

The corrole ring: Synthesis, functionalisation and reactions of a biomimetic macrocycle

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Declaration

I declare that the work presented in this thesis was carried out exclusively by me under the supervision of Professor H M Marques, Professor J P Michael and Doctor M A Fernandes. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



C Zipp

13th day of June 2013

Abstract

The lability of cobalt(III) in vitamin B₁₂ is thought to come about as a function of its coordination environment. The thermodynamics and kinetics of ligand substitution reactions of vitamin B_{12a} were compared to those of a synthetic, more electron rich, corrole-based biomimetic model.

The feasibility of corrole synthesis was established with the synthesis of several corroles with different *meso* substituents. The biomimetic model was designed such that the central *meso* position bore a substituent with a terminal imidazole (referred to as the 'tail') which might act as an axial ligand for a coordinated cobalt ion while the remaining two *meso* positions bore water-solubilising glucose substituents. Unfortunately, the biomimetic model was water soluble below pH 4 only. This rendered the model unsuitable for the present study and these water solubilising groups were not incorporated into the final model. The model system used in this work is [10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-diphenylcorrolato]cobalt(III), referred to as DPTC-Co

Intermediates of the 'tail' *meso* substituent were found to be polymorphic and five pairs of polymorphs were identified. Polymorphism arose from differences in weak intermolecular forces and these differences were evaluated.

The stability constants for the binding of various neutral *N*-, *P*- and *S*-donor ligands and anionic *N*-, *S*-, *I*- and *C*-donor ligands to both vitamin B_{12a} and DPTC-Co were determined in a buffered 80:20 methanol:water solvent system. The more stable binding of neutral ligands to DPTC-Co and anionic ligands to vitamin B_{12a} indicates that the interaction between the metal and an incoming ligand is indeed affected by the metal's coordination environment. Cobalt(III) in DPTC-Co appeared to favour softer ligands while harder ligands were favoured by vitamin B_{12a}.

Kinetic studies showed that the coordination of cyanide to cobalt in vitamin B_{12a} was faster than in DPTC-Co. The reaction between cyanide and vitamin B_{12a} was found to be entropically driven while the reaction with DPTC-Co was enthalpically driven. This suggests that while the reaction between cyanide and vitamin B_{12a} is faster, the reaction between cyanide and DPTC-Co is electronically more labile.

The coordination environment of cobalt has been seen to significantly affect its chemistry. Coordination by the more electron rich corrole macrocycle led to a softer and more electronically labile metal than when coordinated by the corrin macrocycle of vitamin B_{12a}.

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List of abbreviations and symbols

[]	Molar concentration
A	Absorbance
A_0	Initial absorbance
A_1	Final absorbance
AA	Atomic Absorption
A. U.	Arbitrary units
CP	Chemically pure
DFT	Density functional theory
IR	Infra-red
K	Equilibrium constant
K_a	Acid dissociation constant
k	Rate constant
log	Logarithm to the base 10
NMR	Nuclear magnetic resonance
pH	Negative logarithm of proton concentration
pK_a	Negative logarithm of the acid dissociation constant
QTAIM	Quantum Theory of Atoms in Molecules
TD-DFT	Time-dependent density functional theory
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV-vis	Ultra violet-visible
α, β, γ	Visible bands (α, β) and Soret band (γ) in the UV-visible spectrum of vitamin B ₁₂
ϵ	Molar extinction coefficient
λ	Wavelength (nm)
μ	Ionic strength (M)
ν	IR stretching frequency (cm ⁻¹)

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Part 1

A brief history of vitamin B₁₂ and corrole chemistry and the aims of this project

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1.1 Vitamin B₁₂

A vitamin B₁₂ deficiency can be a life threatening condition. Deficiency of this water-soluble vitamin can result in pernicious anaemia, a variety of neurological conditions and general ill health. In the 1850s, pernicious anaemia was fully described by Addison¹ and in 1926 an anti-pernicious anaemia factor was discovered by Whipple, Minot and Murphy.¹ This factor was later discovered to be vitamin B₁₂, reported simultaneously in 1948 by Folkers and associates at the Merck Laboratories in the United States² and Smith and co-workers at the Glaxo Laboratories in the United Kingdom.³ The crystal structure of cyanocobalamin, or vitamin B₁₂, was finally determined in 1955 by Hodgkin⁴ while the first total synthesis of vitamin B₁₂ was completed by Woodward and Eschenmoser in 1973.⁵

Subsequent to its discovery, the interest in vitamin B₁₂ was enormous. The vitamin was keenly studied and its biological purpose as a precursor for an enzyme cofactor, or coenzyme – a small molecule which is required by the enzyme for efficient catalysis of oxidation-reduction or group transfer reactions⁶ – was elucidated with the discovery of a purine-containing derivative⁷ of pseudo-B₁₂ or dicyanocobalamin. This light-sensitive cofactor is required by the glutamate mutase enzyme in bacteria.¹ There are around a dozen enzymes that are known to require vitamin B₁₂-derived coenzymes.⁶ In mammalian systems vitamin B₁₂ coenzymes are necessary for only two enzyme-mediated processes involving alkylation reactions.⁶ The first is the conversion of propionyl-CoA to succinyl-CoA during the oxidation of odd-numbered chain fatty acids. The enzyme responsible for this skeletal rearrangement is methylmalonyl-CoA mutase which requires an adenosylcobalamin coenzyme (as in Figure 1.1.1). The second is the synthesis of methionine in the biosynthesis of S-adenosylmethionine which is a biological methylating agent.⁶ Methionine synthetase or homocysteine methyltransferase is the enzyme which catalyses the conversion of homocysteine to methionine via the transfer of a methyl group. This enzyme requires a methylcobalamin coenzyme. The structure of vitamin B₁₂ and its derivatives is illustrated in Figure 1.1.1 below.

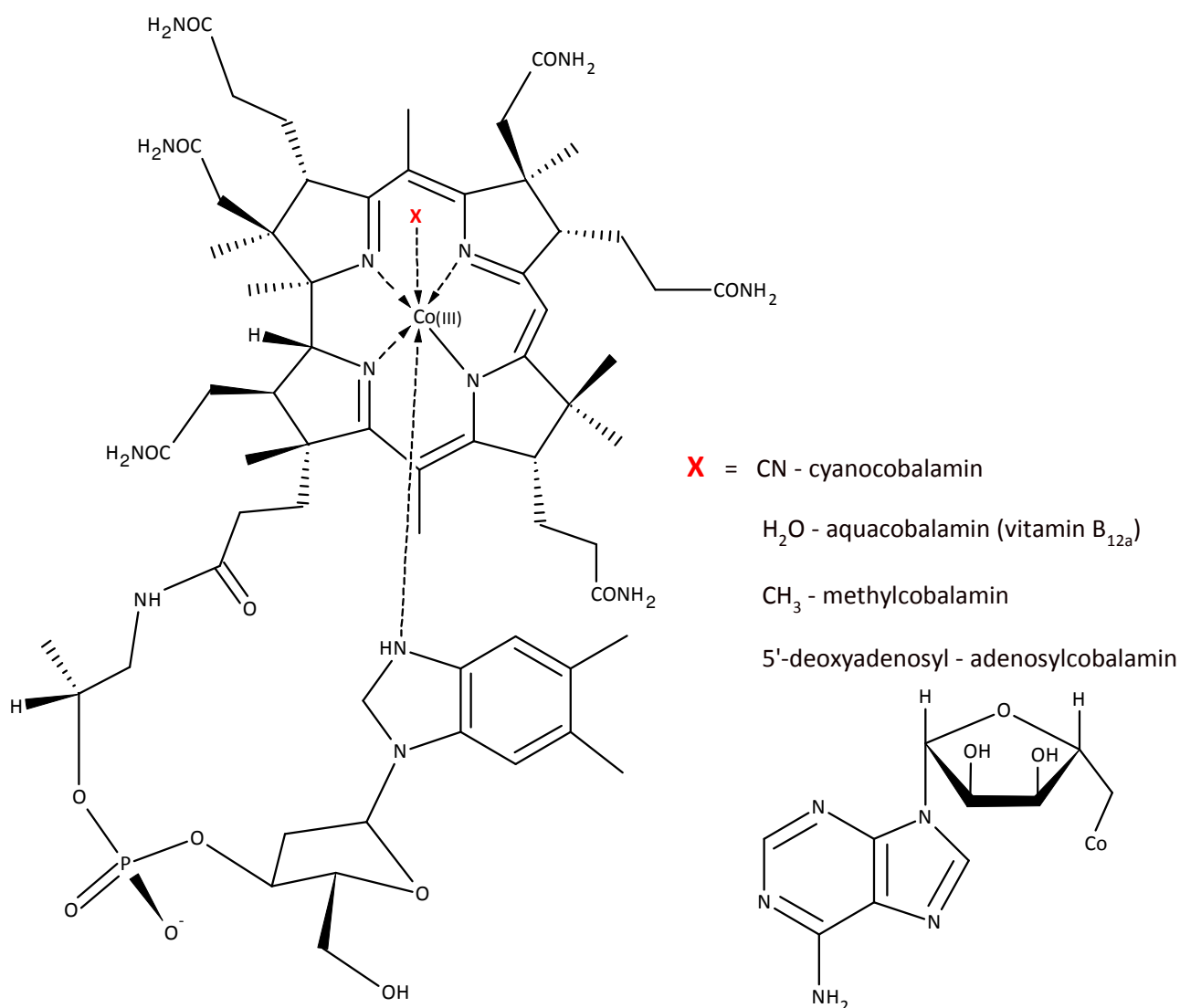


Figure 1.1.1 Vitamin B₁₂ and its derivatives

While the biological role of vitamin B₁₂ was a popular subject, so was its chemistry. Vitamin B₁₂ is the largest, most complex vitamin and contains a biologically-rare cobalt(III) ion encased in a corrin ring. The four pyrrole nitrogens of the corrin ring provide four equatorial ligands. One axial ligand is provided by a 5,6-dimethylbenzimidazole nucleotide group (DMBz) while the other axial ligand differs from derivative to derivative as illustrated in Figure 1.1.1.

The structure of vitamin B₁₂ is a curiosity. The corrin ring is present instead of the biologically-prolific porphyrin macrocycle and a biologically-rare metal ion, cobalt in the

3+ oxidation state, is found at the centre of the vitamin as opposed to a more common biological metal such as iron, copper or manganese. Vitamin B₁₂, an enzymatic cofactor, catalyses fast reactions, but cobalt (III), a d⁶ low spin transition metal, is the classic example of a kinetically inert metal ion, while it is the low spin d⁷ cobalt (II) ion which is kinetically labile. The rate of substitution of one ligand for another in hexa-coordinated cobalt is dependent on the oxidation state of the metal. The rate of substitution of one water ligand by bulk water in a hexaaqua cobalt is $3.2 \times 10^6 \text{ s}^{-1}$ for the $[\text{Co}(\text{H}_2\text{O})_6]^{2+}$ complex and ten orders of magnitude slower for $[\text{Co}(\text{H}_2\text{O})_6]^{3+}$ complex.⁸ These substitution reactions are also sensitive to the coordination environment of the cobalt ion. Cobalt(III), encased by a porphyrin macrocycle system equivalent to aquacobalamin, reacts more slowly during ligand substitution reactions. The rate constant for the substitution of the axially bound water by iodide in the porphyrin system is $1.6 \text{ M}^{-1} \text{ s}^{-1}$.⁹ In aquacobalamin, a corrin system, the rate constant for the same substitution reaction is three orders of magnitude faster at $2.2 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.⁹

These are significant differences! It is clear that both the oxidation state of the metal and the identity of the coordination environment affect the chemistry of the system. The unexpected activity of cobalt(III) in vitamin B₁₂ is intriguing: why has nature used a normally inert metal ion in a biologically important molecule which is required by biological catalysts, and how has the system been manipulated to enhance this metal's inherent inertness? It is thought that the smaller cavity of the partially aromatic corrin ring increases the electron density of the metal, through a *cis* inductive effect that is enhanced by the increased proximity of the electron rich nitrogen donors. This may result in a cobalt(III) metal centre with partial cobalt(II) character, increasing the lability of the system.^{10,11}

1.2 Project background

Given that the nature of the cobalt ion's environment affects the lability of the system, the chemists in the bioinorganic research laboratories at the University of the Witwatersrand have perturbed the vitamin B₁₂ system in a variety of different ways, as indicated in Figure 1.2.1, in order to determine from where the lability of vitamin B₁₂ originates.

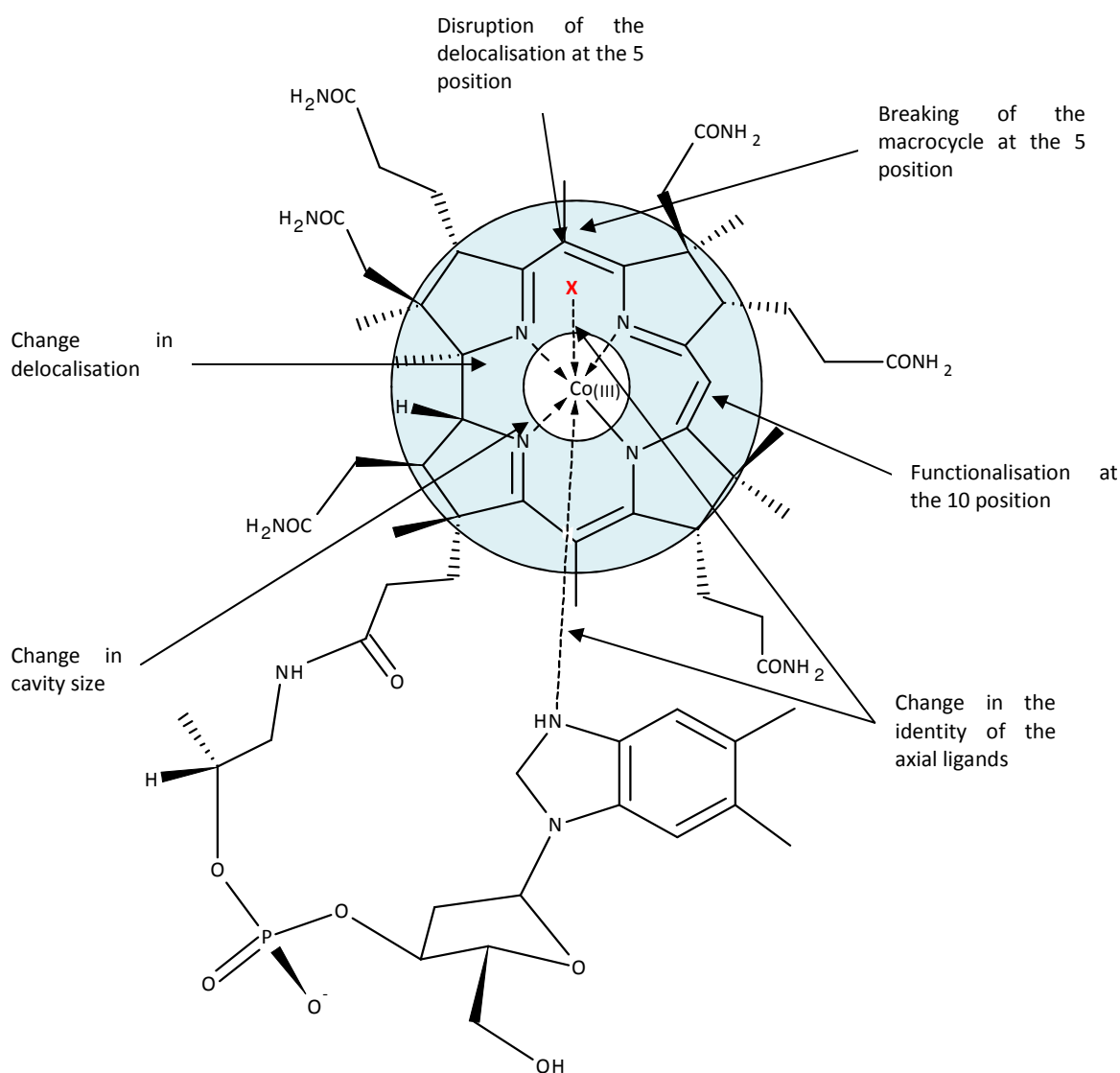


Figure 1.2.1 Perturbation of the vitamin B₁₂ system

Chemaly and co-workers disrupted the delocalisation of the corrin ring at the 5 position of aquacyanocobyrinic acid hetamethyl ester, or aquacyanocobester, to form stable yellow aquacyanocobyrinic acid hetamethyl ester, or stable yellow aquacyanocobester.^{12,13} It has been found that cobalt in aquacyanocobester is both kinetically more labile and thermodynamically softer than in the stable yellow aquacyanocobester, indicating the importance of the delocalised electron cloud of the corrin ring in the labilisation of the cobalt ion.^{12,13} Nowakowska and co-workers disrupted the corrin ring by cleaving the macrocycle at the 10 position, forming 5-seco-dicyanocobester.¹⁴ The now acyclic ligand surrounding the cobalt ion is able to adjust to the steric demands of the cobalt ion. It was found that there was a small decrease in the stability constants for the binding of various ligands when compared to stable yellow aquacyanocobester.¹⁴ These preliminary results, together with those of Chemaly and co-workers, suggest that a change in the electronic structure of the cobalt's coordination environment is more important than the topology of the corrin ring.

Knapton and co-workers explored the effect of functionalization of the 10 position. Both 10-chloro^{9,10} and 10-nitroso¹⁵ derivatives of vitamin B₁₂ were prepared. The π -delocalised system of the 10-chloro derivatives were found to be more electron rich due to π donation from the chloro group at the C10 position.⁹ The coordination of anionic ligands was more favourable in the case of the aqua 10-chloro vitamin B₁₂ derivative than to aquacobalamin itself and the converse was true of the binding of neutral *N*-donor ligands.¹⁰ The electron withdrawing nitroso group, on the other hand, was found to deactivate the metal ion towards substitution reactions.¹⁵ These results indicate that the electronic structure of the corrin ring influences the ability of the coordinated metal to bind axial ligands.

The size of the macrocyclic cavity was altered by Mathura and co-workers through the use of a porphyrin based biomimetic model, *N*-acetyl-Co(III) microperoxidase-8.¹⁶ The coordination of neutral *N*-donor ligands to the porphyrin biomimetic was favoured over aquacobalamin while the converse was true for anionic ligands, indicating the effect of the change in the residual charge on the metal centre (+2 in the case of the corrin and +1

for the porphyrin).¹⁶ The nature of the ligand was found to affect the kinetics of the ligand exchange reaction in the two different macrocyclic systems. These results, together with the results discussed above, highlight that the nature of the coordination environment of the metal ion plays an important role in the chemistry of cobalt(III).

The electronic nature of the macrocycle in vitamin B₁₂ is clearly central to its chemistry. This work seeks to further explore this hypothesis through the use of an *aromatic* macrocycle with a cavity size comparable to that of the corrin ring. The corrole ring answers this description and is the basis of the biomimetic model designed in this work.

1.3 Corroles: history and nomenclature

Corroles are fully aromatic tetrapyrrole macrocycles containing a direct pyrrole-pyrrole bridge. These macrocycles are the link between the fully delocalised porphyrin and the partially delocalised corrin ring of vitamin B₁₂. This family of macrocycles is illustrated in Figure 1.3.1. As a result of the absence of one of the methine bridges of the porphyrin system, corroles have a smaller cavity than porphyrins,¹⁷ and a more electron-rich π system than corrins¹⁸ due to a fully aromatic system containing 18 π electrons delocalised over 19 atoms. The corrole obeys Hückel's $4n+2$ rule and thus conforms to Hückel's rule for aromaticity. In addition, there is a decrease in symmetry, from the D_{4h} symmetry of an unsubstituted porphyrin to C_{2v} of the related corrole.^{17,18} Corroles are stronger acids than their porphyrin and corrin counterparts due to the presence of one 'pyridine-like' nitrogen atom and three 'pyrrole-like' nitrogens (porphyrins have two of each type while corrins have three 'pyridine-like' and one 'pyrrole-like' nitrogen).¹⁷ This allows for a tri-anionic system, while porphyrins are di-anionic and corrins are mono-anionic. Together with the small cavity size of corrole macrocycles, the tri-anionic nature allows for complexation with metals in both very high and very low formal oxidation states.^{18,19} Interestingly, corrole rings are often completely planar, while porphyrins tend to bend and buckle slightly. This may be due to the removal of one of the methyl groups in the formation of the direct pyrrole-pyrrole link which results in a more rigid (and planar) resonating system.

The numbering system used in corrole chemistry is similar to that of other macrocycles. The carbon backbone of the corrole is numbered from the pyrrole-pyrrole bridge with the 5, 10 and 15 positions representing the methine bridges or *meso* positions. The hydrogen-bearing pyrrolic carbons are known as the β positions while the remaining pyrrolic carbons are known as the α positions. Both the *meso* and β positions can be functionalised.

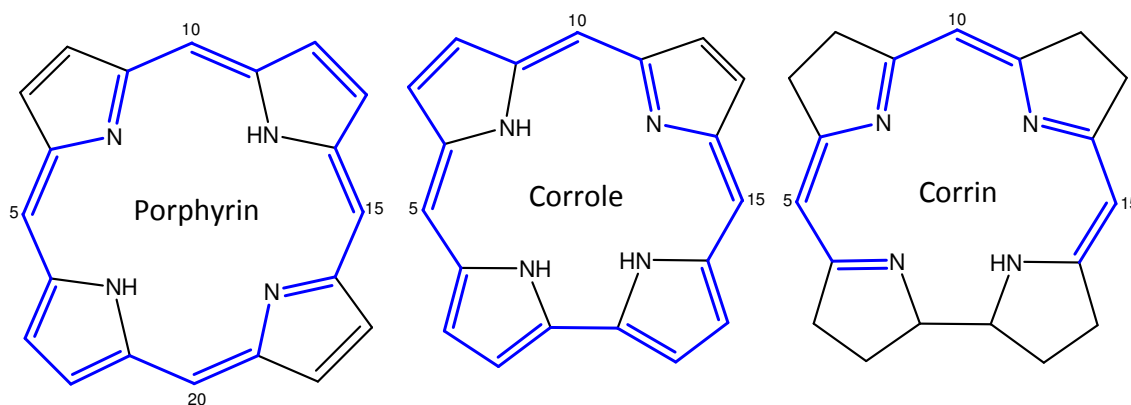


Figure 1.3.1 Three tetrapyrrole macrocycles and the conventional numbering scheme

Corroles were first synthesised in 1964 by Johnson and Kay;²⁰ however it was only after 1999, when the first ‘one-pot’ synthesis was reported simultaneously by Paolesse and co-workers²¹ and Gross and co-workers,²² that there was a dramatic increase in the number of corrole-based articles in the literature. The advent of an easy synthetic route to corroles led to an interest in the properties and applications of these macrocycles. In particular, 5,10,15-triarylcorroles were of great interest due to the reactivity and oxidative sensitivity of the carbon atoms in the *meso* position.²³ As a result of this chemistry, *meso*-substituted corroles are robust and stable towards oxidation.^{18,23} Increased stability and electronic character allows for complexation with a wide variety of metals including metal ions with high formal oxidation states such as iron(IV), cobalt(IV) and cobalt(V)^{17,22,24} where corroles act as tetradentate trianionic ligands.²² In addition to the stabilization of these high formal oxidation state metals, metal-corrole systems have shown remarkable lability with respect to the substitution reactions of axial ligands.¹⁹

1.4 Corrole applications

With the discovery of the interesting chemistry of corrole systems, several applications for these molecules were quickly discovered which are summarised in a comprehensive review of corrole based applications by Aviv and Gross.²³ The ability of corroles to coordinate to metal ions with very high oxidation states allows for their use in catalysis.^{17,18,23,25,26} Corroles have been used to catalyse oxidation reactions such as the hydroxylation²³ and hydroperoxidation²³ of alkanes; epoxidation reactions;^{23,25} sulfoxidation^{18,23} as well as reduction reactions such as oxygen reduction,^{23,26} carbon dioxide reduction to yield useful products;²³ decomposition of reactive oxygen species such as hydrogen peroxide and peroxyxynitrite, one of the most damaging reactive oxygen species generated in organisms during oxidative stress.²³ In addition to redox catalysis, corroles have been used in the catalysis of group transfer reactions, such as carbene and nitrene transfer to olefins^{18,23} and C-H and N-H insertions of carbenes.²³

Another area of corrole chemistry application is in the sensor arena. Corroles have been found to be useful gas sensors in the detection of carbon monoxide levels due to the selective binding of diatomic oxygen or carbon monoxide depending on the oxidation state of the co-ordinated cobalt ion (cobalt(II) and(III) respectively).²³ Optical pH sensors utilise corrole systems due to the potential for three different protonation states²³ while they have also been used in the construction of ion selective and liquid-membrane electrodes.²³

Together with porphyrins and phthalocyanines, corroles have been used in dye sensitized solar cells.²³ While corroles have been shown to be potential dyes in these systems, optimisation in this field is required to increase the efficiency of corrole systems so that they are comparable to existing solar cell systems.²³

With the publication of the preparation of water-soluble corroles,^{22,23} corroles have also been identified to have potential medicinal applications.^{18,23} These systems have shown promising anti-tumour activity by preventing cell proliferation and tumour

progression.^{18,23} The oxidation of lipoproteins, which plays an important role in the development of atherosclerosis was reduced by the antioxidant properties of a water soluble iron corrole.¹⁸ The fluorescent properties of corroles also allow for their potential use as imaging agents for *in vitro* investigations of cancerous tissue.^{17,18,23}

1.5 Corroles as biomimetic macrocycles

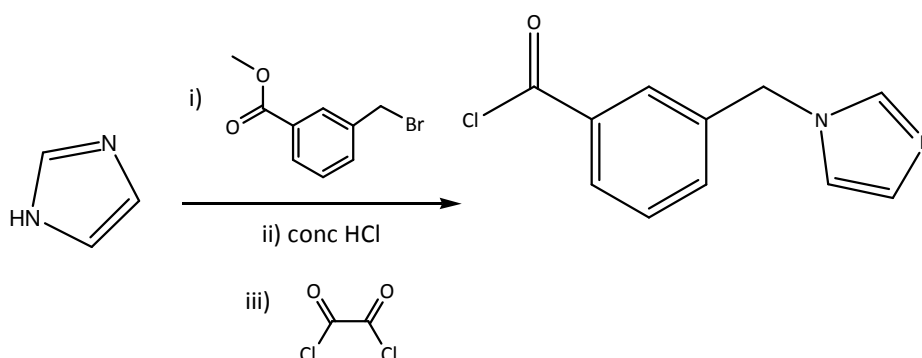
The world was first introduced to the concept of biomimetics by Otto Schmitt in the 1950s in his attempt to create a mechanical device that copied the electrical action of a nerve.²⁷ Later, in the 1970s, the following definition for biomimetics appeared in Webster's Dictionary:

"The study of the formation, structure, or function of biologically produced substances and materials (as enzymes or silk) and biological mechanisms and processes (as protein synthesis or photosynthesis) especially for the purpose of synthesizing similar products by artificial mechanisms which mimic natural ones."²⁷

The use of biomimetics, however, is an age-old phenomenon with humans attempting to replicate nature. The manner in which they clothe themselves, the tools which they use and the quest for flight are but a few examples of humans' mimicry of nature.^{27,28} This broad field of study covers a variety of disciplines including chemistry, physics, medicine and engineering.^{27,28}

There is a great deal of interest in the synthesis of macrocyclic biomimetic systems which are used for the discovery of mechanistic and functional details of biological macrocycles.²⁹ These systems involve the synthesis of a macrocycle with a tail motif which can act as an axial ligand for the co-ordinated metal ion. A lot of work has been done in this area with porphyrins, which are used as biomimetic systems for haem biochemistry.²⁹⁻³⁵ The models have been used to mimic enzymatic catalytic cycles in biology in order to understand mechanistic details^{31,36} and to determine the possible nature of intermediates in said cycles.^{31,32,35} This is often achieved through the synthesis of a system which mimics the active site of an enzyme, such as cytochrome c oxidase.^{34,35} Tailed corroles have also been synthesised as a starting point for corrole ring-based biomimetics of haem-proteins.³⁷ In the case of corrole-based analogues, the effect of the change in cavity size (when compared to that of porphyrins) is of interest.

Collman and co-workers proposed a synthetic route for a tailed porphyrin in 1998.²⁹ This route involved the synthesis of an imidazole acid chloride tail which was then coupled to a porphyrin bearing amine moieties.²⁹ The synthesis of the acid chloride tail is given below in Scheme 1.5.1. This tail has been used by several other research groups in the synthesis of mainly porphyrin^{30-33,35-38} but also corrole³⁷ biomimetic systems.



Scheme 1.5.1 Collman's imidazole acid chloride tail synthesis

Water solubility plays a key role in the synthesis of a successful biomimetic system. With the water solubility of enzymes, proteins, polypeptides, amino acids and in particular, vitamin B₁₂ and the metallated corrin ring at the heart of this vitamin, it is important that any biomimetic model be water-soluble as well. Several water-soluble corroles have been synthesised to date.³⁹⁻⁴³ These corroles contain either pyridinium or sulfonate moieties.^{22,40-43} Figure 1.5.1 below illustrates the water-soluble corroles synthesised.

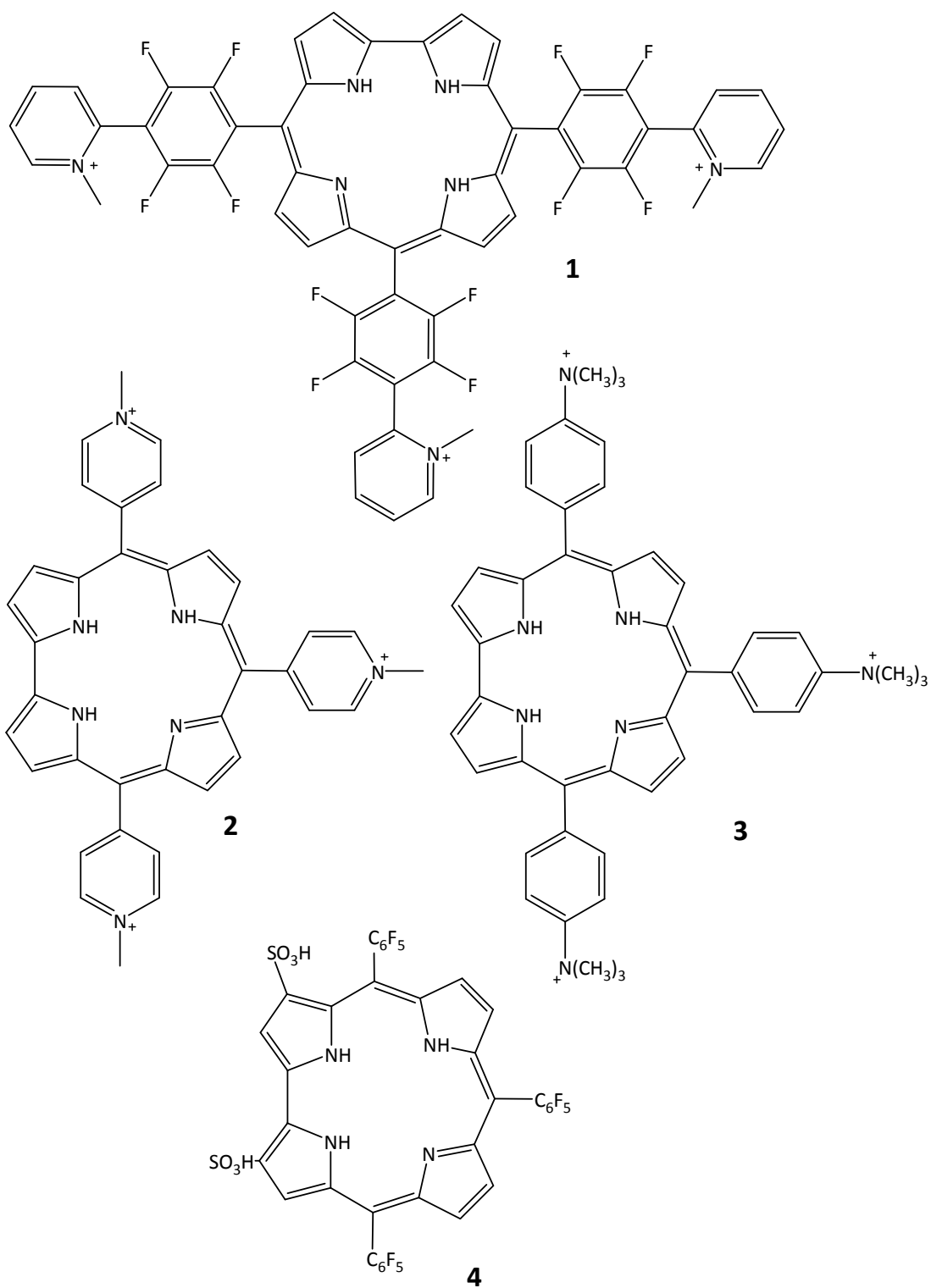


Figure 1.5.1 Water-soluble corroles. (1) methylation of 5,10,15-tris[4-(2-pyridyl)-2,3,5,6-tetrafluorophenyl]corrole²² (2) 4-pyridinium corrole⁴¹ (3) quaternary ammonium corrole⁴¹ (4) bis-sulfonic acid corrole derivative⁴³

1.6 Project aims

The work reported here aimed to investigate the synthesis of a corrole-based biomimetic system of vitamin B₁₂ and the ligand exchange reactions of this system compared to those of aquacobalamin. The central question is how does the coordination environment of cobalt affect its chemistry?

The chemistry of the corrole macrocycle has not previously been explored in the bioinorganic research laboratory at the University of the Witwatersrand. As such, determination of the feasibility of the synthesis and purification of these macrocycles was the first major aim of this study. The effect of the incorporation of large substituents at the *meso* positions on the stability of the macrocycle also needed to be determined.

The second major aim of this work was to design and synthesise a corrole based system reminiscent of vitamin B₁₂. As a biomimetic system, this model required firstly a long substituent which could act as an axial ligand for a coordinated cobalt ion; secondly, a water-solubilising system was to be designed and incorporated into the biomimetic model so that the reactions could be studied in aqueous media. The third major aim of this work was thus to synthesise a water-soluble corrole. Other work in the bioinorganic research laboratory on the synthesis of water-soluble porphyrins involved the incorporation of glucose moieties as water solubilising agents.⁴⁴ As a result, this water-solubilising system was to be used in an attempt to synthesis water-soluble corroles.

In order to answer the central question of this study, the stability constants and kinetic parameters of ligand substitution reactions were determined for both vitamin B_{12a} and the biomimetic model, the fourth major aim of this work. This required an understanding of both the solution chemistry of the model.

Finally, the fifth aim of this study was to gain insight into the nature of the corrole-cobalt-ligand complexes through analysis of absorption spectra calculated using DFT methods in an attempt to understand the electronic structure of these complexes.

The hypothesis of this work is that the increased electron density of the fully delocalised corrole system (compared to the partially delocalised corrin system) will affect the chemistry of the coordinated cobalt ion resulting in a system that is both more kinetically labile and with a softer metal ion than vitamin B_{12a}.

1.7 References

- (1) Okuda, K. *J. Gastroenterol. Hepatol.* **1999**, *14*, 301-308.
- (2) Rickees, E. L.; Brink, N. G.; Koniuszy, F. R.; Wood, T. R.; Folkers, K. *Science* **1948**, *107*, 396-397.
- (3) Smith, E. L. *Nature* **1948**, *161*, 638-639.
- (4) Hodgkin, D. C.; Kamper, J.; Trueblood, J. G.; Prosen, R. J. *Nature* **1955**, *176*, 325-330.
- (5) Woodward, R. B. *Pure & Appl. Chem.* **1973**, *33*, 145-177.
- (6) Voet, D.; G., V. J. *Biochemistry*; 3rd (Wiley International Edition) ed.; John Wiley & Sons, Inc., 2004.
- (7) Barker, H. A.; Weissbach, H.; Smyth, R. D. *Proc. Natl. Acad. Sci. USA* **1958**, *44*, 1093-1097.
- (8) Ducommun, Y.; Zbinden, D.; Merbach, A. E. *Helv. Chim. Acta* **1982**, *65*, 1385-1390.
- (9) Brown, K. L.; Cheng, S.; Zou, X.; Zubkowski, J. D.; Valente, E. J.; Knapton, L.; Marques, H. M. *Inorg. Chem.* **1997**, *36*, 3666-3675.
- (10) Knapton, L.; Marques, H. M. *Dalton Trans.* **2005**, 889-895.
- (11) Perry, C. B.; Fernandes, M. A.; Brown, K. L.; Zou, X. A.; Valente, E. J.; Marques, H. M. *Eur. J. Inorg. Chem.* **2003**, 2095-2107.
- (12) Chemaly, S. M.; Florczak, M.; Dirr, H.; Marques, H. M. *Inorg. Chem.* **2011**, *50*, 8719-8727.
- (13) Chemaly, S. M.; Kendall, L.; Nowakowska, M.; Pon, D.; Perry, C. B.; Marques, H. M. *Inorg. Chem.* **2012**.
- (14) Nowakowska, M., Personal Communication.
- (15) Marques, H. M.; Knapton, L.; Zou, X.; Brown, K. L. *J. Chem. Soc., Dalton Trans.* **2002**, 3195-3200.
- (16) Mathura, S.; de Sousa, A. S.; Perry, C. B.; Navizet, I.; Marques, H. M. *J. Inorg. Biochem.* **2013**, Submitted.
- (17) Gryko, D. T. *Eur. J. Org. Chem.* **2002**, 1735-1743.
- (18) Aviv-Harel, I.; Gross, Z. *Chem. Eur. J.* **2009**, *15*, 8382-8394.
- (19) Joseph, C. A.; Ford, P. C. *J. Am. Chem. Soc.* **2005**, *127*, 6737-6743.

- (20) Johnson, A. W.; Kay, I. T. *J. Chem. Soc.* **1965**, 1620-1629.
- (21) Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F.; Boschi, T.; Smith, K. M. *Chem. Commun.* **1999**, 1307-1308.
- (22) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem. Int. Ed.* **1999**, *38*, 1427-1429.
- (23) Aviv, I.; Gross, Z. *Chem. Commun.* **2007**, 1987-1999 and references therein.
- (24) Kerber, W. D.; Goldberg, D. P. *J. Inorg. Biochem.* **2006**, *100*, 838-857.
- (25) Collman, J. P.; Zeng, L.; Decréau, R. A. *Chem. Commun.* **2003**, 2974-2975.
- (26) Collman, J. P.; Kaplun, M.; Decréau, R. A. *J. Chem. Soc., Dalton Trans.* **2006**, 554-559.
- (27) Vincent, J. F. V.; Bogatyreva, O. A.; R., B. N.; Bowyer, A.; Pahl, A.-K. *J. R. Soc. Interface* **2006**, *3*, 471-482.
- (28) Bar-Cohen, Y. In *SPIE Smart Structures Conference*; SPIE: San Diego, CA, 2005; Vol. 5759-02.
- (29) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenninger, R. *J. Org. Chem.* **1998**, *63*, 8084-8085.
- (30) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenninger, R.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 8082-8083.
- (31) Liu, J.-G.; Ohta, T.; Yamaguchi, S.; Ogura, T.; Sakamoto, S.; Maeda, Y.; Naruta, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 9262-9267.
- (32) Didier, A.; Michaudet, L.; Ricard, D.; Baveux-Chambenoît, V.; Richard, P.; Boitrel, B. *Eur. J. Org. Chem.* **2001**, 1917-1926.
- (33) Young, R.; Chang, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 898-909.
- (34) Decréau, R. A.; Collman, J. P.; Yang, Y.; Yan, Y.; Devaraj, N. K. *J. Org. Chem.* **2007**, *72*, 2794-2802.
- (35) Liu, J.-G.; Naruta, Y.; F., T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1836-1840.
- (36) Collman, J. P.; Sunderland, C. J.; Boulatov, R. *Inorg. Chem.* **2002**, *41*, 2282-2291.
- (37) Collman, J. P.; Decréau, R. A. *Org. Lett.* **2005**, *7*, 975-978.
- (38) Berto, T. C.; Praneeth, V. K. K.; Goodrich, L. E.; Lehnert, N. *J. Am. Chem. Soc.* **2009**, *131*, 17116-17126.
- (39) Mahammed, A.; Weaver, J. J.; Gray, H. B.; Abdelas, M.; Gross, Z. *Tetrahedron Lett.* **2003**, *44*, 2077-2079.

- (40) Mahammed, A.; Gross, Z. *Dalton Trans.* **2010**, 39, 2998-3000.
- (41) Fu, B.; Huang, J.; Ren, L.; Weng, X.; Zhou, Y.; Du, Y.; Wu, X.; Zhou, X.; Yang, G. *Chem. Commun.* **2007**, 3264-3266.
- (42) Haber, A.; Agadjanian, H.; Medina-Kauwe, L. K.; Gross, Z. *J. Inorg. Biochem.* **2008**, 102, 446-457.
- (43) Mahammed, A.; Goldberg, I.; Gross, Z. *Org. Lett.* **2001**, 3, 3443-3446.
- (44) Riley, D. *Post Doctoral Report*, University of the Witwatersrand, 2010.

Part 2

Synthesis of a corrole-based biomimetic model

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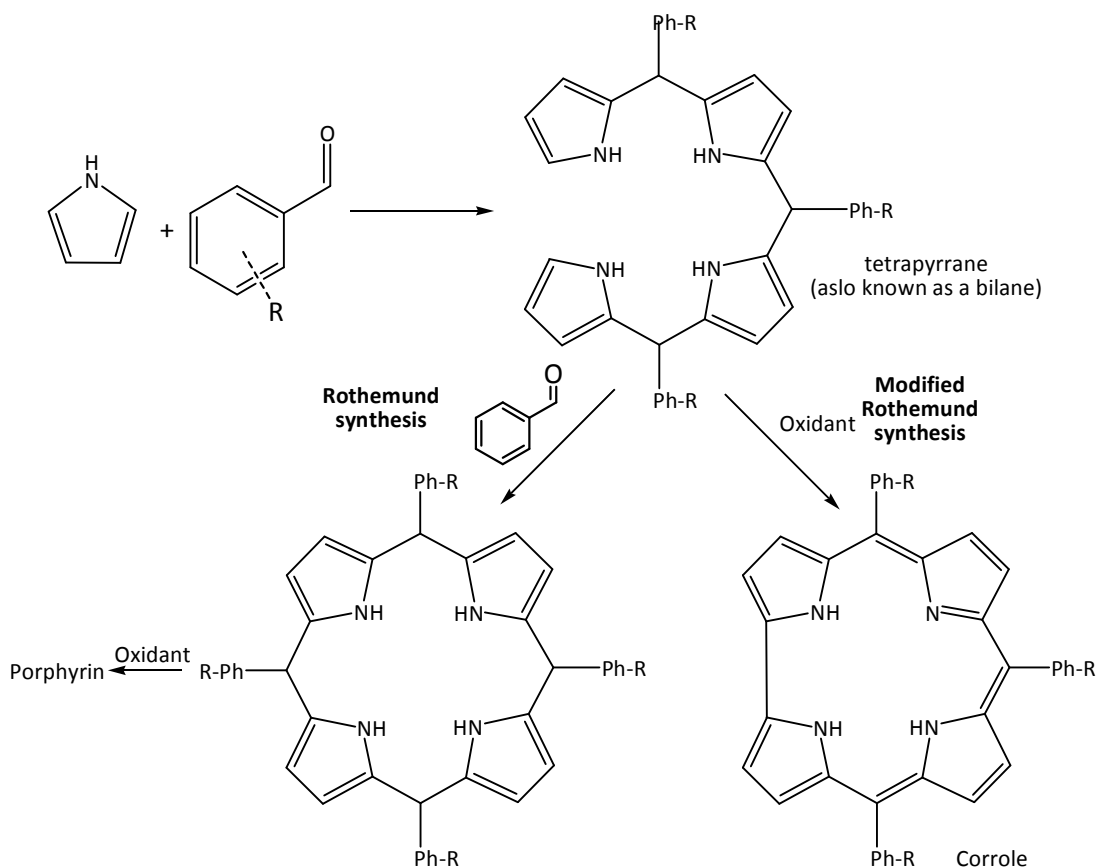
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2.1 Introduction

2.1.1 Synthetic approaches: 'One-pot' syntheses

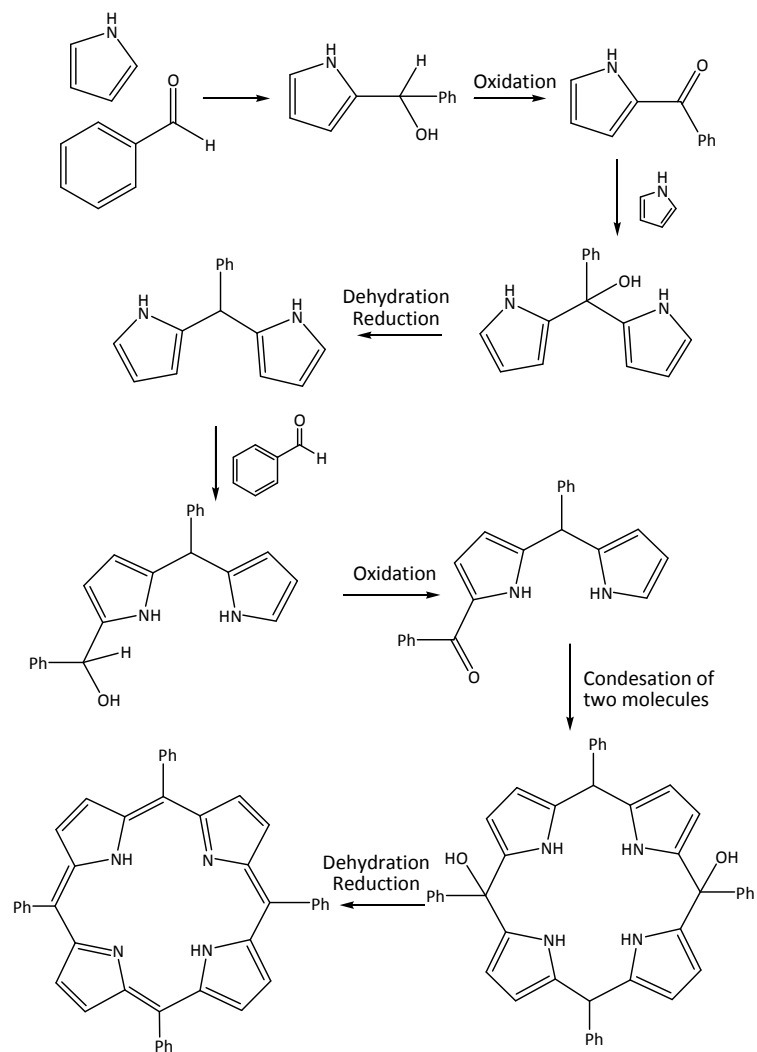
Prior to the discovery of a one-pot synthetic route for the synthesis of corroles there was little interest in these macrocycles owing to their laborious and inefficient synthesis. With the publication of the first easy and feasible routes to corroles in 1999, interest has increased, and the number of publications on the subject has exploded.¹ There are two general synthetic approaches in corrole synthesis. The first is the 'one-pot' route, while the second follows a step-wise or 'lego' approach, where building blocks of the macrocycle are synthesised and then assembled to form the desired macrocycle.

The basis for corrole synthesis stems from the Rothemund reaction, developed in the 1930s, which uses the condensation of a 1:1 ratio of pyrrole and an aldehyde to form a porphyrin.² The modified Rothemund reaction manipulates the reaction conditions by using a 3:1 ratio of pyrrole and an aldehyde in an attempt to suppress the formation of porphyrin and promote corrole formation. The yields of these reactions are generally low (below 10%).^{3,4} A typical reaction scheme for the synthesis of 5,10,15-triphenylcorrole is illustrated below in Scheme 2.1.1. The first step involves an acid catalysed electrophilic substitution reaction yielding pyrrole-aldehyde condensation oligomers of various lengths. The second step is the oxidative ring closure to form the macrocycle of interest.⁵ It is thought that the second step proceeds through the oxidation (atmospheric oxygen in aerobic systems or a chemical oxidant in anaerobic systems) of a tetrapyrane (also known as a bilane) intermediate.



Scheme 2.1.1 Rothemund and modified Rothemund syntheses in the synthesis of tetraarylporphyrins and triarylcorroles

Together with low yields, the modified Rothemund reaction yields a mixture of products as illustrated in Figure 2.1.1, including the corresponding *N*-confused porphyrin and the sapphyrin. While the details of the reaction mechanism have not been fully investigated,⁴ a speculative mechanism is given below in Scheme 2.1.2, as described by Badger and co-workers.⁶



Scheme 2.1.2 Proposed reaction mechanism for the modified Rothemund reaction

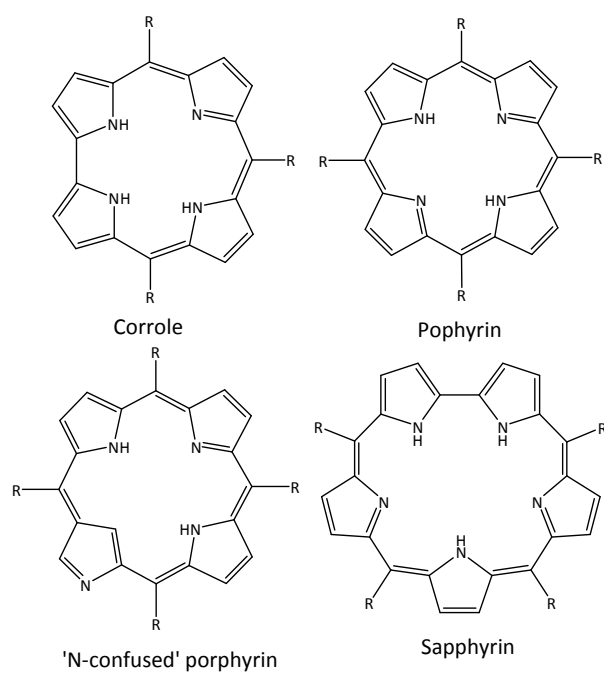


Figure 2.1.1 Products of the modified Rothemund reaction.

The one-pot syntheses^{3,4,7-9} that have revolutionised corrole chemistry vary substantially. Two different methodologies were published in 1999. In spite of the differences between these two methodologies and other methodologies that arose after 1999, the molecular basis of one-pot A₃ corrole synthesis remains the same. This entails two independent steps, the first of which involves the reaction between pyrrole and benzaldehyde derivatives. This reaction is acid-catalysed electrophilic substitution and results in a mixture of aldehyde-pyrrole polymers of various lengths with alternating pyrrole and aldehyde subunits. The second step involves the oxidative ring closure of the polymers and subsequent aromatisation to yield a variety of macrocycles based on the length and identity of the polymer chain produced in the first step.⁵ The desired polymer for corrole synthesis is composed of the condensation of four pyrrole and three aldehyde subunits. This is known as a bilane or tetrapyrane.⁵ The various one-pot synthetic methodologies vary in the first step, but are similar in that the second step is generally achieved with the use of an oxidant such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or *p*-chloranil (tetrachloro-1,4-benzoquinone) in an organic solvent such as chloroform or dichloromethane.

The work of Paolesse and coworkers³ altered the pyrrole:benzaldehyde molar ratio typically used in porphyrin synthesis from approximately 1:1¹⁰ to 3:1 in an effort to limit the number of aldehyde units (becoming *meso* substituents) to three (forming a corrole), preventing the inclusion of a fourth aldehyde (which would form a porphyrin). They later expanded on this synthesis in 2001⁴ with the synthesis of A₃ corroles bearing different *meso* substituents which could be further functionalised. In these systems, all eight of the β substituents were the same as were the three *meso* substituents. Corrole yields were low, typically well below 10%.

Gross and coworkers⁷ used a solvent-free approach in the presence of a solid support. Equimolar quantities of pyrrole and aldehyde were heated for several hours in the presence of florisil, alumina or silica. The black tar-like product was then washed with dry dichloromethane and oxidised with DDQ in the presence of air. Later, Gross and coworkers found that the presence of the solid support and the use of heat were

unnecessary⁸ as rapid mixing of pyrrole and fluorinated aldehyde led to a highly exothermic reaction and the reaction was complete within minutes. DDQ oxidation was still required but subsequent purification was easier with the formation of fewer by-products than in equivalent reactions which occur in the presence of solvent. This is thought to be due to the very short reaction times and the simplicity of the reaction procedure.⁸ Yields were found to be highly dependent on the electronic nature of the aldehyde, with electron-poor aldehydes performing poorly. Yields also varied with scale, with the yield decreasing significantly with upscaling, where the use of the solid support was imperative. In the case of fluorinated aromatic aldehydes, yields varied between 8% and 11%. With the use of benzaldehyde, tetraphenylporphyrin was obtained with no corrole detected, highlighting the limitation of a method which is only effective in the presence of highly electron-rich aldehydes. Gross's methodology was expanded on by Collman and Decréau in 2003,⁹ with an increase of yields of up to 15% with the use of a short burst microwave radiation followed by DDQ oxidation. Again, this synthesis was successful with the use of electron-rich aldehydes only. In spite of this limitation, this method allows for fast synthesis of A₃ corroles bearing electron-rich *meso* substituents. The use of the term 'solvent-free' is perhaps misleading as the workup and oxidation stage of the procedure involved the use of up to 200 ml of dichloromethane for a 1.9 mmol scale reaction and up to two column chromatographic purification steps were used to afford pure product.

Another solvent-free approach has been developed by Collman and Decréau⁹ which also makes use of electron-poor aldehydes as well as a pyrimidyl-aldehyde. This synthesis makes use of microwave irradiation instead of conventional heating and refluxing methods, with increased yields after very short irradiation periods.⁹

It must be noted that the two reported solvent-free methods were effective only in the presence of electron-poor aldehydes where an increase in strongly electron-withdrawing groups, such as fluorine, increase the 'activating inductive effect'⁹ on the aldehyde, making it more reactive towards pyrrole. In the case of non-fluorinated aldehydes, the

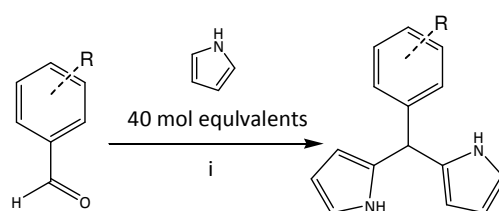
modified Rothemund reaction remains the most effective 'one-pot' synthetic route for corrole synthesis.⁹

While 'one-pot' syntheses were desired for their ease of preparation and quick results, there was little control as to the ratio of desired product and undesired by-products. In particular, the only means of influencing the corrole:porphyrin ratio in favour of corrole appeared to be by control of the pyrrole:aldehyde ratios.

In 2006, Koszarna and Gryko published an efficient synthetic method for the synthesis of *meso*-substituted corroles using a water:methanol solvent system in the presence of catalytic HCl⁵ as opposed to a purely organic solvent system as had been used in previously published syntheses. Gryko's method was found to be very efficient due to the selectivity of intermediates formed based on their solubility in the 1:1 methanol:water mixture in the presence of 0.1 equivalents of hydrochloric acid. The difference in solubility of the starting materials and the desired bilane product together with other intermediates was exploited. The starting materials and dipyrromethane intermediate (two pyrrole and one aldehyde subunit) were soluble in the water:methanol mixture. The bilane, on the other hand, was less soluble in this solvent system and thus precipitated from solution, effectively halting the reaction at the bilane stage. The bilane could then be isolated and oxidised to the corrole macrocycle. In this way, the synthesis of porphyrins and other core-modified porphyrins was greatly reduced.⁵ The use of *p*-chloranil as opposed to DDQ as oxidant was found to increase corrole yields. This synthetic strategy was found to increase corrole yields significantly from well below 20% to between 13% and 56% depending on the identity of the starting materials.

2.1.2 Synthetic approaches: The 'lego' approach

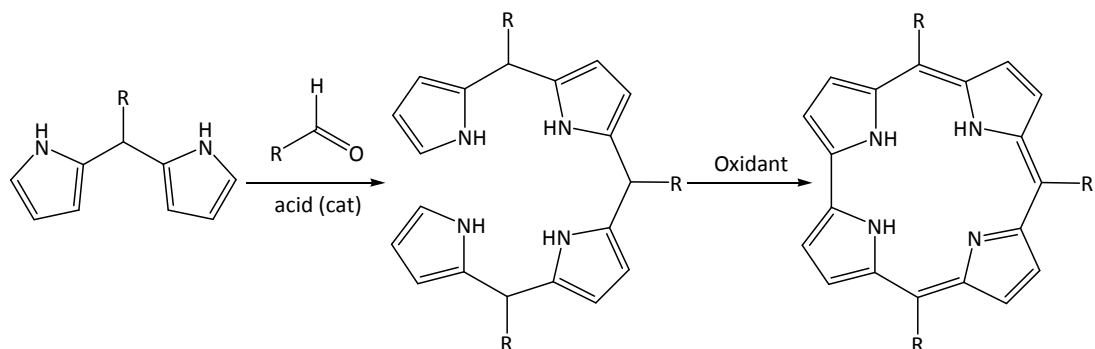
Control over the formation of the corrole macrocycle over the porphyrin or other macrocycles is possible in a step-wise approach, with the synthesis of parts of the macrocycle, which would then be fused to form the desired corrole. This will be referred to as the 'lego' approach. The 'lego' approach has been used by many research groups in the synthesis of porphyrins and other core-modified porphyrins, such as corroles. Two pyrrole units linked by a methine bridge, commonly known as a dipyrromethane, is one of the first intermediates in the building of the desired macrocycle. Dipyrromethanes are synthesised from pyrrole and an aldehyde in the presence of a catalytic amount of acid,¹¹ often trifluoroacetic acid (TFA), as indicated in Scheme 2.1.3 from the method published by Lee and Lindsey in 1994.¹¹ This method allows for the design of macrocycles with different *meso*-substituents. This efficient synthesis (both in terms of time and yield – generally not less than 50%) has been reported by several groups^{11,12} and the dipyrromethane product has been identified as an important precursor for corrole synthesis.^{5,13,14} Dipyrromethane synthesis requires a large excess of pyrrole (typically a 40:1 ratio of pyrrole to aldehyde is used) to prevent the formation of oligomers,¹¹ while the short reaction time and low temperature (15 minutes at room temperature) prevent pyrrole polymerisation.



Scheme 2.1.3 Dipyrromethane synthesis¹¹ i) cat. TFA, 15 minutes

Dipyrromethane units can then be condensed with an aldehyde under acidic conditions and in the presence of a chemical oxidant to yield a porphyrin or, if the ratios are adjusted, a corrole^{5,11,13} as in Scheme 2.1.4. Gryko and Jadach reported the preparation of a series of corroles using dipyrromethanes with various *meso*-substituents with a selection of aldehydes with varied results (between 0% and 22%) but notably with low

porphyrin formation (between 0% and 12%).¹³ They reached several conclusions on this 2+1 condensation. Firstly, a high concentration of substrates and very low concentration of TFA as catalyst favours corrole formation over porphyrin formation.¹³ Secondly, they used a variety of substituted dipyrromethanes and aldehydes and found that a range of aryl substituents, including those bearing methoxy, alcohol, ester, nitro, halogens, nitrile and thionated functional groups, was tolerated in this reaction.¹³



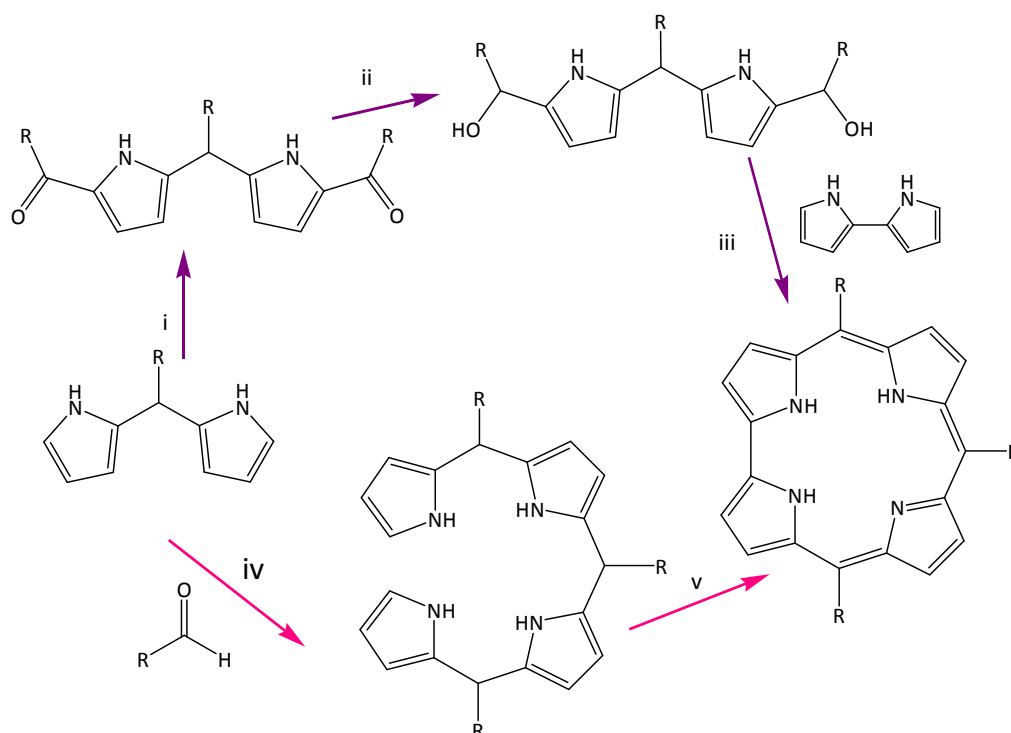
Scheme 2.1.4 Corrole synthesis from dipyrromethanes

In an alternative 'lego' approach two pyrrole rings are coupled together first to form the 2,2'-bipyrrole subunit before construction of the rest of the macrocycle. There are several routes to the synthesis of 2,2'-bipyrrole from pyrrole. One method involves the dimerisation of pyrroles using palladium acetate with a reported 44% yield.¹⁵ This synthesis required the preparation of 1-benzoylpyrrole which was then heated with palladium acetate followed by hydrolysis of the benzyl moieties with a methanol-water solution containing hydrochloric acid.¹⁵ In another synthesis reported by Fu and Gribble, 2,2'-bipyrrole was prepared in a 53% yield from the synthesis of pyrrolyl ketoalcohol followed by treatment with ammonium acetate in an ammonium hydroxide-ethanol solution.¹⁶

The corrole macrocycle is constructed from the acylation and subsequent reduction of dipyrromethane to form a dicarbinol. This is then coupled with 2,2'-bipyrrole in a [2+2] condensation to yield a corrole,^{14,17} with decreased chance of porphyrin formation. Acylation of dipyrromethane occurs through deprotonating with a Grignard reagent followed by reaction with the desired acid chloride as in Scheme 2.1.5. Both the di- and mono-acylated dipyrromethanes can be recovered, typically in a 5:1 ratio.¹⁴ The

monoacylated dipyrromethane can be treated with a Grignard reagent and acid chloride again to yield the diacylated product. Reduction yields the dicarbinol which can be coupled with 2,2'-bipyrrole to result in a corrole system in up to 12% yield.^{14,17}

Alternatively, Koszarna and Gryko's methanol:water⁵ method can be used with a dipyrromethane instead of pyrrole with benzaldehyde to form the bilane in a methanol:water solution followed by ring closing and oxidation using *p*-chloranil.



Scheme 2.1.5 Synthesis of corroles from dipyrromethane. Purple – acylation of dipyrromethane and subsequent coupling with bipyrrole^{14,17} where the dipyrromethane substituent is at position 10 in the corrole product; pink – water:methanol synthesis⁵ with the dipyrromethane substituent at positions 5 and 15 in the corrole product. i) EtMgBr (5 mol equiv.), RCOCl (2.5 mol equiv.); ii) NaBH₄ (50 mol equiv.), THF:CH₃OH 3:1 or NaBH₄ (20 mol equiv.), THF:CH₃OH 10:1 (anhydrous); iii) NH₄Cl (2.5 mol equiv.), BF₃.Et₂O (0.2 mol equiv.), CH₃CN; iv) CH₃OH:H₂O 1:1, cat. HCl; v) *p*-chloranil (1 mol equiv.)

The final intermediate in the macrocycle synthesis is a bilane, as indicated in Schemes 2.1.1, 2.1.2 and 2.1.4. In these schemes, the bilane is synthesised and oxidised *in situ*. Isolation and purification of the bilane prior to the oxidative ring closure would ensure that porphyrin formation is not possible. Bilane cyclisation can occur via either a base or acid catalysed mechanism.^{18,19}

2.1.3 A₂B and ABC corroles

'One-pot' syntheses, as discussed above, are an attractive means for synthesis of gram quantities of corroles in a short time. There is, however, little control of the synthesis of the desired product as opposed to a mixture of undesired structural isomers in the synthesis of *meso*-substituted A₂B or ABC corrole systems (Figure 2.1.2). The statistical ratios of products from A₂B corrole synthesis, as illustrated in Figure 2.1.3, would be expected. The synthesis of a specific *meso*-substituted ABC corrole would be even more difficult with an increased number of possible outcomes. More control would be possible using the 'Lego' approach, with the synthesis of parts of the macrocycle, which would then be linked together to form the desired corrole.

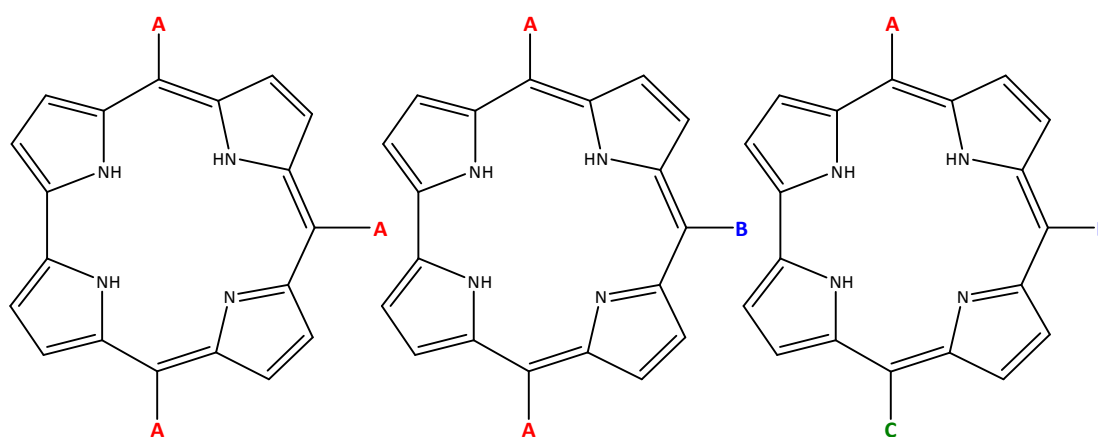


Figure 2.1.2 A₃, *trans* A₂B and ABC corroles

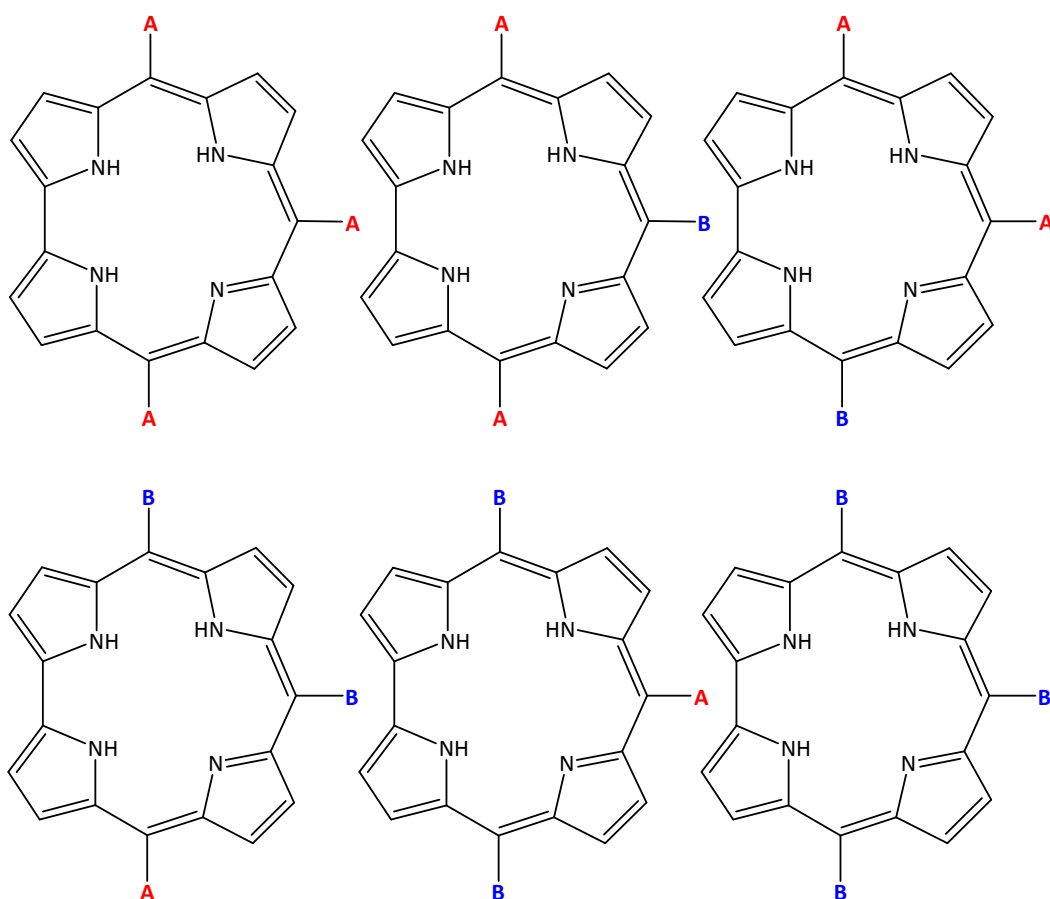
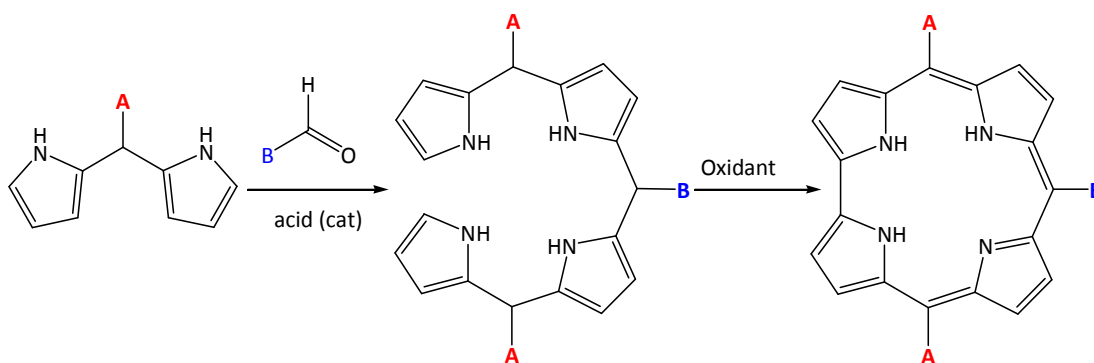


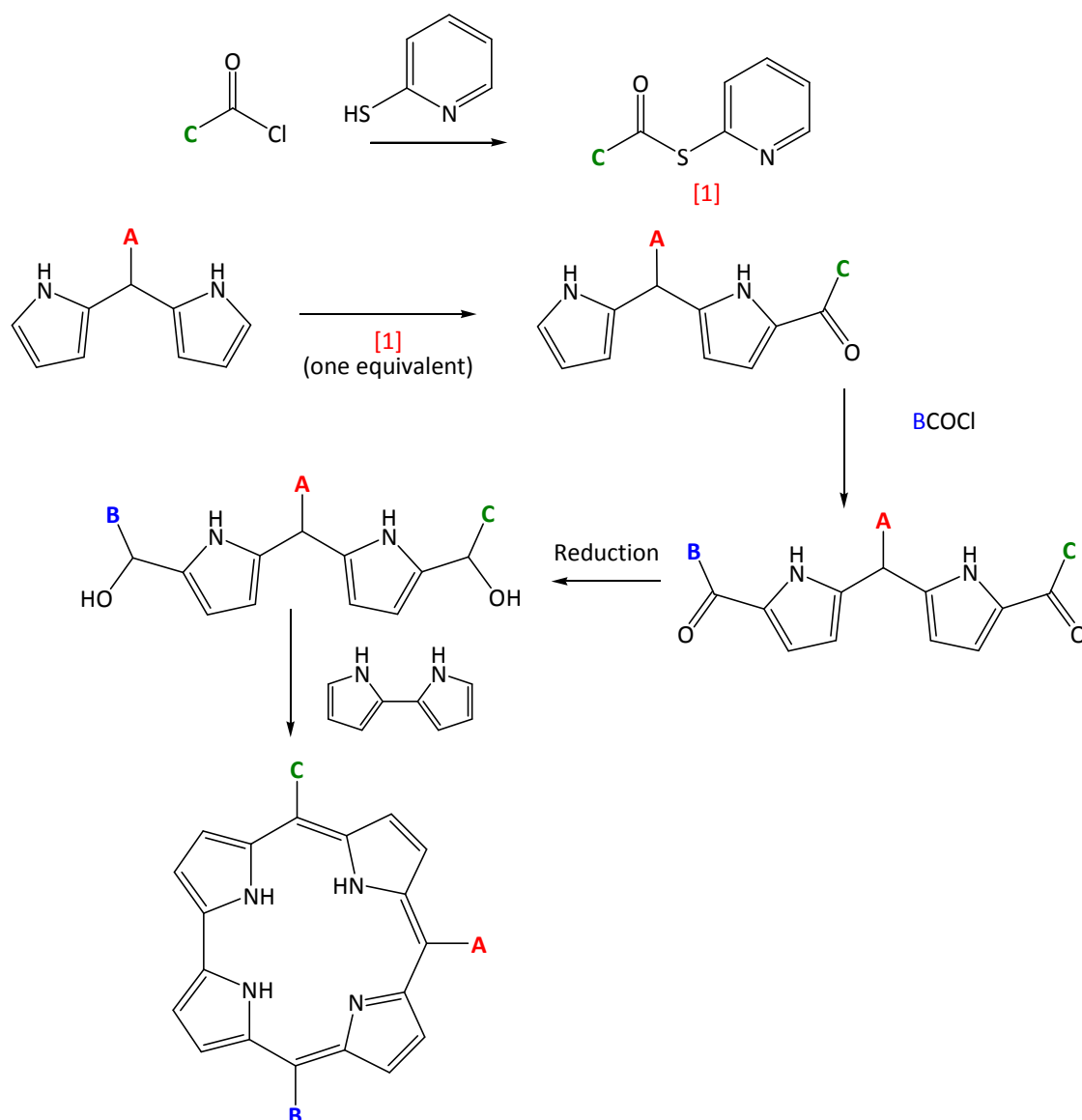
Figure 2.1.3 Possible products of a modified Rothemund synthesis of a *meso*-substituted A₂B corrole

Synthesis of A₂B and ABC corroles have been reported in the literature using one of the techniques described in the previously given Schemes 2.1.4 and 2.1.5 through the use of aldehydes with groups differing from that on the 5 position of the dipyrromethane. In such a way, *trans*-A₂B corroles can be synthesised as in Scheme 2.1.6 as reported by several research groups.^{5,11,13,14}

Scheme 2.1.5 illustrates the use of dicarbinols in a condensation with 2,2'-bipyrrole.¹⁷ In addition to generating the monoacylated dipyrromethane as a by-product of the diacylation process, this monoacylated species can be synthesised in the first step of a sequential acylation process.^{14,17} This could allow for the introduction of a third group, C, in the quest for an ABC corrole. This is illustrated in Scheme 2.1.7 below. Similarly, should A = B, a *cis*-A₂B corrole would result.



Scheme 2.1.6 Synthesis of trans-A2B corrole systems



Scheme 2.1.7 Synthesis of an ABC corrole by sequential acylation^{14,17} i) CH_2Cl_2 ; ii) EtMgBr , THF; iii) EtMgBr , THF; iv) NH_4Cl , $\text{BF}_3 \cdot \text{Et}_2\text{O}$

2.1.4 Superstructured corroles

Tailed macrocyclic systems have been used as biomimetic systems in the study of mechanism and structure-function relationships of haemproteins including haemoglobin, myoglobin, cytochrome P450 and cytochrome C oxidase.^{20,21} While the majority of these studies have focused on the porphyrin, the corrole has been used in such biomimetic studies as well.²⁰

There are numerous porphyrin sub-classes of 'superstructures' bearing different arrangements of covalently linked molecules which are used to study different haemproteins (examples are given in Figure 2.1.4). Picket fence and capped macrocycles have been used as myoglobin analogues,²⁰ capped or picket fence macrocycles capable of coordinating a second metal ion in have been used to study cytochrome c oxidase,²²⁻²⁶ while macrocycles bearing a tail that can act as an axial ligand for a coordinated metal are used as cytochrome P450 analogues²⁷ and to study the effect of the axial ligand on the properties of the metallated macrocycle.^{20,28} These superstructures are most often constructed from incorporating a synthetic handle into the macrocycle which can then later be functionalised.²¹

A more rigid functionality can be synthesised to yield pillared or hangman macrocycles (Figure 2.1.4) which are often used to direct ligands, such as water, into the required position through hydrogen bonding and other intermolecular forces,²⁹ or for electron and proton transfer for the activation of dioxygen.^{30,31}

While these examples are largely based on porphyrins, similar structures have been synthesised around corrole macrocycles.^{20,31} In this work, the superstructure of interest is the tailed structure with a terminal ligand capable of coordinating to a metal as an axial ligand.

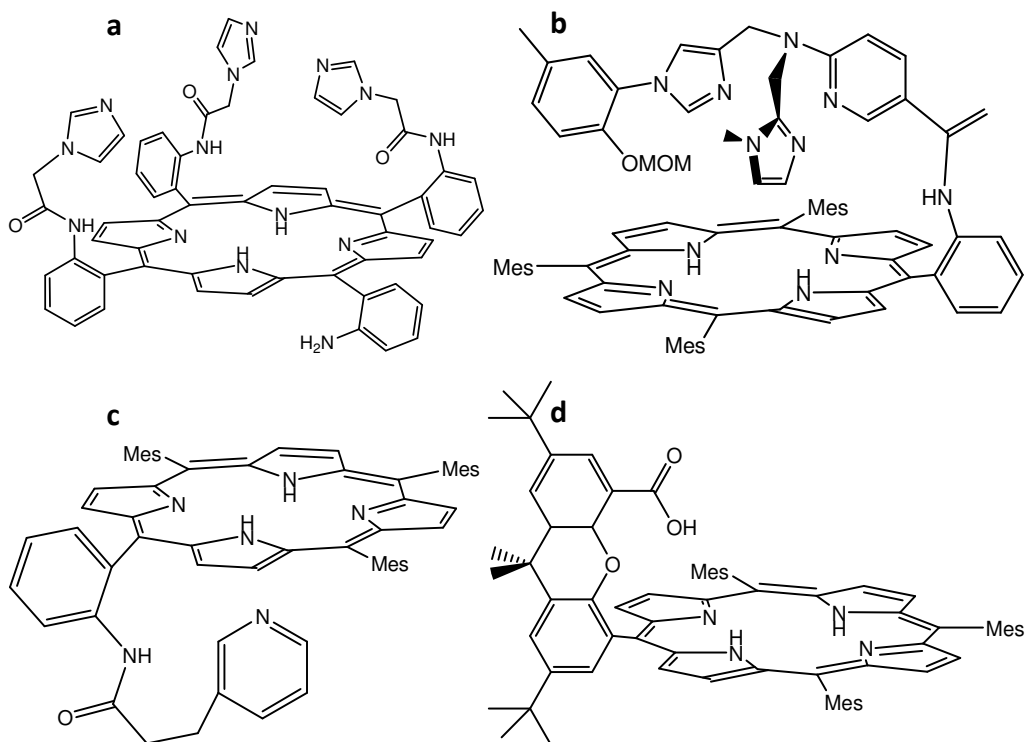


Figure 2.1.4 Macrocylic superstructures **a** picket fence porphyrin;³² **b** capped porphyrin;²⁴ **c** tailed porphyrin;²⁸ **d** hangman porphyrin³⁰

2.1.5 Water solubility

The synthesis of water-soluble macrocycles is important in the study of biomimetic systems, as this allows the biomimetic system to be studied in the same environment as the water-soluble biological system of interest.

The similarities between corroles and the corrin macrocycle of vitamin B₁₂ have been noted,³³⁻³⁵ making the study of the corrole a potential aid in the understanding of vitamin B₁₂ chemistry. As mentioned above, biomimetic systems and their biological counterparts must be studied in similar environments, and thus the insolubility of corroles in aqueous media must be addressed. Several water-soluble corroles have been synthesised to date,^{7,36-41} examples of which are illustrated in Figure 2.1.5. These species rely on the presence of charged species to increase water solubility. Quaternary ammonium,³⁸ *N*-methylpyridinium^{7,38,41} salts and water-solubilising systems based on sulfonic acids⁴⁰ remain charged across the pH spectrum, increasing water solubility.

Numerous water-soluble porphyrins have been synthesised, using similar water-solubilising systems such as *N*-methylpyridinium salts,⁴²⁻⁴⁴ sulfonic acids,⁴⁴ and quaternary ammonium salts.⁴⁵ Other water-solubilising systems include polyethylene glycol (PEG) halides,⁴⁶ sugars⁴⁷ and organic solubilising agents known as ‘swallowtail’ substituents, which prevent $\pi\cdots\pi$ interactions and stacking, thus inhibiting aggregation and precipitation.⁴⁸

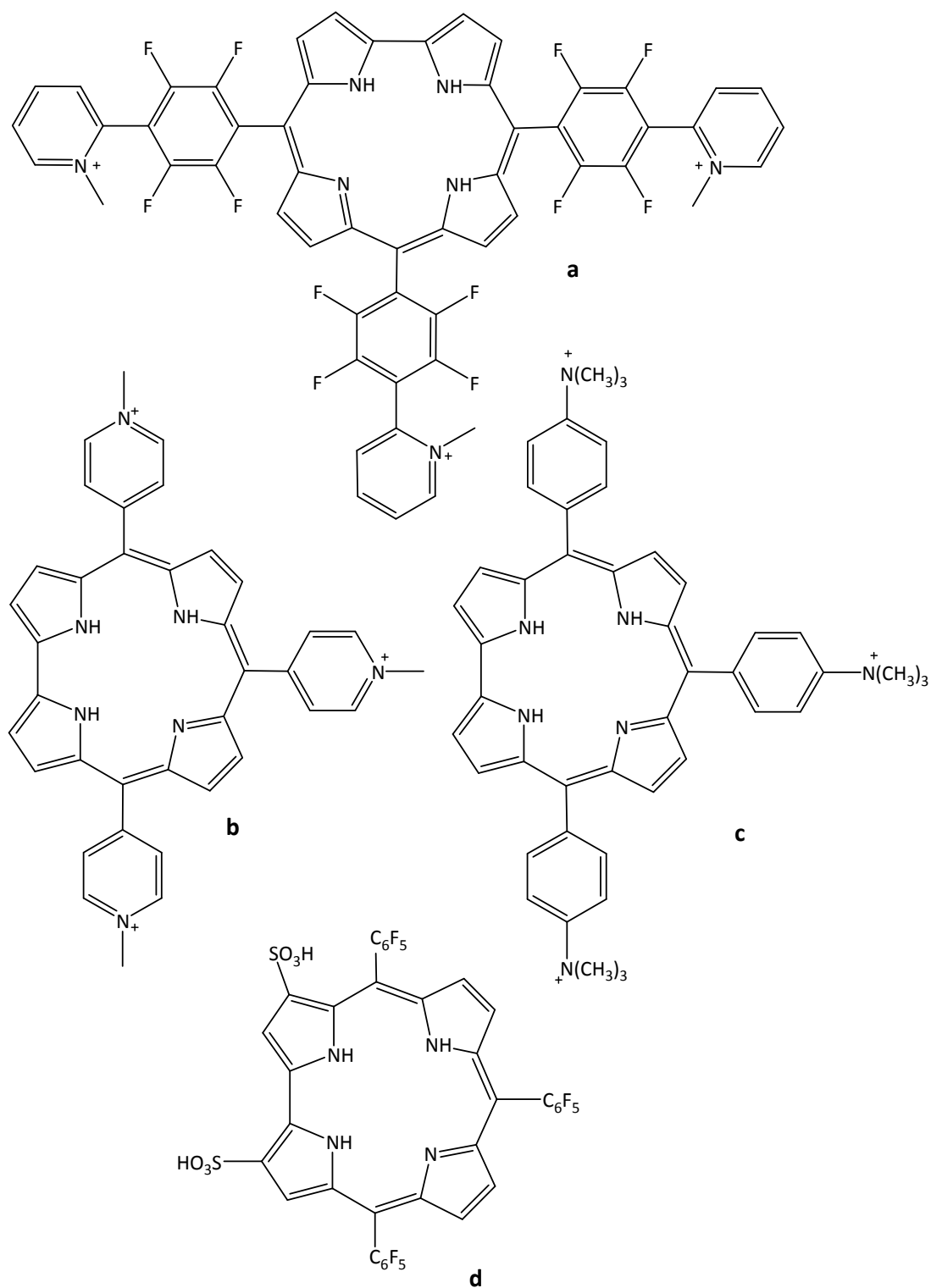


Figure 2.1.5 Examples of corroles with different water-solubilising functionalities: **a** methylation of 5,10,15-tris[4-(2-pyridyl)-2,3,5,6-tetrafluorophenyl]corrole⁷ **b** 4-pyridinium corrole³⁸ **c** quaternary ammonium corrole³⁸ **d** bis-sulfonic acid corrole derivative⁴⁰

2.1.6 Metallated corroles

One of the first examples of corrole synthesis using substituted pyrrole involved the building of the corrole structure around a cobalt metal ion.⁴⁹ In this case the metal acted as a template and was an integral part of the building of the macrocycle. Corrole macrocycles synthesised as outlined in the previous section, without a templating metal ion, are excellent chelators of many metal ions of different sizes and oxidation states.⁵⁰

Bilanes can act as excellent chelators, and can be cyclised to form a corrole macrocycle during coordination with a metal carrier under basic conditions.⁵⁰ In some cases, the oxocorrole is formed, with an ethereal bridge replacing one of the methine bridges.^{50,51} This method requires that the metal ion is able to catalyse the ring closure.⁵⁰ Cobalt is particularly effective in the catalysis of ring formation from pyrrole derivatives and ring closure of bilanes, and thus there are many methods available for metallation of corroles with cobalt.⁵⁰

Alternatively, metallation can occur after the macrocycle has been formed. During the metallation, the macrocycle is treated with a metal carrier, generally at reflux in a solvent such as methanol or pyridine. Various metal carriers can be used such as metal acetates for cobalt, vanadium, titanium, niobium, manganese, palladium, zinc, nickel and copper;⁵⁰ metal chlorides for chromium, molybdenum, rhenium, iron, cobalt, rhodium, indium, tin and phosphorus;⁵⁰ and metallocarbonyls for chromium, molybdenum, manganese, iron and rhodium.⁵⁰

2.2 Determining the feasibility of corrole synthesis

2.2.1 One-pot syntheses

In the present work, the one-pot syntheses reported by Paolesse,^{3,4} a modified Lindsey method¹⁰ and a solvent free approach^{7,8} were attempted with pyrrole and benzaldehyde in the synthesis of 5,10,15-triphenylcorrole with poor results.

Paolesse's one-pot methodology^{3,4} was followed on a 20 mmol scale with the dissolution of benzaldehyde and pyrrole (3 mole equivalents) in acetic acid. After three hours of heating at reflux and a work-up of deionised water and treatment with sodium chloride, a black precipitate was obtained which was purified by column chromatography. Although NMR spectroscopic analysis indicated the presence of both 5,10,15,20-tetraphenylporphyrin and 5,10,15-triphenylcorrole, separation of the very small amount of corrole from the numerous other products was not achieved, in spite of the use of various solvent systems during chromatographic separation.

The Lindsey method¹⁰ for porphyrin synthesis was modified by altering the ratio of pyrrole:benzaldehyde from 1:1 in the typical Lindsey approach to 3:1 in an effort to promote corrole formation over porphyrin formation. The pyrrole and benzaldehyde were added to chloroform in the presence of catalytic $\text{BF}_3(\text{OEt})_2$ under an argon atmosphere. After one hour, DDQ was added and the reaction mixture was stirred for a further hour. This resulted in the formation of 5,10,15,20-tetraphenylporphyrin in 8% yield. Crystal structures of two polymorphs of this porphyrin were determined. While not novel structures^{52,53}, the polymorphs highlight the ability of the plane of the porphyrin to buckle and bend, as illustrated in Figure 2.2.1, which is typical of porphyrins, but not of corroles.

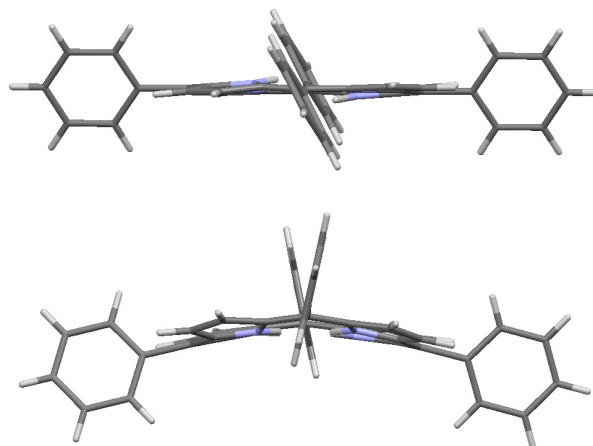


Figure 2.2.1 X-Ray crystal structures of two polymorphs of tetraphenylporphyrin illustrating the ability of the porphyrin core to bend

As expected, the solvent-free approaches outlined by Gross and coworkers^{7,8} was unsuccessful as the aldehyde used was not fluorinated. This reaction was performed on a 2.5 mmol scale and after rapid mixing of the pyrrole and aldehyde and subsequent oxidation in dichloromethane, no corrole was detected.

Successful corrole synthesis was achieved when Gryko's water:methanol method was used to synthesise 5,10,15-triphenylcorrole. Pyrrole and benzaldehyde (2:1 molar ratio) were dissolved in a 1:1 methanol:water mixture in the presence of concentrated HCl (approximately 1% of the total volume) and allowed to stir at room temperature in the absence of light. Subsequent extraction of the bilane into chloroform and oxidation using *p*-chloranil was performed. After purification 5,10,15-triphenylcorrole was obtained in a 19% yield. 5,10,15,20-Tetraphenylporphyrin was also isolated, but in low yield.

The corrole was identified by its characteristic UV-vis spectrum (as in Figure 2.2.2) as well as through mass spectrometry and NMR spectroscopy. The parent ion was observed at $m/z = 526.98$ ($[M+H]^+$). The NMR spectra of the corrole and analogous porphyrin are easily distinguished as the four-fold symmetry of the porphyrin results in a more simplified NMR spectrum with only three distinct signals for the protons in the β positions at 8.92 ppm; the protons in the *ortho* positions of the *meso* phenyl substituents at 8.29 ppm and a complex multiplet representing the remaining *meta* and *para* protons in the 7.86-7.75 ppm region. In contrast, the corrole spectrum is more complex with four

separate doublets of the β protons at 8.97, 8.88, 8.60 and 8.56 ppm and two doublets and a multiplet from the *meso* substituents at 8.37, 8.17 and 7.85-7.68 ppm. The three pyrrolic protons present in the inner core of the macrocycle were observed up-field at -0.49 ppm in deuterated chloroform. Coupling of NMR signals was only evident at very low concentrations of corrole (approximately 1 mg of material in approximately 1 ml. At higher concentrations, broad signals with no multiplet resolution were observed. It is thought that this arose from stacking of macrocycles in solution such that there was significant $\pi\cdots\pi$ interaction between macrocycles.

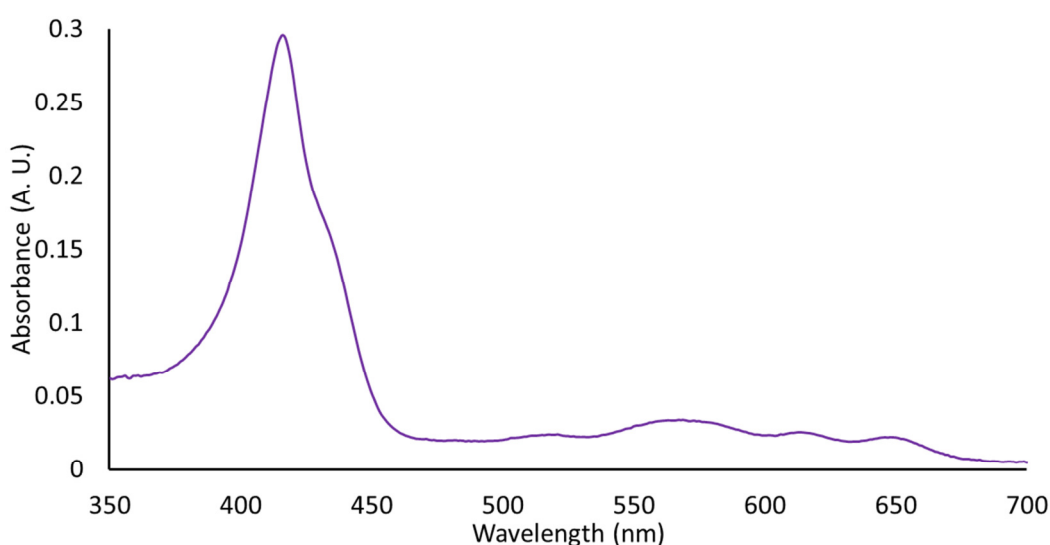


Figure 2.2.2 UV-vis spectrum of 5,10,15-triphenylcorrole in dichloromethane

Two crystal structures of the corrole, illustrated in Figure 2.2.3, were determined, one of which was a solvate with hexane. These structures indicate that the macrocycle is very closely packed in the solid state. Unlike the porphyrin, where molecules are staggered in the unit cell, corrole molecules experience greater overlap, lying 0.1 Å closer to one another than in the porphyrin structure. This observation is in line with the observations from the concentration dependence of the NMR spectroscopic measurements. While neither corrole structure is novel,^{54,55} the solvated structure contained a hexane molecule in the asymmetric unit cell while the published structure with the same unit cell parameters, contains a disordered methanol molecule.⁵⁴ Unlike in the case of the porphyrin, the macrocycle is almost planar in both structures, with one pyrrole ring tilted slightly out of the macrocyclic plane due to the repulsion of the inner core hydrogens.

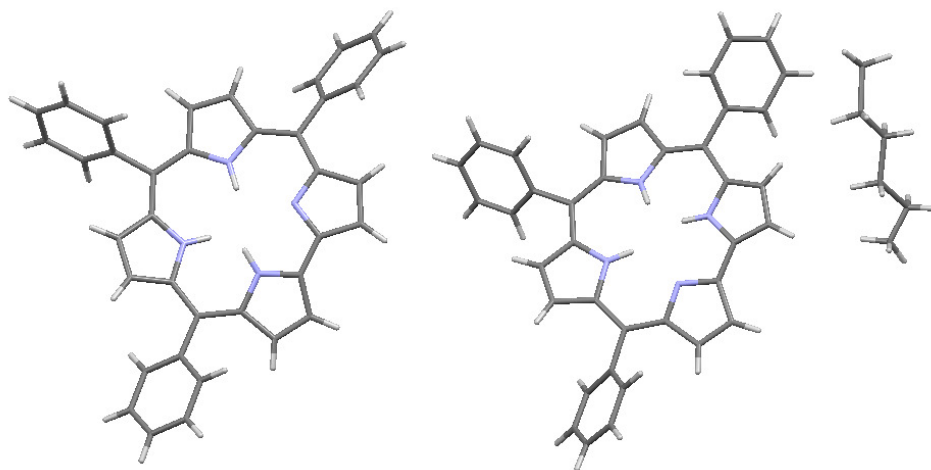


Figure 2.2.3 Two X-Ray crystal structures of 5,10,15-triphenylcorrole, one a solvate containing hexane.

The corrole was metallated with cobalt(II) acetate in the presence of triphenylphosphine to give a five-coordinate complex with one triphenylphosphine ligand in 51% yield, confirmed by single crystal X-ray diffraction (Figure 2.2.4 below), in agreement with the structure published by Paolesse and co-workers in 1999.³ The parent ion was observed in the mass spectrum at $m/z = 844.82$ ($[M+H]^+$) and the characteristic change in UV-vis spectrum upon metal complexation was observed (Figure 2.2.5). The presence of the large triphenylphosphine ligand ensured that the macrocycles did not aggregate in solution or in the solid state. As a result, the NMR spectroscopic analysis produced signals with clear resolution of multiplets in the proton NMR spectrum. The clear splitting of proton signals was also an indication of the diamagnetic nature of the cobalt ion in the 3+ oxidation state.

When compared to the NMR spectrum of 5,10,15-triphenylcorrole, a general up-field shift was observed as in Figure 2.2.6. Proton NMR signals of the β protons shifted from 8.97, 8.88, 8.60 and 8.56 ppm in the metal free corrole to 8.59, 8.32, 8.09 ppm (integrating for four β protons) in the metallated corrole. In addition, the position of the signals of the protons of the triphenylphosphine ligand experienced a very large up-field shift. Triphenylphosphine protons, generally observed between 7.4 and 7.3 ppm, were observed at 7.04, 6.70 and 4.72 ppm in the proton NMR spectrum. This significant change in chemical shift is due to the shielding effect of the cobalt ion. In general, low-oxidation state d-block metals have highly shielded nuclei.⁵⁶ In addition to the effect of the metal,

the identity of the macrocyclic ligand also affects the chemical shift. Porphyrins have been observed to induce up-field shifts of axial ligands in cobalt porphyrins owing to the strong shielding effect of the macrocycle.⁵⁷ Strong shielding effects with large up-field shifts in the positions of the protons of axial amine and amino-ester ligands in cobalt(III) porphyrins have also been observed.⁵⁸

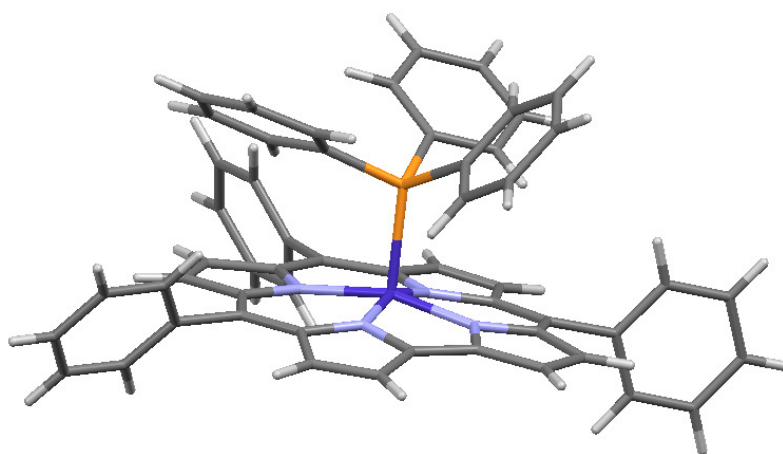


Figure 2.2.4 X-Ray crystal structure of triphenylphosphine [5,10,15-triphenylcorrolato]cobalt(III)

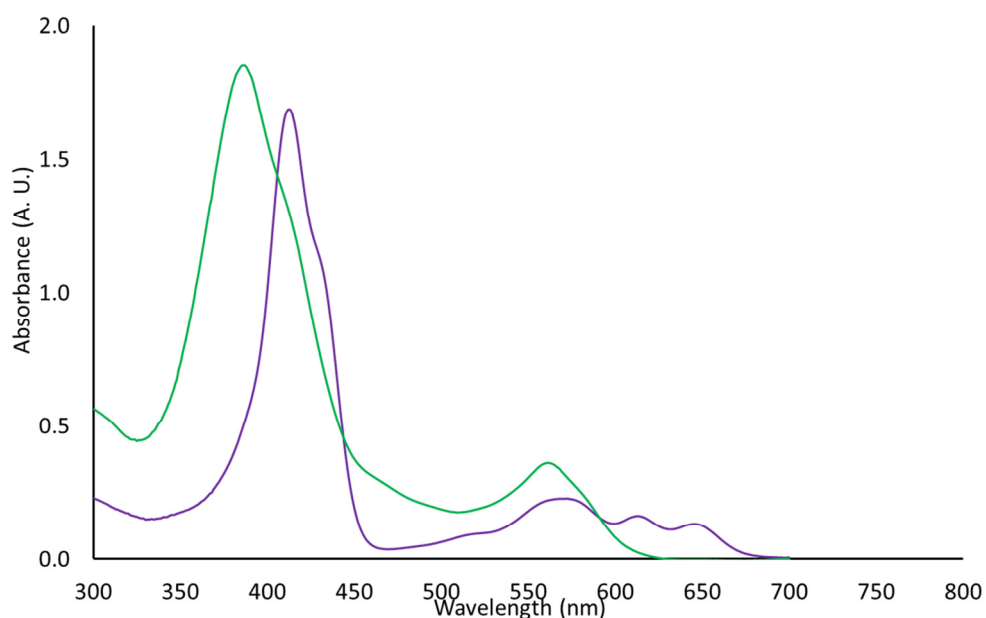


Figure 2.2.5 UV-vis spectra of 5,10,15-triphenylcorrole (purple) and triphenylphosphine [5,10,15-triphenylcorrolato]cobalt(III) (green) in dichloromethane

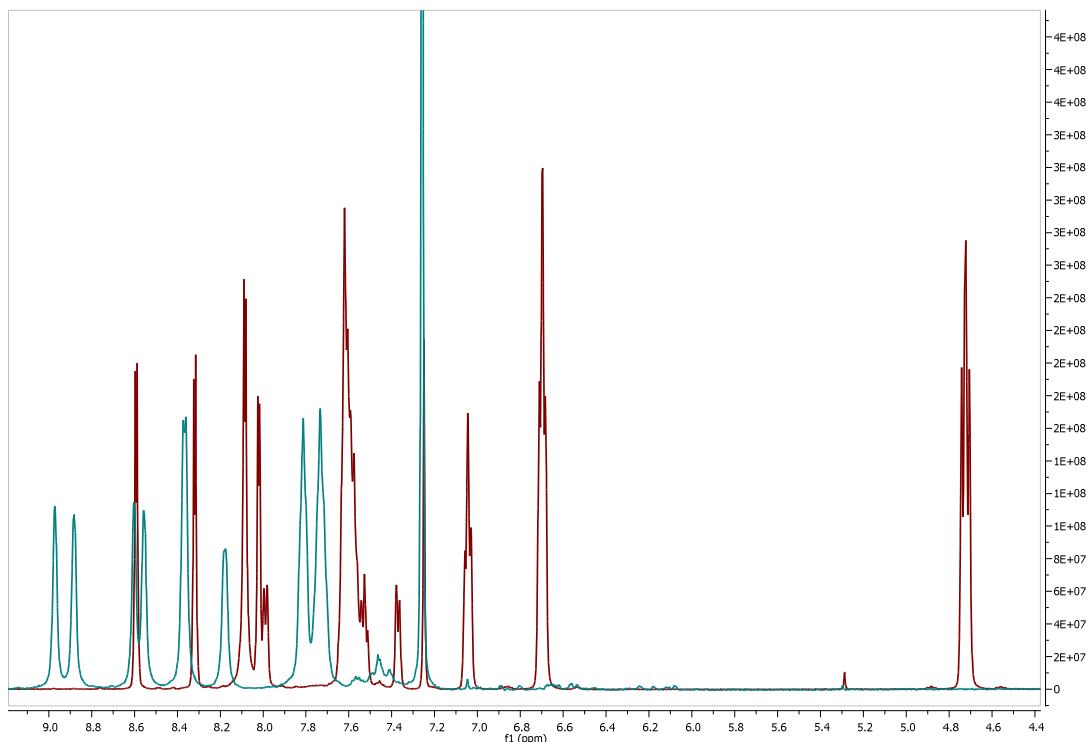


Figure 2.2.6 NMR spectra of 5,10,15-triphenylcorrole (blue) and its metallated counterpart, triphenylphosphine [5,10,15-triphenyl corrolato]cobalt(III) (red) in CDCl_3

The Gryko procedure was also used for the preparation of 5,10,15-tri(2-nitrophenyl)corrole from pyrrole and 2-nitrobenzaldehyde. The yield was significantly lower than in the synthesis of 5,10,15-triphenylcorrole at only 4.5%. NMR spectroscopy confirmed the product as 5,10,15-tri(2-nitrophenyl)corrole with the presence of signals corresponding to the β protons and the *meso* aromatic protons between 8.91 and 7.81 ppm. A general up-field shift of signals in the proton spectrum was observed when compared to 5,10,15-triphenylcorrole, which is in agreement with the literature.²⁰ The parent ion was observed in the mass spectrum at $m/z = 662$ ($[\text{M}+\text{H}]^+$). Unfortunately, the corrole did not crystallise to yield diffraction-quality crystals.

2.2.2 Lego approaches

The synthesis of A₂B and ABC corroles using a one-pot synthetic method yields mixtures of corrole isomers each in low yield, as illustrated in Figure 2.1.2 in **Section 2.1**. A variety of approaches has been established for the synthesis of A₂B and ABC corroles in which the chances of obtaining mixtures of isomers is limited. In these synthetic strategies, the macrocycle is assembled in steps to favour the desired corrole. The basis for many of these step-wise or 'lego' approaches is the synthesis of a dipyrromethane.¹¹

In this work, dipyrromethane was synthesised together with the related polymeric trimer and tetramer. The production of the longer chain species was limited, but not avoided, by the large excess of pyrrole (40 mole equivalents) as well as the short reaction time used (15 minutes). The brown solid was isolated in 57% yield and was identified as 2,2-(phenylmethylene)bis(1*H*-pyrrole), a simple aryl dipyrromethane, from the NMR spectra where no aldehyde signals from the benzaldehyde starting material were observed and the methine proton was observed as a singlet at 5.43 ppm in the proton NMR spectrum and at 43.97 ppm in the carbon NMR spectrum. The positions of the pyrrole signals experienced an up-field shift with three signals observed at 6.65, 6.15 and 5.90 ppm instead of the two signals of unsubstituted pyrrole at 6.74 and 6.24 ppm.

Dipyrromethanes can be used in a number of synthetic pathways towards corroles such as those detailed in Scheme 2.1.5 in **Section 2.1.2**. In the present work, the most efficient route for the synthesis of A₂B corroles was found to be Gryko's methanol:water synthesis⁵ from which 10-(4-methoxyphenyl)-5,15-diphenylcorrole was synthesised in fair yield. Unfortunately, the resultant material was not crystalline, but the corrole was identified by mass spectrometry, the typical corrole-type UV-vis spectrum and the characteristic corrole NMR spectrum with a singlet at 4.09 ppm of the methoxy group. The parent ion was observed at $m/z = 557.06$ ($[M+H]^+$) in the mass spectrum.

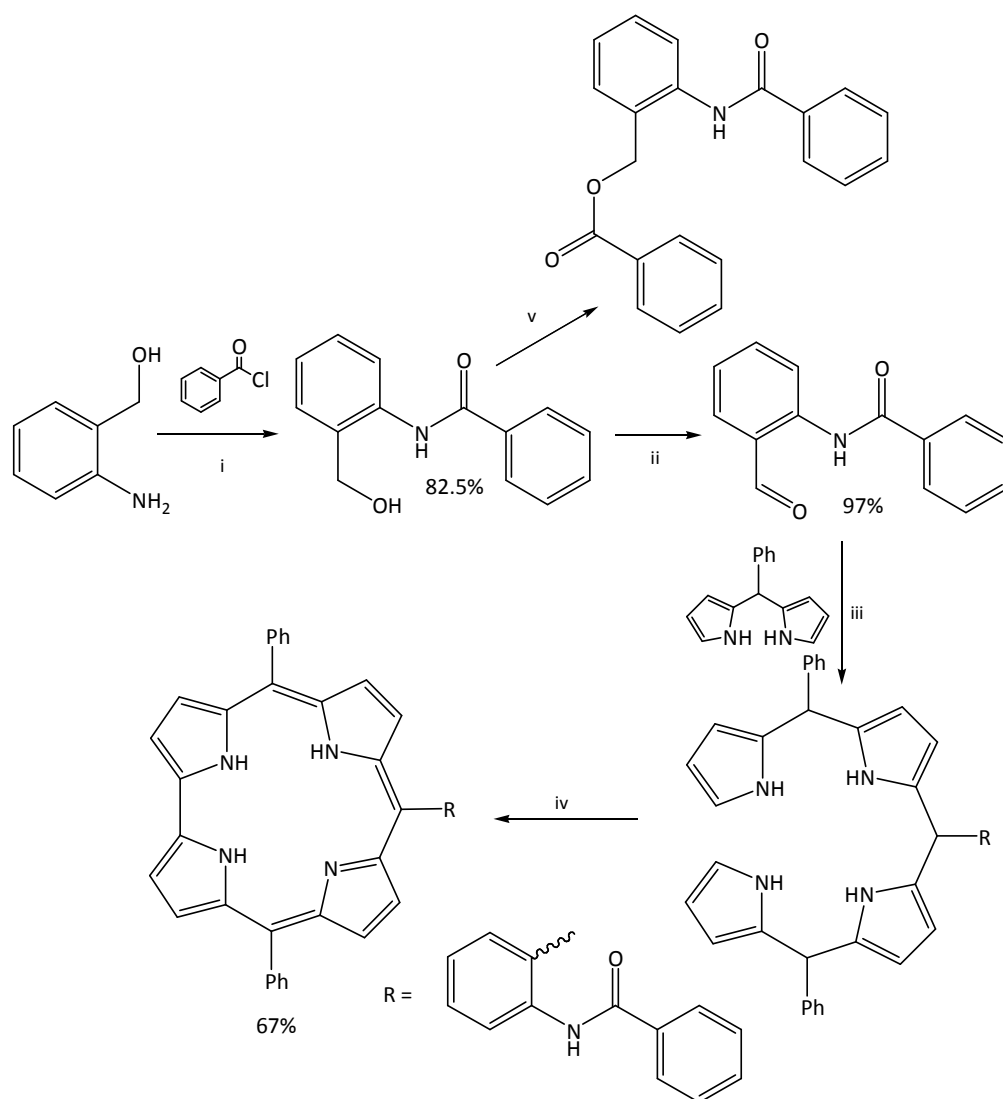
2.2.3 Introducing a bulky *meso* substituent at the 10 position

The ease of synthesis of both A₃ and A₂B corroles using the water:methanol synthetic procedure⁵ having been established, the feasibility of incorporating a bulky substituent at the 10 position was investigated.

As in Scheme 2.2.1 below, *N*-[2-(hydroxymethyl)phenyl]benzamide was synthesised from 2-aminobenzyl alcohol (a novel crystal structure (Figure 2.2.7a) was published in *Acta Crystallographica Section E*,⁵⁹ see **Appendix 2.4** and **Digital Appendix 2.2.1**) and benzoyl chloride in 82% yield, based on the work of Fürstner and Jumbam.⁶⁰ The amide was identified in the NMR spectrum from the down-field NH signal at 9.82 ppm in the proton NMR spectrum and the carbonyl signal at 165.76 ppm in the carbon spectrum. The parent ion was observed at $m/z = 227.0944$ ($[M]^+$) in the high resolution mass spectrum. Subjecting the alcohol to high temperatures for an extended period of time (80°C, overnight) resulted in the formation of a brown resin with the crystallisation of benzoic acid. Recrystallisation of the resin from an aqueous solution of hydrochloric acid yielded colourless needle-like crystals. The product, 2-(benzamido)benzyl benzoate, was identified in the proton NMR spectrum from the absence of the hydroxyl proton which was present at 4.07 ppm in the proton spectrum of *N*-[2-(hydroxymethyl)phenyl]benzamide. In addition, the methylene proton signal experienced a down-field shift from 4.66 ppm in *N*-[2-(hydroxymethyl)phenyl]benzamide to 5.40 ppm as a result of the presence of the more electron rich carboxylic ester. The signals in the aromatic region integrated for 14 aromatic protons, indicating the incorporation of a third phenyl ring.

Subsequent oxidation of *N*-[2-(hydroxymethyl)phenyl]benzamide to the aldehyde, *N*-(2-formylphenyl)benzamide, was achieved in 97% yield using manganese dioxide in chloroform over a 12 hour period. The presence of the aldehyde was confirmed by the down-field aldehyde proton signal at 12.11 ppm in the proton spectrum as well as the carbonyl peak at 195.92 ppm in the carbon NMR spectrum, typical for aldehyde signals. The parent ion was observed at $m/z = 225.0786$ ($[M]^+$) in the high resolution mass spectrum.

The corrole was synthesised from *N*-(2-formylphenyl)benzamide and the dipyrromethane 2,2-(phenylmethylene)bis(1*H*-pyrrole) using the methanol:water method⁵ in 67% yield. The NMR spectrum, while complex, was typical for a corrole macrocycle with signals from the β protons at 8.98, 8.89, 8.60 and 8.52 ppm and signals from the aromatic substituent maintained. The UV-vis spectrum was also characteristic of a corrole. Mass spectrometry data also confirmed the synthesis of the macrocycle with the parent ion present at $m/z = 646.42$ ($[M+H]^+$); and the orientation of the bulky substituent in relation to the plane of the macrocycle was determined from a crystal structure (Figure 2.2.7d).



Scheme 2.2.1 Synthesis of 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole from 2,2-(phenylmethylene)bis(1*H*-pyrrole) and *N*-[2-(hydroxymethyl)phenyl]benzamide using the water:methanol synthesis method⁵ i) CH₂Cl₂ (dry), pyridine, RT, 3hrs then acid work-up; ii) PCC in CH₂Cl₂ and THF, 2.5 hrs or MnO₂, CH₂Cl₂, overnight; iii) CH₃OH:H₂O 1:1, cat. HCl, 1 hr; iv) *p*-chloranil (1 mol equiv.), overnight; v) 80°C overnight then recrystallisation of the brown resin from an HCl solution

N-[2-(Hydroxymethyl)phenyl]benzamide, *N*-(2-formylphenyl)benzamide and 2-(benzamido)benzyl benzoate were all found to be crystalline and polymorphic. Polymorphism was found to have resulted from differences in the van der Waals associations in the solid state, as discussed in **Part 3**. The corrole synthesised was also crystalline. These structures are illustrated in Figure 2.2.7. The crystal structure of the corrole, 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole (a solvated structure with one molecule of dichloromethane per asymmetric unit), like 5,10,15-triphenylcorrole, experienced $\pi\cdots\pi$ interactions between neighbouring molecules both in the solid state and in solution.

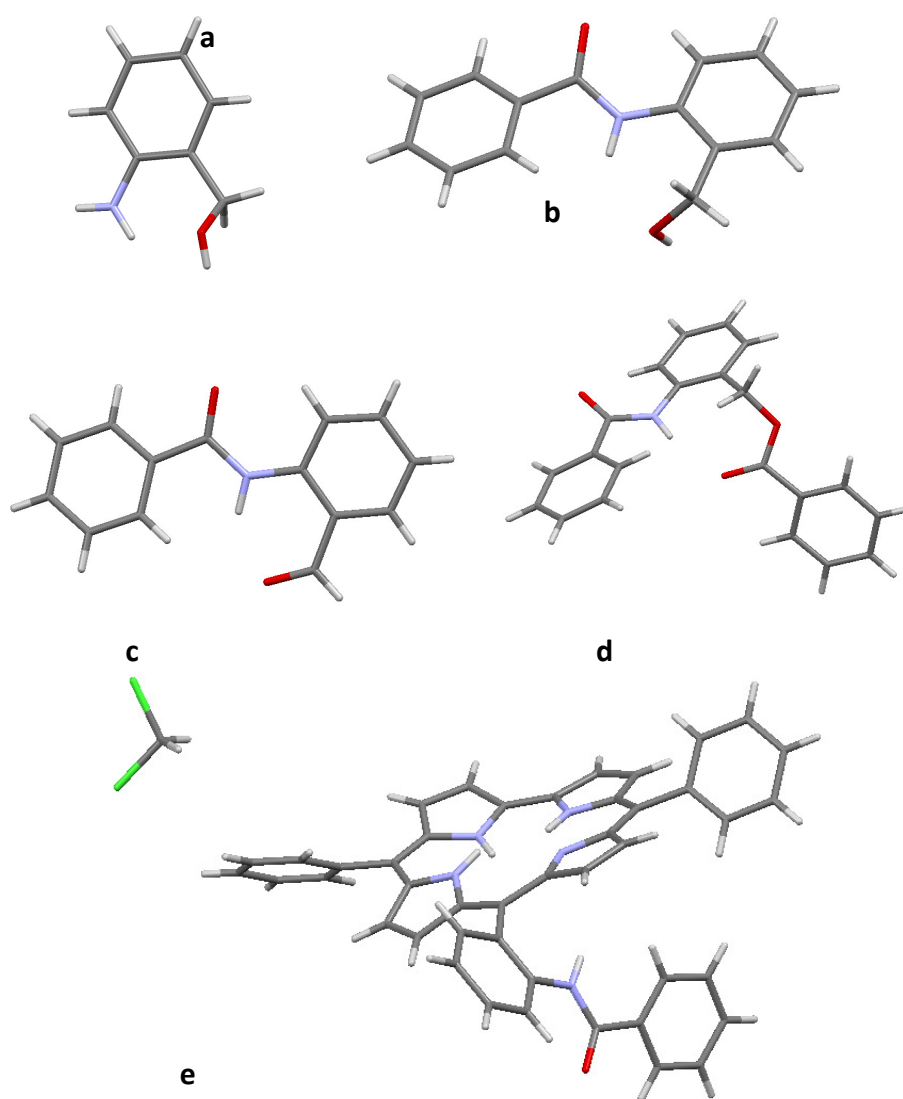


Figure 2.2.7 X-Ray crystal structures of **a** 2-aminobenzyl alcohol, **b** *N*-[2-(hydroxymethyl)phenyl]benzamide (polymorph 1), **c** *N*-(2-formylphenyl)benzamide (polymorph 1); **d** 2-(benzamido)benzyl benzoate (polymorph 2) and **e** 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole

2.3 Design of the target molecule, a tailed corrole

Various routes to simple model corroles have been attempted and Gryko's method⁵ found to be successful. The next synthetic objective was the design and synthesis of a corrole bearing a 'tail' substituent such that the terminus of the tail might act as an axial ligand for a coordinated cobalt metal ion. This system could be used as a biomimetic model of vitamin B₁₂. Molecular mechanics provides a useful tool for the prediction of molecular orientation and total energy of a system. In this section, the principles of molecular mechanics are outlined and the basis for the choice of a suitable 'tailed' corrole as a target for synthesis is justified.

2.3.1 Molecular mechanics: an introduction

Molecular modelling, which includes both quantum and mechanical based modelling methods, can be defined as the mimicking of the behaviour of molecules or molecular systems.⁶¹ Quantum mechanical calculations involve the study of the distribution, interactions and movements of electrons in a system, assuming the Born-Oppenheimer approximation. Molecular mechanics, on the other hand, does not take these electronic motions into account, but rather calculates the energy of a system as a function of the positions of nuclei in the system, where it is assumed that the electron density is distributed based on the position of the nuclei.⁶¹ While quantum mechanical methods are favoured for calculations of the properties of molecules including the prediction of electronic spectra and the investigation of chemical reactions, these complex calculations are both computationally expensive and time consuming when conducted on large molecules. Molecular mechanics, on the other hand, provides a very time-efficient means of determining the ground state structure of a large system which might be beyond the practical capabilities of quantum methods.

Molecular mechanics, or force field methods, makes use of a force field which is a collection of parameters and equations which describe nuclei and their relationships with neighbouring nuclei in the form of bond stretches, angle bends, torsional rotations and

non-bonded interactions (both electrostatic and van der Waals)⁶¹ as illustrated in Figure 2.3.1. These parameters assume that atoms are spherical and bonds act as springs. Equation 2.3.1 gives an example of the simplest force field, where the total energy of a system is given by the summation of these four terms. Bond stretches and angle bends are often modelled using harmonic potentials which describe the change in energy as the bond length or bonding angle deviates from a predetermined reference value, $l_{i,0}$ or $\theta_{i,0}$. Torsions are modelled to describe the changes in energies with the rotation of bonds and non-bonded interactions are calculated from the sum of Coulomb potentials (changes in electrostatic interactions) and Lennard-Jones potentials (changes in van der Waals interactions) for pairs of atoms i and j either in different molecules or separated by at least three atoms if in the same molecule.⁶¹ The use of Coulomb and Lennard-Jones potentials is just one method scheme used to describe the non-bonded interactions. More complex force fields may take other physical parameters in to account, such as cross-terms and hydrogen bonding effects.⁶²

$$V(\mathbf{r}^N) = \sum_{bonds} \frac{k_i}{2} (l_i - l_{i,0})^2 + \sum_{angles} \frac{k_i}{2} (\theta_i - \theta_{i,0})^2 + \sum_{torsions} \frac{V_n}{2} (1 + \cos(n\omega - \gamma))^2 + \sum_{i=1}^N \sum_{j=i+1}^N \left(4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right)$$

Equation 2.3.1

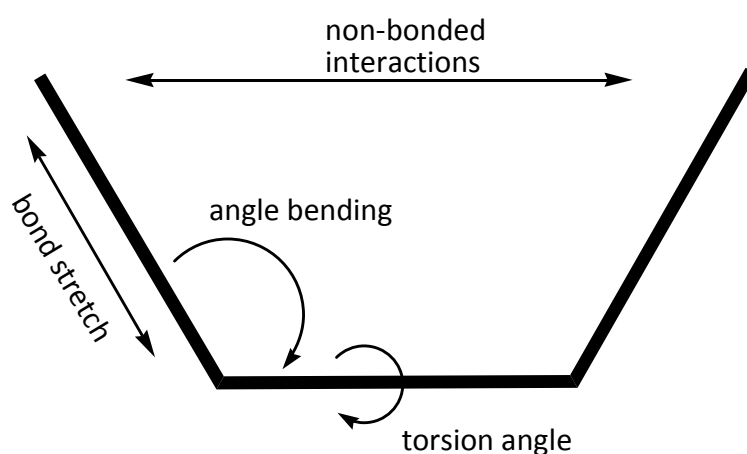


Figure 2.3.1 Physical parameters used in a molecular mechanics force field

One of the beauties of molecular mechanics is that these parameters are largely transferable for similar systems. Force fields make use of predefined atom types. These atom types not only give the atom's element, but also information about the atom's bonding environment, such as hybridisation, bonding to electronegative elements (a carbonyl carbon may be different to an sp^2 carbon in a hydrocarbon) or protonation state. In this way atom types do not need to be redefined for every molecule and every calculation; rather, atom types can be used for a variety of different molecules or classes of molecules.⁶¹

2.3.2 Molecular mechanics: new atom types in the AMBER force field

The AMBER, or Assisted Model Building with Energy Refinement, force field was designed for the modelling of large biomolecules such as proteins and nucleic acids⁶² and has been modified to be suitable for smaller organic molecules for use in the pharmaceutical industry (the general AMBER force field – GAFF).⁶³ Parameters for the study of cobalt corrinoids using the general AMBER force field were also developed based on bond lengths, bond angles and torsion angles from X-ray crystallographic data of reported cobalamin structures (WITSGAFF).⁶⁴

Crystallographic data of corroles bearing phenyl groups at the *meso* positions and coordinated to a cobalt metal ion was required to determine the average bond lengths, angles and torsions. A search of the CSD⁶⁵ yielded ten such structures from which eight new atom types were defined as illustrated in Figure 2.3.2. From analysis of bond lengths, bonding angles and torsions, the pyrrolic carbons (α and β - CAP) were seen to display similar bonding patterns except for the carbons at the bipyrrrole bridge, CAB. The carbons at the *meso* positions were defined as CAM and each nitrogen in the core of the macrocycle was assigned individual atom types NC1, NC2, NC3 and NC4. Cobalt was assigned the atom type Co3 to differentiate it from previously assigned cobalt atom types in the WITSGAFF force field.

The values of k_i , the spring constants, for each atom type were estimated from previous studies and based on standard values for organic systems. Parameters were set and a general corrole structure was subjected to geometry optimisation and single point energy calculations. All bond lengths, angles and torsions were measured and compared to the crystallographic data. If these values were within one standard deviation of the crystallographic data, k_i was accepted, otherwise values of k_i were adjusted so that the measurements were in accord with experimental data. This parameter data is tabulated in **Appendix 2.3**.

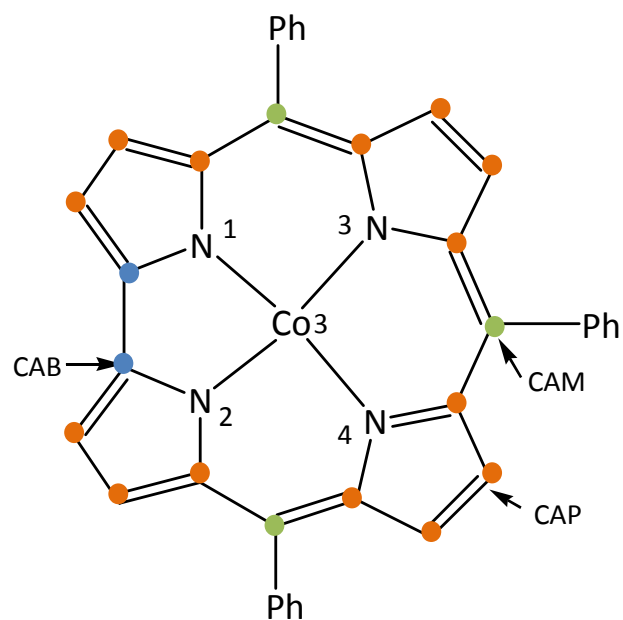


Figure 2.3.2 New atom types defined for molecular mechanical calculations of cobalt corroles using GAFF – Co3, NC1, NC2, NC3, NC4, CAP (pyrrolic carbons; orange dots), CAM (*meso* carbons, green dots) and CAB (bipyrrrole bridge carbons, blue dots)

2.3.3 Molecular mechanics: evaluation of potential systems

Calculations were performed using the HyperChem suite of programmes.⁶⁶ The atom types and parameters for the AMBER force field available in HyperChem⁶² were used together with the newly assigned atom types. Geometry optimisation was carried out using the Polak-Ribière conjugate gradient algorithm with a convergence criterion of 0.05 kCal Å⁻¹ mol⁻¹. Single point energies were calculated using the semi-empirical Zindo/S method.⁶⁷

A variety of tailed systems, flanked by the *meso* phenyl substituent at the 10 position and a terminal nitrogen donor (imidazole or benzimidazole), were evaluated. These systems included both aliphatic and aromatic functionalities (some examples are given in Figure 2.3.3). Systems were evaluated based on the value of the calculated single point energy (where lower values were favoured), the tilt angle of the *N*-donor base to the corrole plane as well as the deformation of the corrole ring from planarity (which was considered unfavourable).

A tailed system featuring an amide and phenyl ring (meta arrangement) between the *meso* phenyl ring and the terminal imidazole (Figure 2.3.4 and **f** in Figure 2.3.3 below) was chosen as the target biomimetic system. Although this system did not have the lowest relative single point energy (the more flexible ether and aliphatic chain system – **g** in Figure 2.3.3 – had a lower single point energy), this system had several advantages. Firstly, there was little distortion of the plane of the corrole macrocycle. Secondly, the cobalt-imidazole bond was perpendicular to the plane of the macrocycle. Thirdly the tail had intermediate flexibility, being less flexible than the aliphatic based systems and less rigid than the anthracene systems. This suggested that the tail would be able to rotate in solution and move into a position favourable for coordination to the cobalt metal. Fourthly, there was literature precedence for this substituent in both porphyrin^{21,22,25,27,28,68} (or bearing substituents on the imidazole moiety^{23,25,69,70}) and corrole²⁰ chemistry.

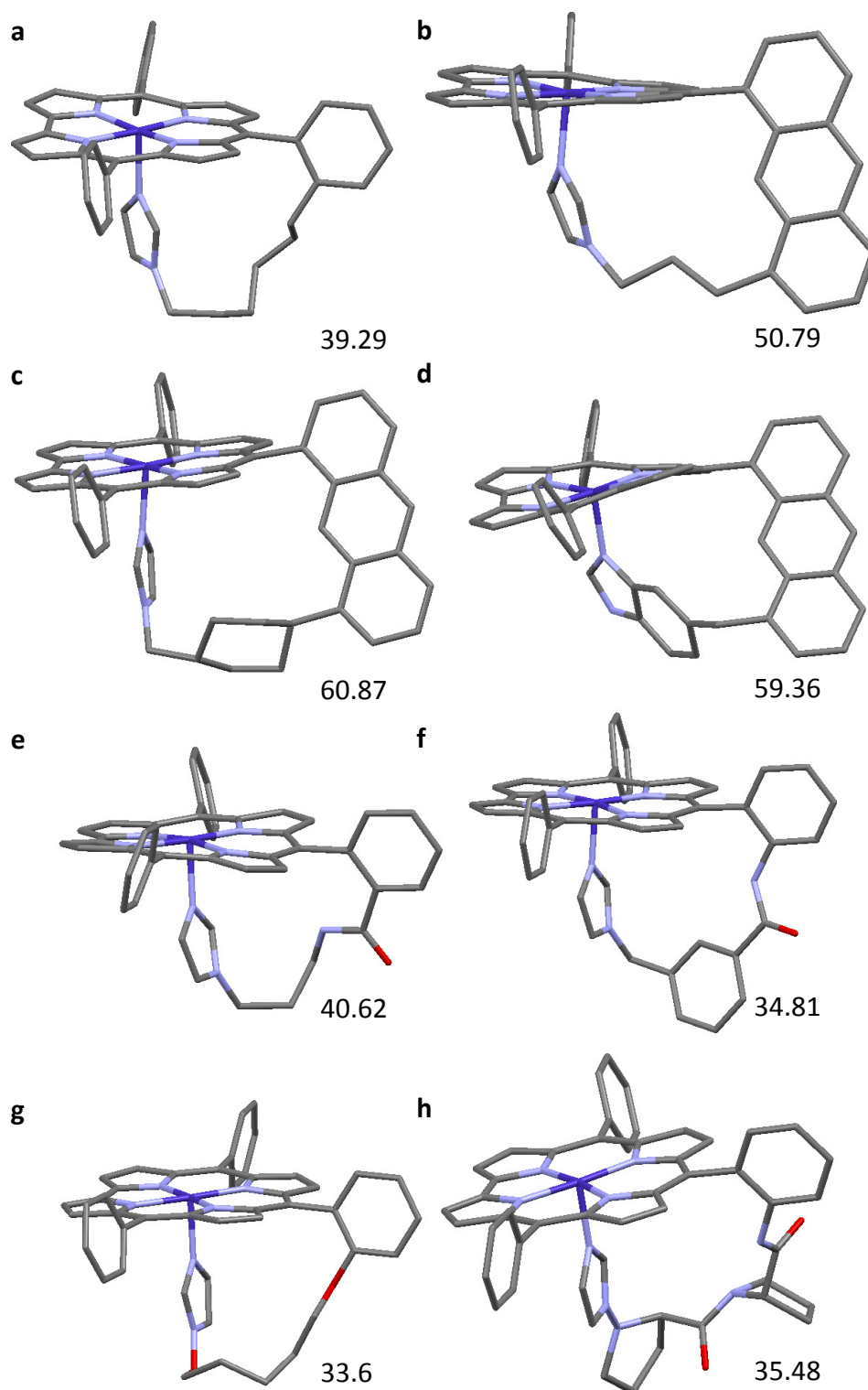


Figure 2.3.3 A selection of modelled systems containing a six carbon aliphatic chain, b anthracene and a three carbon chain, c anthracene and a cyclohexane ring in the chair conformation, d anthracene and benzimidazole, e amide and a three carbon chain, f amide and a phenyl ring (meta arrangement), g two ethers and a 5 carbon chain, h a two proline dipeptide. Calculated single point energies (kCal mol⁻¹) are given. Hydrogens have been omitted for clarity.

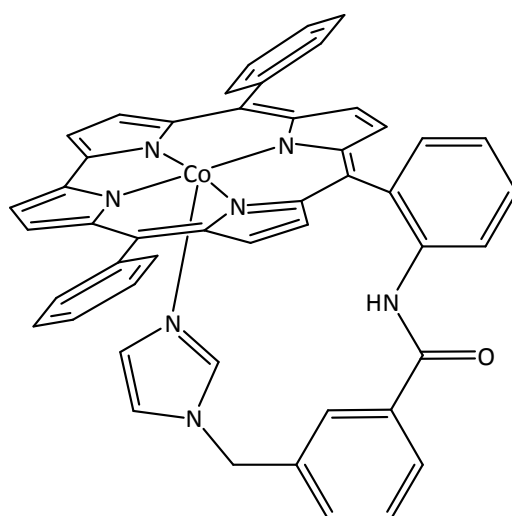
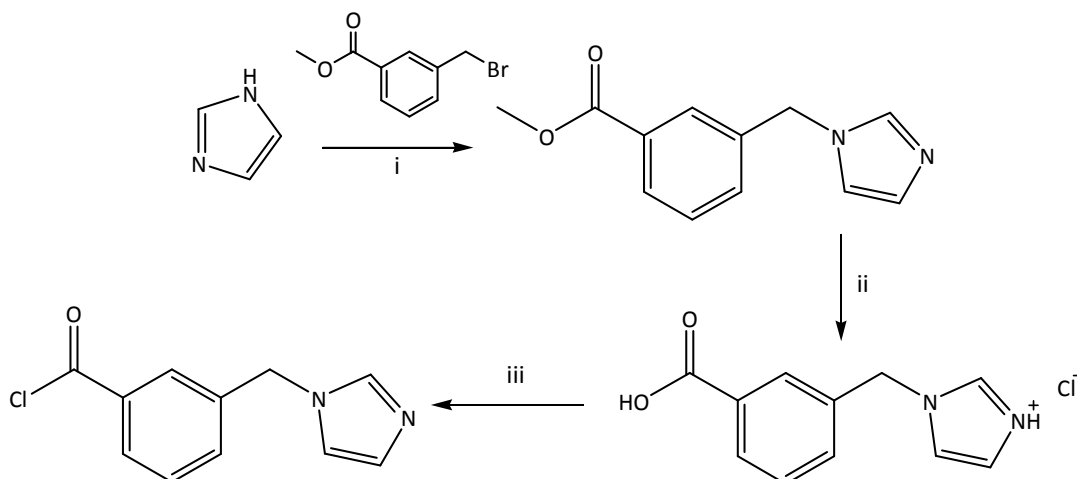


Figure 2.3.4 [10-(2-{[4-(1*H*-imidazol-1-yl)methyl]benzoyl}amino)phenyl]-5,15-diphenylcorrolato-cobalt(III), the synthetic target

2.4 Synthesis of the biomimetic tailed corrole

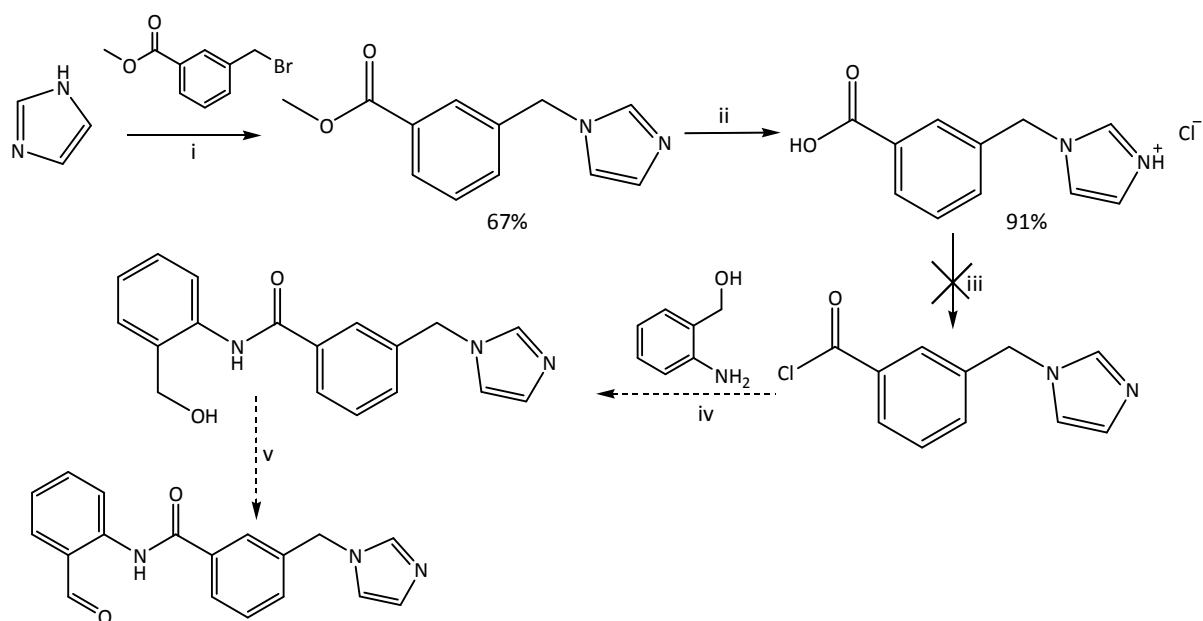
2.4.1 Adapting Collman's synthesis

In the synthesis of superstructures of porphyrin or corrole derivatives, the macrocycle is generally synthesised with functionality that can later be further functionalised. In this way the macrocycle backbone is in place before the superstructure can be prepared. 5,10,15-Tris(*o*-aminophenyl)corrole and 5,10,15,20-tetrakis(*o*-aminophenyl)-porphyrin with various acid chlorides are commonly used in the preparation of macrocyclic superstructures.^{20,21,32,69} Collman's synthesis is described in Scheme 2.4.1



Scheme 2.4.1 Collman's synthesis of a functionalised acid chloride⁷¹ for the preparation of macrocyclic biomimetic models i) DMF, 8hrs; ii) HCl (32%), reflux, 2 hrs; iii) CH₃CN (dry, degassed, under N₂), oxalyl chloride, reflux, 1 hr

The approach in this work was different. As the yields of corrole synthesis are typically low, preparation of intermediates bearing the elements of the final superstructure would allow for synthesis of the superstructure corrole in one step, potentially increasing the overall yield of the synthetic pathway. As such, an aldehyde bearing the tail motif (discussed here) and dipyrromethane bearing a water-solubilising motif (discussed in **Section 2.5.2**) were prepared. These intermediates could then be used in the synthesis of a corrole with the superstructure motifs already in place as in Scheme 2.4.2.



Scheme 2.4.3 Attempted synthesis of the tailed aldehyde with the preparation of an acid chloride based on Collman's synthesis⁷¹ i) DMF, 8hrs; ii) HCl (32%), reflux, 2 hrs; iii) CH₃CN (dry, degassed), oxalyl chloride, reflux, 1 hr; iv) CH₂Cl₂ (dry), triethylamine, 0°C, 10 min, then room temperature, 2 hrs; v) MnO₂, CHCl₃, 20 hrs

Saponification of the ester, methyl 3-(1*H*-imidazol-1-ylmethyl)benzoate, was achieved in hydrochloric acid at reflux. The resultant white powder, isolated as the hydrochloride salt of the free carboxylic acid in 91% yield, crystallised in the *P2₁/c* space group. Proton NMR spectroscopic analysis indicated the loss of the methoxy protons as well as a down-field shift of the imidazole protons from 7.58, 7.10 and 6.92 ppm to 9.18 and 7.76-7.66 ppm, consistent with the presence of a charged imidazole species. This, together with the clear evidence from the X-ray crystal structure (Figure 2.4.1) and the increased water solubility of the compound indicated the successful synthesis of the hydrochloride salt of the acid. Carbon NMR spectroscopic analysis indicated a shift in the position of the carbonyl carbon from 166.45 ppm in the ester to 168.91 ppm in the acid. The parent ion (with the chloride counter-ion) was present in the mass spectrum at $m/z = 237.15$ ($[M+H]^+$).

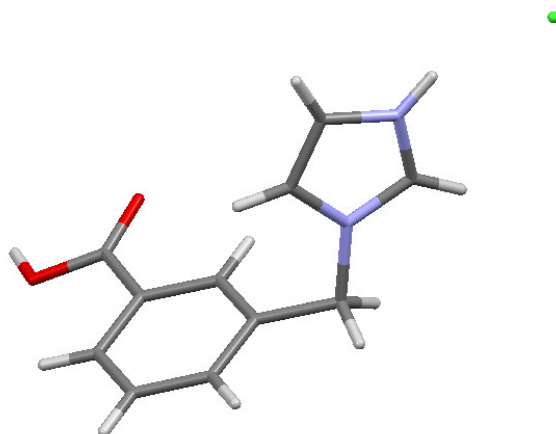


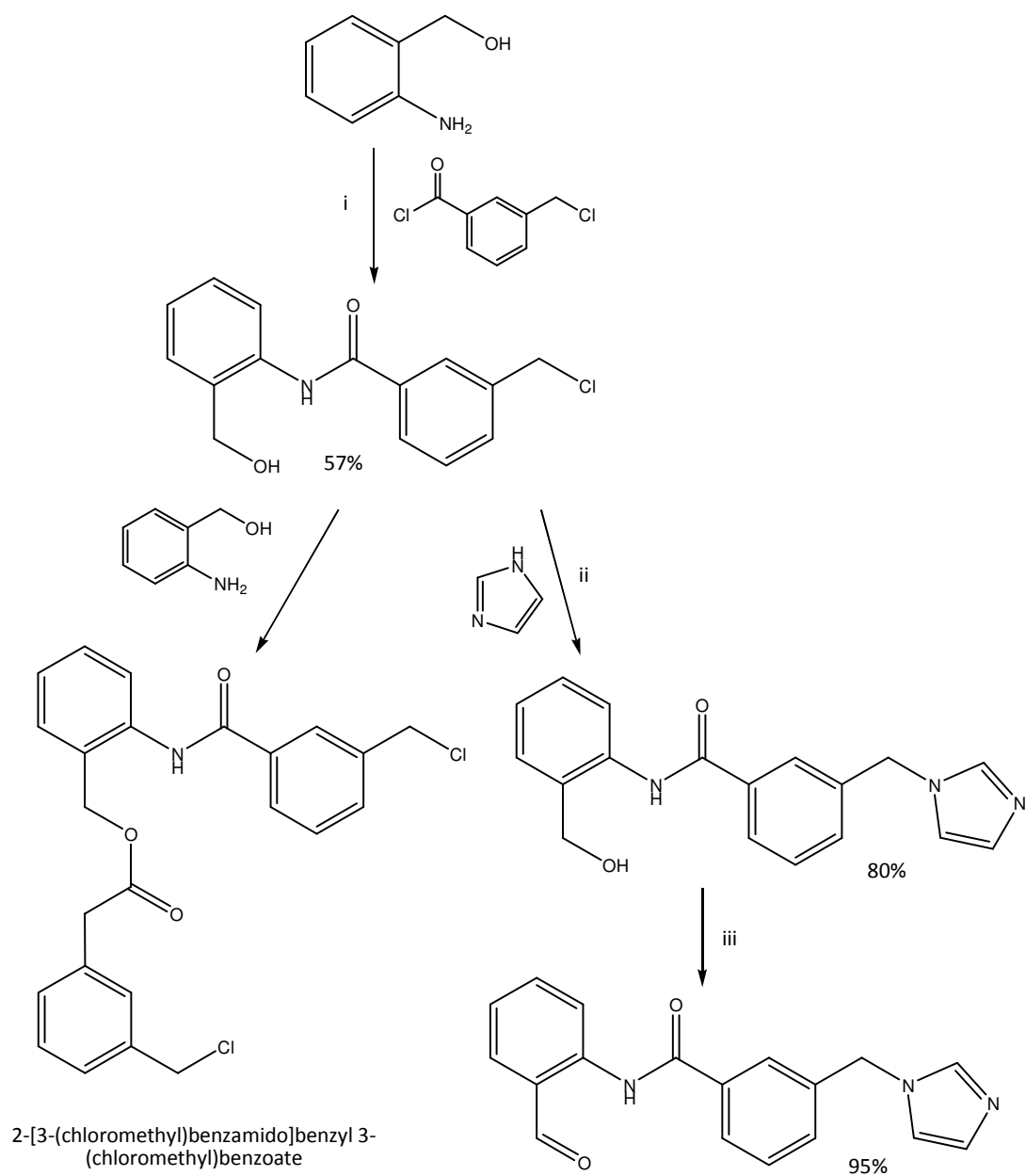
Figure 2.4.1 X-ray crystal structure of 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride (the chloride is indicated in green)

Synthesis of the acid chloride from the carboxylic acid could not be achieved, despite numerous attempts. Various factors were investigated, including solvent, chlorinating agent (oxalyl chloride and thionyl chloride) and base (organic, inorganic and an ion exchange resin were used). The use of a coupling agent (1,1'-carbonyldiimidazole) was also unsuccessful. In light of this difficulty, a new strategy was devised.

2.4.2 An alternative strategy

The difficulty of synthesising the required acid chloride was overcome by using a starting material with the acid chloride in place already – 3-(chloromethyl)benzoyl chloride. The new synthetic scheme is illustrated in Scheme 2.4.4 below. This synthetic route has the advantage of being much shorter, with the aldehyde prepared in three steps, as opposed to the five steps required by the Collman-based⁷¹ synthesis. 3-(Chloromethyl)benzoyl chloride was first coupled to 2-aminobenzyl alcohol in dichloromethane in the presence of triethylamine in 57% yield. The off-white solid product, 3-(chloromethyl)-*N*-[2-(hydroxymethyl)phenyl]benzamide, was identified from the proton NMR spectrum where the presence of a singlet at 9.70 ppm confirmed the formation of the amide bond. In addition to the presence of the expected ion peak at $m/z = 275.0702$ ($[M]^+$) in the mass spectrum, the product crystallised, yielding diffraction-quality crystals from which the structure of the molecule was determined, as in Figure 2.4.2a.

This reaction was found to be time sensitive. The product was isolated in a 57% yield after two hours. If the reaction was allowed to proceed for more than three hours, no 3-(chloromethyl)-*N*-[2-(hydroxymethyl)phenyl]benzamide was isolated, but rather, the 3-(chloromethyl)benzoyl chloride added to 2-aminobenzyl alcohol twice to yield 2-[3-(chloromethyl)benzamido]benzyl 3-(chloromethyl)benzoate as in Scheme 2.4.4. This product crystallised to yield the structure presented in Figure 2.4.2b. The product was also identified from the proton NMR spectra where no alcoholic proton was observed, three signals for methylene protons were present at 5.41, 4.66 and 4.61 ppm, integrating for a total of six protons and in the aromatic region, multiplet signals integrated for twelve aromatic protons in the 8.13-8.03, 7.63-7.61, 7.56-7.43 and 7.27-7.21 ppm regions, indicating the incorporation of a third phenyl ring.



Scheme 2.4.4 Synthesis of the tailed aldehyde from 3-(chloromethyl)benzoyl chloride. i) CH_2Cl_2 (dry), triethylamine, 0°C , 10 min, then room temperature, 2 hrs; ii) DMF, 8hrs; iii) MnO_2 , CHCl_3 , 20 hrs; iv) as in ii) with reaction time > 3 hrs

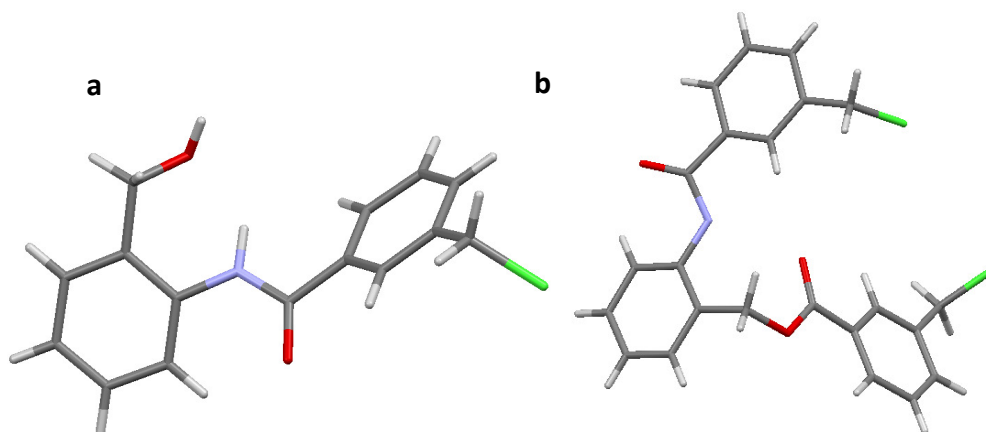


Figure 2.4.2 X-Ray crystal structures of **a** 3-(chloromethyl)-*N*-[2-(hydroxymethyl)phenyl]benzamide and **b** 2-[3-(chloromethyl)benzamido]benzyl 3-(chloromethyl)benzoate

Imidazole was then coupled to 3-(chloromethyl)-*N*-[2-(hydroxymethyl)phenyl]benzamide in DMF based on Berto's synthesis.²⁸ The yield of the product, *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide was found to be largely dependent on the base used during work-up. Use of triethylamine to basify the work-up solution resulted in crude material that required further purification by column chromatography. The yield was 57%. The use of ammonia solution, however, resulted in pure product being isolated in 80% yield which required no further purification. The product was identified by analysis of the NMR spectra from the presence of proton and carbon signals due to the imidazole at 7.38, 7.20 and 7.00 ppm in the proton NMR spectrum and 123.25, 119.42 ppm in the carbon NMR spectrum as well as a shift in the methylene protons from 4.61 ppm (CH₂-Cl) to 4.71 (CH₂-imidazole) in the proton NMR spectrum. The parent ion was present at $m/z = 307.1316$ ($[M]^+$) in the high resolution mass spectrum.

The alcohol was oxidised to the aldehyde using manganese dioxide in chloroform over a 20 hour period. The presence of DMF in the alcohol from the previous reaction prevented the formation of the aldehyde, so care was taken to ensure that the DMF was removed from the alcohol during the work-up, washing and drying stages. The aldehyde product, *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide was obtained in a 95% yield and the loss of the alcoholic proton and the presence of the aldehyde proton at 12.11 ppm in the proton NMR spectrum and the carbonyl carbon at 195.98 ppm in the carbon

spectrum validated the success of the reaction. The parent ion was present at $m/z = 305.1164$ ($[M]^+$) in the high resolution mass spectrum.

Both the alcohol and the aldehyde were found to be crystalline and polymorphic solids. Crystal structures of two polymorphs of both the alcohol *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide and the aldehyde *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide were determined and one structure each of both the alcohol and the aldehyde are presented in Figure 2.4.3. As with *N*-[2-(hydroxymethyl)phenyl]benzamide and *N*-(2-formylphenyl)benzamide in **Section 2.2.3**, polymorphism was found to have resulted from differences in the van der Waals associations in the solid state, as discussed in **Part 3**.

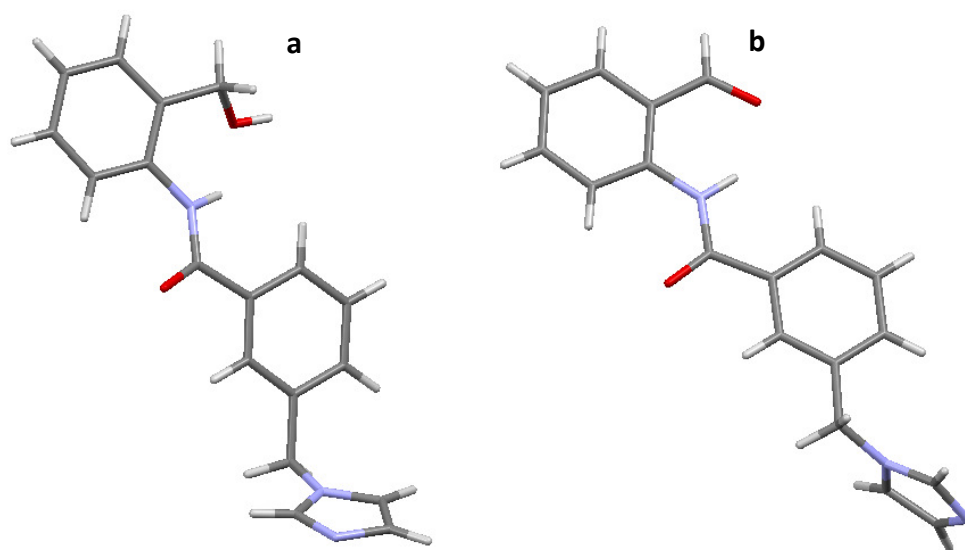
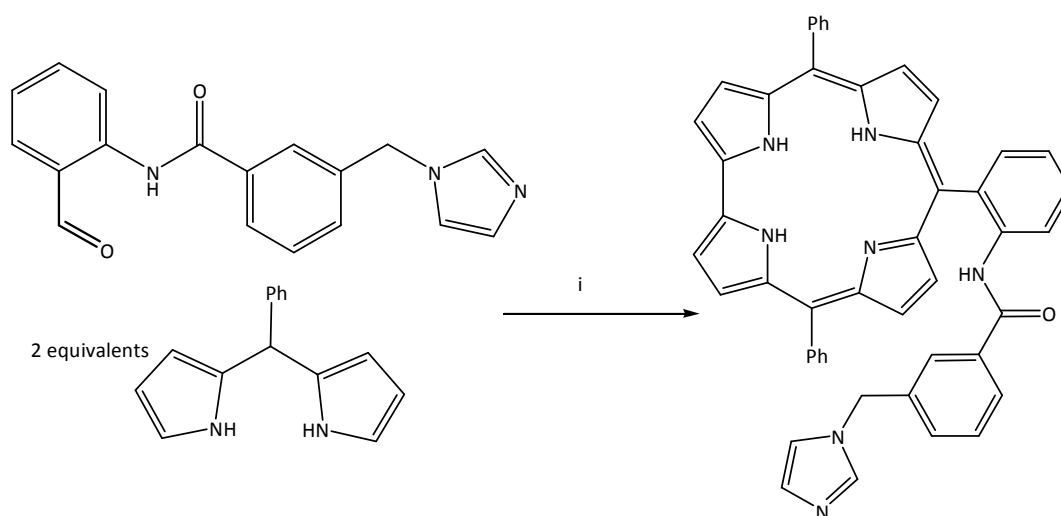


Figure 2.4.3 X-Ray crystal structures of **a** *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 1) and **b** *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 2)

2.4.3 Completing the synthesis of a tailed corrole

The tailed aldehyde, *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide and 2,2-(phenylmethylene)bis(1*H*-pyrrole) were used in Gryko's methanol:water corrole synthesis⁵ according to the method described previously and illustrated in Scheme 2.4.5 below. The product corrole, 10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-diphenylcorrole, referred to in this work as diphenyl tailed corrole or DPTC, was a very dark green/purple solid and appeared to be microcrystalline, but did not yield diffraction quality crystals. The UV-vis spectrum was that of a typical corrole spectrum and the parent ion was observed at $m/z = 726$ ($[M+H]^+$) in the mass spectrum. NMR spectra indicated the inclusion of the tail with the presence of NH amide signal at 9.04 ppm in the proton NMR spectrum and amide carbonyl signal at 163.61 ppm in the carbon NMR spectrum. Signals from the methylene group were present in both the proton and carbon NMR spectra at 3.09 and 21.03 ppm respectively. The typical corrole NMR signals of the β protons were present at 8.85, 8.83, 8.46 and 8.40 ppm.



Scheme 2.4.5 Synthesis of 10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-diphenylcorrole i) CH₃OH:H₂O 1:1, cat. HCl, 1 hr then *p*-chloranil (1 mol equiv.), overnight

The corrole was metallated with cobalt using excess cobalt acetate in the presence of excess sodium acetate under reflux for approximately two hours, until UV-vis analysis indicated the full conversion of the corrole into its metallated species. The UV-vis spectrum of the metallated corrole, [10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]-

amino}phenyl)-5,15-diphenylcorrolato]cobalt(III), referred to as diphenyl tailed corrole cobalt (DPTC-Co) in this work, was solvent dependent as discussed in **Part 4, Section 4.3.4**. In addition, the presence of strong ligands, such as cyanide or imidazole, induced colour and spectroscopic changes, discussed in **Part 4, Section 4.6**. This suggested the metal had been coordinated by the corrole ligand. The presence of the parent ion at $m/z = 782.44$ ($[M+H]^+$) also indicated that the metal had been coordinated by the macrocycle. As observed in the case of 5,10,15-triphenylcorrole, coordination of cobalt resulted in a general up-field shift of the signals as a result of the shielding effect of the cobalt ion, such as the shift in the signals of the β protons which shifted from 8.85, 8.83, 8.46 and 8.40 ppm in the metal free corrole to 8.80, 8.40 (integrating for four β protons) and 8.19 ppm in the metallated species.

2.5 Synthesis of water-soluble corroles

2.5.1 Sugars as macrocyclic water-solubilising agents

Sugars have been used in the preparation of synthetic water-soluble porphyrins and phthalocyanines by numerous research groups, including those of Maillard and co-workers⁷²⁻⁷⁴ and Sol and co-workers.⁷⁵ In addition to the water-solubilising properties of the free OH groups, the steric bulk of the sugars was found to decrease aggregation, thus increasing water solubility as well.⁷³

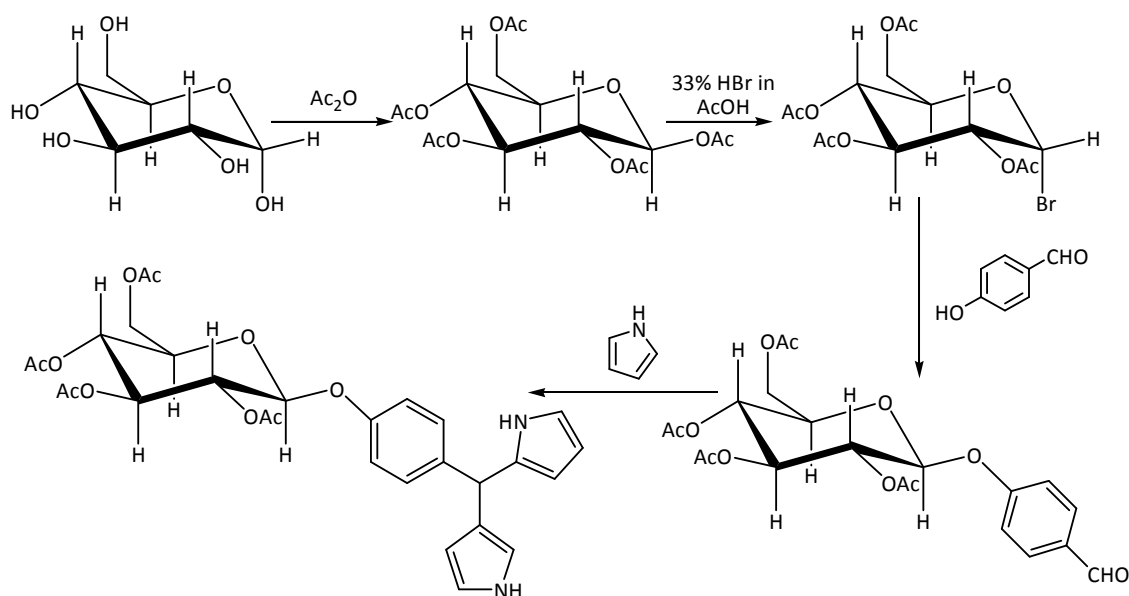
Maillard and co-workers found that the solubility of their synthetic porphyrins in neutral water increased as the number of free hydroxyl groups increased. They also found that the solubility was dependent on the geometry, and thus solvation, of the atropisomers about the phenyl-porphyrin axis (sugars were in the *ortho* position on the *meso* phenyl substituents) in question.⁷²

Glycosylation of metallated porphyrins has been found to have potent catalytic activity in the epoxidation of asymmetric alkenes. The presence of the chiral sugars near the metal centre was found to impart stereoselectivity during the catalytic process.^{74,76}

Glycosylation of porphyrins is evident in nature as well, with the isolation of a tolyporphyrin, a porphyrin derivative in the porphyrin family, bearing C-glycosyl substituents from a blue-green alga.⁷⁷ This tolyporphyrin was found to have significant anti-cancer properties and was found to reverse the effects of increased P-glycoprotein expression associated with multidrug resistance.⁷⁷

2.5.2 Synthesis of precursors for water-soluble corroles

A protocol for the preparation of a dipyrromethane bearing an acylated glucose moiety had been established in our laboratory (Scheme 2.5.1) as part of a potential water-solubilising system for porphyrins.⁷⁸ As the feasibility of this chemistry had been established, it was used as a basis for this work.



Scheme 2.5.1 Acylation of glucose and preparation of dipyrromethane bearing acylated glucose

There are numerous methods for the acylation of glucose using a variety of different reagents, solvents and experimental conditions. Two different synthetic pathways were investigated; the acylation of glucose firstly in acetic anhydride with a catalytic amount of sulphuric acid⁷⁹ and secondly in acetic anhydride in the presence of anhydrous ferric chloride.⁸⁰ These methods both reported excellent yields from gram scale reactions.

In the first synthetic route,⁷⁹ D-glucose was suspended in acetic anhydride at 0°C in the presence of a catalytic amount of sulphuric acid for two and a half hours. The product, penta-acylated glucose, crystallised from the pale yellow oil obtained. Recrystallisation from hot ethanol yielded a mixture of α and β anomers of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose in a 93% yield.

The second synthetic route made use of anhydrous ferric chloride.⁸⁰ Ferric chloride (0.09 mole equivalents) was dissolved in acetic acid. Ferric chloride acts as a Lewis-acid catalyst and dissolves in various inorganic and organic solvents capable of electron donation. The addition of the Lewis-acid generates ion pairs and acylium cation (acetic anhydride ionises to a small extent only in the absence of a catalyst) required for the acylation of sugars.⁸⁰ D-Glucose was added to the ferric chloride solution and after seven minutes of stirring, the reaction mixture was rapidly cooled by pouring into a large volume of iced water. The product precipitated out and was recrystallised from hot ethanol to afford pure 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose in an 80% yield.

In both cases, NMR spectroscopic analysis of the products indicated pure 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose, with the presence of five singlets between 2.19 and 2.02 ppm integrating for a total of 15 protons, indicating the presence of five acetyl groups. The five carbonyl carbons were also present in the carbon NMR spectrum between 170.63 and 168.75 ppm while the five methyl carbons were present between 20.87 and 20.44 ppm. The carbonyl and two C-O stretches indicative of carboxylic esters were observed in the FTIR spectrum at 1738, 1371 and 1217 cm⁻¹ respectively. The ratio of the α and β anomers, however, varied dramatically. The acid catalysed route yielded an α : β ratio of 2:1 while that for the ferric chloride route was 1:10. The α and β anomers presented distinctly different NMR spectra. The NMR signal for the anomeric proton in the equatorial or β position is at 5.72 ppm and experiences a down-field shift when the acetyl group is in the axial or α position to 6.33 ppm. The effect of the position of the anomeric acetyl group on the other four protons in the pyranose ring is marked, with shifts in the positions of signals depending on the spatial interaction with the bulky anomeric group as illustrated in Table 2.5.1 (the numbering scheme can be found in Figure 2.5.1). In the α anomer, the protons occupying axial positions on the same side of the pyranose ring as the axial acetyl group (H3 and H5) experience down-field signal shifts. When in the equatorial position, the β anomer acetyl group does not interact with the protons on the pyranose ring to the same degree, with protons H3 and H5 experiencing an up-field shift while H4 shifted down-field. In spite of the mixture of α and β anomers, 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose crystals examined were of the β anomer, and crystallised in the

P_{212121} space group with the same unit cell as a previously published structure.⁸¹ The parent ion was observed at $m/z = 408$ ($[M+H]^+ + H_2O$) in the mass spectrum. As a mixture of anomers, the product melted over a temperature range of 97-100°C, between the reported melting point of the α anomer at 88-90°C⁸² and that of the β anomer at 110-112°C.⁸³

Table 2.5.1 Proton NMR signal positions (taken from the centre of the signal) for selected protons in the α and β anomers of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose

Proton	Signal position (ppm)	
	α anomer	β anomer
H1	6.33	5.72
H2	5.12	5.12
H3	5.47	5.12
H4	5.12	5.27
H5	4.12	3.84

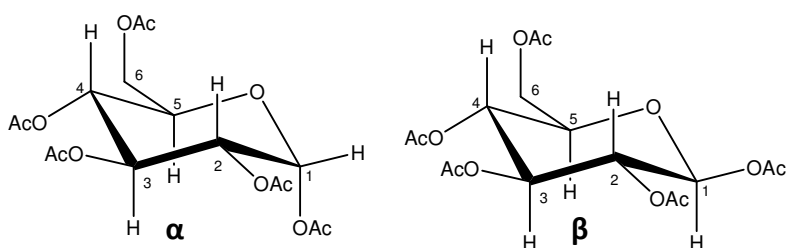


Figure 2.5.1 The α and β anomers of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose and the associated numbering scheme

Bromination of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose at the C1 position was found to produce the α anomer product only, irrespective of the α : β ratio of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose. As the fraction of either α or β anomer was inconsequential, the higher yielding first route for the acylation of D-glucose using a catalytic amount of sulphuric acid was chosen as the method of choice. Bromination at the C1 position can be achieved using a variety of synthetic routes. Three routes were investigated.

In the first synthetic route investigated, 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose was dissolved in dichloromethane under an inert atmosphere. An excess of 33% hydrobromic

acid in acetic acid was added and the reaction mixture was stirred in the dark overnight. Subsequent work-up and concentration *in vacuo* yielded a colourless oil from which the product was obtained in 84% yield when recrystallised from ether and hexane (1:1 v/v).⁸⁴ The second synthetic route⁸⁵ followed a similar procedure, except that a larger excess of hydrobromic acid was used and the reaction mixture was stirred for two hours, exposed to light. Similarly, the product was obtained in 97% yield when recrystallised from ether and hexane (1:1 v/v).

The third synthetic route did not use dichloromethane as a solvent. Instead, 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose was suspended in 33% hydrobromic acid in acetic acid at 0°C. The suspension was allowed to warm to room temperature and the reaction mixture was stirred for 45 minutes, after which time the acylated reactant had reacted to completion.⁷⁸ A colourless oil was obtained after concentration *in vacuo* after the work-up. The product was obtained in 96% yield when recrystallised from ether and hexane (1:1 v/v).

Bromination using the third route was favoured due to the short reaction time and high yield. The product was identified from the characteristic down-field shift of the anomeric proton to 6.62 ppm and the loss of one acetyl CH₃ group in the proton NMR spectrum and one carbonyl carbon and CH₃ carbon in the carbon NMR spectrum. The appearance of a band at 735 cm⁻¹ in the FTIR spectrum was indicative of a C-Br stretch. In addition, the uniformity of the NMR spectrum indicated that one anomer was present, suggesting a potential S_N1 type substitution reaction mechanism. XRD analysis of the crystals indicated that the α anomer was present, with a unit cell in agreement with a structure in the literature where the bromine clearly occupies an axial position in the α anomer.⁸⁶ The white crystals decomposed to yield a watery brown solid on standing at room temperature or when kept at approximately -18°C. To avoid this decomposition, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was used immediately in subsequent reactions.

With the bromine in place at the C1 position, the protected sugar could be coupled to *p*-hydroxybenzaldehyde. This was achieved through the deprotonation of the hydroxyl group using 1M sodium hydroxide, based on the work presented by Rackwitz in 1981⁸⁷. 2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranosyl bromide in acetone was added dropwise and the reaction mixture was stirred overnight at room temperature. The resultant product, 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside, was an off-white solid which was recrystallised from dichloromethane and hexane (1:1 v/v) to give a 55% yield.

The reaction resulted in an inversion of the stereochemistry at the anomeric position with the product identified as the β anomer from XRD analysis. NMR spectroscopic data indicated the presence of an aromatic aldehyde with a down-field singlet at 9.93 ppm and carbonyl peak at 190.73 in the carbon NMR spectrum, characteristic of an aldehyde as well as aromatic signals in the 7.86-7.10 ppm and 161.21-116.75 ppm regions in the proton and carbon spectra respectively together with the signals from the acylated sugar. FTIR spectra indicated the loss of the C–Br stretch, and the presence of a C–H stretch characteristic of aldehydes at 2974 cm⁻¹ not observed in the spectra of either the penta-acylated or the brominated precursors. A strong and broad signal at 1736 cm⁻¹ was indicative of the acetyl protecting groups and the aldehyde carbonyls. The parent ion was observed at $m/z = 475$ ($[M+H]^+ + Na$) in the mass spectrum.

XRD analysis of 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside crystals grown from dichloromethane confirmed the structure of the aldehyde and the fact that the β anomer had formed as Figure 2.5.2a clearly illustrates the phenyl ring occupying the equatorial position. Crystals grown from methanol were not of the aldehyde, but of the associated dimethyl acetal shown in Figure 2.5.2b. The acetal may have formed from a slightly acidic crystallisation solvent system, but this observation could not be repeated, in spite of the use of a variety of acidified alcohols as crystallisation media. The novel structure of the dimethyl acetal was published in Acta Crystallographica Section E – see **Appendix 2.4 and Digital Appendix 2.2.2.**⁸⁸

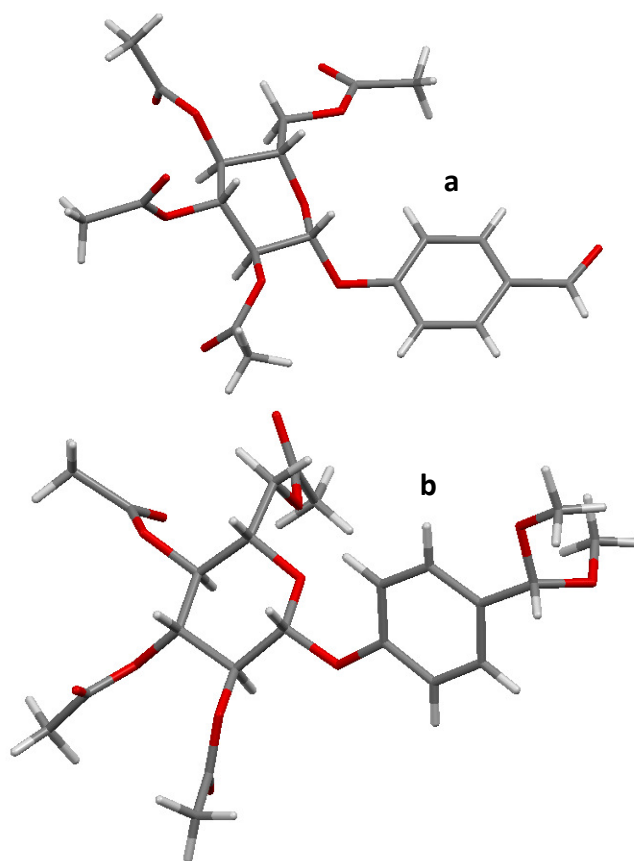


Figure 2.5.2 X-Ray crystal structures of **a** 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside and **b** the associated dimethyl acetal.

The synthesis of a dipyrromethane, discussed in **Section 2.2.2**, requires pyrrole and an aldehyde. With the aldehyde in place in 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, a dipyrromethane bearing the protected sugar was synthesised. As in the synthesis of 2,2-(phenylmethylene)bis(1*H*-pyrrole), a large excess of pyrrole was used (40 mole equivalents) as both solvent and reactant.¹¹ The product, purified by column chromatography and recrystallisation from ethyl acetate and hexane (1:1 v/v), was identified as the β anomer from a crystal structure from SCXRD analysis as in Figure 2.5.3. The proton NMR spectrum of 4-[di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside indicated the successful synthesis of the product with the maintenance of the sugar and acetyl peaks, the loss of the aldehyde singlet and the introduction of the pyrrolic protons in the 6.68-5.89 ppm region and protons on the pyrrolic nitrogens at 7.95 ppm. N-H stretch bands were observed at 3404 and 3350 cm⁻¹

in the FTIR spectrum. The parent ion was present at $m/z = 568.46$ ($[M]^+$) in the high resolution mass spectrum.

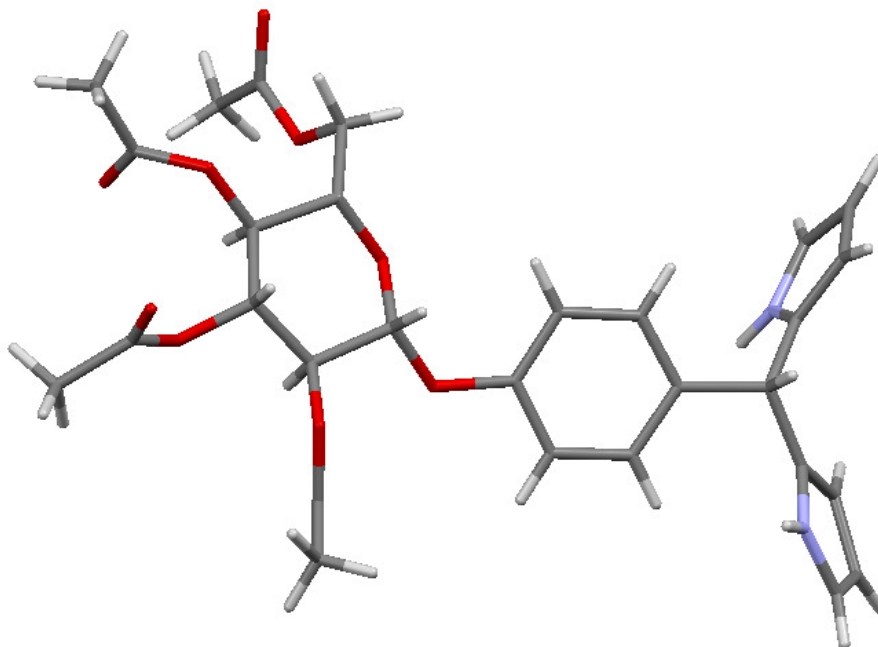


Figure 2.5.3 X-Ray crystal structure of 4-[di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

2.5.3 Completing the synthesis of water-soluble corroles

The dipyrromethane bearing a protected sugar moiety could be used in the synthesis of an A₂B corrole as described in **Section 2.2.2**. Two corroles bearing protected sugar groups, as shown in Figure 2.5.4, were synthesised.

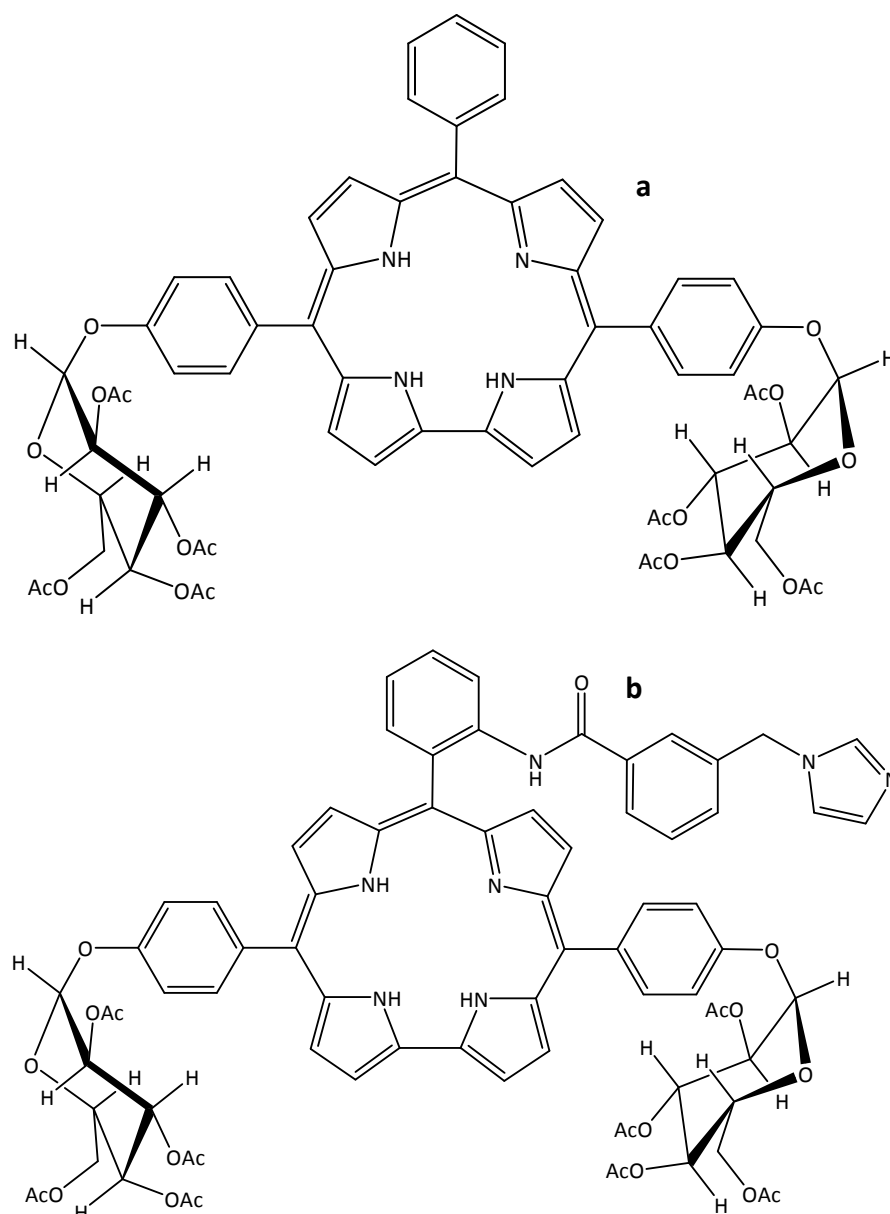


Figure 2.5.4 Corroles bearing sugar groups **a** 10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside)corrole **b** 10-(2-[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside)corrole

In the first case, benzaldehyde and the sugar dipyrromethane, 4-[di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside, were coupled to form a corrole using Koszarna and Gryko's methanol:water synthetic method.⁵ The corrole was identified from the UV-vis spectrum typical of corroles while the proton NMR spectrum indicated the presence of the protected sugar groups with the acetyl protons present between 2.19 and 2.01 ppm. Unfortunately no crystals of diffraction quality could be grown, although a variety of solvents and conditions were used.

In the second case, the tailed aldehyde (the synthesis of which is detailed in **Section 2.4.2**), *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide, was used in the place of benzaldehyde in the methanol:water corrole synthesis. Although no crystal structure could be obtained, the corrole was identified from the UV-vis spectrum and the parent ion was observed in the mass spectrum at $m/z = 1419$ ($[M+H]^+$). NMR spectroscopic data indicated the maintenance of the protected sugar groups with the acetyl methyl groups present between 2.17 and 2.10 ppm in the proton NMR spectrum and the carbonyl carbons between 170.67 and 169.48 ppm and the methyl carbons between 20.80 and 20.64 ppm in the carbon NMR spectrum. The amide proton of the tail was observed at 9.03 ppm while the amide carbonyl carbon was observed at 156.64 ppm, indicating the maintenance of the tail.

Removal of the acetyl protecting groups was achieved using excess sodium methoxide in methanol.^{89,90} The deprotection of the alcohol groups was achieved in the case of both sugar-containing corroles, however, separation of the corroles from the resultant acetate salt was not achieved in either case. The deprotected product 10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole was found to be water-soluble across the pH range. 10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole, on the other hand was soluble below pH 4 only. In addition, deprotected corroles appeared to be light-sensitive and degraded in solution overnight. The presence of sugars, sensitive to acidic and basic conditions, presented another potential problem as many of the inorganic studies were to

be carried out at high pH or under conditions of varying pH (such as pK_a studies in **Part 4, Section 4.4**).

Owing to these significant limitations as well as the difficulty experienced in purification of the deprotected corroles, it was decided that the more simple 10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-diphenylcorrole (prepared as in **Section 2.4.3**) was a better choice for the thermodynamic and kinetic studies where the corrole was to be compared to vitamin B₁₂. Although this corrole, bearing no water-solubilising groups, was soluble in various organic solvents only, it was possible to study both vitamin B₁₂ and the corrole biomimetic model in a methanol:water mixture, as described in **Part 4 Section 4.3.5**. As a result, the synthesis of sugar-bearing corroles was not furthered, and efforts were focused on the chosen biomimetic model, [10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-diphenylcorrolato]cobalt(III) (Figure 2.5.5).

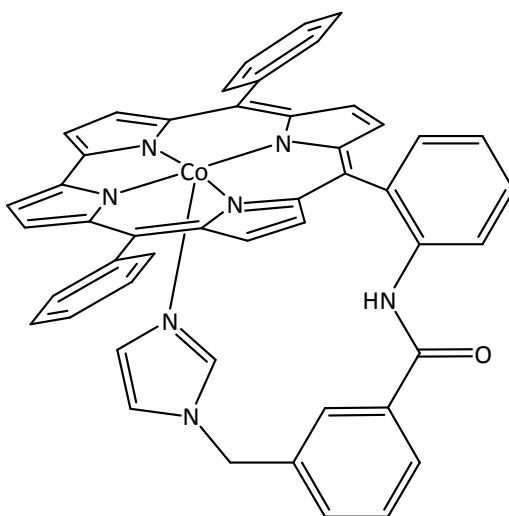


Figure 2.5.5 A biomimetic model of vitamin B₁₂: [10-(2-([4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino)phenyl)-5,15-diphenylcorrolato]cobalt(III)

2.6 Summary and conclusions

The feasibility of synthesising a corrole-based vitamin B₁₂ biomimetic system was established first with the synthesis of simple, model corroles, including 5,10,15-triphenylcorrole, 5,10,15-tri(2-nitrophenyl)corrole and 10-(4-methoxyphenyl)-5,15-diphenylcorrole. The synthesis of 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole suggested that a large, bulky *meso* substituent could be incorporated into the corrole with no loss of stability or significant decrease in yield.

The corroles prepared in the feasibility study were synthesised using Kozarna and Gryko's methanol:water method.⁵ This method was found to be far superior to the one-pot methods proposed in 1999 and the early 2000s.^{3,4,9,13} This method was versatile in that it could be used in the preparation of both A₃ and *trans* A₂B corroles.

The significant $\pi\cdots\pi$ overlap of the macrocycles in both the solid state and in solution was brought to light by the discovery of the concentration-dependence of the signal resolution in the NMR spectra. This was also confirmed by the close intermolecular packing of the corroles in the solid state in crystal structures of 5,10,15-triphenylcorrole and 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole. The $\pi\cdots\pi$ stacking could be interrupted when the corrole was metallated and an axial ligand coordinated to the cobalt ion was present, as in the case of triphenylphosphine [5,10,15-triphenylcorrolato]cobalt(III).

A vitamin B₁₂ biomimetic system was designed with the aid of molecular mechanics. The HyperChem suite of programs⁶⁶ was used to evaluate the relative single-point energies of a variety of corroles bearing a 'tail' substituent acting as an axial ligand for the coordinated cobalt. The low relative single-point energy of the structure, the lack of distortion of the macrocyclic plane and orthogonal binding of the axial imidazole contributed to the choice of the tailed corrole superstructure illustrated in Figure 2.6.1. The same tail motif has been favoured by several research groups for both porphyrin^{21,22,25,27,28,68} and corrole²⁰ based biomimetic models.

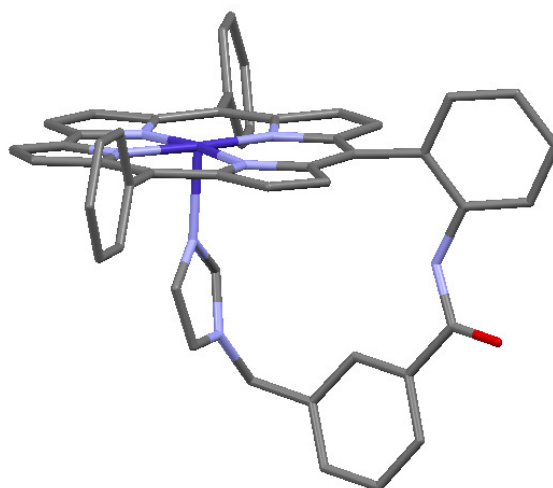


Figure 2.6.1 A biomimetic model of vitamin B₁₂: [10-(2-{{4-(1*H*-imidazol-1-ylmethyl)benzoyl}amino}phenyl)-5,15-diphenylcorrolato]cobalt(III)

Synthesis of the tailed substituent was achieved, not with the five step synthetic strategy based on Collman's synthesis of acid chlorides for biomimetic porphyrin-based models,⁷¹ but rather with a shorter, more efficient synthetic route starting with 3-(chloromethyl)benzoyl chloride, eliminating the need to synthesise the acid chloride intermediate, 3-[(1*H*-imidazol-1-yl)methyl]benzoyl chloride.

The aldehyde required for corrole synthesis was synthesised in three steps from the condensation of this 3-(chloromethyl)benzoyl chloride and 2-aminobenzyl alcohol followed by the coupling of imidazole to the terminus. The alcohol was oxidised to the aldehyde which, together with 2,2-(phenylmethylene)bis(1*H*-pyrrole), was used in the synthesis of a tailed corrole, 10-(2-{{4-(1*H*-imidazol-1-ylmethyl)benzoyl}amino}phenyl)-5,15-diphenylcorrole. The corrole was also successfully metallated using cobalt(II) acetate.

The alcohol and aldehyde intermediates of both 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole and 10-(2-{{4-(1*H*-imidazol-1-ylmethyl)benzoyl}amino}phenyl)-5,15-diphenylcorrole were found to be polymorphic and will be discussed in the next part of this thesis, **Part 3**.

A sugar-based water-solubilising system was used in the preparation of two water-soluble corroles. This involved the preparation of a dipyrromethane bearing an acylated glucose substituent, which was used in conjunction with either benzaldehyde or *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide in the synthesis of 10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole and 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole.

Deprotection of the glucose hydroxyl groups yielded corroles soluble in water. In the case of 10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole, the deprotected product was soluble in aqueous solutions of varying pH as well as methanol. Deprotection of 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole, however, yielded a corrole soluble in aqueous solutions below pH 4 only. This limitation, together with the difficulties experienced in the purification of the deprotected corroles, led to the water-solubilising system not being used in the final biomimetic model. The simpler [10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrolato]cobalt(III), soluble in methanol:water mixtures, was prepared as the biomimetic model instead. A comparison of the physical and inorganic chemistry of the biomimetic model and vitamin B_{12a} will be discussed in **Part 4**.

2.7 General experimental methods

Materials and general methods used in this work are reported in this section.

2.7.1 Materials and purification methods

Reagents and solvents used in this work are reported in **Appendix 1.2**. Reagents and solvents were used as received unless otherwise stated. Benzaldehyde was dried over magnesium sulphate overnight, filtered, and distilled under N₂ at reduced pressure. The pure liquid was stored under N₂. Pyrrole was dried over calcium hydride overnight, then distilled using fractional distillation using a Vigreux column under N₂ or Ar. The pure liquid was stored under N₂ or Ar, covered in foil, in the freezer. When dry solvents were required, acetonitrile, dichloromethane and dimethylformimide were distilled from calcium hydride; diethyl ether and tetrahydrofuran were distilled from sodium wire; and toluene was distilled from sodium lumps. Deionised water, purified using a Direct Q UV 3 Millipore and further purified using a Millipore MilliQ unit, was used throughout this work.

2.7.2 General laboratory techniques and equipment

Evaporation of solvent under reduced pressure was performed on a Büchi Rotavapor R-210 with a Büchi B-491 heating bath at approximately 30°C. This is referred to as evaporation *in vacuo*.

Thin-layer Chromatography (TLC) was carried out using silica gel TLC plates with fluorescent indicator (254 nm), 0.2 mm layer thickness (Fluka); Aluminum oxide on TLC-PET foils with fluorescent indicator (254 nm), 0.2 mm layer thickness, pH 9.9 (Fluka) or Alugram reverse phase Silica C18 with fluorescent indicator (254 nm), 0.15 mm layer thickness (Macherey-Nagel)

Separation of compounds by column chromatography was performed using flash silica-gel 60 (particle size 0.04-0.063 mm).

2.7.3 NMR spectroscopy

Proton NMR data were recorded at 300.13 MHz and carbon NMR data were recorded at 75.47 MHz on a Bruker AVANCE 300 spectrometer. Spectra of corrole macrocycles were recorded on a Bruker ULTRASHIELD 500 PLUS spectrophotometer where proton NMR data were recorded at 500.13 MHz and carbon NMR data were recorded at 125.77 MHz. All samples were dissolved in CDCl₃ unless otherwise stated. Chemical shifts are reported on the δ scale (parts per million (ppm)) relative to the internal standard 0.03% tetramethylsilane (¹H) and the central CDCl₃ line at 77.00 ppm (¹³C). NMR spectroscopic data were processed using the MestReNova software suite.⁹¹ Selected NMR spectra can be found in **Appendix 2.1**.

2.7.4 Melting point

Melting points were recorded using a melting point apparatus with microscope fitted with a JMinst 628 digital thermometer. Samples were placed in a capillary tube sealed at one end. Melting points were recorded as the temperature at which the solid melted to form a uniform liquid (2°C/minute heating rate). Melting points are reported without correction.

2.7.5 Fourier-Transform Infra-Red spectroscopy

Infra-red spectra were recorded on a Bruker Tensor27 infra-red spectrophotometer fitted with a Diamond ATR device. No sample preparation was required. The acquisition of spectra was facilitated by Bruker OPUS software.⁹² Selected FTIR spectra can be found in **Appendix 2.1**.

2.7.6 HPLC

HPLC analysis was performed using a Phenomenex Luna 5 μ Silica column (250 x 4.60 mm, 5 μ m) and a phenomenex silica Security Guard guard column (4.0 mm length x 3.0 mm internal diameter), Dionex UltiMate 3000 pump and Dionex UltiMate 3000 Photodiode array detector. 20 μ l samples were injected onto the column and eluted using an isocratic elution method. Collection of chromatograms was facilitated by the Chromeleon software suite.⁹³

2.7.7 Mass Spectrometry

Low resolution mass spectra were recorded using either an APCI or ESI ion source in both the negative and positive modes on a Finnigan LXQ linear ion trap mass spectrometer using a direct injection method. High resolution data were collected in the positive mode using an EI ion source on a Thermo Fisher high resolution magnetic sector DFS mass spectrophotometer with a resolution of 3000, a mass range of 100 amu (8 kV) and a scan rate of 6 sec/decade. Data are reported as mass to charge ratios or m/z .

2.7.8 Single crystal X-ray diffraction

Single crystal X-ray diffraction intensity data collection, crystal structure solution and refinement were carried out by the author. Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_{α} radiation (50kV, 30mA) using the APEX 2⁹⁴ data collection software. The collection method involved ω -scans of width 0.5° and 512x512 bit data frames. Data reduction was carried out using the program *SAINT+*⁹⁵.

X-ray diffraction data of certain structures were collected on a Bruker X8 PROTEUM X-ray diffractometer equipped with a Microstar copper rotating anode generator, Montel Optics, a PLATINUM 135 CCD detector, and an Oxford CryoStream Plus system. The

collection method involved ω -scans of width 0.5°. Data reduction was carried out using the program *SAINT+*⁹⁵.

Crystal structures was solved by direct methods using *SHELXTL*⁹⁶. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using *SHELXTL*, *PLATON*⁹⁷ and *ORTEP-3*⁹⁸.

Ortep diagrams and crystallographic information for all novel crystal structures can be found in **Appendix 2.2** and crystallographic information tables of bond lengths, angles, torsions and hydrogen bonding parameters can be found in **Digital Appendix 2.1** while the raw data can be found in **Digital Appendix 2.2**.

2.8 Experimental procedures: Determining the feasibility of corrole synthesis

2.8.1 One-pot syntheses

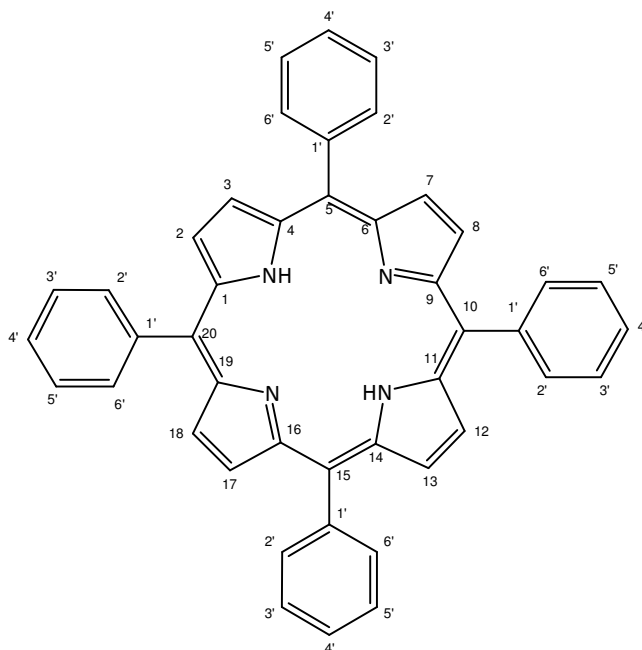
(a) Gross's solvent-free synthesis^{7,8}

A solution of freshly distilled pyrrole (0.173 ml, 2.5 mmol) and benzaldehyde (0.254 ml, 2.5 mmol) in dichloromethane (2 ml) was vigorously stirred at room temperature for 1 minute. The tar-like mixture was dissolved in dichloromethane (50 ml) and oxidised with DDQ (0.283 g, 1.25 mmol) for one hour. From NMR spectroscopic analysis of the crude material no macrocycle was identified.

(b) Paolesse's one-pot synthesis³

Freshly distilled pyrrole (4.2 ml, 60.5 mmol) and benzaldehyde (2.0 ml, 20 mmol) were added to acetic acid (250 ml). The stirred solution was heated to reflux for 3 hours. A colour change from colourless to a dark black-green was noted. The reaction mixture was cooled to room temperature. Deionised water (250 ml) was added. The precipitate was filtered off through a glass fritted funnel. Solid NaCl was added to the filtrate. The resultant precipitate was filtered off. The combined precipitates were separated by column chromatography on flash silica gel with dichloromethane as eluent. 5,10,15,20-Tetraphenylporphyrin, 5,10,15-triphenylcorrole, 2,2-(phenylmethylene)bis(1*H*-pyrrole) and other unidentifiable products were detected from NMR spectroscopic analysis. Multiple chromatographic separations using different eluents (ethyl acetate:hexane (1:4 v/v) containing 1% triethylamine; ethyl acetate:hexane (1:4 v/v); ethyl acetate:petroleum ether (1:4 v/v) containing 1% triethylamine; ethyl acetate; methanol) were unsuccessful in separating the low yield of corrole from the other products.

(c) Preparation of 5,10,15,20-tetraphenylporphyrin – the Lindsey method¹⁰



Freshly distilled pyrrole (0.208 ml, 3.0 mmol) and benzaldehyde (0.102ml, 1.0 mmol) were added to dry chloroform (400 ml). Argon was bubbled through the solvent for 15 minutes. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (168 μl) was added. An immediate colour change from colourless to yellow-green was observed. The flask was covered in foil and was stirred at room temperature for 1 hour after which time the solution was orange. DDQ (173 mg, 0.76 mmol) was washed into the flask with chloroform (150 ml). The colour of the solution immediately changed to black. The reaction mixture was stirred for an hour at room temperature, then concentrated *in vacuo*. The resulting mixture was separated by column chromatography on flash silica gel with ethyl acetate: hexane (1:9 v/v) containing 1% triethylamine as eluent to yield tetraphenylporphyrin as a purple-black solid (14.1 mg, 8%).

MP > 250°C (literature: not reported).

^1H (300 MHz, CDCl_3) δ (ppm): 8.92 (s, 8H, pyrrole H β), 8.29 (dd, J = 7.1, 1.8 Hz, 8H, H $_{\text{ar}}$ *ortho*), 7.86-7.75 (m, 12H, H $_{\text{ar}}$ *meta* + *para*)

^{13}C (75 MHz, CDCl_3) δ (ppm): 142.21 (C1'), 134.62 (C2' & C6'), 131.24(C β), 127.76 (C4'), 126.74 (C3' & C5'), 120.20 (C5, C10, C15 & C20).

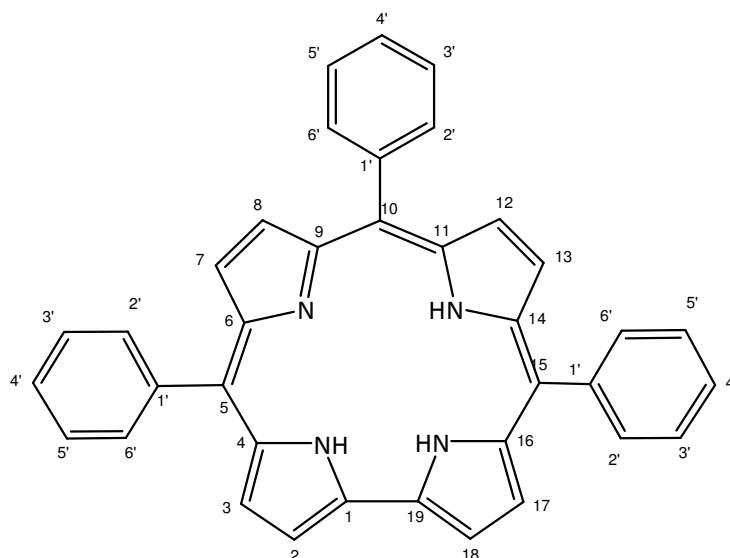
LRMS (ESI) m/z : 615.25 ($[\text{M}+\text{H}]^+$); calc.: 615.25 ($[\text{M}+\text{H}]^+$).

$\nu_{\max}$ (cm^{-1}): 3314 (w, NH stretch); 980 (s, NH bend); 964 (porphyrin skeleton ring vibration); 794 (s, C-H β out of plane bend); 694 (v s, NH bend in plane)

SCXRD	Polymorph 1 - TPHPOR01 *		Polymorph 2 – TPHPOR10	
	Space group	<i>P</i> -1	Space group	<i>I</i> -42 <i>d</i>
	a (Å)	6.42	a (Å)	15.07
	b (Å)	10.36	b (Å)	15.07
	c (Å)	12.29	c (Å)	13.72
	α (°)	95.05	α (°)	90.00
	β (°)	99.38	β (°)	90.00
	γ (°)	101.20	γ (°)	90.00
	R (%)	4.45	R (%)	4.15

* CSD identification code

(d) Preparation of 5,10,15-triphenylcorrole – Gryko's methanol:water method⁵



Freshly distilled pyrrole (0.700 ml, 10 mmol) and benzaldehyde (0.510 ml, 5 mmol) were dissolved in methanol (200 ml). Hydrochloric acid (32%, 4.25 ml) in water (200 ml) was added to the reaction flask which was stoppered and kept in the dark. The mixture was stirred at ambient temperature for 3 hours after which time an orange precipitate had formed. The reaction mixture was extracted into chloroform. The red organic layer was washed with water twice, dried with Na_2SO_4 and diluted with chloroform to a volume of

600 ml. *p*-Chloranil (1.23 g, 5 mmol) was added and the reaction mixture was refluxed for 1 hour in the dark. The black reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The crude product mixture was separated by column chromatography on flash silica gel with dichloromethane as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo*. A dark purple-black powder was obtained (83.2 mg; 19%).

MP > 250°C (literature: not reported⁵).

¹H (500 MHz, CDCl₃) δ (ppm): 8.97 (d br, 2H, pyrrole Hβ), 8.88 (d br, 2H, pyrrole Hβ), 8.60 (d br, 2H, pyrrole Hβ), 8.56 (d br, 2H, pyrrole Hβ), 8.37 (d, *J* = 5.6 Hz, 4H, H_{ar}), 8.17 (d br, 2H, H_{ar}), 7.85–7.68 (m, 9H, H_{ar}), –0.49 (s br, 3H, 3 x NH).

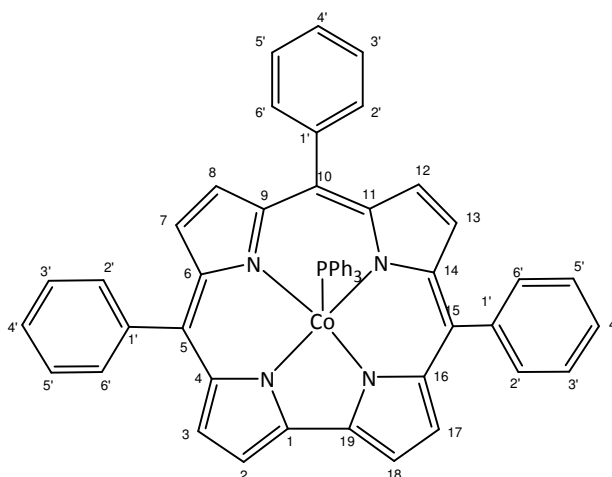
¹³C (126 MHz, CDCl₃) δ (ppm): 143.13, 142.14, 140.86, 139.82, 139.29, 135.96, 135.03, 131.55, 128.05, 127.40, 125.97, 122.65, 118.72, 115.81, 109.73.

LRMS (APCI) *m/z*: 526.98 ([M+H]⁺) 524.91 ([M–H][–]); calc.: 527.22 ([M+H]⁺).

***v*_{max}** (cm^{–1}): 2942 (s, NH stretch); 2844 (s, CH stretch); 1716 (w, C=N stretch); 1454 (m, C=C stretch); 1344 (m, CH bend), 1047 and 1013 (CN stretch and aromatic ring stretches and bends)

SCXRD	Polymorph 1 - JEFBEC		Polymorph 2 - solvate	
	Space group	<i>P</i> 2 ₁ / <i>c</i>	Space group	<i>C</i> 2/ <i>c</i>
	<i>a</i> (Å)	5.71	<i>a</i> (Å)	20.78
	<i>b</i> (Å)	19.01	<i>b</i> (Å)	19.46
	<i>c</i> (Å)	23.90	<i>c</i> (Å)	15.94
	α (°)	90.00	α (°)	90.00
	β (°)	90.47	β (°)	90.41
	γ (°)	90.00	γ (°)	90.00
	<i>R</i> (%)	6.66	<i>R</i> (%)	12.75

(e) Preparation of triphenylphosphine [5,10,15-triphenylcorrolato]cobalt(III)³



5,10,15-Triphenylcorrole (25 mg, 0.0475 mmol), cobalt(II) acetate (25 mg, 0.1 mmol) and triphenylphosphine (25 mg, 0.095 mmol) were refluxed with stirring in methanol (25 ml) for 1 hour in the dark. The reaction was monitored using UV-vis spectroscopy. The solvent was evaporated *in vacuo* and the crude product was separated using column chromatography on flash silica gel with dichloromethane as eluent. The red fraction was collected and concentrated *in vacuo*. The solid was recovered (0.0205 g, 51.1%) and recrystallised from a hexane: dichloromethane (1:1 v/v) solvent system as deep red block-like crystals.

MP > 250°C (literature: not reported³).

¹H (500 MHz, CDCl₃) δ (ppm): 8.59 (d, *J* = 4.3 Hz, 2H, pyrrole H β), 8.32 (d, *J* = 4.7 Hz, 2H, pyrrole H β), 8.09 (d, *J* = 4.7 Hz, 4H, pyrrole H β), 8.02 (d, *J* = 3.9 Hz, 2H, H_{ar}), 7.99 (d, *J* = 7.2 Hz, 1H, H_{ar}), 7.69-7.47 (m, 11H, H_{ar}), 7.37 (d, *J* = 7.3 Hz, 1H, H_{ar}), 7.04 (t, *J* = 6.8 Hz, 3H, *para*-H_{ar} PPh₃), 6.70 (dd, *J* = 7.3, 6.0 Hz, 6H, *meta*-H_{ar} PPh₃), 4.72 (dd, *J* = 9.7, 8.5 Hz, 6H, *ortho*-H_{ar} PPh₃).

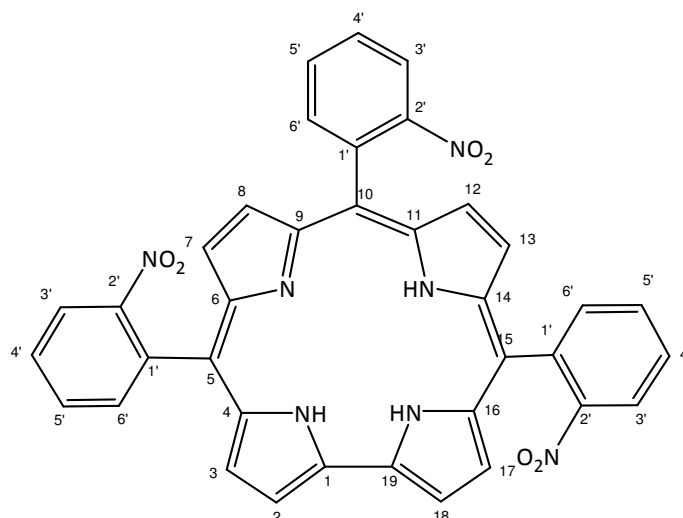
¹³C (126 MHz, CDCl₃) δ (ppm): 146.27; 145.59; 145.56; 145.01; 143.41; 141.88 (C α + *meso*) 136.44, 131.77 (C_{ar} PPh₃), 131.70 (C_{ar} PPh₃), 131.53 (C β pyrrole), 130.89 (C_{ar}), 130.73 (C_{ar}), 129.84, 129.29 (C_{ar} PPh₃), 129.27 (C_{ar} PPh₃), 128.54; 127.61; 127.35; 127.12; 127.08; 126.99; 126.96 (C_{ar} & C_{ar} PPh₃) 125.38; 124.73; 124.37; 124.28; 124.25; 124.10; 123.04; 123.00; 118.57 (C β pyrrole).

LRMS (APCI) *m/z*: 844.79 ([M+H]⁺); calc.: 845.22 ([M+H]⁺).

$\nu_{\max}$ (cm⁻¹): 2947 (s, CH stretch); 1715 (w, C=N stretch); 1427 (m, C=C stretch); 1311 (m, CH bend), 1050 and 1015 (CN stretch and aromatic ring stretches and bends)

SCXRD	KIMQOM
Space group	<i>P</i> -1
a (Å)	8.84
b (Å)	13.12
c (Å)	18.20
α (°)	94.33
β (°)	92.29
γ (°)	97.72
R (%)	3.22

(f) Preparation of 5,10,15-tri(2-nitrophenyl)corrole – Gryko's methanol:water method⁵



Freshly distilled pyrrole (0.697 ml, 10 mmol) and 2-nitrobenzaldehyde (0.756 g, 5 mmol) were dissolved in methanol (200 ml). Hydrochloric acid (32%, 4.25 ml) in water (200 ml) was added to the reaction flask which was stoppered and kept in the dark. The reaction mixture was stirred at ambient temperature for 3 hours after which time an orange precipitate had formed. The reaction mixture was extracted into chloroform. The red organic layer was washed with water twice, dried with Na₂SO₄ and diluted with chloroform to a volume of 600 ml. *p*-Chloranil (1.23 g, 5 mmol) was added and the

reaction was refluxed for 1 hour in the dark. The black reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The crude product mixture was separated by column chromatography on flash silica gel with dichloromethane as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo* and a green-black solid was obtained (0.0745 g, 4.5%).

MP > 250°C (literature: not reported²⁰).

¹H (500 MHz, CDCl₃) δ (ppm): 8.91 (dd, *J* = 10.2, 3.9 Hz, 2H, pyrrole H β), 8.64-8.54 (m, 2H, pyrrole H β), 8.33 (dt, *J* = 25.0, 7.9 Hz, 8H, pyrrole H β and H_{ar}), 8.27-8.22 (m, 2H, H_{ar}), 7.98-7.81 (m, 6H, H_{ar}), -1.98 (s, 3H, 3 x NH).

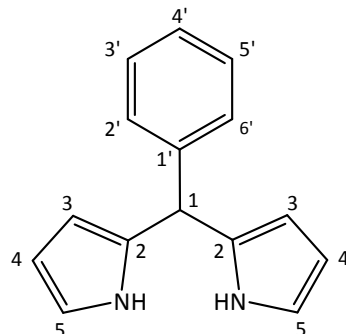
¹³C (126 MHz, CDCl₃) δ (ppm): 152.37, 152.25, 137.11, 137.06, 136.02, 133.71, 131.76, 131.67, 131.59, 131.50, 131.41, 131.19, 131.00, 129.21, 129.14, 126.76, 125.85, 125.74, 124.60, 124.54, 124.45, 124.03, 123.90, 116.35, 105.65, 105.52.

LRMS (ESI) *m/z*: 662 ([M+H]⁺); calc.: 662 ([M+H]⁺).

ν_{max} (cm⁻¹): 2981 (s, NH stretch); 2906 (s, CH stretch); 1701 (w, C=N stretch); 1541 (m, N=O stretch); 1456 (m, C=C stretch); 1344 (m, CH bend), 1062 and 1045 (CN stretch and aromatic ring stretches and bends)

2.8.2 Lego approach

(a) Preparation of 2,2-(phenylmethylene)bis(1*H*-pyrrole) (dipyrromethane)¹¹



Benzaldehyde (0.2 ml, 2 mmol) was dissolved in a large excess of freshly distilled pyrrole (5.6 ml, 80 mmol) and was degassed by bubbling argon through the solution for 10 minutes. Trifluoroacetic acid (16 μ l, 0.1 mmol) was added. The solution was stirred at room temperature for 15 minutes and then diluted with dichloromethane (100 ml) and washed with aqueous sodium hydroxide solution (0.1 N, 100 ml). The organic layer was dried with Na₂SO₄ and concentrated *in vacuo* to remove the excess pyrrole. The brown oil was separated by column chromatography on flash silica gel with hexane: ethyl acetate (4:1 v/v) containing 1% triethylamine as eluent. The desired product (0.252 g, 56.7%) was obtained as a brown solid alongside excess pyrrole and the associated trimer.

MP 98-100°C (literature: 98-99°C⁹⁹).

¹H (300 MHz, CDCl₃) δ (ppm): 7.84 (br s, 2H, NH), 7.36-7.12 (m, 5H, aromatic), 6.65 (dd, J = 4.1, 2.6, 2H, H5), 6.15 (dd, J = 5.9, 2.8, 2H, H4), 5.90 (br s, 2H, H3), 5.43 (s, 1H, PhCH).

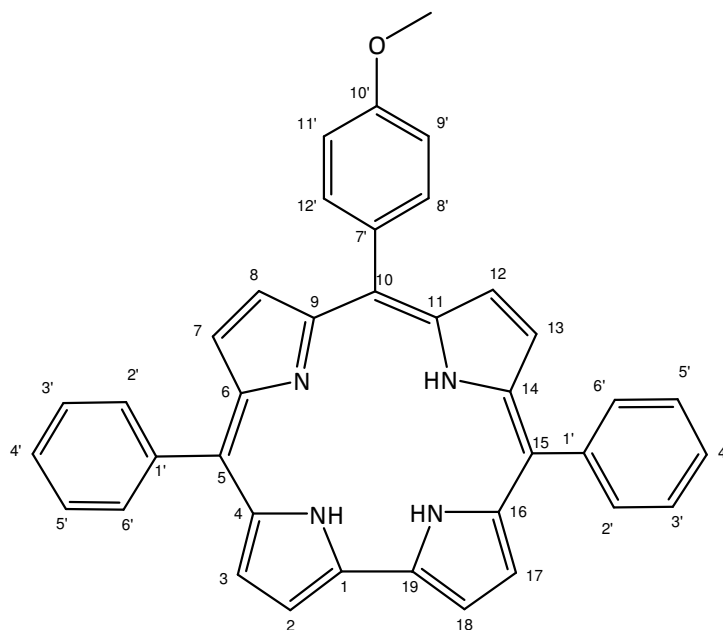
¹³C (75 MHz, CDCl₃) δ (ppm): 142.10 (C1'), 132.54 (C2), 128.68 (C2' and C6'), 128.44 (C3' and C5'), 127.02 (C4'), 117.28 (C5), 108.44 (C4), 107.27 (C3), 43.97 (PhCH).

LRMS (ESI) m/z : 223.10 ([M+H]⁺); calc.: 223.12 ([M+H]⁺).

HRMS (EI) m/z : 222.1150; calc.: 222.1157.

ν_{max} (cm⁻¹): 3363 (s, N-H stretch), 3339 (s, Ar C-H stretch), 2962 (w, C-H stretch), 1554 (m, Ar ring stretch), 1398 (w, C-H bend), 886 (s, Ar C-H bend), 777 (s, Ar C-H bend).

(b) Preparation of 10-(4-methoxyphenyl)-5,15-diphenylcorrole⁵



2,2'-(Phenylmethylene)bis(1*H*-pyrrole) (0.222 g, 1 mmol) and 4-methoxybenzaldehyde (0.061 ml, 0.5 mmol) were dissolved in methanol (50 ml). Hydrochloric acid (32%, 2.5 ml) in water (50 ml) was added to the reaction flask which was stoppered and kept in the dark. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was extracted into chloroform. The organic layer was washed with water twice, dried with Na₂SO₄ and diluted with chloroform to a volume of 250 ml. *p*-Chloranil (0.369 g, 1.5 mmol) was added and the reaction mixture was stirred at ambient temperature overnight in the dark. The black reaction mixture was concentrated *in vacuo*. The crude product mixture was separated by column chromatography on flash silica gel with dichloromethane as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo* to give a black solid product (0.0794 g, 29%).

MP > 250°C (literature: not reported⁵).

¹H (500 MHz, CDCl₃) δ (ppm): 8.97 (d broad, 2H, pyrrole H β), 8.88 (d broad, 2H, pyrrole H β), 8.58 (d broad, 4H, pyrrole H β), 8.37 (d broad, 4H, H_{ar}), 8.09 (d broad, 2H, H_{ar}), 7.81 (s, 5H, H_{ar}), 7.72 (s, 3H, H_{ar}), 4.09 (s, 3H, CH₃).

¹³C (126 MHz, CDCl₃) δ (ppm): 140.75, 136.57, 131.84, 130.82, 130.76, 129.60, 129.25,

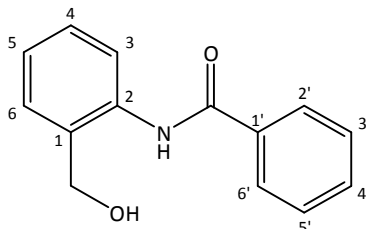
128.92, 128.45, 128.31, 128.04, 127.87, 127.57, 127.39, 126.03, 117.57, 115.66, 113.99, 112.81, 55.35 (CH₃).

LRMS (APCI) m/z : 557.06 ([M+H]⁺); calc.: 557.23 ([M+H]⁺).

$\nu_{\max}$ (cm⁻¹): 2976 (s, NH stretch); 2871 (s, CH stretch); 1683 (w, C=N stretch); 1510 (m, C=C stretch); 1350 (m, CH bend), 1247 (C-O stretch); 1058 and 1018 (CN stretch and aromatic ring stretches and bends)

2.8.3 Introducing a bulky *meso* substituent at the 10 position

(a) Preparation of *N*-[2-(hydroxymethyl)phenyl]benzamide⁶⁰



2-Aminobenzyl alcohol (5 mmol, 0.615 g) and benzoyl chloride (6 mmol, 0.635 ml) were dissolved in dry dichloromethane (15 ml) in the presence of pyridine (6.25 mmol, 0.552 ml).⁶⁰ The reaction mixture was stirred at room temperature for 3 hours. HCl (0.1 N, 10 ml) was added and the aqueous layer was extracted into dichloromethane. The organic layer was washed with aqueous saturated NaHCO₃ solution (20 ml) and water (10 ml) and dried with Na₂SO₄. The off-white solid crystallised on evaporation of solvent *in vacuo* (0.937 g, 82.5%).

MP 94-95°C (literature: 93-94°C¹⁰⁰)

¹H (300 MHz, CDCl₃) δ (ppm): 9.82 (s, 1H, NH), 8.14 (d, *J* = 8.1 Hz, 1H, H₆), 7.84 (d, *J* = 7.3 Hz, 2H, H_{2'} & H_{6'}), 7.47 (d, *J* = 7.4 Hz, 2H, H_{3'} & H_{5'}), 7.38 (t, *J* = 7.5 Hz, 1H, H_{ar}), 7.30-7.20 (m, 1H, H_{ar}), 7.06 (dd, *J* = 7.3, 1.2 Hz, 1H, H_{ar}), 6.99 (dd, *J* = 10.7, 4.0 Hz, 1H, H_{ar}), 4.66 (s, 2H, CH₂), 4.07 (s, 1H, OH).

¹³C (75 MHz, CDCl₃) δ (ppm): 165.76 (C=O), 137.78 (C₂), 134.51 (C_{1'}), 131.89 (C₁), 129.67 (C_{ar}), 128.94 (C_{ar}), 128.76 (C_{2'} & C_{6'}), 128.62 (C_{ar}), 127.13 (C_{3'} & C_{5'}), 124.25 (C_{ar}), 122.13 (C_{ar}), 64.60 (CH₂).

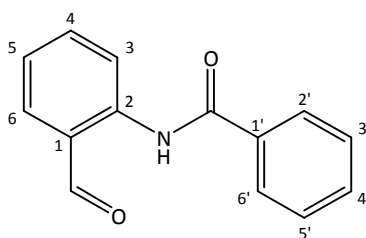
LRMS (ESI) *m/z*: 228.08 ([M+H]⁺); calc.: 228.10 ([M+H]⁺).

HRMS (EI) *m/z*: 227.0944 ([M]⁺); calc.: 227.0946.

ν_{max} (cm⁻¹): 3292 (m, br, O-H and N-H stretch (H-bonded)); 3054 (Aromatic stretch); 1656 (C=O stretch); 1588 (N-H bend)

SCXRD	Polymorph 1		Polymorph 2	
	Space group	$P2_1/n$	Space group	$P2_1/n$
	a (Å)	12.51	a (Å)	5.20
	b (Å)	7.33	b (Å)	13.24
	c (Å)	12.66	c (Å)	17.04
	α (°)	90.00	α (°)	90.00
	β (°)	100.05	β (°)	90.125
	γ (°)	90.00	γ (°)	90.00
	R (%)	4.2%	R (%)	5.6%

(b) Preparation of *N*-(2-formylphenyl)benzamide



N-[2-(Hydroxymethyl)phenyl]benzamide (455 mg, 2 mmol) and manganese(IV) oxide (2.608 g, 30 mmol) were stirred in chloroform (10 ml) for 12 hours. The reaction mixture was filtered through celite with chloroform as eluant. The solvent was removed *in vacuo*. The oily residue crystallised when placed under high vacuum. The off-white solid was recrystallised from methanol and hexane (0.436 g, 96.9%).

MP 67-69°C and 71-72°C (literature: 67-68°C¹⁰¹). Melting points are of the two different polymorphs.

¹H (300 MHz, CDCl₃) δ (ppm): 12.11 (s, 1H, CHO), 10.03 (s, 1H, NH), 8.97 (d, J = 8.4 Hz, 1H, H₃), 8.19-7.97 (m, 3H, H_{3'}, H_{4'} & H_{5'}), 7.78-7.65 (m, 2H, H_{ar}), 7.57 (dd, J = 10.5, 4.5 Hz, 2H, H_{ar}), 7.32-7.24 (m, 1H, H_{ar}).

¹³C (75 MHz, CDCl₃) δ (ppm): 195.92 (CHO), 166.17 (C=O amide), 141.28 (C₂), 136.42 (C₁), 136.22 (C_{1'}), 134.34 (C_{ar}), 132.23 (C_{ar}), 128.90 (C_{ar}), 127.53 (C_{ar}), 123.07 (C_{ar}), 122.01 (C_{ar}), 119.99 (C_{ar}).

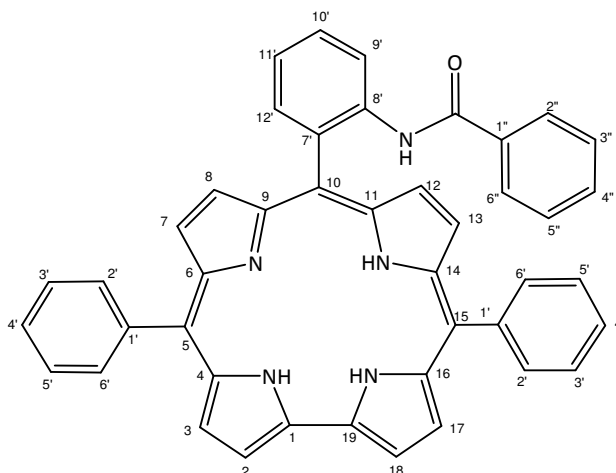
LRMS (APCI) m/z : 226.04 ($[M+H]^+$); calc.: 226.08 ($[M+H]^+$).

HRMS (EI) m/z : 225.0786 ($[M]^+$); calc.: 225.0790.

$\nu_{\max}$ (cm^{-1}): 3318 (w, N-H stretch); 1741 (m, C=O); 1526 (s, N-H stretch)

SCXRD	Polymorph 1		Polymorph 2	
	Space group	$P2_1/n$	Space group	
	a (Å)	4.55	a (Å)	9.09
	b (Å)	15.10	b (Å)	9.52
	c (Å)	16.15	c (Å)	18.48
	α (°)	90.00	α (°)	90.00
	β (°)	96.51	β (°)	90.00
	γ (°)	90.00	γ (°)	90.00
	R (%)	4.21	R (%)	4.13

(c) Preparation of 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole



2,2-(Phenylmethylene)bis(1*H*-pyrrole) (0.053 g, 0.24 mmol) and *N*-[2-formylphenyl]-benzamide (0.027 g, 0.12 mmol) were dissolved in methanol (15 ml). Hydrochloric acid (32%, 4.25 ml) in water (15 ml) was added to the reaction flask which was stoppered and kept in the dark. The reaction mixture was stirred at ambient temperature for 1 hour after which time a red precipitate had formed. The reaction mixture was extracted into chloroform. The amber organic layer was washed with water twice, dried with Na_2SO_4 and diluted with chloroform to a volume of 60 ml. *p*-Chloranil (0.08 g, 0.33 mmol) was added and the reaction was stirred at ambient temperature in the dark overnight. The

crude product mixture was concentrated *in vacuo* and separated by column chromatography using flash silica gel with dichloromethane as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo* to yield a green-black solid (0.0525 g, 67%).

MP > 250°C.

¹H (500 MHz, CDCl₃) δ (ppm): 8.98 (s*, 2H, pyrrole Hβ), 8.89 (s*, 2H, pyrrole Hβ), 8.60 (s*, 2H, pyrrole Hβ), 8.52 (s*, 2H, pyrrole Hβ), 8.32 (s*, 1H + 2H, NH + H_{ar}), 8.00 (d*, J = 18.6 Hz, 2H, H_{ar}), 7.81 (s*, 5H, H_{ar}), 7.72 (s*, 2H, H_{ar}), 7.58-7.41 (m, 3H, H_{ar}), 6.87 (s*, 1H, H_{ar} tail), 6.58 (s*, 4H, H_{ar} tail), -1.13 (s, 3H, 3 x NH). *signals presented as very broad peaks with very poor resolution. It is expected that these signals are in fact multiplets.

¹³C (126 MHz, CDCl₃) δ (ppm): 207.13(C=O), 143.25, 139.95, 139.88, 139.51, 135.89, 135.07, 135.01, 131.30, 131.07, 128.71, 128.41, 128.16, 128.06, 126.21, 126.16, 126.13, 118.88, 116.10, 116.07.

LRMS (APCI) m/z: 646.42 ([M+H]⁺); calc.: 646.26 ([M+H]⁺).

v_{max} (cm⁻¹): 2981, 2964, 2947 (m, N-H stretch); 2873, 2877 (m, aromatic stretch); 1668 (w, C=O); 1058, 1031 (N-C stretch)

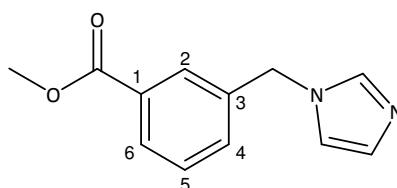
SCXRD

Space group	<i>P</i> ₋₁
a (Å)	9.93
b (Å)	13.74
c (Å)	14.12
α (°)	101.98
β (°)	104.12
γ (°)	100.50
R (%)	5.42

2.9 Experimental procedures: Synthesis of the biomimetic tailed corrole

2.9.1 Adapting Collman's synthesis

(a) Preparation of methyl 3-(1*H*-imidazol-1-ylmethyl)benzoate ⁷¹



Methyl 3-(bromomethyl)benzoate (2.29 g, 10 mmol) and imidazole (2.72 g, 40 mmol) in DMF (3 ml) were stirred at room temperature for 8 hours. The reaction mixture was diluted with water (50 ml) and extracted into dichloromethane (3 x 50 ml). The combined organic fractions were extracted into an aqueous hydrochloric acid solution (10%, 3 x 50 ml). The acidic solution was neutralised with ammonia solution and it became cloudy. The product was extracted into ethyl acetate (3 x 50 ml) and dried over Na₂SO₄. The solvent was removed *in vacuo* to yield a yellow oil (1.442 g, 66.7%).

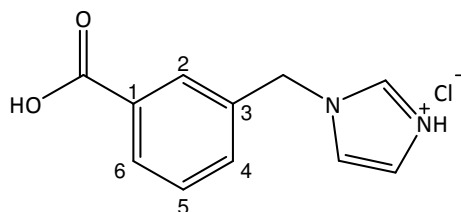
¹H (300 MHz, CDCl₃) δ (ppm): 8.00 (d, *J* = 7.6 Hz, 1H, H₆), 7.88 (s, 1H, H₂), 7.58 (s, 1H, H₂_{imid}), 7.44 (t, *J* = 7.7 Hz, 1H, H₅), 7.33 (d, *J* = 7.8 Hz, 1H, H₄), 7.10 (s, 1H, H₄_{imid}), 6.92 (s, 1H, H₅_{imid}), 5.17 (s, 2H, CH₂), 3.91 (s, 3H, CH₃).

¹³C (75 MHz, CDCl₃) δ (ppm): 166.45 (C=O), 137.36 (C₂_{imid}), 136.64 (C₃), 131.67 (C₁), 130.90 (C₂), 129.96 (C₄ or C₅ or C₆), 129.45 (C₄ or C₅ or C₆), 129.17 (C₄ or C₅ or C₆), 128.41 (C₄_{imid}), 119.20 (C₅_{imid}), 52.27 (CH₂), 50.37 (CH₃).

LRMS (ESI) *m/z*: 217.32 ([M+H]⁺); calc: 217.09 ([M+H]⁺).

ν_{max} (cm⁻¹): 1716 (s, C=O stretch); 1670 (s, N=C stretch); 1284 (s, C-N stretch)

(b) Preparation of 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride⁷¹



Methyl 3-(1*H*-imidazol-1-ylmethyl)benzoate (1.140 g, 5.3 mmol) was refluxed in hydrochloric acid (32%, 10 ml) for 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent was removed *in vacuo* to yield a white solid. Hot acetonitrile (20 ml) was added to the solid and filtered. The precipitate was collected and dried under high vacuum (0.9759 g, 91.5%). The white solid was recrystallised from methanol and hexane.

MP 210-212°C (literature: not reported⁷¹).

¹H (300 MHz, MeOD) δ (ppm): 9.18 (s, 1H, H2_{imid}), 8.08 (d, J = 1.1 Hz, 1H, H2), 8.06 (m, 1H, H6), 7.76-7.66 (m, 2H, H4_{imid} & H5_{imid}), 7.64 (t, J = 1.6 Hz, 1H, H4), 7.58 (dd, J = 11.4, 4.5 Hz, 1H, H5), 5.59 (s, 2H, CH₂).

¹³C (75 MHz, MeOD) δ (ppm): 168.91 (C=O), 136.73 (C2_{imid}), 136.14 (C_{ar}), 134.04 (C_{ar}), 133.12 (C_{ar}), 131.42 (C_{ar}), 130.68 (C_{ar}), 130.61 (C_{ar}), 123.45 (C5_{imid}), 121.63 (C4_{imid}), 53.41 (CH₂).

LRMS (EI) m/z : 203.21 ([M+H]⁺-Cl⁻); calc.: 203.08 ([M+H]⁺-Cl⁻).

HRMS (EI) m/z : 202.0731 ([M]⁺-Cl⁻); calc.: 202.0742 (-Cl⁻).

$\nu_{\max}$ (cm⁻¹): 3017 (very br, O-H stretch carboxylic acid (hydrogen bonded)); 1704 (s, C=O); 1565 (s, N=C stretch); 1191 (s, N-C stretch)

SCXRD

Space group	$P2_1/c$		
a (Å)	12.01	α (°)	90.00
b (Å)	7.67	β (°)	100.41
c (Å)	12.40	γ (°)	90.00
R (%)	3.95		

(c) Attempted preparation of 3-(1*H*-imidazol-1-ylmethyl)benzoyl chloride

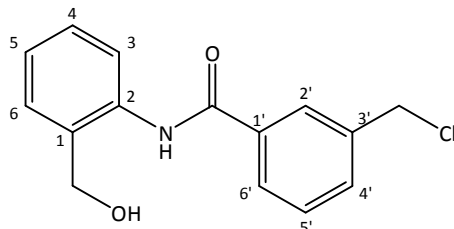
Route 1:⁷¹ 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride (1.011 g, 5 mmol) was suspended in dry, degassed acetonitrile (25 ml). Oxalyl chloride (2.5 ml, 32.3 mmol) was added. The reaction was refluxed for one hour. The reaction was allowed to cool. Ether was added and an off-white solid precipitated. NMR and FTIR spectra confirmed this as starting material. On the addition of a drop of DMF to the solvent system, the white solid did not precipitate and no product was detected in the resultant material. The neither the use of dichloromethane instead of acetonitrile nor the use of thionyl chloride instead of oxalyl chloride affected the outcome.

Route 2: 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride (0.202 g, 0.92 mmol) was suspended in dry, degassed acetonitrile (5 ml) with a drop of DMF. Oxalyl chloride (0.5 ml) was added, and the evolution of gas was observed. The reaction mixture was refluxed for 1 hour and then allowed to cool to room temperature. 2-Aminobenzyl alcohol (0.740 g, 6.01 mmol) and pyridine (0.552 ml) were added and the reaction mixture was stirred at room temperature for three hours. Hydrochloric acid (0.1 N, 10 ml) was added to work the reaction up. The aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic layers were washed with a saturated aqueous solution of NaHCO₃ (20 ml) and water (10 ml) and then dried over Na₂SO₄. Solvent was removed *in vacuo* to yield an orange solid. The material was passed through a silica plug with a dichloromethane eluent to give a yellow solution which was concentrated *in vacuo*. The desired product was not isolated from the crude reaction mixture either in this case or when thionyl chloride was used as the chlorinating agent or if Amberlite IR-4B(OH) resin was used as a base in dichloromethane reaction mixture in the absence of pyridine.

Route 3: Carbonyldiimidazole (CDI - 0.811 g, 5 mmol) was added to dry THF (10 ml) under argon. 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride (1.011 g, 4.60 mmol) was added and the reaction mixture was refluxed for 2.5 hours. 2-Aminobenzyl alcohol (0.640 g, 5.2 mmol) was added and the solution was refluxed overnight under a blanket of argon. Solvent was removed *in vacuo*. The desired product was not isolated.

2.9.2 An alternative strategy

(a) Preparation of 3-(chloromethyl)-*N*-[2-(hydroxymethyl)phenyl]benzamide



3-(Chloromethyl)benzoyl chloride (0.71 ml, 5 mmol) and 2-aminobenzyl alcohol (0.615 g, 5 mmol) were added to dry dichloromethane (15 ml). Freshly distilled triethylamine (0.767 ml, 0.557 g, 5.5 mmol) was added dropwise to the reaction mixture at 0°C. The solution was stirred at 0°C for 10 minutes and then at room temperature for 2 hours. Water was added and the organic layer was separated, dried over Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on flash silica gel with hexane: ethyl acetate (1:1 v/v) as eluent. The desired product was obtained as an off-white solid (0.793 g, 57.5%).

MP 98-99°C (literature: not reported).

¹H (300 MHz, CDCl₃) δ (ppm): 9.70 (s, 1H, NH), 8.21 (d, *J* = 8.0 Hz, 1H, H₆), 7.92 (s, 1H, H_{2'}), 7.81 (d, *J* = 7.8 Hz, 1H, H_{6'}), 7.56 (d, *J* = 7.8 Hz, 1H, H₃), 7.44 (dd, *J* = 9.5, 5.9 Hz, 1H, H₄ or H₅), 7.37-7.29 (m, 1H, H₄ or H₅), 7.15 (dd, *J* = 7.5, 1.4 Hz, 1H, H_{4'}), 7.06 (td, *J* = 7.4, 1.1 Hz, 1H, H_{5'}), 4.75 (d, *J* = 5.8 Hz, 2H, CH₂OH), 4.61 (s, *J* = 4.8 Hz, 2H, CH₂Cl), 3.00 (t, *J* = 5.8 Hz, 1H, OH).

¹³C (75 MHz, CDCl₃) δ (ppm): 165.02 (C=O), 138.28 (C₁, C₂, C_{1'} or C_{3'}), 137.73 (C₁, C₂, C_{1'} or C_{3'}), 135.18 (C₁, C₂, C_{1'} or C_{3'}), 131.95 (C₁, C₂, C_{1'} or C_{3'}), 129.40 (C_{ar}), 129.24 (C_{ar}), 129.15 (C_{ar}), 128.66 (C_{ar}), 127.53 (C_{ar}), 126.80 (C_{ar}), 124.38 (C_{ar}), 122.18 (C_{ar}), 64.80 (CH₂OH), 45.62 (CH₂Cl).

LRMS (ESI) *m/z*: 277 ([M+H]⁺); calc.: 277 ([M+H]⁺).

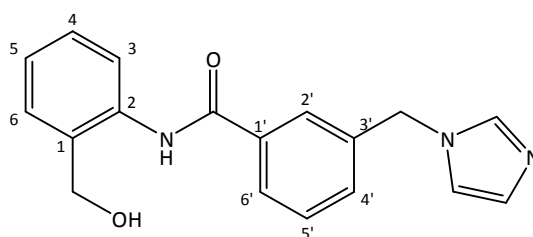
HRMS (EI) *m/z*: 275.0702 ([M]⁺); calc.: 275.0713.

ν_{max} (cm⁻¹): 3217 (m, br, O-H stretch); 3028 (w, N-H stretch); 1740, (very s, C=O); 1653 (s, N-H bend) 747 (s, C-Cl stretch)

SCXRD

Space group	P2 ₁ /n
a (Å)	4.19
b (Å)	26.02
c (Å)	12.18
α (°)	90.00
β (°)	90.00
γ (°)	90.00
R (%)	3.93

(b) Preparation of *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)-benzamide²⁸



3-(Chloromethyl)-*N*-[2-(hydroxymethyl)phenyl]benzamide (4.183 g, 15.17 mmol) and imidazole (10.329 g, 0.52 mol) in DMF (15 ml) were stirred at room temperature for 20 hours. The reaction was diluted with water (100 ml) and extracted into dichloromethane (3 x 100 ml). The combined organic fractions were extracted into a hydrochloric acid solution (10%, 3 x 100 ml). The acidic solution was neutralised with ammonia solution and it became cloudy. The product was extracted into chloroform (3 x 50 ml) and washed with water (6 x 100 ml) to remove any DMF present. The solution was then dried over Na₂SO₄ and the solvent was removed *in vacuo* to yield a yellow solid (3.723 g, 80%).

MP 144-146°C

¹H (300 MHz, MeOD) δ (ppm): 7.92-7.77 (m, 4H, H₃, H₄, H₅ & H₆), 7.53 (t, *J* = 7.6 Hz, 1H, H_{5'}), 7.47 (d, *J* = 7.8 Hz, 1H, H_{6'}), 7.38 (d, *J* = 7.5 Hz, 1H, H_{4_{imid}}), 7.33 (td, *J* = 7.8, 1.5 Hz, 1H, H_{4'}), 7.20 (td, *J* = 7.5, 1.1 Hz, 1H, H_{5_{imid}}), 7.16 (s, 1H, H_{2'}), 7.00 (s, 1H, H_{2_{imid}}), 5.33 (s, 2H, CH₂OH), 4.71 (s, 2H, CH_{2_{imid}}).

¹³C (75 MHz, MeOD) δ (ppm): 166.04 (C=O), 137.76 (C_{2_{imid}}), 136.13 (C₁, C₂, C_{1'} or C_{3'}),

134.94 (C₁, C₂, C_{1'} or C_{3'}), 132.96 (C₁, C₂, C_{1'} or C_{3'}), 130.64 (C₁, C₂, C_{1'} or C_{3'}), 128.97 (C_{ar}), 128.00 (C_{ar}), 127.78 (C_{ar}), 127.66 (C_{ar}), 126.38 (C_{ar}), 126.24 (C_{ar}), 126.19 (C_{ar}), 124.98 (C_{ar}), 123.25 (C_{4imid}), 119.42 (C_{5imid}), 62.00 (CH₂OH), 49.66 (CH₂-imid).

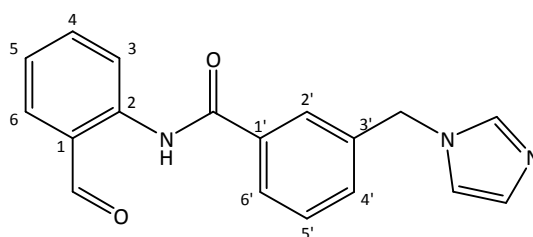
LRMS (ESI) *m/z*: 308 ([M+H]⁺); calc.: 308 ([M+H]⁺).

HRMS (EI) *m/z*: 307.1316 ([M]⁺); calc.: 307.1321.

***v*_{max}** (cm⁻¹): 3028 (m, very broad, O-H stretch and N-H stretch); 1739 (m, C=O stretch); 1664 (s, N-H bend); 1619 (m, C=N stretch)

SCXRD	Polymorph 1		Polymorph 2	
	Space group	P2 ₁ 2 ₁ 2 ₁	Space group	P2 ₁ /n
	a (Å)	4.25	a (Å)	13.48
	b (Å)	11.36	b (Å)	6.63
	c (Å)	31.12	c (Å)	18.55
	α (°)	90.00	α (°)	90.00
	β (°)	90.00	β (°)	108.54
	γ (°)	90.00	γ (°)	90.00
	R (%)	5.47	R (%)	4.43

(c) Preparation of *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide



N-[2-(Hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (0.7633 g, 2.5 mmol) and manganese(IV) oxide (4.347 g, 50 mmol) were stirred in chloroform (50 ml) for 20 hours. The reaction mixture was filtered through celite with chloroform as eluent. The solvent was removed *in vacuo*. The oily residue crystallised when placed under high vacuum. The off-white solid was recrystallised from methanol and hexane (0.7225 g, 95%).

MP 149-150°C

¹H (300 MHz, CDCl₃) δ (ppm): 12.11 (s, 1H, CHO), 10.00 (s, 1H, NH), 8.90 (d, *J* = 8.5 Hz, 1H, H3), 8.00 (d, *J* = 7.7 Hz, 1H, H6), 7.92 (s, 1H, H2_{imid}), 7.77 (d, *J* = 7.6 Hz, 1H, H6'), 7.68 (t, *J* = 7.9 Hz, 1H, H4 or H5), 7.63 (s, 1H, H2'), 7.54 (t, *J* = 7.7 Hz, 1H, H4' or H5'), 7.37 (t, *J* = 8.0 Hz, 1H, H4 or H5), 7.30 (t, *J* = 7.5 Hz, 1H, H4' or H5'), 7.10 (d, *J* = 0.7 Hz, 1H, H4_{imid}), 6.99 (d, *J* = 0.9 Hz, 1H, H5_{imid}), 5.25 (s, 2H, CH₂).

¹³C (75 MHz, CDCl₃) δ (ppm): 195.98 (CHO), 165.37 (C=O amide), 140.89 (C2), 137.29 (C2_{imid}), 136.35 (C1, C1' or C3'), 136.22 (C1, C1' or C3'), 135.12 (C1, C1' or C3'), 130.86 (C_{ar}), 130.00 (C_{ar}), 129.61 (C_{ar}), 126.94 (C_{ar}), 126.72 (C_{ar}), 123.31 (C_{ar}), 121.98 (C_{ar}), 119.81 (C4_{imid}), 119.26 (C5_{imid}), 50.42 (CH₂).

LRMS (ESI) *m/z*: 307.22 ([M+H]⁺); calc.: 306.12 ([M+H]⁺).

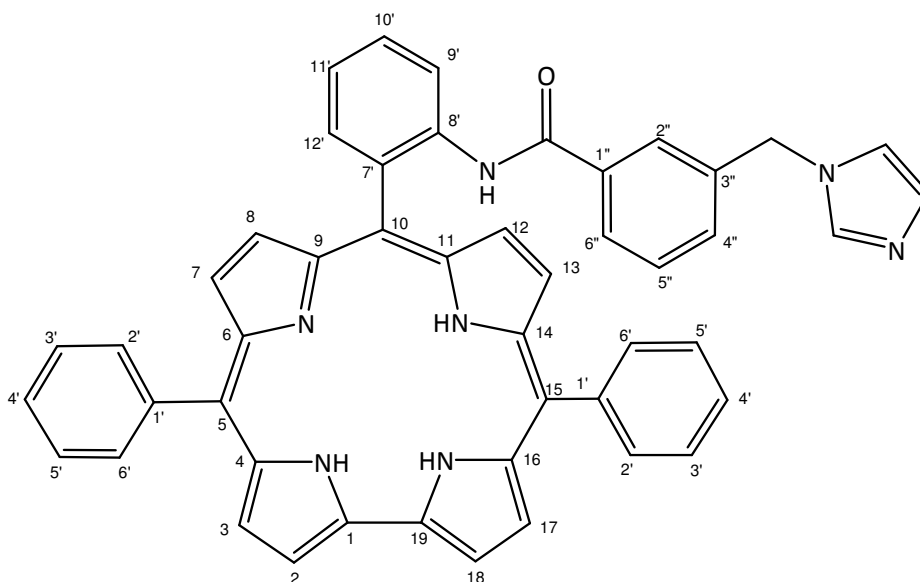
HRMS (EI) *m/z*: 305.1164 ([M]⁺); calc.: 305.1164.

***v*_{max}** (cm⁻¹): 3458 (w, N-H stretch); 1738 (s, C=O stretch); 1659 (m, C=N stretch); 1286 (C-N stretch)

SCXRD	Polymorph 1		Polymorph 2	
	Space group	P2 ₁ /n	Space group	C2/c
	a (Å)	8.25	a (Å)	30.30
	b (Å)	8.24	b (Å)	8.27
	c (Å)	22.00	c (Å)	26.56
	α (°)	90.00	α (°)	90.00
	β (°)	95.56	β (°)	117.35
	γ (°)	90.00	γ (°)	90.00
	R (%)	4.09	R (%)	5.83

2.9.3 Completing the synthesis of a tailed corrole

(a) Preparation of 10-(2-[[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino]phenyl)-5,15-diphenylcorrole



2,2'-(Phenylmethylene)bis(1*H*-pyrrole) (1.112 g, 5 mmol) and 3'-(1*H*-imidazol-1-ylmethyl)-*N*-(2-formylphenyl)benzamide (0.763 g, 2.5 mmol) were dissolved in methanol (150 ml). Hydrochloric acid (32%, 7.5 ml) in water (150 ml) was added to the reaction flask which was stoppered and kept in the dark. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was extracted into chloroform. The organic layer was washed with water twice, dried with Na₂SO₄ and diluted with chloroform to a volume of 500 ml. *p*-Chloranil (1.000 g, 4 mmol) was added and the reaction mixture was stirred for 6 hours in the dark. The black reaction mixture was concentrated *in vacuo*. The crude product mixture was separated by column chromatography on flash silica gel with hexane: ethyl acetate (1:1 v/v) as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo* and a dark green solid was obtained (0.1911 g, 10.5%).

MP > 250°C.

¹H (500 MHz, CDCl₃) δ (ppm): 9.04 (d, *J* = 8.3 Hz, 1H, NH), 8.85 (t, *J* = 3.5 Hz, 2H, pyrrole H_β), 8.83 (d, *J* = 4.6 Hz, 2H, pyrrole H_β), 8.46 (d, *J* = 4.0 Hz, 2H, pyrrole H_β), 8.40 (d, *J* =

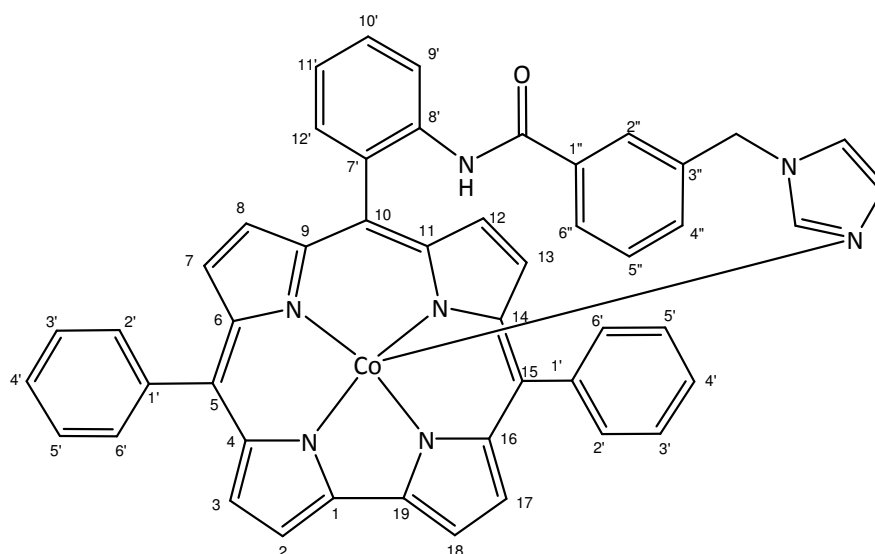
4.6 Hz, 2H, pyrrole H β), 8.34 (d broad, 4H, H2' & H6'), 8.26 (s, 1H, H2_{imid}), 7.80 (t, $J = 7.3$ Hz, 6H, H3', H4' & H6'), 7.71 (d, $J = 7.4$ Hz, 2H, H_{ar}), 7.70-7.65 (m, 1H, H_{ar}), 7.76 (s, 1H, H2''), 7.43 (t, $J = 7.3$ Hz, 1H, H_{ar}), 7.09 (t, $J = 7.7$ Hz, 1H, H2''), 6.77 (d, $J = 7.3$ Hz, 1H, H5_{imid}), 3.90 (s, 2H, CH₂) 1.20 (s broad, 3H, 3 x NH).

¹³C (126 MHz, CDCl₃) δ (ppm): 163.61 (C=O), 143.52, 140.73, 140.09, 138.04, 137.56, 136.07, 136.01, 135.86, 135.29, 135.13, 133.86, 131.77, 131.21, 130.49, 129.03, 128.98, 128.94, 128.66, 128.50, 128.14, 127.95, 127.41, 126.02, 125.84, 123.14, 122.73, 121.14, 120.91, 119.77, 117.18, 116.49, 114.59, 112.71, 111.16, 101.89, 21.03 (CH₂).

LRMS (ESI) m/z : 726 ([M+H]⁺); calc.: 726 ([M+H]⁺).

v_{max} (cm⁻¹): 2964, 2927, 2862 (m, N-H stretch); 1737 (w, C=O stretch); 1085 (s, broad, aromatic out of plane bend

(b) Preparation of [10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrolato]cobalt(III)



10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrole (0.191 g, 0.263 mmol) was dissolved in methanol (200 ml). Cobalt(II) acetate (10 mol equiv, 0.656 g, 2.633 mmol) and sodium acetate (10 mol equiv, 0.358 g, 2.633 mmol) were added and the reaction mixture was heated at reflux for two hours with the round bottomed flask covered in foil. The reaction mixture was concentrated *in vacuo* upon cooling to room temperature. The solid was dissolved in ethyl acetate and washed with water (three

times) and concentrated *in vacuo* to give a black solid (0.176 mg, 85.5%).

MP > 250°C.

¹H (500 MHz, CDCl₃) δ (ppm): 8.96 (d, *J* = 8.4 Hz, 1H, NH), 8.80 (d, *J* = 4.1 Hz, 2H, pyrrole Hβ), 8.40 (d, *J* = 4.0 Hz, 4H, pyrrole Hβ), 8.19-8.10 (m, 5H, pyrrole Hβ + H_{ar}), 8.01 (d, *J* = 4.0 Hz, 2H, H_{ar}), 7.94 (d, *J* = 7.2 Hz, 1H, H_{2imid}), 7.88 (d, *J* = 7.7 Hz, 1H, H_{2''}), 7.73 (d, *J* = 12.5 Hz, 6H, H_{ar}), 7.65 (d, *J* = 6.0 Hz, 3H, H_{ar}), 7.35 (t, *J* = 7.3 Hz, 2H, H_{ar}), 7.20 (t, *J* = 7.7 Hz, 2H, H_{ar}), 6.78 (d, *J* = 7.3 Hz, 1H, H_{ar}), 3.99 (s, 2H, CH₂).

¹³C (126 MHz, CDCl₃) δ (ppm): 163.08 (C=O), 154.09; 153.19; 150.71; 148.22; 147.59; 142.76; 139.29; 139.18; 136.61; 135.50; 135.43; 134.19; 134.01 (quaternary C), 130.06 (pyrrole Cβ), 129.84 (pyrrole Cβ), 129.74, 129.61, 129.59, 129.36, 129.04, 128.84, 128.29, 128.14, 127.70, 127.55, 126.78, 126.16, 125.75, 124.81, 123.28, 122.31, 120.63 (pyrrole Cβ), 119.83 (pyrrole Cβ), 118.96, 118.25, 114.07, 49.98 (CH₂).

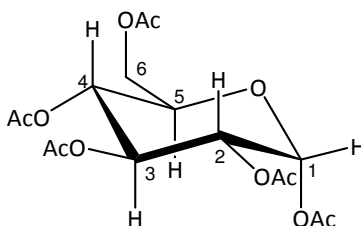
LRMS (APCI) *m/z*: 782.44 ([M+H]⁺); calc.: 782.20 ([M+H]⁺).

ν_{max} (cm⁻¹): 3406 (w, N-H stretch); 1673 (s, C=O stretch); 1578, 1518 (C=N stretch); 1441 (C-N stretch); 1051, 1012, 983 (s, aromatic out of plane bend)

2.10 Experimental procedures: Synthesis of water-soluble corroles

2.10.1 Synthesis of precursors for water-soluble corroles

(a) Preparation of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose



Route 1:⁷⁹ D-Glucose (1.9912 g, 11.05 mmol) was suspended in acetic anhydride (11 ml). The reaction mixture was cooled to 0°C in an icebath containing coarse salt. The reaction mixture was treated with sulfuric acid (95%, 100 μ l) resulting in a yellow solution. The reaction mixture was stirred at room temperature for 2.5 hours after which time the solution was dark orange-red and all of the glucose had dissolved. The reaction mixture was diluted with water (40 ml) and ethyl acetate (50 ml). The organic phase was separated and washed with water (3 x 50 ml) and saturated NaHCO₃ solution (3 x 50 ml). The organic fraction was dried with Na₂SO₄ and concentrated *in vacuo* to yield a yellow oil. The product was placed under high vacuum. The white solid that precipitated from the oil was recrystallised from hot ethanol and rapidly cooled by being placed in an ice bath. The white crystals were filtered off, washed with cold hexane and dried under vacuum to yield a mixture of the α and β products (α : β = 2:1; 4.024 g, 93.3%).

Route 2:⁸⁰ Ferric chloride (78 mg, 0.481 mmol) was added to acetic acid (6 ml) to afford a dark brown solution. D-Glucose (1.005 g, 5.58 mmol) was added portionwise with stirring. The reaction was observed to be exothermic. The reaction mixture was allowed to stir until all of the glucose had dissolved (approximately 10 minutes). The reaction solution was poured with stirring into ice-water (100 ml). After some time a white solid precipitated which was filtered off and recrystallised from hot ethanol and water and rapidly cooled in an ice bath. The white crystalline product was filtered off and dried under vacuum to yield a mixture of the α and β products (α : β = 1:10; 1.742 g, 80%).

Analysis below is of product from Route 1.

MP 97-100°C (literature: 88-90°C (α)⁸²; 110-112°C (β)⁸³).

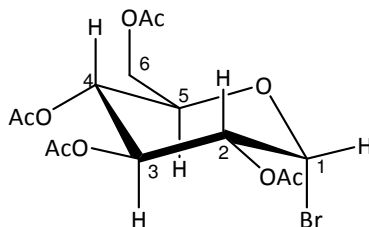
¹H (300 MHz, CDCl₃) δ (ppm): 6.33 (d, J = 3.7 Hz, 1H, H1 α), 5.72 (d, J = 8.2 Hz, 0.5H, H1 β), 5.54-5.40 (m, 1H, H3 α), 5.29-5.25 (m, 0.5H, H4 β), 5.12 (m, 2H + 1H, H2 & H4 α + H2 & H3 β), 4.39-4.20 (m, 1H + 0.5H, H6a α + β), 4.20-4.02 (m, 2H + 0.5H, H5 & H6b α + H6b β), 3.84 (ddd, J = 9.9, 4.4, 2.2 Hz, 0.5H, H5 β), 2.19 (s, 3H, OAc α), 2.12 (s, 1.5H, OAc β), 2.10 (s, 3H, OAc α), 2.09 (s, 1.5H, OAc β), 2.05 (s, 3H, OAc α), 2.04 (s, 3H, 2xOAc β), 2.03 (s, 3H, OAc α), 2.02 (s, 3H + 1.5H, OAc α + β).

¹³C (75 MHz, CDCl₃) δ (ppm): 170.63 (C=O), 170.23 (C=O), 169.65 (C=O), 169.39 (C=O), 168.75 (C=O), 89.06 (C1), 69.82 (C3), 69.18 (C5), 67.87 (C4), 67.73 (C2), 61.44 (C6), 20.87 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.69 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.66 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.56 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.44 ($\underline{\text{C}}\text{H}_3\text{CO}$).

LRMS (ESI) m/z : 408 ($[\text{M}+\text{H}_2\text{O}]^+$); calc.: 408 ($[\text{M}+\text{H}_2\text{O}]^+$).

ν_{max} (cm⁻¹): 1738 (s, C=O stretch); 1371 (s, C-O stretch); 1217 (s, C-O stretch)

(b) Preparation of 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide



Route 1:⁸⁴ 1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose (1.008 g, 2.582 mmol) was dissolved in dry dichloromethane (10 ml). Argon was bubbled through the solution for 10 minutes. A solution of hydrobromic acid (33%) in glacial acetic acid (5 ml) was added. The reaction was stirred under argon overnight in the darkroom at room temperature. The reaction was diluted with dichloromethane (20 ml) and poured onto ice. The organic layer was washed with cold water (2 x 20 ml) and a cold saturated solution of NaHCO₃ (2 x 30 ml) and finally brine (2 x 20 ml). The organic fractions were dried with Na₂SO₄ and concentrated *in vacuo* to yield a yellow oil. An off-white solid precipitated from the oil under vacuum. A white crystalline solid (1.055 g, 84%) was obtained after recrystallisation from ether and hexane (1:1 v/v).

Route 2:⁸⁵ 1,2,3,4,6-Penta-O-acetyl-D-glucopyranose (2.000 g, 5.12 mmol) was dissolved in dry dichloromethane (15 ml). A solution of hydrobromic acid (33%) in glacial acetic acid (12 ml) was added. The reaction was stirred under argon for 2 hours after which time the reaction mixture was partitioned between dichloromethane (20 ml) and water (20 ml). The aqueous layer was re-extracted with dichloromethane (3 x 20 ml) and the organic fractions were washed with a saturated solution of NaHCO₃ until a pH of 8 had been obtained. The organic fractions were dried with Na₂SO₄ and concentrated *in vacuo* to yield a colourless oil. If allowed to stand, a solid precipitated from the oil. A white crystalline solid (2.035 g, 96.5%) was obtained after recrystallisation from ether and hexane (1:1 v/v).

Route 3:⁷⁸ 1,2,3,4,6-Penta-O-acetyl-D-glucopyranose (2.004 g, 5.132 mmol) was added portionwise to a solution of hydrobromic acid (33%) in glacial acetic acid (5.134 ml) at 0°C. Once all of the acetylated glucose had been added, the suspension was allowed to warm to room temperature. The reaction was stirred for 45 minutes after which time all of the acetylated glucose had dissolved and the solution was dark yellow in colour. The reaction was quenched with ice cold water (15 ml) and extracted into dichloromethane (2 x 25 ml). The organic fractions were combined and washed with a saturated solution of NaHCO₃ (2 x 25 ml) and dried with Na₂SO₄. The solvent was evaporated *in vacuo* to afford a colourless oil. The solid was crystallised from the oil from ether: hexane (1:1 v/v) and allowed to rapidly cool in an ice bath to afford a white crystalline solid. The product was filtered off and dried to yield the α anomer (1.885 g, 89.3%).

The product, irrespective of the synthetic method, if left to stand at room temperature, or in the freezer, decomposed to form a brown oil; therefore, the product was used immediately for the subsequent synthesis.

Analysis below is of the product from route 3.

MP 88-90°C (literature: 86-88°C¹⁰²)

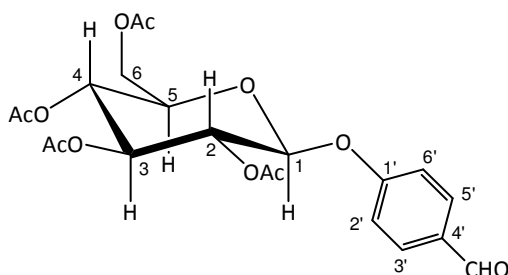
¹H (300 MHz, CDCl₃) δ (ppm): 6.62 (d, J = 4.0 Hz, 1H, H1), 5.56 (t, J = 9.7 Hz, 1H, H3), 5.24-5.08 (m, 1H, H4), 4.84 (dd, J = 10.0, 4.0 Hz, 1H, H2), 4.37-4.32 (m, 1H, H6a), 4.29-4.27 (m,

1H, H5), 4.17-4.09 (m, 1H, H6b), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc).

^{13}C (75 MHz, CDCl_3) δ (ppm): 170.62 (C=O), 169.82 (C=O), 169.75 (C=O), 169.44 (C=O), 86.57 (C1), 72.11 (C5), 70.55 (C2), 70.13 (C3), 67.48 (C4), 60.93 (C6), 20.90 (CH_3CO), 20.78 (CH_3CO), 20.64 (CH_3CO), 20.61 (CH_3CO)

ν_{max} (cm^{-1}): 1738 (s, C=O stretch); 1362 (C-O stretch); 1222 (C-O stretch); 735 (C-Br)

(c) Preparation of 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside⁸⁷



2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl bromide (2.032 g, 4.942 mmol) in acetone (5 ml) was added dropwise into a solution of *p*-hydroxybenzaldehyde (0.627 g, 5.133 mmol) in aqueous sodium hydroxide solution (1M, 5.1 ml). The reaction mixture was stirred at room temperature overnight. The acetone was removed *in vacuo* and the product was extracted into chloroform (3 x 20 ml). The organic fractions were washed with a 1 M sodium hydroxide solution (3 x 20 ml) and then water until neutral. The organic fraction was dried with Na_2SO_4 and the solvent was removed *in vacuo* and an off-white solid precipitated out (1.229 g, 55%). The solid was recrystallised from dichloromethane: hexane (1:1 v/v).

MP 141-143°C (literature: 140-142°C¹⁰³)

^1H (300 MHz, CDCl_3) δ (ppm): 9.93 (s, 1H, CHO), 7.86 (d, $J = 8.6$ Hz, 2H, H3' & H5'), 7.10 (d, $J = 8.6$ Hz, 2H, H2' & H4'), 5.31 (t, $J = 7.7$ Hz, 2H, H2 & H3), 5.24-5.19 (m, 2H, H1 & H4), 4.30 (dd, $J = 12.4, 5.2$ Hz, 1H, H6a), 4.22-4.11 (m, 1H, H6b), 3.92 (dt, $J = 16.6, 7.1$ Hz, 1H, H5), 2.12 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.02 (s, 3H, OAc).

^{13}C (75 MHz, CDCl_3) δ (ppm): 190.73 (CHO), 170.48 (C=O), 170.17 (C=O), 169.37 (C=O),

169.22 (C=O), 161.21 (C1'), 139.24 (C4'), 131.80 (C3' & C5'), 116.75 (C2' & C6'), 97.98 (C1), 72.50 (C2 or C3), 72.26 (C5), 70.98 (C2 or C3), 68.09 (C4), 61.85 (C6), 22.61 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.72 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.63 ($\underline{\text{C}}\text{H}_3\text{CO}$), 20.56 ($\underline{\text{C}}\text{H}_3\text{CO}$).

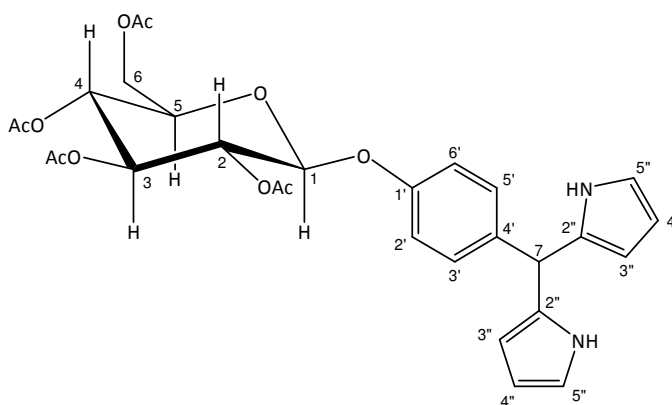
LRMS (ESI) m/z : 475 (+Na) ($[\text{M}+\text{Na}]^+$); calc.: 475 ($[\text{M}+\text{Na}]^+$).

ν_{max} (cm^{-1}): 3456 (w, aldehyde); 3016, 2948 (w, C-H stretch aldehyde); 1736 (s, C=O stretch); 1365 (s, C-O stretch); 1155 (s, C-O stretch)

SCXRD

Space group	P1
a (Å)	5.85
b (Å)	8.95
c (Å)	11.41
α (°)	102.17
β (°)	94.08
γ (°)	101.85
R (%)	7.64

(d) Preparation of 4-[Di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside^{11,78}



A solution of 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside (0.800 g, 1.77 mmol) and a large excess of freshly distilled pyrrole (5.0 ml, 71.4 mmol) was degassed by bubbling argon through the solution for 10 minutes. Trifluoroacetic acid (60 μl , 0.375 mmol) was added. The solution was stirred at room temperature for 15 minutes under

argon and then diluted with dichloromethane (200 ml) and washed with aqueous sodium hydroxide solution (0.1 N, 200 ml). The organic layer was washed with H₂O (200 ml), dried with Na₂SO₄ and concentrated *in vacuo* to remove the excess pyrrole. The brown oil was separated by column chromatography on flash silica gel with hexane: ethyl acetate (1:1 v/v) containing 1% triethylamine as eluent. The desired product (0.589 g, 58.6%) was obtained as an off-white solid alongside excess pyrrole and the associated trimer.

MP 156-158°C (literature: 146-148°C¹⁰⁴)

¹H (300 MHz, CDCl₃) δ (ppm): 7.95 (s (broad), 2H, 2xNH), 7.13 (d, *J* = 8.6 Hz, 2H, H3' & H5'), 6.93 (d, *J* = 8.7 Hz, 2H, H2' & H6'), 6.68 (dd, *J* = 4.0, 2.5 Hz, 2H, H5''), 6.15 (dd, *J* = 5.8, 2.8 Hz, 2H, H4''), 5.89 (m, 2H, H3''), 5.43 (s, 1H, H7), 5.34-5.21 (m, 2H, H2 & H3), 5.18 (d, *J* = 9.8 Hz, 1H, H1 or H4), 5.06 (dd, *J* = 5.2, 2.4 Hz, 1H, H1 or H4), 4.33-4.22 (m, 1H, H6a), 4.15 (dd, *J* = 12.3, 2.2 Hz, 1H, H6b), 3.84 (d, *J* = 9.9 Hz, 1H, H5), 2.05 (s, 6H, 2xOAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc).

¹³C (75 MHz, CDCl₃) δ (ppm): 170.59 (C=O), 170.25 (C=O), 169.40 (C=O), 169.31 (C=O), 155.72 (C1'), 137.22 (C2''), 132.44 (C4' or C3' & C5'), 129.53 (C4' or C3' & C5'), 117.27 (C2' & C6' or C5''), 117.06 (C2' & C6' or C5''), 108.48 (C3'' or C4''), 107.19 (C3'' or C4''), 99.12 (C1), 72.73 (C2 or C3), 72.06 (C5), 71.17 (C2 or C3), 68.28 (C4), 61.94 (C6), 43.25 (C7), 20.69 (CH₃CO), 20.63 (CH₃CO), 20.61 (CH₃CO), 20.58 (CH₃CO).

LRMS (ESI) *m/z*: 569 ([M+H]⁺); calc.: 569 ([M+H]⁺).

HRMS (EI) *m/z*: 568.2048 ([M]⁺); calc.: 568.2057.

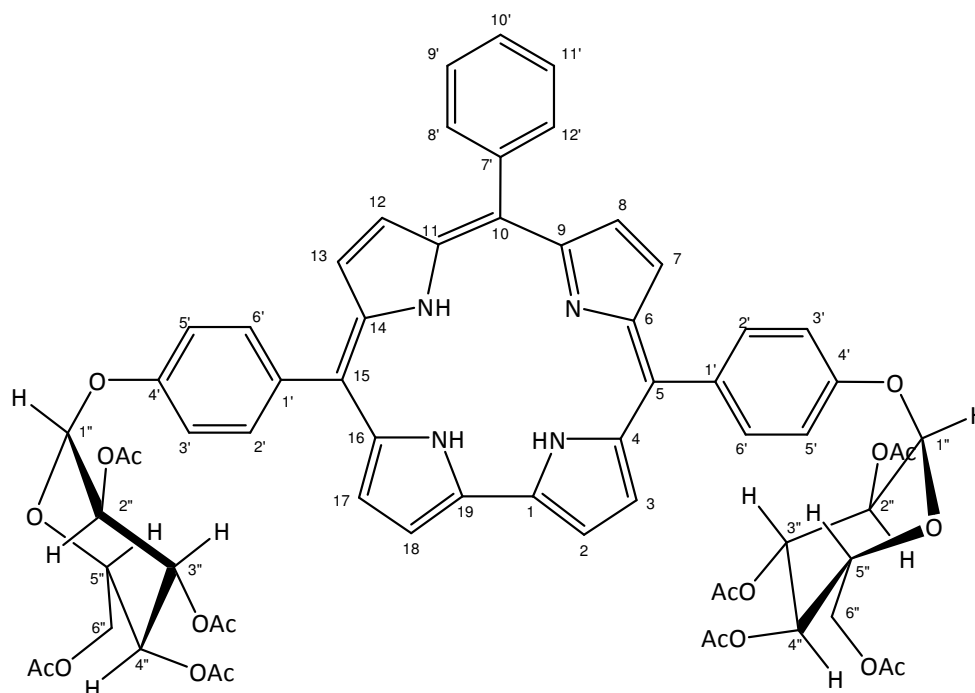
$\nu_{\max}$ (cm⁻¹): 3399, 3345 (w, N-H stretch); 1743 (s, C=O stretch); 1509 (m, C=N stretch); 1365 (); C-N stretch); 1213 (s, C-O stretch); 1036 (s, C-O stretch); 718 (s, aromatic out of plane bend)

SCXRD

Space group		<i>P2</i> ₁	
a (Å)	12.65	α (°)	90.00
b (Å)	7.07	β (°)	93.74
c (Å)	16.47	γ (°)	90.00
R (%)	4.04		

2.10.2 Completing the synthesis of water-soluble corroles

(a) Preparation of 10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole



Benzaldehyde (0.036 ml, 0.35 mmol) and 4-[di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside (0.398 g, 0.7 mmol) were dissolved in methanol (35 ml). Hydrochloric acid (32%, 1.75 ml) in water (35 ml) was added to the reaction flask which was stoppered and kept in the dark. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was extracted into chloroform. The organic layer was washed with water twice, dried with Na₂SO₄ and diluted with chloroform to a volume of 170 ml. *p*-Chloranil (0.170 g, 0.7 mmol) was added and the reaction was stirred for 5 hours in the dark. The black reaction mixture was concentrated *in vacuo*. The crude product mixture was separated by column chromatography on flash silica gel with hexane: ethyl acetate (1:1 v/v) as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo* to give a green-black solid (0.2596 g, 60.8%).

MP > 250°C.

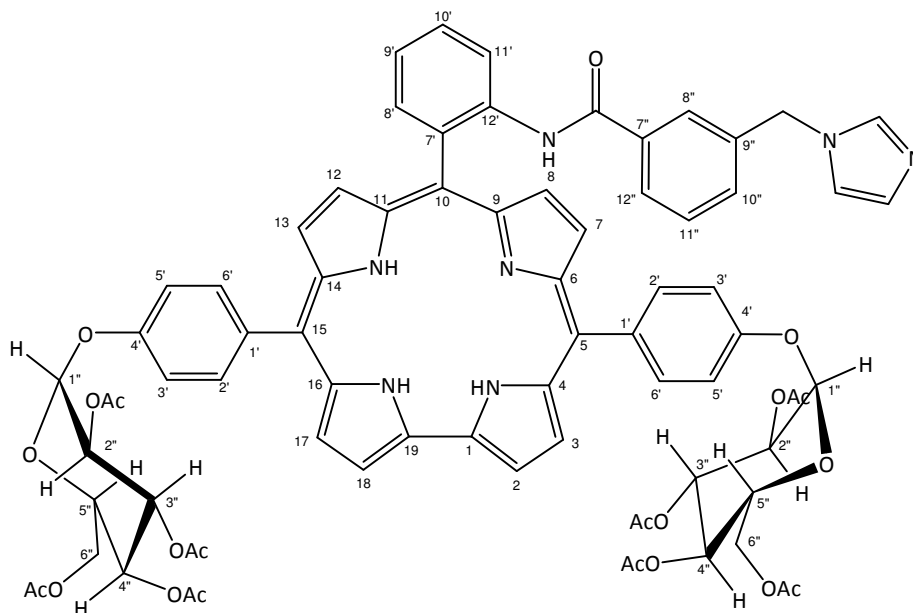
^1H (500 MHz, CDCl_3) δ (ppm): 8.93 (d, $J = 4.0$ Hz, 2H, pyrrole H β), 8.84 (d, $J = 4.6$ Hz, 2H, pyrrole H β), 8.54 (d, $J = 3.8$ Hz, 4H, pyrrole H β), 8.28 (d, $J = 8.4$ Hz, 4H, H $_{ar}$), 8.15 (d, $J = 5.5$ Hz, 2H, H $_{ar}$), 7.74 (d, $J = 5.7$ Hz, 3H, H $_{ar}$), 7.44 (d, $J = 8.4$ Hz, 4H, H $_{ar}$), 5.49-5.38 (m, 3H, H2', H3', H1' or H4'), 5.36-5.24 (m, 3H, H2', H3', H1' or H4'), 5.23-5.13 (m, 2H, H2', H3', H1' or H4'), 4.43-4.38 (m, 1H, H6'a, H6'b or H5'), 4.34-4.26 (m, 1H, H6'a, H6'b or H5'), 4.25-4.14 (m, 1H, H6'a, H6'b or H5'), 4.08-4.01 (m, 1H, H6'a, H6'b or H5'), 2.19 (s, 6H, CH $_3$), 2.15-2.11 (m, 6H, CH $_3$), 2.10 (s, 6H, CH $_3$), 2.07-2.01 (m, 6H, CH $_3$).

^{13}C (126 MHz, CDCl_3) δ (ppm): 171.15; 170.64; 170.32; 170.24; 169.47; 169.40; 169.30 (C=O), 142.13; 135.94; 135.08; 134.67; 130.96; 129.75; 129.44; 127.42; 127.30; 126.86; 125.96; 117.32; 116.51; 116.20; 116.06; 109.87; 108.39; 108.06 (C $_{ar}$), 99.14 (C1'), 72.87 (C2' or C3'), 72.73 (C2' or C3'), 72.28 (C5'), 71.36 (C2' or C3'), 71.16 (C2' or C3'), 68.44 (C4'), 68.28 (C4'), 62.12 (C6'), 60.39 (C6'), 21.04; 20.79; 20.67; 20.64; 20.61 (CH $_3$).

LRMS (APCI) m/z : No parent ion was detected but the observed 567.33 fragment may correspond to the corrole fragment after the loss of the two sugar groups.

ν_{max} (cm^{-1}): 2983 (w, br, N-H stretch); 1749 (s, C=O stretch); 1375 (m, C=N stretch); 1218, 1039 (s, C-O stretch)

(b) Preparation of 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole



4-[Di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside (1.137 g, 2 mmol) and 3'-(1*H*-imidazol-1-ylmethyl)-*N*-(2-formylphenyl)benzamide (0.305 g, 1 mmol) were dissolved in methanol (100 ml). Hydrochloric acid (32%, 5 ml) in water (100 ml) was added to the reaction flask which was stoppered and kept in the dark. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was extracted into chloroform. The organic layer was washed with water twice, dried with Na₂SO₄ and diluted with chloroform to a volume of 500 ml. *p*-Chloranil (0.490 g, 2 mmol) was added and the reaction was stirred for 5 hours in the dark. The black reaction mixture was concentrated *in vacuo*. The crude product mixture was separated by column chromatography on flash silica gel with ethyl acetate as eluent. The corrole-containing fractions (identified using UV-vis spectroscopy) were combined and evaporated to dryness *in vacuo* to give a black solid (0.300 g, 21%).

MP > 250°C.

¹H (500 MHz, CDCl₃) δ (ppm): 9.03 (d, *J* = 7.8 Hz, 1H, NH), 8.83 (d, *J* = 18.8 Hz, 2H, pyrrole H β), 8.78 (s, 2H, pyrrole H β), 8.40 (d, *J* = 10.2 Hz, 2H, pyrrole H β), 8.37 (s, 2H, pyrrole H β), 8.24 (d broad, 5H), 7.77 (t broad, 2H, H_{ar}), 7.72 (d, *J* = 6.0 Hz, 1H, H_{ar}), 7.43 (d, *J* = 4.5 Hz, 6H, H_{ar}), 7.12 (t broad, 1H, H_{ar}), 6.80 (d, *J* = 6.5 Hz, 1H, H_{ar}), 5.42 (dd, *J* = 19.0, 8.6 Hz,

6H, H2', H3', H1' or H4'), 5.31 (d, $J = 16.1$ Hz, 2H, H2', H3', H1' or H4'), 4.46-4.35 (m, 2H, H6'a), 4.30 (t, $J = 11.7$ Hz, 2H, H6'b), 4.04 (s, $J = 19.3$ Hz, 2H, H5'), 2.17 (dd, $J = 22.1, 15.4$ Hz, 9H, CH₃), 2.10 (s, 15H, CH₃).

¹³C (126 MHz, CDCl₃) δ (ppm): 170.67; 170.64; 170.33; 169.48 (C=O); 156.64 (C=O), 138.01; 136.04; 135.32; 133.80; 130.57; 129.11; 129.01; 128.27; 125.95; 119.89; 116.46; 114.65 (C_{ar}), 99.22 (C1'), 99.15 (C1'), 72.86 (C2' or C3'), 72.28 (C5'), 71.36 (C2' or C3'), 68.41 (C4'), 62.09 (C6'), 20.80; 20.78; 20.76; 20.68; 20.64 (CH₃).

LRMS (ESI) m/z : 1419 ([M+H]⁺); calc.: 1419 ([M+H]⁺).

ν_{max} (cm⁻¹): 3398 (w, N-H stretch); 1735 (s, C=O stretch); 1445 (C=N stretch); 1309 (C-N stretch); 1216 (s, C-O stretch); 962 (aromatic out of plane bend)

(c) Deprotection of acetyl groups⁹⁰

10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole (0.355 g, 0.7 mmol) and K₂CO₃ (790 mg, 8.2 mol equivalents, 5.74 mmol) were dissolved in methanol (10 ml). The reaction mixture was stirred for 2.5 hours at room temperature until TLC indicated that no starting material remained. The reaction mixture was concentrated *in vacuo* to yield a green solid and a large quantity of salt. A large C18 column was prepared with water followed by 50 % methanol in water, followed by water. The product was dissolved in minimal water and loaded onto the column. Salts were flushed off the column with water until no residue was detected when using silver nitrate. The corrole was flushed off the column with methanol and concentrated *in vacuo*. The corrole was found to still contain excess salts. In spite of the presence of the impurity, the reaction appeared to yield the product in quantitative yield as all of the material was soluble in aqueous solution. Meaningful NMR spectroscopic data could not be collected as the acetate peak in the proton spectrum overwhelmed the spectrum and smaller signals could not be discerned from the baseline.

The same procedure was carried out for the deprotection of 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole. Similarly, the salts overwhelmed the NMR spectra and no meaningful information was gained, but the parent ion was observed in the mass spectrum (**LRMS** (ESI) *m/z*: 1083 – [M+H]⁺; calc.: 1083.14 – [M+H]⁺).

2.11 References

- (1) Aviv, I.; Gross, Z. *Chem. Commun.* **2007**, 1987-1999.
- (2) Rothmund, P. *J. Am. Chem. Soc.* **1936**, *58*, 625-627.
- (3) Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F.; Boschi, T.; Smith, K. M. *Chem. Commun.* **1999**, 1307-1308.
- (4) Paolesse, R.; Nardis, S.; Sagone, F.; Khoury, R. G. *J. Org. Chem.* **2001**, *66*, 550-556.
- (5) Koszarna, B.; Gryko, D. T. *J. Org. Chem.* **2006**, *71*, 3707-3717.
- (6) Badger, G. M.; Jones, R. A.; Laslett, R. L. *Aust. J. Chem.* **1964**, *17*, 1028-1035.
- (7) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem. Int. Ed.* **1999**, *38*, 1427-1429.
- (8) Gross, Z.; Galili, N.; Simkhovich, L.; Saltsman, I.; Botoshansky, M.; Blser, D.; Boese, R.; Goldberg, I. *Org. Lett.* **1999**, *1*, 599-602.
- (9) Collman, J. P.; Decréau, R. A. *Tetrahedron Lett.* **2003**, *44*, 1207-1210.
- (10) Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guillard, R., Eds.; Academic Press: New York, 2000; Vol. 1.
- (11) Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427-11440.
- (12) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391-1396.
- (13) Gryko, D. T.; Jadach, K. *J. Org. Chem.* **2001**, *66*, 4267-4275.
- (14) Roa, P. D.; Dhanalekshmi, S.; Little, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323-7344.
- (15) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1980**, 49-50.
- (16) Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 7352-7354.
- (17) Decréau, R. A.; Collman, J. P. *Tetrahedron Lett.* **2003**, *44*, 3323-3327.
- (18) Dolphin, D.; Johnson, A. W.; Leng, J.; van der Broek, P. *J. Chem. Soc. (C)* **1966**, 880-884.
- (19) Licoccia, S.; Di Vona, M. L.; Paolesse, R. *J. Org. Chem.* **1998**, *63*, 3190-3195.
- (20) Collman, J. P.; Decréau, R. A. *Org. Lett.* **2005**, *7*, 975-978.
- (21) Young, R.; Chang, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 898-909.
- (22) Liu, J.-G.; Naruta, Y.; F., T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1836-1840.

- (23) Decréau, R. A.; Collman, J. P.; Yang, Y.; Yan, Y.; Devaraj, N. K. *J. Org. Chem.* **2007**, *72*, 2794-2802.
- (24) Liu, J.-G.; Naruta, Y.; Tani, F.; Chishiro, T.; Tachi, Y. *Chem. Commun.* **2004**, 120-121.
- (25) Collman, J. P.; Decréau, R. A. *J. Org. Chem.* **2004**, *69*, 3546-3549.
- (26) Collman, J. P.; Sunderland, C. J.; Boulatov, R. *Inorg. Chem.* **2002**, *41*, 2282-2291.
- (27) Liu, J.-G.; Ohta, T.; Yamaguchi, S.; Ogura, T.; Sakamoto, S.; Maeda, Y.; Naruta, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 9262-9267.
- (28) Berto, T. C.; Praneeth, V. K. K.; Goodrich, L. E.; Lehnert, N. *J. Am. Chem. Soc.* **2009**, *131*, 17116-17126.
- (29) Yeh, C.-Y.; Chang, C. K.; Nocera, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1513-1514.
- (30) Dogutan, D. K.; Bediako, D. K.; Teets, T. S.; Schwalbe, M.; Nocera, D. G. *Org. Lett.* **2010**, *12*, 1036-1039.
- (31) Dogutan, D. K.; Stoian, S. A.; McGuire, R.; Schwalbe, M.; Teets, T. S.; Nocera, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 131-140.
- (32) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenninger, R.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 8082-8083.
- (33) Gross, Z. *J. Biol. Inorg. Chem.* **2001**, *6*, 733-738.
- (34) Hush, N. S.; Woolsey, I. S. *J. Chem. Soc., Dalton Trans.* **1974**, 24-34.
- (35) Dolphin, D.; Harris, R. L. N.; Huppertz, J. I.; Johnson, A. W.; Kay, I. T. *J. Chem. Soc. (C)* **1966**, 30-40.
- (36) Mahammed, A.; Weaver, J. J.; Gray, H. B.; Abdelas, M.; Gross, Z. *Tetrahedron Lett.* **2003**, *44*, 2077-2079.
- (37) Mahammed, A.; Gross, Z. *Dalton Trans.* **2010**, *39*, 2998-3000.
- (38) Fu, B.; Huang, J.; Ren, L.; Weng, X.; Zhou, Y.; Du, Y.; Wu, X.; Zhou, X.; Yang, G. *Chem. Commun.* **2007**, 3264-3266.
- (39) Haber, A.; Agadjanian, H.; Medina-Kauwe, L. K.; Gross, Z. *J. Inorg. Biochem.* **2008**, *102*, 446-457.
- (40) Mahammed, A.; Goldberg, I.; Gross, Z. *Org. Lett.* **2001**, *3*, 3443-3446.
- (41) Kupersmidt, L.; Okun, Z.; Amit, T.; Mandel, S.; Saltsman, I.; Mahammed, A.; Bar-Am, O.; Gross, Z.; Youdim, M. B. H. *J. Neurochem.* **2010**, *113*, 363-373.
- (42) Pasternack, R. F.; Spiro, E. G.; Teach, M. *J. Inorg. Nucl. Chem.* **1974**, *36*, 599-606.

- (43) Gibson, E. A.; Duhme-Klair, A.-K.; Perutz, R. N. *New J. Chem.* **2010**, *34*, 1125-1134.
- (44) Budimir, A.; J., K.; Fábián, I.; Lente, G.; Bányai, I.; Batinić-Haberle, I.; Biruš, M. *Dalton Trans.* **2010**, *39*, 4405-4410.
- (45) Munakata, H.; Kanzaki, T.; Nakagawa, S.; Imai, H.; Uemori, Y. *Chem. Pharm. Bull.* **2001**, *49*, 1573-1580.
- (46) Mewis, R. E.; Savoie, H.; Archibald, S. J.; Boyle, R. W. *Photodiagnosis Photodynamic Therapy* **2009**, *6*, 200-206.
- (47) Ho, C.-M.; Zhang, J.-L.; Zhou, C.-Y.; Chan, O.-Y.; Yan, J. J.; Zhang, F.-Y.; Huang, J.-S.; Che, C.-M. *J. Am. Chem. Soc.* **2010**, *132*, 1886-1894.
- (48) Borbas, K. E.; Morz, P.; Hamblin, M. R.; Lindsey, J. S. *Bioconjugate Chem.* **2006**, *17*, 638-653.
- (49) Paolesse, R.; Licoccia, S.; Bandoli, G.; Dolmella, A.; Boschi, T. *Inorg. Chem.* **1994**, *33*, 1171-1176.
- (50) Erben, C.; Will, S.; Kadish, K. M. In *The Porphyrin Handbook*; 1st ed.; Kadish, K. M., Smith, K. M., Guillard, R., Eds.; Academic Press: New York, 2000; Vol. 2, p 233-300.
- (51) Paolesse, R. *Synlett.* **2008**, 2215-2230.
- (52) Hamor, M. J.; Hamor, T. A.; Hoard, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 1938-1942.
- (53) Silvers, S. J.; Tulinsky, A. *J. Am. Chem. Soc.* **1967**, *89*, 3331-3337.
- (54) Paolesse, R.; Marini, A.; Nardis, S.; Froiio, A.; Mandoj, F.; Nurco, D. J.; Prodi, L.; Montalti, M.; Smith, K. M. *J. Porphyr. Phthalocya.* **2003**, *7*, 25-36.
- (55) Ding, T.; Harvey, P. D.; Ziegler, C. J. *J. Porphyr. Phthalocya.* **2005**, *9*, 22-27.
- (56) Shriver, D. F.; Atkins, P. W. *Inorganic Chemistry*; 3rd ed.; Oxford University Press: Oxford, 2002.
- (57) Simonato, J.-P.; Chappellet, S.; Pécaut, J.; Baret, P.; Marchon, J.-C. *New J. Chem.* **2001**, *25*, 714-720.
- (58) Gouedard, M.; Gaudemer, F.; Gaudemer, A.; Riche, C. *J. Chem. Res. (S)* **1978**, 30-31.
- (59) Zipp, C. F.; Fernandes, M. A.; Marques, H. M.; Michael, J. P. *Acta Crystallogr.* **2012**, *E68*, o174.
- (60) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991-6010.

- (61) Leach, A. R. *Molecular modelling: Principles and applications*; Addison Wesley Longman Limited: Singapore, 1998.
- (62) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765-784.
- (63) Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J. Comp. Chem.* **2004**, *25*, 1157-1174.
- (64) Marques, H. M.; Ngoma, B.; Egan, T. J.; Brown, K. L. *J. Mol. Struct.* **2001**, *561*, 71-91.
- (65) Allen, F. H. *Acta Crystallogr., Sect. B* **2002**, *58*, 380-388.
- (66) HyperChem; 8.0.5 ed.; Hypercube Ltd.: Gainesville, FL, USA.
- (67) Anderson, W. P.; Edwards, W. D.; Zerner, M. C. *Inorg. Chem.* **1986**, *25*, 2728-2732.
- (68) Karlin, K. D. *Nature* **2010**, *463*, 168-169.
- (69) Didier, A.; Michaudet, L.; Ricard, D.; Baveux-Chambenoît, V.; Richard, P.; Boitrel, B. *Eur. J. Org. Chem.* **2001**, 1917-1926.
- (70) Collman, J. P.; Sunderland, C. J.; Boulatov, R. *Inorg. Chem.* **2002**, *41*, 2282-2291.
- (71) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenninger, R. *J. Org. Chem.* **1998**, *63*, 8084-8085.
- (72) Maillard, P.; Guerquin-Kern, J.-L.; Huel, C.; Momenteau, M. *J. Org. Chem.* **1993**, *58*, 2774-2780.
- (73) Maillard, P.; Guerquin-Kern, J.-L.; Momenteau, M.; Gaspard, S. *J. Am. Chem. Soc.* **1989**, *111*, 9125-9127.
- (74) Oulmi, D.; Maillard, P.; Guerquin-Kern, J.-L.; Huel, C.; Momenteau, M. *J. Org. Chem.* **1995**, *60*, 1554-1564.
- (75) Sol, V.; Blais, J. C.; Bolbach, G.; Carré, V.; Granet, R.; Guilloton, M.; Spiro, M.; Krausz, P. *Tetrahedron Lett.* **1997**, *38*, 6391-6394.
- (76) Vilain, S.; Maillard, P.; Momenteau, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1697-1698.
- (77) Prinsep, M. R.; Caplan, F. R.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 385-387.
- (78) Riley, D. *Post Doctoral Report*, University of the Witwatersrand, 2010.

- (79) Dinev, Z.; Wardak, A. Z.; Brownlee, R. T. C.; Williams, S. J. *Carbohydrate Research* **2006**, *341*, 1743-1747.
- (80) Dasgupta, F.; Singh, P. P.; Srivastava, H. C. *Carbohydrate Research* **1980**, *80*, 346-349.
- (81) Jones, P. G.; Sheldrick, G. M.; Kirby, A. J.; Glenn, R. Z. *Kristallogr.* **1982**, *161*, 245-251.
- (82) Bernardes, G. J. L.; Thompson, S.; Chalker, J. M.; Errey, J. C.; El Oualid, F.; Claridge, T. D. W.; Davis, B. G.; Grayson, E. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 2244-2247.
- (83) Rajaganesh, R.; Mohan Das, T.; Ravinder, P.; Subramanian, V. *Carbohydrate Research* **2011**, *346*, 2327-2336.
- (84) Rodebaugh, R.; Fraser-Reid, B. *Tetrahedron* **1996**, *52*, 7663-7678.
- (85) Floyd, N.; Vijayakrishnan, B.; Koeppe, J. R.; Davis, B. G. *Angew. Chem. Int. Ed.* **2009**, *48*, 7798-7802.
- (86) Takai, M.; Watanabe, H.; Hayashi, J.; Watanabe, S. *Bull. Fac. Eng. Hokkaido Univ.* **1976**, *79*, 101 as cited in the CSD.
- (87) Rackwitz, H.-R. *Carbohydrate Research* **1981**, *88*, 223-232.
- (88) Zipp, C. F.; Fernandes, M.; Marques, H. M.; Michael, J. P. *Acta Crystallogr.* **2012**, *E68*, o1202.
- (89) Mikata, Y.; Shinohara, Y.; Yoneda, K.; Nakamura, Y.; Esaki, K.; Tanahashi, M.; Brudzińska, I.; Hirohara, S.; Yokoyama, M.; Mogami, K.; Tanase, T.; Kitayama, T.; Takashiba, K.; Nabeshima, K.; Takagi, R.; Takatani, M.; Okamoto, T.; Kinoshita, I.; Doe, M.; Hamazawa, A.; Morita, M.; Nishida, F.; Sakakibara, T.; Orvig, C.; Yano, S. *J. Org. Chem.* **2001**, *66*, 3783-3789.
- (90) Ul Islam, R. *Post Doctoral report*, University of the Witwatersrand, 2010.
- (91) MestReNova; 6.0.2-5475 ed.; Mestrelab Research S. L.: Santiago de Compostela, 2009.
- (92) OPUS; 5.5 build 5.5.60 ed.; Bruker Optik GmbH: Ettlingen, Germany, 2005.
- (93) Chromeleon; 6.80SR7 build 2528 ed.; Dionex Corporation: 2005.
- (94) Bruker; APEX2; 2.0-1 ed.; Bruker AXS Inc.: Madison, Wisconsin, USA, 2005.
- (95) Bruker; SAINT+; 6.0 (includes XPREP and SADABS) ed.; Bruker AXS Inc.: Madison, Wisconsin, USA, 2005.

- (96) Bruker; SHELXTL; 5.1 (includes XS, XL, XP, XSELL) ed.; Bruker AXS Inc.: Madison, Wisconsin, USA, 1999.
- (97) Spek, A. L. *J. Appl. Cryst.* **2003**, *36*, 7-13.
- (98) Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565.
- (99) Lindsey, J. S.; Yu, L.; Thamyongkit, P.; Bhise, A. D. 2007; Vol. US2007/155963 A1.
- (100) Kirino, O.; Yamamoto, S.; Kato, T. *Agric. Biol. Chem.* **1980**, *44*, 2143-2147.
- (101) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. *Adv. Synth. Cat.* **2011**, *353*, 401-410.
- (102) Berthold, H. J.; Franke, S.; Thiem, J.; Schotten, T. *J. Org. Chem.* **2010**, *75*, 3859-3862.
- (103) Ling Luo, H.; Yang, W.; Li, Y.; Fan Yin, S. *Chem. Nat. Compounds* **2010**, *46*, 412-416.
- (104) Lv, F.; He, X.; Lu, L.; Wu, L.; Liu, T. *J. Porphyr. Phthalocya.* **2011**, *15*, 217-222.

Part 3

Polymorphism *N*-phenylbenzamide derivatives

The relationship between the polymorphic intermediates of 10-[2-(benzoylamino)-phenyl]-5,15-diphenylcorrole and 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}-phenyl)-5,15-diphenylcorrole was explored in two publications which are presented here. The chemistry of DPTC-Co and how it compared to that of vitamin B₁₂ is presented in **Part 4**.

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3.1 Polymorphism and the power of weak interactions

3.1.1 Polymorphism

The phenomenon of polymorphism was discovered in the 1830s when Friedrich Wöhler and Justus von Liebig observed the formation of different crystal habits of benzamide under different experimental conditions.¹ In chemistry and materials chemistry polymorphism is thus defined as “A solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state.”² There are, however, numerous definitions of polymorphism in the literature.²⁻⁶ The arrangement of molecules in the crystal lattice can have implications on the physical properties of the molecule, including solubility, bioavailability, melting point, physical, mechanical and chemical stability and crystalline morphology and habit.⁵⁻⁷ In turn, the presence of polymorphs of a material can have serious implications in the application of that material, be it in the materials or pharmaceutical sphere and there is great need for the understanding of the changing characteristics of a material under different conditions.

Polymorphism may be attributed to the interplay between intra- and intermolecular forces which can result in one of two differences in the crystal lattice, either differences in the molecular conformation or differences in intermolecular interactions and arrangement of the molecule in the crystal lattice. These differences give rise to either conformational or packing polymorphism.⁷ Pseudopolymorphism, on the other hand, arises from the inclusion of another molecule in the lattice during solvation or hydration of the structure. The formation of different polymorphs of a compound is very sensitive to the crystallisation environment and different polymorphs can arise from changes in solvent, temperature or pressure as these factors affect the processes and rates of nucleation, crystal growth and phase transformation.⁶

The polymorphs of a compound are either monotropically or enantiotropically related. In the case of monotropic polymorphs, one polymorph is stable over the entire temperature and pressure range and all other polymorphs are metastable to this polymorph. This stable polymorph does not undergo any phase transitions to form other polymorphs and the metastable polymorphs need to be kinetically trapped if they are to be observed.⁸ In the case of enantiotropic polymorphs, the stability of one polymorph over another is sensitive to temperature and pressure and polymorphs can interconvert under favourable conditions.

The relationship between polymorphs, be it monotropic or enantiotropic, can be better understood by analysis of the thermodynamic relationship between the polymorphs of a compound. The relative stability of a family of polymorphs at a particular temperature depends on the free energies of each crystallographic system. Clearly, in order for polymorphs to exist at all, the differences in the energies of these different forms must be small. In a monotropic system, both the Gibbs free energy and the enthalpy of one polymorph, say polymorph I, is always lower in energy compared to another polymorph, polymorph II. At the temperature at which the Gibbs energy of the polymorph equals that of the melt, melting will occur. In a monotropic system, the highest melting point will be observed for the most stable polymorph, with the remaining polymorphs melting in the order of decreasing stability. No spontaneous phase change from polymorph I to the metastable polymorph II will occur. Polymorph II is kinetically assessable only. In the case of an enantiotropic system, the Gibbs free energy of polymorph I is lower than that of polymorph II in a specific temperature range. The temperature at which the free energies of two polymorphs is equal is known as the thermodynamic transition point after which the free energy of polymorph II is lower than that of polymorph I. Below this point polymorph II is metastable to polymorph I, while above this temperature polymorph I is metastable relative to polymorph II. This transition point occurs before the melting point and thus the two forms are thermodynamically assessable before the melting point.⁹

3.1.2 Promoting polymorphism

Differences in the physical properties of polymorphs can lead to the favouring of one polymorph over another for a particular application. There is, therefore, great interest in the chemistry behind the promotion, or the suppression, of a particular polymorph of a compound.

There are several stages of the crystallisation process. The first stage is the preparation of a supersaturated solution of the molecule of interest. Under these conditions aggregation of molecules can occur. Aggregation leads to the formation of nuclei, the seed of crystallisation. This stage is known as nucleation. This is followed by the growth phase. The nucleation and the growth phases are important in the determination of the properties of the final crystal including size, morphology and crystal packing, or polymorphism.¹⁰ Variation of the crystallisation environment can affect these stages and lead to the growth of different polymorphic phases.

Polymorphism can be controlled, to a certain degree, using a variety of different approaches. These include solvent choice, temperature control and the use of additives. These approaches rely on the promotion of some interactions over others, or the disruption of interactions to favour others. Growth of different phases of a polymorphic system can be achieved in using a number of different crystallisation environments such as different solvent systems, different temperatures or pressures, the addition of additives or surfactants and even the size of the crystallisation vessel.^{11,12}

Crystallisation at different temperatures can lead to different polymorphic forms. Computational simulations and theoretical studies suggest that the mechanism of nucleation differs with temperature. It has been found that at temperatures higher than the critical point of a metastable phase, nucleation resulted in crystal like aggregates or clusters while at lower temperatures, liquid-like crystals were favoured.¹⁰

Different solvent systems (including solvents at different pHs) or additives can disrupt the nucleation phase or the rate of crystal growth during the crystallisation process. Through intermolecular interactions, solvents and chemical additives are used to intermolecularly 'block' functional groups or inhibit interactions that would play key roles in the crystal packing of a particular polymorph. In this way, other intermolecular interactions between the molecules of the compound of interest can arise leading to different crystal packing arrangements.¹² Additives can also be used to stabilise intermolecular interactions leading to the polymorph of interest.¹³

Containment, or crystallisation in a restricted space, is a technique used to limit heterogeneous nucleation, and can be achieved using a variety of different techniques. This can occur in capillary tubes where small solution volumes allow for very few nucleation sites, allowing a polymorphic phase to grow without competition from other phases. The varying size of the crystallisation nucleus of different phases can be exploited when crystals are grown within nano-polymers or glass matrices, a technique called nanoscopic confinement. Crystallisation at the edge of a drop of solution, a technique called contact line crystallisation, can be used to grow metastable polymorphic phases that grow at the liquid surface.¹²

These techniques often involve disruption or promotion of certain intermolecular forces over others. As intermolecular forces play such a central role in the crystallisation process, as well as in the stabilising of different packing motifs in the crystal lattice, an understanding of the intermolecular forces at play is important.

3.1.3 Weak interactions

The packing of molecules in a crystal lattice comes about as a result of numerous intermolecular forces that exist between neighbouring molecules and aims to reduce repulsive interactions and maximise attractive interactions. In addition to the classic strong intermolecular forces, such as dipole-dipole interactions and hydrogen bonds, a host of weaker interactions also exist between molecules. These weak interactions include dispersion forces and several classes of weak hydrogen bonds.

The hydrogen bond was defined by Linus Pauling in the 1960s as a stabilising interaction that occurs between X-H and Y where X and Y are electronegative atoms such as oxygen, nitrogen or fluorine.¹⁴ A more global definition was put forward by Pimentel stating that a hydrogen bond exists if there is evidence of a bonding interaction between X-H and Y and this bond involves the hydrogen atom already bonded to X.¹⁵ Importantly, in this definition the chemical identity on X and Y were not stipulated. Later, Nishio and Hirota subdivided hydrogen bonds into four types based on hard soft acid base theory; namely conventional hydrogen bonds between hard acids and hard bases; $X-H\cdots\pi$ bonds between hard acids and soft bases; $C-H\cdots X$ bonds between soft acids and hard bases; and $C-H\cdots\pi$ bonds between soft acids and soft bases.¹⁶ These weak interactions have been acknowledged to be particularly important in chemistry and biology as their low binding energies allow for fast, energetically inexpensive rearrangements in ambient conditions.¹⁷ The weaker $C-H\cdots X$ and $C-H\cdots\pi$ bonds will be discussed in more detail.

Shortly after the descriptions of hydrogen bonds were put forward, Sutor introduced the idea of a $C-H\cdots O$ hydrogen bond, rather than just a $C\cdots O$ short contact.¹⁸ Her suggestion was initially lambasted, but countless research papers have since agreed that the $C-H\cdots O$ interaction is indeed a type of hydrogen bond.¹⁹⁻²² $C-H\cdots X$ interactions increase in strength as the acidity of the C-H hydrogen increases.^{23,24} It has been noted that the strength of the interaction between C-H and X is more dependent on the nature of the proton donor and less so on the nature of the acceptor.²⁰ Interestingly, computational

studies have shown that the binding energy of strong hydrogen bonds is very sensitive to the distance between the donor and acceptor groups, and less so in the case of C-H...X interactions, particularly C-H...O hydrogen bonds. This led to the suggestion by Gu and co-workers that certain C-H...O hydrogen bonds may be stronger than the classic hydrogen bonds after a certain distance of separation of the donor and acceptor groups.²⁰

C-H...X hydrogen bonds, such as the C-H...O bond, play an important role in solid state chemistry given the high probability of the presence of oxygen in an organic molecule or organometallic complex. As such, a full understanding of the packing and stabilisation of a crystal structure can only be achieved when these weak interactions are taken into account.¹⁹ In spite of their small energetic contribution to the stabilisation of a crystal lattice, C-H...O interactions can play “steering” or “directing” roles in the packing of the crystal structure, such as in the case of 3,5-dinitrocinnamic acid (VIII) where the arrangement of the molecule in the lattice not only accommodates the strong hydrogen bonds, but also allows for a network of stabilising C-H...O bonds.^{19,23}

Similar to the C-H...X hydrogen bond, the strength of C-H... π interactions depends on the hydrogen donating ability of the C-H group as well as the electron density of the π group. Large stabilising effects are achieved through ‘activation’ of the C-H group by electron withdrawing groups while aromatic π systems lead to stronger interactions than aliphatic π systems.^{21,22} C-H... π interactions have a dual nature in that they have both electrostatic and dispersion terms. The directionality of these attractive interactions distinguishes them from London dispersion forces.^{17,21,22}

C-H... π interactions play an important role in the conformation that more flexible molecules adopt in the solid state.^{21,22,25} These interactions have been found to play a determining role in the conformational preference of crownphanes to adopt an eclipse-*trans* conformation, a conformation that typically would be regarded as unstable.²⁵ In other examples highlighted by Nishio’s comprehensive reviews on the subject, C-H... π bonding has been found to stabilise the seemingly less stable conformations of several

different compounds including the *gauche* conformations of 1-pentyne and n-butyl cyanide, the folded conformation of levopimaric acid and the folded conformation of 80-benzhydrylideneamino-1,10-binaphthyl-2-ol, stabilised by cooperative C-H $\cdots$ π bonding.^{21,22} In addition to their importance in crystallography and conformational effects, C-H $\cdots$ π bonding has been cited as being important in a number of disciplines including solid state reactions, chiral discrimination, molecular recognition and gas-phase inclusion chemistry.^{21,22}

These weak interactions are important not only in the solid state, but in solution as well, as they have been noted to persist in solution or in the liquid phase.^{20,26} They are thus thought to play important roles in the conformation and three-dimensional structure of various biomolecules including DNA,²⁷ proteins²⁸ and carbohydrates.^{20-22,29}

Visualisation and the understanding of these weak interactions have been revolutionised with the use of Hirshfeld and electrostatic potential (ESP) surfaces. Desiraju suggested that crystal structures need to be visualised in their entirety and not from the point of view of selected interactions which have been presumed to be the most important.³⁰ One approach to address this need for visualisation in crystallography is the use of the Hirshfeld surface, introduced in 1997 by Spackman and Byrom.³¹ The Hirshfeld surface defines a volume occupied by a molecule in a crystal lattice with respect to the proximity of neighbouring molecules by partitioning the electron density in the crystal into molecular fragments. In this way, information about the intermolecular interactions can be determined.^{32,33} This Hirshfeld surface is based on Hirshfeld's "stockholder partitioning scheme" where atoms in molecules were defined as spherically averaged electron densities of individual atoms. The Hirshfeld surface represents a smooth boundary which does not overlap with neighbouring boundaries and encapsulates the electron density of the molecule of interest. This boundary is defined as the region where the ratio of electron density of the molecule of interest to the electron density of the neighbouring molecules in the crystal is 0.5.^{32,34}

Different information can be mapped onto the Hirschfeld surface, such as electrostatic potentials, ESP, normalised contact distances, d_{norm} , as well as shape indices or curvedness.³²⁻³⁵ ESP maps give an indication of the distribution of electron density, and thus charge distribution, in a molecule by determining the attractive or repulsive response of the molecule to a point positive charge that is moved over the surface of the molecule. When ESP information is mapped onto a Hirschfeld surface, the charge distribution at the surface of the molecule, the surface being the area of the molecule in contact with its environment, can give an indication of the areas of the molecule that would favour both strong and weak intermolecular interactions with neighbouring molecules. ESP mapped surfaces can also be used to understand how the charge distribution changes with changes in substitution or even conformation.^{32,36}

Normalised contact distances, on the other hand, give an indication of the presence of close contacts by determining if the electron density in an area of the molecule is being either drawn beyond the van der Waal's radius or pushed into the electron cloud surrounding the molecule. These distances are defined in terms of the distance between a point on the surface and the nearest nucleus in a neighbouring molecule and the distance between a point on the surface and the closest atom within the molecule together with the van der Waal radii of the atoms involved.^{32,35} This information can be mapped onto a Hirschfeld surface as blue areas of the surface beyond the van der Waal radius, white areas at the van der Waal surface as defined by the radii and red areas of close contacts, where the surface is closer to the nuclei than the van der Waal radii, and is useful in pin-pointing the areas of interaction between a molecule and its neighbouring molecules.

While these visualisation tools aid in the assignment of close contacts, the intricacies of the packing of the crystal structure cannot be fully appreciated or understood without the quantification of the energies of these contacts, and their contribution to the total lattice energy of the structure.

3.1.4 Quantifying weak interactions

When structures are evaluated in crystal engineering, typically the atom-to-atom interactions between a molecule and its neighbours are evaluated and ranked according to the interaction type. The following order of weak interactions is used: classic hydrogen bonds ($\text{N-H}\cdots\text{O}$; $\text{O-H}\cdots\text{O}$; $\text{O-H}\cdots\text{N}$) > weak hydrogen bonds ($\text{C-H}\cdots\text{O}$; $\text{C-H}\cdots\text{N}$; $\text{C-H}\cdots\pi$) > dipole $\cdots$ dipole interactions > $\pi\cdots\pi$ interactions. The weaker dispersion forces are often disregarded entirely as interactions of this type usually require significant overlap between molecules and are difficult to quantify. In the atom-to-atom approach, the interactions are not quantified in any way.

It has been suggested that a more appropriate way of evaluating structures would be by determining the total interaction energy of a molecule (referred to as the reference molecule) with its neighbours by means of pairwise calculations.^{37,38} This can be achieved using a number of different approaches such as, in increasing complexity and accuracy, atom-atom potential methods such as the use of Lennard-Jones potentials; semi-classical density sums (SCDS) methods; DFT methods or the more computationally demanding *ab initio* methods.³⁹ In addition to the evaluation of crystal structures, the accurate quantification of the interactions between molecules is important in crystal structure prediction. The use of advanced and very accurate DFT methods has, for example, led to spectacular successes in the prediction of crystal structures in the last five years.⁴⁰⁻⁴²

Gavezzotti's Coulomb London Pauli (CLP) approach⁴³ as implemented in the CLP package has been used in this work. CLP models include atom-atom (AA-CLP) and SCDS (PIXEL) methods, and can be used to calculate the lattice energy as a sum of the interaction energies within a crystallographic system.⁴³ AA-CLP and PIXEL both make use of a series of mathematical expressions to calculate the energetic contributions of repulsion, dispersion, polarisation and Coulombic effects between pairs of atoms in neighbouring molecules to the total energy of the intermolecular interactions. AA-CLP and Pixel differ in the manner in which the atomic charges and the energetic contribution of the Coulombic

interactions are calculated. AA-CLP makes use of a Mulliken population analysis on an extended Hückel wavefunction in order to calculate atomic charges. These atom based point charges are then used to evaluate the contribution of Coulombic effects to the stability of a structure^{37,43} PIXEL, on the other hand, uses a semi classical density sums method (SCDS) where the contribution of Coulombic effects to the total energy is evaluated by summing the electrostatic interaction energy between the electron density of the reference molecule and its neighbours. The molecular electron density required for such a calculation is typically obtained by an *ab initio* MP2/6-31G(d,p) calculation. In order to increase the speed of the calculation, the electron density is condensed into points referred to as pixels. A “pixel-by-pixel” approach then allows for the determination of the interaction of each pixel with its environment.⁴⁴ This approach allows for a better description of the electrostatic properties of a molecule and consequently enables far more accurate determinations of interaction energies when compared to AA-CLP, but is far more computationally demanding.⁴⁵

DFT methods are even more computationally demanding when determining lattice energies of a crystalline system. Energy calculations for pairs of molecules can be more accurately determined from a calculation of the orbital interactions between pairs of molecules. The stability is, however, often overestimated, leading to a basis set superposition error (BSSE) for which a correction, referred to as the counterpoise method,⁴⁶ is required. The error is caused by the mixing or overlap of basis sets at the interface between the two neighbouring molecules, thereby lowering the energy of the system. This is particularly problematic when pairs of molecules experience a large area of overlap. Without a BSSE correction, calculated molecule...molecule interaction energies resemble those determined using AA-CLP's less accurate predecessor, OPROP when the UNI^{47,48} force field is used. OPROP with the UNI force field was designed to ignore the energy contribution of the Coulombic interactions to the lattice energy by allowing the other contributions such as repulsion and dispersion to be overestimated. This may seem an unusual approach, but the approximation allowed lattice energies to be calculated relatively quickly and led to the advances in crystal structure prediction in the

1990's.⁴² In most cases, the results obtained using OPRP have been found to be reasonable for molecular crystals. Traditionally, the description of functionals used in DFT methods is not designed to deal with dispersion effects. As a consequence, interaction energies between molecules with considerable π overlap are usually significantly underestimated. To correct for this, several modified functionals, such as the M06 or M06-2X functionals, have been proposed and have been found to produce better results in systems containing dispersion forces.⁴⁹ However, even these are inaccurate in systems where dispersion effects are very significant, and a newer approach has now been proposed in which classical DFT (typically the BP3LYP functional) is combined with empirical parameters which describe the energy contribution of the dispersion forces (known as DFT-D).⁵⁰ The dispersion corrections in DFT-D and PIXEL have been shown to be almost equivalent.⁵¹

PIXEL calculations are now considered one of the methods of choice for determining the partitioned energies of interaction in a crystal structure, and a prerequisite in the study of polymorphism and crystal structures in general.⁵¹ PIXEL is not without its disadvantages. As a computationally demanding method, the use of PIXEL is limited to relatively small systems and thus atom-atom methods such as AA-CLP remain the only option for larger systems.

3.2 A structural and theoretical analysis of a polymorphism inducing substructure

3.2.1 Polymorphs of *N*-[2-(hydroxymethyl)phenyl]benzamide

The research paper that follows, *Polymorphs of N-[2-(Hydroxymethyl)phenyl] benzamide: Structural Characterization and Analysis of Molecule...Molecule Interactions by Means of Atom–Atom Potentials and DFT*, focuses on the relationship between the two polymorphs of *N*-[2-(hydroxymethyl)phenyl] benzamide. The nature of the intermolecular forces involved in the stabilisation of the crystal lattice, and the ranking of these interactions in terms of their contribution to the overall lattice energy of the crystal structure, was analysed using DFT, PIXEL and atom-atom potential (OPROP) methods. The synthesis, characterisation, crystal structure determination and accidental, yet fortuitous, discovery of the polymorphs were carried out by the author. DFT calculations were carried out by Dr C. B. Perry and OPROP and PIXEL calculations were carried out by Dr M. A. Fernandes. The paper was submitted on 30 December 2010 and published in the peer-review journal *Crystal Growth & Design* on 29 March 2011. The supplementary information can be found in **Appendix 3.1**.

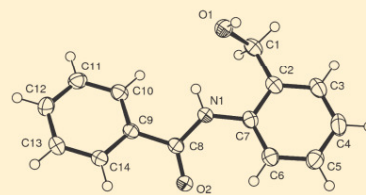
Polymorphs of *N*-[2-(Hydroxymethyl)phenyl]benzamide: Structural Characterization and Analysis of Molecule ··· Molecule Interactions by Means of Atom–Atom Potentials and DFT

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Supporting Information

ABSTRACT: Two polymorphs of *N*-[2-(hydroxymethyl)phenyl]benzamide have been identified and their structures elucidated. Both crystallize in $P2_1/n$ but with different unit cell parameters and crystal packing. The less stable polymorph II undergoes a first order phase transition to polymorph I at 85 °C, as determined using variable temperature powder diffraction studies. The arrangement of molecules in both structures is characterized by intramolecular ring-forming $N-H \cdots O(H)$ and chain-forming intermolecular $O-H \cdots O=C$ hydrogen bonds. It is, however, the nature of the dispersive interactions due to π overlap that differentiates the two structures. In polymorph I, these exist in a molecule ··· molecule interaction that also accommodates the $O-H \cdots O=C$ hydrogen bond. Calculations using atom–atom potential methods, and corroborated using DFT methods, indicate that the interaction energy of this pair of molecules accounts for at least half of the total lattice energy of the structure. Carrying out the equivalent calculations on polymorph II shows that the dispersive interactions due to π overlap and the $O-H \cdots O=C$ hydrogen bond are separated into two different molecule ··· molecule interactions. This suggests that determining the distinctive interactions between pairs of molecules may provide some insight into how to inhibit them and, hence, favor the growth of other crystal forms.



N-[2-(Hydroxymethyl)phenyl]benzamide is an intermediate in several synthetic pathways, including the synthesis of oxazines (as well as being a product of oxazine hydrolysis),^{1–3} and in the synthesis of biomimetic models in our laboratory. In addition, it has been synthesized as a potential antifungal agent.⁴ The *ortho*-amino benzyl alcohol moiety is a useful synthon en route to compounds with applications in medicine; for example, 2-hydroxymethylphenylcarbamoyl-(*S*)-prolyl-(*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide is used in pain management and treatment.⁵ The polymorphic behavior of the title compound is therefore of interest.

Several definitions of polymorphism have been proposed, including a general definition that polymorphism occurs when more than one structure or arrangement of the lattice results in an energy minimum under different conditions.⁶ Differences in crystal structure may be due to differences in molecular conformation or to differences in intermolecular interactions, resulting in an alternative packing arrangement. Nonetheless, the differences in energy between the polymorphs must be small for the polymorphs to exist. Typically, only the atom-to-atom interactions between molecules are examined in most current reports involving polymorphism and crystal engineering. Structures are therefore evaluated according to the presence of classical hydrogen bonds (such as $N-H \cdots O$, $O-H \cdots O$, $O-H \cdots N$), weak hydrogen bonding interactions ($C-H \cdots O$, $C-H \cdots N$, $C-H \cdots \pi$, etc.), obvious dipole ··· dipole interactions, and $\pi \cdots \pi$ interactions. Often, their identification and significance depends on the discretion of the researcher involved. The actual energetic contribution of each interaction is ranked according to interaction type but otherwise not quantified. It has been suggested that perhaps a better approach would

be to evaluate structures in terms of the total interaction energy of one molecule with all its neighbors within the structure as pairwise energies.^{7,8} Different methods of quantifying these interactions have been discussed and compared.⁹ In this work, two different polymorphs have been compared, first, using the usual atom-to-atom approach and, subsequently, using an atom–atom potential method, a semiclassical density sums method (PIXEL^{10–13}), and DFT methods with several functionals.

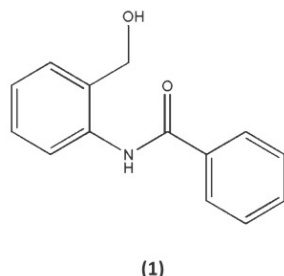
N-[2-(Hydroxymethyl)phenyl]benzamide (**1**) was synthesized by benzylation of 2-aminobenzyl alcohol according to an established method¹⁴ as part of an extended synthesis of a biomimetic target molecule to be reported elsewhere. The product was characterized by ¹H- and ¹³C NMR, IR, single crystal XRD, and melting point; results were found to be in agreement with the literature.² Slow evaporation of the compound from an 1:1 ethyl acetate/hexane solvent system led to blocklike crystals (Figure S1a in the Supporting Information) of the more stable polymorph I. Recrystallization as a purification method of the same reaction product from a subsequent synthesis (slow evaporation from dichloromethane at room temperature) led to the serendipitous discovery of needle-like crystals (Figure S1b) of the less stable polymorph II. Further recrystallization attempts using the same reaction product in the same container led to the formation of polymorph I, suggesting that crystallization conditions rather than just the presence of

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reaction impurities contributed to the formation of this polymorph. Both polymorphs have been structurally characterized using X-ray diffraction; both crystallize in monoclinic $P2_1/n$ with different crystal packing and hence different unit cell parameters (Table 1).



As a consequence of the discovery of polymorph II, many crystallization attempts were made using several solvents (dichloromethane, dichloromethane/hexane, ethyl acetate, ethyl acetate/hexane, methanol, toluene, isopropanol), temperatures, and crystallization methods (slow cooling, slow evaporation, and precipitation) in order to understand the crystallization conditions required; all resulted in the crystallization of polymorph I, perhaps because, to preserve the small amount of polymorph II available, it was used as the starting material and, despite all precautions, seeded the crystallization experiments.

We have, in addition, also attempted sublimation methods using polymorph I as a starting material which appear to lead to a solid-state reaction which will be reported elsewhere. Our inability to grow new crystals of polymorph II places this structure in the realm of disappearing polymorphs.²²

The molecules in the two polymorphs are conformationally similar (Figure 1, weighted rmsd = 0.1448 Å). Tables comparing the bond lengths and angles within the two molecules are reported in the Supporting Information (Table S1). The largest difference between the two molecules is a ca. 6° difference in the C7–N1–C8–C9 torsion angle, 177.42(12)° and –177.0(2)° for polymorphs I and II, respectively, with the remaining conformational differences arising as a consequence. Single point DFT calculations on the isolated molecules with the B3LYP (3.6 kJ mol^{−1}),^{23–26} X3LYP (3.3 kJ mol^{−1}),²⁷ CAM-B3LYP (2.0 kJ mol^{−1}),²⁸ M06 (2.2 kJ mol^{−1}),²⁹ and M06–2X (2.4 kJ mol^{−1})³⁰ functionals [all with 6-31++G(d,p)] using Gaussian-09³¹ consistently indicate that the conformation in polymorph II is about 3 kJ mol^{−1} higher in energy. The fact that the two molecules have virtually the same energy suggests that the difference in energy between the two polymorphs is almost entirely due to packing differences.

The molecule contains two groups (an alcohol and an amide group) which are capable of forming classical hydrogen bonds. The N–H component of the amide group in both structures is involved in an intramolecular hydrogen bond with the lone pairs of the alcohol group [–N–H···O(H); graph set ^{32,33} S(6); Table 2] in both structures, probably as a consequence of the molecular conformation being almost identical. Coincidentally, the conformation of the molecule is also stabilized by an intramolecular C–H···O interaction [–C(6)–H···O=C; graph set S(6)] in both structures. The alcohol group in both structures forms chains of molecules along the *b*-axis (coinciding with the 2-fold screw axis in both cases) by hydrogen bonding to the amide

Table 1. Crystallographic Information for Polymorphs I and II^a

	I	II
formula	C ₁₄ H ₁₃ NO ₂	C ₁₄ H ₁₃ NO ₂
formula weight	227.25	227.25
temperature (K)	173(2)	173(2)
wavelength (Å)	0.71073	0.71073
crystal system	monoclinic	monoclinic
space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> (Å)	12.5115(4)	5.1936(6)
<i>b</i> (Å)	7.3273(2)	13.2328(14)
<i>c</i> (Å)	12.6648(4)	17.0316(17)
β (deg)	100.052(2)	90.125(4)
cell volume (Å ³)	1143.23(6)	1170.5(2)
ρ _{calc} (g/cm ³)	1.320	1.290
<i>Z</i>	4	4
data/parameters	2230/155	2296/155
<i>R</i> ₁ / <i>wR</i> ₂	0.042/0.098	0.056/0.119
GOF	1.007	1.053

^a Data collection, APEX2;¹⁵ cell refinement, APEX2; data reduction, SAINT;¹⁶ program used to solve structure, SHELXS97;¹⁷ program used to refine structure, SHELXL97;¹⁷ molecular graphics, ORTEP-3 for Windows¹⁸ and SCHAKAL99;¹⁹ software used to prepare material for publication, WinGX²⁰ and PLATON.²¹

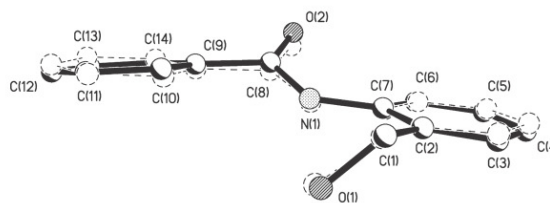


Figure 1. Least squares overlay of the *N*-[2-(hydroxymethyl)phenyl]benzamide molecule in the two polymorphs (dotted lines for polymorph II).

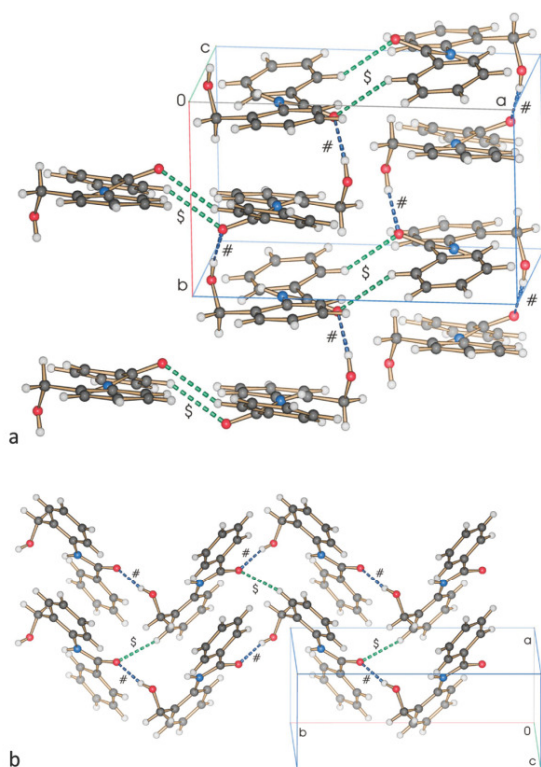
oxygen of a neighboring molecule [–O–H···O=C; graph set C(8); Figure 2]. The relative orientation between the molecules in both cases is, however, very different. The angle between the molecular least-squares planes between neighboring molecules in this chain is 12.7° in polymorph I—hence, the molecules almost stack on each other—while it is 72.9° in polymorph II. There is, therefore, significant π overlap between molecules within the hydrogen bonded chain in polymorph I. For polymorph II, significant π overlap occurs between molecules on different hydrogen bonded chains related by translation along the *a* axis. However, neither structure contains distinctive ring π ··· π interactions: the ring Cg···Cg distances are much shorter between molecules in polymorph I (shortest distance 4.1558(8) Å—along the *b* axis) compared to those in polymorph II (shortest distance 4.9480(16) Å—along the *a* axis). This has significant consequences for the lattice energies (see below). However, the most direct consequence is that the cell axis is almost twice the length along *b* in polymorph II compared to polymorph I.

Finally, there are intermolecular C–H···O interactions between molecules related by centers of inversion in polymorph

Table 2. Hydrogen-Bond Geometry for Polymorphs I and II (Å, deg)^a

D–H...A	D–H	H...A	D...A	D–H...A
Form I				
N1–H1N...O1	0.88	2.13	2.822(1)	135
O1–H1O...O2 ⁽ⁱ⁾	0.84	1.96	2.791(1)	168
C6–H6...O2	0.95	2.37	2.901(2)	115
C14–H14...O2 ⁽ⁱⁱ⁾	0.95	2.58	3.435(2)	150
Form II				
N1–H1N...O1	0.88	2.03	2.752(3)	138
O1–H1O...O2 ⁽ⁱⁱⁱ⁾	0.84	1.94	2.763(3)	166
C6–H6...O2	0.95	2.34	2.899(3)	117
C3–H3...O2 ^(iv)	0.95	2.62	3.529(3)	160

^a(i) $(\frac{3}{2} - x, \frac{1}{2} + y, \frac{3}{2} - z)$; (ii) $(1 - x, -y, 1 - z)$; (iii) $(\frac{3}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$; (iv) $(\frac{5}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$.

**Figure 2.** Intermolecular hydrogen bonding in polymorphs (a) I and (b) II between the alcohol and amide groups (OH...O=C; #). These form chains along *b* in both structures. C–H...O=C interactions (\$) link the chains in an alternating manner in both structures. Also visible is the significant π overlap between molecules of the hydrogen bonded chain in I. In II the π overlap occurs between molecules on neighboring chains related by translation along *a*. The diagrams show that I is composed of layers while II has a zigzag type packing.

I [$-\text{C}(14)-\text{H}\cdots\text{O}=\text{C}$; graph set $\text{R}_2^2(10)$; Figure 2; Table 2] forming hydrogen bonded dimers and alternately linking the

hydrogen bonded chains to form a sheet of molecules parallel to (10–1). Since the molecules in the chain almost stack on each other along the hydrogen bonded chain (viewed down the *b* axis) and are then involved in these centrosymmetric dimers, the structure is layerlike when viewed down the *c* axis. By comparison, molecules in polymorph II are involved in a long and hence weak C–H...O interactions [$-\text{C}(3)-\text{H}(3)\cdots\text{O}=\text{C}$; graph set $\text{C}(7)$], which effectively weaves molecules on neighboring $-\text{O}-\text{H}\cdots\text{O}=\text{C}$ chains together along the *a* axis. This coincides with the significant π overlap between these molecules that was previously mentioned. The crystal packing in polymorph II is best described as zigzag.

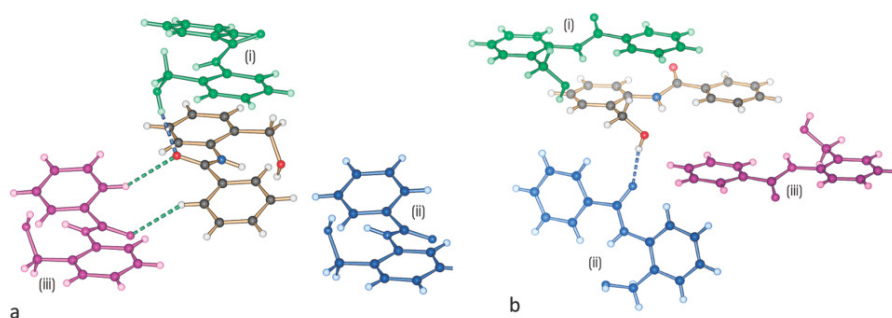
To determine the thermodynamic relationship between the two polymorphs, crystals of each type were investigated using DSC, “high temperature” powder diffraction, and hot stage microscopy. It was found that polymorph I persisted until its melting point of 95 °C and so is the more stable of the two polymorphs. Comparison of the crystal densities at –100 °C also indicates that polymorph I (1.320 g cm^{-3}) should be more stable than polymorph II (1.290 g cm^{-3}), as higher crystal densities usually indicate stronger molecular interactions between the molecules in a structure.^{34–36} All three techniques indicate that polymorph II changes to polymorph I at about 85 °C, retaining the crystal habit but in a non-single-crystal-to-single-crystal manner. As a consequence, the crystal after phase transitions yields a powder diffraction pattern when exposed to X-rays on a single crystal diffractometer (Figure S7 in the Supporting Information). This suggests that the phase transition is first order; this is not surprising, as the cell volume of polymorph II at –100 °C is almost 30 Å^3 larger than that of polymorph I. In addition, a phase change from the zigzag structure of polymorph II to the layered structure of polymorph I requires large molecular movements, which are difficult to accommodate.

While the evaluation of the hydrogen bonding and other weak interactions often gives significant insight into the nature and difference of two polymorphs, evaluating the structures using lattice energy calculations and the resulting molecule...molecule interactions allows these to be quantified. For this purpose, two different lattice energy calculation methods were used: OPROP³⁷ and PIXEL,^{9–13,38} which are both modules of the OPIX³⁷ program package. In order to carry out these calculations, all O–H, N–H, and C–H distances were normalized at 1.0 Å, 1.0 Å, and 1.08 Å, as prescribed in the OPIX manual. Using OPROP with the UNI^{39,40} force field to calculate the lattice energy suggests that polymorph I ($-149.1 \text{ kJ mol}^{-1}$) is more stable than polymorph II ($-143.2 \text{ kJ mol}^{-1}$) by about 5.9 kJ mol^{-1} . The equivalent calculation using PIXEL suggests that the lattice energy difference between polymorph I ($-129.7 \text{ kJ mol}^{-1}$) and II ($-127.0 \text{ kJ mol}^{-1}$) is about 2.7 kJ mol^{-1} .

Molecule...molecule interaction energies from these calculations are given in Table 3. Calculations using OPROP and, hence, an atom–atom potential method reveal very distinctive differences in the interactions in the two structures. Polymorph I has a pattern in which one interaction is much stronger ($-78.7 \text{ kJ mol}^{-1}$ —a little more than half the calculated lattice energy) than the two next most significant interactions (both around -15 kJ mol^{-1}). In the strong interaction, the molecules are orientated such that the intermolecular O–H...O=C hydrogen bond is formed. This orientation also allows for significant π overlap (within the chain as shown in Figure 2) and, hence, significant stabilization due to dispersive forces (Figure 3). The next two molecular geometries around the central molecule

Table 3. Molecule···Molecule Interactions Energies Contributing the Most to the Stability of Polymorph I and II Calculated Using OROP, PIXEL, and Various DFT Functionals (kJ mol^{−1})^a

symmetry	OPIX		DFT					
	OPROP/UNI	pixel	M06	M06-2X	M06-2X/6-311++G(d,p)	X3LYP	CAM-B3LYP	B3LYP
Form I								
$3/2 - x, -1/2 + y, 3/2 - z$	−78.7	−62.7	−81.6	−80.4	−86.6	−28.3	−37.5	20.6
$2 - x, -y, 1 - z$	−17.6	−23.1	−17.1	−19.2	−22.9	−6.4	−9.4	−2.1
$1 - x, -y, 1 - z$	−14.2	−21.1	−10.2	−11.7	−15.4	−1.5	−3.9	2.5
$-1/2 + x, -1/2 - y, -1/2 + z$	−10.9	−14.6	−12.7	−14.0	−18.1	−8.9	−10.1	−6.9
$2 - x, -y, 2 - z$	−10.8	−7.2	−6.9	−6.4	−10.3	0.8	−0.2	3.1
$3/2 - x, -1/2 + y, 1/2 - z$	−8.7	−8.3						
$-1/2 + x, -1/2y, 1/2 + z$	−6.5	−7.5						
$x, y, -1 + z$	−4.1	−6.0						
Form II								
$1 + x, y, z$	51.2	27.9	38.0	36.2	38.2	5.6	0.0	11.6
$1/2 - x, -1/2 + y, 3/2 - z$	−35.5	−38.2	−38.8	−40.1	−40.6	−29.8	−33.0	−26.1
$1 - x, 2 - y, 2 - z$	−16.1	−18.6	−13.7	−15.5	−15.7	−5.3	−7.5	−14.1
$-1/2 - x, -1/2 + y, 3/2 - z$	−13.9	−19.1	−18.5	−19.4	−19.8	−14.0	−15.3	−11.6
$-1/2 + x, 5/2 - y, -1/2 + z$	−10.6	−13.1	−12.7	−13.2	−13.8	−4.9	−6.1	−3.1
$-x, 2 - y, 2 - z$	−7.1	−6.5						
$-3/2 + x, 5/2 - y, -1/2 + z$	−4.0	−7.9						

^a All DFT calculations were carried out using a 6-31++G(d,p) basis set, unless otherwise indicated.**Figure 3.** Arrangement of the three molecules with the greatest contribution to the stability of (a) polymorph I; (i) molecules involved in both (OH···O=C) hydrogen-bonding and significant π overlap ($3/2 - x, -1/2 + y, 3/2 - z$; −78.7 kJ/mol); (ii) molecules interacting through weak C–H···O(H) interactions ($2 - x - y, 1 - z$; −17.6 kJ/mol); (iii) molecules involved in C–H···O=C interactions ($1 - x, -y, 1 - z$; −14.2 kJ mol^{−1}); and (b) polymorph II; (i) molecules involved in significant π overlap ($-1 + x, y, z$; −51.2 kJ mol^{−1}); (ii) molecules involved in (OH···O=C) hydrogen-bonding ($1/2 - x, -1/2 + y, 3/2 - z$; −35.5 kJ mol^{−1}); (iii) molecules interacting through weak C–H···O(H) interactions ($1 - x, 2 - y, 2 - z$; −16.1 kJ mol^{−1}).

contain C–H···O interactions. These, however, contribute much less significantly to the stability of the structure. The pattern of the three most significant interactions in polymorph I is therefore very strong···weak···weak. In polymorph II, the strongest interaction geometry of polymorph I (the −78.7 kJ mol^{−1} interaction) is broken up into two separate interactions, in which the orientation allowing for significant π overlap (and hence dispersion) contributes −51.2 kJ mol^{−1} to the lattice energy, while the orientation coinciding with the intermolecular O–H···O=C hydrogen bond contributes −35.5 kJ mol^{−1}. The sum of these two interactions contributes more than half of the calculated lattice energy. The next strongest interaction contributes −16.1 kJ mol^{−1} and allows for C–H···O interactions between the

molecules. The pattern of the three most significant interactions in polymorph II is therefore strong···strong···weak. Analyzing the molecule···molecule interaction energies from the calculations using PIXEL results in the patterns described above for both polymorphs but with very different interaction energies. The very strong···weak···weak pattern is still very distinct for polymorph I. PIXEL is also capable of breaking down interactions into their energetic components and indicates that dispersion contributes a very significant −60.2 kJ mol^{−1}, while electrostatics and polarization contribute −78.6 kJ mol^{−1} to the most stable molecule···molecule interaction. These are counterbalanced by a repulsion energy of 76.0 kJ mol^{−1}. For polymorph II, the orientation coinciding with π overlap contributes half the

energy ($-27.9 \text{ kJ mol}^{-1}$) of its atom–atom potential (UNI) calculated equivalent ($-51.2 \text{ kJ mol}^{-1}$). In this case, PIXEL indicates that dispersion contributes almost all the stabilization ($-46.6 \text{ kJ mol}^{-1}$), while electrostatics and polarization contribute about -7.7 kJ mol^{-1} ; this is counterbalanced by a repulsion energy of 26.4 kJ mol^{-1} . As a consequence, the hydrogen bonding interaction is, at $-38.2 \text{ kJ mol}^{-1}$, more significant in this calculation. Nevertheless, the molecule...molecule interaction pattern is still strong...strong...weak, although less distinctly so.

For comparison purposes, DFT calculations were carried out on the five most significant interactions identified with the atom potential (UNI) calculation using the hybrid DFT functionals B3LYP, X3LYP, CAM-B3LYP, M06, and M06-2X (Table 3). The functionals CAM-B3LYP, X3LYP, M06, and M06-2X have been reported as being able to model structures containing dispersion forces, with M06 and M06-2X probably being the current state of the art. B3LYP is a commonly used DFT functional which has not been optimized for dispersion forces; it has been included for comparison. In the case of the M06, M06-2X, X3LYP, and CAM-B3LYP functionals, the very strong...weak...weak sequence of interactions in polymorph I is found, but with much lower energies when using the X3LYP and CAM-B3LYP functionals, indicating that these two functionals do not handle dispersion forces well in this particular case. Results using the M06 and M06-2X functionals reproduce the numbers obtained using the atom potential method (UNI) almost exactly. B3LYP's inability to model dispersion produces a large positive energy for this interaction, as well as the most important dispersion dominated molecule...molecule interaction of polymorph II. Carrying out the equivalent calculations for polymorph II using X3LYP and CAM-B3LYP results in very small ($\approx 0 \text{ kJ mol}^{-1}$ in the case of CAM-B3LYP) or positive energies ($\approx 6 \text{ kJ mol}^{-1}$ in the case of X3LYP) for what is the strongest molecule...molecule interaction (the π overlap geometry) from OPROP, illustrating the deficiencies in modeling dispersion effects with these two functionals. Using the M06 and M06-2X functionals does yield values similar to those for OPROP and PIXEL. The energy of the second most important molecule...molecule interaction coinciding with the $\text{O}-\text{H}\cdots\text{O}=\text{C}$ intermolecular hydrogen bond is more consistently calculated with all the methods used. Calculations with the M06 and M06-2X functionals result in energies comparable to those of the atom potential method with an interaction sequence of strong...strong...weak. In this case, the orientation encouraging π overlap and the orientation allowing for the intermolecular $\text{O}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bond have almost identical energies. As a final check, the M06-2X calculation was repeated for both structures using a larger, triple- ζ basis set [6-311++G(d,p)]. Almost identical results were obtained for polymorph II but somewhat larger energies for I. When modeling dispersion dominated interactions using high level DFT methods, the use of a large basis set is generally desirable. However, the results show that the choice of basis set may indeed influence the energies obtained but does not seem to affect the sequence of energies in this case.

Calculations of this kind—even if just OPROP is used—are very useful, as they can give significant insight into the forces keeping the molecules in a crystal together. The above molecule...molecule energy comparison and interpretation is admittedly especially easy in this case, as the two polymorphs are so distinctly different in this way. Applying the same approach to another polymorphic system may not lead to such clear-cut differences. Had only the usual analysis of the hydrogen bonding geometries and $\pi\cdots\pi$

interactions (as reported by the usual $\text{Cg}\cdots\text{Cg}$ distance) been carried out in this case, then the true nature of the packing forces within each polymorph would not have been known. In particular, the significance of the π -overlapped molecule...molecule geometry (and hence the contribution of dispersion to these structures) would have been overlooked. In this work, knowledge of the importance of the strongest molecule...molecule interaction ($-78.7 \text{ kJ mol}^{-1}$) to the stability of polymorph I led to attempts to disrupt it by attempting crystallization experiments with many different solvents as possible intercalating agents, but without success. In addition, attempts were made to crystallize at higher temperatures (around 85°C) to try and force out the more open (lower density) structure of polymorph II, but also without success. In fact, as mentioned earlier, polymorph II converts to polymorph I at around 85°C . Despite these failures, knowledge of the most significant interactions in a structure does allow one to target them and possibly inhibit their crystallization.

In summary, the conformationally flexible molecule, *N*-[2-(hydroxymethyl)phenyl]benzamide, has been found to crystallize out as two polymorphs. Both crystallize in the same space group and have almost equivalent molecular conformations (due to the presence of a $\text{N}-\text{H}\cdots\text{O}$ intramolecular hydrogen bond), but different crystal packing and hence cell dimensions. We have only once successfully crystallized polymorph II, making the structure another example of a disappearing polymorph. Attempts to recrystallize this polymorph using different solvents and techniques have so far only yielded polymorph I, indicating that it is the more stable of the two. Further examination using lattice energy calculations show polymorph I to be more stable by $3\text{--}6 \text{ kJ mol}^{-1}$, depending on the calculation method used. This has been confirmed using DSC and powder diffraction, which indicate that polymorph II converts to polymorph I at 85°C . The usual examination of hydrogen bonding and $\pi\cdots\pi$ interactions suggests the structures are held together by similar interactions. However, calculating the molecule...molecule interaction energies for both structures reveals that the two polymorphs have very different packing arrangements. Most significantly, the most stable molecule...molecule geometry in polymorph I is one in which significant π overlap occurs together with a $\text{O}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bond. This particular molecule...molecule interaction accounts for more than half of the lattice energy in the structure and is, as a consequence, very distinctive. In the less stable polymorph II, stabilization derived from this one geometry is split into two different geometries—one with π overlap and one corresponding to the $\text{O}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bond. Knowledge of a very stable interaction geometry in polymorph I provides, in principle, a means to inhibit it and encourage the growth of an alternative. However, our attempts to do so have so far been unsuccessful. Nonetheless, the knowledge of the most important molecule...molecule geometries should allow techniques that inhibit particular interactions to be developed, which will be another useful tool in crystal engineering.

■ ASSOCIATED CONTENT

S Supporting Information. Infrared, PXRD, and DSC data, and crystal coordinates as CIF files for polymorphs I and II. This material is available free of charge via the Internet at <http://pubs.acs.org>. The CIF files can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) as CCDC-805594 and CCDC-805595.

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REFERENCES

- Witkop, B.; Patrick, J. B.; Kissman, H. M. *Chem. Ber.* **1952**, *85*, 949.
- Dixon, W. J.; Hibbert, F.; Mills, J. F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1503.
- Auwers, K. *Chem. Ber.* **1904**, *37*, 2254.
- Kirino, O.; Yamamoto, S.; Kato, T. *Agric. Biol. Chem.* **1980**, *44*, 2143.
- Walpole, C.; Ko, S. Y.; Brown, M.; Beattie, D.; Campbell, E.; Dickenson, F.; Ewan, S.; Hughes, G. A.; Lemaire, M.; Lerpiniere, J.; Patel, S.; Urban, L. *J. Med. Chem.* **1998**, *41*, 3159.
- O'Neill, M. H. *Pharm. Tech.* **2003**, 44.
- Dunitz, J. D.; Gavezzotti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1766.
- Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth Des.* **2005**, *5*, 2180.
- Dunitz, J. D.; Gavezzotti, A. *Chem. Soc. Rev.* **2009**, *38*, 2622.
- Gavezzotti, A. *J. Phys. Chem.* **2002**, *B106*, 4145.
- Gavezzotti, A. *J. Phys. Chem.* **2003**, *B107*, 2344.
- Gavezzotti, A. *CrystEngComm* **2003**, *5*, 429.
- Gavezzotti, A. *CrystEngComm* **2003**, 5.
- Furstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991.
- Bruker. APEX2, 2.0-1 ed.; Bruker AXS Inc.: Madison, WI, USA, 2005.
- Bruker. SAINT+, 6.0 (includes XPREP and SADABS) ed.; Bruker AXS Inc.: Madison, WI, USA, 2005.
- Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.
- Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
- Keller, E. University of Freiberg, Germany, 1999.
- Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.
- Spek, A. L. *Acta Crystallogr., Sect. D* **2009**, *65*, 148.
- Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193.
- Vosko, S. H.; Wilk, L.; Nusait, M. *Can. J. Phys.* **1980**, *58*, 1200.
- Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
- Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
- Xu, X.; Goddard, W. A. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 2673.
- Yanai, T.; Tew, D. P.; Handy, N. C. *Chem. Phys. Lett.* **2004**, *393*, 51.
- Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
- Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
- Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian Inc.: Wallingford, CT, 2009.
- Bernstein, J.; Davis, R. E.; Shimon, L.; Chang, N.-L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1555.
- Etter, M. C.; MacDonald, J. C.; Bernstein, J. *Acta Crystallogr., Sect. B* **1990**, *46*, 256.
- Sathishkumar, R.; Mahapatra, S.; Thakur, T. S.; Desiraju, G. R. *Curr. Sci. India* **2010**, *99*, 1807.
- Desiraju, G. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 8342.
- Thakur, T. S.; Desiraju, G. R. *Cryst. Growth Des.* **2008**, *8*, 4031.
- Gavezzotti, A. *OPiX*, A computer program package for the calculation of intermolecular interactions and crystal energies; University of Milano: 2003.
- Gavezzotti, A. *J. Chem. Theory Comput.* **2005**, *1*, 834.
- Filippini, G.; Gavezzotti, A. *Acta Crystallogr., Sect. B* **1993**, *49*, 868.
- Filippini, G.; Gavezzotti, A. *J. Phys. Chem.* **1994**, *98*, 4831.

3.2.2 A polymorphism inducing substructure and its polymorphic derivatives

The manuscript that follows, *Polymorph diversity: phenylbenzamide as a moiety that encourages polymorphism*, investigates *N*-phenylbenzamide as a potential polymorphism enhancing group. In a more systematic study, the molecule...molecule interactions of five pairs of polymorphs, derivatives of *N*-[2-(hydroxymethyl)phenyl] benzamide, were analysed using the PIXEL CPL method and the most stabilising interactions were ranked and assessed. The synthesis, characterisation, crystal structure determination and discovery of the polymorphic structures were carried out by the author. The generation of Hirschfeld and electron density diagrams onto which the electrostatic potential was mapped, intramolecular energy calculations using Gaussian-09 and PIXEL (SCDS) calculations were carried out by Dr M. A. Fernandes. The paper was submitted on 13 February 2013 to *Crystal Growth & Design* and awaits review. The supplementary information can be found in **Appendix 3.2** and **Digital Appendix 3.1**.

Polymorphic diversity: *N*-phenylbenzamide as a moiety which may encourage polymorphism

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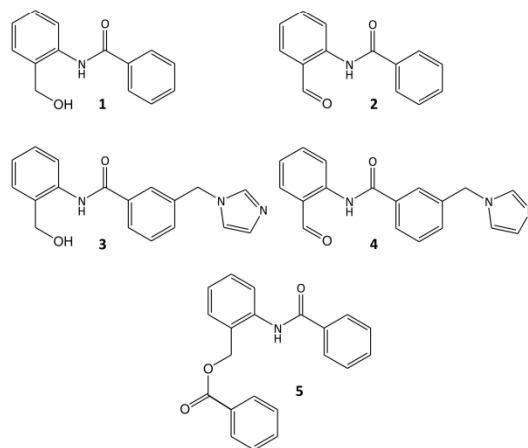
ABSTRACT: In this work we identify and describe a moiety which may be capable of encouraging the formation of polymorphs. Four new *N*-phenylbenzamide-based compounds have been synthesized yielding four pairs of polymorphs upon recrystallization. The structures of these have been discussed and compared with the previously reported polymorphs of *N*-(2-(hydroxymethyl)phenyl)benzamide. The results indicate that the conformation of the *N*-phenylbenzamide group is generally constant, but is able to alter its conformation as required by the crystal packing. The *N*-phenylbenzamide group is capable of N-H...O hydrogen bonding, but requires a change in conformation which is generally resisted by the molecule. As a consequence, weak forces such as C-H...O, C-H...N, C-H... π and π ... π interactions play significant but varying roles in these structures. One possible reason for the varying nature of the π ... π interactions may be due to the variation of the electrostatic potential across the *N*-phenylbenzamide group in which negative and positive regions alternate across the face of the molecule. It is the combination of all these attributes that possibly leads to polymorphism being observed in the structures reported here, and the results suggest that compounds containing a carboxylic acid or aniline group can be altered by a simple chemical modification and have their ability to form polymorphs enhanced.

INTRODUCTION

Polymorphism is a phenomenon in which a molecule adopts various packing arrangements in the solid state. Polymorphism can be both a bane as well as a panacea in various applications. It is particularly important in the pharmaceutical industry as the chemical stability and bioavailability can depend significantly on the polymorph that a drug adopts. In the case of solid-state chemistry, polymorphs offer the opportunity to study the affect of the crystal environment on a solid-state reaction, an example being the solid-state reactivity of *o*-ethoxy-*trans*-cinnamic acid.¹⁻³ As a consequence, the analysis of the intermolecular forces at work in a crystal structure is important in the understanding of the driving force in the crystallization of one polymorph over another. This is usually done by the analysis of close contacts and the interpretation of crystal packing in terms of hydrogen bonding (such as O-H...O and N-H...O) and weak interactions (such as C-H...O, C-H...N and C-H... π) using an atom-to-atom approach. The problem with this approach is that the contribution of π ... π interactions to the stability of a structure is often overlooked. An alternative (and complimentary) approach is to quantify and rank the interaction energies between pairs of molecules according to their contribution to the stability of a crystal structure. This has been shown to provide a more comprehensive picture of the forces within a crystal, and a better understanding of the relationship between polymorphs.^{4,5}

In this work we report on a set of compounds which contain a moiety which seems to have a propensity for forming polymorphs (Scheme 1). The compounds were synthesized as precursors to further products in a vitamin B₁₂ biomimetic model synthesis project. The crystal structures of these compounds

have been obtained by single crystal X-ray diffraction, and evaluated by carrying out lattice energy calculations using *PIXEL*. A key feature to note is that compounds **1** and **3** contain an alcohol group and as a consequence are capable of strong hydrogen bonding, while this group has been replaced by an aldehyde group in compounds **2** and **4** which is not capable of strong hydrogen bonding. For compound **5**, the alcohol group has been converted into a benzyl ester in order to see if polymorphism is suppressed by substitution at this point.



Scheme 1

EXPERIMENTAL

Synthesis

N-(2-Formylphenyl)benzamide (**2**) was synthesized from the oxidation of compound **1**. N-[2-(Hydroxymethyl)phenyl]benzamide (compound **1** - the synthesis of which has been reported in our previous paper;⁷ 455 mg, 2 mmol) and manganese(IV) oxide (2.608 g, 30 mmol) were stirred in chloroform (10 ml) for 12 hours, open to air. The reaction mixture was filtered through celite with chloroform as eluant. The solvent was removed *in vacuo*. The oily residue crystallized when placed under high vacuum. An off-white solid was obtained (0.436 g, 96.9%). Recrystallization from methanol/hexane (1:1 v/v) yielded colorless needles of polymorph **2a** while recrystallization from dichloromethane yielded colorless needles of polymorph **2b**. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 12.11 (s, 1H), 10.03 (s, 1H), 8.97 (d, J = 8.4 Hz), 8.19-7.97 (m, 3H), 7.78-7.65 (m, 2H), 7.57 (dd, J = 10.5, 4.5 Hz, 2H), 7.32-7.24 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 195.92, 166.17, 141.28, 136.42, 136.22, 134.34, 132.23, 128.90, 127.53, 123.07, 122.01, 119.99.

N-[2-(Hydroxymethyl)phenyl]-3-(1H-imidazol-1-ylmethyl)benzamide (**3**) was synthesized from the coupling of imidazole to a phenylbenzamide derivative, based on an established procedure⁶ using 3-(chloromethyl)-N-[2-(hydroxymethyl)phenyl]benzamide which was synthesized from 3-(chloromethyl)benzoyl chloride and 2-aminobenzyl alcohol using the same methodology used for the synthesis of compound **1**.⁷ 3-(Chloromethyl)-N-[2-(hydroxymethyl)phenyl]benzamide (4.183 g, 15.17 mmol) and imidazole (10.329 g, 0.52 mol) in DMF (15 ml) were stirred at room temperature for 20 hours. The reaction was diluted with water (100 ml) and extracted into dichloromethane (3 x 100 ml). The combined organic fractions were extracted into a hydrochloric acid solution (10%, 3 x 100 ml). The acidic solution was neutralized with ammonia solution until neutral and became cloudy. The product was extracted into chloroform (3 x 50 ml) and washed with water (6 x 100 ml) to remove any DMF present. The solution was then dried over Na₂SO₄ and the solvent was removed *in vacuo* to yield a yellow solid (3.723 g, 80%). Recrystallization from acetone yielded colorless plates of polymorph **3a** while recrystallization from acetone/ethyl acetate (1:1 v/v) yielded colorless needles of polymorph **3b**. ¹H NMR (300 MHz, MeOD) δ (ppm): 7.92-7.77 (m, 4H), 7.53 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.33 (td, J = 7.8, 1.5 Hz, 1H), 7.20 (td, J = 7.5, 1.1 Hz, 1H), 7.16 (s, 1H), 7.00 (s, 1H), 5.33 (s, 2H), 4.71 (s, 2H). ¹³C NMR (75 MHz, MeOD) δ (ppm): 166.04, 137.76, 136.13, 134.94, 132.96, 130.64, 128.97, 128.00, 127.78, 127.66, 126.38, 126.24, 126.19, 124.98, 123.25, 119.42, 62.00, 49.66.

N-(2-Formylphenyl)-3-(1H-imidazol-1-ylmethyl)benzamide (**4**) was synthesised from the oxidation of compound **3**. N-[2-(Hydroxymethyl)phenyl]-3-(1H-imidazol-1-ylmethyl)benzamide (compound **3**; 0.7633 g, 2.5 mmol) and manganese(IV) oxide (4.347 g, 50 mmol) were stirred in chloroform (50 ml) for 20 hours. The reaction mixture was filtered through celite with chloroform as eluent. The solvent was removed *in vacuo*. The oily residue crystallized when placed under high vacuum. An off-white solid was obtained (0.7225 g, 95%). Recrystallization of the solid from chloroform yielded colorless plates of polymorph **4a** while vapour diffusion of hexane into chloroform yielded colorless needles of polymorph **4b**. ¹H NMR(300 MHz,

CDCl₃) δ (ppm): 12.11 (s, 1H), 10.00 (s, 1H), 8.90 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.92 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.63 (s, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 0.7 Hz, 1H), 6.99 (d, J = 0.9 Hz, 1H), 5.25 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 195.98, 165.37, 140.89, 137.29, 136.35, 136.22, 135.12, 130.86, 130.00, 129.61, 126.94, 126.72, 123.31, 121.98, 119.81, 119.26, 50.42.

2-(Benzamido)-benzyl benzoate (**5**) was synthesized inadvertently from compound **1**. Upon heating compound **1** at a constant temperature of 80°C, a brown resin formed from which benzoic acid crystallized. Recrystallization of the resin from a hydrochloric acid solution yielded colorless needle-like crystals. ¹H NMR(300 MHz, CDCl₃) δ (ppm): 9.76 (s, 2H), 8.14 - 7.97 (m, 10H), 7.66 - 7.35 (m, 16H), 7.23 (dd, J = 14.2, 6.6 Hz, 3H), 5.40 (s, 4H).

Crystal growth

The discovery of polymorphs was done by simply noting if a different habit had been obtained after recrystallizing a compound from a different solvent. Crystal structures of the polymorphs of **1** have been previously reported,⁷ and as a consequence only basic crystallographic information are given in Table 1. Crystallographic information on the new compounds **2-5** are given in Table 2. ORTEP diagrams for polymorphs of **2-5** are given in Figure 1.

Crystal structure solution and refinement

Intensity data for compounds **2-4** were collected at -100(2) °C on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA). The collection method involved ω -scans of width 0.5° and 512x512 bit data frames. Intensity data for **5a** and **5b** were collected at -100(2) °C on a Bruker X8 Proteum diffractometer equipped with a PLATINUM 135 CCD detector and Motel 200 optics, using Cu K_α radiation (45kV, 20mA) from a Microstar rotating-anode generator. The collection method involved ω -scans of width 0.5° and 1024x1024 bit data frames.

All crystal structures were solved by direct methods. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 . Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. The crystal structures of **2b** and **4b** contain molecules displaying disorder. In the case of **2b**, molecule **B** is located over a crystallographic centre of inversion and as a consequence was refined with its occupancy set to 0.5 and with its bond lengths and angles constrained to match those of ordered molecule **A**. The alternative orientation of the molecule is therefore generated by the centre of inversion. The imidazole group on molecule **B** of polymorph **4b** was also found to be disordered and consequently refined in two orientations with the dominant orientation having an occupancy of 0.617(15). Software used in this work were as follows: Data collection: APEX2⁸; cell refinement: SAINT⁹; data reduction: SAINT; program used to solve structure: SHELXS-97¹⁰; program used to refine structure: SHELXL-97¹⁰; molecular graphics: ORTEP-3 for Windows¹¹ and SCHAKAL-99¹²; software used to prepare material for publication: WinGX¹³ and PLATON.¹⁴

Calculations

Relative intramolecular energies were calculated with the M06-2X¹⁵ DFT functional and the 6-31++G(d,p) basis set, using Gaussian-09.¹⁶ In the calculation, the crystal geometry of the C, O and N atoms were kept frozen while the H atom positions were allowed to optimize. This was done because H atoms in crystal structures determined by X-ray diffraction methods are geometrically and not experimentally placed.

Lattice and molecule...molecule interaction energies were calculated using *PIXEL*¹⁷ as incorporated with the April 2012 version of the *CLP* package.¹⁸ The calculations were carried out as prescribed within the *CLP* manual. The calculation was initialized by geometrically normalizing bonds involving H to neutron distances within *CLP*, followed by the calculation of an *ab initio* MP2/6-31G(d,p) molecular electron density using Gaussian-09.¹⁶ This molecular electron density description was then used as input by *PIXEL* to carry out the calculations. As *PIXEL* is only capable of working with a maximum of two molecules in the asymmetric unit, lattice energy calculations for compound **2** were carried out using *AA-CLP* which is also incorporated in the *CLP* package, as this atom-atom potential method is capable of working with more than two molecules. This change in calculation method was necessary as polymorph **2b** contains 3 molecules in the asymmetric unit when the inversion symmetry is removed. As a consequence of this limitation, *PIXEL* based molecule...molecule interaction energies were calculated only for the ordered molecule of **2b**.

Hirshfeld and electron density surfaces on which the electrostatic potential was mapped, were generated using CrystalExplorer¹⁹ coupled with HF/6-31G(d,p) wave function calculations using Gaussian-09.¹⁶

Table 1. Crystallographic Information for the previously-published polymorphs of **1**⁷

	1a	1b
Formula	C ₁₄ H ₁₃ NO ₂	C ₁₄ H ₁₃ NO ₂
Formula weight	227.5	227.5
Temperature (K)	173(2)	173(2)
Crystal system	Triclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> (Å)	12.5115(4)	5.1936(6)
<i>b</i> (Å)	7.3273(2)	13.2328(14)
<i>c</i> (Å)	12.6648(4)	17.0316(17)
α (°)	90	90
β (°)	100.052(2)	90.125(4)
γ (°)	90	90
Cell volume (Å ³)	1143.23(6)	1170.5(2)
ρ_{calc} (g/cm ³)	1.320	1.290
<i>Z</i>	4	4
<i>Z'</i>	1	1

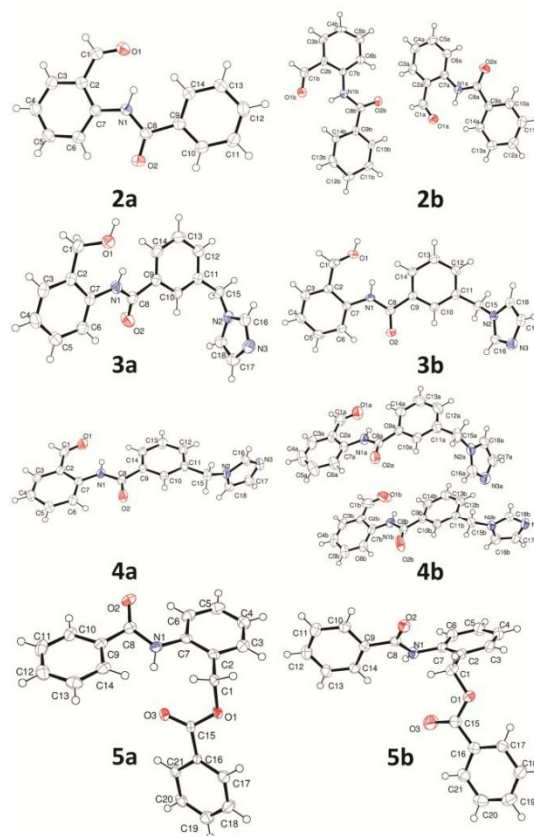


Figure 1. ORTEP Diagrams (50% probability level) for the polymorphs of compounds **2-5**.

RESULTS AND DISCUSSION

Molecular structures

ORTEP diagrams for the structures analysed in this work are shown in Figure 1. Selected torsion angles for these structures as well as those of compound **1** which were reported in a previous paper are given in Table 3. In general, the phenylbenzamide component adopts a planar conformation. The conformation of the amide group (defined by the *bcd*f torsion angle in Table 3) is almost constant and seemingly unaffected by crystal packing. The phenyl group is also almost planar with the amide group in compounds **1-4** and **5a**, and this may be due to an intramolecular hydrogen bond which forms between the amide hydrogen and the alcohol, aldehyde or ester oxygen atom. The only exception is in **5b**, where the benzamide group is rotated to take advantage of intermolecular hydrogen bonding. In this case the substituted phenyl group rotates by about 90° so that it is almost perpendicular to the benzamide group. The benzamide group also adopts a different orientation as indicated by the least squares overlay of the molecules in **5a** and **5b** (Figure 2c). This difference has a significant effect on the hydrogen bonding and crystal packing of compound **5** as will be discussed further

in the text. The other conformational difference between the molecules reported here is due to differences in the orientation of the substituent to the phenylbenzamide component in various compounds. The phenylbenzamide conformation in molecules **3a** and **3b** is almost identical, but the added imidazole substituent is orientated in the opposite direction in each molecule (Figure 2a) resulting in different hydrogen bond patterns in each structure. Since the alcohol group is involved in strong hydrogen bonding, its orientation has been assumed to be constant while the imidazole has been treated as being flexible. Using this assumption, it is found that the core phenylbenzamide component adopts an almost identical conformation in the two polymorphs resulting in an RMSD of 0.0415 Å when all the non-hydrogen atoms of the phenylbenzamide component are used in the calculation (Figure 2a).

Polymorphs **4a** and **4b** crystallize with one and two molecules (defined as molecules **A** and **B**) in the asymmetric unit, respectively. All three molecules adopt a different conformation (Figure 2b). The imidazole group in molecule **B** of **4b** was found to be disordered, but the dominant orientation [0.617(15) occupancy] has a similar conformation to the molecule in **4a**. Molecule **A** in **4b** adopts a conformation in which the imidazole is more perpendicular with the phenylbenzamide moiety and hence significantly different to the other two molecules (Figure 2b). A consequence of the imidazole disorder in **4b** is that the direction from which the imidazole can act as acceptor to a proton donor is altered. Each orientation therefore stabilizes a different hydrogen bond motif.

The relative energies of molecules in polymorphs **1a-5b** as calculated with M06-2X/6-31++G(d,p) functional and basis set using *Gaussian-09* are given in Table 4. The energies of the disordered molecules in **2b** and **4b** are not included. As can be seen the energy difference between each pair of conformers is very small. In general the larger the molecule the greater the energy difference between the conformers. It is interesting to

note that the energy difference for the two very different conformations of **5** is only about 14 kJ/mol. One reason for the **5a** conformation having a lower energy may be due to stabilization by the intramolecular hydrogen bond.

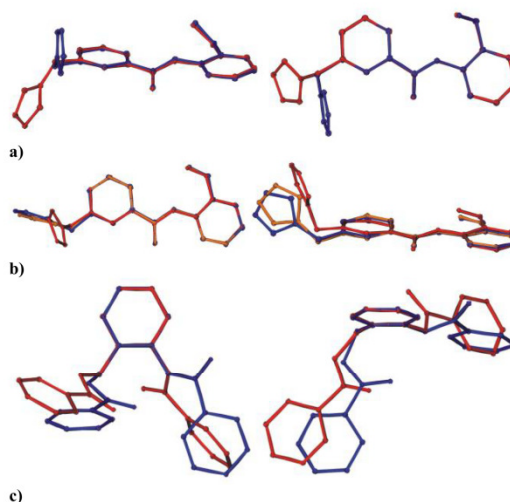


Figure 2. a) Superimposition (by least squares fit of atoms C1-C7 and N1 atoms) for compound **3-5** shown in two views. a) molecules of compound **3a** in blue and **3b** in red; b) molecules of compound **4a** in blue and the two molecules in the asymmetric unit of **4b** in red and orange; c) molecules of compound **5a** in blue and **5b** in red.

Table 2. Crystallographic Information for compounds **2-5**. Two polymorphs have been found for each of these compounds.

	2a	2b	3a	3b	4a	4b	5a	5b
Formula	C ₁₄ H ₁₁ NO ₂	C ₁₄ H ₁₁ NO ₂	C ₁₈ H ₁₇ N ₃ O ₂	C ₁₈ H ₁₇ N ₃ O ₂	C ₁₈ H ₁₅ N ₃ O ₂	C ₁₈ H ₁₅ N ₃ O ₂	C ₂₁ H ₁₇ NO ₃	C ₂₁ H ₁₇ NO ₃
Formula weight	225.24	225.24	307.35	307.35	305.33	305.33	331.36	331.36
Temperature (K)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2/ <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> bca
a (Å)	4.5532(1)	3.8949(1)	13.4793(8)	4.2509(7)	8.2469(2)	30.2956(11)	5.9682(3)	8.7529(4)
b (Å)	15.0996(4)	25.1426(8)	6.6293(4)	11.363(3)	8.2333(2)	8.2672(3)	12.0166(6)	9.5545(4)
c (Å)	16.1510(5)	16.8477(5)	18.5481(12)	31.115(6)	22.0039(5)	26.5597(9)	22.9633(12)	39.9926(17)
α (°)	90	90	90	90	90	90	90	90
β (°)	96.515(2)	95.522(2)	108.540(2)	90	95.544(2)	117.346(2)	90.091(4)	90
γ (°)	90	90	90	90	90	90	90	90
Cell volume (Å ³)	1103.23(5)	1642.20(8)	1571.41(17)	1502.9(5)	1487.1	5908.8(4)	1646.87(14)	3377.6(3)
ρ _{calc} (g/cm ³)	1.356	1.367	1.299	1.358	1.364	1.373	1.336	1.316
Z	4	6	4	4	4	16	4	8
Z'	1	1.5	1	1	1	2	1	1
Data/Parameters	2650/158	2575/145	3786/216	2769/209	3585/212	6444/423	2512/227	2867/229
R1/wR2	0.042/0.10	0.040/0.07	0.044/0.11	0.050/0.13	0.041/0.10	0.052/0.10	0.060/0.17	0.035/0.09
GOF	1.030	0.870	1.060	1.009	1.012	1.011	1.112	1.073

Table 3. Selected torsion angles (°) for molecules in polymorphs 1-5. Also included are the interplanar angles between the least squares planes defined by two phenyl rings in the phenylbenzamide moiety.

	abcd	bcdf	bcde	edfg	Bz/Ph interplanar angle
1a	157.2	177.4	-1.2	31.9	13.6
1b	169.9	-177.0	1.8	21.1	2.7
2a	-175.8	177.3	-2.7	8.0	11.7
2b-m1	-179.7	175.9	-3.6	-6.2	8.9
2b-m2	-174.5	178.5	-0.6	-5.9	3.9
3a	159.9	-176.1	3.3	23.6	6.9
3b	163.9	-178.2	-1.5	25.5	9.6
4a	176.3	-179.5	0.8	-0.1	3.9
4b-m1	169.7	-173.9	5.7	17.0	11.1
4b-m2	172.7	-178.2	1.8	-3.2	10.3
5a	149.8	-176.1	3.4	32.3	5.0
5b	61.2	172.1	-7.0	20.6	78.5

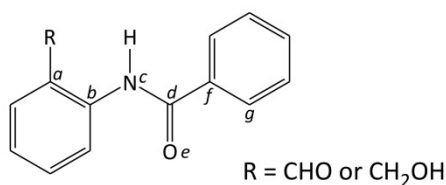


Table 4. Conformation energies for molecules in polymorphs of 1b-5b (kJ/mol) relative to polymorphs 1a-5a as calculated with M06-2X/6-311++G(d,p) using *Gaussian-09*. The calculation was only carried out for the ordered molecule for polymorphs 2b and 4b.

Compound	Polymorph b
1	0.9
2	0.4
3	7.1
4	11.2
5	13.8

Crystal packing

The dominant influences on these crystal structures are O-H...O hydrogen bonding, C-H...O and C-H... π interactions, and dispersion forces (usually referred to as π ... π interactions) between neighbouring aromatic rings. It is the interplay between these that determines the nature of each polymorph. As mentioned in our previous paper,⁷ the extent of the influence of the π ... π interactions in these molecules is easily overlooked if the usual ring centre to ring centre (Cg...Cg) measurement is done. The extent of the contribution of the π ... π interactions to the stability of each polymorph is instead more easily determined by calculation of the weak interactions acting between the molecules using a program such as *PIXEL*.¹⁷ *PIXEL* as a

consequence has been used to evaluate all the structures reported here. The results of these calculations are listed in Table 6 for the similar compounds 1 and 2, Table 7 for compounds 3 and 4, and Table 8 for compound 5. At least two most important interactions as calculated by *PIXEL* have been drawn and these can be found in the electronic supporting information.

It should be noted that for simplicity we refer to π ... π interactions as any interaction in which the molecules receive significant stabilization by significant π overlap over another molecule regardless of whether the aromatic ring centroid to aromatic ring centroid distance (usually referred to as Cg...Cg distances) is exceptionally short. An examination of molecule...molecule interaction energies from the *PIXEL* calculations show that the most significantly stabilized molecule...molecule interactions incorporate very significant favorable contributions from Coulombic, polarization as well as dispersion effects (Tables 6-8).

The crystal structures of the polymorphs of 1 have previously been reported by us and as a consequence only the key characteristics of these structures relevant to this discussion are presented here.

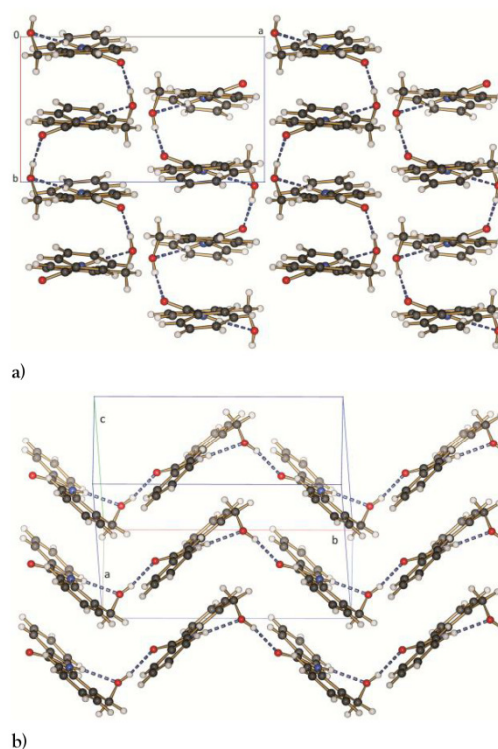


Figure 3. Intermolecular hydrogen bonding in the polymorphs of 1. a) Crystal packing of 1a down the c axis; the hydrogen bonded chain along the b axis together with the π ... π overlap between the molecules can be clearly seen. b) These interactions in 1b are separated from each other leading to hydrogen bonded chains along the b axis which then interact with neighboring chains through π ... π interactions.

Since strong hydrogen bonding, if possible, contributes significantly to the stability of a structure, it almost always has to be present. There are very few exceptions with an example in this work being the polymorphs of **5**. As a consequence, hydrogen bonding in **1** links these molecules into chains in each polymorph as shown in Figure 3. Strong hydrogen bonding is a very directional interaction as the best hydrogen donating group will interact best with the best available hydrogen accepting group so as to form the strongest hydrogen bond possible in a structure.²⁰ It is by nature an atom...atom interaction that determines the point of contact between two molecules in a structure. As can be seen in Figure 3, hydrogen bonding forces the molecules together to form chains but does not control the orientation of the molecules with respect to each other. By contrast, $\pi\cdots\pi$ interactions are at their strongest when the molecules involved overlap significantly over each other with the best stabilization occurring when the repulsive electrostatic interactions between the molecule is at a minimum. Compound **1** in the two polymorphs has adopted two approaches to stabilize the structure via $\pi\cdots\pi$ interactions. In **1a**, the influence of the $\pi\cdots\pi$ interactions causes the molecules to overlap within a hydrogen bonding chain, while in **1b** it is the $\pi\cdots\pi$ interactions between the chains of molecules which stabilize the structure. In other words, the different packing in the two structures is due to the different application of $\pi\cdots\pi$ interactions to the stability of each structure. C-H...O interactions act to further stabilize each structure. The combination of the $\pi\cdots\pi$ and O-H...O hydrogen bonding between molecules in **1a** results in a significant interaction energy between these molecules, with this geometry contributing -62.8 kJ/mol while the next most significant molecule...molecule interaction only contributes -23.5 kJ/mol to the structure (Table 6). By contrast, the separation of the O-H...O and $\pi\cdots\pi$ interaction results in a structure in which the interactions of a reference molecule with its neighbors are more uniform in strength. In this case the molecule...molecule interactions between hydrogen bonded molecules contributes -37.8 kJ/mol to the structure, while the $\pi\cdots\pi$ overlap contributes -27.8 kJ/mol to the structure. It is interesting to note that *PIXEL* attributes the strength of the $\pi\cdots\pi$ interaction as being almost entirely due to dispersion (Table 6). Also, the sum of these interactions (-65.6 kJ/mol) is almost identical to the energy of the combined interaction present in **1a** (-62.8 kJ/mol). The geometries of the two most stabilizing interactions are illustrated in Figure S1 in the supplementary information.

The alcohol group present in compound **1** has been replaced by an aldehyde group in compound **2**. Compound **2** also crystallizes as two polymorphs with their crystallographic details shown in Table 2. A feature common to the two polymorphs is the centrosymmetrically C-H...O hydrogen bonded dimer highlighted in Figures 4 and 5. The differences between polymorphs **2a** and **2b** depends on how these arrange in each structure. *PIXEL* calculations indicate that these dimers are moderately significant to the stability of the structure contributing -17.4 kJ/mol in **2a** and -17.9 kJ/mol in **2b**. They provide a useful feature for the comparison of the two structures and may also provide a kinetic path towards the structures during crystallization by aligning pairs of molecules in this way before the molecules start stacking through $\pi\cdots\pi$ interactions. The issue is not discussed here, but it is interesting to note that the success of crystal structure prediction over the last few years has shown that the overall thermodynamic stability of the crystal structure is more important than any individual interaction, as accurate lattice energies are the primary selection criterion used in the

prediction procedure.^{21,22} The existence of polymorphs in which strong hydrogen bonding is absent in one of the polymorphs is a key example of this (see compound **5** and the discussion of the polymorphs of *p*-tosylhydrazine in reference 23). The significant influence of kinetics is, however, revealed through the existence of the phenomenon of polymorphism. The $\pi\cdots\pi$ interaction between molecules which stack on each other upon cell translation along the *a* axis (the molecules therefore being eclipsed on each other along the stacking direction) contributes -31.2 and -28.7 kJ/mol (calculated for the ordered molecule) to structures **2a** and **2b**, respectively. The lack of strong hydrogen bonding in the polymorphs of **2** allows the molecules to arrange in different ways. Polymorph **2a** crystallizes with one molecule in the asymmetric unit in which the C-H...O hydrogen bonded dimer is transposed according to the space group operations along the *b* and *c* axes. By contrast, **2b** crystallizes with one and half molecules in the asymmetric unit where one molecule is disordered over a centre of inversion. The ordered molecules (molecule A) outnumber the disordered molecules (molecule B) by a ratio of 2:1. In this structure the molecules act as 'host' and 'guest' with respect to each other. The ordered molecules form the 'host' structure, while the disordered molecules include themselves in channels created by the 'host' structure as shown in Figure 5. The presence of the disordered molecule leads to the layered structure of **2a** being converted to the cross hatched structure of **2b**. The orientation of the disordered molecules (shown in green) relative to the ordered molecules can be clearly seen in Figure 5b. It is interesting to note that the disordered molecules do form C-H...O interactions with the 'host' molecules, but as the interactions are strongest between the phenyl groups and the amide oxygen (Figure 5a), they effectively allow the molecule to rotate along its length, and therefore do influence the orientation of these molecules which leads to the observed disorder. With respect to whether the disordered molecule is related by an inversion or translation to the next molecule along the stack axis, *PIXEL* calculations indicate that inversion is slightly favoured suggesting that the molecules might be arranging with inversion symmetry along the disordered stack. This is discussed further below when the lattice energies of the various polymorphs are considered. A list of weak interactions present in the polymorphs of **2** is given in Table 5, while the geometries of these interactions are listed in Tables S1 and S2 in the supplementary information. In general, the *PIXEL* calculations indicated that the environments around each molecule in **2a** and **2b** as measured molecule...molecule interaction energies is relatively uniform, though slightly stronger interactions are present in **2a**. The geometries of the two most stabilizing interactions are illustrated in Figure S2 in the supplementary information.

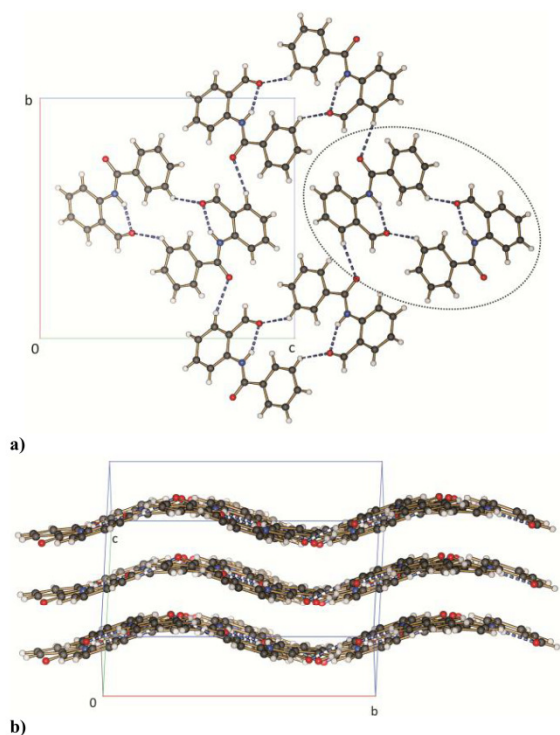


Figure 4. a) Crystal packing of compound **2a** viewed down the *a* axis; the common C-H...O dimer present in both polymorphs of **2** is indicated. b) These molecules interact through C-H...O interactions to form a layered structure with $\pi\cdots\pi$ interactions between the layers.

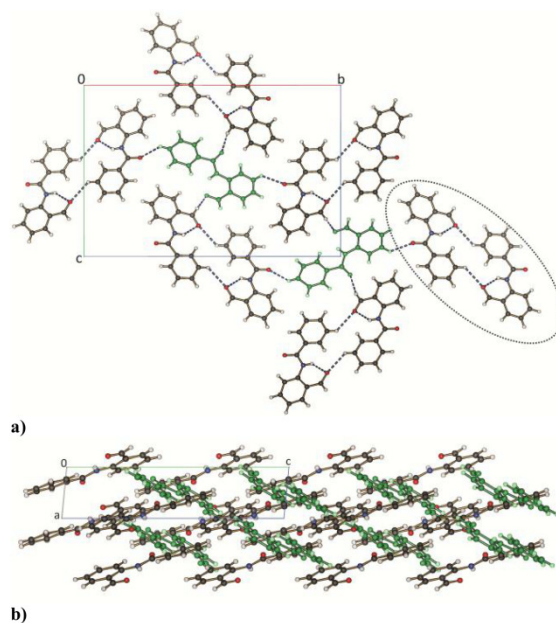


Figure 5. a) Crystal packing of compound **2b** composed of ordered and disordered molecules viewed down the *a* axis; the common C-H...O dimer of **2** is highlighted and is composed of the ordered molecules. These create host channels into which the disordered guest arrange in two orientations (one orientation shown in green). C-H...O and $\pi\cdots\pi$ interactions can be clearly seen but the orientation of the disordered molecules create a crosshatched arrangement of molecules as in b).

Compound **3** is an imidazole-containing derivative of compound **1**. The conformation is, on the whole, different in polymorphs **3a** and **3b** with the imidazole pointing in opposite direction in each molecule (Figure 2). In both polymorphs, the alcohol group hydrogen bonds to the more basic imidazole group (the strongest hydrogen acceptor in the molecule) of a neighbouring molecule rather than to another alcohol group. These hydrogen bonds in **3a** result in the molecules arranging in the form of a spiral resembling a tightly coiled spring in the direction of the *b* axis of the unit cell in which each molecule is symmetrically related to the next by a 2_1 screw axis (Figure 6). Spirals of hydrogen bonded molecules interact with neighbouring molecules through C-H...O interactions involving an imidazole ring hydrogen and the amide oxygen atom, or through C-H... π interactions in which a phenyl group acts as hydrogen donor and the imidazole as π acceptor. The hydrogen bonding is similar in **3b** but the spiral is now stretched out to form a chain like structure in which each molecule is situated behind the previous one along the *b* axis (Figure 7). Here the molecules are also aligned by a 2_1 screw axis but are spaced further apart. Molecules in each of these chains then interact through π ... π interactions with molecules related by translation along the *a* axis in an arrangement very similar to polymorph **1b** (Figure 2b). Noteworthy is that **3a** crystallizes in a centrosymmetric space group ($P2_1/n$) while **3b** crystallizes in a chiral space group ($P2_12_12_1$). According to the *PIXEL* calculations (Table 7), the molecule...molecule interaction contributing most to the structure of **3a** is the one associated with the hydrogen bonded pattern (-67.8 kJ/mol). There is also a centrosymmetric dimer similar to the one mentioned in the polymorphs of **2** which is held together by two C-H...O and two C-H... π interactions (-48.8 kJ/mol), and which brings neighbouring hydrogen bonded chains together (Figure 6b). The most important molecule...molecule interactions in **3b** are those associated with the hydrogen bonding (-73.7 kJ/mol) as well as the π ... π interaction in which the molecules overlap by translation along the *a* axis (-39.6 kJ/mol). The geometries of the two most stabilizing interactions are illustrated in Figure S3 in the electronic supplementary information.

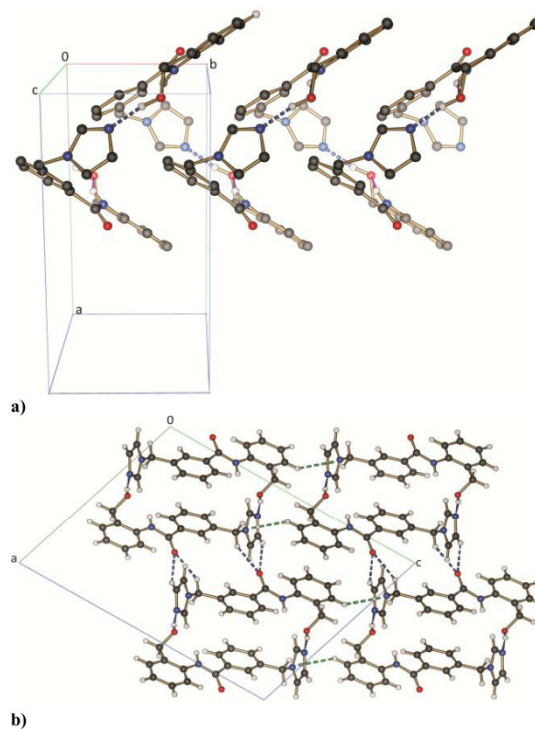


Figure 6. a) O-H...N hydrogen bonded spiral down the *b* axis present in **3a**. b) These interact with neighboring spirals through C-H... π and C-H...O interactions.

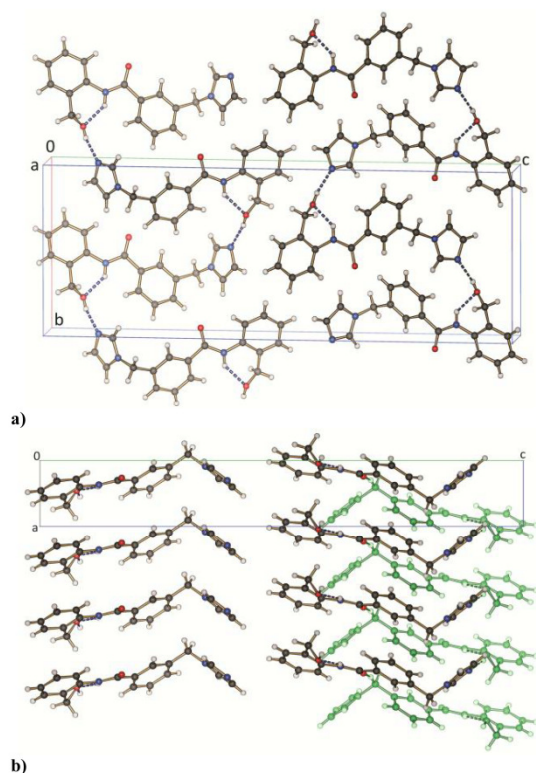


Figure 7. a) The O-H...N spirals present in **3a** are stretched out to form a more layer-like chain in **3b**. b) These interact with each other through $\pi\cdots\pi$ interactions in a manner similar to **1b**. These $\pi\cdots\pi$ stacks are related to each other by a 2_1 screw axis down the *b* axis as shown in green.

Table 5. List of intermolecular interaction types present in the polymorphs of 1-5. The presence of hydrogen bonds and $\pi\cdots\pi$ interactions was determined using *PLATON*. The presence of $\pi\cdots\pi$ interactions was also determined by visual inspection of the molecule...molecule interactions with significant π overlap contributing 15 kJ/mol or more to the stability of the structure as determined by *PIXEL*. Strong intramolecular hydrogen bonding, if present, has also been indicated.

Polymorph	Interactions
1a	NH...O (intra), O-H...O, C-H...O, $\pi\cdots\pi$
1b	NH...O (intra), O-H...O, C-H...O, $\pi\cdots\pi$
2a	NH...O (intra), C-H...O, C=O... π , $\pi\cdots\pi$
2b	NH...O (intra), C-H...O, $\pi\cdots\pi$
3a	NH...O (intra), O-H...N, C-H...O, C-H... π
3b	NH...O (intra), O-H...N, C-H...O, $\pi\cdots\pi$
4a	NH...O (intra), C-H...N, C-H...O, $\pi\cdots\pi$
4b	NH...O (intra), C-H...O, C-H...N, C=O... π , C-H... π , $\pi\cdots\pi$
5a	NH...O (intra), C-H...O, C-H... π , $\pi\cdots\pi$
5b	NH...O (inter), C-H...O, C-H... π , $\pi\cdots\pi$

Molecules in **4a** pack in a zig-zag like pattern while those in **4b** pack as layers. Compound **4** is an imidazole-containing derivative of compound **2** and related to compound **3** by conversion of the alcohol to an aldehyde. Strong hydrogen bonding is, as a consequence, absent in both structures and is instead replaced by C-H...N interactions. These in **4a** occur between imidazole groups located on the folds of the zig-zag pattern and link molecules in neighbouring stacks together. Molecules in **4b** form C-H...O linked layers composed of either **A** or **B** molecules. These are then linked together by C-H...N interactions between neighbouring imidazole groups. Both structures contain molecules held together by $\pi\cdots\pi$ interactions. These in **4a** act between pairs of molecules (dimers) related by centers of inversion, while in **4b** they bind four molecules together to form a tetramer in which the sequence of molecules is A...B...B...A (Figure 9). This tetramer stacks on its neighbours to create the layered packing, but is rotated by about 90° with respect to the tetramer below and above it so that only partial overlap occurs between neighbouring tetramers. Weak interactions present in **4a** and **4b** are listed in Table 5. *PIXEL* calculations indicate that the two most significant molecule...molecule interactions in **4a** involve a C-H...O stabilized centrosymmetric dimer (-36.7 kJ/mol) followed by the centrosymmetric $\pi\cdots\pi$ interaction (-36.6 kJ/mol). The most significant molecule...molecule interactions in **4b** involve a $\pi\cdots\pi$ interaction within the tetramer (-49.0 kJ/mol) as well as two arrangements which support C-H...O interactions along the *b* axis of the unit cell which stabilise the structure by -32.9 and -32.3 kJ/mol respectively (Table 7). The geometries of the three most stabilizing interactions of **4a** and two most stabilizing interactions of **4b** are illustrated in Figure S4 in the supplementary information.

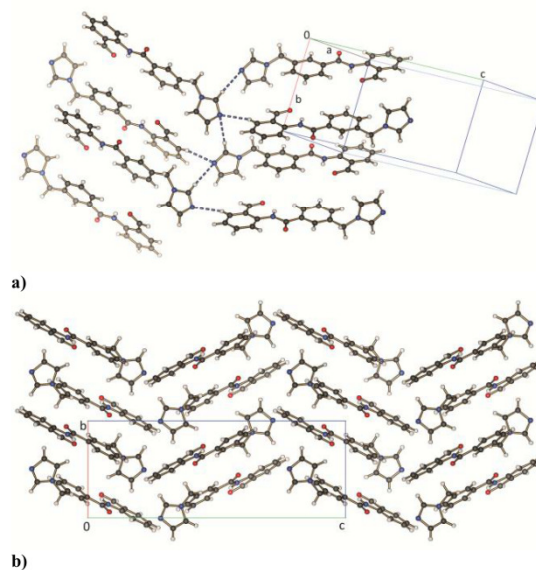


Figure 8. a) A dominant $\pi\cdots\pi$ interaction leads to the formation molecular dimers in **4a**. These are brought together by together by the C-H...N interactions between imidazoles on neighboring dimers. b) The geometry adopted by C-H...N interactions also result in zig-zag like packing.

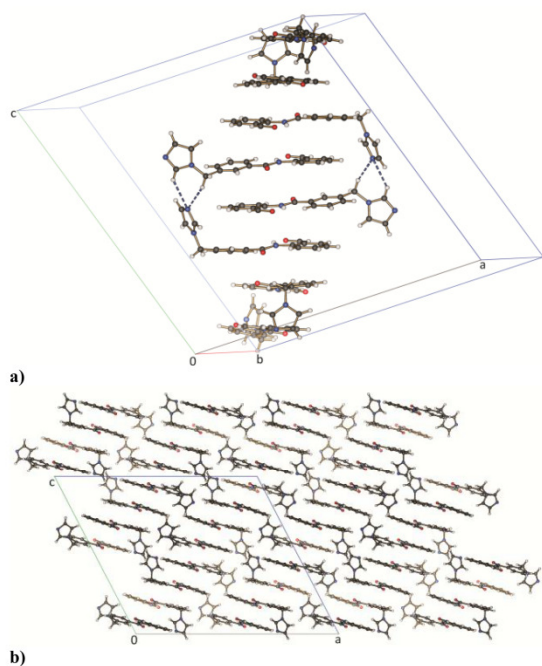


Figure 9. The structure of **4b** is dominated by $\pi\cdots\pi$ interactions. a) The strongest of these result in a tetramer of π stacked molecules which can be viewed as the building unit of this structure. Reinforcing this formation are C-H $\cdots$ N interactions between imidazoles on molecules within the tetramer. b) The layered structure is created by the assembly of tetramers which are rotated by about 90° with respect to the neighboring ones above and below them which results in the layered structure.

Compound **5** is derived from compound **1** by esterification of the alcohol group with benzoic acid. The molecule adopts a very different conformation in polymorphs **5a** and **5b** especially around the amide group. The conformation of the phenylbenzamide is almost planar in **5a** while the phenyl and benzamide groups are twisted almost perpendicularly to each other in **5b**. This leads to different hydrogen bond behavior in each structure: the almost planar conformation of the phenylbenzamide group leads to intramolecular N-H $\cdots$ O hydrogen bonding in **5a** resulting in molecules which are not connected by strong intermolecular hydrogen bonding, while the twisted conformation in **5b** allows chains of N-H $\cdots$ O hydrogen bonded molecules to be formed along the *b* axis. This phenomenon in which a compound is able to crystallize as a close packed structure with no hydrogen bonding, and another in which hydrogen bonding is present is very rare,²³ and is a consequence of the two different molecular conformation adopted by **5**. Polymorph **5a** can be described as being made up of C-H $\cdots$ O stabilized layers of molecules which stack along the *c* axis. These C-H $\cdots$ O interactions within each layer link up chains of molecules along the *a* and *b* axis (Figure 10a). These layers are linked together by C-H $\cdots\pi$ and $\pi\cdots\pi$ interactions between benzoate groups on the edges of neighboring layers (Figure 10b). The chains of **5b** are

not only stabilized by N-H $\cdots$ O hydrogen bonding, but also by additional C-H $\cdots$ O and C-H $\cdots\pi$ interactions (Figure 11a). There are also $\pi\cdots\pi$ interactions between the benzoate groups on neighboring chains. C-H $\cdots\pi$ interactions are present between the benzamide groups on adjacent chains (Figure 11b). For **5a**, PIXEL calculations indicate that the most important molecule $\cdots$ molecule geometry (-50.4 kJ/mol) is the one in which molecules are linked together along the *a* axis by C-H $\cdots$ O and C-H $\cdots\pi$ interactions. The molecules also partially overlap allowing dispersion to contribute (-67.6 kJ/mol; see Table 8) significantly to the interaction energy. For comparison, the molecule $\cdots$ molecule geometry supporting the C-H $\cdots$ O hydrogen bonded chain along the *b* axis (Figure 10a) only contributes about -34.0 kJ/mol. This is due to dispersion (-39.4 kJ/mol) contributing less to this interaction because the molecules along the chain only overlap moderately. The next most important molecule $\cdots$ molecule interaction (-38.8 kJ/mol) is one in which the benzoate groups on neighboring layers interact through $\pi\cdots\pi$ and C-H $\cdots\pi$ interactions as shown in Figure 10b. A key difference between the two polymorphs is that the strength of interactions around a molecule in **5a** is relatively uniform, while in **5b** there is a dominant interaction followed by much weaker ones. For **5b**, the strongest molecule $\cdots$ molecule interaction is between molecules involved in the N-H $\cdots$ O hydrogen bonded chain (-71.0 kJ/mol) along the *b* axis. The strength of this interaction is also due to the presence of a C-H $\cdots\pi$ and two C-H $\cdots$ O interactions between the molecules. The next strongest geometry contributes only -21.1 kJ/mol, and supports the C-H $\cdots\pi$ interaction between neighboring N-H $\cdots$ O chains. The geometries of the three most stabilising interactions are illustrated in Figure S5 in the supplementary information.

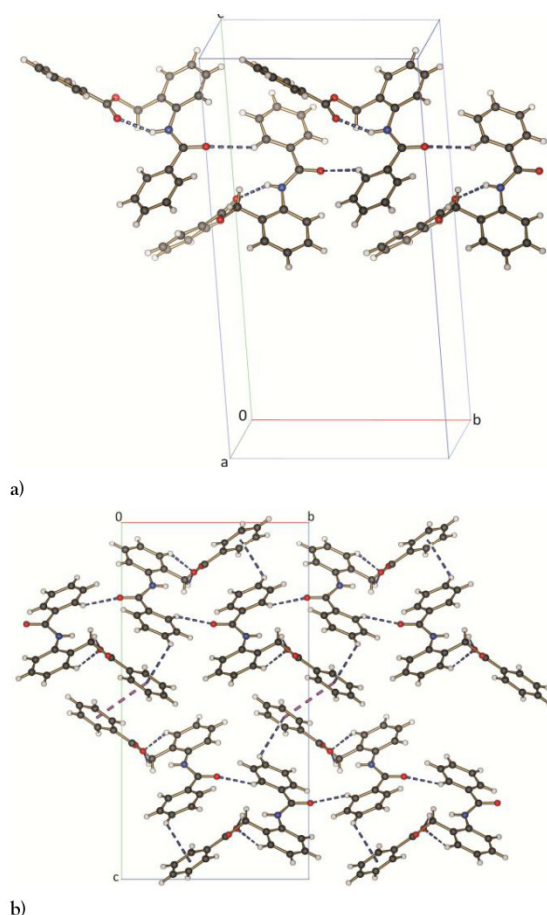


Figure 10. a) C-H...O bound chain along the *b* axis of polymorph **5a**. b) Neighboring chains are held together by C-H... π and π ... π interactions between benzyl esters on neighboring molecules. Strong N-H...O interactions are prevented from occurring in this structure due to the planar conformation of the phenylbenzamide group.

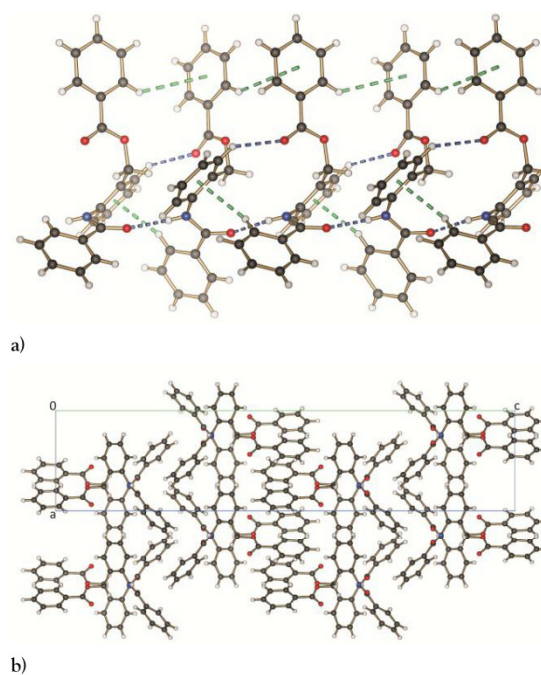


Figure 11. a) The molecular conformation adopted by **5b** allows strong N-H...O hydrogen bonding to occur, resulting in the formation of a chain of hydrogen bonded molecules down the *b* axis. Molecules within this chain are also kept together by C-H... π and C-H...O interactions. b) As in **5a**, neighboring chains are held together by π ... π interactions between the benzyl ester groups.

Lattice energy calculations

Lattice energies for polymorphs **1a-5b** is given in Table 9. With the exception of compound **2**, all of these were calculated using *PIXEL*. The lattice energies for compound **2** were calculated using the atom-atom potential method *AA-CLP* as *PIXEL* cannot calculate a lattice energy for a structure containing more than two molecules. In order to calculate a lattice energy for **2b**, in which the presence of the disordered molecule causes problems, the symmetry of the structure was lowered from $P2_1/c$ to $P2_1$ and the *a* axis doubled allowing the disordered molecule to be treated as an ordered molecule in one of two possible orientations with respect to the molecule stacked above and below it. This allowed a lattice energy to be calculated using the assumption that the molecules stack by cell translation above and below it (a kind of eclipsed geometry) leading to a lattice energy of -119.7 kJ/mol, or the assumption that molecules along the stack are related to each other by a center of inversion which lead to a calculated lattice energy of -121.8 kJ/mol. This difference suggests that the disordered molecules are probably related by a center of inversion along the stack.

In general, the relative energies given in Table 9 show that the energy difference between various polymorphs is less than 4 kJ/mol. The only exception is for **4b** where the difference is almost 15 kJ/mol. This difference may be because only the intramolecular energy of the ordered molecule was taken into

account in the calculation. Refining a disordered molecule often results in a structure whose conformation is less than ideal, and in this case resulted in intramolecular energies that were significantly higher than that of the ordered molecule. The energies of the disordered molecule were therefore omitted from the calculation but the overall result has been kept to allow comparison with the energies of the other compounds. The most interesting calculations are for compounds **3** and **5**. In both cases the intramolecular energy of the second polymorph is significantly higher than that of the first polymorph but the final relative energies differ by less than 3 kJ/mol. It is interesting to note that the significant change in conformation for **5b** results in the molecule being at a significantly higher energy, but that the advantage in forming the intermolecular N-H...O pattern compensates significantly resulting in a lower lattice energy.

Table 9. Intramolecular, lattice and relative energies of compounds **1** to **5** (kJ mol⁻¹). With the exception of compound **2**, lattice energies were calculated using *PIXEL*, while the relative intramolecular energies were calculated with the M06-2X DFT functional using Gaussian-09 and a 6-31++G(d,p) basis set. The lattice energies for **2** were calculated with *AA-CLP*.

Polymorph	M06-2X	Lattice Energy	Relative Energy
1a	0	-130.6	-130.6
1b	0.90	-127.5	-126.6
2a	0	(-118.7)	(-118.7)
2b	0.36	(-119.7)/(-121.8)	(-119.34)/(-121.44)
3a	0	-196.4	-196.4
3b	7.07	-200.4	-193.3
4a	0	-156.7	-156.7
4b	11.21	-153.2	-142.0
5a	0	-154.3	-154.3
5b	13.79	-166.1	-152.3

Phenylbenzamide as a promoter of polymorphism

The diversity of polymorphs presented so far raises the question whether the phenylbenzamide component is able to encourage polymorphism or not. In order to check for a general trend, a search for structures containing the phenylbenzamide group was carried out in the Cambridge Structural Database²⁴ (CSD; Version 5.34, 2013 release with Nov 2012 update) resulting in 982 unique compounds (including compound **1** as Refcodes AWEWAB and AWEWAB01) after the removal of obvious duplicate entries (such as AWEWAB01 in this case). Of these, 23 compounds have at least one reported polymorph, three have been reported for 8-Methoxy-N-phenyl-1-naphthamide (TAWRIT, TAWRIT01 and TAWRIT02), one compound has been reported to exist as two DMF solvate polymorphs (PIWBUT and PIWBUT01), and one reported as two polymorphs of a co-crystal (FENDUJ and FENDUJ01). The FENDUJ01 co-crystal may also contain solvent which is absent

in the structure included in the CSD but a search for voids does suggest that some solvent molecules may be present. A full list of Refcodes for these 23 compounds is given in the electronic supplementary information.

Only 23 polymorphic structures out of 982 compounds suggests that the phenylbenzamide group is incapable of encouraging polymorphism. However, it is likely that this group is interesting to researchers working on compounds for synthetic purposes and therefore not searching for polymorphs. Given the lack of an extensive number of reported polymorphs reasons have to be found as to why the phenylbenzamide moiety might have a propensity for forming polymorphs.

From the examination of crystal structures of compounds **1-5**, and ignoring the molecule specific O-H...O and O-H...N hydrogen bonding present in the structures of compounds **1** and **3** respectively, it is clear that a wide variety of intermolecular interactions is possible ranging from N-H...O hydrogen bonding involving the amide group, to C-H...O and C-H... π interactions and finally π ... π interactions (or at least interactions with a significant dispersion component as calculated with *PIXEL*). The interplay of the various interactions may therefore play a role in encouraging polymorphism.

Another clear phenomenon noted when examining these structures and those displaying polymorphism in the CSD, is that the phenylbenzamide group can easily bend and twist leading to various conformations and conformational polymorphism.

Finally, the phenylbenzamide group has a special electronic property that becomes apparent when the electrostatic potential is plotted on the electron density surface of a molecule. The ESP diagrams for compounds **1** and **2** are shown in Figure 12. All four of these diagrams also indicate a π ... π interaction present in each of the structures. The diagrams are colored such that blue represents the electropositive areas in which hydrogen atoms usually present, while red represents electronegative areas where the nitrogen atom, oxygen atoms and the π electron charge of the benzene rings is present. What is clear when the electrostatic potential diagram of any of these molecules is scanned from left to right is an alternating sequence of positive and negative areas. This means that a molecule interacting with it in a π ... π manner will be able to find a number of orientations to do so, and we believe this to be another factor which encourages polymorphism. This is especially clear when the two π ... π interactions shown in Figure 12 for compound **2** are examined. In each case the upper molecule has maintained its orientation but has located itself on a different area of the lower molecule. It is interesting to note that the electrostatic potential of the molecule is blurred out when mapped onto a Hirshfeld surface as shown in Figure 12. The diagrams also show that the mapping of electrostatic potential onto the Hirshfeld surface is sensitive to crystal packing.

So, do we believe that the phenylbenzamide group encourages polymorphism? Considering that this group is capable of a variety of weak interactions and is also conformationally flexible enough to allow different interactions to become dominant in a structure, and that the electrostatic surface of the group is complex enough to allow a variety of π ... π interactions to occur, we believe it to be a strong possibility. The fact that we were able to find the five pairs of polymorphs discussed in this work without undue effort makes the possibility interesting. If nothing else, the possibility is appealing because of the ease with which benzoic acids and aniline type compounds can be converted to the phenylbenzamide group. It may therefore be possible to convert

a compound that is reluctant to form polymorphs to one that does so easily. Such modification of compounds might also find

application in the pharmaceutical industry as amides are a common functional group in biological systems.

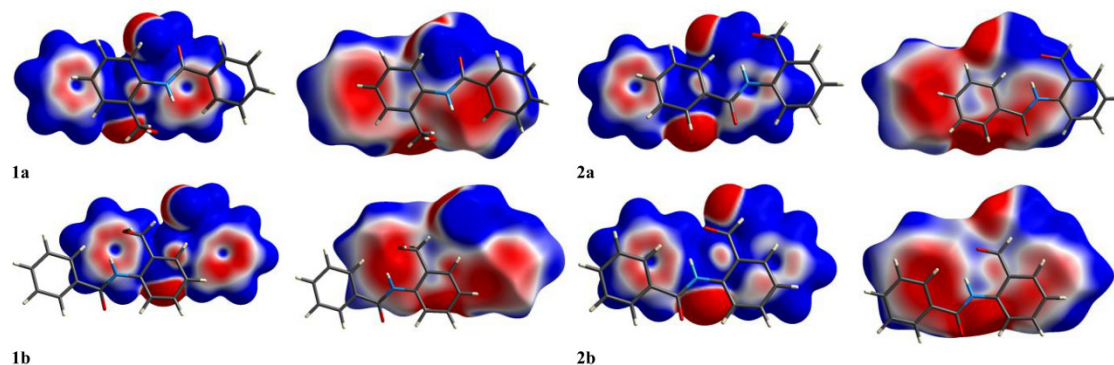


Figure 12 Electron density (left; 0.008 isosurface level) and Hirshfeld surface diagrams (right) on which the electrostatic potential is mapped. The colors range from -50 kJ/mol (-0.019 au) shown in red, 0 kJ/mol in white and +50 kJ/mol (+0.019 au) in blue for compounds 1 and 2 (polymorphs have been indicated).

Table 6. Molecule...molecule interaction energies contributing most to the stability to the polymorphs of 1 and 2 as calculated using *PIXEL* (kJ mol⁻¹).

Symmetry (molecule pair)	Total	Coulombic	Polarization	Dispersion	Repulsion
Polymorph 1a					
1.5-x, -0.5+y, 1.5-z	-62.8	-54.1	-24.1	-60.4	75.8
2-x, -y, 1-z	-23.5	-11.3	-4.3	-25.1	17.1
1-x, -y, 1-z	-20.3	-6.5	-6.2	-27.9	20.2
0.5+x, -0.5-y, 0.5+z	-14.8	-7.6	-2.8	-10.9	6.5
1.5-x, 0.5+y, 0.5-z	-8.3	-2.0	-0.5	-8.0	2.1
2-x, -y, 2-z	-7.5	1.3	-1.9	-14.6	7.7
Polymorph 1b					
1.5-x, 0.5+y, 0.5-z	-37.8	-46.3	-21.6	-26.5	56.6
1+x, y, z	-27.8	-2.6	-5.0	-46.1	25.9
2.5-x, 0.5+y, 0.5-z	-19.9	-11.8	-3.6	-12.5	8.0
1-x, 2-y, -z	-18.6	-7.1	-2.7	-22.0	13.2
0.5+x, 1.5-y, 0.5+z	-13.1	-5.3	-1.6	-13.7	7.5
1.5+x, 1.5-y, 0.5+z	-7.9	-2.7	-1.5	-11.7	8.1
Polymorph 2a					
1+x, y, z	-31.2	-5.5	-3.7	-50.7	28.7
-0.5-x, 0.5+y, 1.5-z	-19.0	-12.8	-4.7	-16.8	15.2
1-x, 1-y, 1-z	-17.4	-7.9	-5.1	-23.6	19.1
0.5-x, 0.5+y, 1.5-z	-12.9	-4.3	-2.1	-15.7	9.2
0.5+x, 0.5-y, -0.5+z	-12.8	-5.2	-1.3	-12.5	6.4
-x, 1-y, 1-z	-7.4	2.2	-0.9	-12.0	3.3
Polymorph 2b (ordered molecule only)					
1+x, y, z	-28.7	-2.6	-3.9	-55.4	33.2
-x, 1-y, -z	-17.9	-7.7	-3.8	-19.6	13.1
x, 1.5-y, 0.5+z	-10.0	-4.6	-1.8	-11.5	7.9
1-x, 1-y, -z	-9.0	-2.0	-0.7	-10.7	4.4
1+x, 1.5-y, -0.5+z	-8.4	-2.5	-0.9	-8.4	3.5

Table 7. Molecule...molecule interaction energies contributing most to the stability to the polymorphs of 3-4 as calculated using *PIXEL* (kJ mol⁻¹).

Symmetry (molecule pair)	Total	Coulombic	Polarization	Dispersion	Repulsion
Polymorph 3a					
0.5-x, 0.5+y, 0.5-z	-67.8	-95.6	-55.2	-55.3	138.3
1-x, -y, 1-z	-48.8	-31.3	-12.5	-39.8	34.8
x, 1+y, z	-34.4	-12.8	-4.3	-32.7	15.3
1-x, 1-y, 1-z	-21.9	-14.1	-7.9	-27.6	27.6
0.5+x, 0.5-y, -0.5+z	-19.3	-10.7	-3.9	-18.2	13.5
1.5-x, 0.5+y, 0.5-z	-19.1	-8.5	-2.8	-20.0	12.2
1-x, 1-y, -z	-14.4	-5.4	-1.1	-10.5	2.6
Polymorph 3b					
1-x, 0.5+y, 1.5-z	-73.7	-86.8	-43.9	-45.9	103.0
1+x, y, z	-39.6	-6.6	-10.3	-67.9	45.2
2-x, 0.5+y, 1.5-z	-32.6	-15.7	-9.2	-33.5	25.8
0.5+x, 0.5-y, 2-z	-11.6	-4.6	-3.8	-17.0	13.8
1.5-x, 1-y, 0.5+z	-7.9	-3.2	-1.8	-8.4	5.5
0.5-x, 1-y, 0.5+z	-7.2	-3.6	-0.8	-4.5	1.8
Polymorph 4a					
-x, -y, -z	-36.7	-21.8	-6.5	-31.0	22.6
1-x, -y, -z	-36.6	-2.0	-7.0	-72.1	44.5
1-x, 1-y, -z	-32.9	-11.9	-4.8	-38.6	22.4
-x, 1-y, -z	-30.1	-13.3	-6.4	-43.9	33.6
1+x, y, z	-28.4	-17.3	-5.3	-24.6	18.9
1.5+x, 0.5-y, 0.5+z	-17.5	-13.6	-5.1	-10.1	11.3
-0.5-x, 0.5+y, -0.5-z	-17.4	-13.7	-5.1	-11.1	12.5
0.5+x, 0.5-y, 0.5+z	-16.0	-2.7	-3.6	-20.6	11.0
1.5-x, 0.5+y, 0.5-z	-8.9	-0.7	-0.9	-11.7	4.4
Polymorph 4b					
1-x, 1-y, 1-z (m1_m2)	-49.0	-14.5	-5.7	-70.9	42.1
1-x, -y, 1-z (m2_m2)	-32.9	-11.0	-5.7	-33.9	17.7
x, 1+y, z (m2_m2)	-32.3	-22.6	-8.0	-30.6	28.9
0.5-x, 0.5+y, 0.5-z (m1_m1)	-31.3	-11.2	-5.4	-43.4	28.6
1-x, 1-y, 1-z (m2_m2)	-28.1	0.6	-3.3	-55.6	30.2
x, 1+y, z (m1_m1)	-27.6	-22.7	-9.3	-29.2	33.6
x, y, z (m2_m1)	-24.8	-19.3	-8.1	-15.9	18.5
0.5-x, -0.5-y, 1-z (m1_m2)	-21.2	-12.6	-3.7	-10.4	5.5
0.5-x, 0.5-y, 1-z (m1_m1)	-20.8	-8.9	-1.6	-15.8	5.4
1-x, -y, 1-z (m1_m2)	-16.2	-6.3	-2.3	-10.9	3.3
x, 1-y, 0.5+z (m2_m1)	-15.7	-4.9	-1.3	-13.6	4.1
0.5-x, 0.5-y, 1-z (m1_m2)	-15.6	-4.7	-3.8	-15.7	8.6
1-x, y, 1.5-z (m2_m2)	-8.8	-3.0	-2.6	-15.4	12.1

Table 8. Molecule...molecule interaction energies contributing most to the stability to the polymorphs of 3-5 as calculated using *PIXEL* (kJ mol⁻¹).

Symmetry (molecule pair)	Total	Coulombic	Polarization	Dispersion	Repulsion
Polymorph 5a					
1+x, y, z	-50.4	-21.0	-9.0	-67.6	47.3
2-x, 1-y, 2-z	-38.9	-13.3	-4.5	-52.1	31.0
2-x, 0.5+y, 1.5-z	-34.0	-14.3	-7.9	-39.4	27.5
3-x, 0.5+y, 1.5-z	-17.7	-3.6	-3.9	-26.1	15.9
1-x, 1-y, 2-z	-13.6	-2.6	-1.8	-18.3	9.1
1-x, 2-y, 2-z	-8.9	-4.0	-1.5	-11.8	8.5
Polymorph 5b					
0.5-x, 0.5+y, z	-71.0	-55.2	-24.6	-67.0	75.8
0.5+x, 1.5-y, 1-z	-21.1	-7.3	-3.1	-28.2	17.6
-x, 2-y, 1-z	-18.1	-7.6	-3.2	-33.7	26.4
1-x, 2-y, 1-z	-15.0	-4.7	-3.4	-23.8	17.0
0.5+x, y, 0.5-z	-14.2	-4.5	-2.7	-20.2	13.3
1+x, y, z	-12.6	-3.1	-2.1	-15.7	8.3
-x, 0.5+y, 0.5-z	-9.5	-2.7	-1.4	-10.8	5.4

IN SUMMARY

The comparison of 5 pairs of polymorphs of five similar phenylbenzamide derivatives indicated that the structures are all unique. Strong O-H...O and O-H...N hydrogen bonds are present in the structures of compounds 1 and 3 respectively, while N-H...O hydrogen bonding is present in structure 5b but absent in structure 5a. Through the conformation of the phenylbenzamide is generally planar and consistent in the structures reported here, the molecule in 5b adopts a different conformation so as to allow an intermolecular N-H...O hydrogen. This N-H...O hydrogen bond is present as an intramolecular interaction in 5a. Examination of polymorphs of other compounds in the CSD indicates that phenylbenzamide can adopt a variety of conformations and form conformational polymorphs. Other weak forces such as C-H...O, C-H...N, C-H... π and π ... π interactions compete with each other resulting in polymorphs that have very little in common with each other or with the polymorphs of the other compounds reported here. An interesting observation is that π ... π interactions play a very significant role in most of the structures, but that the extent and nature of the interaction differs from structure to structure. A possible reason for this is revealed when the electrostatic potential is mapped onto the electron density of the phenylbenzamide group indicating an alternating pattern of positive and negative regions across the molecule. Neighboring molecules as a consequence can align to form π ... π interactions in a variety of orientations. The ease with which we have identified these five pairs of polymorphs, the variety of interactions adopted by each structure, the flexibility in π ... π interactions formed, and the variety of possible conformations adopted, suggests that the phenylbenzamide group may encourage polymorphism.

ASSOCIATED CONTENT

Crystal coordinates as CIF files for polymorphs 2a to 5b have deposited as supporting information. This material is available free of charge via the internet at <http://pubs.acs.org>. The CIF files can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) as 873577-873579. This material is available free of charge via the internet at <http://pubs.acs.org>.

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REFERENCES

- (1) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996-2000.
- (2) Fernandes, M. A.; Levendis, D. C.; Schoening, F. R. L. *Acta Crystallogr., Sect. B* **2004**, 60, 300-314.
- (3) Fernandes, M. A.; Levendis, D. C.; Schoening, F. R. L. *Acta Crystallogr., Sect. B* **2004**, 60, 315-324.
- (4) Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth Des.* **2005**, 5, 2180-2189.
- (5) Dunitz, J. D.; Gavezzotti, A. *Angew. Chem. Int. Ed.* **2005**, 44, 1766-1787.
- (6) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenninger, R. *J. Org. Chem.* **1998**, 63, 8084-8085.
- (7) Zipp, C.F.; Fernandes, M.A.; Marques, H.M.; Michael, J.P.; Perry, C.B. *Cryst. Growth Des.* **2011**, 11, 1431-1436.
- (8) Bruker. APEX2, 2.0-1 ed.; Bruker AXS Inc.: Madison, WI, USA, 2005.
- (9) Bruker. SAINT+, 6.0 (includes XPREP and SADABS) ed.; Bruker AXS Inc.: Madison, WI, USA, 2005.
- (10) Sheldrick, G. M., *Acta Crystallogr., Sect. A* **2008**, 64, 112-122.
- (11) Farrugia, L. J., *J. Appl. Crystallogr.* **1997**, 30, 565.
- (12) Keller, E. University of Freiberg, Germany, 1999.
- (13) Farrugia, L. J., *J. Appl. Crystallogr.* **1999**, 32, 837-838.
- (14) Spek, A. L., *Acta Crystallogr., Sect. D* **2009**, 65, 148-155.
- (15) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, 120, 215-241.
- (16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian Inc.; Wallingford, CT, 2009.
- (17) (a) Gavezzotti, A. *J. Phys. Chem. B*, **2003**, 107, 2344-2353. (b) Gavezzotti, A. *Z. Kristallogr.* **2005**, 220, 499-510.
- (18) Gavezzotti, A., *New J. Chem.* **2011**, 35, 1360-1368.
- (19) (a) Wolff, S. K.; Grimwood, D. J.; McKinnon, J. J.; Turner, M. J.; Jayatilaka, D.; Spackman, M.A. *CrystalExplorer* (Version 3.0); University of Western Australia, Australia, 2012. (b) Spackman, M. A.; McKinnon, J. J.; Jayatilaka, D. *CrystEngComm*, **2008**, 10, 377-388.
- (20) Etter, M. C., *Acc. Chem. Res.* **1990**, 23, 120-126.
- (21) Neumann, M. A.; Leusen, F. J. J.; Kendrick, J. *Angew. Chem. Int. Ed.* **1990**, 23, 120-126.
- (22) Bardwell, D. A.; Adjiman, C. S.; Arnautova, Y. A.; Bartashevich, E.; Boerrigter, S. X. M.; Braun, D. E.; Cruz-Cabeza, A. J.; Day, G. M.; Della Valle, R. G.; Desiraju, G. R.; van Eijck, B. P.; Facelli, J. C.; Ferraro, M. B.; Grillo, D.; Habgood, M.; Hofmann, D. W. M.; Hofmann, F.; Jose, K. V. J.; Karamertzanis, P. G.; Kazantsev, A. V.; Kendrick, J.; Kuleshova, L. N.; Leusen, F. J. J.; Maleev, A. V.; Misquitta, A. J.; Mohamed, S.; Needs, R. J.; Neumann, M. A.; Nikylov, D.; Orendt, A. M.; Pal, R.; Pantelides, C. C.; Pickard, C. J.; Price, L. S.; Price, S. L.; Scheraga, H. A.; van de Streek, J.; Thakur, T. S.; Tiwari, S.; Venuti, E.; Zhitkov, I. K. *Acta Crystallogr. Sect. B* **2011**, 67, 535-551.
- (23) Nangia A., *Acc. Chem. Res.* **2008**, 41, 595-604.
- (24) Allen, F.H., *Acta Crystallogr., Sect. B* **2002**, 58, 380-388.

3.3 Conclusions

This work was a result of the unexpected, yet fortuitous discovery of five pairs of polymorphs of the alcohol and aldehyde intermediates of 10-[2-(benzoylamino)-phenyl]-5,15-diphenylcorrole and 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrole as in Figure 3.5.1. The structures of these were explored and discussed in two papers in *Crystal Growth & Design*.

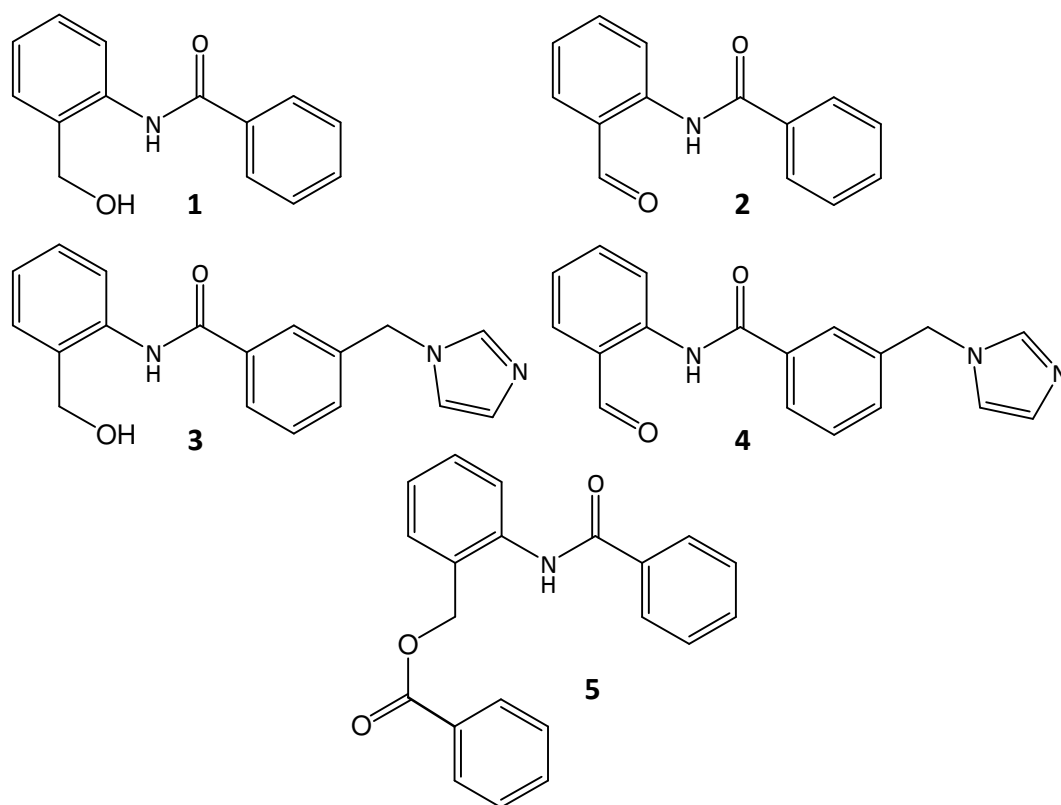


Figure 3.5.1 Polymorphic *N*-phenylbenzamide derivatives evaluated in this work. **1** N-[2-(hydroxymethyl)phenyl]-benzamide; **2** N-(2-formylphenyl)benzamide; **3** N-[2-(hydroxymethyl)-3-(1*H*-imidazol-1-ylmethyl)phenyl]-benzamide; **4** N-(2-formyl-3-(1*H*-imidazol-1-ylmethyl)phenyl)-benzamide; **5** 2-(benzamido)-benzyl benzoate

The results reported in the 2013 paper indicate that *N*-phenylbenzamide is a conformationally flexible and electrostatically non-uniform functional group. These properties allow for a wide variety of potential N-H $\cdots$ O, C-H $\cdots$ O, C-H $\cdots$ π and $\pi\cdots\pi$ interactions. It is believed that it is as a consequence of this that the *N*-phenylbenzamide derivatives explored in this work were found to be polymorphic. It was also suggested

that this functional group may encourage polymorphism in a wider variety of derivatives. With the importance of polymorphism in many spheres including pharmaceuticals and materials science, the discovery of a molecular group that could promote polymorphism is of great significance.

Quantitative analysis of the intermolecular interactions in a crystal structure has been shown to provide invaluable insights into the forces that shape the packing of a crystal lattice. In contrast to the traditional atom-to-atom approach to crystal analysis, the quantification of intermolecular interactions between pairs of molecules in the lattice highlights the importance of the weaker hydrogen bond interactions such as $X-H\cdots\pi$, $C-H\cdots X$ and $C-H\cdots\pi$ bonds as well as $\pi\cdots\pi$ interactions in the stabilisation of crystal structures. Often, the differences between polymorphs of a compound lie not with differences in the strong classical hydrogen bonding, but rather in the weaker interactions. This was found to be the case for compounds **1** and **3** where the strong hydrogen bond was maintained, but differences in the two polymorphs of each compound arose from different $C-H\cdots O$ and $\pi\cdots\pi$ interactions. In the case of the aldehyde derivative **2** and **4**, where strong intermolecular hydrogen bonding was absent, differences between polymorphs again arose from $C-H\cdots O$ and $\pi\cdots\pi$ interactions. Large conformational differences between molecules in the polymorphs of compound **5** led to significant differences between the two polymorphs. In the case of the first polymorph, the conformation of the molecule in the crystal lattice did not allow for the formation of an intermolecular hydrogen bond and the structure was stabilised by weak interactions. A conformational change in the second polymorph allowed for strong $N-H\cdots O$ hydrogen bonding to occur. The phenomenon of a polymorphic compound crystallising as a close packed structure with no hydrogen bonding in one case, and with hydrogen bonding present in the other case is very rare,⁵² and is as a consequence of the differences in molecular conformation adopted by **5**.

A useful result of the 2011 paper is that knowledge of the intermolecular forces, together with their energetic contribution to the stabilisation of crystal structure, may offer

information on structure determining interactions, providing useful insights into methods for the suppression or promotion of one polymorph over another. Experiments could then be tailored to either promote or prevent these interactions through the use of different crystallisation methods and solvents.

3.4 References

- (1) Wöhler, F.; von Liebig, J. *Ann. Pharm.* **1832**, 3, 249-282.
- (2) McCrone, W. C. In *Physics and Chemistry of the Organic Solid State*; Wiley Interscience: New York, 1965; Vol. II, p 725-726.
- (3) Almarsson, O.; Zaworotko, M. J. *Chem. Commun.* **2004**, 1889-1896.
- (4) Bhatt, P. M.; Desiraju, G. R. *Chem. Commun.* **2007**, 2057-2059.
- (5) O'Neill, M. H. *Pharm. Tech.* **2003**, 44-56.
- (6) Bernstein, J.; Davey, R. J.; Henck, J.-O. *Angew. Chem. Int. Ed.* **1999**, 38, 3440-3461.
- (7) Datta, S.; Grant, D. J. W. *Nature* **2004**, 3, 42-57.
- (8) Morris, K. R.; Griesser, U. J.; Eckhardt, C. J.; Stowell, J. G. *Adv. Drug Deliv. Rev.* **2001**, 48, 91-114.
- (9) Grunenberg, A.; Henck, J.-O.; Siesler, H. W. *Int. J. Pharm.* **1996**, 129, 147-158.
- (10) Erdemir, D.; Lee, A. Y.; Myerson, A. S. *Acc. Chem. Res.* **2009**, 42, 621-629.
- (11) Dressler, D. H.; Mastai, Y. *Cryst. Growth Des.* **2007**, 7, 847-850.
- (12) Llinàs, A.; Godman, J. M. *Drug Discov. Today* **2008**, 13, 198-210.
- (13) Blagden, N.; Davey, R. J. *Cryst. Growth Des.* **2003**, 3, 873-885.
- (14) Pauling, L. *The Nature of the Chemical Bond*; Cornell University Press: Ithaca, NY, 1960.
- (15) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; W. H. Freeman: San Francisco, CA, 1960.
- (16) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, 45, 7201-7245.
- (17) Melandri, S. *Phys. Chem. Chem. Phys.* **2011**, 13, 13901-13911.
- (18) Sutor, J. J. *Chem. Soc.* **1963**, 1105-1110.
- (19) Desiraju, G. R. *Acc. Chem. Res.* **1991**, 24, 290-296.
- (20) Gu, Y.; Kar, T.; Scheiner, S. J. *Am. Chem. Soc.* **1999**, 121, 9411-9422.
- (21) Nishio, M. *Phys. Chem. Chem. Phys.* **2011**, 13, 13873-13900, and references therein.
- (22) Takahashi, O.; Kohno, Y.; Nishio, M. *Chem. Rev.* **2010**, 110, 6049-6076, and references therein.
- (23) Desiraju, G. R.; Sharma, C. V. K. M. *J. Chem. Soc., Chem. Comm.* **1991**, 1239-1241.

- (24) Desiraju, G. R. *Chem. Commun.* **2005**, 2995-3001.
- (25) Tsuzuki, S.; Houjou, H.; Nagawa, Y.; Hiratani, K. *J. Chem. Soc. Perkin Trans. 2* **2001**, 1951-1955.
- (26) Marques, M. P. M.; Amorim da Costa, A. M.; Ribeiro-Claro, P. J. A. *J. Phys. Chem. A* **2001**, *105*, 5292-5297.
- (27) Metzger, S.; Lippert, B. *J. Am. Chem. Soc.* **1996**, *118*, 12467-12468.
- (28) Musah, R. A.; Jensen, G. M.; Rosenfeld, R. J.; McRee, D. E.; Goodin, D. B.; Bunte, S. W. *J. Am. Chem. Soc.* **1997**, *119*, 9083-9084.
- (29) Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1993**, *115*, 4540-4547.
- (30) Desiraju, G. R. *Chem. Commun.* **1997**, 1475-1482.
- (31) Spackman, M. A.; Btrom, P. G. *Chem. Phys. Lett.* **1997**, *267*, 215-220.
- (32) Spackman, M. A.; Jayatilaka, D. *CrystEngComm* **2009**, *11*, 19-32.
- (33) McKinnon, J. J.; Spackman, M. A.; Mitchell, A. S. *Acta Crystallogr. B* **2004**, *60*, 627-668.
- (34) Spackman, M. A.; McKinnon, J. J.; Jayatilaka, D. *CrystEngComm* **2008**, *10*, 377-388.
- (35) McKinnon, J. J.; Jayatilaka, D.; Spackman, M. A. *Chem. Commun.* **2007**, 3814-3816.
- (36) Cockroft, S. L.; Perkins, J.; Zonta, C.; Adams, H.; Spey, S. E.; Low, C. M. R.; Vinter, J. G.; Lawson, K. R.; Urch, C. J.; Hunter, C. A. *Org. Biomol. Chem.* **2007**, *5*, 1062-1080.
- (37) Dunitz, J. D.; Gavezzotti, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1766-1787.
- (38) Dunitz, J. D.; Gavezzotti, A. *Cryst. Growth Des.* **2005**, *5*, 2180-2189.
- (39) Dunitz, J. D.; Gavezzotti, A. *Chem. Soc. Rev.* **2009**, *38*, 2622-2633.
- (40) Bardwell, D. A.; Adjiman, C. S.; Arnautova, Y. A.; Bartashevich, E.; Boerrigter, S. X. M.; Braun, D. E.; Cruz-Cabeza, A. J.; Day, G. M.; Della Valle, R. G.; Desiraju, G. R.; van Eijck, B. P.; Facelli, J. C.; Ferraro, M. B.; Grillo, D.; Habgood, M.; Hofmann, D. W. M.; Hofmann, F.; Jose, K. V. J.; Karamertzanis, P. G.; Kazantsev, A. V.; Kendrick, J.; Kuleshova, L. N.; Leusen, F. J. J.; Maleev, A. V.; Misquitta, A. J.; Mohamed, S.; Needs, R. J.; Neumann, M. A.; Nikylov, D.; Orendt, A. M.; Pal, R.; Pantelides, C. C.; Pickard, C. J.; Price, L. S.; Price, S. L.; Scheraga, H. A.; van de Streek, J.; Thakur, T. S.; Tiwari, S.; Venuti, E.; Zhitkov, I. K. *Acta Crystallogr. Sect. B* **2011**, *67*, 535-551.
- (41) Price, S. L. *CrystEngComm* **2004**, *6*, 344-353.

- (42) Neumann, M. A.; Leusen, F. J. J.; Kendrick, J. *Angew. Chem. Int. Ed.* **1990**, *23*, 120-126.
- (43) Gavezzotti, A. *New J. Chem.* **2011**, *35*, 1360-1368.
- (44) Gavezzotti, A. *J. Phys. Chem. B* **2002**, *106*, 4145-4154.
- (45) Gavezzotti, A. *CrystEngComm* **2003**, *5*, 429-438.
- (46) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553-566.
- (47) Filippini, G.; Gavezzotti, A. *Acta Crystallogr., Sect. B* **1993**, *49*, 868.
- (48) Filippini, G.; Gavezzotti, A. *J. Phys. Chem.* **1994**, *98*, 4831.
- (49) Marom, N.; Tkatchenko, A.; Rossi, M.; Gobre, V. V.; Hod, O.; Scheffler, M.; Kronik, L. *J. Chem. Theory Comput.* **2011**, *7*, 3944-3951.
- (50) Civalleri, B.; Zicovich-Wilson, C. M.; Valenzano, L.; Ugliengo, P. *CrystEngComm* **2008**, *19*, 405-410.
- (51) Maschio, L.; Civalleri, B.; Ugliengo, P.; Gavezzotti, A. *J. Phys. Chem. A* **2011**, *115*, 11179-11186.
- (52) Nangia, A. *Acc. Chem. Res.* **2008**, *41*, 595-604.

Part 4

Reactions of a corrole-based biomimetic model

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4.1 The inorganic chemistry of corroles

4.1.1 Metals in corroles

Corroles, aromatic corrins, and core-contracted porphyrins have received much attention since corrole synthesis was revolutionised in 1999.^{1,2} Corroles, with three ionisable pyrrolic nitrogens in the inner core of the macrocycle, form trianions. This results in a system rich in π electrons, which in a small binding cavity, is a strong σ donor.³ As a result, corroles are able to stabilise metals with high oxidation states, a feat not achieved by the dianionic porphyrin or monoanionic corrin.³⁻⁷ In addition, the trianionic nature of the corrole results in low-valent metal complexes with significantly higher reactivity than porphyrin counterparts.⁸ The coordination of metals by corroles is of great interest as metallocorroles have been found to play important roles in catalysis, medicine, sensors and energy generation.^{4,9}

The complexation of a wide variety of metals by corroles has been studied.⁶ In spite of the small coordination cavity, a variety of different metals can be coordinated without distortion of the planarity of the macrocycle¹⁰ (although non-innocent corroles are often saddled^{3,11}). Palmer observed that while the number of reported first-row transition metal corrole complexes is high, the coordination of second- and third-row transition metals is more limited.³ Complexes of all of the first-row transition metals except scandium have been reported. Second-row transition metallocorroles, including Nb, Mo, Ru, Rh and Ag corroles have been reported while Re, Ir and Au are the only third-row transition metals complexes reported.⁶ Main group metals, B, Al, Ga, In, Sn, Ge, As, Bi, Sb and P have also been complexed by corrole macrocycles.^{4,6,8} The trianionic nature of the corrole is unable to stabilise metals in the 2+ oxidation state. As a result, complexes of such metals (such as Mg^{II} , Co^{II} , Zn^{II} , Fe^{II} or Ni^{II}) which are commonly found in porphyrin chemistry, are rare in corrole chemistry.⁸

The most common coordination numbers observed in corrole complexes are five and six. A few four-coordinate systems have been reported including Cu^{III} and Ag^{III} systems. Five-

coordinate systems are favourable as the displacement of the metal above the plane of the macrocycle is beneficial not only for the metal, but also for the macrocycle. Strong σ donation from the electron rich corrole decreases the Lewis acidity of the coordinated metal, thus decreasing the affinity for a second axial ligand. In spite of this, six-coordinate systems are common and they exhibit remarkable planarity of the macrocycle, a property which has been shown to affect the physical and chemical properties of the system.⁴

The coordination of metals in high formal oxidation states by porphyrins results in unstable, transient complexes, while similar corrole complexes are stable.^{6,7,12} High-valent metallocorroles are thus useful as stable biomimetic systems in the study of high-valent intermediates in haem biochemistry.¹² The first high-valent metallocorrole was reported in 1981 where chromium was found to be coordinated in the 5+ oxidation state.¹³ It has been established that the electronic nature of the corrole ring, dictated by the electronic properties of the *meso* and β substituents, together with the oxidation state of the metal and the presence of axial ligands, can be either innocent, or non-innocent.¹² In electron rich systems, the corrole macrocycle is said to be innocent, in that a true high-valent metal centre is present, while in electron poor corrole systems, the macrocycle is in fact partially oxidised and is thus non-innocent.³ These electron-poor systems, as a result of the partial oxidation, tend to display saddled macrocycles.^{3,11} The presence of a strong field axial ligand has been shown to stabilise high-valent metal centres, and in these cases, the corrole ligand appears to be innocent.¹⁴

In addition to acting as a tetradentate ligand, examples of corroles acting as tridentate, dianionic ligands have been reported for Rh^I complexes^{15,16} as well as $(oxo)V^{IV}$ and $(oxo)Ti^{IV}$ complexes¹⁷ where the metal coordinates through three of the four nitrogen donors.

4.1.2 Corrole and vitamin B₁₂ spectra

In the spectroscopy of corroles, as with the UV-vis spectroscopy of porphyrin, the bands of lower energy and intensity are known as the α or Q bands (500-700 nm region) while the bands of higher energy and higher intensity are known as β or Soret bands (300 - 500 nm region)³ as illustrated in Figure 4.1.1. Extinction coefficients are often lower for corroles than for related porphyrin macrocycles.³ The spectra of corroles have been adequately rationalised by the four-orbital model,¹⁸ which was shown by Gouterman in the 1960s to apply to porphyrins.^{19,20} In metalloporphyrins, the majority of the transitions observed in the UV-vis spectra are due to $\pi \rightarrow \pi^*$ transitions of the metal and ligand.^{21,22} In the electronic spectra of metallocorroles, however, the observed bands are often due to the $\pi \rightarrow \pi^*$ transitions of the corrole ligand rather than transitions involving the metal and axial ligands.^{21,23}

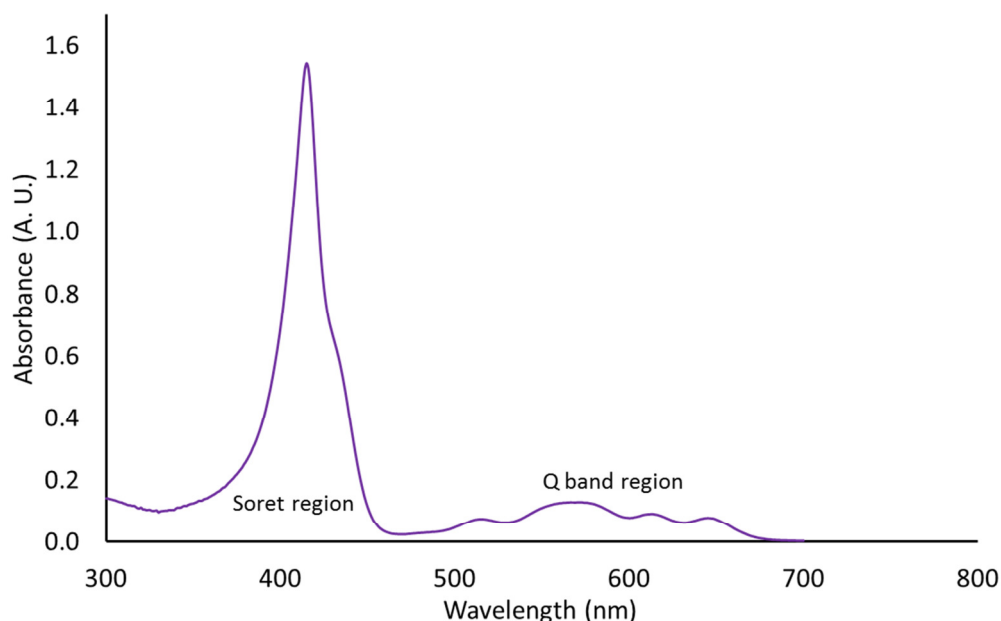


Figure 4.1.1 The UV-vis spectrum of triphenyl corrole in dichloromethane

The spectrum of vitamin B₁₂ is characterised by the strongly-absorbing γ band in the 350 nm region and the less strongly absorbing β and α bands in the 420-600 nm region.²⁴ A weakly-absorbing δ band in the 300-350 nm region and the E and D bands in the 390-420 nm region are also present (Figure 4.1.2). A number of electronic transitions are

responsible for these bands in the UV-vis spectrum including internal transitions of electrons in either the corrin ring or the axial ligands, charge transfer transitions between either the corrin and the metal ion or the axial ligands and the metal ion as well as $d-d$ transitions of the metal ion. It has been found, however, that the bands above 300 nm in the UV-vis spectrum are due to $\pi \rightarrow \pi^*$ transitions within the corrin ring.²⁵ While these transitions are due to the transition of electrons within the corrin ring, they are sensitive to the nature of the axial ligands.²⁶

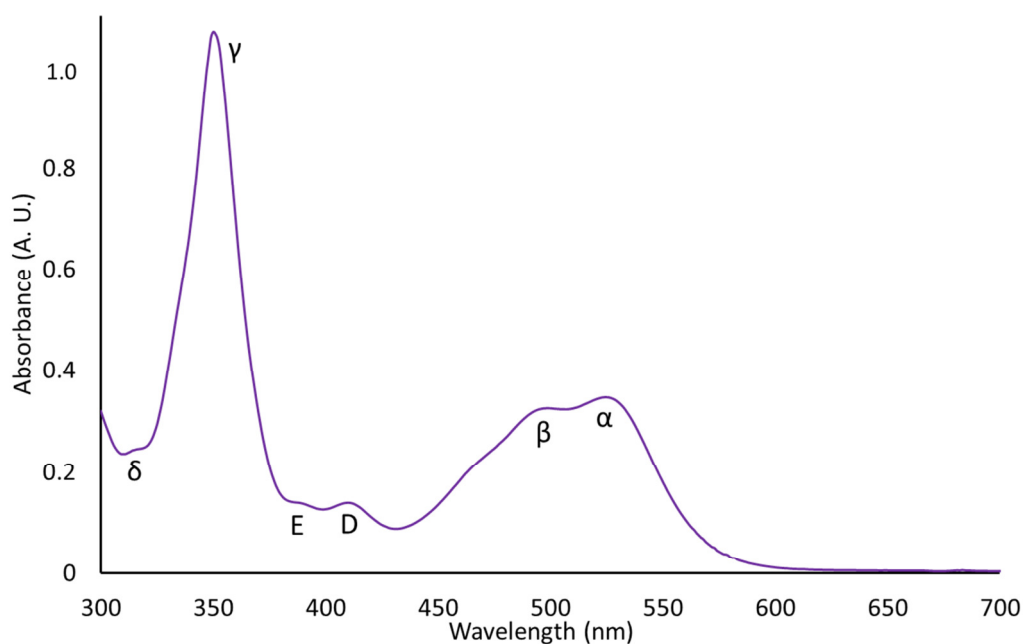


Figure 4.1.2 The UV-vis spectrum of vitamin B_{12a} in water

‘Atypical’ spectra, as in Figure 4.1.3, with the γ band appearing at longer wavelengths and significantly reduced intensity together with the appearance of other bands of similar or greater intensity in the 300-350 nm region, arise upon coordination of certain ligands at the β position including ethyl, vinyl and methyl groups,²⁷ sulfites, isoamyl and selenocyanide,²⁸ as well as iodide²⁹ and thiosulfate.³⁰ The spectra of substituted cobalamins become increasingly ‘atypical’ as the polarisability of the β ligand increases and Perry and Marques suggest that the ‘atypical’ spectra arise from the separation of the components of the typical γ band due to the change in donation of electron density from the more electron donating, polarisable β ligands.²⁸

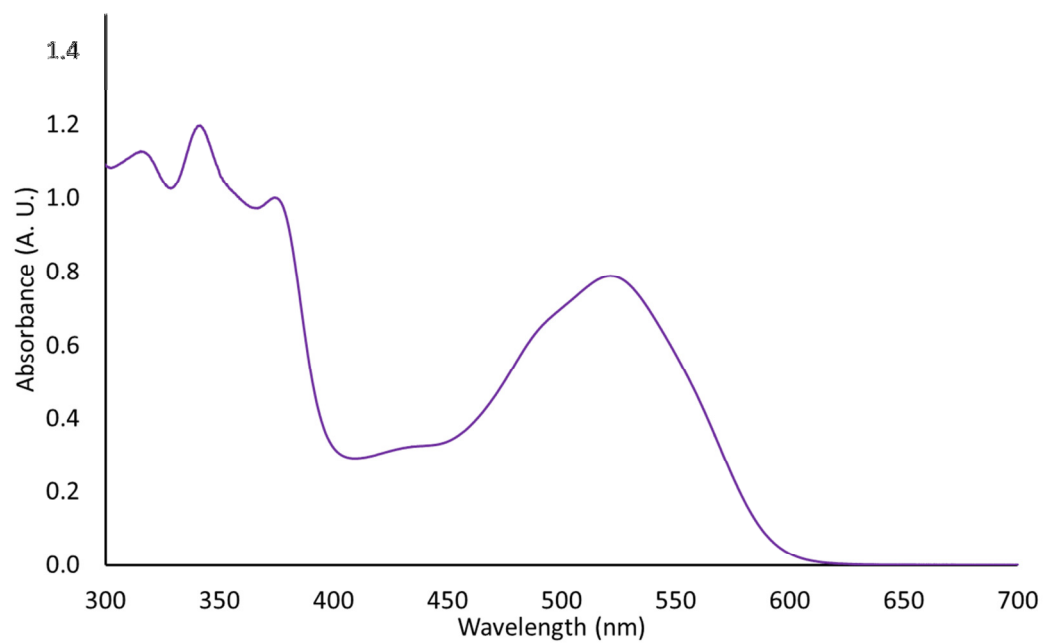


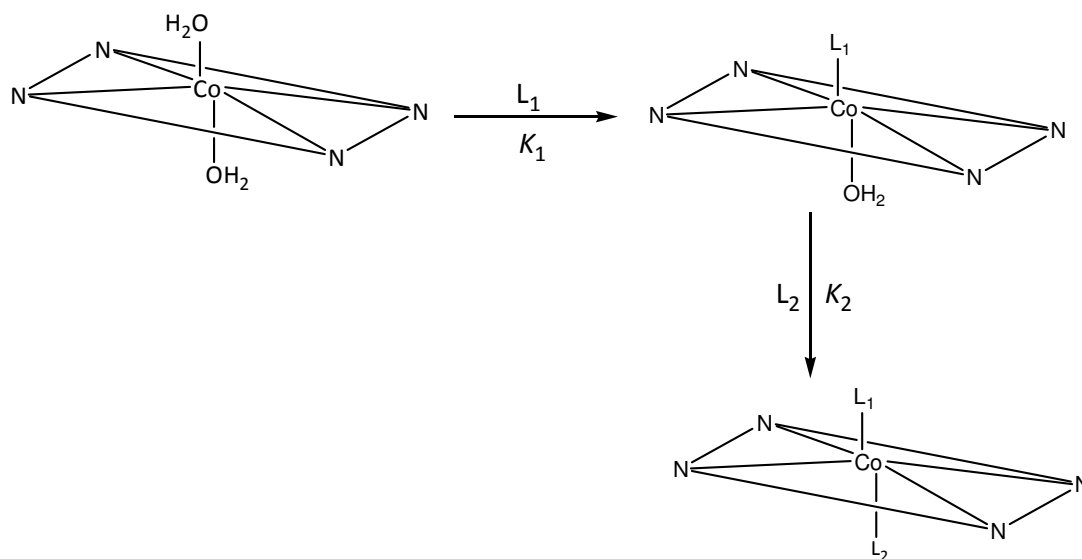
Figure 4.1.3 UV-vis spectrum of methylcobalamin, an 'atypical' cobalamin spectrum

4.1.3 Ligand substitution reactions of corroles

While the literature available on the substitution reactions of vitamin B_{12a} is vast, the same cannot be said for reactions involving a corrole macrocycle. Only one example of a substitution reaction in aqueous media has been published – the binding of human serum albumin (HSA) to the gallium and manganese complexes of the water soluble 2,17-bis-sulfonato-5,10,15(trispentafluorophenyl)corrole where it was found that HSA binds to both the free base and metallated corroles very strongly, such that the stability constants for these reactions could not be determined by UV-vis titrations.³¹

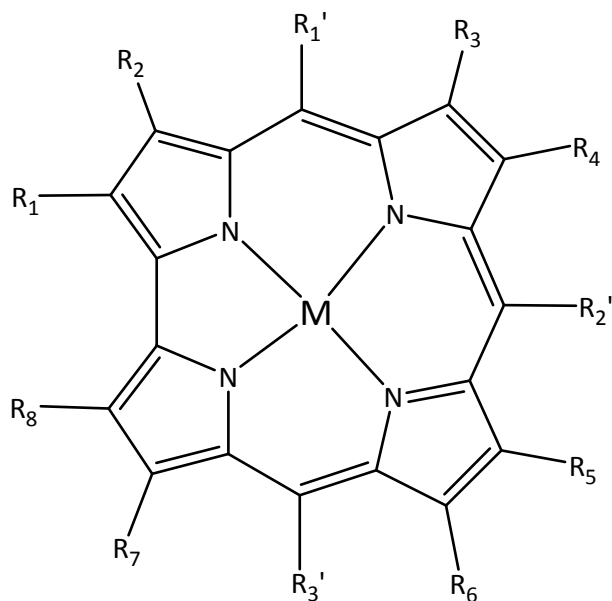
The reactions of various corroles with pyridine and carbon monoxide,³²⁻³⁵ substituted pyridines^{36,37} and various anions³⁸⁻⁴⁰ in organic solvents have been discussed in various publications. Figure 4.1.4 illustrates the corroles used in each study and the stability constants for the various ligands bound to cobalt corroles are presented in Tables 4.1.1 and 4.1.2, while those bound to manganese corroles are in Table 4.1.3.

Log K_2 values (as defined in scheme 4.1.1) are for the coordination of one ligand to the metal ion *trans* to an existing ligand. In the case of the cobalt systems **3** and **4**,³⁶ an increase in the pK_a of the base resulted in an increase of log K as well (Table 4.1.1), indicating that an increase in electron density at the donor nitrogen of the ligand results in increased affinity between the cobalt ion and the ligand. This illustrates that the affinity of nitrogen donor ligand for H⁺ parallels its affinity for the cobalt ion. The values of log K_1 were found to be considerably higher than for log K_2 for system **4**. log K_2 values for system **3**, with one pyridine ligand in place prior to the substitution reactions, were found to be similar, but slightly higher than the log K_2 values of system **4**. This demonstrates that the ligand *trans* to the incoming ligand plays a more important role in the determination of log K_2 than the *cis* effects of the length of the aliphatic chain substituted at the β positions of the corrole ring.



Scheme 4.1.1 Generalised reaction for ligand substitution reactions where the metal is coordinated by a macrocycle. K_1 is the stability constant for the binding of the first ligand while K_2 is the stability constant for the binding of the second ligand

Results from Guillard,^{32,34} Kadish³³ and Murakami³⁶ (Table 4.1.1) indicate that the substitution pattern at both the *meso* and β positions of the corrole ring affect the properties of the coordinated cobalt(III) ion. The presence of aliphatic substituents at the β positions and hydrogens at the *meso* positions on the corrole ring led to low stability constants for the coordination of pyridine (systems **3**, **4**³⁶ and **5**³⁴). The addition of aromatic groups at the *meso* positions increased K (system **1**³²⁻³⁴). The introduction of aromatic substituents at some of the β positions increased $\log K$ further (systems **6** - **8**³⁴), with electron withdrawing groups on some of the β positions (*o*-OMePh in system **8**) increasing the $\log K$ to a greater extent than the electron donating groups (*p*-OMePh in system **6**). The use of aromatic substituents at six of the eight β positions results in the highest $\log K$ for the series (system **9**³⁴).



- 1** - $R_1' = R_3' = \text{H}$; $R_1 = R_2 = R_7 = R_8 = R_2' = \text{Ph}$; $R_3 = R_4 = R_5 = R_6 = \text{Me}$; $\text{M} = \text{Co}$
- 2** - $R_1' = R_2' = R_3' = \text{H}$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = \text{Me}$; $\text{M} = \text{Mn}$
- 3** - $R_1' = R_2' = R_3' = \text{H}$; $R_1 = R_2 = R_7 = R_8 = \text{Me}$; $R_3 = R_4 = R_5 = R_6 = \text{Et}$; $\text{M} = \text{Co} \cdots \text{Py}$
- 4** - $R_1' = R_2' = R_3' = \text{H}$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = \text{Et}$; $\text{M} = \text{Co}$
- 5** - $R_1' = R_2' = R_3' = \text{H}$; $R_1 = R_2 = R_3 = R_6 = R_7 = R_8 = \text{Me}$; $R_4 = R_5 = \text{Et}$; $\text{M} = \text{Co}$
- 6** - $R_1' = R_3' = \text{H}$; $R_2' = \text{Ph}$; $R_3 = R_4 = R_5 = R_6 = \text{Me}$; $R_1 = R_2 = R_7 = R_8 = p\text{-OMePh}$; $\text{M} = \text{Co}$
- 7** - $R_1' = R_2' = R_3' = \text{H}$; $R_1 = R_2 = R_7 = R_8 = \text{Ph}$; $R_3 = R_6 = \text{Me}$; $R_4 = R_5 = \text{Et}$; $\text{M} = \text{Co}$
- 8** - $R_1' = R_3' = \text{H}$; $R_2' = \text{Ph}$; $R_3 = R_4 = R_5 = R_6 = \text{Me}$; $R_1 = R_2 = R_7 = R_8 = o\text{-OMePh}$; $\text{M} = \text{Co}$
- 9** - $R_1' = R_3' = \text{H}$; $R_1 = R_2 = R_3 = R_6 = R_7 = R_8 = R_2' = \text{Ph}$; $R_4 = R_5 = \text{Me}$; $\text{M} = \text{Co}$
- 10** - $R_1' = R_3' = \text{Mes}$; $R_2' = \text{Ph}$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = \text{H}$; $\text{M} = \text{Mn}$
- 11** - $R_1' = R_2' = R_3' = \text{H}$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = \text{Me}$; $\text{M} = \text{Co} \cdots \text{PPh}_3$
- 12** - $R_1' = R_2' = R_3' = x\text{-Ph}$; $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = \text{Me}$; $\text{M} = \text{Co} \cdots \text{PPh}_3$

Figure 4.1.4

Corroles used in the study of ligand binding in organic solvents in the literature. **1** – Guillard and co-workers,^{32,34} Kadish and co-workers;^{33,40} **2** – Licoccia and co-workers;³⁷ **3, 4** – Murakami and co-workers;³⁶ **4-9** – Guillard and co-workers;³⁴ **10** – Chen and co-workers,³⁸ Shen and co-workers;³⁹ **11, 12** – Adamian and co-workers³⁵

Table 4.1.1 Stability constants for various ligands bound to substituted cobalt corroles (as in Figure 4.1.4) from the literature

Corrole	Solvent	Ligand	log K_1 ; log K_2	Reference
1	PhCN	Chloride	2.88	Kadish ⁴⁰
3*	Acetone	Pyridine	1.6	Murakami ³⁶
		4-cyanopyridine	1.01	
		4-aminopyridine	2.74	
		4-methylpyridine	2.1	
		3-methylpyridine	1.9	
		2-methylpyridine	-0.8	
		3-acetylpyridine	2.28	
		3-hydroxypyridine	1.5	
4	Acetone	Pyridine	4.2; 1.6	Murakami ³⁶
		4-cyanopyridine	3.29; 0.82	
		4-aminopyridine	5.9; 2.65	
		4-methylpyridine	4.8; 2.0	
		3-methylpyridine	4.5; 1.75	
		2-methylpyridine	2.0; -1.0	
		3-acetylpyridine	5.03; 2.06	
		3-hydroxypyridine	4.3; 1.1	
1	CH ₂ Cl ₂	Pyridine	4.90; 2.10	Guilard, ^{32,34}
		CO	4.2	Kadish ³³
5	CH ₂ Cl ₂	Pyridine	3.78; 2.00	Guilard ³⁴
		CO	3.7	
6	CH ₂ Cl ₂	Pyridine	4.95; 2.17	Guilard ³⁴
		CO	4.3	
7	CH ₂ Cl ₂	Pyridine	5.01; 2.19	Guilard ³⁴
		CO	3.9	
8	CH ₂ Cl ₂	Pyridine	5.32; 2.38	Guilard ³⁴
		CO	4.3	
9	CH ₂ Cl ₂	Pyridine	5.48; 2.19	Guilard ³⁴
		CO	4.8	

* Stability constants given are log K_2 values. The ligand *trans* to the incoming ligand was pyridine

The *cis* influence was investigated in a series of corroles bearing methyl substituents at the β positions and phenyl groups with different substituents at the *meso* positions (system **12**). The *cis* influence investigates how a change in the equatorial ligand system affects the chemistry, in particular the thermodynamics of ligand substitution, at the axial position through donation of electron density from the equatorial macrocyclic ligand to the metal.⁴¹ Adamian and co-workers³⁵ found that the stability constant, K_2 for the binding of pyridine *trans* to triphenyl phosphine increased as the Hammett substituent constant increased. This result was in line with Guillard's results with differing electron donating or withdrawing groups at the β positions.³⁴ This suggests electron withdrawal from the β or *meso* positions decreases the electron density of the metal ion, resulting in a more positively charge metal centre which readily accepts electrons from an incoming ligand, leading to higher stability constants.

Table 4.1.2 Stability constants for pyridine bound to substituted cobalt corroles already bearing a triphenylphosphine axial ligand from Adamian and co-workers³⁵

Corrole	Solvent	Meso substituent	log K_2
11	Benzene	H	2.29
12	Benzene	Ph	1.54
		<i>p</i> -OMePh	1.30
		<i>p</i> -MePh	1.40
		<i>p</i> -ClPh	1.54
		<i>m</i> -ClPh	1.72
		<i>o</i> -ClPh	1.62

The binding of ligands to corrole-coordinated manganese occurs at much higher ligand concentrations compared to cobalt corroles as Table 4.1.3 illustrates. Licoccia³⁷ suggests that equilibrium lies in favour of the unligated, or ligand free species, as penta coordination of manganese may be satisfied through interactions between different neighbouring macrocycles. Binding of neutral ligands was poor but coordination of anionic ligands (in system **10**^{38,39}) yielded large stability constants.

Table 4.1.3 Stability constants for various ligands bound to substituted manganese corroles (as in Figure 4.1.4) from the literature

Corrole	Solvent	Ligand	log <i>K</i>	Reference
2	CHCl ₃	Pyridine	1.17	Licoccia ³⁷
		4-methylpyridine	1.91	
		4-vinylpyridine	0.81	
10	PhCN	Acetate	4.5	Chen ³⁸
10	PhCN	Cyanide	4.7	Shen ³⁹
		Thiocyanate	4.2	
		Chloride	4.8	

4.1.4 Electrochemical studies

The ability of corrole to stabilise a wide variety of metals in a variety of different oxidation states has resulted in many, many electrochemical studies on different corrole systems. As one might expect, changes in solvent, axial ligands, and the *meso* and β substituents affect the redox behaviour of the corrole.³⁹ The use of coordinating solvents, or the presence of axial ligands dramatically changes the redox behaviour of metallocorroles. In the case of cobalt corroles, the presence of an axial ligand prevents the formation of corrole dimers which is often observed in non-coordinating solvents.^{6,42} It has been observed that, as with porphyrins, the presence of aryl substituents at the *meso* positions results in systems that are harder to oxidise and easier to reduce than corroles bearing alkyl β substituents.^{6,39} The electronic properties of these substituents also affect the electrochemistry of the system. An increase in the electron withdrawing ability of the substituent results in an increase in both the reduction and oxidation half-wave potentials.³⁵

Kadish and co-workers observed that metallocorroles are more difficult to reduce, and easier to oxidise, than similar porphyrins with the same metal ions.^{6,35,42-44} In addition, the reduction of cobalamins^{45,46} generally occurs at higher potentials than the reduction of corroles. This suggests that the trivalent corrole macrocycle is able to better stabilise metals in high oxidation states than the divalent porphyrin, or the monovalent corrin.

4.1.5 Bismacrocycle systems

The synthesis, characterisation and catalytic properties of bisporphyrin, biscallole and corrole-porphyrin dyads have also been reported.^{32,38,47-51} These dyads consist of two macrocycles linked in a face-to-face fashion through either a flexible or rigid linker as illustrated in Figure 4.1.5. The use of corroles in these dyads became popular following increased ease of synthesis with the several one-pot synthetic routes and the discovery of the interesting chemistry which corroles possess, including the stabilisation of metal in high oxidation states.⁴⁷ The first cofacial biscallole was reported in 1998 by Jérôme and co-workers.⁴⁷

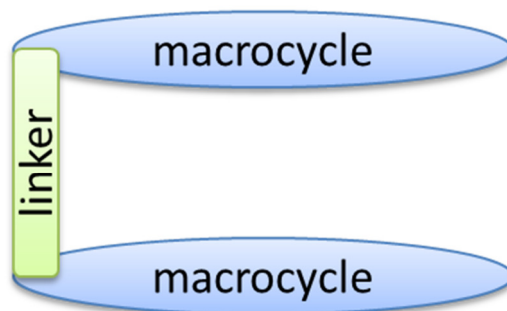


Figure 4.1.5 Cartoon of the structure of bismacrocycle dyads. The linker is often a polyaromatic or aromatic system. The two macrocycles can be of the same type (biscallole or bisporphyrin) or of different types (corrole-porphyrin dyads). The macrocycles can both be metallated or free base, or only one of the two macrocycles can contain a metal.

Bismacrocycles have been utilised as catalysts in oxidation reactions, including the four-electron reduction of dioxygen to water^{47,48} and the microscopic reverse of nitrogen fixation,⁴⁷ where the substrate, or guest, is encapsulated between the two macrocycles.³⁸ Bismacrocycles are of great interest as they provide a system which can readily bind small molecules, such as oxygen or carbon monoxide, which may require two metal binding sites in order to undergo the desired reaction, mimicking metal cluster chemistry in biological systems such as cytochrome oxidase and nitrogenase.⁵¹ This encapsulation is highly dependent on several factors, including the identity of the linker molecule, the metals coordinated by the macrocycles, and the solvent.³⁸ The length and structure of the linker is used to control the distance between the two macrocycles, and thus the $\pi\cdots\pi$

interactions of the macrocycle.⁵⁰ The flexibility of the linker also serves to control the manner in which the dyad opens and closes to accept the guest substrate.

The identity of the bridging linker affects the ligand binding properties of the metallated corroles. In a comparison of a corrole with two of its related biscalcoroles, differing by the identity of the linker, the stability constant for the binding of pyridine was slightly higher for the monocalcorole ($\log K = 4.90$) than for an anthracenyl-linked biscalcorole ($\log K = 4.84$) while that for the biphenylenyl linked biscalcorole was almost two orders of magnitude lower ($\log K = 3.14$).³² The binding of carbon monoxide, on the other hand yielded very different results, with the highest stability constant determined for the phenylenyl linker dimer ($\log K = 31.3$), followed by the anthracenyl-linked dimer ($\log K = 15.0$) and finally the monocalcorole ($\log K = 7.1$).³²

4.2 General Methods

Materials and general methods used in this study are reported in this section. Details of methods specific to particular experiments are detailed in the appropriate sections to follow.

4.2.1 Materials

Deionised water, purified using a Direct Q UV 3 Millipore and further purified using a Millipore MilliQ unit, was used throughout this study unless otherwise stated. Water used for the preparation of cobalt and vitamin B_{12a} standards as well as any water used for atomic absorption measurements was purified using a Micropure RO system with UV sterilizer and further purified using a MilliQ mixed bed ion exchange system for a final purity of >18 mΩ.

Reagents and buffers used in this work are reported in **Appendix 1.2**. Buffers were adjusted to the required pH using concentrated solutions of either sodium hydroxide or orthophosphoric acid. Vitamin B_{12a} studies were performed using hydroxocobalamin acetate. Atomic Absorption studies were performed using chlorohydrate dihydroxocobalamin. The corrole used in all studies was synthesised as reported in **Part 2 Sections 2.4.3 and 2.9.3**.

4.2.2 pH measurements

pH measurements were performed using a Metrohm High-precision 780 pH meter and Metrohm Unitrode combination pH electrode. Metrohm ready-to-use buffer solutions at pH 4, 7 and 9 were used to calibrate the electrode using a 3 buffer calibration.

4.2.3 UV-vis spectroscopy

UV-vis spectra of ligand binding assay experiments were recorded on either a Cary 1E UV-vis Spectrophotometer, fitted with a circulating water bath maintained at $\pm 25.0 \pm 0.1^\circ\text{C}$, or Cary 300 Bio UV-vis Spectrophotometer, fitted with a Cary Dual Cell Peltier accessory from Varian, set at 25.0°C . Spectra of the pK_a titration were recorded on a Cary 3E UV-vis Spectrophotometer, fitted with a circulating water bath maintained at $25.0 \pm 0.1^\circ\text{C}$. All spectrophotometers were fitted with cuvette holders for 1 cm path length cuvettes. Matched Helma standard quartz cuvettes with Teflon stoppers, were used for ligand binding assays. A 1 cm path length, 1.5 ml volume quartz self-masking flow cell was used for the pK_a titration, together with a standard quartz cuvette as a reference cell. Spectra were recorded with a spectral band width of 2 nm, signal averaging time of 0.5 s, data interval of 1.00 nm and scan rate of $120.00 \text{ nm min}^{-1}$. Collection of spectra was facilitated by the Scan application of the Cary WinUV software suite.⁵²

4.2.4 Kinetics

Kinetic data were collected on an Applied Photophysics stopped flow reaction analyser with a 1 cm cell pathlength, using an ozone-free xenon ARC lamp and pbp Spectra kinetic monochromator with a spectral band width of 2.3 nm. The reaction between the chromophore (DPTC-Co or vitamin B_{12a}) and cyanide was monitored at four different temperatures and five ligand concentrations under pseudo first order conditions. The temperature of the reaction cell was controlled using a LKB BrommaMultitemp thermostatic circulator.

4.2.5 Data Analysis

Spectroscopic data from ligand binding assays and kinetic analysis were analysed using SigmaPlot⁵³ in the determination of observed equilibrium or stability constants (K_obs) and rate constants (k_obs).

Where K_{obs} was found to be less than 4, the binding isotherm in Equation 4.2.1 was used (derivation of Equation 4.2.1 can be found in **Appendix 4.1**); A is the absorbance at a particular ligand concentration $[L]$, A_0 is the initial absorbance, A_1 is the final absorbance and K_{obs} is the equilibrium constant. A_0 , A_1 and K_{obs} are variables which were solved for using a non-linear least squares and an iterative process.

$$A = \frac{A_0 + A_1 K_{obs} [L]}{1 + K_{obs} [L]}$$

Equation 4.2.1

Where $\log K_{obs}$ was found to be greater than 4, the cobalt, or chromophore concentration was taken into account with the data fitted to the binding isotherm in Equation 4.2.2 (derivation of Equation 4.2.2 can be found in **Appendix 4.1**).⁵⁴ A_0 is the initial absorbance, A_1 is the final absorbance, $[M]_T$ is the total metal concentration, $[L]_T$ is the total ligand concentration, FL is an expression for the free ligand concentration and K_{obs} is the equilibrium constant. A_0 , A_1 and K_{obs} are variables which were solved for using a non-linear least squares and an iterative process.

$$A = \frac{A_0 + A_1 K_{obs} [L]_{free}}{1 + K_{obs} [L]_{free}}$$

where

$$[L]_{free} = \frac{-(1 + K_{obs} [M]_T - K_{obs} [L]_T) + \sqrt{(1 + K_{obs} [M]_T - K_{obs} [L]_T)^2 + 4K_{obs} [L]_T}}{2K_{obs}}$$

Equation 4.2.2

The final stability constants were determined from the sum of the weighted K_{obs} values obtained for each wavelength at which there was a large spectroscopic change (typically four wavelengths – two examples of which can be found in **Appendix 4.6** (determination of K) and **Digital Appendices 4.2.1** and **4.2.2** (raw data) while all other examples can be found in **Digital Appendices 4.3.1** and **4.3.2** (determination of K)). The error was calculated from the sum of weighted relative percentage error reciprocals using Microsoft Excel.

pH-independent stability constants were determined by taking the fraction of available ligand (a protonated ligand cannot bind to the metal) as well as the fraction of aqua complex of the chromophore (the hydroxocobalamin cannot undergo ligand substitution reactions⁵⁵⁻⁵⁷) into account using Equation 4.2.3 (as detailed in **Appendix 4.2**), where pK_{aL} refers to the pK_a of the conjugate acid of a ligand and pK_{aM} refers to the pK_a of the equilibrium between the aqua and hydroxo complexes of the chromophore.

$$K = K_{obs}(1 + 10^{pK_{aL}-pH})(1 + 10^{pH-pK_{aM}})$$

Equation 4.2.3

Kinetic data were fitted to one of two different equations. A simple exponential, as in equation 4.2.4 was used in all cases except for the data obtained for the reaction between DPTC-Co and cyanide at 10°C at low cyanide concentration, where a double exponential for two sequential first order reactions, as in Equation 4.2.5, was used. In Equation 4.2.4, A_0 is the initial absorbance, A_1 is the final absorbance, t is the time in seconds and k is the observed first order rate constant to be determined. In Equation 4.2.5, ε_A , ε_B and ε_C are the extinction coefficients of species A, B and C, t is the time in seconds and k_1 and k_2 are the observed first order rate constants to be determined. This equation determines the fraction of species A, B and C in solution at any given time from the summation of their contribution to the overall absorbance.

$$A = (A_0 - A_1)e^{-kt} + A_1$$

Equation 4.2.4

$$A = \varepsilon_A e^{-k_1 t} + \varepsilon_B \left(\frac{k_1}{k_2 - k_1} e^{-k_1 t} - e^{-k_2 t} \right) + \varepsilon_C \left(\frac{k_1 e^{-k_2 t} - k_2 e^{-k_1 t}}{k_2 - k_1} + 1 \right)$$

Equation 4.2.5

pH-independent rate constants were determined by taking the fraction of aqua complex of the chromophore into account using Equation 4.2.6 (derived in **Appendix 4.3**), where pK_{aL} refers to the pK_a of the conjugate acid of the ligand and pK_{aM} refers to the pK_a of the equilibrium between the aqua and hydroxo complexes of the chromophore. The hydroxo complex is kinetically inert to substitution in the case of both vitamin B_{12a}⁵⁵⁻⁵⁷ and iron(III) porphyrins.^{58,59} We therefore assume that this is also true for cobalt(III) corroles. Weighted k values have been not reported as the values of the errors did not represent

the scatter of the data; rather, averaged values of k and the statistical deviation have been reported.

$$k^{II} = k_{obs}^{II}(1 + 10^{pK_{aL}-pH})(1 + 10^{pH-pK_{aM}})$$

Equation 4.2.6

4.2.6 DFT methods

DFT calculations were carried out using Gaussian-09.⁶⁰ Calculations were performed by Dr Isabelle Navizet and Dr Christopher Perry using the cluster at the Centre for High Performance Computing, Cape Town and the LAN cluster. Interpretation of the results is by the author with the assistance of Navizet and Perry.

4.3 Effect of solvents on spectra of metallated and free base DPTC

4.3.1 Introduction

The polarity of a solvent, together with the solute-solvent interactions particular to that solvent, can affect UV-vis spectra of chromophores insofar as the position, shape and relative intensities of absorption bands are concerned.⁶¹ This is a consequence of the interaction between the solvent and the chromophore and can result in a change in the energy between the excited and the ground state of the chromophore.⁶¹

Solvatochromism is described as the pronounced change in electronic absorption bands due to a change in solvent polarity.⁶² Solvatochromism is a complex phenomenon which results from a variety of different processes that occur between the solvent and solute.⁶³ Changes in the absorption band positions, shapes and intensities in the UV-vis spectra of a chromophore are as a result of several factors, including how the orientation and dynamics of the chromophore are affected by the solvent.⁶³ Positive solvatochromism is characterised by bathochromic shifts in absorption band position with an increase in solvent polarity, while negative solvatochromism is characterised by hypsochromic shifts in absorption band position with an increase in solvent polarity.⁶¹

The effect of solvent on the spectra of various corroles and metallated corroles has been observed. One of the most widely studied metallocorroles is the four coordinate copper corrole and its derivatives (the corroles studied by Lu and coworkers are illustrated in Figure 4.3.1). These copper corroles have been studied under different solvent conditions where it has been reported that solvent choice can affect the oxidation state of the coordinated copper metal ion.⁶⁴ In cobalt corroles, solvent choice has also been shown to affect the electrochemical and spectroscopic properties of the corroles.⁶⁵ A negative solvatochromism effect was observed for iridium(III) containing corroles where an increase in solvent polarisability resulted in a hypsochromic shift of the Soret bands.⁶⁶

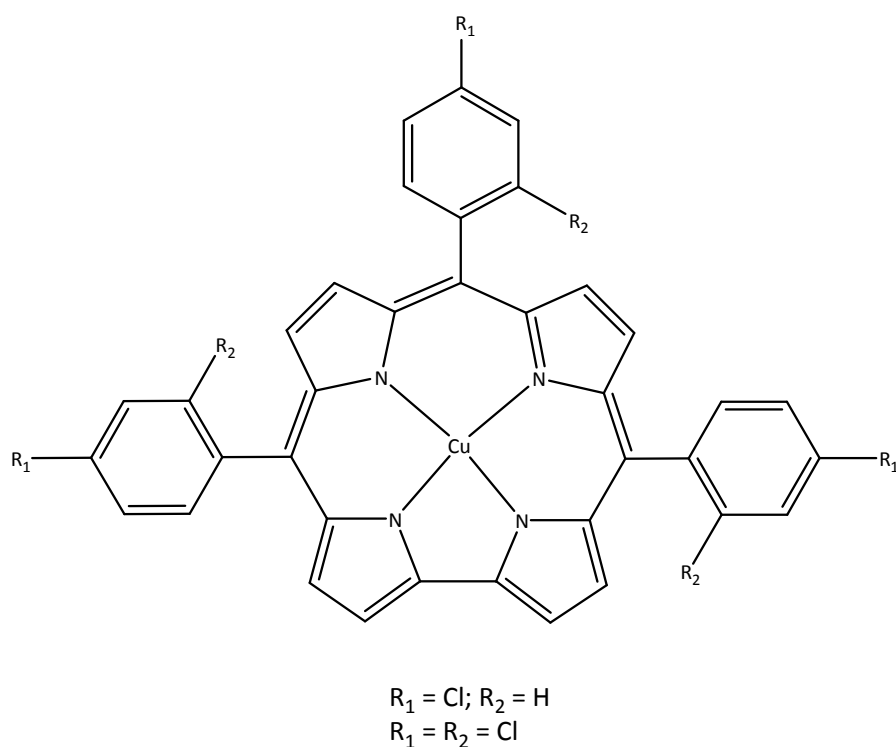


Figure 4.3.1 Copper corroles studied by Lu and co-workers⁶⁴

In vitamin B₁₂ chemistry, it has been reported that solvent choice affects absorption spectra of various cobalt(III) containing corrinoids (negative solvatochromism)⁶⁷ with differences in the position of the γ band of up to 8 nm observed for dicyanocobyrinic acid heptamethyl ester.⁶⁸ In addition, the Co(III)/Co(II) redox potential is solvent sensitive.⁶⁹ Solvent choice also affects stability constants^{69,70} and kinetics of ligand substitution reactions.^{71,72} In porphyrin chemistry, the effect of solvent has also been reported with solvent choice affecting stability constants,^{73,74} aggregation,⁷⁵ and UV-vis spectra.^{76,77}

4.3.2 Methods particular to solvent effects

This section deals with the effect of solvent on both DPTC and DPTC-Co. In the first case, the effect of a range of different solvents on the spectrum of the unmetallated and metallated DPTC was observed. In the second case, the stability of the metallated corrole in methanol:water solutions of varying ratios was determined as a function of light exposure after 48 hours. This investigation led to the choice of an 80:20 methanol:water (v/v) solvent system for all further investigations in this study. It was observed that the spectrum of the metallated DPTC in this chosen solvent system changed over time; in the third case, therefore, the kinetics of this change was observed over a 72 hour period.

In the case of both DPTC and DPTC-Co, concentrated solutions of the chromophore were prepared in ethyl acetate; 10 µl of chromophore solution was added to 4 ml of solvent. The spectrum of each solution was recorded as indicated in **Section 4.2.3**.

The stability of DPTC-Co in various methanol:water solutions was determined by preparing a concentrated solution of the corrole dissolved in methanol; 50 µl of the chromophore was added to solutions of varying methanol:water ratios; 10 ml of each solution was prepared. The spectroscopic changes were monitored as a function of time and light exposure.

It was observed that the spectrum of DPTC-Co in 80:20 methanol:buffer solution changed over time. The kinetics for this slow change in the spectrum were monitored at 388 and 437 nm and were recorded using the kinetics program in the Cary WinUV suite.⁵²

The rate constant was calculated by standard non-linear least squares methods in SigmaPlot by fitting the experimental data to Equation 4.3.1 where A is the absorbance at a particular wavelength, A_0 is the initial absorbance, a is a scaling factor, k is the first order rate constant to be determined and t is the time (s).

$$A = A_0 + ae^{-kt}$$

Equation 4.3.1

4.3.3 The spectra of free base DPTC

The spectrum of the free base DPTC is highly dependent on the choice of solvent. The absorption maxima of the free base corrole in a selection of solvents are given in Table 4.3.1 while the spectra are presented in Figure 4.3.2. The hydrogen bonding ability of the solvent influences the general shape of the spectrum with hydrogen-bonding solvents having a broadening, hypochromic effect on the absorption bands. A similar phenomenon has been observed for a metallated porphyrin by Pesternack and co-workers.⁷⁸ In their case, the increase in the fraction of water in acetone:water mixtures led to broader peaks with diminished intensity.

Solvents can be grouped into three classes according to their effects on the spectrum of DPTC: non-polar (hexane, ethyl acetate and dichloromethane), intermediate polarity (THF and acetone) and polar (acetonitrile and methanol).

The most intense bands in the Soret region presented with defined shoulders (lower in energy than the main band) while the Q band region contained two defined peaks when DPTC was present in non-polar organic solvents. In solvents of intermediate polarity, the main Soret band diminished in intensity and experienced a bathochromic shift. The shoulder was less defined than in non-polar solvents. Additional broad, higher energy bands in the Soret region appeared. The Q bands were less defined, with similar intensity. In polar organic solvents such as methanol and acetonitrile, the Soret bands broadened and were lower in intensity. The shoulder was poorly defined. Q bands were less defined and lower in intensity compared to both the non-polar and intermediate solvents.

Table 4.3.1 Absorption maxima for the free base DPTC in a selection of solvents

Solvent	Hydrogen bonding ability	Polarity ($E_T(30)^{61}$)	Absorbance at wavelength (nm)			
			415	435	583	611
Hexane	None	31.0	2.116	1.561	0.539	0.488
Ethyl acetate	Weak acceptor	38.1	1.631	1.052	0.309	0.275
Dichloromethane	None	40.7	2.034	1.285	0.347	0.338
THF	Acceptor	37.4	0.728	0.637	0.336	0.284
Acetone	Acceptor	42.2	0.634	0.554	0.274	0.223
Acetonitrile	Acceptor	45.6	0.837	0.602	0.165	0.137
Methanol	Donor and acceptor	55.4	1.107	0.721	0.195	0.171

The changes in the electronic spectra of *N*-acetylmicroperoxidase-8 upon $\pi\cdots\pi$ dimerization were investigated by Munro and Marques.⁷⁹ $\pi\cdots\pi$ dimers experienced shifts in the electronic spectra when compared to the spectrum of the monomer. In the case of *N*-acetylmicroperoxidase-8, $\pi\cdots\pi$ dimerization occurred as a function of ionic strength and resulted in a broadening and decrease in intensity of bands in the UV-vis spectrum.⁷⁹ In the case of DPTC, both NMR (recorded in non-coordinating deuterated chloroform) and crystallographic data indicated that the corrole may interact with its neighbours in solution as well as in the solid state through significant $\pi\cdots\pi$ interactions as discussed in **Part 2, Section 2.2.1**. A very low concentration of DPTC was used for the collection of the spectra in Figure 4.3.2, thus decreasing the possibility of $\pi\cdots\pi$ dimerization. This was assumed as the solution chemistry and Beer-Lambert behaviour of DPTC has not been explored. Study of the Beer-Lambert behaviour of DPTC in a variety of solvents would be required to explore the possibility of $\pi\cdots\pi$ dimerization or aggregation. The decrease in intensity and the broadening of the absorption bands seen in Figure 4.3.2 is speculated to occur as a result of the perturbation of the HOMO-LUMO gap as a result of hydrogen bonding between the macrocyclic inner core hydrogens and solvents capable of hydrogen bonding.

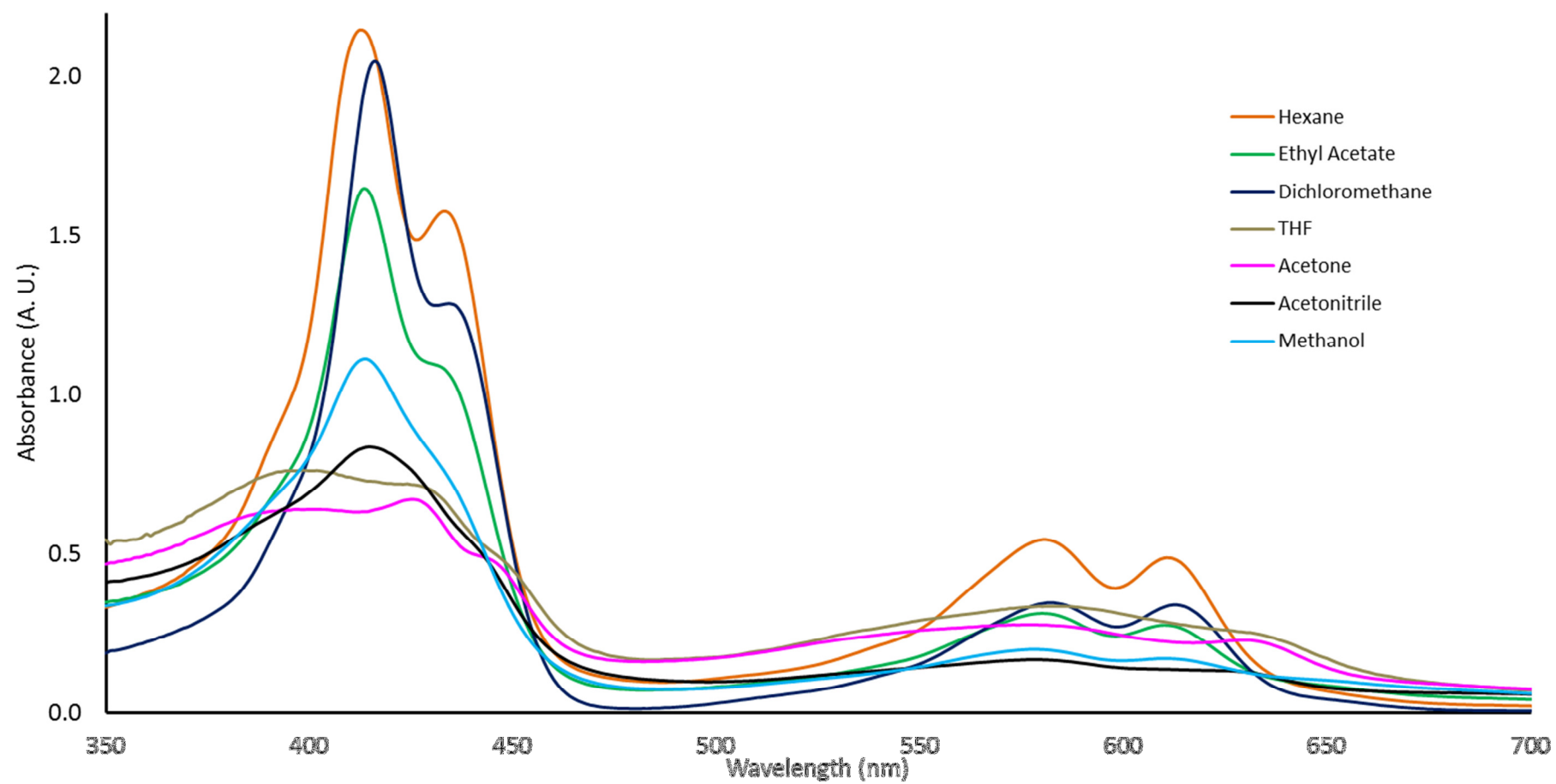


Figure 4.3.2 The effect of solvent on the spectrum of the free base DPTC ([DPTC] $\approx$ 0.6 mM)

4.3.4 The spectra of DPTC-Co

The spectra of DPTC-Co depend on the coordinating ability of the solvent, with solvent coordination resulting in a dramatic shift of the Soret from the 380 nm region to the 450 nm region. In addition, the appearance of a lower energy shoulder was observed to occur. The Q band region also experienced a considerable change with the Q band shifting from the 550 to the 600-640 nm region. The spectra of DPTC-Co in various solvents are presented in Figure 4.3.3 below.

Solvents can be grouped into two main groups according to their effect on the spectrum of DPTC-Co. Non-coordinating solvents include dichloromethane, hexane and ethyl acetate while the coordinating solvents include acetone, methanol, acetonitrile and THF.

The spectra of DPTC-Co in non-coordinating solvents differ only in intensity, or extinction coefficient, with a strongly absorbing Soret band at 388 nm and weakly absorbing, broad Q band at 555 nm. Coordinating solvents induced a large spectroscopic change with the splitting of the Soret band. In both acetonitrile and acetone, this band was split to yield a pronounced shoulder at 453 nm while in methanol and THF this shoulder was not seen. It is thought that the Soret at 388 nm is indicative of a five-coordinate species, while the multiple bands in the 440 nm region are due to the presence of a six-coordinate species. The broadening and decrease in intensity of the spectra in coordinating solvents, in particular acetonitrile, may be due to aggregation. A study of the Beer's Law behaviour of DPTC-Co in different solvents would be required to rationalise the observed spectra. Such a study would also indicate if the splitting of the Soret band in the 450 nm region is a result of the solvation of the macrocycle or aggregation. A similar large bathochromic shift of the Soret was observed by Adamian and co-workers upon the change from a five-coordinate to six-coordinate cobalt corrole system during the binding of pyridine to a corrole with an existing triphenylphosphine axial ligand.³⁵

The position of the Q bands was also found to be solvent dependent. In acetonitrile and acetone, Q bands were present in the 543 nm and 622 nm region with an additional Q

band at 582 nm in acetonitrile. In methanol and THF Q bands were present at 536, 575 and 608 nm.

The ratio of the 388 nm:438 nm peak heights (Table 4.3.2) is remarkably different for the four coordinating solvents. As the availability of the electron pair on the donor atom (oxygen in the case of acetone, THF and methanol and nitrogen in the case of acetonitrile) increases, the ratio of the 388 nm:438 nm Soret intensity decreases, indicative of an increase in the fraction of six-coordinate species in solution. The soft nature of the cobalt in DPTC-Co has a greater affinity to the soft, diffuse lone pair of the acetonitrile than to the harder, less diffuse lone pairs of acetone.

Table 4.3.2 The ratio of the 388 nm Soret to the 438 nm Soret with differing solvents

Solvent	Polarity ($E_T(30)^{61}$)	Absorbance (A.U.) at		
		wavelength (nm)		388 nm:438 nm
		388	438	
THF	37.4	1.292	0.992	1.307
Acetone	42.2	1.460	0.736	1.984
Acetonitrile	45.6	0.817	1.318	0.620
Methanol	55.4	1.121	1.287	0.871

There does not appear to be any correlation between solvent properties and either the ratio of band heights or band positions. The solvent properties examined include polarity, dielectric constant, Gutmann donor number, refractive index, molar transition energies ($E_T(30)$), dipole moments, Hildebrand solubility parameters, Kamlet-Taft hydrogen donor, acceptor and polarizability parameters and partition coefficients.

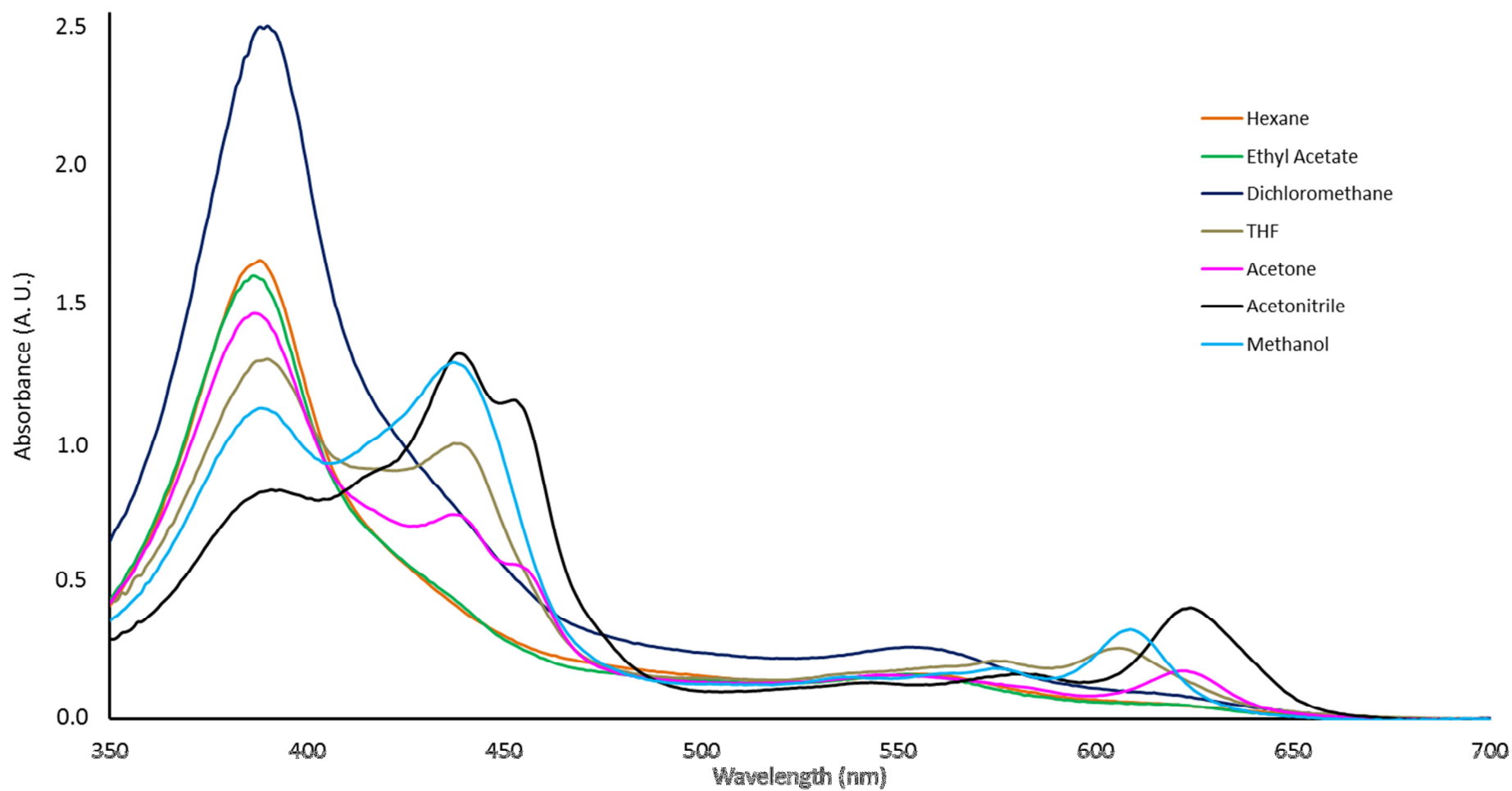


Figure 4.3.3 The effect of solvent on the spectrum of DPTC-Co ([DPTC-Co] $\approx$ 0.05 mM)

4.3.5 The stability of DPTC-Co in methanol:water solvent systems

This study aimed to compare a synthesised biomimetic system to vitamin B_{12a}. As such, the composition and ionic strength of the solvent system in which the stability constants were to be determined needed to be the same for the biomimetic and vitamin B_{12a}. Unfortunately, DPTC-Co was not water soluble, but rather was soluble in methanol and methanol:water mixtures. Therefore, the stability of DPTC-Co when exposed to light after 48 hours was determined in a range of methanol:water mixtures. The spectra of the initial solution, after 48 hours exposed to light and after 48 hours with no light exposure are presented in Figure 4.3.4 below.

The stability of DPTC-Co was poor, with a degree of precipitation in solutions with less than 40% methanol, regardless of the extent of light exposure. In a 20:80 methanol:water solvent system, DPTC-Co precipitated out of solution immediately, while in 40:60 methanol:water, DPTC-Co precipitated out of solution after 48 hours. In 60:40 methanol:water, DPTC-Co showed greater stability, with the decrease in absorption of the chromophore occurring to a lesser extent while in 80:20 methanol:water, DPTC-Co showed the greatest stability with little change in the absorbance of the chromophore. There was a light dependant change in the Soret band at 380 nm. After light exposure, a collapse of the 380 nm Soret is observed, with an increase in the intensity of the 440 nm Soret. As discussed in **Section 4.3.4** above, this is thought to be an effect of the coordinating behaviour of the solvent. Owing to the relative stability of the system, 80:20 methanol:water was chosen as the solvent system that was to be used throughout this study.

Water is a highly polar and coordinating solvent. It is therefore surprising that the spectra of DPTC-Co in solvents with high water content exhibited the spectrum indicative of the five-coordinate species only. Owing to the insolubility of DPTC-Co in water, and the precipitation of material in high water content solvent systems, it appears that DPTC-Co may form an aggregate or dimer that sterically prevents the water from coordinating to the cobalt metal centre.

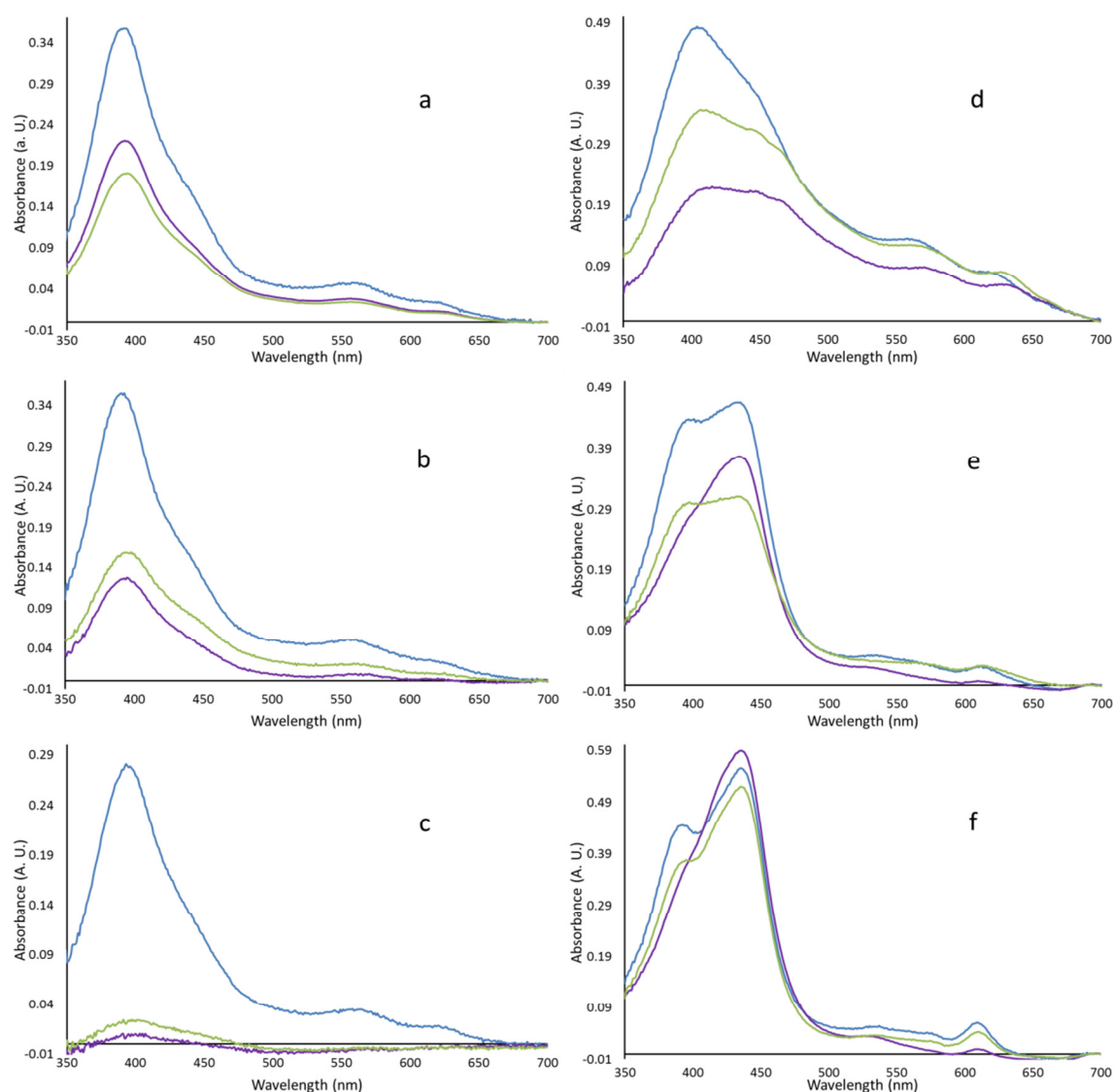


Figure 4.3.4 The stability of DPTC-Co in methanol:water mixtures. Blue – time zero; purple – 48 hrs light exposure; green – 48 hrs no light exposure. Methanol:water mixtures: **a** - 5:95; **b** - 10:90; **c** - 20:80; **d** - 40:60; **e** - 60:40; **f** - 80:20 ([DPTC-Co] $\approx$ 0.02 mM)

The observed change in spectrum of DPTC-Co in 80:20 methanol:water was monitored as a function of time over two hours. The change in absorbance at 388 and 437 nm as well as the calculation of the associated rate constants for the first 2000 s are illustrated in Figure 4.3.5. It is thought that there is an equilibrium between the five-coordinate and six-coordinate DPTC-Co species in solution as in Scheme 4.3.1.

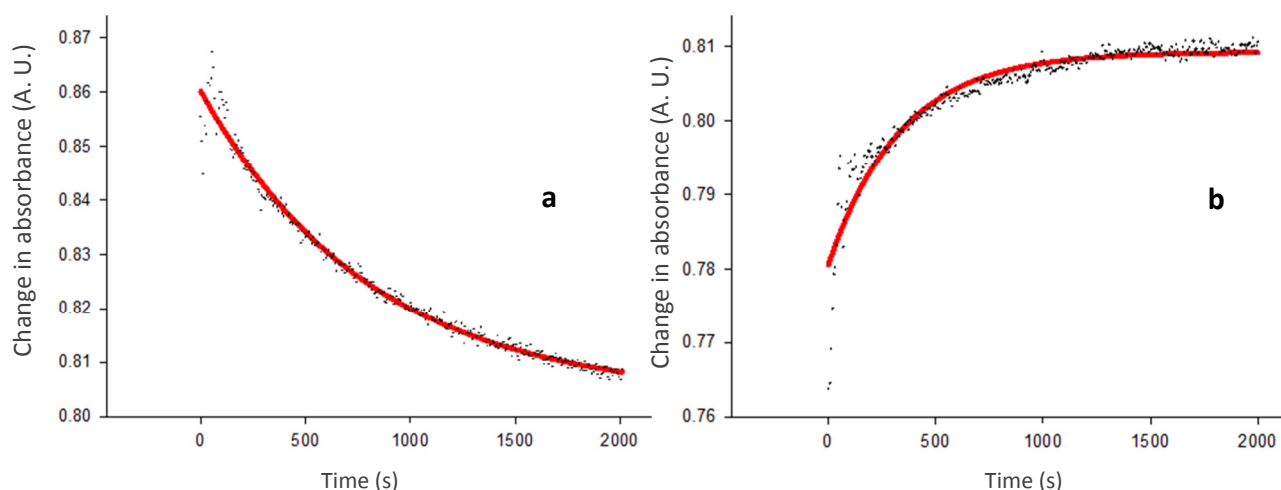
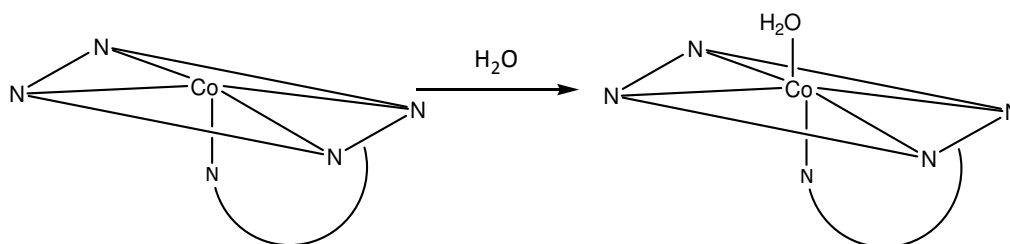


Figure 4.3.5 The change in absorbance of DPTC-Co in 80:20 methanol:water solvent system over 2000 s at **a** – 388 nm and **b** – 437 nm at $\pm 25.0^\circ\text{C}$. Black circles indicate the experimentally determined absorbances. Red line indicates the calculated curve for $k = 1.2 \pm 0.3 \times 10^{-3} \text{ s}^{-1}$ in **a** and $k = 3.0 \pm 0.1 \times 10^{-3} \text{ s}^{-1}$ in **b** from Equation 4.3.1



Scheme 4.3.1 Schematic representation of the conversion of five-coordinate DPTC-Co to six-coordinate DPTC-Co

Moreno-Esparza and co-workers studied the kinetics and thermodynamics of the binding of iodide to aquacobalamin as a function of varying methanol:water solvent mixtures.⁸⁰ While many substitution reactions have been studied in an aqueous environment, it has been suggested that water is an inappropriate solvent to use as a mimic of vitamin B₁₂'s biological environment as biological microenvironments are often partially hydrophobic in nature.⁸⁰ This suggests that the use of a methanol:water solvent system is quite appropriate in the study of vitamin B_{12a}.

4.3.6 Conclusions

The spectra of both the metallated and the unmetallated DPTC are solvent dependent.

DPTC was found to be soluble in a wide range of organic solvents. The hydrogen bonding capabilities of the solvent influenced the spectra, with the use of non-hydrogen bonding, non-polar solvents resulting in spectra with sharp bands of high intensity. The use of solvents with hydrogen bonding capabilities resulted in broader, less defined peaks of lower intensity.

The coordinating ability of the solvent affected the spectra of DPTC-Co. The use of non-coordinating solvents (dichloromethane, ethyl acetate and hexane) resulted in spectra with one intensely absorbing Soret and one Q band in the 555 nm region. The use of coordinating solvents resulted in very different spectra with multiple Soret bands of varying intensity as well as more intense Q bands in the 600-650 nm region. The position of the Soret appears to indicate the coordination environment of the cobalt ion. Five-coordinate species exhibited a strongly absorbing Soret in the 390 nm region, while the Soret or multiple Soret bands of the six-coordinate species appeared in the 440 nm region. The spectrum of the five-coordinate species and that of a mixture of five- and six-coordinated species is given in Figure 4.3.6.

The solvent of choice for the study of both the DPTC-Co biomimetic and vitamin B_{12a} was 80:20 methanol:water. Lower methanol content led to precipitation and the absorption peaks of the spectra became broad with a dramatic decrease in intensity. The conversion of the five to the six-coordinate DPTC-Co species was slow with a rate constant of approximately $2.0 \times 10^{-3} \text{ s}^{-1}$ at 25°C.

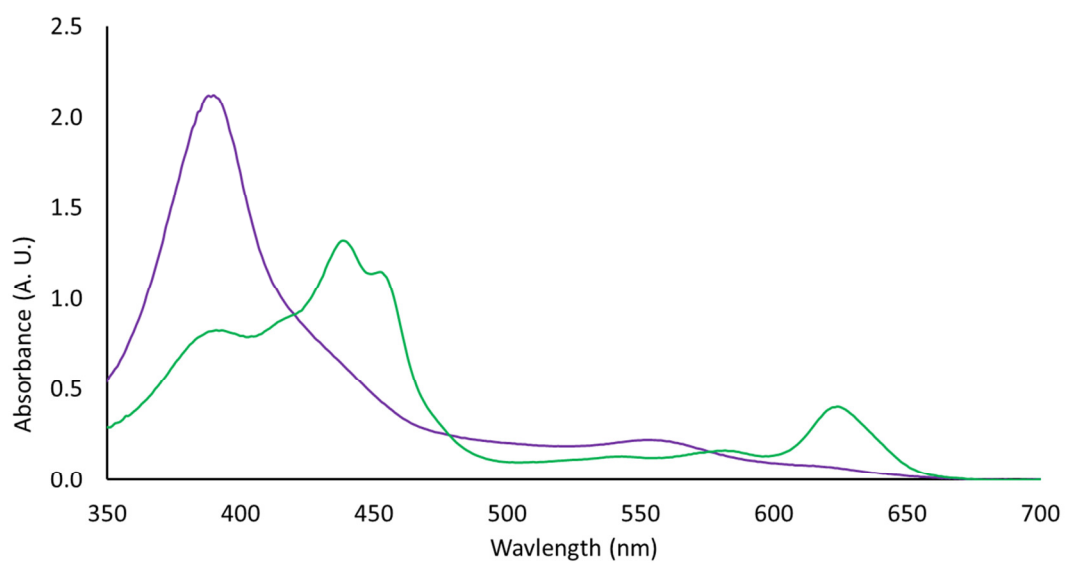
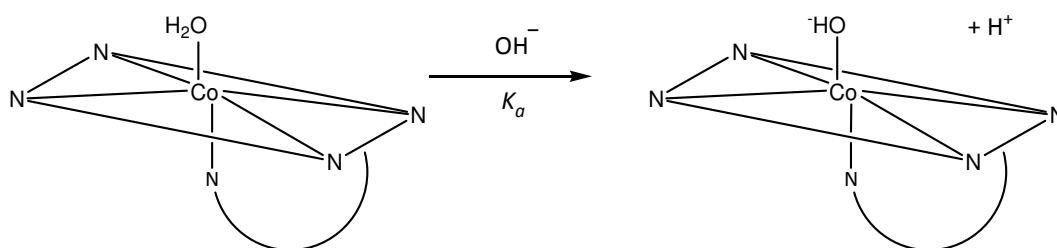


Figure 4.3.6 Electronic spectra of five-coordinate DTPC-Co in dichloromethane (purple) and six-coordinate DPTC-Co in acetonitrile (green)

4.4 pK_a determination in an 80:20 methanol:water solvent system

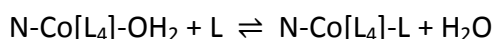
4.4.1 Introduction

The pK_a for the aqua/hydroxo equilibrium for a corrin or corrole coordination complex, as illustrated in Scheme 4.4.1, can be determined from the spectroscopic changes accompanied with the change in pH.



Scheme 4.4.1 The aqua/hydroxocobalamin equilibrium

This pK_a is determined for a number of reasons. The observed stability constant for the exchange of an axial ligand needs to be corrected for the pK_a of the aqua/hydroxo equilibrium in order to obtain a pH-independent stability constant for ligand substitution reactions of the following type:



where N is an axial nitrogen donor ligand covalently bound to a macrocycle, L_4 . The macrocycle provides four equatorial ligands to coordinate the cobalt. When determining the kinetics of such reactions with vitamin B_{12a} , the hydroxo complex ($N\text{-Co}[L_4]\text{-OH}^-$) has been found to be inert to substitution in the case of both vitamin B_{12a} ⁵⁵⁻⁵⁷ and iron(III) porphyrins;^{58,59} as such, these rate constants are pH dependent. The observed rate constants have to be corrected for the effect of pH. Stability constants also have to be corrected for this pH effect. Therefore it is assumed that the reactions of cobalt(III) corroles are pH-dependent as well. The pK_a of the DPTC-Co can be compared to that of

vitamin B_{12a} and this may provide insight into the effect that the macrocycle has on the nature of the cobalt-oxygen bond.

In addition to the equilibrium illustrated in Scheme 4.4.1, vitamin B_{12a} possesses several other pK_a s, including that of the deprotonation and subsequent coordination of the benzimidazole ligand to the cobalt as well as the deprotonation of the phosphate group of the nucleotide linker. DPTC-Co is expected to possess two pK_a s, for the deprotonation of the aqua species to yield the hydroxo form as well as the deprotonation of the imidazole base and subsequent coordination as an axial ligand.

4.4.2 Methods particular to the pK_a determination

The pK_a of vitamin B_{12a} was determined in both aqueous (multi-component buffer) and 80:20 methanol:multi-component buffer solvent systems. The pK_a of DPTC-Co was determined in 80:20 methanol:multi-component buffer only. Table 4.4.1 describes the composition of the multi-component buffered solutions used in the pK_a titrations. The buffer solution was prepared and diluted to yield either a 80:20 water:buffer or 80:20 methanol:buffer solvent system. The ionic strength was not adjusted through the addition of an inert metal salt and therefore ionic strength is reported as an average of the ionic strength of the multi-component buffer solution as a function of pH over the course of the titration.

Table 4.4.1 Composition of the buffered solutions used in the pK_a titrations

Buffer	Concentration (M, $\times 10^{-3}$)	Final concentration after dilution (M, $\times 10^{-3}$)
MOPS	5.045	1.009
TRIS	5.399	1.080
CHES	5.142	1.028

The required solvent was added to a double walled titration cell fitted with a lid with openings for the pH electrode and a drawn-out capillary tube such that the system was sealed to minimise the evaporation of methanol. The temperature of the cell was maintained at $25 \pm 0.1^\circ\text{C}$ by circulating water from a temperature controlled water bath through the outer sleeve of the double walled titration cell. The solvent circulated from the cell to the 1.5 ml volume quartz self-masking flow cell through 0.4 mm silicon tubing by a Watson-Marlow 101U peristaltic pump at a rate of 90 revolutions per minute. Chromophore was added either as a solid (vitamin B_{12a}) or in solution (concentrated solution of DPTC-Co in ethyl acetate). The pH was adjusted to between 3 and 4 using a concentrated solution of orthophosphoric acid after which an initial UV-vis spectrum was recorded. The pH was gradually increased by the addition of drops of concentrated

sodium hydroxide using a drawn-out capillary tube and the solution was allowed to equilibrate. Spectra were recorded after each pH adjustment.

The pK_a was calculated by non-linear least squares methods in SigmaPlot by fitting the data to Equation 4.4.1 where A is the absorbance at a particular wavelength, A_0 is the initial absorbance, A_1 is the absorbance at 100% dihydroxocobalamin conversion and K_a is the acid dissociation constant to be determined.

$$A = \frac{10^{-pH} A_0 + 10^{-pK_a} A_1}{10^{-pH} + K_a}$$

Equation 4.4.1

The reported pK_a was calculated from the sum of the weighted pK_a values obtained for each wavelength at which there was a large spectroscopic change. The error was calculated from the sum of weighted relative percentage error reciprocals. An example of this can be found in **Appendix 4.4** and the accompanying raw spectroscopic data can be found in **Digital Appendices 4.1.1** and **4.1.2**.

4.4.3 pK_a of vitamin B_{12a}: the effects of solvent

The pK_a of Vitamin B_{12a} for the aqua/hydroxo equilibrium (Scheme 4.4.1) was determined in both aqueous and 80:20 methanol:buffer solvent systems with an average ionic strength of 0.8 mM.

At pH 4, in aqueous media, spectroscopic maxima were present at 350, 410, 498 and 525 nm, representing the γ , D, β and α bands respectively. As the pH of the solution increased, all of the above-mentioned bands underwent a bathochromic shift to 357, 416, 510 and 536 nm respectively, with well-defined isosbestic points at 331, 365, 430, 475 and 540 nm. The γ band underwent a hypochromic shift while the D, β and α bands underwent hyperchromic shifts as the pH increased. No spectroscopic changes were observed above pH 9, indicating the full conversion of aquacobalamin to hydroxocobalamin. The spectroscopic changes of Vitamin B_{12a} in aqueous solution with varying pH are illustrated in Figure 4.4.1.

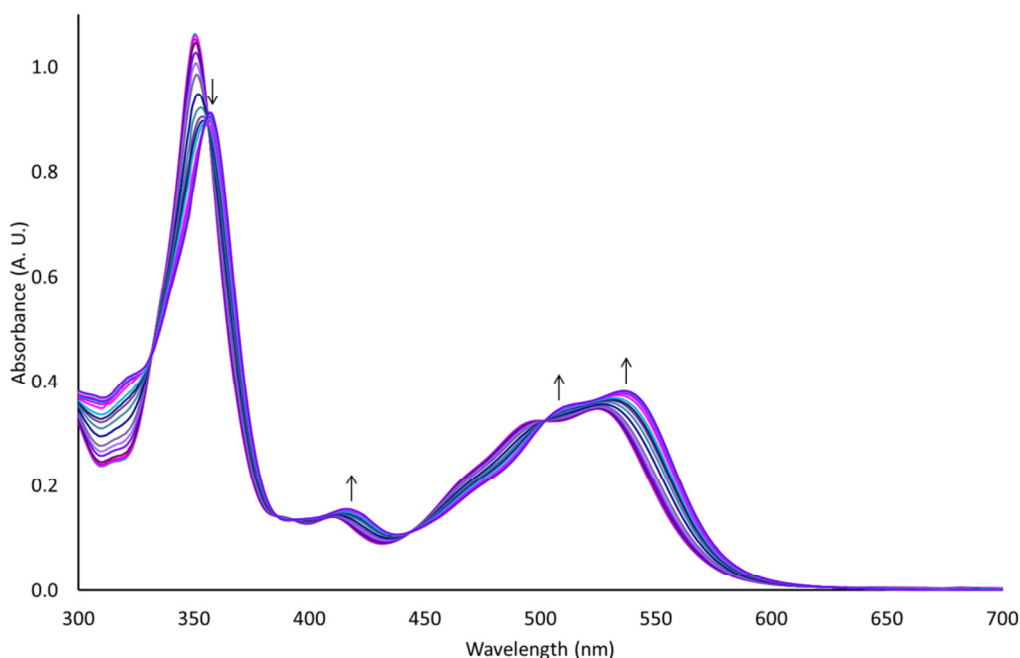


Figure 4.4.1 Spectroscopic changes of vitamin B_{12a} in aqueous solution with varying pH

Similar spectroscopic changes were observed during the pK_a titration of vitamin B_{12a} in the 80:20 methanol:buffer solvent system. The characteristic γ , D, β and α bands present

at 350, 410, 498 and 525 nm, respectively, in an aqueous solvent system at pH 4 shifted slightly (apart from the γ band which remains unchanged at 350 nm) to lower wavelengths at 350, 408, 496 and 523 nm for the γ , D, β and α bands, respectively, in the 80:20 methanol:buffer solvent system. As in the aqueous system, the increase in pH resulted in the γ band experiencing a hypochromic shift and the D, β and α bands experiencing hyperchromic shifts. This change in absorption intensity was accompanied by a bathochromic shift of the whole spectrum with maxima at 356, 418, 510 and 534 nm for the γ , D, β and α bands respectively, with clear isosbestic points at 338, 356, 455 and 498 nm. Above pH 9 there was no change in the absorption spectrum indicating the complete conversion of aquacobalamin to hydroxocobalamin.

The pK_a for vitamin B_{12a} in aqueous solution ($\mu = 0.8$ mM) was determined to be 7.462 ± 0.007 while in a 80:20 methanol:buffer solvent system ($\mu = 0.8$ mM), the pK_a was determined to be 7.40 ± 0.02 . The pK_a in 80:20 methanol:buffer solvent system was marginally lower than when determined in aqueous solution. The solvating ability and dielectric constant of a solvent are important factors that affect the equilibrium position of the dissociation constant.⁸¹⁻⁸³ Water has a high dielectric constant (78.36)⁶¹ and is able to stabilise the ions produced during an acid dissociation reaction. Methanol has a lower dielectric constant (32.66)⁶¹ and is thus less able to stabilise the produced ions. It has been observed in small organic systems such as 4-(2-pyridylazo)resorcinol⁸¹ and L-Norvaline⁸³ that a decrease in the dielectric constant of a solvent results in a decrease in the pK_a .

Examples of the experimental data and fit are given in Figures 4.4.2 (aqueous solvent system) and 4.4.3 (80:20 methanol:buffer solvent system). In both cases, the pK_a showed a slight wavelength dependence. Reported pK_a s are a weighted average of the five wavelengths considered. Details can be found in **Appendix 4.4**.

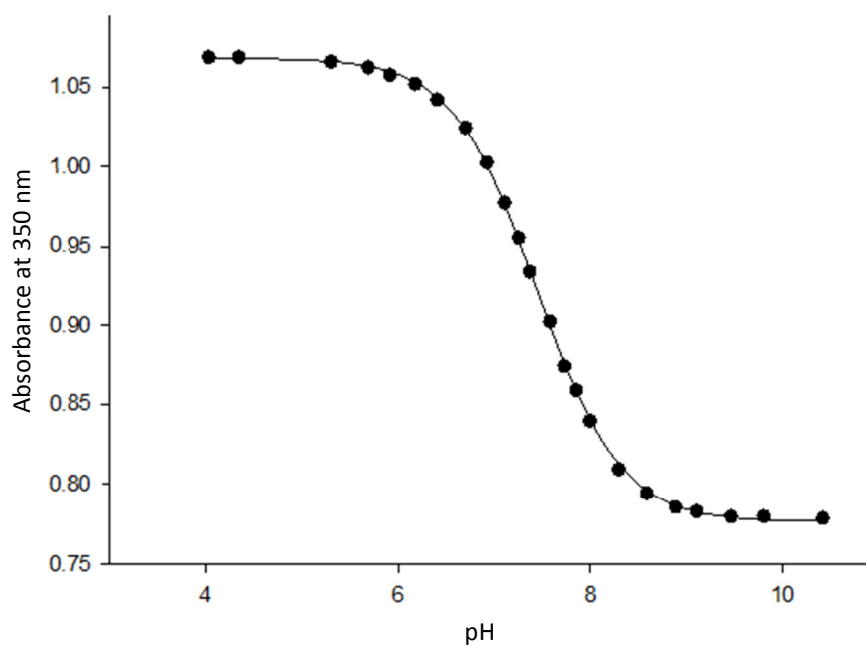


Figure 4.4.2 Absorbance changes of vitamin B_{12a} in aqueous solution with varying pH at 350 nm. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve for $pK_a = 7.462 \pm 0.007$ from Equation 4.4.1

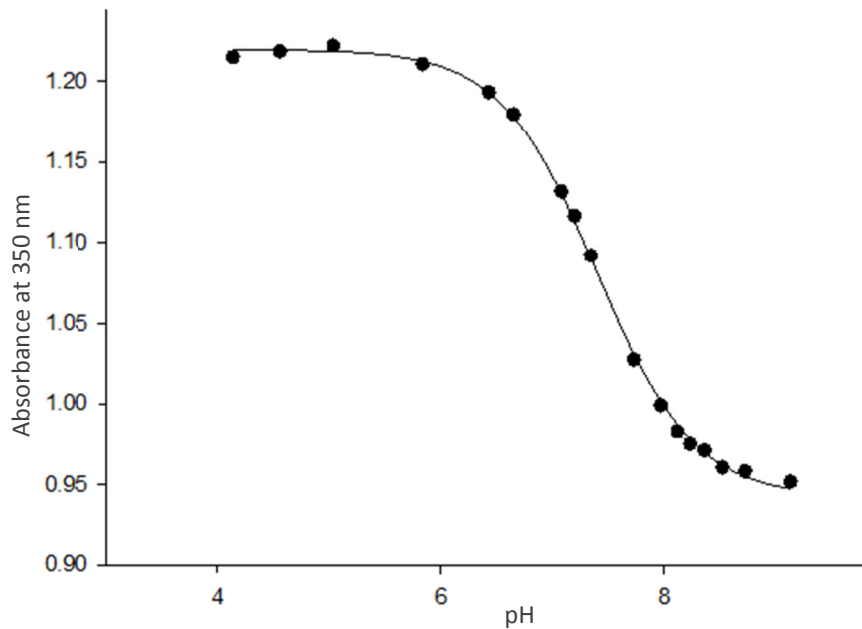


Figure 4.4.3 Absorbance changes of vitamin B_{12a} in 80:20 methanol:buffer solution with varying pH at 350 nm. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve for $pK_a = 7.40 \pm 0.02$ from Equation 4.4.1 (details can be found in **Appendix 4.4**)

4.4.4 pK_a of vitamin B_{12a}: the effects of ionic strength

The ionic strength of the solvent plays an important role in the pK_a of a system. A variety of inert salts have been used as supporting electrolytes, such as perchlorates^{41,84} and nitrates.⁸⁵ In some instances, chloride salts have also been used,^{55,86-88} but the use of a chloride salt as an inert salt as a supporting electrolyte is inappropriate as chloride is known to bind to vitamin B_{12a}.^{29,85} The pK_a increases as the ionic strength (with non-chloride salts) increases as in Figure 4.4.4. As the ionic strength of a solvent system increases, so the polarity of the solvent system increases.⁶¹ It is known that the ionic strength, and thus polarity, of the reaction medium can affect both the kinetics^{61,71,89} and equilibrium constant^{89,90} of a reaction.

Table 4.4.2 pK_a of aquacobalamin with varying ionic strength

Solvent	Ionic strength, μ (M)	pK_a	Reference
Water	0.0007*	7.462 ± 0.007	This work
80:20 methanol:water	0.0008*	7.40 ± 0.02	This work
Water	0.042 (NaCl)	7.75	Hanania ⁸⁶
Water	0.047 (Phosphate)	7.8	Hayward ⁹¹
Water	0.054 (NaCl)	7.6 ± 0.3	Randall ⁸⁷
Water	0.2 (NaClO ₄)	7.8 ± 0.1	Betterton ⁸⁴
Water	0.5 (KCl)	7.8	Rubinson ⁸⁸
Water	0.5 (NaNO ₃)	8.09 ± 0.02	Brown ⁸⁵
Water	1.0 (KCl)	8.1	Reenstra ⁵⁵
Water	Not specified	7.5	Smith ⁹² and Fantes ⁹³

* ionic strength is reported as an average of the ionic strength of the multicomponent buffer solution as a function of pH over the course of the titration.

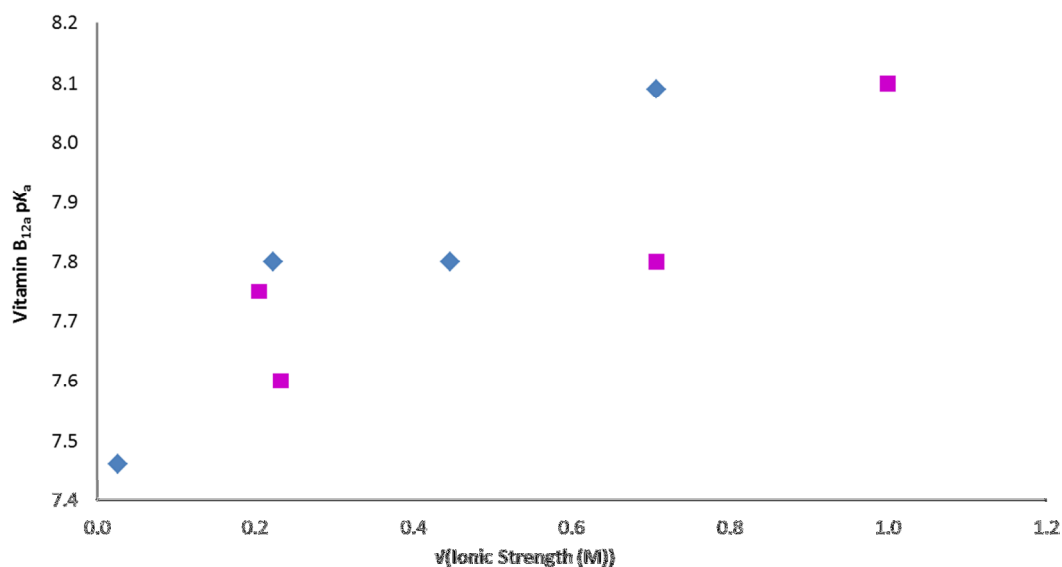


Figure 4.4.4 The increase in pK_a of vitamin B_{12a} in aqueous solution with ionic strength (M). Ionic strength was adjusted using non-chloride salts (blue diamonds) or chloride salts (purple squares).

An increase in ionic strength results in an increase of the polarity of the solution. In a more polar solution, the formation of more polar, or charged species, would be favoured over the formation of less polar, or neutral species. Aquacobalamin carries a net charge of 1+ while hydroxocobalamin is neutral. Formation of the neutral hydroxocobalamin would become increasingly less favourable with increasing ionic strength, thus driving the pK_a up.

4.4.5 pK_a of DPTC-Co

The pK_a of DPTC-Co was determined in a 80:20 methanol:buffer solvent system with an average ionic strength of 0.8 mM.

At pH 3.5 a single broad Soret at 434 nm and three Q bands at 525, 643 and 694 nm were present as in Figure 4.4.5. The absorbance of the spectra decreased as the pH was raised from 3.5 to 7.5. The Soret shifted slightly to 435 nm while the Q bands shifted to 521, 626 and 701 nm. At pH 8.6 a Q band of significant intensity appeared at 621 nm. This Q band increased in intensity as the pH increased to 9.2 while the Soret became less broad and the maximum absorbance shifted from 434 nm to 437 nm with a gradual increase in absorbance. The Q band at 701 nm decreased in intensity and a new Q band appeared at 583 nm. At pH 9.8 a shoulder on the Soret appeared at 453 nm. As pH increased to 10.5 the Soret at 437 nm became more narrow and increased in intensity and the shoulder at 453 nm became more distinct. The Q bands at 583 and 621 nm increased in intensity while the Q band at 701 nm decreased in intensity further. There was no change in the spectrum at higher pH indicating the complete conversion of the aqua species to the hydroxo species. Two sets of isosbestic points were observed. Between pH 3.5 and pH 7.5, isosbestic points were observed at 377 and 697 nm. Clear isosbestic points between pH 8.6 and 11.7 were present at 335, 434, 465, 545 and 648 nm. The spectra of DPTC-Co with increasing pH are given in Figure 4.4.5. The experimental and calculated data for the change in absorbance at 621 nm between pH 6.9 and pH 11.7 is presented in Figure 4.4.6. The pK_a for the aqua- hydroxo-DPTC-Co equilibrium was determined to be 9.76 ± 0.06 .

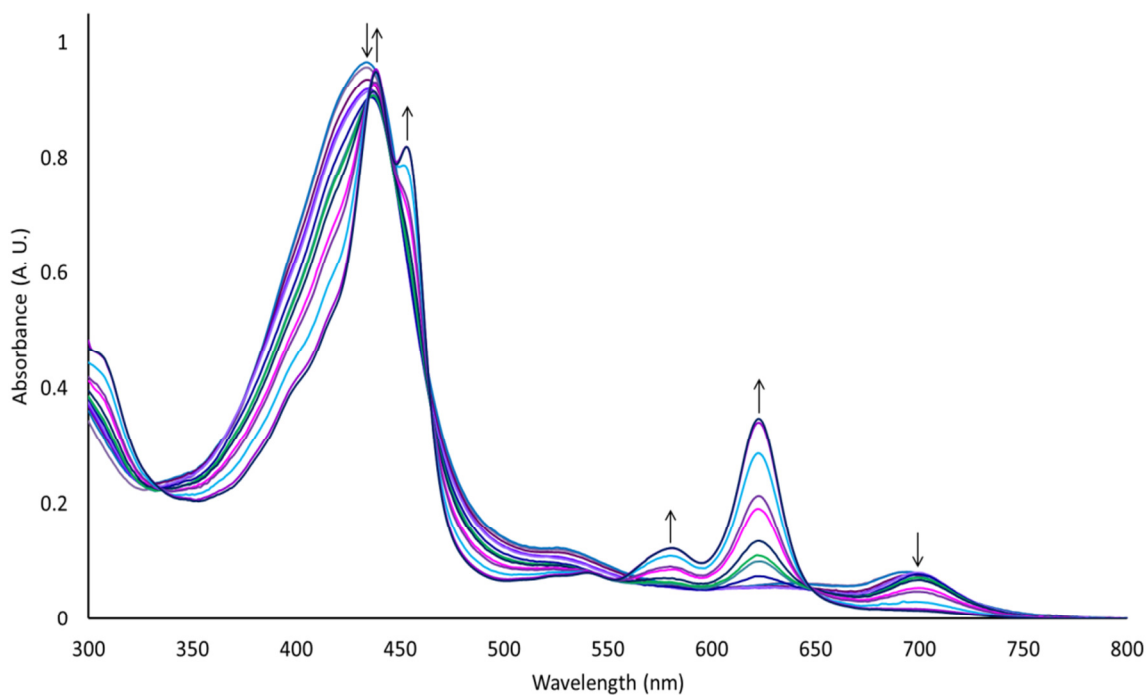


Figure 4.4.5 Spectroscopic changes of DPTC-Co in aqueous 80:20 methanol:buffer solution with varying pH (raw data can be found in **Digital Appendix 4.1.1**)

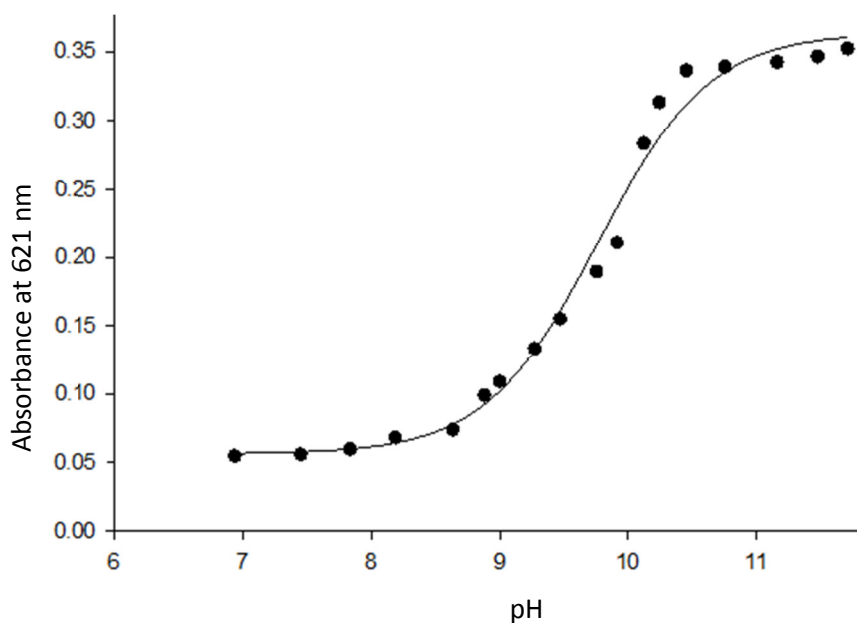


Figure 4.4.6 Absorbance changes of DPTC-Co in 80:20 methanol:buffer solution with varying pH between 6.9 and 11.7 at 621 nm. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve for $pK_a = 9.76 \pm 0.06$ in Equation 4.4.1 (details can be found in **Appendix 4.4**)

The pK_a for DPTC-Co (9.76 ± 0.06) is considerably higher than the pK_a for vitamin B_{12a} (7.40 ± 0.02) in the same solvent system and with the same ionic strength. A high pK_a value indicates that the DPTC-Co hydroxo species is less stable than hydroxocobalamin, the corresponding vitamin B_{12a} species.

Two series of experiments were conducted by Marques, Brown and co-workers involving a change in the electronic nature of vitamin B₁₂'s corrin ring through the addition of either an electron donating⁸⁵ or electron withdrawing⁹⁴ group at the C10 position. The introduction of an electron donating chloro group decreased the pK_a from 8.09 ($\mu = 0.5$ M NaNO₃) in vitamin B_{12a} to 7.65 ($\mu = 0.5$ M NaNO₃),⁸⁵ while a strongly electron withdrawing nitro group increased the pK_a to 10.71 ($\mu = 2.2$ M NaClO₄).⁹⁴ These were unexpected results.

The interpretation of the often used example of the difference in the first pK_a s of [Fe^{III}(H₂O)₆] ($pK_a = 2.19$) and [Fe^{II}(H₂O)₆] ($pK_a = 10.1$)⁹⁵ is that as the charge on the metal centre increases, the metal-oxygen bond becomes more polarised. This results in the electron density in the oxygen-hydrogen bond being pulled closer to the oxygen atom, resulting in a weaker, longer oxygen-hydrogen bond which therefore undergoes heterolytic cleavage more readily. As the charge on the metal decreases, the metal-oxygen bond is polarised to a lesser extent, resulting in a shorter, stronger oxygen-hydrogen bond which requires a much higher pH for deprotonation. This classic interpretation would suggest that as the charge on the cobalt in vitamin B₁₂ derivatives increased, through the addition of an electron withdrawing group such as the nitro group, the pK_a would have decreased. As this was not the case, it appears that the classic interpretation is not applicable to more complex, electron-rich macrocyclic systems. Marques, Brown and co-workers explained the observed unexpected increase in pK_a as being a result of the cobalt-oxygen bond in 10-nitrosoaquacobalamin becoming more ionic due to the cobalt(III) like character of the metal. Consequently, the charge on the oxygen was found to increase (from semi-empirical molecular orbital calculations) resulting in a stronger oxygen-hydrogen bond, requiring a higher pH for deprotonation.⁹⁴

Brown and Marques's findings that an increase in electron density on the macrocycle led to a decrease in pK_a does not support the findings that the pK_a of the more electron rich corrole containing system was considerably higher than that of vitamin B₁₂. In this case, the choice of solvent system, 80:20 methanol:water, may have affected the pK_a through a charge neutralisation effect. The aqua DPTC-Co species has a net charge of zero from cobalt(III) coordinated to the trianionic corrole macrocycle. The hydroxo species has a net charge of 1-. In a primarily organic solvent environment, the presence of a charged species would not be favourable, driving the pK_a up, making the charged species more difficult to attain. In the case of vitamin B_{12a}, aquacobalamin, with a charge of 1+ would be less favourable than the neutral hydroxocobalamin, thus the pK_a is low. The difference in the pK_a of vitamin B_{12a} in water and 80:20 methanol:water is admittedly small (7.462 ± 0.007 (water; $\mu = 0.8$ mM) vs 7.40 ± 0.02 (80:20 methanol:water; $\mu = 0.8$ mM)), but this may be due to a culmination of low ionic strength and a highly organic medium at the threshold pK_a value for this system.

The presence of two sets of spectroscopic changes of DPTC-Co with increasing pH, each accompanied by a set of isosbestic points, suggests that there is more than one pK_a in the given pH range. At low pH there appears to be a second pK_a as illustrated in the experimental and calculated data for the change in absorbance at 400 nm for the full pH range in Figure 4.4.7. There is a significant change in absorbance at the isosbestic points for the second pK_a , 335, 434, 465, 545 and 648 nm, below a pH of 8.6. An example of this is given for the absorbance for the isosbestic point at 545 nm in Figure 4.4.8. The second pK_a was determined to be approximately 6.7 ± 0.2 .

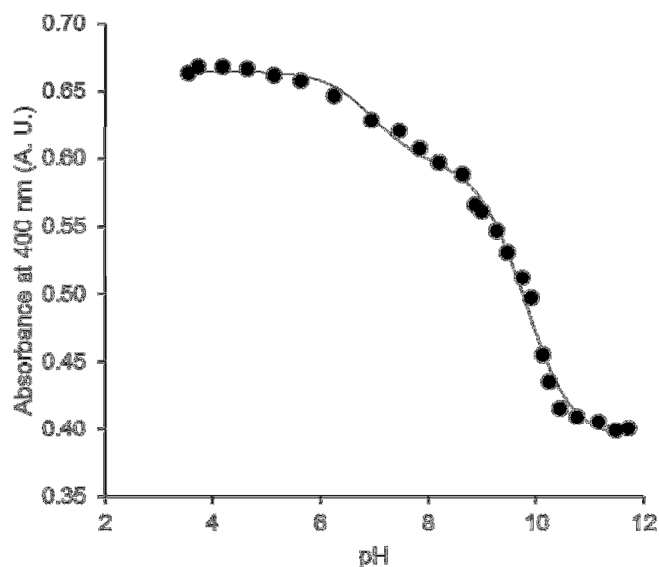


Figure 4.4.7 Absorbance changes of DPTC-Co in 80:20 methanol:buffer solution with varying pH between 3.5 and 11.7 at 400 nm. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve

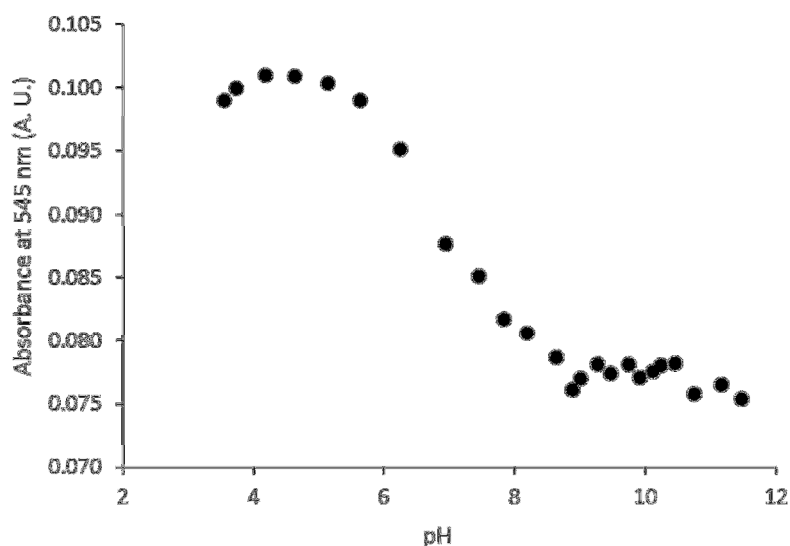


Figure 4.4.8 Observed absorbance changes of DPTC-Co in 80:20 methanol:buffer solution with varying pH at 545 nm, an isosbestic point for the second pK_a

In order to verify if this was a true pK_a the stability constants for the coordination of nitrite to DPTC-Co at various values of pH was determined as in Table 4.4.3. The observed stability constants were corrected for the fraction of aqua-DPTC-Co using the first determined pK_a of DPTC-Co of 9.76 ± 0.06 . Above a pH of 8.78 the stability constant decreased with increasing pH, but experienced little variation after the correction factor

was applied. Below pH 8.29 the stability constant increased with decreasing pH and the observed $\log K$ did not change when the correction factor was applied. This indicates that there is a third species present at low pH in addition to the aqua and hydroxo DPTC-Co species.

Table 4.4.3 The pH dependence of the stability constant of the coordination of DPTC-Co and nitrite

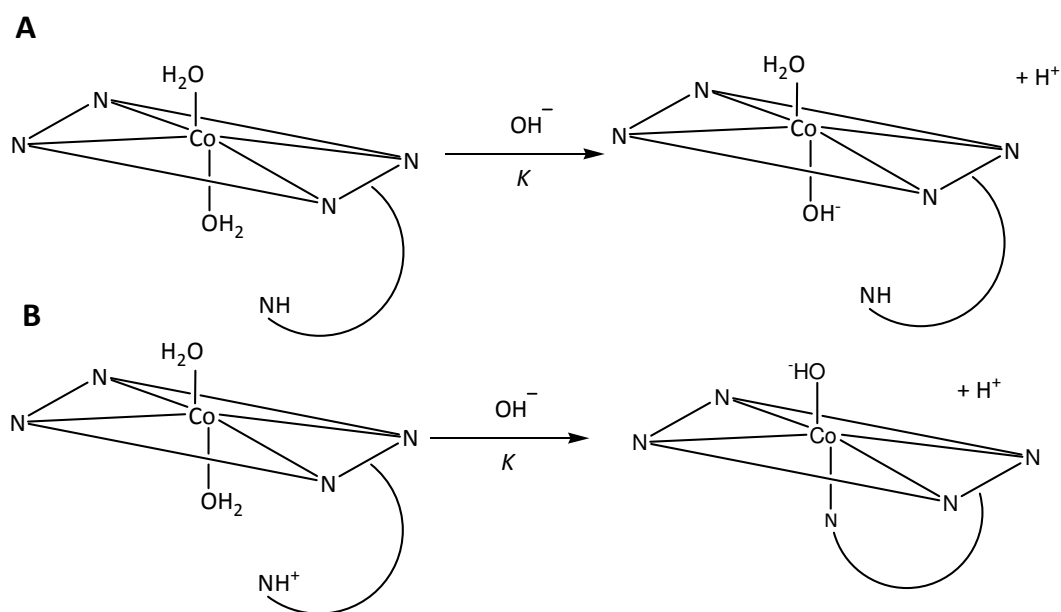
pH	$\log K_{\text{obs}}$	$\log K$	μ (M)*
6.04	8.77 ± 0.05	8.77 ± 0.05	0.013
6.47	6.6 ± 0.1	6.6 ± 0.1	0.004
7.10	4.29 ± 0.02	4.29 ± 0.02	0.011
7.49	3.56 ± 0.02	3.56 ± 0.02	0.017
8.29	3.39 ± 0.04	3.40 ± 0.04	0.023
8.78	2.95 ± 0.05	3.00 ± 0.05	0.006
9.51	2.86 ± 0.02	3.06 ± 0.02	0.016
10.02	2.62 ± 0.03	3.06 ± 0.03	0.021
10.91	1.80 ± 0.03	2.97 ± 0.03	0.019

*Ionic strength was calculated from the concentration of the charged buffer species at the experimental pH

The second pK_a might be due to one of the following equilibria: the deprotonation of one axially bound water in the diaqua species or the deprotonation and coordination of the imidazole base as illustrated in Scheme 4.4.2. The deprotonation of one water in the diaqua species seems unlikely, as the fraction of the diaqua species is likely to be low, and thus the deprotonation of one axially bound water would not contribute to large spectroscopic changes. The pK_a for the corresponding equilibrium for diaquacobalamin is 6.0.⁹¹

The deprotonation and subsequent coordination of the imidazole base of the tail of DPTC-Co is a more likely candidate, although the value for the pK_a is unexpectedly high. The pK_a for the corresponding equilibrium in vitamin B_{12a}, the coordination of the benzimidazole base, is -2.4.⁹¹ This is significantly lower than the pK_a of the conjugate acid of free benzimidazole at 5.56 (25°C, $\mu = 0.1$ M).⁹⁶ The histidine involved in the corresponding pK_a

in the case of the iron porphyrin containing acetyl-microperoxidase 8, is 3.21 (25°C, $\mu = 0.1 \text{ M NaClO}_4$).⁹⁷ Again, this is significantly lower than the pK_a for the conjugate acid of free histidine at 5.97 (25°C, $\mu = 0.0 \text{ M}$).⁹⁶ Reduction of the pK_a values from the free ligands to the coordinated ligands indicates competition between the metal ion and protons in solution for the nitrogen containing ligands. The pK_a of the conjugate acid of free imidazole is 6.99 (25°C, $\mu = 0.0 \text{ M}$)⁹⁶ while the pK_a for the coordinated base in DPTC-Co is 6.7 ± 0.2 . Such a minimal reduction in the pK_a might suggest that the design of the imidazole containing tail is not optimal for the coordination of the cobalt metal. This might be due to insufficient flexibility in the tail, and thus the angle of the interaction between the imidazole and the cobalt may be unfavourable for the optimal orbital overlap.



Scheme 4.4.2 Possible equilibria for the second pK_a . **A** – the deprotonation of one axially bound water in the diaqua species **B** – the deprotonation of the imidazole base

4.4.6 Conclusions

The pK_a of vitamin B_{12a} was determined in both water and 80:20 methanol:water at very low ionic strength and the pK_a of DPTC-Co was determined in 80:20 methanol:water at similarly low ionic strength.

The pK_a of vitamin B_{12a} was highly dependent on the ionic strength of the medium, with an increase in pK_a with increasing ionic strength. The pK_a was less dependent on the polarity of the solvent, as a very small difference was observed between the pK_a determined in water (7.462) and in 80:20 methanol:water (7.40).

Two pK_a s were observed for DPTC-Co. The first, representing the deprotonation of the aqua species leading to the hydroxo species was high at 9.76. This pK_a was significantly higher than the vitamin B₁₂ pK_a . In vitamin B_{12a}, deprotonation of the axially bound water results in an overall neutral molecule, with a decrease in the charge at the metal centre. In the case of DPTC-Co, the neutral molecule becomes charged upon deprotonation. In a methanol rich solvent system, a neutral system would be favoured over a charged system, thus resulting in the deprotonation of water bound to vitamin B_{12a} occurring more readily than in the case of DPTC-Co. The second pK_a was found to be 6.7 and may represent the deprotonation and coordination of the imidazole tail. This was unexpectedly high, and may be as a result of poor flexibility of coordination of the tail to the cobalt ion.

4.5 Corrole solution chemistry – Beer's law and determination of the extinction coefficient

4.5.1 Introduction

The Beer-Lambert law is a fundamental law which combines the work of Beer, correlating the light absorbed with the concentration of the chromophore present in solution, and that of Lambert, correlating the amount of light absorbed with the distance travelled through the light absorbing medium.⁹⁸ Beer's law states that the measured absorbance of monochromatic light⁹⁹ is proportional to the concentration of the chromophore. This holds true as long as the chromophore does not undergo any change that might affect the extinction coefficient, or the amount of light absorbed by the chromophore at a particular wavelength. Such changes include dimerization or polymerisation or changes due to the existence of a concentration-dependant equilibrium.¹⁰⁰ The deviation of linearity of the change in absorbance with increasing concentration can thus be used in establishing the concentrations for which the chromophore of interest is monomeric. In addition, the use of this relationship can be used in the determination of the extinction coefficient, ϵ , of the chromophore.

The extinction coefficient of a chromophore can be used in calculating the exact concentration of the chromophore in solution. It follows that ϵ must be determined accurately. This can be done in several ways. The most reliable method requires that a crystal structure of the chromophore has been determined so that the exact nature of the solid is known i.e. if the solid is solvated or not. The crystal of the chromophore can then be very accurately weighed and dissolved in an appropriate solvent and the UV-vis spectrum recorded. In the absence of a crystal structure, various analytical methods can be used. These include ICP-OES (inductively coupled plasma optical emission spectrometry) and graphite furnace atomic absorption. The latter was used in this study.

Atomic Absorption (AA) involves the atomisation of the sample. Free atoms in the gas phase absorb electromagnetic radiation from an element-specific hollow-cathode lamp and are excited to high energy states. As in other spectrophotometric techniques, the amount of absorbed radiation is determined from the difference between the initial and final radiation intensities. Correlation of the absorbance and concentration of standard samples can be used in the determination of the exact concentration of an unknown sample.¹⁰¹ In this work, the concentration of cobalt was determined for both vitamin B₁₂ samples of known concentration and DPTC-Co samples of unknown concentrations.

The use of AA for the determination of cobalt samples with complex matrices has been established¹⁰² and thus vitamin B_{12a} itself, and not a conventionally used cobalt standard – a simple cobalt salt – was used to establish a calibration curve in this analysis.

4.5.2 Methods particular to solution chemistry

The solution chemistry and Beer-Lambert behaviour of DPTC-Co was determined spectrophotometrically. DPTC-Co was dried under high vacuum and a sample of 7.65 mg was weighed out on a six figure balance. The DPTC-Co sample was dissolved in 5 ml of ethyl acetate to yield a concentrated stock solution with a concentration (determined from weighing) of 1.957×10^{-3} M.

DPTC-Co was added in known aliquots to a cuvette containing 2.5 ml of 80:20 methanol:buffer solution at pH 9.5. A reference cuvette containing 80:20 methanol:buffer solution only was used. The change in absorbance with increasing concentration of DPTC-Co was monitored at 388, 437 and 610 nm.

4.5.3 Beer-Lambert behaviour of DPTC-Co

The increase in absorbance of the chromophore with increasing concentration of DPTC-Co is illustrated in Figure 4.5.1. The change in absorbance at 388, 437 and 610 nm was monitored as a function of increasing DPTC-Co concentration. The change in absorbance increased linearly across the $0.00\text{--}5.70 \times 10^{-5}$ M concentration range (Figure 4.5.2 – see **Appendix 4.5** for data and statistical analysis), indicating that DPTC-Co was present as a monomer in 80:20 methanol:buffer solution below a concentration of 5.70×10^{-5} M and absorbance of 2.16 A. U. - well above the concentration used in the pK_a and stability constant experiments carried out in this study.

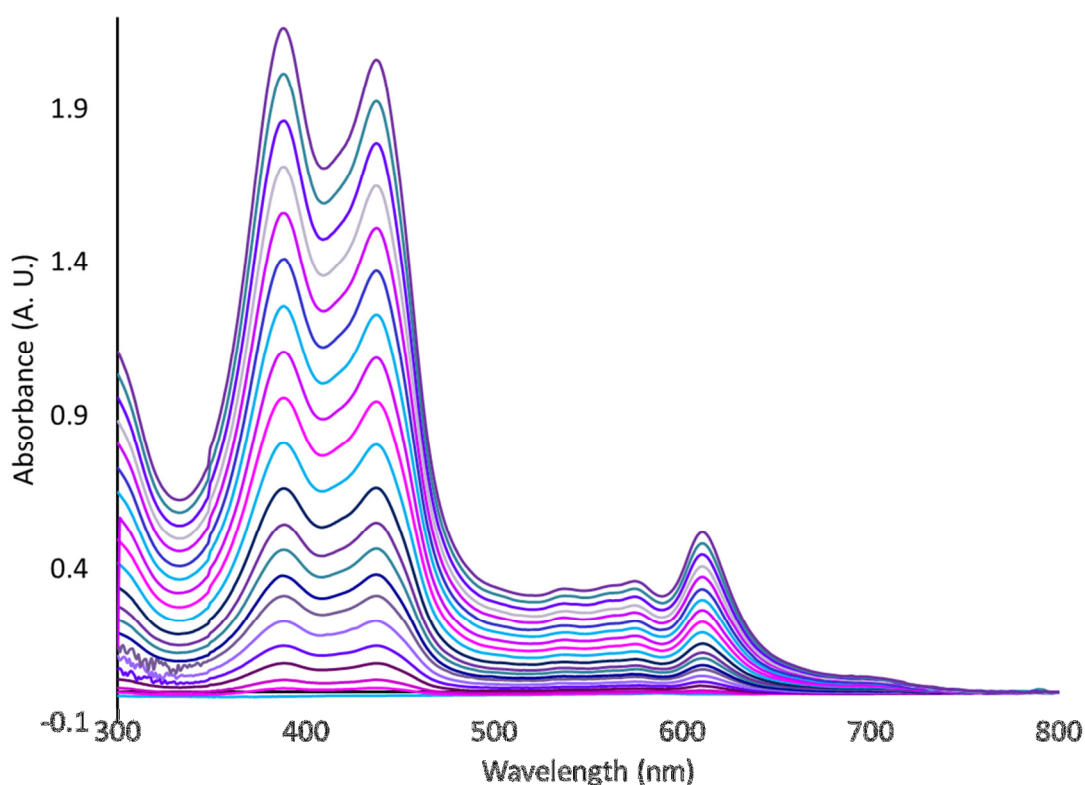


Figure 4.5.1 The increase in absorbance of DPTC-Co with increasing concentration

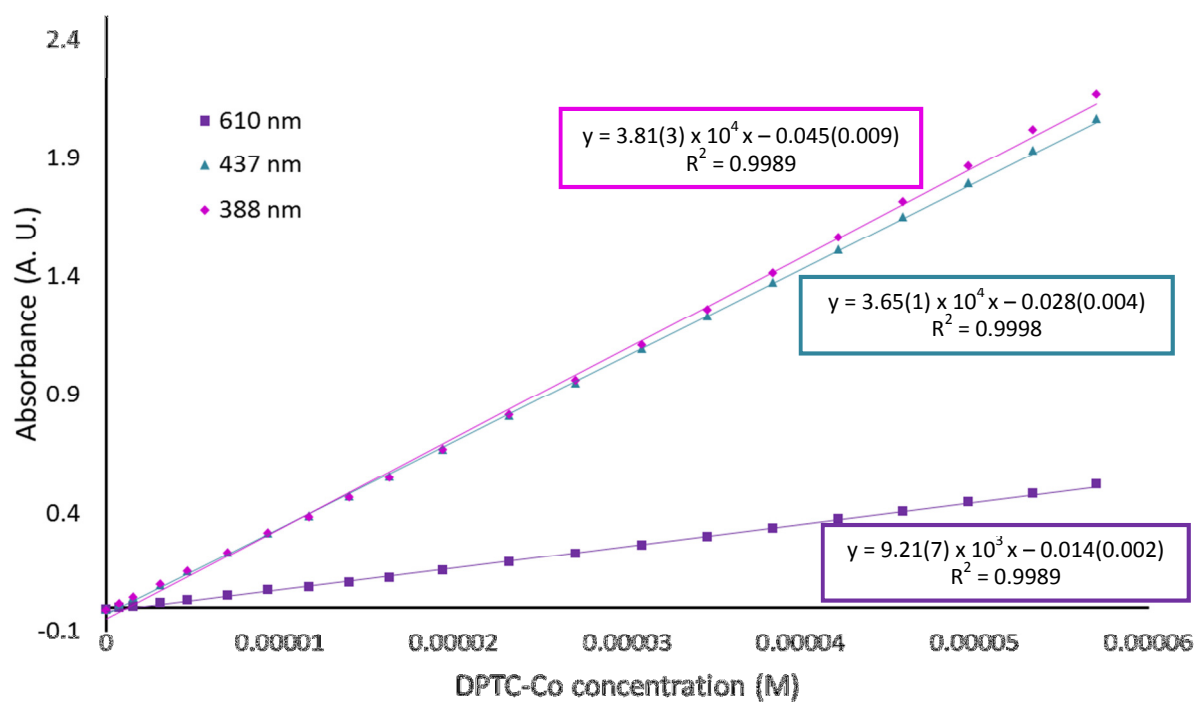


Figure 4.5.2 The linear increase in absorbance with increasing DPTC-Co concentration, indicating that Beer's Law is obeyed and DPTC-Co is present as a monomer in solution (details on the statistical analysis can be found in **Appendix 4.5**)

4.5.4 Methods particular to the determination of cobalt concentration by atomic absorption

Cobalt concentration of vitamin B_{12a} standards and DPTC-Co samples were determined using atomic absorption spectroscopy.

Vitamin B_{12a} samples were prepared using chlorohydrate dihydroxocobalamin in water purified using a Micropure RO system with UV sterilizer and further purified using a MilliQ mixed bed ion exchange system for a final purity of >18 mΩ. Six standards with concentrations between 0.05 and 6 ppm cobalt were prepared. Samples of each standard were treated with a few sodium cyanide crystals and placed in a thermostatted circulating water bath at 25°C for three hours. Once the hydroxocobalamin had completely converted to dicyanocobalamin, the spectrum of each sample was recorded. The concentration of dicyanocobalamin was calculated from the extinction co-efficient, ϵ , at 367 nm ($3.04 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$).²⁴ DPTC-Co samples of between approximately 0.1 and 0.4 ppm were prepared in dichloromethane.

Atomic absorption spectra were recorded on a PG-900 atomic absorption spectrophotometer using a graphite furnace fitted with a pyrolytically coated HGA-76 graphite tube. Collection of spectra was facilitated by the AAWin software suite, where absorption was monitored at 240.7 nm. The line spectrum characteristic of cobalt, using a Photron hollow-cathode lamp single element cobalt lamp, was reported as the integral of the absorption profile. Sample volumes of 10 µl were injected into the graphite tube in the furnace. Samples were subjected to a heating program (as in Table 4.5.1) and the absorption due to cobalt was recorded. The drying stage of the heating program removed the solvent. The pyrolysis stage aimed to strip the sample from matrix components – in this case, the organic material (corrin or corrole macrocycles) encasing the cobalt ion and was in essence a calcination stage. The atomisation stage was a high temperature stage where free cobalt atoms in the gas phase were excited from the ground state to higher energy states. The energy absorbed by the electrons in this process was recorded as an absorption spectrum. The cleaning phase removed any residue remaining on the graphite

tube.¹⁰⁰ Non-specific absorption of radiation was corrected for by subtracting the absorbance recorded from a deuterium lamp. This is known as deuterium background correction.¹⁰⁰

Table 4.5.1 Heating program used in the determination of cobalt concentration by graphite furnace atomic absorption

Step	Temperature (°C)	Ramp (°C/s)	Hold (s)	Argon flow rate	Step type
1	120	3	5	Maximum	Drying
2	750	5	12	Maximum	Pyrolysis
3	2300	0	3	Off	Atomisation
4	2300	0	4	Maximum	Cleaning
5	25	-	45	Maximum	Cooling

Vitamin B_{12a} and DPTC-Co samples were run a number of times until three absorbances had a relative percentage error below 5%. Blank samples (water for vitamin B_{12a} analysis and dichloromethane for DPTC-Co analysis) were run between every sample. A calibration curve was established using the calculated concentrations and averaged observed absorbances of the vitamin B_{12a} standards that fell within the linear range of absorbance. The concentrations of cobalt in the DPTC-Co samples were calculated from the equation of the linear calibration curve.

4.5.5 Determination of cobalt concentration by atomic absorption

A calibration curve for the cobalt absorbance in standard vitamin B_{12a} samples was established and is detailed in Table 4.5.2 and Figure 4.5.3. Above 0.2 ppm cobalt, the curve deviated from linearity. A concentration range of 0-0.2 ppm was used for the calibration curve used in the determination of the concentration of cobalt in DPTC-Co. Equation 4.5.1, where A is the atomic absorbance and $[Co]$ is the cobalt concentration, was used to determine the concentration of cobalt on DPTC-Co. The cobalt concentrations in DPTC-Co samples can be found in Table 4.5.3 below. The concentration of sample 3 was not calculated as its absorbance lay beyond the linear range of the calibration curve.

$$A = 2.2721[Co] + 0.1382$$

Equation 4.5.1

Table 4.5.2 Atomic absorption of cobalt in vitamin B_{12a} standards at 240.7 nm

Standard	0	1	2	3	4	5	6
Concentration ($\times 10^{-6}$ M)	0	0.6678	1.368	3.388	9.079	12.07	22.30
Concentration (ppm)	0	0.0394	0.0806	0.1997	0.5351	0.7115	1.3144
Absorbance 1	0.122	0.248	0.332	0.595	0.824	0.900	1.031
Absorbance 2	0.115	0.245	0.337	0.574	0.853	0.899	1.030
Absorbance 3	0.119	0.239	0.328	0.584	0.832	0.926	1.001
Average absorbance	0.119	0.244	0.332	0.584	0.836	0.908	1.021
Standard deviation	0.004	0.005	0.005	0.011	0.015	0.015	0.017
Relative standard deviation (%)	3.0	1.9	1.4	1.8	1.8	1.7	1.7

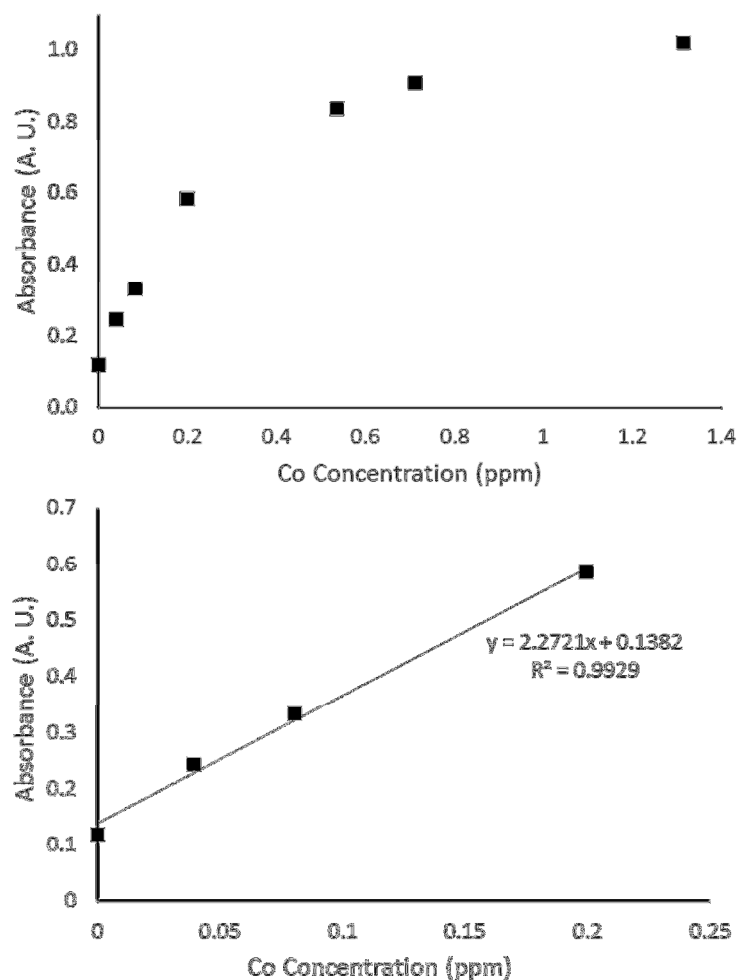


Figure 4.5.3 Atomic absorption calibration curve established from vitamin B_{12a} standards

Table 4.5.3 Atomic absorption of cobalt in DPTC-Co samples at 240.7 nm

Sample	1	2	3
Absorbance 1	0.344	0.596	0.813
Absorbance 2	0.333	0.588	0.800
Absorbance 3	0.333	0.606	0.796
Average absorbance	0.337	0.597	0.803
Standard deviation	0.006	0.009	0.009
Relative standard deviation (%)	1.886	1.511	1.107
Concentration (ppm)	0.087	0.202	
Concentration ($\times 10^{-6}$ M)	1.482	3.424	

4.5.6 Determination of the extinction coefficient, ϵ

The extinction coefficient, ϵ , is a measure of a molecule's ability to absorb light at a particular wavelength¹⁰⁰ and is characteristic of a molecule as well as the solvent in which the molecule is dissolved. The concentration of chromophore can be determined from the Beer-Lambert Law (Equation 4.5.2) where A is the absorbance at a particular wavelength, ϵ is the extinction coefficient ($\text{M}^{-1} \text{cm}^{-1}$), b is the path length of the cell (cm) and c is the concentration (M).

$$A = \epsilon bc$$

Equation 4.5.2

There is a linear increase in absorbance with concentration provided that the chromophore absorbs light as a monomer in solution and does not aggregate, or take part in a concentration-dependent equilibrium¹⁰⁰ which would result in deviations from linearity. ϵ can therefore be determined from the gradient of the change in absorbance with increasing concentration. From Figure 4.5.2, ϵ can be determined for the three wavelengths of interest. The determined ϵ values from the Beer's Law experiment are as follows: $3.81 \pm 0.03 \times 10^4 \text{ M}^{-1} \text{cm}^{-1}$ (388 nm), $3.65 \pm 0.01 \times 10^4 \text{ M}^{-1} \text{cm}^{-1}$ (437 nm) and $9.21 \pm 0.07 \times 10^3 \text{ M}^{-1} \text{cm}^{-1}$ (610 nm).

The ϵ determined from a Beer's Law experiment is dependent on the accuracy of the concentration of the stock chromophore solution. As the concentration of DPTC-Co was not accurately known, ϵ was determined for the DPTC-Co samples used in AA analysis. Spectra of DPTC-Co samples 1 and 2 were recorded in dichloromethane and ϵ was determined (the concentration of sample 3 could not be determined as it lay beyond the linear region of the calibration curve – **Section 4.5.5**). The same known volume of DPTC-Co was added to 2.5 ml dichloromethane and 2.5 ml 80:20 methanol:buffer solvent system (pH 9.5). The concentration of DPTC-Co in dichloromethane was determined from ϵ (dichloromethane) and this concentration was used to determine ϵ in 80:20 methanol:buffer solvent system (pH 9.5) (Tables 4.5.4 and 4.5.5). The value of ϵ at 388

nm obtained from AA was used in the determination of DPTC-Co concentrations in stability constant titrations (**Section 4.6**).

There is a large difference between ϵ (388 nm) for DPTC-Co determined from AA ($3.18 \pm 0.03 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) and that determined from Beer's Law ($3.81 \pm 0.03 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). It is unexpected that ϵ determined from Beer's Law is higher than that determined from the AA results. If moisture was present or the crystal lattice contained included solvent in the weighed sample which was used for the Beer's Law experiment it would increase the mass of the sample resulting in a higher calculated concentration. The absorbance of DPTC-Co would be lower than expected, resulting in a smaller calculated value of ϵ .

Table 4.5.4 Determination of ϵ from AA DPTC-Co samples in dichloromethane

Sample	UV-vis Absorbance (A. U.)	Concentration (ppm)	Concentration (M x 10 ⁻⁶)	ϵ (M ⁻¹ cm ⁻¹ x 10 ⁴)
1	1	0.344	0.0906	4.79
	2	0.333	0.0857	5.06
	3	0.333	0.0857	5.06
2	1	0.596	0.201	5.32
	2	0.588	0.200	5.42
	3	0.606	0.206	5.21
Average ϵ (M ⁻¹ cm ⁻¹)				5.14
Standard deviation				0.225
Relative standard deviation (%)				4.37

Table 4.5.5 Determination of ϵ from AA DPTC-Co samples in 80:20 Methanol:buffer (pH 9.5)

Solvent	UV-vis absorbance (A. U.), wavelength (nm)	Concentration (M x 10 ⁻⁵)	ϵ AA (M ⁻¹ cm ⁻¹ x 10 ⁴)
Dichloromethane	1.064, 389	2.07	5.14
80:20 Methanol: buffer (pH 9.5)	0.657, 388	2.07	3.18

4.5.7 Conclusions

The linear relationship between absorbance and concentration from the Beer's law experiment indicates that DPTC-Co exists as a monomer in solution below a concentration of 5.7×10^{-5} M. The extinction coefficient at 388 nm was determined to be $3.81 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$.

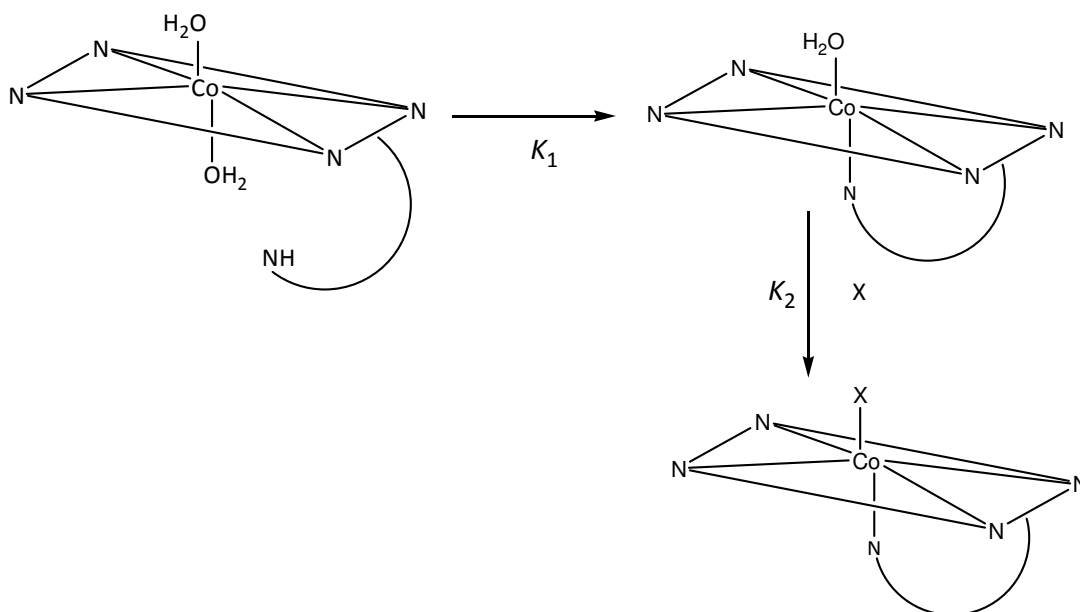
Atomic absorption methods were used to determine the exact concentration of cobalt in DPTC-Co samples. The concentration of DPTC-Co was determined from correlation of the observed AA absorbances with a standard calibration curve, constructed from vitamin B₁₂ samples of known concentration. Consequently, the extinction coefficient of DPTC-Co in dichloromethane was determined to be $5.14 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ at 389 nm. This was used in determination of the extinction coefficient of DPTC-Co in 80:20 methanol:buffer at pH 9.5 and found to be $3.18 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ at 388 nm.

The large difference between the extinction coefficients determined using the two different methods is of concern, and cannot be adequately rationalised. In spite of the uncertainties in the calculated extinction coefficients, the value determined from AA analysis was used in the calculation of DPTC-Co throughout this work.

4.6 Determination of stability constants of DPTC-Co and vitamin B_{12a} with various neutral and anionic ligands

4.6.1 Introduction

A stability, formation or binding constant, is an equilibrium constant which provides a measure of the interaction between, in the case of this work, an incoming ligand and a metal in the formation of a complex. This study is concerned with the formation of complexes of vitamin B_{12a} and DPTC-Co with a variety of ligands, as in Scheme 4.6.1. In vitamin B₁₂ chemistry, stability constants determined for ligand substitution reactions are K_2 values (but are generally referred to as K) as the experiments are carried out at a pH at which the nitrogenous base of the tail is coordinated to the cobalt (K_1).



Scheme 4.6.1 Generalised reaction for ligand substitution reactions (where K_2 is to be determined) where the cobalt metal is coordinated by either the corrin ring of vitamin B_{12a} or the corrole ring of DPTC

Stability constants give a direct indication of both the sign and magnitude of the Gibbs energy of the formation of the complex as ΔG° is directly proportional to $\log K$ in Equation 4.6.1. Analysis of stability constants as a function of temperature allows for the

determination of the change in enthalpy and change in entropy of the system from the van't Hoff plot of Equation 4.6.2. This information can be used in deducing the driving force of a reaction, bonding (related to enthalpy changes) or disorder (related to changes in entropy). This study determined stability constants at 25°C only. The determination of K as a function of temperature over a meaningfully large temperature range presented a problem given the high fraction of methanol in the solvent system; thus determination of the enthalpic and entropic contributions to the energy of the reactions was not determined.

$$\Delta G^\circ = -RT \ln K$$

Equation 4.6.1

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

Equation 4.6.2

The ligand exchange reactions of vitamin B₁₂ have been studied extensively. The same cannot be said for the reactions of metallocorroles. As discussed in **Section 4.1.3**, the ligand exchange reactions of about a dozen metallocorroles with a selection of ligands have been studied in organic solvent systems.³²⁻³⁷ While these studies aimed to determine the effect of ligand basicity and the effect of substitution of both the β and *meso* positions of the corrole framework, the present study aimed to compare the stability constants of vitamin B_{12a} with those of the corrole-containing biomimetic system, DPTC-Co, such that the effect of the increased delocalised electron system of the macrocycle on the chemistry of the coordinated cobalt metal ion could be deduced.

4.6.2 Methods particular to the determination of stability constants

All ligand binding assays were performed using a 80:20 methanol:buffer solvent system. The buffer used varied depending on the pH at which the experiment was carried out, but the concentration remained constant at 0.05 M. No inert salt was added to adjust the ionic strength; rather this was determined from the concentration of the charged buffer species at the pH at which the experiment was conducted. The initial pH of the DPTC-Co or vitamin B_{12a} solution was recorded. Initial spectra of either DPTC-Co or vitamin B_{12a} with no ligand present were first recorded. Cobalt concentrations were calculated using the extinction co-efficient, ϵ , at 388 nm ($3.18 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) for DPTC-Co (see **Section 4.5**) and at 350 nm ($2.61 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) for vitamin B_{12a}.²⁹ A known volume of standard ligand solution was added to the cuvette using a 10, 50, 100 or 250 μl micro syringe. The cuvette was inverted to ensure mixing and the spectrum was recorded after allowing for equilibration. Additions were made until there was no further change in the spectrum. The final pH was recorded. Spectra were corrected for the dilution effect by multiplying the recorded absorbance by the ratio of the total and initial volume. An example of the raw and corrected data can be found in **Digital Appendices 4.2.1** and **4.2.2**.

In the case of out-of-cell titrations, equal volumes of solvent and chromophore were added to the required number of 10 ml vials. Ligand was added such that the total volume of ligand added increased across the series of vials. Vials were capped, sealed with parafilm and placed in a thermostatted circulating water bath maintained at 25°C for 2-3 hours before the spectra were recorded. Once again, the spectra were corrected for the dilution effect as explained above.

Table 4.6.1 below provides details of all of the ligand binding assays undertaken. Ligand concentration ranges are for the ligand concentration in the cuvette. Stability constants presented in **Sections 4.6.3** and **4.6.4** were determined using Equations 4.2.1 and 4.2.2 as described in **Section 4.2.4** and details on the determination of K can be found in **Appendix 4.6** and **Digital Appendices 4.3.1** and **4.3.2**.

Table 4.6.1 Summary of ligand binding assays: ligands, ligand concentration ranges and cobalt concentrations

Ligand	Ligand concentration range (M)	pH	[Cobalt] (M x 10 ⁻⁵)
DPTC-Co			
<i>Neutral ligands</i>			
Ethanolamine	1.23 x 10 ⁻⁶ -4.25 x 10 ⁻⁴	9.50	2.018
Pyridine	5.95 x 10 ⁻⁷ -4.54 x 10 ⁻⁴	9.16	2.711
4-Dimethylaminopyridine (DMAP)	1.46 x 10 ⁻⁶ -2.78 x 10 ⁻⁴	9.51	2.056
N-Methylimidazole	1.26 x 10 ⁻⁶ -3.38 x 10 ⁻⁴	9.46	2.166
Thiophene	6.24 x 10 ⁻³ -0.422	9.52	2.185
Thiourea	3.60 x 10 ⁻³ -4.88 x 10 ⁻²	9.47	1.924
Trimethylphosphite	7.93 x 10 ⁻⁷ -2.74 x 10 ⁻⁵	9.44	1.748
Trimethylphosphite	7.36 x 10 ⁻⁷ -3.61 x 10 ⁻⁵	9.44	2.799
(DMAP competition experiment)			
Trimethylphosphite	9.64 x 10 ⁻⁷ -4.73 x 10 ⁻⁵	9.50	2.258
(Pyridine competition experiment)			
<i>Anionic ligands</i>			
Cysteine	7.85 x 10 ⁻⁷ -2.10 x 10 ⁻⁴	9.86	2.084
Sodium cyanide	6.09 x 10 ⁻⁷ -2.10 x 10 ⁻⁵	9.57	2.198
Sodium cyanide (DMAP competition experiment - in cell)	6.07 x 10 ⁻⁷ -2.09 x 10 ⁻⁵	9.59	1.669
Sodium cyanide (DMAP competition experiment - out of cell)	8.37 x 10 ⁻⁷ -2.48 x 10 ⁻⁵	9.51	1.957
Sodium nitrite	8.05 x 10 ⁻⁵ -1.14 x 10 ⁻²	9.51	2.459
Sodium azide	1.17 x 10 ⁻⁴ -1.65 x 10 ⁻²	9.51	1.943
Sodium thiocyanate	2.47 x 10 ⁻⁴ -9.47 x 10 ⁻²	9.50	2.601

Table 4.6.1 continued

Ligand	Ligand concentration range (M)	pH	[Cobalt] (M x 10 ⁻⁵)
Vitamin B_{12a}			
<i>Neutral ligands</i>			
Ethanolamine	1.39 x 10 ⁻³ -0.188	8.13	4.835
Pyridine	9.88 x 10 ⁻³ -1.12	7.21	4.273
4-Dimethylaminopyridine (DMAP)	2.70 x 10 ⁻⁵ -2.15 x 10 ⁻²	9.10	7.833
N-Methylimidazole	4.20 x 10 ⁻⁵ -5.49 x 10 ⁻³	7.09	2.76
Thiophene	0.245-2.88	9.14	4.609
Thiourea	2.27 x 10 ⁻³ -3.75 x 10 ⁻²	7.08	5.857
Trimethylphosphite	6.06 x 10 ⁻⁶ -2.15 x 10 ⁻⁴	7.08	4.144
<i>Anionic ligands</i>			
Cysteine	4.00 x 10 ⁻⁵ -1.73 x 10 ⁻³	6.01	4.308
Cyanide	5.85 x 10 ⁻⁶ -1.38 x 10 ⁻⁴	7.11	6.277
Cyanide	9.59 x 10 ⁻⁵ - 3.56 x 10 ⁻³	7.09	3.185
(azide competition experiment)			
Cyanide	9.60 x 10 ⁻⁵ -4.37 x 10 ⁻³	7.09	3.172
(nitrite competition experiment)			
Nitrite	8.11 x 10 ⁻⁷ -6.46 x 10 ⁻⁵	7.12	3.658
Azide	1.63 x 10 ⁻⁶ -1.01 x 10 ⁻⁴	7.11	2.308
Thiocyanate	8.00 x 10 ⁻⁷ -2.73 x 10 ⁻⁴	7.12	2.499
Iodide	6.57 x 10 ⁻⁵ -1.54 x 10 ⁻³	6.99	3.628

4.6.3 The effect of solvent on stability constants

The stability constant for the binding of ethanolamine to DPTC-Co was determined in dichloromethane, methanol and 80:20 methanol:buffer. The change in spectrum of DPTC-Co in 80:20 methanol:water was of concern; thus the stability constant for the binding of ethanolamine was determined in both fresh and 'aged' (used more than one day after preparation) solutions. The log K values are compared in Table 4.6.2.

The log K for the binding of ethanolamine in dichloromethane is significantly larger than in more polar, coordinating solvents. In dichloromethane, a non-polar and non-coordinating solvent, DPTC-Co is found as the five-coordinate species only. In coordinating solvents, both the five- and six-coordinate species are present. During the binding of a ligand, the ligand can bind directly to the five-coordinate species, while in the case of the six-coordinate species, displacement of the coordinated solvent must occur before the ligand is able to bind, resulting in a lower observed log K . Similarly, this can be rationalised by looking at the donor numbers (DN) of the solvents. Gutmann's donor number is a semiquantitative measure of the Lewis basicity of a solvent and indicates the ease of solvation of a cation or Lewis acid by a solvent.⁶¹ The DN for dichloromethane is 1 while that for methanol is 18.⁶¹ During the coordination of a ligand to a metal centre, as the donor number decreases, competition between solvent and ligand decreases, therefore the stability of the complex increases, increasing log K .¹⁰³

The log K for the reaction in methanol and the corrected log K in aged methanol:buffer solution differ by about 0.35 units. The corrected log K value for the reaction in fresh 80:20 methanol:buffer solution, however, is greater than in methanol or in the aged 80:20 methanol:buffer solution. Methanol, although a poor ligand, is able to bind to the coordinated cobalt metal centre in DPTC-Co with a log K of -1.60 ± 0.08 (from the out of cell titration of methanol in dichloromethane) and as discussed in **Section 4.3.5**, the kinetics for the binding of methanol appear to be slow. In pure methanol and the aged methanol:buffer solution, the coordination of ethanolamine involves first the displacement of the methanol axial ligand followed by the coordination of ethanolamine.

This is an energy intensive process, resulting in a decrease in the $\log K$ value. Fresh methanol:buffer solutions, containing a mixture of five- and six-coordinate DPTC-Co species, yield higher $\log K$ values as only a fraction of DPTC-Co is present as the six-coordinate species requiring the displacement of methanol before the binding of ethanolamine.

Table 4.6.2 pH-independent stability constants for the binding of ethanolamine to DPTC-Co in various solvents

Solvent	$\log K_{\text{obs}}$	$\log K$
Dichloromethane	6.08 ± 0.04	6.08 ± 0.04
Methanol	4.79 ± 0.05	4.79 ± 0.05
80:20 methanol:buffer (fresh, pH 9.5)	4.65 ± 0.02	5.15 ± 0.02
80:20 methanol:buffer (aged, pH 9.5)	4.31 ± 0.02	4.81 ± 0.02

In the present study, stability constants for the ligand substitution reactions of DPTC-Co were determined using freshly prepared solutions, rather than the ‘aged’ solutions due to several concerns including the moderate instability of the corrole to light and air and the irreproducibility of preparing ‘aged’ solutions. As the focus of this work was to study the trends in $\log K$ values for vitamin B_{12a} versus the corrole, there was a need for a simple, reproducible system.

The effect of increasing the fraction of methanol on the stability constant of the binding of *N*-methylimidazole to vitamin B_{12a} was also determined. Table 4.6.3 and Figure 4.6.1 illustrate the change in $\log K$ with increasing methanol concentration. As the concentration of methanol in the solvent system increases and the polarity decreases, the $\log K$ decreases in an apparently sigmoidal fashion. Hamza observed that binding constants of pyridine derivatives to aquacyanocobyrinic acid are solvent dependent where it was found that an increase in polarity led to an increase in the value of K .⁶⁷

Table 4.6.3 Solvent dependant stability constants for the binding of *N*-methylimidazole to vitamin B_{12a}

% methanol:buffer solvent	v/v methanol in solvent	Polarity ($E_T(30)^{61,104}$) ^a	$\log K_{\text{obs}}$	$\log K$ (μ (M))
0		63.1	3.81 ± 0.04	4.32 ± 0.04 (0.019)
20		61	3.84 ± 0.04	4.32 ± 0.04 (0.021)
40		59.3	3.71 ± 0.05	4.21 ± 0.05 (0.019)
60		57.3	3.56 ± 0.06	4.04 ± 0.06 (0.022)
80		56.3	3.51 ± 0.05	3.99 ± 0.05 (0.022)

^a Approximate values determined from Figure 3(B) from Smithrud et al¹⁰⁴

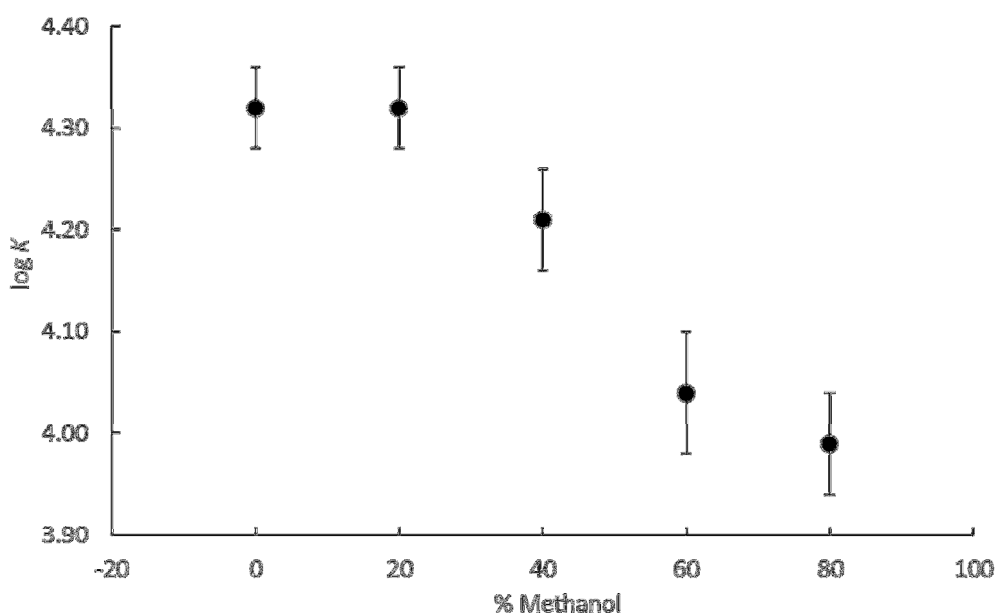
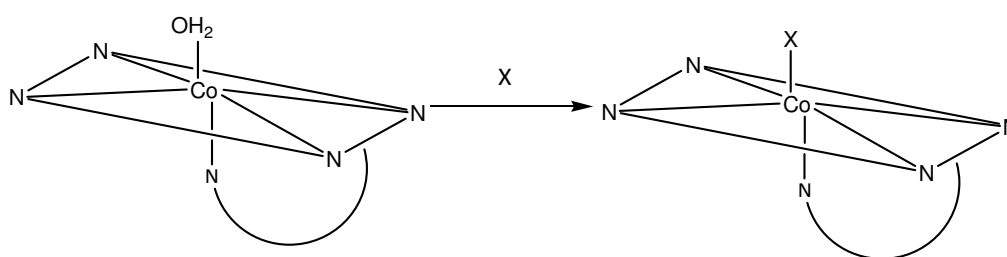


Figure 4.6.1 The dependence of the stability constant for the binding of *N*-methylimadazole to vitamin B_{12a} on percentage methanol (v/v) in a methanol:buffer solution

For purposes of comparing vitamin B_{12a} and the biomimetic model, the stability constants of ligand substitution reactions of vitamin B₁₂ were conducted in 80:20 methanol:water solutions due to the dependence of $\log K$ on solvent composition.

4.6.4 The binding of neutral and anionic ligands to DPTC-Co and vitamin B_{12a}

The binding of a variety of both neutral and anionic ligands with DPTC-Co and vitamin B_{12a} were studied in the 80:20 methanol:buffer solvent system. A summary of the observed and corrected stability constants for the generalised reaction in Scheme 4.6.1 are presented in Tables 4.6.4 and 4.6.5. The ligand concentration ranges and pH used can be found in Table 4.6.1.



Scheme 4.6.1 Generalised reaction for ligand substitution reactions where the cobalt metal is coordinated by either the corrin ring of vitamin B₁₂ or the corrole ring of DPTC

The stability constants for the strong binding of trimethylphosphite to DPTC-Co and cyanide to DPTC-Co and vitamin B_{12a} were determined initially from standard ligand substitution reactions for which very high, and thus very unreliable, stability constants were determined ($\log K \gg 4$, in square brackets in Tables 4.6.4 and 4.6.5). Competition reactions, where a strong binding ligand (pyridine or DMAP in the case of trimethylphosphite and DMAP, azide or nitrite in the case of cyanide) was initially coordinated to the chromophore and this ligand was then replaced by trimethylphosphite or cyanide, were used to determine a more reliable stability constant.

Table 4.6.4 Summary of the stability constants for the coordination of neutral ligands to vitamin B_{12a} and DPTC-Co

Ligand	Vitamin B ₁₂ log <i>K</i> _{obs}	Vitamin B ₁₂ log <i>K</i> (μ (M))	DPTC-Co log <i>K</i> _{obs}	DPTC-Co log <i>K</i> (μ (M))
<i>Neutral ligands</i>				
Ethanolamine	1.41 ± 0.05	3.60 ± 0.05 (0.023)	4.65 ± 0.02	5.15 ± 0.02 (0.016)
Pyridine	0.26 ± 0.04	0.48 ± 0.04 (0.013)	4.01 ± 0.02	4.11 ± 0.02 (0.011)
4-Dimethylaminopyridine (DMAP)	1.70 ± 0.02	3.99 ± 0.02 (0.010)	4.81 ± 0.02	5.32 ± 0.02 (0.016)
<i>N</i> -Methylimidazole	3.51 ± 0.05	3.99 ± 0.05 (0.011)	5.23 ± 0.04	5.41 ± 0.04 (0.015)
Thiophene	-0.8 ± 0.2	1.0 ± 0.2 (0.010)	0.89 ± 0.04	1.09 ± 0.04 (0.016)
Thiourea	1.59 ± 0.02	1.76 ± 0.02 (0.011)	1.9 ± 0.1	2.1 ± 0.1 (0.015)
Trimethylphosphite	4.60 ± 0.07	4.77 ± 0.07 (0.011)	[6.7 ± 0.1]	[6.9 ± 0.1 (0.015)]
Trimethylphosphite (DMAP competition experiment)	-	-	6.44 ± 0.08	11.8 ± 0.1 (0.015)
Trimethylphosphite (Pyridine competition experiment)	-	-	6.25 ± 0.07	10.36 ± 0.09 (0.016)

Table 4.6.5 Summary of the stability constants for the coordination of anionic ligands to vitamin B_{12a} and PDTC-Co

Ligand	Vitamin B ₁₂ log <i>K</i> _{obs}	Vitamin B ₁₂ log <i>K</i> (μ (M))	PDTC-Co log <i>K</i> _{obs}	PDTC-Co log <i>K</i> (μ (M))
<i>Anionic ligands</i>				
Cysteine	4.1 ± 0.1	6.5 ± 0.1 (0.011)	5.4 ± 0.2	5.7 ± 0.2 (0.020)
Cyanide	[5.1 ± 0.1]	[7.3 ± 0.1 (0.011)]	[7.7 ± 0.4]	[8.1 ± 0.4 (0.017)]
Cyanide (DMAP competition experiment - in cell)	-	-	7.6 ± 0.7	13.1 ± 0.7 (0.017)
Cyanide (DMAP competition experiment - out of cell)	-	-	7.7 ± 0.6	13.2 ± 0.6 (0.016)
Cyanide (azide competition experiment)	4.06 ± 0.03	12.53 ± 0.07 (0.011)	-	-
Cyanide (nitrite competition experiment)	3.09 ± 0.04	11.9 ± 0.5 (0.011)	-	-
Nitrite	6.5 ± 0.4	6.7 ± 0.4 (0.012)	2.86 ± 0.02	3.06 ± 0.02 (0.016)
Azide	6.17 ± 0.05	6.35 ± 0.05 (0.011)	2.63 ± 0.02	2.82 ± 0.02 (0.016)
Thiocyanate	4.55 ± 0.04	4.73 ± 0.04 (0.012)	1.12 ± 0.05	1.31 ± 0.05 (0.016)
Iodide	3.82 ± 0.02	3.96 ± 0.02 (0.010)	2.09 ± 0.03; -0.02 ± 0.02	2.33 ± 0.03 (0.017) 0.22 ± 0.02

The stability constants determined for the binding of various ligands to aquacobalamin in the 80:20 methanol:buffer solvent system were different, and in some cases considerably different, from those determined in aqueous media, as reported in the literature. These differences are summarised in Table 4.6.6 below. As mentioned in **Section 4.3.5**, the ideal solvent system for the study of vitamin B₁₂, and correlation to biological systems, may not be an aqueous solvent system, but rather a multi-component system containing a more non-polar solvent, such as methanol.⁸⁰

Balt and co-workers, as well as Moreno-Esparza and co-workers, have studied the reactions of vitamin B_{12a} in multicomponent solvent systems using varying dioxane-water,^{71,105} acetonitrile-water^{105,106} and methanol-water mixtures.⁸⁰ In all cases it was observed that there was a marked difference in both the thermodynamic and kinetic parameters as the identity of the solvent mixture changes. Balt and co-workers found that in dioxane-water mixtures the rate constant for the binding of thiosulfate to aquacobalamin decreased from 500 to approximately 160 M⁻¹ s⁻¹ as the concentration of dioxane increased from 0 to 8 M⁷¹ while the rate constant for the reaction between thiourea and aquacobalamin decreased from 214 to 7.5 M⁻¹ s⁻¹ as the fraction of dioxane increased.¹⁰⁵ In acetonitrile-water mixtures the stability constants for the binding of thiocyanate to aquacobalamin increased from log *K* = 3.30 to 4.17 as the fraction of acetonitrile increased from 0 to 80%,¹⁰⁶ while the rate constant for the binding of thiourea to aquacobalamin varied from 14.0 to 227 s⁻¹.¹⁰⁵ Moreno-Esparza and co-workers found that the stability constant for the binding of iodide to aquacobalamin increased from log *K* = 1.41 to 3.95 as the methanol fraction increased from 0 to 100%.⁸⁰

Table 4.6.6 Stability constants in 80:20 methanol:water and in aqueous media for the binding of a variety of ligands to aquacobalamin

Ligand	Log <i>K</i> (25°C)	
	80:20 methanol:water solvent system*	Aqueous solution
Pyridine	0.48 ± 0.04	1.23 ⁴¹
<i>N</i> -methylimidazole	4.05 ± 0.05	4.44 ¹⁰⁷
Thiourea	1.59 ± 0.03	1.1 ¹⁰⁸
Trimethylphosphite	4.77 ± 0.07	5.0 ¹⁰⁹
Cysteine	6.5 ± 0.1	6.0 or 8.3 ¹¹⁰
Cyanide	12.54 ± 0.07	≥ 12 ⁹¹
Nitrite	6.7 ± 0.4	5.34 ⁴¹
Azide	6.35 ± 0.05	4.85 ⁴¹
Thiocyanate	4.73 ± 0.04	3.03 ⁴¹
Iodide	3.97 ± 0.02	1.4 ⁸⁰
	3.12 ^{80**}	

* This work

** $\mu = 0.15$ M NaClO₄

From Tables 4.6.4 and 4.6.5 it is clear that the stability constants of the neutral ligands are higher in aqueous solutions (thiourea is an exception) while those of the anionic ligands are higher in the 80:20 methanol:water solvent system, although it must be noted that the ionic strength of the determined stability constants varies. Balt and co-workers found that the log *K* for the substitution of water by thiocyanate on vitamin B₁₂ increased from 3.30 to 4.17 as the fraction of acetonitrile in the solvent system increased.¹⁰⁶ The fraction of dioxane had a less dramatic effect on the stability constant for the binding of thiourea, increasing from 13 to 17 dm³ mol⁻¹.¹⁰⁵ Moreno-Esparza and co-workers found that the stability constant for the binding of iodide to vitamin B_{12a} was enormously dependent on the composition of the solvent, increasing from 26 in 100% water to 9.0 × 10³ dm³ mol⁻¹ in 100% methanol.⁸⁰

While dioxane⁷¹ and acetonitrile¹⁰⁵ have been shown to not displace the water in aquacobalamin, a methanol-cobalamin complex has been shown to form with a stability

constant of $3.7 \text{ dm}^3 \text{ mol}^{-1}$ in methanol-rich solvent systems.⁸⁰ The complex formation was characterised by a subtle shift in the position of the γ band from 350 to 351 nm and a decrease in intensity. Moreno-Esparza concluded that the increase in the stability constants with decreasing polarity of solvent arises as a result of the formation of an outer-sphere complex which is more stable at lower solvent polarity due to the charge neutralisation as a result of the reaction between aquacobalamin (bearing a charge of 1+) and iodide resulting in a neutral iodocobalamin species.⁸⁰ Thus, the binding of the anionic iodide was found to be more favourable in solvents with higher methanol composition.

Aquacobalamin has an overall charge of 1+ with a charge of 2+ at the metal centre. The coordination of an anionic ligand results in a neutral complex. In solvent systems with low water content, such as the 80:20 methanol:water solvent system used in this study, the formation of a neutral complex would be far more favourable than in a purely aqueous solvent system, resulting in higher stability constants in less polar solvent systems, as in Table 4.6.5. The binding of neutral ligands, on the other hand, does not affect the charge of the complex. The hydrogen bonding abilities of the solvent decrease as the fraction of the more non-polar solvent increases. This might affect the stability of the complexes of neutral ligands, resulting in lower stability constants in the 80:20 methanol:water solvent system than in purely aqueous systems.

4.6.5 The UV-vis spectroscopic changes of DPTC-Co upon ligand binding

The absorption bands in the Soret region have been assigned the labels Soret 1, Soret 2, Soret 3 etc. while similarly the bands in the Q band region have assigned Q1, Q2 etc. as illustrated in Figure 4.6.2, a spectrum recorded during the coordination of ethanolamine to DPTC-Co. An absorption band of low intensity at a wavelength lower than that of Q1 was also observed, but is not discussed.

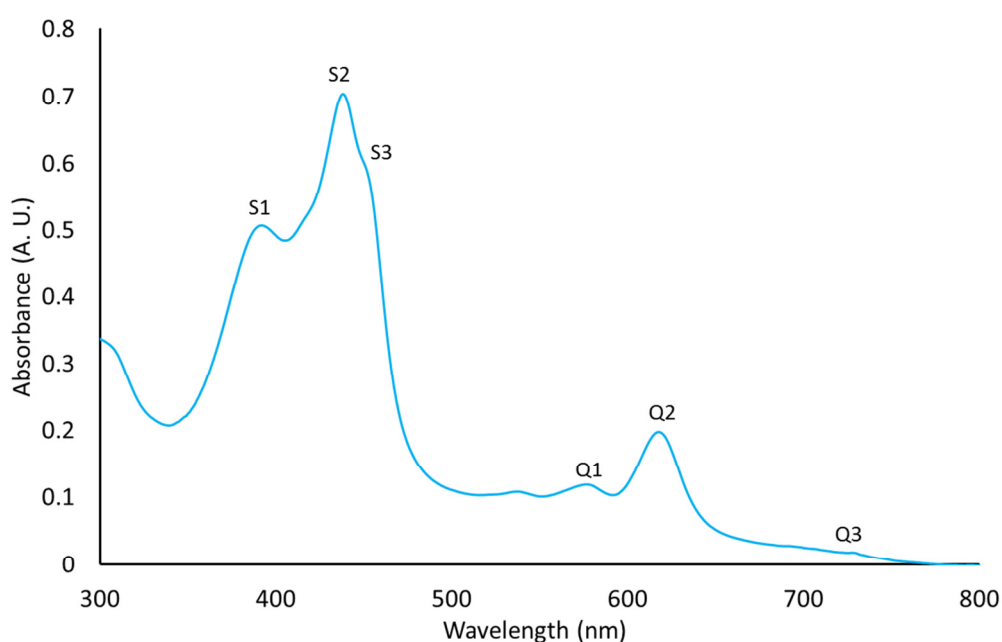


Figure 4.6.2 Assignment of absorption bands of DPTC-Co. The spectrum was recorded during the coordination of ethanolamine to DPTC-Co

The binding of neutral *N* donor ligands (ethanolamine, pyridine, DMAP and *N*-methylimidazole) to DPTC-Co yields similar spectroscopic changes, with the collapse of the 388 nm Soret and the appearance of a well-defined shoulder on the 438 nm Soret (experiencing a small shift from 437 nm as in Figure 4.6.3). In all cases, there was an increase in the intensity of the 438 nm Soret. There was little variation in the position of the shoulder with ethanolamine and *N*-methylimidazole complexes at 452 nm, the DMAP complex at 451 nm and pyridine complex at 450 nm. The Q bands experienced both an increase in intensity and a bathochromic shift. The Q band at 577 nm in DPTC-Co shifted

to 579 nm in all cases except the *N*-methylimidazole complex where it shifted to 580 nm. There was variation in the 611 nm Q band which shifted to 617 nm (pyridine complex), 619 nm (DMAP complex), 620 nm (ethanolamine complex) and 622 nm (*N*-methylimidazole complex). Table 4.6.7 summarises the shifts in the Soret and Q bands as well as the isosbestic points for the binding of *N*-donor neutral ligands. Spectra representative of the binding of neutral *N*-donor ligands (the spectroscopic changes for the binding of DMAP) are illustrated in Figure 4.6.3 below.

Table 4.6.7 Shifts in wavelength of the Soret and Q bands and isosbestic points upon binding of neutral *N*-donor ligands to DPTC-Co

Ligand	Wavelength (nm)					Isosbestic points (nm)
	Soret 1	Soret 2	Soret 3	Q 1	Q 2	
Water	388	437	-	577	611	
Ethanolamine	-	438	452	579	620	347, 421, 504, 543, 560
Pyridine	-	438	450	579	617	347, 425, 545, 557
DMAP	-	438	451	579	619	331, 419, 476, 570, 590, 605
<i>N</i> -methyl-imidazole	-	438	452	580	622	329, 414, 483, 575, 591, 610

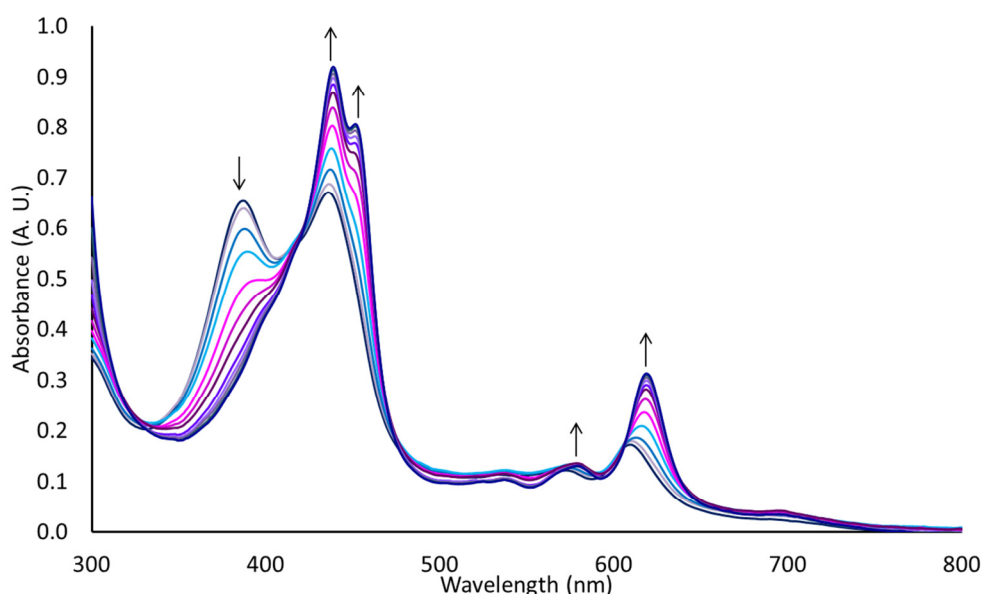


Figure 4.6.3 Spectroscopic changes associated with the binding of DMAP to DPTC-Co, representative of the changes observed for the binding of nitrogen donors

The binding of trimethylphosphite to DPTC-Co (Figure 4.6.4) yields very different spectroscopic changes compared to the binding neutral *N*-donors. The binding of trimethylphosphite to DPTC-Co was achieved by exchanging a bound pyridine or DMAP ligand with the trimethylphosphite ligand. These competition experiments were carried out as the log *K* for trimethylphosphite in the absence of a competing ligand was too high to determine with any accuracy. There was a decrease in intensity of the Soret and Q bands upon substituting the competition ligand with trimethylphosphite. Soret 2 shifted from 438 to 443 nm while two shoulders, Soret 1 and Soret 3, appeared at 414 and 461 nm. The Q bands at 577 and 611 nm shifted to 587 and 633 nm. Isosbestic points were seen at 308, 418, 459, 566, 584, 595 and 625 nm.

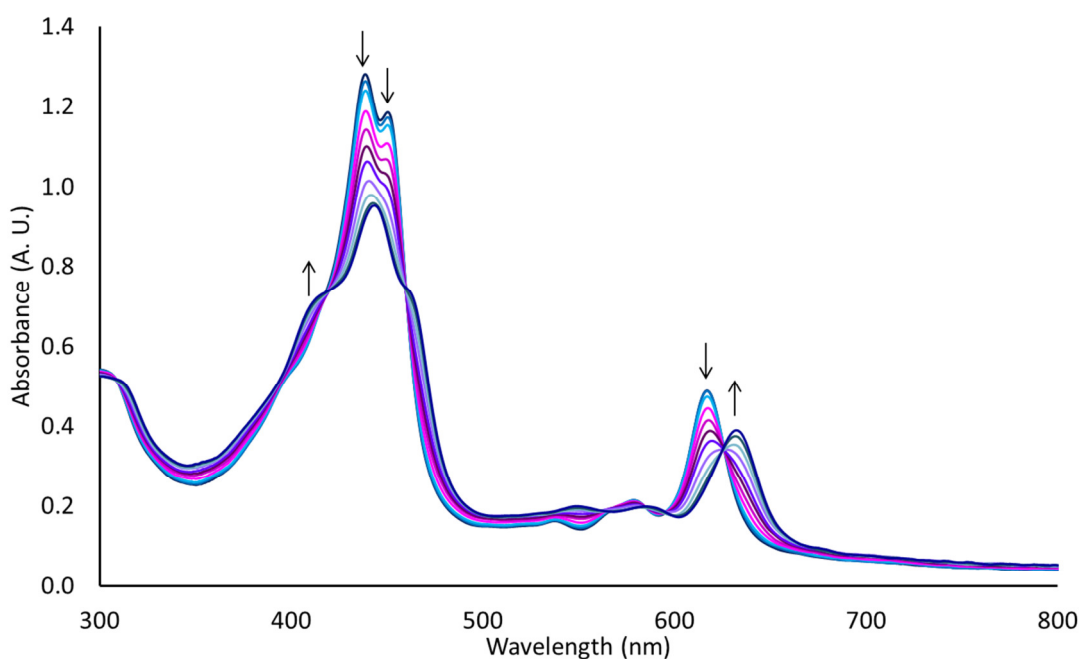


Figure 4.6.4 Spectroscopic changes associated with the displacement of pyridine by trimethylphosphite on DPTC-Co

Thiourea and thiophene, while both sulfur donors, bound to DPTC-Co yielding different spectra. The spectroscopic changes were not as drastic as in the case of the neutral *N*- or *P*-donor ligands. The binding of thiourea led to the collapse of Soret 1 at 388 nm. Soret 2 at 437 nm underwent a decrease in intensity as well as a bathochromic shift to 439 nm. Q bands 1 and 2 increased in intensity and shifted to the red from 577 nm to 587 nm and 611 nm to 631 nm for Q band 1 and 2 respectively. The isosbestic point at 356 nm was

clear while those at 450, 604 and 615 nm were less so. The spectroscopic changes can be seen in Figure 4.6.5.

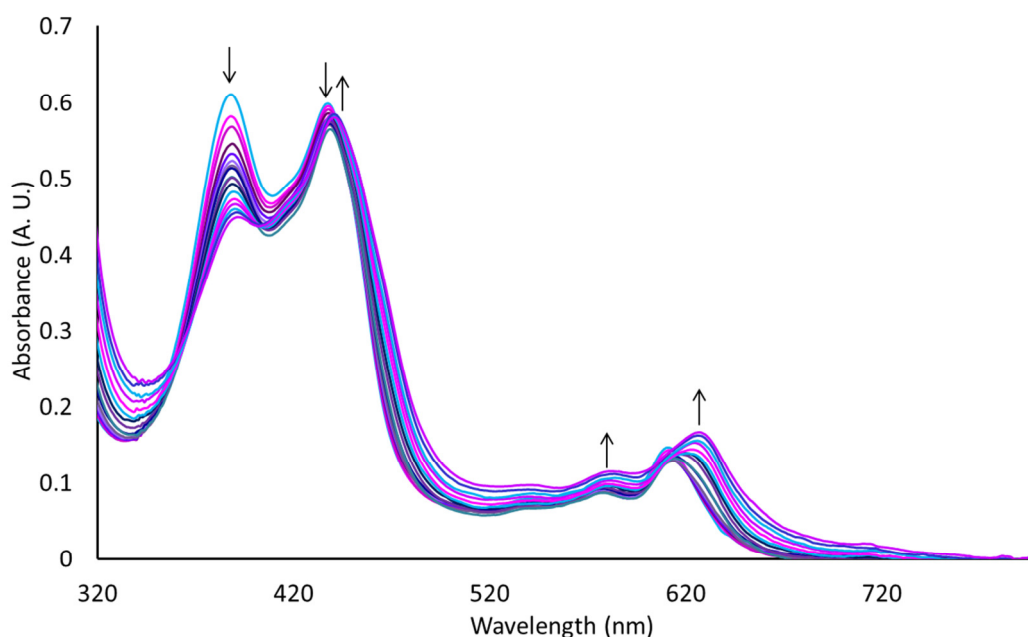


Figure 4.6.5 Spectroscopic changes associated with the binding of thiourea to DPTC-Co

Thiophene bound to DPTC-Co with a general decrease in the intensity of all of the bands with one isosbestic point only as in Figure 4.6.6. The shifts in wavelength of Soret and Q bands were subtle. The wavelength of Soret 1 did not change while Soret 2 shifted from 437 to 438 nm. Q band 1 shifted to the blue from 577 to 574 while Q band 2 shifted to the red from 611 to 614 nm. The single isosbestic point was at 630 nm. The general decrease in the UV-vis spectrum may be indicative of the thiophene ligand interacting with the metal in DPTC-Co through π -stacking. Evaluation of the Hill plot indicated that one ligand had coordinated to the metal centre as the gradient of the plot was nearly equal to one (0.9548). Of course, this might also be an indication a 1:1 DPTC-Co:thiophene π -stacked arrangement.

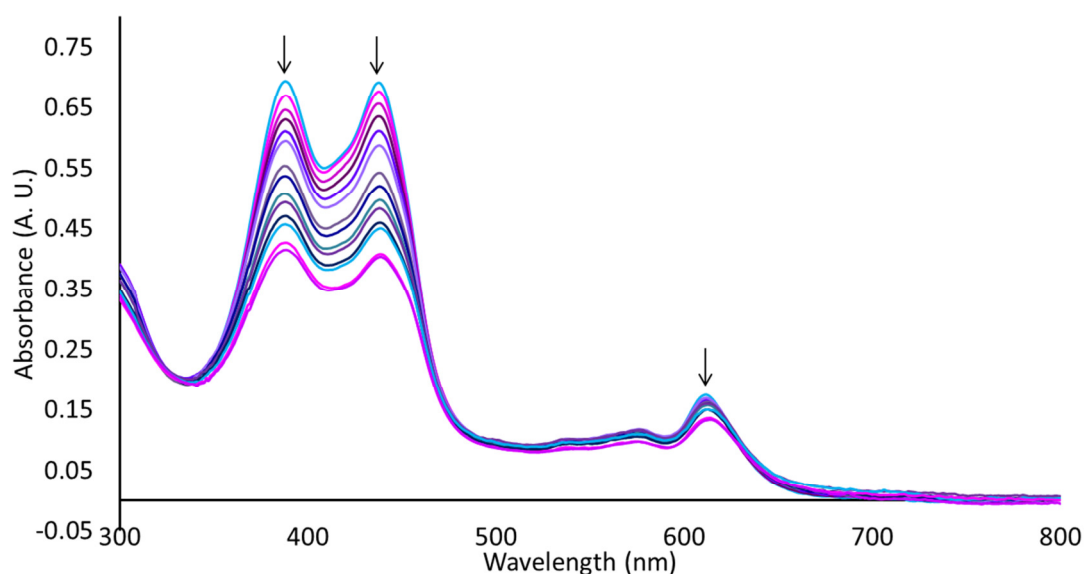


Figure 4.6.6 Spectroscopic changes associated with the binding of thiophene to DPTC-Co

Anionic *N*- and *S*-donor ligands (cyanide, nitrite, azide and thiocyanate) bound to DPTC-Co to yield similar spectra. There was a collapse of Soret 1 at 388 nm. Unlike the neutral *N*-donors, Soret 2 did not have a defined shoulder, but rather was broad and experienced either a blue shift or no shift at all with an increase in intensity. Unlike the neutral ligands, Q bands 1 and 2 did not increase in intensity, but rather decreased in intensity with the appearance of Q band 3 in the 710 nm region. The changes in Soret and Q band positions, as well as the isosbestic points, are listed in Table 4.6.8 while spectra representative of the binding of anionic *N*- and *S*-donor ligands (the spectroscopic changes for the binding of thiocyanate) are illustrated in Figure 4.6.7.

Table 4.6.8 Shifts in wavelength of the Soret and Q bands and isosbestic points upon binding of anionic *N*- and *S*-donor ligands to DPTC-Co

Ligand	Wavelength (nm)				Isosbestic points (nm)
	Soret 1	Soret 2	Q 2	Q 3	
Water	388	437	611	-	
Azide	-	437	614	710	351, 405, 516, 637
Nitrite	-	436	637	706	348, 403, 522, 635
Thiocyanate	-	437	615	709	339, 408, 506, 637
Cyanide	-	434	638	710	351, 405, 516, 637
Cyanide (DMAP comp)	-	434	638	700	342, 433, 467, 516, 652

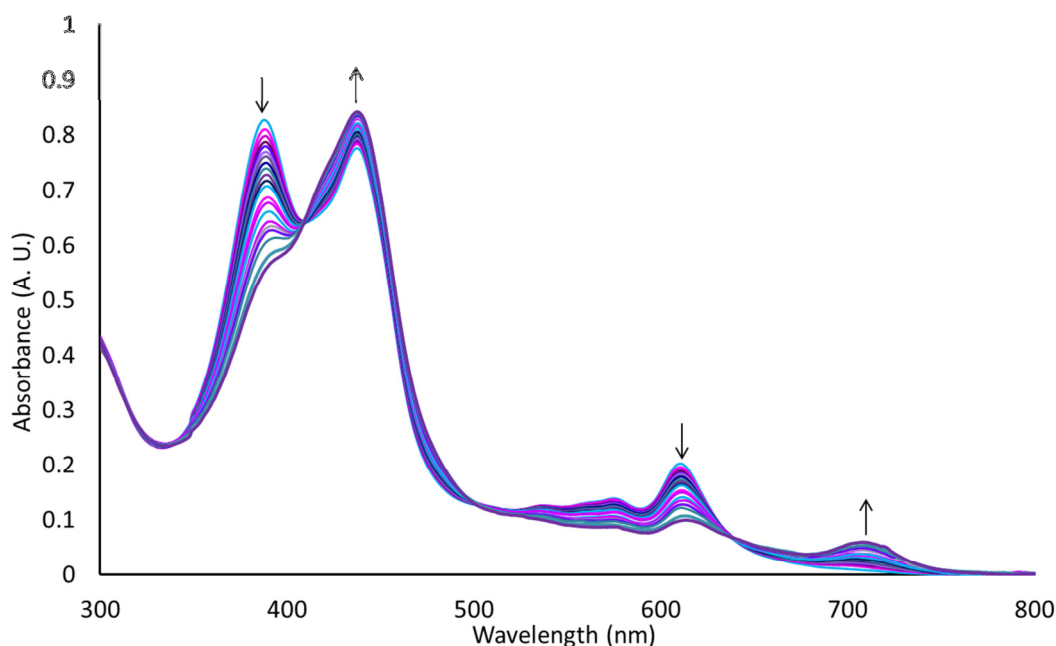


Figure 4.6.7 Spectroscopic changes associated with the binding of thiocyanate to DPTC-Co

Cysteine has 3 pK_{as} at 1.7, 8.36 and 10.74 for the deprotonation of the carboxylic acid, thiol and amine respectively.⁹⁶ The titration of DPTC-Co with cysteine was conducted at a pH of 9.8 where the fraction of the thiolate was 0.97 and the unprotected amine was 0.12. The binding of cysteine can thus be considered to involve the binding of thiolate, an anionic ligand. In spite of this, the spectroscopic changes are reminiscent of the binding of neutral *N*-donor ligands (Figure 4.6.8). There was an increase in absorbance of all maxima except the initial Soret at 388 nm. Soret 2 experienced a small shift to the red from 437 to 439 nm (as in the neutral *N*-donors). The shoulder appeared at 435 nm. Q bands 1 and 2 shifted from 538 to 539 nm and 611 to 621 nm respectively, again similar to the spectroscopic changes observed upon binding of neutral *N*-donor ligands. Isosbestic points were observed at 399, 430, 473, 560, 677 and 739 nm.

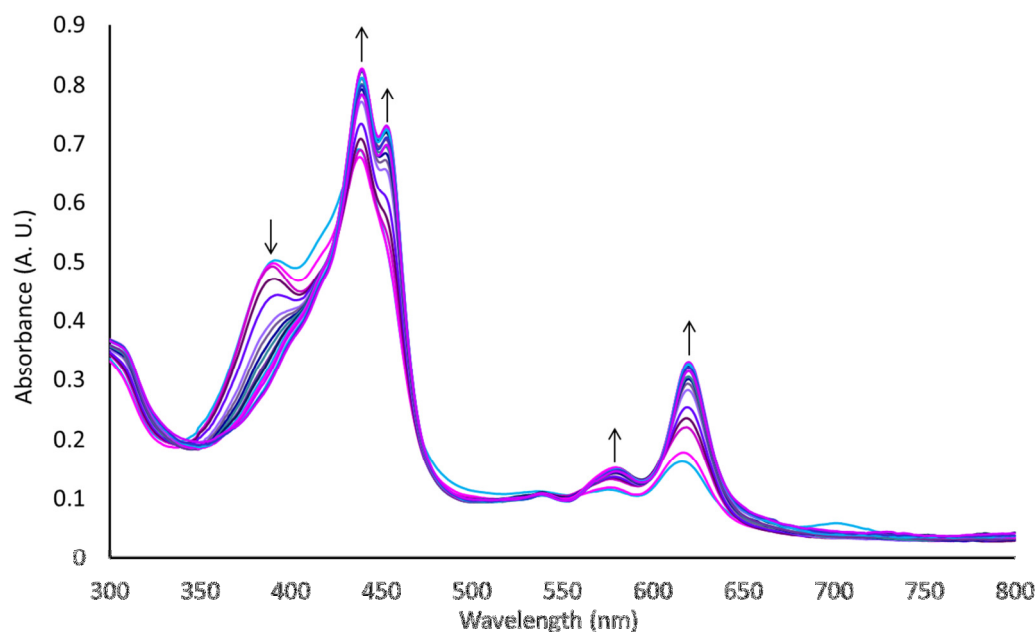


Figure 4.6.8 Spectroscopic changes associated with the binding of cysteine to DPTC-Co at pH 9.8

Iodide coordinated to DPTC-Co weakly. At low iodide concentrations ($0-2.05 \times 10^{-5}$ M), a general decrease in the intensity of the spectrum was observed with no shift in peak position; thus no isosbestic points were observed. At higher iodide concentrations, a marked increase in intensity of Soret 1 and decrease in intensity of Soret 2 was observed. Q band 1 increased in intensity while Q band 2 decreased in intensity. There was no change in peak position except for Q band 2 which shifted from 611 to 614 nm. Isosbestic points were observed at 420, 455, 597 and 620 nm. This may indicate the formation of an outer-sphere complex preceding the actual binding of iodide to the metal centre. Spectroscopic changes at high iodide concentrations are presented in Figure 4.6.9 and the binding isotherm at 385 nm is illustrated in Figure 4.6.10.

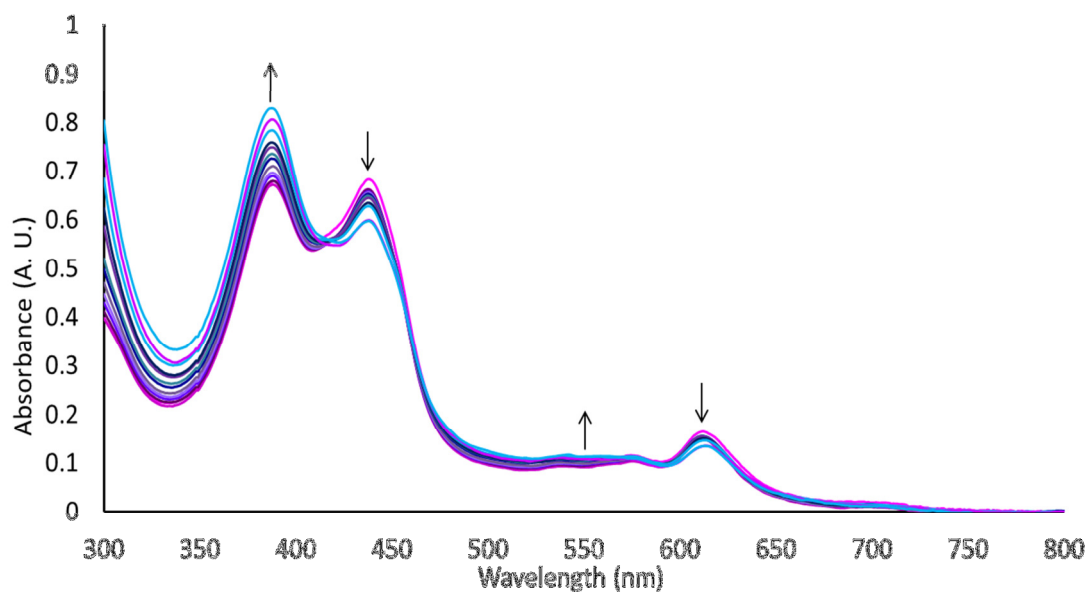


Figure 4.6.9 Spectroscopic changes associated with the binding of iodide to DPTC-Co at high iodide concentration

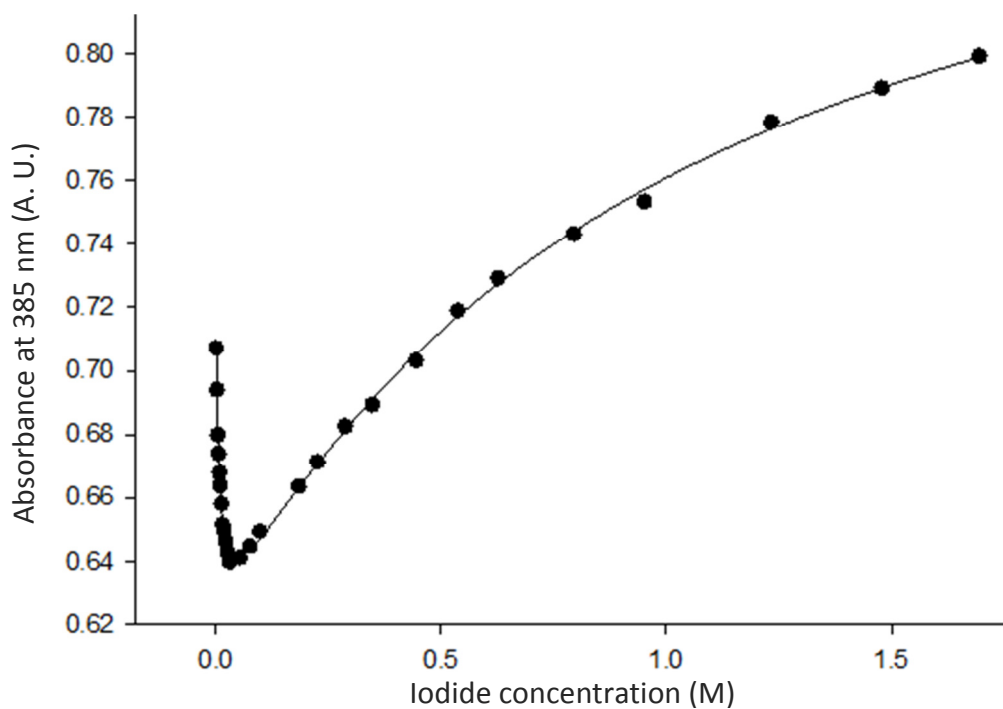


Figure 4.6.10 Change in absorbance at 385 nm with increasing concentration of iodide. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve from Equation 4.2.1

In general, the binding of both neutral and anionic ligands to DPTC-Co resulted in a collapse of Soret 1, believed to indicate the decrease in the fraction of the five-coordinate species with an increase in the fraction of the six-coordinate species. The appearance of a shoulder, Soret 3, appears to be indicative of the coordination of strong neutral ligands and cysteine. The position of Q band 2 varied as the identity of the donor atom of the ligand changed and a low energy Q band (Q3) appeared during the binding of several anionic ligands. This suggests that the electronic transitions responsible for the absorption bands in the Q band region arise as a result of the interaction between the ligand and the biomimetic model. This hypothesis was explored using time dependent DFT calculations and is discussed in **Section 4.7**.

4.6.6 The UV-vis spectroscopic changes of vitamin B_{12a} upon ligand binding

The binding of neutral *N*-donor ligands (ethanolamine, pyridine, DMAP and *N*-methylimidazole) to vitamin B_{12a} yielded similar spectroscopic shifts; the change in intensity, however, differed for the 4 ligands. In the case of the ethanolamine complex, there was an increase in absorbance of the γ band. The D, β and α bands experienced a decrease in intensity. The binding of pyridine on the other hand caused a decrease in absorbance of the γ band and an increase in the D, β and α bands with more distinct β and α bands. Coordination of *N*-methylimidazole produced an increase in absorbance of all of the maxima. The binding of DMAP, in a manner similar to ethanolamine, resulted in an increase in absorbance of the γ band and a decrease of the β and α bands. The D band, however, increased in intensity. Titrations of ethanolamine and DMAP with vitamin B_{12a} were conducted at pH 8 and 9, respectively, while the titrations of both pyridine and *N*-methylimidazole were conducted at pH 7. The spectroscopic shifts and isosbestic points are summarised in Table 4.6.9 below while representative spectra are illustrated in Figure 4.6.11.

Table 4.6.9 Shifts in wavelength of the γ , D, β and α bands and isosbestic points upon binding of neutral *N*-donor ligands to Vitamin B_{12a}

Ligand	Wavelength (nm)				Isosbestic points (nm)
	γ	D	β	α	
Water (pH 7)	351	409	502	523	
Water (pH8/9)	354	418	509	532	
Ethanolamine	356	411	508	532	348, 393, 468, 498, 555
Pyridine	356	411	505	531	337, 354
<i>N</i> -Methylimidazole	357	411	506	535	309, 352, 396, 406, 417, 500, 512, 526
DMAP	358	415	509	535	351, 419, 537

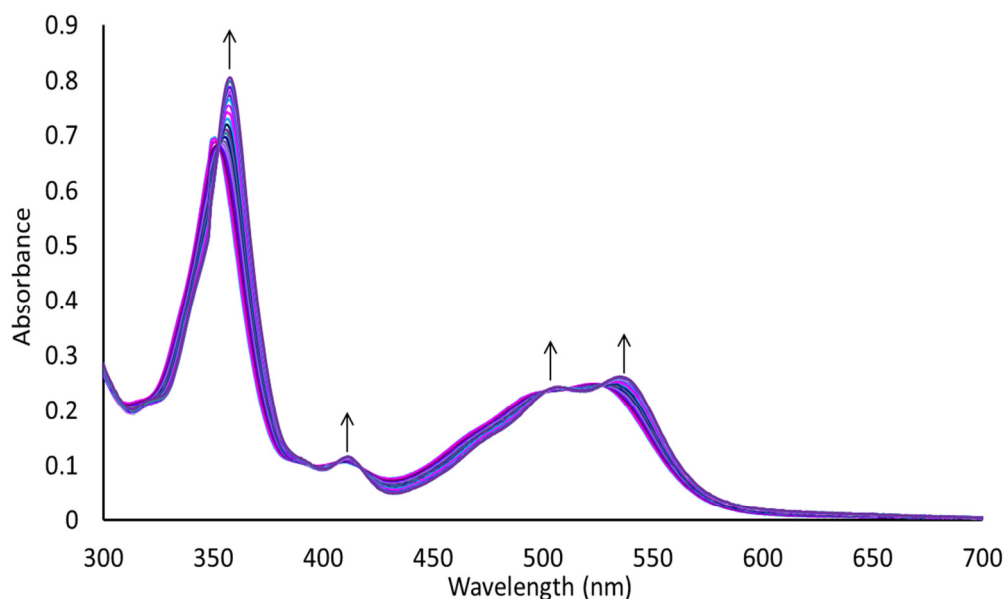


Figure 4.6.11 Spectroscopic changes associated with the binding of *N*-methylimidazole to vitamin B_{12a} at pH 7.1

The formation of the trimethylphosphite complex was accompanied by large bathochromic spectroscopic shifts as illustrated in Figure 4.6.12. The γ band shifted from 351 to 363 nm. The D band shifted from 409 to 411 as observed for the coordination of ethanolamine, pyridine and *N*-methylimidazole. The β and α bands shifted from 502 to 522 nm and 523 to 540 nm respectively. The D band increased in intensity while the absorbance of the γ , β and α bands decreased. Clear isosbestic points were observed at 326, 358, 482 and 552 nm.

The binding of thiourea and thiophene to vitamin B_{12a} led to similar spectroscopic changes. The initial spectra of vitamin B_{12a} differed as the titrations were conducted at different pH values. The thiourea titration was conducted at pH 7.1 while the thiophene titration was conducted at pH 9.1. The binding of thiourea resulted in the γ band decreasing in intensity, and shifting from 351 to 353 nm. The D band shifted from 409 to 407 with an increase in intensity. The β and α bands became indistinct and shifted from 502 and 523 nm to yield one broad band at 530 nm with a decrease in intensity. Clear isosbestic points were observed at 335, 358, 440 and 537 nm. In the case of the coordination of thiophene, the γ band decreased in intensity, but did not experience a shift from 354 nm. The D band shifted from 418 to 414 with an increase in intensity. The β

and α bands became indistinct and shifted from 509 and 532 to yield one broad band at 532 nm with a decrease in intensity. Isosbestic points were observed at 348, 361, 482 and 552 nm. The stability constant for the coordination of thiophene to vitamin B_{12a} was very low, with an observed log K of -0.8. Owing to the low binding constant and the insolubility of thiophene in 80:20 methanol:water solutions at high thiophene concentrations, saturation of the metal was not observed as seen in the binding isotherm in **Digital Appendix 4.3.2**. Spectroscopic changes representative of the binding of sulfur donors are illustrated in Figure 4.6.13.

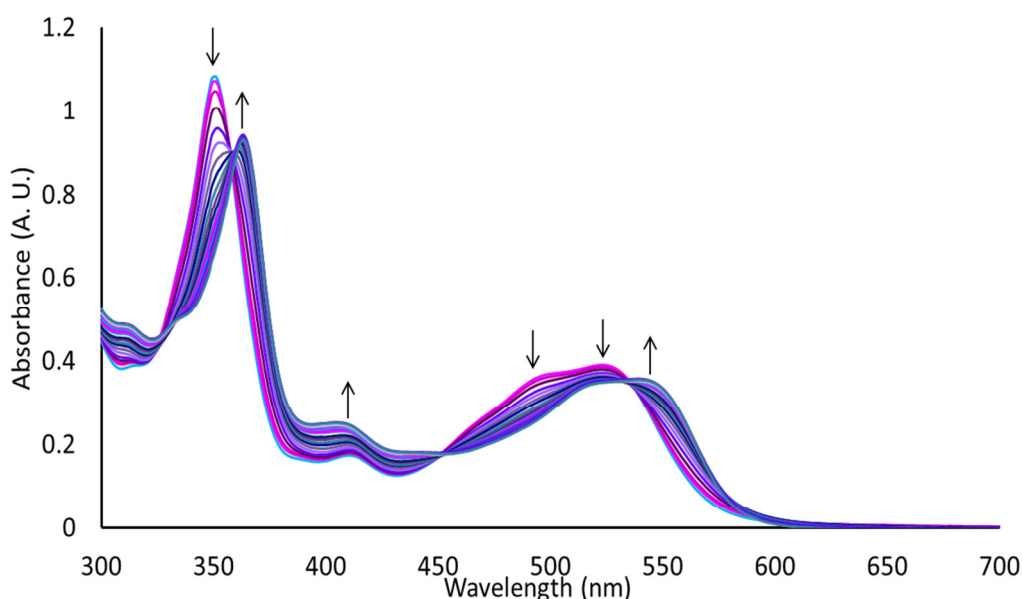


Figure 4.6.12 Spectroscopic changes associated with the binding of trimethylphosphite to vitamin B_{12a}

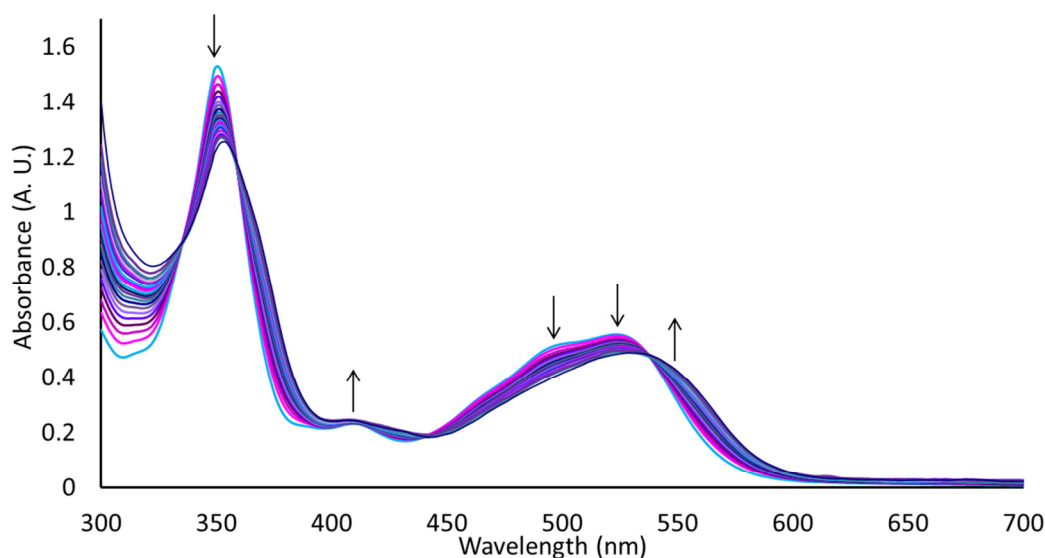


Figure 4.6.13 Spectroscopic changes associated with the binding of thiourea to vitamin B_{12a} at pH 7.1

The binding of anionic *N*- and *S*-donor ligands (cyanide, nitrite, azide and thiocyanate) to DPTC-Co led to similar spectra. This was not the case when bound to vitamin B_{12a}. These titrations were all carried out at pH 7 with γ , D, β and α bands of aquacobalamin present at 351, 409, 502 and 523 nm respectively.

The binding of azide led to a decrease in intensity of the γ band at 358 nm with the appearance of a broad shoulder at 348 nm. The D band at 417 nm increased in intensity. The β band at 514 nm decreased in intensity while the α band at 537 increased in intensity. Isosbestic points were observed at 344, 356, 445 and 527 nm.

When nitrite was coordinated to vitamin B_{12a} the γ band at 355 nm increased in intensity. The D band at 413 nm increased in intensity. The β band at 505 nm and the α band at 531 both increased in intensity and became more distinct. Isosbestic points were observed at 341, 352, 420 and 486 nm.

In the case of the thiocyanate complex, the γ band at 534 nm decreased in intensity. The absorbance of the D band at 411 nm increased. The β and α bands at 511 nm and 533 nm both decreased in intensity. Isosbestic points were observed at 338, 353, 439 and 528 nm.

A large bathochromic shift of the γ band to 360 nm with an increase in absorbance was observed upon formation of the cyanide complex. The position of the D band did not change, but an increase in absorbance was observed. The β band at 517 nm decreased in intensity while the α band at 548 nm increased in intensity. Isosbestic points were observed at 323, 354, 444 and 534 nm. As the stability constant for the formation of the cyanide complex was very large, two competition experiments were carried out using azide and nitrite as competing ligands. A summary of the spectroscopic changes of these experiments can be found in Table 4.6.10.

Table 4.6.10 Spectroscopic changes associated with the binding of cyanide to vitamin B_{12a} in competition reactions

Competing ligand	Wavelength (nm)				Isosbestic points (nm)
	γ	D	β	α	
Water	351→360	409→409	502→517	523→548	323, 354, 444, 534
Nitrite	354→360	413→409	504→517	531→548	355, 404, 449, 449, 539
Azide	356→360	417→409	514→517	537→548	353, 389, 542, 600

The binding of iodide led to an 'atypical'²⁹ vitamin B₁₂ spectrum as in Figure 4.6.14. The γ decreased in intensity substantially with a shift from 351 to 355 nm. Shoulders appeared on either side of the γ band at 321 and 373 nm, characteristic of atypical vitamin B₁₂ spectra.²⁹ The D band gave way to two bands at 418 and 439 with decreased intensity. The β band collapsed while the α band decreased in intensity at 529 nm and a new band appeared at 557 nm. Isosbestic points were observed at 336, 363, 395, 417, 446, 542 and 597 nm.

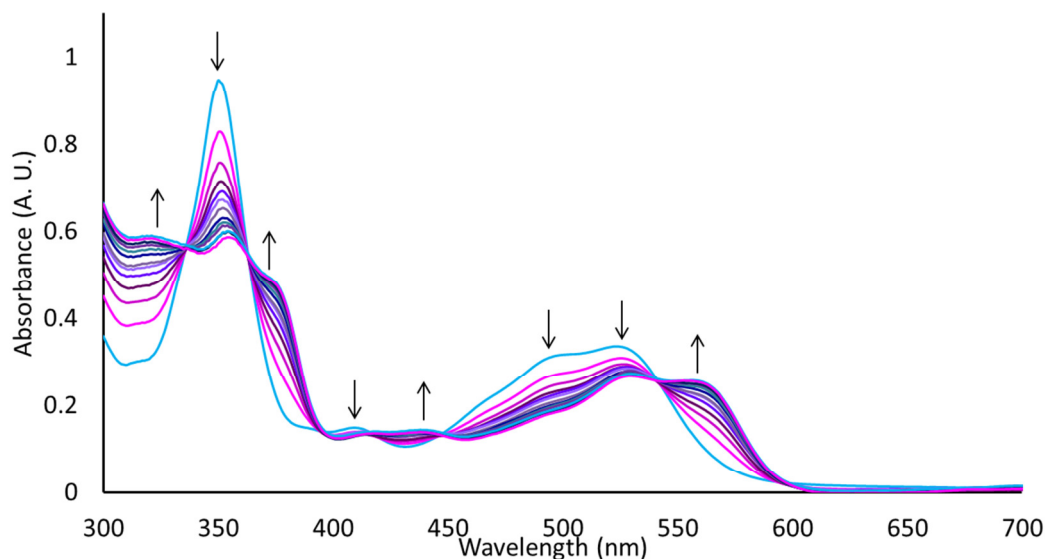


Figure 4.6.14 The 'atypical' spectroscopic changes associated with the binding of iodide to vitamin B_{12a}

The coordination of cysteine at pH 6.0 also yielded an 'atypical' spectrum (Figure 4.6.15).¹¹⁰ The absorbance of the γ band was greatly reduced with new bands appearing at 332 and 369 nm. There was an increase in the absorbance of the D band together with a large bathochromic shift from 408 to 430 nm. The β band collapsed and the α band

decreased in intensity and shifted from 522 to 528 nm and a new band appeared at 554 nm. Isosbestic points were observed at 338, 362, 447 and 531 nm.

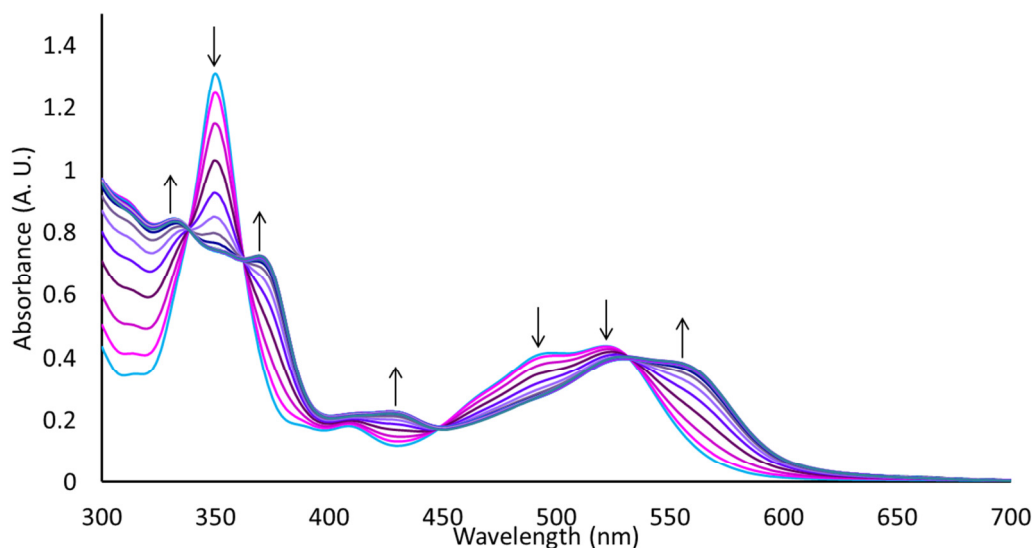


Figure 4.6.15 The 'atypical' spectroscopic changes associated with the binding of cysteine to vitamin B_{12a} at pH 6.0

The spectroscopic changes observed during the binding of ligands to vitamin B_{12a} were, in general, smaller than those observed for the DPTC-Co reactions. In general, the α and β bands experienced a bathochromic shift upon the binding of both neutral and anionic ligands. The position and intensity of the γ band varied as the ligand varied. An increase in intensity with little change in position was observed for neutral *N*-donor ligand complexes and the nitrite complex, while an increase in intensity with a significant bathochromic shift was observed for the cyanide complex. The γ band decreased in intensity with a significant bathochromic shift in position for the trimethylphosphite complex and decreased in intensity for the neutral *S*-donor ligand, azide and thiocyanate complexes with little change in position. 'Atypical' spectra were observed for the iodo and cysteine complexes.

4.6.7 The effect of the corrole ring on the coordinated metal

There is a linear correlation between the $\log K$ values for vitamin B₁₂ and DPTC-Co complexes, as illustrated in Figures 4.6.14 and 4.6.15; as $\log K$ of DPTC-Co complexes increases, the $\log K$ of vitamin B₁₂ complexes increases as well. This suggests that the cobalt coordinated by either the corrole or corrin ring coordinates to the ligands in a similar fashion. In Figure 4.6.16 the data points (except that for cyanide) lie below the $\log K_{\text{corrole}} = \log K_{\text{B}_{12}}$ line. This indicates that the stability constants are higher for B₁₂ complexes than for DPTC-Co complexes. In Figure 4.6.17 all of the data points lie above the $\log K_{\text{corrole}} = \log K_{\text{B}_{12}}$ line, indicating that the stability constants are higher for DPTC-Co complexes than for B₁₂ complexes. The very large $\log K$ value for the coordination of cyanide to both DPTC-Co and B₁₂ and the coordination of trimethylphosphite to DPTC-Co makes determination of their exact values very difficult, even when determined from competition experiments. These $\log K$ values are approximate therefore and the presence of the cyanide data point above the $\log K_{\text{corrole}} = \log K_{\text{B}_{12}}$ line in Figure 4.6.16 cannot be considered significant.

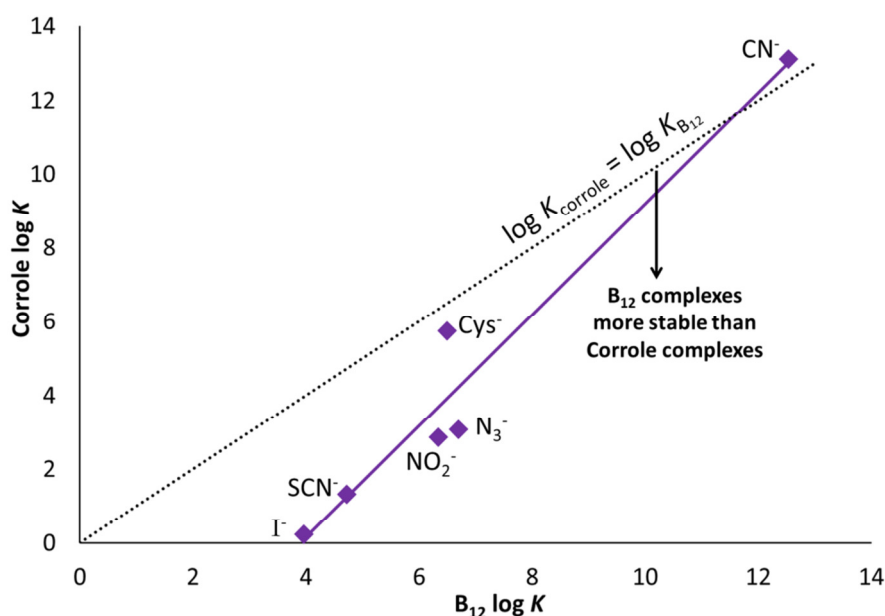


Figure 4.6.16 The correlation between the stability constants for DPTC-Co and vitamin B₁₂ complexes with anionic ligands.

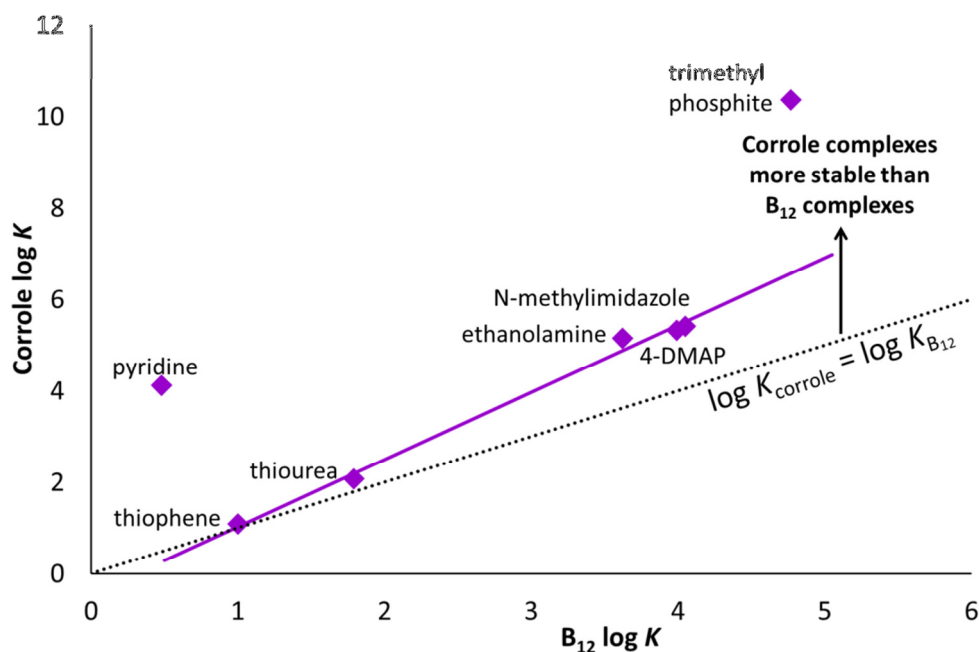


Figure 4.6.17 The correlation between the stability constants for DPTC-Co and vitamin B_{12} complexes with neutral ligands.

As mentioned previously, the corrin ring has one ionisable nitrogen of the four nitrogen donors which coordinate cobalt(III) with a net 2+ charge on the metal centre. In the corrole ring, on the other hand, three of the four coordinating nitrogens are ionisable. When coordinated to cobalt(III), the complex is neutral. The electrostatic interaction between the positively charged metal centre of vitamin B_{12} and the harder ionic ligands results in higher $\log K$ values than for the neutral corrole biomimetic system. Similarly, the neutral DPTC-Co system interacts more strongly with the softer neutral ligands than the charged vitamin B_{12} system. This suggests that the interaction between the metal and the incoming ligand can be modified by the nature of the equatorial macrocyclic ligand and that cobalt, when coordinated by the corrole ring in DPTC-Co is softer, possessing more cobalt(II) character, than when coordinated by the corrin ring in vitamin B_{12} .

The $\log K$ values for the binding of both pyridine and trimethylphosphite (even if the latter is an approximate value) are considerably higher for the DPTC-Co complex than the vitamin B_{12} complex and therefore these values deviate significantly from the linear relationship in Figure 4.6.17. The lower than expected values for the coordination of pyridine and trimethylphosphite by vitamin B_{12} are probably due to the steric interactions

between the bulky ligand and the metal centre, crowded by sterically large acetamide groups above the plane of the corrin ring. As no crystallographic data were available, DFT modelling had to be relied upon to explore the structure. The interaction between pyridine and cobalt in vitamin B₁₂, as determined by DFT calculations, is illustrated in Figure 4.6.18.

One might expect a similarly low log *K* value for the binding of DMAP to vitamin B_{12a} as the steric bulk of this ligand is very similar to that of pyridine. From comparison of the p*K*_a values for the conjugate acids of these ligands, 5.2 (pyridine) and 9.55 (DMAP) (Table 4.6.11), it is evident that there is a very strong inductive effect from the dimethylamino group *para* to the nitrogen of the pyridine ring. The increased electron density on the nitrogen enhances the attraction between the nitrogen and the proton, thus increasing the basicity of the ligand. DMAP is better able to interact with the cobalt in vitamin B₁₂, in spite of the steric restrictions, due to the increased attraction between the electron rich nitrogen and the positive metal centre. This is evident from a comparison of the cobalt-ligand bond lengths determined from the geometry-optimised DFT structures. The pyridine-cobalt bond length is 2.045 Å while there was a 0.018 Å decrease to 2.027 Å when DMAP was bound to cobalt. In addition to the shortening of the nitrogen-cobalt bond, there was an increase in the non-bonded interaction distance between the hydrogen atoms on C2 and C6 of the ligand and C5 and C15 of the corrin macrocycle from 2.340 and 2.538 Å (pyridine) to 2.349 and 2.559 Å (DMAP) as illustrated in Figure 4.6.18. These changes in bond lengths indicate that the increased basicity of DMAP encourages strong coordination to the coordinated cobalt, in spite of the steric constraints, illustrating that the electronic effects overcome the steric effects during the coordination of pyridine derivatives.

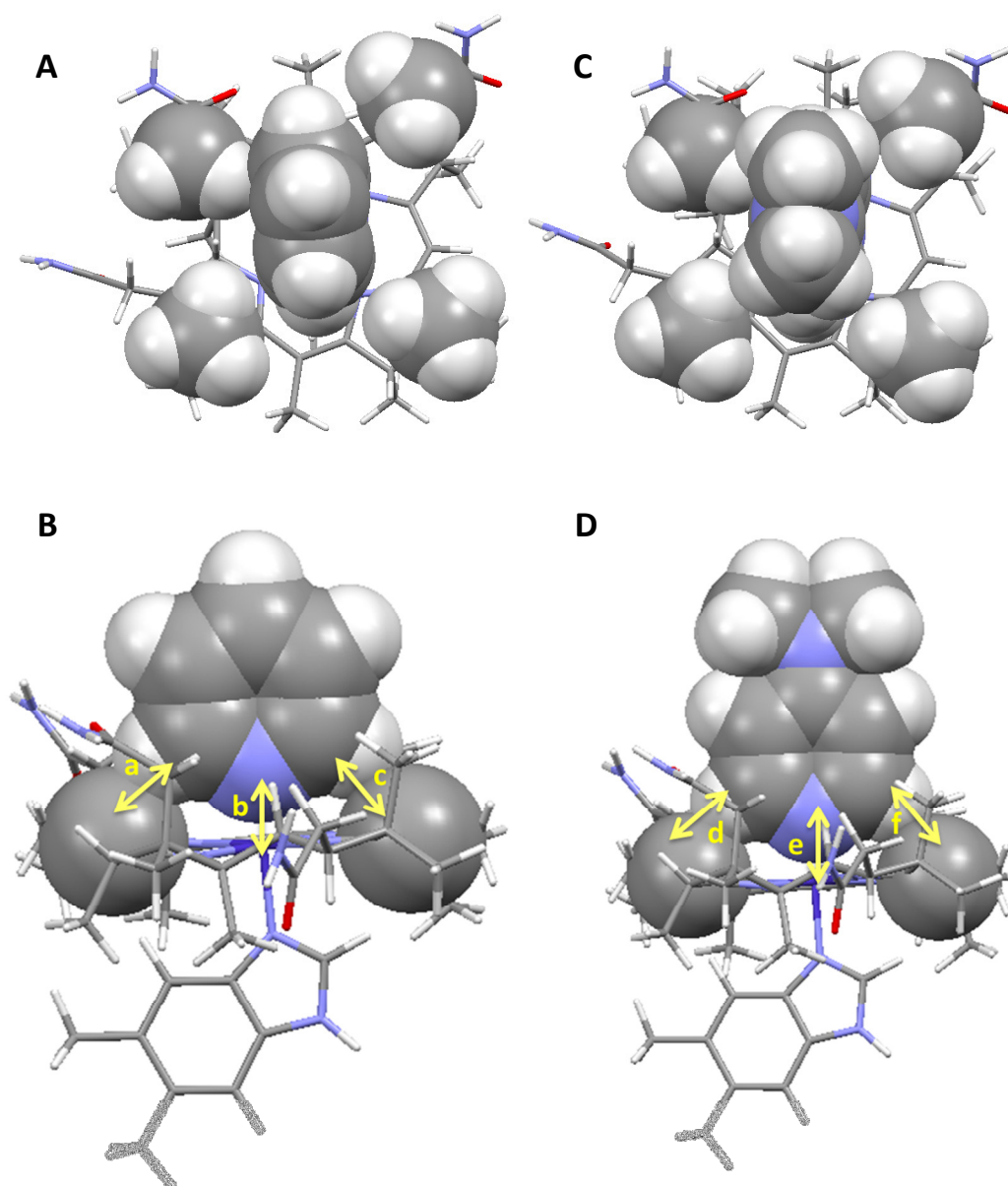


Figure 4.6.18 DFT geometry optimised B_{12} complexes with pyridine (**A** and **B**) and DMAP (**C** and **D**) viewed from the β face and from the side illustrating bond lengths (in Å) a – 2.340; b – 2.045; c – 2.538; d – 2.349; e – 2.027; f – 2.559

The pK_a values for the ligands used in this study are presented in Table 4.6.11. An increase in the pK_a of the conjugate acids of the anionic ligands led to an increase in the stability constant for the formation of both the DPTC-Co and vitamin B_{12} complex as in Figure 4.6.19. This suggests that there is a correlation between the affinity of the Lewis base (the ligand) to both the Lewis acid proton and the Lewis acid metal; thus when coordinating to anionic ligands, Co(III) acts in a similar manner to the hard proton, i.e. the interaction between the ligand and the metal has ionic character. This is evident from the QTAIM

studies on the DPTC-Co model, discussed in **Section 4.7.4**, where the data suggested that the bond between the cobalt and the anionic nitrite ligand had a high degree of ionic character. The large stability constants of cyanide with DPTC-Co and vitamin B₁₂ deviated from the linear relationship in Figure 4.6.19, indicating that the cyanide-cobalt bond differed from the nature of the other Co-anionic ligand bonds. QTAIM data highlighted this difference, indicating that the Co-CN bond had significant covalent character.

Table 4.6.11 pK_a values for the conjugate acids of ligands used in this study

Ligand	pK_a (μ – M)	Reference
<i>Neutral ligands</i>		
Trimethylphosphite	3.4	Chemaly ¹⁰⁹
Pyridine	5.20 (0.0)	NIST database ⁹⁶
N-Methylimidazole	7.10 (0.1)	NIST database ⁹⁶
Ethanolamine	9.50 (0.0)	NIST database ⁹⁶
DMAP	9.55 (0.1)	NIST database ⁹⁶
Thiourea	21.1 (DMSO)	Jakab ¹¹¹
Thiophene		
<i>Anionic ligands</i>		
Iodide	-9.5	McCoubrey ¹¹²
Thiocyanate	-1.3 (0.0)	NIST database ⁹⁶
Nitrite	3.15 (0.0)	NIST database ⁹⁶
Azide	4.62 (0.0)	NIST database ⁹⁶
Cysteine	1.7, 8.36, 10.74 (0.0)	NIST database ⁹⁶
Cyanide	9.21 (0.0)	NIST database ⁹⁶

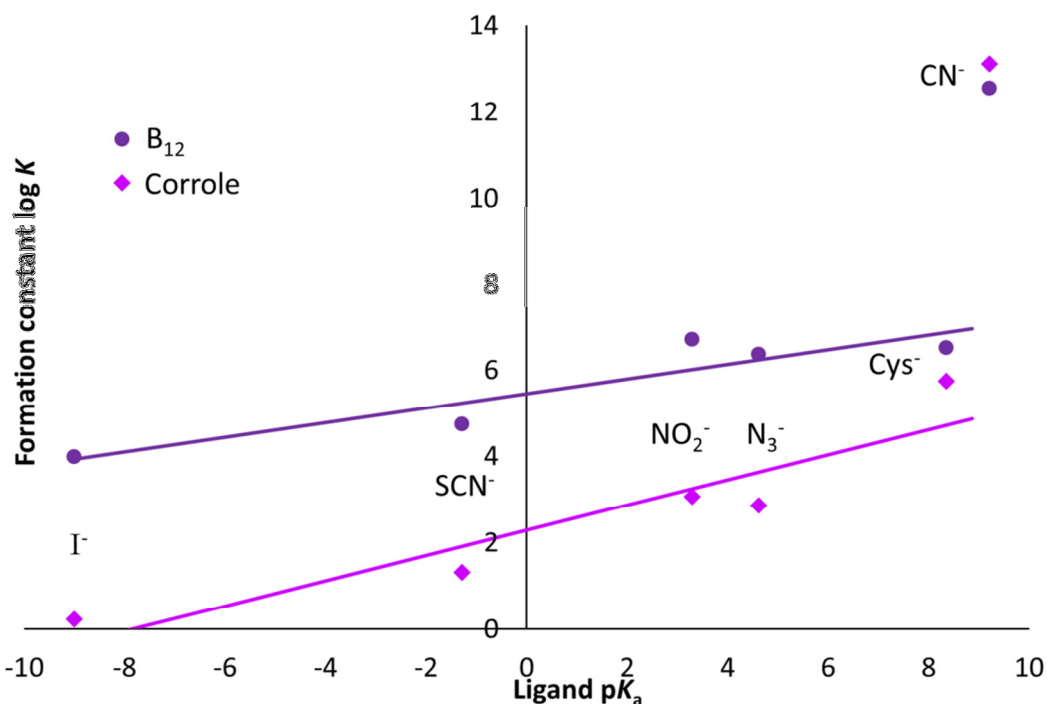


Figure 4.6.19 The correlation between the stability constants for DPTC-Co and vitamin B_{12} complexes with anionic ligand pK_a

The stability constants of DPTC-Co and vitamin B_{12a} complexes with neutral ligands, however, decrease with increasing ligand pK_a (the pK_a of the conjugate acid of the ligands) as in Figure 4.6.20. The inverse correlation suggests that in this case the metal does not behave in a manner similar to the ionic interaction between the hard proton and the Lewis base. This suggests that the interaction between the metal and the ligand in DPTC-Co and vitamin B_{12} complexes has significant covalent character. QTAIM data, however, indicates that the Co-ligand bond has significant ionic character, although ρ , indicative of bond length and strength, shows that the neutral ligands bind to the cobalt with short, strong bond lengths, with the exception of trimethylphosphite, a bulky, sterically demanding ligand. The negative trend might be misleading, however, as the series of neutral ligands considered varied enormously in terms of their basicity, polarisability, size and the nature of the donor atom. In spite of the negative trend (highlighting the misleading nature of this 'trend'), the $\log K$ of the binding of DMAP, an electron donating ligand was over an order of magnitude higher than the binding of pyridine for both the DPTC-Co and vitamin B_{12} systems. This result is in agreement with Murakami's findings³⁶ where the $\log K$ increased with increasing basicity of pyridine ligands.

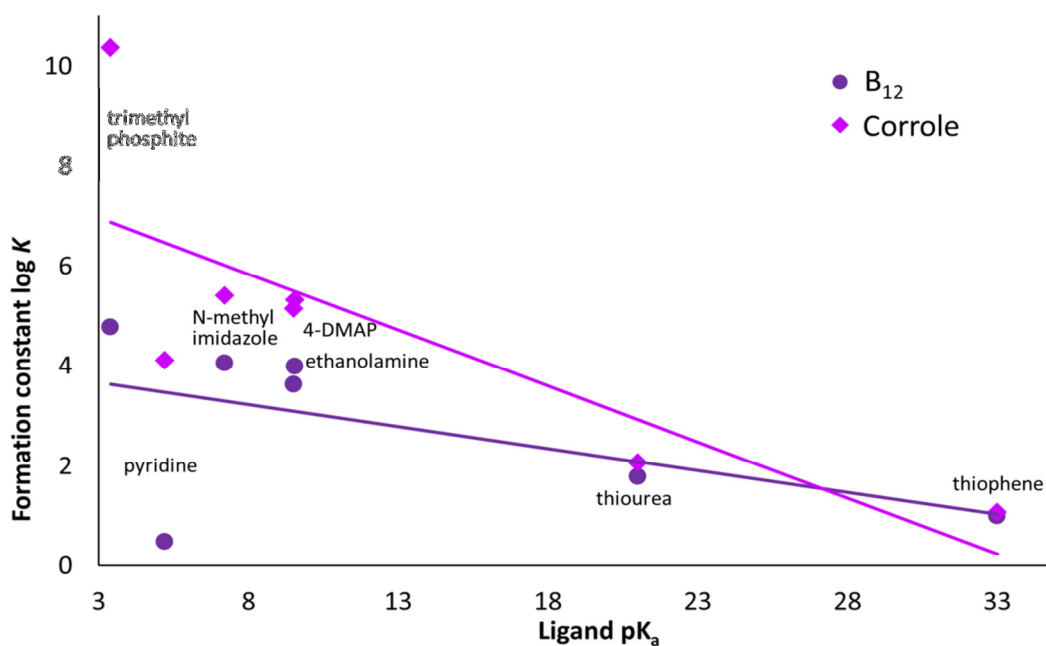


Figure 4.6.20 The correlation between the stability constants for DPTC-Co and vitamin B_{12} complexes with neutral ligand pK_a

The stability constants for the formation of complexes with sulfur donors thiourea and thiophene were low. Sulfur, a soft ligand, might be expected to form strong complexes with the softer than expected $Co(III)$ in the corrin and corrole systems. Thiourea contains a thioketone where the lone pairs are delocalised into the double bond, ensuring that they are held more closely to the sulfur nucleus and are less available for bonding to the metal. Thiophene on the other hand is an aromatic thioether. The lone pairs on the sulfur are delocalised into the aromatic system of the molecule, and thus are unavailable for bonding to the cobalt metal.

Guilard³⁴ and Adamian³⁵ found that within a series of corroles bearing different β and *meso* substituents, the presence of electron withdrawing substituents, decreasing the donation of electron density to the metal, resulted in an increase in the $\log K$ for the coordination of pyridine. The decrease in electron density at the metal centre would result in a harder, more positively charged metal ion which would more readily accept electrons from an incoming ligand than would a softer, more electron rich metal ion. This is in direct contrast with what has been observed in this study. The introduction of the electron rich corrole ring, donating electron density to the coordinated cobalt, should

result in a softer, more electron rich metal compared the cobalt vitamin B₁₂ system, coordinated by a less electron rich corrin ring. In this study, the binding of neutral ligands occurred more readily with the electron donating corrole system, with higher stability constants, than in the B₁₂ system.

In the systems studied by Guilard and Adamian, comparison was made between similar systems, using either pyridine as the incoming ligand and different corrole macrocycles, or with the same corrole macrocycle and different pyridine derivatives as incoming ligands. In this way, the effect of a change in basicity of the ligand, or in the electron donating or withdrawing properties of the corrole ring substituents could be observed. In the present study, the two systems and the range of ligands used were markedly different and many factors influenced the binding of ligands. These include the steric constraints of the β face of vitamin B_{12a} from the bulky propionic substituents together with their electron donating properties, the differences in the identity of the lower or α ligand as well as the difference in the length of the delocalised system, and therefore planarity and conformation, of the corrin and corrole macrocycles. With these differing factors, it was not possible to draw similar conclusions to those in the literature.^{34,35}

It must be noted that the log *K* values for the binding of ligands to DPTC-Co (which are, in essence, log *K*₂ values, as discussed in **Section 4.6.1**) determined in this study, are substantially higher than those observed previously. The log *K* and log *K*₂ for the binding of pyridine to various corroles in organic solvents varied from 3.78-5.48 and 1.6-2.38 for log *K* and log *K*₂, respectively³²⁻³⁷ while the binding of pyridine to DPTC-Co had a log *K* of 4.11. This is in the region expected for the binding of one pyridine molecule to yield a five-coordinate system. The pyridine complex with DPTC-Co, at pH 9.2 (the pH of the ligand substitution reaction with pyridine) is expected to be six-coordinate, a result verified by DFT calculations (discussed in **Section 4.7**).

4.6.8 Conclusions

The binding of ligands to cobalt in corrin and corrole-containing systems is solvent dependent. The charge of both the ligand as well as the metal centre in the macrocycle dictates the solvent effect. In the case of DPTC-Co, containing a neutral metal centre, the increase in polarity and coordinating ability of the solvent decreases the efficiency of a neutral ligand binding to the cobalt. In the case of vitamin B₁₂, containing a positively charged metal centre, anionic ligands have been found to bind more efficiently in solvents with lower polarities, while the opposite is true for neutral ligands.

The spectroscopic changes observed upon complexation of the different ligands were similar for ligands of the same class (neutral *N*-donor; neutral *S*-donor; anionic *N*- and *S*-donor) for both the corrole and corrin systems. The binding of iodide and cysteine to vitamin B_{12a} resulted in 'atypical' spectra while the binding of cysteine to DPTC-Co gave spectra similar to the binding of the neutral *N*-donor ligands. Two processes were observed during the binding of iodide to DPTC-Co, indicating the potential formation of an outer-sphere complex.

The stability constants of the binding of a range of ligands to both the corrole containing DPTC-Co and the corrin containing vitamin B_{12a} systems indicate that cobalt acts in a similar fashion towards ligands when coordinated by either the corrin or corrole ring. The binding of anionic ligands was favoured by the charged metal centre in vitamin B_{12a}, while the neutral cobalt in DPTC-Co favoured neutral ligands. This suggested that the metal in DPTC-Co was softer in nature than that in Vitamin B_{12a}, highlighting the ability of the coordination environment of the cobalt to affect its chemistry. The steric constraints of the β face of vitamin B_{12a} affect the binding of bulky ligands, such as pyridine; however, the steric effects can be overcome as the electron donating ability, or basicity, of the ligand increases, as in the case of DMAP.

The log *K* of the anionic ligand increased as the p*K*_a increased for both corrole and corrin systems while the opposite occurred for neutral ligands. This may indicate a difference in

the character of the metal-ligand bond. QTAIM analysis indicated that the binding of anionic ligands occurred through a more ionic interaction, with long bond lengths while a more covalent interaction, with shorter bond lengths was observed during the binding of neutral ligands.

4.7 Correlation between DFT calculated and experimental UV-vis spectra – insights into the effect of ligand binding on the electronic structure of the DPTC-Co system

4.7.1 Introduction

DFT, or density functional theory, is a computational method based on the two Hohenberg-Kohn theorems. The first theorem states that there is a one-to-one mapping between the ground state electron density of a system and its wavefunction and the second that the ground state electron density minimises the total electronic energy of a system. The fundamental postulate of quantum mechanics is that any physical system can be fully described by its wavefunction. Consequently, the first Hohenberg-Kohn theorem allows for the physical properties of a system to be described by the electron density of that system. From the second theorem, the energy of the ground state can be determined from determination of the ground state electron density.¹¹³ The calculated electron density distributions are expressed in terms of Kohn-Sham orbitals.

Several functionals, or the mathematical relationships between energy and electron density, for the calculation of the electron density distribution have been designed, differing in the way this electron density-energy relationship is described.¹¹⁴ As the choice of functional can drastically alter the outcome of DFT calculations, there is much debate as to the best choice of functional for the study of macrocycles.^{14,114-116} In general, the consensus is that while hybrid functionals appear to give good results, a series of functionals should be used and the results compared to available experimental data. In any event, in the absence of experimental data, it is very difficult to determine the accuracy of computational data.

Various DFT-based studies have been performed on corrole complexes, with the majority focused on fundamental studies of different corroles with respect to their molecular and electronic structure.^{18,114,117-126} Some of the main conclusions about the molecular

structure of corroles include the following: corroles are relatively planar compared to porphyrins;¹²¹ five-coordinate structures often display doming at the metal centre;^{121,124} saddling, unlike in the case of porphyrins, is uncommon for corroles with the exception of copper corroles^{121,124} (which have been extensively studied^{14,115,127-129}); ruffling of the macrocycle is impossible.^{121,122}

The electronic structure of corroles is similar to porphyrins in some respects and the electronic structure of the four frontier orbitals described by the four-orbital model proposed by Gouterman^{19,20} can be used to describe corroles as well as porphyrins.¹⁸

The innocence or non-innocence of the corrole ligand has been extensively debated, where the use of DFT has highlighted the metal-corrole ligand orbital mixing leading to non-innocence of the corrole.^{14,116,120,127,130-134} There is general agreement that the corrole ligand is able to act as both an innocent and a non-innocent ligand and the corrole's environment (*meso* and β substitution patterns, the type of metal and the presence and type of axial ligand) plays an important role in this distinction.

DFT calculations have also been used in the determination of reaction mechanisms and the reactivity of metallated corrole systems. In many cases, manganese and iron corroles have been studied as biomimetic models in order to gain insight into the reaction mechanisms of cytochrome P450 compound I^{135,136} and chloroperoxidase compound I and II intermediates.^{133,137}

Time-dependant DFT (TD-DFT) calculations have been used in the calculation of excited states of corrole systems. This has been used to rationalise experimental spectroscopic data.¹³⁸⁻¹⁴³ The changes in substitution pattern of the corrole backbone at the *meso* and β positions in free-base corroles are evident in the position of the Q bands. TD-DFT results indicate that this is as a result of the change in the energy gap between the LUMO and LUMO-1 orbitals. The substitution of nitro groups in the β positions stabilises the LUMO orbitals resulting in the Q bands being red-shifted.¹⁴⁰ The spectra of metallocorroles are also sensitive to varying substitution of aryl groups at the *meso* positions – a feature not

observed in porphyrin spectroscopy.^{138,141} This sensitivity results in 'hyper-spectra', or the splitting of the Soret band as a result of significant ligand-to-metal charge transfer contributing to transitions in the Soret region, a phenomenon also not observed for porphyrins.^{138,139,141}

Alemayehu¹³⁸ noted that while TD-DFT calculations often provide good representations of experimental data in cases where the corrole, metal and substituents can be viewed as a single chromophore, the presence of substituents with lone pairs in the corrole system can result in unsatisfactory calculated spectra displaying nonphysical, strong transitions which arise from the excitations of these lone pairs.

Bader's quantum theory of atoms in molecules (QTAIM) is used to gain insights into the nature of bonding in chemical systems.^{144,145} QTAIM uses the distribution of electron density, ρ , and the gradient vector field of ρ , $\nabla\rho$, to study the topology of the electron density in describing the bonding in a system. A bond is characterised by the presence of both a bond path and a bond critical point. A bond path is a line in space at which the distribution of electron density is higher than at the neighbouring lines or space. The point on this line at which the gradient, $\nabla\rho$, vanishes is known as a bond critical point. The value of ρ at the bond critical point gives an indication of the strength of the bond, while its position indicates the polarity of the bond.¹⁴⁴ The ratio of electron potential energy density, $V(\mathbf{r})$ and kinetic energy density, $G(\mathbf{r})$, $|V(\mathbf{r})|/G(\mathbf{r})$ is used to classify the bond as covalent, ionic or of intermediate character.¹⁴⁶

4.7.2 Methods particular to DFT methods

A simplified model of DPTC-Co (Figure 4.7.1) was used for DFT studies. A variety of ligands, representative of those used for the experimental determination of stability constants, were used as the upper axial ligand. Wavefunction files for use in QTAIM analysis of ρ were generated using DFT methods using Gaussian-09.⁶⁰ Geometry optimisations were carried out at the BP86^{147,148} level of theory using the TZVP^{149,150} basis set. BP86 is a generalised gradient approximation functional which is considered to be one of the best functionals for the study of cobalamins.¹⁵¹

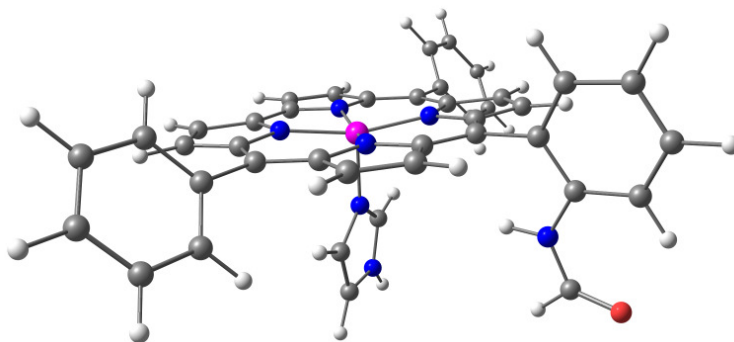


Figure 4.7.1 Simplified DPTC-Co model used for DFT calculations

TD-DFT single point excitation energies for the first 30 excited states were calculated using the hybrid density functional CAM-B3LYP¹⁵² with TZVP^{149,150} basis set. Preliminary calculations using the BP86 functional showed poor correlation with experimental spectra. The hybrid CAM-B3LYP functional, on the other hand, reproduced experimental results more closely. The resultant calculated electronic spectra were compared and contrasted with experimental data.

Wavefunction files, were generated using Gaussian by performing a single point calculation on previously geometry-optimised structures, were used as input for QTAIM calculations. ρ , a measure of the electron density at a bond critical point, $G(\mathbf{r})$, the kinetic energy density, and $V(\mathbf{r})$, the electron potential energy were evaluated using the AIMALL and AIM2000 program suite.^{153,154}

4.7.3 Calculated UV-vis spectra of a DPTC-Co model

TD-DFT calculations were carried out for the DPTC-Co model coordinated to one of several ligands – methanol, ethanolamine, pyridine, trimethylphosphite, imidazole, nitrite, cyanide and a thiolate (H_3CS^-), a model of cysteine as well as the five-coordinate species and a diaqua species.

Table 4.7.1 illustrates the differences between the calculated and experimental spectra. There is good correlation (in bold in Table 4.7.1) of the distance between the Soret and final Q band in the experimental spectra with that in the calculated TD-DFT spectra of DPTC-Co complexes with neutral ligands and the thiolate.

The distance between the Soret and last Q band was not reproduced for the complexes of anionic ligands, cyanide and nitrite, the diaqua nor the five-coordinate species. Scaling of the x-axis of the calculated spectrum (using a multiplication factor) improved the correlation slightly in the case of the five-coordinate species while in the case of the diaqua, cyanide and nitrite complexes, the position of the calculated Q band of highest wavelength in the TD-DFT spectra corresponded to a much more weakly absorbing Q band at lower wavelengths, rather than to the more intense Q band at a higher wavelength in the experimental spectrum.

Table 4.7.1 TD-DFT and experimental spectra of DPTC-Co with various ligands

Ligand	TD-DFT					Experimental		
	Soret 1	Soret 2	Q band	Soret 1 – Q band	Soret 2 – Q band	Soret	Q band	Soret – Q band
Five-coordinate	366		503	137		388	554	166
Methanol	373	381	556	183	175	437	611	174
Ethanolamine	371	393	568	197	175	438	616	178
Imidazole	377	394	575	198	181	438	622	184
Pyridine	361	392	572	211	180	438	617	179
Trimethylphosphite	377	400	586	209	186	443	633	190
Cyanide	382	407	586	204	179	434	711	277
Nitrite	388	408	586	198	178	436	706	270
Cysteine / thiolate	388	421	602	214	181	439	621	182
Diaqua species	364	378	548	184	170	434	694	260

Two different scaling factors were applied to the TD-DFT data to ensure overlap of the Soret and final Q band in the calculated and experimental spectra (Yang indicated that their calculated data had been shifted by a ‘constant energy offset’ to correlate with their experimental data¹⁴²). In the case of the DPTC-Co complexes with neutral ligands and the thiolate, the wavelength of all of the peaks was shifted to higher wavelengths. The wavelengths of the peaks of the complexes with anions (cyanide, and nitrite), the diaqua species and five-coordinate species were adjusted through a multiplication scaling factor. The scaling factors used are summarised in Table 4.7.2.

Table 4.7.2 Scaling factors applied to TD-DFT data

Ligand	Scaling factor
Methanol	$\lambda + 55$
Ethanolamine	$\lambda + 50$
Imidazole	$\lambda + 45$
Pyridine	$\lambda + 45$
Trimethylphosphite	$\lambda + 45$
Cysteine / thiolate	$\lambda + 20$
Cyanide	$\lambda \times 1.065$
Nitrite	$\lambda \times 1.065$
Five-coordinate	$\lambda \times 1.15$
Diaqua species	$\lambda \times 1.06$

Comparison of the TD-DFT spectrum of the five-coordinate species with the experimental spectrum of DPTC-Co in dichloromethane suggests that the hypothesis of the existence of a five-coordinate species in non-coordinating solvents (**Section 4.3.4**) is valid. The general peak shape and position of the TD-DFT spectrum was reflected in the experimental spectrum as seen in Figure 4.7.2. In addition to the peak shape and position, TD-DFT predicted one principle Soret peak for the five-coordinate species, while at least two Soret peaks at longer wavelengths were predicted for the six-coordinate systems (an example of which is illustrated in Figure 4.7.3) as seen in the experimental spectra of DPTC-Co coordinated to neutral ligands.

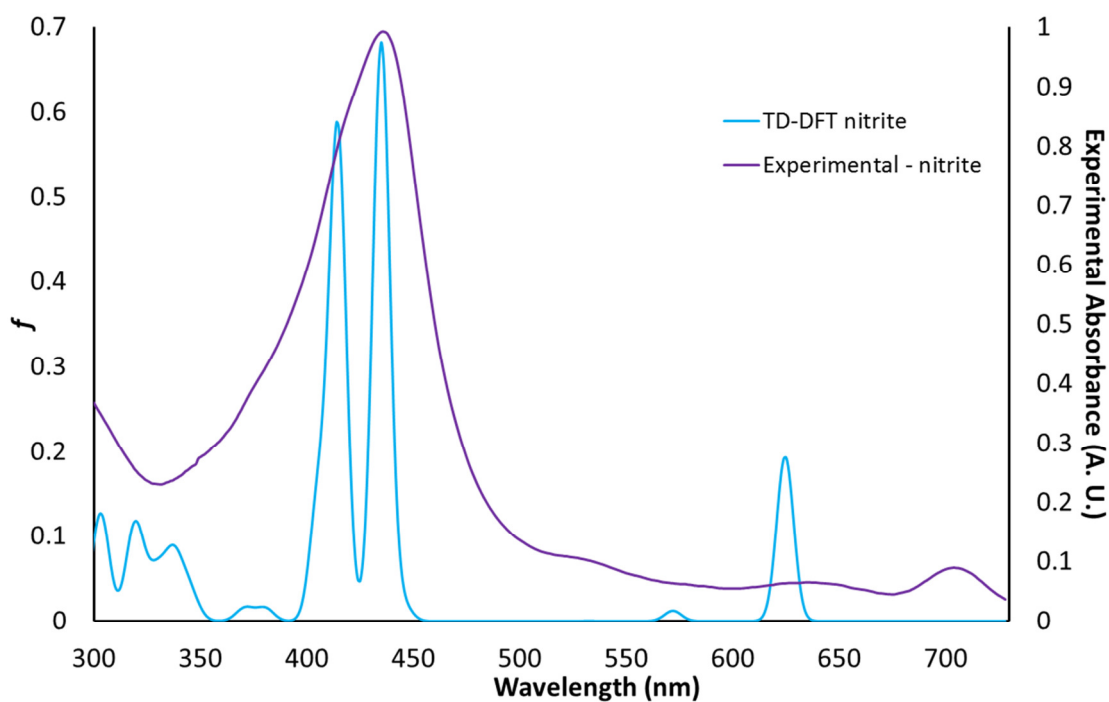


Figure 4.7.2 TD-DFT (scaled x1.06) and experimental spectra of five-coordinate DPTC-Co

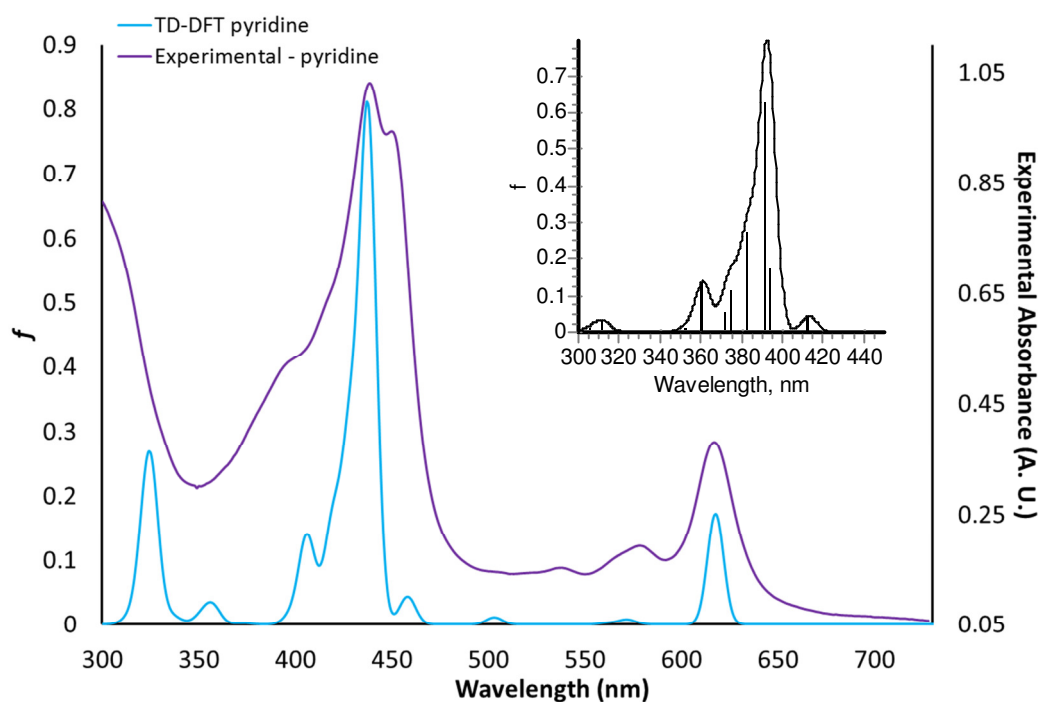


Figure 4.7.3 TD-DFT (shifted +45 nm) and experimental spectra of DPTC-Co coordinated to pyridine. The insert indicates the positions of the predicted electronic transitions, where a transition can be seen that corresponds to the higher energy shoulder (Soret 3) in the experimental spectrum

Two Soret bands were predicted in the TD-DFT spectra of DPTC-Co coordinated to cyanide and nitrite as well as to two water molecules in the diaqua species (compared to the experimental spectrum of DPTC-Co at pH 3.5). Experimentally, the coordination of these ligands yielded one broad Soret in the 430 nm region. Figure 4.7.4 illustrates the TD-DFT and experimental spectra of the coordination of cyanide, where it is clear that the two predicted Soret bands lie in the same region as the experimentally observed Soret. This one broad Soret band may be a combination and broadening of the two calculated Soret bands. The calculated Q band of lowest energy, while significantly different from the experimental data, coincides with a less intensely absorbing Q band in the experimental data.

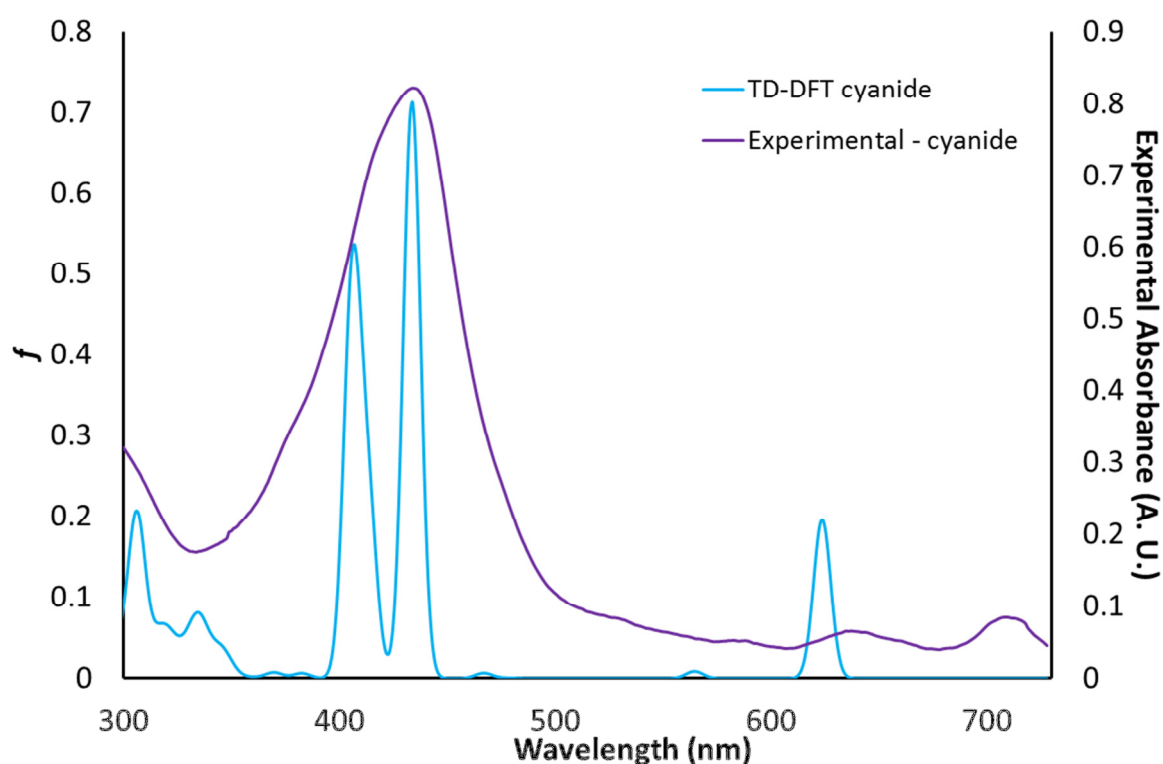


Figure 4.7.4 TD-DFT (scaled x1.065) and experimental spectra of DPTC-Co coordinated to cyanide

TD-DFT calculations are also used to gain insight into the nature of the electronic transitions attributed to each peak in the UV-vis spectrum. These transitions vary as the axial ligand changes. In the case of the cyanide complex, the electron density distribution of the HOMO-2 to LUMO+2 orbitals are represented in Figure 4.7.5. Electron density in the HOMO-2 orbital is found in the π bonding orbitals of the pyrrole groups as well as in

the d_{yz} metal orbital and the σ orbital of the cyanide ligand. In the HOMO-1 orbital, electron density is asymmetrically distributed about the corrole in the π bonding orbitals of the corrole backbone ring and in the d_{xz} metal orbital. The HOMO orbital contains electron density distributed around the corrole backbone with a small amount of electron density found on the imidazole axial ligand and the *meso* phenyl rings. The LUMO orbital contains π bonding electron density symmetrically distributed around the corrole ring, while this symmetry is lost in the LUMO+1 with more electron density on the side of the 10 *meso* position. Electron density of the LUMO+2, on the other hand, is found on the phenyl ring and amide tail of the *meso* position at carbon 10.

Figure 4.7.6 illustrates the electron density distribution of the HOMO-2 – LUMO+2 orbitals of the aqua complex which differs considerably from the cyano complex. Like the LUMO+2 of the cyanide complex, the electron density of the HOMO-2 is found exclusively on the phenyl ring and amide tail of the *meso* group at the 10 position. A symmetric distribution of π bonding electron density around the corrole backbone is found in the HOMO-1 orbital. The HOMO contains electron density at the *meso* positions, pyrrole-pyrrole bridge and the pyrrolic nitrogens with a small amount of electron density on the cobalt metal and water ligand. Electron density is symmetrically distributed on the α - β pyrrole bonds and *meso* positions of the corrole ring in the LUMO. The LUMO+1 orbital features electron density at the *meso* positions and pyrrole-pyrrole bridge as well as the pyrrolic nitrogens and the α - β bonds of the pyrrole units on either side of the 10 position. Electron density is also found in the d_z^2 orbital of the cobalt ion and on both the water and imidazole ligands. The majority of the electron density of the LUMO+2 is found in an antibonding arrangement between the d_z^2 orbital of the cobalt and σ orbitals of the imidazole and water ligands. Little electron density is found on the pyrrolic nitrogen of the inner core of the corrole ring.

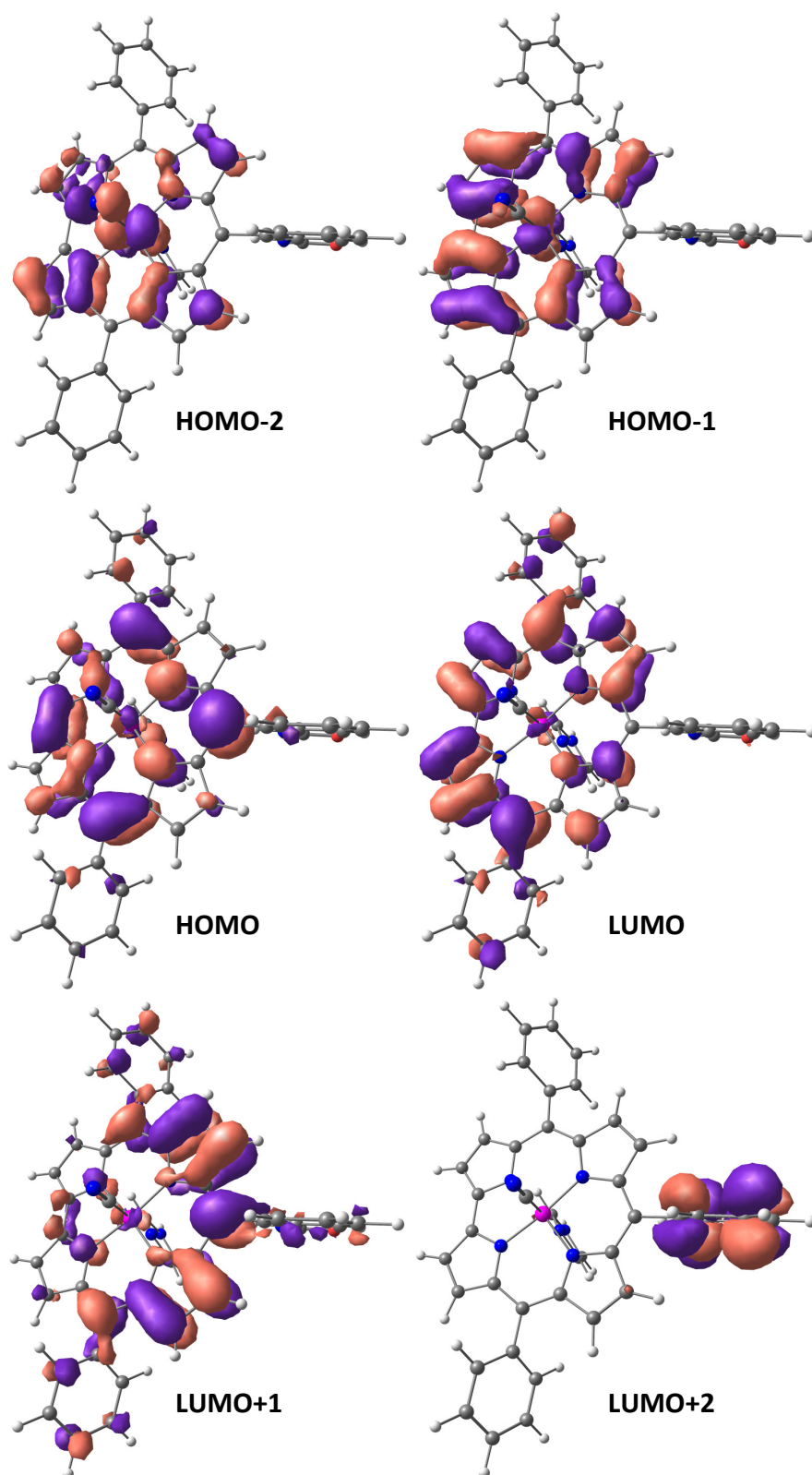


Figure 4.7.5 HOMO-2 – LUMO+2 orbitals of the DPTC-Co cyanide complex

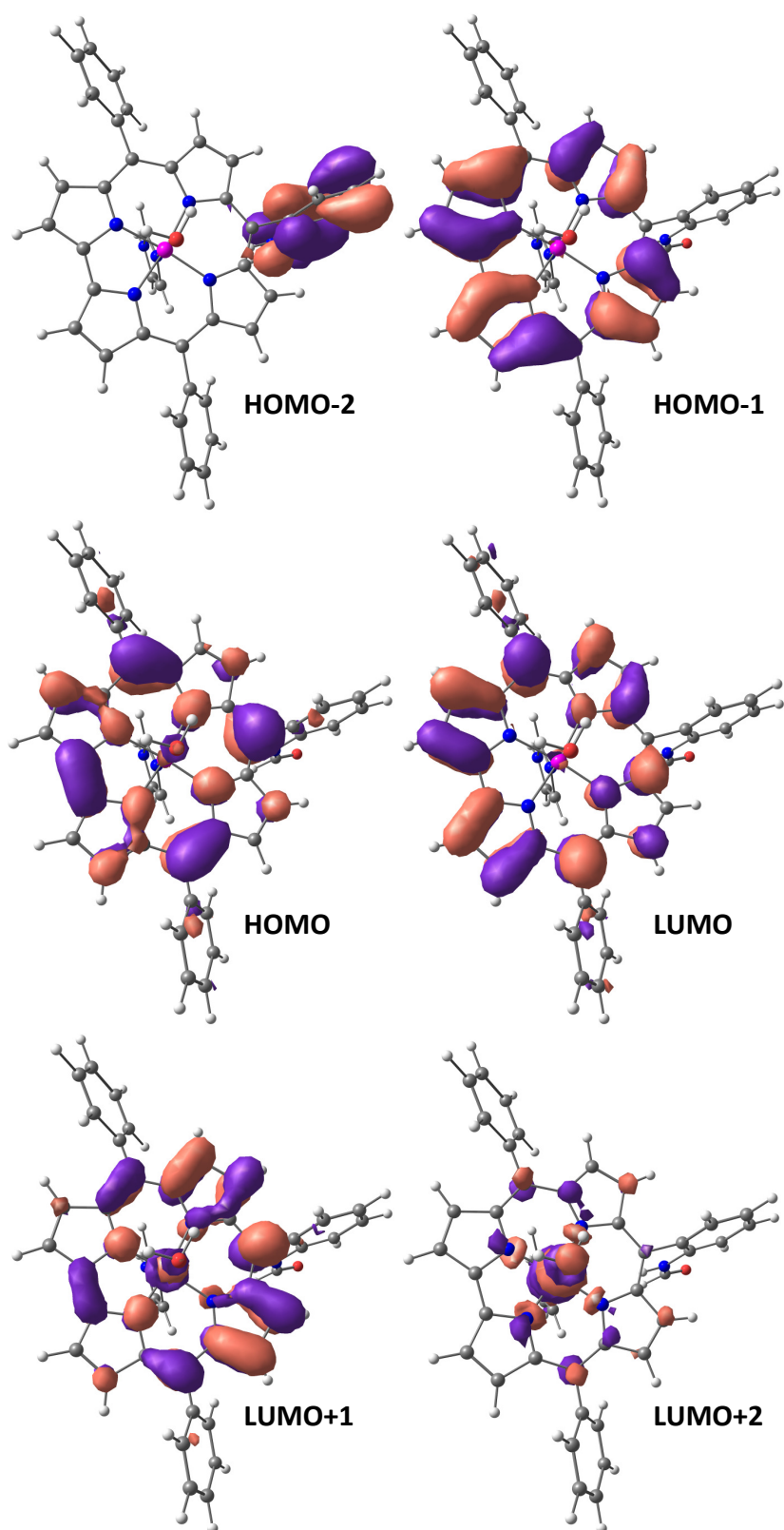


Figure 4.7.6 HOMO-2 – LUMO+2 orbitals of the DPTC-Co aqua complex

The energies of the HOMO and LUMO, as well as the energy gap between them, varied significantly as the identity of the axial ligand varied as illustrated in Figure 4.7.7. Table 4.7.3 lists the energies of the HOMO, LUMO and the HOMO-LUMO gap for the various complexes. These data can be divided into four categories: the thiolate complex; complexes with anionic ligands (nitrite and cyanide); complexes with neutral ligands (methanol, ethanolamine, pyridine, trimethylphosphate and imidazole) and the five-coordinate and diaqua species. While the HOMO-LUMO gap is the smallest for the thiolate complex, both the HOMO and LUMO energies are the highest. The complexes of the anionic ligands have the next lowest HOMO-LUMO gap even though the HOMO and LUMO energies are high (just below that for the thiolate). The neutral ligand coordination complexes have intermediate HOMO, LUMO and HOMO-LUMO gap energies. The five-coordinate and diaqua species have the highest HOMO-LUMO gap energy and the lowest HOMO energies. The LUMO of the five-coordinate species has the lowest energy while that of the diaqua species is higher, lying between that of the neutral ligand complexes and the anion complexes.

Table 4.7.3 Relative HOMO, LUMO and band gap energies (in electron volts) of DFT calculated complexes

Ligand	HOMO	LUMO	Energy gap
Thiolate	-0.0979	0.0508	0.1487
Nitrite	-0.1036	0.0471	0.1507
Cyanide	-0.1045	0.0467	0.1512
Trimethylphosphite	-0.2007	-0.0486	0.1521
Imidazole	-0.1982	-0.0444	0.1538
Pyridine	-0.2017	-0.0474	0.1543
Ethanolamine	-0.2033	-0.048	0.1553
Methanol	-0.2066	-0.0494	0.1572
Water	-0.2086	-0.0511	0.1575
Five-coordinate	-0.2181	-0.0516	0.1665
Diaqua species	-0.2167	-0.0059	0.2108

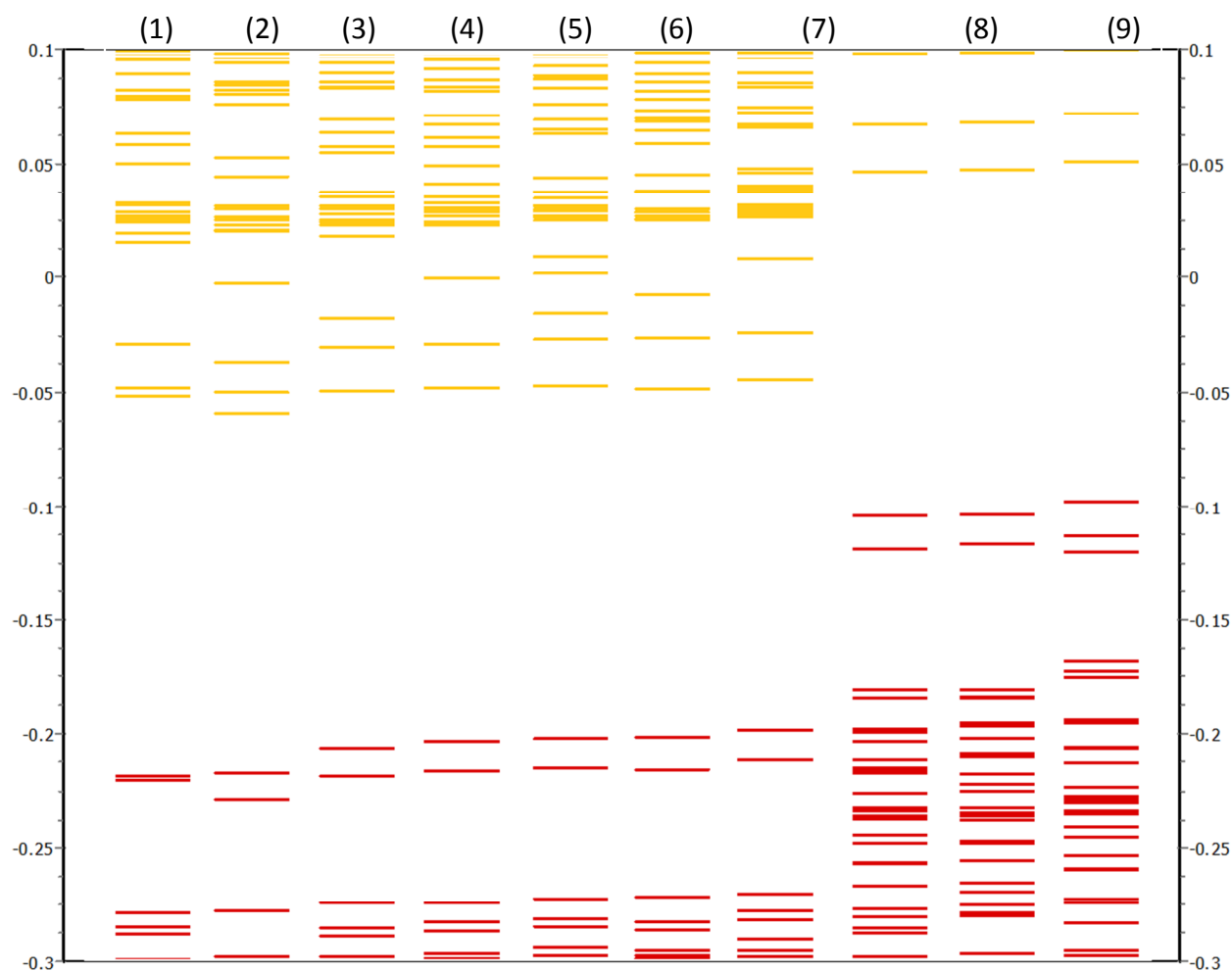


Figure 4.7.7 Energy level scheme for the DPTC-Co and its complexes. Red lines indicate the energy levels of occupied orbitals while yellow lines represent unoccupied orbitals. Energy is given in electron volts. (1) five-coordinate species (2) diaqua species; (3) methanol complex; (4) ethanolamine complex; (5) pyridine complex; (6) trimethylphosphite complex; (7) imidazole complex; (8) cyanide complex; (9) nitrite complex; (10) thiolate complex

The Q band was found to arise from a HOMO $\rightarrow$ LUMO transition in all cases, except for the five-coordinate and diaqua species. A good linear correlation between the position of the Q band and the HOMO-LUMO energy gap was observed (Figure 4.7.8) with an observed hypsochromic shift of the Q band with an increase in the HOMO-LUMO energy difference. This indicates that as the gap between the HOMO and the LUMO increases, more energy is required for the excitation of an electron from the HOMO into the LUMO and thus the Q band appears at a position of higher energy and lower wavelength. The presence of an outlier, the diaqua species, was unsurprising as this Q band arose from a combination of two transitions: HOMO $\rightarrow$ LUMO and HOMO-1 $\rightarrow$ LUMO+1. The Q band of the five-coordinate species (arising from a HOMO-1 $\rightarrow$ LUMO), whilst present at a considerably lower wavelength, did not deviate from the linear relationship. As can be seen in Figure 4.7.7, the energy difference between the HOMO and HOMO-1 energy levels is minimal, and thus the HOMO-LUMO energy gap is very similar to the HOMO-1-LUMO energy gap.

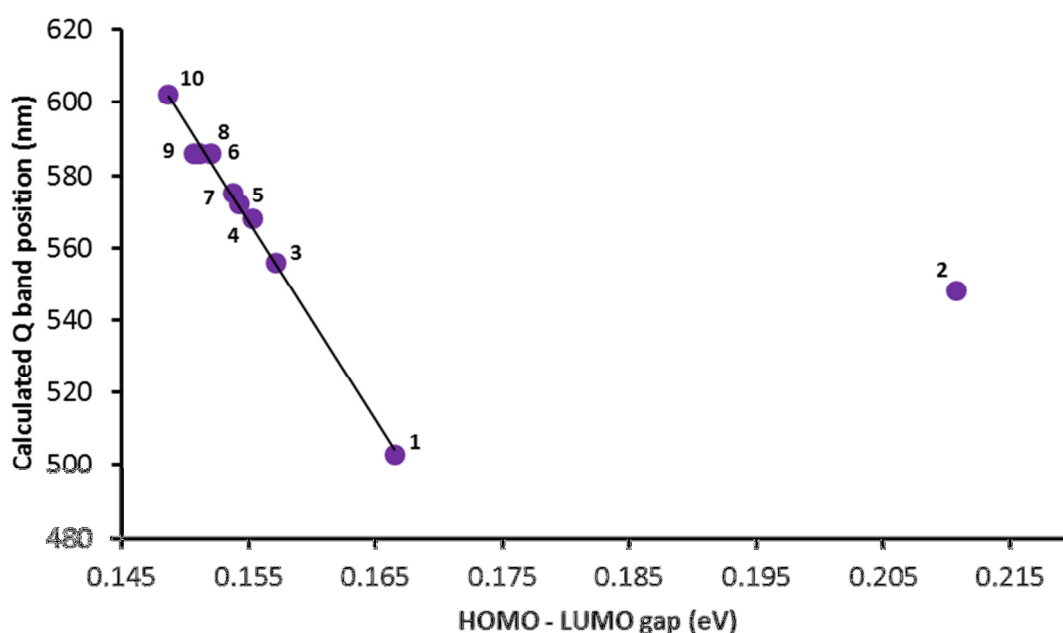


Figure 4.7.8 Correlation between the calculated Q band position and the HOMO-LUMO energy gap. The diaqua species deviates from the trend as this Q band arises from not one, but two electronic transitions. (1) five-coordinate species (2) diaqua species; (3) methanol complex; (4) ethanolamine complex; (5) pyridine complex; (6) trimethylphosphite complex; (7) imidazole complex; (8) cyanide complex; (9) nitrite complex; (10) thiolate complex

The HOMO → LUMO transitions resulting in the Q band in all cases (except the five-coordinate and diaqua species) can be divided into three categories, depending on the HOMO and LUMO states. These categories are the same as those used above, in the analysis of the energies of the HOMO, LUMO and HOMO-LUMO gap. The complexes with neutral ligands (methanol, ethanolamine, imidazole, pyridine and trimethylphosphite) exhibited transitions involving the movement of electron density from the corrole ring in the ground state to the metal and the two axial ligands in the excited state. The thiolate complex exhibited a transition of the electron density from the sulfur atom in the thiolate ligand and the metal in the ground state to the corrole ring in the excited state. The third category contains the complexes of anionic ligands, cyanide and nitrite. Coordination of these ligands resulted in Q bands corresponding to the transition of electron density from the inner corrole ring (atoms involved in coordination to the metal and the atoms bridging the pyrrole subunits) to the outer corrole with little involvement of the electron density on the metal or either of the axial ligands. The Q bands of the five-coordinate species did not arise from a HOMO → LUMO transition and those of the diaqua species arose from two different transitions. Interestingly, the systems with transitions involving movement of electron density from the macrocycle to or from the metal and ligands also showed good correlation of the distance between the Soret and Q band with the calculated and experimental spectra (Table 4.7.1). This illustrates that a superficial resemblance of experimental spectra does not necessarily suggest a similar redistribution of electron density during an electronic transition.

In the first category of HOMO → LUMO transitions, the calculated orbitals were very similar for all of the ligand complexes investigated. The HOMO and LUMO orbitals of the imidazole DPTC-Co complex are illustrated in Figure 4.7.9. The electron density in the HOMO is situated in the π orbitals of the pyrrolic nitrogens, the π orbitals of the methyl groups bridging the pyrrole subunits as well as the pyrrole-pyrrole bridge. In the LUMO, electron density was found in the antibonding d_z^2 orbital of the cobalt ion and the σ orbitals of the donor atoms in both the axial ligands and the equatorial nitrogen ligands of the corrole macrocycle.

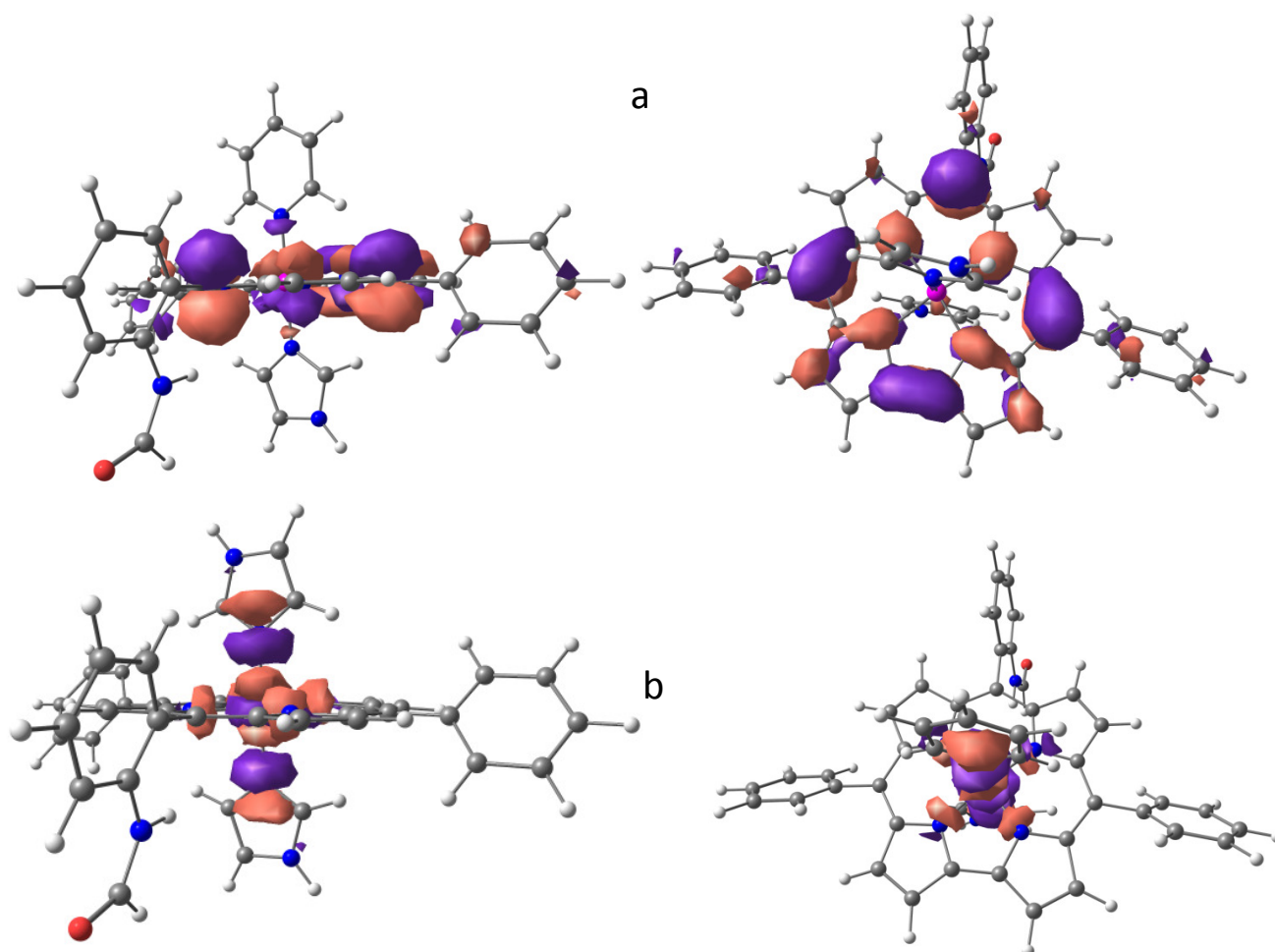


Figure 4.7.9 Orbitals of the HOMO (a) and LUMO (b) of the DPTC-Co imidazole complex

The HOMO and LUMO orbitals of the thiolate complex (Figure 4.7.10) differed substantially from those in Figure 4.7.9. In the HOMO, electron density was situated in the d_{xz} orbitals of the cobalt ion, the sulfur lone pairs and the p orbital of the methyl group of the ligand. In the HOMO $\rightarrow$ LUMO transition, electron density moved from the metal and axial ligand to an asymmetric distribution in π^* orbitals over the macrocycle.

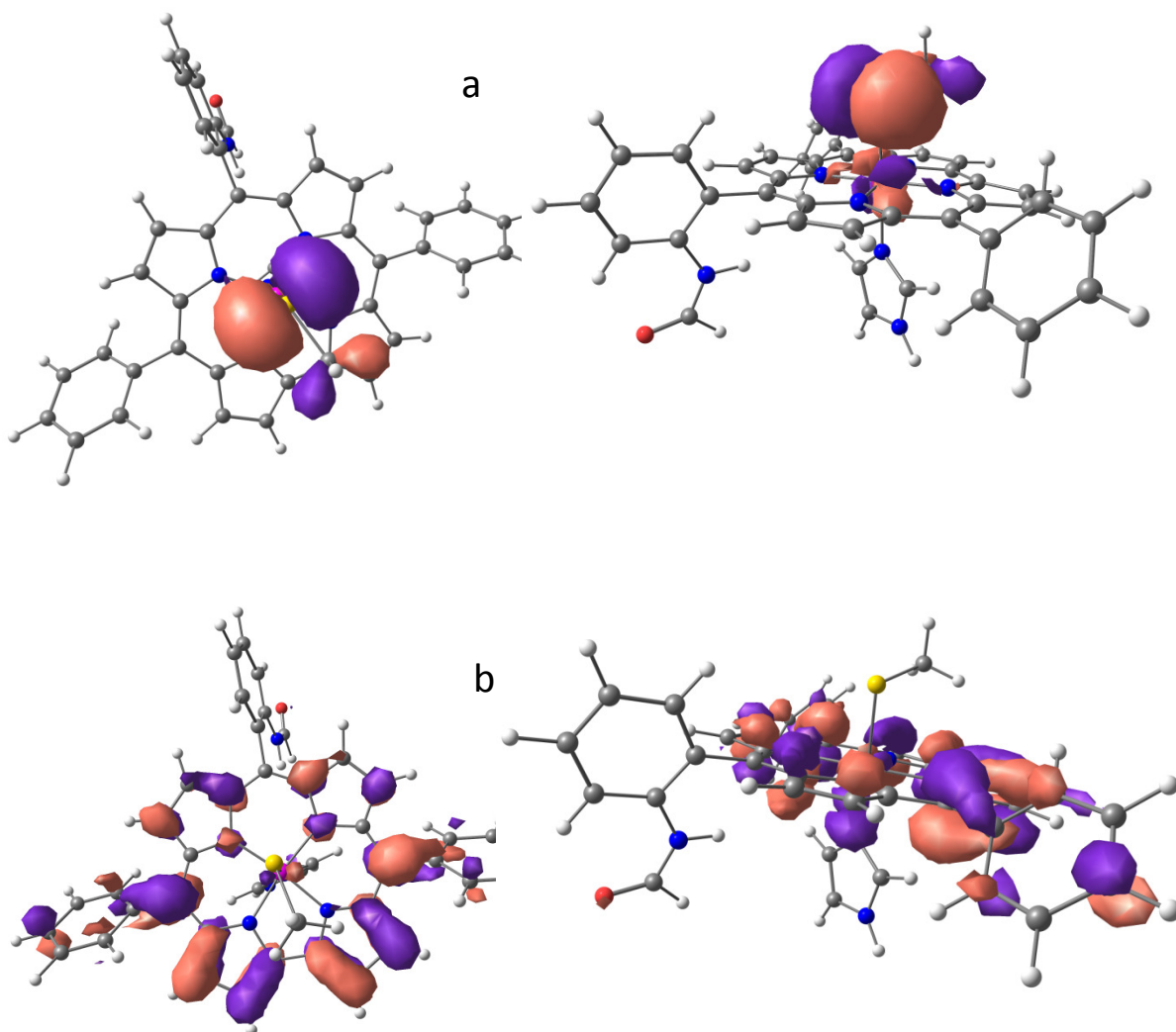


Figure 4.7.10 Orbitals of the HOMO (a) and LUMO (b) of the DPTC-Co thiolate complex

The Q bands of the complexes with the anions (cyanide and nitrite) did not entail electron movement involving the metal or axial ligands (Figure 4.7.11). In the HOMO, the majority of electron density was found on the pyrrolic nitrogens and the atoms involved in the linkage of the pyrrole subunits. In the LUMO, electron density moved to the π^* orbitals of the bonds within the pyrrole subunits.

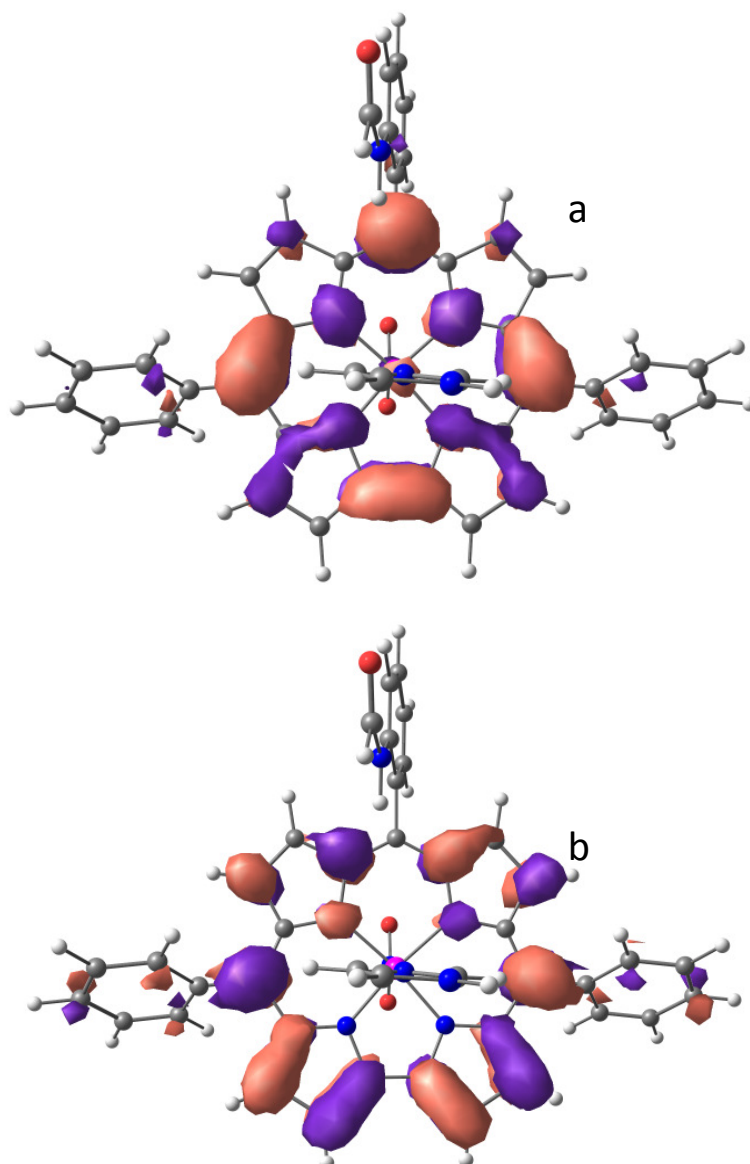


Figure 4.7.11 Orbitals of the HOMO (a) and LUMO (b) of the DPTC-Co nitrite complex

The Q bands of the five-coordinate and diaqua species did not involve different transitions. In the case of the five-coordinate species, a HOMO $\rightarrow$ LUMO+1 transition was observed. Like the anion complexes represented in Figure 4.7.11, this involved movement of the electron density around the macrocycle; however, some electron density was observed in the d_{z^2} orbital of the cobalt ion in the HOMO as in Figure 4.7.12. In the case of the diaqua species, the Q band was composed of two transitions: HOMO $\rightarrow$ LUMO and HOMO-1 $\rightarrow$ LUMO+1. The HOMO $\rightarrow$ LUMO transition involved movement of electron density from π bonds on the pyrrolic nitrogens and the bonds linking the pyrrole subunits to an asymmetric distribution of the π electrons of the pyrrole rings with both bonding

and antibonding orbitals present. On the other hand, the HOMO-1 $\rightarrow$ LUMO+1 transition involved electron density moving from π orbitals of the pyrrole subunits to the antibonding orbitals of the d_{z^2} orbital of the cobalt ion and the σ bonds of the axial water ligands and the equatorial nitrogen atoms of the corrole ring as in Figure 4.7.13.

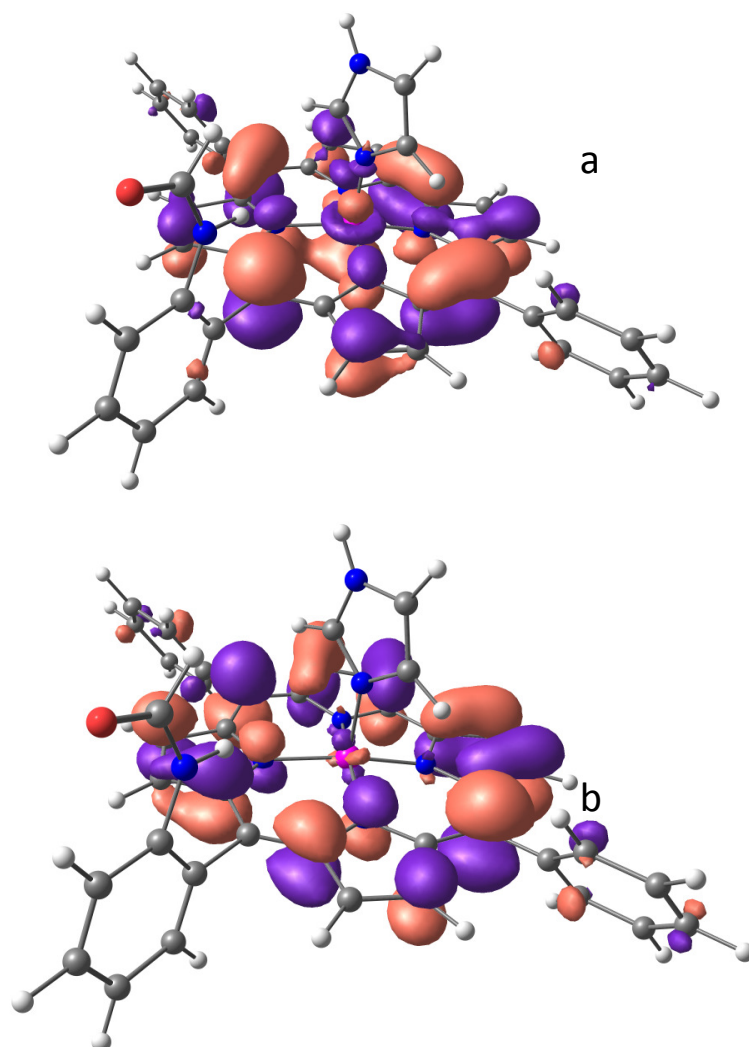


Figure 4.7.12 Orbitals of the HOMO (a) and LUMO+1 (b) of the five-coordinate DPTC-Co species

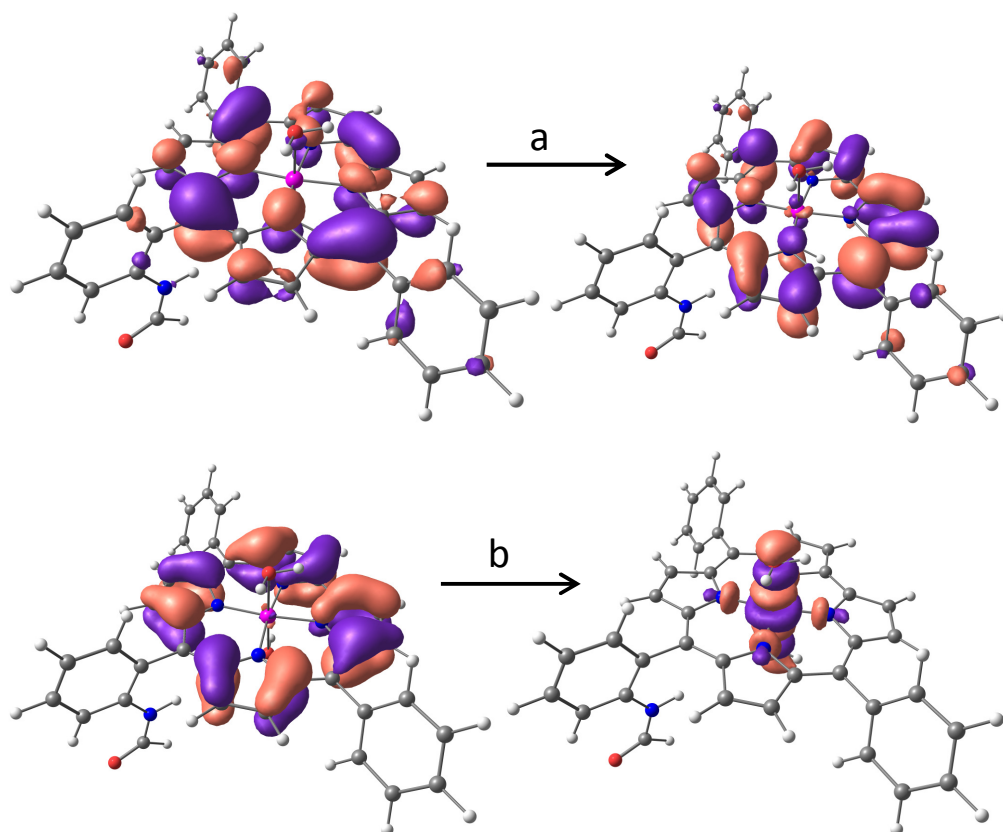


Figure 4.7.13 HOMO→LUMO (a) HOMO-1→LUMO+1 (b) of the diaqua DPTC-Co complex

Analysis of the full TD-DFT spectrum calculated for the pyridine DPTC-Co model indicated that the Q band arose from the movement of electron density from the corrole in the ground state to the metal and axial ligands in the excited state. The Soret, a result of multiple transitions (as has been reported in the literature^{139,140}), arose from movement of electron density from the corrole to the atoms in the tail extending from the central phenyl ring; from the corrole and cobalt ion to the pyridine ligand as well as movement of electron density around the corrole ring. Bands in the UV region were due to transitions involving electron density moving from the metal and macrocycle to the metal and ligand; from the tail subunit to the metal and axial ligands as well as from the metal and macrocycle to other areas of the macrocycle. Several of these transitions involved the transfer of electron density from the ligand (axial and equatorial) to the metal as well as metal centred excitations as has been seen in TD-DFT studies on corrole containing systems in the literature.^{138,139,141} Figure 4.7.14 illustrates the multiple transitions that occur in the Soret and UV regions of the spectrum of the pyridine complex.

In contrast, analysis of the full TD-DFT spectrum of the nitrite complex indicated that both the Q band and Soret, while comprising several transitions, arose from movement of electron density around the corrole macrocycle and did not involve the metal or axial ligands. The UV bands, however, involved many transitions including the movement of electron density from the metal and macrocycle onto the nitrite ligand; from the metal and corrole to the corrole; from the metal and nitrite ligand to the corrole as well as from the corrole macrocycle to the peripheral phenyl rings. The TD-DFT spectrum is illustrated in Figure 4.7.15 where multiple transitions occur in the Soret and UV region.

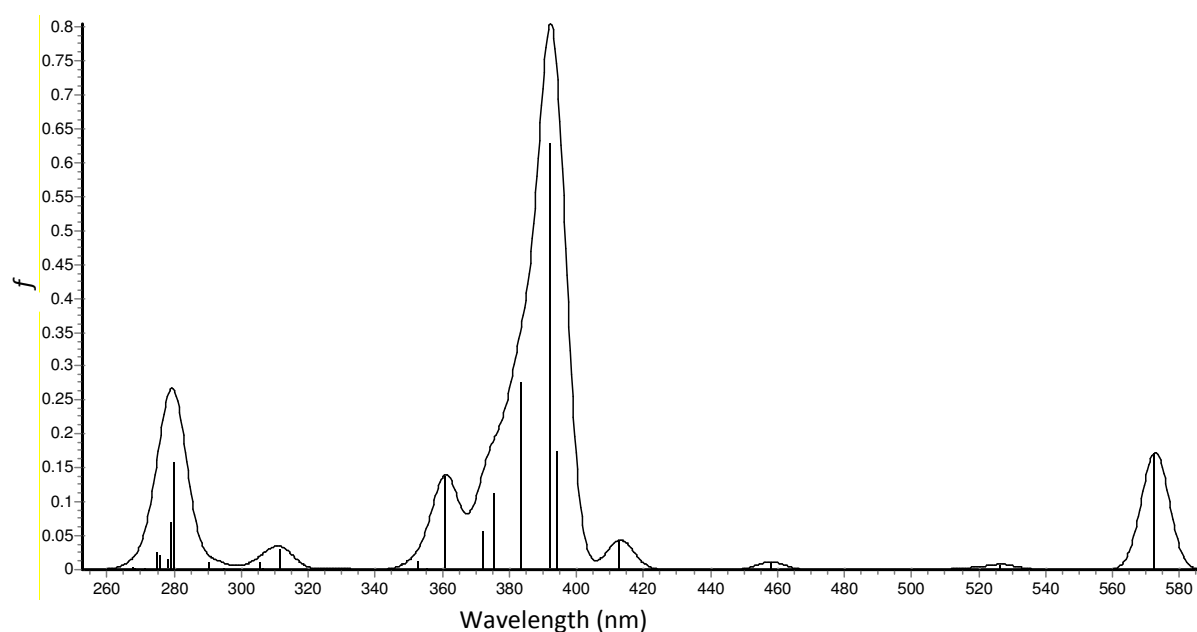


Figure 4.7.14 TD-DFT spectrum of the DPTC-Co pyridine complex

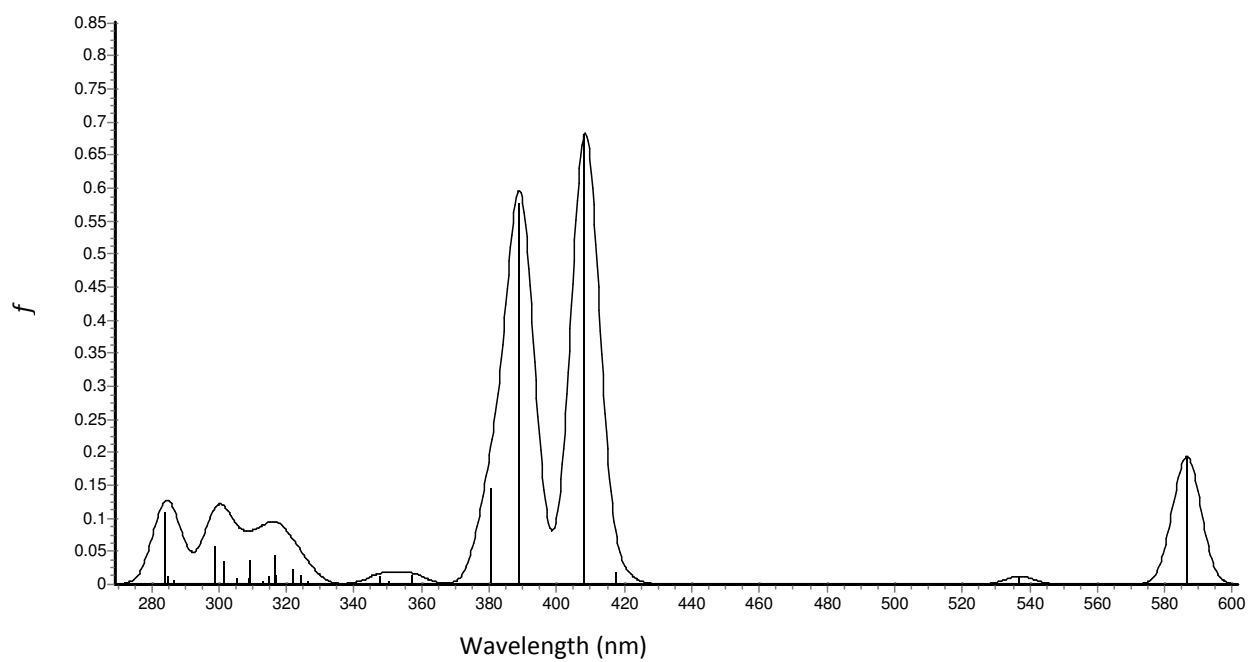


Figure 4.7.15 TD-DFT spectrum of the DPTC-Co nitrite complex

4.7.4 The character of the cobalt-ligand bond from QTAIM calculations

QTAIM calculations were used to gain insight into the nature of the bonding between the metal and its ligands in DPTC-Co ligand complexes, based on the value of ρ , the electron density, at the bond critical point. The simplified DPTC-Co model used for TD-DFT calculations was used for QTAIM calculations with imidazole, cyanide, nitrite, water, trimethylphosphite, pyridine and the thiolate, H_3CS^- as ligands. The bonding parameters for the five-coordinate species were determined. A summary of the parameters obtained from the QTAIM calculations are given in Table 4.7.4.

The electron density at the bond critical point of a bond, ρ , indicates the strength of the bond between two atoms, with an increase in ρ indicating an increase in the bond strength and a decrease in the bond length. The $|V(\mathbf{r})|/G(\mathbf{r})$ ratio characterises the bonding characteristics as ionic ($|V(\mathbf{r})|/G(\mathbf{r}) < 1$), covalent ($|V(\mathbf{r})|/G(\mathbf{r}) > 2$), or intermediate ($1 < |V(\mathbf{r})|/G(\mathbf{r}) < 2$).¹⁵⁵ From the data in Table 4.7.3, it is clear that all of the bonds examined were of intermediate character, with significant ionic character, with the exception of the cobalt-ligand bonds in the complexes with softer cyanide, thiolate and trimethylphosphite ligands which were more covalent in nature.

The nature of the cobalt-imidazole tail bond is predominantly ionic. The nature of the cobalt-ligand bond is less ionic than the cobalt-tail bonds (except in the case of the aqua species). This suggests that the variable ligands form stronger complexes with the cobalt than the axial tail ligand, and that water is a poor ligand for the corrole cobalt complex. The cobalt-tail bond is least ionic in the case of the five-coordinate system (with the exception of the poor water ligand) and becomes weaker and longer in length as the nature of the variable axial ligand changes, increasing in length in the following series of complexes: water < imidazole < pyridine < trimethylphosphite < nitrite < thiolate < cyanide. $|V(\mathbf{r})|/G(\mathbf{r})$ of the cobalt-tail bond does not change according to the same series, but decreases and becomes more ionic as follows: water > trimethylphosphite > pyridine > imidazole > thiolate > cyanide > nitrite. These series illustrate the following: firstly,

water is a poor ligand for the DPTC-Co model, with a short, strong cobalt-tail bond; secondly, the ionic nature of the bond is not the only factor in the determination of the bond length, as illustrated by the difference in the position of trimethylphosphite and pyridine complexes as well as the complexes with anionic ligand (cyanide, nitrite and the thiolate); thirdly, the binding of anionic ligands lengthens the Co-tail bond in a more ionic interaction.

As the length of the Co-variable axial ligand bond length increases in the following series of complexes: cyanide < nitrite < imidazole < pyridine < water < trimethylphosphite < thiolate, ρ decreases with the exception of trimethylphosphite and thiolate, containing third row donor atoms, with necessarily longer bond lengths given the larger covalent radii of these donor atoms.

Figure 4.7.16 illustrates the decrease in bond length of the cobalt-ligand bond with the increase in ρ , indicating the increase in bond strength of the cobalt-ligand bond. The cobalt-S bond of the thiolate complex and the cobalt-P bond of trimethylphosphite complex are the exceptions to the almost linear trend, with a much longer than expected bond length for the electron density found between cobalt and sulfur and cobalt and phosphorous. It appears that ligands with third row donor atoms would form a series parallel to the trend observed for the ligands containing smaller second row donor atoms, due to the larger covalent radii of the third row sulfur and phosphorous donor atoms compared to the smaller second row oxygen and nitrogen donor atoms in the other ligands.

The identity of the variable axial ligand affects the bonding of the tail ligand, illustrating the *trans* influence. This is highlighted in Figure 4.7.17 where a decrease in the Co-variable ligand bond results in a lengthening of the Co-tail bond, which becomes more ionic in nature.

There appears to be a correlation between the $\log K$ for the binding of ligands to DPTC-Co and the calculated Co-ligand bond length. Although data for only four ligand DPTC-Co

complexes are available there appears to be a general increase in the bond length as the binding of the ligand becomes less favourable, as illustrated in Figure 4.7.18. From this correlation, the binding of nitrite deviates from the trend which might be as a result of the interaction between the ligand and the solvent (solvent effects are not taken into account during the QTAIM calculations).

Table 4.7.4 QTAIM bonding parameters for the DPTC-Co model

Ligand	Bond	ρ	$ V(r) /G(r)$	Bond length
Five-coordinate	Co-tail	0.10610	1.15864	1.90214
	Co-ligand	-	-	-
Imidazole	Co-tail	0.08860	1.12949	1.96698
	Co-ligand	0.09026	1.13241	1.96056
Cyanide	Co-tail	0.06015	1.11541	2.12224
	Co-ligand	0.13462	1.42471	1.85273
Nitrite	Co-tail	0.06627	1.11994	2.0829
	Co-ligand	0.10408	1.21250	1.94489
Thiolate	Co-tail	0.06280	1.12014	2.10657
	Co-ligand	0.08092	1.52044	2.29132
Pyridine	Co-tail	0.08824	1.13205	1.97024
	Co-ligand	0.08482	1.13590	1.99294
Trimethylphosphite	Co-tail	0.07316	1.13736	2.05218
	Co-ligand	0.09887	1.48842	2.19066
Water	Co-tail	0.10566	1.14800	1.90082
	Co-ligand	0.05080	1.06943	2.1256

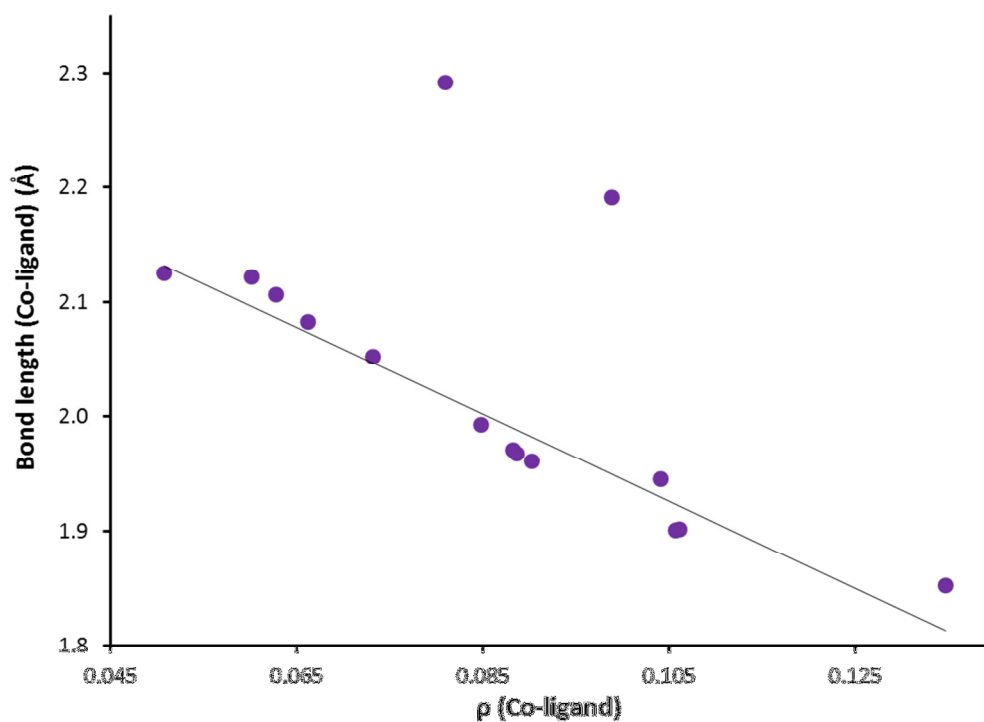


Figure 4.7.16 The correlation between Co-ligand and Co-tail bond length and ρ . The thiolate and trimethylphosphite complexes deviate from the trend due to the larger van der Waal radii of third row donor atoms compared to second row donor atoms

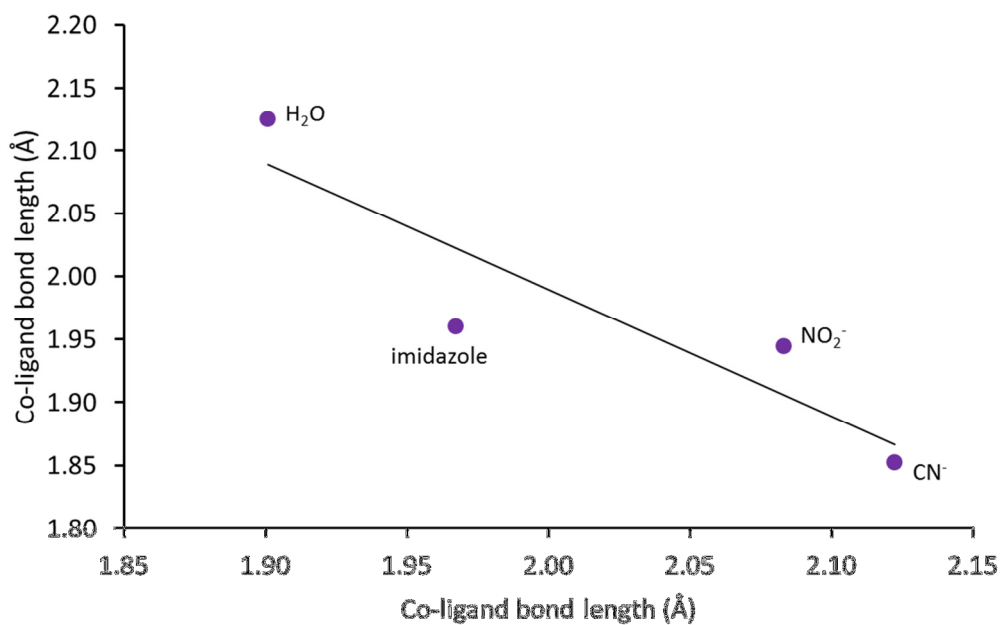


Figure 4.7.17 The *trans* influence is evident from the increase in the Co-tail bond length as the Co-ligand bond length decreases

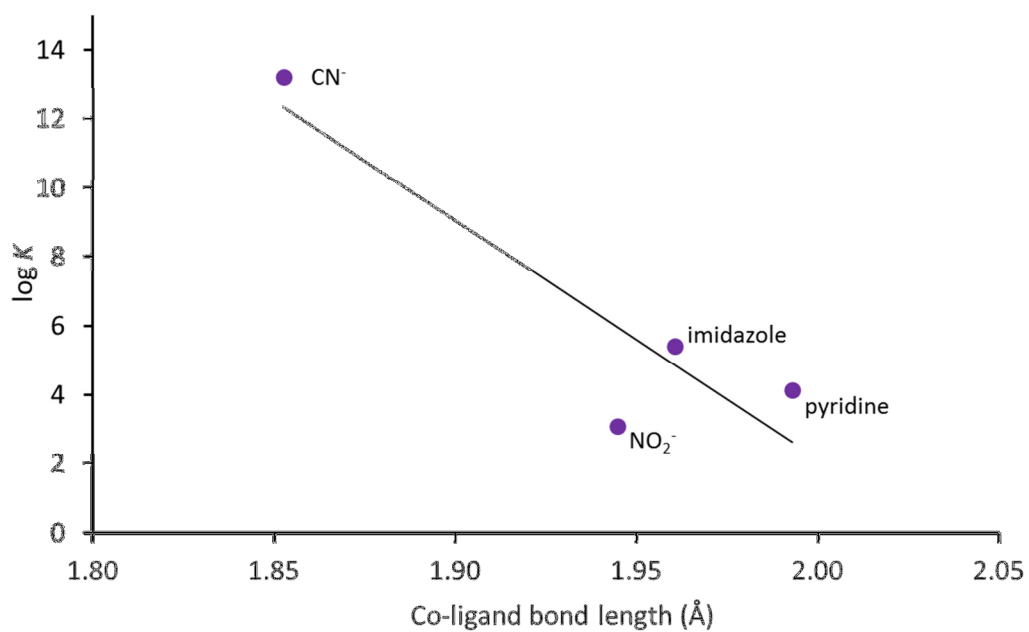


Figure 4.7.18 The correlation between the stability constant for the binding of the ligand to DPTC-Co and the Co-ligand bond length

4.7.6 Conclusions

TD-DFT calculations were carried out on a variety of ligands complexed to a simplified model of DPTC-Co. These calculations provided evidence for the existence of a five-coordinate species as the calculated and experimental spectra were very similar. The addition of a second axial ligand resulted in the splitting of the Soret band as seen in the experimental spectra of DPTC-Co complexes with neutral ligands as well as a thiolate (a cysteine model).

The distance between the most red-shifted Q band in the calculated and experimental spectra correlated well and there was good agreement between these spectra, after shifting the calculated peaks along the wavelength axis, for neutral ligands and cysteine. A multiplication scaling factor was applied to the calculated spectra of the cyanide and nitrite complexes and the five-coordinate and diaqua species for fair correlation to the experimental data. The correlation between the experimental and calculated UV-vis spectra provided more evidence for the hypothesis that DPTC-Co exists as a five-coordinate species in non-coordinating environments and as a six-coordinate species in the presence of a coordinating solvent or compound.

Analysis of the Kohn-Sham orbitals revealed a large variation in the HOMO-LUMO energy gap as the axial ligand was varied. There was good correlation between the position of the Q band and the energy difference between the HOMO and the LUMO, except in the case of the diaqua species, where the Q band was found to arise from a combination of two transitions. The origin of the Q band was found, in general, to arise from a HOMO → LUMO transition. The nature of the molecular orbitals involved in these transitions varied as the nature of the ligand varied. The Soret and UV regions of the spectra were complex with multiple transitions accounting for the Soret bands and bands in the UV region. The electronic transitions responsible for these bands varied with the identity of the ligand. In the case of the transitions in the Soret region, in the pyridine complex, electron density on the ligand was involved in the transitions while in the case of nitrite, transitions arose from changes in the distribution of electron density on the corrole ring.

QTAIM calculations provided an indication of the bonding character of the metal-ligand interaction, in particular the bond between the cobalt and the imidazole containing tail. The binding of anionic ligands lengthens this bond, becoming more ionic in nature. The binding of neutral ligands occurs through a more covalent interaction with shorter bond lengths. The poor binding of water, clear from the ease of its substitution in the experimental ligand substitution reactions discussed in **Section 4.6**, was also clear.

Comparison of TD-DFT and QTAIM data of the DPTC-Co model and a similar vitamin B₁₂ model would shed light on the electronic differences between the corrole system and the corrin system. As computational chemistry was not the main focus of this work, this was considered beyond the scope of the project.

4.8 The kinetics of the coordination of cyanide to DPTC-Co and vitamin B_{12a}

4.8.1 Introduction

Cobalt(III) is the classic example of an inert metal ion. When coordinated by the corrin ring in vitamin B_{12a}, however, rates of substitution reaction increase remarkably. The substitution of a water ligand by thiocyanate on the $[\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2]^{2+}$ complex occurs slowly with a second order rate constant of $8.6 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$.¹⁵⁶ The analogous reaction with vitamin B_{12a} occurs extremely quickly with a second order rate constant nine orders of magnitude larger.⁸⁴ This remarkable increase in the lability of the inert cobalt ion is believed to be a function of its coordination environment.^{28,41,85,94,157}

In this work, the differences between the corrole ring in DPTC-Co and the corrin ring in vitamin B_{12a} on the rate of reaction were determined in the substitution reaction of water by cyanide. The rates of substitution reactions with various ligands have been determined for vitamin B_{12a},^{26,55,57,158,159} its derivatives^{41,85,94,160} and model compounds¹⁶¹ and the effect of varying environmental factors such as ionic strength and solvent composition^{71,72,80,105,106,162,163} have been studied extensively. Determination of kinetic parameters can give insights into the mechanistic details of a reaction^{159,164,165} as well as insights into the effect of different substituents and different incoming ligands with respect to steric demand, charge and electron donating or withdrawing abilities.

The kinetics of substitution reactions in corrole-containing systems, on the other hand, has not been extensively investigated, although the kinetics of the catalytic activity of various corrole-containing systems has been well documented. For example, the kinetics of the catalysis of oxidation of hydrocarbons,¹⁶⁶⁻¹⁶⁸ hydrogen atom transfer (HAT)^{169,170} and nitrogen atom transfer¹⁷¹ reactions as well as the catalytic activity of corrole based antioxidants¹⁷² have been recorded. The kinetics of the re-association of NO to a variety of *meso*-substituted nitrosyl iron corrole complexes during flash photolysis reactions

illustrated the increased lability of iron in the corrole complex compared to an analogous porphyrin complex with a second order rate constant five orders of magnitude larger for the corrole complex.¹⁷³ While no correlation was found between the electronic properties of the *meso* substituents and the reaction rates, the rates were found to decrease slightly with the use of different coordinating solvents such as THF, acetonitrile and pyridine.¹⁷³

4.8.2 Methods particular to kinetics

All kinetic studies were performed using a 80:20 methanol:buffer solvent system at pH 9.5 (CHES buffer, 0.05M). No inert salt was added to adjust the ionic strength; rather it was determined from the concentration of the charged buffer species at the pH at which the experiment was conducted. Cyanide solutions were prepared in the 80:20 methanol:buffer solvent system and the pH was not adjusted further. Vitamin B_{12a} solution was freshly prepared using hydroxocobalamin acetate. DPTC-Co solution was also freshly prepared by adding DPTC-Co dissolved in ethyl acetate (due to DPTC-Co limited solubility in methanol and methanol:water mixtures) to the methanol:buffer solvent system.

Equal volumes of chromophore and cyanide were injected into the reaction cell and the change in absorbance was monitored with time. The reaction between cyanide and DPTC-Co was monitored at 434 nm while the reaction between cyanide and vitamin B_{12a} was monitored at 361 nm or in one case, at 540 nm. Vitamin B_{12a} reactions were repeated in triplicate while eight DPTC-Co reactions were carried out. The pH of the reaction mixture was recorded from which the concentration of free cyanide was determined. As the pH of the initial cyanide solutions was not pH corrected, the final pH after 1:1 mixing of chromophore and cyanide solution was highly dependent on the cyanide concentration. The use of highly concentrated cyanide solutions increased the pH of the reaction mixture dramatically (by 1.5 pH units in some cases).

The dead time, or the average age of the reaction solution at the time of earliest observation,¹⁷⁴ of stopped flow apparatus is known to be solvent dependent¹⁷⁵ and is affected by temperature, the viscosity of the solvent system, the volume of solvent delivered to the reaction chamber as well as the efficiency of mixing in the reaction chamber.¹⁷⁴ The dead time of the instrument used is known to be approximately 2 ms in aqueous solutions; it was found to be much longer, approximately 60 ms, in the 80:20 methanol:buffer solvent system used in this study as data collected between 0 and 60 ms was consistently irreproducible and apparently random irrespective of ligand

concentration and the identity of the chromophore. All data below 60 ms were discarded before the data were analysed.

First order rate constants were determined as outlined in **Section 4.2.5**. Examples of raw data collected for the determination of rate constants can be found in **Digital Appendices 4.4.1** and **4.4.2** and examples of the results and regression analysis of the standard non-linear least squares curve fitting data can be found in **Appendix 4.7**. Second order rate constants were determined from the slope of the linear relationship between the first order rate constant and free cyanide concentration at a particular temperature. The linear relationship between the second order rate constants and the inverse of temperature was determined in Eyring plots such that the enthalpy and entropy of activation for the reaction between the chromophore and cyanide were determined as in Equation 4.8.1. k_{II} is the pH-independent second order rate constant, h is Planck's constant, k_B is the Boltzman constant, R is the gas constant, T is the temperature and $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are the enthalpy and entropy activation energy parameters, respectively.

$$\ln \frac{k_{II}h}{k_B T} = \frac{-\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R}$$

Equation 4.8.1

4.8.3 The coordination of cyanide to DPTC-Co

The reaction between DPTC-Co and cyanide was monitored at four temperatures (9.9, 15.0, 19.7 and 25.0°C) and at five cyanide concentrations (0.2908, 0.7270, 1.454, 1.890 and 2.326×10^{-3} M). The progression of the reaction between cyanide and DPTC-Co was monitored at 434 nm, the Soret of cyanoDPTC-Co. The increase in absorbance as DPTC-Co was complexed by cyanide was small, in spite of DPTC-Co concentrations yielding an initial maximum absorbance of approximately 1 A. U. This was as a result of the small change in absorbance at 434 nm (an approximate 18% increase) upon coordination of cyanide to DPTC-Co. In the case of vitamin B₁₂, large changes in absorbance were observed as the absorbance of cyanocobalamin at 361 nm experienced an approximately 50% increase in absorbance compared to aquacobalamin. In light of the limited availability of DPTC-Co as well as the increased complexity of the solvent system with the addition of more DPTC-Co pre-dissolved in ethyl acetate, the concentration of DPTC-Co was not increased. This had the unfortunate result of yielding rather noisy data with relatively large errors in the calculated rate constants and activation parameters.

At 9.9°C and low cyanide concentrations an initial process, accompanied by a decrease in absorbance, preceded the binding of cyanide to DPTC-Co. The rate of this initial process as well as the rate of the complex formation were determined using a double exponential fraction to accommodate two sequential first order reactions (Equation 4.2.5 in **Section 4.2.5**). This is illustrated in Figure 4.8.1. This initial process was within the dead time of the instrument at high cyanide concentrations and at higher temperatures, and could not be determined under these conditions. The first order rate constant for this initial process, k_1^I could be determined at three ligand concentrations at 9.9°C to be $2.1 \pm 0.3 \times 10^4$. These data, together with the determined second order rate constant, k_{II}^I , from the linear relationship between k_1^I and cyanide concentration, are given in Table 4.8.1 and Figure 4.8.2.

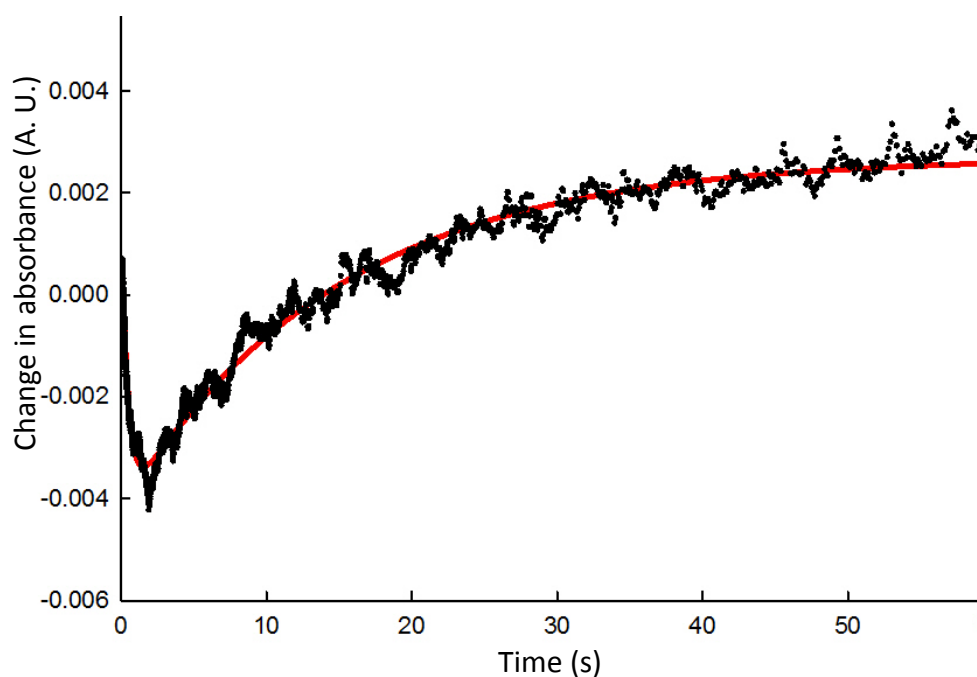


Figure 4.8.1 The change in absorbance at 434 nm with time for the coordination of cyanide to DPTC-Co in the 80:20 methanol:water solvent system at 9.9°C and ligand concentration of 2.908×10^{-4} M. Black circles indicate the experimentally determined absorbances. Red line indicates the best fit curve for $k_1^I = 4.2 \pm 0.6$ from Equation 4.2.5

Table 4.8.1 First and second order rate constants determined for the observed initial process during the coordination of cyanide to DPTC-Co at 9.9°C at varying ligand concentrations.

Cyanide concentration ($\times 10^{-3}$ M)	pH	Free cyanide concentration ($\times 10^{-3}$ M)	k_1^I (s^{-1})
0.2908	9.649	0.1509	4.2 ± 0.6
0.7270	9.679	0.3899	10 ± 2
1.454	9.712	0.8072	18 ± 2
k_{II}^I ($M^{-1} s^{-1}$)			$2.1 \pm 0.3 \times 10^4$

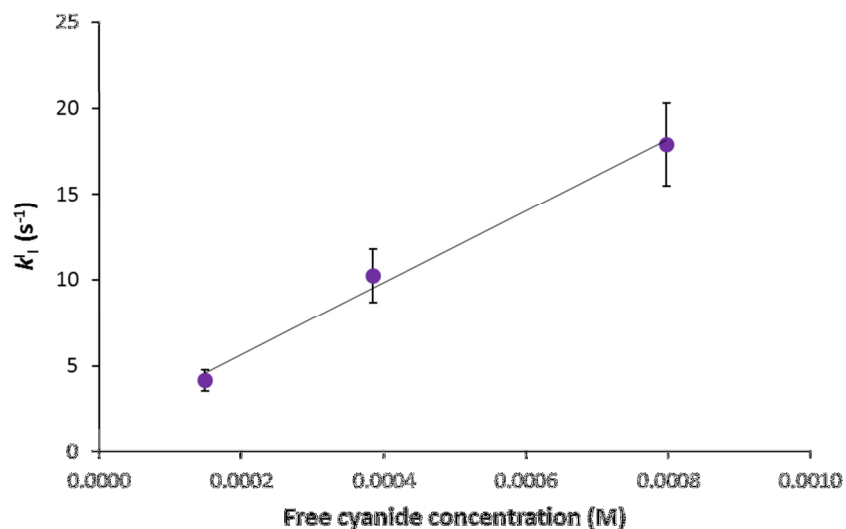


Figure 4.8.2 The linear relationship between the first order rate constant and ligand concentration for the fast initial process during the complexation of cyanide to DPTC-Co at 9.9°C. $k_{II}^I = 2.1 \pm 0.3 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ with goodness of fit $r^2 = 0.9919$

This fast initial process might involve either the formation of an outer-sphere complex prior to the binding of cyanide or some sort of rearrangement to allow for the binding of cyanide. As observed in Figure 4.3.4 (**Section 4.3**), an equilibrium is established between the five- and six-coordinated DPTC-Co species in the 80:20 methanol:water solvent system. The slow conversion of five- to six-coordinate species occurs with an associated increase in absorbance of the six-coordinate Soret at 437 nm. Conversely, a decrease in the fraction of six-coordinate species would result in a decrease in intensity of this Soret. In figure 4.8.1, the initial decrease in absorbance may be as a result of the formation of an inner-sphere complex with either an initial dissociation of the water ligand or a significant weakening of the water-Co bond, followed by the coordination of cyanide with a sharp increase in absorbance.

The main event, the change in absorbance due to the binding of cyanide to DPTC-Co was evaluated to determine the first order rate constants using a simple exponential (Equation 4.2.4) in all cases where the fast initial process was not observed (high cyanide concentrations and temperatures higher than 9.9°C). An example of the data determined at 15°C is presented in Figures 4.8.3, 4.8.4 and Table 4.8.2 below. There is evidence of a reverse reaction that occurs during the coordination of cyanide to DPTC-Co as illustrated

by the non-zero intercept in Figure 4.8.4. The reverse reaction is evident at all temperatures. Second order rate constants were plotted against $1/T$ in an Eyring plot to determine the activation energies $\Delta H^\ddagger$ and $\Delta S^\ddagger$ as in Table 4.2.3 and Figure 4.8.5.

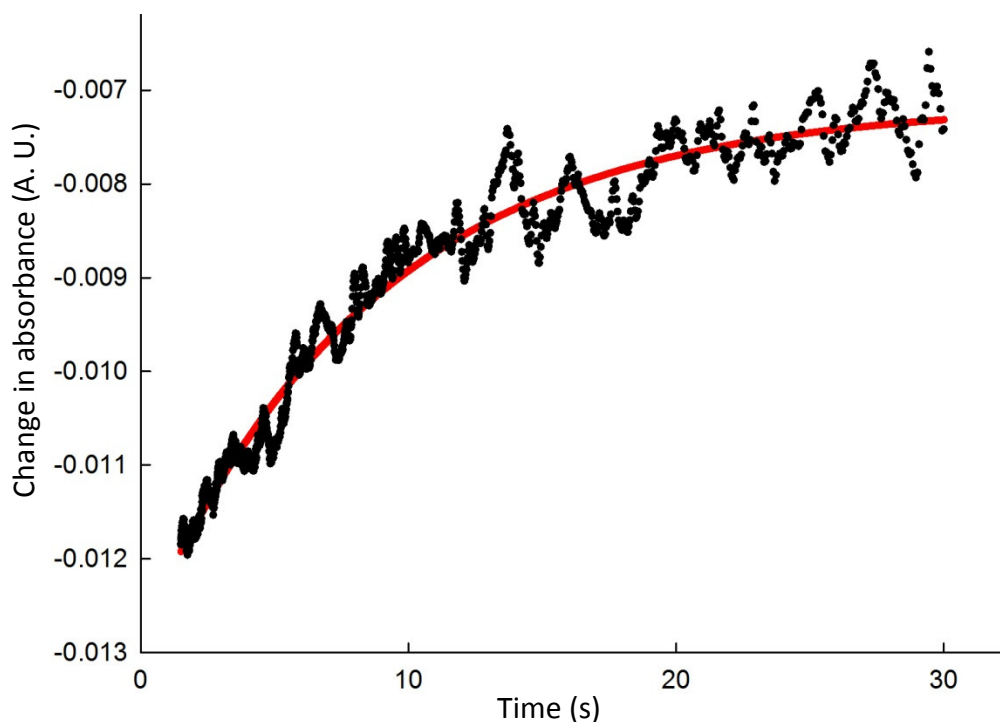


Figure 4.8.3 The change in absorbance at 434 nm with time for the coordination of cyanide to DPTC-Co in the 80:20 methanol:water solvent system at 15.0°C and ligand concentration of 2.908×10^{-4} M. Black circles indicate the experimentally determined absorbances. Red line indicates the best fit curve for $k_1 = 0.26 \pm 0.05$ from Equation 4.2.4

Table 4.8.4 First and second order rate constants determined for the formation of cyanoDPTC-Co at 15.0°C at varying ligand concentrations.

Cyanide concentration ($\times 10^{-3}$ M)	pH	Free cyanide concentration ($\times 10^{-3}$ M)	k_1 (s^{-1})
0.2908	9.649	0.1744	0.26 ± 0.05
0.7270	9.679	0.4480	0.43 ± 0.06
1.454	9.712	0.9219	0.60 ± 0.08
1.890	9.733	1.219	0.98 ± 0.07
2.326	9.754	1.526	1.0 ± 0.2
k_{11} ($M^{-1} s^{-1}$)			610 ± 101
k_r (s^{-1})			0.2 ± 0.1

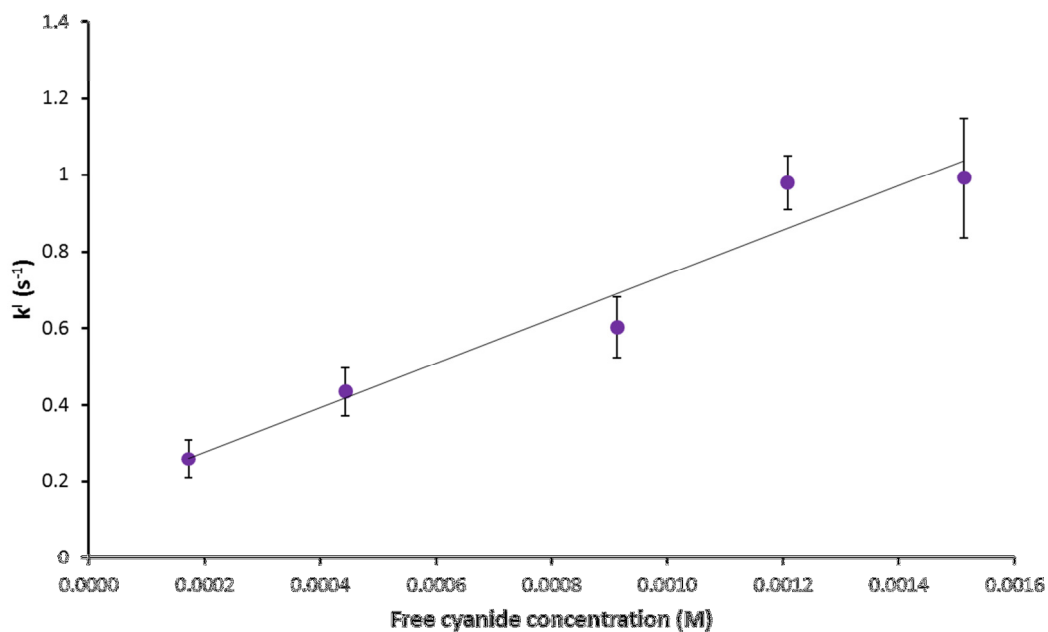


Figure 4.8.4 The linear relationship between the first order rate constant and ligand concentration for the formation of cyanoDPTC-Co at 9.8°C. $k_{\text{f}} = 610 \pm 101 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{r}} = 0.2 \pm 0.1 \text{ s}^{-1}$ with goodness of fit $r^2 = 0.9794$

Table 4.8.5 The temperature dependence of k_{f} , k_{r} and the determined activation energy parameters

Temperature (°C)	$k_{\text{f}} (\text{M}^{-1} \text{ s}^{-1})$	$k_{\text{r}} (\text{M}^{-1} \text{ s}^{-1})$
9.9	402 ± 40	0.13 ± 0.04
15.1	610 ± 101	0.2 ± 0.1
19.7	728 ± 70	0.28 ± 0.08
25.1	995 ± 148	0.7 ± 0.2
$\Delta H^{\ddagger} (\text{kJ/mol})$	39 ± 3	75 ± 16
$\Delta S^{\ddagger} (\text{J/K.mol})$	-58 ± 11	3 ± 55

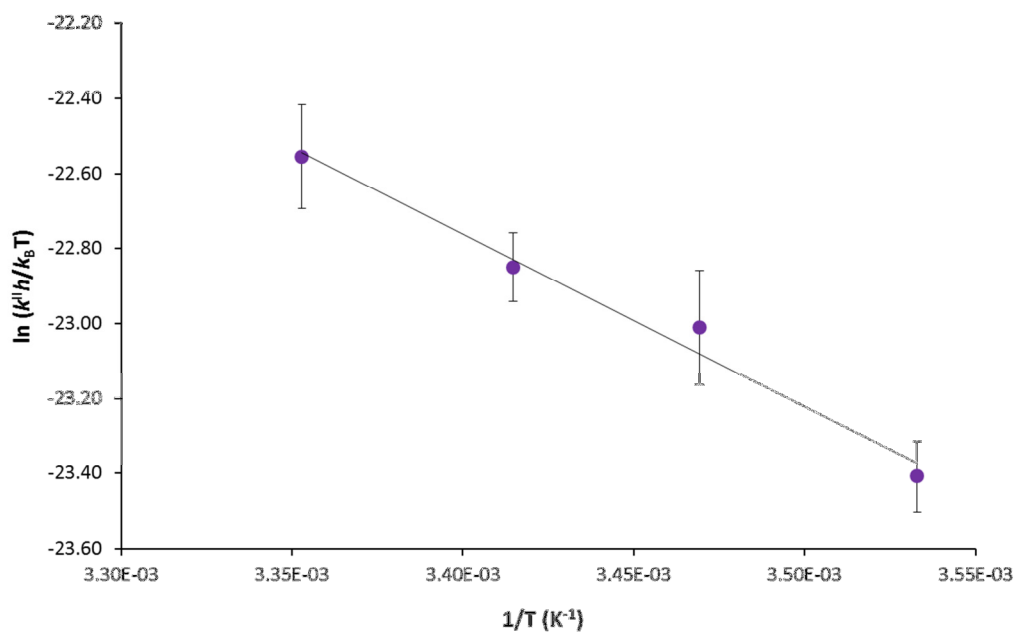


Figure 4.8.5 Temperature dependence of k_{II} for the formation of the cyanide DPTC-Co complex with goodness of fit $r^2 = 0.9788$

The presence of an identifiable reverse reaction was unexpected. With the incredibly high affinity of cyanide for DPTC-Co ($\log K$ is approximately 13) it is unexpected that the reverse aquation of DPTC-Co would occur. With the data and evidence available, this observation cannot be rationalised.

4.8.4 The coordination of cyanide to Vitamin B_{12a}

The reaction between vitamin B_{12a} and cyanide was monitored at four temperatures (9.8, 15.1, 19.8 and 25.2°C) and at five cyanide concentrations (1.048, 2.514, 5.238, 7.857 and 10.48 x 10⁻² M). As the concentrations of cyanide were high, the pH of the reaction mixtures were significantly higher than the pH of the buffered solvent system (at approximately pH 9.5). Consequently, the fraction of aquacobalamin, the reactive cobalamin species, was extremely low and the reactions had to be monitored for between 300 and 1000 seconds.

The progression of the reaction was monitored at 361 nm, the γ band of cyanocobalamin. The absorbance increased as the reaction between aquacobalamin and cyanide progressed, but decreased with the subsequent formation of dicyanocobalamin as illustrated in Figure 4.8.6. The data were fitted to a double exponential to accommodate two sequential first order reactions (Equation 4.2.5 in **Section 4.2.5**). The two first order rate constants determined, k^I and k^{II} , were found to be very similar indicating a cross correlation or compensation effect of k^I and k^{II} with very large p values, indicating that the results were not significant, and effectively meaningless.

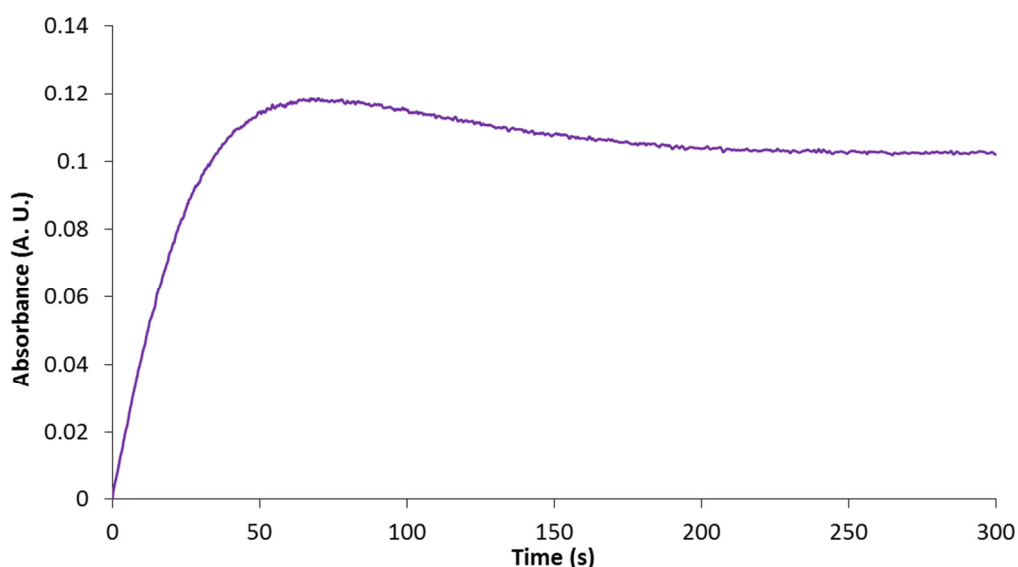


Figure 4.8.6 The change in absorbance at 361 nm with time for the conversion of aquacobalamin to cyanocobalamin and subsequent conversion to dicyanocobalamin in the 80:20 methanol:water solvent system at 25.2°C and ligand concentration of 0.1048 M

As a consequence of the unreliable results of the determination of k^I and k^{II} , the data representing the formation of cyanocobalamin from aquacobalamin only were used in the determination of the first order rate constant. An example of the data determined at 9.8°C is presented in Figures 4.8.7, 4.8.8 and Table 4.8.4 below. Second order rate constants were plotted against $1/T$ in an Eyring plot to determine the activation energies $\Delta H^\ddagger$ and $\Delta S^\ddagger$ as in Table 4.2.5 and Figure 4.8.9.

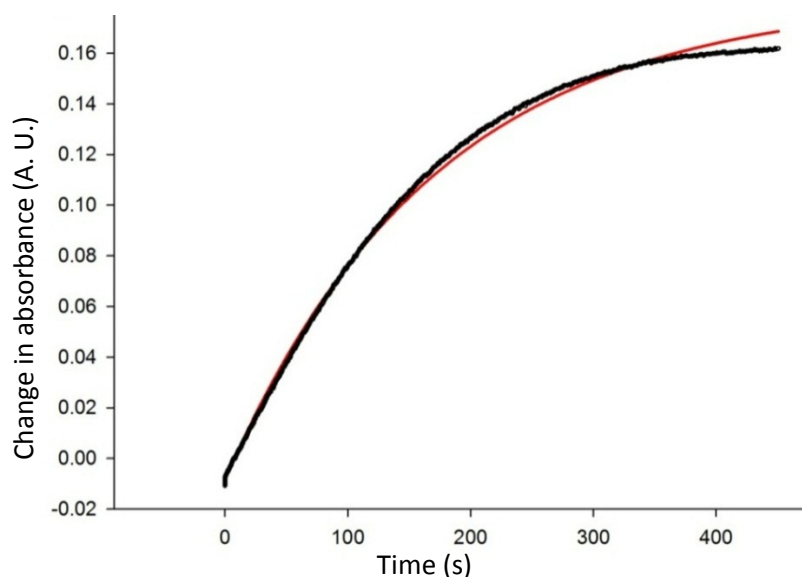


Figure 4.8.7 The change in absorbance at 361 nm with time for the conversion of aquacobalamin to cyanocobalamin in the 80:20 methanol:water solvent system at 9.8°C and ligand concentration of 2.514×10^{-2} M. Black circles indicate the experimentally determined absorbances. Red line indicates the best fit curve for $k_1 = 10.7 \pm 0.1$ from Equation 4.2.4

Table 4.8.4 First and second order rate constants determined for the formation of cyanocobalamin from aquacobalamin at 9.8°C at varying ligand concentrations.

Cyanide concentration ($\times 10^{-2}$ M)	pH	Free cyanide concentration ($\times 10^{-2}$ M)	k_1 (s^{-1})
1.048	10.214	0.8358	2.93 ± 0.04
2.514	10.659	2.304	10.7 ± 0.1
5.238	10.904	4.980	21.2 ± 0.1
7.857	11.107	7.610	34.0 ± 0.2
10.48	11.252	10.24	46.3 ± 0.3
k_{II} ($M^{-1} s^{-1}$)			458 ± 11

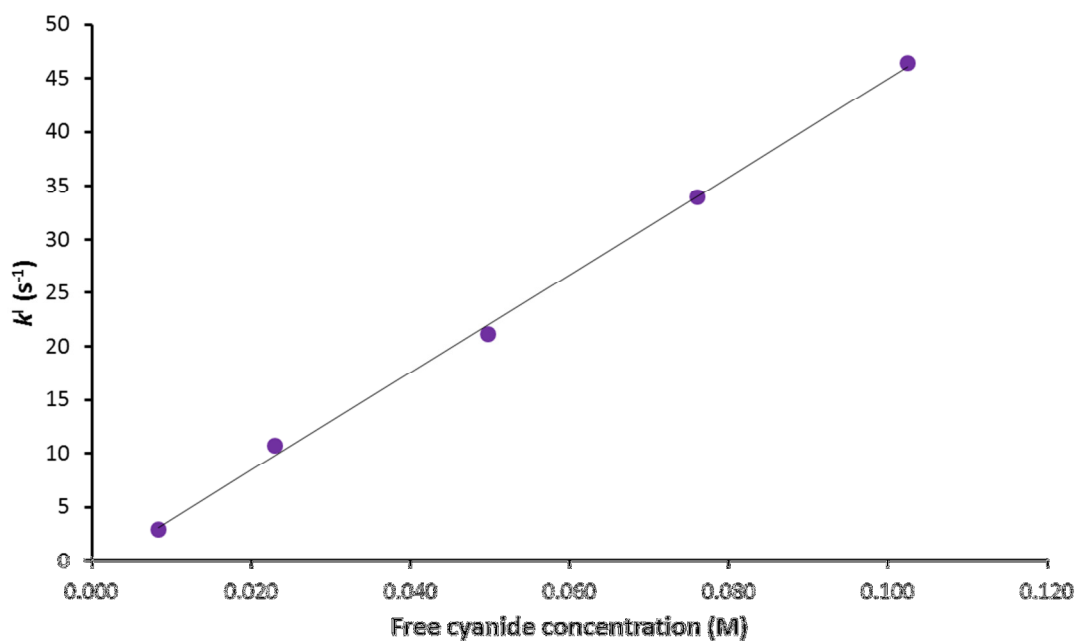


Figure 4.8.8 The linear relationship between the first order rate constant and ligand concentration for the formation of cyanocobalamin at 9.8°C. $k_{II} = 458 \pm 11$ with goodness of fit $r^2 = 0.9975$

Table 4.8.5 The temperature dependence of k_{II} and the determined activation energy parameters for the formation of cyanocobalamin

Temperature (°C)	k_{II} ($M^{-1} s^{-1}$)
9.8	458 ± 11
15.1	794 ± 31
19.8	1364 ± 47
25.2	2982 ± 86
$\Delta H^\ddagger$ (kJ/mol)	82 ± 5
$\Delta S^\ddagger$ (J/K.mol)	96 ± 19

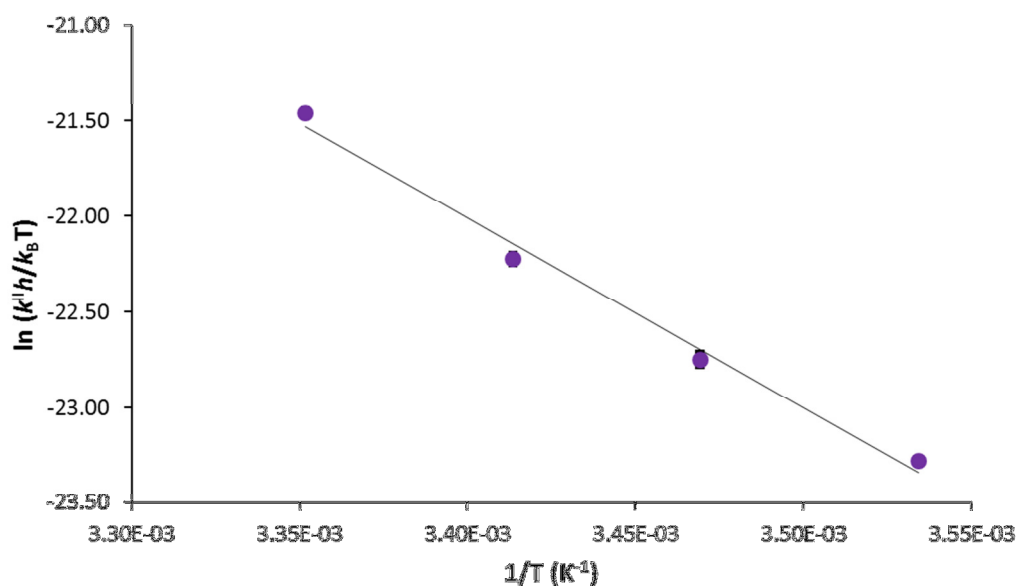


Figure 4.8.9 Temperature dependence of k_{II} for the formation of cyanocobalamin with goodness of fit $r^2 = 0.9871$

The unfortunate observation of two reactions, the formation of cyanocobalamin as well as dicyanocobalamin, might have been avoided if the reaction was monitored at a different wavelength. The reaction was monitored at 540 nm, an isosbestic point for the conversion of cyanocobalamin to dicyanocobalamin, at 20.3°C with a cyanide concentration of 0.04958M upon mixing. At this wavelength, the change in absorbance due to the formation of dicyanocobalamin was observed to a lesser extent. The second order rate constants for this reaction at 20°C determined at 361 and 540 nm were within error at 1364 ± 47 and 1453 ± 123 respectively. The signal to noise ratio, however, was large with a small change in absorbance at this wavelength. Therefore, although the determination of rate constants from the data representing the formation of cyanocobalamin from aquacobalamin only did not fit the data as well as might have been expected as the formation of dicyanocobalamin became apparent, as is evident in Figure 4.8.7, the rate constants determined at a different wavelength are identical within error, and thus the determined rate constants (at 361 nm) are used in this discussion.

4.8.5 The effect of environment on vitamin B_{12a} kinetics

That the environment in which a reaction takes part affects the kinetics is a well-known fact. Balt and co-workers, in a six part series, documented the effect of ionic strength and solvent composition on the kinetics of axial ligand substitution reactions of aquacobalamin with various anionic and neutral ligands in acetonitrile:water and dioxane:water mixtures^{71,72,105,106,160,162,163} while Moreno-Esparza and co-workers investigated the binding of iodide to aquacobalamin in varying methanol:water mixtures.⁸⁰

It was found that ionic strength affected both k_1 and k_{-1} in the reaction between aquacobalamin and thiosulfate with k_1 decreasing from over $1100 \text{ M}^{-1} \text{ s}^{-1}$ to approximately $100 \text{ M}^{-1} \text{ s}^{-1}$ and k_{-1} increasing from approximately 0.02 to 0.04 s^{-1} as the ionic strength increased from 0 to 0.8 M NaClO_4 .⁷¹ This was not unexpected as reactions involving ionic species are known to be influenced by the ionic nature of the reaction media;^{71,105} however, the increase in k_{-1} deviated from the trend expected from Debye-Hückel theory where it was expected to remain constant. The 'Winstein special salt effect' explains this increase as being a result of competition between the non-coordinating ClO_4^- ion and the leaving group in the second coordination sphere during the transition state favouring the reformation of the aqua complex.^{71,164}

The composition of the solvent and the ionic strength affects the kinetics of the system to a similar degree.^{71,105} The solvent effect, however, is more complex than the ionic strength effect. The polarity and dielectric constant,^{71,80,106,163} hydrogen bonding capabilities,⁷² the structure of the bulk solvent,¹⁶² viscosity as well as heats of evaporation or fluidity¹⁷⁶ all affect the kinetics and the mechanisms at play in the system in different ways. These solvent effects can either stabilise or destabilise the products and transition state depending on the nature of the solvent as well as the nature of the reactants and products (such as electronic structure, hydrogen bonding capabilities and size^{80,162}). Balt and co-workers found that the first order rate constant for the substitution of water by thiosulfate⁷¹ and various neutral sulfur donor ligands^{72,105} on vitamin B_{12a} decreased as

the mole fraction of dioxane in water increased. Similarly, substitution by thiocyanate in acetonitrile:water mixtures displayed the same trend.¹⁰⁶ In these cases, there was a complex non-linear relationship between the thermodynamic transfer enthalpies and entropies (δmH and δmS) with varying solvent composition, although the change in the transfer Gibbs energy (δmG°) displayed a less complex change with solvent composition due to the compensation effect between the changes in enthalpy and entropy.¹⁰⁵ Moreno-Esparza studied the binding of iodide to aquacobalamin in methanol:water mixtures. This system showed a parabolic change in the rate of substitution with varying methanol concentrations, with a general decrease in rate with increasing methanol concentration in water dominant systems. In methanol dominant systems, however, the rate increased dramatically at very high methanol concentrations with the rate at 100% methanol three times that at 0% methanol.⁸⁰ In this case, unlike in Balt's studies with non-coordinating solvents such as acetonitrile and dioxane, methanol binds to aquacobalamin when the concentration of methanol is much greater than that of water. Moreno-Esparza noted that the presence of significant amounts of methanol-bound cobalamin affected the mechanism of the reaction as there was evidence of an outer sphere complex mechanism in methanol dominant systems, but not in water dominant systems. In addition, in water dominant solvent systems, evidence of the reverse reaction was found which was attributed to the 'reversible solvent expulsion from the outer-sphere complex'.⁸⁰

The rate of the substitution of water by cyanide on vitamin B_{12a} is dependent on solvent. Marques and co-workers⁵⁷ and Reenstra and Jencks⁵⁵ investigated the reaction between cyanide and vitamin B_{12a}. The activation energies $\Delta H^\ddagger$ and $\Delta S^\ddagger$ of the coordination of cyanide to vitamin B_{12a} in different solvent systems are given in Table 4.8.6.

Table 4.8.6 Activation energies and kinetic data for the addition of cyanide to aquacobalamin in different solvents

Solvent (μ , M)	$\Delta H^\ddagger$ (kJ/mol)	$\Delta S^\ddagger$ (kJ/K.mol)	k_{II} ($M^{-1} s^{-1}$; 25°C)
Water (1.0) ^{55,57}	52 $\pm$ 1	-25 $\pm$ 4	250
80:20 methanol:water (0.025*)	82 $\pm$ 5	96 $\pm$ 19	2.98(9) $\times 10^2$

*This work - ionic strength was calculated from the concentration of the charged buffer species at the experimental pH

The data in Table 4.8.6 is fairly surprising with respect to Balt and Moreno-Esparza's results. Similar to Moreno-Esparza's reaction of iodide with aquacobalamin, the rate of cyanide substitution is much higher in the methanol rich solvent system than in the aqueous system. Unlike in the case of the iodide reaction where the rate at 80% methanol in water is just over half that at 0% methanol,⁸⁰ the rate of the cyanide reaction in 80% methanol is significantly faster at just under 12 times that of the reaction in water. In addition to the differences in solvent composition, these reactions were carried out at different ionic strengths. Balt found a marked decrease in the observed rate constant as the ionic strength increased from 0 to 0.8 M NaClO₄⁷¹ indicating that the low ionic strength used in this investigation was likely to increase the reaction rate. The rate of cyanide substitution is therefore greatly influenced by both the solvent composition and the ionic strength.

Analysis of the activation energies reveals that the reaction in water is enthalpically driven while that in 80% methanol is entropically driven. The significant change in enthalpy of activation suggests a change in the position of the transition state along the reaction coordinate. The large positive change in enthalpy of activation in the methanol rich system is indicative of a late transition state in which the breaking of the cobalt-water bond occurs before significant cobalt-cyanide bonding can occur whereas the smaller change in enthalpy of activation in the aqueous system suggests an early transition state where significant cyanide-cobalt bond formation occurs as the cobalt-water bond is broken. The remarkable change in entropy of activation suggests that the system in aqueous media is significantly more ordered than in more non-polar media. Balt noted that the fraction of non-polar co-solvent broke down the ordered structure of bulk water

and significantly changed the solvation of vitamin B_{12a}.¹⁶³ Reenstra⁵⁵ and Marques⁵⁷ suggested that unfavourable entropic contributions may be as a result of increased nucleophilic participation by the incoming ligand, leading to a more ordered system and a more concerted mechanism. A change in solvent structure may contribute to the favourable increase in $\Delta S^\ddagger$. Nucleophilic participation may occur to a lesser extent in a more non-polar environment, decreasing the ordered nature of the system.

Balt and co-workers, in a study on aquanitritocobaloxime and thiourea in water:dioxane mixtures postulated that the reaction mechanism changed from I_A to I_D as the solvent composition became more non-polar.¹⁶⁰ Moreno-Esparza also postulated a change in mechanism with changing methanol concentration with a reversible aquation of the cobalt at low methanol concentration and an outer sphere complex mechanism at high methanol concentrations.⁸⁰ Reenstra⁵⁵ and Marques⁵⁷ suggested that differences in the nucleophilic participation result in a more concerted mechanism and this nucleophilic participation is likely to be affected by solvent composition. These findings suggest that the large differences in the data in Table 4.8.6 may arise from differences in mechanism, although insufficient data have been collected to determine if this is the case or not. Analysis of the kinetics at varying methanol concentrations would be required to answer this question more fully.

4.8.6 The lability of cobalt in vitamin B_{12a} and a biomimetic model

The second order rate constants and parameters of activation for the coordination of cyanide to cobalt in vitamin B_{12a} and DPTC-Co are summarised in Table 4.8.7. Analysis of the second order rate constants indicates that the reactions of vitamin B_{12a} with cyanide are similar to those of DPTC-Co at low temperatures and two to three times faster at higher temperatures. Superficially, one might conclude that cobalt in the corrin ring of vitamin B_{12a} is more labile than in the corrole ring of DPTC-Co. Analysis of the activation parameters, however, reveals a different picture.

The effect of changes in the electronic nature of a system on the kinetics is evident in the enthalpic contribution to the activation energy, and not the contribution of entropy of activation. Environmental changes, such as the effect of solvent, manifest themselves in both the enthalpic and entropic contributions to the activation barrier.¹⁶⁴ This suggests that the rates of the reaction of cyanide with either DPTC-Co or vitamin B_{12a} cannot be compared as the systems' interactions with the environment are different due to the differences in the interaction between the macrocycle and the solvent as a result of differences in the charges of vitamin B_{12a} and DPTC-Co. As such, comparison of the enthalpies of activation may highlight the electronic differences between the two systems and thus the electronic effect of a change in macrocycle on the coordinated cobalt metal ion.

Equation 4.8.1 illustrates that an increase in enthalpy of activation decreases the rate of the reaction while an increase in entropy of activation has the opposite effect. In the case of the corrin ring, the reaction is entropy driven. On the other hand, the reaction with the corrole ring is enthalpy driven.

Table 4.8.7 Second order rate constants and activation parameters for the coordination of cyanide to cobalt in vitamin B_{12a} and the biomimetic model, DPTC-Co

Macrocycle	Temperature (°C)	k_{II} (M ⁻¹ s ⁻¹)	$\Delta H^\ddagger$ (kJ/mol)	$\Delta S^\ddagger$ (kJ/K.mol)
Corrin	9.8	458 ± 11	82 ± 5	96 ± 19
	15.1	794 ± 31		
	19.8	1364 ± 47		
	25.2	2982 ± 86		
Corrole	9.9	402 ± 40	39 ± 3	-58 ± 11
	15.1	610 ± 101		
	19.7	728 ± 70		
	25.1	995 ± 148		

Changes in entropy of activation in these two systems are significantly different. The large positive value in the case of vitamin B_{12a} indicates a favourable increase in the disorder of the system upon coordination of cyanide. In the case of the corrole, the large negative value indicates an ordering of the system. In both cases, anionic free cyanide ligand would be solvated prior to coordination. While the numbers of degrees of freedom of the cyanide would decrease upon coordination, the dispersion of the water molecules of solvation around the cyanide into bulk solvent would be entropically favourable.

The differences between the two systems are in the charges of the metallated macrocycles. Vitamin B_{12a}, with an overall charge of 1+, would experience an ordered array of solvent around the charged molecule. Coordination of an anionic ligand would result in the charge neutralisation of the chromophore and the ordered network of solvent molecules that surrounded vitamin B_{12a} would become less ordered. The hydrogen bonding interactions between the solvent and the acetamide side chains would remain unchanged. In a solvent system rich in methanol, the neutralisation of a charged system would also be far more favourable than in an aqueous system, as discussed in **Section 4.8.5**. DPTC-Co, overall neutral, would not have the ordered network of solvent as in the case of vitamin B_{12a}. Coordination of an anionic ligand, however, would result in an overall charge of 1-. The formation of a charged species in a predominantly organic

solvent system, as opposed to the neutralisation of charged species, as with vitamin B_{12a}, would be entropically unfavourable. More energy would be required to create an ordered network of solvent molecules to separate the charged species in solution. In addition to this, the presence of a five-coordinate species as well as a six-coordinate DPTC-Co in solution in 80:20 methanol:water will affect the change in entropy of activation. In the case of vitamin B_{12a} where we assume 100% six-coordinate species, the release of the bound water into the bulk solvent during the coordination of the cyanide ligand is entropically favourable. In the presence of a five-coordinate DPTC-Co species the cyanide ligand can bind directly to the metal ion without the release of solvent into bulk solvent – an entropically unfavourable event. It would be interesting to determine the effect that the binding of a neutral ligand has on the change in entropy of the transition state. Would the change in entropy of activation be more favourable with the formation of a neutral product as opposed to a charged product?

Changes in enthalpy of activation also vary in these two systems. In the corrin system, the change in enthalpy is large, positive and energetically unfavourable. In the corrole system, however, the change in enthalpy of activation, while still positive, is much lower and thus more favourable. In this way, cobalt in DPTC-Co might be envisaged to be more electronically labile than in vitamin B_{12a}. While the changes in bonding are similar in both systems with the breaking of an oxygen-cobalt bond and the formation of a carbon-cobalt bond, the strength of these bonds as well as the time along the reaction coordinate at which these events occur may vary.

The binding of cyanide to vitamin B_{12a} is known to follow a dissociative interchange mechanism, I_D.^{55,57} A large positive change in enthalpy of activation, as in the case of the vitamin B_{12a} system, is indicative of a late transition state, whereas a smaller enthalpy of activation change, as seen in the reaction with the corrole suggests an early transition state, as illustrated in Figure 4.8.10. In an early transition state, the coordination of cyanide occurs as the weak cobalt-water bond breaks. This mechanism is less dissociative in nature with the production of a species more seven coordinate in nature. During a late transition state more energy is required to break the stronger cobalt-water bond before

the cyanide ligand can bind to the cobalt ion. This results in a more dissociative mechanism with a species more five-coordinate in nature forming as the breaking of the water-cobalt bond occurs to a larger extent before cyanide coordination. This highlights the lability of the cobalt ion in the biomimetic model as the coordination of cyanide occurs at an earlier stage of the transition state than in the case of vitamin B_{12a}. The position of the transition state along the reaction coordinate also affects the entropy of activation of the system. Early transition states, while enthalpically favourable, are entropically unfavourable. The formation of a species with seven coordinate character constrains both the entering and leaving ligands, thus decreasing the change in entropy of activation. Conversely, as the change in enthalpy of activation increases in a late transition state, the change in entropy of activation increases as the formation of a species with five-coordinate character, as one ligand leaves and another enters, is less restrictive and ordered, and thus more favourable. In this way, there exists a compensation effect between the changes in entropy and enthalpy of activation¹⁷⁶ and this system is no exception.

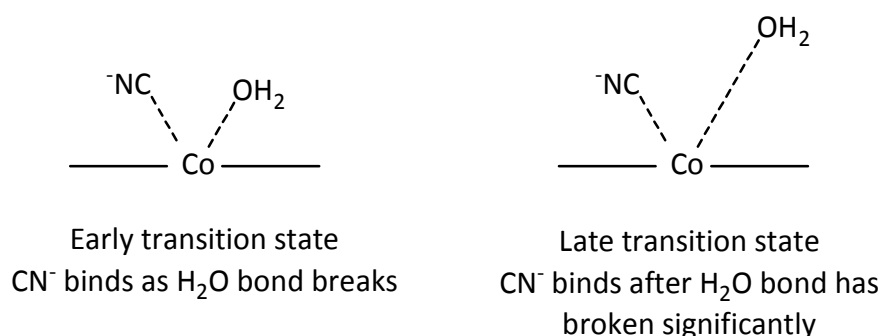


Figure 4.8.10 Early transition state typically has more seven coordinate character while a late transition state has more five-coordinate character

As discussed in Section 4.8.3, a very fast initial process is observed at low temperature and low ligand concentration. It was postulated that the observed decrease in absorbance may indicate the formation of the five-coordinate species or significant weakening of the cobalt-water bond prior to the coordination of cyanide. The formation of a five-coordinate species would suggest a dissociative mechanism as opposed to a dissociative interchange mechanism, while the significant weakening of the cobalt-water bond before cyanide is able to bind suggests a late transition state. These theories contradict the activation energy data determined from the Eyring plot indicating an early transition state

mechanism. Without further evidence, it is not possible to determine the nature of the species involved in the fast initial reaction. Acquisition of spectra from a diode array detection system coupled with stopped flow techniques at low temperature (the use of a methanol rich solvent system would facilitate the study of this system at temperatures below zero) would allow for a better understanding of the nature of this species and the mechanism involved. In this discussion, it is assumed that the mechanism involved in the reaction with vitamin B₁₂ is the same as that with DPTC-Co and this may not be the case.

4.8.7 Conclusions

The rate of cyanide coordination is dependent on the nature of the solvent system as well as the nature of the electronic environment of the cobalt ion. The second order rate constant for the binding of cyanide is higher in the vitamin B₁₂ system than in the DPTC-Co system. Although faster, the reaction between vitamin B₁₂ and cyanide is entropically driven, while that between DPTC-Co and cyanide is enthalpically driven and very entropically unfavourable. When regarded in this light, it is clear that cobalt in DPTC-Co is more electronically labile than in the corrin ring of vitamin B_{12a}.

During the coordination of cyanide to DPTC-Co at low temperature and low cyanide concentration, evidence of an initial fast reaction was present. This fast reaction may involve the formation of an outer sphere complex or the formation of a five-coordinate system prior to the formation of the cobalt-cyanide bond. There was also evidence of a reverse reaction, which occurred at all temperatures and ligand concentrations, which was unexpected given the very high formation constant observed for the formation of the cyanoDPTC-Co complex.

A large environmental dependence was observed for the reaction of vitamin B_{12a} with cyanide. The rate of reaction was considerably faster in the methanol rich solvent system of low ionic strength compared to the reaction in a purely aqueous and highly ionic medium. The differences in rate and activation energy parameters point to a potential change in mechanism with difference in solvent system as well as ionic strength.

This kinetics study is far from complete and must be considered an initial study. In spite of this, the effects of both the greater environment (solvent and ionic strength) and the electronic environment of the coordinated metal in the different macrocycles are clear. It appears that the increased electron donation from the corrole ring to the cobalt ion affects the lability of the metal.

4.9 References

- (1) Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F.; Boschi, T.; Smith, K. M. *Chem. Commun.* **1999**, 1307-1308.
- (2) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem. Int. Ed.* **1999**, 38, 1427-1429.
- (3) Palmer, J. H. *Struct. Bond.* **2012**, 142, 49-90.
- (4) Aviv-Harel, I.; Gross, Z. *Chem. Eur. J.* **2009**, 15, 8382-8394.
- (5) Joseph, C. A.; Ford, P. C. *J. Am. Chem. Soc.* **2005**, 127, 6737-6743.
- (6) Erben, C.; Will, S.; Kadish, K. M. In *The Porphyrin Handbook*; 1st ed.; Kadish, K. M., Smith, K. M., Guillard, R., Eds.; Academic Press: New York, 2000; Vol. 2, p 233-300.
- (7) Paolesse, R. In *The Porphyrin Handbook*; 1st ed.; Kadish, K. M., Smith, K. M., Guillard, R., Eds.; Academic Press: New York, 2000; Vol. 2, p 201-232.
- (8) Aviv-Harel, I.; Gross, Z. *Coord. Chem. Rev.* **2011**, 255, 717-736.
- (9) Aviv, I.; Gross, Z. *Chem. Commun.* **2007**, 1987-1999 and references therein.
- (10) Paolesse, R.; Licoccia, S.; Boschi, T. *Inorg. Chim. Acta* **1990**, 178, 9-12.
- (11) Alemayehu, A.; Hansen, L. K.; Ghosh, A. *Inorg. Chem.* **2010**, 49, 7608-7610.
- (12) Ghosh, A.; Steene, E. J. *Inorg. Biochem.* **2002**, 91, 423-436.
- (13) Murakami, Y.; Matsuda, Y.; Yamada, S. *J. Chem. Soc., Dalton Trans.* **1981**, 855-861.
- (14) Ghosh, A. *J. Biol. Inorg. Chem.* **2006**, 11, 712-724.
- (15) Saltsman, I.; Goldberg, I.; Gross, Z. *Tetrahedron Lett.* **2003**, 44, 5669-5673.
- (16) Saltsman, I.; Simkhovich, L.; Balazs, Y. S.; Goldberg, I.; Gross, Z. *Inorg. Chim. Acta* **2004**, 357, 3038-3046.
- (17) Licoccia, S.; Paolesse, R.; Tassoni, E.; Polizio, F.; Boschi, T. *J. Chem. Soc., Dalton Trans.* **1995**, 3617-3621.
- (18) Ghosh, A.; Wondimagegn, T.; Parusel, B. J. *J. Am. Chem. Soc.* **2000**, 122, 5100-5104.
- (19) Gouterman, M. *J. Mol. Spectrosc.* **1961**, 6, 138-163.
- (20) Gouterman, M.; Wagnière, G. H. *J. Mol. Spectrosc.* **1963**, 11, 108-127.
- (21) Hush, N. S.; Woolsey, I. S. *J. Chem. Soc., Dalton Trans.* **1974**, 24-34.
- (22) Edwards, L.; Dolphin, D. H. *J. Mol. Spectrosc.* **1970**, 35, 90-109.

- (23) Hush, N. S.; Dyke, J. M.; Williams, M. L.; Woolsey, I. S. *J. Chem. Soc., Dalton Trans.* **1974**, 395-399.
- (24) Hill, J. A.; Pratt, J. M.; Williams, R. J. P. *J. Chem. Soc.* **1964**, 5149-5153.
- (25) Day, P. *Theoret. Chim. Acta (Berl.)* **1967**, 7, 328-341.
- (26) Pratt, J. M. *Inorganic Chemistry of Vitamin B₁₂*; Academic Press: London, 1972.
- (27) Hill, H. A. O.; Pratt, J. M.; Williams, R. J. P. *Proc. Roy. Soc. A* **1965**, 288, 352-358.
- (28) Perry, C. B.; Marques, H. M. S. *Afr. J. Chem.* **2005**, 9-15.
- (29) Pratt, J. M.; Thorp, R. G. *J. Chem. Soc. (A)* **1966**, 187-191.
- (30) Chemaly, S. M. *Dalton Trans.* **2008**, 5766-5773.
- (31) Mahammed, A.; Gray, H. B.; Weaver, J. J.; Sorasaene, K.; Gross, Z. *Bioconjugate Chem.* **2004**, 15, 738-746.
- (32) Guillard, R.; Jérôme, F.; Barbe, J.-M.; Gros, C. P.; Ou, Z.; Shao, J.; Fischer, J.; Weiss, R.; Kadish, K. M. *Inorg. Chem.* **2001**, 40, 4856-4865.
- (33) Kadish, K. M.; Ou, Z.; Shao, J.; Gros, C. P.; Barbe, J.-M.; Jérôme, F.; Bolze, F.; Burdet, F.; Guillard, R. *Inorg. Chem.* **2002**, 41, 3990-4005.
- (34) Guillard, R.; Gros, C. P.; Bolze, F.; Jérôme, F.; Ou, Z.; Shao, J.; Fischer, J.; Weiss, R.; Kadish, K. M. *Inorg. Chem.* **2001**, 40, 4845-4855.
- (35) Adamian, V. A.; D'Souza, F.; Licoccia, S.; Di Vona, M. L.; Tassoni, E.; Paolesse, R.; Boschi, T.; Kadish, K. M. *Inorg. Chem.* **1995**, 34, 532-540.
- (36) Murakami, Y.; Yamada, S.; Matsuda, Y.; Sakata, K. *Bull. Chem. Soc. Jpn.* **1978**, 51, 123-129.
- (37) Licoccia, S.; Morgante, E.; Paolesse, R.; Polizio, F.; Senge, M. O.; Tondello, E.; Boschi, T. *Inorg. Chem.* **1997**, 36, 1564-1570.
- (38) Chen, P.; Ojaimi, M. E.; Gros, C. P.; Richard, P.; Barbe, J.-M.; Guillard, R.; Shen, J.; Kadish, K. M. *Inorg. Chem.* **2011**, 50, 3479-3489.
- (39) Shen, J.; Ojaimi, M. E.; Chkounda, M.; Gros, C. P.; Barbe, J.-M.; Shao, J.; Guillard, R.; Kadish, K. M. *Inorg. Chem.* **2008**, 47, 7717-7727.
- (40) Kadish, K. M.; Shao, J.; Ou, Z.; Frémond, L.; Zhan, R.; Burdet, F.; Barbe, J.-M.; Gros, C. P.; Guillard, R. *Inorg. Chem.* **2005**, 44, 6744-6754.
- (41) Knapton, L.; Marques, H. M. *Dalton Trans.* **2005**, 889-895.

- (42) Kadish, K. M.; Adamian, V. A.; Van Caemelbecke, E.; Gueletii, E.; Will, S.; Erben, C.; Vogel, E. *J. Am. Chem. Soc.* **1998**, *120*, 11986-11993.
- (43) Van Caemelbecke, E.; Will, S.; Autret, M.; Adamian, V. A.; Lex, J.; Gisselbrecht, J.-P.; Gross, M.; Vogel, E.; Kadish, K. M. *Inorg. Chem.* **1996**, *35*, 184-192.
- (44) Kadish, K. M.; Koh, W.; Tagliatesta, P.; Sazou, D.; Paolesse, R.; Licoccia, S.; Boshi, T. *Inorg. Chem.* **1992**, *31*, 2305-2313.
- (45) Kunze, S.; Zobi, F.; Kurz, P.; Spingler, B.; Alberto, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 5025-5029.
- (46) Zheng, D.; Yan, L.; Birke, R. L. *Inorg. Chem.* **2002**, *41*, 2548-2555.
- (47) Jérôme, F.; Gros, C. P.; Tardieux, C.; Barbe, J.-M.; Guillard, R. *Chem. Commun.* **1998**, 2007-2008.
- (48) Volpe, M.; Hartnett, H.; Leeland, J. W.; Wills, K.; Ogunshun, M.; Duncombe, B. J.; Wilson, C.; Blake, A. J.; McMaster, J.; Love, J. B. *Inorg. Chem.* **2009**, *48*, 5195-5207.
- (49) Gros, C. P.; Brisach, F.; Meristoudi, A.; Espinosa, E.; Guillard, R.; Harvey, P. D. *Inorg. Chem.* **2007**, *46*, 125-135.
- (50) Guillard, R.; Gros, C. P.; Barbe, J.-M.; Espinosa, E.; Jérôme, F.; Tabard, A. *Inorg. Chem.* **2004**, *43*, 7441-7455.
- (51) Kadish, K. M.; Shao, J.; Ou, Z.; Zhan, R.; Burdet, F.; Barbe, J.-M.; Gros, C. P.; Guillard, R. *Inorg. Chem.* **2005**, *44*, 9023-9038.
- (52) Varian; 3.00(182) ed.; Sax Software Corp.: Australia, 2002.
- (53) SigmaPlot; 11.0.0.75 ed.; Systat Software: San Jose, CA, 2008.
- (54) Marques, H. M.; Munro, O. Q.; Crawcour, M. L. *Inorg. Chim. Acta* **1992**, *196*, 221-229.
- (55) Reenstra, W. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 5780-5791.
- (56) Conn, J. B.; Wartman, T. G. *Science* **1952**, *115*, 72-73.
- (57) Marques, H. M.; Brown, K. L.; Jacobsen, D. W. *J. Biol. Chem.* **1988**, *263*, 12378-12383.
- (58) Marques, H. M. *Inorg. Chem.* **2005**, *44*, 6146-6148.
- (59) Marques, H. M.; Baldwin, D. A.; Pratt, J. M. *J. Inorg. Biochem.* **1987**, *29*, 77-91.
- (60) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.

- Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; Gaussian Inc.: Wallingford CT, 2009.
- (61) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*; 4th ed.; Wiley Verlag Chemie: Weinheim, 2011.
- (62) Muller, P. *Pure & Appl. Chem.* **1994**, *66*, 1077-1184.
- (63) Marini, A.; Muñoz-Losa, A.; Biancardi, A.; Mennucci, B. *J. Phys. Chem. B* **2010**, *114*, 17128-17135.
- (64) Lu, G.; Lin, W.; Fang, Y.; Zhu, W.; Ji, X.; Ou, Z. *J. Porphyr. Phthalocya.* **2011**, *15*, 1265-1274.
- (65) Kadish, K. M.; Shao, J.; Ou, Z.; Gros, C. P.; Bolze, F.; Barbe, J.-M.; Guliard, R. *Inorg. Chem.* **2003**, *42*, 4062-4070.
- (66) Palmer, J. H.; Gross, Z.; Gray, H. B. In *United States Patent Application Publication* 2010; Vol. US 2010/0305335 A1.
- (67) Hamza, M. S. A. *J. Inorg. Biochem.* **1998**, *69*, 269-274.
- (68) Markwell, A. J.; Pratt, J. M.; Shaikjee, M. S.; Toerien, J. G. *J. Chem. Soc., Dalton Trans.* **1987**, 1349-1357.
- (69) Murakami, Y.; Hisaeda, Y.; Kajihara, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3642-3646.
- (70) Hamza, M. S. A.; Pratt, J. M. *J. Chem. Soc., Dalton Trans.* **1996**, 3721-3725.
- (71) Balt, S.; van Herk, A. M. *Transition Met. Chem.* **1983**, *8*, 152-154.
- (72) Balt, S.; De Bolster, M. W. G.; Van Garderen, C. J.; Van Herk, A. M.; Lammers, K. R.; Van Der Velde, E. G. *Inorg. Chim. Acta* **1985**, *106*, 43-47.
- (73) Stynes, H. C.; Ibers, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 5125-5127.

- (74) Rillema, D. P.; Wicker, C. M. J.; Morgan, R. D.; Barringer, L. F.; Scism, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 1276-1281.
- (75) Das, R. R.; Pasternack, R. F.; Plane, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3312-3316.
- (76) George, R. G.; Padmanabhan, M. *Proc. Indian Acad. Sci. (Chem. Sci.)* **2003**, *115*, 263-271.
- (77) Weinkauf, J. R.; Cooper, S. W.; Schweiger, A.; Wamser, C. C. *J. Phys. Chem. A* **2003**, *107*, 3486-3496.
- (78) Pasternack, R. F.; Spiro, E. G.; Teach, M. *J. Inorg. Nucl. Chem.* **1974**, *36*, 599-606.
- (79) Munro, O. Q.; Marques, H. M. *Inorg. Chem.* **1996**, *35*, 3768-3779.
- (80) Moreno-Esparza, R.; Lopez, M.; Peannell, K. H. *J. Chem. Soc., Dalton Trans.* **1992**, 1791-1795.
- (81) Ghasemi, J.; Niazi, A.; Kubista, M.; Elbergali, A. *Anal. Chim. Acta* **2002**, *455*, 335-342.
- (82) Baggesgaard-Rasmussen, H. *Z. Analyt. Chem.* **1936**, *105*, 269.
- (83) Fazary, A. E.; Ibrahim, S. E.; Ju, Y. *J. Chem. Eng. Data* **2009**, *54*, 2532-2537.
- (84) Betterton, E. A., PhD Thesis, University of the Witwatersrand, 1982.
- (85) Brown, K. L.; Cheng, S.; Zou, X.; Zubkowski, J. D.; Valente, E. J.; Knapton, L.; Marques, H. M. *Inorg. Chem.* **1997**, *36*, 3666-3675.
- (86) Hanania, G. I. H.; Irvine, D. H. *J. Chem. Soc.* **1964**, 5694-5697.
- (87) Randall, W. C.; Alberty, R. A. *Biochem.* **1967**, *6*, 1520-1525.
- (88) Robinson, K. A.; Parekh, H. V.; Itabashi, E.; Mark, H. B. *Inorg. Chem.* **1983**, *22*, 458-463.
- (89) Pettine, M.; Gennari, F.; Campanella, L.; Casentini, B.; Marani, D. *Geochim. Cosmochim. Acta* **2012**, *83*, 37-47.
- (90) Fiala, J.; Vlček, A. *Inorg. Chim. Acta* **1980**, *42*, 85-94.
- (91) Hayward, G. C.; Hill, H. A. O.; Pratt, J. M.; Vanston, N. J.; Williams, R. J. P. *J. Chem. Soc.* **1965**, 6485-6493.
- (92) Smith, E. L.; Fantes, K. H.; Ball, S.; Waller, J. G.; Emery, W. B.; Anslow, W. K.; Walker, A. D. *Biochem. J.* **1952**, *52*, 389-395.
- (93) Fantes, K. H.; Page, J. E.; Parker, L. F. J.; Smith, E. L. *Proc. Roy. Soc. B* **1950**, *136*, 592-609.

- (94) Marques, H. M.; Knapton, L.; Zou, X.; Brown, K. L. *J. Chem. Soc., Dalton Trans.* **2002**, 3195-3200.
- (95) Yatsimirskii, K. B.; Vasil'ev, V. P. *Instability Constants of Complex Compounds*; Pergamon Press: Elmsford, NY, 1960.
- (96) Martell, A. E.; Smith, R. M.; NIST Standard Reference Database 2004; Vol. 46 Version 8.0.
- (97) Munro, O. Q.; Marques, H. M. *Inorg. Chem.* **1996**, *35*, 3752-3767.
- (98) Malinin, D. R.; Yoe, J. H. *J. Chem. Ed.* **1961**, *38*, 129-131.
- (99) Wentworth, W. E. *J. Chem. Ed.* **1966**, *43*, 262-264.
- (100) Harris, D. C. *Quantitative Chemical Analysis*; 7th ed.; W. H. Freeman and Company: New York, 2007.
- (101) Beaty, R. D.; Kerber, J. D. *Concepts, Instrumentation and Techniques in Atomic Absorption Spectrophotometry*; 2nd ed.; The Perkin-Elmer Corporation: Norwalk, CA, 1993.
- (102) Barfoot, R. A. *Analyst* **1980**, *105*, 551-557.
- (103) Rounaghi, G. H.; Ghaemi, A. *Eur. J. Chem.* **2012**, *9*, 2472-2482.
- (104) Smithrud, D. B.; Sanford, E. M.; Chao, I.; Ferguson, S. B.; Carcanague, D. R.; Evanseck, J. D.; Houk, K. N.; Diederich, F. *Pure & Appl. Chem.* **1990**, *62*, 2227-2236.
- (105) Balt, S.; Van Herk, A. M.; Koolhaas, W. E. *Inorg. Chim. Acta* **1984**, *92*, 67-74.
- (106) Balt, S.; de Bolster, M. W. G.; Van Herk, A. M. *Inorg. Chim. Acta* **1985**, *107*, 13-17.
- (107) Mathura, S., Personal Communication.
- (108) Firth, R. A.; Hill, H. A. O.; Pratt, J. M.; Thorp, R. G.; Williams, R. J. P. *J. Chem. Soc. (A)* **1969**, 381-386.
- (109) Chemaly, S. M. *J. Inorg. Biochem.* **1991**, *44*, 17-25.
- (110) Hill, H. A. O.; Pratt, J. M.; Thorp, R. G.; Ward, B.; Williams, R. J. P. *Biochem. J.* **1970**, *120*, 263-269.
- (111) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724-1727.
- (112) McCoubrey, J. C. *Trans. Faraday Soc.* **1955**, *52*, 743-747.
- (113) Hohenberg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864-871.
- (114) Ghosh, A.; Taylor, P. R. *Curr. Opin. Chem. Biol.* **2003**, *7*, 113-124.

- (115) Pierloot, K.; Zhao, H.; Vancoillie, S. *Inorg. Chem.* **2012**, *49*, 10316-10329.
- (116) Roos, B. O.; Veryazov, V.; Conradie, J.; Taylor, P. R.; Ghosh, A. *J. Phys. Chem. B Lett.* **2008**, *112*, 14099-14102.
- (117) Cho, S.; Lim, J. M.; Hiroto, S.; Kim, P.; Shinokubo, H.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2009**, *131*, 6412-6420.
- (118) Conradie, J.; Ghosh, A. *Inorg. Chem.* **2011**, *50*, 4223-4335.
- (119) Ghosh, A.; Jynge, K. *Chem. Eur. J.* **1997**, *3*, 823-833.
- (120) Tangen, E.; Ghosh, A. *J. Am. Chem. Soc.* **2002**, *124*, 8117-8121.
- (121) Thomas, K. E.; Alemayehu, A.; Conradie, J.; Beavers, C.; Ghosh, A. *Acc. Chem. Res.* **2012**, *45*, 1203-1214.
- (122) Thomas, K. E.; Conradie, J.; Hansen, L. K.; Ghosh, A. *Inorg. Chem.* **2011**, *50*, 3247-3251.
- (123) Harmer, J.; Van Doorslaer, S.; Gromov, I.; Bröring, M.; Jeschke, G.; Schweiger, A. *J. Phys. Chem. B* **2002**, *106*, 2801-2811.
- (124) Rovira, C.; Kunc, K.; Hutter, J.; Parrinello, M. *Inorg. Chem.* **2001**, *40*, 11-17.
- (125) Yamauchi, S.; Tanabe, M.; Ohba, Y.; Sugisaki, K.; Toyota, K.; Sato, K.; Takui, T.; Saltsman, I. *Chem. Phys. Lett.* **2012**, *521*, 64-68.
- (126) Zakharieva, O.; Veeger, C. *J. Mol. Struct.: THEOCHEM* **2005**, *723*, 171-182.
- (127) Steene, E.; Dey, A.; Ghosh, A. *J. Am. Chem. Soc.* **2003**, *125*, 16300-16309.
- (128) Thomas, K. E.; Alemayehu, A.; Conradie, J.; Beavers, C.; Ghosh, A. *Inorg. Chem.* **2011**, *50*, 12844-12851.
- (129) Thomas, K. E.; Wasbotten, I. H.; Ghosh, A. *Inorg. Chem.* **2008**, *47*, 10469-10478.
- (130) Ghosh, A.; Steene, E. *J. Biol. Inorg. Chem.* **2001**, *6*, 739-752.
- (131) Lai, W.; Cao, R.; Dong, G.; Shaik, S.; Yao, J.; Chen, H. *J. Phys. Chem. Lett.* **2012**, *3*, 2315-2319.
- (132) Schwalbe, M.; Dogutan, D. K.; Stoian, S. A.; Teets, T. S.; Nocera, D. G. *Inorg. Chem.* **2011**, *50*, 1368-1377.
- (133) Steene, E.; Wondimagegn, T.; Ghosh, A. *J. Phys. Chem. B* **2001**, *105*, 11406-11413.
- (134) Ye, S.; Tuttle, T.; Bill, E.; Simkhovich, L.; Gross, Z.; Thiel, W.; Neese, F. *Chem. Eur. J.* **2008**, *14*, 10839-10851.
- (135) de Visser, S. P.; Ogliaro, F.; Gross, Z.; Shaik, S. *Chem. Eur. J.* **2001**, *7*, 4954-4960.

- (136) Latifi, R.; Valentine, J. S.; Nam, W.; de Visser, S. P. *Chem. Commun.* **2012**, 48, 3491-3493.
- (137) Steene, E.; Wondimagegn, T.; Ghosh, A. *J. Inorg. Biochem.* **2002**, 88, 113-118.
- (138) Alemayehu, A.; Conradie, J.; Ghosh, A. *Eur. J. Inorg. Chem.* **2011**, 1857-1864.
- (139) Reith, L. M.; Himmelsbach, M.; Schoefberger, W.; Knör, G. *J. Photochem. Photobiol. A: Chem.* **2011**, 218, 247-253.
- (140) Stefanelli, M.; Pomarico, G.; Tortora, L.; Nardis, S.; Fronczek, F. R.; McCandless, G. T.; Smith, K. M.; Manowong, M.; Fang, Y.; Chen, P.; Kadish, K. M.; Rosa, A.; Ricciardi, G.; Paolesse, R. *Inorg. Chem.* **2012**, 51, 6928-6942.
- (141) Wasbotten, I. H.; Wondimagegn, T.; Ghosh, A. *J. Am. Chem. Soc.* **2002**, 124, 8104-8116.
- (142) Yang, Y.; Jones, D.; von Haimberger, T.; Linke, M.; Wagnert, L.; Berg, A.; Levanon, H.; Zacarias, A.; Mahammed, A.; Gross, Z.; Heyne, K. *J. Phys. Chem. A* **2012**, 116, 1023-1029.
- (143) Ziegler, C. J.; Sabin, J. R.; Geier III, G. R.; Nemykin, V. N. *Chem. Commun.* **2012**, 48, 4743-4745.
- (144) Bader, R. F. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, U.K., 1990.
- (145) Bader, R. F. W. *Acc. Chem. Res.* **1985**, 18, 9-15.
- (146) Espinosa, E.; Alkorta, I.; Elguero, J.; Molins, E. *J. Phys. Chem.* **2002**, 117, 5529-5542.
- (147) Becke, A. D. *Phys. Rev. A* **1988**, 38, 3098-3100.
- (148) Perdew, J. P. *Phys. Rev. B* **1986**, 33, 8822-8824.
- (149) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, 97, 2571-2577.
- (150) Schaefer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, 100, 5829-5235.
- (151) Jensen, K. P.; Ryde, U. *Coord. Chem. Rev.* **2009**, 253, 769-778.
- (152) Yanai, T.; Tew, D. P.; Handy, N. C. *Chem. Phys. Lett.* **2004**, 393, 51-57.
- (153) Biegler-König, F. W.; Schönbohm, J.; Bayles, D.; *AIM2000*, 1 ed. <http://www.gauss.fh-bielefeld.de/aim2000>.
- (154) Keith, T. A.; *AIMAll*, 08.05.04 ed. <http://aim.tkgristmill.com>, 2008.
- (155) Espinosa, E.; Molins, E.; Lecomte, C. *Chem. Phys. Lett.* **1998**, 285, 170-173.
- (156) Jackson, W. G.; Jurisson, S. S.; McGregor, B. C. *Inorg. Chem.* **1985**, 24, 1788-1790.

- (157) Knapton, L., PhD Thesis, University of the Witwatersrand, 2005.
- (158) Hill, H. A. O.; Pratt, J. M.; Williams, R. J. P. *Chem. Br.* **1969**, 5, 156-161.
- (159) Thusius, D. *J. Am. Chem. Soc.* **1971**, 93, 2629-2635.
- (160) Balt, S.; De Bolster, M. W. G.; Van Herk, A. M. *Inorg. Chim. Acta* **1987**, 137, 167-171.
- (161) Ablov, A. V. *Coord. Chem. Rev.* **1975**, 17, 253-279.
- (162) Balt, S.; Van Herk, A. M. *Inorg. Chim. Acta* **1986**, 125, 27-30.
- (163) Balt, S.; Van Herk, A. M. *J. Chem. Soc., Faraday Trans. 1* **1986**, 82, 3331-3341.
- (164) Langford, C. H.; Gray, H. B. *Ligand Substitution Processes*; W. A. Benjamin, Inc.: New York, 1965.
- (165) Hasinoff, B. B. *Can. J. Chem.* **1974**, 52, 910-914.
- (166) Biswas, A. N.; Das, P.; Agarwala, A.; Bandyopadhyay, D.; Bandyopadhyay, P. *J. Mol. Cat. A: Chem.* **2012**, 326, 94-98.
- (167) Bose, S.; Pariyar, A.; Biswas, A. N.; Das, P.; Bandyopadhyay, P. *Cat. Commun.* **2011**, 12, 1193-1197.
- (168) McGown, A. J.; Kerber, W. D.; Fujii, H.; Goldberg, D. P. *J. Am. Chem. Soc.* **2009**, 131, 8040-8048.
- (169) Zdilla, M.; Dexheimer, J. L.; Abu-Omar, M. M. *J. Am. Chem. Soc.* **2007**, 129, 11505-11511.
- (170) Zdilla, M.; Abu-Omar, M. M. *Inorg. Chem.* **2008**, 47, 10718-10722.
- (171) Golubkov, G.; Gross, Z. *J. Am. Chem. Soc.* **2005**, 127, 3258-3259.
- (172) Okun, Z.; Gross, Z. *Inorg. Chem.* **2012**, 51, 8083-8090.
- (173) Joseph, C. A.; Lee, M. S.; Iretskii, A. V.; Wu, G.; Ford, P. C. *Inorg. Chem.* **2006**, 45, 2075-2082.
- (174) Harvey, R. A. *Anal. Biochem.* **1969**, 29, 58-67.
- (175) Balny, C.; Travers, F.; Barman, T.; Douzou, P. *Proc. Natl. Acad. Sci. USA* **1985**, 82, 7495-7499.
- (176) Bennetto, H. P.; Caldin, E. F. *J. Chem. Soc. (A)* **1971**, 2198-2207.

Part 5

Conclusions and future prospects

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5.1 Overview

The nature of the equatorial macrocyclic ligand of vitamin B₁₂ affects the chemistry of the normally inert d⁶ cobalt(III) metal ion. One consequence of this is that the ligand substitution reactions of aquacobalamin (vitamin B_{12a}) are fast.

Evidence in favour of this hypothesis indicates that a decrease in the electron density of the corrin ring through either the disruption of the corrin's delocalised system^{1,2} or the introduction of an electron withdrawing substituent on the corrin ring³ led to relative deactivation of the metal centre towards substitution, with a decrease in the stability constants of the binding of ligands and a decrease in the associated reaction rates observed. On the other hand, an increase in the electron density on the macrocycle as a result of the introduction of an electron donating substituent^{4,5} resulted in the more favourable binding of anionic ligands when compared to aquacobalamin, while the binding of neutral *N*-donor ligands was less favourable. It is clear that perturbation of the electron density of the corrin ring influences the ligand substitution reaction of the coordinated cobalt ion.

In the present study the electron density of the macrocycle was increased further with the use of a fully aromatic macrocycle, the corrole ring, in a system mimicking the structure of vitamin B₁₂.

5.2 The synthesis of a biomimetic macrocycle

The feasibility of corrole synthesis was established with the synthesis of several corroles, of both the A₃ and A₂B type, using Gryko and Koszarna's methanol:water method.⁶ The introduction of a bulky *meso* amide substituent was achieved with the synthesis of 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole with no effect on the stability of the system.

The design of the biomimetic model incorporated a substituent that might act as an axial ligand (Figure 5.1.1) for the coordinated metal as well as water solubilising groups. The axial ligand, or tail substituent was designed using molecular mechanics modelling with the HyperChem suite of programs⁷ and a protected glucose based water solubilising system⁸ was investigated.

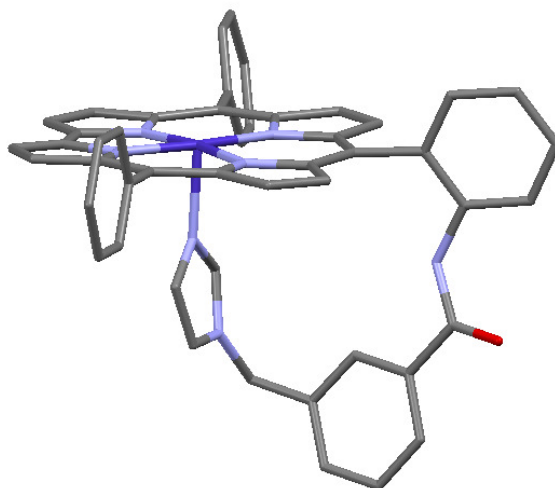
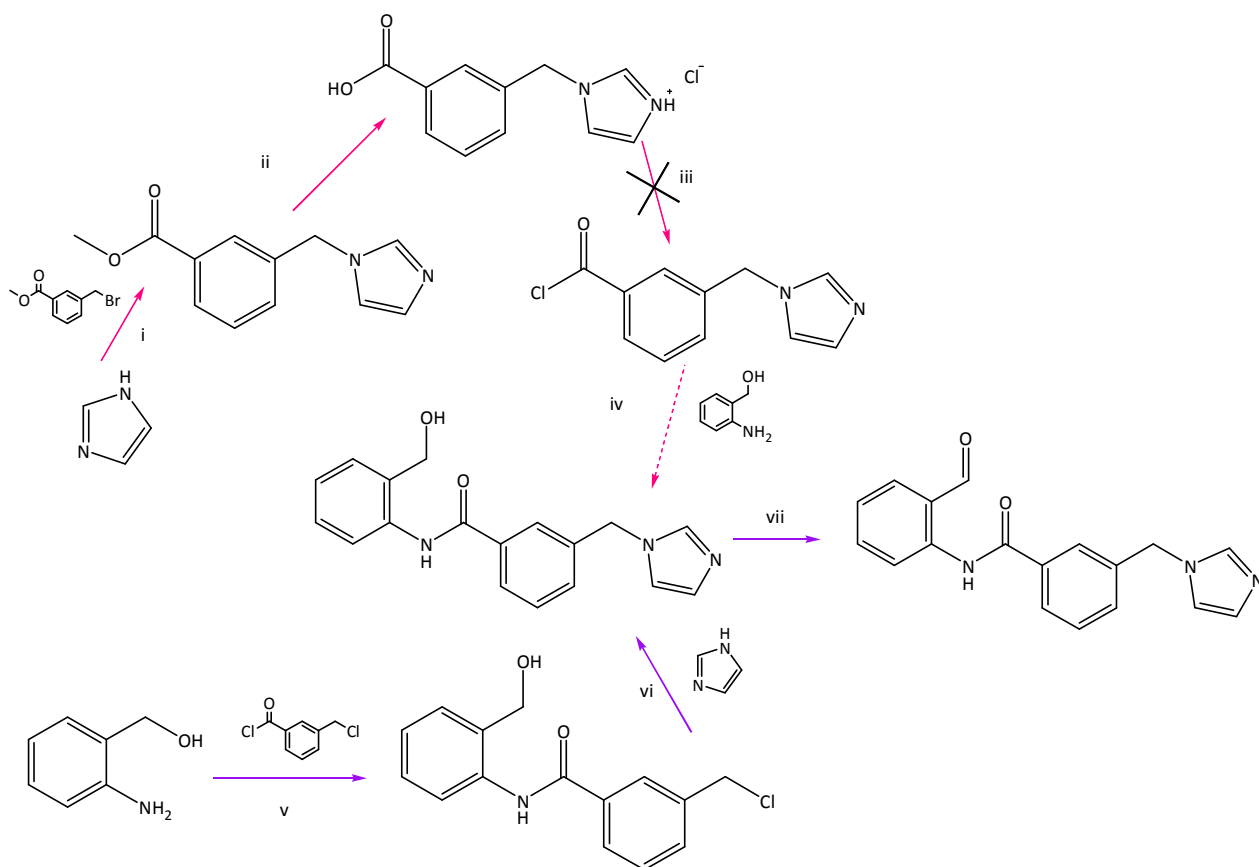


Figure 5.1.1 A biomimetic model of vitamin B₁₂: [10-(2-[[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrolato]cobalt(III), referred to as DPTC-Co in this work

Collman's synthesis of an imidazole-containing acid chloride⁹ was unsuccessful and led to a revision of the proposed synthetic route for the tail substituent (Scheme 5.1.1). Intermediates of this tail substituent as well as intermediates of the shorter tail corrole, 10-[2-(benzoylamino)phenyl]-5,15-diphenylcorrole, were found to be polymorphic. Analysis of molecule...molecule interactions and quantification of the weak interactions in the crystal lattice indicated that packing polymorphism arose primarily from differences in the weak dispersion forces as opposed to differences in hydrogen bonding.



Scheme 5.1.1 Synthesis of the tailed aldehyde. The pink pathway represents the use of Collman's synthesis of an imidazole containing acid chloride. This route was unsuccessful. The purple pathway illustrates the alternative synthesis using 3-(chloromethyl)benzoyl chloride. i) DMF, 8hrs; ii) HCl (32%), reflux, 2 hrs; iii) CH₃CN (dry, degassed), oxalyl chloride refluxed, 1 hr; iv) CH₂Cl₂ (dry), triethylamine, 0°C, 10 min, then room temperature, 2 hrs; v) CH₂Cl₂ (dry), triethylamine, 0°C, 10 min, then room temperature; vi) 2 hrs; DMF, 8hrs; vii) MnO₂, CHCl₃, 20 hrs.

Two sugar-bearing corroles were successfully synthesised. Deprotection of the glucose groups by removal of the acetyl protecting groups of 10-phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole, a corrole bearing two glucose substituents at the 5 and 15 positions, yielded a water soluble corrole. Deprotection of the protected glucose groups in 10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole, a more complex structure with two glucose substituents at the 5 and 15 positions, and the biomimetic tail at the 10 position, yielded a corrole soluble in aqueous solution below pH 4 only. In light of this significant limitation, the biomimetic model used throughout the rest of this work, [10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrolato]-cobalt(III), referred to as DPTC-Co, did not bear the glucose moieties.

5.3 A comparison of the reactions of vitamin B_{12a} and the biomimetic system

Reactions of vitamin B_{12a} and the biomimetic model were studied in 80:20 methanol:water due to the insolubility of the model in aqueous solutions.

The pK_a of vitamin B_{12a} was determined in both aqueous and 80:20 methanol:water solvent systems at similarly low ionic strength. The value was found to be highly dependent on the ionic strength of the medium (reported values vary from 7.6 ($\mu = 0.054$ M)¹⁰ to 8.1 ($\mu = 1.0$ M)¹¹) and less dependent on the identity of the solvent (aqueous - 7.462 ± 0.007 ; methanol:water - 7.40 ± 0.02 ($\mu = 0.8$ mM)). The pK_a for the aqua/hydroxo equilibrium as well as an equilibrium attributed to the base-on/base-off equilibrium were observed for DPTC-Co at 9.76 ± 0.06 and 6.7 ± 0.2 ($\mu = 0.8$ mM), respectively.

The stability constants for the binding of several ligands to Co(III) in both vitamin B_{12a} and DPTC-Co were determined. Vitamin B_{12a} formed more stable complexes with anionic ligands than DPTC-Co, while the opposite was true for the binding of neutral ligands. An increase in the electron density of the coordination environment thus affects the chemistry of the cobalt metal. This suggests that cobalt in DPTC-Co is softer in character than in vitamin B_{12a}, favouring softer ligands over harder anionic ligands. Analysis of the DPTC-Co system using Bader's quantum theory of atoms in molecules, QTAIM, indicated that the cobalt-ligand bond was more ionic in character in the case of anionic ligand complexes and more covalent in character in the case of neutral ligand complexes. In addition, an increase in cobalt ligand bond length was accompanied by a decrease in the experimentally determined stability constant for the small sample of ligands used QTAIM analysis.

The coordination of cyanide to vitamin B_{12a} occurred at a faster rate than to DPTC-Co. While the reaction with vitamin B_{12a} is entropically driven, enthalpically it is unfavourable. The reaction between DPTC-Co and cyanide, on the other hand is entropically favourable

and enthalpically more favourable than in the case of vitamin B_{12a}. These findings suggest that cobalt(III) in DPTC-Co is electronically more labile than in vitamin B_{12a}.

These findings suggest that the coordination environment of vitamin B_{12a} does indeed affect the chemistry of substitution reactions on cobalt. An increase in the electron density of the coordinating macrocycle appears to result in a softer, more electron rich metal which is enthalpically more labile than in vitamin B_{12a}.

5.4 Future prospects

This study aimed to lay the foundation for an extensive study of corroles as biomimetic models of vitamin B₁₂. As such, there are almost limitless future prospects for this work.

From a synthetic point of view, the incorporation of a water solubilising substituent is of great importance. The solvent dependence of the thermodynamics and kinetics of the substitution reactions of vitamin B_{12a} observed in this work is significant. The study of a corrole biomimetic model in aqueous solution will allow for a more holistic comparison of the chemistry of vitamin B₁₂ and the model.

The significantly high pK_a of 6.7 ± 0.2 , for what is thought to be the equilibrium between the base-on and base-off DPTC-Co species, may indicate that the designed 'tail' substituent may not allow for optimal axial coordination to the cobalt ion. Determination of the crystal structure of DPTC-Co may have given us insight into the geometry of this coordination, but unfortunately, a crystal of diffraction quality could not be grown. This is a matter which will require attention in the future, with the possible design and synthesis of a different 'tail' substituent.

The thermodynamics of the substitution reactions of various ligands with DPTC-Co and vitamin B_{12a} was investigated. The use of a broad variety of ligands made it difficult to correlate the determined stability constants with physical data of the ligands, such as pK_a or Hammett constants. This work would benefit from the use of a series of related ligands, such as a range of pyridine or imidazole derivatives substituted with different electron-withdrawing or -donating functional groups. In addition, the study of the coordination of these ligands to DPTC-Co at various temperatures would allow for the determination of thermodynamic parameters such as ΔH and ΔS which would allow for a better understanding of the effect of the increased electron density of the *cis* macrocyclic ligand. However, this presupposes the successful synthesis of a water-soluble corrole as work with a predominantly methanol solution above 25°C is impractical.

TD-DFT and QTAIM analysis of both the biomimetic model and vitamin B₁₂ would allow for a comparison of these two systems. This may provide insights into the differences in the electronics of the two systems. Calculation of the charge density on cobalt in these two systems would also provide useful insight into the hypothesised *cis*-influence of the macrocyclic ligand on the coordinated metal.

The study of the kinetics of the binding of cyanide to DPTC-Co indicated that the reaction was entropically unfavourable. The effect on the activation parameters upon the binding of a neutral ligand may reveal more clues as to the mechanism involved. As mentioned earlier, the use of a purely aqueous solvent system may also affect the activation parameters significantly.

The corrole macrocycle has proved to be a good system for the study of the effect of the coordination environment on a coordinated cobalt ion. As Prof. Marques often reminds me, this is only part one! There are many more avenues to explore in this work, of which just a few have been mentioned.

5.5 References

- (1) Chemaly, S. M.; Florczak, M.; Dirr, H.; Marques, H. M. *Inorg. Chem.* **2011**, *50*, 8719-8727.
- (2) Chemaly, S. M.; Kendall, L.; Nowakowska, M.; Pon, D.; Perry, C. B.; Marques, H. M. *Inorg. Chem.* **2012**.
- (3) Marques, H. M.; Knapton, L.; Zou, X.; Brown, K. L. *J. Chem. Soc., Dalton Trans.* **2002**, 3195-3200.
- (4) Brown, K. L.; Cheng, S.; Zou, X.; Zubkowski, J. D.; Valente, E. J.; Knapton, L.; Marques, H. M. *Inorg. Chem.* **1997**, *36*, 3666-3675.
- (5) Knapton, L.; Marques, H. M. *Dalton Trans.* **2005**, 889-895.
- (6) Koszarna, B.; Gryko, D. T. *J. Org. Chem.* **2006**, *71*, 3707-3717.
- (7) HyperChem; 8.0.5 ed.; Hypercube Ltd.: Gainesville, FL, USA.
- (8) Riley, D. *Post Doctoral Report*, University of the Witwatersrand, 2010.
- (9) Collman, J. P.; Bröring, M.; Fu, L.; Rapt, M.; Schwenninger, R. *J. Org. Chem.* **1998**, *63*, 8084-8085.
- (10) Randall, W. C.; Alberty, R. A. *Biochem.* **1967**, *6*, 1520-1525.
- (11) Reenstra, W. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 5780-5791.

Appendix 1

Reagents

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A1.1	Reagents used in Part 2	344
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A1.1 Reagents used in Part 2

Reagents used in the syntheses described in Part 2 are listed in Table A1.1. Reagents were used as received unless otherwise stated. Solvents and their purification methods are listed in Table A1.2.

Table A1.1 Reagents used in Part 2

Reagent	Grade	Supplier
<i>Fine Chemicals</i>		
Glacial Acetic Acid	CP	N.T. Laboratory suppliers
Acetic anhydride	CP	Merck
2-Aminobenzyl alcohol	CP	Aldrich
2-Aminophenol	CP	Merck
Benzaldehyde	99.5%	Aldrich
Benzoyl chloride	CP (redistilled)	Sigma-Aldrich
Boron trifluoride diethyl etherate	CP	Sigma-Aldrich
1,1'-Carbonyldiimidazole (CDI)	CP	Aldrich
3-(Chloromethyl)benzoyl chloride	CP	Acros Organic
Dess-Martin periodinane (DMP)	97%	Aldrich
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)	98%	Aldrich
D-+-Glucose	CP	Sigma
Imidazole	CP	Merck
Methyl 3-(bromomethyl)benzoate	CP	Aldrich
4-Methyl imidazole	98%	Aldrich
<i>o</i> -Nitro benzaldehyde	98%	Aldrich
Oxalyl chloride	CP	Merck
<i>p</i> -Chloranil	99%	Aldrich
<i>p</i> -Methoxy benzaldehyde	CP	Merck
<i>p</i> -Nitro benzaldehyde	AR	British Drug Houses
Pyridine	99.8%	Aldrich

Table A1.1 continued

Pyridinium chlorochromate (PCC)	98%	Aldrich
Pyrrole	98%	Aldrich
Thionyl Chloride	CP	Merck
Triethylamine	UnivAR	SAARCHEM
Triphenylphosphine	98%	Merck
γ -Butyrolactone	AR	SMM Chemicals Pty Limited
Phenol	AR	Aldrich
<i>Inorganic Chemicals</i>		
Ammonium Chloride	UnivAR	SAARCHEM
Ammonium hydroxide	UnivAR	SAARCHEM
Cobalt (II) acetate	CP	Merck
Ferric chloride	UnivAR	SAARCHEM
33% Hydrobromic acid in glacial acetic acid	CP	Merck
Hydrochloric acid 32%	CP	ACE
Magnesium turnings	CP	Aldrich
Manganese (IV) oxide	85%	Sigma-Aldrich
Nitric acid 55%	CP	ACE
Pd/C	Unknown % Pd	
Potassium Carbonate (anhydrous)	CP	Glass World
$\text{SnCl}_2 \cdot \text{H}_2\text{O}$	CP	AnalaR
Sodium carbonate (anhydrous)	UnivAR	Merck
Sodium chloride	UnivAR	Merck
Sodium hydrogen carbonate	CP	Merck
Sodium hydroxide	UnivAR	Merck
Sulphuric acid	95%	Merck
Trifluoroacetic acid	CP	Sigma-Aldrich
Sodium Acetate	CP	Associated Chemical Enterprises cc.

Table A1.1 continued

<i>Purification, drying and gases</i>		
Silica for Flash Chromatography	230-400 mesh	Fluka Analytical
(silica gel 60)	ASTM	
Micro sieves	4 Å	Merck
Sodium sulphate	CP	ACE
Calcium Hydride	95%	Sigma-Aldrich
Sodium metal lumps	UnivAR	SAARCHEM
Celite 545	125.3 µm, 71%	Aldrich
Amberlite IR-4B(OH) resin	AG	BDH Laboratory Reagents
Argon	UP	Afrox
Hydrogen	UP	Afrox
Nitrogen	UP	Afrox

Table A1.2 Solvents used in this work

Solvent	Grade	Supplier
Acetone	CP	Promark Chemicals
Acetonitrile	HPLC	Merck
Chloroform	Univ AR	Merck
Chloroform -d	99.8 atom % D	Sigma-Aldrich
Dimethyl Sulfoxide -d6	99.5 atom % D	Sigma-Aldrich
Methanol - d	99.8 atom % D	Sigma-Aldrich
Dichloromethane	CP	Sigma-Aldrich
Dichloromethane	HPLC	Sigma-Aldrich
Diethyl ether	CP	Merck
Dimethyl formamide	Univ AR	SAARCHM
Ethanol	Absolute	Sigma-Aldrich
Ethyl Acetate	98% UniLAB	Merck
Hexane	99%	Sigma-Aldrich
Hexane	HPLC	Sigma-Aldrich
Methanol	CP	Sigma-Aldrich
Methanol	HPLC	Sigma-Aldrich
1-Propanol	99%	Pro Analysis
2-Propanol	CP	Merck
Tetrahydrofuran	98%	Merck
Toluene	99%	ACE

A1.2 Reagents used in Part 4

Reagents used in the solution and inorganic chemistry described in Part 4 are listed in Table A1.3. Reagents were used as received unless otherwise stated. The buffers used in this work are listed in Table A1.4.

Table A1.3 Reagents used in Part 4

Reagent	Grade	Supplier
L-Ascorbic acid	CP	Sigma-Aldrich
Chlorohydrate dihydroxocobalamin	CP	Roussel Uclaf
L-Cysteine	CP, 97%	Aldrich
4-Dimethylaminopyridine	Reagent plus	Aldrich
Ethanolamine	CP	Aldrich
Hydroxocobalamin acetate	CP	Roussel Uclaf
Methanol	HPLC	Sigma-Aldrich
N-Methylimidazole	CP	Sigma-Aldrich
Orthophosphoric acid	CP	Aldrich
Pyridine	99.8%	Aldrich
Sodium azide	CP	Riedel-De Haën
Sodium cyanide	CP	Merck
Sodium dithionite	CP	BDH Chemicals
Sodium hydroxide	UnivAR	Merck
Sodium iodide	Unilab	SAAR CHEM
Sodium nitrite	UnivAR	SAAR CHEM
Sodium thiocyanate	CP	Riedel-De Haën
Thiophene	CP	Fluka
Thiourea	CP	Merck
Trimethylphosphite	CP	Sigma-Aldrich

Table A1.4 Buffers used in this study

Buffer	Supplier		pK _a (25°C)	Suitable buffering range
CAPS	Sigma		10.40	9.7-11.1
CHES	Sigma		9.50	8.6-10.0
HEPES	Sigma		7.48	6.8-8.2
MES	Sigma		6.10	5.5-6.7
MOPS	Sigma		7.14	6.5-7.9
Sodium Acetate	Associated Chemical Enterprises cc.		4.76	3.6-5.6
TRIS	Merck		8.06	7.5-9.0

Appendix for Part 2

Synthesis of a corrole-based biomimetic model

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A2.1	Selected NMR and FTIR spectra	351
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A2.3	New AMBER atom types	378
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A2.1 Selected NMR and FTIR spectra

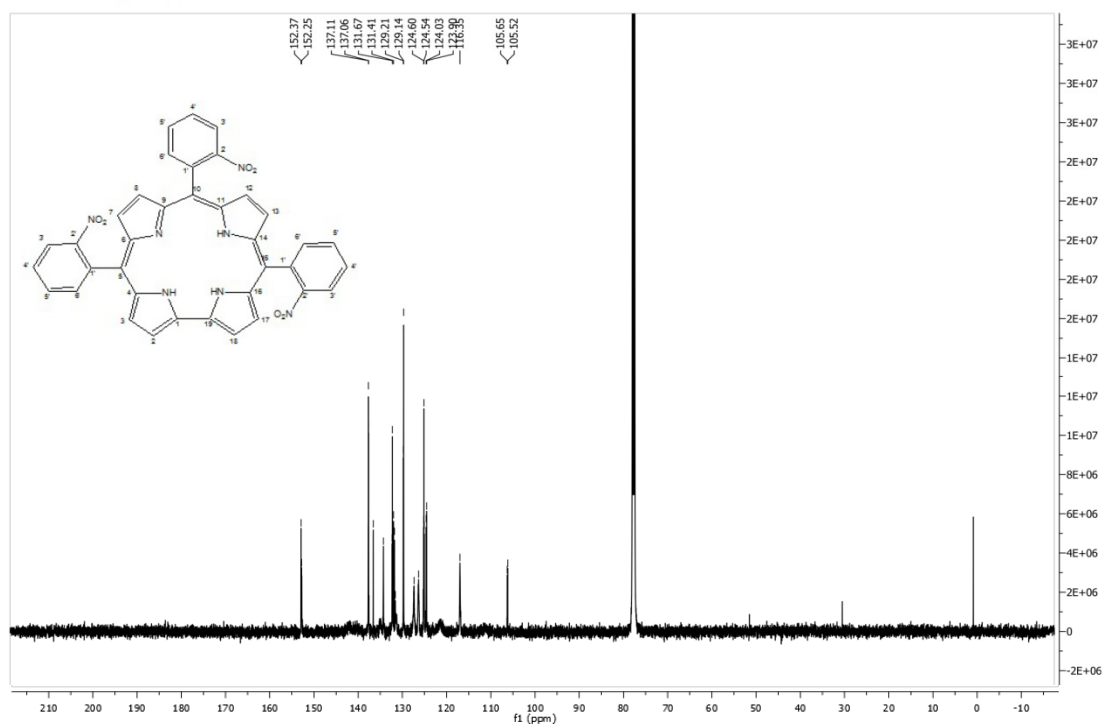
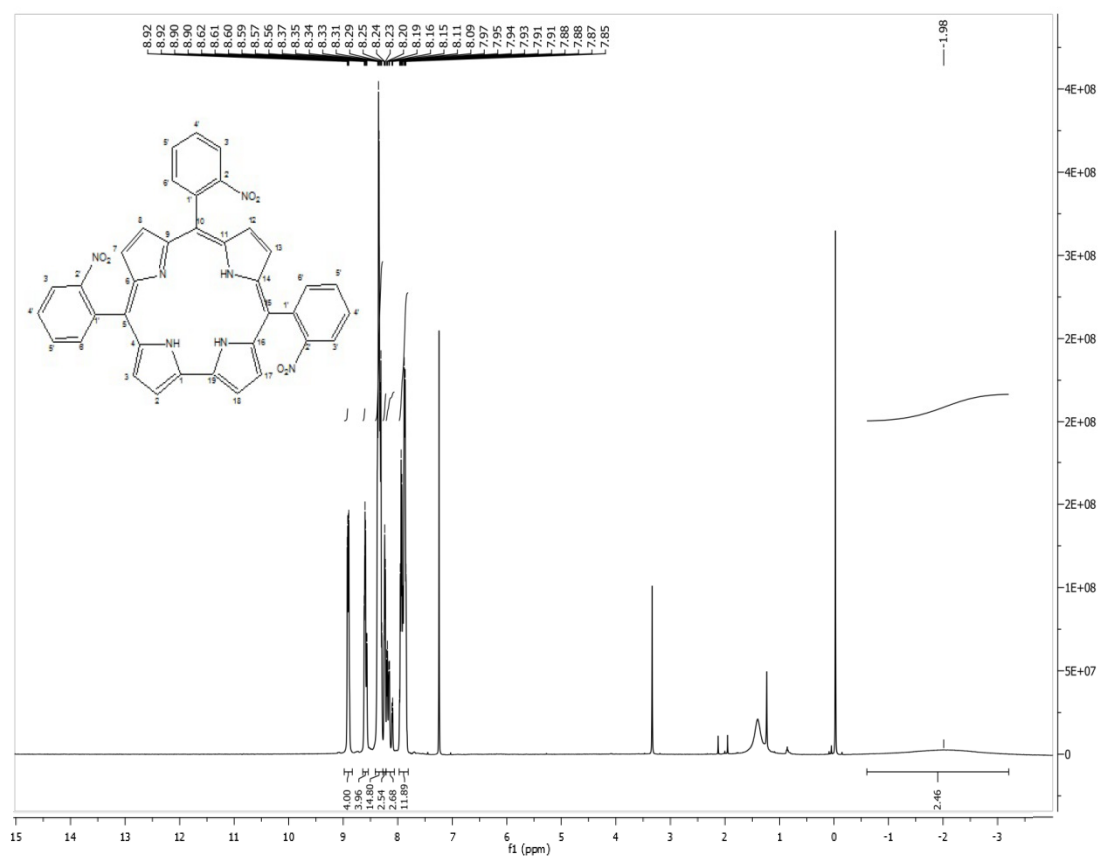
Proton and carbon NMR spectra are given for the following compounds:

- 5,10,15-Tri(*o*-nitrophenyl)corrole
- *N*-[2-(Hydroxymethyl)phenyl]benzamide
- *N*-(2-Formylphenyl)benzamide
- 10-[2-(Benzoyl(amino)phenyl)-5,15-diphenylcorrole
- 3-(Chloromethyl)-*N*-[2-(hydroxymethyl)phenyl] benzamide
- *N*-[2-(Hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide
- *N*-(2-Formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide
- 10-(2-{[4-(1*H*-Imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrole
- [10-(2-{[4-(1*H*-Imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15diphenyl-corrolato]cobalt(III)
- 4-Formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside
- 4-[Di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside
- 10-Phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole
- 10-(2-{[4-(1*H*-Imidazol-1-ylmethyl)- benzoyl]amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole

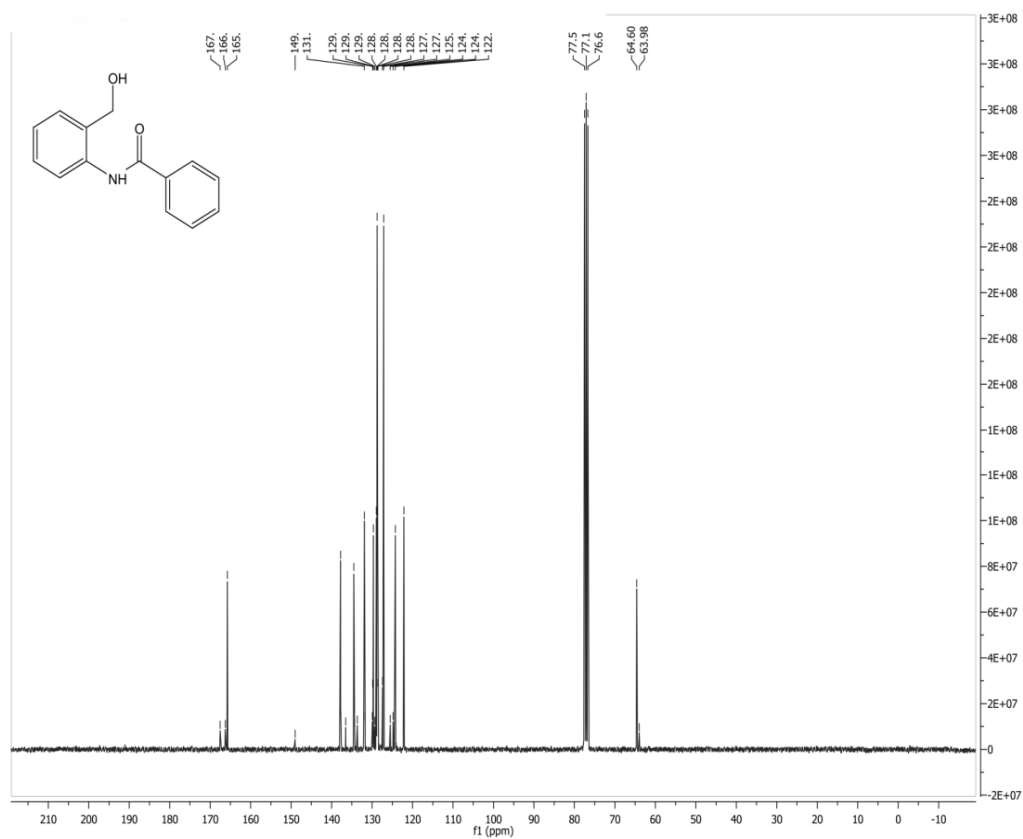
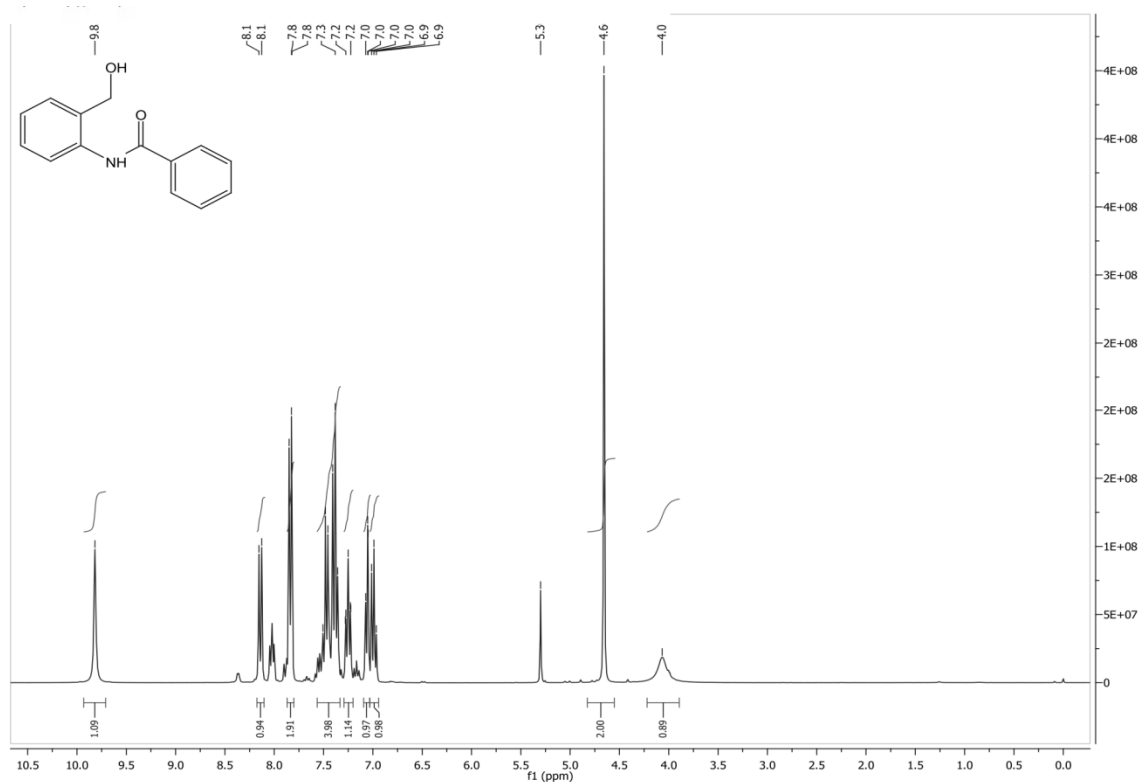
FTIR spectra are given for the following compounds:

- 1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose
- 2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranosyl bromide
- 4-Formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

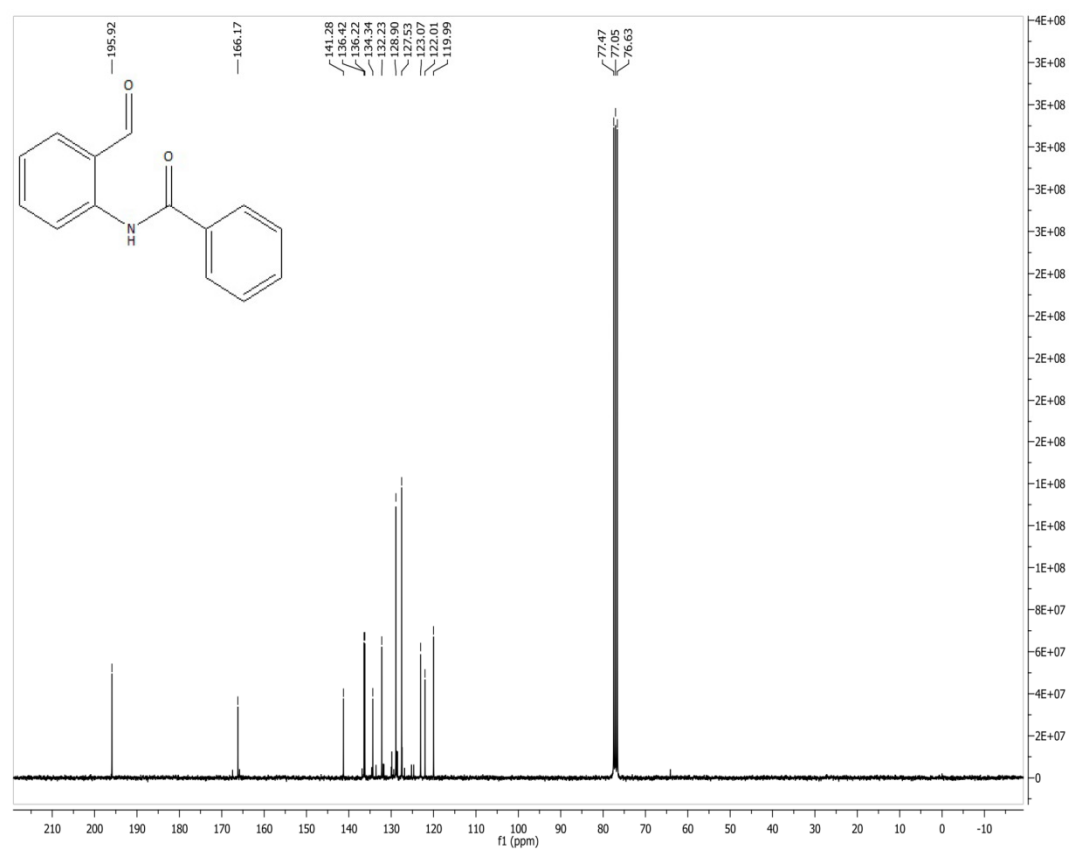
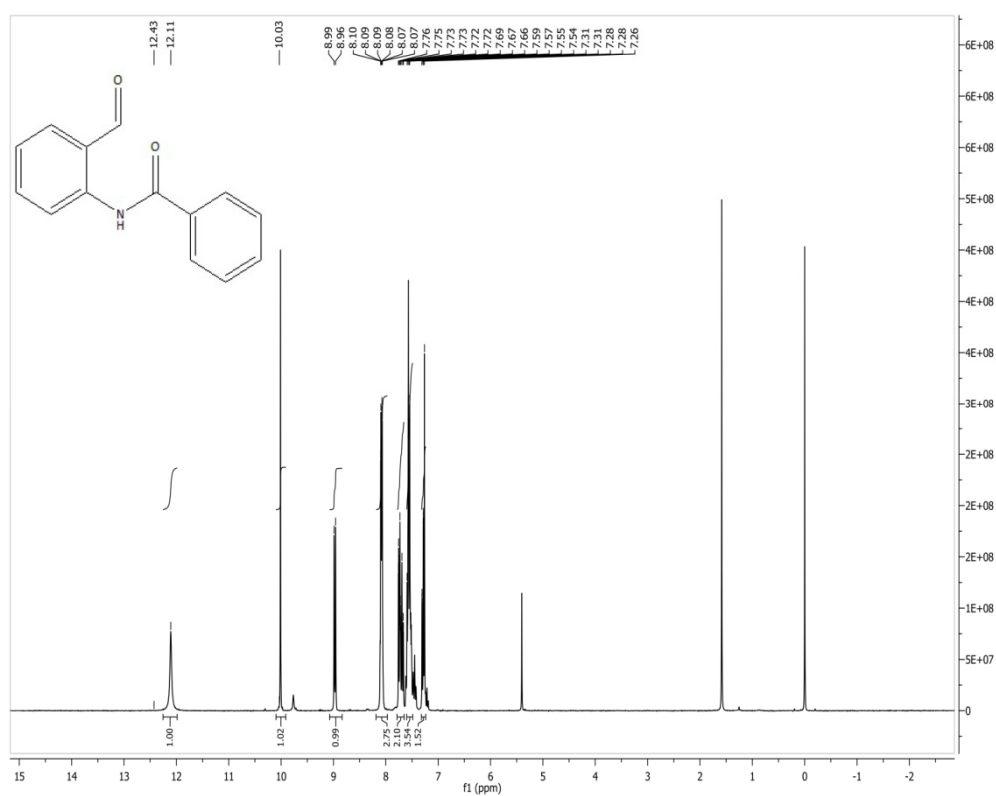
5,10,15-Tri(*o*-nitrophenyl) corrole



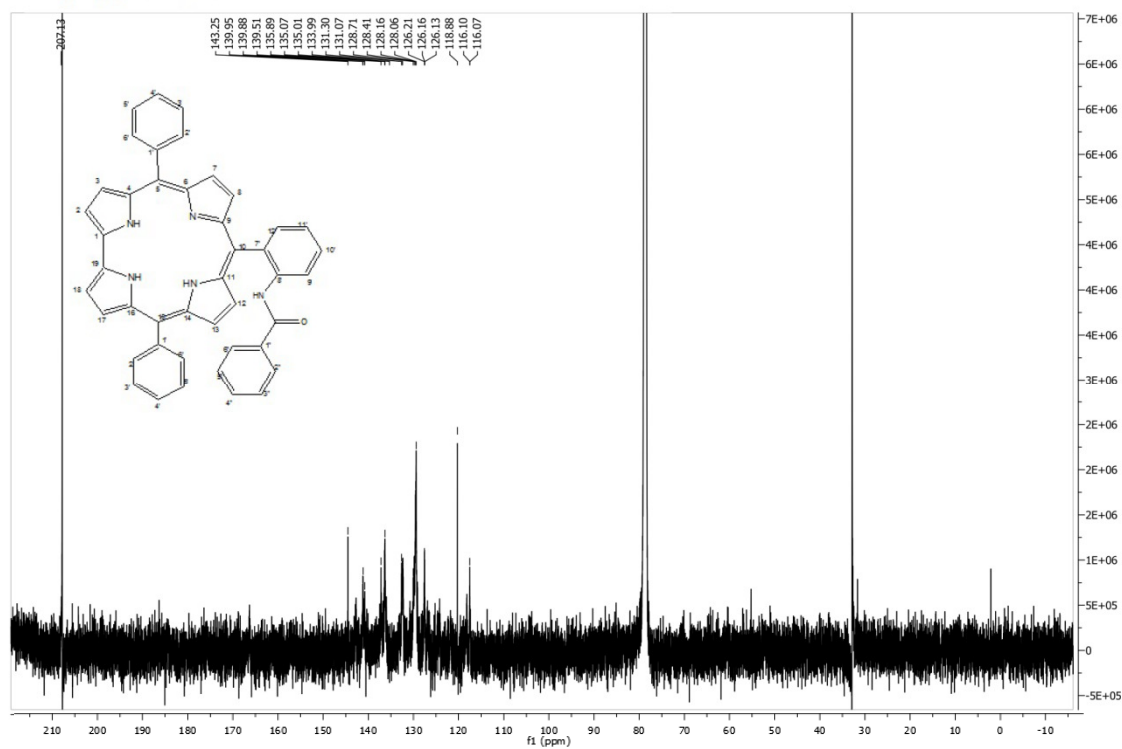
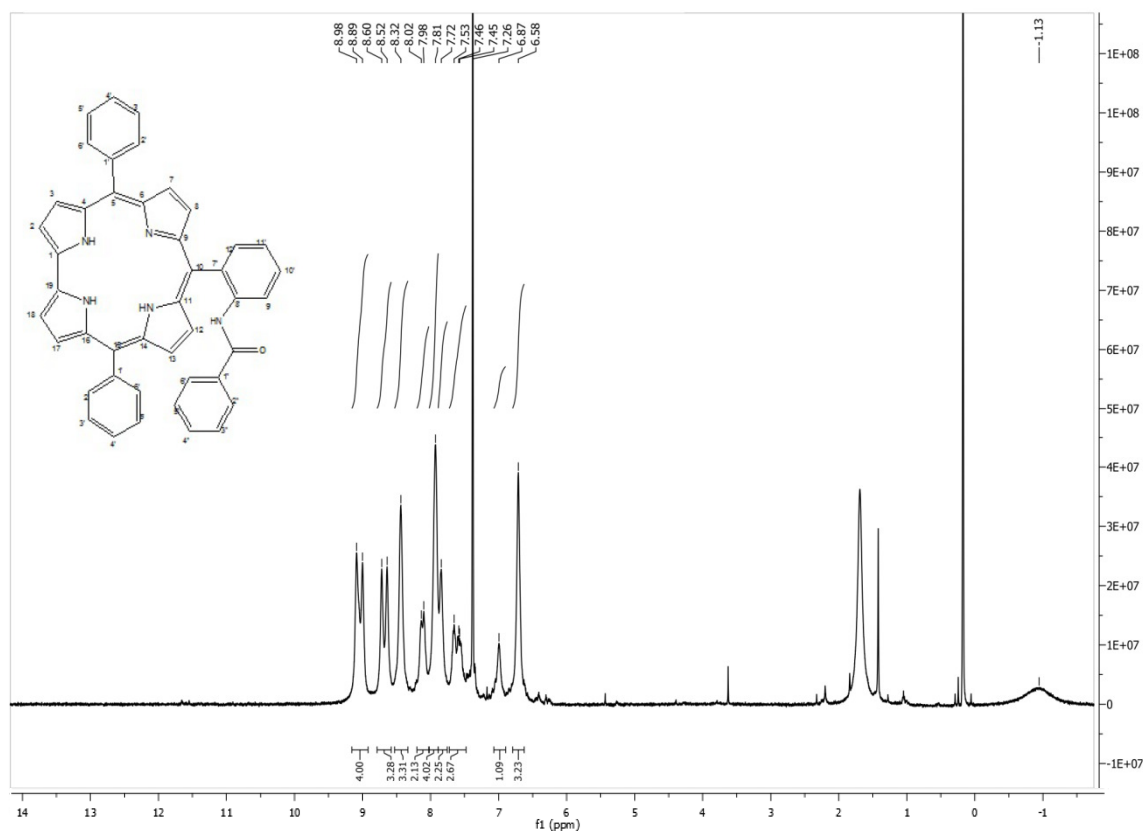
N-[2-(Hydroxymethyl)phenyl]benzamide

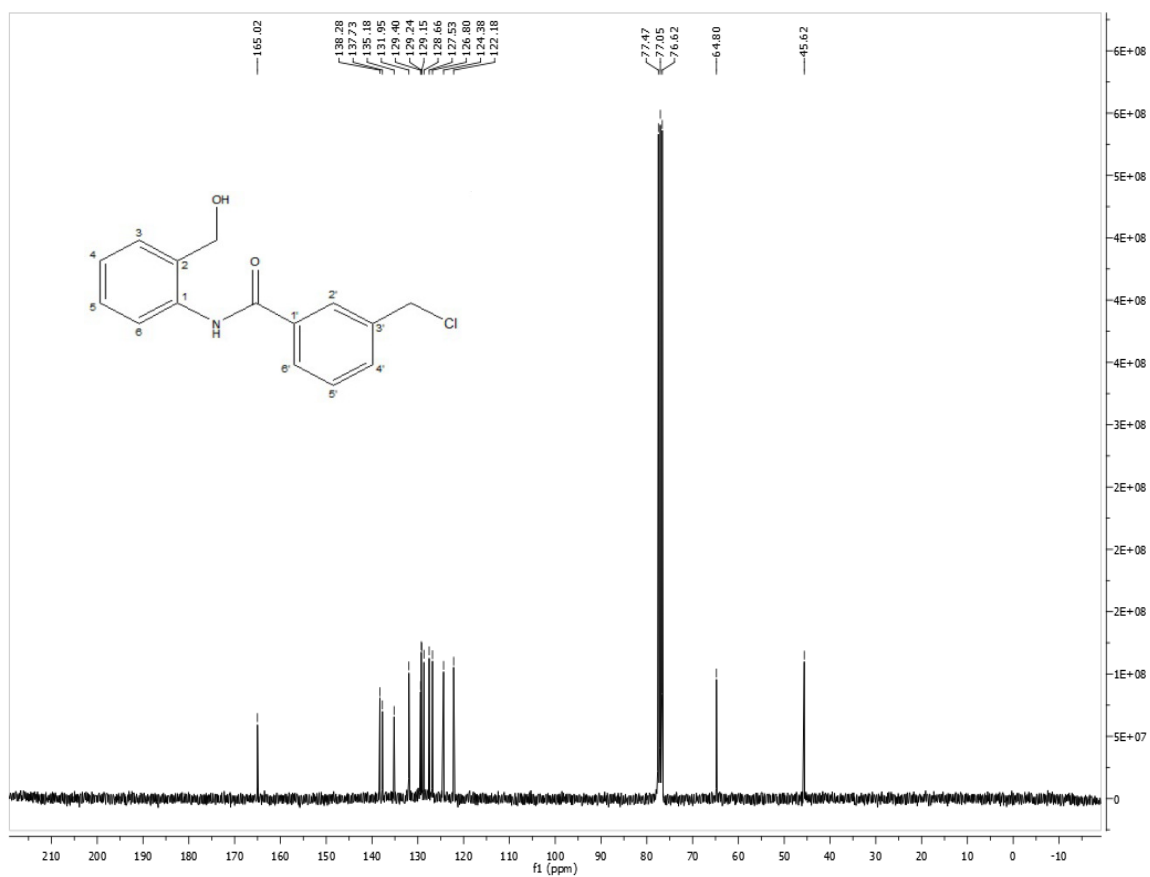
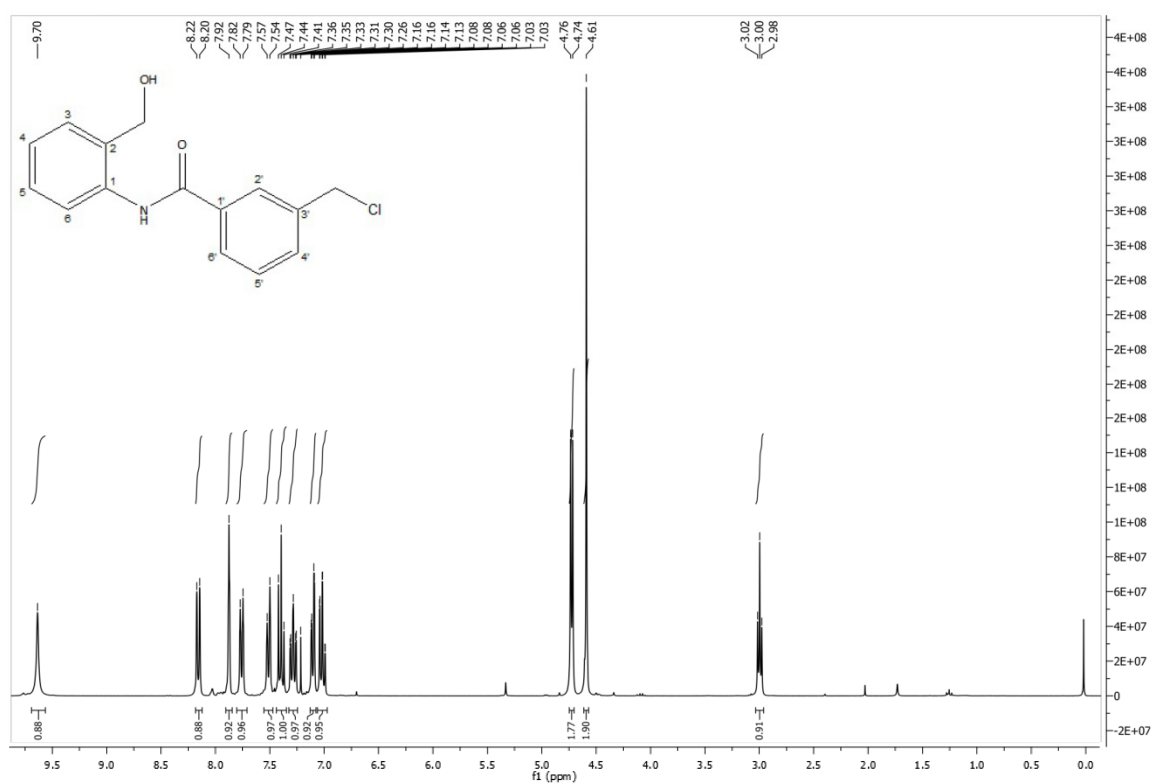


N-[2-Formylphenyl]benzamide

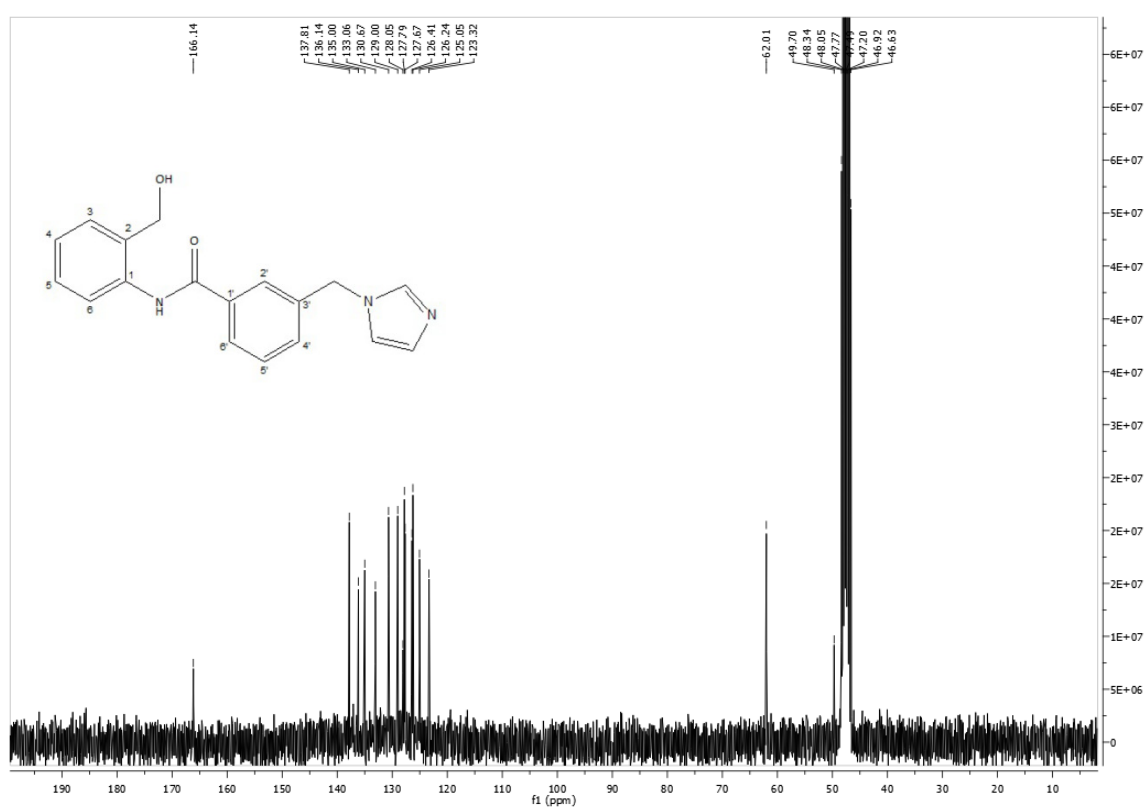
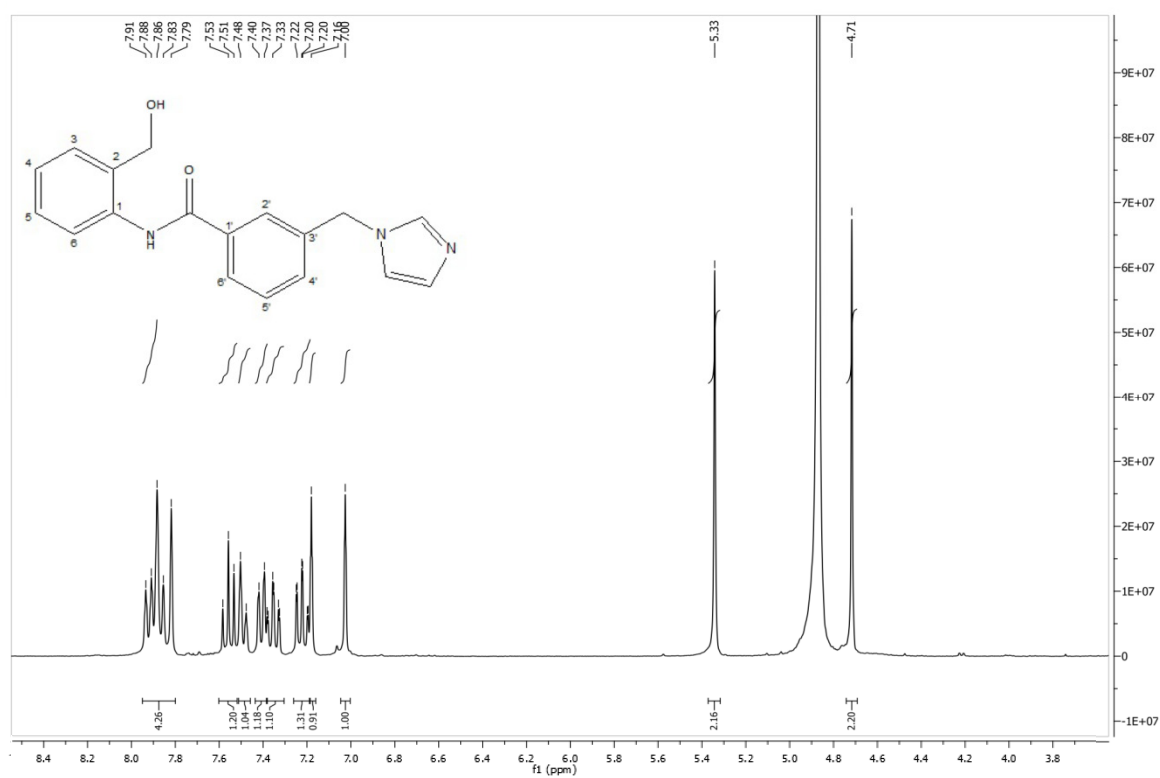


10-[2-(Benzoyl(amino)phenyl)-5,15-diphenylcorrole]

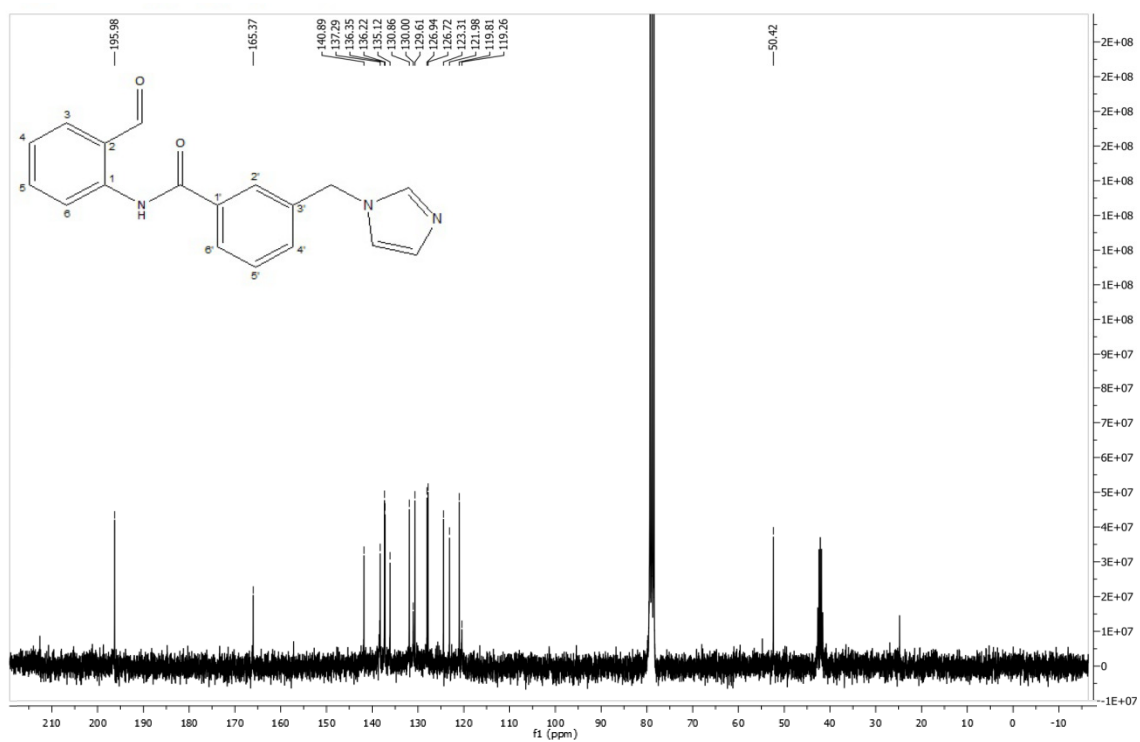
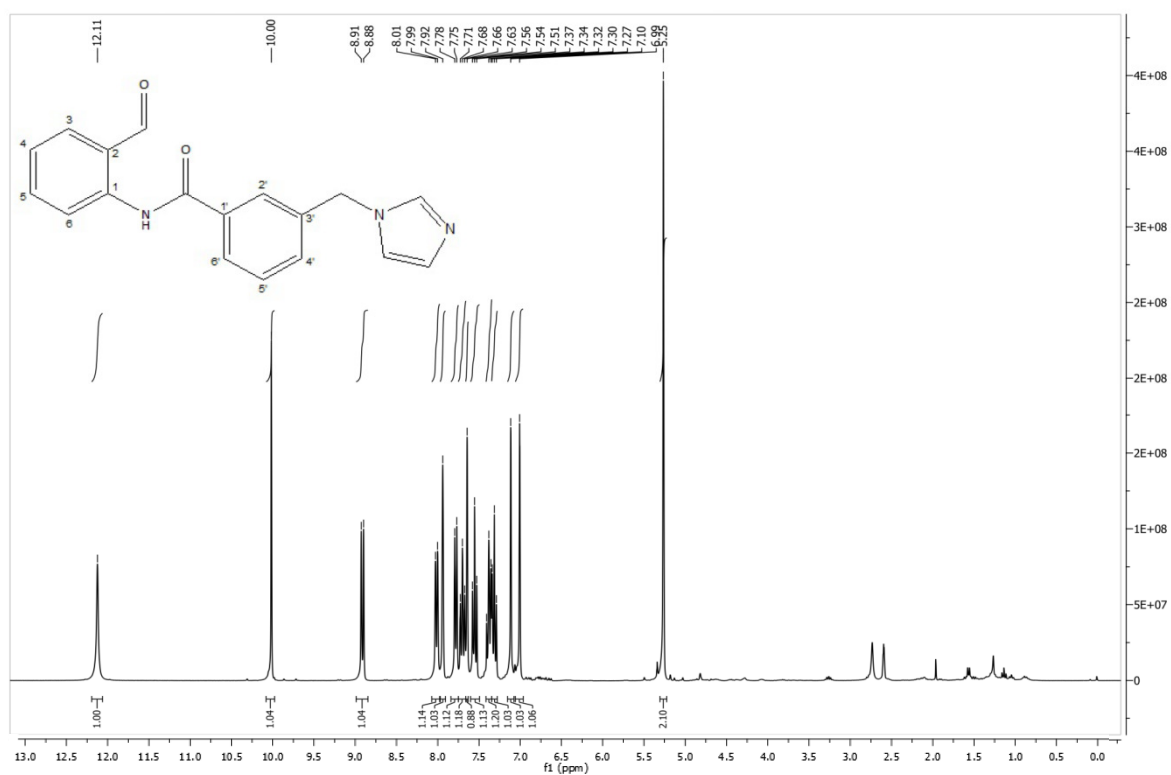




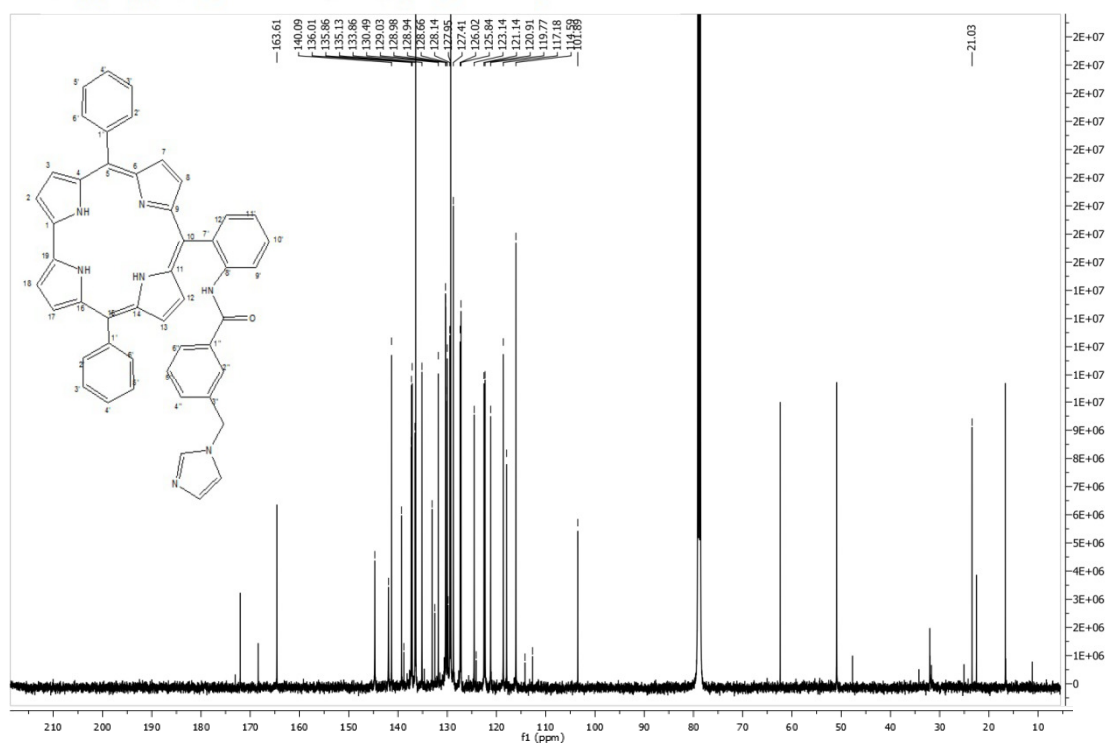
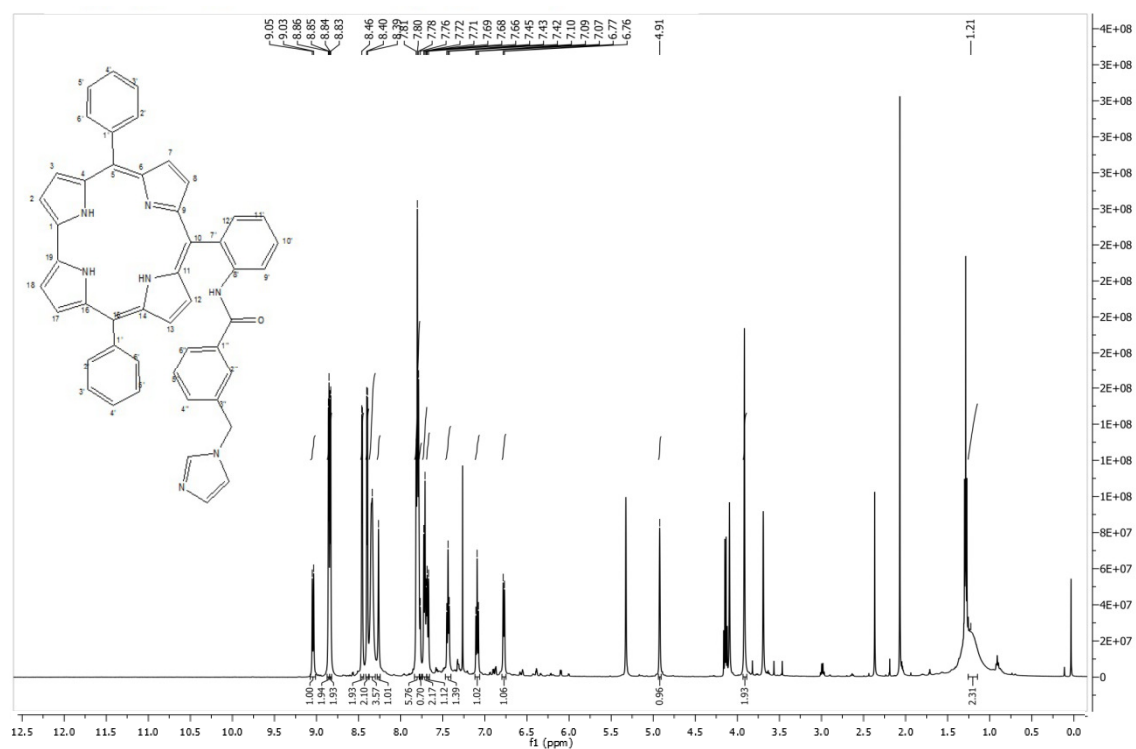
N-[2-(Hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide



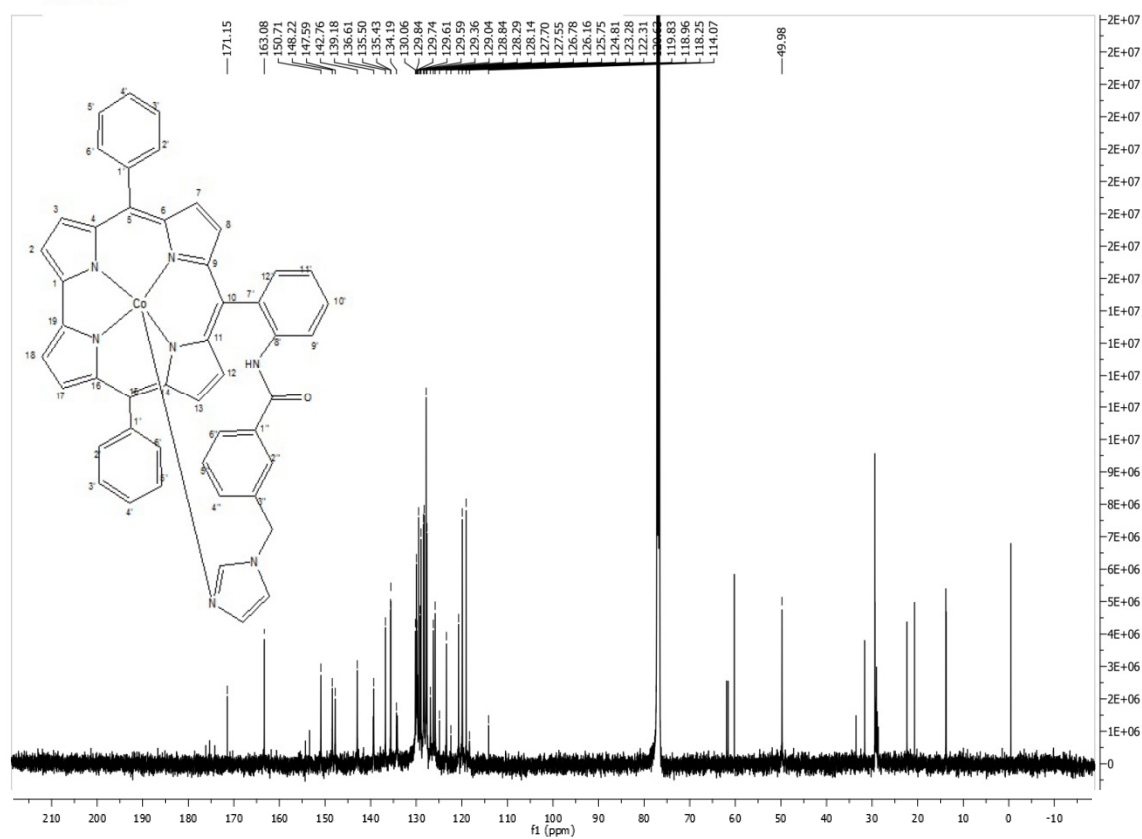
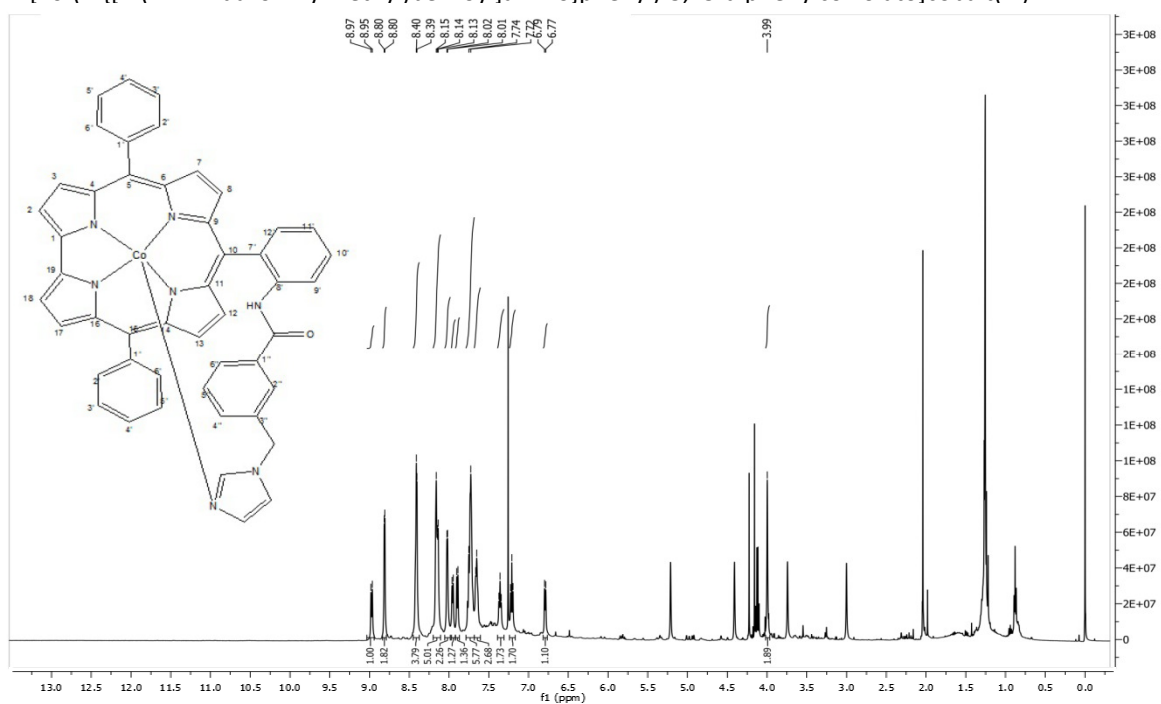
N-[2-Formylphenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide



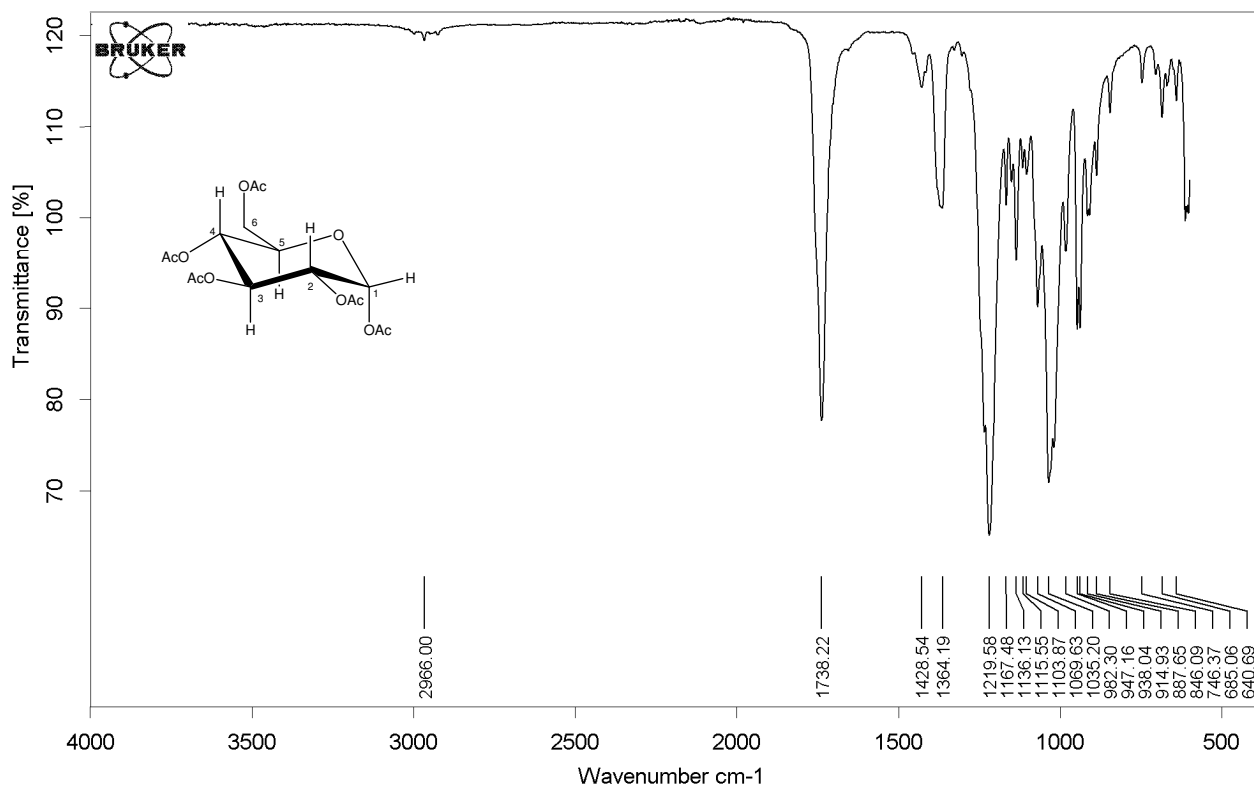
10-(2-[[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino]phenyl)-5,15-diphenylcorrole



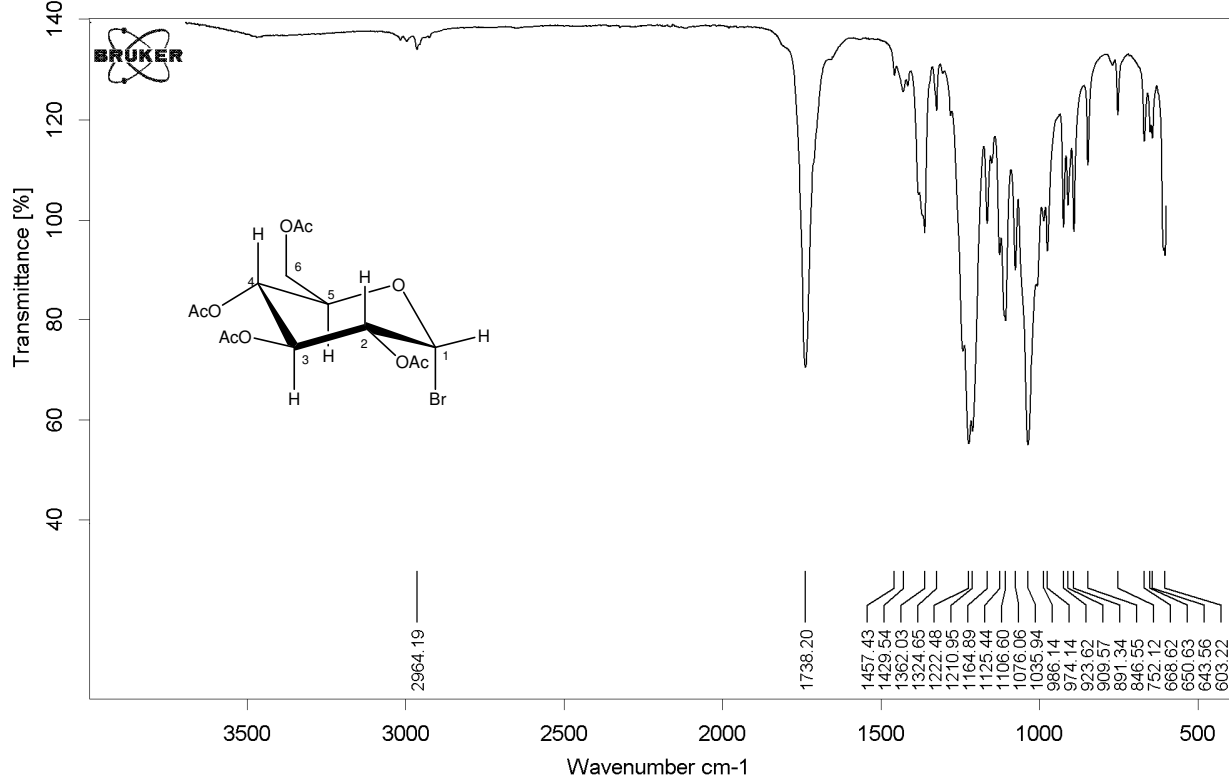
[10-(2-{[4-(1*H*-imidazol-1-ylmethyl)benzoyl]amino}phenyl)-5,15-diphenylcorrolato]cobalt(III)



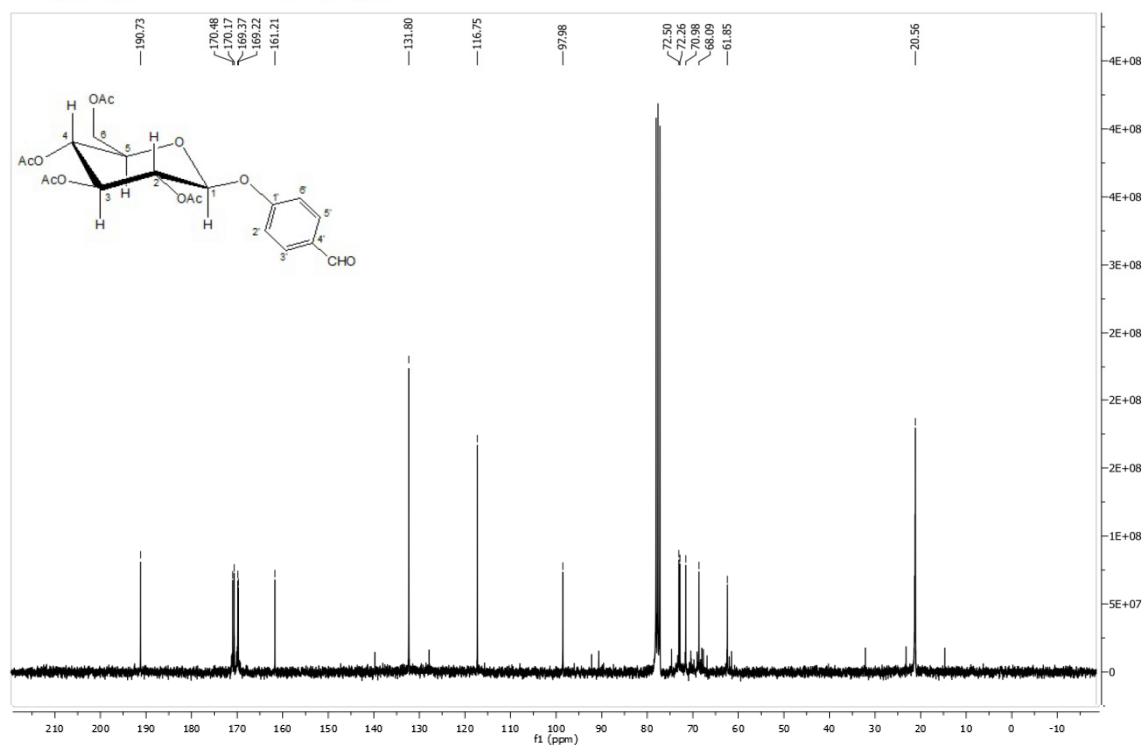
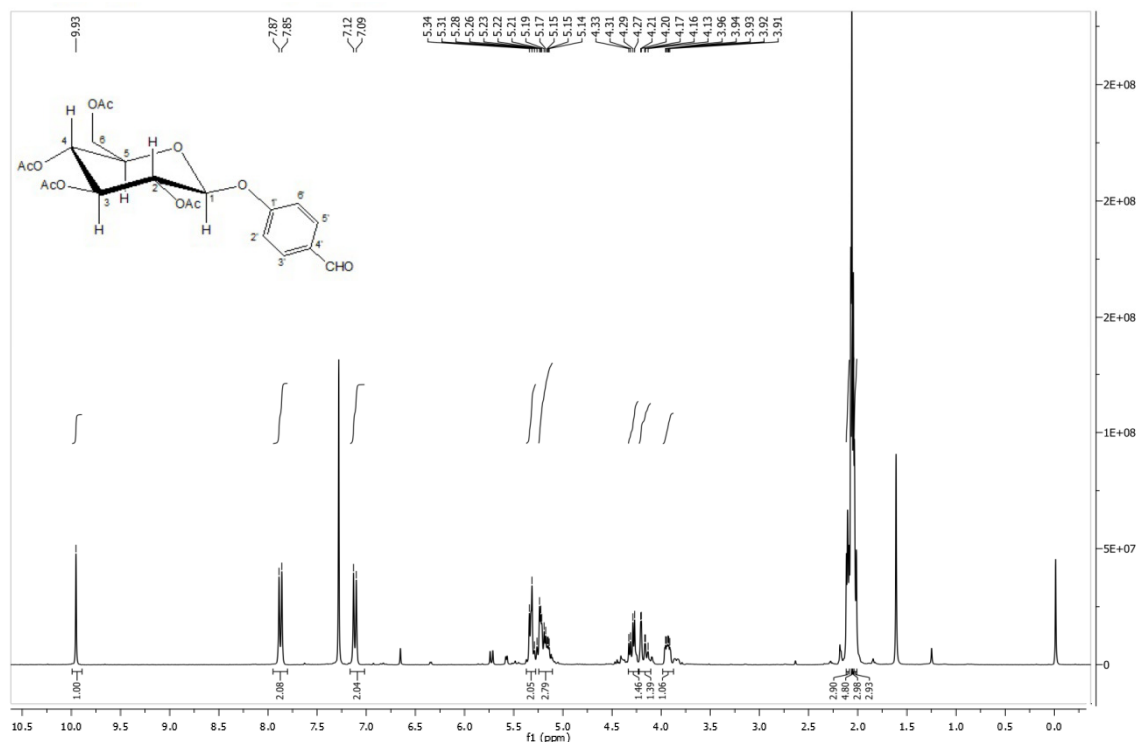
1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose



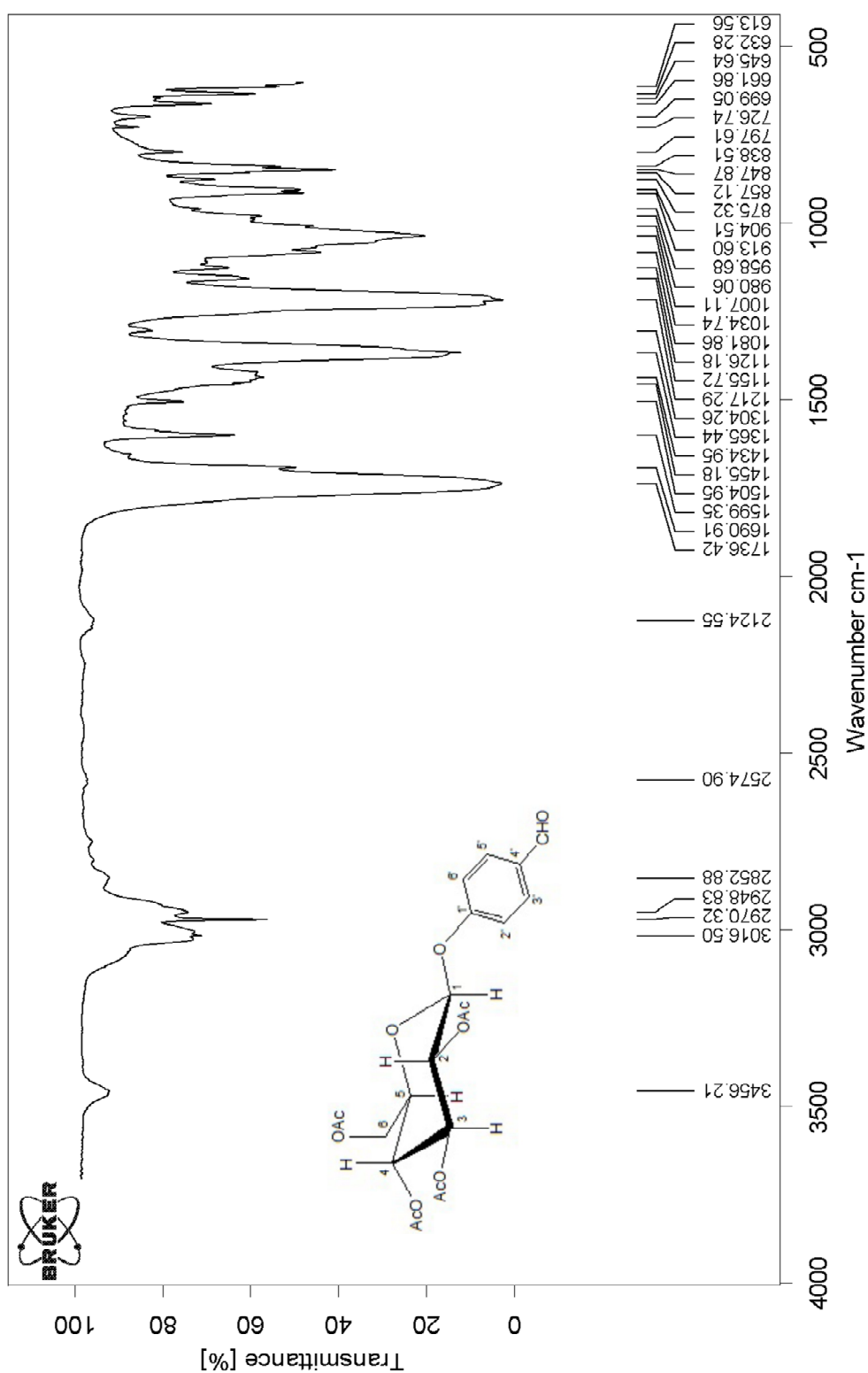
2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranosyl bromide



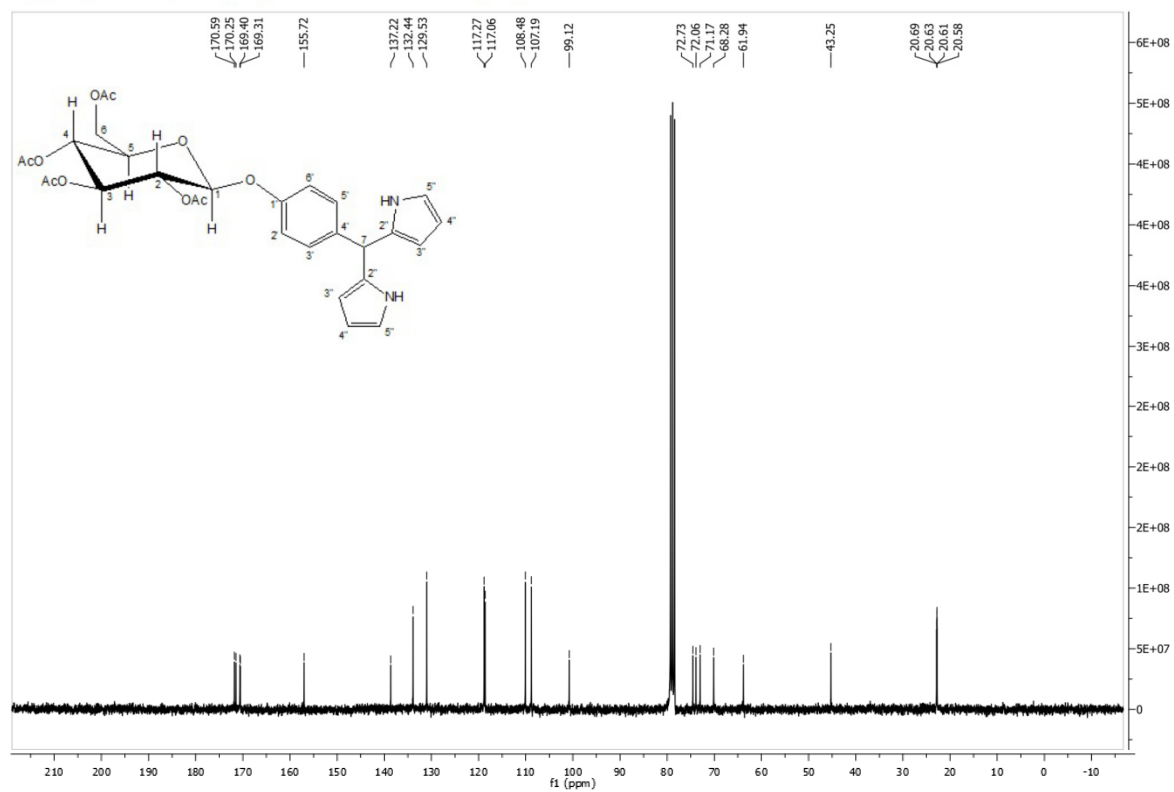
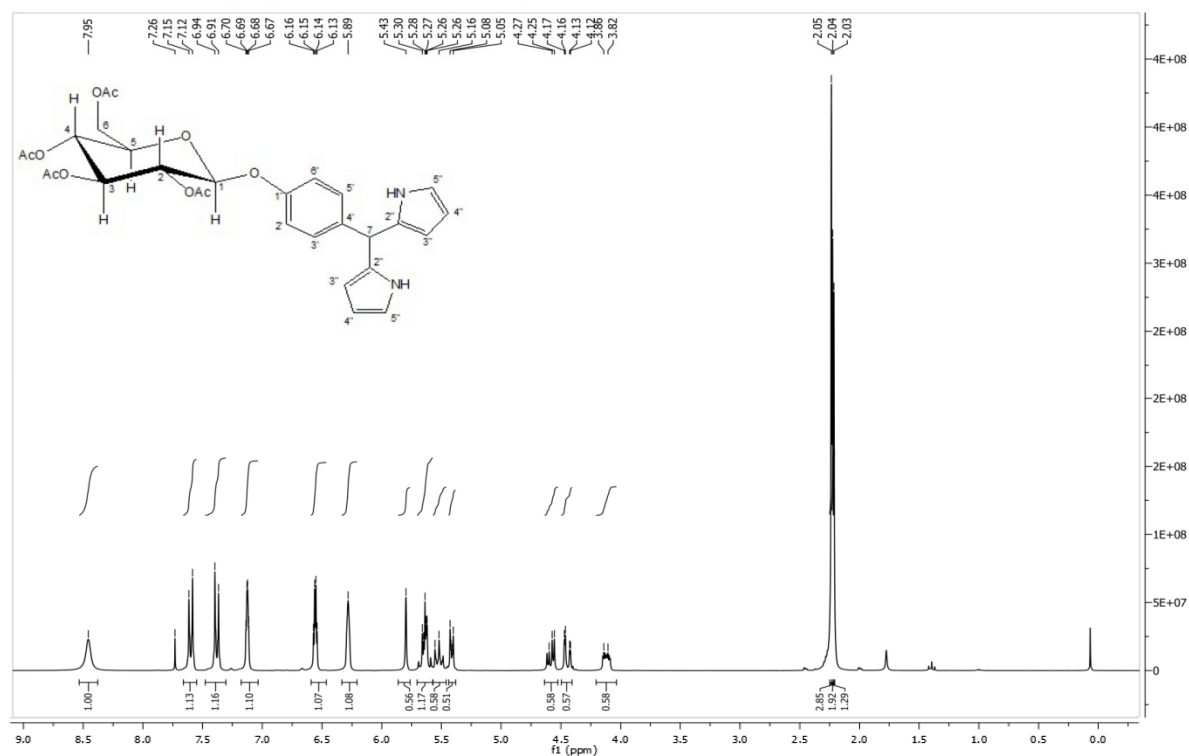
4-Formylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside



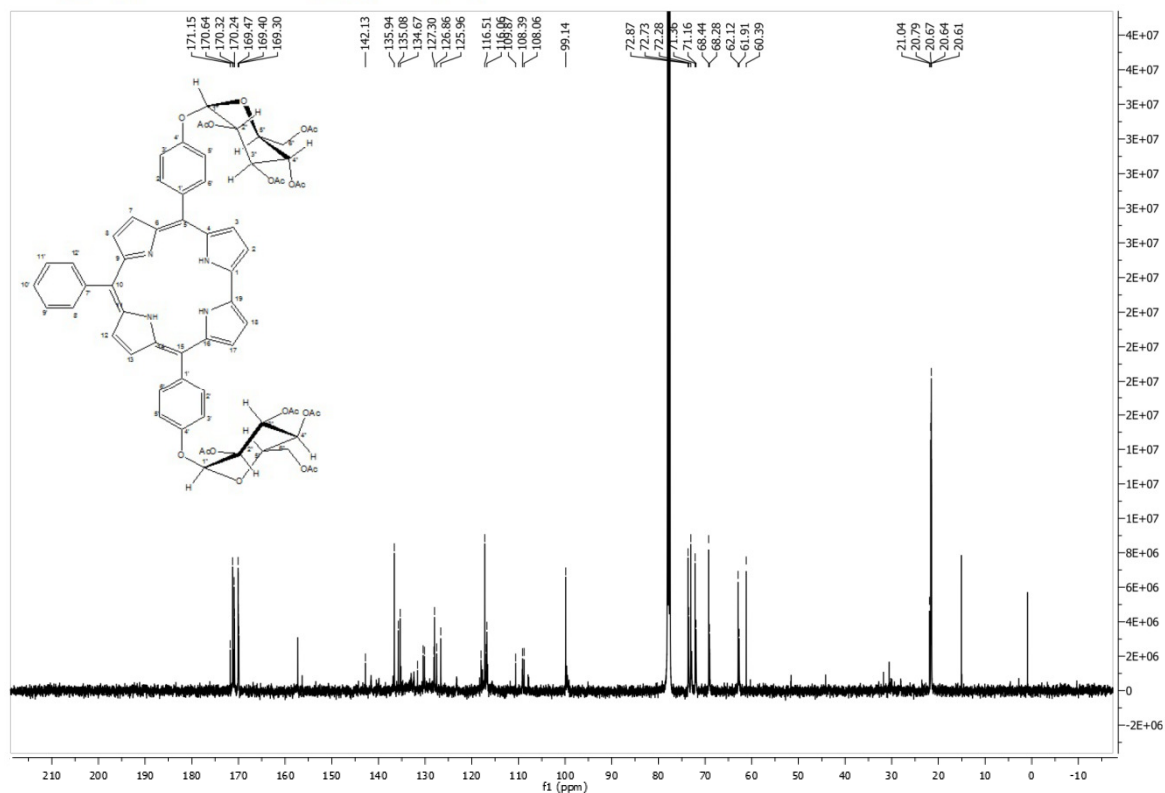
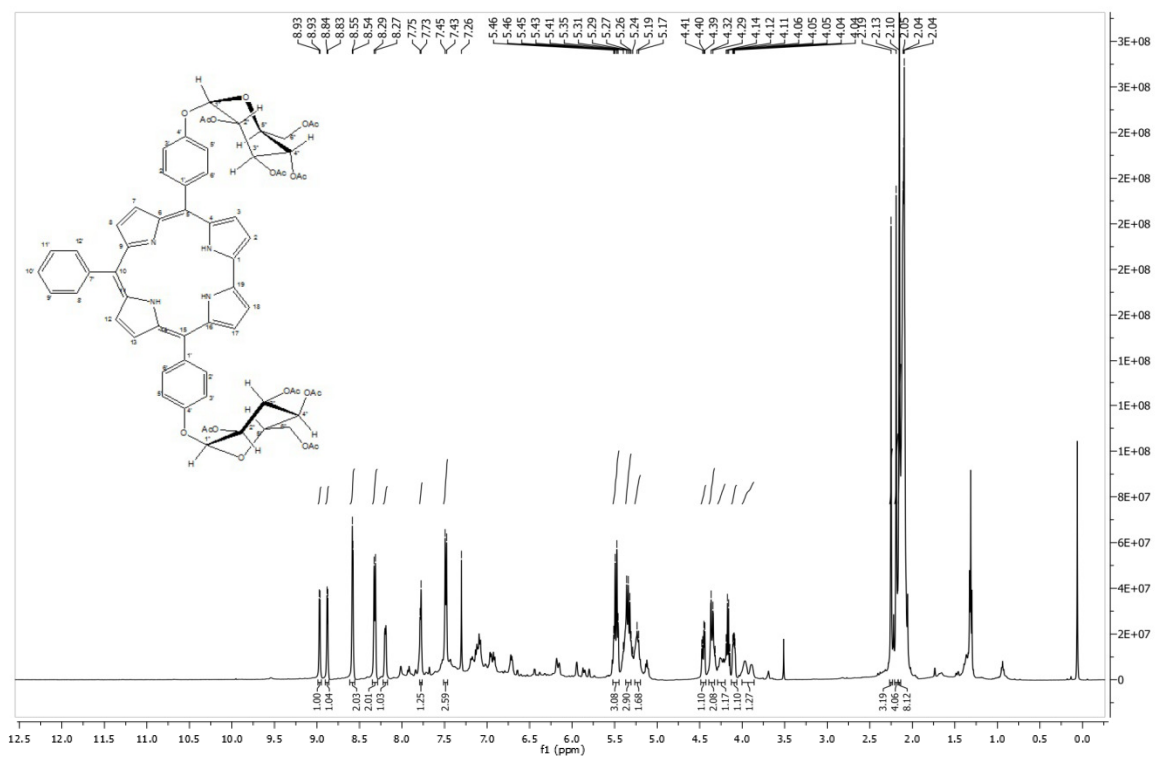
4-Formylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside



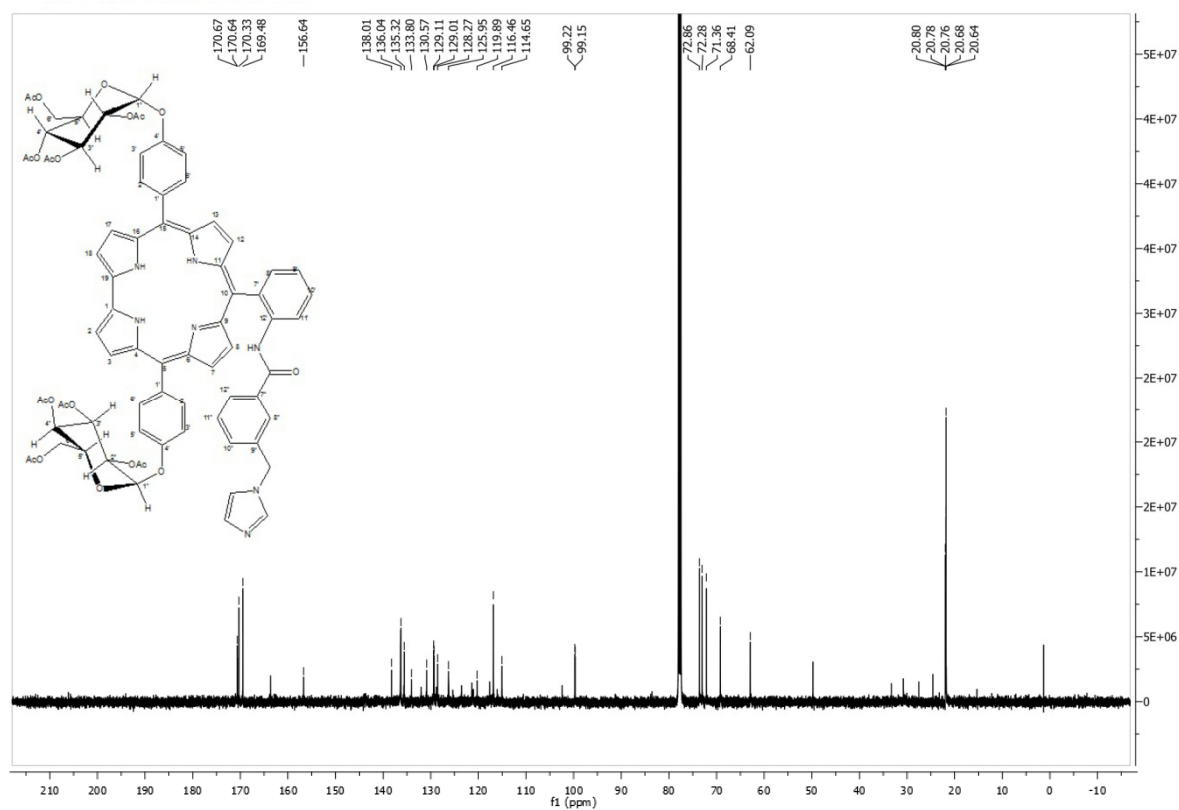
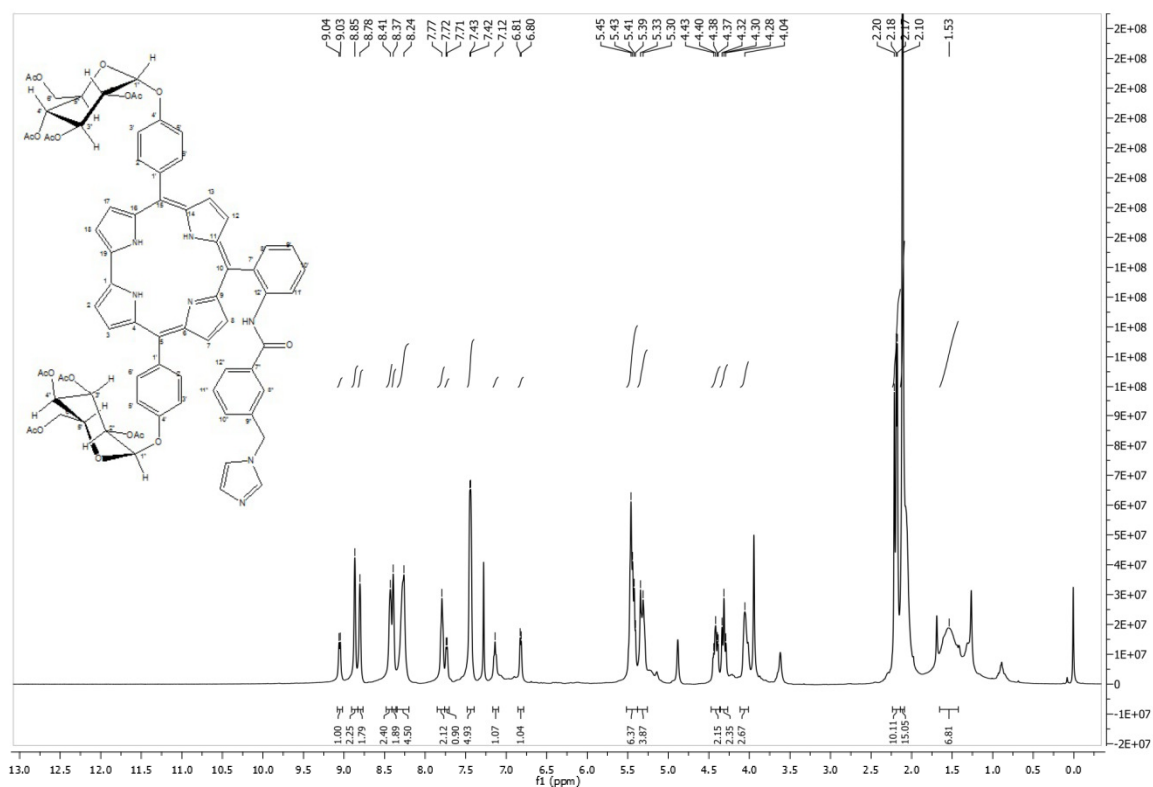
4-[Di(1H-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside



10-Phenyl-5,15-(diphenyl-2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside)corrole



10-(2-{{4-(1*H*-imidazol-1-ylmethyl)benzoyl}amino}phenyl)-5,15-(diphenyl-2'',3'',4'',6''-tetra-*O*-acetyl- β -D-glucopyranoside)corrole



A2.2 Crystallographic data

Ortep diagrams and tables of crystallographic data for the following crystal structures discussed in **Part 2** are given:

- 5,10,15-Triphenylcorrole hexane solvate
- 2-Aminobenzyl alcohol
- *N*-[2-(Hydroxymethyl)phenyl] benzamide (polymorphs 1 and 2)
- *N*-(2-Formylphenyl)benzamide (polymorphs 1 and 2)
- 2-(Benzamido)benzyl benzoate (polymorphs 1 and 2)
- 10-[2-(Benzoyl(amino)phenyl)-5,15-diphenylcorrole
- 1-(3-Carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride
- 3-(Chloromethyl)-*N*-[2-(hydroxymethyl)-phenyl] benzamide
- 2-[3-(Chloromethyl)benzamido]benzyl 3-(chloromethyl)-benzoate
- *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorphs 1 and 2)
- *N*-(2-Formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorphs 1 and 2)
- 4-Formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside
- 4-(Dimethoxymethyl)phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside
- 4-[Di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Full crystallographic details including atomic coordinates, bond lengths and angles, anisotropic displacement factors, hydrogen coordinates, torsion angles and hydrogen bonding parameters for all of the above structures can be found in **Digital Appendix 2.1**

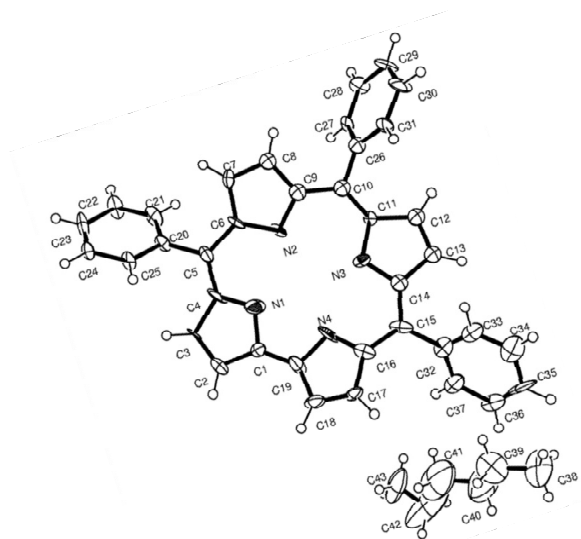


Figure A2.1 Ortep diagram (50% probability level) of 5,10,15-triphenylcorrole hexane solvate

Table A2.1 Crystallographic information for 5,10,15-triphenylcorrole hexane solvate

Parameter	
Ref code	9c_czhmm9
Formula	C ₃₉ H ₃₄ N ₄ O ₂
Formula weight	590.70
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C2
<i>a</i> , <i>b</i> , <i>c</i> (Å)	20.783(2), 19.4630(19), 15.9381(16)
α , β , γ (deg)	90.00, 90.414(5), 90.00
Cell volume (Å ³)	6446.9(12)
ρ_{calc} (g cm ⁻³)	1.217
<i>Z</i>	8
Data/parameters	11256/793
<i>R</i> ₁ / <i>wR</i> ₂	0.1275/0.3391
GOF	1.223

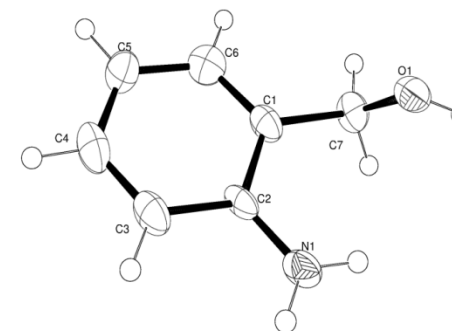


Figure A2.2 Ortep diagram (50% probability level) of 2-aminobenzyl alcohol

Table A2.2 Crystallographic information for 2-aminobenzyl alcohol

Parameter	
Ref code	10c_czhmm17
Formula	C ₇ H ₉ NO
Formula weight	123.15
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	Pna21
<i>a</i> , <i>b</i> , <i>c</i> (Å)	22.583(6), 6.0505(14), 4.6832(12)
α , β , γ (deg)	90.00, 90.00, 90.00
Cell volume (Å ³)	639.9(3)
ρ_{calc} (g cm ⁻³)	1.278
<i>Z</i>	4
Data/parameters	852/83
<i>R</i> ₁ / <i>wR</i> ₂	0.0829/0.1832
GOF	1.142

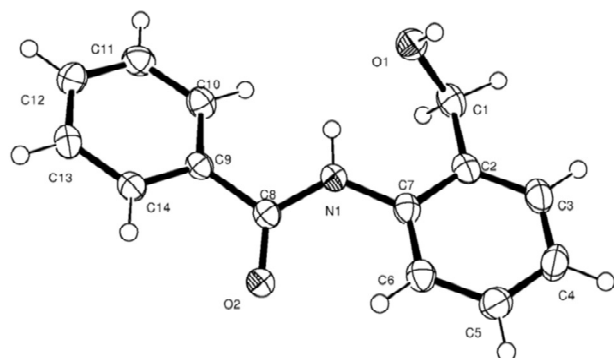


Figure A2.3 Ortep diagram (50% probability level) of *N*-[2-(hydroxymethyl)phenyl] benzamide (polymorph 1)

Table A2.3 Crystallographic information for *N*-[2-(hydroxymethyl)phenyl] benzamide (polymorph 1)

Parameter	
Ref code	10c_czhmm4
Formula	C ₁₄ H ₁₃ NO ₂
Formula weight	227.25
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P2 ₁ /n
<i>a</i> , <i>b</i> , <i>c</i> (Å)	12.5115(4), 7.3273(2), 12.6648(4)
α , β , γ (deg)	90.00, 100.052, 90.00
Cell volume (Å ³)	1143.23
ρ_{calc} (g cm ⁻³)	1.320
<i>Z</i>	4
Data/parameters	2230/155
<i>R</i> ₁ / <i>wR</i> ₂	0.042/0.098
GOF	1.007

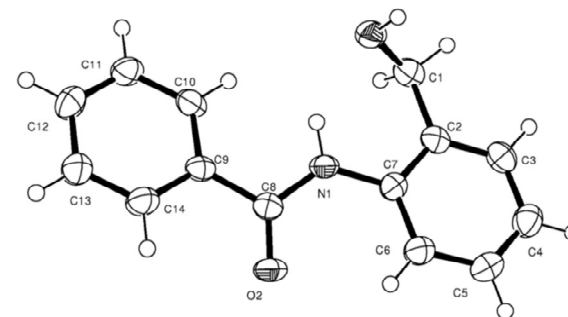


Figure A2.4 Ortep diagram (50% probability level) of *N*-[2-(hydroxymethyl)phenyl] benzamide (polymorph 2)

Table A2.4 Crystallographic information for *N*-[2-(hydroxymethyl)phenyl] benzamide (polymorph 2)

Parameter	
Ref code	10c_czhmm11
Formula	C ₁₄ H ₁₃ NO ₂
Formula weight	227.25
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P2 ₁ /n
<i>a</i> , <i>b</i> , <i>c</i> (Å)	5.1936(6), 13.2328(14), 17.0316(17)
α , β , γ (deg)	90.00, 90.125(4), 90.00
Cell volume (Å ³)	1170.5(2)
ρ_{calc} (g cm ⁻³)	1.290
<i>Z</i>	4
Data/parameters	2296/155
<i>R</i> ₁ / <i>wR</i> ₂	0.056/0.119
GOF	1.053

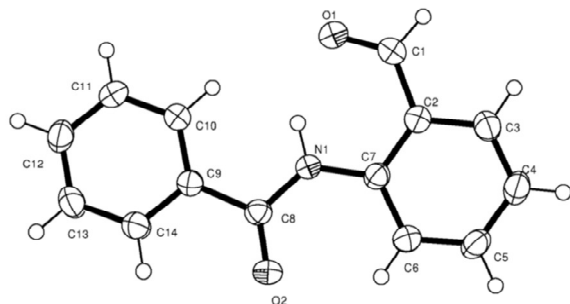


Figure A2.5 Ortep diagram (50% probability level) of *N*-(2-formylphenyl)benzamide (polymorph 1)

Table A2.5 Crystallographic information for *N*-(2-formylphenyl)benzamide (polymorph 1)

Parameter	
Ref code	10c_czhmm9
Formula	C ₁₄ H ₁₁ NO ₂
Formula weight	225.24
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	4.5532(1), 15.0996(4), 16.1510(5)
α , β , γ (deg)	90.00, 969.515(2), 90.00
Cell volume (Å ³)	1103.23(5)
ρ_{calc} (g cm ⁻³)	1.356
<i>Z</i>	4
Data/parameters	2650/158
<i>R</i> ₁ / <i>wR</i> ₂	0.042/0.104
GOF	1.030

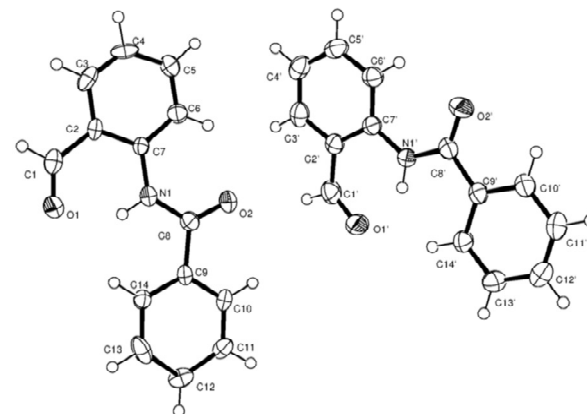


Figure A2.6 Ortep diagram (50% probability level) of *N*-(2-formylphenyl)benzamide (polymorph 2)

Table A2.6 Crystallographic information for *N*-(2-formylphenyl)benzamide (polymorph 2)

Parameter	
Ref code	11c_czhmm15
Formula	C ₁₄ H ₁₁ NO ₂
Formula weight	225.24
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	3.8949(1), 25.1426(8), 16.8477(5)
α , β , γ (deg)	90.00, 95.522(2), 90.00
Cell volume (Å ³)	1642.20(8)
ρ_{calc} (g cm ⁻³)	1.367
<i>Z</i>	6
Data/parameters	2575/145
<i>R</i> ₁ / <i>wR</i> ₂	0.040/0.070
GOF	0.870

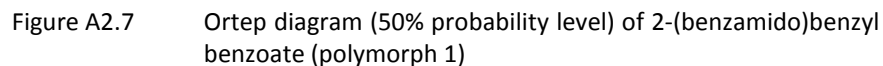


Table A2.7 Crystallographic information for 2-(benzamido)benzyl benzoate (polymorph 1)

Figure A2.8 Ortep diagram (50% probability level) of 2-(benzamido)benzyl benzoate (polymorph 2)

Table A2.8 Crystallographic information for 2-(benzamido)benzyl benzoate (polymorph 2)

371

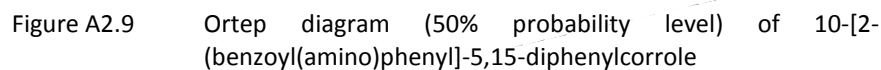


Table A2.9 Crystallographic information for 10-[2-(benzoyl(amino)phenyl)-5,15-diphenylcorrole

Figure A2.10 Ortep diagram (50% probability level) of 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride

Table A2.10 Crystallographic information for 1-(3-carboxybenzyl)-1*H*-imidazol-3-ium hydrochloride

372

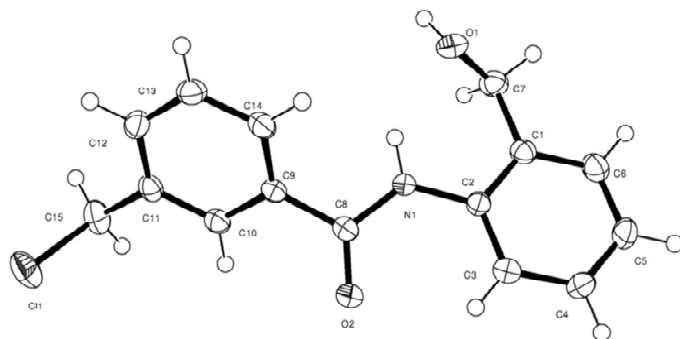


Figure A2.11 Ortep diagram (50% probability level) of 3-(chloromethyl)-*N*-[2-(hydroxymethyl)-phenyl] benzamide

Table A2.11 Crystallographic information for 3-(chloromethyl)-*N*-[2-(hydroxymethyl)-phenyl] benzamide

Parameter	
Ref code	11c_czhmm18
Formula	C ₁₅ H ₁₀ ClNO ₂
Formula weight	271.69
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	4.1899(4), 26.023(3), 12.1764(14)
α , β , γ (deg)	90.00, 90.01, 90.00
Cell volume (Å ³)	1327.6(2)
ρ_{calc} (g cm ⁻³)	1.359
<i>Z</i>	4
Data/parameters	3190/173
<i>R</i> ₁ / <i>wR</i> ₂	0.0393/0.0895
GOF	1.027

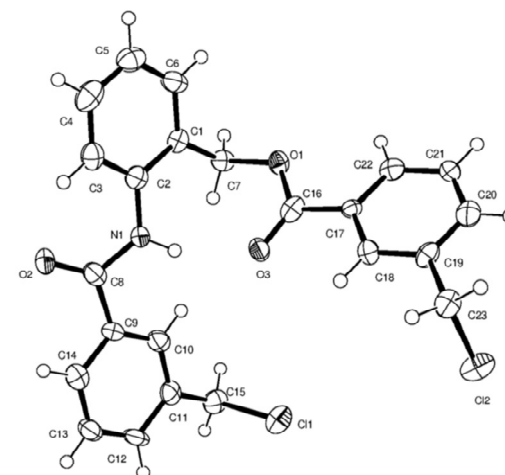


Figure A2.12 Ortep diagram (50% probability level) of 2-[3-(chloromethyl)benzamido]benzyl 3-(chloromethyl)-benzoate

Table A2.12 Crystallographic information for 2-[3-(chloromethyl)benzamido]benzyl 3-(chloromethyl)-benzoate

Parameter	
Ref code	11c_czhmm25
Formula	C ₂₃ H ₁₈ Cl ₂ NO ₃
Formula weight	427.28
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	<i>F</i> dd2
<i>a</i> , <i>b</i> , <i>c</i> (Å)	38.968(4), 46.919(5), 4.3266(3)
α , β , γ (deg)	90.00, 90.00, 90.00
Cell volume (Å ³)	7910.6(13)
ρ_{calc} (g cm ⁻³)	1.435
<i>Z</i>	16
Data/parameters	4217/262
<i>R</i> ₁ / <i>wR</i> ₂	0.0550/0.0687
GOF	0.729

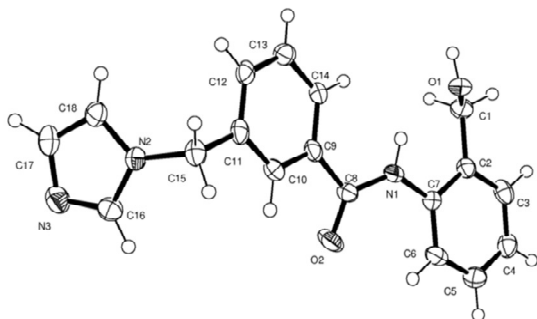


Figure A2.13 Ortep diagram (50% probability level) of *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 1)

Table A2.13 Crystallographic information for *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 1)

Parameter	
Ref code	11c_czhmm20
Formula	C ₁₈ H ₁₇ N ₃ O ₂
Formula weight	307.35
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> , <i>b</i> , <i>c</i> (Å)	4.2509(7), 11.363(3), 31.115(6)
α , β , γ (deg)	90.00, 90.00, 90.00
Cell volume (Å ³)	1502.9(5)
ρ_{calc} (g cm ⁻³)	1.358
<i>Z</i>	4
Data/parameters	2769/209
<i>R</i> ₁ / <i>wR</i> ₂	0.050/0.127
GOF	1.009

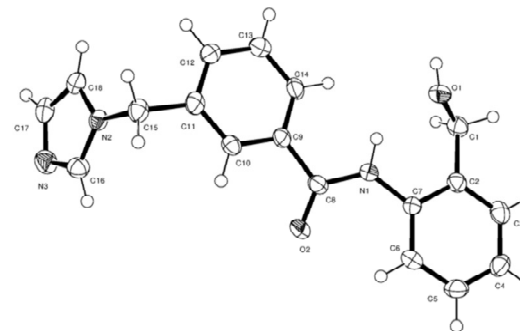


Figure A2.14 Ortep diagram (50% probability level) of *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 2)

Table A2.14 Crystallographic information for *N*-[2-(hydroxymethyl)phenyl]-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 2)

Parameter	
Ref code	11c_czhmm27
Formula	C ₁₈ H ₁₇ N ₃ O ₂
Formula weight	307.35
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	13.4793(8), 6.6293(4), 18.5481(12)
α , β , γ (deg)	90.00, 108.540(2), 90.00
Cell volume (Å ³)	1571.41(17)
ρ_{calc} (g cm ⁻³)	1.299
<i>Z</i>	4
Data/parameters	3786/216
<i>R</i> ₁ / <i>wR</i> ₂	0.044/0.113
GOF	1.060

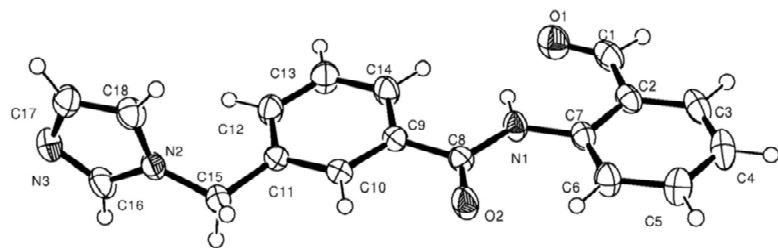


Figure A2.15 Ortep diagram (50% probability level) of *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 1)

Table A2.15 Crystallographic information for *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 1)

Parameter	
Ref code	11c_czhmm24
Formula	C ₁₈ H ₁₅ N ₃ O ₂
Formula weight	305.33
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	8.2469(2), 8.2333(2), 22.0039(5)
α , β , γ (deg)	90.00, 95.544(2), 90.00
Cell volume (Å ³)	1487.06(6)
ρ_{calc} (g cm ⁻³)	1.364
<i>Z</i>	4
Data/parameters	3585/212
<i>R</i> ₁ / <i>wR</i> ₂	0.0409/0.102
GOF	1.012

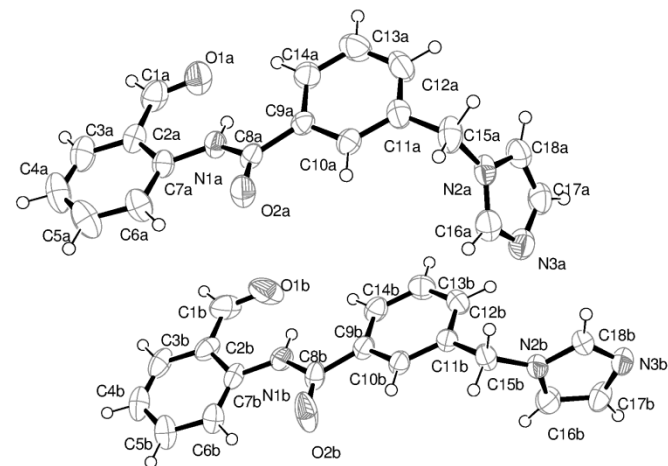


Figure A2.16 Ortep diagram (50% probability level) of *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 2)

Table A2.16 Crystallographic information for *N*-(2-formylphenyl)-3-(1*H*-imidazol-1-ylmethyl)benzamide (polymorph 2)

Parameter	
Ref code	11c_czhmm23
Formula	C ₁₈ H ₁₅ N ₃ O ₂
Formula weight	305.33
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>C</i> 2/ <i>c</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	30.2956(11), 8.2672(3), 26.5597(9)
α , β , γ (deg)	90.00, 117.346(2), 90.00
Cell volume (Å ³)	5908.8(4)
ρ_{calc} (g cm ⁻³)	1.373
<i>Z</i>	16
Data/parameters	6444/423
<i>R</i> ₁ / <i>wR</i> ₂	0.052/0.122
GOF	1.011

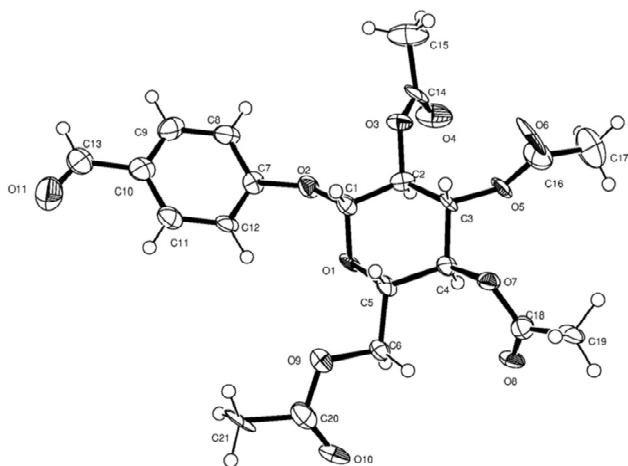


Figure A2.17 Ortep diagram (50% probability level) of 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Table A2.17 Crystallographic information for 4-formylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Parameter	
Ref code	11c_czhmm10
Formula	C ₂₁ H ₂₃ O ₁₁
Formula weight	451.39
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P1
<i>a</i> , <i>b</i> , <i>c</i> (Å)	5.8522(18), 8.948(3), 11.414(3)
α , β , γ (deg)	102.172(7), 94.084(8), 101.852(7)
Cell volume (Å ³)	567.7(3)
ρ_{calc} (g cm ⁻³)	1.320
<i>Z</i>	1
Data/parameters	2333/293
<i>R</i> ₁ / <i>wR</i> ₂	0.0750/0.1946
GOF	1.108

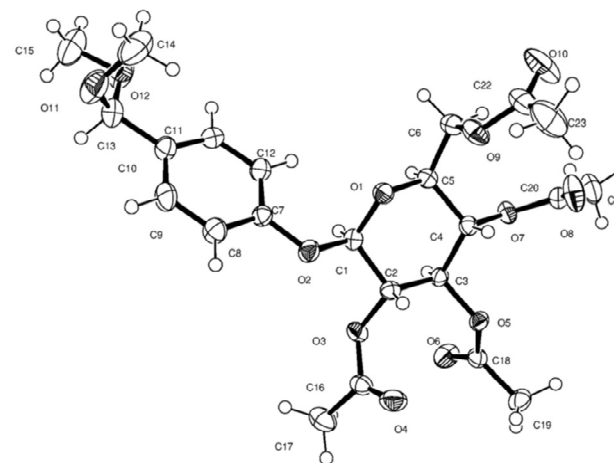


Figure A2.18 Ortep diagram (50% probability level) of 4-(dimethoxymethyl)phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Table A2.18 Crystallographic information for 4-(dimethoxymethyl)phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Parameter	
Ref code	11c_czhmm8
Formula	C ₂₃ H ₃₀ O ₁₂
Formula weight	498.47
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> , <i>b</i> , <i>c</i> (Å)	7.9004(2), 10.9961(3), 29.2289(8)
α , β , γ (deg)	90.00, 90.00, 90.00
Cell volume (Å ³)	2539.22(12)
ρ_{calc} (g cm ⁻³)	1.304
<i>Z</i>	4
Data/parameters	3493/322
<i>R</i> ₁ / <i>wR</i> ₂	0.0424/0.0948
GOF	0.966

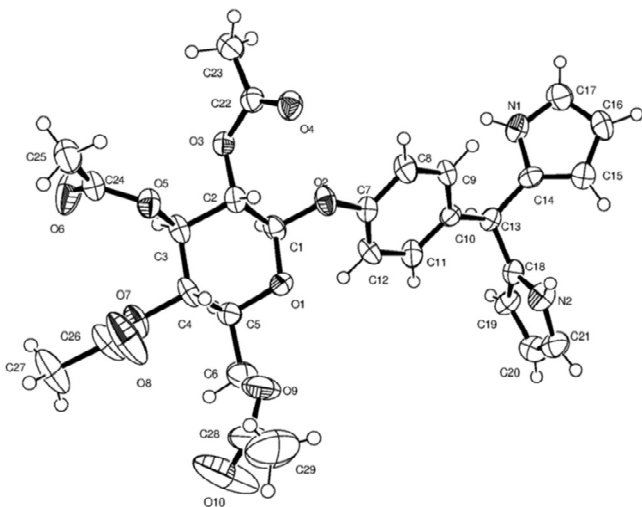


Figure A2.19 Ortep diagram (50% probability level) of 4-[di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Table A2.19 Crystallographic information for 4-[di(1*H*-pyrrol-2-yl)methyl]phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

Parameter	
Ref code	c11_czhmmp1
Formula	C ₂₉ H ₃₂ N ₂ O ₁₀
Formula weight	568.57
Temperature (K)	173 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁
<i>a</i> , <i>b</i> , <i>c</i> (Å)	12.652(5), 7.069(5), 16.465(5)
α , β , γ (deg)	90.00, 93.741(5), 90.00
Cell volume (Å ³)	14.69.4(13)
ρ_{calc} (g cm ⁻³)	1.285
<i>Z</i>	2
Data/parameters	3147/374
<i>R</i> ₁ / <i>wR</i> ₂	0.0404/0.0952
GOF	1.066

A2.3 New AMBER atom types

The parameters for the AMBER atom types defined in this work are reported in Table A2.20.

Table A2.20 Summary of the newly defined atom types and their associated parameters

Atom Types		
Atom type	Mass (g mol ⁻¹)	Comment
co3	58.93	Cobalt 3+
nc1	14.01	Corrole N
nc2	14.01	Corrole N
nc3	14.01	Corrole N
nc4	14.01	Corrole N
cam	12.01	<i>meso</i> position carbon in corrole
cap	12.01	pyrrole carbon in corrole

Table A2.20 continued

Parameters for bond stretching			
Atom type 1	Atom type 2	Force constant (kcal mol ⁻¹ Å ⁻²)	Equilibrium bond length (Å)
co3	nc1	300.0	1.87
co3	nc2	300.0	1.87
co3	nc3	300.0	1.89
co3	nc4	300.0	1.89
nc1	cap	470.0	1.38
nc2	cap	470.0	1.38
nc3	cap	470.0	1.38
nc4	cap	470.0	1.38
cap	cap	478.0	1.41
cap	cam	478.0	1.40
cam	ca	478.0	1.49
cap	ha	344.3	1.087

Table A2.20 continued

Parameters for angle bending					
Atom type 1	Atom type 2	Atom type 3	Force constant (kcal mol ⁻¹ radian ⁻²)	Equilibrium angle (radians)	Comment
nc1	cap	cap	70.2	108.00	
nc2	cap	cap	70.2	108.00	
nc3	cap	cap	70.2	108.00	
nc4	cap	cap	70.2	108.00	
nc1	cap	cam	70.2	119.00	
nc2	cap	cam	70.2	119.00	
nc3	cap	cam	70.2	119.00	
nc4	cap	cam	70.2	119.00	
cap	nc1	cap	67.1	108.00	
cap	nc2	cap	67.1	108.00	
cap	nc3	cap	67.1	108.00	
cap	nc4	cap	67.1	108.00	
co3	nc1	cap	31.5	126.00	half c3-na-ca
co3	nc2	cap	31.5	126.00	half c3-na-ca
co3	nc3	cap	31.5	126.00	half c3-na-ca
co3	nc4	cap	31.5	126.00	half c3-na-ca
cap	cap	cap	67.2	108.00	
cap	cap	cap	67.2	108.00	

Table A2.20 continued

cap	cap	ha	48.5	120.01			
cap	cap	cam	34.0	129.00	half ca-ca-ca		
cap	cam	cap	67.2	123.0			
cap	cam	ca	67.2	118.0			
cam	ca	ca	67.2	121.0			
nc1	co3	nc2	30.0	81.0			
nc1	co3	nc3	30.0	90.0			
nc1	co3	nc4	30.0	171.0			
nc3	co3	nc4	30.0	95.0			
nc3	co3	nc2	30.0	185.0			
nc4	co3	nc2	30.0	91.0			
Parameters for torsion angle rotation							
Atom type 1	Atom type 2	Atom type 3	Atom type 4	½ Vn	γ	N	Comment
co3	nc1	cap	cap	4	1.2	180	based on **-ca-na-**-
co3	nc2	cap	cap	4	1.2	180	based on **-ca-na-**-
co3	nc3	cap	cap	4	1.2	180	based on **-ca-na-**-
co3	nc4	cap	cap	4	1.2	180	based on **-ca-na-**-
co3	nc1	cap	cam	4	1.2	180	based on **-ca-na-**-
co3	nc2	cap	cam	4	1.2	180	based on **-ca-na-**-
co3	nc3	cap	cam	4	1.2	180	based on **-ca-na-**-
co3	nc4	cap	cam	4	1.2	180	based on **-ca-na-**-

Table A2.20 continued

**	co3	**	**	6	0	180	all torsions about metal set to zero
nc1	cap	cap	cap	4	14.5	180	based on **-ca-ca-**
nc2	cap	cap	cap	4	14.5	180	based on **-ca-ca-**
nc3	cap	cap	cap	4	14.5	180	based on **-ca-ca-**
nc4	cap	cap	cap	4	14.5	180	based on **-ca-ca-**
nc1	cap	cap	nc2	4	14.5	180	based on **-ca-ca-**
nc1	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
nc2	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
nc3	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
nc4	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
nc1	cap	cam	cap	4	14.5	180	based on **-ca-ca-**
nc2	cap	cam	cap	4	14.5	180	based on **-ca-ca-**
nc3	cap	cam	cap	4	14.5	180	based on **-ca-ca-**
nc4	cap	cam	cap	4	14.5	180	based on **-ca-ca-**
nc1	cap	cam	ca	4	14.5	180	based on **-ca-ca-**
nc2	cap	cam	ca	4	14.5	180	based on **-ca-ca-**
nc3	cap	cam	ca	4	14.5	180	based on **-ca-ca-**
nc4	cap	cam	ca	4	14.5	180	based on **-ca-ca-**
cap	cap	cap	cap	4	14.5	180	based on **-ca-ca-**
cap	cap	cap	cam	4	14.5	180	based on **-ca-ca-**
cap	cap	cam	cap	4	14.5	180	based on **-ca-ca-**

Table A2.20 continued

cap	nc1	cap	cap	4	1.2	180	based on **-ca-na-**
cap	nc2	cap	cap	4	1.2	180	based on **-ca-na-**
cap	nc3	cap	cap	4	1.2	180	based on **-ca-na-**
cap	nc4	cap	cap	4	1.2	180	based on **-ca-na-**
cap	nc1	cap	cam	4	1.2	180	based on **-ca-na-**
cap	nc2	cap	cam	4	1.2	180	based on **-ca-na-**
cap	nc3	cap	cam	4	1.2	180	based on **-ca-na-**
cap	nc4	cap	cam	4	1.2	180	based on **-ca-na-**
cap	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
cap	cap	cam	ca	4	14.5	180	based on **-ca-ca-**
cap	cam	ca	ca	4	7.0	180	based on **-ca-ca-** $\frac{1}{2}$ $\frac{1}{2}V_n$ to prevent phenyl distortions
ha	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
cam	cap	cap	ha	4	14.5	180	based on **-ca-ca-**
cam	ca	ca	ha	4	14.5	180	based on **-ca-ca-**
cam	ca	ca	ca	4	14.5	180	based on **-ca-ca-**

Table A2.20 continued

Out-of-plane bending parameters for sp^2 hybridised atoms						
Atom type 1	Atom type 2	Atom type 3	Atom type 4	$\frac{1}{2} V_n$	γ	N
**	**	ca	ha	1.10	180.00	2.00
**	cam	ca	**	1.10	180.00	2.00
cap	ca	cam	cap	1.10	180.00	2.00
ha	cap	cap	cap	1.10	180.00	2.00
cap	nc1	cap	cap	1.10	180.00	2.00
cap	nc2	cap	cap	1.10	180.00	2.00
cap	nc1	cap	cam	1.10	180.00	2.00
cap	nc2	cap	cam	1.10	180.00	2.00
cap	nc3	cap	cam	1.10	180.00	2.00
cap	nc4	cap	cam	1.10	180.00	2.00
Parameters for nonbonded interactions between pairs of atoms						
Atom	$\frac{1}{2}(\text{min energy nuclear separation}) (\text{\AA})$	Well depth (kcal mol ⁻¹)	Comments			
co3	2.000	0.0440	Co(III) preliminary values - CSD vdW radius			
nc1	1.824	0.1700	Corrole N			
nc2	1.824	0.1700	Corrole N			
nc3	1.824	0.1700	Corrole N			
nc4	1.824	0.1700	Corrole N			
cam	1.908	0.0860	<i>meso</i> carbon in corrole			
cap	1.908	0.0860	pyrrole carbon in corrole			

A2.4 Publications

The structure report, *(2-Aminophenyl)methanol*, that follows discusses the hydrogen bonding in the crystal lattice resulting in hydrogen bonded layers of molecules. Crystal structure determination was carried out by the author. The paper was written with the assistance of Dr M. A. Fernandes. The report was submitted on 11 November 2011 and published in *Acta Crystallographica Section E* in January 2012. The supplementary materials for this report can be found in **Digital Appendix 2.2.1**

(2-Aminophenyl)methanol

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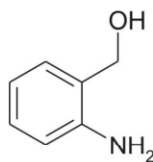
Received 11 November 2011; accepted 13 December 2011

Key indicators: single-crystal X-ray study; $T = 173$ K; mean $\sigma(\text{C}-\text{C}) = 0.003$ Å; R factor = 0.030; wR factor = 0.075; data-to-parameter ratio = 8.7.

The crystal structure of the title compound, $\text{C}_7\text{H}_9\text{NO}$, displays $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds which link molecules related by translation along the b axis, and $\text{O}-\text{H}\cdots\text{N}$ and further $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds which link molecules related by the 2_1 screw axis along the c axis. The resulting combination is a hydrogen-bonded layer of molecules parallel to (011).

Related literature

For the use of amines in the pharmaceutical industry, see: Morissette *et al.* (2004). For the use of amines in crystal engineering, see: Bernstein *et al.* (1999). For hydrogen-bond motifs, see: Bernstein *et al.* (1995); Etter *et al.* (1990).



Experimental

Crystal data

$\text{C}_7\text{H}_9\text{NO}$
 $M_r = 123.15$
 Orthorhombic, Pna_21
 $a = 22.6222$ (9) Å
 $b = 6.0675$ (2) Å
 $c = 4.7005$ (2) Å
 $V = 645.19$ (4) Å³
 $Z = 4$
 Mo $K\alpha$ radiation
 $\mu = 0.09$ mm⁻¹
 $T = 173$ K
 $0.46 \times 0.20 \times 0.07$ mm

Data collection

Bruker APEXII CCD
 diffractometer
 4682 measured reflections
 715 independent reflections
 681 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.078$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.030$
 $wR(F^2) = 0.075$
 $S = 1.09$
 715 reflections
 82 parameters
 1 restraint
 H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.12$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.13$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$\text{O1}-\text{H1}\cdots\text{N1}^i$	0.85	1.94	2.791 (2)	172
$\text{N1}-\text{H1B}\cdots\text{O1}^i$	0.91	2.28	3.135 (2)	156
$\text{N1}-\text{H1A}\cdots\text{O1}^{ii}$	0.87	2.19	3.0585 (17)	175

Symmetry codes: (i) $-x + 1, -y + 1, z - \frac{1}{2}$; (ii) $x, y - 1, z$.

Data collection: APEX2 (Bruker, 2005); cell refinement: SAINT (Bruker, 2005); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997) and SCHAKAL99 (Keller, 1999); software used to prepare material for publication: WinGX (Farrugia, 1999) and PLATON (Spek, 2009).

This work was supported by the National Research Foundation, Pretoria (NRF, GUN 2053652 & 77122), the South African Research Chairs Initiative and the University of the Witwatersrand.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: FJ2480).

References

- Bernstein, J., Davey, R. J. & Henck, J.-O. (1999). *Angew. Chem. Int. Ed. Engl.* **38**, 3440–3461.
 Bernstein, J., Davis, R. E., Shimon, L. & Chang, N. L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
 Bruker (2005). APEX2 and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
 Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* **B46**, 256–262.
 Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
 Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
 Keller, E. (1999). SCHAKAL99. University of Freiberg, Germany.
 Morissette, S. L., Almarsson, O., Peterson, M. L., Remenar, J. F., Read, M. J., Lemmo, A. V., Ellis, S., Cima, M. J. & Gardner, C. R. (2004). *Adv. Drug Deliv. Rev.* **56**, 275–300.
 Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
 Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.

The structure report, *4-(Dimethoxymethyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside*, that follows reports on the solid state structure and intermolecular interactions of the enantiomerically pure compound. Crystal structure determination was carried out by the author. The paper was written with the assistance of Dr M. A. Fernandes. The report was submitted on 22 February 2012 and published in *Acta Crystallographica Section E* in March 2012. The supplementary materials for this report can be found in **Digital Appendix 2.2.2**

4-(Dimethoxymethyl)phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside

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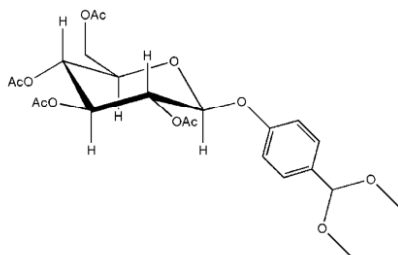
Received 22 February 2012; accepted 14 March 2012

Key indicators: single-crystal X-ray study; $T = 173$ K; mean $\sigma(\text{C}-\text{C}) = 0.004$ Å; R factor = 0.042; wR factor = 0.102; data-to-parameter ratio = 10.8.

The enantiomerically pure title compound, $\text{C}_{23}\text{H}_{30}\text{O}_{12}$, crystallizes in the chiral space group $P2_12_12_1$. The *O*-acetylated-glucopyranoside moiety adopts a chair conformation. Numerous C—H...O interactions as well as a C—H... π interaction are present in the crystal structure.

Related literature

For similar compounds, see: Bin *et al.* (2008); Ansari *et al.* (2006). For the use of sugars as water-solubilizing agents in macrocyclic chemistry, see: Sol *et al.* (1997); Maillard *et al.* (1993); Oulmi *et al.* (1995). For the role of sugars in biological systems, especially proteins, see: Floyd *et al.* (2009).



Experimental

Crystal data

$\text{C}_{23}\text{H}_{30}\text{O}_{12}$
 $M_r = 498.47$
Orthorhombic, $P2_12_12_1$
 $a = 7.9004$ (2) Å
 $b = 10.9961$ (3) Å
 $c = 29.2289$ (8) Å
 $V = 2539.22$ (12) Å³
 $Z = 4$
Mo $K\alpha$ radiation
 $\mu = 0.11$ mm⁻¹
 $T = 173$ K
 $0.45 \times 0.32 \times 0.10$ mm

Data collection

Bruker APEXII CCD
diffractometer
13406 measured reflections
3493 independent reflections
2644 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.053$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.042$
 $wR(F^2) = 0.102$
 $S = 0.97$
3493 reflections
322 parameters
H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.25$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.20$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

C_g is the centroid of the C7—C12 ring.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$C2-H2\cdots O11^i$	1.00	2.44	3.347 (3)	151
$C12-H12\cdots O4^{ii}$	0.95	2.45	3.321 (3)	152
$C19-H19A\cdots O3^{iii}$	0.98	2.54	3.510 (3)	171
$C19-H19C\cdots O8^{iv}$	0.98	2.49	3.414 (3)	157
$C21-H21C\cdots O10^{iv}$	0.98	2.29	3.252 (4)	168
$C23-H23C\cdots C_g^v$	0.98	2.71	3.615 (4)	153

Symmetry codes: (i) $-x, y + \frac{1}{2}, -z + \frac{1}{2}$; (ii) $x - 1, y, z$; (iii) $x + \frac{1}{2}, -y + \frac{1}{2}, -z$; (iv) $x + \frac{1}{2}, -y + \frac{1}{2}, -z$; (v) $x, y + 1, z$.

Data collection: APEX2 (Bruker, 2005); cell refinement: SAINT (Bruker, 2005); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997) and SCHAKAL99 (Keller, 1999); software used to prepare material for publication: WinGX (Farrugia, 1999) and PLATON (Spek, 2009).

This work was supported by the National Research Foundation, Pretoria (NRF, GUN 2053652), the South African Research Chairs Initiative and the University of the Witwatersrand.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: MW2057).

References

- Ansari, F. L., Sultana, S., Corrente, A. M. & Parvez, M. (2006). *Acta Cryst.* **E62**, o3139–o3141.
- Bin, Y., Zhao, F., Zhang, F. & Wang, R.-J. (2008). *Acta Cryst.* **E64**, o63.
- Bruker (2005). APEX2 and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
- Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
- Floyd, N., Vijayakrishnan, B., Koeppe, J. R. & Davis, B. G. (2009). *Angew. Chem. Int. Ed.* **48**, 7798–7802.
- Keller, E. (1999). SCHAKAL99. University of Freiberg, Germany.
- Maillard, P., Guerquin-Kern, J.-L., Huel, C. & Momenteau, M. (1993). *J. Org. Chem.* **58**, 2774–2780.
- Oulmi, D., Maillard, P., Guerquin-Kern, J.-L., Huel, C. & Momenteau, M. (1995). *J. Org. Chem.* **60**, 1554–1564.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Sol, V., Blais, J. C., Bolbach, G., Carré, V., Granet, R., Guilloton, M., Spiro, M. & Krausz, P. (1997). *Tetrahedron Lett.* **38**, 6391–6394.
- Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.

Appendix for Part 3

Polymorphism *N*-phenylbenzamide derivatives

Table of contents

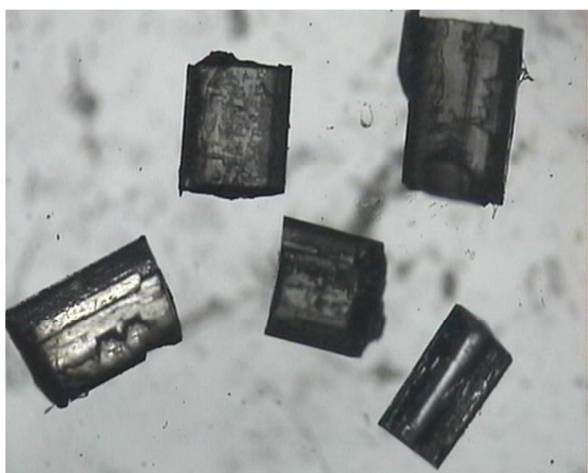
A3.1	Supplementary information for paper 1	390
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A3.1 Supplementary information for paper 1

Supplementary information for:

Polymorphs of *N*-[2-(hydroxymethyl)phenyl]benzamide: structural characterization and analysis of molecule...molecule interactions by means of atom-atom potentials and DFT

Caitlin. F. Zipp, Manuel. A. Fernandes*, Helder M. Marques, Joseph. P. Michael and Christopher B. Perry



a



b

Figure S1. Microscope photographs of (a) block-like crystals of the more stable polymorph I, and (b) the needle-like crystals of the meta-stable polymorph II.

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Single crystal experimental, solution and refinement procedure:

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_{α} radiation (50kV, 30mA) using the APEX 2 (Bruker, 2005a) data collection software. The collection method involved ω -scans of width 0.5° and 512x512 bit data frames. Data reduction was carried out using the program *SAINT+* (Bruker, 2005b) and face indexed absorption corrections were made using *XPREP* (Bruker, 2005b).

The crystal structure was solved by direct methods using *SHELXTL* (Bruker, 1999). Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. ORTEP diagrams for the two polymorphs are given in Figure S2. Selected bond lengths and angles are given in Table S1.

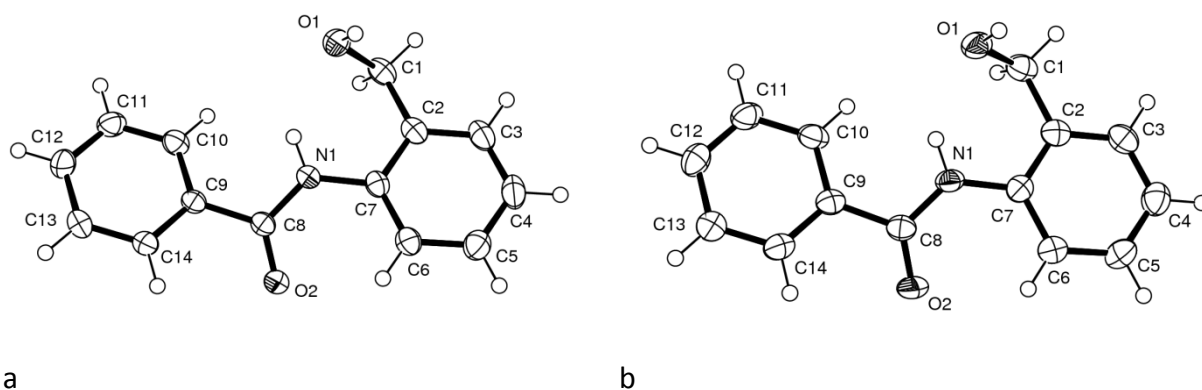
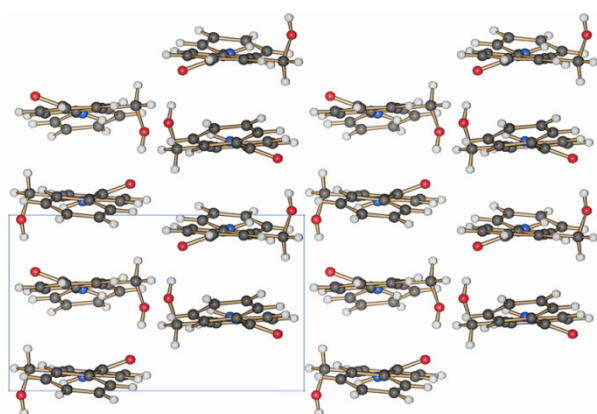


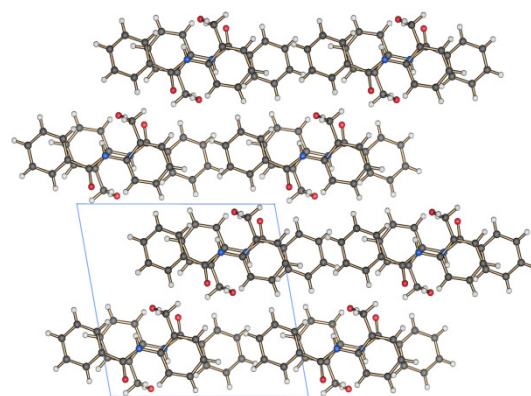
Figure S2. ORTEP Diagrams (50% probability level) for polymorphs (a) I and (b) II.

Table S1. Selected bond lengths (Å) and torsion angles (°) for polymorphs I and II.

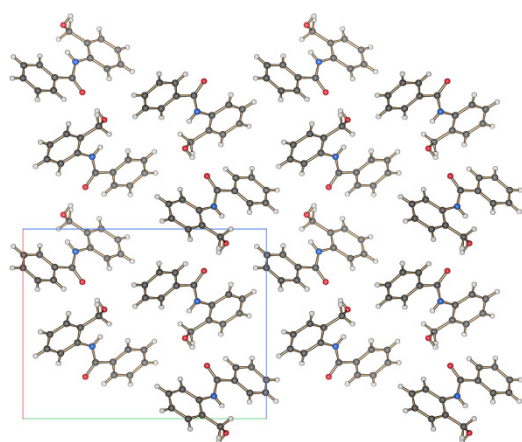
	I	II
C(1)-O(1)	1.4337(17)	1.429(3)
C(1)-C(2)	1.5039(18)	1.515(3)
C(2)-C(7)	1.4075(18)	1.392(3)
C(7)-N(1)	1.4175(16)	1.413(3)
C(8)-N(1)	1.3522(16)	1.351(3)
C(8)-O(2)	1.2371(15)	1.226(3)
C(8)-C(9)	1.4951(18)	1.499(3)
O(1)-C(1)-C(2)-C(3)	-125.23(13)	-134.2(2)
O(1)-C(1)-C(2)-C(7)	55.83(16)	48.6(3)
C(5)-C(6)-C(7)-N(1)	-179.31(12)	179.2(2)
C(3)-C(2)-C(7)-N(1)	177.87(12)	-178.6(2)
C(1)-C(2)-C(7)-N(1)	-3.16(18)	-1.5(4)
O(2)-C(8)-C(9)-C(10)	-149.19(13)	-158.2(3)
N(1)-C(8)-C(9)-C(10)	32.11(18)	20.6(4)
O(2)-C(8)-C(9)-C(14)	31.93(18)	21.1(4)
N(1)-C(8)-C(9)-C(14)	-146.77(12)	-160.1(2)
O(2)-C(8)-N(1)-C(7)	-1.2(2)	1.8(4)
C(9)-C(8)-N(1)-C(7)	177.42(12)	-177.0(2)
C(6)-C(7)-N(1)-C(8)	-24.8(2)	-20.1(4)
C(2)-C(7)-N(1)-C(8)	157.25(13)	160.9(3)



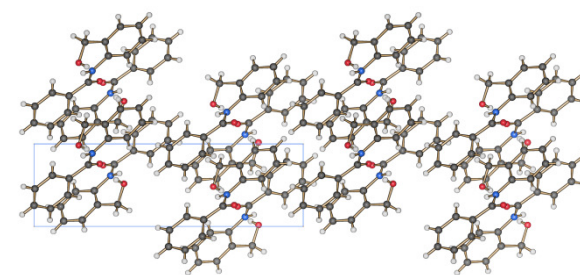
a



b



c



d

Figure S3. Packing diagrams for the two polymorphs of *N*-[2-(hydroxymethyl)phenyl]benzamide: views down the *a* axis for polymorphs I (a) and II (c); views down the *b* axis for polymorphs I (b) and II (d).

IR data:

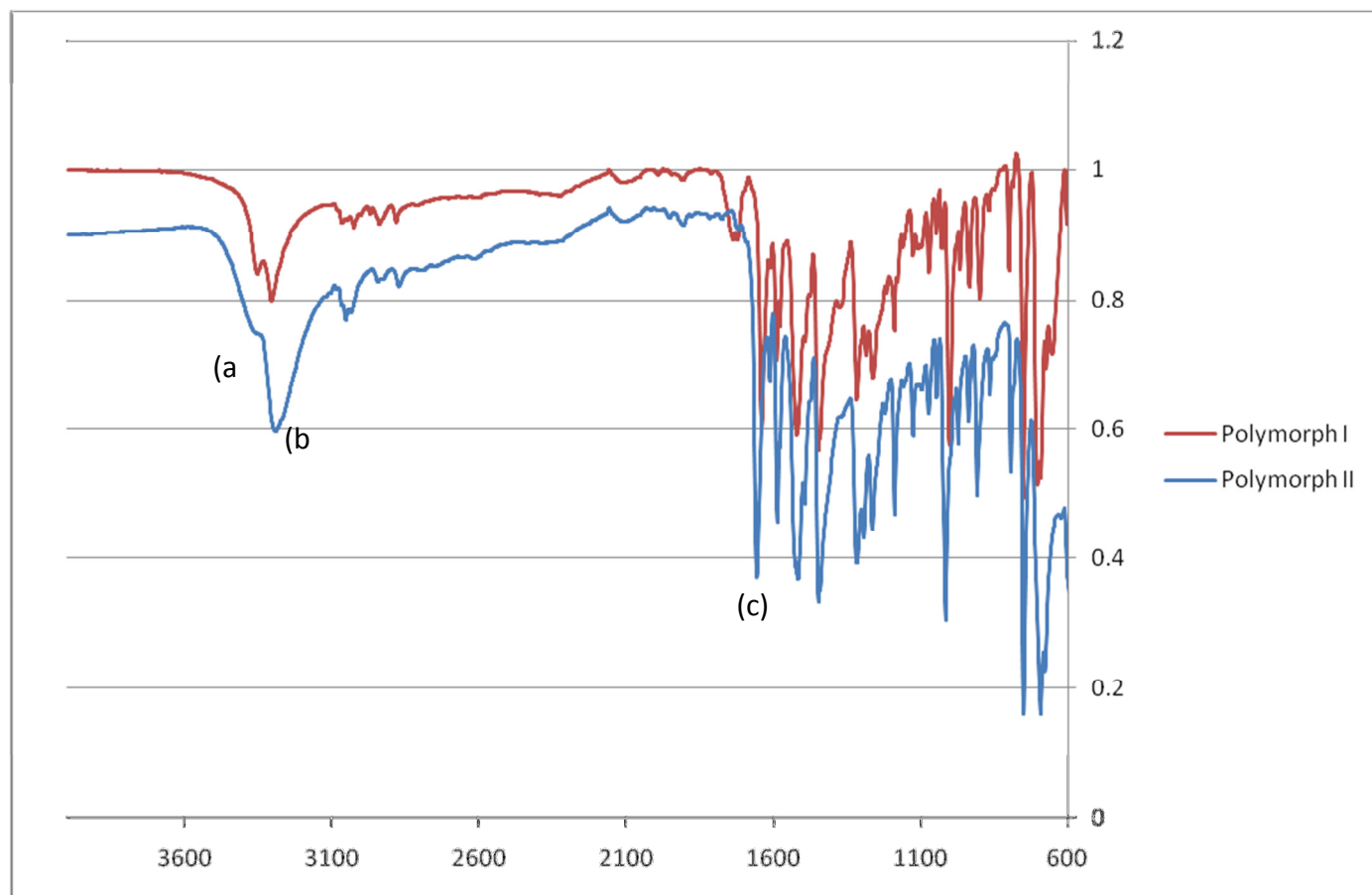


Figure S4. Solid-state IR spectra for the two polymorphs: polymorph I (upper plot) in red; polymorph II (lower plot) in blue. Selected band assignments are as follows: (a) N-H stretch, (b) O-H stretch and (c) C=O stretch.

Powder diffraction patterns:

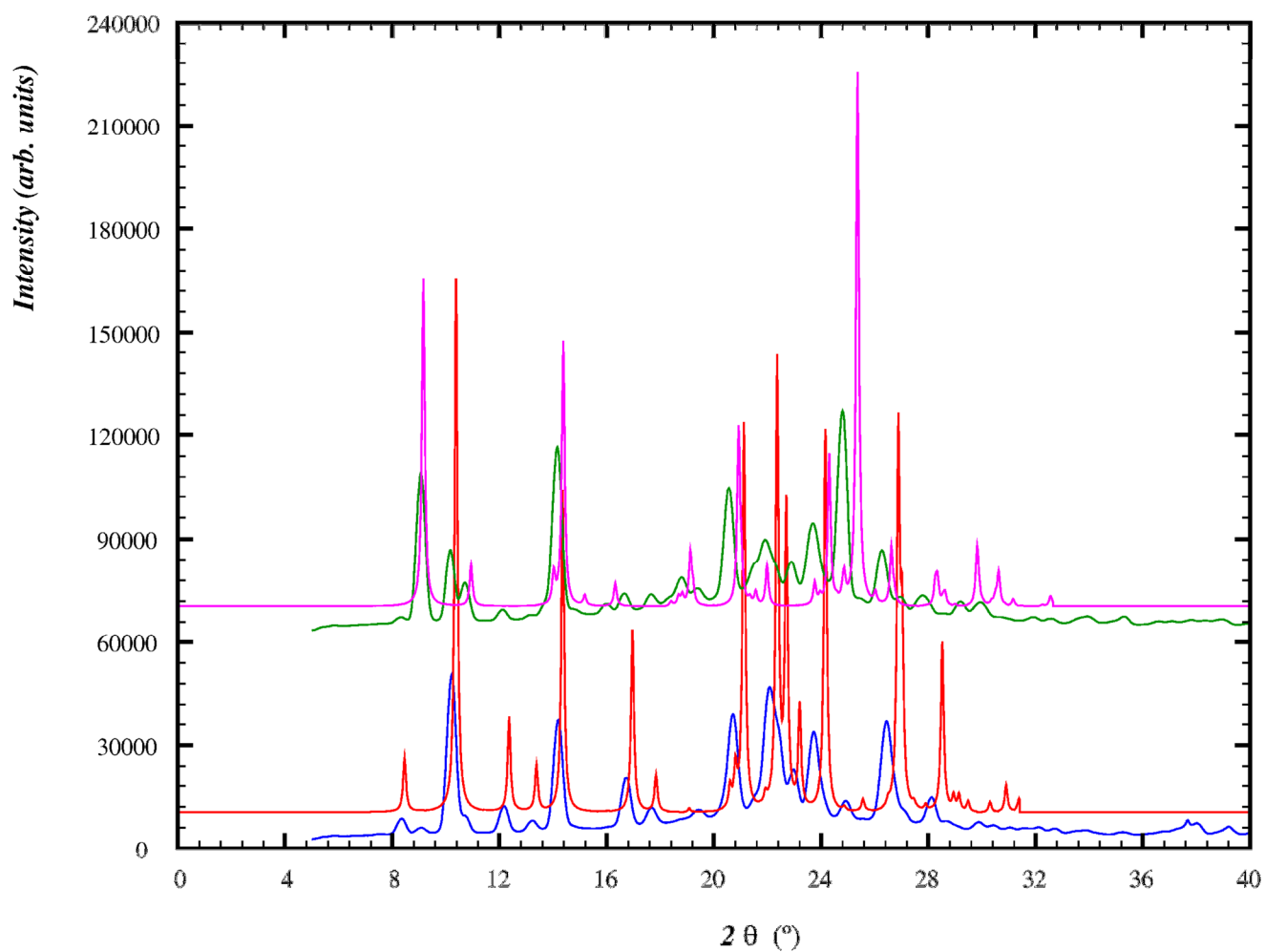
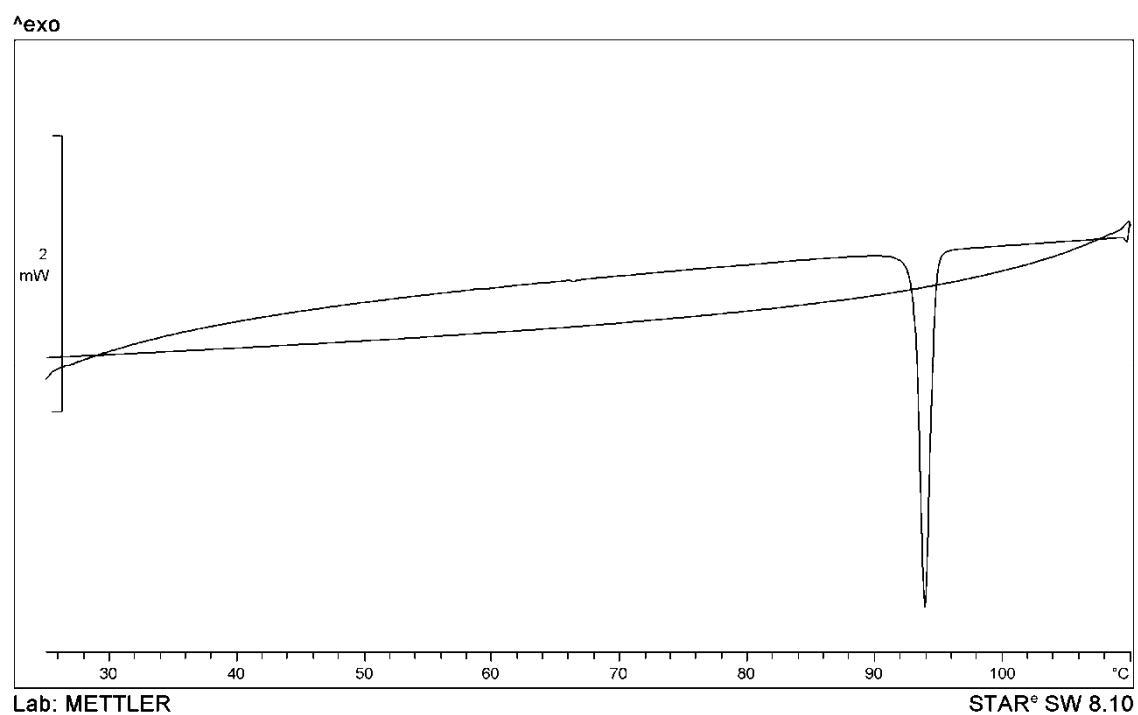
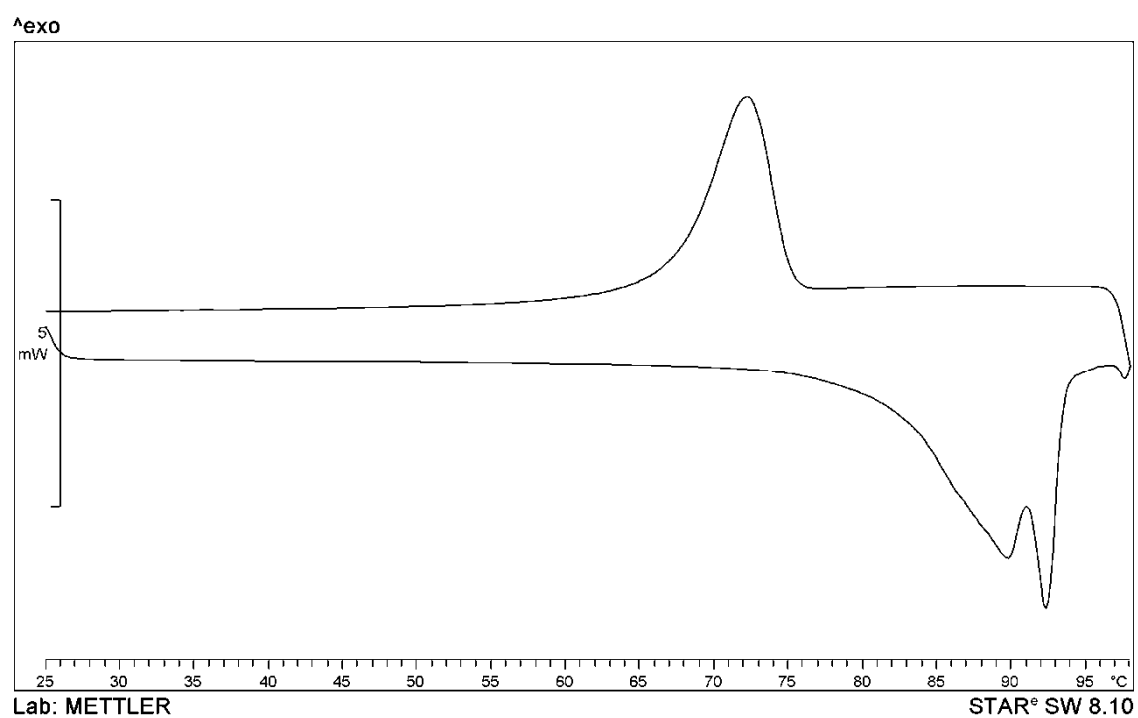


Figure S5. Powder patterns for the two polymorphs. Lower diffractograms: measured data for polymorph II at 30°C (blue) with calculated pattern (using -100°C coordinates) of polymorph II (red) overlaid. Upper diffractograms: measured data for polymorph I at 88°C (post phase transition; green) with calculated pattern (using -100°C coordinates) of polymorph I (pink) overlaid.

DSC data:



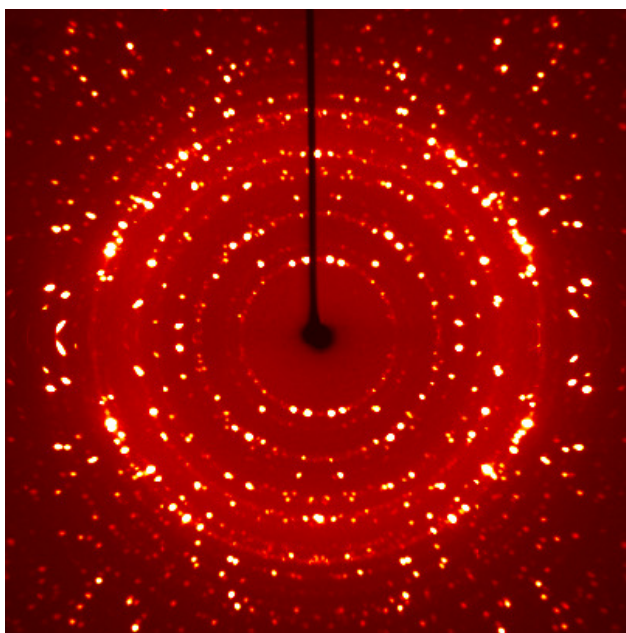
a



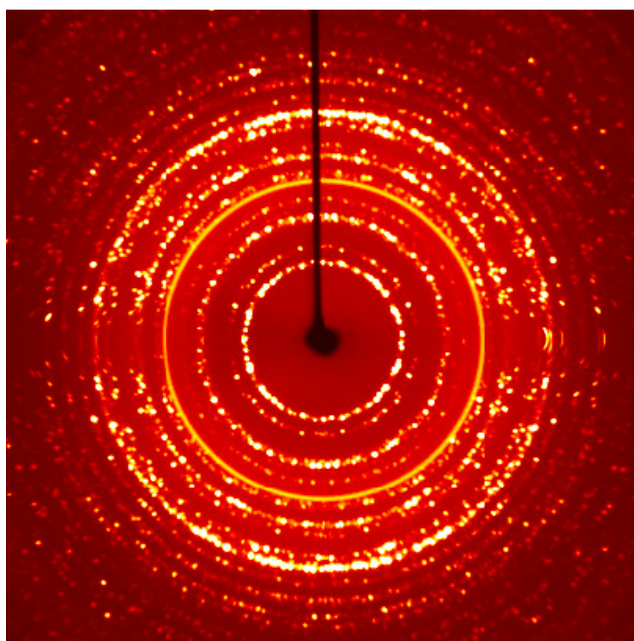
b

Figure S6. DSC scans for polymorphs I (a) and II (b).

X-ray rotation snapshots:



a



b

Figure S7. X-ray CCD snapshots taken on a Bruker Proteum X8 diffractometer with Cu anode by rotating a crystal 360° around the phi axis, just before the phase transition (around 80°C) where it diffracts as a single crystal, and after the phase transition (around 90°C) where the crystal has broken down into small crystallites and hence diffracts as a powder. X-ray snapshots taken between these temperatures have elements of both pictures. This is consistent with the broad phase transition peak that can be seen on the DSC in Figure S6 above.

A3.2 Supplementary information for paper 2

Supplementary information for:

Polymorphic diversity: *N*-phenylbenzamide as a moiety which may encourage polymorphism

Caitlin F. Zipp, Heinrich W. Dirr, Manuel A. Fernandes,* Helder M. Marques and Joseph P. Michael

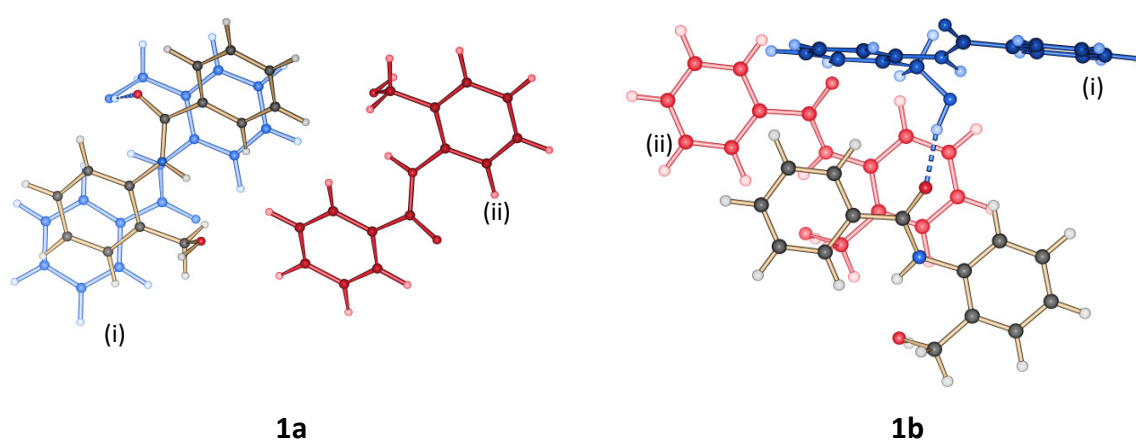


Figure S1. Orientations with highest interaction energies in the polymorphs of **1**. **1a** (i) $1.5-x, -0.5+y, 1.5-z$; $-62.8 \text{ kJ mol}^{-1}$ (ii) $2-x, -y, 1-z$; $-23.5 \text{ kJ mol}^{-1}$; **1b** (i) $1.5-x, 0.5+y, 0.5-z$; $-37.8 \text{ kJ mol}^{-1}$ (ii) $1+x, y, z$; $-27.8 \text{ kJ mol}^{-1}$.

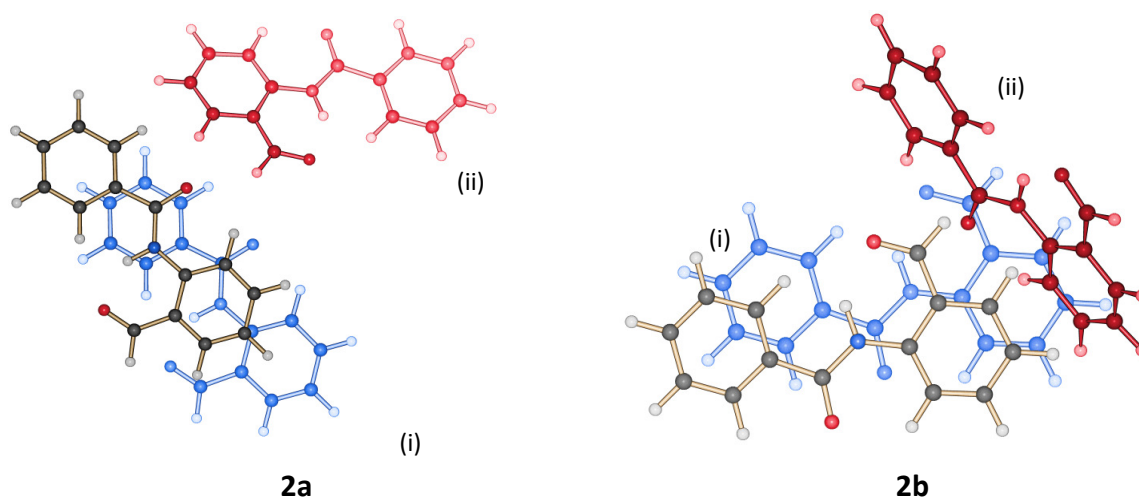


Figure S2. Orientations with highest interaction energies in the polymorphs of **2**. **2a** (i) $1+x, y, z$; $-31.2 \text{ kJ mol}^{-1}$ (ii) $-0.5-x, 0.5+y, 1.5-z$; $-19.0 \text{ kJ mol}^{-1}$; **2b** (i) $1+x, y, z$; $-28.7 \text{ kJ mol}^{-1}$ (ii) $-x, 1-y, -z$; $-17.9 \text{ kJ mol}^{-1}$.

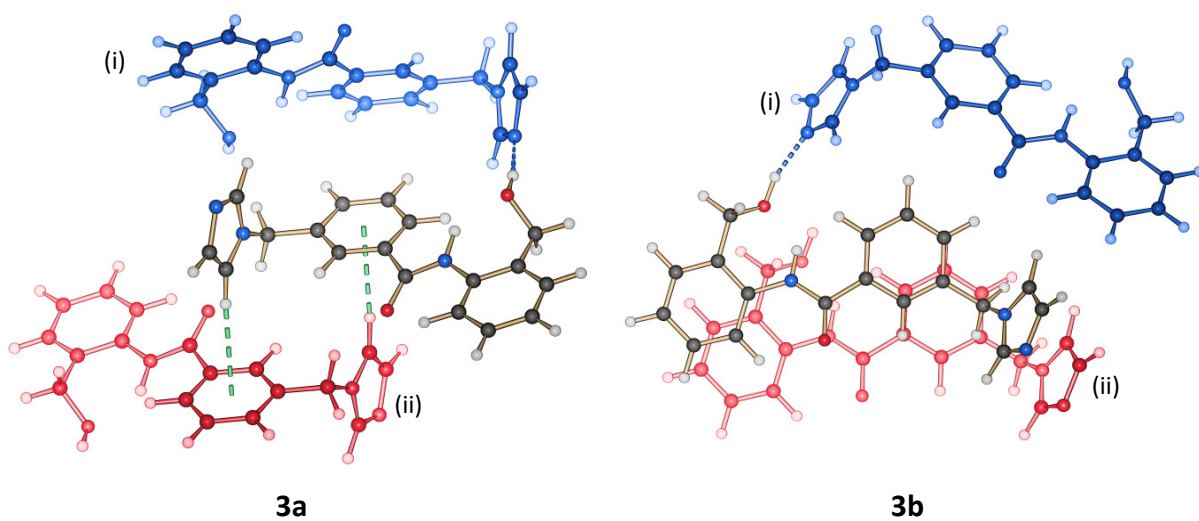


Figure S3. Orientations with highest interaction energies in the polymorphs of **3**. **3a** (i) 0.5-x, 0.5+y, 0.5-z; -67.8 kJ mol⁻¹ (ii) 1-x, -y, 1-z; -48.8 kJ mol⁻¹; **3b** (i) 1-x, 0.5+y, 1.5-z; -73.7 kJ mol⁻¹ (ii) 1+x, y, z; -39.6 kJ mol⁻¹.

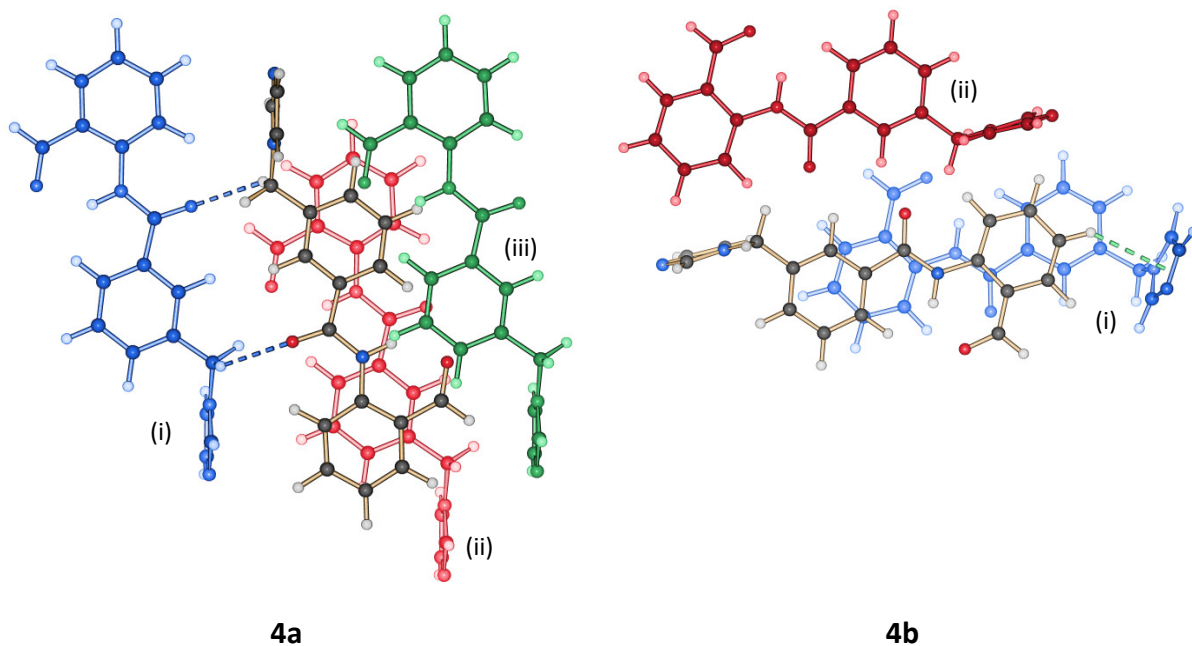


Figure S4. Orientations with highest interaction energies in the polymorphs of **4**. **4a** (i) -x, -y, -z; -36.7 kJ mol⁻¹ (ii) 1-x, -y, -z; -36.6 kJ mol⁻¹; (iii) 1-x, 1-y, -z; -32.9 kJ mol⁻¹; **4b** (i) 1-x, 1-y, 1-z (m1_m2); -49.0 kJ mol⁻¹; (ii) 1-x, -y, 1-z (m2_m2); -32.9 kJ mol⁻¹.

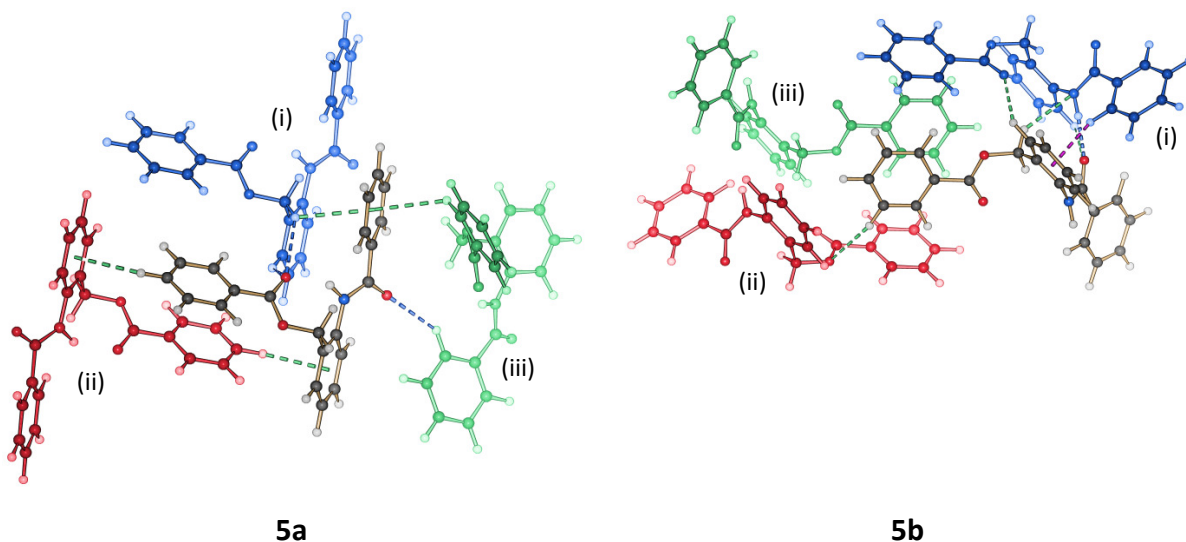


Figure S5. Orientations with highest interaction energies in the polymorphs of **5**. **5a** (i) 1+x, y, z; -50.4 kJ mol⁻¹ (ii) 2-x, 1-y, 2-z; -38.9 kJ mol⁻¹; (iii) 2-x, 0.5+y, 1.5-z; -34.0 kJ mol⁻¹; **5b** (i) 0.5-x, 0.5+y, z; -71.0 kJ mol⁻¹ (ii) 0.5+x, 1.5-y, 1-z; -21.1 kJ mol⁻¹; (iii) -x, 2-y, 1-z; -18.1 kJ mol⁻¹.

Table S1. O-H...O and C-H...O interaction geometries for polymorphs of 1-5 (Å, °).

<i>D</i> -H... <i>A</i>	<i>D</i> -H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> -H... <i>A</i>
Polymorph 1a^a				
N1-H1N...O1	0.88	2.13	2.822(1)	135
O1-H1O...O2 ⁽ⁱ⁾	0.84	1.96	2.791(1)	168
C6-H6...O2	0.95	2.37	2.901(2)	115
C14-H14...O2 ⁽ⁱⁱ⁾	0.95	2.58	3.435(2)	150
Polymorph 1b^a				
N1-H1N...O1	0.88	2.03	2.752(3)	138
O1..H1O...O2 ⁽ⁱⁱⁱ⁾	0.84	1.94	2.763(3)	166
C6-H6...O2	0.95	2.34	2.899(3)	117
C3-H3...O2 ^(iv)	0.95	2.62	3.529(3)	160
Polymorph 2a				
N1-H1N...O1	0.92	2.48	3.407(2)	166
C3-H3...O2 ^(v)	0.95	2.28	2.890(2)	121
Polymorph 2b				
N1A-H1NA...O1A	0.88	1.98	2.707(2)	139
N1B-H1NB...O1B	0.88	1.96	2.681(4)	139
C1A-H1A...O1B ^(vi)	0.95	2.60	3.506(3)	161
C5B-H2B...O2A ^(vii)	0.95	2.43	3.143(1)	132
Polymorph 3a				
N1-H1N...O1	0.87	2.02	2.707(2)	135

O1-H1O...N3 ⁽ⁱ⁾	0.95	1.75	2.691(2)	169
C15-H15A...O2 ^(viii)	0.99	2.49	3.379(2)	149
C15-H15B...O1 ⁽ⁱ⁾	0.99	2.34	3.250(2)	152
C17-H17...O2 ^(xi)	0.95	2.44	3.260(2)	145
Polymorph 3b				
N1-H1N...O1	0.88	1.98	2.692(3)	138
O1-H1O...N3 ^(x)	0.84	1.93	2.756(3)	168
C15-H15B...O2 ^(xi)	0.99	2.41	3.339(3)	157
Polymorph 4a				
N1-H1N...O1	0.91	1.92	2.682(2)	140
C3-H3...N3 ^(xii)	0.95	2.57	3.385(2)	144
C15-H15A...O2 ^(xiii)	0.99	2.52	3.089(2)	117
C15-H15B...O1 ^(xiv)	0.99	2.59	3.514(2)	156
C16-H16...N3 ^(xv)	0.95	2.59	3.538(2)	173
Polymorph 4b				
N1A-H1C...O1A	0.88	1.96	2.680(2)	138
N1B-H1D...O1B	0.88	1.94	2.671(2)	139
C1A-H1A...O2A ^(xvi)	0.95	2.43	3.334(3)	159
C1B-H1B...O2B ^(xvi)	0.95	2.46	3.373(3)	161
C10A-H10A...O1A ^(xvii)	0.95	2.50	3.402(2)	159
C15B-H15C...N3A	0.99	2.49	3.428(3)	158
C16A-H16A...O1A ^(xvii)	0.99	2.49	3.331(3)	147
Polymorph 5a				
N1-H1...O3	0.88	2.05	2.845(4)	150
C3-H3...O3 ^(xii)	0.95	2.50	3.327(5)	142
Polymorph 5b				
N1-H1...O2 ^(xviii)	0.89	2.00	2.869(2)	162
C3-H3...O3 ^(xix)	0.95	2.51	3.313(2)	142

a - extracted from reference 7 (i) ($\frac{3}{2}-x, \frac{1}{2}+y, \frac{3}{2}-z$); (ii) ($1-x, -y, 1-z$); (iii) ($\frac{3}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$); (iv) ($\frac{5}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$); (v) ($-\frac{1}{2}-x, \frac{1}{2}+y, \frac{3}{2}-z$); (vi) ($-x, 1-y, 1-z$); (vii) ($x, \frac{3}{2}-y, \frac{1}{2}+z$); (viii) ($1-x, 2-y, 1-z$); (ix) ($1-x, 1-y, 1-z$); (x) ($1-x, -\frac{1}{2}+y, \frac{3}{2}-z$); (xi) ($2-x, -\frac{1}{2}+y, \frac{3}{2}-z$); (xii) ($-1+x, y, z$); (xiii) ($-x, -y, -z$); (xiv) ($\frac{3}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$); (xv) ($-\frac{1}{2}-x, -\frac{1}{2}+y, -\frac{1}{2}-z$); (xvi) ($x, 1+y, z$); (xvii) ($x, -1+y, z$); (xviii) ($\frac{1}{2}-x, \frac{1}{2}+y, z$); (xix) ($\frac{1}{2}-x, -\frac{1}{2}+y, z$).

Table S2. C-H... π and C=O... π interaction geometries for polymorphs of 1-5, where applicable (Å, °).

<i>D</i> -H... <i>A</i>	<i>H</i> ... <i>Cg</i> or <i>X</i> ... <i>Cg</i>	<i>C</i> ... <i>Cg</i>	C-H... <i>Cg</i> or C-X... <i>Cg</i>
Polymorph 2a			
C8=O2...Cg ⁽ⁱ⁾	3.971(1)	3.572(2)	62.35(7)
Polymorph 3a			
C3-H3...Cg ⁽ⁱⁱ⁾	2.90	3.640(2)	136
C5-H5...Cg ⁽ⁱⁱⁱ⁾	2.75	3.585(2)	147
C18-H18...Cg ^(iv)	2.98	3.927(2)	176
Polymorph 4b			
C1A=O1A...Cg ^(v)	3.787(2)	3.546(2)	69.35(1)
C4B-H4B...Cg ^(vi)	2.92	3.690(3)	139
C13B-H13B...Cg ^(vii)	2.96	3.814(5)	150
Polymorph 5a			
C19-H19...Cg ^(viii)	2.88	3.731(5)	150
Polymorph 5b			
C14-H14...Cg ^(ix)	2.89	3.690(2)	143

(i) Cg = C9-C10-C11-C12-C13-C14, (-1+x, y, z); (ii) Cg = N2-C16-N3-C17-C18, (-½+x, ¾-y, ½+z); (iii) Cg = C2-C3-C4-C5-C6-C7, (½-x, -½+y, ¾-z); (iv) Cg = C9-C10-C11-C12-C13-C14, (1-x, 2-y, 1-z); (v) Cg = C9A-C10A-C11A-C12A-C13A-C14A, (½-x, ½+y, ½-z); (vi) Cg = N2A-C16A-N3A-C17A-C18A, (1-x, 1-y, 1-z); (vii) Cg = N2B-C16B-C17B-N3B-C18B, (x, 1+y, z); (viii) Cg = C2-C3-C4-C5-C6-C7, (2-x, 1-y, 2-z); (ix) Cg = C2-C3-C4-C5-C6-C7, (½-x, -½+y, z).

Appendix for Part 4

Reactions of a corrole-based biomimetic model

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A4.1 Derivation of equations for the determination of stability constants

The binding isotherm of a system with $\log K < 4$

An equilibrium exists between the chromophore (M) and free ligand in solution:



The equilibrium constant can be defined as:

$$K = \frac{[ML]}{[M][L]}$$

From Beer's Law (where b is the path length of the cell) the initial and final absorbances can be defined:

$$A_0 = \varepsilon_M b [M]_0$$

$$A_1 = \varepsilon_{ML} b [ML]_1$$

At any point during the titration:

$$A = \varepsilon_M b [M] + \varepsilon_{ML} b [ML]$$

$$[M]_0 = [M] + [ML]$$

$$[ML]_1 = [M]_0 = [M] + [ML]$$

$$\therefore A = \varepsilon_M b ([M]_0 - [ML]) + \varepsilon_{ML} b [ML]$$

$$A = \varepsilon_M b [M]_0 - \varepsilon_M b [ML] + \varepsilon_{ML} b [ML]$$

$$A - \varepsilon_M b [M]_0 = [ML] (\varepsilon_M b + \varepsilon_{ML} b)$$

$$\therefore [ML] = \frac{A - \varepsilon_M b [M]_0}{\varepsilon_{ML} b - \varepsilon_M b}$$

$$[ML] = \frac{A - A_0}{\varepsilon_{ML} b - \varepsilon_M b}$$

Equation A4.1

Similarly:

$$A = \varepsilon_M b [M] + \varepsilon_{ML} b [ML]$$

$$A = \varepsilon_M b [M] + \varepsilon_{ML} b ([ML]_1 - [M])$$

$$A = \varepsilon_M b [M] + \varepsilon_{ML} b [ML]_1 - \varepsilon_{ML} b [M]$$

$$A - \varepsilon_M b [M]_1 = [M] (\varepsilon_M b - \varepsilon_{ML} b)$$

$$\therefore [M] = \frac{A - \varepsilon_M b[M]_1}{\varepsilon_M b - \varepsilon_{ML} b}$$

$$[M] = \frac{A - A_1}{\varepsilon_M b - \varepsilon_{ML} b}$$

Equation A4.2

Considering the equilibrium constant:

$$K = \frac{[ML]}{[M][L]}$$

Substituting in equations A4.1 and 4.12:

$$K = \frac{A - A_0}{\varepsilon_{ML} b - \varepsilon_M b} \cdot \frac{1}{L} \cdot \frac{\varepsilon_M b - \varepsilon_{ML} b}{A - A_1}$$

$$K = \frac{A - A_0}{\varepsilon_{ML} b - \varepsilon_M b} \cdot \frac{1}{L} \cdot \frac{\varepsilon_{ML} b - \varepsilon_M b}{A_1 - A}$$

$$K = \frac{A - A_0}{A_1 - A} \cdot \frac{1}{L}$$

$$K[L] = \frac{A - A_0}{A_1 - A}$$

$$\therefore K[L] = \frac{A_0 - A}{A - A_1}$$

Assuming that $[L]_0 \approx [L]$ and K is small:

$$K[L] = \frac{A_0 - A}{A - A_1}$$

$$A_0 - A = K[L](A - A_1)$$

$$A_0 - A = K[L]A - K[L]A_1$$

$$K[L]A + A = K[L]A_1 + A_0$$

$$A(K[L] + 1) = K[L]A_1 + A_0$$

$$\therefore A = \frac{A_0 + A_1 K[L]}{1 + K[L]}$$

Equation A4.3

The binding isotherm of a system with $\log K > 4$

If K is large, $[L]_{free} \neq [L]_T$. An expression for $[L]_{free}$ can be derived.

$$[L]_{free} = [L]_T - [ML]$$

$$[ML] = [M]_T - [M]$$

$$[M]_T = [ML] + [M]$$

From the equilibrium constant:

$$[M]_T = [ML] + \frac{[ML]}{K[L]_{free}}$$

$$[M]_T = [ML] \left(1 + \frac{1}{K[L]_{free}} \right)$$

$$[M]_T = [ML] \left(\frac{1 + K[L]_{free}}{K[L]_{free}} \right)$$

$$\therefore [ML] = \frac{[M]_T K [L]_{free}}{1 + K [L]_{free}}$$

$$\therefore [L]_{free} = [L]_T - \frac{[M]_T K [L]_{free}}{1 + K [L]_{free}}$$

$$\therefore [L]_{free} (1 + K [L]_{free}) = [L]_T (1 + K [L]_{free}) - [M]_T K [L]_{free}$$

$$[L]_{free} + K [L]_{free}^2 = [L]_T + K [L]_T [L]_{free} - [M]_T K [L]_{free}$$

$$K [L]_{free}^2 + (1 + [M]_T K - [L]_T K) [L]_{free} - [L]_T = 0$$

This has the form:

$$a_1 [L]_{free}^2 + a_2 [L]_{free} + a_3 = 0$$

where $a_1 = K$; $a_2 = 1 + [M]_T K - [L]_T K$ and $a_3 = -[L]_T$

$$\therefore [L]_{free} = \frac{-a_2 \pm \sqrt{a_2^2 - 4a_1 a_3}}{2a_1}$$

$$[L]_{free} > 0$$

$$\therefore [L]_{free} = \frac{-a_2 + \sqrt{a_2^2 - 4a_1 a_3}}{2a_1}$$

Substituted into equation A4.3:

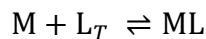
$$A = \frac{A_0 + A_1 K [L]_{free}}{1 + K [L]_{free}}$$

$$\begin{aligned}
A &= \frac{A_0 + A_1 K \left(\frac{-a_2 + \sqrt{a_2^2 - 4a_1 a_3}}{2a_1} \right)}{1 + K \left(\frac{-a_2 + \sqrt{a_2^2 - 4a_1 a_3}}{2a_1} \right)} \\
&= \frac{A_0 + A_1 K \left(\frac{-(1 + [M]_T K - [L]_T K) + \sqrt{(1 + [M]_T K - [L]_T K)^2 + 4K[L]_T}}{2K} \right)}{1 + K \left(\frac{-(1 + [M]_T K - [L]_T K) + \sqrt{(1 + [M]_T K - [L]_T K)^2 + 4K[L]_T}}{2K} \right)} \\
&= \frac{A_0 + A_1 \frac{1}{2} \left(-(1 + [M]_T K - [L]_T K) + \sqrt{(1 + [M]_T K - [L]_T K)^2 + 4K[L]_T} \right)}{1 + \frac{1}{2} \left(-(1 + [M]_T K - [L]_T K) + \sqrt{(1 + [M]_T K - [L]_T K)^2 + 4K[L]_T} \right)}
\end{aligned}$$

Equation A4.4

A4.2 Derivation of equations for the correction of K taking free ligand and metal into account

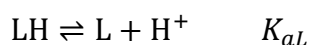
An equilibrium exists between the chromophore (M) and free ligand in solution:



The equilibrium constant can be defined as:

$$K = \frac{[ML]}{[M][L]}$$

An equilibrium also exists for the ligand:



Assume L and not LH binds to M

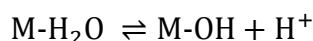
$$\begin{aligned} K_{aL} &= \frac{[L][H^+]}{[LH]} \\ [L_T] &= [L] + [LH] \\ [L_T] &= [L] + \frac{[L][H^+]}{K_{aL}} \\ [L_T] &= [L] \left(1 + \frac{[H^+]}{K_{aL}} \right) \\ [L] &= \frac{[L_T]}{1 + \frac{[H^+]}{K_{aL}}} \\ \therefore [L] &= \frac{[L_T]}{1 + 10^{pK_a - pH}} \end{aligned}$$

Equation A4.5

Thus the fraction of available ligand is given by:

$$\frac{1}{1 + 10^{pK_a - pH}}$$

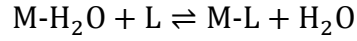
In addition to the equilibrium between protonated and deprotonated ligand, there exists an equilibrium between the aqua and hydroxo form of the metal as follows:



The equilibrium constant can be defined as:

$$K_{aM} = \frac{[M-OH][H^+]}{[M-H_2O]}$$

M-H₂O and not M-OH is able to undergo ligand substitution reactions as follows:



$$K = \frac{[ML]}{[M-H_2O][L]}$$

Thus:

$$K = \frac{[ML]}{[M_T][L]}$$

$$[M_T] = [M-H_2O] + [M-OH]$$

$$[M_T] = [M-H_2O] + \frac{K_{aM}[M-H_2O]}{[H^+]}$$

$$[M_T] = [M-H_2O] \left(1 + \frac{K_{aM}}{[H^+]} \right)$$

$$[M-H_2O] = \frac{[M_T]}{1 + \frac{K_{aM}}{[H^+]}}$$

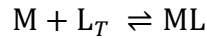
$$\therefore [M-H_2O] = \frac{[M_T]}{1 + 10^{pH - pK_{aM}}}$$

Equation A4.6

Thus the fraction of available chromophore is given by:

$$\frac{1}{1 + 10^{pH - pK_{aM}}}$$

From the equilibrium between the chromophore and ligand we have:



Taking the free ligand (Equation A4.5) and free chromophore (Equation A4.6) into account:

$$K = \frac{[ML]}{[M][L]}$$

$$K = \frac{[ML]}{[M][L]} (1 + 10^{pK_a - pH}) (1 + 10^{pH - pK_{aM}})$$

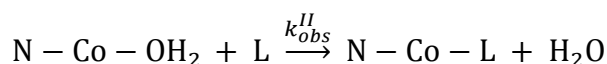
Thus:

$$K = K_{obs} (1 + 10^{pK_a - pH}) (1 + 10^{pH - pK_{aM}})$$

Equation A4.7

A4.3 Derivation of equations for the determination of pH-independent k values

The reaction between the metal and an incoming ligand has an associated rate constant as follows:



where

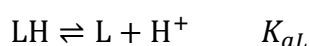
$$\frac{d[N - Co - L]}{dt} = k_{obs}^{II}[N - Co - OH_2][L]$$

where k_{obs}^{II} is the observed second order rate constant. Under pseudo first order conditions, where $[L] \gg [N - Co - L]$, such that:

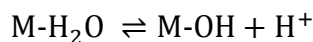
$$\frac{d[N - Co - L]}{dt} = k_{obs}^I[N - Co - OH_2] \quad \text{and} \quad k_{obs}^I = k_{obs}^{II}[L]$$

k_{obs}^I changes with increasing ligand concentration in a linear fashion and from the gradient of this plot, k_{obs}^{II} is determined. If the intercept does not pass through the origin, the value of the intercept corresponds to the first order rate constant of the reverse reaction, the hydrolysis of $[N - Co - L]$ by water.

k_{obs}^{II} will vary with pH for two reasons. Firstly, there exists an equilibrium for the incoming ligand:



where only L , and not LH^+ , will react with cobalt(III). Secondly, an equilibrium exists between the aqua and hydroxo form of the metal as follows:



where the hydroxo complex is inert to substitution.

As in Appendix 4.2, Equations A4.5 and A4.6, expressions for the free ligand and aqua form of the metal are taken into account:

$$k^{II} = k_{obs}^{II}(1 + 10^{pK_{aL}-pH})(1 + 10^{pH-pK_{aM}})$$

Equation A4.8

A4.4 Wavelength dependence of pK_a values

The spectroscopic changes of DPTC-Co and vitamin B₁₂ in a buffered 80:20 methanol:water solvent system associated with the increase in pH are illustrated in Figures A4.1 and A4.3 respectively. The raw absorbance data for these two titrations can be found in **Digital Appendix 4.1**. The transposed data used for the determination of the stability constant can be found in Tables A4.1 and A4.2 and the binding isotherms are illustrated in Figure A4.2 and A4.4. pK_a values were calculated by non-linear least squares methods by fitting the data to Equation 4.4.1 (**Section 4.4**)

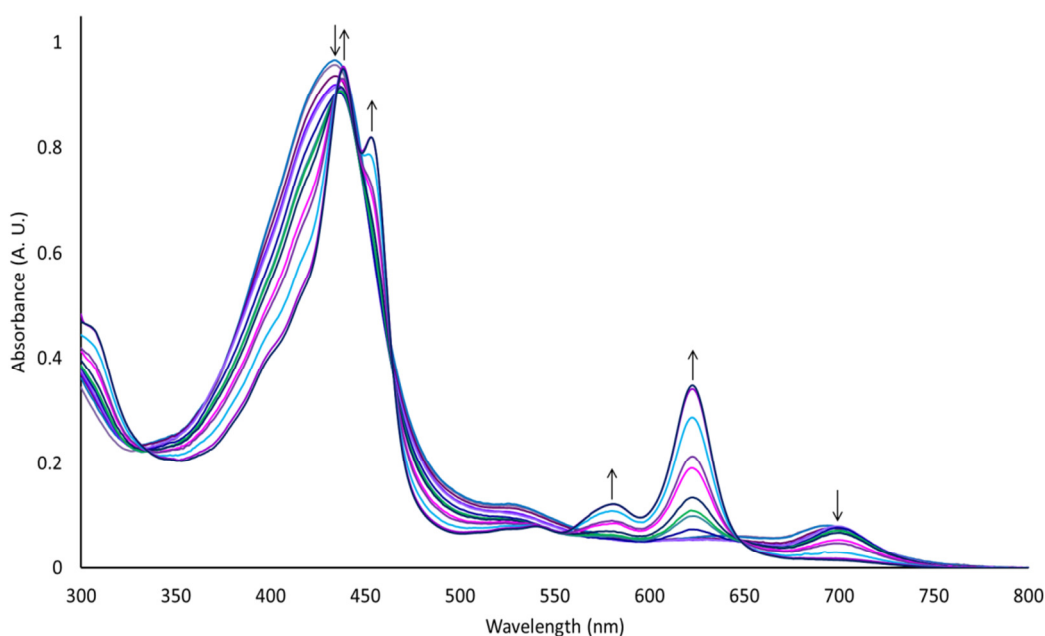


Figure A4.1 Spectroscopic changes of DPTC-Co in aqueous 80:20 methanol:buffer solution with varying pH

Table A4.1 Transposed data for the determination of the pK_a s of DPTC-Co at specific wavelengths and the weighted overall pK_a s and associated errors

pH	Absorption at wavelength (nm)						
	300	400	425	452	579	621	696
3.545	0.334	0.664	0.927	0.680	0.061	0.059	0.081
3.73	0.343	0.669	0.937	0.686	0.061	0.058	0.082
4.187	0.351	0.669	0.934	0.686	0.062	0.058	0.082
4.632	0.354	0.667	0.928	0.686	0.062	0.058	0.080
5.14	0.356	0.662	0.922	0.682	0.062	0.058	0.078
5.625	0.357	0.658	0.916	0.678	0.061	0.057	0.078
6.255	0.359	0.647	0.901	0.669	0.060	0.056	0.077
6.939	0.363	0.629	0.882	0.657	0.056	0.055	0.078
7.451	0.366	0.621	0.874	0.656	0.056	0.056	0.080
7.835	0.367	0.607	0.862	0.654	0.055	0.060	0.079
8.187	0.370	0.597	0.853	0.658	0.056	0.068	0.078
8.636	0.370	0.588	0.844	0.658	0.057	0.074	0.076
8.881	0.375	0.566	0.821	0.673	0.061	0.099	0.071
9.001	0.378	0.562	0.814	0.676	0.064	0.109	0.071
9.272	0.386	0.547	0.796	0.695	0.071	0.134	0.066
9.47	0.392	0.531	0.777	0.708	0.077	0.155	0.061
9.753	0.404	0.512	0.753	0.729	0.085	0.190	0.053
9.913	0.410	0.498	0.735	0.742	0.090	0.211	0.047
10.121	0.437	0.456	0.680	0.788	0.109	0.284	0.030

TableA4.1 continued

10.241	0.475	0.436	0.655	0.803	0.117	0.314	0.023
10.452	0.474	0.416	0.632	0.816	0.122	0.337	0.018
10.753	0.457	0.409	0.625	0.814	0.121	0.340	0.015
11.158	0.460	0.406	0.621	0.815	0.122	0.343	0.015
11.475	0.463	0.400	0.612	0.814	0.123	0.347	0.014
11.707	0.471	0.401	0.611	0.815	0.126	0.352	0.016
K_1	No fit	1.072×10^{-7}	2.787×10^{-7}	3.740×10^{-7}	9.997×10^{-8}	No fit	No fit
err		3.768×10^{-8}	1.121×10^{-7}	2.251×10^{-7}	7.320×10^{-8}		
1/Rel % Error		2.844×10^{-2}	2.486×10^{-2}	1.662×10^{-2}	1.366×10^{-2}		
Sum (1/Rel % Error)	8.358×10^{-2}						
Weighted K_1 fraction		3.647×10^{-8}	8.289×10^{-8}	7.436×10^{-8}	1.634×10^{-8}		
Weighted error fraction		1.282×10^{-8}	3.334×10^{-8}	4.476×10^{-8}	1.196×10^{-8}		
Weighted K_1	2.101×10^{-7}						
Weighted err	1.029×10^{-7}						
pK_1	6.68						
σ	0.17						
K_2	1.619×10^{-10}	1.596×10^{-10}	1.584×10^{-10}	1.918×10^{-10}	1.763×10^{-10}	1.163×10^{-10}	1.456×10^{-10}
err	3.377×10^{-11}	1.785×10^{-11}	1.640×10^{-11}	2.509×10^{-11}	2.242×10^{-11}	1.737×10^{-11}	1.670×10^{-11}
1/Rel % Error	4.795×10^{-2}	8.941×10^{-2}	9.660×10^{-2}	7.645×10^{-2}	7.863×10^{-2}	6.693×10^{-2}	8.720×10^{-2}

TableA4.1 continued

Sum (1/Rel % Error)	0.543	2.627×10^{-11}	2.818×10^{-11}	2.699×10^{-11}	2.552×10^{-11}	1.433×10^{-11}	2.338×10^{-11}
Weighted K_2 fraction	1.430×10^{-11}	2.938×10^{-12}	2.917×10^{-12}	3.531×10^{-12}	3.246×10^{-12}	2.140×10^{-12}	2.681×10^{-12}
Weighted error fraction	2.981×10^{-12}						
Weighted K_2	1.590×10^{-10}						
Weighted err	2.043×10^{-11}						
pK₂	9.80						
σ	0.05						

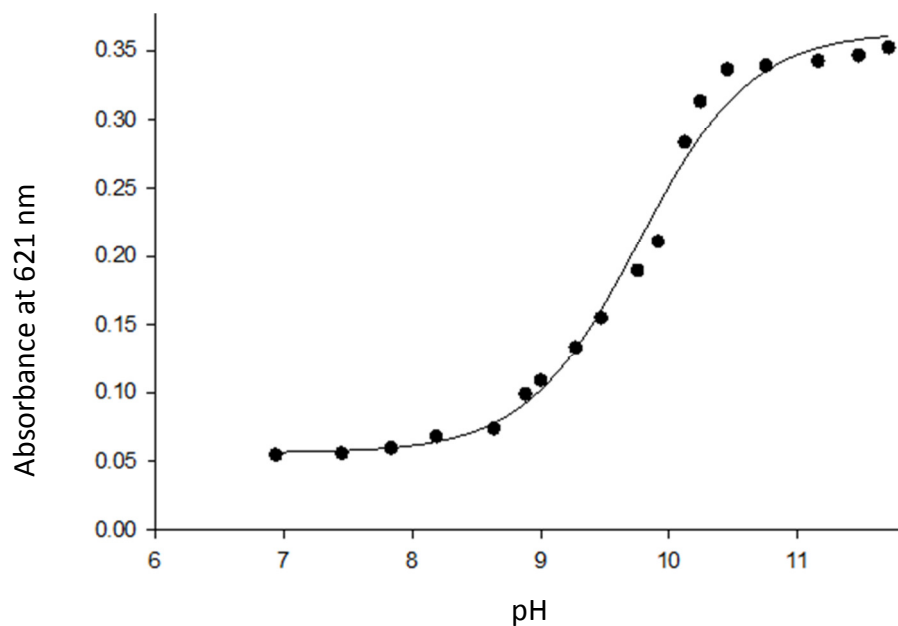


Figure A4.2 Absorbance changes of DPTC-Co in 80:20 methanol:buffer solution with varying pH between 6.9 and 11.7 at 621 nm. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve for $pK_a = 9.76 \pm 0.06$ in Equation 4.4.1 (Section 4.4)

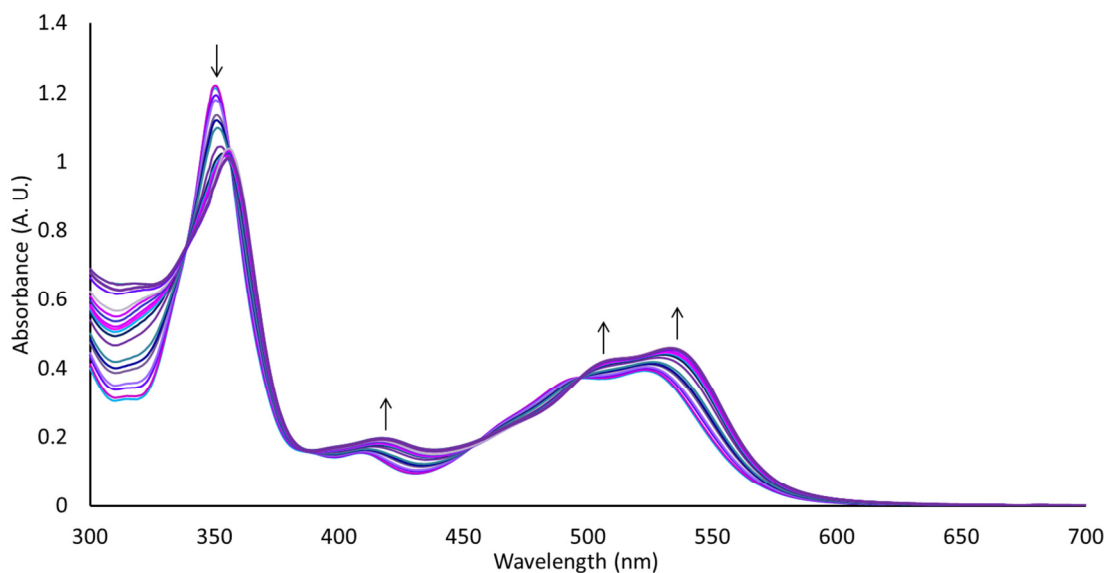


Figure A4.3 Spectroscopic changes of vitamin B_{12a} in aqueous 80:20 methanol:buffer solution with varying pH

Table A4.2 Transposed data for the determination of the pK_a of vitamin B_{12a} at specific wavelengths and the weighted overall pK_a and associated errors

pH	Absorption at wavelength (nm)					
	310	350	425	480	530	550
4.138	0.304	1.215	0.102	0.310	0.375	0.187
4.559	0.310	1.218	0.102	0.311	0.378	0.190
5.036	0.313	1.222	0.103	0.311	0.379	0.193
5.837	0.322	1.210	0.105	0.310	0.382	0.197
6.429	0.338	1.193	0.111	0.307	0.387	0.207
6.651	0.350	1.179	0.114	0.304	0.392	0.215
7.079	0.387	1.132	0.126	0.297	0.404	0.237
7.198	0.401	1.117	0.131	0.294	0.408	0.245
7.344	0.419	1.092	0.137	0.290	0.415	0.256
7.730	0.467	1.028	0.153	0.281	0.431	0.285
7.970	0.493	0.999	0.162	0.276	0.440	0.301
8.119	0.506	0.983	0.165	0.274	0.444	0.309
8.233	0.513	0.975	0.166	0.272	0.446	0.314
8.361	0.520	0.971	0.168	0.272	0.449	0.319
8.522	0.529	0.961	0.170	0.271	0.452	0.324
8.725	0.536	0.958	0.172	0.270	0.454	0.328
9.133	0.550	0.952	0.174	0.270	0.457	0.334

Table A4.2 continued

K_a	3.774×10^{-8}	3.952×10^{-8}	4.118×10^{-8}	4.381×10^{-8}	3.928×10^{-8}	3.740×10^{-8}
Err	1.822×10^{-9}	1.307×10^{-9}	8.685×10^{-10}	1.648×10^{-9}	1.962×10^{-9}	1.663×10^{-9}
Rel % Error	4.828	3.306	2.109	3.761	4.995	4.446
1/Rel % Error	0.207	0.302	0.474	0.266	0.200	0.225
Sum (1/Rel % Error)	1.675					
Weighted K_a fraction	4.667×10^{-9}	7.137×10^{-9}	1.166×10^{-8}	6.957×10^{-9}	4.696×10^{-9}	5.023×10^{-9}
Weighted error fraction	2.25×10^{-10}	2.360×10^{-10}	2.459×10^{-10}	2.616×10^{-10}	2.346×10^{-10}	2.233×10^{-10}
Weighted K_a	4.014×10^{-8}					
Weighted err	1.427×10^{-9}					
pK_a	7.40					
σ	0.02					

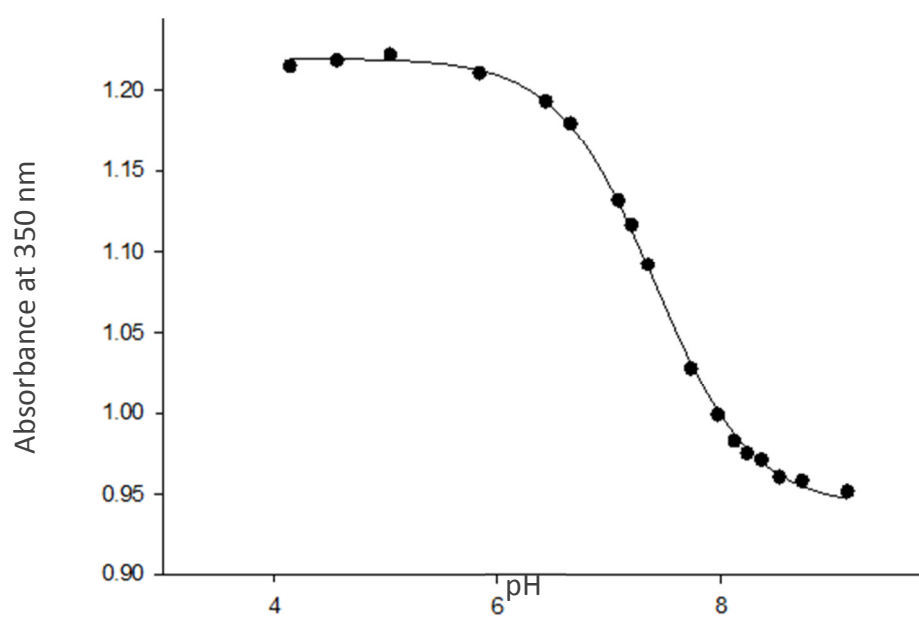


Figure A4.4 Absorbance changes of vitamin B_{12a} in 80:20 methanol:buffer solution with varying pH at 350 nm. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve for $pK_a = 7.40 \pm 0.02$ from Equation 4.4.1 (**Section 4.4**)

A4.5 Beer's Law

The data pertaining to the determination of the extinction coefficient of DPTC-Co (as in Figure 4.5.2, **Section 4.5.3**) is presented in Table A4.3.

Table A4.3 The increase in absorbance with increasing DPTC-Co concentration at specific wavelengths

DPTC-Co concentration (M x 10 ⁻⁵)	Absorbance (A. U.) at wavelength (nm)		
	388	437	610
0	-0.013	-0.011	-0.006
0.0782	0.013	0.014	-0.001
0.156	0.040	0.040	0.006
0.313	0.094	0.093	0.022
0.469	0.151	0.151	0.034
0.702	0.231	0.232	0.053
0.935	0.313	0.313	0.074
1.167	0.379	0.382	0.088
1.399	0.463	0.467	0.109
1.630	0.546	0.552	0.128
1.938	0.663	0.665	0.157
2.321	0.811	0.806	0.194
2.702	0.958	0.946	0.229
3.082	1.108	1.089	0.267
3.460	1.257	1.229	0.300
3.837	1.410	1.372	0.335
4.213	1.559	1.511	0.375
4.587	1.711	1.649	0.409
4.959	1.862	1.788	0.448
5.330	2.017	1.927	0.483
5.700	2.164	2.062	0.521

The regression statistics and ANOVA tests for the fit of the data to the linear best-fit line are summarised in Table A4.4

Table A4.4 Statistical analysis of the linear relationship between increase in absorbance and concentration of DPTC-Co at specific wavelengths

Data from wavelength (nm)

388

Regression Statistics

Multiple R

0.999463503

R Square

0.998927294

Adjusted R Square

0.998870836

Standard Error

0.02405253

Observations

21

ANOVA

df

SS

MS

F

Significance F

Regression

1

10.2359542

10.2359542

17693.21627

1.11334E-29

Residual

19

0.01099196

0.00057852

Total

20

10.2469461

Coefficients

Standard Error

t Stat

P-value

Lower 95%

Upper 95%

Lower 95.0%

Upper 95.0%

Intercept

-0.0449737

0.00850066

-5.29061327

4.17129E-05

-0.06276579

-0.0271816

-0.06276579

-0.02718161

X Variable 1

38136.2730

286.704728

133.0158497

1.11334E-29

37536.19315

38736.352

37536.1931

38736.3529

437

Regression Statistics

Multiple R

0.999878434

R Square

0.999756883

Adjusted R Square

0.999744087

Standard Error

0.010948913

Observations

21

Table A4.4 continued

ANOVA					
	<i>df</i>	<i>SS</i>	<i>MS</i>	<i>F</i>	<i>Significance F</i>
Regression	1	9.366431377	9.366431377	78132.575	8.3589E-36
Residual	19	0.002277695	0.000119879		
Total	20	9.368709073			

	<i>Coefficients</i>	<i>Standard Error</i>	<i>t Stat</i>	<i>P-value</i>	<i>Lower 95%</i>	<i>Upper 95%</i>	<i>Lower 95.0%</i>	<i>Upper 95.0%</i>
Intercept	-0.0281717	0.003869572	-7.280315528	6.600E-07	-0.0362708	-0.020072	-0.0362708	-0.0200725
X Variable 1	36480.531	130.5103901	279.5220492	8.358E-36	36207.3702	36753.69	36207.370	36753.693

610

Regression Statistics	
Multiple R	0.999423459
R Square	0.998847251
Adjusted R Square	0.998786579
Standard Error	0.006019241
Observations	21

ANOVA					
	<i>df</i>	<i>SS</i>	<i>MS</i>	<i>F</i>	<i>Significance F</i>
Regression	1	0.596487352	0.596487352	16463.33226	2.20577E-29
Residual	19	0.000688394	3.62313E-05		
Total	20	0.597175746			

	<i>Coefficients</i>	<i>Standard Error</i>	<i>t Stat</i>	<i>P-value</i>	<i>Lower 95%</i>	<i>Upper 95%</i>	<i>Lower 95.0%</i>	<i>Upper 95.0%</i>
Intercept	-0.0136525	0.002127324	-6.417705541	3.74112E-06	-0.018105	-0.009199	-0.018105	-0.009199
X Variable 1	9206.0790	71.74899619	128.3095174	2.20577E-29	9055.9067	9356.2514	9055.9067	9356.2514

A4.6 Wavelength dependence of stability constants

The spectroscopic changes associated with the coordination of DMAP to DPTC-Co are illustrated in Figure A4.5 and to vitamin B_{12a} in Figure A4.7. The raw absorbance data and data corrected for dilution for these two titrations can be found in **Digital Appendix 4.2**. The transposed data used for the determination of the stability constant can be found in Tables A4.5 and A4.6 and the binding isotherms are illustrated in Figure A4.6 and A4.8. The final stability constants were determined from the sum of the weighted K_{obs} values obtained for each wavelength at which there was a large spectral change. pH-independent stability constants, K , were determined using Equation A4.7. Stability constants were determined using Equation A4.3. In the case of $K > 4$ (as in this case) stability constants were determined using Equation A4.4. The error was calculated from the sum of weighted relative percentage error reciprocals using Microsoft Excel. These are examples of the determination of the stability constants for the binding of DMAP to DPTC-Co and to vitamin B_{12a}. The transposed data and binding isotherms for the binding of other ligands can be found in **Digital Appendix 4.3**.

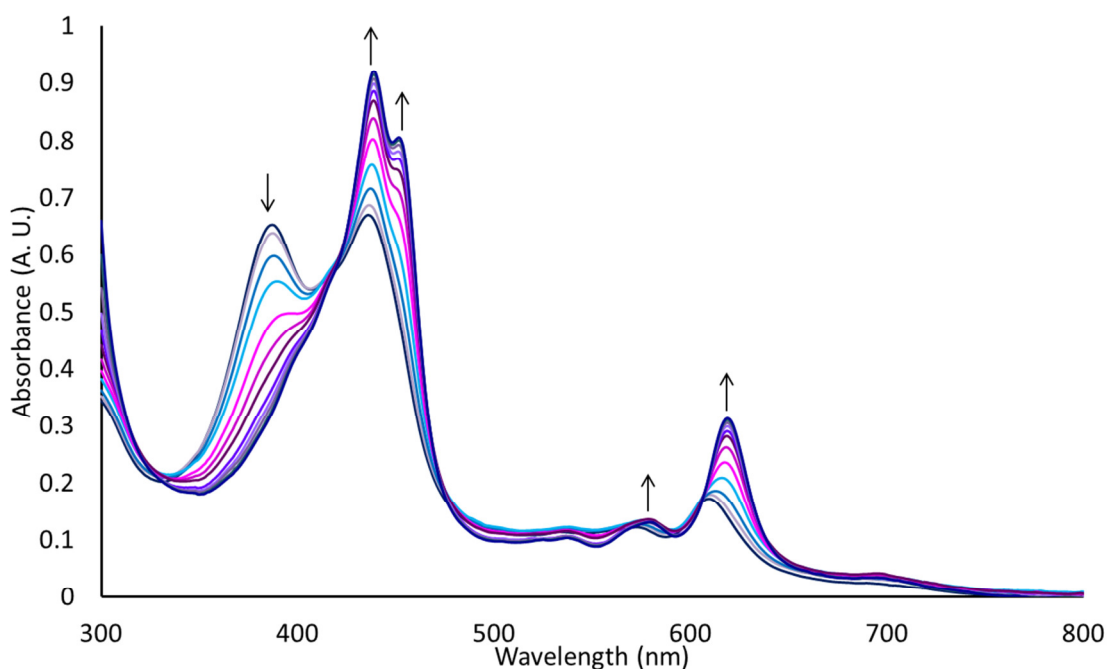


Figure A4.5 Spectroscopic changes associated with the binding of DMAP to DPTC-Co

Table A4.5 Transposed data for the determination of the stability constant for the binding of DMAP to DPTC-Co at specific wavelengths and the weighted overall stability constant and associated errors

DMAP concentration ($M \times 10^{-5}$)	Absorption at wavelength (nm)			
	385	437	450	617
0.000	0.650	0.669	0.517	0.150
0.146	0.635	0.687	0.538	0.163
0.509	0.593	0.716	0.573	0.180
1.088	0.544	0.757	0.624	0.209
2.163	0.475	0.800	0.675	0.236
3.576	0.426	0.833	0.717	0.262
5.656	0.390	0.862	0.750	0.280
9.016	0.353	0.877	0.768	0.287
12.251	0.337	0.888	0.781	0.296
16.582	0.327	0.897	0.791	0.301
22.400	0.316	0.904	0.798	0.306
27.824	0.310	0.909	0.803	0.309
<i>K</i>	55165.215	67366.170	71190.250	69850.143
err	1301.937	2878.137	2483.448	3795.229
[Metal] ($M \times 10^{-6}$)	9.710	4.630	7.270	8.130
Err ($\times 10^{-6}$)	1.920	2.180	1.970	3.500
Relative % Error	2.360	4.272	3.488	5.433
1/Rel % Error	0.424	0.234	0.287	0.184
Sum (1/Rel % Error)	1.128			
Weighted <i>K</i> fraction	20713.102	13972.581	18083.832	11392.028
Weighted error fraction	488.843	596.961	630.848	618.973
Weighted <i>K</i>	64161.543			
Weighted err	2335.626			
Corrected weighted <i>K</i>	210196.294			
Corrected weighted error	7651.624			
Log <i>K</i>	5.32			
σ	0.02			

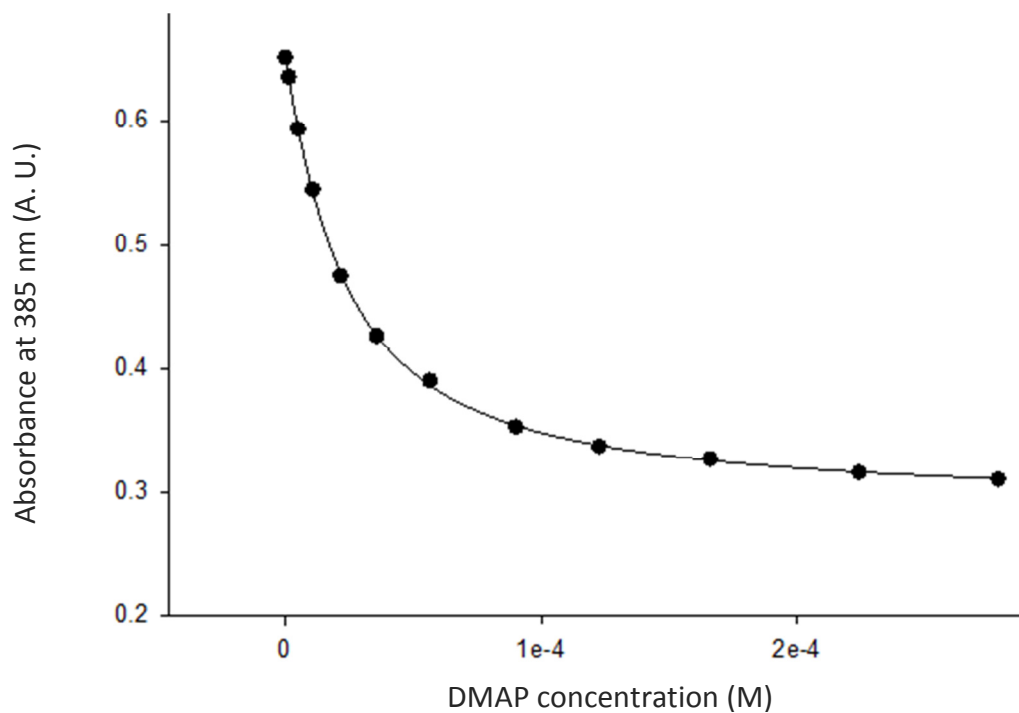


Figure A4.6 Change in absorbance at 385 nm with increasing concentration of DMAP during the coordination of DMAP to DPTC-Co. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve from Equation A4.4

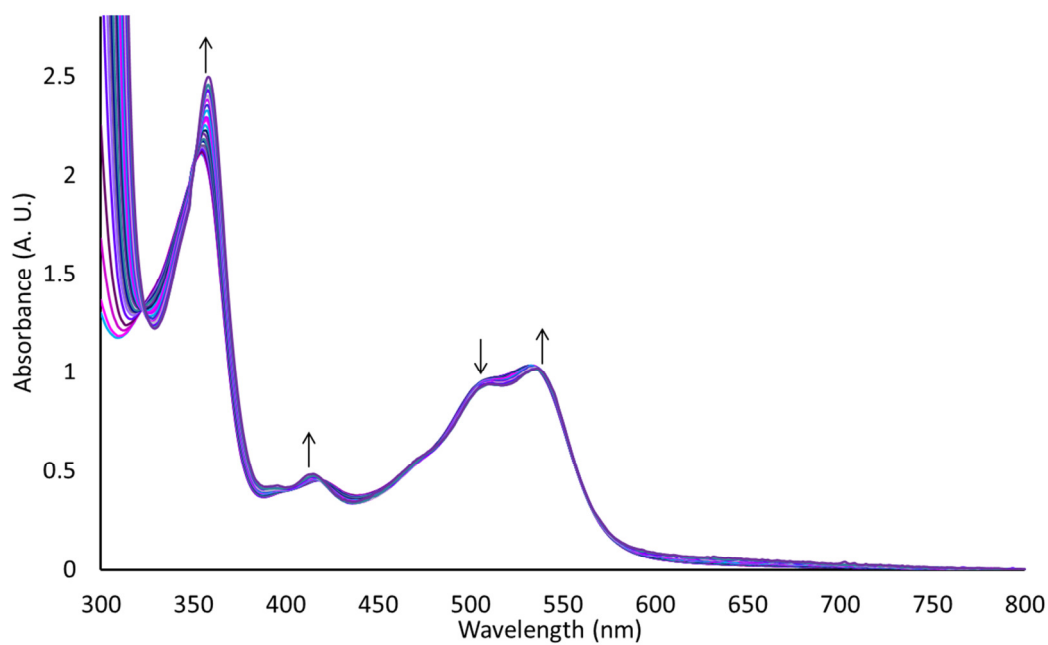


Figure A4.7 Spectroscopic changes associated with the binding of DMAP to vitamin B_{12a}

Table A4.6 Transposed data for the determination of the stability constant for the binding of DMAP to vitamin B_{12a} at specific wavelengths and the weighted overall stability constant and associated errors

DMAP concentration (M x 10 ⁻³)	Absorption at wavelength (nm)			
	357	370	411	520
0.000	2.063	0.963	0.433	0.985
0.027	2.065	0.963	0.434	0.986
0.162	2.077	0.968	0.433	0.987
0.430	2.081	0.971	0.433	0.987
0.960	2.101	0.983	0.439	0.987
1.481	2.120	0.996	0.436	0.984
1.995	2.133	1.008	0.437	0.983
2.500	2.158	1.018	0.437	0.983
2.998	2.162	1.031	0.438	0.979
4.210	2.194	1.052	0.439	0.978
5.377	2.224	1.076	0.446	0.975
6.502	2.247	1.090	0.443	0.972
7.587	2.281	1.107	0.444	0.972
8.634	2.292	1.124	0.446	0.964
10.623	2.323	1.145	0.447	0.962
12.481	2.351	1.169	0.451	0.957
14.223	2.376	1.186	0.451	0.952
15.857	2.395	1.206	0.455	0.949
18.844	2.418	1.221	0.454	0.946
21.504	2.441	1.244	0.460	0.937
<i>K</i>	57.573	45.038	19.687	No fit
err	2.715	1.805	12.008	
Relative % Error	4.716	4.008	60.992	
1/Rel % Error	0.212	0.249	0.016	
Sum (1/Rel % Error)	0.478			
Weighted <i>K</i> fraction	25.545	23.510	0.675	
Weighted error fraction	1.205	0.942	0.412	
Weighted <i>K</i>	49.730			
Weighted err	2.559			
Corrected weighted <i>K</i>	9758.509			
Corrected weighted error	502.110			
Log <i>K</i>	3.99			
σ	0.02			

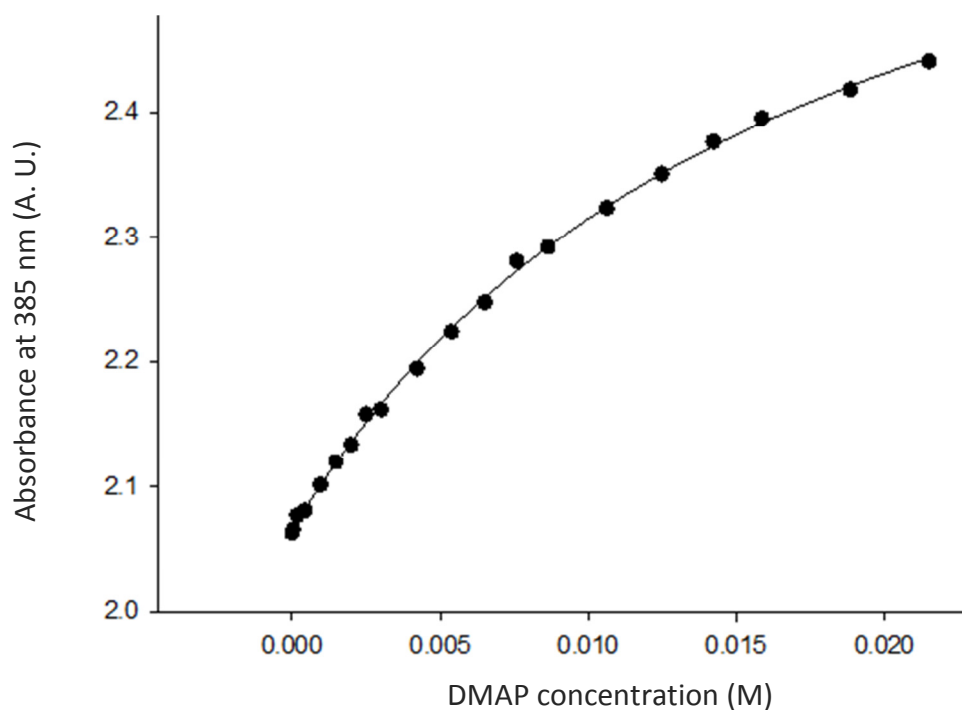


Figure A4.8 Change in absorbance at 385 nm with increasing concentration of DMAP during the coordination of DMAP to vitamin B_{12a}. Solid circles indicate the experimentally determined absorbances. Solid line indicates the best fit curve from Equation A4.4

A4.7 Kinetic data

Examples of the raw data collected for the determination of the rate of cyanide coordination to both DPTC-Co and vitamin B_{12a} can be found in **Digital Appendix 4.4** together with the data corresponding to the calculated best fit curve. An example of the change in absorbance at 434 nm with time for the coordination of cyanide to DPTC-Co is given in Figure A4.9. This is followed by a summary of the results and regression analysis of the standard non-linear least squares curve fitting data. Similarly, an example of the change in absorbance at 361 nm with time for the coordination of cyanide to vitamin B_{12a} is given in Figure A4.10, followed by a summary of the results and regression analysis of the standard non-linear least squares curve fitting data.

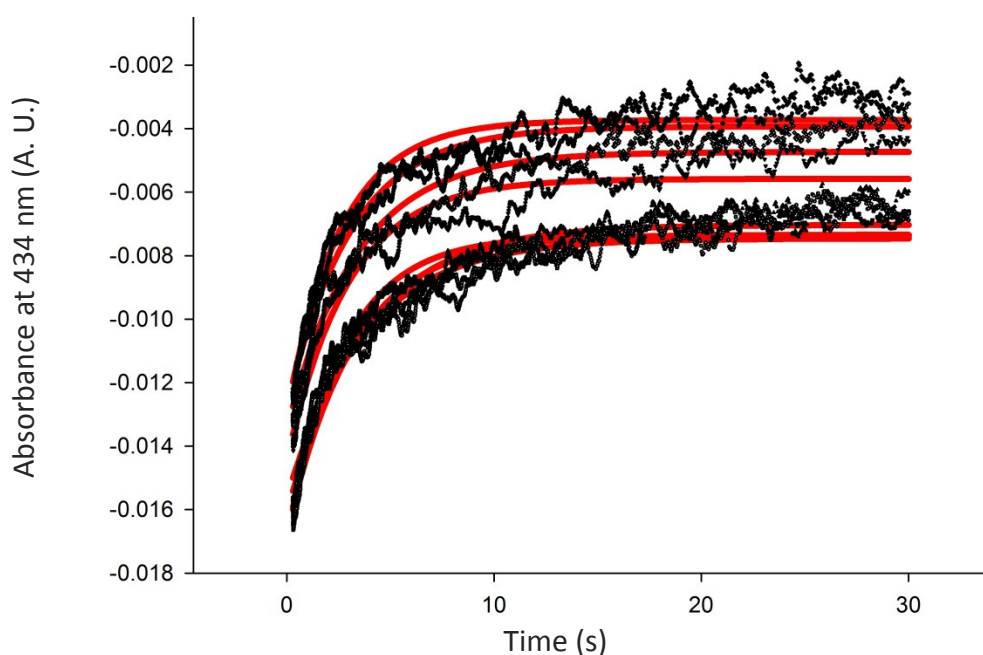


Figure A4.9 The change in absorbance at 434 nm with time for the coordination of cyanide to DPTC-Co in the 80:20 methanol:water solvent system at 15.0°C and ligand concentration of 1.454×10^{-3} M. Black circles indicate the experimentally determined absorbances. Red line indicates the best fit curve for $k_1 = 0.60 \pm 0.08$ from Equation 4.2.4 (**Section 4.2**)

NonLinear Regression - Global Curve Fitting

Data Source: Data 3 in 15C.JNB

Equation: User-Defined, FirstOrder Kinetics

$$f = (A1-Ainf)*exp(-k*x) + Ainf$$

Data Set Specifications:

Data Set	Independent Variable	Dependent Variable
1	Column 1	Column 2
2	Column 1	Column 3
3	Column 1	Column 4
4	Column 1	Column 5
5	Column 1	Column 6
6	Column 1	Column 7
7	Column 1	Column 8
8	Column 1	Column 9

Global Parameters:

A Global Parameter is shared across all data sets.

Global Goodness of Fit:

R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.98943327	0.97897820	0.97895072	0.00049639

Analysis of Variance:

Analysis of Variance:

	DF	SS	MS
Regression	24	1.80024893	0.07501037
Residual	17592	0.00433465	0.00000025
Total	17616	1.80458358	0.00010244

Corrected for the mean of the observations:

	DF	SS	MS	F	P
Regression	23	0.20186314	0.0087766635619	72749789	<0.00000001
Residual	17592	0.00433465	0.00000025		
Total	17615	0.20619779	0.00001171		

Statistical Tests:

Normality Test (Kolmogorov-Smirnov) Failed (P = <0.00000001)

K-S Statistic = 0.02963206 Significance Level = 0.05000000

Constant Variance Test Failed (P = <0.00000001)

Data Set 1:

Number of Observations = 2202

Rsqr = 0.98186976

Residual Sum of Squares = 0.00034859

Parameter Estimates:

	Coefficient	Std. Error	t	P
A1	-0.01279099	0.00003179	-402.37808466	<0.00000001
Ainf	-0.00392938	0.00002203	-178.38014045	<0.00000001
k	0.32109269	0.0032853597	73465344	<0.00000001

Data Set 2:

Number of Observations = 2202

Rsqr = 0.95536714

Residual Sum of Squares = 0.00076841

Parameter Estimates:

	Coefficient	Std. Error	t	P
A1	-0.01562762	0.00002915	-536.14650268	<0.00000001
Ainf	-0.00745889	0.00002410	-309.54186915	<0.00000001
k	0.26730948	0.0029931989	30592388	<0.00000001

Data Set 3:**Number of Observations** = 2202**Rsqr** = 0.96870461**Residual Sum of Squares** = 0.00061069**Parameter Estimates:**

	Coefficient	Std. Error	t	P
A1	-0.01449059	0.00003258	-444.79672667	<0.00000001
Ainf	-0.00557982	0.00002157	-258.73677722	<0.00000001
k	0.33699067	0.00342946	98.26348514	<0.00000001

Data Set 4:**Number of Observations** = 2202**Rsqr** = 0.97628653**Residual Sum of Squares** = 0.00049467**Parameter Estimates:**

	Coefficient	Std. Error	t	P
A1	-0.01612161	0.00002920	-552.14341504	<0.00000001
Ainf	-0.00703041	0.00002405	-292.35988785	<0.00000001
k	0.26834084	0.00269891	99.42555201	<0.00000001

Data Set 5:**Number of Observations** = 2202**Rsqr** = 0.98368814**Residual Sum of Squares** = 0.00035820**Parameter Estimates:**

	Coefficient	Std. Error	t	P
A1	-0.01700430	0.00003413	-498.19216354	<0.00000001
Ainf	-0.00737700	0.00002079	-354.77717693	<0.00000001
k	0.36803328	0.00347575	105.88606132	<0.00000001

Data Set 6:**Number of Observations** = 2202**Rsqr** = 0.97541776**Residual Sum of Squares** = 0.00053970**Parameter Estimates:**

	Coefficient	Std. Error	t	P
A1	-0.01674328	0.00003110	-538.40151235	<0.00000001
Ainf	-0.00734194	0.00002248	-326.57810541	<0.00000001
k	0.30712213	0.00296419	103.61085827	<0.00000001

Data Set 7:**Number of Observations** = 2202**Rsqr** = 0.97118899**Residual Sum of Squares** = 0.00058477**Parameter Estimates:**

	Coefficient	Std. Error	t	P
A1	-0.01296525	0.00003478	-372.82044067	<0.00000001
Ainf	-0.00372517	0.00002052	-181.56991226	<0.00000001
k	0.38080141	0.00375382	101.44369644	<0.00000001

Data Set 8:**Number of Observations** = 2202**Rsqr** = 0.96747578**Residual Sum of Squares** = 0.00062961**Parameter Estimates:**

	Coefficient	Std. Error	t	P
A1	-0.01350197	0.00003059	-441.31329530	<0.00000001
Ainf	-0.00473295	0.00002285	-207.17049557	<0.00000001
k	0.29689951	0.00307565	96.53220545	<0.00000001

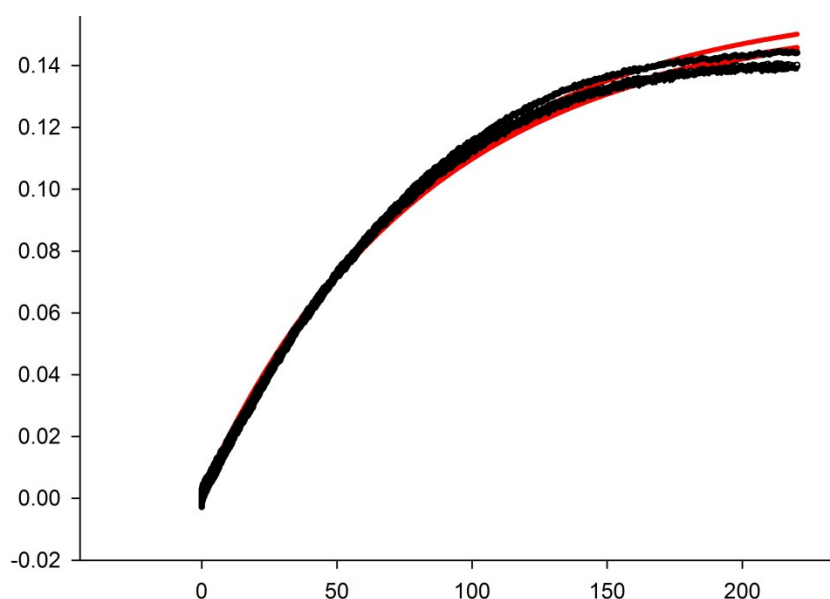


Figure A4.10 The change in absorbance at 361 nm with time for the coordination of cyanide to vitamin B_{12a} in the 80:20 methanol:water solvent system at 15.0°C and ligand concentration of 5.238×10^{-2} M. Black circles indicate the experimentally determined absorbances. Red line indicates the best fit curve for $k_1 = 0.60 \pm 0.08$ from Equation 4.2.4 (**Section 4.2**)

NonLinear Regression - Global Curve Fitting

Data Source: Data 3 in 15C.JNB

Equation: User-Defined, FirstOrder Kinetics

$$f = (A1 - Ainf) * \exp(-k * x) + Ainf$$

Data Set Specifications:

Data Set	Independent Variable	Dependent Variable
1	Column 1	Column 2
2	Column 1	Column 3
3	Column 1	Column 4

Global Parameters:

A Global Parameter is shared across all data sets.

Global Goodness of Fit:

R	Rsqr	Adj Rsqr	Standard Error of Estimate
0.99957028	0.99914074	0.99914002	0.00131562

Analysis of Variance:

Analysis of Variance:

	DF	SS	MS
Regression	9	32.95097370	3.66121930
Residual	9543	0.01651761	0.00000173
Total	9552	32.96749132	0.00345137

Corrected for the mean of the observations:

	DF	SS	MS	F	P
Regression	8	19.20656131	2.400820161387066	29798840	<0.00000001
Residual	9543	0.01651761	0.00000173		
Total	9551	19.22307893	0.00201268		

Statistical Tests:

Normality Test (Kolmogorov-Smirnov) Failed (P = <0.00000001)

K-S Statistic = 0.08845325 Significance Level = 0.05000000

Constant Variance Test Failed (P = <0.00000001)

Data Set 1:

Number of Observations = 3184

Rsqr = 0.99915235

Residual Sum of Squares = 0.00582444

Parameter Estimates:

	Coefficient	Std. Error	t	P
A1	-0.00173579	0.00003413	-50.85521176	<0.00000001

Ainf	0.16125699	0.00017260934	28321100	<0.00000001
k	0.01218945	0.00002679454	92277753	<0.00000001

Data Set 2:

Number of Observations = 3184

Rsqr = 0.99911739

Residual Sum of Squares = 0.00545796

Parameter Estimates:

	Coefficient	Std. Error	t	P
A1	0.00226126	0.0000341866	16469476	<0.00000001
Ainf	0.15591067	0.00016880923	63790016	<0.00000001
k	0.01238420	0.00002845435	32063170	<0.00000001

Data Set 3:

Number of Observations = 3184

Rsqr = 0.99915021

Residual Sum of Squares = 0.00523521

Parameter Estimates:

	Coefficient	Std. Error	t	P
A1	0.00114349	0.0000341133	51909357	<0.00000001
Ainf	0.15586504	0.00017413895	8939764	<0.00000001
k	0.01211337	0.00002822429	26470308	<0.00000001