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The coordination chemistry of some cobalt corrinoid and iron porphyrin complexes

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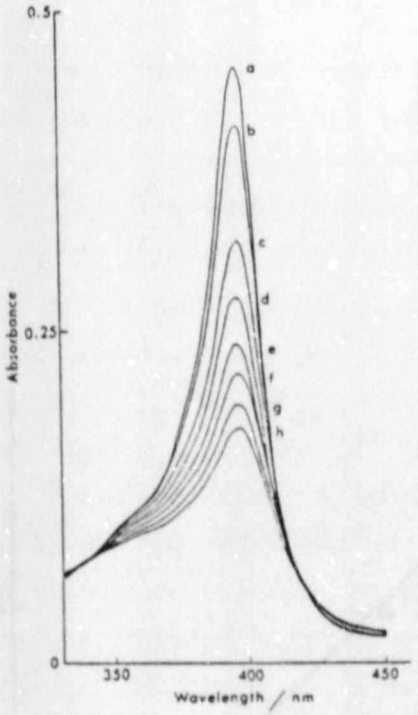

Fig. 7.7 Spectral changes for a titration of ca. 2 x 10^{-6} M MP-8 in 20% MeOH:H_2O (v/v) solution, pH 7.4 at 25°C, with caffeine.

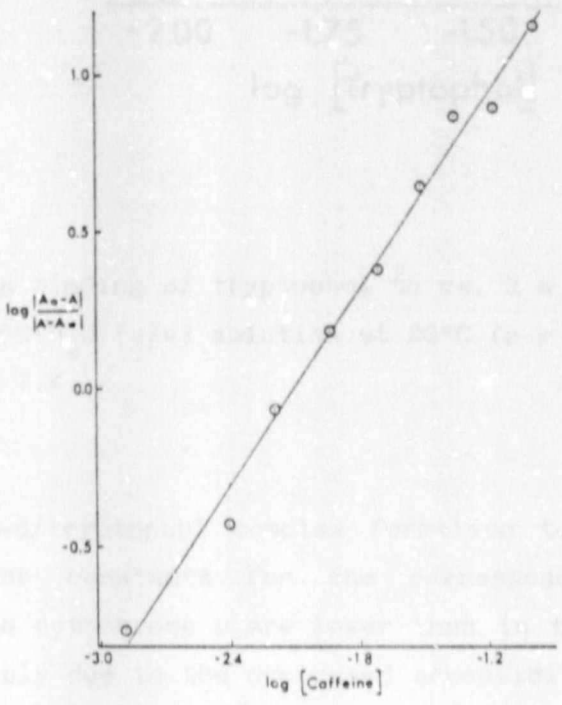

Fig. 7.8 The binding of caffeine to ca. 2 x 10^{-6} M MP-8 in 20% MeOH:H_2O (v/v) solution at 25°C (μ = 0.1 (phosphate)) at pH 7.4.

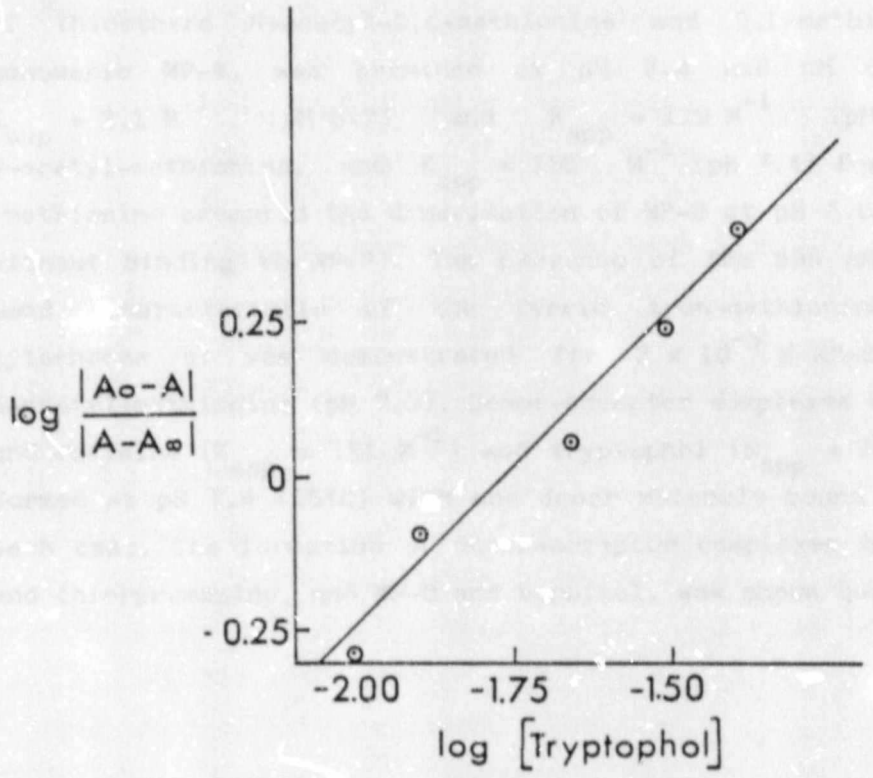

Fig. 7.9 The binding of tryptophol to ca. 2 x 10^{-6} M MP-8 in 20% MeOH:H_2O (v/v) solution at 25°C (μ = 0.1 (phosphate)) at pH 7.4.

holds for MP-8/tryptophol complex formation too) it can be seen that formation constants for the corresponding donor-acceptor complexes with cytochrome c are lower than in the model complexes. This is probably due to the decreased accessibility of the haem in cytochrome c; binding also requires the cleavage of the Fe-S bond. Other effects largely absent in the corresponding model complexes include disruption by hydrophobic reagents of the ordered water structure within the haem crevice, and bonding with the protein.

7.6 Summary

Equilibrium studies of microperoxidase-8 (MP-8) in aqueous methanol solution were used to assess its potential as a model for cytochrome c, and possibly cytochrome P-450. A Beer's Law plot confirmed that ca. 2×10^{-6} M MP-8 in 20% MeOH:H_2O (v/v) solution at pH 7.4 (25°C) was ≥ 97% monomeric. The formation of 1:1 complexes of thioethers N-acetyl-D,L-methionine and D,L-methionine with monomeric MP-8, was examined at pH 7.4 and pH 6.7 (25°C): K_{app} = 2.1 M^{-1} (pH 6.7) and K_{app} = 1.9 M^{-1} (pH 7.4) for N-acetyl-methionine, and K_{app} = 155 M^{-1} (pH 7.4) for methionine (methionine promoted the dimerisation of MP-8 at pH 6.0 and pH 6.7 without binding to MP-8). The presence of the 695 nm absorption band (characteristic of the ferric iron-methionine bond in cytochrome c) was demonstrated for 2×10^{-5} M MP-8 in 1.6 M N-acetyl-methionine (pH 7.0). Donor-acceptor complexes between MP-8 and caffeine (K_{app} = 151 M^{-1}) and tryptophol (K_{app} = 60 M^{-1}) were formed at pH 7.4 (25°C) with one donor molecule bound to MP-8 in each case. The formation of donor-acceptor complexes between MP-8 and chlorpromazine, and MP-8 and barbital, was shown qualitatively.

CHAPTER 8 - SUMMARY AND CONCLUSIONS

The aim of this dissertation was to investigate the rôle of conformational change in the protein's control of the active site in haemoproteins and enzymes, by studying:

(i) cobalt corrinoid cofactors for the B_{12}-dependent isomerase reactions,

(ii) the reactivity of the iron-methionine bond in cytochrome c, and

(iii) the usefulness of MP-8 as a model for cytochrome c.

(i)

The thermolytic homolysis of prepared organocobalamins: methyl, ethyl and cyclobutylcobalamin, and of adenosylcobalamin, was examined under nitrogen and oxygen at pH 6 and 7, 96 °C. Half-lives ($t_{½}$) for the homolytic fission of the Co-C bond in organocobalamins increase in the following ligand order:
ethyl (ca. 9 min) < cyclobutyl (ca. 75 min) < adenosyl (ca. 180 min) < methyl (ca. 80 hrs). This order supports a proposal (Pratt, 1984) that steric control by the protein of the Co-$\hat{C}_{\alpha}$-C_{β} bond angle induces homolysis of the Co-C bond in isomerase enzymes.

These values were used to provide an estimate of $t_{½}$ ca. 10 years for the rate in the protein-free coenzyme at room temperature. Comparison with published data on B_{12}-dependent isomerases shows that the Co-C bond in the coenzyme is labilised by $\leqslant 10^5$ when bound by the apoenzyme and by a further $\geqslant 10^5$ in the presence of substrate to achieve the overall labilisation of $\geqslant 10^{10}$ (i.e. $t_{½} \sim 2.5$ ms) required for the enzymatic reaction.

(ii)

The integrity of the iron-methionine 80 bond in cytochrome c is essential for its physiological activity. An Fe-S bond length increase may be associated with the known protein conformational

change, on reduction of cytochrome c (Moore, 1982). The presence of the bond can be monitored using a charge-transfer band in the near infra-red (695 nm).

The alkaline isomerisation of cytochrome c (from Type III to Type IV), thought to play a regulatory rôle in vivo, induces Fe-S bond cleavage and a protein conformational change, resulting in a more open haem crevice structure. The pK_a of the alkaline isomerisation for horse-heart cytochrome c was confirmed to be ca. 9.05 (25 °C) in this work. Extinction coefficients for Type III and Type IV at 695 nm were determined as 867 and 83 M^{-1} cm^{-1}, respectively.

Binding studies were conducted near the pK_a of the alkaline isomerisation by monitoring the intensity of the 695 nm absorbance band. The perchlorate anion binds to cytochrome c at 25 °C with K_{eq} ca. 5×10^{-3} M^{-1} (1:1 complex). The resulting Fe-S bond cleavage can be attributed both to direct coulombic and to indirect chaotropic effects. Donor-acceptor interactions are known to be important in vivo (e.g. in the functioning of cytochrome P-450). Caffeine and tryptophol were found to form donor-acceptor complexes with the haem of cytochrome c at 25 °C with K_{eq} ca. 6×10^{-4} M^{-1} (1:1 complex) and K_{eq} ca. 9×10^{-2} M^{-1} (1:2 complex), respectively. The following compounds also effect cleavage of the Fe-S bond, probably by donor-acceptor interactions with the haem: chlorpromazine, procaine, indole acetic acid, tryptophan, barbital, salicylic acid and benzoic acid. In addition to donor-acceptor interactions, both hydrogen bonding with the protein and chaotropic effects are likely, due to these hydrophobic molecules.

(iii)

The enzymatic digestion of cytochrome c yields haem-peptides with peptide chain lengths varying from 6 to 80 amino acids. An improved method for the preparation and purification of the haem-octapeptide, MP-8, was developed in this work. For a rapid test of MP-8 purity, the TLC solvent system: 88 mℓ water/88 mℓ sec-butanol/ 0.2 mℓ 0.88 M ammonia/0.114 g KCN was found to give good separation of MP-8 (R_{B12} = 2.3), MP-11 (close to the baseline) and a smaller haem-peptide impurity (R_{B12} = 3.1 - 3.3). HPLC analysis of the MP-8 product showed it to be superior purity to a

commercial product.

A Beer's Law Plot confirmed that ca. 2×10^{-6} M MP-8 is $\geq$ 97 % monomeric in 20 % MeOH:H_2O (v/v) at pH 7.4, 25 °C. These conditions were used in binding studies with thioethers and drugs.

Haem-peptide/thioether adducts are useful as models for the Fe-S bond in cytochrome c. The formation of 1:1 thioether complexes with MP-8 was examined spectroscopically at 397.2 nm. For the MP-8/D,L-methionine adduct, K_{app} is ca. 155 M^{-1} at pH 7.4 (25 °C), and for MP-8/N-acetyl-D,L-methionine, K_{app} is ca. 1.9 M^{-1} at pH 7.4 and is ca. 2.1 M^{-1} at pH 6.7 (25 °C). The 695 nm absorbance band (which in cytochrome c is indicative of the presence of the iron-methionine band) is exhibited by the MP-8/N-acetyl-methionine adduct.

The formation of 1:1 donor-acceptor MP-8/drug complexes was examined spectroscopically at 397.2 nm. Caffeine binds to MP-8 with a binding constant K_{app} ca. 151 M^{-1} at pH 7.4 and ca. 240 M^{-1} at pH 6.7 (25 °C). Tryptophol binds to MP-8 with K_{app} ca. 60 M^{-1} at pH 7.4 (25 °C). Both chlorpromazine and barbital bind to MP-8, probably by donor-acceptor interactions. Although comparison to cytochrome c is complicated by a difference in experimental conditions for MP-8 and cytochrome c, the binding constants are several orders of magnitude lower for the haemoprotein, where the haem is enclosed in a hydrophobic crevice, less accessible to the drug molecules.

APPENDIX - Derivation of equations for the kinetic studies (Chapter 4) and equilibrium studies (Chapters 5 and 7)

(a) Kinetic Studies

In Chapter 4, values for the half-life ($t_{½}$) of decomposition for various organocobalamins and organocobinamides were determined from plots of $\ell og|A_\infty - A|$ against time.

The derivation of the equation is as follows:

The rate law for a first order reaction in a reactant, A, is

$$-d[A]/dt = k_1[A] \quad ,$$

which may be integrated to give

$$\ell n[A]_t = -k_1 t + \ell n[A]_o \quad .$$

The plot of $\ell n[A]_t$ against t would be expected to be linear for a first order reaction in A; from the slope is obtained the rate constant, k_1. Using ℓog_{10} instead of ℓn simply alters the k_1 by a constant, 2.30.

The reaction followed in Chapter 4 was homolytic fission of the cobalt-carbon (Co-C) bond in organocorrinoids e.g. Co(III) - R $\rightleftharpoons$ Co(II) + R$^\cdot$.

The loss of Co(III) (or the increase in Co(II)) for homolytic fission under nitrogen was monitored spectroscopically by following the loss of peaks due to Co(III) or the increase in the intensity of peaks due to Co(II). The reaction under oxygen was monitored by following the increase in peaks due to Co(III) (from the oxidation of Co(II)).

The concentration of Co(III) present at time t is proportional to $|A-A_\infty|$, where A is the absorbance of a peak due to Co(III), and A_∞ the absorbance of the final species on completion of homolytic fission. Alternatively, the Co(III) concentration is proportional to $|A_\infty - A|$, where A is the absorbance of a peak due to the formation of Co(II); A_∞ denotes complete formation of Co(II). Thus $\ell og|A_\infty - A|$ or $\ell og|A-A_\infty|$ are plotted against t.

(b) Equilibrium Studies

Ligand binding studies with cytochrome c or MP-8 were described in Chapters 5 and 7. The following abbreviations are used below: M, denotes a monomeric porphyrin species; D, the dimeric species; n, the number of ligand molecules, L, bound to the monomer or dimer; A denotes absorbance with A_o or A_∞ referring to the absorbance of the initial or final species, respectively; $[Fe]_{TOT}$, the concentration of iron porphyrin units; and ϵ_M and ϵ_{ML_n}, the extinction coefficients of the monomer and the monomer with n ligands bound, respectively.

(i) The equation for binding n ligands to a monomer

If the equilibrium is represented by

$$M + nL \rightleftharpoons ML_n \quad ,$$

the equilibrium constant is

$$K_{app} = \frac{[ML_n]}{[M][L]^n} \quad ,$$

which can be rearranged as

$$\log K_{app} = \log \frac{[ML_n]}{[M]} - n \log[L] \qquad (1)$$

Varying [L]:

Since

$$A = \epsilon_M[M] + \epsilon_{ML_n}[ML_n] \qquad (2)$$

and

$$[Fe]_{TOT} = [M] + [ML_n] \qquad (3)$$

it follows that

$$[ML_n] = [Fe]_{TOT} - [M]$$

and

$$A = \epsilon_M[M] + \epsilon_{ML_n}([Fe]_{TOT} - [M])$$

$$\therefore A = [M](\epsilon_M - \epsilon_{ML_n}) + \epsilon_{ML_n}[Fe]_{TOT}$$

$$\therefore [M] = \frac{A - \epsilon_{ML_n}[Fe]_{TOT}}{\epsilon_M - \epsilon_{ML_n}} \quad .$$

Since $A_o = \epsilon_M[Fe]_{TOT}$

$$\therefore \quad \epsilon_M = \frac{A_o}{[Fe]_{TOT}} \qquad (4)$$

Since $A_\infty = \epsilon_{ML_n}[Fe]_{TOT}$

$$\therefore \quad \epsilon_{ML_n} = \frac{A_\infty}{[Fe]_{TOT}} \qquad (5)$$

It follows that

$$[M] = \frac{(A - A_\infty)}{(A_o - A_\infty)}[Fe]_{TOT} \qquad (6)$$

Solving (3) for $[ML_n]$ and substituting the resulting equation, together with (4) and (5), into (2) yields

$$[ML_n] = \frac{(A_o - A)}{(A_o - A_\infty)}[Fe]_{TOT} \qquad (7)$$

Substituting (6) and (7) into (1) yields

$$\log K_{app} = \log \frac{(A_o - A)}{(A - A_\infty)} - n \log [L]$$

$$\therefore \log \frac{(A_o - A)}{(A - A_\infty)} = \log K_{app} + n \log [L].$$

A plot of $\log \frac{(A_o - A)}{(A - A_\infty)}$ against $\log [L]$ should

be linear with slope = n and intercept = $\log K_{app}$.

(ii) <u>The calculation of A for weakly binding or sparingly soluble ligands</u>

For the equilibrium

$$M + nL \rightleftharpoons ML_n \quad ,$$

the equilibrium constant is

$$K_{app} = \frac{[ML_n]}{[M][L]^n} \quad ;$$

rearranging gives

$$\frac{[ML_n]}{[M]} = K_{app}[L]^n \qquad (8)$$

Substituting (6) and (7) into (8) gives

$$\frac{(A_o - A)}{(A - A_\infty)} = K_{app}[L]^n \qquad (9)$$

Multiplying the RHS of (9) by $\frac{(A_o - A_\infty)}{(A_o - A_\infty)}$, and rearranging gives

$$\frac{1}{(A_o - A)} = \frac{1}{K_{app}[L]^n(A_o - A_\infty)} + \frac{1}{(A_o - A_\infty)} \quad .$$

A plot of $\frac{1}{(A_o - A)}$ against $\frac{1}{[L]^n}$ should be linear with

$$\text{slope} = \frac{1}{K_{app}(A_o - A_\infty)} \text{ and intercept} = \frac{1}{(A_o - A_\infty)} \quad .$$

(iii) <u>Proton loss involving the monomeric species, on binding n ligands</u>

For the equilibrium

$$MH + nL \rightleftharpoons ML_n + H^+ \quad ,$$

the equilibrium constant is

$$K_{eq} = \frac{[ML_n][H^+]}{[MH][L]^n} = K_{app}[H^+] \quad ;$$

$$\therefore \log K_{eq} = \log K_{app} + npH \quad .$$

A plot of $\log K_{app}$ against pH should be linear with slope = -n and intercept = $\log K_{eq}$.

(iv) The equation for dimerisation induced by the binding of n ligands

For the equilibrium

$$2M + nL \rightleftharpoons DL_n \quad ,$$

and the equilibrium constant is

$$K_{app} = \frac{[DL_n]}{[M]^2[L]^n} \quad ;$$

$$\therefore \log K_{app} = \log \frac{[DL_n]}{[M][M]} - n \log [L] \qquad (10)$$

Substituting (6) and (7) into (10) gives

$$\log K_{app} = \log \frac{(A_o - A)/2}{(A - A_\infty)[M]} - n \log[L]$$

A plot of $\log \frac{(A_o - A)/2}{(A - A_\infty)[M]}$ against $\log [L]$

should be linear with slope = n and

intercept = $\log K_{app}$.

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