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Steric effects in vitamin B12 complexes

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B_{12r} present as determined by UV-visible spectroscopy.

Further evidence of the intermediacy of a strained adenosylcobalamin species is provided by the ribonucleotide reductase reaction. Ribonucleotide reductase catalyses a different type of reaction to the isomerase reactions (see Table 1.1) but there is evidence that the first step in its reaction mechanism is homolytic fission.[154] Observation of the kinetics of the reaction at 525nm using UV-visible spectroscopy showed that the reaction proceeds in two steps, an initial fast step, followed by a slow step. It was concluded that 'either both phases of the reaction produce cob(II)alamin, or the product of the initial fast reaction has a spectrum resembling that of cob(II)alamin'.[154] The species formed in the initial fast reaction might be the strained adenosylcobalamin which would have a spectrum very similar to that of B_{12r} in the 525nm region.

In section 9.2 a sterically strained form of adenosylcobalamin was postulated as an intermediate in the enzymatic isomerization reactions; in this section evidence (from UV-visible spectroscopy) is provided for such an intermediate.

9.4 Mechanism of the isomerization step

In the last few years a great deal of progress towards an understanding of the mechanism of the rearrangement step catalysed by isomerase enzymes has been made, both by model studies and by study of the enzyme reactions themselves.

The formation of the Co-C bond in cyclopropylmethylcobalamin inhibits the otherwise facile cyclopropylmethyl rearrangement and

suggests that rearrangement of the substrate while attached to the cobalt during the isomerase enzyme reactions is unlikely (Chapter 8). Model cobalamin[26-31] and cobaloxime[20,32-34] compounds with the same carbon-skeletons as the substrates of α-methyleneglutarate mutase and methylmalonyl-coenzyme A mutase have been prepared and it has been shown that rearrangement is associated with cleavage of the Co-C bond[20,26-34] but that B_{12r} remains in close proximity to the substrate free radical[20,33,34] during the rearrangement.

The enzymes dioldehydrase, glycerol dehydrase, ethanolamine ammonia lyase and ribonucleotide reductase all show similar ESR spectra which have been interpreted as arising from B_{12r} and an organic free radical at a distance of ≥ 10Å from each other with both dipolar coupling and isotropic exchange between B_{12r} and the organic free radical.[135-139] This means that there is overlap between the atomic orbitals of the cobalt (II) ion and the substrate radical even though they are separated by a distance of ≥ 10Å. It appears likely that rearrangement occurs within this structure and that the cobalt ion removes electron density from and places a positive charge on the substrate free radical during the rearrangement.

CHAPTER 10 - SUMMARY AND CONCLUSIONS

The aims of this thesis were:-

1) To study the steric effects, as opposed to the electronic effects, of the organoligand on the spectra, equilibria and reactions of alkylcobalamins.

2) To search for an alkylcobalamin which undergoes homolytic fission at room temperature to use as a model for the enzyme-induced homolytic fission of adenosylcobalamin.

3) To study the rearrangement of cyclopropylmethylcobalamin to 3-butenylcobalamin in order to show whether or not rearrangement of an organoligand σ-bonded to cobalamin is likely.

In order to determine the steric effects of organoligands the alkylcobalamins with the following series of ligands were studied. For series 1 (methyl < ethyl < isopropyl) there is increasing substitution on C_α of the alkyl ligand. For series 2 (ethyl ~ n-propyl < isobutyl < neopentyl) there is increasing substitution on C_β of the alkyl ligand and hence increasing steric interactions between the substituents of C_β and the propionamide side-chains of the corrin ring. For series 3 (cyclopropyl< cyclobutyl < cyclopentyl < cyclohexyl) the bond angle of the cycloalkyl ligand increases giving rise to increasing steric distortion around C_α (Chapter 4) In all three series the increase in steric interaction between the organoligand on one hand

and the cobalt atom and corrin ring on the other gives rise to parallel changes in the spectra, equilibria (both pH-dependent and pH-independent) and lability of the Co-C bond.

The spectra of the five-coordinate, protonated, 'base-off' (E) forms show parallel changes in the αβ region, in the region around 375nm and in the band at 303nm for all three series. In the αβ region there is an increase in the ratio of extinction coefficients at 440nm and 460nm, in the 374-390nm region the band shifts gradually from lower to higher wavelength and the band at 303nm gradually increases in intensity. The spectra of the six-coordinate, 'base-on' (A) forms show a gradual shift of the αβ band from 522nm to 510nm (Chapter 4). The pKa values for the series of alkylcobalamins increase for all three series; for series 1 the pKa's vary from 2,5 to ≥ 4,5 (ΔpKa ≥ 2,0), for series 2 the pKa's vary from 3,9-4,7 (ΔpKa = 1,8) and for series 3 the pKa's vary from 2,8-4,7 (ΔpKa = 1,9)(Chapter 4). The ratio of five-coordinate unprotonated, 'base-off' (C) forms to six-coordinate base-on (A) forms increases with increasing steric compression within the series (Chapter 5). The alkylcobalamins in the series show increasing ease of decomposition (by homolytic fission and/or β-elimination) such that isopropylcobalamin, neopentylcobalamin, cyclopentylcobalamin and cyclohexylcobalamin rapidly decompose at room temperature in neutral solution (Chapter 6 and 7). The five-coordinate, protonated, 'base-off' (E) forms are much more stable (towards breaking of the Co-C bond) than the corresponding six-

coordinate (A) complexes. This can be ascribed to relief of steric strain in the five-coordinate relative to the six-coordinate forms.

There are no fundamental differences between primary and secondary groups (methyl ≡ cyclopropyl, ethyl ≡ cyclobutyl), between alkylcobalamins and cycloalkylcobalamins (isopropyl ≡ cyclopentyl and cyclohexyl) or between substitution on C_α and C_β (neopentyl ≡ cyclopentyl). Series 1, 2 and 3 can be combined into a single series without introducing any significant anomalies in the orders of spectra, equilibria or reactivity and adenosylcobalamin can be given a definite position in this series.

It is proposed that steric repulsion in the organocobalamins is partially relieved by lengthening of the Co-C bond (Chapter 4) and by conversion of the six-coordinate, 'base-on' complex to a five-coordinate, unprotonated, 'base-off' complex with concomitant movement of the cobalt atom out of the plane of the corrin ring (Chapter 4 and 5). Hence increasing steric distortion leads to the Co-C bond becoming longer and to increasing stability of the five-coordinate over the six-coordinate forms. This is supported by X-ray crystallographic evidence for the lengthening of the Co-C bond in isopropylcobaloxime (compared to methylcobaloxime)[74] and for the existence of a five-coordinate methylcobalt complex with the BAE ligand where the cobalt atom is displaced above the plane of the equatorial ligands.[71] It is shown that there are two different forms of 'base-off' organocobalamins present in neutral

aqueous solution (Chapter 5) which show small but significant differences in spectra. It is suggested that the unprotonated benzimidazole is not coordinated in either form but is completely free in one form and held close to the corrin ring by hydrophobic bonding in the other.

Neopentylcobalamin in neutral solution at 25°C is stable under nitrogen but is decomposed by oxygen to give B_{12a} and by hydrogen donors such as thiols and isopropanol to give B_{12r} and neopentane. These reactions are attributed to reversible homolytic fission of the Co-C bond to give a low steady-state concentration of B_{12r} and neopentyl radicals, followed by abstraction of a hydrogen atom by the neopentyl radical to give neopentane (Chapter 6). It has been proposed that adenosylcobalamin is labilized towards homolytic fission during the isomerase reactions by distortion of the cobalt coordination sphere due to changes in conformation of the apoenzyme on binding the substrate.[147] The labilization of the Co-C bond of neopentylcobalamin towards homolytic fission, caused by the lengthening and weakening of the Co-C bond as a result of steric compression, provides a model and hence support for the proposed mechanism of homolysis of adenosylcobalamin by the isomerase enzymes (Chapter 9).

Cyclopropylmethylcobalamin was shown to isomerize to 3-butenylcobalamin very slowly at room temperature ($t_{\frac{1}{2}} \sim 1$ month) but more rapidly in the

presence of light ($t_{\frac{1}{2}}$ = five minutes) or on heating to 60°C ($t_{\frac{1}{2}}$= 165 minutes) and without any significant effect of oxygen (Chapter 8). Since the cyclopropylmethyl free radical isomerizes very rapidly at -120°C[123] this shows that the formation of the Co-C bond actually inhibits the rearrangement and suggests that rearrangement of the substrate while attached to the cobalt during the enzyme reactions is unlikely.

Finally, aspects of the mechanism of isomerase enzymes are discussed in the context of steric effects in organocobalamins. It is suggested that an intermediate in the reaction mechanism of isomerase enzymes is an enzyme-bound, sterically-distorted form of adenosylcobalamin that this might have a UV-visible spectrum similar to those of the five-coordinate forms of sterically-distorted alkylcobalamins, eg. neopentylcobalamin and cyclohexylcobalamin, with bands at ~440nm and ~375nm. A survey of the published spectra of the enzyme-substrate complex for isomerase enzymes does, in fact, reveal the presence of hitherto unexplained bands at ~440nm and ~380nm, in agreement with the proposed occurrence of a distorted form of aderosylcobalamin as an intermediate (Chapter 9).

Appendix 1 - Preparation of Organic Starting Materials

Reagents

The reagents used were: lithium aluminium hydride (Merck ('for synthesis'), cyclopropanecarboxylic acid (Merck 'for synthesis'), phosphorous tribromide (Hopkin and Williams Analar), zinc bromide (Hopkin and Williams general purpose reagent).

Solvents

Diethyl ether and dichloromethane were Hopkin and Williams Analar reagents. Ether was dried over calcium chloride and then over sodium turnings.

Preparation of cyclopropylmethanol[1,2]

Ten grams lithium aluminium hydride was added to 360ml ether with stirring. The mixture was cooled in ice water and 19ml cyclopropanecarboxylic acid in 300ml ether was added at a rate such as to produce gentle reflux. After standing for half an hour with continued stirring and cooling of the reaction mixture, water was added to decompose the excess lithium aluminium hydride. Ten per cent sodium hydroxide (300ml) was then added and the white precipitate which formed filtered off. The ether layer was collected and the aqueous layer extracted with ether. The ether extract was combined with the ether layer and dried over sodium sulphate. The ether was distilled off and the fraction boiling from 114°C - 118°C (630 mmHg) was collected. The yield (based on cyclopropanecarboxylic acid) was forty per cent.

Preparation of cyclopropylmethyl bromide[2]

Cyclopropylmethanol (4,5ml) in 112ml ether was added slowly to 8,0ml stirred, ice-cooled phosphorous tribromide. The mixture was stirred for forty minutes and then excess phosphorous tribromide decomposed by addition of ice. The ether layer was separated, washed with water and dried over calcium chloride. The fraction boiling at 100-104°C 630 mmHg was collected. The yield (based on cyclopropylmethanol) was thirty-two per cent.

Preparation of 3-butenyl bromide[2]

A mixture of 10ml forty-eight per cent hydrobromic acid and 20g zinc bromide was cooled on ice. To this was added dropwise 3ml cyclopropylmethanol. The mixture was left to stir for one hour on ice and then one hour at room temperature. Then ice water (25ml) was added and the reaction mixture extracted with ether. The ether extract was dried over sodium sulphate and distilled. The fraction boiling from 91-93°C (630 mmHg) was collected. The yield (based on cyclopropylmethanol) was thirty-eight per cent.

Characterization of products

Products were characterized using infra-red (IR) and nuclear magnetic resonance (NMR) spectroscopy. IR spectra were recorded on a Jasco IRA-1 diffraction grating spectrometer. Band positions are quoted in cm^{-1} and the following abbreviations are used: s = strong, m = medium, w = weak and b = broad. NMR spectra were recorded using a Hitachi-Perkin-Elmer R-20A NMR spectrometer (60MHz). Resonances are quoted: δppm (multiplicity, numb- protons, assignment).

Cyclopropylmethanol

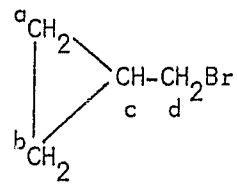
IR (thin film) 3360(b); 3060(s); 2990(s); 2900(s); 2860(s); 2040(w); 1940(w); 1460(m); 1420(s); 1400(m); 1300(m); 1240(m); 1180(w); 1140(w); 1105(w); 1085(w); 1020(s); 920(w); 905(m); 895(w); 807(m); 780(w).

The IR spectrum was the same as that obtained by other workers.[3]

Cyclopropylmethyl bromide

IR (thin film) 3120(m); 3050(s); 2900(w); 1470(w); 1450(s); 1380(m); 1270(w); 1235(s); 1210(w); 1180(w); 1120(w); 1100(w); 1065(m); 1035(s); 980(s); 920(s); 850(s) 805(m); 775(s).

NMR (CCl_4) 0,40(m,2H,a); 0,75(m,2H,b) 1,20(m,1H,c); 3,30(d,2H,d)

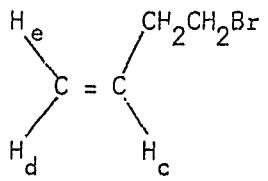


The IR and NMR spectra are similar to those of cyclopropylmethyl chloride.[2,4]

3-Butenyl bromide

IR (thin film) 3020(m); 3000(s); 2990(w); 1650(m); 1450(m); 1440(s); 1425(w); 1320(w); 1280(s); 1220(s); 1120(w); 1080(w); 1040(w); 1005(s); 935(s); 820(w); 770(w).

NMR($CDCl_3$) 2,55(q,2H,b); 3,30(t,2H,a); 4,85(s,1H,d);
5,05(s,1H,e); 5,6 (m,1H,c).



The IR spectrum is similar to that obtained by other workers.[2]

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Appendix 2

UV-visible Spectra of Organocobalamins

A. pH=1

Ligand	Maxima λ/nm(10^{-4} ε)					
methyl	495(s)	460		374	330(s)	303
	(0,69)	(0,93)		(0,90)	(1,3)	(2,2)
ethyl		455(s)	440	380		303
		(0,82)	(0,84)	(0,91)		(3,0)
n-propyl		455(s)	441	381		303
		(0,86)	(0,88)	(0,94)		(2,8)
isopropyl		460(s)	442	382		303
		(1,0)	(1,1)	(1,2)		(>3,2)
cyclopropyl	495(s)	460	440(s)	374	325(s)	303
	(0,68)	(0,83)	(0,80)	(0,83)	(1,7)	(2,0)
isobutyl		455(s)	439	384,5		303
		(0,77)	(0,85)	(0,92)		(2,9)
cyclobutyl		455(s)	438	378		303
		(0,74)	(0,84)	(0,86)		(2,7)
cyclopropylmethyl		455(s)	442	382		303
		(0,79)	(0,83)	(0,99)		(2,7)
3-butenyl		455	440(s)	378		303
		(0,78)	(0,74)	(0,88)		(2,4)
neopentyl		460(s)	438	388,5		303
		(0,76)	(0,93)	(1,0)		(3,0)
cyclopentyl		460(s)	440	382		303
		(0,77)	(0,83)	(0,90)		(3,1)
cyclohexyl		460(s)	442	384		303
		(0,73)	(0,93)	(0,93)		(>3,3)
adenosyl	495(s)	458		376	347(s)	
	(0,53)	(0,88)		(0,82)	(0,97)	

(s) denotes shoulder

B. pH=6-7

Ligand	Maxima λ/nm($10^{-4}\varepsilon$)						
methyl	585(s)	518	500(s)	430(s)	372	342	310
	(0,55)	(0,87)	(0,80)	(0,40)	(1,1)	(1.3)	(1,3)
ethyl		506	485(s)	440(s)	375(s)	342	305
		(0,91)	(0,76)	(0,50)	(0,97)	(1,3)	(1,7)
n-propyl		510		440(s)	375(s)	343	305
		(0,95)		(0,47)	(0,97)	(1,3)	(1,6)
isopropyl		500(s)		442	382	340(s)	305
		(0,70)		(0,90)	(1,2)	(1,2)	(>3,0)
cyclopropyl	550(s)	522	500(s)	440(s)	375(s)	342	305
	(0,60)	(0,87)	(0,77)	(0,42)	(0,95)	(1,4)	(1,3)
isobutyl		519		442	378(s)	338(s)	305
		(0,88)		(0,51)	(0,90)	(1,2)	(1,6)
cyclobutyl		510		440(s)	375(s)	345(s)	303
		(0,87)		(0,57)	(0,91)	(1,4)	(1,9)
cyclopropylmethyl		510		440(s)	375(s)	342	305
		(0,83)		(0,47)	(0,98)	(1,3)	(1,5)
3-butenyl		510		440	375(s)	342	305
		(0,84)		(0,43)	(0,92)	(1,2)	(1,4)
neopentyl		498		438	387(s)	346	304
		(0,81)		(0,77)	(1,0)	(1,4)	(2,7)
cyclopentyl		500		440	377(s)	344	302
		(0,74)		(0,74)	(1,2)	(1,4)	(3,1)
cyclohexyl		500(s)		440	377(s)	345	303
		(0,67)		(0,92)	(0,97)	(1,2)	(>3,3)
adenosyl	550(s)	522	500(s)	440(s)	374	340	305
	(0,65)	(0,84)	(0,76)	(0,49)	(1,1)	(1,2)	(1,3)

(s) denotes shoulder

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