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Coenzyme B_{12} model studies: An HSAB approach to the equilibria and kinetics of axial ligation of alkyl(aquo)-cobaloximes by imidazole and cyanide

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Abstract. Kinetics and equilibria of the axial ligation of alkyl(aquo)cobaloximes by imidazole and cyanide have been measured spectrophotometrically in aqueous solutions of ionic strength 1·0 M at 25°C as a function of *p*H. Comparison of K_{IMD} and K_{CN^-} of CH_3, C_2H_5 and $BrCH_2$ cobaloximes indicates that their stability is in the order $BrCH_2 > CH_3 > C_2H_5$. As the electron-withdrawing capacity of the alkyl group *trans* to water increases, the electron density of the cobalt(III) decreases and thus it becomes a stronger Lewis acid and binds more strongly to imidazole and cyanide. The association and dissociation rate constants are better correlated to the relative softness of the ligand showing that cyanide binds 30 times faster than imidazole. These complexes are isolated and are characterized by IR and ^{1}H NMR spectra.

Keywords. Alkyl cobaloximes; association constants; hand and soft acids and bases; rhodoximes; dissociation constants.

1. Introduction

Vitamin B_{12} coenzyme as well as methyl cobalamines are octahedral Co(III) compounds containing direct Co–C bond which occupy an axial coordination position relative to a corrinoid ring system [1,2]. The cobaloximes $RCo(DH)_2OH_2$ (where DH = mono anion of dimethyl glyoxime) are often studied as models for cobaloximes and the alkyl complexes have been the subject of extensive kinetic mechanistic studies [3–9]. The activity has been motivated by the possibility that axial base release may be involved in biological mechanisms. One of the principal advantages in investigating, is the solubility of these compounds in non-coordinating solvents. Under such conditions, it is possible to observe the substitution process uncomplicated by the intermediacy of solvato complexes [10].

The ligand substitution reaction of vitamin B_{12}, and its derivatives [11–15] and B_{12} model compounds, the cobaloximes [16,17], are of interest from the point of view of the mechanisms of inorganic ligand substitution reactions and the possibility that such reactions may play an important role in coenzyme B_{12} catalysed reactions. Such ligation changes may indeed be important in enzymatic reactions involving B_{12} [18–25]. Randaccio *et al* [26–28] studied the structural and solution properties of rhodoximes, compared the cobaloximes and rhodoximes and discussed the basis of electronic and steric effects.

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These studies have furnished a foundation for understanding the mechanism of the Co–C bond cleavage in the vitamin B_{12} coenzyme. Marques *et al*[29] and Randaccio *et al*[30,31] studied the molecular mechanism of modelling of the cobaloximes. Variation of the rate constants for the alkylation of tributylphosphono cobaloxime by some alkylchlorides is explained using the Taft equation[32]. Mixed ligand complexes of $[CNCo(DH)_2L]^-$ (L = imidazole primaryamines, pyridine etc.) are prepared[32–35]. Based on the changes in the νCN and ^{13}C and ^{15}N chemical shifts with the basicity of *trans* axial ligand, we expect that Co to CN π bonding is important in these cyano (ligand) complexes.

We have used imidazole, since imidazole rings (nucleic acid, proteins, antibiotics and cofactors) are present in biological systems playing significant roles in acid/base chemistry, catalysis, H-bonding and metal complexation[36]. Here we report the ligation reactions of imidazole or cyanide with bromomethyl, methyl and ethyl aquocobaloximes.

$$RCo(DH)_2H_2O + L \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} RCo(DH)_2L + H_2O, \quad (1)$$

where R = CH_3, C_2H_5 or $BrCH_2$, L = imidazole, cyanide.

In this work we have taken biologically relevant ligands in an attempt to evaluate the extent of metal to ligand π donation in the metal–ligand bond as a basis for studies on the kinetic *trans* effect on the alkyl cobalt complexes.

2. Materials and methods

Alkyl halides (Sigma), buffer salts, KCl and solvents (BDH) of the highest commercially available purity were used without further purification. Doubly distilled water was used throughout. The $RCo(DH)_2OH_2$ complex (R = CH_3, C_2H_5 or $BrCH_2$) was synthesized directly from dimethyl glyoximes, cobaltous acetate and CH_3Br, C_2H_5Br or CH_2Br_2 as described previously[37]. The complexes were characterized by ^{13}C and ^1H NMR spectra.

$BrCH_2Co(DH)_2IMD$ (IMD = Imidazole) complex[38,39] was prepared by suspending 200 mg (0·50 mM) of $BrCH_2Co(DH)_2OH_2$ in 50 ml of methanol and treated with 50 mg (0·86 mM) of imidazole. The resulting golden yellow solution was stirred at room temperature for 6 h. The methanol was removed under reduced pressure and water was added to induce precipitation as a yellow powder. The product was recrystallized from methanol, water, washed with water, ethanol and ether and dried *in vacuo*.

Proton NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz NMR spectrometer. Samples were prepared by dissolving 30 mg of $BrCH_2Co(DH)_2OH_2$ or $BrCH_2Co(DH)_2IMD$ in DMSO-d_6. Proton and ^{13}C NMR spectra were referred to external standard TSP in DMSO-d_6. Infrared spectra were obtained on a Perkin–Elmer FTIR-1605 spectrometer using KBr pellets.

Electronic spectra were recorded on a UV-1601 PC spectrometer and single wavelength measurements were made on Elico single beam spectrophotometer SL 171 model. The sample compartment of which was thermostated at $25 \pm 0{\cdot}1$°C. Apparent formation constants for the $RCo(DH)_2IMD$ complexes were determined spectrophotometrically as described previously[40,41]. Complex formation was monitored at visible wavelength 436–455 nm depending on the alkyl group. Cobaloxime concentration used was $1{\cdot}25 \times 10^{-3}$ M in visible wavelength range in 1·0 cm path-length cells. Samples containing KCN or imidazole at various concentration were prepared. HCl, chloroacetic

acid, formate, acetate, phosphate or *tris* buffer (0·2 M) as needed, to maintain *p*H (1·0 to 9·0) and KCl (ionic strength 1·0 M) were used. Samples were incubated at 25°C ± 0·1°C until equilibrium was reached as determined by the cessation of absorbance changes. The *p*H of the sample was measured after completion of the absorbance measurements, using a Digisum *p*H-meter equipped with a combined glass electrode. Formation constants were determined from the absorbance data as described previously [37,42].

3. Results and discussions

The IR spectra of $BrCH_2Co(DH)_2OH_2$ shows a broad peak at 3130 cm^{-1}. The absence of a broad peak at 3130 cm^{-1} in $BrCH_2Co(DH)_2IMD$ indicates that water is replaced by imidazole. Appearance of a peak at 430 cm^{-1} indicates that imidazole is coordinated to cobalt through N. The peak at 514 cm^{-1} is due to the coordination of C=N to Co(III). Peak shifts due to (C=C) and (C=N) frequencies of the complex in the region 1450–1650 cm^{-1} indicates that at least one of the ring nitrogen of imidazole is involved in metal ion coordination. The low intensity band at 2360 cm^{-1} is due to intramolecular hydrogen bonding in the parent complex $RCo(DH)_2IMD$.

Imidazole exhibits the following ^1H NMR signals, C2-H (7·3 δ), C4-H (6·75 δ) and C5-H (6·75 δ) and N-H (12·93 δ). These signals upon coordination to metal ion are shifted downfield (C2-H 7·42 δ, C4-H 7·24 δ, C5-H 6·97 δ). Upon coordination the equivalence of protons C4-H and C5-H of imidazole at 6·75 δ is lost and separate signals are obtained downfield. In addition, there is a signal at 2·07 ppm corresponding to 4 equatorial methyls and signal at 3·37 ppm to $BrCH_2$.

The molar conductivity of ~ 10^{-3} M solutions of the complexes in methanol show that they are non-electrolytes.

3.1 *Spectrophotometric determination of equilibrium constants (K_f) for ligation – Formation constants for the alkyl (IMD) cobaloxime*

Apparent equilibrium constants K_f^{app} for the formation of alkyl cobaloxime adduct from $RCo(D_2H_2)OH_2$ and ligand L from (2), where $(L)_{free}$ is the equilibrium ligand concentration were determined by spectrophotometric measurements of solution of $RCo(D_2H_2)OH_2$ ($1{\cdot}25 \times 10^{-3}$ M) at varying ligand concentrations at 435–455 nm. The data at a given *p*H were analysed with a computer by using linear regression based on (3). Figure 1 shows the concentration dependence binding of imidazole to $C_2H_5Co(DH)_2OH_2$. As the concentration of imidazole increases the absorbance decreases,

$$K_f^{app}\,[RCo(DH)_2L]/[RCo(DH)_2OH_2][L]_{free}, \tag{2}$$

$$A = A_0 - (\Delta\varepsilon[RCo(DH)_2OH_2][L]_{free} + 1/K_f^{app}), \tag{3}$$

where A_0 is the absorbance of $RCo(DH)_2OH_2$ in the absence of added ligand. $\Delta\varepsilon$ is the difference between the molar absorptivity of $RCo(DH)_2OH_2$ and $RCo(DH)_2L$ at the wavelength used and $[RCo(DH)_2OH_2]$ is the total concentration of cobalt containing species. K_f^{app} values were determined at *p*H 8·0 to 4·0 for imidazole. The anticipated dependence of K_{imd}^{app} was demonstrated for all complexes as shown in figure 2. Slopes of

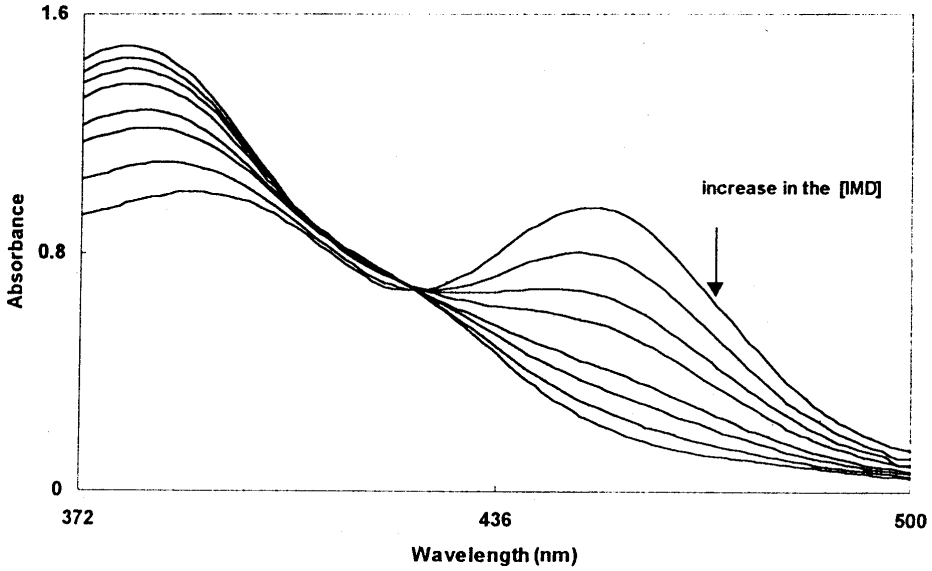

Figure 1. Binding of $C_2H_5Co(DH)_2OH_2$ with varying concentrations of imidazole at *p*H = 6·5 and 25°C.

the plots of log K_{imd}^{app} vs *p*H varied from 0·97 to 0·998. Values of K_{imd} were determined from each measurement as,

$$K_{IMD} = K_{IMD}^{app}/\alpha_{IMD}, \tag{4}$$

where α_{IMD} is the fraction of imidazole present as free base calculated using *pKa* = 7·241 at 25°C for imidazole as

$$\alpha_{IMD} = K_a/(K_a + [H^+]). \tag{5}$$

Values of K_{IMD} thus determined were independent of measurement of wavelength and complex concentration. A minimum of five values of K_{IMD} were determined for each complex and averaged to provide the K_{IMD}. Figure 3 shows the *p*H dependence of binding of imidazole. Keeping the cobaloxime and ligand concentration constant, spectra were recorded at different *p*H, and clearly show that as the *p*H is increased, binding of imidazole to $BrCH_2Co(DH)_2OH_2$ increases.

3.2 *Formation constants for the alkyl(cyano)cobaloximes*

Apparent formation constants for the $[BrCH_2Co(DH)_2CN^-]$ were calculated as

$$K_{CN}^{app} = [RCo(DH)_2CN^-]/[RCo(DH)_2OH_2][CN^-]_T,$$

where $[CN^-]_T$ is the total ligand concentration of cyanide species (i.e. $[CN^-]_T = [CN^-] + [HCN]$), K_{CN}^{app} values are *p*H dependent, in general, due to the ionization of HCN (*pKa* of HCN at 25°C = 9·04), from the equilibria in scheme 1 below and the law of mass action.

$$BrCH_2Co(DH)_2OH_2 + CN^- \rightleftarrows [BrCH_2Co(DH)_2CN^-].$$
$$K_a \uparrow\downarrow \pm H^+$$
$$HCN$$

Scheme 1.

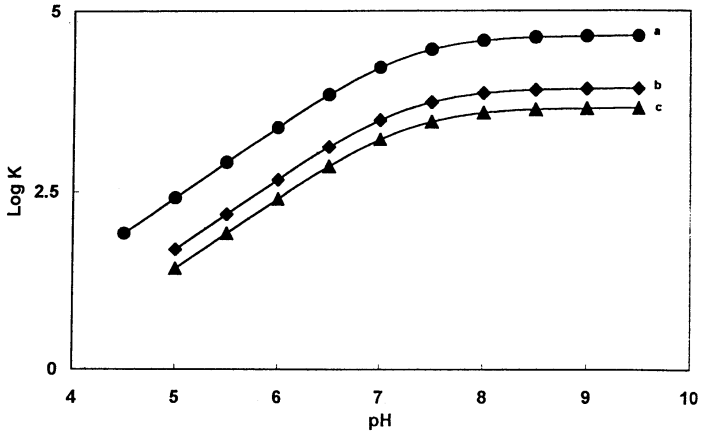

Figure 2. Dependence of log K on pH for the formation of $BrCH_2Co(DH)_2IMD$ (**a**), $CH_3Co(DH)_2IMD$ (**b**), and $C_2H_5Co(DH)_2IMD$ (**c**) at 25°C.

The dependence of K_{CN}^{app} on H^+ concentration may be readily derived as

$$K_{CN}^{app} = K_a K_{CN}/([H^+] + K_a). \quad (6)$$

Since K_{CN} values are quite large only the limiting behaviour for $[H^+] \gg K_a$ could be observed,

$$\lim_{[H^+]>>K_a} K_{CN}^{app} = K_a^* K_{CN}/[H^+]. \quad (7)$$

The pH independent behaviour for $[H^+] \ll K_a$ could be demonstrated when

$$\lim_{[H^+]\to 0} K_{CN}^{app} = K_{CN}.$$

Thus for each measurement of K_{CN}^{app}, a value of K_{CN} could be calculated from (7) using the measured pH and K_a for HCN and these values were averaged to obtain the estimation of KCN summarized in table 1. The failure to observe any positive deviation of K_{CN}^{app} from the strictly linear decrease with pH for $BrCH_2Co(DH)_2OH_2$ suggests that any binding of HCN itself must be quite weak indeed.

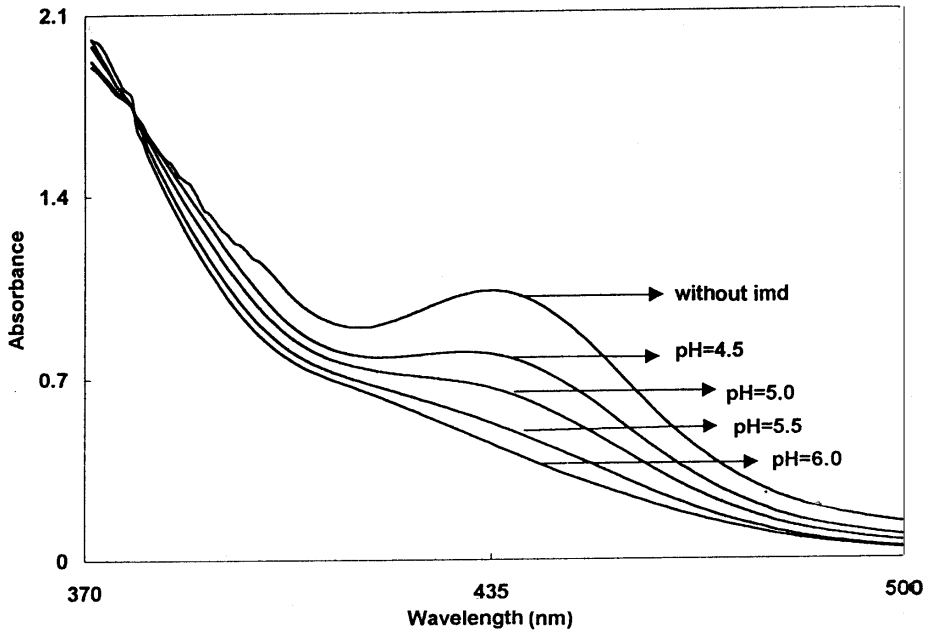

Figure 3. Dependence of *p*H on the binding of $BrCH_2Co(DH)_2OH_2$ with $4{\cdot}3 \times 10^{-3}$ M imidazole at 25°C.

Table 1. Formation constants for $RCo(DH)_2IMD$ and $[RCo(DH)_2CN^-]$.

				Log K^{app}_{IMD} values at different *p*H values										
(R=)	K_{IMD}	*K_{CN}	K_{CN}/K_{IMD}	4·5	5·0	5·5	6·0	6·5	7·0	7·5	8·0	8·5	9·0	9·5
$BrCH_2$	47334	$12{\cdot}8 \times 10^8$	27036	1·91	2·41	2·90	3·39	3·84	4·21	4·46	4·58	4·63	4·65	4·65
CH_3	8512	$1{\cdot}06 \times 10^8$	12400	–	1·68	2·18	2·66	3·11	3·49	3·73	3·86	3·90	3·92	3·92
C_2H_5	4580	$4{\cdot}7 \times 10^7$	10300	–	1·41	1·91	2·39	2·84	3·22	3·47	3·59	3·63	3·65	3·65

*ref. [37]

3.3 *Direct determination of ligation rates (k_{on})*

For the imidazole and cyanide, the second-order rate constant for ligation to $BrCH_2Co(DH)_2OH_2$ was determined from absorbance measurements at 436 nm obtained under pseudo-first-order conditions with ligand concentration in atleast tenfold excess over $BrCH_2Co(DH)_2OH_2$ concentration. The *p*H was maintained at 4·5 with CH_3COOH–CH_3COONa buffer in case of imidazole, whereas in case of CN^- *p*H 2·0 was maintained with KH_2PO_4-H_3PO_4. The reactions were initiated by adding a small volume of $BrCH_2Co(DH)_2OH_2$ solution in 25% methanol to cuvettes containing buffer, KCl and ligand to the thermostated cell compartment of a UV 1601PC spectrometer maintained at $25{\cdot}0 \pm 0{\cdot}1$°C. Figure 4 shows the time-dependent binding of imidazole to $BrCH_2Co(DH)_2OH_2$ at *p*H 6·0. First-order rate constants (k_{obs}) were obtained by the

method previously described [43]. Second-order rate constants $k_{\|(obs)}$ for ligation were obtained from the slopes of graphs of k_{obs} vs ligand concentration. Significant ordinate intercepts on such plots (k_{off}), were generally too small to be accurately determined,

$$k_{obs} = k_{on}^{app}\,[L]_{total} + k_{off}.$$

Non-zero ordinate intercepts of such plots when present gave values for the reverse rate constant k_{off} according to

$$k_{obs} = k_f[L] + k_{-f}.$$

In this measurement of k_{on} the plots of k_{obs} vs [IMD] showed no significant deviation from linearity at increasing IMD concentration (up to 1:35 ratio). It is observed that at *p*H 4·5, as the concentration of ligand increases the rate of formation of complex k_f also increases (figure 5).

In case of cyanide at *p*H 2·0, as the concentration of cyanide increases, the rate of formation of complex increases (figure 6). In case of cyanide binding to $BrCH_2Co(DH)_2OH_2$ initially (1 to 2 *p*H) as *p*H increases the rate increases then remains constant even the *p*H increases to 6·0 (figure 7).

Rate constant for ligand dissociation from $[BrCH_2Co(DH)_2IMD]$ (figure 8) or $[BrCH_2Co(DH)_2CN]^-$ were also obtained from the change in absorbance at suitable wavelength of a solution of $BrCH_2Co(DH)_2IMD$ or CN^- (generated *in situ*).

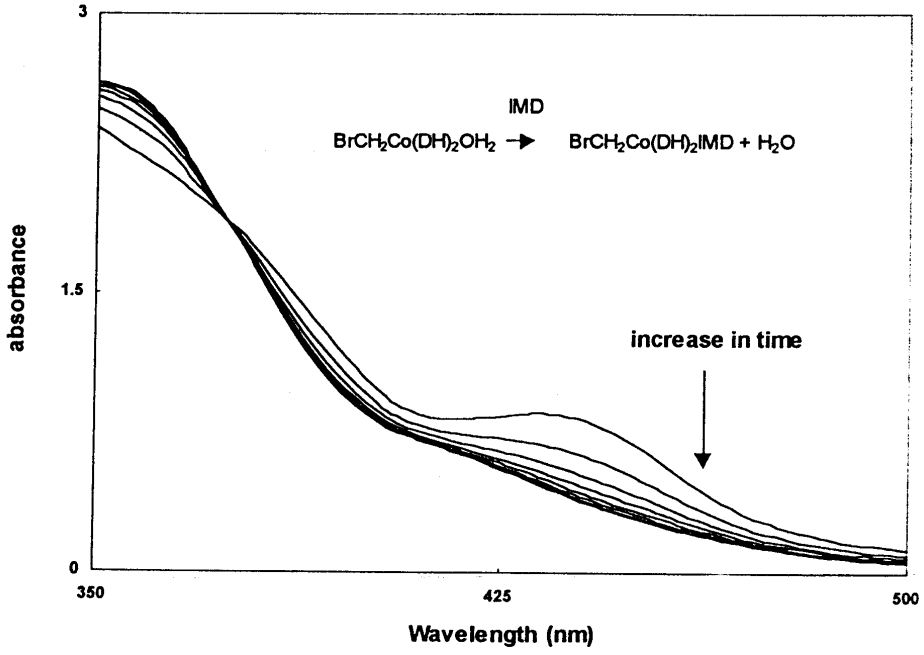

Figure 4. Kinetics of association of $BrCH_2Co(DH)_2OH_2$ with IMD at *p*H = 6·0 and 25°C.

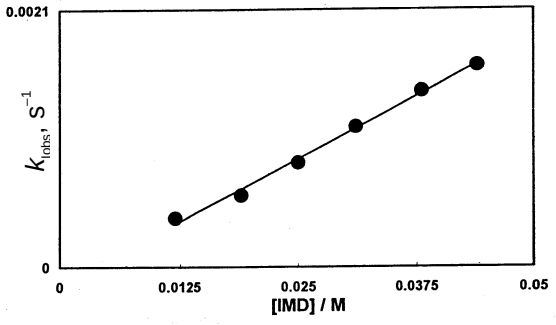

Figure 5. Dependence of [IMD] on the pseudo first-order rate constants, k_{obs}, for the formation of $BrCH_2(DH)_2IMD$ at *p*H 4·5 and 25°C, the gradient $k_{||} = 4{\cdot}04 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}.

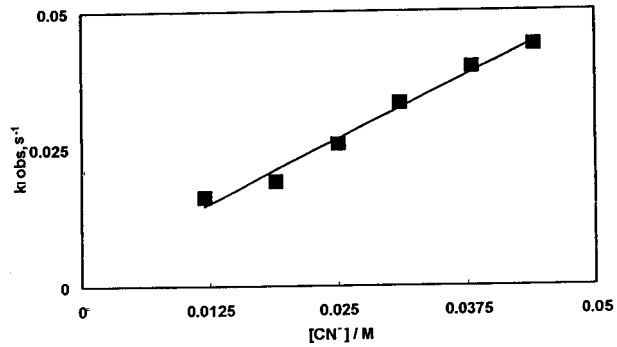

Figure 6. Dependence of [CN^-] on the pseudo first-order rate constants, k_{obs}, for the formation of [$BrCH_2Co(DH)_2CN^-$] at *p*H 2·0 and 25°C, the gradient $k_{||} = 9{\cdot}35 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}.

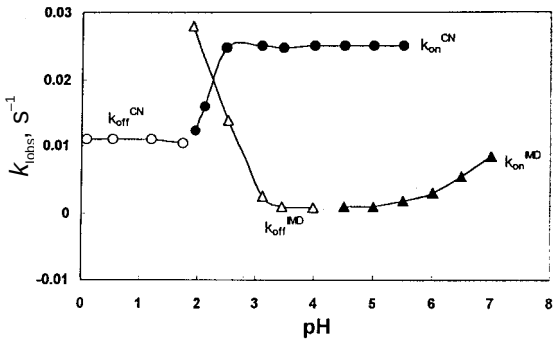

Figure 7. Comparative dependence of *p*H on pseudo first-order rate constants, k_{on} (association), and k_{off} (dissociation) for $BrCH_2Co(DH)_2IMD$ and [$BrCH_2Co(DH)_2CN^-$].

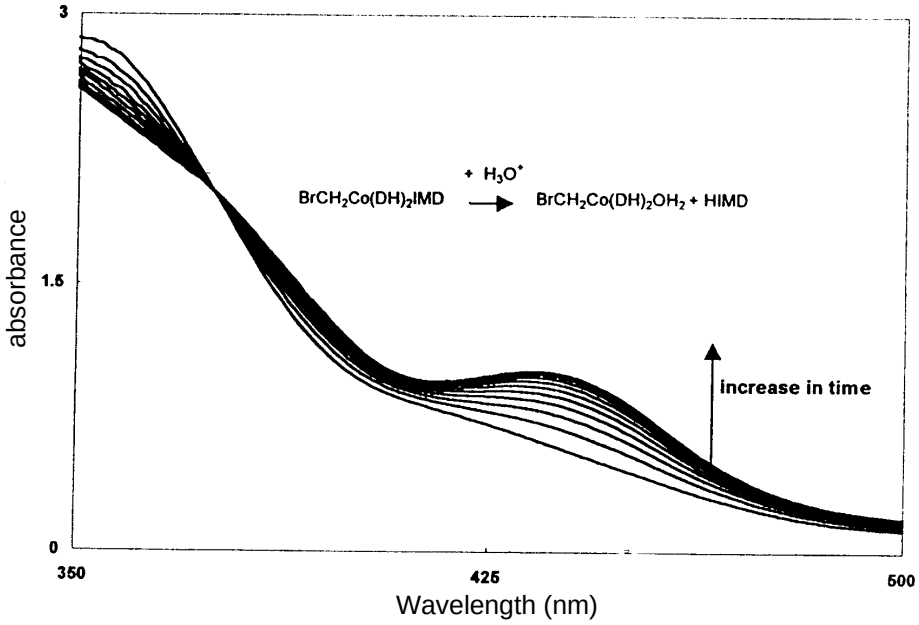

Figure 8. Dissociation kinetics of $BrCH_2Co(DH)_2IMD$ into $BrCH_2Co(DH)_2OH_2$ at *p*H = 3·0 and 25°C.

3.4 *Evidence for axial ligation by IMD or CN^-*

Evidence for axial ligation has been obtained from cyclic reaction in which the regeneration of $BrCH_2Co(DH)_2OH_2$ was demonstrated spectrophotometrically in dissociation kinetic experiments. As the *p*H is lowered all the imidazole bound to cobaloxime is taken out and aquo complex regenerated.

$$BrCH_2Co(DH)_2H_2O + IMD \xrightarrow{p\text{H}>7\cdot0} BrCH_2Co(DH)_2IMD + H_2O$$

$$\uparrow \qquad\qquad p\text{H} < 4\cdot0 \qquad\qquad \downarrow$$

$$IMDH^+$$

The ligation reaction of $BrCH_2Co(DH)_2OH_2$ in excess ligand is first-order with respect to $BrCH_2Co(DH)_2OH_2$ concentration. No buffer catalysis is observed with phosphate and acetate buffer concentration up to 0·5 M. Plots of pseudo-first-order rate constants (k_{obs}) for ligation with $BrCH_2Co(DH)_2OH_2$ vs concentration of imidazole at *p*H 4·5 are linear up to 0·05 M (IMD) and indicate that the reactions are also first order with respect to ligand concentration.

Rate of association of imidazole to $BrCH_2Co(DH)_2OH_2$ gives simple monophasic kinetics and plots of k_{obs} against ligand concentration are linear with intercepts not significantly different from zero. The kinetics of ligand addition to $BrCH_2Co(DH)_2OH_2$ is strongly dependent upon *p*H since only the deprotonated imidazole or CN^- will coordinate to Co(III) and all ligand substitution reactions of B_{12} and alkyl aquo cobaloximes reported to date are second-order with rate-limiting addition of L. The

substitution of H_2O proceeds through an unstable five-coordinate intermediate. Figure 7 shows the dependence of pseudo first-order rate constants for association and dissociation as functions of *p*H for both imidazole and cyanide.

3.5 *The mechanism of ligation reaction of $BrCH_2Co(DH)_2OH_2$*

First-order kinetic dependence on incoming ligand concentration in ligation reactions is accounted for in each of the following detailed mechanistic schemes.

(1) *SN^2 mechanism*

$$CH_2BrCo(DH)_2OH_2 + IMD \rightleftarrows CH_2BrCo(DH)_2IMD + H_2O$$

(2) *Outer-sphere complexation mechanism (equivalent to an I_d process)*

$$BrCH_2Co(DH)_2OH_2 + IMD \xrightarrow{K_{on}^{IMD}} [CH_2BrCo(DH)_2H\text{-}OH\ldots\ldots IMD]$$
$$\downarrow K$$
$$CH_2BrCo(DH)_2IMD + H_2O.$$

Plots of pseudo first-order rate constants (k_{obs}) against ligand concentrations are linear and not passed through the origin (figure 5). This indicates that there is a reversible reaction taking place and along with complex formation, some dissociation is also taking place. This is expected at low *p*H (below 7·0, IMD pK_a is 7·241). Since the reactions are fast above 7·0 *p*H, it is not possible to study the reaction kinetics by conventional spectrophotometric techniques.

At low *p*H (4·5) the graphs of k_{obs} against ligand concentration have non-zero ordinate intercepts at [ligand] $\rightarrow 0$, which indicates significant contributions from reverse rate constants (k_{-f}). Values of k_{-f} obtained from such plots or from independent measurements of $BrCH_2Co(DH)_2L$ dissociation were used to calculate the values of the apparent equilibrium constants.

The *p*H dependence of the apparent equilibrium constants for ligation, K_f^{app}, from *p*H 4·5 to 8·0, is consistent indicating that the IMD free base is the sole ligating species. As the *p*H is decreased, K^{app} decreases. The dependence of *p*H on the binding of imidazole to $RCo(DH)_2OH_2$ is seen in figure 3. This may be because of the competition of H^+ with Co(III) to bind with imidazole. Hence at lower *p*H most of the imidazole is protonated and not available for binding with cobalt. At higher *p*H imidazole (free base) available is maximum and binds to cobalt(III). Thus the K_f^{app} is large at higher *p*H. Above 8·0 or 9·0 *p*H K_f^{app} is *p*H independent as after 8·0 *p*H imidazole is completely free base and available for binding.

Comparison of K_{IMD} or K_{CN} of CH_3, C_2H_5 and $BrCH_2$ cobaloximes indicates that the order of K_{IMD} is $CH_2Br > CH_3 > C_2H_5$ (figure 2). As the electron-withdrawing capacity of the alkyl group *trans* to the water increases, it is difficult to displace water and with increasing electron-withdrawing power of the alkyl group, electron density on the cobalt decreases and Co(III) becomes a stronger Lewis acid and binds more strongly to the N donor ligand. This is proposed by Bresciani *et al*[44]. This is further supported by the

association kinetics of the $BrCH_2$ complex. In CH_3 and C_2H_5 cobaloximes, imidazole or CN^- bind to cobalt instantaneously, whereas in $BrCH_2$ cobaloxime, IMD or CN^- bind to Co(III) slowly. This is supported by the large $t^{1/2}$ of $BrCH_2Co(DH)_2IMD$ complex, whereas it is difficult to measure rate constants for CH_3 or C_2H_5 complexes by conventional spectrophotometry. The rate of displacement of pyridine in alkyl rhodoximes increases with increase in σ donor power of the alkyl group [44]. Dependence of the equilibrium constants for ligation of bromomethyl cobaloximes by imidazole and cyanide up on the pK_a values of the conjugate acids of the ligands indicates that the equilibrium constant of ligation of imidazole is smaller than that of the cyanide (table 1). This can be explained based on the stronger $Co \rightarrow CN^-$ back bonding in the cyanide complex.

Soft (or class b) character has been assigned to alkyl cobaloximes [45–47], vitamin B_{12} and methyl cobalt corrins [48]. This is supported by the observed greater ligand affinity to $CH_3Co(DH)_2OH_2$ of the soft thiolate anions as opposed to that of the hard primary amines [49,50]. In contrast, most of the Co(III) complexes, e.g. $[Co(NH_3)_5OH_2]^{+3}$, are hard acids [49] (with the interesting exceptions of the soft acids $[Co(CN)_5H_2O]^{-2}$ and $[Co(NH_3)_5SO_3]^+$). It appears that the presence of one or more soft or unsaturated ligands is sufficient to confer softness to a cobalt complex. Further, more softness appears to be directly related to the ability of a cobalt complex to stabilize a carbon–cobalt bond as seen in the cobaloximes, the cobalt corrins and even pentacyano Co(III). In the present study also, comparison of binding constants of $BrCH_2Co(DH)_2IMD$ and $[BrCH_2Co(DH)_2CN]^-$ indicates that the higher stability of $[BrCH_2Co(DH)_2CN]^-$ is due to soft–soft interaction between Co(III) and CN^-. Though both the ligands CN^- and imidazole can form metal to ligand π back-bonding, there is an enormous increase in the stability of the CN^- complex compared to that of the IMD complex [K_{CN}/K_{IMD} = 27036]. This can be attributed to the fact that IMD is a hard base whereas CN^- is a soft base.

Table 2. First-order rate constants for the axial ligation of $BrCH_2Co(DH)_2OH_2$ by L at 25·0 ± 0·1°C.

Conc. (M)	k_{on} (s^{-1})	$k_{\|\|}$ ($dm^3\ mol^{-1}\ s^{-1}$)	*p*H	k_{on} (s^{-1})	*p*H	k_{off} (s^{-1})
L = imidazole						
0·012	4×10^{-4}		4·5	$8{\cdot}92 \times 10^{-4}$	1·9	$2{\cdot}79 \times 10^{-2}$
0·019	$5{\cdot}88 \times 10^{-4}$		5·0	$1{\cdot}42 \times 10^{-4}$	2·53	$1{\cdot}4 \times 10^{-2}$
0·025	$8{\cdot}5 \times 10^{-4}$		5·5	$1{\cdot}8 \times 10^{-3}$	3·12	$2{\cdot}5 \times 10^{-3}$
0·031	$1{\cdot}14 \times 10^{-3}$	$3{\cdot}35 \times 10^{-3}$	6·0	$3{\cdot}06 \times 10^{-3}$	3·45	$9{\cdot}0 \times 10^{-4}$
0·038	$1{\cdot}43 \times 10^{-3}$		6·5	$5{\cdot}53 \times 10^{-3}$	3·98	$8{\cdot}32 \times 10^{-4}$
0·044	$1{\cdot}64 \times 10^{-3}$		7·0	$8{\cdot}44 \times 10^{-3}$		
L = cyanide						
0·012	0·016		1·95	0·0124	0·08	0·011
0·019	0·0189		2·13	0·016	0·54	0·011
0·025	0·0256		2·5	0·0247	1·2	0·011
0·031	0·0331	0·858	3·1	0·025	1·74	0·0105
0·038	0·0397		3·47	0·0248		
0·044	0·0438		4·0	0·025		
			4·5	0·025		
			5·0	0·025		

Rate constants are better correlated with the relative softness of the ligand among imidazole and CN^-. At *p*H 4·5 the rates of formation of imidazole complex is slow [$k_{obs} = 8{\cdot}92 \times 10^{-4}$ s^{-1}], whereas the rate of formation of the CN^- complex is fast ($2{\cdot}5 \times 10^{-2}$ s^{-1}). [$K_{obs}^{CN}/K_{obs}^{IMD} = 28$]. $[BrCH_2Co(DH)_2CN]^-$ formation is 28 times faster than $BrCH_2Co(DH)_2IMD$ (table 2). Even if we compare the dissociation rates, it tells that CN^- binds more strongly than imidazole. Bound CN^- can be completely removed from cobalt ($k_{obs} = 0{\cdot}011$ s^{-1}) at 0 *p*H whereas imidazole can be removed only at 1·9 *p*H ($k_{obs} = 0{\cdot}02792$ s^{-1}).

4. Conclusions

Alkylcobaloximes of the type $[RCo(DH)_2OH_2]$, where R = CH_3, C_2H_5 or $BrCH_2$ are prepared and their binding, association and dissociation rate constants with imidazole and cyanide are studied as functions of *p*H. Association of these ligands with alkylcobaloximes are explained based on the HSAB principle.

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