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Equilibria and kinetics for *p*H-dependent axial ligation of alkyl(aquo) cobaloximes with aromatic and aliphatic N-donor ligands

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Abstract. Equilibria and kinetics of the reaction of bromomethyl(aquo) cobaloxime with histamine, histidine, glycine and ethyl glycine ester and iodomethyl(aquo) cobaloxime with cyanide, imidazole and substituted imidazoles were studied as a function of *p*H at 25°C, 1·0 M ionic strength (KCl) by spectrophotometry technique. The rate of substitution of H_2O varies with the *pKa* of the incoming ligand, thus establishing the existence of nucleophilic participation of the ligand in the transition state. Dissociation kinetic reactions were also studied as a function of *p*H. Binding and kinetic data were interpreted based on the basicity, steric crowd of the entering ligand and HSAB principle. To compare the rate constants of the entering ligands *p*H independent second-order rate constants were calculated.

Keywords. Alkylcobaloximes; histamine; histidine; imidazoles; equilibrium constants.

1. Introduction

The key step in the mechanism of action of many enzymes, which require Vit-B_{12} coenzyme, is generally accepted as the homolytic cleavage of the Co–C bond [1–3]. It is widely believed that structural and conformational changes in coenzyme B_{12} lead to acceleration in Co–C bond cleavage rates [4–6]. The axial ligation reactions of metallo-porphyrin ions in aqueous solution are dependent upon the particular metal ion [7–12], equatorial ligands [13] and the axial ligands [14–18]. The study of simple models of the B_{12} coenzyme, such as the cobaloximes, $RCo(DH)_2L$, where L = neutral ligand and R = alkyl group, has furnished a significant amount of data [19,20] that have provided a foundation for understanding the behaviour of cobalamins [21]. These cobaloximes have been the subject of extensive kinetic and mechanistic studies [22,23]. This activity has been motivated by the possibility that axial base release may be involved in biological mechanisms. Contrary to this, as models for coenzyme B_{12}, cobaloximes can be faulted on a number of counts including electrochemical [24], kinetic [25,26] and structural properties [20,27,28]. The $(DH)_2$ equatorial ligand system is not as electron donating as the corrin in coenzyme B_{12} or the

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schiff-base equatorial ligands of other B_{12} models[29]. Compared to both cobalamins and other model systems, cobaloximes have stronger Co–C bonds[29] and shorter Co–L (L = pyridine or substituted pyridines) bonds[20]. Eldik *et al*[30] studied the ligand substitution reactions of *trans*-$[Co(en)_2Me(H_2O)]^{2+}$ a simple model for coenzyme B_{12}, with cyanide and imidazole as entering ligands and found that these ligands displace the coordinated water molecule trans to the methyl group and form the six coordinate complex. There is a need to study ligand substitution reactions trans to the axial alkyl ligand in coenzyme B_{12} and various model complexes. Since it is known that methyl cobaloximes and coenzyme B_{12} undergo substitution of their axial benzimidazole ligand with a protein histidine residues during complexation to the enzyme methionine synthase and methyl malonyl coenzyme A mutase, respectively[31,32].

Since binding of cobaloximes with amino acids, imidazoles and histamine are more closely related to the structural and bonding characteristics of corrin systems involved in biological mechanisms, we decided to explore the kinetics and equilibria of the axial ligation of the alkyl(aquo)cobaloximes with the aromatic ligands imidazole, substituted imidazoles, histamine, histidine and aliphatic ligands (glycine, ethyl glycine ester).

2. Materials and methods

Histamine (histamine dihydrochloride), histidine (histidine monohydrochloride), glycine, ethyl glycine ester were obtained from Sigma and imidazole, 1-methyl imidazole, 2-methyl imidazole, 2-ethyl imidazole, 1,2-di methyl imidazole were obtained from Acros. KCl, HPLC grade methanol, acetic acid, HCl, phosphoric acid, formic acid were obtained from Fluka. Dipotassium hydrogen phosphate, potassium dihydrogen phosphate, potassium phosphate, *tris*(hydroxymethyl)aminomethane (Tris), sodium acetate, potassium hydroxide were obtained from Acros. Double-distilled, deionized water was used throughout.

To maintain appropriate *p*H 0·2M buffers of HCl (0–1·5 *p*H), KH_2PO_4 and H_3PO_4 (2·0 *p*H), HCOOH and KOH (2·5–3·0 *p*H), CH_3COOH and CH_3COONa (3·5–5·5 *p*H), K_2HPO_4 and KH_2PO_4 (6·0–8·0 *p*H), Tris and HCl (8·5–9·0 *p*H), K_2HPO_4 and K_3PO_4 (9·5–11·5 *p*H) were used.

Alkyl(aquo) cobaloximes were prepared by modified procedure of Brown *et al*[33]. All manipulations were performed under minimal illuminations due to photolability of the carbon–cobalt bond[14]. These alkyl(aquo) cobaloximes are photolabile, particularly in solution. Soluble in alcohols and DMSO, less so in chloroform or water and virtually insoluble in ether and hydrocarbon solvents.

*p*H values were determined with a Digisun digital *p*H meter equipped with a combined glass electrode. The electrode was standardized at two *p*H values (*p*H = 4 and 9·2) with standard buffer solutions. UV and visible spectra were recorded on a Hitachi U-3410, the sample compartment of which is provided with a thermostat and the concentrations of bromomethyl(aquo) cobaloximes (0·00125 M) was fixed at 436 nm and iodomethyl(aquo) cobaloximes (0·001 M) was fixed at 442 nm. For axial ligation single wavelength measurements were made on an Elico single beam spectrophotometer SL 171 model. The sample compartment of which was thermostated at 25 ± 0·1°C.

3. Results and discussion

3.1 *Determination of dissociation constants of the ligands*

Values for the *pKa* of the conjugate acid of ligands are obtained by potentiometric titration at 25 ± 0·1°C. Values of *pKa*'s are obtained by a linear least-squares fit of the data to (1) below, derived from (2), where α_L is the fraction of the total ligand present as the free base (or unprotonated) species as shown in (3).

$$pH = pKa + \log [(\alpha_L)/(1-\alpha_L)], \tag{1}$$

$$Ka = [L^-]\,[H^+]/[HL], \tag{2}$$

$$\alpha_L = Ka/(Ka + [H^+]). \tag{3}$$

Ka is the dissociation constant of the ligand.

3.2 *Determination of equilibrium constants*

Apparent equilibrium constants (K_{app} values, see (4) below) for the axial ligation of alkyl(aquo) cobaloximes (scheme 1) were determined by spectrophotometric measurements. Solutions containing $RCo(DH)_2(OH_2)$, an appropriate buffer (0·2 M) to maintain *p*H, KCl to maintain ionic strength (1·0 M) and varying concentrations of ligand are taken in 3 mm cuvettes and allowed to equilibrate in a thermostated holder at 25 ± 0·1°C for 15 min prior to addition of cobaloxime.

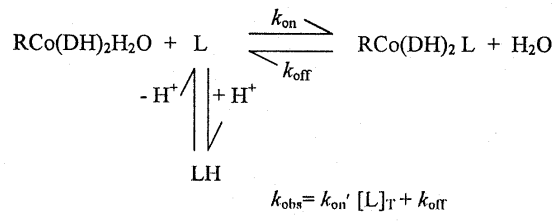
$$K_{app} = \frac{[RCo(DH)_2L]}{[RCo(DH)_2H_2O][L]_{free}}. \tag{4}$$

Final absorbance readings are taken after equilibrium is established as indicated by the time independence of the readings.

For such experimental setups, at a given *p*H, (5) is applied as follows

$$\Delta A = \Delta A_{max}\,[L]_f/(1/K_{app} + [L]_f), \tag{5}$$

where ΔA is the difference in absorbance between solutions containing cobaloxime and added ligand (L) and solutions containing only cobaloxime at the same concentration, ΔA_{max} is the maximum absorbance change thus obtained at high $[L]$, and $[L]_f$ is the



(R=$BrCH_2$ or ICH_2)

Scheme 1.

equilibrium concentration of the ligand in both ionization states. The data are analysed by a least-squares fit to the rearranged form of (5) to give

$$\Delta A = \Delta A_{max} - \{1/K_{app}\,(\Delta A/[L]_f)\}, \tag{6}$$

$$[L]_f = [L]_T - (C_T.\Delta A/\Delta A_{max}). \tag{7}$$

$[L]_f$ is calculated from (7) using the measured value of ΔA_{max}, $[L]_T$ is the total concentration of added ligand and C_T is the total concentration of cobaloxime. Values of K_{app} are obtained from the least-squares fit of (6) i.e., the plot of ΔA vs $\Delta A/[L]_f$ and the slope is $-1/K_{app.}$

The values for the equilibrium constants for axial ligation with respect to unprotonated ligand are calculated from the relation $K_{eq} = K_{app}/\alpha_L$, where α_L is calculated from (3).

3.3 *Determination of ligation rates (k_{on})*

For each ligand L, at various *p*H values, first-order rate constants (k_{obs}) are determined from the absorbance measurements at the same wavelength used for K_{app} determinations under pseudo-first order condition with L being, at least in 10-fold excess over cobaloxime concentration .

Reaction progress is monitored by measurements of the change in the absorbance upon addition of alkyl(aquo) cobaloxime to a 3 ml cuvette, which contain KCl to maintain unit ionic strength, necessary buffer (0·2 M) to maintain *p*H and ligand in the thermostated (25 ± 0·1°C) cell compartment of Elico SL171 model. First order rate constants (k_{obs}) are obtained by least-squares fits of the data to (8) below

$$\ln (A_t - A_\infty) = k_{obs}t, \tag{8}$$

where A_t is the absorbance at time t and A_∞ is the final absorbance.

Second-order rate constants, k_{on}, at a given *p*H for a given ligand are obtained from the slopes of least-squares fits of the data,

$$k_{obs} = k_{on}'\,[L]_T + k_{off}, \tag{9}$$

where $[L]_T$ is the total concentration of L present. Values of $k_{on,}$ the *p*H independent second-order ligation rate constant are calculated from $k_{on} = k_{on}'/\alpha_L$, where α_L is defined above.

3.4 *Determination of k_{off}*

Ligand dissociation rate constants, k_{off} (scheme 1), are measured spectrophotometrically by addition of a small volume of a solution containing preformed $RCo(DH)_2L$ to cuvettes containing KCl buffer (0·2 M) in the thermostated (25 ± 0·1°C) cell compartment of the spectrophotometer .

Absorbance is continuously monitored at the same wavelength (436 nm or 442 nm) used for K_{app} and k_{obs} measurements. Triplicate measurements are made at each *p*H and first-order rate constants, k_{off}, are determined as above (8). In all cases, the ligand dissociation proceeds to ≥ 99% completion at both *p*Hs. All plots of (8) are satisfactorily

linear (correlation coefficients $\geq 0{\cdot}998$). All determinations were averaged to obtain a final value of $k_{off.}$

Imidazole, substituted imidazoles, histamine, histidine, glycine, ethyl glycine ester undergo protonation of N-atom with acid dissociation constants, *pKa* in the range of 6–10. The values of the equilibrium constant K_{app} for the reaction of the glycine, ethyl glycine ester, histidine and histamine with bromomethyl cobaloximes and K_{app} values for the reaction of imidazole and substituted imidazoles with iodomethyl cobaloximes are given in table 1. Logarithmic plots of log K_{app} vs *p*H are shown in figure 1 which indicates that as the *p*H increases the K_{app} increases and the affinity for ligands increases in the order Glyest < Gly < Hisamn < Hisdn for bromomethyl(aquo) cobaloxime and 2Etimd < 1,2-diMeimd < 2-Meimd < Imd < 1-Meimd << CN^- for iodomethyl (aquo) cobaloxime. If we compare the *p*H dependent binding plots of glycine and ethyl glycine ester in both cases K_{app} increases with increase in *p*H and after certain *p*H they become *p*H independent, glycine shows *p*H dependence up to 10 *p*H and later becomes *p*H independent, whereas ethyl glycine ester binding is *p*H dependent up to 8 *p*H and later becomes *p*H independent. The binding of histidine to bromomethyl(aquo) cobaloxime has been shown in figure 2.

The equilibrium constants for the ligation of $ICH_2Co(DH)_2OH_2$ by imidazole, substituted imidazoles and CN^- is also dependent upon the *pKa* values of the ligands. In case of imidazole and 1-meimidazole the *p*H dependent binding constants are measured from *p*H 5·0 to 8·5, which demonstrate the *p*H dependent and *p*H independent binding of these ligands to $ICH_2Co(DH)_2OH_2$, whereas in case of 2-Meimd, 2-Etimd and 1,2 Dimeimd, the binding constants cannot be measured below *p*H 6·5 as they bind weakly to Co(III) of cobaloxime. If we compare the binding constants of various ligands with $ICH_2Co(DH)_2OH_2$ they are in the order $K_{CN^-} >> K_{1\text{-Meimd}} > K_{Imd} > K_{2\text{-Meimd}} > K_{1,2\text{-Dimeimd}} > K_{2\text{-Etimd}}$. Though 2-Meimd, 1,2Dimeimd and 2-Etimd are more basic than

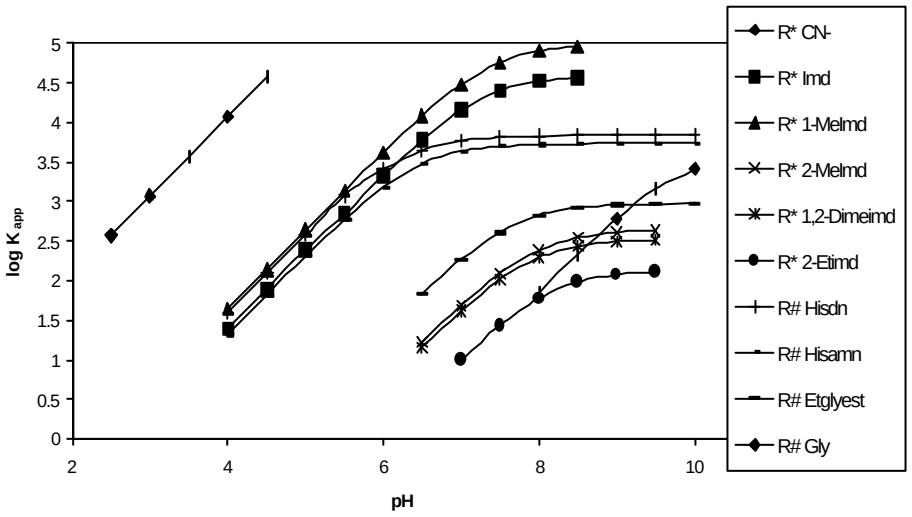


Figure 1. Dependence of log K_{app} on *p*H for the axial ligation of $RCo(DH)_2OH_2$ by different ligands at 25°C (R* – ligation with ICH_2 complex; $R^{\#}$ – ligation with $BrCH_2$ complex).

Table 1. Formation constants (log k) for the axial ligation of $RCo(DH)_2OH_2$ by L at 25°C.

	*p*H															
L	2·5	3·0	3·5	4·0	4·5	5·0	5·5	6·0	6·5	7·0	7·5	8·0	8·5	9·0	9·5	10·0	K_{eq}
R=CH₂Br																	
Hisdn	–	–	–	1·60	2·10	2·58	3·08	3·41	3·65	3·77	3·81	3·83	3·84	3·84	3·84	–	6900
Hisamn	–	–	–	1·32	1·82	2·31	2·78	3·18	3·48	3·64	3·70	3·72	3·73	3·74	3·74	–	5480
EtGlyest	–	–	–	–	–	–	–	–	1·83	2·27	2·61	2·83	2·93	2.96	2·97	2·98	958
Gly	–	–	–	–	–	–	–	–	–	–	–	–	2·33	2·79	3·16	3·41	3979
R=CH₂I																	
CN–	2·57	3·07	3·57	4·07	4·57	–	–	–	–	–	–	–	–	–	–	–	$13·6 \times 10^8$
1-Meimd	–	–	–	1·64	2·14	2·64	3·13	3·62	4·08	4·48	4·76	4·90	4·96	–	–	–	98400
Imd	–	–	–	1·39	1·89	2·64	2·84	3·33	3·78	4·15	4·40	4·52	4·57	–	–	–	39300
2-Meimd	–	–	–	–	–	–	–	–	1·22	1·69	2·09	2·39	2·54	2·61	2·63	–	440
1,2-Dimeimd	–	–	–	–	–	–	–	–	1·51	1·61	2·01	2·29	2·43	2·49	2·51	–	336
2-Etimd	–	–	–	–	–	–	–	–	–	0·99	1·43	1·77	1·98	2·08	2·11	–	135

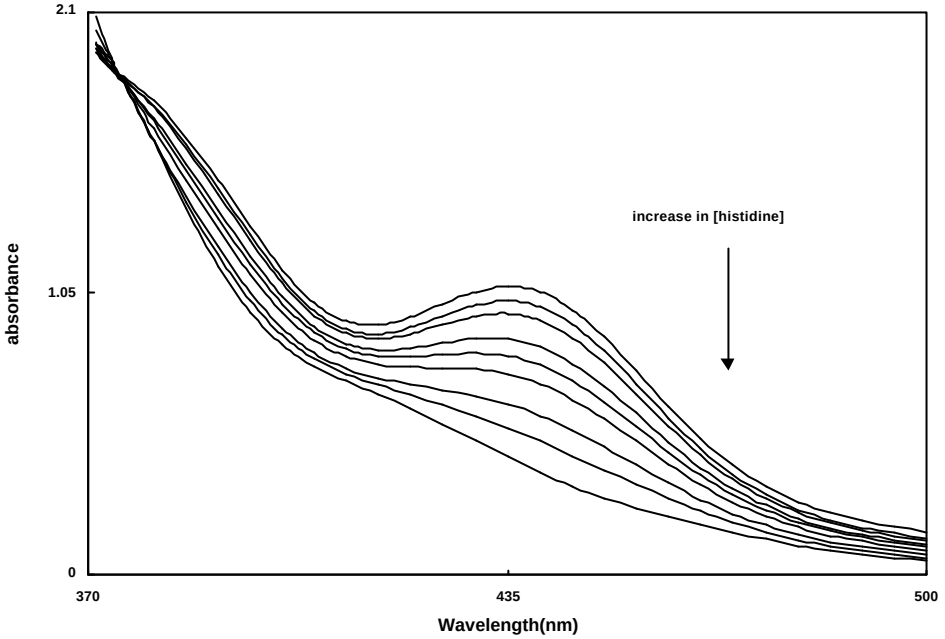


Figure 2. Binding of $BrCH_2Co(DH)_2OH_2$ with varying concentrations of histidine at *p*H = 7·5 and 25°C, isosbestic point = 380 nm.

Hisdn and Imd, they form less stable complexes. This is due to steric hindrance caused by the methyl or ethyl at the C_2 of imidazole. Similar trends are observed [34] in the study of $[CNCo(DH)_2L]$ (where *L* = 2-substituted imidazoles) and in the binding of $P(n\text{-but})_3$ to cobaloximes [35]. Though the *P* in $P(n\text{-but})_3$ is soft and more basic than imidazoles it binds weakly, this indicates that steric hindrance plays a dominant role.

In the case of histamine and histidine there is no increase in K_{app} at the *p*H above the *pKa* of the ligand. This clearly indicates that in these ligands the binding is through the endocyclic nitrogen. If it binds through NH_2 group at higher *p*H, there should be an increase in K_{app} even at higher *p*H. With histidine, the coordination is through the nitrogen of the imidazole ring, though there is a possibility of COO^- and NH_2 coordination, the NH_2 is mostly protonated below 8·0 *p*H, hence not available for binding.

A soft or class b character has been assigned to cobaloximes (III) [36] and is consistent with the observed greater ligand affinity of cyanide, imidazole [37,38], histidine or histamine than the hard glycine or ethyl glycine ester. Furthermore, softness appears to be related to the ability of a cobalt complex to stabilize a Co–C bond. Co(III) to ligand $\boldsymbol{p}$ bonding is used to explain the reverse order for the dependence of ligation strength upon ligand basicity. The order of $RCo(DH)_2L$ stability is attributed to the ability of imidazoles or histidine or histamine to accept electrons into higher energy unfilled $\boldsymbol{p}^*$ anti bonding orbitals through $d\boldsymbol{p} \rightarrow p\boldsymbol{p}$ back bonding, whereas primary amine (glycine or ethyl glycine ester) cannot accept electrons in either fashion. The reverse order for the dependence of $RCo(DH)_2L$ stability on ligand basicity among two series of ligands, aromatic (histamine, histidine, imidazole and substituted imidazoles) and aliphatic (glycine and ethyl glycine ester) is not unexpected based on the following reasons.

(1) An increase in basicity is associated with increased ability for σ donation for example glycine form more stable complexes than ethyl glycine ester, since glycine is more basic (*pKa* 9·74) than ethyl glycine ester (*pKa* 7·62).
(2) An increase in basicity is associated with decreased ability for the aromatic ligands to function as π acceptors.

The values of $K_{Hisdn} > K_{Hisamn}$, though histamine is slightly more basic than histidine. Histidine and histamine bind to Co(III), via N $\rightarrow$ Co(III) donor as well as Co(III) $\rightarrow$ N π bond. Histidine is a better π acceptor than histamine, hence histidine forms more stable complexes than histamine.

The plot of pseudo first-order rate constant k_{obs} against histidine, histamine or imidazole concentration is linear with a very small intercept, which may indicate that a small dissociation is accompanied by the complex formation (figure 3). This appears to be more likely at lower *p*H (i.e. much below the pK_a of imidazole, histidine or histamine) this is probably due to the protonation of ligand. The kinetic studies cannot be taken at high *p*H by conventional methods due to fast reactions. This is supposed by the observed high binding constant values at high *p*H. In case of histidine and histamine, as the *p*H is increased the rate of formation of complex increases. In case of histamine there is not much change in the k_{obs} even the *p*H is increased up to 7·0 *p*H. In both the cases, as the *p*H is decreased from 4·0 *p*H initially the rate of dissociation is constant but after reaching 2·5 *p*H there is a sudden increase in the dissociation rate constant. That means the bound histamine or histidine comes out from the complex at lower *p*H easily. This supports the very low binding constant at lower *p*H and high binding constant at higher *p*H (table 1).

The plots of k_{obs} vs concentration of glycine and ethyl glycine ester give straight lines with non-zero intercepts. The rate of dissociation (k_{off}) increases with decreasing *p*H (figure 4). For glycine the plot of k_{obs} vs *p*H increases with *p*H linearly. Whereas in case of ethyl glycine ester it is sigmoidal that is from *p*H 7 to 8 it increases slowly and then increases suddenly from 8 to 8·5, after which it is steady and there is no change in the k_{obs} with increase in *p*H. This can be explained that at high *p*H it reaches saturation, it means there is no effect of *p*H on the rate of formation (table 2).

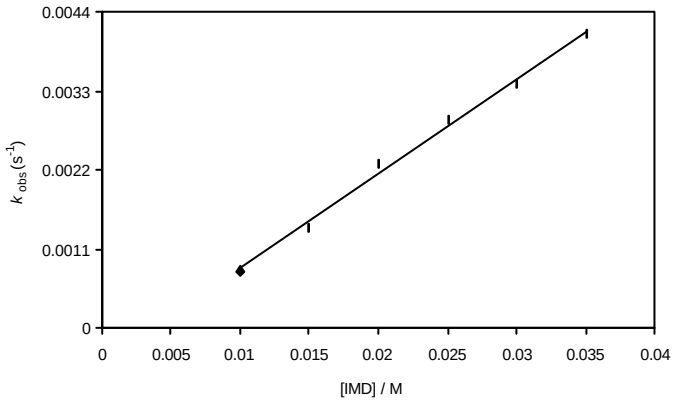


Figure 3. Dependence of [IMD] on pseudo first-order rate constants, k_{obs}, for the formation of $ICH_2Co(DH)_2$ IMD at *p*H = 5 and 25°C, the gradient $k_{on}' = 0{\cdot}132\ dm^3\ mol^{-1}\ s^{-1}$.

Table 2. Kinetic data for the axial ligation of bromomethyl(aquo)cobaloxime by different ligands at 25°C.

	k_{obs} (s^{-1})				k_{off} (s^{-1})			k_{obs} (s^{-1})				
*p*H	Histidine ($\times 10^3$)	His ($\times 10^3$)	Ethyl glycine ester ($\times 10^2$)	Glycine ($\times 10^3$)	*p*H	Histidine ($\times 10^3$)	His ($\times 10^3$)	C:L*	Histidine ($\times 10^3$)	His ($\times 10^3$)	Ethyl glycine ester ($\times 10^3$)	Gly ($\times 10^3$)
4·5	0·90	0·60	–	–	1·5	8·10	9·50	1:10	1·00	0·76	6·26	1·04
5·0	1·00	0·76	–	–				1:15	1·80	1·33	7·30	1·25
5·5	1·80	1·60	–	–	2·0	5·00	5·30	1:20	2·40	1·76	7·92	1·42
6·0	2·90	2·20	–	–				1:25	3·06	2·20	8·45	1·64
6·5	4·00	3·80	–	–	2·5	3·20	1·80	1:30	3·84	2·60	9·16	1·78
7·0	5·08	4·76	0·63	–				1:35	–	–	9·87	2·02
7·5	6·60	6·10	0·73	–	3·0	1·10	1·10					
8·0	9·50	6·13	0·89	1·04				k_{on}' (s^{-1})	0·11	0·07	0·1	0·03
8·5	–	–	1·50	2·91	3·5	1·02	0·90					
9·0	–	–	1·64	5·40				α	0.06	0·04	0·193	0·02
9·5	–	–	1·65	7·40	4·0	0·890	0.65	k_{on} (dm^3 mol^{-1} s^{-1})	2·00	1·93	0·57	1·71
10·0	–	–	–	9·90								
10·5	–	–	–	12·8								

*Ratio of $[BrCH_2Co(DH)_2OH_2]$ ($1{\cdot}25 \times 10^{-3}$) M and [L]M.

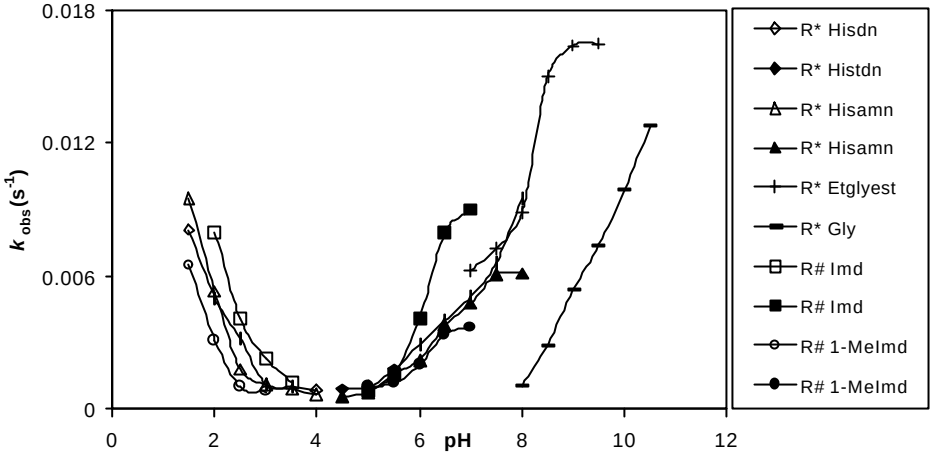


Figure 4. Dependence of k_{obs} on *p*H for the axial ligation of $[RCo(DH)_2OH_2]$ and dependence of k_{off} on *p*H for the dissociation of *L* from $[RCo(DH)_2L]$ complex at 25°C. (R* – $BrCH_2$; $R^{\#}$ – ICH_2).

Figure 4 shows the pseudo first-order rate constants for the formation (k_{obs}) and dissociation (k_{off}) as a function of *p*H (table 3). For Imd k_{obs} increases slowly up to 3·5 *p*H and then there is a sharp rise. For CN^- there is a slow increase between 1·0 and 1·5 *p*H then rises sharply between 2·0 and 3·0 *p*H. Later it is steady and there is not much increase in k_{obs} with increase in *p*H. These kinetic data are supported by binding data. The rate of dissociation of Imd and CN^- *trans* to the $[ICH_2Co(DH)_2L]$ complex increases with decrease in *p*H. Imidazole can be removed completely at *p*H 2·0 whereas CN^- is removed at 0·0 *p*H. This also supports the fact that CN^- binds more strongly than imidazole.

The kinetics of substitution of the axial base in alkylcobaloximes and related cobalt complexes has been studied under a variety of conditions [39,40]. In none of the studies was the mechanism established conclusively although in all cases strong evidence was provided that the intimate mechanism is dissociative (Id or D).

In coordinating solvents 'pentacoordinate' species are formed involving pentacoordinate alkylcobalt complexes and solvent. In view of the evidence presented above for the existence of pentacoordinate alkylcobaloximes and the ligation kinetic studies of others, both on alkyl cobalt complexes with other equatorial ligand system [41] and on cobaloxime(III) complexes [42,43], an SN^1 mechanism appears to be operative.

The small dependence of k_{on} upon ligand basicity within each series of ligands is clearly related to the fact that while the reacting complex is a soft acid the ligand is hard. The rate constants are better correlated with the relative softness of the ligand among the ligands we have studied.

The small difference in the rate of ligand substitution despite large differences in the stabilities of the Co(III) complexes [44] and aquo cobalamine have been taken to indicate the lack of significant activation of the transition state by the incoming ligand and, conversely, domination of the transition state activation by the leaving ligand (i.e., a dissociative interchange mechanism Id) [45]. The stability of pentacoordinate alkyl cobalt complexes and the evidence that both the dominant soft Co(III) complexes,

Table 3. Kinetic data for the axial ligation of iodomethyl(aquo)cobaloxime by different ligands at 25°C.

k_{obs} (s^{-1})				k_{off} (s^{-1})				k_{obs} (s^{-1})			
*p*H	Imd ($\times 10^3$)	1-Me Imd ($\times 10^3$)	CN^- ($\times 10^2$)	*p*H	CN^- ($\times 10^2$)	Imd ($\times 10^3$)	1-Me Imd ($\times 10^3$)	C:L*	Imd ($\times 10^3$)	1-Me Imd ($\times 10^3$)	CN^-
1·5	–	–	1·42	0·0	1·17	–	–	1:10	0·8	0·7	0·01
2·0	–	–	1·78								
2·5	–	–	2·98	0·5	1·01	–	–	1:15	1·4	1·1	0·02
3·0	–	–	3·46								
3·5	–	–	3·5	1·0	0·75	–	–	1:20	2·3	1·5	0·02
4·0	–	–	–								
4·5	–	–	–	1·5	–	–	6·50	1:25	2·9	1·9	0·03
5·0	0·8	1·0	–								
5·5	1·6	1·2	–	2·0	–	80·0	3·1	1:30	3·4	2·3	0·03
6·0	4·1	2·0	–								
6·5	8·0	3·4	–	2·5	–	4·1	1·0	1:35	4·1	2·7	0·04
7·0	9·0	3.7	–								
				3·0	–	2·2	0·8	k_{on}' (s^{-1})	0·132	0·8	1·034
				3·5	–	1·2	–				
								α	0·006	0·001	$2·8 \times 10^{-6}$
								k_{on} (dm^3 mol^{-1} s^{-1})	23·07	567·15	$3·8 \times 10^7$

*Ratio of $[ICH_2Co(DH)_2OH_2]$ ($1·00 \times 10^{-3}$) M and [L]M.

$[Co(CN)_5H_2O]^{2-}$ and $[Co(NH_3)_5SO_3]^+$, undergo SN^1 ligand substitution reactions [46,47], clearly favor this mechanism for the ligation reaction of $BrCH_2Co(DH)_2OH_2$. The coordination between the softness of a cobalt(III) complex and the stability of its pentacoordinate species permits SN^1 mechanism for ligand substitution [48].

To compare the rate constants of the various ligands for the formation of complex with $BrCH_2Co(DH)_2OH_2$ and $ICH_2Co(DH)_2OH_2$, we have calculated the second order rate constant, k'_{on} from the slopes of the pseudo first-order rate constants as a function of concentration of the ligand. Since this is also *p*H-dependent for better comparison we have calculated k_{on}, the *p*H independent second-order rate constant. The order of k_{on} is as follows: CN^- >> 1-Meimd [28] > Imd > Hisdn > Hisamn > Gly > Etglyest. This is in accordance with the basicity order of the ligands. Though the basicity of glycine and ethyl glycine ester are larger than imidazole, histidine or histamine k_{on} are much smaller. But within glycine and ethyl glycine ester again they follow the basicity order, k_{on} of glycine > ethyl glycine ester. This can be explained based on π bonding and HSAB principle.

4. Conclusions

In the ligation reaction of $BrCH_2Co(DH)_2OH_2$ and $ICH_2Co(DH)_2OH_2$ the π-accepting ligands (cyanide, imidazole, histidine or histamine) react more rapidly than the purely σ donors (glycine or ethyl glycine ester). The greater reactivities of the cyanide, imidazole, histidine and histamine compound to glycine or ethyl glycine ester are discussed based on the basicity , $d\pi$–$p\pi$ back bonding and HSAB principle. From these studies we also found that there is severe steric strain between substituent at the C_2 of a coordinated imidazole and the cobaloxime.

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