

Kinetics and mechanism of the interaction of N donor ligands with iodomethyl(aquo)cobaloxime

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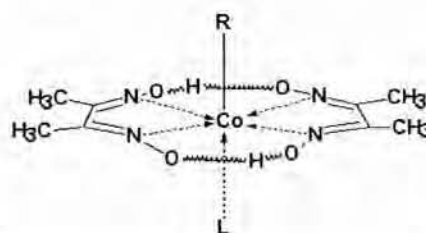
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The equilibrium constants, rate constants and activation parameters for axial ligation of alkyl(aquo)cobaloximes by N donor ligands in the presence of 0.2 M buffer (to maintain pH) and 1.0 M KCl (to maintain ionic strength) have been determined spectrophotometrically at 442 nm. The rates and activation parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) for the reactions have been estimated from the effect of concentration of ligand and temperature on the kinetics of these reactions. From the results of experimentally determined rates and activation parameters of cobaloximes, it can be concluded that the reactivity of metal complexes is greatly influenced by the ligand field effect of the co-ordinated groups and the presence of pi acceptor ligand, which provides a low energy pathway for electron transfer from a pi donor ligand anion leading to rate enhancement. The small negative $\Delta S^\ddagger$ and low $\Delta H^\ddagger$ values suggest the operation of a dissociative interchange (Id) substitution mechanism at the Co(III) center.

The B₁₂ based enzymes are the only ones thus far known whose co-factors contain a metal-carbon bond. Cobaloximes containing a cobalt-carbon σ bond in one of the axial positions and dimethyl glyoximate in the equatorial position are widely used as models for co-enzyme B₁₂. Cobaloximes are capable of reproducing certain chemical properties of the naturally occurring system¹⁻⁸ and are found useful in understanding some basic features of the more complex biologically important rearrangements thereby providing clues into the elusive mechanisms of B₁₂ catalysed enzymatic processes via radical intermediates⁹. The key step in the above rearrangement reactions is considered to be the making and breaking of Co-C bond¹⁰. These model complexes have shown that the ligand in the *trans* position to Co-C bond has a strong *trans* influence on the axial alkyl ligand and the nature of the alkyl group has an influence on the thermodynamic stability^{11,12} of the bond; equilibrium constants, kinetics and mechanism

of the substitution reactions¹³. In order to establish the factors affecting the ligand substitution reactions¹⁴⁻¹⁶ and to establish a suitable mechanism for the Co-C bond breaking, a large amount of work has been done.

Reasonable hypothesis about the nature of the transition state could be formulated utilising the thermal activation parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$). The Co-C bond cleavage is influenced by the basicity of the ligand and steric crowd of the ligand. Hence in the present note we have chosen ligands with varying basicities and sterically crowded 3,5-dimethyl pyrazole. Recently, Van Eldik *et al.*¹⁷⁻¹⁹, studied the ligand substitution reactions of *trans* [Co(en)₂Me(H₂O)]²⁺ with cyanide and imidazole as incoming ligands and also the mechanistic study on the reactions of alkyl(aquo)cobaloximes with azole and suggested that an interchange dissociative (Id) substitution mechanism operates where azoles participate in the transition state.



R = ICH₂

L = Alanine, alanine methylester, pyrazole or 3,5-dimethylpyrazole

Experimental

L-alanine, L-alaninemethylester, pyrazole and 3,5-dimethylpyrazole, obtained from Sigma, were used without further purification. KCl, and HPLC grade methanol were obtained from Fluka. Doubly distilled, deionized water was used throughout; to maintain appropriate pH, 0.2M buffers were used in the range 1.0 to 9.0 and were prepared as reported earlier¹⁴⁻¹⁶.

ICH₂Co(DH)₂OH₂ was prepared using a procedure of Brown *et al.*²⁰ All manipulations were performed under minimal illuminations due to photolability of organo cobalt bond. All work with the alkyl (aquo)cobaloximes was performed in dim light (in dark room) and solutions were covered with

aluminium foil. pH measurements were made with a Digisun digital pH meter equipped with a combined glass electrode. The electrode was standardized at two pH values (4 and 9.2) with standard buffer solutions.

UV and visible spectra were recorded on a Elico BL 198 Bio spectrophotometer, the sample compartment of which is provided with a thermostat and the concentrations of iodomethyl(aquo)cobaloximes (0.0006 M) was fixed at 442 nm.

Results and discussion

Determination of equilibrium constants

All the pK_a values of the ligands studied were determined potentiometrically. Apparent equilibrium constants, K_{app} (Eq.1) for the axial ligation of iodomethyl(aquo)cobaloxime were determined by spectrophotometric measurements at 442 nm (λ_{max} of iodomethyl(aquo) cobaloxime). In a 3 ml cuvette, solutions containing cobaloxime, an appropriate buffer (0.2 M) to maintain pH, KCl to maintain unit ionic strength and varying concentrations of ligand were taken in a cell block maintained at $25 \pm 0.1^\circ\text{C}$. Solutions were allowed to temperature equilibrate in the spectrophotometer cell block for at least 15 min. prior to addition of cobaloxime.

$$K_{app} = \frac{[\text{ICH}_2\text{Co}(\text{DH})_2\text{L}]}{[\text{ICH}_2\text{Co}(\text{DH})_2\text{H}_2\text{O}] [\text{L}]_{\text{free}}} \quad \dots(1)$$

Final absorbance readings were taken after equilibrium was established as indicated by the time independence of the readings. UV-visible scan of the complex with alanine, at different concentrations of ligand shows an isosbestic point at 421 nm showing that a single product i.e., $\text{ICH}_2\text{Co}(\text{DH})_2\text{L}$ is formed.

K_{eq} was calculated by a linear plot of ΔA versus $\Delta A/[\text{L}]_f$. Values of K_{app} were obtained from the least-squares fit of the plot of ΔA versus $\Delta A/[\text{L}]_f$ and the slope is $-1/K_{app}$. The values for the equilibrium constants for axial ligation with respect to unprotonated ligand were calculated from the relation $K_{eq} = K_{app}/\alpha_L$, where

$$\alpha_L = K_a/(K_a + [\text{H}^+]) \quad \dots(2)$$

The values of equilibrium constant (K_{app}) for the axial ligation of $\text{ICH}_2\text{Co}(\text{DH})_2\text{H}_2\text{O}$ by various N donor ligands are given in Table 1. The pH dependent binding constants were measured from 1.0 to 6.0 for pyrazole and dimethylpyrazole and for other ligands

from 6.0 to 12.0, which demonstrate pH-dependent and pH-independent binding of ligands to $\text{ICH}_2\text{Co}(\text{DH})_2\text{H}_2\text{O}$. If we observe pH-dependent and pH-independent binding plots (Fig. 1), K_{app} values increase up to a certain value of pH and after this they are pH-independent. This may be because of the competition of H^+ with $\text{Co}(\text{III})$ to bind with ligand. Hence, at lower pH most of ligand is protonated and not available for binding with cobalt. At higher pH, ligand available is maximum and binds to $\text{Co}(\text{III})$, so the K_{app} is larger at higher pH. A soft or class b character has been assigned to cobaloximes²¹ and is

Table 1 — Formation constants for the axial ligation of iodomethyl(aquo)cobaloxime $\text{ICH}_2\text{Co}(\text{DH})_2\text{OH}_2$ by N donor ligands at 25°C in aqueous solution [ionic strength 1.0M(KCl)]

pH	R= ICH_2			
	ALA	AME	PY	DMPY
1.0	-	-	1.0595	-
1.5	-	-	1.5340	-
2.0	-	-	1.9606	-
2.5	-	-	2.2868	0.7619
3.0	-	-	2.4764	1.2462
3.5	-	-	2.5589	1.6997
4.0	-	-	2.5886	2.0791
4.5	-	-	2.5984	2.3320
5.0	-	-	-	2.4568
5.5	-	-	-	2.8051
6.0	-	1.9534	-	2.5206
6.5	-	2.4395	-	-
7.0	-	2.8966	-	-
7.5	-	3.2822	-	-
8.0	2.3012	3.6271	-	-
8.5	2.7891	3.6746	-	-
9.0	3.2497	3.7260	-	-
9.5	3.6431	3.7436	-	-
10.0	3.9155	-	-	-
10.5	4.0869	-	-	-
11.0	4.1229	-	-	-
11.5	4.1317	-	-	-
$K_{eq}(\text{M}^{-1})$	13799.42	5649.80	401.00	338.42

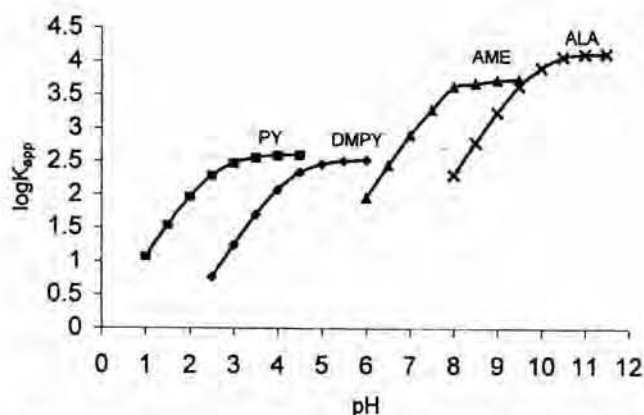


Fig. 1 — Dependence of apparent equilibrium constants (K_{app}) on the pH for the axial ligation of Iodomethyl(aquo)cobaloxime ($ICH_2Co(DH)_2OH_2$) by N donor ligands at 25°C in aqueous solution, ionic strength 1.0M (KCl)

consistent with its observed greater ligand affinity of cyanide and imidazoles²²⁻²⁴. Similar trends were observed for all the ligands studied. If we compare the equilibrium constants (K_{eq}) of various ligands they are in the order $K_{ALA} > K_{AME} > K_{PY} > K_{DMPY}$.

The order of stability depends on ligand basicity and steric hindrance among two series of ligands¹⁶, aromatic (PY and DMPY) and aliphatic (ALA and AME). Though DMPY is more basic than pyrazole, it forms less stable complexes than pyrazole due to steric hindrance of the substituents (methyl group) at C₃ and C₅, though P in P(*n*-but)₃ is soft²⁵ and more basic than imidazole, it binds weakly due to steric hindrance; this indicates that steric hindrances play a vital role. The decrease in stability with steric hindrance can also be well explained in case of alanine and alanine methyl ester. If we compare the pH dependent binding plots of alanine and alanine methyl ester, in both the cases K_{app} increases with increase in pH and after certain pH they become pH-independent; alanine shows pH dependence up to 9.5 and later becomes pH-independent, whereas alanine ester binding will be pH-dependent up to 7.5 and later it becomes pH-independent.

For each ligand L, the absorbance measurements were carried out at various pH values, first order rate constants (k_{obs}) are determined by monitoring the decrease in absorbance at the same wavelength used for K_{app} determinations under pseudo-first order condition¹⁵ with L, in at least 10 fold excess over cobaloxime concentration (0.0006 M). First order rate constants (k_{obs}) were obtained by least-squares fits of the data to Eq. (3)

Table 2 — Kinetic data showing dependence of $k_{obs}(s^{-1})$ on pH for the axial ligation of Iodomethyl(aquo)cobaloxime by N donor ligands at 25°C.

pH	$k_{obs}(s^{-1})$			
	ALA	AME	PY	DMPY
2.0	-	-	0.0008	-
2.5	-	-	0.0017	-
3.0	-	-	0.0021	-
3.5	-	-	0.0028	0.0001
4.0	-	-	-	0.0002
4.5	-	-	-	0.0009
5.0	-	-	-	0.0010
9.0	0.0002	-	-	-
9.5	0.0003	0.0003	-	-
10.0	0.0007	0.0004	-	-
10.5	0.0008	0.0005	-	-
11.0	-	0.0006	-	-

$$\ln [A_t]/[A_\infty] = k_{obs} t \quad \dots(3)$$

where A_t is the absorbance at time t and A_∞ is the final absorbance. At constant temperature, constant pH and fixed concentration of complex, the plot $\ln[A_t]/[A_\infty]$ versus time, for different ligand concentrations, is curved at the initial stage and subsequently linear indicating that the reaction is not a single step process, but a two step consecutive process may be assumed. In order to show that the rates are dependent on pH, rates were determined at different pH (Table 2), it is observed that the rate is enhanced tremendously near the pK_a of the ligand (Fig. 2).

The second order rate constants k_{on}' was determined by plotting k_{obs} versus the [ligand], the slope of which is k_{on}' . Since this is also pH-dependent we have calculated k_{on} , pH-independent second order rate constant (Table 3) using the equation $k_{on} = k_{on}'/\alpha_L$. In order to calculate activation parameters the substitution reaction was studied at varying ligand concentrations, at fixed complex concentration and at a fixed pH. The reaction was studied at 15, 20, 25, 30 and 35°C. The rates showed dependence on ligand concentration as well as on temperature and the results are included in Table 4. Figure 3 shows the temperature dependence of substitution reaction. The

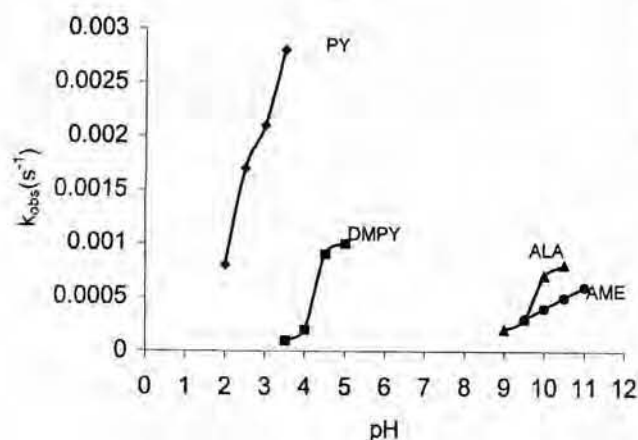


Fig. 2 — Dependence of pseudo first order rate constant on pH in aqueous solution at 25°C, ionic strength 1.0M KCl

Table 3 — Data for the determination of k_{on} (pH independent second order rate constant) for the axial ligation of $[\text{ICH}_2\text{Co}(\text{DH})_2\text{OH}_2]$ with N donor ligands at 25°C in aqueous solution [ionic strength 1.0 M KCl]

	$k_{\text{obs}}(\text{s}^{-1})$			
C:L	ALA	AME	PY	DMPY
1:10	0.0002	0.0003	0.0017	0.002
1:15	0.0004	0.0005	0.0021	0.003
1:20	0.0005	0.0006	0.0026	0.004
1:25	0.0006	0.0007	0.0030	0.005
1:30	0.0007	0.0008	0.0035	0.006
$k_{\text{on}}(\text{s}^{-1})$	0.04	0.04	0.09	0.0333
α	0.1288	0.9808	0.4827	0.3546
	(pH = 9.0)	(pH = 9.5)	(pH = 2.5)	(pH = 4.0)
$k_{\text{on}}(\text{s}^{-1})$	0.3105	0.0407	0.1864	0.0939

Table 4 — Data for the determination of second order rate constant (k_{on}) for the axial ligation of $[\text{ICH}_2\text{Co}(\text{DH})_2\text{OH}_2]$ with alanine ($\text{p}K_a = 9.83$) at different temperatures in aqueous solution, pH=9.0, ionic strength 1.0 M (KCl)

C:L	$10^3[\text{Ala}]$ (mol dm ⁻³)	k_{obs} at different temperatures(°C)				
		15	20	25	30	35
1:10	6.0	0.00005	0.00010	0.00020	0.00030	0.00040
1:15	9.0	0.00007	0.00020	0.00040	0.00050	0.00060
1:20	12.0	0.00009	0.00025	0.00050	0.00070	0.00080
1:25	15.0	0.00010	0.00030	0.00060	0.00080	0.00100
1:30	18.0	0.00020	0.00040	0.00070	0.00090	0.00150
k_{on}		0.0854	0.1809	0.3105	0.3881	0.6731

activation parameters for the axial ligation ($\Delta S^\ddagger$ and $\Delta H^\ddagger$) were calculated from standard Eyring plot and are given in Table 5. Van Eldik *et al.*¹⁷ determined the activation parameters ($\Delta S^\ddagger$, $\Delta H^\ddagger$ and $\Delta V^\ddagger$) for the reaction of *trans* $[\text{Co}^{\text{III}}(\text{en})_2(\text{Me})\text{H}_2\text{O}]^{2+}$ with cyanide and imidazole as $49 \pm 4 \text{ kJ mol}^{-1}$, $-38 \pm 15 \text{ JK}^{-1} \text{ mol}^{-1}$ and $+7.0 \pm 0.6 \text{ cm}^3 \text{ mol}^{-1}$ and $53 \pm 2 \text{ kJ mol}^{-1}$, $-22 \pm 7 \text{ JK}^{-1} \text{ mol}^{-1}$ and $+4.7 \pm 0.1 \text{ cm}^3 \text{ mol}^{-1}$ and concluded that an interchange dissociative, Id mechanism in which the entering nucleophile could be weakly bound in the transition state was operative. In the present study we have investigated the displacement of the axial H_2O molecule in $[\text{ICH}_2\text{Co}(\text{DH})_2\text{OH}_2]$ by alanine and found the low activation enthalpy of $71 \pm 2 \text{ kJ mol}^{-1}$ and low negative activation entropy of $-30 \pm 2 \text{ JK}^{-1} \text{ mol}^{-1}$ respectively and an isokinetic plot of $\Delta H^\ddagger$ versus $\Delta S^\ddagger$ support the dissociative nature of the substitution process.

The kinetics of substitution of the axial base in alkylcobaloximes and related cobalt complexes has

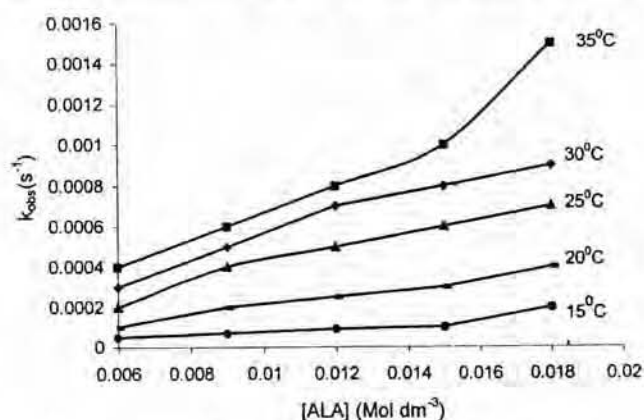


Fig. 3 — Plot of k_{obs} versus $[\text{ALA}]$, at pH = 9.0, in aqueous solution, at different temperatures, ionic strength 1.0M KCl

Table 5 — Activation parameters

System	$\Delta H^\ddagger$ (kJmol ⁻¹)	$\Delta S^\ddagger$ (JKmol ⁻¹)	Ref.
Cyanide	53±0.6	-127±3	39
Imidazole	71±1	-25±4	37
Cysteine	88±4	+35±1.3	38
Pyrazole	83±1	+24±3	19
Alanine	71±2	-30±2	Present work

been studied under a variety of conditions^{26,27}. In none of the studies was the mechanism established conclusively although in all cases strong evidence was given that the intimate mechanism is dissociative (Id or D). In most of these studies, the exchanges were performed in water with H₂O as the leaving group. There is considerable evidence in the recent literature that this is the case for the alkylcobalt corrins^{28,29} and alkylcobaloximes among B₁₂ model chelate system³⁰. 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 and on cobaloxime(III) complexes^{31,32}, an S_N¹ mechanism appears to be operative. Nevertheless there is substantial evidence that Co(III) complexes are stabilized enough to exist as penta-coordinate species³³.

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 overall small variation of ligation rates with ligand is probably indicative of an early transition state with rather large ligand to metal.

The incoming ligand and leaving ligand (water) are just loosely bound to cobalt in the transition state. It is difficult to distinguish between a transition state in which both ligands are loosely bound (i.e., Id mechanism), and one in which the leaving ligand has completely dissociated (i.e. S_N¹ mechanism)³⁴.

The stability of pentacoordinate alkyl cobalt complexes and the evidence that both of the dominant soft Co(III) complexes, [Co(CN)₅H₂O]²⁻ and [Co(NH₃)₅SO₃]⁺ undergo ligand substitution reaction as S_N¹ mechanism^{35,36} clearly favours this mechanism for ligation reaction of RCo(DH)₂OH₂. The

coordination between the softness of a cobalt(III) complex and the stability of its pentacoordinate species permitting an S_N¹ mechanism for ligand substitution³⁴ and our evidence supporting to the soft character of RCo(DH)₂OH₂ support the conclusion that the ligation reaction of RCo(DH)₂OH₂ probably proceed via S_N¹ mechanism.

Conclusions

The binding of ALA and AME to ICH₂Co(DH)₂OH₂ follow basicity order, whereas PY forms more stable complexes than DMPY due to steric hindrance of the substituent at C₃ and C₅ of DMPY. It can be concluded from the kinetic and thermodynamic data that an Interchange (Id) substitution mechanism operates during the homolysis of Co-C bond in cobaloximes in which the nucleophile participates in the transition state.

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