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KINETICS AND MECHANISMS OF SUBSTITUTION REACTIONS OF OCTAHEDRAL MACROCYCLIC AMINE COMPLEXES

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A. INTRODUCTION

It has been known for quite some time that certain transition metals, mainly Co, Fe, Cu, Mo and Mn, are present in biological systems. An understanding of their mode of action, though valuable, is not easily obtainable mainly because of the very complexity of these living systems. The so-called "model systems" approach was then devised in the hope that the knowledge obtained from the simpler systems could be extrapolated to give an understanding of the natural reactions in real systems. In particular, this "model" approach for the vitamin B_{12} group has attracted the greatest attention in recent years[1,2]. Essentially, most of these B_{12} model compounds are cobalt(III) complexes containing various macrocyclic quadridentate amine ligands. The recent success in the synthesis of a great many macrocyclic amine ligands by metal template reactions[3,4] has further stimulated research activities in various aspects of these model compounds. This paper attempts to summarize the recent advances in the rapidly expanding field of kinetic and mechanistic studies of octahedral macrocyclic amine complexes. Attention is paid mainly to cobalt(III) complexes containing relatively simple macrocycles, but reference is also made to other metal complexes when appropriate.

B. ABBREVIATIONS AND NOMENCLATURE

In general, an octahedral cobalt(III) amine complex is represented in this article by

[CoLAX], where L denotes either four monodentate or two bidentate or one quadridentate amine ligand, A a monodentate orienting ligand, and X a monodentate leaving group. The charge carried by the complex is in most cases not specified. Except as indicated, the first-order acid hydrolysis rate constant is represented by k_1 (sec^{-1}) and the second-order base hydrolysis rate constant is represented by k_2 ($M^{-1}.sec^{-1}$). The extent of acid hydrolysis of [CoLAX] is governed by the thermodynamic equilibrium constant K (M) which is defined by $[CoLAOH_2]_e[X]_e/[CoLAX]_e$, where $[species]_e$ represents the concentration of the species concerned at equilibrium. On the other hand, the stability constant of [CoLAX] with respect to acid hydrolysis is denoted by Q (M^{-1}), which is the reciprocal of K.

Ligand abbreviations used in this article are: bipy, 2,2′-bipyridyl; DMSO, dimethylsulphoxide; DPSO, diphenylsulphoxide; en, ethylenediamine; imid, imidazole; py, pyridine; terpy, 2,2′,2″-terpyridine, and tu, thiourea. R is used to designate an alkyl group. In addition, the structural formulae for some of the dioximes and macrocyclic amine ligands are illustrated in Table 1.

TABLE 1

Abbreviations for some dioximes and macrocyclic amine complexes

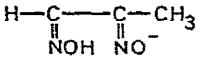
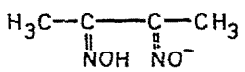
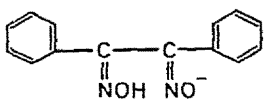
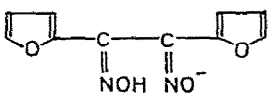
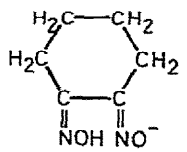
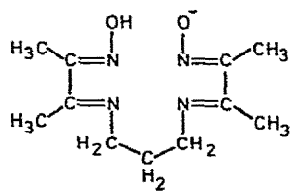
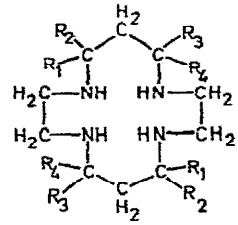
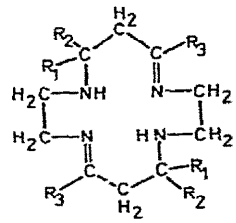
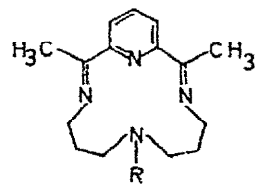
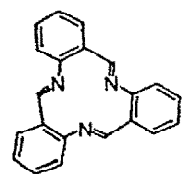
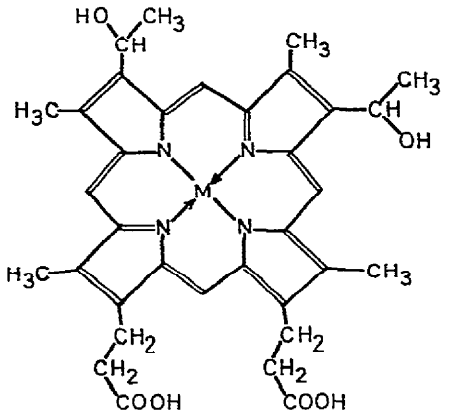
Abbreviation	Name	Structural formula
MH	Methylglyoximato	
DH	Dimethylglyoximato	
Df	Benzylglyoximato	
Dfur	α-Furildioximato	
Nioxim	1,2-Cyclohexanedionedioximato	
(DOH)(DO)pn	Diacetylmonoximeimino-diacetylmonoximatoiminopropane	

TABLE 1 (continued)

Abbreviation	Name	Structural formula
cyclam	1,4,8,11-Tetra-azacyclo-tetradecane	
teta	*meso*-5,7,7,12,14,14-Hexamethyl-cyclam	cyclam: $R_1=R_2=R_3=R_4=H$
tetb	DL isomer of teta	teta and tetb: $R_1=R_2=R_3=CH_3$, $R_4=H$
trans-cyclam-diene	1,4,8,11-Tetra-azacyclo-tetradeca-4,11,diene	
meso-trans[14]diene	*meso*-5,7,7,12,14,14-Hexamethyl-*trans*-cyclam-diene	
DL-*trans*[14]diene	DL isomer of *meso-trans*[14]diene	*trans*-cyclam-diene: $R_1=R_2=R_3=H$ *trans*[14]diene: $R_1=R_2=R_3=CH_3$
CR	2,12-Dimethyl-3,7,11,17-tetra-azabicyclo[11.3.1]-heptadeca-1(17),2,11,13,15-pentaene	 CR: R=H
$CR-CH_3$	7-Methyl-CR	$CR-CH_3$: $R=CH_3$
TRI	Tribenzo[*b,f,j*][1,5,9]tri-azacyclododecine	



Structure I. M^{III} haematoporphyrin IX.

Coordination of haematoporphyrin IX of structure I is usually achieved by the ionization of the two amino protons. This di-negatively charged porphyrin is abbreviated as HP. Cobalamins and cobinamides are structurally closely related corrinoids of general structure II. In particular, the cobalamin molecule with the terminal benzimidazole taking up the fifth coordination position, Y, is represented without specification of charge by the abbreviation CBM–. Thus vitamin B_{12}, cyanocobalamin, is represented by CBM–CN.

C. MECHANISMS OF SUBSTITUTION REACTIONS OF OCTAHEDRAL COBALT(III) AMINE COMPLEXES

It seems appropriate here to recapitulate briefly the currently accepted mechanisms of substitution reactions of octahedral cobalt(III) amine complexes[5–14]. All these reactions are essentially dissociative in nature (S_N1) and they can be represented by the following general reaction scheme[14].

$$\text{complex} + \text{reagent} \underset{\text{(fast)}}{\overset{K_{rs}}{\rightleftharpoons}} \text{reactive species} \tag{1}$$

$$\text{reactive species} \xrightarrow[\text{(rate-determining)}]{k_{rs}} \text{product} \tag{2}$$

where K_{rs} represents the equilibrium constant for step (1) and k_{rs} the first-order dissociative rate constant for step (2).

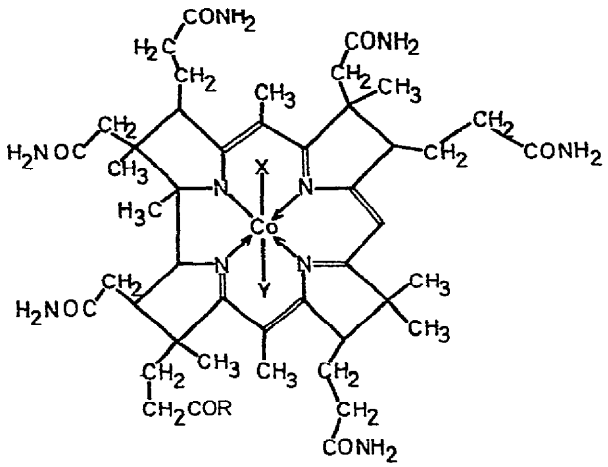
The general rate law is given by

$$\text{Rate} = \frac{k_{rs}K_{rs}[\text{reagent}]\,[\text{complex}]}{1 + K_{rs}[\text{reagent}]} \tag{3}$$

The more reactive species generated in step (1) can be broadly classified into three different types.

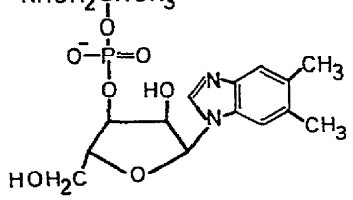
(*a*) *Reactive species in the form of ion-pairs*

This is a common phenomenon for reactions in non-aqueous solvents[15] where ion-pair



Cobinamide: R = $NHCH_2CH(OH)CH_3$

Cobalamin: R = $NHCH_2CHCH_3$



Structure II. Corrinoid.

formation plays a very important role. Many anation reactions of aquo complexes have been shown to proceed via the more reactive ion-pair between the complex and the entering anion[14,16]. Spontaneous acid hydrolysis could be regarded in the limit as the reaction occurring within the ion-multiplet between the complex and the solvent molecules. Here the reactive species is simply the solvated complex itself. Activation processes within these ion-pairs are essentially dissociative in nature.

(*b*) *Reactive species containing good leaving groups*

Most cation-induced hydrolysis reactions of these complexes are believed to involve the formation of reactive species with good leaving groups. For example, the acid-catalysed hydrolyses of $[Co(NH_3)_5F]^{2+}$ and $[Co(NH_3)_5(NO_2)]^{2+}$ have been interpreted in terms of the more reactive $[Co(NH_3)_5(FH)]^{3+}$ (ref. 17) and $[Co(NH_3)_5(HNO_2)]^{3+}$ (ref. 18) respectively. Most hydroxo complexes are known to exchange very slowly with the solvent water. The reactions are rapidly accelerated by acid owing to the formation of the more reactive aquo complexes[19]. The Hg^{2+} (ref. 20) and Ag^{+} (ref. 21) induced hydrolysis reactions of various halo-complexes involve the rapid generation of the good leaving groups HgX^{+} and AgX respectively.

(*c*) *Reactive species containing good labilizing groups*

Most anion-induced hydrolysis reactions of these complexes have been shown to in-

volve the generation of reactive species with good labilizing groups. The extensively studied base-catalysed hydrolysis of cobalt(III)–amine complexes is overwhelmingly believed to involve the strongly labilizing amido group[9,13,14].

The life-time of the five-coordinate intermediate generated in step (2) is closely related to the nature of the reactive species. Most probably it is promoted by the presence of good leaving and labilizing groups. In reactions involving these two types of reactive species, a limiting S_N1 mechanism characterized by nucleophilic competition reactions[22–25] is usually obeyed. In the absence of either of these types of assistance, the reactions are best described[6,10,26] in terms of Langford's dissociative interchange mechanism (I_d).

Although the general rate expression (3) has been found to be followed by some ligand substitution reactions in non-aqueous solvents[15], many other substitution reactions of cobalt(III)–amine complexes are known to appear in either one of the two following limiting cases. One is where K_{rs}[reagent] $\gg 1$ and the reactions become zero-order with respect to the reagent concentration, i.e. Rate = k_{rs}[complex]. This condition is always encountered in the spontaneous acid hydrolysis of these complexes in aqueous solution. The other limiting case is where K_{rs}[reagent] $\ll 1$ and the reactions become second-order with Rate = $k_{rs}K_{rs}$[reagent] [complex]. This rate expression is followed by most base hydrolyses of these complexes[9,14]. Depending on the nature of the reactants, anation reactions have been found to obey either the general or the limiting rate expression.

For some reactions, when ion-multiplets are formed as the reactive species, the rate expression (3) will have to be modified to include the appropriate higher-order reagent concentration terms.

Sometimes if more than one reactive species is generated in step (1), the generalized rate law (3) will simply be a summation of similar expressions, each corresponding to one particular reactive species.

The generalized kinetics and mechanisms discussed above are known to be followed by conventional cobalt(III) ammine- and ethylenediamine-type complexes. Within the domain of macrocyclic amine complexes, where some biologically important conjugated macrocycles are included, it would be desirable to see if the same reaction pattern is followed in their substitution reactions.

D. SUBSTITUTION REACTIONS OF SATURATED MACROCYCLIC AMINE COMPLEXES

(*i*) *1,4,8,11-Tetra-azacyclotetradecane complexes*

In acid solution (pH $\leqslant 2$), where base hydrolysis is not appreciable, *trans*-[Co(cyclam)AX] partially aquates with complete retention of configuration to an equilibrium mixture as represented by the equation

$$\textit{trans}\text{-}[Co(cyclam)AX] + H_2O \overset{K}{\rightleftharpoons} \textit{trans}\text{-}[Co(cyclam)A(OH_2)] + X \qquad (4)$$

This behaviour is quite different from that of bis-ethylenediamine and tetra-ammine complexes, where the aquation reactions are usually complete. The aquation equilibrium constants for some of the chloro-cyclam complexes are collected in Table 2. It is clear from Table 2 that those complexes containing neutral orienting ligands, such as NH_3 and H_2O, are exceptionally stable with respect to the release of the coordinated chloride. An expla-

TABLE 2

Equilibrium constants for the following reaction in 0.01 *M* nitric acid
trans-[Co(cyclam)ACl] + H_2O ⇌ *trans*-[Co(cyclam)AOH_2] + Cl^-

A	$10^3 \times K$ (*M*)	Ref.
CN^-	24.0 [a]	28
Cl^-	8.0 [b]	27
NO_2^-	2.7 [c]	28
$\underline{N}CS^-$	1.4 [d]	29
NH_3	Very small [e]	30
OH_2	Very small [e]	27, 31

[a] At 67.0°.
[b] At 60.5°.
[c] At 33.2°.
[d] At 82.5°; in 0.01 *M* perchloric acid.
[e] No estimation was made; the amount of coordinated chloride liberated is negligibly small.

nation based on the thermodynamic nephelauxetic effect[32] of these amine ligands on the central cobalt(III) ion will be presented later in the text.

Some of the rate constants and activation parameters for the aquation of cyclam and related amine complexes are collected in Table 3, from which some regularities among these amine complexes become prominent. In each of these amine series, the labilizing power of the non-labile orienting ligand A follows the same order: $OH^- > NO_2^- > Cl^- \sim CN^- > NH_3 > \underline{N}CS^-$. This means that the electronic influence of each of these ligands on the aquation activation processes is independent of the nature of the amine ligands L. This seems to indicate that essentially the same mechanism is followed by the aquation reactions of corresponding members of these amine complexes. As discussed in great detail previously[14], all these reactions are essentially dissociative. For the cyclam series, all the aquation reactions have negative entropies of activation[14]. This is consistent with the development of tetragonal pyramidal activated complexes in these dissociative activation processes[49]. The alternative trigonal-bipyramidal activated complexes are less favourable in terms of the steric requirement of the macrocyclic amine ligand. A closer examination of the activation parameters in Table 3 shows that, with the exception of the chloro–ammine complex, which is of a different charge type, the pre-exponential terms ($\log_{10} B$) are practically constant for the aquation of *trans*-[Co(cyclam)ACl]$^+$. For this series of complexes, where the leaving group is the same and the environment *cis* to the leaving group is the same, when a tetragonal pyramid is developed in the transition state there is very little solvation disturbance around the back of the molecule where the *trans* ligand A is situated. All the solvation changes are concentrated around the leaving group, which would not vary much from one member to another in the same series. This uniform solvation change is reflected by the narrow range of the value of $\log_{10} B$ (11.4–12.4) for the aquation reactions of these complexes as compared to the much larger variation of $\log_{10} B$ in the reactions of bis-ethylenediamine and tetra-ammine complex were stereochemical changes and hence larger solvation changes occur.

A comparison of the kinetic data in Table 3 shows that the aquation rate constants of

TABLE 3

First-order rate constants and activation parameters for the aquation of *trans*-[CoLAX]

L	A	X	k_1 (25°C, sec^{-1})	E_a [a] (kcal.$mole^{-1}$)	$\log_{10} B$ [a]	Steric change (%)	Ref.
(cyclam)	OH^-	Cl^-	1.2×10^{-2}	19.4	12.4	0	27
$(en)_2$	OH^-	Cl^-	1.6×10^{-3}	26.2	16.4	75	33
(cyclam)	NO_2^-	Cl^-	4.3×10^{-5}	21.5	11.5	0	28
$(en)_2$	NO_2^-	Cl^-	9.8×10^{-4}	21.6	12.8	0	34
$(NH_3)_4$	NO_2^-	Cl^-	2.7×10^{-2}	19.2	12.5	0	35
(cyclam)	Cl^-	Cl^-	1.1×10^{-6}	24.9	12.3	0	27
$(en)_2$	Cl^-	Cl^-	3.5×10^{-5}	26.7	15.0	35	36–38
$(NH_3)_4$	Cl^-	Cl^-	1.8×10^{-3}	25.5	16.0	55	39
(cyclam)	CN^-	Cl^-	4.8×10^{-7}	24.5	11.6	0	28
$(en)_2$	CN^-	Cl^-	8.2×10^{-5}	22.6	12.4	0	40
$(NH_3)_4$	CN^-	Cl^-	9.8×10^{-4}	21.3	12.6	0	41
(cyclam)	NH_3	Cl^-	7.3×10^{-8} [b]			0	42
$(en)_2$	NH_3	Cl^-	3.4×10^{-7}	23.6	10.9	0	43
$(NH_3)_4$	NH_3	Cl^-	1.7×10^{-6}	23.7	11.6	0	44
(cyclam)	NCS^-	Cl^-	3.2×10^{-8}	25.5	11.4	0	45
$(en)_2$	NCS^-	Cl^-	4.6×10^{-8}	30.4	14.9	60	46
$(NH_3)_4$	NCS^-	Cl^-	3.6×10^{-6}	26.4	13.7	[c]	45
(cyclam)	NO_2^-	Br^-	5.5×10^{-4}	21.5	12.6	0	47
$(en)_2$	NO_2^-	Br^-	4.2×10^{-3}	22.8	14.4	0	48
$(NH_3)_4$	NO_2^-	Br^-	7.2×10^{-2}	19.4	13.1	0	35

[a] $k_1 = B \exp(-E_a/RT)$ (sec^{-1}).
[b] First-order rate constant for the substitution of the coordinated chloride by thiocyanate.
[c] It was shown[45] that the reaction was accompanied by stereochemical change.

cyclam complexes are slower than those of the corresponding bis-ethylenediamine analogues. *Trans*-[Co(cyclam)(OH)Cl]$^+$ is exceptionally labile in this respect. A special mechanism for the aquation of this complex will be discussed later in the text. This reduced reactivity of cyclam complexes is in most cases due to a less favourable entropy of activation which is not adequately compensated in some cases by the corresponding decrease in the activation energy. A comparison of the relative reduction in the aquation rate constant of the π-donating chloro- and the π-accepting cyano-complexes is most interesting. That this reduction is greater for *trans*-[Co(cyclam)(CN)Cl]$^+$ (170 times at 25°C) than *trans*-[Co(cyclam)Cl_2]$^+$ (32 times at 25°) seems to imply that the π-conjugative effect of orienting ligands is not the only dominating factor which decides reaction rates and mechanisms. When the duality of reaction mechanisms was formulated in early days by

Ingold and co-workers[7,34] it was assumed that the π-conjugative effect of orienting ligands was the decisive factor affecting reaction rates and mechanisms. If this assumption were true the steric restrictions of the cyclic ligand on the formation of trigonal-bipyramidal intermediates would seriously reduce the reactivity of the chloro- but not the cyano-cyclam complex. The reduction in the aquation rate for *trans*-$[Co(cyclam)Cl_2]^+$ should have been greater than that for *trans*-$[Co(cyclam)(CN)Cl]^+$.

The base hydrolysis of cyclam complexes, like that of other conventional cobalt(III) amine complexes, is very rapid. A comparison of the rate constants and activation parameters for the base hydrolysis of cyclam and bis-ethylenediamine complexes is made in Table 4. In general, both series demonstrate the same kinetic dependence on the nature of A with $Cl^- > NH_3 > \underline{N}CS^- \sim NO_2^- \sim CN^- > OH^-$, and for a given orienting ligand A, the cyclam complex is always more reactive. It can be seen that, with the exception of Cl^-, this is exactly the reverse order of reactivity compared with the order for the aquation reactions of these complexes. This seems to indicate that the base hydrolyses of these amine complexes depend in the opposite sense on the electronic effect of the non-labile ligand A as compared with their aquation reactions. Based on this observation alone it would be rather tempting to suggest that the base hydrolysis is bimolecular as distinct from the unimolecular aquation mechanism. However, it has been discussed in great detail previously[14] that sufficient evidence has now been accumulated to support the S_N1CB mechanism[9] of Basolo and Pearson for the base hydrolysis of cobalt(III)–amine complexes. The electronic effect of these non-labile ligands A is largely swamped by the strongly labilizing amido group on the reactivity of these complexes.

TABLE 4

Second-order rate constants and activation parameters for the base hydrolysis of some [CoLA.Cl] complexes

L	A	k_2 (0° C, M^{-1}.sec^{-1})	E_a (kcal.mole^{-1})	$\log_{10} B$	Ref.
(cyclam)	Cl^-	7.4×10^3	14.2	15.2	53
$(en)_2$	Cl^-	8.5×10	23.2	20.5	54
(cyclam)	NH_3	4.0×10^2	22.9	20.9	42
$(en)_2$	NH_3	1.3			55
(cyclam)	$\underline{N}CS^-$	3.2×10	21.7	18.8	45
$(en)_2$	$\underline{N}CS^-$	3.5×10^{-1}	23.2	18.7	46
(cyclam)	NO_2^-	2.8×10	20.0	17.5	47
$(en)_2$	NO_2^-	8.0×10^{-2}	24.4	18.4	34
(cyclam)	CN^-	0.81	23.2	18.2	41
$(en)_2$	CN^-	1.3×10^{-1}	23.2	17.7	40
(cyclam)	OH^-	1.3×10^{-1}	22.7	17.3	53
$(en)_2$	OH^-	1.7×10^{-2}	22.8	16.4	54

One of the outstanding features of the base hydrolyses of cyclam complexes is the demonstration[50] of general base catalysis in the hydrolysis of *trans*-$[Co(cyclam)Cl_2]^+$. It was shown that the rate of hydrolysis of this dichloro complex increases linearly with the concentration of "free base" in a series of buffer solutions maintained at constant pH (i.e., constant hydroxide ion concentration) and constant ionic strength. This increase in rate, though small, is significant in demonstrating that the hydroxide ion is not the only specific reagent to facilitate "base" hydrolysis. This unambiguously rules out the bimolecular mechanism for these reactions. The presence of general base catalysis requires that the amido-conjugate base *trans*-$[Co(cyclam\text{-}H)Cl_2]$ cannot be generated at a rate very much faster than the rate of base hydrolysis[51]. This requirement allowed Poon and Tobe to investigate the relationship between amine proton exchange and base hydrolysis of this complex cation[50]. It was found that the base hydrolysis is accompanied by the exchange of one amine proton. This is fully consistent with the S_N1 CB mechanism. In fact the activation energy for the base hydrolysis of *trans*-$[Co(cyclam)Cl_2]^+$ is so small that it is out of place for a base hydrolysis but is of the right magnitude for an amine–proton exchange reaction[13]. This implies that the formation of the amido-conjugate base becomes the rate-determining step in the base hydrolysis of the dichloro complex.

For the hydrolysis of *trans*-$[Co(cyclam)(NO_2)X]$, where $X = NO_3^-$, Br^- and Cl^-, it was found that the plot of $\log k_1$ against $\log k_2$ is linear, with a slope of magnitude 0.86 (Fig.1)[52], which is the same slope as that for the linear free energy plot of $\log k_1$ against $\log K$. On the other hand the linear plot of $\log k_2$ against $\log K$ has a slope of unity[52]. This seems to imply, following Langford's arguments for the penta-ammine cobalt(III) system[26], that there is a slightly greater dissociative character associated with base hydrolysis than with acid hydrolysis of *trans*-$[Co(cyclam)NO_2X]$. This is consistent with the idea[14] that the presence of a good labilizing group, such as an amido group, could stabilize and increase the lifetime of a five-coordinate intermediate and could promote a limiting dissociative aquation of the conjugate base (i.e. base hydrolysis of the amine complex). The spontaneous aquation of these complexes, on the other hand, would follow a dissociative interchange mechanism. The presence of a π-withdrawing NO_2^- group may even demand a slightly greater water participation in the transition state in assisting the final

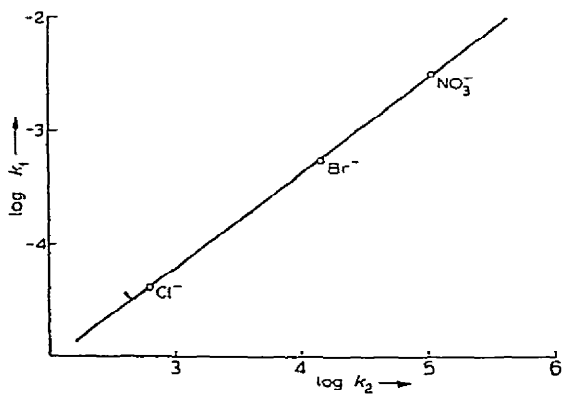


Fig.1. The plot of $\log k_1$ vs. $\log k_2$ for the hydrolysis of *trans*-$[Co(cyclam)(NO_2)X]$ at 25°C.

scission of the stretched Co–X bond than does Langford's penta-ammine series. This may perhaps explain the value of the slope, slightly smaller than unity, obtained in the plot of log k_1 against log K.

When the thermodynamic and kinetic stability of these saturated amine complexes are compared (Tables 2, 3 and 4), a general pattern appears. For a given pair of A and X the thermodynamic stability of *trans*-[CoLAX] with respect to *trans*-[CoLA(OH_2)] decreases[28,30,32,35,45,47] along the following closely related series of L: cyclam > $(en)_2$ > $(NH_3)_4$. Kinetically, the aquation rate constants of analogous complexes would increase but the base hydrolysis rate constants decrease along the same series[32]. This systematic variation in these thermodynamic and kinetic properties was found to correlate well with the ability of these amine ligands to expand the 3*d* electron cloud away from the cobalt(III) ion[32]. In other words, the variation in these properties is closely related to the positions of these amine ligands in the nephelauxetic series, viz. cyclam > en > NH_3. The expansion of the 3*d* shell and hence the demand of donor lone-pair electrons by the central cobalt(III) ion is greatest in cyclam and least in tetra-ammine complexes. This idea is strongly supported by the observed greater acidity of aquo-cyclam complexes compared with the corresponding bis-ethylenediamine complexes, which are in turn more acidic than the tetra-ammine analogues[32]. The relatively greatest attraction of water lone-pair electrons by cobalt(III) in cyclam complexes indirectly weakens the O–H bond of the aquo ligand and, therefore, renders their aquo complexes most acidic. This kind of thermodynamic nephelauxetic effect in strengthening the metal–ligand bond would be expected to be more pronounced for negatively charged ligands, such as Cl^- and OH^- than for neutral molecules, such as OH_2 and NH_3, since the electron pairs from the former donors are relatively more "basic". This immediately explains the gradual decrease in the thermodynamic stability of *trans*-[CoLAX] with respect to *trans*-[CoLA(OH_2)], which is reflected by the gradual increase in the extent of aquation of these complexes, along the above amine series. For example, the aquation of *trans*-[Co(cyclam) (NCS) Cl]$^+$ only proceeds to about 35% at equilibrium at 82.5°; the aquation of *trans*-[Co$(en)_2$(NCS)Cl]$^+$ is virtually complete but further aquation of *trans*-[Co$(en)_2$(NCS)(OH_2)]$^{2+}$ is not noticeable; for the aquation of the tetra-ammine complex, not only is the release of the chloride complete but the release of the coordinated thiocyanate also occurs to a great extent[45]. Furthermore, it would be expected that the nephelauxetic effect would increase with the charge of the complex. This may explain the thermodynamic inertness of aquo- and ammine-cyclam complexes towards aquation compared with other lower-charge cyclam complexes shown in Table 2. For unimolecular aquation reactions, the tendency of a metal complex to expel a leaving group depends largely on the extent to which the ground state electronic repulsion around the central metal ion can be reduced in the transition state. A comparison of the relative nephelauxetic effect of these amine ligands suggests that the cyclam complexes in which the 3*d* electron cloud has already been expanded to the greatest extent would have the least tendency to expel the leaving group in order to gain a further delocalization of these metal electrons into the vacated orbital in the transition state. The aquation rate is, therefore, slowest. When the labilizing powers of the orienting ligands are compared it is interesting to note that Cl^- and CN^- are grouped together although they are so different in their π-conjugative effect, being operative in opposite directions, and in their ligand field strength. They are, however, very similar in their nephelauxetic effect on the central co-

balt(III) ion. It seems, therefore, highly probable that the kinetic nephelauxetic effect would play a significant role, at least in the chloro- and cyano-cobalt(III) amine complexes, in affecting the rates and mechanisms of these aquation reactions. The effect on the rate of base hydrolysis is slightly more complicated. Assuming an S_N1 CB mechanism[9,13,14] the rate constant is directly proportional to the product of K_a and k_{cb}, where K_a is the acid ionization constant (amine proton) of the complex and k_{cb} is the aquation rate of the conjugate base. The greater tendency by cobalt(III) to attract donor electron density in cyclam than in the corresponding bis-ethylenediamine and tetra-ammine complexes indirectly weakens the N–H bond and, therefore, would probably increase the value of K_a. This is supported by the greater amine proton exchange rate[32,56] of *trans*-$[Co(cyclam)(OH_2)_2]^{3+}$ compared with those of the equally charged $[Co(en)_3]^{3+}$ and $[Co(NH_3)_6]^{3+}$. The effect on the value of k_{cb} is less obvious. Since k_{cb} represents the dissociative aquation rate constant of the conjugate base, its value would be smallest in cyclam complexes. On the other hand, the greater tendency by cobalt(III) in cyclam relative to other amine complexes to attract electron density would increase the value of k_{cb} by enhancing both the σ- and π-donating ability of the amido group in the cyclam conjugate base. In view of the great labilizing power of amido groups in the aquation of these conjugate bases in general, it could tentatively be argued that the latter influence of the two above-mentioned opposing effects on the value of k_{cb} seems greater. The net effect would be for both K_a and k_{cb} to be greater in cyclam complexes and this would lead to a faster base hydrolysis compared with those of the other two corresponding amine complexes.

Apart from the electronic effect discussed above, other effects, such as solvation and steric effects, also seem to play an important role in affecting the stability of these amine complexes. The effect of replacing four ammonia by two ethylenediamine molecules and then by one cyclam is certainly to increase the size of the complex, which is accordingly accompanied by a decrease in the solvation energy. This reduction in solvation energy would increase with the charge of the complex. Therefore, the solvation effect would also contribute by increasing the thermodynamic stability of *trans*-[CoLAX] with respect to *trans*-$[CoLA(OH_2)]$ and the acidity of the latter with increasing chelation of the amine ligands. This effect, however, would predict wrongly that both aquation and base hydrolysis, which are essentially dissociative and hence would involve a creation of charge in the transition state, would be suppressed by increasing chelation. Another direct consequence of replacing two ethylenediamine molecules by one cyclam is to render the latter complexes rigid towards stereochemical change. The probable influence of this kind of steric effect is to reduce the entropy of activation, which would lead to reduction of the reaction rate of cyclam complexes with respect to that of the bis-ethylenediamine analogues. Again, this effect cannot differentiate between aquation and base hydrolysis. It seems, therefore, that the electronic effect, and in particular the nephelauxetic effect, is primarily responsible for the thermodynamic and kinetic stability of cyclam and the related saturated-amine complexes in aqueous solution.

The apparent abnormal behaviour[30] in the acid hydrolysis of *trans*-$[Co(cyclam)(NH_3)Cl]^{2+}$ is well accounted for in terms of the nephelauxetic influence of cyclam on this complex ion. In aqueous acidic solution the hydrolysis of this complex leads to the release of the coordinated ammonia rather than the chloride. This is contrary to the conventional observation that the coordinated ammonia in octahedral cobalt(III) amine complexes is

thermodynamically very stable with respect to substitution by other ligands. The release of ammonia from coordination under normal kinetic conditions has never been observed. A detailed investigation showed that the reaction scheme, as represented by the following equations, was much more complicated than the observed substitution of ammonia by a water molecule.

$$trans\text{-}[Co(cyclam)(NH_3)Cl]^{2+} + H_2O \underset{(fast)}{\overset{K}{\rightleftharpoons}} trans\text{-}[Co(cyclam)(NH_3)(OH_2)]^{3+} + Cl^- \quad (5)$$

$$trans\text{-}[Co(cyclam)(NH_3)Cl]^{2+} + H_2O \overset{k_1}{\rightarrow} trans\text{-}[Co(cyclam)(OH_2)Cl]^{2+} + NH_3 \quad (6)$$

$$trans\text{-}[Co(cyclam)(NH_3)Cl]^{2+} + OH^- \overset{k_2}{\rightarrow} trans\text{-}[Co(cyclam)(OH)Cl]^{+} + NH_3 \quad (7)$$

$$trans\text{-}[Co(cyclam)(OH)Cl]^{+} + H^+ \underset{(fast)}{\rightleftharpoons} trans\text{-}[Co(cyclam)(OH_2)Cl]^{2+} \quad (8)$$

$$NH_3 + H^+ \underset{(fast)}{\rightleftharpoons} NH_4^+ \quad (9)$$

Detailed kinetic studies[42] showed that the coordinated chloride was in fact some 2×10^3 times more labile than the coordinated ammonia at 25°. The apparent abnormal behaviour was due entirely to the thermodynamically unfavourable equilibrium constant K in eqn. (5), which shifts the equilibrium almost entirely to the left and makes the hydrolysis of the coordinated chloride unnoticeable. The much increased lability of the coordinated ammonia can be understood in terms of the relatively unfavourable nephelauxetic effect of neutral ligands in cyclam complexes relative to those in bis-ethylenediamine and tetra-ammine analogues. In basic solution the hydrolysis is normal, giving *trans*-$[Co(cyclam)(NH_3)(OH)]^{2+}$ as the first reaction product. Here both reactant and product are of the same charge and the hydrolysis reaction is, therefore, not discriminated against by the nephelauxetic effect.

The faster aquation of *trans*-$[Co(cyclam)(OH)Cl]^+$ as compared to that of *trans*-$[Co(en)_2(OH)Cl]^+$ seems out of place in terms of the above discussion of nephelauxetic effect. It was proposed[28] that this exceptionally fast reaction was facilitated by the internal transfer of a proton from one of the cyclam secondary nitrogens to the coordinated hydroxo group. In the course of this rapid exchange a *cis* amido group was momentarily generated, which could facilitate the dissociation of the chloride ligand and profitably stabilize the resulting tetragonal-pyramidal intermediate (Fig.2). This proposition implies that both aquation and base hydrolysis of the *trans*-hydroxo-cyclam complex proceed by

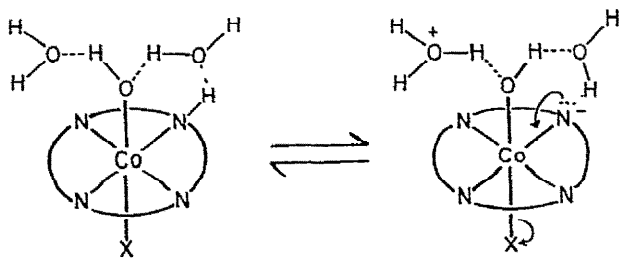


Fig.2. The internal conjugate base mechanism for the aquation of *trans*-[Co(cyclam)(OH)X].

essentially the same amido conjugate base mechanism. This idea is supported by the observation that both aquation and base hydrolysis of *trans*-$[Co(cyclam)(OH)Cl]^+$ are faster by the same factor (7.5 and 8.0 respectively at 25°) than those of *trans*-$[Co(en)_2(OH)Cl]^+$.

The acid-catalyzed hydrolysis of *trans*-$[Co(cyclam)(NO_2)_2]^+$ shows a peculiar maximum rate at ca. 11.5–12.0 *M* sulphuric acid[57]. The reason behind this is not clear. It was suggested that the variation of activity coefficients of various ions in strongly acidic solution might be responsible for this peculiar behaviour[57].

The anation reactions of *cis*- and *trans*-$[Co(cyclam)Cl(OH_2)]^{2+}$ by Cl^- and NCS^- have been shown[27,58] to follow the general rate equation (3). Analysis of the kinetic data showed[14] that these reactions were best described in terms of a limiting S_N1 mechanism rather than an ion-pair mechanism, otherwise an unrealistically large ion-pair formation constant would have to be assumed for the ion association between *trans*-$[Co(cyclam)(OH_2)Cl]^{2+}$ and NCS^-. It is interesting to note that the relative effectiveness of NCS^- compared to water in capturing the five-coordinate $[Co(cyclam)Cl]^{2+}$ depends largely on the origin of the intermediate, being 4.9×10^4 at 59.0°C when the intermediate was formed from a *trans* substrate and 4.3×10^2 at 25° from a *cis* substrate. This large difference in the discrimination factor has been taken to indicate that square pyramids are generated in the dissociation of *cis*- and *trans*-$[Co(cyclam)Cl(OH_2)]^{2+}$. If trigonal-bipyramidal intermediates were generated, then steric and electronic considerations would require the coordinated chloride to be in the trigonal plane so that essentially the same form of these intermediates would be derived from both isomers. Consequently, the competition ratios should not be so greatly different. On the other hand, the square pyramids generated from these two isomers would be sufficiently different to permit such a large difference in the competition ratios (Fig. 3). These large competition ratios, especially for the *trans* isomer, where the relative effectiveness of H_2O, Cl^- and NCS^- in trapping the five-coordinate $[Co(cyclam)Cl]^{2+}$ is in the ratio of 1:180:49,000 respectively, imply that these inter-

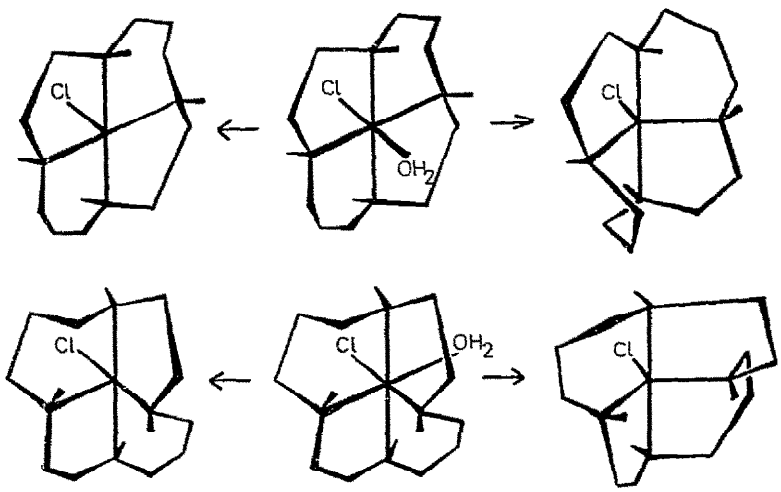


Fig.3. Skeletal relationship between the trigonal-bipyramidal and square-pyramidal five-coordinate intermediates resulting from the release of water from *cis*- and *trans*-$[Co(cyclam)Cl(OH_2)]^{2+}$.

mediates have exceptionally long lifetimes to enable them to differentiate between various incoming nucleophiles.

As far as the reactions of other metal complexes are concerned, very little experimental work has been done. Some of the available kinetic data are summarized in Table 5. It is noticed that the behaviour of the chromium(III) complexes is, in some respects, quite similar to that of the corresponding cobalt(III) complexes. For example, the aquation of *cis*-$[Cr(cyclam)Cl_2]^+$ is some 10^3 times faster than that of the *trans* isomer. This compares well with the factor of 10^4 in the cobalt(III) system[58]. The aquation of *trans*-$[Cr(cyclam)Cl_2]^+$ is slower than that of *trans*-$[Cr(en)_2Cl_2]^+$, whereas the base hydrolysis of these complexes varies in the opposite sense. This is reminiscent of the similar behaviour of the well studied cobalt(III) complexes. On the other hand, the behaviour of the hydroxochloro complexes is quite different in these two systems. Here both aquation and base hydrolysis of the chromium(III)–cyclam complexes are slower than those of the corresponding bis-ethylenediamine analogues. In any case, the lack of sufficient kinetic data does not allow a general discussion on the behaviour of these chromium(III) and rhodium(III) cyclam complexes to be made.

(ii) Other complexes

Closely related to cyclam are the Curtis macrocycles. The kinetics of substitution reactions of their metal complexes have attracted a great deal of attention in recent years. Endicott and co-workers first noticed that the aquation rates for *trans*-dichloro complexes with the isomerically related ligands teta, teta″ and tetb (see Table 1 for abbreviations) were very similar and that the aquation rate of *trans*-$[Co(teta)(NCS)_2]^+$ was faster than that of the corresponding dichloro and dibromo complexes[60,61]. These observations are rather astonishing in the sense that these different isomeric dichloro complexes, in particular the teta and tetb complexes, have quite different steric environments at the reaction site. If the faster aquation rate, by two orders of magnitude, for *trans*-$[Co(teta)Cl_2]^+$ compared with that for *trans*-$[Co(cyclam)Cl_2]^+$ was correctly ascribed to steric crowding in the former it becomes difficult to understand the similarity in rates for the teta and tetb

TABLE 5

Hydrolysis-rate constants of some chromium(III) and rhodium(III) complexes of the type [M(cyclam)-A.Cl] at 25°C

M	A	k_1 (sec^{-1})	k_2 ($M^{-1}.sec^{-1}$)	Ref.
Cr	*trans*-Cl^-	2×10^{-8}	1.3	59
Cr	*trans*-OH^-		9×10^{-3}	59
Cr	*cis*-Cl^-	2.5×10^{-5}	7.2	59
Cr	*cis*-OH^-	2.0×10^{-4}	4.1×10^{-2}	59
Rh	*trans*-Cl^-		2×10^{-9} [a]	13
Rh	*trans*-OH^-		6×10^{-12} [a]	13
Rh	*cis*-Cl^-		7.2×10^{-4} [a]	13

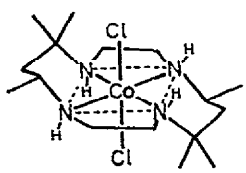
[a] At 0°C.

TABLE 6

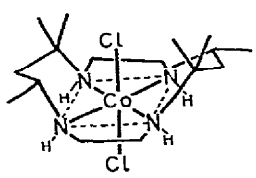
First-order rate constants and activation parameters for the release of the coordinated chloride of *trans*-$[CoLCl_2]^+$

L	k_1 (25°C, sec^{-1})	k'_1 (25°C, sec^{-1})	$\Delta H^{\neq}$ (kcal.$mole^{-1}$)	$\Delta S^{\neq}$ (cal.deg^{-1}.$mole^{-1}$)	Ref.
(cyclam)	1.1×10^{-6}		24.6	−3	27
(teta)	9.3×10^{-4}		25.6	13	62
(teta)	2.65×10^{-4}		27.4	16.9	61
(tetb)	4.2×10^{-3}		28.3	25	62
(tetb)		3.4×10^{-4}	39.5	58	62
(tetb)	2.1×10^{-4}				61

complexes. The aquation and isotopic chloride exchange kinetics of these complexes were investigated by Chau and Poon[14,62]. Their studies confirmed that the two chlorines are kinetically equivalent in *trans*-$[Co(teta)Cl_2]^+$, III, but kinetically different in the tetb-complex IV. The relative reactivity of these coordinated chlorides (from Chau and Poon's data in Table 6) follows the order: k_1 (tetb) > k_1 (teta) > k'_1 (tetb) > k_1 (cyclam). It was concluded that this reactivity order clearly demonstrated the steric acceleration of unimolecular aquation of these complexes. Here k_1 (tetb) was assigned to be associated with the release of the up-plane chlorine (structure IV), where it is sterically embraced by both *gem*-dimethyl groups, and k'_1 (tetb) was assumed to be associated with that of the other chlorine. The alternative assignment of k_1 (tetb) to be associated with the sterically less congested down-plane chlorine, which would then imply an S_N2 mechanism for these reactions, was considered highly unlikely, otherwise the cyclam complex would have been more reactive than these teta and tetb complexes. The kinetically greater lability of *trans*-$[Co(teta)(NCS)_2]^+$ as compared to the corresponding dihalo complexes is nicely correlated with its much reduced thermodynamic stability with respect to *trans*-$[Co(teta)(NCS)(OH_2)]^{2+}$. This kind of ground state destabilization of a coordinated thiocyanate has never been found in other saturated amine complexes of cobalt(III). Steric effect should not be the sole explanation because the corresponding dibromo complex is thermodynamically much more stable. One possibility is that the complex under investigation was an S-bonded thiocyanato complex. It is known that a coordinated S-bonded thiocyanate is kinetically much more labile than a coordinated chloride in the cobalt(III)—cyclam system[45].



Structure III. *trans*-$[Co(teta)Cl_2]^+$



Structure IV. *trans*-$[Co(tetb)Cl_2]^+$

Tobe's correlation[49] of activation entropy with aquation stereochemistry is obeyed by cyclam complexes, but these sterically congested systems seriously deviate from this rule. In fact, the highly positive entropies of activation in these Curtis systems could be taken as an indication of a relaxation of the ground state steric constraints in the dissociative transition state. The observation that $\Delta S^{\neq\prime}$(tetb) > $\Delta S^{\neq}$(tetb) > $\Delta S^{\neq}$(teta) > $\Delta S^{\neq}$(cyclam) (Table 6) is fully consistent with this proposition[62]. In the ground state of the tetb complex, both *gem*-dimethyl groups would probably be frozen in particular positions to avoid the maximum crowding with the embraced up-plane chlorine. The removal of this chlorine in the transition state would release this kind of steric constraint and allow free rotation of both *gem*-dimethyl groups. The removal of the down-plane chlorine would probably release the constraints by the simultaneous downward movement of the two six-membered chelate rings in order to "spread out" both *gem*-dimethyl groups. The motion of the chelate rings together with the free rotation of the methyl groups would seriously disturb the solvating water molecules. Thus, it would be expected that $\Delta S^{\neq\prime}$(tetb) would be larger than $\Delta S^{\neq}$(tetb), which would be more positive than the $\Delta S^{\neq}$ of the slightly less strained teta and the relatively strain-free cyclam complexes.

The above discussion of steric constraints in the ground state of these Curtis complexes is also supported by the reduced thermodynamic stability of *trans*-$[Co(teta)Cl_2]^+$ with respect to *trans*-$[Co(teta)Cl(OH)_2)]^{2+}$ than the corresponding cyclam analogue. This difference could be attributed to the possibility that a coordinated water might effectively reduce the ground state steric interaction between this axial ligand and the *gem*-dimethyl groups with respect to a coordinated chloride in the teta complex. This possibility arises because a water molecule may orient itself in such a way that both hydrogen atoms are pointing away from the *gem*-dimethyl groups. This leaves only the oxygen atom, which, has a much smaller van der Waals radius than a chloride, to face these methyl groups directly.

Although it appears that stereo-retention is characteristic of ligand substitution reactions of cyclam and its hexamethylated complexes, it was noticed that the anation of *cis*-$[Co(tetb)(OH_2)_2]^{3+}$ by Cl^- gave exclusively *trans*-$[Co(tetb)Cl(OH_2)]^{2+}$ as the first detectable product[63]. Since *trans*-$[Co(tetb)(OH_2)_2]^{3+}$ was not sufficiently labile to be the reaction intermediate, an S_N2 mechanism with a chloride attack from the rear was suggested to account for this anation reaction[63]. It must, however, be noted that the same anation reaction could still be explained in terms of a possibly labile *cis*-$[Co(tetb)Cl(OH_2)]^{2+}$ intermediate which may isomerize too rapidly to escape detection. To be consistent with the general concept that all the ligand substitution reactions of saturated amine complexes of cobalt(III) are essentially dissociative, it seems that the following mechanism may explain the steric course of the above anation reaction more satisfactorily than an S_N2 mechanism. It was pointed out by Endicott[64] that for the same isomeric configuration of tetb, designated as α, $[Co(tetb)(OH_2)_2]^{3+}$ readily assumed a *cis* geometry while all the $[Co(tetb)X_2]^+$ complexes very much preferred a *trans* configuration. This was explained in terms of electrostatic repulsion between neighbouring X^-—X^- groups which would tend to separate these negative groups as far as possible[64]. Since this kind of ligand electrostatic repulsion is so important, it seems reasonable to expect that in the ion-pair of $\{cis\text{-}[Co(tetb)(OH_2)_2]^{3+}, X^-\}$ the X^- group would be best situated at the organic part of the molecule at the rear (Fig.4). As soon as the trigonal bipyramidal

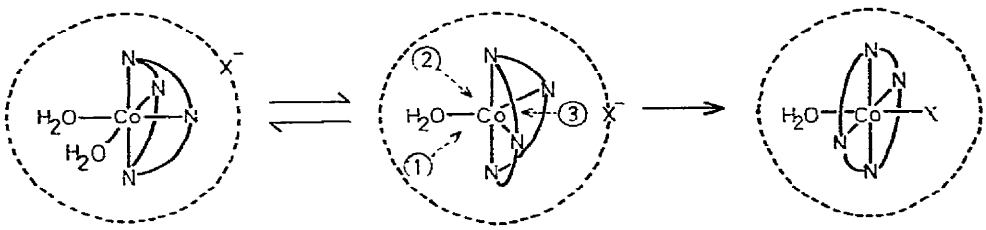


Fig.4. Steric course for the unimolecular anation of *cis*-$[Co(tetb)(OH_2)_2]^{3+}$.

intermediate is formed, the entrance of a water molecule in positions 1 or 2 leads back to the original *cis* diaquo complex, whereas the entrance of X^- from position 3 would give exclusively a *trans* product. The mechanism can also explain the steric course in the decomposition of *cis*-$[Co(tetb)(CO_3)]^+$ by various acids. The reaction with HBr gives a mixture of *cis*-$[Co(tetb)(OH_2)_2]^{3+}$ and *trans*-$[Co(tetb)Br(OH_2)]^{2+}$, while the decomposition by HCl gives exclusively[63] *trans*-$[Co(tetb)Cl(OH_2)]^{2+}$. As soon as the carbonate group is decomposed, essentially the same five-coordinate $[Co(tetb)(OH_2)]^{3+}$ intermediate, as shown in Fig.4, will be generated. Since Cl^- is a harder base and hence a better nucleophile than Br^- for the hard cobalt(III) in these complexes it is not surprising if we expect Cl^- to be more effective than water in trapping the five-coordinate intermediate and gives exclusively *trans*-$[Co(tetb)Cl(OH_2)]^{2+}$. On the other hand, Br^- may not be effective enough to gain full control of the intermediate and this would result in a mixture of *trans*-$[Co(tetb)Br(OH_2)]^{2+}$ and *cis*-$[Co(tetb)(OH_2)_2]^{3+}$. The very poorly coordinating ClO_4^- cannot compete at all with water for the five-coordinate intermediate, but its being situated at position 3 would have the effect of blocking the entrance of water from this position. The consequence is that only *cis*-$[Co(tetb)(OH_2)_2]^{3+}$ is formed, as observed, in the decomposition of *cis*-$[Co(tetb)(CO_3)]^+$ by $HClO_4$.

E. SUBSTITUTION REACTIONS OF UNSATURATED MACROCYCLIC AMINE COMPLEXES

It is well known that many of the unusual features of the chemistry of vitamin B_{12} have been attributed to some extent to the presence of cobalt(III)—N(imine) groups through which the central metal ion shares pseudo-aromaticity with the encircling amine macrocycle. In fact, the extensive electronic interaction between the cobalt atom and some of these highly unsaturated ligand systems renders the formalism of a cobalt(III) oxidation state unrealistic. It becomes desirable to investigate the systematic changes in the chemistry of these macrocyclic amine complexes with progressive unsaturation in the ligand systems. It is hoped that the knowledge derived from the simpler model systems may be extrapolated to an understanding of the much more complex in vivo systems. We are concerned here only with the variation in the kinetics and mechanisms of substitution reactions with the extent of unsaturation of these amine complexes.

The simplest unsaturated macrocycles, which are closely related to cyclam and its hexamethylated analogues, are Curtis *cis*- and *trans*[14]diene, where a pair of azomethine linkages are sited *cis* or *trans* to each other in the macrocycle. Most of the studies, however, have been concentrated on the electrochemical[65,66] and redox[67] behaviour of their cobalt(II), nickel(II) and copper(II) complexes. The corresponding studies on the kinetics of ligand substitution reactions have been rather sparse.

Kernohan and Endicott[61] first reported the aquation kinetics of complexes of the type *trans*-[Co(*meso-trans*[14]diene)X_2], where X = Cl^-, Br^- and NCS^-. They noted that these reactions are not very sensitive to the nature of X. The aquation rate constants for these three complexes lie within a factor of 5. A factor of 2×10^4 has been found for the reactions of the corresponding saturated teta complexes.

The reason behind the insensitivity of reaction rate to the nature of the axial ligands is not clear at this stage. It may be tempting to attribute this effect to the presence of a pair of cobalt(III)–N(imine) bonds which enables an electronic delocalization between the cobalt ion and the macrocyclic ring. This kind of electronic delocalization might render the electronic effect of the axial ligands much less important here than it would be in other saturated amine systems in affecting reaction rates. However, this generalization is thwarted by the even greater dependence of the aquation rate of cobalamins[68–70] on the nature of X than other conventional saturated cobalt(III) amine complexes. The hundred-fold increase in the reactivity of *trans*-[Co(*meso-trans*[14]diene)Cl_2]$^+$ over *trans*-[Co(teta)Cl_2]$^+$ was reasonably attributed to the possibility that the cobalt(III)–N(imine) groups help increase the lifetime of a five-coordinate intermediate species[61]. If this interpretation is correct, it is difficult to explain the similarity in the aquation rates of the dibromo complexes in these two systems and the even slower aquation rate of *trans*-[Co(*meso-trans*[14]diene)-$(NCS)_2$]$^+$ compared with the saturated teta analogue. This apparent inconsistency could easily be accounted for in terms of a more general proposition to be discussed later in the concluding section of this paper.

The observed[61] similarity in the equation rates for the *meso*- and DL-*trans*-dichloro-*trans*[14]diene complexes is rather surprising. With reference to the previous discussion concerning the differences in the reactivity of teta and tetb complexes, this observation is found difficult to reconcile with the prediction made on the basis of steric effects on octahedral substitution reactions.

The acid hydrolysis of *cis*-[Co(DL-*trans*[14]diene)(CO_3)]$^+$ was studied in conjunction with the related tetb analogue. It was found, as shown in Table 7, that the hydrolysis rates increase in the following order[67]: *cis*-[Co(tetb)(CO_3)]$^+$ < *cis*-[Co(DL-*trans*-[14]diene)-(CO_3)]$^+$ < *cis*-[Co$(en)_2(CO_3)$]$^+$. The following mechanism was suggested to explain these decarboxylation reactions.

$$cis\text{-}[CoL(CO_3)]^+ + H_3O + \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} cis\text{-}[CoL(HCO_3)(OH_2)]^{2+} \tag{10}$$

$$cis\text{-}[CoL(HCO_3)(OH_2)]^{2+} \overset{k_b}{\rightarrow} cis\text{-}[CoL(OH)(OH_2)]^{2+} + CO_2 \tag{11}$$

$$cis\text{-}[CoL(OH)(OH_2)]^{2+} + H^+ \underset{\text{(fast)}}{\rightleftharpoons} cis\text{-}[CoL(OH_2)_2]^{3+} \tag{12}$$

There are two possibilities. One possibility is that equilibrium (10) is rapidly established and that the hydrolysis of the bicarbonato group (i.e. k_b) becomes the rate-determining step. The other alternative is that the acid-catalyzed ring opening of the chelated carbonato ligand (i.e. k_a) is the rate-determining step. Kernohan and Endicott attempted to explain the above reactivity order of these carbonato complexes by pointing out that the decrease in the hydrolysis rate was closely related to the increase in the ground state steric constraints of these complexes[63]. The replacement of the chelated carbonato ligand by two

TABLE 7

First-order rate constants[63] for the acid hydrolysis of complexes of the type *cis*-$[CoL(CO_3)]^+$ at 73°C

L	k_1 (sec^{-1})
(tetb)	2.82×10^{-3}
(DL-*trans*[14]diene)	2.35×10^{-1}
$(en)_2$	2×10^2

monodentate groups would even enhance this kind of steric repulsive interaction between the amine methyl groups and the other two coordination positions. Consequently the pre-equilibrium constant (10) would be least favourable for the tetb complex than the DL-*trans*[14]diene complex which, in turn, is not as favourable as the relatively strain-free bis-ethylenediamine analogue. Such a description assumes that these systems follow the first decarboxylation mechanism. The hydrolysis rate constant could then be approximated as the product of the pre-equilibrium constant and the hydrolysis rate constant (k_b) of the bicarbonato complex. Unless a bimolecular mechanism is also assumed for the hydrolysis of these bicarbonato intermediates the above discussion of steric constraints would make the value of k_b greatest for tetb and least for the $(en)_2$ complexes. In order to account for the observed reactivity order of these carbonato complexes, another assumption, namely that the effect of steric constraints on the equilibrium constant is greater than that on k_b, has to be made. This, however, may not be justified. On the other hand, if the alternative mechanism that the ring opening of the chelated carbonate ligand is the rate-determining step and if a dissociative mechanism is assumed for this reaction, the above steric argument would not stand, otherwise the reversed order of reactivity would have been expected. At present, it is not possible to decide which mechanism is closest to the truth for these decarboxylation reactions. However, it may be of interest to note that sufficient evidence has now been accumulated to support the second mechanism for the acid hydrolysis of the related $[Co(NH_3)_4(CO_3)]^+$ system[71].

The substitution reactions of a more extended conjugated macrocyclic amine complex, *trans*-$[Co(CR{-}CH_3)Cl_2]^+$, have recently been investigated by Poon and Wan. This particular macrocyclic ligand has the merit that it is half way between a saturated ring and a fully conjugated macrocycle. Unfortunately, at this time there is only a very limited amount of information available for discussion.

In aqueous acidic solution, the stereo-retentive hydrolysis of the first chloride is too fast to be followed by conventional techniques. The release of the second chloride leads to the formation of a pair of metastable five-coordinate complexes $[Co(CR{-}CH_3)(OH_2)]^{3+}$ and $[Co(CR{-}CH_3)(OH)]^{2+}$ in equilibrium[72]. This conclusion was supported by the isolation and characterization[73] of $[Co(CR{-}CH_3)OH](Cl,ClO_4)$. The aquo five-coordinate compound could then slowly take up another water molecule to give the final *trans*-$[Co(CR{-}CH_3)(OH_2)_2]^{3+}$ product. These reactions, therefore, unambiguously support a limiting S_N1 mechanism with an excessively long-life five-coordinate intermediate.

Very recently, the exchange reactions of *trans*-$[NiLS_2]$, where L represents either $CR{-}CH_3$ or CR, and S represents either *N,N'*-dimethylformamide or water, with the cor-

responding solvent molecule were studied by Rusnak and Jordan[74]. For a given S, the exchange rate is not significantly affected by the presence of an additional methyl group in one of these closely related macrocycles. The complication arising from the rapid spin state inter-conversion of these systems in solution[74] does not allow, at the present stage of experimental information, any conclusion to be drawn concerning the mechanism of these exchange reactions.

Closely related to the above work is the water exchange reaction[75] of $[Ni(TRI)(OH_2)_3]^{2+}$. As shown in Table 8, the replacement of some of the coordinating water molecules in $[Ni(OH_2)_6]^{2+}$ by various rigid and highly conjugated amine macrocycles has little effect on the water exchange rates, whereas the replacement of these water molecules by other relatively simple saturated amines significantly increases the reaction rates. The reason behind this behaviour remains largely unexplained.

Only a few kinetic studies on ligand substitution reactions of pseudo-aromatic corrinoids, metalloporphyrins and phthalocyanine metal complexes have been reported. Probably the main difficulty is that these reactions are usually too fast to be followed by conventional techniques. At present, we shall confine our discussion to relatively simple and "free"* macrocyclic complexes. The reactions of more complexed and naturally occurring macrocyclic complexes, such as ferrihaemoprotein in which the iron-containing porphyrin moiety is covalently joined to a long protein chain, have been discussed elsewhere[81–83].

Randall and Alberty first reported the kinetics of ligand substitution reactions of aquocobalamin by thiocyanate, azide, cyanate and imidazole[68,69]. These reactions were later re-examined in greater detail by Thusius[70,84]. It was found, as shown in Table 9, that the anation rate constant (k_{-1}) is virtually independent of the nature of the incoming group This contrasts sharply with the variation by a factor as large as 5×10^{11} in the stability

TABLE 8

First-order rate constants for the water exchange reactions of some nickel(II) complexes at 25°C.

Complex	k_1 (sec^{-1})	Ref.
$[Ni(OH_2)_6]^{2+}$	3.2×10^4	76
$[Ni(TRI)(OH_2)_3]^{2+}$	3.8×10^4	75
$[Ni(CR)(OH_2)_2]^{2+}$	4.5×10^4	74
$[Ni(CR{-}CH_3)(OH_2)_2]^{2+}$	5.2×10^4	74
$[Ni(terpy)(OH_2)_3]^{2+}$	5.2×10^4	77
$[Ni(bipy)(OH_2)_4]^{2+}$	4.9×10^4	76
$[Ni(bipy)_2(OH_2)_2]^{2+}$	6.6×10^4	76
$[Ni(NH_3)(OH_2)_5]^{2+}$	2.5×10^5	78, 79
$[Ni(NH_3)_2(OH_2)_4]^{2+}$	6.1×10^5	79
$[Ni(NH_3)_3(OH_2)_3]^{2+}$	2.5×10^6	79
$[Ni(en)(OH_2)_4]^{2+}$	4.4×10^5	80
$[Ni(en)_2(OH_2)_2]^{2+}$	5.4×10^6	80

* The term "free" here implies those macrocyclic complexes which are not covalently linked to long protein chains.

TABLE 9

Some kinetic and thermodynamic data for the following reaction at 25.5°C, $\mu = 0.5\ M$

$$CBM{-}X + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CBM{-}OH_2 + X$$

X	k_1 (sec^{-1})	k_{-1} ($M^{-1}.sec^{-1}$)	K^a (M)	Ref.
Br^- [b]	5.9×10^2	1.0×10^3	5.3×10^{-1}	70
I^-	3.5×10^1	1.4×10^3	3.1×10^{-2}	70
SCN^-	1.8	2.3×10^3	8.3×10^{-4}	84
SCN^-	1.8	7.1×10^3	8.3×10^{-4}	68
NCO^-	1.1	0.47×10^3	1.9×10^{-3}	70
NCO^- [c]	9.5×10^{-1}	0.73×10^3	1.9×10^{-3}	69
$S_2O_3^{2-}$	3.5×10^{-2}	0.2×10^3	1.4×10^{-4}	70
N_3^-	2.9×10^{-2}	1.2×10^3	1.8×10^{-5} [d]	70
N_3^-	3×10^{-2}	1.7×10^3	1.8×10^{-5} [d]	69
$imid^0$	6×10^{-4}	0.027×10^3	2.6×10^{-5} [e]	69
SO_3^{2-}	$\leqslant 1 \times 10^{-5}$	$\leqslant 0.2 \times 10^3$	4.5×10^{-8} [f]	70
HSO_3^-	($\sim 80\ M^{-1}.sec^{-1}$) [g]	0.17×10^3	$\sim 4.5 \times 10^{-1}$ [d]	70
CN^-	10^{-9}	1.5×10^3	10^{-12} [g]	89

[a] Taken from thermodynamic stability constants of ref. 85, unless otherwise stated, at ambient temperature and $\mu = 0.5\ M\ KNO_3$ (except for $X = S_2O_3^{2-}$ where the ionic strength was maintained with $NaClO_4$).
[b] At 26°C.
[c] Extrapolated from values determined at other temperatures.
[d] Ref. 70.
[e] Ref. 86.
[f] Ref. 87; $\mu = 0.35$, acetate buffer at pH = 5.0.
[g] Ref. 88.

constant (the reciprocal of K) of the corresponding cobalamins. This weak response of the anation rate constant to the variation in the nucleophilicity of the incoming group eliminates the possibility of a classical bimolecular mechanism for these reactions. A linear free energy relationship of a straight line plot between log k_1 and log K with unit slope, as shown in Fig.5, strongly supports a dissociative mechanism for these aquation reactions. The observation that the entropies of activation for the hydrolysis of these cobalamins are all close to zero could be taken as an indication of a square-pyramidal intermediate in these dissociative activation processes. The generation of a trigonal-bipyramidal intermediate would have seriously disturbed the solvating water molecules and would have given rise to higher positive values for this activation parameter.

The Hg^{2+}-catalyzed hydrolysis of alkyl cobalamins and alkyl cobinamides were recently investigated by Williams and co-workers[90]. It was found that the replacement of one hydrogen atom in the coordinated methyl group to give either ethyl or *n*-propyl is accompanied by a reduction in the hydrolysis rate by a factor of as much as 10^4. This is probably due to serious steric hindrance for the approach of Hg^{2+} to the coordinating carbon atom. Consequently, the effective concentration of the reactive species which contains the labile leaving group $-C(Hg)H_2R^+$ and hence the hydrolysis rate of the alkyl-cobalamin is reduced. This is a thermodynamic steric effect. The kinetic steric effect is probably

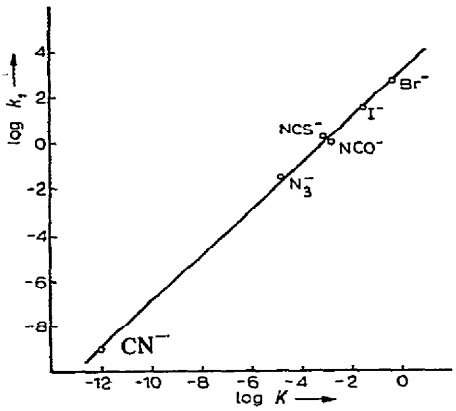


Fig.5. A linear free energy relationship in the substitution reactions of cobalamins – the plot of log k_1 vs. log K at 25°C for the reaction

$$\text{CBM–X} + \text{H}_2\text{O} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{CBM–OH}_2 + \text{X}$$

where X = uni-negative ligand.

felt when the isopropyl complex was found to be 400 times more reactive than the *n*-propyl analogue[90]. Steric compression between the secondary alkyl ligand and the corrin ring would surely contribute to a great extent to weaken the cobalt(III)–carbon bond to facilitate its dissociation in the transition state.

Another systematic study of the substitution kinetics of cobalamins is the aquation of complexes of the type *trans*-[Co(corrin)A(NH_3)]. As shown in Table 10, both the thermodynamic and kinetic stabilities of these complexes depend similarly on the nature of the ligand A. In particular, the general pattern that complexes with neutral orienting ligands are much less reactive than those with negatively charged ligands is reminiscent of the similar reactivity pattern for the cyclam and CR–CH_3 systems. This seems to indicate that the reactivity of these complexes, saturated or otherwise, depends to a large extent on the amount of negative charge donated to the central cobalt atom by these orienting ligands.

TABLE 10

Some thermodynamic and kinetic data[91] for the reaction
trans-[Co(corrin)A.NH_3] + H_2O ⇌ *trans*-[Co(corrin)A(OH_2)] + NH_3

A	k_1 (30°C, sec^{-1})	K [a] (M)
OH_2	1.4×10^{-5}	$\leqslant 10^{-9}$
Bzm [b]	8.6×10^{-5}	10^{-7}
CN^-	$\geqslant 3 \times 10^{-1}$	3×10^{-4}
SO_3^{2-}	$\geqslant 3 \times 10^{-1}$	3×10^{-1}
CH_3^-	$\geqslant 3 \times 10^{-1}$	10

[a] Ambient temperature.
[b] *trans*-[Co(corrin)(Bzm)NH_3] = CBM–NH_3.

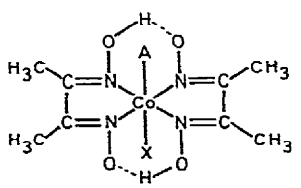
An interesting feature of the hydrolysis reactions of cobalamins is that these reactions are not catalyzed by base[70]. It is not clear whether this insensitivity to base hydrolysis is due to the absence of any amine proton in cobalamins which is required by the S_N1 CB mechanism or due to the extensive electronic delocalization in cobalamins compared with conventional cobalt(III)–amine complexes. It is hoped that the results on the base hydrolyses of *trans*-$[Co(CR)Cl_2]^+$ and of *trans*-$[Co(CR–CH_3)Cl_2]^+$ presently being investigated may help to answer the above question.

Ligand substitution reactions of metalloporphyrins, just like those of the cobalamin system, appear to be fast or "instantaneous". The kinetics of substitution reactions of *trans*-$[Co(HP)(OH_2)_2]^+$ by thiocyanate and cyanate were investigated by Fleischer et al.[92]. As is common to other cobalt(III)–amine complexes, the second anation step is much faster than the first, indicating that *trans*-$[Co(HP)X(OH_2)]$, where $X = NCS^-$ and CN^-, is kinetically much more labile than the higher-charged *trans*-$[Co(HP)(OH_2)_2]^+$. The first-order anation rate constant usually increases linearly with the nucleophile concentration but then gradually tails off at a higher ligand concentration. This behaviour is not compatible with a classical bimolecular mechanism. It is, however, consistent with either an ion-pair or a dissociative–competitive mechanism[14]. Analysis of the kinetic data showed that these reactions were best described in terms of the latter mechanism with a rate-determining generation of the five-coordinate $[Co(HP)(OH_2)]^+$ intermediate (k_1 = 17.4 sec^{-1} at 25°)[92]. The anation of *trans*-$[Fe(HP)(OH_2)_2]^+$ has also been studied. It was found that this iron complex is just as reactive as the cobalt analogue toward substitution reactions and essentially the same dissociative mechanism is probably operative in both systems.

F. SUBSTITUTION REACTIONS OF PSEUDO-MACROCYCLIC AMINE COMPLEXES

It is well known that the two bidentate dimethyl-glyoximato anions in $[Co(DH)_2AX]$ are linked together by chelating internal hydrogen bonds which render these complexes pseudo-macrocyclic[93–95]. With only a few exceptions[96], most of these complexes are known[97] to have a *trans* configuration with a planar arrangement of the "macrocycle" V. To mark the many striking similarities in the chemistry of these complexes with that of the corresponding cobalamins, they are usually referred to as cobaloximes[1]. The kinetics of substitution reactions of cobaloximes have been investigated most extensively by Ablov and co-workers and Syrtsova and co-workers.

Some of the aquation kinetic data are collected in Table 11. Many of these reactions were studied in mixed solvents consisting of water with varying amounts of organic sol-



Structure V. *trans*-$[Co(DH)_2AX]$

TABLE 11

Kinetics and activation parameters for the aquation of *trans*-$[Co(DH)_2AX]$ at 25°C in aqueous solution

A	X	k_1 (sec^{-1})	E_a (kcal.$mole^{-1}$)	$\log_{10} B$	Ref.
SO_3^{2-}	Cl^-	1.97×10^{-5}	24.1	13.0	98
SO_3^{2-}	Br^-	3.85×10^{-5}	22.1	11.8	98
SO_3^{2-}	I^-	6.48×10^{-5}	20.1	10.5	98
SO_3^{2-}	I^-	2.15			99
HSO_3^-	Cl^-	6.76×10^{-5}	13.9	6.08	100
NO_2^-	Cl^-	1.03×10^{-4}	23.3	13.1	101
NO_2^-	Br^-	1.15×10^{-4}	23.7	13.4	101
NO_2^-	N_3^-	$\sim 3 \times 10^{-5}$ [a]			102
NO_2^-	NCS^-	$\sim 5 \times 10^{-6}$			102
NO_2^-	HSO_3^-	$\sim 7 \times 10^{-4}$			102
NO_2^-	$urea^0$	2.22×10^{-4}	14.0 [b]	6.62	103
Cl^-	Cl^-	2.7×10^{-4}	23.9	14.0	104
Cl^-	Cl^-	3.0×10^{-4} [c]	24.1	14.1	105
Cl^-	$urea^0$	1.63×10^{-4}	15.5 [b]	7.59	103
Br^-	Br^-	3.8×10^{-4}			104
Br^-	Br^-	1.5×10^{-4} [c]	24.4	14.1	105
Br^-	$urea^0$	1.74×10^{-4}	14.9 [b]	7.18	103
I^-	Cl^-	6×10^{-5}			102
I^-	Br^-	7.2×10^{-5}			102
I^-	I^-	1.1×10^{-5} [c]	25.9	14.0	104
I^-	NCS^-	$\leq 6 \times 10^{-5}$ [d]			102
I^-	HSO_3^-	$\leq 5 \times 10^{-6}$ [e]			102
I^-	$urea^0$	2.93×10^{-4} [f]	12.6 [b]	5.72	103
NCS^-	NCS^-	1×10^{-8} [c]	32.2	15.7	106
tu^0	tu^0	6.3×10^{-3} [c]	15.4	9.1	107
H_2O^0	Cl^-	1.0×10^{-4}	25.2	14.5	105, 108, 109
H_2O^0	Br^-	4.7×10^{-5}			109
H_2O^0	Br^-	3.7×10^{-5} [c]	27.8	16.0	105
H_2O^0	I^-	4.5×10^{-6}	27.2	14.6	105

[a] At 35°C.
[b] Converted from the published data in kJ.$mole^{-1}$.
[c] Extrapolated from data at other temperatures.
[d] At 20°C.
[e] At 15°C.
[f] In 25% ethanol.

vents such as methanol, ethanol, ethylene glycol and dioxan. It was found that the aquation rate decreased as the proportion of these organic solvents was increased[100,108,110–112]. In some cases, the plot of log k_1 against $1/D$, where D represents the bulk dielectric constant of a mixed solvent, is linear[110]. In other cases, a linear plot of k_1 against water concentration in these mixed solvents was noted[112]. Since the leaving group bears the same negative charge as these reacting ionic complexes, it was argued that these linear plots were not consistent with an S_N1 mechanism but corresponded well with an associative mechanism for these reactions. It should, however, be noted that the composition of a mixed solvent in the neighbourhood of the solute may be quite different from that of the overall solution. The bulk dielectric constant of a mixed solvent might not be a true measure of the effective dielectric constant in the vicinity of the reacting species. On the other hand, the solvent ionizing power parameter Y of Grunwald and Winstein[113], which is derived from kinetic data based on the limiting S_N1 solvolysis of *tert.*-butyl chloride in various mixed solvents, seems to give a better representation of a solvent property when near a reacting molecule. It was found that a linear plot of log k_1 against Y with a slope of magnitude 0.2 was obtained for the aquation of *trans*-$[Co(DH)_2(HSO_3)Cl]^-$ in a range of binary mixed solvents[114]. A similar relationship has also been found to exist in the aquation of some well-studied systems, such as *cis*- and *trans*-$[Co(en)_2Cl_2]^+$ and $[Co(NH_3)_5Cl]^{2+}$, which are known to react by a dissociative mechanism. Since the dioxime complex has a charge which is opposite to that of the conventional amine complexes, it becomes dangerous to take this similarity in the Grunwald–Winstein relationships as an indication of a similar reaction mechanism for these systems. Furthermore, since these Y parameters were derived from the reaction of a neutral, though polar, molecule, they may not be a good measure of the same solvent property for reactions of charged species. In fact, as the nature of a solvent is changed many factors, some recognized, such as dielectric constant, others unrecognized, are changed, possibly affecting the reaction rate of a substrate in opposite senses. It is difficult to understand the influence of reaction medium on reactivity even at the qualitative level[115]. Since the electronic and structural properties of the planar $Co(DH)_2$ moiety are intermediate between those of Co(cyclam) and Co(corrin), it seems rather surprising if the former complexes react by an associative mechanism whereas dissociative activation processes are followed by the latter two systems. Closer examination of the kinetic data in Table 11 shows that the aquation rates of these dioxime complexes, with the probable exceptions of isothiocyanato and thiourea complexes, do not seem to depend greatly on the nature of the groups A and X. For the series of complexes with X = Cl^-, the reactivity decreases in the following order of A: $Cl^- > NO_2^- \approx OH_2 > HSO_3^- \approx I^-$. However, the difference is small, differing at most by a factor of five. The position of SO_3^{2-} as an orienting ligand is not clear because of the great discrepancy in the aquation data of *trans*-$[Co(DH)_2(SO_3)I]^{2-}$ reported by Syrtsova and Korletyanu[98] and Tsiang and Wilmarth[99]. In view of the well known strongly labilizing influence of SO_3^{2-} in cobaltamine chemistry the kinetic result of Wilmarth seems rather reasonable. When X = urea, the reactivity order is reversed with $Cl^- \leqslant Br^- < NO_2^- < I^-$. Here, the spread is even smaller than for the chloro complexes, differing by a factor of less than two. Similarly, the variation in aquation rates with the nature of the leaving group is very much smaller than that observed with saturated amine complexes. This kind of non-uniform variation of the reactivity order with the nature of A and X and the small difference in

rate constants of these halo complexes seems to indicate that the cobalt(III) ion in these dioxime complexes lies somewhere in the middle of the "hard" and "soft" spectrum of transition metal ions. A small variation in some minor factors, such as the electronic or steric effect, may be sufficient to change the reactivity order of these halo complexes.

Such an increase in the cobalt(III) soft character in these dioxime complexes is further substantiated by the observation[116] that the aquation rate of *trans*-$[Rh(DH)_2(HSO_3)Cl]^-$ was slower than the cobalt(III) analogue only by a factor of ten at 25°C. A factor of 270 has been found for the much harder *trans*-dichloro bis-ethylenediamine complexes[9,117].

The aquation kinetics of a series of substituted dioxime complexes of the type *trans*-$[Co(dioxime)_2(HSO_3)Cl]^-$ are collected in Table 12. It is clear that the replacement of one or both methyl groups in dimethylglyoxime by a variety of substituents does not greatly affect the reactivity of these complexes. It is quite probable that the methyl groups and all their substituents lie in the same basal plane of the pseudo-macrocycle in such a way that the steric environments above and below this dioxime plane do not vary greatly among this series of dioxime complexes. Furthermore, the electronic effect of these various substituents which are rather far from the reaction centre may not have any significant influence on the reactivity of the complexes.

The hydrolysis of these dioxime complexes is, in general, catalyzed by base but to a

TABLE 12

First-order rate constants and activation parameters for the aquation of *trans*-$[Co(dioxime)_2(HSO_3)Cl]^-$ in 0.05 *M* nitric acid

Dioxime	Medium	$10^5 \times k_1$ (25°C, sec^{-1})	E_a (kcal.$mole^{-1}$)	$\log_{10} B$	Ref.
(MH)[a]	Water	7.14[b]	13.8	6.08	118
(MH)[a]	62% ethanol	3.5[b]	14.0		118
(DH)[c]	Water	6.76	13.9	6.08	100
(DH)[a]	Water	5.4[b]	13.0		119
(DH)[c]	60% ethanol	3.29	13.9	5.63	100
(DH)[a]	60% ethanol	2.6[b]	13.7		119
(Df)[d]	61.9% ethanol	2.6[b]	16.2	7.3	120
(Df)[a]	60% ethanol	2.1[b]	14.1		119
(Df)[e]	61.9% ethanol	4.1[b]	14.5	6.2	120
(Dfur)[a]	60% ethanol	2.7[b]	14.9		119
(Nioxim)[a]	Water	8.0[b]	14.4		119
(Nioxim)[a]	60% ethanol	5.2[b]	14.0		119

[a] NH_4^+ salt of the complex ion.
[b] Extrapolated from values at other temperatures.
[c] Na^+ salt of the complex ion.
[d] Compound supplied as $H[Co(Df)_2(HSO_3)Cl]$.
[e] Na^+ salt of the corresponding bromo complex ion.

much lesser extent than the conventional cobalt(III) amine complexes. For example, the k_2/k_1 ratio for *trans*-$[Co(DH)_2(NO_2)Br]^-$ has been found[95] to be 2×10^2 at 10°C. This is very much smaller than the corresponding ratio of 2×10^7 for the cyclam analogue[47]. This large difference in the k_2/k_1 ratio for these two systems is certainly consistent with the postulate that the rapid base hydrolysis of cobaltamines is due to the presence of a strongly labilizing amido group in the amido conjugate base[9]. Such a labilizing source is absent in the corresponding bis-dimethylglyoximato conjugate base. Analysis of the kinetic data for the base hydrolysis of *trans*-$[Co(DH)_2(NH_3)X]$, where $X = Cl^-$ and Br^-, showed that the slightly faster base hydrolysis of the bromo complex was due almost entirely to a slightly larger conjugate base formation constant than that for the chloro complex. The specific aquation rate constants of the chloro and bromo conjugate bases are virtually identical (2.2×10^{-4} and 2.1×10^{-4} sec^{-1} at 25°C respectively). This lack of rate response of the conjugate bases to the nature of the leaving group was taken to indicate an S_N2 CB mechanism for the base hydrolysis of these cobaloxime complexes[121]. It was thought that a bimolecular aquation of the conjugate base is favoured by strong hydrogen bonding between an incoming water molecule and the deprotonated dioxime ligand[121]. It should be noted that such a lack of rate response to the nature of the leaving halides must not be taken too seriously as an indication of a bimolecular mechanism. As explained previously, it could simply be due to a delicate balance between softness and hardness of the cobalt(III) ion in such a way that it is not "sensitive" enough to differentiate between different coordinated halides in these dioxime complexes.

Some of the anation kinetics of *trans*-$[Co(DH)_2A(OH_2)]$ by various nucleophiles are collected in Table 13. Two generalized features of these kinetic data are noted. First, for a given orienting ligand A, the variation of the anation rate constants with the nature of the incoming group is small. This immediately rules out a bimolecular mechanism for these reactions. By virtue of the principle of microscopic reversibility, the hydrolysis reactions of *trans*-$[Co(DH)_2AX]$ are likely to be dissociative. Secondly, the kinetic *trans*-effect exerted by SO_3^{2-} is about 10^4 times greater than that exerted by NO_2^- and I^-. These latter two orienting ligands have similar *trans* influence on the lability of the leaving group. The anation of *trans*-$[Co(DH)_2(SO_3)(OH_2)]^-$ by SO_3^{2-} gives rise to a limiting rate at about 0.1 *M* SO_3^{2-} concentration. Since ion-pair formation between the reagent and the substrate of like charge is unlikely, this kinetic behaviour is best explained in terms of a dissociative–competition mechanism. Analysis of the kinetic data showed that SO_3^{2-} is some 650 times more reactive than water in trapping the five-coordinate $[Co(DH)_2(SO_3)]^-$ intermediate. If we now consider the anation reactions of this sulphitoaquo complex by other incoming groups, it was found that these second-order anation rate constants are faster than the SO_3^{2-} limiting anation rate by an order of magnitude. This seems to indicate that a limiting S_N1 mechanism does not occur in these other anation reactions. It is possible that these reactions follow a dissociative–interchange mechanism and that this interchange process is affected by the presence of other electrolytes in some sort of medium effect. It is well known that the aquation rates of *trans*-$[Co(dioxime)_2(HSO_3)Cl]^-$, where dioxime = DH and Df, depend on the nature of other electrolytes present in the reaction solution[119,123].

The kinetics of substitution reactions of alkyl-cobaloximes are relatively sparse. Some of the anation kinetics of *trans*-$[Co(DH)_2(CH_3)(OH_2)]$ are shown in Table 14. As in the

TABLE 13

Second-order rate constants for the following anation reaction at 25°C

$$trans\text{-}[Co(DH)_2A(OH_2)] + X \underset{k_1}{\overset{k}{\rightleftharpoons}} trans\text{-}[Co(DH)_2AX] + H_2O$$

A	X	k (M^{-1}.sec^{-1})	Ref.
SO_3^{2-}	SO_3^{2-}	0.56 [a]	99
SO_3^{2-}	tu^0	8.34	99
SO_3^{2-}	NCS^-	8.31	99
SO_3^{2-}	N_3^-	7.30	99
SO_3^{2-}	HSO_3^-	6.06	99
SO_3^{2-}	I^-	5.50	99
SO_3^{2-}	py^0	5.00	99
SO_3^{2-}	$S_2O_3^{2-}$	1.45	99
NO_2^-	HSO_3^-	8.5×10^{-3}	102
NO_2^-	NCS^-	5.8×10^{-4}	102
NO_2^-	N_3^-	5.7×10^{-4}	102
NO_2^-	N_3^-	1.5×10^{-3}	122
NO_2^-	Br^-	1.6×10^{-4}	102
NO_2^-	NO_2^-	1×10^{-4} [b]	102
NO_2^-	Cl^-	8×10^{-5}	102
I^-	HSO_3^-	3.4×10^{-3}	102
I^-	NCS^-	1.2×10^{-3}	102
I^-	Br^-	3.0×10^{-4}	102
I^-	Cl^-	2.3×10^{-4}	102

[a] Limiting first-order anation rate constant in sec^{-1}.
[b] Extrapolated from data at other temperatures.

TABLE 14

Some kinetic and thermodynamic data[124] for the reaction

$$trans\text{-}[Co(DH)_2(CH_3)(OH_2)] + X \underset{k_1}{\overset{k}{\rightleftharpoons}} trans\text{-}[Co(DH)_2(CH_3)X] + OH_2$$

X	k (10°C, M^{-1} sec^{-1})	K [a] (M)	k_1 [b] (10°C, sec^{-1})
NCS^-	49.6	1.04×10^{-2}	5.2×10^{-1}
N_3^-	34.7	4.9×10^{-3}	1.7×10^{-1}
py^0	29.9	2.08×10^{-4}	6.2×10^{-3}
CN^-	14.0	1×10^{-6}	1.4×10^{-5}
NH_3^0	3.1	2.75×10^{-4}	8.5×10^{-4}

[a] The corresponding formation constants ($Q = 1/K$) were given in the original reference.
[b] Calculated from $k_1 = k.K$.

anation of other macrocyclic amine complexes, the reaction rate does not greatly depend on the nature of the incoming group[124]. This again supports a dissociative activation for these reactions. From these anation rate constants and the appropriate formation constants, the first-order aquation rate constants of *trans*-$[Co(DH)_2(CH_3)X]$ could be deduced and are collected in the last column of Table 14. It was found that, for uni-negative leaving groups, a linear correlation between log k_1 and log K with a slope close to unity was obtained. Such a linear free energy relationship would strongly support a dissociative mechanism for these hydrolysis reactions. In the case of other alkyl analogues, it was found that while the thiocyanate and azide anation rates increased rather substantially with the nature of R: methyl < ethyl < isopropyl, there is little change in their formation constants[124]. This variation in free energy of activation with little change in relative ground state free energies is probably best explained in terms of steric effects in the reactions of these complexes. The steric repulsion between the large isopropyl group and the dioxime macrocycle would have a greater tendency to expel the leaving group, thus making possible a greater distortion of the tetragonal transition state so as to release this ground state steric repulsion. Such a steric acceleration is consistent with a dissociative mechanism for the reactions of these alkylcobaloximes. The greater kinetic *trans* influence of these alkyl groups relative to SO_3^{2-} could be taken to indicate the importance of σ-bond donation by non-labile ligands in affecting the reactivity of these complexes.

The kinetics of Hg^{2+}-catalyzed hydrolysis of alkylaquocobaloximes were investigated by Adin and Espenson[125]. The reactivity pattern is reminiscent of that of cobalamins. Substituents at the α carbon atom are accompanied by a marked decrease in rate, i.e. methyl > ethyl > isopropyl. This is probably due to steric hindrance of the formation of the reactive *trans*-$[Co(DH)_2(OH_2)(R\,Hg)]^{2+}$ intermediate. On the other hand, any alkyl substituent at the β carbon atom does not have any significant effect on the reaction rates, i.e. ethyl $\approx$ *n*-propyl $\approx$ isobutyl.

The anation reactions of another pseudo-macrocyclic *trans*-$[Co\{(DOH)(DO)pn\}R(OH_2)]$ complex by imidazole, benzimidazole and triphenylphosphine in acetone solution have recently been investigated[126], and the reactions have been satisfactorily explained in terms of the dissociative–competition mechanism. The kinetic *trans*-effect of these orienting alkyl groups increases in the following order: phenyl < methyl < benzyl $\approx$ ethyl < *n*-propyl. This is just the order of increasing σ-donor character of these alkyl groups and the observation is, therefore, consistent with a dissociative mechanism.

The ligand exchange reactions of *trans*-$[Co(DH)_2(CH_3)X]$ have been shown to be dependent on the nature of X in the following reactivity order[127,128]: CO, CH_3CN, DPSO > DMSO > $(CH_3)_2S$ > $O(CH_2CH_2)_2S$ (S-bonded) > $(CH_3)_3N$ > $P(OCH_3)_3$ > $P(C_6H_5)_3$. This reactivity order clearly shows that the $[Co(DH)_2(CH_3)]$ moiety is considerably "soft". The dissociative nature of these exchange reactions was confirmed by the fact that the exchange rate of *trans*-$[Co(DH)_2(CH_3)\{P(OCH_3)_3\}]$ is independent of $P(OCH_3)_3$ concentration in the solution. Although the importance of the σ-effect of these alkyl groups has been unambiguously recognized, the marked stability of the phosphite and phosphine complexes seemed to indicate that the metal-to-ligand π-bond may also be important in affecting the reactivity of these dioxime complexes.

G. CONCLUSION

An overall digestion of the previous discussion shows that some regularities begin to appear as the extent of conjugation in the macrocyclic ring is increased. Thus, accompanying this stepwise increase in the extent of unsaturation of the following macrocycles, cyclam, teta, tetb < *trans*[14]diene < bisdioximes < CR, CR–CH_3 < corrin < porphyrin, the central cobalt(III) ion progressively increases its "soft" character. This could probably be understood in terms of the enhanced polarizability of the central metal ion as the extent of electronic delocalization between the metal ion and the encircling macrocycle is increased. Thus, the aquation rate constants of *trans*-$[Co(cyclam)Br_2]^+$ and *trans*-$[Co(cyclam)(NO_2)Br]^+$ are faster than their chloro analogues by a factor of 20 and 500 respectively at 25°C. This indicates that the cobalt(III) ion in the Co(cyclam) moiety is essentially "hard". This factor of k_{Br}/k_{Cl} is reduced nearly to unity in *trans*[14]diene and $(DH)_2$ complexes. This is a direct consequence of the possibility that the central metal ion in these complexes is under a delicate balance of "hard" and "soft" character such that it becomes insufficiently sensitive to differentiate between the various coordinated halides. A small variation in some other factors, such as the electronic effect of a non-labile ligand, may be sufficient to tip the balance to one particular side. This may largely be responsible for the non-uniform reactivity order of the leaving halide ligands in these complexes. In any case, the gross difference between the reactivities of these halide ligands is usually very small. In cobalamins and other fully conjugated macrocyclic amine systems, the cobalt(III) ion has become so "soft" that iodide is a poorer leaving group than bromide and a factor of 17 for the k_{Br}/k_I ratio has been found[70] for the aquation of these halo-cobalamins at 25°.

One distinctive consequence of this gradual increase in the cobalt(III) "soft" character in these macrocyclic amine complexes is that the lability towards substitution reactions is accordingly increased. Some relevant kinetic data for comparison are collected in Table 15.

Assuming that the steric effect affecting the aquation rate of *meso-trans*[14]diene complexes can be roughly equated to the same effect in the teta system, obtained by comparing the aquation rates of the latter complexes with those of the corresponding cyclam analogues, it is possible to obtain a reasonable estimate of the aquation rates of some fictitious steric-free *trans*-cyclam-diene complexes allowing a comparison of the electronic effect of these various macrocycles to be made. By such a method, the aquation rates of *trans*-[Co(*trans*-cyclam-diene)Cl_2]$^+$ and *trans*-[Co(*trans*-cyclam-diene)Br_2]$^+$ were estimated to be 4×10^{-5} and 3×10^{-5} sec^{-1} respectively at 25°C. Therefore, as the extent of unsaturation is gradually increased from cyclam to *trans*-cyclam-diene to $(DH)_2$ complexes, the aquation rates increase accordingly by the ratio of 1:36:270 for the dichloro and by a much smaller ratio of 1:1.5:10 for the dibromo complexes. This observation suggests that the lability of bromo complexes is not very sensitive to the "hard" and "soft" character of the central metal ion and that, therefore, the change-over of the reactivity order of coordinated halides with increasing softness of the cobalt(III) ion must arise by the much greater susceptibility of chloride and iodide towards this "soft" and "hard" character in the opposite directions.

Since cyanide and chloride are very similar in their labilizing power in cyclam complexes[28], it can be concluded from Table 15 that *trans*-[Co(corrin)(CN)(NH_3)] is some

TABLE 15

The first-order aquation rate constants of some macrocyclic amine complexes at 25°C

Complex	k_1 (sec^{-1})	Ref.
trans-$[Co(cyclam)Cl_2]^+$	1.1×10^{-6}	27
trans-$[Co(teta)Cl_2]^+$	9.3×10^{-4}	62
trans-[Co(*meso-trans*[14]diene)$Cl_2]^+$	3.6×10^{-2}	61
trans-$[Co(DH)_2Cl_2]^-$	3×10^{-4}	105
trans-$[Co(cyclam)Br_2]^+$	2×10^{-5}	129
trans-$[Co(teta)Br_2]^+$	3.8×10^{-2}	62
trans-[Co(*meso-trans*[14]diene)$Br_2]^+$	5.1×10^{-2}	62
trans-$[Co(DH)_2Br_2]^-$	3.8×10^{-4}	104
trans-$[Co(DH)_2Br_2]^-$	1.5×10^{-4}	105
CBM–Br	5.9×10^{2}	70
trans-$[Co(cyclam)Cl(NH_3)]^{2+}$	4.6×10^{-11} [a]	42
trans-$[Co(corrin)(CN)(NH_3)]$	$\geq 3 \times 10^{-1}$ [a,b]	91

[a] For the release of the coordinated NH_3.
[b] At 30°C.

4×10^9 more reactive than the corresponding cyclam analogue.

The reason behind this increasing lability with increasing extent of unsaturation of these macrocyclic amine complexes is not immediately clear. The recent success in the isolation of the stable five-coordinate $[Co(CR{-}CH_3)(OH_2)]^{3+}$ intermediate[73] in the aquation of *trans*-$[Co(CR{-}CH_3)(OH_2)Cl]^{2+}$ and the identification of some five-coordinate alkyl- and sulphito-cobinamides[130] in aqueous solution seem to suggest that reactions are essentially dissociative and that the variation in the kinetic lability of these complexes is governed primarily by the increasing thermodynamic stability of the five-coordinate intermediate with increasing extent of unsaturation in these encircling amine ligands around the central cobalt(III) ion.

At the present stage of limited experimental information, it is premature to try to draw any simple correlation between model systems synthesized in laboratories and complexed systems in vivo. It is hoped that this article has served the purpose of summarizing all the available but scattered experimental data into a more integrated picture in order to stimulate further research in this field of chemistry.

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