Proton Exchange and Base Hydrolysis of *syn,anti-cis*-Dichloro(1,4,7,10-tetra-azacyclododecane)cobalt(III) Cations

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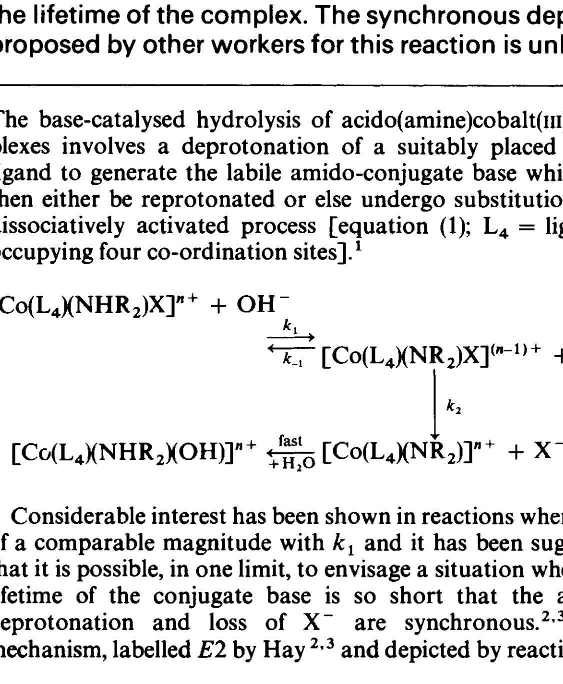
Studies of the exchange of amine protons between *syn,anti-cis*-$[Co(cyclen)Cl_2]^+$ (cyclen = 1,4,7,10-tetra-azacyclododecane) and D_2O in deuteriated buffer solutions show that extensive exchange takes place between the solvent and the protons on the nitrogen *trans* to the co-ordinated chlorides, within the lifetime of the unreacted complex. In the ^1H n.m.r. spectrum of the complex ion in $[^2H_6]$dimethyl sulphoxide, the chemical shift of one of the protons on a nitrogen *trans* to chlorine is very sensitive to the presence of added Cl^- presumably because of ion association and hydrogen bonding. The second-order rate constant for the exchange of this proton, 6.9×10^7 dm³ mol⁻¹ s⁻¹, is only *ca.* 3 times greater than that for the exchange of the other, 2.5×10^7 dm³ mol⁻¹ s⁻¹. There is no exchange of the protons on the mutually *trans* nitrogens during the lifetime of the complex. The synchronous deprotonation–chloride dissociation pathway proposed by other workers for this reaction is unlikely.

The base-catalysed hydrolysis of acido(amine)cobalt(III) complexes involves a deprotonation of a suitably placed amine ligand to generate the labile amido-conjugate base which can then either be reprotonated or else undergo substitution by a dissociatively activated process [equation (1); L_4 = ligand(s) occupying four co-ordination sites].[1]

$$\begin{array}{l}[Co(L_4)(NHR_2)X]^{n+} + OH^- \\ \qquad \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [Co(L_4)(NR_2)X]^{(n-1)+} + H_2O \\ \qquad\qquad\qquad\qquad \downarrow k_2 \qquad\qquad (1) \\ [Co(L_4)(NHR_2)(OH)]^{n+} \xleftarrow[+H_2O]{fast} [Co(L_4)(NR_2)]^{n+} + X^- \end{array}$$

Considerable interest has been shown in reactions where k_2 is of a comparable magnitude with k_1 and it has been suggested that it is possible, in one limit, to envisage a situation where the lifetime of the conjugate base is so short that the acts of deprotonation and loss of X^- are synchronous.[2,3] This mechanism, labelled *E*2 by Hay[2,3] and depicted by reaction (2),


(2)

would require that the systems obey the criteria for rate-limiting deprotonation, *i.e.*, general base catalysis, primary isotope effects, no proton exchange in the recovered unreacted substrate, *etc.* Unusually low enthalpies of activation, once thought to be an excellent criterion,[4] have now been found in cases where $k_{-1} \gg k_{-2}$[5] and are no longer to be relied upon. In addition, it would also have to meet the criteria for rate-limiting Co–X bond breaking, *i.e.*, a rate that is sensitive to the nature of X. (In a two-stage process where $k_2 \gg k_{-1}$, the observed rate constant would be independent of k_2 and, in the first approximation, independent of the nature of the leaving group.)

The base hydrolysis of *cis*-$[Co(cyclen)X_2]^+$ (cyclen = 1,4,7,10-tetra-azacyclododecane; X = Cl or Br) has been found to meet some of these criteria and it has been suggested by Hay and Norman[2] that this system is an example of the *E*2 mechanism for base hydrolysis.

As part of a general examination of the relationship between the rates of proton exchange of acido–amine complexes of transition-metal ions and their sensitivity towards base-catalysed hydrolysis, we have had cause to examine the *cis*-$[Co(cyclen)Cl_2]^+$ system and to study the proton-exchange criterion as applied to the question of the *E*2 mechanism. Our results are reported in this paper.

Experimental

Preparation of cis-*Dichloro*(1,4,7,10-*tetra-azacyclododecane*)*cobalt*(III) *Chloride*.—$Li(OH)\cdot H_2O$ (0.1 g, 2.4 mmol) was added to a suspension of cyclen·4HCl (0.25 g, 0.8 mmol) in anhydrous methanol (10 cm³); when all had dissolved a solution of $CoCl_2\cdot 6H_2O$ (0.187 g, 0.8 mmol) in methanol (10 cm³) was added and methanol-saturated air passed through the brownish solution for 1 h. A dark blue-violet precipitate, which was probably the insoluble $[CoCl_4]^{2-}$ salt, was filtered off and discarded. The filtrate was warmed to boiling point for 10 min and the resulting very fine violet precipitate was filtered off, washed with methanol and diethyl ether, and dried (0.068 g, 25% yield) (Found: C, 28.3; H, 5.80; N, 16.6. $C_8H_{20}Cl_3CoN_4$ requires C, 28.5; H, 5.95; N, 16.6%).

Proton Exchange Kinetics.—A buffer solution (12 cm³) of CH_3CO_2D and CH_3CO_2Na in D_2O (pD = 5.01, I = 0.10 mol dm⁻³) was thermostatted at 0 °C and *cis*-$[Co(cyclen)Cl_2]Cl$ (0.04 g) was added with vigorous stirring. After a suitable known time the reaction was quenched by adding perchloric acid (12 cm³, 3 mol dm⁻³) and the mixture left to stand at 0 °C for a few minutes. The precipitated dichloro-perchlorate was filtered off, washed with ice-cold 0.5 mol dm⁻³ perchloric acid, ethanol, and diethyl ether, and then air dried. The procedure was repeated at a series of different times. A second set of runs at pD 5.96 and I = 0.01 mol dm⁻³ was carried out at 3 °C using stronger solutions of the complex (0.06 g in 8 cm³).

The dried perchlorates were dissolved in $[^2H_6]$dimethyl sulphoxide to which anhydrous LiCl had been added, the ^1H

n.m.r. spectrum measured, and the areas under the peaks integrated. The fraction of exchange, α, was determined by comparing the area under the appropriate peak, A, with that under the standard (2 H) amine peak at δ 7.13, A_s, so that $1 - \alpha = 2A/A_s$. The first-order rate constant, $k_{obs.}$, was obtained from the slope of the plot of ln $(1 - \alpha)$ against time and converted to the second-order rate constant by dividing by $[OD^-]$ ($[OD^-] = 10^{\log K_{D_2O}{}^{I,T} + pD}$). Literature values for $K_{D_2O}{}^{0,T}$, the ionic product of D_2O at zero ionic strength,[6] were combined with relevant values for the activity coefficients at the ionic strength used,[6] it being assumed that isotopic effects in this instance were negligible.

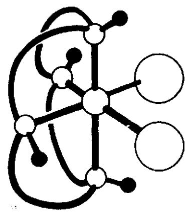
pD *Measurements*.—Using a Radiometer PM26 pH meter with a glass electrode and a saturated calomel electrode calibrated against potassium hydrogenphthalate and borax buffers at 0 °C, the pH reading was converted to pD using the empirical relationship, pD = 'pH reading' + 0.40.[7,8]

^1H N.m.r spectra were measured with a Varian XL200 FT spectrometer.

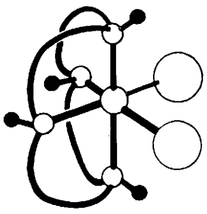
Results and Discussion

The complex *cis*-$[Co(cyclen)Cl_2]^+$ was prepared as its chloride salt by the oxidation of a buffered solution of $CoCl_2$ and the ligand in methanol rather than by the method of Collman and Schneider[9] where the oxidation was carried out in the presence of NO_2^- and the complex *cis*-$[Co(cyclen)(NO_2)_2]^+$ then converted to the dichloro-species by reaction with concentrated HCl. The ^1H n.m.r. spectrum of the perchlorate salt in $[^2H_6]$dimethyl sulphoxide shows, apart from the multiplet due to CH_2 protons between δ 2.1 and 3.6, two broad peaks of equal area at δ 6.44 and 7.13 which are assigned to the amine protons. This at first suggested that the two protons on nitrogens *trans* to Cl were in equivalent environments, which is consistent with either (**I**), where both protons *trans* to Cl point away from each other (*syn,syn*) or (**II**), where both protons point towards each other (*anti,anti*), a structure analogous to that of the known complex *cis*-$[Co(cyclam)Cl_2]Cl$ (cyclam = 1,4,8,11-tetra-azacyclotetradecane).[10] However, this simple ^1H n.m.r. spectrum is misleading, and the greater breadth of the peak at δ 6.44 should have given rise to suspicion. The ^1H n.m.r. spectrum of the chloride salt in $[^2H_6]$dimethyl sulphoxide has the same methylene proton peaks but the amine proton peaks, still with the same chemical shifts, are in the peak area ratio 3:1. Addition of further chloride, as LiCl, causes one of the two overlapping peaks at δ 7.13 to shift further downfield so that there are three proton peaks at δ 6.44(1 H), 7.13(2 H), and 8.26(1 H). It is therefore clear that the complex has structure (**III**) (*syn,anti*), the chemical shifts of the *syn* and *anti* protons being fortuitously similar in the solution of the perchlorate. The downfield shift of one of these peaks in the presence of Cl^- is due to hydrogen bonding in the chloride ion pair[11] and, assuming that the chloride anion prefers a site as far from the co-ordinated chlorides as possible, this identifies the protons at δ 7.13 as those on the mutually *trans* nitrogens, that at δ 6.44 as the *syn* proton and the other at δ 8.26 as the *anti* proton. The *cis*-$[Co(cyclen)Cl_2]^+$ cation used in this work therefore has the same structure as that reported for the dinitro-[12] and carbonato-[13] complexes.

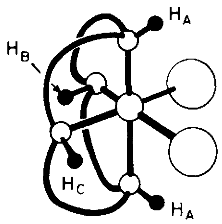
The proton-exchange kinetics of the system could not be studied using the *N*-deuteriated complex, as was possible in the case of β-*cis*-$[Co\{RR(SS)\text{-}2,3,2\text{-tet}\}Cl_2]^+$ [14] (2,3,2-tet = 1,9-diamino-3,7-diazanonane) and, more recently, in that of *cis*-$[Co\{RRRR(SSSS)\text{-cyclam}\}Cl_2]^+$ (cyclam = 1,4,8,11-tetraazacyclotetradecane),[5] because a shortage of material prevented the background studies required to develop a method of preparing the *N*-deuteriated material. Consequently the exchange was followed by dissolving the ^1H substrate in D_2O solutions of deuteriated buffers and examining the areas under the N–H peaks in the unreacted material, recovered as its perchlorate salt. This is not a particularly satisfactory approach because it would not distinguish between the complete absence of exchange required by the *E*2 mechanism and the small amount of exchange observed when $k_2 \sim k_{-1}$. However, since extensive exchange could be observed in the recovered unreacted material, this objection could be ignored.



(I)



(II)



(III)

The *cis*-$[Co(cyclen)Cl_2]^+$ cation is extremely labile with respect to base hydrolysis, the rate constant (2.1×10^7 dm^3 mol^{-1} s^{-1} at 25 °C and I = mol dm^{-3})[2] being the largest reported for a dichloro-complex of a saturated macrocyclic tetra-amine ligand. The complex is also labile with respect to spontaneous aquation ($k = 4.3 \times 10^{-3}$ s^{-1} at 25 °C),[2] although not as labile as the corresponding cyclam species;[5] thus it was necessary to carry out the exchange study at as low a temperature as possible and at as high a pH as possible. Even so it was not feasible to work under conditions where the amount of reaction through the uncatalysed path was negligible. Therefore, it was not possible to determine the ratio k_2/k_{-1} from the relationship between the fraction of exchange and the fraction of reaction (base hydrolysis) and thence obtain k_1,[5] and it was necessary to make a direct evaluation of k_1 which required working at a known constant pD and being able to measure accurately the time between initiating and quenching the reaction.

The main proton-exchange experiments were carried out at pD = 5.00 in CH_3CO_2D–CH_3CO_2Na buffers in D_2O at 0 °C. The ^1H n.m.r. spectra of the $[^2H_6]$dimethyl sulphoxide solutions of the recovered perchlorates (with LiCl added to separate the signals from the *syn*- and *anti*-amine protons) showed that the areas under the peaks at δ 7.13, assigned to the protons on the mutually *trans* nitrogens, and those in the region δ 2.1—3.6, assigned to the methylene protons, remained unchanged. The areas under the other two amine peaks decreased at different rates. Calibration was made against the area under the 2 H peak at 7.13. $k_{obs.}$ for the exchange of the proton at δ 8.26 is 1.6×10^{-3} s^{-1} at pD = 5.0 (0 °C) which, with $K_{D_2O} = 2.31 \times 10^{-16}$ mol^2 dm^{-6} gives a second-order rate constant, $k_1(H_B) = 6.9 \times 10^7$ dm^3 mol^{-1} s^{-1}, while $k_{obs.}$ for the proton at δ 6.23 was 5.9×10^{-4} s^{-1} and therefore $k_1(H_C) = 2.5 \times 10^7$ dm^3 mol^{-1} s^{-1}.

A second series of experiments at higher pD showed that the first sample, precipitated after 180 s, had virtually completely exchanged the proton at δ 8.26, but there was only 40% exchange at the other. This is consistent with a value of 2.0×10^7 dm^3 mol^{-1} s^{-1} for $k_1(H_C)$ which, considering the different experimental conditions and the experimental error, is in good agreement with the value obtained at pD = 5.0 and the assumption that the proton exchange is indeed first-order with respect to $[OH^-]$. No exchange was observed of the protons on the mutually *trans* nitrogens.

Since the *E*2 mechanism requires that every act of deprotonation is accompanied by loss of Cl^- and since the base-catalysed hydrolysis is irreversible under the conditions of the experiment, such a mechanism will be characterized by the absence of any exchange, in the recovered unreacted material, of the proton involved, and by complete exchange of one such proton in the recovered reaction product. The observation of extensive exchange of H_B and H_C in the recovered unreacted material demonstrates conclusively that these protons are not involved in an $E2$ mechanism and, if indeed one is occurring in this system, it must involve the protons on the mutually *trans* nitrogens (H_A). It was not possible to test this directly by examining the recovered product but it is thought unlikely that these protons are involved and, as in the case of *cis*-$[Co(cyclam)Cl_2]^+$, where there is no suggestion of an $E2$ mechanism[5] and in the case of the cation β-*cis*-[Co{*RR*(*SS*)-2,3,2-tet}$Cl_2]^+$, where the recovered product could also be examined,[14] they remain bound throughout the act of base hydrolysis.

Using the literature value for $\Delta H^\ddagger$ (51 kJ mol^{-1}),[2] k_{OH} at 0 °C is estimated to be 3.3×10^6 dm^3 mol^{-1} s^{-1}; this will be considerably greater than the value for the reaction of the ^1H complex with OD^- in D_2O which is the value that must be used together with k_1 in order to estimate k_2/k_{-1}. This rate constant has never been measured but, if the system has a similar isotope effect to others, k_{OD} can be estimated to lie within the range 1.4×10^6—1.8×10^6 dm^3 mol^{-1} s^{-1}. Using the expression, $k_{OH} = k_1k_2/(k_{-1} + k_2)$, $k_2/k_{-1} < 0.03$ for H_B and <0.08 for H_C, the actual values depending, amongst other things, on the way that the base hydrolysis partitions between the two pathways. The system is therefore well within the limiting case of $k_{-1} \gg k_2$ and should not, as reported,[2] be sensitive to general base catalysis. However, it is possible that the reported enthalpy of activation is too large, so that k_{OH} at 0 °C is not as small as that estimated above.

It is of interest to note that, in spite of the very large difference in the extent to which the *syn* and *anti* protons are affected by ion association and hydrogen bonding with chloride ions in dimethyl sulphoxide solution, their rate constants for proton exchange differ only by a factor of *ca.* 3. This suggests that ion association with the base hydroxide does not constitute an important contribution to the act of deprotonation. A similar observation has been made in the case of the species *cis*-$[Co(en)_2X_2]^+$ (en = ethylenediamine).[11]

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