Isomerization in the 1,4,7,10,13,16-Hexaazacyclooctadecanecobalt(III) System $[Co(hexacyclen)]^{3+}$, and Ion-Association Enhancement of the Unstable Facial Isomer

Graeme H. SEARLE
Department of Physical and Inorganic Chemistry, University of Adelaide,
Adelaide, S.A. 5001, Australia

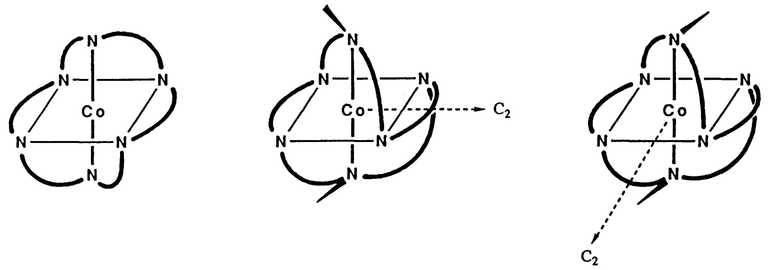
(Received March 29, 1989)

The substitution reaction $[Co(NH_3)_5(H_2O)]^{3+}$+hexacyclen·$3H_2SO_4$+6base+charcoal gives *mer*-[Co(hexacyclen)]$^{3+}$ as the major product, and the equilibrium proportion of the *fac* isomer is $<1\%$. The commercial hexacyclen contains linpen (the open chain analogue of hexacyclen, generated by an elimination reaction in the Richman-Atkins cyclization synthesis procedure), so that the synthesis of complex yields [Co(linpen)]$^{3+}$ isomers as co-products which complicate the isolation of the pure [Co(hexacyclen)]$^{3+}$ isomers. Procedures are now given for obtaining the *mer* and *fac* isomers pure. In particular, the unstable *fac* isomer is obtained by isomerization of the *mer* in base in the presence of the strongly associating anion PO_4^{3-}. This yields the new equilibrium mixture *mer*:*fac*:hydrolysis products=71:18:11, wherein the *fac* proportion is enhanced twenty times, enabling the pure *fac* isomer to be obtained in quantity. For the base-catalyzed isomerization reaction *fac*→*mer* in NaOH solutions at 50 °C, procedures are given for following the reaction by analyses of samples using ion-exchange HPLC (Na_2SO_4 elution) and by spectrophotometry. The mechanism must involve intramolecular bond rupture, but the kinetic results are not consistent with a simple S_N1CB mechanism, and a two-step process involving an intermediate is indicated.

The cobalt(III) complex system [Co(hexacyclen)]$^{3+}$ formed by the sexadentate macrocyclic ligand hexacyclen[1] has considerable stereochemical interest since it can exist in several types of isomers (Fig. 1). The ligand can wrap around the cobalt to give the alternative topological arrangements described as *fac* and *mer*. The *fac* has all chelate ring linkages facial and is of approximate symmetry D_{3d}, whereas the *mer* has two meridional linkages and four facial linkages, and has approximate symmetry D_2 in the topological sense (with ring conformations ignored). Thus the *mer* topology is dissymmetric, Δ or Λ.[2] Additionally for the *mer*, diastereoisomers arise for each of these optical configurations due to the different orientations possible for the N-H bonds at the nitrogen centers coupling the *mer* rings.[2] In acidic conditions where these N-H hydrogen dispositions are prevented from interconverting via hydrogen exchange (and the conformations of the *mer* rings are hence constrained), the effective symmetry of each of the *mer* diastereoisomers is reduced to C_2. Thus there are three geometrically distinct species: the *fac* and the two *mer* racemates *mer*-($\Lambda\delta/\Delta\lambda$) and *mer*-($\Lambda\lambda/\Delta\delta$).

This [Co(hexacyclen)]$^{3+}$ system is stereochemically analogous to the $[Co(dien)_2]^{3+}$ system.[1,4] The isomer *sym*-[Co(hexacyclen)]$^{3+}$ corresponds to *sym-fac*-$[Co(dien)_2]^{3+}$. The *mer* isomers of the two complexes are related topologically, as the dien ligands in *mer*-$[Co(dien)_2]^{3+}$ can be coupled together by ethylene bridges in alternative ways to give the Δ and Λ enantiomeric topologies of *mer*-[Co(hexacyclen)]$^{3+}$. Also, in both of these *mer* complexes the alternative N-H orientations give rise to analogous optical isomerism, in the δ and λ *enantiomers* of *mer*-$[Co(dien)_2]^{3+}$, and in the δ and λ *diastereoisomers* of each of Δ and Λ *mer*-[Co(hexacyclen)]$^{3+}$.

The isomerism of this [Co(hexacyclen)]$^{3+}$ system has been largely elucidated experimentally in previous studies.[5-7] Preparations by substitution reactions between a Co(III)-ammine complex and hexacyclen in the presence of charcoal give all the possible isomers in admixture. The *fac* and *mer* complexes are



fac (D_{3d}) Λ-*mer*, δ-NH (C_2) Λ-*mer*, λ-NH (C_2)

Fig. 1. Isomers and diastereoisomers of [Co(hexacyclen)]$^{3+}$. The *mer* diastereoisomers occur as racemates, $\Lambda\delta/\Delta\lambda$ and $\Lambda\lambda/\Delta\delta$, and only one optical form is shown for each.

then separable by chromatography on SP-Sephadex cation-exchange resin,[5,8] and the results show that coordination of this ligand is highly stereospecific: the *mer* topology (both diastereoisomers) occurs at $>99\%$ proportion at equilibrium, and the *fac* is barely detectable. SP-Sephadex chromatography under acidic conditions has given a partial separation of the *mer* diastereoisomers (each as racemate) and shows these forms to be in comparable proportions,[5] and the ^{13}C NMR spectrum also shows that the isolated *mer* complex contains the NH diastereoisomers in similar amounts.[6]

Isomerizations of CoN_6^{3+}-type complexes have been studied quite extensively.[9–14] The general catalysis of these reactions by charcoal (heterogeneous reaction) or by base (homogeneous reaction) is well-established, but the mechanisms of these processes have not been settled. Several features of this $[Co(hexacyclen)]^{3+}$ system make it attractive for a study of isomerization within a CoN_6^{3+} framework: (1) the system has only two geometric isomers *fac* and *mer*; (2) the *fac* should isomerize essentially completely to *mer* ($>99\%$) so that only one forward reaction should be observed; and (3) the coupling of all the chelate rings in the macrocyclic ligand should restrict the possible modes of ring movements. The present work thus aimed to establish the occurrence or otherwise of the isomerization between the *fac*- and *mer*-$[Co(hexacyclen)]^{3+}$ isomers, and to determine the base dependence of this reaction, and it was hoped that this base dependence might provide some definite evidence concerning the reaction mechanism.

This work required pure samples of the *fac* and *mer* (diastereoisomer mixture) isomers, but isolation of the *fac* from an equilibrium synthetic mixture ($<1\%$) is clearly an impractical means of obtaining this isomer in quantity. It has been demonstrated with the $[Co(dien)_2]^{3+}$ system that ion-association with phosphate anion can markedly shift the equilibrium position and enhance the proportions of more strongly associating isomers, particularly the *sym-fac*,[15] so that the second aim of the work has been to demonstrate that the ion-association effect can also be applied to the analogous hexacyclen complex system to obtain the unstable *fac* isomer in quantity in an isomerization process.

Royer and co-workers have reported interesting observations on isomerizations from the *mer* isomers of $[Co(hexacyclen)]^{3+}$ (and in two other cobalt(III) systems with analogous symmetrical hexaaza macrocycles).[7] Their work is complementary to our results reported herein.

Experimental

^{13}C NMR Spectra. 20.1-MHz NMR spectra of the complexes, broad-band proton-decoupled, were recorded on solutions in acidified D_2O on a Bruker WP-80 DS spectrometer locked to deuterium. An 8192 data table was used. A capillary of *t*-butyl alcohol provided a reference signal: 618.9 Hz, δ 30.79 for CH_3 downfield from $SiMe_4$. (This reference signal was measured for a *t*-butyl alcohol capillary in $CDCl_3$ against $SiMe_4$ as internal reference). As with other cobalt(III) (3+)-charged complexes previously studied, the chemical shifts of the resonances of the $[Co(hexacyclen)]^{3+}$ isomers showed insignificant variations with different anions (generally <0.1 in δ).

Synthesis of *mer*-$[Co(hexacyclen)]Br_3 \cdot H_2O$. A mixture of $[Co(NH_3)_5(H_2O)](ClO_4)_3$ (1.84 g, 0.004 mol), hexacyclen $\cdot$ $3H_2SO_4$ (2.32 g, 5% excess; Aldrich 98%), $LiOH \cdot H_2O$ (1.06 g) and freshly ground charcoal (0.2 g) in water (60 ml) was heated over a steam bath for 3 h. The charcoal was filtered off, and the orange solution was applied to a column (4.5 cm diam.×40 cm) of SP-Sephadex C-25 cation-exchange resin.

The column was eluted with 0.1 M Na_3PO_4 (1 M=1 mol dm^{-3}) when bands separated as follows:

(1) a fast-moving barely detectable orange band containing *fac*-$[Co(hexacyclen)]^{3+}$ and a trace of $[Co(linpen)]^{3+}$ (**A**) (See Results);

(2) a second very weak orange band;

(3) the main orange-red band of *mer*-$[Co(hexacyclen)]^{3+}$;

(4) considerable purple material extending down most of the column.

The *mer* effluent from band (3) was collected, diluted two times, and applied directly to a column of Dowex 50W-X2 cation-exchange resin, 200—400 mesh, H^+ form (3×4 cm). The complex was washed on with 0.1 M HBr then washed with 1 M HBr to remove all Na^+, then was eluted off with 3 M HBr. The effluent was rotary evaporated to near dryness, and air was sucked through the flask to remove HBr. A little water was added to dissolve the product, followed by gradual addition of ethanol, and crystallization of the diastereoisomer mixture was encouraged by scratching the flask. The resulting orange crystals were filtered off, washed with ethanol and acetone, and air-dried to constant weight. Yield 1.51 g, 66%. Found: C, 25.2; H, 5.4; Br, 43.5; N, 14.5%. Calcd for *mer*-$[Co(C_{12}H_{30}N_6)]Br_3 \cdot H_2O$: C, 25.1; H, 5.6; Br, 41.7; N, 14.6%. The product may have contained a small amount of isomer $[Co(linpen)]^{3+}$ (**D**), although this was not evident in the ^{13}C NMR spectrum. ^{13}C NMR in D_2O/HBr of the approximately 1 : 1 NH-diastereoisomer mixture: δ 60.5 (2 carbons), 57.0, 55.8, 55.6, 55.2, 53.2, 52.8*, 51.4, 50.6, 50.1, 49.0. [*δ 52.6 for the nitrate salt].

The *mer* isomer could also be obtained from Dowex resin as the less soluble nitrate salt, and HNO_3 eluent concentration was restricted to 1.5 M maximum to avoid precipitation of complex on the resin. Found: C, 26.8; H, 6.1; N, 23.3%. Calcd for *mer*-$[Co(C_{12}H_{30}N_6)](NO_3)_3 \cdot 2H_2O$: C, 26.7; H, 6.3; N, 23.4%.

The *mer* was also obtained as the perchlorate salt by absorbing the complex on a column of Biorex-70 weak-acid cation-exchange resin, 50—100 mesh, Na^+ form, and eluting off with 0.1 M $HClO_4$. Crystallization from the evaporated solution was completed by the addition of ethanol, and the $NaClO_4$ remained in the mother liquor from filtering off the complex.[6]

The *mer* complex could be separated into the two NH-diastereoisomers (as the racemates $\Delta\delta/\Lambda\lambda$ and $\Lambda\lambda/\Delta\delta$) by chromatography down SP-Sephadex using 0.2 M Na_2SO_4/H_2SO_4 pH 2 as eluent.[5] Under these acidic conditions two approximately equal but incompletely separated bands were obtained, relative R_x(*mer-1*)/(*mer-2*)$=1.2_4$. These were collected and the overlap portion was discarded. The two components were isolated as chlorides using Dowex resin with 3 M HCl elution, and characterized by their ^{13}C NMR spectra in D$_2$O/HCl: for the first eluted diastereoisomer *mer-1* δ 57.0, 55.6 (2 carbons), 53.2, 50.5, 49.1; for *mer-2* δ 60.4 (2 carbons), 55.2, 52.6, 51.6, 50.1.

The combined effluents of the *fac* isomer from the first weak orange Sephadex band (1) from several preparations were worked up using the Dowex/HCl procedure. The ^{13}C NMR spectrum showed that this band (1) contained *fac*-[Co(hexacyclen)]$^{3+}$ (δ 56.1) together with the [Co(linpen)]$^{3+}$ (**A**) isomer (δ 57.6, 57.2 (2 carbons), 55.4, 42.3), but the total amount obtained was very small.

Preparation of *fac*-[Co(hexacyclen)]Cl$_3$ by Isomerization from *mer*. Two solutions of *mer*-[Co(hexacyclen)]Br$_3$·H$_2$O in 0.1 M Na$_3$PO$_4$ (1.80 g in 80 ml, giving [Co] 0.04 M) in stoppered flasks were heated at 80 °C for 12 h. The solutions were diluted (250 ml) and acidified to pH 2 using 1 M HCl, and were then applied to separate columns (4.5×30 cm) of SP-Sephadex cation-exchange resin. The acidification was necessary to avoid partial elution of the *fac* isomer by PO$_4^{3-}$ during the application. After washing on with water, the columns were eluted with 0.1 M Na$_3$PO$_4$, when bands separated in the following order:

(1) (first eluted) light-orange *fac*-[Co(hexacyclen)]$^{3+}$ with a trace of [Co(linpen)]$^{3+}$ (**A**);
(2) very weak yellow;
(3) deep orange-red *mer*-[Co(hexacyclen)]$^{3+}$;
(4) a yellow continuum, containing "*mer*";
(5) pink-carmine;
(6) olive-green precipitate.

The *fac* effluents (1) from the two columns were collected and combined, diluted two times, and acidified to pH 2. This solution was applied to a column of Dowex 50W-X2 resin, 200—400 mesh, H$^+$ form (3×3 cm). After washing on with 0.1 M then washing with 1 M HCl to remove Na$^+$, the complex was eluted off with 3 M HCl, and the effluent was evaporated to dryness. Ethanol was added to enable the yellow-orange solid to be removed by filtration. This product was washed with ethanol and acetone, and air-dried to constant weight. Yield 0.43 g, 16%. Found: C, 33.7; H, 7.1; Cl, 25.1; N, 19.6%. Calcd for *fac*-[Co(C$_{12}$H$_{30}$N$_6$)]Cl$_3$: C, 34.0; H, 7.1; Cl, 25.1; N, 19.8%.

The *mer* effluents band (3) from the columns were combined, diluted, and applied directly (without acidification) to a Dowex 50W-X2 column (3×4 cm). The *mer* was recovered as the bromide salt as described previously. Recovery 2.17 g, 60%.

The two isomers could also be obtained as the nitrate salts, although these are less soluble than the halides, and a lower concentration of HNO$_3$ had to be used (1.5 M maximum) for the elution from Dowex to avoid precipitation of the complexes on the resin. Yields of nitrates from one isomerizaton run: *fac* 15%, *mer* recovery 60%. Found for *fac*: C, 27.5; H, 6.0; N, 24.2%. Calcd for *fac*-[Co(C$_{12}$H$_{30}$N$_6$)](NO$_3$)$_3$·H$_2$O: C, 27.6; H, 6.2; N, 24.2%.

The first-obtained *fac*-[Co(hexacyclen)]Cl$_3$ products contained trace amounts of [Co(linpen)]Cl$_3$ (**A**) as shown by small peaks in the ^{13}C NMR spectrum at δ 57.2 and 42.6. [Co(linpen)]$^{3+}$ (**A**) was not apparent however when *mer*-[Co(hexacyclen)]Br$_3$ which had been recovered from previous isomerization runs was used. Recrystallization of the total *fac*-[Co(hexacyclen)]Cl$_3$ from warm 0.01 M HCl by partial rotary evaporation and addition of some ethanol gave the pure *fac* product, when the [Co(linpen)]Cl$_3$ (**A**) was retained in the mother liquor. Rechromatography of this mother liquor gave a substantial separation of the two components: pale orange *fac*-[Co(hexacyclen)]$^{3+}$ eluted first and was isolated pure from the first portion of the band effluent. The latter portion of the band contained yellow [Co(linpen)]$^{3+}$ (**A**), as the major component (^{13}C NMR peaks from **A** at δ 57.6, 57.3 two carbons, 55.4, 42.6) plus some *fac*-[Co(hexacyclen)]$^{3+}$ (δ 56.1). A trace of the *mer* isomer was also evident in this re-chromatography, this *mer* being formed by re-isomerization.

The material within the yellow continuum (4) seems to be a derivative from *mer*-[Co(hexacyclen)]$^{3+}$. On isolation (Dowex/HCl), this material apparently reverted to *mer* since the ^{13}C NMR spectrum then obtained was identical to that of *mer*-[Co(hexacyclen)]$^{3+}$.

The precipitate (6) seems to form only in the Na$_3$PO$_4$ solution, and is deposited at the column head. It dissolves and is eluted if the column is slightly acidified.

Determination of Conditions for Optimum Isomerization of *mer*- to *fac*-[Co(hexacyclen)]$^{3+}$. *mer*-[Co(hexacyclen)](NO$_3$)$_3$·2H$_2$O was dissolved in 0.1 M Na$_3$PO$_4$ (0.408 g of complex, chromatographically pure on SP-Sephadex, in 20 ml giving [Co] ca. 0.04 M). The solution was heated in a stoppered flask at 80±2 °C and samples were removed with a calibrated pipette (2.96 ml) at various times (2, 5, 8, 12, 24 h) and acidified (0.7 ml of 1 M HCl). Acidification was necessary to quench the isomerization and to prevent elution by PO$_4^{3-}$ during application to Sephadex. The samples were eluted down SP-Sephadex columns (1.2×20 cm) using 0.1 M Na$_3$PO$_4$, and the effluents of the separated *fac* and *mer* isomers were made up to standard volumes with 0.1 M Na$_3$PO$_4$ (*fac* made up to 10 ml, *mer* to 50 ml). Cobalt in these solutions was determined by atomic absorption at 240.7 nm using a dinitrogen monoxide-acetylene flame, against solutions of [Co(en)$_3$](ClO$_4$)$_3$ in 0.1 M Na$_3$PO$_4$ as standards. Moles of total hydrolysis products in the samples were calculated by the difference (initial–final) [Co(hexacyclen)]$^{3+}$.

Kinetics of Isomerization of the *fac* Isomer. (a) HPLC Using Strong-Acid Cation-Exchange. The analytical procedure was developed from that described by Larsen.[16,17] The apparatus comprised a Waters HPLC system (Model 5000 solvent delivery unit, U6K injector, 481 variable-wavelength detector), and chromatograms were recorded and integrated using a Hewlett-Packard integrator model 3380S. The column used for HPLC was a Waters Protein-Pak SP-5PW, of dimensions 7.5 mm i.d.×75 mm, having capacity 300 nmol of 3+ complex.[16] All solutions were prepared with distilled and Milli-Q treated water, and were filtered through an all-glass filter unit fitted with a 0.45 μm membrane (Millipore MF type). The HPLC eluent was 0.2 M Na$_2$SO$_4$/pH 2 with H$_2$SO$_4$.

Runs were carried out at NaOH concentrations 0.05, 0.1, and 0.5 M (I=1.0 with NaCl). Reaction solutions were prepared of about 0.010 g of *fac*-[Co(hexacyclen]Cl$_3$ in 3 ml of the NaOH solution giving [Co] about 0.007 M, and held at 50.0 °C. Constant samples 0.2 ml were removed at intervals, about ten for each run, using an auto pipette (Gilsen "Pipetman" P200) and placed on small columns (5 mm×15 mm) of SP-Sephadex C25, and washed on with water.

At the completion of the run, all these columns were then eluted totally with 0.2 M Na_2SO_4/pH 2, and each effluent was collected and weighed accurately (ca. 4 g). This prechromatography, which conveniently quenched the samples, was necessary to ensure the removal of any strongly retained complexes prior to the HPLC,[16] and the weighing of the effluents permitted normalization between the samples in each run. Each effluent was filtered through a Millex HV4 filter (using a Pasteur pipette and a dry syringe). Constant samples of the effluents 100 μl (Hamilton syringe) were injected for HPLC. Flow rate was 1.0 ml min^{-1}. Detection was at 480 nm, approximately the band I maxima for *fac* and *mer* (but was also checked at 250 nm when similar results were obtained). Chromatograms were recorded from 0—15 min, with full scale absorption in the range 0—0.1 absorption units. This procedure gave about 40 nmol of $[Co(hexacyclen)]^{3+}$ in each injection.

HPLC elution gave (in general) three completely separated peaks due to the isomers *fac, mer-1,* and *mer-2,* with typical retention times 3.9, 8.6, and 11.0 min respectively. The amounts of the *fac* and total *mer* components in the different samples were measured as the products of integrated peak area times mass of Sephadex effluent, where the peaks for the *mer* NH-diastereoisomers *mer-1* and *mer-2* were summed. This procedure normalized the different samples taken over a run.

The optical isomers of *mer*-$[Co(hexacyclen)]^{3+}$ were not separated by this HPLC procedure: there was no sign of any separation of the four diastereoisomeric/optical species using HPLC with 0.15 M sodium di-μ-(R,R)tartrato(4−)-diantimonate(III)/H_2SO_4 pH 2 eluent.[18] Partial resolutions have however been achieved on Sephadex columns using this eluent or sodium (+)-tartrate.[5,7]

(b) Spectrophotometric Runs. Isomerization runs in 0.1 and 0.5 M NaOH solution at 50 °C (I=1.0 M with NaCl) were followed using a Varian-Cary 219 UV/Vis spectrophotometer with timer, wavelength programmer and cell programmer accessories. Absorbances at wavelengths 520, 478, and 416 nm were measured and stored using the Varian 219/210 spectrophotometer "Master Kinetic Storage Programme" on an Apple IIe computer.

The complex *fac*-$[Co(hexacyclen)]Cl_3$ was weighed (about 0.008 g) and transferred to an appropriate amount (about 5.4 g) of the NaOH/NaCl solution giving [Co] about 0.0034 M. After dissolution, this solution was transferred to a 1 cm cell in a thermostatted holder 50 °C in the spectrophotometer and the recording cycle was started. Recordings were taken at intervals of 15 min (0.1 M NaOH) or 10 min (0.5 M NaOH) and were continued until the absorptions had reached maxima (at 22 h for 0.1 M NaOH, 11 h for 0.5 M NaOH). Absorbance changes for the run in 0.1 M NaOH at 50 °C were: at 478 nm, 0.25 (ε=71) to 0.94 (ε=274) (cf. in 0.01 M HCl at 20 °C, ε_{478}=62 for *fac*, 241 for *mer*); at 416 nm, 0.13 to 0.47.

Results and Discussion

Possible Pathways for Isomerization in $[CoN_6]^{3+}$ Complexes. In the isomerization of $[Co(dien)(medien)]^{3+}$ on charcoal in water the bis complexes $[Co(dien)_2]^{3+}$ and $[Co(medien)_2]^{3+}$ are also generated, and this must involve complete dissociation of ligands.[10] However, isomerizations in some other circumstances appear to be exclusively intramolecular: the homogeneous isomerization of $[Co(dien)(medien)]^{3+}$ in base is not accompanied by generation of the bis complexes and thus differs clearly from the charcoal reaction above,[10] and Δ-$[Co(pn)_3]^{3+}$ [1] with charcoal racemizes faster than coordinated pn exchanges with pn from the solution.[9] For such intramolecular reactions two alternative mechanisms have been envisaged:[20b] Co–N bond rupture whereby a five-coordinate intermediate is generated in which reattachment can occur at a different position, and a twist process wherein six-coordination is preserved. These alternatives should properly be viewed as the limiting mechanisms of a range.

The experimental observations on isomerizations in a number of $[CoN_6]^{3+}$ systems have been interpreted on the basis of predominantly intramolecular bond-rupture mechanisms: $[Co(en)_3]^{3+}$ racemization under both charcoal and homogeneous conditions,[12] $[Co(dien)(medien)]^{3+}$ and $[Co(dien)_2]^{3+}$ homogeneous,[10,13] *u-fac*-$[Co(daes)_2]^{3+}$ charcoal racemization,[1,11] and $[Co(tacd)_2]^{3+}$ homogeneous.[1,14] This bond-rupture mechanism more easily accommodates both the observed base dependence of the isomerization rates for these systems, and the occurrence under some conditions of hydrolytic by-products which have been presumed to be $[CoN_6(OH)]^{2+}$ species.[10]

For the racemization of $[Co(en)_3]^{3+}$ in the presence of both charcoal and base, Spiro has deduced that the dominant pathway is through the conjugate base and a five-coordinate intermediate, and it was also shown that a Co(III)-Co(II) electron-exchange process is significant only for solutions containing added $[Co(en)_3]^{2+}$ + en.[12] Although this latter pathway is less important than was earlier considered for the $[Co(en)_3]^{3+}$ system,[21] such a scheme has to be retained as plausible for the isomerization of $[Co(dien)(medien)]^{3+}$ on charcoal since it can accommodate the complete dissociations of ligands.[10]

As well as the above bond-rupture proposals, twist processes remain an intriguing possibility because there is evidence for their occurrence with isomerizations in some complexes of Cr(III)[22,23] and Cr(I)[24] and Fe(II).[25] Although there is little direct evidence for their occurrence in some other Co(III) systems previously studied,[26–28] an interesting situation has been reported recently with the sexadentate complex $[Co(stn)]^{3+}$ which racemizes homogeneously in base and also in the solid state.[1,29] The catalysis of the homogeneous racemization of this complex by hydroxide indicates that deprotonation at a secondary nitrogen is a first step. A bond rupture as a second step can not be seen to lead to inversion of the absolute configuration about the metal, which has therefore been attributed to a trigonal twist (Bailar twist) process. In this system the racemization has to involve inversion of the absolute configurations of all three asymmetric nitrogens "simultaneously," so that deprotonation at one nitrogen site initially must precede the twist act.[29,30] However, with tris-bidentate complexes (without such ring-coupling) a purely twist process does not readily accommodate the observed base catalysis and the formation of some hydrolysis co-products in Co(III) systems.

Significance of Isomerization in [Co(hexacyclen)]$^{3+}$. The occurrence or otherwise of isomerization between the *fac* and *mer* [Co(hexacyclen)]$^{3+}$ isomers would seem to be definitive in establishing two aspects of the isomerization mechanism. Firstly, no twist process (of the Bailar or Ray-Dutt types) can be envisaged for the *fac* isomer due to the coupling of the chelate rings,[7] so that any isomerization *fac*$\rightleftarrows$*mer* has presumably to be attributed to a Co–N bond-rupture process. Secondly, if the isomerization is base-catalyzed, as with the other CoN_6^{3+} systems studied, this catalysis should probably be attributable to deprotonation occurring at a *s*-NH center (since hexacyclen has only secondary amine sites). These considerations should be relevant also if the reaction proceeded through a labile Co(II) intermediate, in a redox pathway occcurring under charcoal conditions.

Preparation of *mer*-[Co(hexacyclen)]$^{3+}$. Various preparative procedures for [Co(hexacyclen)]$^{3+}$ were examined in anticipation of obtaining the *fac* isomer in greater proportion than that reported previously, $<1\%$.[5,6] However this was not realized and the *fac* was sometimes barely detectable on the Sephadex among co-products of the reactions (including [Co(linpen)]$^{3+}$ isomers, see below). We therefore sought to isolate from the synthesis only the pure *mer* isomer (both diastereoisomers), and thence to obtain the *fac* by isomerization. The linear hexamine linpen,[1] which is the open-chain analogue of hexacyclen, is a troublesome contaminant of hexacyclen, and additional steps in the isolation procedure for [Co(hexacyclen)]$^{3+}$ are necessary to remove [Co(linpen)]$^{3+}$.

The substitution reaction $[Co(NH_3)_5(H_2O)](ClO_4)_3$+hexacyclen·$3H_2SO_4$+6LiOH in water with charcoal[5] seemed to give the cleanest product mixture, although considerable hydrolysis by-products were unavoidable.

All the products were then separated by cation-exchange chromatography on SP-Sephadex. We found Na_3PO_4 eluent[6] to be more satisfactory for this preparative work than Na_2SO_4/H^+,[5] as the Na_3PO_4 is highly discriminating[31] and effects the best separation of the *fac*- and *mer*-[Co(hexacyclen)]$^{3+}$ isomers[32] from [Co(linpen)]$^{3+}$ co-products (see below) of the substitution synthesis. Also, in the basic conditions of Na_3PO_4 elution the darkly-colored hydrolysis by-products from the synthesis, or from isomerization reactions for [Co(hexacyclen)]$^{3+}$ as below, elute slowly so that the *mer* (diastereoisomer mixture) can be readily separated ahead of them. (With Na_2SO_4/H^+ elution, the by-products appear mainly as two pink bands between the *fac* and *mer* bands. These same hydrolysis product bands were observed from samples from isomerization reactions carried out in 0.1 M Na_3PO_4 separated on Sephadex with Na_2SO_4/H^+). With Na_3PO_4, the *fac* and *mer* bands are also darkened in color, and we ascribe this to some deprotonation at coordinated nitrogen sites.[17,33] Although the isomerization is base-catalyzed, this was not a problem in the Sephadex/Na_3PO_4 chromatography to obtain the two isomers pure, as we found that the amount of *fac* →*mer* change occurring in 0.1 M Na_3PO_4 pH 12 was negligible over several hours at room temperature, as samples of *fac* then isolated showed no *mer* by ^{13}C NMR.

From its Sephadex/Na_3PO_4 effluent, the *mer* NH-diastereoisomer mixture could be isolated as its bromide or nitrate salt by using Dowex strong-acid cation-exchange resin.

The *mer* diastereoisomers could be subsequently separated by Sephadex chromatography by using acidic conditions, Na_2SO_4/H^+ eluent.[5,7] Experimentally the diastereoisomers are designated as *mer-1* and *mer-2* according to their elution order from Sephadex, but their identities as ($\Lambda\delta/\Delta\lambda$) or ($\Lambda\lambda/\Delta\delta$) remain unknown.[7]

Preparation of *fac*-[Co(hexacyclen)]$^{3+}$ by Isomerization. The cation-exchange elution order of the isomers *fac*$\gg$*mer* with Na_3PO_4 or Na_2SO_4 indicates that the *fac* associates more strongly with these eluent anions.[8,31] Consequently, under conditions where equilibrations between isomers can occur, i.e. in water with charcoal or base,[10,14] the proportion of *fac* should be enhanced in the presence of associating anions such as PO_4^{3-} or SO_4^{2-}. Such enhancements have been demonstrated previously with *s*-*fac*-[Co(dien)$_2$]$^{3+}$[15] and *trans*-[Co(tacd)$_2$]$^{3+}$,[14] and where a less stable isomer preferentially associates with an added anion the shift in equilibrium position may be substantial. Thus in [Co(dien)$_2$]$^{3+}$ the *s-fac* proportion formed in synthesis changed from 8% in water (with counter-anions present Cl^-, NO_3^-, or ClO_4^-, all weakly associating) to 59% with added Na_3PO_4 at 20 °C.[15]

This enhancement effect has now been used in the [Co(hexacyclen)]$^{3+}$ system to obtain the unstable *fac* isomer by allowing the *mer* to isomerize in 0.1 M Na_3PO_4 at 80 °C. The time for optimum conversion was determined from small-scale tests which showed that equilibrium was reached by 12 h. The proportions under these conditions were *mer* : *fac* : hydrolysis products=71 : 18 : 11 (see below), so that ion-association enhances the *fac* proportion by about twenty times. Larger scale mixtures thus isomerized were separated by Sephadex/Na_3PO_4 chromatography, and the recovered *mer* was recycled.

Isomerization in Na_2SO_4+charcoal (pH 5) gave little if any *fac* enhancement. These results suggest that in the equilibrium substitution syntheses on charcoal,[5,6] the ca. 1% *fac* obtained actually represents an enhancement by ion-association with SO_4^{2-} which was the counter anion present, and which is moderately associating.[15] Thus in the presence of only weakly associating anions, the equilibrium *fac* proportion would be expected to be ≪1%.

The Occurrence of $[Co(linpen)]^{3+}$ in $[Co(hexacyclen)]^{3+}$. The complex system $[Co(linpen)]^{3+}$[1] exists in four topological isomers (Fig. 2). These are designated **A**, **B**, **C**, and **D** according to their elution order on Sephadex, and their geometries have been assigned.[34] Our first-isolated *fac*-$[Co(hexacyclen)]^{3+}$ contained $[Co(linpen)]^{3+}$ (**A**) (identified by its chromatographic elution on SP-Sephadex[8] and by its ^{13}C NMR spectrum being closely similar to those of authentic **A**).

The linpen must have been present as an impurity in the starting hexacyclen·$3H_2SO_4$ material, and indeed the ^{13}C NMR spectrum of the hexacyclen·$3H_2SO_4$ (after conversion to hexacyclen·6HCl) showed a peak (δ 43.7) which can be attributed to the main resonance (three carbons of the five different carbons present) of authentic linpen·6HCl. Our recent work on Richman-Atkins cyclization syntheses of cyclic polyamines[35] has demonstrated how a linear analogue can arise as an elimination reaction co-product during a cyclization synthesis, so that linpen has to be expected as a contaminant in hexacyclen.[36]

In the equilibrium substitution preparation of $[Co(hexacyclen)]^{3+}$ all four isomers **A** to **D** should be formed from the linpen. The isomers **D** (73% proportion[34]) and **C** would contaminate *mer*-$[Co(hexacyclen)]^{3+}$, as these all chromatograph similarly.[8] This **D** would then be expected to isomerize to **A** (9% proportion[34]) during the *mer*→*fac* isomerization, and **A** and *fac* chromatograph similarly. Experimentally, **D** was evident in crude samples of *mer* as a yellowish tail to the orange *mer* band on Sephadex chromatography, and initial samples of *fac* contained **A**. However, samples of *fac* obtained from subsequent isomerizations using recycled *mer* were free of **A**, due to the eventual removal of **D** from *mer* by isomerization.

$[Co(linpen)]^{3+}$ contaminants were thus removed as follows: (1) **A**, **B**, and **D** were separable partially from *mer*-$[Co(hexacyclen)]^{3+}$ by Sephadex chromatography;[8] (2) **D** and **C** were partially removed from *mer* by their isomerization to **A** in Na_3PO_4; (3) fractional recrystallization of the final *mer* and *fac* materials removed (**D**+**C**) and **A** respectively.

Conditions for Optimum Isomerization to *fac*-$[Co(hexacyclen)]^{3+}$. The time and yield for optimum isomerization to *fac* were determined from small-scale runs in which pure *mer*-$[Co(hexacyclen)](NO_3)_3$ was allowed to isomerize in 0.1 M Na_3PO_4 at 80 °C. The solutions were sampled at various times and analyzed.

The mole proportions of *mer*, *fac*, and hydrolysis products versus time thus determined (Fig. 3) show that the isomerization is slow. The proportion of *fac* rises gradually, to become constant at 18% at about 12 h. Hydrolysis (or decomposition) occurs concomitantly, rising rapidly at first, then levelling out at 11% at about 5—8 h. It is evident that equilibrium is attained between the two isomers and the hydrolyzed species, at *mer*:*fac*:hydrolysis=71:18:11, by 12 h. However, the faster generation of hydrolyzed products (the crossover in the *fac* and hydrolysis curves) suggests that the isomerization process is not simple.

This 18% proportion of *fac* was expected to be near the optimum, since the effect of PO_4^{3-} on enhancing the least stable *s*-*fac*-$[Co(dien)_2]^{3+}$ reached maximum at 0.08 M Na_3PO_4.[15] Under the equilibration conditions of Na_3PO_4, hydrolysis to the extent of ca. 11%

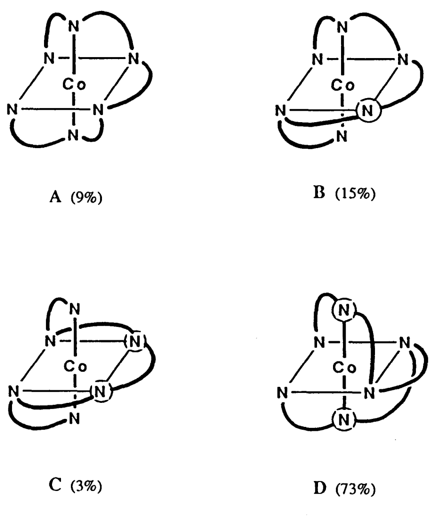


Fig. 2. Topological isomers of Λ-$[Co(linpen)]^{3+}$ and their equilibrium proportions. Diastereoisomers arise from the alternative dispositions (or *R*/*S* configurations) at the circled secondary amines which couple *mer* chelate rings.

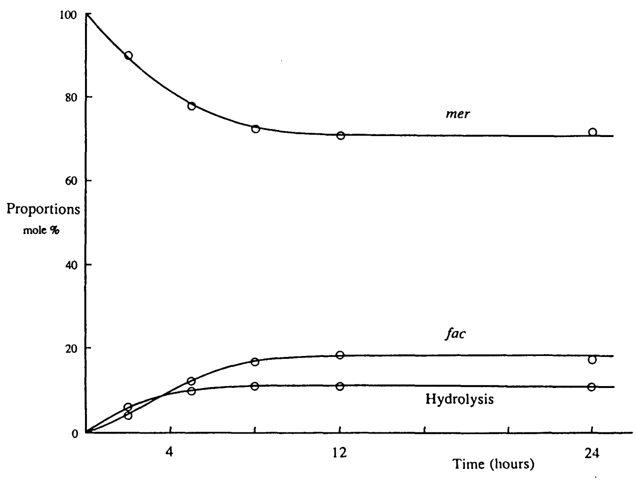


Fig. 3. Isomerization-equilibration of *mer*-$[Co(hexacyclen)](NO_3)_3$ in 0.1 M Na_3PO_4 at 80 °C. Separation is by Sephadex/Na_3PO_4. Equilibrium mole proportions are *mer*:*fac*:hydrolysis=71:18:11%.

seems to be unavoidable in [Co(hexacyclen)]$^{3+}$.

Kinetic Runs on *fac*→*mer* [Co(hexacyclen)]$^{3+}$ Isomerization. (a) Runs Followed by HPLC Analysis of Samples. The reaction was followed at 50 °C, under the NaOH concentration conditions 0.05, 0.1, and 0.5 M NaOH (I=1.0 M, NaCl). The *fac*-[Co(hexacyclen)]$^{3+}$ complex immediately formed darkish red-brown solutions in base (including 0.1 M Na_3PO_4, as used in elution from Sephadex, see above), giving greater absorption at all wavelengths. These initial darkenings were reversible, so that when the solutions were applied to Sephadex or were acidified, they reverted to pale orange. This conforms to the pattern found with other [CoN_6]$^{3+}$ and [CoN_4S_2]$^{3+}$ systems where very rapid and reversible darkenings occur in base at varying pH values depending on the complex, and we attribute these changes to the formation of darkly colored deprotonated species.[17,33)]

In the HPLC procedure, samples from the various solutions removed at intervals were analyzed by HPLC using a strong-acid cation-exchange column. The eluent was Na_2SO_4/H_2SO_4 pH 2, and detection was spectrophotometric. Apparently clean chromatograms were obtained showing completely separated peaks of *fac* and the *mer-1* and *mer-2* diastereoisomers only, over most of the reaction, e.g. up to 12 h for 0.1 M NaOH (Fig. 4).[37)] Of the *mer* diastereoisomer products *mer-1* was always observed in slightly greater amount (*mer-1* ≈60—55%, assuming that the two diastereoisomers have similar absorptions), but our kinetic plots were made with respect to *total mer*.

Elution at pH 4 (Na_2SO_4/H_2SO_4) was also tried. Under these conditions the two *mer*-NH diastereoisomers were not completely separated as the absorption recordings did not achieve baseline between the two peaks, and this indicates that the diastereoisomers interconvert at pH 4 over the time scale of the HPLC analysis (although not at pH 2, as above). This is presumably through base-catalyzed N-H exchange involving the deprotonated species, analogously to the racemization of [Co(dien)$_2$]$^{3+}$.[38)] However, it seems that the isomerization (pH≥4) in the *mer*-[Co(hexacyclen)$_2$]$^{3+}$ is considerably faster than the analogous racemization (pH>7) of *mer*-[Co(dien)$_2$]$^{3+}$.[38)] Although this pH 4 gave similar kinetic plots to those for pH 2, we believe that there are more uncertainties at these higher pH values, as the measured absorptions may have contributions from protonated and deprotonated forms of the two diastereoisomers and from other possible intermediates. In fact, some small shoulders or peaks are evident close to the *fac* peak on the HPLC elution curves, especially in the latter stages of the reactions.

The kinetic plots for disappearance of the *fac* and appearance of the *mer*(total) are irregular for all NaOH concentrations. The amount of *fac* did not decrease in a first order manner, and this was particularly noticeable in the lowest NaOH concentration, 0.05 M, when the *fac* remained nearly constant to about 3 h before decreasing slowly. Also, the 0.1 M NaOH curve for *mer* has a marked hump at 2.5 h (Fig. 5). These observations are consistent with the "*fac*" band in HPLC containing a second species, of a similar *fac* geometry, which builds up slowly, and this is likely to be some longer-lived intermediate.

The irregularities in the *mer* elution kinetic curves

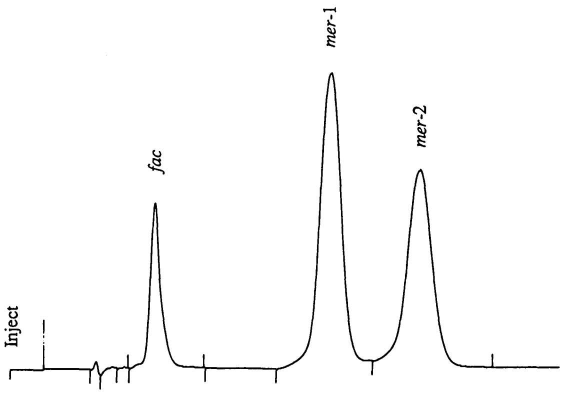


Fig. 4. Typical HPLC chromatogram, Na_2SO_4/H^+ pH 2 elution. (Reaction in 0.1 M NaOH, 50 °C, for 12 h).

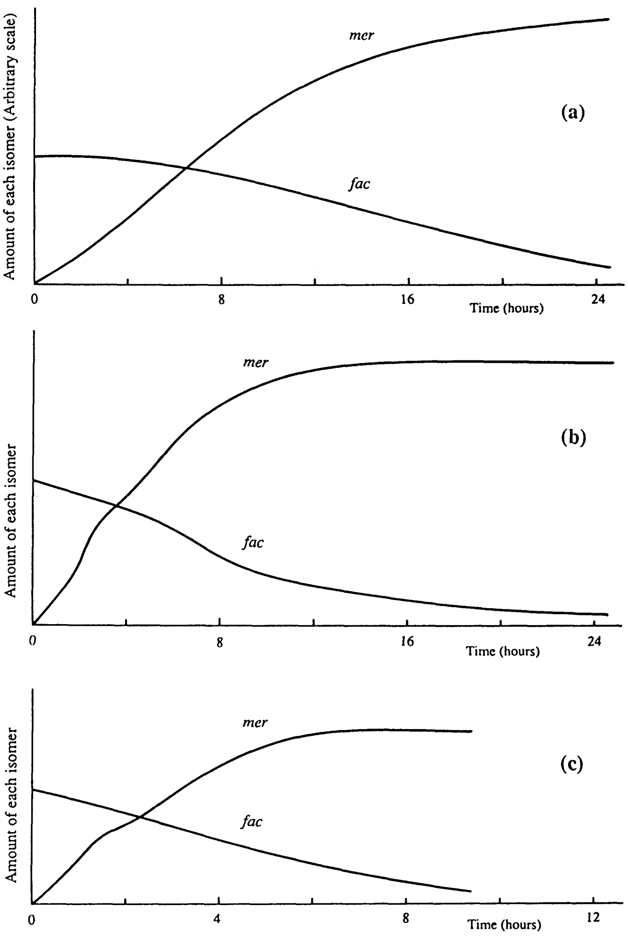


Fig. 5. Kinetic plots from HPLC elutions of isomerization reactions of *fac* at 50 °C: (a) in 0.05 M NaOH; (b) 0.1 M NaOH; (c) 0.5 M NaOH.

were an inflection in the curve for 0.05 M NaOH (≈3 h) and humps for 0.1 M NaOH (≈2.5 h) and 0.5 M NaOH (≈1.5 h) (Fig. 5). Although these irregularities have precluded the precise measurement of reaction rates, the plots of amount of *mer* versus time allow semiquantitative estimates of the rates. For the 0.05, 0.1, and 0.5 M NaOH reactions the half-lives are about 8, 4, and 2 h respectively taking the reactions to be pseudo-first-order, so that there is clearly a base dependence of the rates. The order in hydroxide is approximately first-order, and is in accord with the deprotonation requirement of a bond-rupture process for the *fac*→*mer* isomerization in this system.

(b) Isomerization Followd by Spectrophotometry. Isomerization runs in 0.1 M and 0.5 M NaOH at 50 °C were followed spectrophotometrically. Absorptions were measured at three wavelengths 478 (the λ_{max} for the *mer* isomer where the maximum change occurs), 520, and 416 nm (Fig. 6). Both the initial and the final absorptions were higher at all wavelengths (progressively with increasing OH^- concentration) than those measured in acid (ε_{478} for *fac*: 62 in 0.01 M HCl, initially 71 in 0.1 M NaOH, initially 86 in 0.5 M NaOH). This greater *initial* absorption is attributed to deprotonation.[17,33)]

The *subsequent* increases in absorption do not correspond to a single pseudo-first-order reaction, but the absorptions versus time plots show inflections at early stages of the overall reaction. This is particularly clear in the 0.1 M NaOH reaction (Fig. 7), where the inflection in the absorption occurs at 2—3 h. These inflections correspond to the humps on the HPLC versus time plots for the *fac* and the *mer* isomers for the corresponding isomerizations as followed by Sephadex chromatography and HPLC analysis (Fig. 5). With 0.5 M NaOH, irregularities in the absorption versus time plots are evident up to the first 2 h of the reaction as followed both by in-situ spectrophotometry and Sephadex/HPLC chromatography. These plots for the different NaOH concentrations again demonstrate a base dependence of the overall reaction rate.

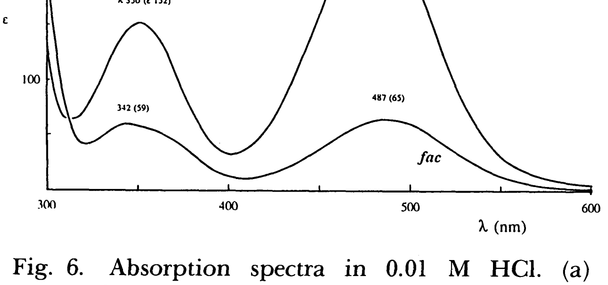


Fig. 6. Absorption spectra in 0.01 M HCl. (a) *mer*-[Co(hexacyclen)]$Br_3 \cdot H_2O$; (b) *fac*-[Co(hexacyclen)]Cl_3.

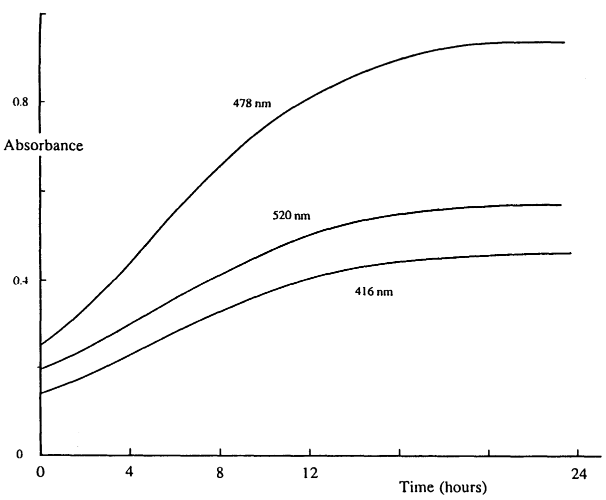


Fig. 7. Absorbance changes during isomerization of *fac* in 0.1 M NaOH at 50 °C.

The occurrence of an inflection (induction period) in the absorbance versus time plots (for different OH^- concentrations and different wavelengths) suggests that the reaction may be described as a series first order scheme **A**→**B**→**C** involving an intermediate **B**.[39)] However, plots of the absorbance data as $\log(A_\infty - A_t)$ versus time gave continuous curves having no linear latter sections. We take these results to indicate that the two steps k_1 and k_2 are of comparable rates, or that the overall reaction involves autocatalysis. The steps are not readily analyzed, since the absorbance is a function of at least three varying species.

The Mode of Isomerization. Since a twist is implausible for the *fac*⇄*mer* isomerization, the reaction presumably proceeds by a bond-rupture process. Also, the observed approximately first-order base dependence suggests that a deprotonated intermediate is involved, and the rapid and reversible darkening in base of both isomers is consistent with this proposal.

A scheme of bond rupture and deprotonation steps which can connect all the *fac* and *mer* isomers is shown in Fig. 8. From *fac*, two enantiomeric trigonal-bipyramidal intermediates can arise, and on re-association these could together yield the racemic components ($\Lambda,\delta + \Delta,\lambda$) of *one* the *mer* diastereoisomers. Inversion of configuration at the equatorial nitrogen center in the intermediate (denoted N* in Fig. 8), which is adjacent to the dissociated nitrogen, is required for the detached rings to change their position on re-association to regain octahedral coordination, and the deprotonation thus required at this N* should make the *fac*→*mer* reaction base dependent. Pi-donor bonding to cobalt of this amide group in the trigonal plane could stabilize the five-coordinate intermediate.[20a,40,41)] Inversion of configuration is required also at the dissociated nitrogen for the *fac* →*mer* change, but such inversions of free amines are rapid (and should occur within the lifetime of the

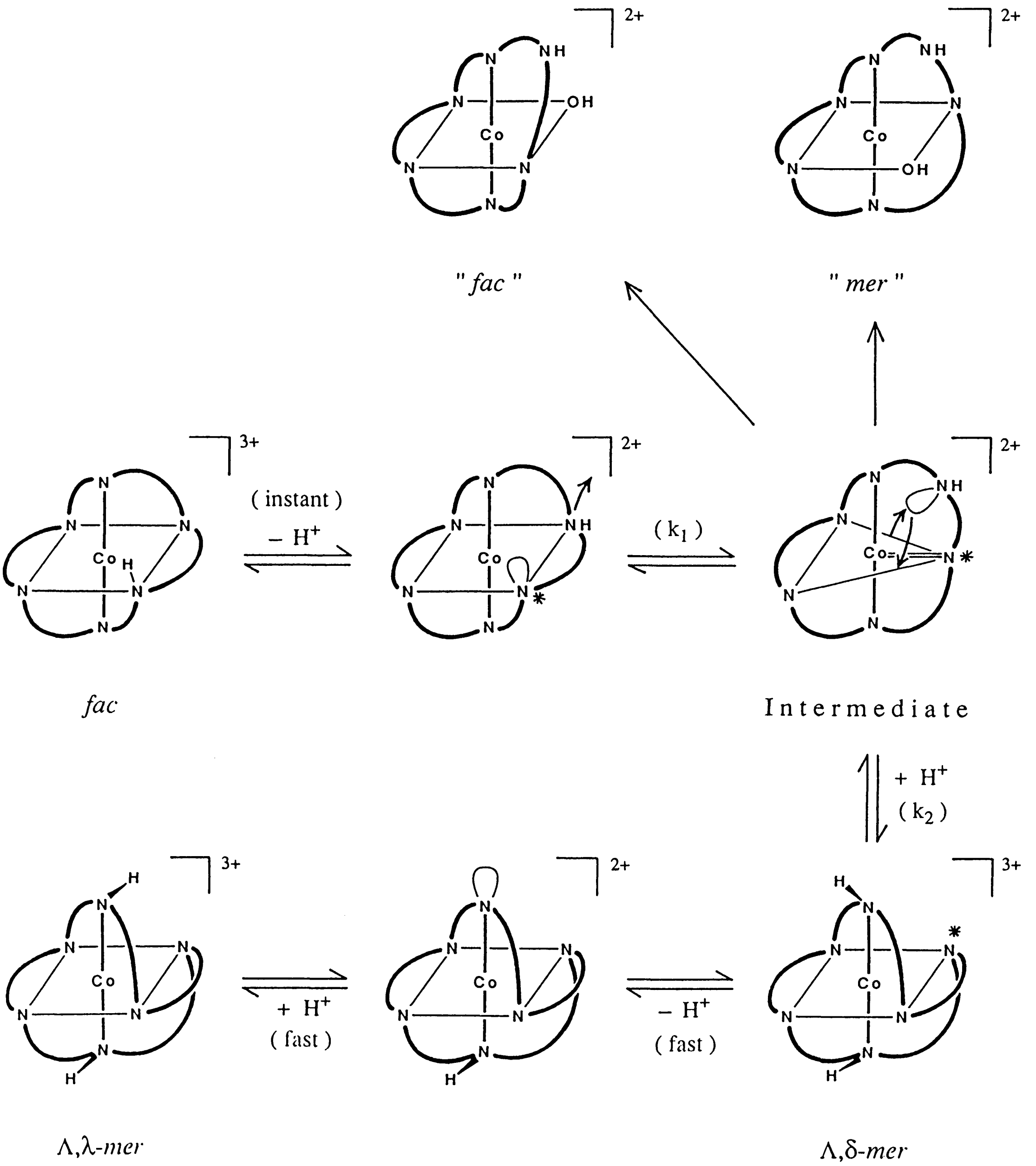


Fig. 8. Bond rupture and deprotonation processes giving *fac* $\rightleftarrows$ *mer* [Co(hexacyclen)]$^{3+}$. Only one enantiomer is shown for the trigonal bipyramid intermediate and for the *mer* diastereoisomers.

trigonal-bipyramid intermediate) and do not exhibit a base dependence.

The HPLC results are consistent with this proposed scheme. The changes in the HPLC "*fac*" peak indicate a slow build up of some intermediate species, since the peak apparently remains constant in magnitude for some time before then decreasing. Also, some residual small peaks (close to the *fac*) become unmasked in the latter stage of reaction when the sharp peak of the octahedral *fac* isomer has largely disappeared. We now identify this intermediate as the proposed trigonal bipyramid, formed slowly by step k_1.

The HPLC *mer* elution versus time plot at 0.05 M NaOH shows an inflection which is consistent with the proposed scheme of consecutive first order reactions involving one intermediate.$^{39)}$ At the higher NaOH concentrations, however, the *mer* elution curves show in addition humps which indicate that some other species becomes involved under these conditions. It is difficult to see that the hump could be due to an increased amount of the *mer* isomer (irregularly generated, from some other intermediate), and it seems more likely that at these higher NaOH concentrations some other species is formed which elutes similarly to the *mer* so that it is masked, but is detected along with the *mer*.

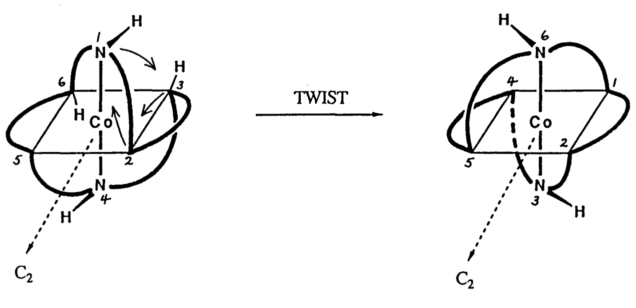
The spectrophotometric kinetic observations are also consistent with the proposed consecutive steps scheme, where the rates k_1 and k_2 are indicated to be comparable.

That the isomerization is slow suggests that the trigonal bipyramid intermediate is long-lived, and competition experiments employing strong nucleophiles might be useful to check this. However the present reacting solutions contained Cl$^-$ and OH$^-$ as potential nucleophiles in concentrations greatly exceeding cobalt, and formation of species such as [Co(hexacyclen)OH]$^{2+}$ is plausible (Fig. 8). These may be the species suggested as contributing to the apparent *mer* hump in the HPLC elution curves for the higher NaOH concentration conditions.

The concomitant formation of hydrolysis products (or other substitution products) could be expected, as the proposed five-coordinate intermediate in the *fac*$\rightleftarrows$*mer* isomerization (with an uncoordinated amino group) is similar to the intermediate in the generally accepted S$_N$1CB mechanism for the base hydrolysis of cobalt(III) amine complexes.40–43) Hydrolysis was especially evident in the isomerization (from *mer*) carried out in phosphate, where the carmine Sephadex band may have contained phosphate-substituted products. It is also relevant that the species *cis*-[Co(en)$_2$(mono-en)(OH)]$^{2+}$ is formed as the main product in the base hydrolysis of *cis*-[Co(en)$_2$(mono-enH)Cl]$^{3+}$, showing that the free amino group of the monodentate-en ligand does not compete favorably with water for the vacant coordination site in the proposed five-coordinate intermediate.42) The formation of [Co(hexacyclen)(OH)]$^{2+}$ may be a parallel situation.

With some macrocyclic complex systems closely analogous to [Co(hexacyclen)]$^{3+}$, Royer and coworkers7) found that equilibrations between *fac* and *mer* isomers were generally facile, and attributed this to the high strain in these macrocyclic structures.44) We believe that these *fac*→*mer* changes can be accommodated by our proposal of a single Co–N bond rupture, and that the more drastic simultaneous breaking of *two* adjacent Co–N bonds as suggested previously7) is not necessary.

Although no twist processes are possible for the direct change *fac*→*mer* [Co(hexacyclen)]$^{3+}$, a twist process can be envisaged for direct inversion of one *mer* diastereoisomer, $\Lambda,\lambda \rightleftarrows \Delta,\delta$ (Fig. 9), and this need not involve deprotonation. Inversion of the other *mer* diastereoisomer Λ,δ does not seem possible directly by a twist, but inversion could occur indirectly through two alternative routes. One path is through the symmetrical *fac* isomer, Λ,δ-*mer*$\rightleftarrows$*fac*$\rightleftarrows\Delta,\lambda$-*mer*, involving deprotonations and inversions at two nitrogen centers (Fig. 8). The second possible route is through the other diastereoisomer Λ,λ involving one deprotonation and NH inversion step, followed by the twist. We can not envisage direct formation of the $(\Lambda,\lambda/\Delta,\delta)$-*mer* diastereoisomer from the *fac*, and we suppose its formation to be via the $(\Lambda,\delta/\Delta,\lambda)$ diastereoisomer (Fig. 8). However, in the present experiments only the total of all the *mer* isomers is calculated, so that the alternative possible routes for the *mer* interconversions are not distinguished.



Λ-*mer*, λ-NH Δ-*mer*, δ-NH

Fig. 9. Possible twist process for *mer*-[Co(hexacyclen)]$^{3+}$ giving inversion around cobalt. The process (as shown) need not involve inversion at a N center, so that it could be independent of pH.

The present HPLC results show that the interconversion of the *mer* diastereoisomers by NH exchange is rapid, being in evidence at pH 4 over 15 min at 20 °C. The inversion of the *mer* diastereoisomers is of interest, since the relative rates of this inversion and the *mer*→*fac* conversion might provide evidence about the possible *mer* twist process. However, isolation of the *mer* in optically active forms has not yet been achieved. Royer7) did however obtain a partial resolution of the *mer* material by Sephadex chromatography using acidified 0.3 M sodium (+)-tartrate as eluent, and CD curves were given of two separated fractions, which were both assigned as having the Λ configuration around the cobalt. However, isolation from solution as the perchlorate salt gave only racemic crystals. The structure reported for these was the diastereoisomer $\Delta,\lambda/\Lambda,\delta$ racemate,45) but the occurrence of racemization during crystallization precluded identification of this solid with the order of elution of the two *mer* diastereoisomers by Sephadex/Na$_2$SO$_4$/H$^+$ chromatography.

Although the pH conditions used for these experiments were not given, the reported results indicate that inversions of configuration around the cobalt $\Delta \rightleftarrows \Lambda$ in the *mer* geometry are facile.7) It is difficult therefore to see that these inversions could proceed via the demonstrated slow *mer*→*fac* pathway involving bond rupture, so that a twist process seems likely for these interconversions within the *mer* geometry.

Results obtained recently by Larsen with isomerization of [Co(aeaps)$_2$]$^{3+}$ in base1,46) have bearing on the present work. For the reaction of different isomers in 1 M NaOH, a sequential process $\mathbf{A} \xrightarrow{k_1\,(\mathrm{fast})} \mathbf{B} \xrightarrow{k_2\,(\mathrm{slow})} \mathbf{C}$ was found, as deduced herein for the [Co(hexacyclen)]$^{3+}$ system. For this thioether system the individual steps could be separated and were quite slow

($t_{1/2}$=85 s and 23 min at 1 °C) and there seemed to be no evidence (no instant darkening) for a preliminary deprotonation at coordinated amine. The product solution **C** contained at least three species at equilibrium, one of which (20% proportion) was found to be [Co(aeaps)(aeaps-H)]$^{2+}$ [1] involving coordination of a carbanion group on one ligand rather than the thioether sulfur as in the reactants. Although this result is thought provoking, it is likely that this situation of alkyl group coordination is unique to a substrate complex with a six-membered ring having a thioether sulfur donor, and the analogous situation in the [Co(hexacyclen)]$^{3+}$ system seems implausible. Nevertheless, these results clearly show that the isomerization process is not simple and that several products may result.

Finally, cobalt(III) complexes of the types [Co(tetars)X_2]$^{n+}$ [1] and [Co(diars)$_2X_2$]$^{n+}$,[1] each with four tertiary arsine donor centers, are very prone to rapid catalytic substitution and topological equilibration which are supposed to occur via electron transfer with a labile cobalt(II) species.[47,48] These cobalt(II) species are presumed to be produced by spontaneous internal reduction of the cobalt atom and the simultaneous oxidation of the bound ligands X, since the isomerizations occur particularly in concentrated solutions, in reducing solvents like alcohols, and in the presence of excess of X^- where X^- is mildly reducing such as Br^- and NCS^-. These catalytic reactions are characterized by erratic kinetic behavior, such as the non-smooth loss of optical activity in substitution, cis→trans isomerization, or racemization reactions.[47,48] However such involvement of cobalt(II) is expected to be much less with isomerizations in cobalt(III)-amine complexes (amine=NH_3, en, dien, dpt[1]) where spontaneous reductions occur only under forcing conditions.[49,50] Although our work with [Co(hexacyclen)]$^{3+}$ did not involve conditions which were found to favour the catalysis in the arsine systems, there was some evidence of erratic behavior so that the involvement of cobalt(II) in catalytic amounts can not be absolutely excluded in the [Co(hexacyclen)]$^{3+}$ system.[53]

Parts of this work were carried out during leaves at the Departments of Chemistry at University of Otago, Dunedin, New Zealand, and James Cook University, Townsville, Australia. The use of facilities at those Departments and helpful discussions with D. A. Buckingham (Otago) and F. R. Keene (James Cook) are gratefully acknowledged. P. McDuie (Adelaide) kindly assisted with the atomic absorption measurements.

References

1) Ligand abbreviations: hexacyclen=1,4,7,10,13,16-hexaazacyclooctadecane; dien=diethylenetriamine; medien=4-methyldiethylenetriamine, or 2,2′-(methylimino)bis[ethylamine], $H_2NCH_2CH_2N(Me)CH_2CH_2NH_2$; linpen= 3,6,9,12-tetraazatetradecane-1,14-diamine, or "linear pentaethylenehexamine"; pn=1,2-propanediamine; daes=bis(2-aminoethyl) sulfide, $H_2NCH_2CH_2SCH_2CH_2NH_2$; tacd=1,4,7-triazacyclodecane; stn=1,1,1-tris(5-amino-2-azapentyl)ethane, or 5,5′,5″-ethylidynetris[4-azapentan-1-amine]; aeaps=(2-aminoethyl)(3-aminopropyl)sulfide, $H_2N(CH_2)_2S(CH_2)_3NH_2$; aeaps-H=$H_2N(CH_2)_2S(CH^-)(CH_2)_2NH_2$; tetars=$Me_2As(CH_2)_3AsPh(CH_2)_2AsPh(CH_2)_3AsMe_2$; diars=*o*-phenylenebis[dimethylarsine]; dpt=4-azaheptane-1,7-diamine, common name "dipropylenetriamine".

2) The absolute configurations of *mer*-[Co(hexacyclen)]$^{3+}$ are defined in terms of skew pairs of the octahedron edges spanned by chelate rings, Ref. 3. Λ-*mer* has 6Λ and 2Δ skew pairs. The different relative NH orientations are designated λ-NH or δ-NH according to their chirality, as with *mer*-[Co(dien)$_2$]$^{3+}$, Ref. 4.

3) IUPAC Commission on Inorganic Chemical Nomenclature, *Inorg. Chem.*, **9**, 1 (1970).

4) F. R. Keene and G. H. Searle, *Inorg. Chem.*, **11**, 148 (1972).

5) Y. Yoshikawa, *Chem Lett.*, **1978**, 109.

6) R. W. Hay, B. Jeragh, S. F. Lincoln, and G. H. Searle, *Inorg. Nucl. Chem. Lett.*, **14**, 435 (1978).

7) D. J. Royer, G. J. Grant, D. G. Van Derveer, and M. J. Castillo, *Inorg. Chem.*, **21**, 1902 (1982).

8) K. Sakakibara, Y. Yoshikawa, and H. Yamatera, *Bull. Chem. Soc. Jpn.*, **52**, 2725 (1979).

9) S. E. Harnung, S. Kallesoe, A. M. Sargeson, and C. E. Schäffer, *Acta Chem. Scand., Ser. A*, **28**, 385 (1974).

10) G. H. Searle, F. R. Keene, and S. F. Lincoln, *Inorg. Chem.*, **17**, 2362 (1978).

11) A. Hammershoi and E. Larsen, *Acta Chem. Scand., Ser. A*, **32**, 485 (1978).

12) P. D. Totterdell and M. Spiro, *J. Chem. Soc., Dalton Trans.*, **1979**, 1324.

13) F. R. Keene, I. A. S. McDonald, and G. H. Searle, *Aust. J. Chem.*, **34**, 1331 (1981).

14) G. H. Searle and M. E. Angley, *Inorg. Chim. Acta*, **49**, 185 (1981).

15) F. R. Keene and G. H. Searle, *Inorg. Chem.*, **13**, 2173 (1974).

16) M. J. Bjerrum and E. Larsen, *Acta Chem. Scand., Ser A*, **39**, 465 (1985).

17) L. R. Gahan, T. W. Hambley, G. H. Searle, M. J. Bjerrum, and E. Larsen, *Inorg. Chim. Acta*, **147**, 17 (1988).

18) Under similar conditions, the optical isomers of each of *u-fac* and *mer*-[Co(dien)$_2$]$^{3+}$ were separable on HPLC, as found also by chromatography on Sephadex columns with this tartrato(4−)diantimonate(III) eluent, Ref. 19.

19) Y. Yoshikawa and K. Yamasaki, *Bull. Chem. Soc. Jpn.*, **45**, 179 (1972); *Coord. Chem. Rev.*, **28**, 205 (1979).

20) F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed., Wiley, New York (1967). a) p. 174; b) pp. 289—291, 313—322.

21) F. P. Dwyer and A. M. Sargeson, *Nature(London)*, **187**, 1022 (1960); F. P. Dwyer and A. M. Sargeson, *J. Phys. Chem.*, **65**, 1892 (1961).

22) G. A. Lawrance and D. R. Stranks, *Inorg. Chem.*, **16**, 929 (1977).

23) G. A. Lawrance and S. Suvachittanont, *Inorg. Chim. Acta Lett.*, **32**, L13 (1979).

24) W. R. Robinson, D. E. Wigley, and R. A. Walton,

Inorg. Chem., **24**, 918 (1985).

25) L. Christiansen, D. N. Hendricksen, H. Toftlund, S. R. Wilson, and C-L. Xie, *Inorg. Chem.*, **25**, 2813 (1986).

26) S. S. Eaton, J. R. Hutchinson, R. H. Holm, and E. L Muetterties, *J. Am. Chem. Soc.*, **94**, 6411 (1972).

27) S. S. Eaton, G. R. Eaton, R. H. Holm, and E. L. Muetterties, *J. Am. Chem. Soc.*, **95**, 1116 (1973).

28) G. A. Lawrance, S. Suvachittanont, D. R. Stranks, P. A. Tregloan, L. R. Gahan, and M. J. O'Connor, *J. Chem. Soc., Chem. Commun.*, **1979**, 757; *Inorg. Chem.*, **19**, 3443 (1980).

29) K. Tomioka, T. Kashihara, U. Sakaguchi, and H. Yoneda, *Chem. Lett.*, **1984**, 1047.

30) The complex tris(2-pyridylmethyl)-1,4,7-triazacyclononaneiron(II), $[Fe(tptcn)]^{2+}$, has topology analogous to that of $[Co(stn)]^{3+}$ but the ring couplings do not involve secondary amines, and recently this complex was elegantly shown to racemize rapidly and without base catalysis, Ref. 25. This probably occurs by a trigonal twist associated with the high-spin state, since this particular ligand gives a "crossover complex" with Fe(II). Such involvement of the high-spin state with Co(III) systems is much less likely.

31) G. H. Searle, *Aust. J. Chem.*, **30**, 2625 (1977).

32) Relative R_x values *fac*/*mer*, measured for minimal loadings of the complexes on small columns as in Ref. 31, are 6.2 for 0.1 M Na_3PO_4 and 2.1 for 0.2 M Na_2SO_4/H_2SO_4 pH 2.

33) R. J. Geue, T. W. Hambley, J. M. Harrowfield, A. M. Sargeson, and M. R. Snow, *J. Am. Chem. Soc.*, **106**, 5478 (1984).

34) Y. Yoshikawa and K. Yamasaki, *Bull. Chem. Soc. Jpn.*, **46**, 3448 (1973); Y. Yoshikawa, *ibid.*, **49**, 159 (1976).

35) G. H. Searle and R. J. Geue, *Aust. J. Chem.*, **37**, 959 (1984).

36) T. J. Atkins, J. E. Richman, and W. F. Oettle, *Org. Synth.*, **58**, 86 (1978).

37) Hydrolysis bands which eluted with this Na_2SO_4/H_2SO_4 eluent between the *fac* and *mer* from the isomerizations in Na_3PO_4 at 80 °C (see above) were not evident.

38) G. H. Searle and F. R. Keene, *Inorg, Chem.*, **11**, 1006 (1972).

39) T. W. Moore and R. G. Pearson, "Kinetics and Mechanism," 3rd ed, Wiley, New York (1981), p. 290.

40) M. L. Tobe, in IUPAC, "Coordination Chemistry-20," ed by D. Banerjea, Pergamon, Oxford (1980), p. 47.

41) D. A. Buckingham, P. A Marzilli, and A. M. Sargeson, *Inorg. Chem.*, **8**, 1595 (1969).

42) R. W. Hay and K. B. Nolan, *J. Chem. Soc., Dalton Trans.*, **1975**, 1621.

43) P. Comba and A. M. Sargeson, *J. Chem. Soc., Chem. Commun.*, **1985**, 51.

44) Equilibrations in 1,4,7,10,13,16-tri-(*R*,*R*)-cyclohexano[*b*,*h*,*n*]hexaazacyclooctadecanecobalt(III), $[Co(TC18N6)]^{3+}$, were reported to be facile at pH>7 and pH<1 and were accompanied by decomposition. With 1,4,8,11,15,18-hexaazacycloheneicosanecobalt(III) $[Co(21N6)]^{3+}$ only the one isomer *fac* was apparent in solution and was partially resolved by chromatography. This isomer apparently racemized in solution (conditions not stated), and it isomerized on crystallization to give one of the three possible *mer* diastereoisomers, Ref. 7.

45) This $\Delta,\lambda/\Delta,\delta$ diastereoisomer was designated as $\Delta(\delta\delta\delta)\Delta(\lambda\lambda\delta)$-*mer*-(1,2) in terms of one enantiomer in Ref. 7.

46) M. J. Bjerrum, M. Gajhede, E. Larsen, and J. Springbϕrg, *Inorg. Chem.*, **27**, 3960 (1988).

47) B. Bosnich, W. G. Jackson, and J. W. McLaren, *Inorg. Chem.*, **13**, 1133 (1974).

48) B. Bosnich, W. G. Jackson, and S. B. Wild, *Inorg. Chem.*, **13**, 1121 (1974).

49) S. Lum, L. Ereshefsky, and C. S. Garner, *J. Inorg. Nucl. Chem.*, **35**, 1591 (1973).

50) Some Co(II) is formed on heating Co(III)-amine complexes: traces of Co(II) are formed on heating $[Co(dien)(en)Cl]Cl_2$ in alcohols,(51) or heating $[Co(en)_3]Cl_3$ in aqueous en;(21,51) substantial Co(II) is generated on heating $[Co(en)_3]Cl_3$(51) or $[Co(en)_2Cl_2]Cl\cdot 2H_2O\cdot HCl$(52) in the solid state.

51) F. P. Dwyer, "Advances in the Chemistry of the Coordination Compounds," (Proceedings Sixth ICCC), ed by S. Kirschner, MacMillan, New York (1961), p. 21.

52) J. Springbϕrg and C. E. Schäffer, *Inorg. Synth.*, **14**, 68 (1973).

53) After heating $[Co(en)_3]Cl_3$ in 0.01 M NaOH at 50 °C for 6 h, the presence of Co(II) was uncertain, being around the detection limit of 2×10^{-4} M. The detection of Co(II) provides no evidence that electron transfer is involved in the mechanism. The test involves acidification with HNO_3, addition of excess KCNS, centrifuging the precipitated $[Co(III)](CNS)_3$, and addition of amyl alcohol to the (pipetted off) supernatant.