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Ligand Substitution Behavior of a Simple Model for Coenzyme B_{12}

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The ligand substitution reactions of *trans*-$[Co^{III}(en)_2(Me)H_2O]^{2+}$, a simple model for coenzyme B_{12}, were studied for cyanide and imidazole as entering nucleophiles. It was found that these nucleophiles displace the coordinated water molecule trans to the methyl group and form the six-coordinate complex *trans*-$[Co(en)_2(Me)L]$. The complex-formation constants for cyanide and imidazole were found to be $(8.3 \pm 0.7) \times 10^4$ and 24.5 ± 2.2 M^{-1} at 10 and 12 °C, respectively. The second-order rate constants for the substitution of water were found to be $(3.3 \pm 0.1) \times 10^3$ and 198 ± 13 M^{-1} s^{-1} at 25 °C for cyanide and imidazole, respectively. From temperature and pressure dependence studies, the activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta V^{\ddagger}$ for the reaction of *trans*-$[Co^{III}(en)_2(Me)H_2O]^{2+}$ with cyanide were found to be 50 ± 4 kJ mol^{-1}, 0 ± 16 J K^{-1} mol^{-1}, and $+7.0 \pm 0.6$ cm^3 mol^{-1}, respectively, compared to 53 ± 2 kJ mol^{-1}, -22 ± 7 J K^{-1} mol^{-1}, and $+4.7 \pm 0.1$ cm^3 mol^{-1} for the reaction with imidazole. On the basis of reported activation volumes, these reactions follow a dissociative mechanism in which the entering nucleophile could be weakly bound in the transition state.

Introduction

Many octahedral organometallic complexes of Co(III), such as cobaloxime[1−9] and Costa's complex[10] (a mixed Schiff base−oxime complex with a uni-negative N_4 equatorial ligand), and those with a Schiff base,[11,12] such as N,N′-ethylenebis(actylacetoneiminato),[13] N,N′-ethylenebis(salicylideneiminato)[14] and the dianion of disalicylidene-O-phenylenediamine[14b], have been suggested as models for the vitamin B_{12} coenzyme because of their similarity to either the nature of the active site or a specific function of the enzyme. Much work has been carried out on these model complexes and has provided a basis for understanding the behavior of the more complex vitamin B_{12} molecule.[9,15] Substitution and Co−C bond cleavage reactions at the axial positions in such models are related to the reactions of the α- and β-positions in the natural cobalamin. Ligand substitution reactions of vitamin B_{12} in general follow a dissociative type of mechanism.[16,17] In the case of the coenzyme, however, evidence for an associative substitution mode was recently reported, and it was postulated that attack of the first nucleophile (cyanide) occurred at the β-(5′-deoxy-5′-adenosyl) site rather than at the α-dimethylbenzimidazole site.[18] To gain further insight into the reasons for this unexpected mechanistic changeover, since it is generally expected that the introduction of a metal−carbon bond will induce a dissociatve substitution reaction in the trans position, we have now turned to the study of model systems that include a cobalt−carbon σ-bond.

Brown et al.[19,20] reported kinetic and equilibrium data for the binding of various nitrogen ligands to methylcobaloxime.

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They also extended their work and studied different alkylcobaloximes to understand the mechanism of axial ligand substitution reactions, the relative importance of metal-to-ligand donation, and the possible existence of stable pentacoordinate species in aqueous solution.[21] The kinetics of the substitution reaction of tetra(4-N-methylpyridyl)porphinediaquacobalt(III) was studied, and it was found that the reaction of this complex with NCS^- occurs via a limiting dissociative (D) mechanism, whereas the reaction with halide ions occurs via a dissociative interchange (I_d) mechanism.[22] The simplest model for coenzyme B_{12} was synthesized by Kofod in 1995[23] and consists of a Co(III) metal center surrounded by five ammine ligands and one methyl ligand. This complex is stable in a solution of high ammonia concentration (ca. 3 M) but undergoes a rapid ligand substitution reaction with ethylenediamine (en) to form *cis*-$[Co(en)_2(Me)NH_3]^{2+}$, which slowly isomerizes to the more stable and isolatable trans isomer.[24] A potential advantage of the planar bis(ethylenediamine) arrangement around the Co(III) center is the flexibility of the chelates, an aspect that has been suggested to be important for the biological activity of the coenzyme.[25]

There is indeed a need to study ligand substitution reactions trans to the axial alkyl ligand in coenzyme B_{12} and various model complexes in comparison to all the work carried out on substitution reactions trans to nonalkyl ligands, since it is known that methylcobalamin and coenzyme B_{12} undergo substitution of their axial benzimidazole ligand with a protein histidine residue during complexation to the enzymes methionine synthase and methyl malonyl coenzyme A mutase, respectively.[26,27]

There have been some discrepancies in the literature regarding the mechanism of the axial ligand substitution reactions of vitamin B_{12}, its derivatives, and model complexes. The D mechanism is favored by some authors,[16] whereas in other reports,[17] the I_d mechanism is favored, since the incoming ligand participates in the transition state. It is well known that high-pressure kinetic techniques[28] can assist the elucidation of inorganic and bioinorganic reaction mechanisms through the calculated activation volume obtained from the pressure dependence of the rate constant. This technique was found to be very efficient in differentiating between I_d and D substitution mechanisms in Co(III) complexes.[17c−e,28,29] This has led us to study the ligand substitution reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ by applying this technique to ligands such as imidazole (ImH) and cyanide (CN^-). ImH is known to be an interesting ligand in bioinorganic chemistry for a variety of reasons, such as the presence of an ImH group of histidine as a ligand in most of the known haemoproteins,[30] and CN^- is considered one of the convenient ligands that can be used to probe both the trans effects of a second axial ligand and the cis effects of the equatorial macrocyclic ligand since it has minimum steric requirements.

In addition, this study will reveal information on the order in which equatorial ligands such as corrin, porphyrin, and cobaloximes exert remarkable cis effects on ligand substitution in the axial position.[31,32] This cis effect was demonstrated by Ponn[33] when the rate constants for the hydrolysis of $Co^{III}(N_4)$ complexes were determined and found to increase with the extent of unsaturation of the equatorial ligand, varying in the ratio of 1:36:270 as N_4 was changed from 1,4,8,11-tetraazacyclotetradecane to 1,4,8,11-tetraazacyclotetradeca-1,7-diene and to cobaloxime. A comparison of the second-order rate constant for substituting the H_2O molecule by an incoming ligand (L) in Co(III) complexes with N-donor equatorial ligands (N_4) shows that the approximate lability ratio of the metal ion toward substitution in the corrin, porphyrin, cobaloxime, and ammine complexes is 10^9:10^6:10^4:1.[17i,22,34]

Experimental Section

Materials. All chemicals used were p.a. grade and used as received without further purification. CAPS buffer was purchased from Sigma. $NaClO_4$ and NaCN were purchased from Merck. ImH was supplied by Aldrich. Ultrapure water was used for all measurements. All preparations and measurements were carried out in diffuse light, since the complex was found to be light sensitive.

trans-$[Co(en)_2(Me)NH_3]S_2O_6$ was prepared as described by Kofod[35] by reacting Co(II) nitrate with methylhydrazine in the presence of NH_3 to give $[Co(NH_3)_5Me](NO_3)_2$ and then reacting this complex with ethylenediamine to give *cis*-$[Co(en)_2(Me)NH_3]^{2+}$, which was isomerized slowly to give *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ and then isolated in the solid form as *trans*-$[Co(en)_2(Me)NH_3]S_2O_6$. This complex, upon dissolving in buffer solutions, gives *trans*-$[Co(en)_2(Me)H_2O]^{2+}$. The complexes were charaterized by elemental analysis and UV−vis and NMR spectroscopy, and the results were in agreement with literature data.[35]

Instrumentation. The pH of the solution was measured using a Mettler Delta 350 pH meter. The pH meter was calibrated with standard buffer solutions at pH 4 and 7. UV−vis spectra were recorded on Shimadzu UV-2101 or Cary 1 spectrophotometers.

Kinetic measurements were carried out on an Applied Photophysics SX 18MV stopped-flow instrument coupled to an online data acquisition system. At least eight kinetic runs were recorded under all conditions, and the reported rate constants represent the mean values. All kinetic measurements were carried out under pseudo-first-order conditions, i.e., the ligand concentration was in at least 10-fold excess. Measurements at high pressure were carried out using a homemade high-pressure stopped-flow unit.[36] The kinetic data were analyzed with the OLIS KINFIT program. All instruments were thermostated to the desired temperature (±0.1 °C).

Potentiometric titrations were carried out to determine the pK_a for $[Co(en)_2(Me)H_2O]^{2+}$. A 2.5×10^{-3} M sample of this complex ($I = 0.1$ M $NaClO_4$) was titrated with $HClO_4$ (3.85×10^{-3} M) at 25 °C.

Equilibrium Measurements. A $1-5 \times 10^{-3}$ M sample of $[Co(en)_2(Me)NH_3]S_2O_6$, dissolved in CAPS or phthalate buffer ($I = 0.1$ M using $NaClO_4$), was placed in a 1.0 cm path length cuvette in the themostated

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cell block of the spectrophotometer for 20−30 min. This solution was titrated by the addition of small volumes of a concentrated stock solution of the ligand, using a Hamilton syringe. The ligand solution was prepared in the same buffer, and the ionic strength was also adjusted to 0.1 M using $NaClO_4$. The titrations were carried out in duplicate and were monitored at several wavelengths where the largest change in absorbance occurred. The values of the equilibrium constant, K, were obtained by fitting the absorbance versus concentration curve, after correction for dilution, to the appropriate equation (see Results and Discussion).

Results and Discussion

The UV−vis spectrum of *trans*-$[Co(en)_2(Me)NH_3]S_2O_6$ dissolved in different buffers at pH 5−11 showed bands at 364 and 470 nm (134 and 80 M^{-1} cm^{-1}, respectively). However, in pure NH_3 solution, these bands are located at 354 and 463 nm (142 and 63 M^{-1} cm^{-1}, respectively), with a shoulder at 290 nm (171 M^{-1} cm^{-1}). These observations suggest that the complex under investigation has an aqua ligand in the trans position when it is dissolved in aqueous buffers, whereas an NH_3 ligands is coordinated trans to the methyl group when the complex is dissolved in high ammonia concentration. This in a good agreement with the results of Kofod et al.,[35] viz., *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ in water exhibits two bands at 365 and 472 nm (137 and 74 M^{-1} cm^{-1}, respectively), and *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ in 5 M NH_3 exhibits two bands at 355 and 464 nm (133 and 56 M^{-1} cm^{-1}, respectively), with a shoulder at 289 nm (156 M^{-1} cm^{-1}).

It was found that *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ decomposes upon exposure to UV light, suggesting that the Co−C bond can be cleaved photochemically. This was observed for all Co(III) complexes containing alkyl groups coordinated to the cobalt atom in the axial position.[37] Preliminary experiments showed that decomposition of this complex by the light beam of the spectrophotometer was negligible. Despite the lower light sensitivity of this complex as compared to other alkylcobalt species, special care was taken to protect this complex from photochemical decomposition, and all solution preparations and measurements were carried out in diffuse light.

In the present study, the displacement of the axial H_2O molecule in *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ by CN^- and ImH was investigated, for which the general reaction can be represented by eq 1, where L is CN^- or ImH.

$$trans\text{-}[Co(en)_2(Me)H_2O]^{2+} + L \underset{k_b}{\overset{k_a}{\rightleftarrows}} trans\text{-}[Co(en)_2(Me)L]^{2+} + H_2O \quad (1)$$

A pH titration of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with base indicated that the pK_a value of the coordinated water molecule must be greater than 12, since there was no change observed in the pH titration curve up to pH 12. This value is in line with that expected for a weakly coordinated water molecule. Also, from the trans effect order in the case of cobalt corrinoids[37] and the kinetic and the equilibrium results of this work, we expect a pK_a value of about 14, since this complex is similar to vinyl and acetylidecobinamide (vinyl and acetylide are coordinated to the cobalt corrinoids in the axial position). Preliminary experiments in which the UV−vis spectrum was scanned at range 250−600 nm showed that at pH 6−11, CN^- and ImH react rapidly with *trans*-$[Co(en)_2(Me)H_2O]^{2+}$. In the case of CN^-, no significant difference in the spectra at pH 6 and 11 was observed, indicating that CN^- is the binding nucleophile. Equilibrium 1 was established within the time required for mixing the solutions and recording the spectra. The values of K were determined spectrophotometrically in duplicate experiments by titrating ca. 5×10^{-3} M *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with a concentrated stock solution of the ligand to minimize the effect of dilution. Figure 1 shows the spectrophotometric titration of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with CN^- at pH 6, $I =$ 0.1 M ($NaClO_4$), and 10 °C. The value of K_1 (k_a/k_b) was determined at pH 6, since the value is large and correction for the acid dissociation of HCN (pK_a = 9.04)[17b] could be made. It is clear from Figure 1 that the reaction is characterized by clean isosbestic points, indicating that a simple equilibrium exists with no sign of the interference of a second equilibrium in this pH range, such as the formation of a dicyano complex. Figure 1 also shows that there is a significant shift in the UV−vis spectrum upon formation of *trans*-$[Co(en)_2(Me)CN]^+$ with λ_{max} values at 331 and 446 nm (235 and 62 M^{-1} cm^{-1}, respectively). Kofod et al.[35] reported λ_{max} values for this complex at 332 and 445 nm (218 and 53 M^{-1} cm^{-1}, respectively), which are in close agreement with our findings. Spectral changes slightly different from those reported in Figure 1 were observed for the reaction with ImH, and λ_{max} occurred at 356 and 464 nm (123 and 64 M^{-1} cm^{-1}, respectively), with a shoulder at 292 nm (167 M^{-1} cm^{-1}).

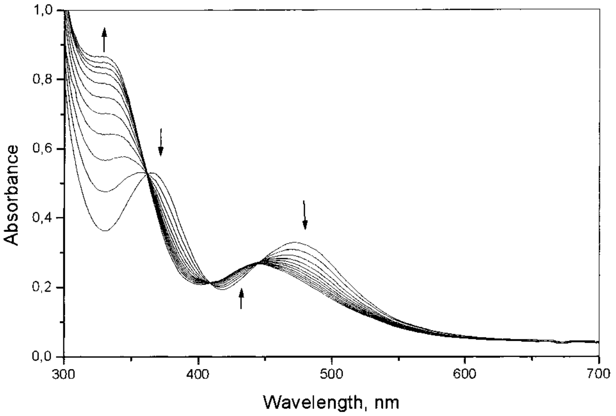

Figure 1. UV−vis spectra of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ in the presence of various concentrations (0.001−0.025 M) of CN^- at pH 6, 10 °C, and $I = 0.1$ M ($NaClO_4$).

The spectrophotometric titrations were monitored by following the increase in absorbance at 332 nm or the decrease in absorbance at 474 nm, where the largest change in absorbance occurred. Typical data for the reaction with CN^- are shown in Figure 2. The solid line represents the fit of the experimental data to eq 2

$$A_x = A_o + A_\infty K[L]/(1 + K[L]) \quad (2)$$

where A_o and A_∞ represent the absorbance at 0% and 100% formation of *trans*-$[Co(en)_2(Me)L]^{2+}$, respectively, and A_x is the absorbance at any given ligand concentration [L]. The values of K and A_∞ were calculated from nonlinear least-squares fits of the data to eq 2. The data were subsequently analyzed by plotting $\log[(A_x - A_o)/(A_\infty - A_x)]$ versus log[L], which resulted in a good linear plot with slopes of 0.95 ± 0.02 and 0.97 ± 0.03 for CN^- and ImH, respectively, indicating that only one ligand is coordinated to the cobalt complex. The intercept of this linear plot gives the value of log K, which is in excellent agreement with the directly determined value described above.

The values of K of CN^- and ImH were found to be $(8.3 \pm 0.7) \times 10^4$ and 24.5 ± 2.2 M^{-1} at 10 °C, respectively, from

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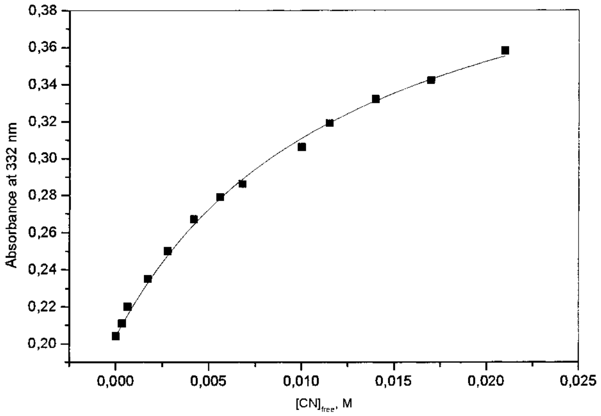

Figure 2. Changes in absorbance at 330 nm upon addition of CN^- to *trans*-$[Co(en)_2(Me)H_2O]^{2+}$. The line is a fit of the data to eq 3 in the text.

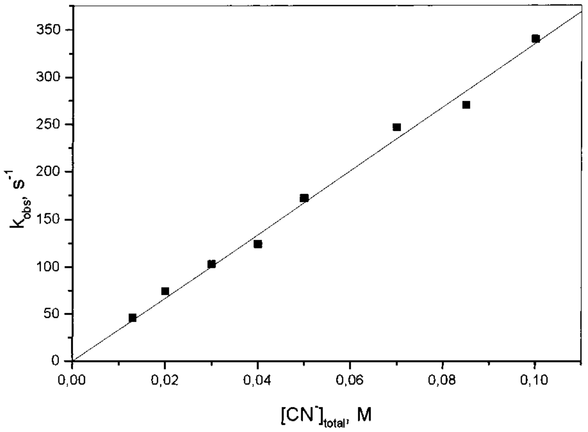

Figure 3. Plot of k_{obs} vs $[CN^-]_{total}$ for the reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and CN^- at pH 11, 10 °C, and $I = 0.1$ M ($NaClO_4$). The best fit of the data (line) gives $k = 3.3 \times 10^3$ M^{-1} s^{-1}.

which it follows that CN^- binds much stronger than ImH to this model complex. Brown et al.[2,38] found values of K for the binding of CN^- to $[Co(corrin)(Me)H_2O]^{2+}$ and $[Co(DMG)_2(Me)H_2O]$ (DMG = dimethylglyoximate) to be 84 and 0.74×10^8 M^{-1}, respectively. It follows that the affinity of CN^- for *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ is 10^3 times greater than for $[Co(corrin)(Me)H_2O]^{2+}$ and 10^3 times smaller than for $[Co(DMG)_2(Me)H_2O]^{2+}$. This comparison nicely demonstrates the cis effect, i.e., the influence of the equatorial ligand on the substitiution reaction of the axial ligand trans to the alkyl group. The trend in the formation constants for the equatorial ligands is corrin $<$ $(en)_2$ $<$ $(DMG)_2$.

Figure 3 shows a plot of k_{obs} versus $[CN^-]$ for the reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with excess CN^- at pH 11 ($[CN^-] = 0.01-0.10$ M, $I = 0.1$ M using $NaClO_4$). The linear plot has a negligible intercept, which indicates that the back reaction does not contribute significantly and that no parallel reaction takes place. The reaction is pseudo-first-order in $[CN^-]$ and has a second-order rate constant of $(3.3 \pm 0.1) \times 10^3$ M^{-1} s^{-1} at 10 °C. This behavior can be expressed by the rate law in eq 3, where L represents CN^-.

$$k_{obs} = k_a[L] \qquad (3)$$

It was found that the second-order rate constant for the reaction between *trans*-$[Co(DMG)_2(Me)H_2O]$ and CN^- is 14 M^{-1} s^{-1},[1] but it was impossible to determine the rate constant for the reaction of CN^- or any nitrogen bases with $[Co(corrin)(Me)H_2O]^+$ because the reaction is too fast to be followed by stopped-flow or temperature-jump techniques.[39] Thus, the order of reactivity of the complexes for the different equatorial ligands is corrin $>$ $(en)_2$ $>$ $(DMG)_2$.

Table 1. Kinetic Data for the Reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with CN^- as a Function of Temperature[a]

T (°C)	$k_a \times 10^{-3}$ (M^{-1} s^{-1})
5.0	2.7 ± 0.1
10.0	3.5 ± 0.2
15.0	5.7 ± 0.3
20.0	8.3 ± 0.3
$\Delta H^{\ddagger}$(kJ mol^{-1})	50 ± 4
$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})	0 ± 15

[a] Experimental conditions: $[Co(en)_2(Me)OH_2] = 1.2 \times 10^{-3}$ M, pH 11, $I = 0.1$ M ($NaClO_4$).

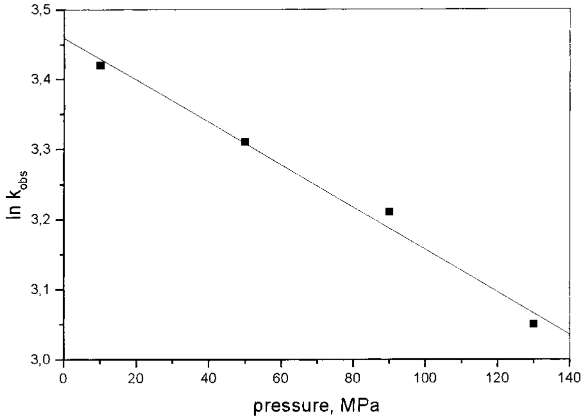

Figure 4. Plot of ln k_{obs} vs pressure for the reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and CN^-. The best fit of the data (line) gives $\Delta V^{\ddagger} = 7.0 \pm 0.6$ cm^3 mol^{-1}.

Costa and co-workers[11,12] attempted to quantitatively order the alkylcobalt chelate complexes in terms of the electrochemical potentials for the reduction of $[Co(chel)R]^{n+}$ to $[Co(chel)R]^{(n-1)+}$ and obtained this order of increasing ease of reduction: N,N′-ethylenebis(acetylaceteneiminato) (bae) $<$ N,N′-ethylenebis(α-methylsalicylideneiminato) $<$ N,N′-ethylenebis(salicylideneiminato) $<$ O-phenylenebis(salicylideneiminato) $<$ cobalamin $<$ bis(dimethylglyoximato) $<$ 1-(diacetylmonooximeiminato)-3-(diacetylmonooximatoiminato)propane.[11,12] This order should also be reflected by the kinetics of ligand exchange on the Co(chel)(R)L complexes if it accurately reflects the relative degree of electron donation of the equatorial chelate to the metal center. It is known that the strongly electron-donating ligands (such as bae) are expected to more easily form a pentacoordinate alkylcobalt complex[37] and exhibit faster axial ligand exchange than the more weakly donating chelate $(DMG)_2$. Further work on saturated amines as equatorial ligands is needed to obtain a complete picture of the cis effect or the role of the equatorial ligands on the reactivity and mechanism of these ligand substitution reactions.

The reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and CN^- was studied as a function of temperature and pressure, for which the results are reported in Table 1 and Figure 4, respectively. Good linear correlations between ln(k/T) versus $1/T$ and between ln k versus pressure were obtained. The activation parameters

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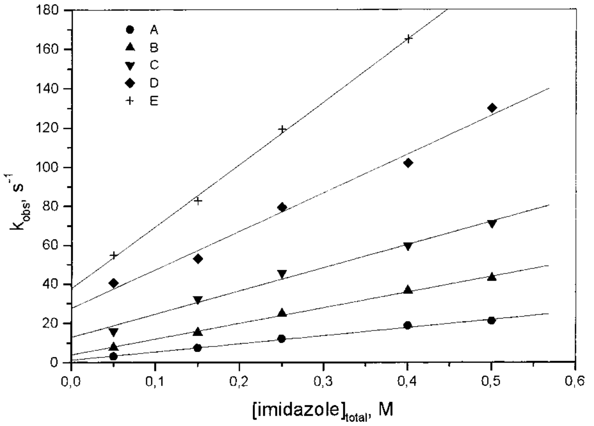

Figure 5. Plot of k_{obs} vs [ImH] for the reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and imidazole as a function of temperature. Experimental conditions: [Co(III)] = 0.003 M, pH 9, $I = 0.1$ M ($NaClO_4$), and $T = 5.0$ °C (A), 12.0 °C (B), 18.0 °C (C), 25.0 °C (D), and 30.0 °C (E).

Table 2: Kinetic Data for the Reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with ImH as a Function of Temperature[a]

T (°C)	k_a ($M^{-1}\,s^{-1}$)	k_b (s^{-1})
5.0	41 ± 2	1.4 ± 0.6
12.0	80 ± 3	4.0 ± 0.8
18.0	119 ± 8	13 ± 2
25.0	198 ± 13	28 ± 4
30.0	319 ± 10	38 ± 2
$\Delta H^‡$ (kJ mol^{-1})	53 ± 2	94 ± 8
$\Delta S^‡$ (J $K^{-1}\,mol^{-1}$)	−22 ± 7	+97 ± 27

[a] Experimental conditions: $[Co(en)_2(Me)OH_2] = 5 \times 10^{-3}$ M, pH 9, $I = 0.1$ M ($NaClO_4$).

$\Delta H^‡$, $\Delta S^‡$, and $\Delta V^‡$ were found to be 50 ± 4 kJ mol^{-1}, 0 ± 16 J K^{-1} mol^{-1}, and +7.0 ± 0.6 cm^3 mol^{-1}, respectively.

The reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and excess ImH at pH 9 ([ImH] = 0.05−0.50 M, $I = 0.1$ M using $NaClO_4$) was studied at different temperatures. The results are shown in Figure 5, from which good linear plots with significant intercepts are obtained within the experimental error limits. Furthermore, the plots do not indicate any saturation at large [ImH]. This behavior can be expressed by the rate law given in eq 4, where k_a and k_b represent the rate constants for the forward and reverse reactions in eq 1, respectively, and L represents ImH. The values of k_a and k_b can be used to calculate K ($K = k_a/k_b$), which turns out to be 20.1 ± 3.2 M^{-1} at 12 °C. This kinetically determined value for K is in good agreement with that obtained spectrophotometrically at the same temperature, viz. $K = 24.5 \pm 2.2$ M^{-1}. The values of k_a and k_b as functions of temperature, along with the corresponding activation parameters, are summarized in Table 2.

$$k_{obs} = k_a[L] + k_b \qquad (4)$$

From a comparison of the values of k_a for the reactions of CN^- and ImH with *trans*-$[Co(en)_2(Me)H_2O]^{2+}$, viz., 3.3×10^3 M^{-1} s^{-1} (at 10 °C) and 198 M^{-1} s^{-1} (at 25 °C), respectively, it is seen that CN^- is a much stronger nucleophile, as expected. The difference in the complex-formation constant K, viz., 8.3×10^4 and 24.5 M^{-1} for CN^- and ImH, respectively, is even 2 orders of magnitude larger due to the significant effect of k_b, the reverse aquation reaction, in the ImH complex.

The high lability of coordinated water in *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ is also expressed by the relatively low and very similar activation enthalpies for the substitution by CN^- and ImH, as compared to the much higher activation enthalpy for the reaction of the ImH complex (i.e., back reaction for the complex formation with ImH). The entropies of activation for the complex-formation reactions were found to be 0 ± 16 and −22 ± 7 J K^{-1} mol^{-1} for CN^- and ImH, respectivly. It is known that $\Delta S^‡$ is usually subjected to large error limits because of the intrinsic extrapolation involved in its determination such that these small absolute numbers are not very significant in terms of the assignment of a mechanism.[41] A significantly more positive value was found for the reverse aquation reaction of the ImH complex, pointing to a dissociative activated transition state.

Table 3: Kinetic Data for the Reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with ImH as a Function of Pressure at 10 °C[a]

P (MPa)	[ImH] (M)	k_{obs} (s^{-1})	k_a ($M^{-1}\,s^{-1}$)	k_b (s^{-1})
10	0.05	5.34	51.5 ± 0.7	2.9 ± 0.2
	0.15	10.9		
	0.25	15.8		
	0.40	23.5		
50	0.05	4.8	47.5 ± 1.8	2.8 ± 0.5
	0.15	10.4		
	0.25	14.5		
	0.40	21.7		
90	0.05	4.36	44.2 ± 0.8	2.3 ± 0.2
	0.15	9.13		
	0.25	13.5		
	0.40	19.9		
130	0.05	4.11	40.4 ± 0.5	2.1 ± 0.1
	0.15	8.19		
	0.25	12.4		
	0.40	18.2		
$\Delta V^‡$ ($cm^3\,mol^{-1}$)			+4.7 ± 0.1	+6.4 ± 0.9

[a] Experimental conditions: $[Co(en)_2(Me)OH_2] = 5 \times 10^{-3}$ M, pH 9, 10 °C, $I = 0.1$ M ($NaClO_4$).

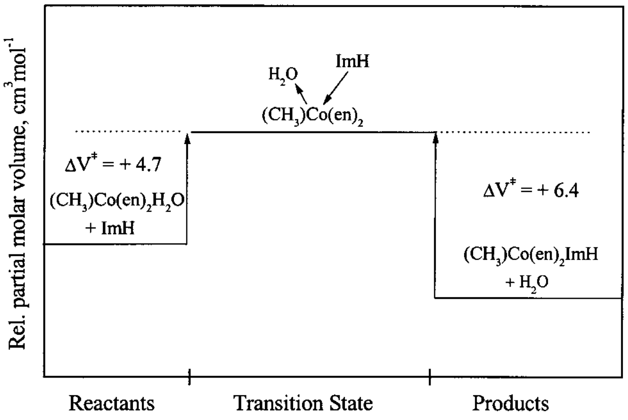

Figure 6. Volume profile for the reaction *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ + ImH $\rightleftarrows$ *trans*-$[Co(en)_2(Me)ImH]^{2+}$ + H_2O.

The pressure dependence of the reaction with ImH was investigated as a function of [ImH], and the data are summarized in Table 3. Plots of ln k_a and ln k_b versus pressure give good linear relationships from which $\Delta V^‡$ was calculated. From $\Delta V^‡$, it is possible to construct a volume profile for the substitution of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ by ImH (see Figure 6), from which it can be seen that the substitution process is dissociatively

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activated. Similar results were reported for reactions of aquacobalamin with different ligands such as HN_3, N_3^-, pyridine and its derivatives, and thiourea and its derivatives.[17c−e] In these cases, $\Delta V^\ddagger$ was found to be in the range between +4 and +8 $cm^3\ mol^{-1}$, i.e., similar to the values found for the reactions of CN^- and ImH with *trans*-$[Co(en)_2(Me)H_2O]^{2+}$, and $\Delta V^\ddagger$ was interpreted in terms of an I_d mechanism. These values are signficantly smaller than those reported for substitution reactions of cobalt(III) porphyrin systems. There it was found that the values of $\Delta V^\ddagger$ for ligand substitution on $[Co(TMPP)(H_2O)_2]^{5+}$ and $[Co(TPPS)(H_2O)_2]^{3-}$, where TMPP = meso-tetrakis(4-N-methylpyridyl)porphine and TPPS = meso-tetrakis(p-sulfonatophenyl) porphine, are +14.4 and +15.4 $cm^3\ mol^{-1}$, respectively,[29,40] and these were assigned to a D mechanism. The volumes of activation in this study are also significantly smaller than those reported for the reaction of $[Co(NH_3)_5(CH_3)]^{2+}$ with ethylenediamine in forming *cis*-$[Co(en)_2(NH_3)(CH_3)]^{2+}$, as well as those for the subsequent cis-to-trans isomerization reaction, for which I_d mechanisms were suggested.[24] It follows from this comparison that the introduction of a single cobalt−carbon bond significantly labilizes the coordinated water molecule in *trans*-$[Co(en)_2(Me)H_2O]^{2+}$, as reflected by its high pK_a value, but apparently does not induce a limiting D mechanism on the basis of the reported $\Delta V^\ddagger$ data (see Results and Discussion).

Thus, on the basis of the volume of activation data and the constructed volume profile, it is reasonable to conclude that the reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with ImH and CN^- follows an I_d mechanism, where the entering nucleophile partially participates in the transition state. The volume changes during the complex-formation reaction are controlled by the lengthening of the Co−H_2O bond, which should be independent of L. The reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and L is presented in eq 5, and the corresponding expression for k_{obs} is given in eq 6

$$trans\text{-}[Co(en)_2(Me)H_2O]^{2+} + L \overset{K_1}{\rightleftharpoons} [Co(en)_2(Me)H_2O]^{2+}\cdot L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} trans\text{-}[Co(en)_2(Me)L]^{2+} + H_2O \quad (5)$$

$$k_{obs} = k_2K_1[L]/(1 + K[L]) + k_{-2} \quad (6)$$

$$k_{obs} = k_2K_1[L] + k_{-2}$$
$$= k_a[L] + k_b \quad (7)$$

The plots of k_{obs} versus [L] are linear within the experimental error limits, indicating that $(1 + K_1[L]) \approx 1$; eq 6 reduces to eq 7, which is in agreement with the empirical rate law of eq 4, where $k_a = k_2K_1$ and $k_b = k_{-2}$. Thus, $\Delta V^\ddagger(k_a) = \Delta V^\ddagger(k_2) + \Delta V(K_1)$, from which it follows that the volume changes associated with $\Delta V^\ddagger(k_2)$ and $\Delta V(K_1)$ contribute to the overall observed value. It is reasonable to expect that $\Delta V(K_1)$ will be somewhat negative,[28,41] depending on the nature of the precursor species formed. On the other hand, $\Delta V^\ddagger(k_2)$ will be positive for an I_d mechanism such that these volume contributions will partially cancel each other to account for the observed value.

However, the possibility of a limiting D mechanism cannot be fully ruled out on the basis of the volume of activation data. Since all observations point to a very labile coordinated water molecule, the ground state trans influence of the methyl group could be so significant that only a relatively small bond lengthening is required to reach the transition state, which will lead to a relatively low value of $\Delta V^\ddagger$. Furthermore, the fact that no limiting rate constant typical for a D mechasnism is reached upon increasing the entering nucleophile concentration (see Figures 3 and 5) cannot be taken as evidence against the existence of a D mechanism, since the limiting rate constant is expected to be very high for the dissociation of a labile water molecule and will most probably not lie in the stopped-flow time range. In terms of the limiting dissociative mechanism outlined in eq 8, the rate law in the absence of any deviation from a linear dependence of k_{obs} on [L] is given in eq 9.

$$trans\text{-}[Co(en)_2(Me)H_2O]^{2+} \rightleftharpoons [Co(en)_2(Me)]^{2+} + H_2O \qquad k_3,k_{-3}$$

$$[Co(en)_2(Me)]^{2+} + L \rightleftharpoons [Co(en)_2(Me)L]^{2+} \qquad k_4,k_{-4} \quad (8)$$

$$k_{obs} = (k_3k_4[L] + k_{-3}k_{-4})/(k_4[L] + k_{-3})$$
$$= k_3k_4[L]/k_{-1} + k_{-4} \quad (9)$$

According to this rate law, $k_a = k_3k_4/k_{-4} = k_3K_4$ such that $\Delta V^\ddagger(k_a) = \Delta V^\ddagger(k_3) + \Delta V(K_4)$. In this case, the volume changes associated with $\Delta V^\ddagger(k_3)$ and $\Delta V(K_4)$ are also expected to partially cancel each other, since $\Delta V^\ddagger(k_3)$ must be significantly positive, ca. 13 $cm^3\ mol^{-1}$, for the dissociation of a water molecule from an octahedral complex and $\Delta V(K_4)$ must be negative for the binding of L.[28,41] Thus, on the basis of the observed volumes of activation, it is not possible to distinguish between an I_d and a D mechanism in this particular case. We can only conclude that significant bond breakage must occur in the transition state, giving it a dissociative character. Weak bond formation with the entering nucleophile in the transition state cannot be ruled out.

By way of comparison, $\Delta V^\ddagger$ data have been reported for complex-formation and ligand substitution reactions in *trans*-$[Rh(DMG)_2(R)H_2O]$, where DMG = dimethylglyoximate and R = CH_3, CH_2Cl, and CF_3CH_2.[42] The data showed a systematic changeover in mechanism from I_d to I_a, i.e., from small positive to small negative volumes of activation along the series of R, as a result of a decrease in the σ-donor property of R. Similar substitution reactions on *trans*-$Co(DMG)_2(CH_3)L$, where L is, for instance, MeOH, Me_2NCHO, Me_2NCHS, Me_2S, or $(MeO)_3P$, exhibit typical $\Delta V^\ddagger$ data of between 6.8 and 16.8 $cm^3\ mol^{-1}$, depending on the size of the leaving group L, in line with a dissociative mechanism.[43]

Furthermore, the I_d mechanism suggested above contradicts the D mechanism favored in cases such as those for the reaction of methylaquacobaloxime with thiols.[3] The operation of a D mechanism was also supported by the presence of five-coordinate species that result from the stabilizing Co−C bond in the Co(III) complexes of bis(salicylaldehyde)ethylenediamine and bis(acetylacetone)ethylenediamine prepared by Costa and co-workers[13,14] and from the crystal structure of pentacoordinate methyl derivatives of these complexes.[44,45] Evidence for the existence of pentacoordinate species among the alkylcobinamides and alkylcobalamins was also found from the temperature dependence of UV−vis and pmr spectra.[46] This evidence

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for the operation of a D mechanism was presented for cobaloxime and corrinoids, where there is a delocalization of electron density from the unsaturated equatorial ligands (DMG and corrin) onto the Co(III) center. This would, in part, induce a partial Co(II) character onto the metal center and could account for the higher kinetic lability and the longer axial bond length to the Co(III) center. However, in the system investigated here, the chelate is fully saturated, and hence, an I_d mechanism, characteristic for Co(III) substitution reactions, could be the more likely mechanism. The reason for the operation of an associative substitution mechanism in coenzyme B_{12} remains unresolved[18] and requires further clarification.

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