Equilibrium, Kinetic and Leaving Group Effect Studies on Ligand Substitution Reactions of a Simple Model for Coenzyme B_{12}

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The ligand substitution reactions of *trans*-$[Co^{III}(en)_2(Me)H_2O]^{2+}$ and *trans*-$[Co^{III}(en)_2(Me)NH_3]^{2+}$ were studied for CN^-, SCN^-, N_3^-, and NH_3 as entering nucleophiles. These nucleophiles displace the coordinated H_2O and NH_3 molecules *trans* to the methyl group and form the six-coordinate complex *trans*-$[Co(en)_2(Me)L]$. The complex-formation constant for the displacement of H_2O by NH_3 was found to be 17.4 ± 1.1 M^{-1} at 20 °C, and those for the displacement of NH_3 by SCN^- and N_3^- were found to be 4.4 ± 1.5 and 3.1 ± 0.4 at 10 °C, respectively. From temperature and pressure dependence studies, activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta V^{\neq}$) for the reaction of *trans*-$[Co^{III}(en)_2(Me)H_2O]^{2+}$ with NH_3 were found to be 62 ± 1 kJ mol^{-1}, +3 ± 5 J K^{-1} mol^{-1} and +5.7 ± 0.3 cm^3 mol^{-1}, respectively, compared to 79 ± 2 kJ mol^{-1}, +40 ± 6 J K^{-1} mol^{-1} and +9.0 ± 0.4 cm^3 mol^{-1} for the reverse aquation reaction of *trans*-$[Co^{III}(en)_2(Me)NH_3]^{2+}$. Based on the reported kinetic and activation parameters, the substitution of coordinated H_2O by NH_3 follows an I_d mechanism in which the entering nucleophile participates in the transition state. The substitution of NH_3 by SCN^-, N_3^- and CN^- proceeds via the intermediate aqua complex such that aquation of the amine complex becomes the rate-determining step at high entering ligand concentration. A detailed comparison with available data in the literature is made.

Introduction

Model complexes for vitamin B_{12} have played an important role in understanding the behavior of the ligand substitution reactions of vitamin B_{12} and the role of the Co−C bond in the coenzyme vitamin B_{12}.[1,2] Many octahedral organometallic complexes of Co^{III}, such as cobaloxime[2−10] and Costa's complex[11] (a mixed Schiff base/oxime complex with a uni-negative N_4 equatorial ligand), those with a Schiff base,[12,13] *N,N′*-ethylenebis(actylacetoneiminato),[14] *N,N′*-ethylenebis(salicylideneiminato)[15] and the dianion of disalicylidene-*O*-phenylenediamine[15] as ligands, have been suggested as models for the vitamin B_{12} coenzyme, to mimic either the nature of the active site or a specific function of the enzyme. These model complexes have shown that the ligand in the *trans* position to the Co−C bond can affect the kinetics and thermodynamic stability of this bond.[16] We recently studied the reaction of cyanide with different alkylcobalamins (RCbl, where R = CF_3, CF_3CH_2, CF_2H, CH_3, CH_2Br) and found that the nature of the alkyl group has an influence on the thermodynamic equilibrium constants, kinetics and mechanism of the substitution reactions of the axial ligand *trans* to the alkyl group.[17]

The simplest model for coenzyme B_{12} was synthesized by Kofod in 1995[18] and consists of a Co^{III} metal center surrounded by five ammine groups and one methyl group as ligands. This complex is only stable in aqueous solution in the presence of a high ammonia concentration (ca. 3 M). We recently suggested that the $[Co(NH_3)_5(Me)]^{2+}$ cation is not favored in being used as a model for vitamin B_{12} due to the necessary presence of a high ammonia concentration and the unfavorable pH.[19] $[Co(NH_3)_5(Me)]^{2+}$ 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 isolable *trans* isomer.[19] The kinetic and activation parameters for the displacement of the four ammonia ligands by two ethylenediamine (en) chelates confirmed the operation of a limiting dissociative reaction mechanism under limiting concentration conditions. The activation parameters also confirmed the operation of a dissociative mechanism for the subsequent *cis* to *trans* isomerization reaction.

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.[20] We studied the ligand substitution reactions of *trans*-$[Co^{III}(en)_2(Me)H_2O]^{2+}$ with CN^- and imidazole. Activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta V^{\neq}$) for the reaction of *trans*-$[Co^{III}(en)_2(Me)H_2O]^{2+}$ with cyanide were found to be 49 ± 4 kJ mol^{-1}, −38 ± 15 J K^{-1} mol^{-1} and +7.0 ± 0.6

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cm^3 mol^{-1}, respectively, compared to 53 ± 2 kJ mol^{-1}, −22 ± 7 J K^{-1} mol^{-1} and +4.7 ± 0.1 cm^3 mol^{-1} for the reaction with imidazole.[21] Based on the reported activation volumes, these reactions follow a dissociative (interchange dissociative, I_d, or limiting dissociative, D) mechanism in which the entering nucleophile could be weakly bound in the transition state.[21] By way of comparison, ligand substitution reactions of vitamin B_{12} in general follow a dissociative (I_d or D) type of mechanism.[22−36] In the case of the coenzyme, however, evidence for an associative substitution mode was reported.[37] In order to gain further insight into the reasons for this unexpected mechanistic changeover, we have now investigated substitution reactions of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ to study the effect of the leaving group on the axial ligand substitution mechanism of these model complexes that include a cobalt−carbon σ-bond. These complexes allow us to mimic the active site of the coenzyme since the ammine ligand *trans* to the Co−Me bond represents the dimethylbenzimidazole moiety in the coenzyme.

Results and Discussion

As mentioned before, the pK_a value of coordinated water in *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ is higher than 12, since there was no change observed in the pH titration curve up to that pH.[21] Furthermore, 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 most of the Co^{III} complexes containing alkyl groups coordinated to the cobalt atom in the axial position.[16] 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 alkylcobalamins, special care was taken to protect this complex from photochemical decomposition.

In the present study, we investigated the displacement of the axial H_2O molecule in *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ by NH_3 in order to make comparisons with our earlier study on the reactions of cyanide and imidazole with this complex.[21] Subsequently, we investigated the displacement of NH_3 in *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ by SCN^-, N_3^- and CN^-, in order to obtain more information on leaving group effects in such systems. The investigated reaction is shown in Equation (1), where X = H_2O for L = NH_3, and X = NH_3 for L = CN^-, SCN^-, N_3^-.

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

Reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with NH_3

Equilibrium Measurements

The UV/Vis spectrum of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ in buffers at pH = 11 shows characteristic bands at 364 (125 M^{-1} cm^{-1}) and 472 nm (74 M^{-1} cm^{-1}). Addition of NH_3 shifts the bands to 354 (133 M^{-1} cm^{-1}) and 464 nm (67 M^{-1} cm^{-1}) with a shoulder at 290 nm (166 M^{-1} cm^{-1}). These changes in the UV/Vis spectra are accompanied by distinct isosbestic points, indicating that a simple equilibrium exists under these conditions. These observations suggest that the aqua ligand in the *trans* position to the methyl group is displaced by ammonia to form the six-coordinate *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ complex.

Preliminary experiments in which the UV/Vis spectrum was scanned in the range 250 to 600 nm, showed that at pH = 11, NH_3 reacts rapidly with *trans*-$[Co(en)_2(Me)H_2O]^{2+}$. Equilibrium (1) was established within the time required for mixing the solutions and recording the spectra. The values of the overall equilibrium constant K were determined spectrophotometrically (in duplicate experiments) by titrating ca. 3×10^{-3} M *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ (I = 0.1 M, $NaClO_4$) with a concentrated stock solution of NH_3 to minimize dilution effects.

The spectrophotometric titration of NH_3 was monitored by following the increase in absorbance at 326 nm or the decrease in absorbance at 380 nm, where the largest change in absorbance occurred. Typical data for the reaction with NH_3 are shown in Figure 1. The solid line represents the fit of the experimental data to Equation (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].

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

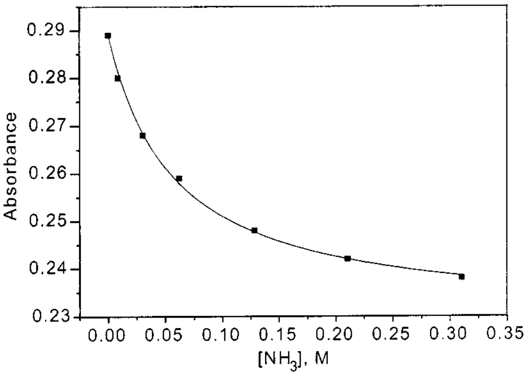

Figure 1. Changes in absorbance at 380 nm on addition of NH_3 to *trans*-$[Co(en)_2(Me)H_2O]^{2+}$; the solid line is a fit of the data to Equation (2) in the text

The values of K and A_∞ were calculated from a non-linear least-squares fit of the data to Equation (2). The data were subsequently also analyzed by plotting log $(A_x - A_o)/(A_\infty - A_x)$ versus log[L], which resulted in a linear plot with slope of 0.99 ± 0.06 for NH_3, indicating that only one ligand (L) is coordinated to the cobalt complex. The intercept of the linear plot gives the value of log K, which is in excellent agreement with the directly determined value described above.

The value of $K(NH_3)$ was found to be 17.4 ± 1.1 M^{-1} at 20 °C. The value of K for the binding of NH_3 to $[Co(corrin)(Me)H_2O]^{2+}$ was reported to be 0.1 M^{-1},[38] from which it follows that the affinity of NH_3 for *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ is almost 200 times higher than for $[Co(corrin)(Me)H_2O]^{2+}$. This comparison demonstrates the *cis* effect, i.e. the influence of the equatorial ligand on the substitution reaction of the axial ligand *trans* to the alkyl group. The observed trend in the formation constants for the equatorial ligands is corrin < $(en)_2$.

Kinetic Measurements

The reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and excess NH_3 at pH = 11 ($[NH_3]$ = 0.1 to 1.25 M, I = 0.1 M using $NaClO_4$) was studied at different temperatures. The results are shown in Figure 2, from which it follows that good linear plots with significant intercepts are obtained within the experimental error limits. Furthermore, the plots do not indicate any saturation at high $[NH_3]$ values. This behavior can be expressed by the rate law given in Equation (3), where k_a and k_b represent the rate constants for the forward and reverse reactions in Equation (1), respectively, L represents NH_3 and X is H_2O (the concentration of water is a constant and taken into k_b). It should be noted that the intercepts in Figure 2 are subjected to large error limits and an alternative procedure was used to determine the rate constant for the reverse reaction more accurately (see further Discussion). The values of k_a and k_b as a function of temperature, along with the corresponding activation parameters are summarized in Table 1.

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

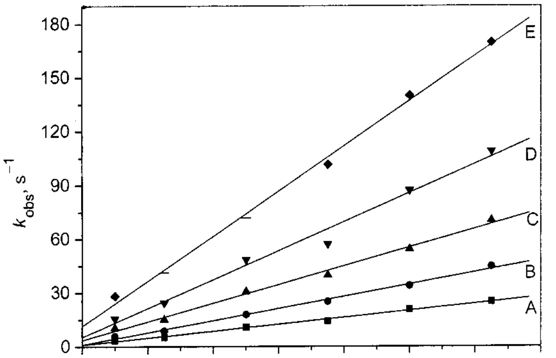

Figure 2. Plot of k_{obs} versus $[NH_3]$ for the reaction between *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ and NH_3 as a function of temperature; experimental conditions: $[Co^{III}]$ = 0.0045 M, pH = 11, I = 0.1 M $NaClO_4$ and temperature = 5.0 (A), 10.0 (B), 15.0 (C), 20.0 (D) and 25.0 °C (E)

The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for the forward reaction (k_a) were found to be 62 ± 1 kJ mol^{-1} and 3 ± 5 J K^{-1} mol^{-1}, respectively, whereas those for the reverse reaction (k_b) were found to be 85 ± 13 kJ mol^{-1} and 60 ± 43 J K^{-1} mol^{-1}, respectively.

Table 1. Kinetic data for the reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with NH_3 as a function of temperature (experimental conditions see footnotes)

T [°C]	k_a [M^{-1} s^{-1}][a]	k_b [s^{-1}][b]	k_b [s^{-1}][c]
5.0	19.1 ± 0.8	1.0 ± 0.6	1.33 ± 0.03
10.0	33.6 ± 1.3	1.1 ± 1.0	2.28 ± 0.06
15.0	51.8 ± 2.1	3.5 ± 1.6	4.45 ± 0.04
20.0	82.2 ± 5.4	4.7 ± 4.1	7.5 ± 0.6
25.0	125.5 ± 3.7	11.5 ± 2.8	13.8 ± 0.9
$\Delta H^{\neq}$ [kJ mol^{-1}]	62 ± 1	85 ± 13	79 ± 2
$\Delta S^{\neq}$ [J K^{-1} mol^{-1}]	+3 ± 5	+60 ± 43	+40 ± 6

[a] $[Co(en)_2(Me)H_2O]$ = 4.5 × 10^{-3} M, pH = 11, I = 0.1 M $NaClO_4$. [b] Values were calculated from the intercepts in Figure 2. [c] Values were calculated from the direct reaction of 9 × 10^{-3} M $[Co(en)_2(Me)NH_3]^{2+}$ in the presence of 0.3 M NH_3, at pH = 11 and 0.1 M $NaClO_4$, with 0.5 M HCl.

We determined the rate and activation parameters for the aquation (k_b) of *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ (in the presence of 0.3 M NH_3) directly by treating this amine complex with 0.5 M HCl to protonate ammonia to form *trans*-$[Co(en)_2(Me)H_2O]^{2+}$. This reaction was found to be independent of the acid concentration as long as the acid is in excess under the selected conditions, and the results for k_b are included in Table 1. The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were found to be 79 ± 2 kJ mol^{-1} and 40 ± 6 J K^{-1} mol^{-1}, respectively, and are more accurate than those determined from the intercepts of Figure 2.

The values of k_a and k_b can be used to calculate K (= k_a/k_b), which turns out to be 11.0 ± 1.6 M^{-1} at 20 °C. The kinetically determined value of K is in close agreement with that obtained spectrophotometrically at the same temperature, viz. 17.4 ± 1.1 M^{-1}.

The high lability of coordinated water in *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ is also seen in the relatively low activation enthalpy for the substitution by NH_3, as compared to the higher activation enthalpy for the aquation reaction of the ammonia complex (i.e. back reaction). The value of the activation enthalpy for the reaction with NH_3 (63 ± 1 kJ mol^{-1}) is close to that obtained previously[21] for the reaction with CN^- and imidazole (50 ± 4 kJ mol^{-1} and 53 ± 2 kJ mol^{-1}, respectively). The activation entropy for the formation of *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ was found to be close to zero, compared to a significantly positive value for the back reaction. It is known that $\Delta S^{\neq}$ is usually subjected to large error limits because of the intrinsic extrapolation involved in its determination, such that small absolute numbers are not very significant in terms of the assignment of a mechanism.[39] The significantly positive value found for the reverse aquation reaction, points to a dissociatively activated transition state.

The pressure dependence of the reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with NH_3 was investigated and the data are summarized in Table 2. Plots of ln k_a versus pressure gave a good linear plot from which $\Delta V^{\neq}$ was found to be +5.7 ± 0.3 cm^3 mol^{-1}. The pressure dependence of the aquation reaction of *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ (in the

Table 2. Kinetic data for the reaction of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with NH_3 as a function of pressure at 5 °C (experimental conditions see footnotes)

p [MPa]	k_a [M^{-1} s^{-1}][a][b]	k_b [s^{-1}][c]
10	3.88 ± 0.16	1.74 ± 0.04
50	3.43 ± 0.22	1.50 ± 0.01
90	3.08 ± 0.12	1.25 ± 0.02
130	2.73 ± 0.22	1.10 ± 0.04
$\Delta V^{\neq}$ [cm^3 mol^{-1}]	+5.7 ± 0.3	+9.0 ± 0.4

[a] $[Co(en)_2(Me)H_2O] = 4.5 \times 10^{-3}$ M, $[NH_3] = 1.5$ M, pH = 11, 5 °C, $I = 0.1$ M $NaClO_4$. [b] Calculated from the equation: $k_{obs} = k_b + k_a[NH_3]$. [c] Determined from the reaction of 1.8×10^{-2} M $[Co(en)_2(Me)NH_3]^{2+}$ in the presence of 0.3 M NH_3 at pH = 11, 0.1 M $NaClO_4$ and 5 °C, with 0.5 M HCl.

presence of 0.3 M NH_3) was also investigated by the direct reaction of 1.8×10^{-2} M $[Co(en)_2(Me)NH_3]^{2+}$ with 0.5 M HCl to protonate the ammonia. A plot of ln k_b versus pressure gave a good linear relationship, from which $\Delta V^{\neq}$ was calculated to be +9.0 ± 0.4 cm^3 mol^{-1} (the data are summarized in Table 2; see Supporting Information, Figure S-1). From the values of $\Delta V^{\neq}$ it is possible to construct a volume profile for the substitution of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ by NH_3 (see Figure 3), from which it can be concluded that the substitution process is dissociatively activated, since the transition state has a significantly higher partial molar volume than the reactant state. Similar results were reported for reactions of *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ with CN^- and imidazole[21] and also for the reaction of aquacobalamin with different ligands such as HN_3, N_3^-, pyridine and its derivatives, and thiourea and its derivatives.[30–32] In all these cases, $\Delta V^{\neq}$ was found to be in the range of +4 to +8 cm^3 mol^{-1}, i.e. similar to the value found for the reaction of NH_3 with *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ in this study, and was interpreted in terms of an I_d mechanism. These values are significantly smaller than those reported for substitution reactions of (porphyrin)cobalt(III) systems. There it was found that $\Delta V^{\neq}$ 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,[40,41] and these were assigned to a limiting D mechanism. 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 $\Delta V^{\neq}$ data.

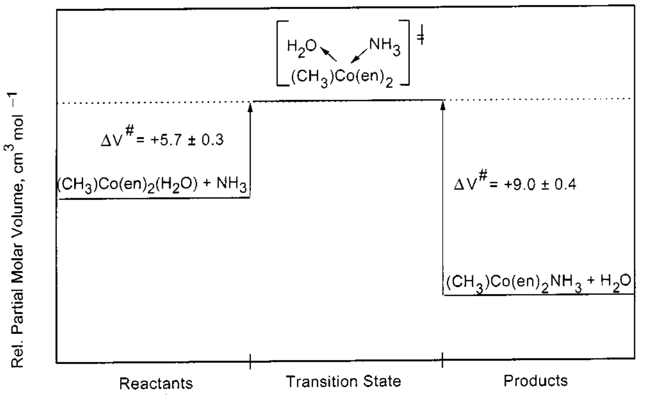

Figure 3. Volume profile for the reaction *trans*-$[Co(en)_2(Me)H_2O]^{2+} + NH_3 \rightleftarrows$ *trans*-$[Co(en)_2(Me)NH_3]^{2+} + H_2O$

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 NH_3 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 $Co-OH_2$ bond that should be independent of the nature of L.

Reaction of *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ with CN^-, SCN^- and N_3^-

The UV/Vis spectrum of *trans*-$[Co(en)_2(Me)NH_3]^{2+}$, dissolved in buffers at pH = 11 in the presence of 1 M NH_3, showed bands at 354 (133 M^{-1} cm^{-1}) and 464 nm (67 M^{-1} cm^{-1}) with a shoulder at 290 nm (166 M^{-1} cm^{-1}). Addition of SCN^- shifts the UV/Vis bands to 356 (208 M^{-1} cm^{-1}) and 464 nm (97 M^{-1} cm^{-1}), whereas addition of N_3^- shifts the UV/Vis bands to 364 (182 M^{-1} cm^{-1}) and 472 nm (98 M^{-1} cm^{-1}).

Spectrophotometric titrations for the reactions with SCN^- and N_3^- were performed in the presence of 1 M NH_3 at 10 °C, and monitored by the increase in absorbance at 461 and 467 nm, respectively. The values of K were calculated from a non-linear least-squares fit of the data to Equation (2) and found to be 4.4 ± 1.5 and 3.0 ± 0.4, respectively. The data were also analyzed by plotting log $(A_x - A_o)/(A_\infty - A_x)$ versus log[L], which resulted in linear plots with slopes of 0.99 ± 0.04 and 0.99 ± 0.09 for SCN^- and N_3^-, respectively, indicating that only one ligand (L) is coordinated to the cobalt complex.

Figure 4 shows a plot of k_{obs} versus $[CN^-]$ for the reaction of *trans*-$[Co(en)_2(Me)NH_3]^{2+}$ (in the presence of 1 M NH_3) with CN^- at pH = 11 ($[CN^-]$ = 0.05 to 1 M), I = 1 M ($NaClO_4$) and 10 °C. This plot shows saturation kinetics (a limiting value of k_{obs} (= k_3) is reached at high $[CN^-]$ values) and exhibits no intercept, indicating that the reverse reaction does not contribute significantly. The suggested mechanism in reaction (4) involves the dissociative formation of a six-coordinate aqua intermediate, followed by the reaction with the entering ligand L. The data in Figure 4 were fitted to Equation (5), and resulted in $k_3 = 2.79 \pm 0.02$ s^{-1}, $k_{-4} \approx 0$ and $k_4/k_{-3} = 73 \pm 3$. The value of k_{obs} increases with increasing cyanide concentration due to the fact that $k_3 >> k_{-4}$. The value of k_4/k_{-3} represents the efficiency of CN^- compared with NH_3 to scavenge the six-coordinate aqua intermediate. The rate law is presented in Equation (5)

$$\begin{aligned}&\textit{trans}\text{-}[\mathrm{Co(en)_2(Me)NH_3}]^{2+} + \mathrm{H_2O} \rightleftarrows\\ &\qquad \textit{trans}\text{-}[\mathrm{Co(en)_2(Me)H_2O}]^{2+} + \mathrm{NH_3} \quad k_3,k_{-3}\\ &\textit{trans}\text{-}[\mathrm{Co(en)_2(Me)H_2O}]^{2+} + \mathrm{L} \rightleftarrows\\ &\qquad \textit{trans}\text{-}[\mathrm{Co(en)_2(Me)L}]^{+} + \mathrm{H_2O} \quad k_4,k_{-4}\end{aligned} \tag{4}$$

$$k_{\mathrm{obs}} = \{k_3k_4[\mathrm{L}] + k_{-3}k_{-4}[\mathrm{NH_3}]\}/\{k_4[\mathrm{L}] + k_{-3}[\mathrm{NH_3}]\} \tag{5}$$

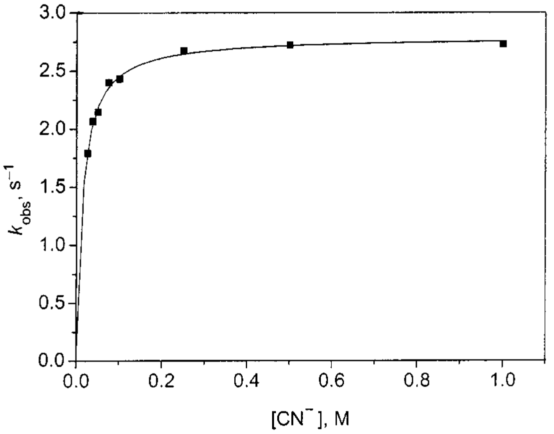

Figure 4. k_{obs} versus $[\mathrm{CN^-}]_{\mathrm{total}}$ for the reaction between *trans*-$[\mathrm{Co(en)_2(Me)NH_3}]^{2+}$ and $\mathrm{CN^-}$ at pH = 11, $[\mathrm{NH_3}]$ = 1 M, 10 °C and I = 1 M ($\mathrm{NaClO_4}$); the best fit of the data (solid line) to Equation (5) gives $k_3 = 2.79 \pm 0.02\ \mathrm{s^{-1}}$, $k_4/k_{-3} = 73 \pm 3$

The reactions of $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$ with *trans*-$[\mathrm{Co(en)_2(Me)NH_3}]^{2+}$ were studied at 10 °C, using a buffer at pH = 9 and I = 1 M $\mathrm{NaClO_4}$. Interestingly, the plot of k_{obs} versus $[\mathrm{SCN^-}]$ results in a decrease of k_{obs} with increasing ligand concentration presumably due to the fact that $k_3 << k_{-4}$ as shown in Figure 5. A Similar plot was obtained for the reaction with $\mathrm{N_3^-}$ (see Supporting Information, Figure S-2). This is characteristic for the dissociative formation of an intermediate and the occurrence of an efficient back reaction. A similar nucleophile concentration dependence was reported for several reversible dissociative ligand substitution reactions, such as the reaction of $[\mathrm{Co(NH_3)_5(Me)}]^{2+}$ with ethylenediamine,[19] the reaction of (N-methylimidazole)cobalamin with N-methylimidazole,[27] and other reactions reported in the literature.[42–46] A nonlinear least-squares fit of the data for $\mathrm{SCN^-}$, revealed that $k_3 = 3.1 \pm 0.2\ \mathrm{s^{-1}}$, $k_{-4} = 19 \pm 4\ \mathrm{s^{-1}}$ and $k_4/k_{-3} = 34 \pm 13$, and those obtained for $\mathrm{N_3^-}$ are $k_3 = 3.1 \pm 0.3\ \mathrm{s^{-1}}$, $k_{-4} = 23 \pm 5\ \mathrm{s^{-1}}$ and $k_4/k_{-3} = 16 \pm 7$. The values of k_4/k_{-3} represent the efficiency of $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$ compared with $\mathrm{NH_3}$ to scavenge the six-coordinate intermediate. The complex-formation constant $K = k_3k_4/k_{-3}k_{-4}$ obtained from the kinetic data for the reaction with $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$ are 5.6 ± 0.5 and 2.2 ± 0.5, respectively, which are in good agreement with the thermodynamically determined values of 4.4 ± 1.5 and 3.0 ± 0.4, respectively.

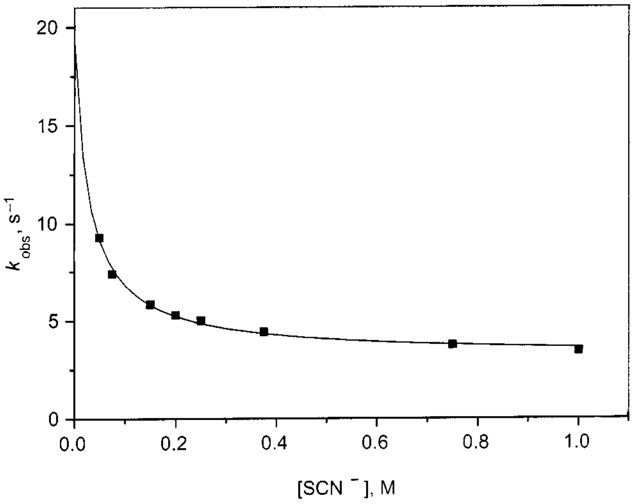

Figure 5. k_{obs} versus $[\mathrm{SCN}]_{\mathrm{total}}$ for the reaction between *trans*-$[\mathrm{Co(en)_2(Me)NH_3}]^{2+}$ and $\mathrm{SCN^-}$ at pH = 9, $[\mathrm{NH_3}]$ = 1 M, 10 °C and I = 1 M $\mathrm{NaClO_4}$; the best fit of the data (solid line) to Equation (5) gives $k_3 = 3.1 \pm 0.2\ \mathrm{s^{-1}}$, $k_{-4} = 19 \pm 4\ \mathrm{M^{-1}\ s^{-1}}$, $k_4/k_{-3} = 34 \pm 13$

By way of comparison, the value of k_3 for the reaction of *trans*-$[\mathrm{Co(en)_2(Me)NH_3}]^{2+}$ with $[\mathrm{CN^-}]$ ($2.79 \pm 0.02\ \mathrm{s^{-1}}$) is close to that obtained when L is $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$, viz. 3.1 ± 0.2 and 3.1 ± 0.3 $\mathrm{s^{-1}}$, respectively, and also in agreement with that obtained for the aquation of *trans*-$[\mathrm{Co(en)_2(Me)NH_3}]^{2+}$ (viz. $2.28 \pm 0.06\ \mathrm{s^{-1}}$) at 10 °C. This suggests that the limiting rate constant reached at high nucleophile concentration for all these reactions, is for aquation of the ammine complex that is controlled by the release of $\mathrm{NH_3}$ (i.e., k_3), for which the mechanism has been discussed above.

The value of k_{-4} for the reaction of $[\mathrm{Co(en)_2(Me)CN}]^{+}$ with $\mathrm{NH_3}$ is close to zero. However, k_{-4} for the reaction of the $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$ complexes with $\mathrm{NH_3}$ is 19 ± 4 and 23 ± 5 $\mathrm{M^{-1}\ s^{-1}}$, respectively. These values indicate that the back reaction contributes significantly in the case of the weaker nucleophiles $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$, and that the reaction is irreversible in the case of the stronger nucleophile $\mathrm{CN^-}$.

The ratio of k_4/k_{-3} for the reaction of $\mathrm{CN^-}$ with $[\mathrm{Co(en)_2(Me)NH_3}]^{2+}$ was found to be 73 ± 3, significantly higher than for the reactions with $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$, viz. 34 ± 13 and 16 ± 7, respectively. The higher ratio in the case of $\mathrm{CN^-}$ is due to its stronger nucleophilicity than $\mathrm{SCN^-}$ and $\mathrm{N_3^-}$, and is therefore a better scavenger for the six-coordinate aqua intermediate in its competition with $\mathrm{NH_3}$ as nucleophile. We conclude that aquation of the ammine complex controls the ligand substitution reactions with the studied nucleophiles and proceeds according to the mechanism outlined in Equation (4).

Experimental Section

Materials: All chemicals were of p.a. grade and used as received. Taps buffer (pH = 9) and Caps buffer (pH = 11) were purchased from Sigma. $\mathrm{NaClO_4}$ was purchased from Fluka. NaSCN, $\mathrm{NaN_3}$, $\mathrm{NH_3}$ and NaCN were purchased from Merck. Ultra pure water was used for all measurements. All preparations and measurements were carried out in diffuse light since the complexes were found to be light sensitive. *trans*-$[Co(en)_2(Me)NH_3]S_2O_6$ was prepared as described by Kofod[47] by treating Co^{II} nitrate with methylhydrazine in the presence of NH_3 to give $[Co(NH_3)_5Me](NO_3)_2$. This complex was treated with ethylenediamine to give *cis*-$[Co(en)_2(Me)NH_3]^{2+}$, followed by a slow isomerization to give *trans*-$[Co(en)_2(Me)NH_3]^{2+}$, which can be isolated in the solid form; *trans*-$[Co(en)_2(Me)H_2O]^{2+}$ was prepared by dissolving *trans*-$[Co(en)_2(Me)NH_3]S_2O_6$ in water at 60 °C for 2 h as previously described. The complexes were characterized by elemental analyses, UV/Vis and NMR spectroscopy, and the results were in agreement with literature data.[47]

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 = 7 and 10. UV/Vis spectra were recorded with Shimadzu UV-2101 and Cary 5 spectrophotometers. Kinetic measurements were carried out with 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 tenfold excess. Measurements at high pressure were carried out using a homemade high-pressure stopped-flow unit.[48] Kinetic data were analyzed with the OLIS KINFIT (Bogart, GA, USA) program. All instruments used were thermostated to the desired temperature (± 0.1 °C). Equilibrium measurements: $3-5 \times 10^{-3}$ M *trans*-$[Co(en)_2(Me)NH_3]S_2O_6$ or *trans*-$[Co(en)_2(Me)H_2O]S_2O_6$, dissolved in Taps buffer pH = 9 or caps buffer pH = 11 (I = 0.1 M using $NaClO_4$), was placed in a 1.0-cm path length cuvette in the thermostated cell block of the spectrophotometer for ca. 20 min. This solution was titrated by 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 to the appropriate equation, after correction for dilution (see further Discussion).

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[1] J. Halpern, *Science* **1985**, *227*, 869.
[2] [2a] N. Bresciani-Pahor, M. Forcolin, L. G. Marzilli, L. Randaccio, M. F. Summers, P. J. Toscano, *Coord. Chem. Rev.* **1985**, *63*, 1. [2b] L. G. Marzilli, M. F. Summers, E. Zangrando, N. Bresciani-Pahor, L. Randaccio, *J. Am. Chem. Soc.* **1986**, *108*, 4830. [2c] L. Randaccio, N. Bresciani-Pahor, E. Zangrando, L. G. Marzilli, *Chem. Soc. Rev.* **1989**, *18*, 225. [2d] S. M. Polson, L. Hansen, L. G. Marzilli, *Inorg. Chem.* **1997**, *36*, 307.
[3] A. L. Crumbliss, W. K. Wilmarth, *J. Am. Chem. Soc.* **1970**, *92*, 2593.
[4] K. L. Brown, S. Satyanarayana, *J. Am. Chem. Soc.* **1992**, *114*, 5674.
[5] K. L. Brown, R. G. Kallen, *J. Am. Chem. Soc.* **1972**, *94*, 1894.
[6] L. G. Marzilli, P. J. Toscano, L. Randaccio, N. Bresciani-Pahor, M. Calligaris, *J. Am. Chem. Soc.* **1979**, *101*, 6754.
[7] L. Randaccio, N. Bresciani-Pahor, P. J Toscano, L. G. Marzilli, *J. Am. Chem. Soc.* **1980**, *102*, 7372.
[8] N. Bresciani-Pahor, L. Randaccio, P. J. Toscano, A. Sandercock, L. G. Marzilli, *J. Chem. Soc., Dalton Trans.* **1982**, 129.
[9] M. F. Summers, P. J. Toscano, N. Bresciani-Pahor, G. Nardin, L. Randaccio, L. G. Marzilli, *J. Am. Chem. Soc.* **1983**, *105*, 6259.
[10] N. Bresciani-Pahor, L. G. Marzilli, L. Randaccio, P. J. Toscano, E. Zangrando, *J. Chem. Soc., Chem. Commun.* **1984**, 1508.
[11] G. Costa, G. Mestroni, E. de Savorgnani, *Inorg. Chim. Acta.* **1969**, *3*, 323.
[12] G. Costa, A. Puxeddu, E. Reisenhofer, *Collect. Czech. Chem. Commun.* **1971**, *36*, 1065.
[13] G. Costa, *Coord. Chem. Rev.* **1972**, *8*, 63.
[14] G. Costa, G. Mestroni, G. Tauzher, L. Stefani, *J. Organomet. Chem.* **1966**, *6*, 181.
[15] [15a] G. Costa, G. Mestroni, L. Stefani, *J. Organomet. Chem.* **1967**, *7*, 493. [15b] A. Bigotto, G. Costa, G. Mestroni, G. Pellizer, A. Puxeddu, E. Reisenhofer, L. Stefani, G. Tauzher, *Inorg. Chim. Acta Rev.* **1970**, 41.
[16] J. M. Pratt, *Inorganic Chemistry of Vitamin B_{12}, Academic Press, London, 1972.*
[17] M. S. A. Hamza, X. Zou, K. L. Brown, R. van Eldik, *Inorg. Chem.* **2001**, *40*, 5440.
[18] P. Kofod, *Inorg. Chem.* **1995**, *34*, 2768.
[19] C. Dücker-Benfer, M. S. A. Hamza, C. Eckhardt, R. van Eldik, *Eur. J. Inorg. Chem.* **2000**, 1563.
[20] L. M. Hansen, P. N. V. Pavan Kumar, D. S. Marynick, *Inorg. Chem.* **1994**, *33*, 728.
[21] M. S. A. Hamza, C. Dücker-Benfer, R. van Eldik, *Inorg. Chem.* **2000**, *39*, 3777, 6145.
[22] D. Thusius, *J. Am. Chem. Soc.* **1971**, *93*, 2629.
[23] F. Nome, J. H. Fendler, *J. Chem. Soc., Dalton Trans.* **1976**, 1212.
[24] D. A. Baldwin, E. A. Betterton, J. M. Pratt, *S. Afr. J. Chem.* **1982**, *35*, 173.
[25] G. Stochel, R. van Eldik, *Inorg. Chem.* **1990**, *29*, 2075.
[26] G. Stochel, R. van Eldik, H. Kunkely, A. Vogler, *Inorg. Chem.* **1989**, *28*, 4314.
[27] A. G. Cregan, N. E. Brasch, R. van Eldik, *Inorg. Chem.* **2001**, *40*, 1430.
[28] W. C. Randall, R. A. Alberty, *Biochemistry* **1967**, *6*, 1520.
[29] W. W. Reenstra, W. P. Jencks, *J. Am. Chem. Soc.* **1979**, *101*, 5780.
[30] F. F. Prinsloo, M. Meier, R. van Eldik, *Inorg. Chem.* **1994**, *33*, 900.
[31] M. Meier, R. van Eldik, *Inorg. Chem.* **1993**, *32*, 2635.
[32] F. F. Prinsloo, E. L. J. Breet, R. van Eldik, *J. Chem. Soc., Dalton Trans.* **1995**, 685.
[33] H. M. Marques, *J. Chem. Soc., Dalton Trans.* **1991**, 339.
[34] H. M. Marques, J. C. Bradley, L. A. Campbell, *J. Chem. Soc., Dalton Trans.* **1992**, 2019.
[35] H. M. Marques, O. Q. Munro, B. M. Cumming, C. Denysschen, *J. Chem. Soc., Dalton Trans.* **1991**, 297.
[36] H. M. Marques, J. C. Bradley, K. L. Brown, H. Brooks, *J. Chem. Soc., Dalton Trans.* **1993**, 3475.
[37] N. E. Brasch, M. S. A. Hamza, R. van Eldik, *Inorg. Chem.* **1997**, *36*, 3216.
[38] W. H. Pailes, H. P. C. Hogenkamp, *Biochemistry* **1968**, *7*, 4160.
[39] [39a] R. van Eldik, A. E. Merbach, *Comments Inorg. Chem.* **1992**, *12*, 341. [39b] R. van Eldik, in *Perspectives in Coordination Chemistry* (Eds.: A. F. Williams, C. Floriani, A. E. Merbach), VCH, Weinheim, ***1992***, p. 55.
[40] S. Funahashi, M. Inamo, K. Ishihara, M. Tanaka, *Inorg. Chem.* **1982**, *21*, 447.

[41] J. G. Leipoldt, R. van Eldik, H. Kelm, *Inorg. Chem.* **1983**, *22*, 4146.
[42] H. E. Toma, J. M. Malin, E. Giesbrech, *Inorg. Chem.* **1973**, *12*, 2084.
[43] J. M. Malin, H. E. Toma, E. Giesbrech, *J. Chem. Educ.* **1977**, *54*, 385.
[44] W. Byers, J. A. Cossham, J. O. Edwards, A. T. Gordon; J. G. Jones, E. T. P. Kenny, A. Mahamed, J. McKnight, D. A. Sweigart, G. A. Tondreau, T. Wright, *Inorg. Chem.* **1986**, *25*, 4767.
[45] K. J. Schneider, R. van Eldik, *Organometallics* **1990**, *9*, 92.
[46] R. A. Henderson, K. E. Oglieve, *J. Chem. Soc., Chem. Commun.* **1994**, 1961.
[47] P. Kofod, P. Harris, S. Larsen, *Inorg. Chem.* **1997**, *36*, 2258.
[48] R. van Eldik, D. A. Palmer, R. Schmidt, H. Kelm, *Inorg. Chim. Acta* **1981**, *50*, 131.

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