Coenzyme B_{12} Model Studies − Kinetics of Axial Ligation of Alkylcobalt Complexes Containing a Tridentate Amino-Oximate Ligand

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The ligand-substitution reaction of $[RCo(LNHpy)(HLNHpy)]^+$ by cyanide was studied in methanol as a solvent, where R = Et (**1**), Me (**2**), CF_3CH_2 (**3**), and bridging CH_2 (**4**), HLNHpy = 2-(2-pyridylethyl)amino-3-butanone oxime and $LNHpy^-$ is its conjugate base. The second-order rate constants for the substitution of the 2-pyridylethyl moiety in $[RCo(LNHpy)(HLNHpy)]^+$ by cyanide were found to be 19.1, 0.25, $2.2\cdot10^{-2}$, and $1.7\cdot10^{-2}$ $\text{M}^{-1}\cdot s^{-1}$ for R = Et, Me, CF_3CH_2, and bridging CH_2, respectively. From the temperature- and pressure-dependence studies of the substitution reaction, the activation parameters ($\Delta H^‡$, $\Delta S^‡$, $\Delta V^‡$) for the reaction of $[RCo(LNHpy)(HLNHpy)]^+$ with cyanide in methanol were found to be, for R = Et: 69 ± 2 $kJ\cdot mol^{-1}$, $+11\pm7$ $J\cdot K^{-1}$ mol^{-1}, $+9.6\pm0.3$ $cm^3\cdot mol^{-1}$; R = Me: 86 ± 4 $kJ\cdot mol^{-1}$, $+31\pm15$ $J\cdot K^{-1}\cdot mol^{-1}$, $+4.3\pm0.2$ $cm^3\cdot mol^{-1}$; R = CF_3CH_2: 73 ± 3 $kJ\cdot mol^{-1}$, -33 ± 10 $J\cdot K^{-1}\cdot mol^{-1}$, $+8.7\pm0.2$ $cm^3\cdot mol^{-1}$; R = bridging CH_2: 80 ± 1 $kJ\cdot mol^{-1}$, -13 ± 3 $J\cdot K^{-1}\cdot mol^{-1}$, $+5.4\pm0.1$ $cm^3\cdot mol^{-1}$, respectively. Based on the reported rate and activation parameters, the mechanism of the ligand-substitution reaction varies between a limiting dissociative and a dissociative interchange type of mechanism depending on the σ-donor and steric effects of the alkyl group.
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Introduction

The discovery of coenzyme B_{12} and the increasing amount of information on its biochemical role[1,2] has led to great efforts in the synthesis and study of model organocobalt complexes with a coordination sphere as similar as possible to that of the corrin ring. Much work has been carried out on organocobalt B_{12} model complexes to achieve a deeper understanding of the behaviour of coenzyme B_{12} by studying *cis* and *trans* effects which significantly influence the physical and chemical properties of vitamin B_{12} and its chemical models.[3−6] The nature of the alkyl group in the axial position has an effect on the Co−C and $Co-N_{(axial)}$ bond lengths, where the latter increase with increasing donor properties of the σ-donor ligand and are significantly influenced by the nature of the equatorial ligand.[7−9] The reaction of cyanide with different alkylcobalamines (RCb1, where R = CF_3, CF_3CH_2, CF_2H, Me, and CH_2Br) showed that the nature of the alkyl group has an influence on the thermodynamic stability constants, as well as on the rate constants of the substitution reactions of the axial ligand *trans* to the alkyl group.[10]

In order to obtain further insight into these reactions, a class of organocobalt complexes *trans*-$[(R)Co(LNHpy)(HLNHpy)]ClO_4$, where HLNHpy is the tridentate ligand 2-(2-pyridyethyl)amino-3-butanone oxime and LNHpy is its conjugated base, were synthesized.[5,11] The alkyl group R was Me, Et, CF_3CH_2, or the intramolecular bridging CH_2 group as shown in Figure 1. The geometry of these compounds is reminiscent of the lariat-type ligands previously reported,[3,12] since they contain a potentially quinquedentate ligand forming an equatorial chelating system bearing a pendant pyridyl group axially coordinated to the cobalt atom. The structural features of these complexes allow better modeling of the displacement of 5,6-dimethylbenzimidazole in coenzyme B_{12} than any other model so far studied. It is further of interest that the geometry of the N−Co−C unit in the Me derivative [Co−C = 1.971(7) Å, Co−N = 2.159(5) Å] is much closer to that of MeCbl [Co−C = 1.979(4) Å, Co−N = 2.162(4) Å] than of any other previously proposed B_{12} model complex.[5]

Ligand-substitution reactions of vitamin B_{12} and its model complexes in general follow a dissociative (I_d or D) type of mechanism.[13−15] In the case of the coenzyme, however, evidence was originally reported for an associative substitution mode, which was later corrected to result from the combination of a rapid substitution of dimethylbenzimi-

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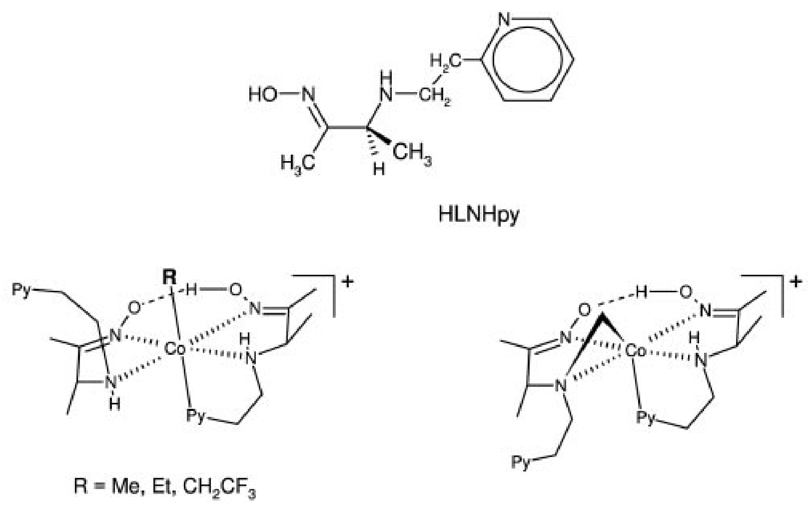


Figure 1. Structures of HLNHpy, which is the tridentate ligand 2-(2-pyridyethyl)amino-3-butanone oxime, and of *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$, where R = Et, Me, CF_3CH_2, and bridging CH_2

dazole and subsequent water-assisted heterolysis of the cobalt−carbon (adenosyl) bond.[16,17] Ligand-substitution reactions of different cobalamins (R = CF_3, CN^-, $NCCH_2$) with cyanide have been studied,[10,18] and it was found that CN^- substitutes the 5,6-dimethylbenzimidazole (DMBz) moiety in all cases. The activation parameters were interpreted in terms of a limiting D mechanism.

Kinetic and mechanistic studies on the substitution behaviour of alkyl derivatives of bis(dimethylglyoximate)-cobalt(III) complexes have been performed extensively.[19−33] Most of these studies have been aimed to asses the role of the σ-bonded alkyl group to Co^{III} in affecting the axial substitution rates in the *trans* position. Typical reactions that have been studied can be represented by Equations (1) and (2), where DH represents the monoanion of dimethylglyoxime, R is an alkyl group, and L and L^I are neutral bases.

$$\textit{trans}\text{-}[RCo(DH)_2H_2O] + L \rightarrow \textit{trans}\text{-}[RCo(DH)_2L] + H_2O \qquad (1)$$

$$\textit{trans}\text{-}[RCo(DH)_2L] + L^I \rightarrow \textit{trans}\text{-}[RCo(DH)_2L^I] + L \qquad (2)$$

In the present study, we investigated the ligand-substitution reactions of *trans*-$[(R)Co^{III}(LNHpy)(HLNHpy)]^+$, where R = Et, Me, CF_3CH_2, and bridging CH_2. These reactions were studied as a function of entering nucleophile concentration, temperature, and pressure in order to elucidate the reasons for the observed lability and the intimate mechanisms of these reactions.

Results and Discussion

The kinetics of the reaction of complexes of the type *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$, R = Et (**1**), Me (**2**) and CF_3CH_2 (**3**), with CN^- were studied in methanol. Cyanide was used as the entering nucleophile, since other less-strong nucleophiles are known to be incapable of replacing any of the axial ligands in these complexes. The reaction of the complex[11] *trans*-$[(CH_2)Co(LNHpy)(HLNpy)]^+$ (**4**) with CN^- was also studied. Complex **4** was characterized to involve a $-CH_2-$ group that forms a three-membered metallacycle,[34,35] in which the other two members are the Co atom and the equatorial nitrogen donor. Complexes containing this type of metallacycle are quite rare[34,35] and scarcely studied. In view of the unusual geometry of this complex, it seemed to be of interest to examine its kinetic properties with reference to the reactivity of the *trans* position with respect to the bridging $-CH_2-$ fragment.

Reaction of *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$ with Cyanide

R = Et

The UV/Vis spectrum of *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+$ shows two bands at 368 and 464 nm (376 and 207 $M^{-1}\cdot cm^{-1}$, respectively) in methanol at 25.0 °C. The substitution reaction of *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+$ occurs by displacement of the axial 2-pyridylethyl ligand by cyanide, which is positioned *trans* to the ethyl group. The product is light-sensitive, suggesting the presence of the alkyl group in the axial position. The product spectrum has a single band at 452 nm (137 $M^{-1}\cdot cm^{-1}$) with a shoulder at 338 nm (441 $M^{-1}\cdot cm^{-1}$); good isosbestic points at 334 and 360 nm were observed during the reaction.

Figure 2 presents a plot of k_{obs} versus $[CN^-]$ for the reaction of $2.5\cdot 10^{-3}$ M *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+$ with cyanide (0.025−0.20 M) at I = 0.5 M (CF_3SO_3Li) in methanol at 25.0 °C. The linear plot has a negligible intercept, indicating that the back reaction does not contribute significantly and that no parallel reaction takes place. The second-order rate constant for the substitution of 2-pyridylethyl by

CN^- was found to be 19.1±0.2 $M^{-1}\cdot s^{-1}$ at 25.0 °C. This behaviour can be expressed by the rate law given in Equation (3).

$$k_{obs} = k_a [CN^-] \quad (3)$$

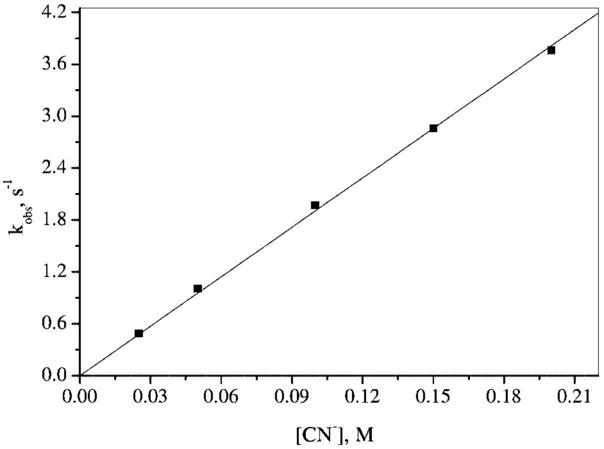


Figure 2. Plot of k_{obs} versus $[CN^-]$ for the reaction of *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+$ with cyanide in methanol; experimental conditions: $[Co^{III}] = 1\cdot10^{-3}$ M, $I = 0.5$ M, $T = 25.0$ °C

The reaction was also studied as a function of temperature and pressure, for which the results are reported in Tables 1 and 2. A plot of ln k_a versus pressure gives a good linear relationship as shown in Figure 3. The activation parameters ($\Delta H^‡$, $\Delta S^‡$, $\Delta V^‡$) were found to be 69±2 $kJ\cdot mol^{-1}$, 11±7 $J\ K^{-1}\cdot mol^{-1}$ and 9.6±0.3 $cm^3\cdot mol^{-1}$, respectively. Based on the reported rate and activation parameters, the ligand-substitution reaction of the complex *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+$ with cyanide follows a dissociative mechanism as presented in reaction [Equation (4)].

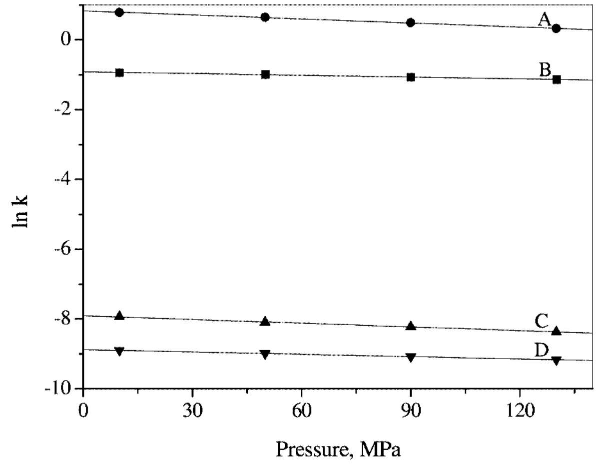


Figure 3. Plots of ln*k* versus pressure for the reaction of *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$ with cyanide in methanol; experimental conditions: A) R = Et, $[Co^{III}] = 2.5\cdot10^{-3}$ M, $[CN^-] = 0.1$ M, $I = 0.5$, $T = 25.0$ °C; B) R = Me, $[Co^{III}] = 2.5\cdot10^{-3}$ M, $[CN^-] = 0.2$ M, $I = 0.5$ M, T= 35.0 °C; C) R = CF_3CH_2, $[Co^{III}] = 1\cdot10^{-3}$ M, $[CN^-] = 0.025$ M, $I = 0.5$ M, $T = 20.0$ °C; D) R = CH_2, $[Co^{III}] = 1\cdot10^{-3}$ M, $[CN^-] = 0.025$ M, $I = 0.5$ M, $T = 15.0$ °C

Table 1. Kinetic data for the reaction of *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$ with cyanide in methanol as a function of temperature

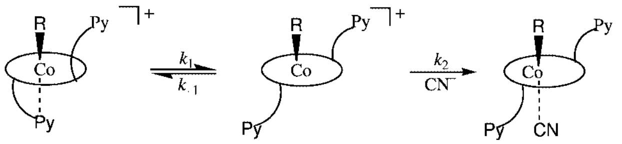
Temp. [°C]	k_a [$M^{-1}\cdot s^{-1}$]			
	R = Et[a]	R = Me[b]	R = CF_3CH_2[c]	R = CH_2[d]
5.0	2.5±0.1	–	–	–
10.0	4.4±0.1	(3.25±0.27)·10^{-2}	–	–
15.0	8.4±0.1	(7.60±0.33)·10^{-2}	(7.70±0.30)·10^{-3}	(4.80±0.08)·10^{-3}
20.0	12.7±0.2	(1.25±0.04)·10^{-1}	(1.43±0.06)·10^{-2}	(8.48±0.26)·10^{-3}
25.0	20.7±0.4	(2.50±0.07)·10^{-1}	(2.32±0.09)·10^{-2}	(1.56±0.09)·10^{-2}
30.0	31.7±0.7	(3.94±0.05)·10^{-1}	(4.06±0.12)·10^{-2}	(2.62±0.09)·10^{-2}
35.0	–	–	(5.80±0.20)·10^{-2}	(4.40±0.08)·10^{-2}
$\Delta H^‡$ [$kJ\cdot mol^{-1}$]	69±2	86±4	73±3	80±1
$\Delta S^‡$, [$J\cdot K^{-1}\cdot mol^{-1}$]	+11±7	+31±15	−33±10	−13±3

[a] *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+ = 1\cdot10^{-3}$ M, $[CN^-] = 0.1$ M and $I = 0.5$ M. [b] *trans*-$[(Me)Co(LNHpy)(HLNHpy)]^+ = 2.5\cdot10^{-4}$ M, $[CN^-] = 0.2$ M and $I = 0.5$ M. [c] *trans*-$[(CF_3CH_2)Co(LNHpy)(HLNHpy)]^+ = 1.0\cdot10^{-3}$ M, $[CN^-] = 0.05$ M and $I = 0.5$ M. [d] *trans*-$[(CH_2)Co(LNHpy)(HLNHpy)]^+ = 2.5\cdot10^{-3}$ M, $[CN^-] = 0.025$ M and $I = 0.5$ M.

Table 2. Kinetic data for the reaction of *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$ with cyanide in methanol as a function of pressure

Presssure [MPa]	k_{obs} [s^{-1}]			
	R = Et[a]	R = Me[b]	R = CF_3CH_2[c]	R = CH_2[d]
10	2.19±0.01	0.39±0.01	(3.57±0.03)·10^{-4}	(1.36±0.08)·10^{-4}
50	1.91±0.02	0.37±0.01	(3.05±0.04)·10^{-4}	(1.25±0.02)·10^{-4}
90	1.63±0.05	0.34±0.01	(2.68±0.03)·10^{-4}	(1.14±0.02)·10^{-4}
130	1.38±0.3	0.32±0.01	(2.32±0.02)·10^{-4}	(1.04±0.02)·10^{-4}
$\Delta V^‡$ [$cm^3\cdot mol^{-1}$]	+9.6±0.3	+4.3±0.2	+8.7±0.2	+5.4±0.1

[a] *trans*-$[(Et)Co(LNHpy)(HLNHpy)]^+ = 2.5\cdot10^{-3}$ M, $[CN^-] = 0.1$ M, $T = 25.0$ °C and $I = 0.5$ M. [b] *trans*-$[(Me)Co(LNHpy)(HLNHpy)]^+ = 2.5\cdot10^{-3}$ M, $[CN^-] = 0.2$ M, $T = 35.0$ °C and $I = 0.5$ M. [c] *trans*-$[(CF_3CH_2)Co(LNHpy)(HLNHpy)]^+ = 1.0\cdot10^{-3}$ M, $[CN^-] = 0.025$ M, $T = 20.0$ °C and $I = 0.5$ M. [d] *trans*-$[(CH_2)Co(LNHpy)(HLNHpy)]^+ = 1.0\cdot10^{-3}$ M, $[CN^-] = 0.025$ M, $T = 15.0$ °C and $I = 0.5$ M.



(4)

R = Me, CF_3CH_2, and Bridging CH_2

The UV/Vis spectra of *trans*-[(R)Co(LNHpy)(HLNHpy)]$^+$ show two bands at 362 and 452 nm (466 and 330 $M^{-1}\cdot cm^{-1}$, respectively) for R = Me, one band at 462 nm (187 $M^{-1}\cdot cm^{-1}$) with a shoulder at 364 nm (256 $M^{-1}\cdot cm^{-1}$) for R = CF_3CH_2, and a single band at 400 nm (509 $M^{-1}\cdot cm^{-1}$) with a shoulder at 472 nm (303 $M^{-1}\cdot cm^{-1}$) for R = bridging CH_2 in methanol at 25.0 °C. The ligand-substitution reactions of *trans*-[(R)Co(LNHpy)(HLNHpy)]$^+$ occurrs by displacement of the axial 2-pyridylethyl ligand, which is located *trans* to the alkyl group, by cyanide. Good isosbestic points at 361 and 328 nm for R = Me, at 364 nm for R = CF_3CH_2, and at 362 and 398 nm for R = bridging CH_2, were obtained upon mixing the complex with cyanide. The UV/Vis spectra of the products show a band at 450 nm (274 $M^{-1}\cdot cm^{-1}$) with a shoulder at 340 nm (554 $M^{-1}\cdot cm^{-1}$) for R = Me, one band at 452 nm (132 $M^{-1}\cdot cm^{-1}$) for R = CF_3CH_2, and one band at 476 nm (233 $M^{-1}\cdot cm^{-1}$) with a shoulder at 372 nm (692 $M^{-1}\cdot cm^{-1}$) for R = bridging CH_2.

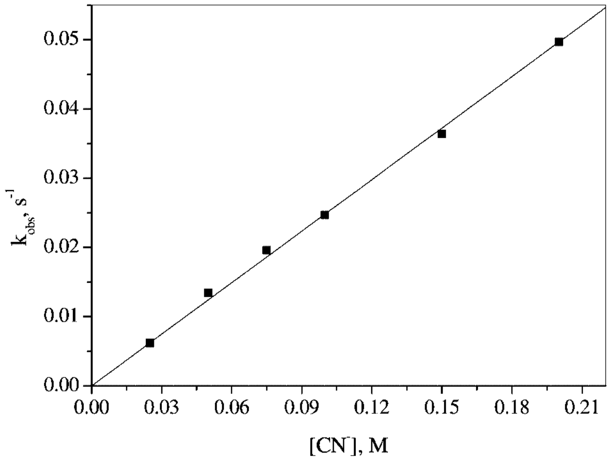


Figure 4. Plot of k_{obs} versus $[CN^-]$ for the reaction of *trans*-[(Me)Co(LNHpy)(HLNHpy)]$^+$ with cyanide in methanol; experimental conditions: $[Co^{III}] = 2.5\cdot10^{-4}$ M, $I = 0.5$ M, $T = 25.0$ °C

Figures 4, 5, and 6 report plots of k_{obs} versus $[CN^-]$ for the reaction of *trans*-[(R)Co(LNHpy)(HLNHpy)]$^+$ with cyanide (0.025−0.20 M) at $I = 0.5$ M (CF_3SO_3Li) in methanol at 25.0 °C. The linear plots have negligible intercepts, indicating that the back reaction does not contribute significantly and that no parallel reaction takes place. The second-order rate constants for the substitution of 2-pyridylethyl by CN^- were found to be 0.25±0.01, $(2.3\pm0.1)\cdot10^{-2}$, and $(1.6\pm0.1)\cdot10^{-2}$ $M^{-1}\cdot s^{-1}$ for R = Me, CH_2CF_3 and bridging CH_2, respectively, at 25.0 °C. This behaviour can be expressed by a rate law similar to that given in Equation (3).

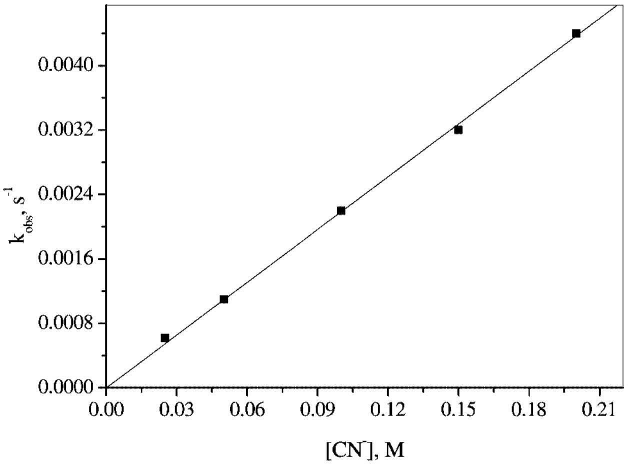


Figure 5. Plot of k_{obs} versus $[CN^-]$ for the reaction of *trans*-[(CF_3CH_2)Co-(LNHpy)(HLNHpy)]$^+$ with cyanide in methanol; experimental conditions: $[Co^{III}] = 1\cdot10^{-3}$ M, $I = 0.5$ M, $T = 25.0$ °C

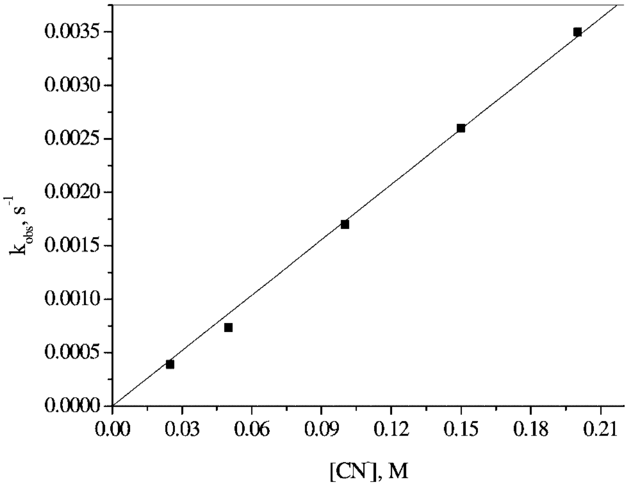


Figure 6. Plot of k_{obs} versus $[CN^-]$ for the reaction of *trans*-[(CH_2)Co(LNHpy)(HLNHpy)]$^+$ with cyanide in methanol; experimental conditions: $[Co^{III}] = 2.5\cdot10^{-3}$ M, $I = 0.5$ M, $T = 25.0$ °C

The reactions were studied as a function of temperature and pressure, for which the results are reported in Tables 1 and 2. Plots of lnk_a versus pressure gave good linear relationships as shown in Figure 3. The activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta V^{\ddagger}$) were found to be 86±4 kJ·mol^{-1}, +31±15 J·K^{-1}·mol^{-1}, and +4.3±0.2 cm^3·mol^{-1} for R = Me; 73±3 kJ·mol^{-1}, −33±10 J·K^{-1}·mol^{-1}, and +8.7±0.2 cm^3·mol^{-1} for R = CF_3CH_2; and 80±1 kJ·mol^{-1}, −13±3 J·K^{-1}·mol^{-1}, and +5.4±0.1 cm^3·mol^{-1} for R = bridging CH_2, respectively. Based on the reported rate and activation parameters, it is reasonable to suggest that ligand substitution in the complexes *trans*-[(R)Co(LNHpy)(HLNHpy)]$^+$ proceeds by a dissociative interchange (I_d) mechanism.

Overall Mechanistic Comparison

It is interesting to compare the structural and solution properties of complexes **1−3** with those of the corresponding alkylcobaloximes. It has been shown that in the latter series, the Co−N$_{(axial)}$ distance increases with the σ-donor property of R. Thus, the order of increasing Co−N$_{(axial)}$ distance is: CF_3CH_2 (2.041 Å) < Me (2.068 Å) < Et (2.081 Å).[36] There is also a defined trend in the rate constant of the axial ligation for a given incoming base. In all the studied cases, it was found that the rate constants increase on increasing the σ-donor strength of the R alkyl group.[19−33,37] By way of example, some data for the axial ligation of a series of alkyl(aqua)cobaloximes by the neutral dimethoxyethylamine base are summarized in Table 3. These data show that the ground-state *trans* influence of a given R group parallels the kinetic *trans* effect of the same group, both effects being controlled by the electronic properties of R. Similarly to that observed in the alkylcobaloximes, it has been shown that the electronic properties of the R group affect the Co−N$_{(axial)}$ bond lengths and control the *trans* influence and *trans* effect in some other complexes with tetradentate chelating systems such as the alkyl derivatives[33,36] of the type $[RCo(DO)(DOH)pnH_2O]^+$ {where (DO)(DOH)pn = *N*^{2},*N*$^{2\prime}$-propanediylbis(2,3-butanedione) 2-imine 3-oxime} and alkylrhodoximes.[38,39]

Table 3. Second-order rate constants for the reaction *trans*-$[(R)Co(DH)_2H_2O]$ + DEA → *trans*-$[(R)Co(DH)_2DEA]$ + H_2O

R[21]	σ*	*k* at 25 °C, $M^{-1}\cdot s^{-1}$
Et	−0.10	81±6
Me	0.00	5.1±0.2
CF_3CH_2	+0.99	$(2.7\pm0.1)\cdot10^{-2}$

Contrary to the cobaloximes, there is no definite trend in the observed Co−N$_{(axial)}$ distances along the series **1**−**3**. In this series the distances are 2.160(6), 2.158(5), and 2.168(5) Å for the CF_3CH_2, Me (mean value of two structurally independent molecules) and Et derivatives, respectively.[5] The difference in the Co−N$_{(axial)}$ distances between the Me and Et derivatives, although smaller than that found in the corresponding alkylcobaloximes, is in agreement with the donating properties of the R groups. However, a shorter Co−N$_{(axial)}$ distance with respect to that observed would be expected for **3**, due to the poorer donor ability of CF_3CH_2. This apparent anomaly can be explained on the basis of the structural features of complexes **1**−**3**, and of the different steric properties of the R groups considered. In particular, it is observed that the flexibility of the ethylene chain bearing the coordinated pyridyl group allows the axial pyridyl residue to rotate around the Co−N$_{(pyridyl)}$ bond. There is clear evidence that the orientation of the pyridyl moiety appreciably influences the length of the Co−N$_{(axial)}$ bond, so that by varying the R group, the trend in the *trans* influence is modified with respect to that expected on the basis of the donating properties of R.

These conformational changes have been observed not only in complexes **1**−**3**, but also in some other alkylcobalt chelates.[3,12,40,41] Hence the Co−N$_{(axial)}$ distances found in complexes **1**−**3** are a result of a compromise between the energies involved either in the torsion or in the stretching of the Co−N$_{(axial)}$ bond.[5] This leads to the conclusion that for compounds **1**−**3** any attempt to correlate the electronic properties of the R group with the ground state *trans* influence, has to be considered as of little use.

The second-order rate constants for substitution of 2-pyridylethyl by cyanide were found to be 19.1, 0.25, $2.2\cdot10^{-2}$, and $1.7\cdot10^{-2}$ $M^{-1}\cdot s^{-1}$ at 25 °C for the series of complexes *trans*-$[(R)Co(LNHpy)(HLNHpy)]^+$, where R = Et, Me, CF_3CH_2, and CH_2, respectively. It seems that this trend reflects the σ-donor properties of R. However, significant differences are observed in the transmission of effects of R when the series **1**−**3** are compared with the corresponding cobaloximes. A comparison of the rate constant ratios Et/Me and CF_3CH_2/Me for cobaloximes and for the series **1**−**3** can illustrate these differences. From the data for the second-order rate constants of complexes **1**−**3** and the data reported in Table 3, these ratios are 15.9 and $5.3\cdot10^{-3}$ for cobaloximes and 76.4 and $88.0\cdot10^{-3}$ for complexes **1**−**3**. From this it follows that in reference to the Me derivatives, the ligation rates in both Et and CF_3CH_2 derivatives are greatly enhanced in **2** and **3** with respect to the corresponding cobaloximes. By assuming that in the latter compounds the effect of R is mainly an electronic one, it can be deduced that steric effects play an important role in affecting the reaction rates also for **1**−**3**. Structural data show that, according to the bending angle (a) values,[42−45] bending away from the neutral base L between the two DH units is significantly smaller than that of the Schiff-base complexes and range between 0 and 3°; the bending angles in complexes **1**−**3**[5] range between 8 and 16°. This is probably due to the higher flexibility of the equatorial system in complexes **1**−**3** with respect to the $Co(DH)_2$ moiety. The increased level of flexibility in the latter compounds can be ascribed to the presence of only one O−H···O bridge (vs. two present in cobaloximes) and to the less-extensive electronic delocalization over the equatorial plane (two conjugated C=N bond vs. four conjugated C=N bond in cobaloximes). Based on the above argument it may be inferred that in approaching the transition state, the bending of the equatorial ligand toward the pyridyl group is permissible and that this contributes to the extension of the Co−N$_{(pyridyl)}$ bond. It is reasonable to expect that these steric effects will be more pronounced in complexes having relatively bulky R groups such as Et and CF_3CH_2.

The activation volume data reported in Table 2 suggest an increasing dissociative character of the ligand-substitution process on going along the series Me < CF_3CH_2 < Et. This order does not reflect the donating properties of R. As suggested above, this order has to be largely ascribed to steric effects. Probably in the case of the large value found for the Et derivative, both electronic and steric effects contribute. By way of comparison, we reported $\Delta V^{\ddagger}$ values for the ligation of cysteine to *trans*-$[(R)Co(DH)_2H_2O]$, where DH = dimethylglyoximate anion for R = CF_3CH_2, Ph, and CH_2Ph, of 0±1, +4.9±0.3, and +5.9±0.4 $cm^3\cdot mol^{-1}$, respectively.[46] The sequence CF_3CH_2 < Ph < CH_2Ph is as expected and corresponds to an increase in the dissociative character of the process with increasing donor properties of R.

The reaction of cyanide with different alkycobalamines (RCbl, where R = CF_3, CF_3CH_2, CF_2H, Me, and CH_2Br) was studied, and it was found that the nature of the alkyl group has a strong influence on the thermodynamic stability constants as well as the rate constants for the substitution reactions of the axial ligand *trans* to the alkyl group.[10] It was found that Co−N and Co−C bond lengths increase in the RCbl series in the order H_2O < CN < CF_3 < CF_2H < Me < adenosyl.[47−50] The second-order rate constants for RCbl with CN^- were found to be 1.1 (25 °C), 217 (10 °C), 483 (5 °C), and $1 \cdot 10^3$ $\text{M}^{-1} \cdot \text{s}^{-1}$ (5 °C), for X= CN^-, CF_3, $NCCH_2$, and CF_2H, respectively.[18] The kinetic *trans* effect was found to decrease in the order nPr ≥ adenosyl ≥ Me ≥ CF_3CH_2 > CF_2H > $NCCH_2$ > CF_3 > CN^-.

The relatively slow reaction rate of complex **4** is consistent with the short $Co-N_{(pyridyl)}$ bond[11] [2.118(3) Å], and the $\Delta V^{\ddagger}$ value suggests an $Co-N_{(pyridyl)}$ bond extension in the transition state similar to that of the Me derivative. Therefore, this complex exhibits no special kinetic properties. Perhaps the only relevant point is the presence of the $-CH_2-$ arm, which imparts a greater rigidity to the system, so that in this case the steric effects become less important.

On the basis of the activation parameters presented in Tables 1 and 2, it is reasonable to conclude that the ligand-substitution reactions of *trans*-[(R)Co(LNHpy)(HLNHpy)]$^+$ with cyanide, where R = Et, Me, CF_3CH_2, and bridging CH_2, follow a dissociative mechanism whose nature can vary from limiting dissociative to a dissociative interchange (I_d) mechanism, depending on the σ-donor and steric properties of the alkyl group, as discussed in detail above. It may be concluded, that the complexes studied here are more suitable than the cobaloximes to examine the influence of steric effects, which have up to now been disregarded in the study of model compounds for coenzyme B_{12}.

Experimental Section

Materials: All chemicals were of analytical reagent grade and used as received. Sodium cyanide was purchased from Merck and lithium trifluoromethanesulfonate from Aldrich. *trans*-[(R)Co(LNHpy)(HLNHpy)]ClO_4 (R = Me, Et, CF_3CH_2) were prepared by reduction of *trans*-[Co(LNHpy)(HLNHpy)]$(ClO_4)_2$ by $NaBH_4$ and addition of alkyl iodide under nitrogen. The remaining complex *trans*-[(CH_2)Co(LNHpy)(HLNHpy)]ClO_4 was prepared by treating *trans*-[$(ClCH_2)$Co(LNHpy)(HLNHpy)]ClO_4 with NaOH. The complexes were characterised by elemental analysis and NMR spectroscopy, and the results were in agreement with those reported in the literatures.[5,11] All preparations and measurements were carried out in the dark since alkylcobaloximes are light-sensitive.

Instrumentation: UV/Vis spectra were recorded with Shimadzu UV-2101 and Hewlett Packard 8452A spectrophotometers. Kinetic measurements were carried out with the Shimadzu instrument. Measurements at elevated pressures (up to 150 MPa) were carried out using the Shimadzu spectrophotometer equipped with a home-made high-pressure unit for slow reactions,[51] and a high-pressure stopped-flow unit for fast reactions.[52] Kinetic data were analyzed with the OLIS KINFIT program. The standard deviations reported for the experimental data were estimated using the ORIGIN program. All instruments were thermostatted to the desired temperature (±0.1 °C). Kinetic measurements were carried out under pseudo-first-order conditions, i.e. the ligand concentration was in at least a 10-fold excess.

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[1] J. Halpern, *Science* **1985**, *227*, 869.

[2] R. Banerjee, *Chemistry and Biochemistry of B_{12}, Wiley & Sons, New York,* **1999**.

[3] A. Gerli, M. Sabat, L. G. Marzilli, *J. Am. Chem. Soc.* **1992**, *114*, 6711.

[4] P. G. Yohannes, N. Bresciani-Pahor, L. Randaccio, E. Zangrando, *Inorg. Chem.* **1988**, *27*, 4738.

[5] R. Dreos, A. Felluga, G. Nardin, L. Randaccio, P. Siega, G. Tauzher, *Eur. J. Inorg. Chem.* **2001**, 267.

[6] B. M. Alzoubi, M. S. A. Hamza, C. Dücker-Benefer, R. van Eldik, *Eur. J. Inorg. Chem.* **2002**, 968.

[7] L. M. Hansen, P. N. V. Paven Kumar, D. S. Marynick, *Inorg. Chem.* **1994**, *33*, 728.

[8] S. J. Moore, A. Kutikev, R. J. Lachicotte, L. G. Marzilli, *Inorg. Chem.* **1999**, *38*, 768.

[9] F. Asaro, R. Dreos, S. Geremia, G. Nardin, G. Pellizer, L. Randaccio, G. Tauzher, S. Vuano, *J. Organomet. Chem.* **1997**, *548*, 211.

[10] M. S. A. Hamza, X. Zou, K. L. Brown, R. van Eldik, *Inorg. Chem.* **2001**, *40*, 5440.

[11] R. Dreos, A. Felluga, G. Nardin, L. Randaccio, P. Siega, G. Tauzher, *Inorg. Chem.* **2001**, *40*, 5541.

[12] L. G. Marzilli, A. Gerli, A. M. Calafat, *Inorg. Chem.* **1992**, *31*, 4617.

[13] [13a] G. Stochel, R. van Eldik, *Inorg. Chem.* **1990**, *29*, 2075. [13b] F. F. Prinsloo, M. Meier, R. van Eldik, *Inorg. Chem.* **1994**, *33*, 900. [13c] M. Meier, R. van Eldik, *Inorg. Chem.* **1993**, *32*, 2635. [13d] F. F. Prinsloo, E. L. J. Breet, R. van Eldik, *J. Chem. Soc., Dalton Trans.* **1995**, 685. [13e] A. G. Gergan, N. E. Brasch, R. van Eldik, *Inorg. Chem.* **2001**, *40*, 1430. [13f] M. S. A. Hamza, C. Dücker-Benfer, R. van Eldik, *Inorg. Chem.* **2000**, *39*, 3777. [13g] B. M. Alzoubi, M. S. A. Hamza, C. Dücker-Benfer, R. van Eldik, *Eur. J. Inorg. Chem.* **2002**, 968.

[14] [14a] H. M. Marques, *J. Chem. Soc., Dalton Trans.* **1991**, 339. [14b] H. M. Marques, J. C. Bradley, L. A. Campbell, *J. Chem. Soc., Dalton Trans.* **1992**, 2019. [14c] H. M. Marques, J. C. Bradley, K. L. Brown, H. Brooks, *J. Chem. Soc., Dalton Trans.* **1993**, 3475. [14d] H. M. Marques, O. Q. Munro, B. M. Cumming, C. de Nysschen, *J. Chem. Soc., Dalton Trans.* **1994**, 297.

[15] [15a] D. Thusius, *J. Am. Chem. Soc.* **1971**, *93*, 2629. [15b] F. Nome, J. H. Fendler, *J. Chem. Soc., Dalton Trans.* **1976**, 1212. [15c] W. C. Randall, R. A. Alberty, *Biochemistry* **1967**, *6*, 1520. [15d] W. W. Reenstra, W. P. Jencks, *J. Am. Chem. Soc.* **1979**, *101*, 5780.

[16] N. E. Brasch, M. S. A. Hamza, R. van Eldik, *Inorg. Chem.* **1997**, *36*, 3216.

[17] M. S. A. Hamza, A. G. Cregan, N. Brasch, R. van Eldik, *Dalton Trans.* **2003**, 596.

[18] M. S. A. Hamza, X. Zou, K. L. Brown, R. van Eldik, *J. Chem. Soc., Dalton Trans.* **2002**, 3832.

[19] A. L. Crumbliss, W. K. Wilmarth, *J. Am. Chem. Soc.* **1970**, *92*, 2593.

[20] K. L. Brown, D. Cernoff, D. J. Keljo, R. G. Kallen, *J. Am. Chem. Soc.* **1975**, *97*, 7338.

[21] K. L. Brown, D. Lyles, N. Pencovici, R. G. Kallen, *J. Am. Chem. Soc.* **1972**, *94*, 6697.

[22] K. L. Brown, A. W. Awtrey, *Inorg. Chem.* **1978**, *17*, 111.

[23] N. Bresciani-Pahor, L. Randaccio, A. C. Sandercock, L. G. Marzilli, *J. Chem. Soc., Dalton Trans.* **1982**, 129.

[24] M. F. Summers, P. J. Toscano, N. Bresciani-Pahor, G. Nardin, L. Randaccio, L. G. Marzilli, *J. Am. Chem. Soc.* **1983**, *105*, 6259.

[25] W. C. Trogler, R. C. Stewart, L. G. Marzilli, *J. Am. Chem. Soc.* **1974**, *96*, 3697.

[26] R. C. Stewart, L. G. Marzilli, *J. Am. Chem. Soc.* **1978**, *100*, 817.

[27] K. L. Brown, R. G. Kallen, *J. Am. Chem. Soc.* **1972**, *94*, 1894.

[28] J. K. Espenson, R. Russell, *Inorg. Chem.* **1974**, *13*, 7.

[29] R. Dreos Garlatti, G. Tauzher, G. Costa, *Inorg. Chim. Acta* **1983**, *70*, 83.

[30] R. Dreos Garlatti, G. Tauzher, G. Costa, *Inorg. Chim. Acta* **1983**, *71*, 9.

[31] R. Dreos Garlatti, G. Tauzher, G. Costa, *Inorg. Chim. Acta* **1981**, *50*, 95.

[32] R. Dreos Garlatti, G. Tauzher, G. Costa, *Inorg. Chim. Acta* **1986**, *121*, 27.

[33] R. Dreos Garlatti, G. Tauzher, G. Costa, *Inorg. Chim. Acta* **1984**, *82*, 197.

[34] S. M. Polson, L. Hansen, L. G. Marzilli, *J. Am. Chem. Soc.* **1996**, *118*, 4804.

[35] L. G. Marzilli, S. M. Polson, L. Hansen, S. G. Moore, *Inorg. Chem.* **1997**, *36*, 3854.

[36] N. Bresciani-Pahor, M. Forcolin, L. G. Marzilli, L. Randaccio, M. F. Summers, P. J. Toscano, *Coord. Chem. Rev.* **1985**, *63*, 1.

[37] F. Mancia, N. H. Keep, A. Nakagawa, P. F. Leadlay, S. McSweeney, B. Rasmussen, P. Boske, O. Diat, P. R. Evans, *Structure* **1996**, 339.

[38] C. Dücker-Benfer, R. Dreos, R. van Eldik, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2245.

[39] L. Randaccio, S. Geremia, R. Dreos-Garlatti, G. Tauzher, F. Asaro, G. Pellizer, *Inorg. Chim. Acta* **1992**, *194*, 1.

[40] R. Cini, S. J. Moore, L. G. Marzilli, *Inorg. Chem.* **1998**, *37*, 6890.

[41] S. Kirota, S. M. Polson, J. M. Puskett, S. J. Moore, M. B. Mitchell, L. G. Marzilli, *Inorg. Chem.* **1996**, *35*, 5645.

[42] A. Clearfield, R. Gopal, R. J. Kline, M. Spiski, O. L. Urban, *J. Coord. Chem.* **1978**, *7*, 163.

[43] M. Calligaris, G. Nardin, L. Randaccio, *Inorg. Nucl. Chem. Lett.* **1972**, *8*, 477.

[44] M. Calligaris, G. Nardin, L. Randaccio, *J. Chem. Soc. A* **1972**, 1433.

[45] M. F. Summers, L. G. Marzilli, N. Bresciani-Pahor, L. Randaccio, *J. Am. Chem. Soc.* **1984**, *106*, 4478.

[46] M. S. A. Hamza, A. Felluga, L. Randaccio, G. Tauzher, R. van Eldik, *Dalton Trans.*, submitted for publication.

[47] L. Randaccio, M. Furlan, S. Geremia, M. Slouf, I. Srnova, D. Toffoli, *Inorg. Chem.* **2000**, *39*, 3403.

[48] T. Wagner, C. E. Afshar, H. L. Cavrell, J. P. Glusker, U. Englert, H. P. C. Hogenkamp, *Inorg. Chem.* **1999**, *38*, 1785.

[49] X. Zou, K. L. Brown, *Inorg. Chim. Acta* **1997**, *267*, 305.

[50] [50a] C. Kratky, G. Färber, K. Gruber, K. Wilson, Z. Dauter, H-F. Nolting, R. Konrat, B. Kraütler, *J. Am. Chem. Soc.* **1995**, *117*, 4654. [50b] M. Rossi, J. P. Glusker, L. Randaccio, M. F. Summers, P. J. Toscano, L. G. Marzilli, *J. Am. Chem. Soc.* **1985**, *107*, 1729.

[51] M. Spitzer, F. Gartig, R. van Eldik, *Rev. Sci. Instrument* **1988**, *59*, 2092−2093.

[52] R. van Eldik, W. Gaede, S. Wieland, J. Kraft, M. Spitzer, D. A. Palmer, *Rev. Sci. Instrument.* **1993**, *64*, 1355−1357.

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