Kinetics and Mechanism of Axial Ligand Substitution of Alkyl Cobaloximes by Substituted Pyridines in Different Solvents

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Keywords: Cobaloximes / Solvent effects / *trans* effect / Ligand-substitution reactions / Nitrogen heterocycles

Ligand-substitution reactions of *trans*-RCo(Hdmg)$_2$S (where R = $PhCH_2$ or CF_3CH_2, Hdmg = dimethylglyoximate, and S = H_2O or MeOH) were studied for the nucleophiles 4-aminopyridine (4-NH_2Py), pyridine (Py) and 4-cyanopyridine (4-CNPy). From the pressure and temperature dependence of the substitution of methanol by 4-NH_2Py, Py, and 4-CNPy, the activation parameters $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta V^{\neq}$ were estimated for the cases where R = $PhCH_2$ and CF_3CH_2. The activation parameters for the substitution of H_2O by Py and 4-CNPy in the case where R = CF_3CH_2 were also found. The kinetic data and activation parameters show that the dissociative character of the reaction decreases on changing the R group from $PhCH_2$ to CF_3CH_2 and the solvent from MeOH to H_2O.

Introduction

The study of the chemical and physical properties of organocobalt compounds, which serve as models for vitamin B_{12}, is of interest both to inorganic and bioinorganic chemists. Various pseudo-octahedral organometallic complexes of Co^{III}, containing equatorial ligands such as dioximes,[1−9] imino groups/oximes[10] and Schiff bases derived from diamines and salicylaldehyde[11] or acetylacetonate[12] have been proposed as models for the vitamin B_{12} coenzyme. Some of us recently studied the reaction of cyanide with various alkylcobalamins (RCbl, where R = CN, $CNCH_2$, CF_3, CF_3CH_2, CF_2H, CH_3, $BrCH_2$) and found that the nature of the alkyl group has an important influence on the thermodynamic equilibrium constants, and the kinetics and mechanism of the substitution reactions of the axial ligand *trans* to the alkyl group.[13,14]

The nature of the axial alkyl group in cobaloximes[2] and in related $[RCo\{(DO)(DOH)pn\}H_2O]^+$ complexes[15] has an effect on the substitution of the ligand in the *trans* position. This substitution is very rapid and involves a dissociative activation mode, similar to the substitution of labile cobalamin complexes. Ligand-substitution reactions of vitamin B_{12} and its models in general follow a dissociative (I_d or D) type of mechanism.[16−28] In the case of the coenzyme, evidence was initially reported for an associative substitution mode, which was, however, recently reinterpreted and instead assigned to a subsequent Co−C heterolysis reaction.[29] An interchange mechanism may involve either associative or dissociative activation (I_a or I_d mechanism), according to the relative importance of bond making and bond breaking in the transition state. Evidence that usually leads to the assignment of a dissociative mechanism includes the absence of any relationship between the nature of the entering nucleophile and the rate constant, an increase in lability with an increase in the electron donating ability of the alkyl group R in the *trans* position, and positive values for both $\Delta V^{\neq}$ and $\Delta S^{\neq}$.

In general, kinetic studies are performed under pseudo first order conditions using a large excess of ligand over the complex. A linear dependence of the observed pseudo first-order rate constant on the concentration of the entering nucleophile has been observed in almost in all cases, both for aquacobalamin and synthetic models in aqueous solution. The first deviation from linearity was reported for the reaction of $[RCo\{(DO)(DOH)pn\}H_2O]^+$ complexes (R = Me and Et).[15] Curvature in the plot of k_{obs} versus ligand concentration generally characterizes multistep processes, such as a limiting dissociative mechanism (D), which involves a pentacoordinate intermediate, or a mechanism in which intermediate species are formed in a rapid pre-equilibrium which precedes the slow substitution step. In the above-mentioned complexes, linear relationships between

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k_{obs} and ligand concentration were found for the substitution of water by a number of nucleophiles. However, curvature was observed for L = imidazole, benzylamine, pyridine and 4-methylpyridine. Since the later four ligands all contain aromatic group, it was tentatively suggested that these are involved in forming the intermediate, perhaps through a π-π interaction with the conjugated system of the (DO)(DOH)pn equatorial ligand.

More recently, a non-linear dependence of k_{obs} on the concentration of the entering ligand has been reported for the reaction of aquacobalamin with substituted pyridines.[16] This was first incorrectly interpreted as evidence for the operation of a limiting dissociative mechanism, but later work clearly demonstrated that the observed deviation was due to the rapid formation of adducts involving the nucleophiles and cobalamin, preceding the slow substitution reaction according to a dissociative interchange mechanism.[17] This finding greatly enhanced our interest in mechanisms associated with the reactions of nucleophiles that contain an aromatic group because of the connection with the biochemistry of vitamin B_{12}. Therefore, in order to obtain a deeper understanding of this phenomenon, we extended the present study to cobaloximes, which are the most widely recognised model systems for the study of vitamin B_{12}. We report kinetic data for ligand-substitution reactions of $RCo(Hdmg)_2S$ with various pyridines, where R = $PhCH_2$ and CF_3CH_2, S = H_2O and MeOH and L = 4-NH_2Py, Py, and 4-CNPy, in order to study the kinetic *trans* effect in alkyl cobalt complexes as a function of nucleophile concentration, temperature and pressure.

Results and Discussion

The ligand-substitution reactions of *trans*-$RCo(Hdmg)_2S$ (where R = CF_3CH_2 and $PhCH_2$) with various nucleophiles L = 4-NH_2Py, Py, and 4-CNPy to form $RCo(Hdmg)_2L$, according to Equation (1), were studied with MeOH and H_2O as solvents.

$$RCo(Hdmg)_2S + L \rightarrow RCo(Hdmg)_2L + S \quad (1)$$

The results fall into two categories: (i) when the incoming ligand is Py or 4-NH_2Py, a non-linear concentration dependence is obtained for both $PhCH_2$ (S = MeOH) and CF_3CH_2 (S = MeOH or H_2O) derivatives, (ii) when the incoming ligand is 4-CNPy, a linear relationship is observed for both the $PhCH_2$ (S = MeOH) and CF_3CH_2 (S = MeOH or H_2O) derivatives. The reaction of $(4-10) \times 10^{-4}$ M *trans*-$RCo(Hdmg)_2(H_2O)$ with an excess of nucleophile (4-NH_2Py and Py) was studied at various temperatures in MeOH and H_2O. The results are shown in Figure 1 (R = CF_3CH_2, L = 4-NH_2Py in MeOH) and Figure 2 (R = CF_3CH_2, L = Py in H_2O); see also Figure S1 (R = $PhCH_2$, L = 4-NH_2Py in MeOH) and Figure S2 (R = CF_3CH_2, L = Py in MeOH) in the Supporting Information (see footnote on the first page of this article). The plots show significant curvature at high nucleophile concentration and negligible intercepts, which can be interpreted (see below) in terms of the interchange mechanism presented in Equations (2) and (3). The corresponding rate law is given in Equation (4), where K represents the equilibrium constant for precursor formation, and k the interchange rate constant. In these cases, k and K can be separated kinetically so that their values can be discussed individually.

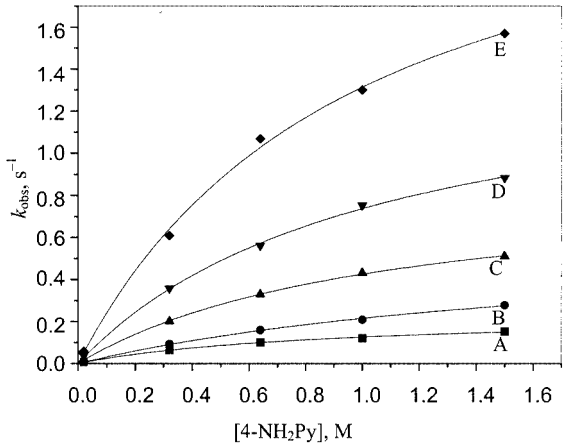

Figure 1. Plots of k_{obs} versus [4-NH_2Py] for the reaction with *trans*-$(CF_3CH_2)Co(Hdmg)_2(MeOH)$ as a function of temperature. Experimental conditions: $[Co^{III}] = 1 \times 10^{-3}$ M and temperature 20.0 (A), 25.0 (B), 30.0 (C), 35.0 (D), and 40.0 °C (E)

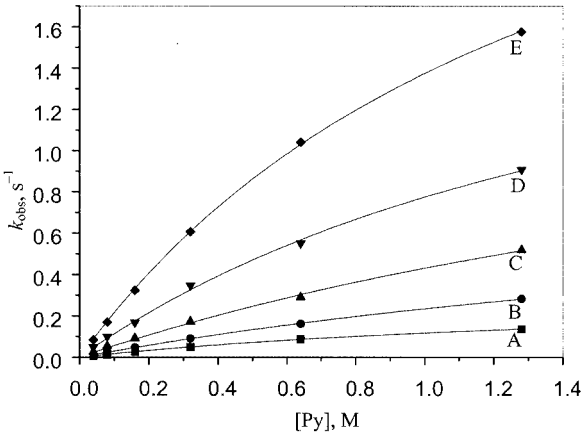

Figure 2. Plots of k_{obs} versus [Py] for the reaction with *trans*-$(CF_3CH_2)Co(Hdmg)_2(H_2O)$ as a function of temperature. Experimental conditions: $[Co^{III}] = 1 \times 10^{-3}$ M, pH = 8.0, I = 0.1 M $NaClO_4$ and temperature 20.0 (A), 25.0 (B), 30.0 (C), 35.0 (D), and 40.0 °C (E)

$$RCo(Hdmg)_2S + L \underset{}{\overset{K}{\rightleftharpoons}} [RCo(Hdmg)_2S.L] \quad (2)$$

$$[RCo(Hdmg)_2S.L] \xrightarrow{k} RCo(Hdmg)_2L + S \quad (3)$$

$$k_{obs} = kK[L]/(1 + K[L]) \quad (4)$$

Figures 3 and S3 (for the latter see the Supporting Information) show plots for k_{obs} versus [L] for the reaction of R = CF_3CH_2 with L = 4-CNPy in MeOH and H_2O, and

R = $PhCH_2$ with L = Py and 4-CNPy in MeOH, respectively. The linear plots have negligible intercepts, which indicate that the back reactions do not contribute significantly and that no parallel reaction takes place. This behaviour can be expressed by the rate law given in Equation (5), from which it follows that the overall second-order rate constant (k_a) is a composite of k and K, and cannot be separated easily.

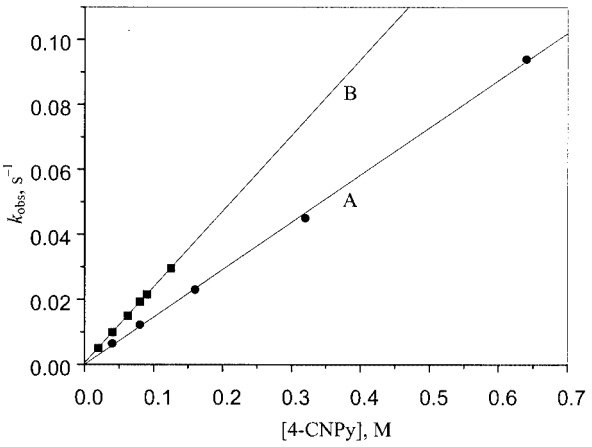

Figure 3. Plots of k_{obs} versus [4-CNPy] for the reaction with *trans*-$(CF_3CH_2)Co(Hdmg)_2S$ where S = MeOH (A) and H_2O (B) as a function of temperature. Experimental conditions: $[Co^{III}] = 1 \times 10^{-3}$ M, (pH = 8.0, I = 0.1 M $NaClO_4$ for S = H_2O) and temperature 25.0 °C

$$k_{obs} = k_a[L] = kK[L] \quad (5)$$

Tables 1, 2, 3, and 4 summarize the kinetic data obtained at different temperatures and pressures for the series of reactions investigated in this study. Plots of $\ln(k_a)$ versus pressure give good linear relationships as shown in Figure 4 for the reactions of *trans*-$(CF_3CH_2)Co(Hdmg)_2(MeOH)$

Table 1. Kinetic data for the reaction of *trans*-$RCo(Hdmg)_2(MeOH)$ with 4-NH_2Py as a function of temperature

R	T, °C	k, s^{-1}	K, M^{-1}	kK, $M^{-1}\,s^{-1}$
$PhCH_2$ [a]	5.0	127 ± 4	0.38 ± 0.02	48 ± 3
	10.0	187 ± 10	0.47 ± 0.03	88 ± 7
	15.0	228 ± 22	0.62 ± 0.07	141 ± 21
	20.0	458 ± 39	0.52 ± 0.06	238 ± 34
	25.0	1017 ± 135	0.35 ± 0.03	356 ± 56
	$\Delta H^{\neq}$, kJ·mol^{-1}			67 ± 2
	$\Delta S^{\neq}$, J·mol^{-1} K^{-1}			+28 ± 7
CF_3CH_2 [b]	20.0	0.24 ± 0.02	1.13 ± 0.16	0.27 ± 0.04
	25.0	0.61 ± 0.05	0.54 ± 0.07	0.33 ± 0.05
	30.0	0.88 ± 0.03	0.94 ± 0.05	0.83 ± 0.05
	35.0	1.50 ± 0.07	0.96 ± 0.09	1.44 ± 0.15
	40.0	2.60 ± 0.16	1.02 ± 0.12	2.65 ± 0.35
	$\Delta H^{\neq}$, kJ·mol^{-1}			90 ± 9
	$\Delta S^{\neq}$, J·mol^{-1} K^{-1}			+49 ± 29

[a] $[PhCH_2Co(Hdmg)_2MeOH] = 4 \times 10^{-4}$ M, [4-NH_2Py] = 0.01−0.64 M in MeOH. [b] $[CF_3CH_2Co(Hdmg)_2MeOH] = 1 \times 10^{-3}$ M, [4-NH_2Py] = 0.02−1.5 M in MeOH.

with 4-NH_2Py, Py and 4-CNPy. Similar plots are presented in Figures S4 and S5 (see the Supporting Information) for the reactions between $RCo(Hdmg)_2H_2O$ and the nucleophiles L = 4-NH_2Py, 4-CNPy, and Py, where R = $PhCH_2$ and S = MeOH, and the nucleophiles L = 4-CNPy and Py, where R = CF_3CH_2 and S = H_2O, respectively. The activation parameters for the substitution of methanol by 4-NH_2Py, Py, and 4-CNPy in the case where R = $PhCH_2$ were found to be $\Delta H^{\neq}$ = 67 ± 2, 77 ± 1 and 80 ± 2 kJ·mol^{-1}, $\Delta S^{\neq}$ = +28 ± 7, +57 ± 5 and +71 ± 6 J·mol^{-1} K^{-1}, and $\Delta V^{\neq}$ = +9.8 ± 0.1, +10.3 ± 0.3 and +13.0 ± 0.3 cm^3 mol^{-1}, respectively. The activation parameters in the case where R = CF_3CH_2 were found to be $\Delta H^{\neq}$ = 90 ± 9, 91 ± 5 and 89 ± 3 kJ·mol^{-1}, $\Delta S^{\neq}$ = +49 ± 29, +42 ± 17 and +36 ± 8 J·mol^{-1} K^{-1}, and $\Delta V^{\neq}$ = +7.5 ± 0.3, +8.6 ± 0.1 and +9.4 ± 0.1 cm^3 mol^{-1}, respectively. The activation parameters for substitution of H_2O by Py and 4-CNPy, where R = CF_3CH_2, were found to be $\Delta H^{\neq}$ = 94 ± 4 and 93 ± 1 kJ·mol^{-1}, $\Delta S^{\neq}$ = +62 ± 14 and +55 ± 4 J·mol^{-1} K^{-1}, and $\Delta V^{\neq}$ = +5.7 ± 0.4 and +7.4 ± 0.1 cm^3 mol^{-1}, respectively. These activation parameters, in particular the values of $\Delta V^{\neq}$, support the operation of a dissociative mechanism.

The discussion of the kinetic data will focus on the observed second-order rate constants for the overall reaction given in Equation (1), which is a composite of K and k, as given in Equations (2) and (3). Although for some systems k and K could be separated kinetically, the activation parameters were always determined for the combined value of kK, i.e. k_a. Little is presently known about the temperature and pressure dependence of the precursor formation step, and for that reason the thermodynamic contributions of K form part of the overall reported parameters. This complication should be kept in mind when interpreting the overall rate and activation parameters.

The reactivity of the cobaloxime complexes shows a strong dependence on the nature of the alkyl substituent R. The lability of these complexes was affected by the electronic and steric properties of the alkyl group. The second-order rate constants for the reaction of *trans*-$(PhCH_2)Co(Hdmg)_2(MeOH)$ with 4-NH_2Py, Py, and 4-CNPy were found to be 356, 182, and 296 $M^{-1}\,s^{-1}$ at 25.0 °C, respectively. However, those obtained for the reaction with *trans*-$(CF_3CH_2)Co(Hdmg)_2(MeOH)$ were 0.330, 0.147 and 0.153 $M^{-1}\,s^{-1}$ at 25.0 °C, respectively. The second-order rate constants for the reaction of *trans*-$(CF_3CH_2)Co(Hdmg)_2(H_2O)$ with Py and 4-CNPy in H_2O were found to be 0.317 and 0.214 $M^{-1}\,s^{-1}$ at 25.0 °C, respectively. This trend shows that the kinetic *trans* effect is greater for R = $PhCH_2$ than for R = CF_3CH_2, in accordance with the donor properties of the alkyl group. For the complexes *trans*-$[RCo(LNHpy)(HLNHpy)]^+$, where HLNHpy is the tridentate 2-(2-pyridylethyl)amino-3-butanone oxime ligand and $LNHpy^-$ its conjugate base, the second-order rate constants for substitution of 2-(pyridylethyl) were found to be 19.1, 0.25, 2.2 × 10^{-2}, and 1.7 × 10^{-2} $M^{-1}\,s^{-1}$ for R = Et, Me, CF_3CH_2, and $-CH_2-$, respectively.[30] The reaction between alkylcobalamins

Table 2. Kinetic data for the reaction of *trans*-RCo(Hdmg)$_2$(S) with L in MeOH and H_2O as a function of temperature

	k_a, M^{-1} s^{-1}			
	R = $PhCH_2$, S = MeOH		R = CF_3CH_2,L = 4-CNPy	
T, °C	L = Py[a]	L = 4-CNPy[b]	S = MeOH[c]	S = H_2O[d]
5.0	18.3 ± 0.1	28 ± 2		
10.0	33.9 ± 0.3	49 ± 2		
15.0	64 ± 1	97 ± 1		
20.0	108 ± 1	173 ± 2	0.073 ± 0.001	0.112 ± 0.001
25.0	182 ± 1	296 ± 3	0.153 ± 0.001	0.214 ± 0.003
30.0			0.254 ± 0.001	0.393 ± 0.004
35.0			0.464 ± 0.003	0.739 ± 0.004
40.0			0.820 ± 0.004	1.390 ± 0.020
$\Delta H^{\neq}$, kJ·mol^{-1}	77 ± 1	80 ± 2	89 ± 3	93 ± 1
$\Delta S^{\neq}$, J·mol^{-1} K^{-1}	+57 ± 5	+71 ± 6	+36 ± 8	+55 ± 4

[a] [$PhCH_2Co(Hdmg)_2MeOH$] = 4 × 10^{-4} M, [Py] = 0.01 M. [b] [$PhCH_2Co(Hdmg)_2MeOH$] = 4 × 10^{-4} M, [4-CNPy] = 0.01 M. [c] [$CF_3CH_2Co(Hdmg)_2MeOH$] = 4 × 10^{-4} M, [4-CNPy] = 0.08 M. [d] [$CF_3CH_2Co(Hdmg)_2H_2O$] = 1 × 10^{-3} M, [4-CNPy] = 0.08 M, pH = 8 and I = 0.1 M $NaClO_4$.

Table 3. Kinetic data for the reaction of *trans*-(CF_3CH_2)Co(Hdmg)$_2$(S) with Py in MeOH and H_2O as a function of temperature

	T, °C	*k*, s^{-1}	*K*, M^{-1}	*kK*, M^{-1} s^{-1}
S = MeOH[a]	20.0	0.88 ± 0.05	0.07 ± 0.01	0.062 ± 0.010
	25.0	1.13 ± 0.05	0.13 ± 0.01	0.147 ± 0.013
	30.0	2.04 ± 0.14	0.12 ± 0.01	0.245 ± 0.026
	35.0	3.36 ± 0.40	0.12 ± 0.02	0.403 ± 0.083
	40.0	9.82 ± 0.89	0.08 ± 0.01	0.786 ± 0.121
	$\Delta H^{\neq}$, kJ·mol^{-1}			91 ± 5
	$\Delta S^{\neq}$, J·mol^{-1} K^{-1}			+42 ± 17
S = H_2O[b]	20.0	0.33 ± 0.01	0.57 ± 0.03	0.188 ± 0.011
	25.0	0.96 ± 0.08	0.33 ± 0.04	0.317 ± 0.047
	30.0	1.71 ± 0.25	0.34 ± 0.07	0.581 ± 0.147
	35.0	2.20 ± 0.19	0.54 ± 0.07	1.188 ± 0.185
	40.0	3.40 ± 0.08	0.68 ± 0.03	2.312 ± 0.117
	$\Delta H^{\neq}$, kJ·mol^{-1}			94 ± 4
	$\Delta S^{\neq}$, J·mol^{-1} K^{-1}			+62 ± 14

[a] [$CF_3CH_2Co(Hdmg)_2MeOH$] = 1 × 10^{-3} M and [Py] = 0.04−4.0 M. [b] [$CF_3CH_2Co(Hdmg)_2(H_2O)$] = 1 × 10^{-3} M, [Py] = 0.04−1.28 M, pH = 8 and I = 0.1 M $NaClO_4$.

(RCb1) and cyanide showed that the kinetic *trans* effect decreases in the order (R =) Pr > Me (ca. 10^4 $M^{-1}s^{-1}$) > CF_3CH_2 > CF_2H (10^3 M^{-1} s^{-1}) > CF_3 > $NCCH_2$ > CN (0.1 M^{-1} s^{-1}).[14] The substitution of H_2O by CN^- for various cobinamides (RCbi) increases in the order (R =) H_2O = DMBz < OH^- < CN^- < CH_2=CH, Me, and Et, with the corresponding rate constants ranging from about 10^3 to about 10^8 M^{-1} s^{-1}.[31]

The pK_{BH+} values for 4-NH_2Py, Py, and 4-CNPy are 9.17,[32] 5.23,[32] and 1.7[33] (estimated), respectively. Both in water and methanol, the second-order rate constants for the ligation of the pyridines are only slightly affected by their basicity. Such a weak sensitivity of the *kK* values is consistent with an I_d mechanism, which is controlled by the breaking of the Co−S bond. Analogously, the substitution rate constants of aquacobalamin by a variety of substituted pyridine ligands were found to be independent of their pK_{BH+} values.[25]

The second-order rate constants for substitution of H_2O in *trans*-(CF_3CH_2)Co(Hdmg)$_2$(H_2O) by Py and 4-CNPy are higher than that found for the corresponding reaction with cysteine,[34] and this was ascribed to metal-to-ligand π bonding. The range of rate constants for axial ligand binding to methylaquacobaloxime are 4.3−7.5 (RNH_2), 12.8−27.3 (RS^-), 49.6−55.2 (RSH), and 92−200 (X-py) M^{-1} s^{-1}.[35] That is, the π-acceptor ligands (X-Py, RS^- and RSH) react more rapidly than pure σ donors (RNH_2). In the ligand-substitution reactions of *trans*-MeCo(Hdmg)$_2$(H_2O), the higher reactivity of the substituted pyridines (as compared to neutral or anionic thiolates) stand in contrast to the opposite reactivity order for these same nucleophiles with various unsaturated carbon electrophiles.[35] The ratio of the second-order rate constants for the reaction of pyridine and 4-CNpy with alkylcobaloxime (R = CF_3CH_2) is 1.48, and that for R = Me is 1.24. The second-order rate constant in the case of R = Me is higher than for R = CF_3CH_2, which is due to the stronger labilization by R = Me.

The second-order rate constants for the substitution of H_2O in *trans*-RCo(Hdmg)$_2$(H_2O) by pyridine were found to

Table 4. Kinetic data for the reaction of *trans*-$RCo(Hdmg)_2S$ with 4-NH_2Py, Py, and 4-CNPy as a function of pressure

	Pressure, MPa	k_{obs}, s^{-1}		
		4-NH_2Py	Py	4-CNPy
R = $PhCH_2$, S = MeOH[a]	10	2.28 ± 0.07	0.98 ± 0.03	1.28 ± 0.03
	50	1.94 ± 0.05	0.83 ± 0.01	1.01 ± 0.05
	90	1.63 ± 0.04	0.68 ± 0.01	0.81 ± 0.01
	130	1.37 ± 0.04	0.58 ± 0.01	0.66 ± 0.06
	$\Delta V^{\neq}$, $cm^3\ mol^{-1}$	+9.8 ± 0.1	+10.3 ± 0.3	+13.0 ± 0.3
R = CF_3CH_2, S = MeOH[b]	10	0.150 ± 0.006	0.107 ± 0.001	0.116 ± 0.006
	50	0.136 ± 0.007	0.093 ± 0.002	0.100 ± 0.006
	90	0.119 ± 0.002	0.082 ± 0.001	0.087 ± 0.001
	130	0.107 ± 0.003	0.072 ± 0.001	0.075 ± 0.004
	$\Delta V^{\neq}$, $cm^3\ mol^{-1}$	+7.5 ± 0.3	+8.6 ± 0.1	+9.4 ± 0.1
R = CF_3CH_2, S = H_2O[c]	10	–	0.135 ± 0.002	0.114 ± 0.003
	50	–	0.127 ± 0.003	0.101 ± 0.004
	90	–	0.115 ± 0.002	0.091 ± 0.002
	130	–	0.104 ± 0.002	0.081 ± 0.002
	$\Delta V^{\neq}$, $cm^3\ mol^{-1}$	–	+5.7 ± 0.4	+7.4 ± 0.1

[a] [$PhCH_2Co(Hdmg)_2MeOH$] = (4−7) × 10^{-4} M, {[4-NH_2Py], [Py] = 0.04 M and at 5.0 °C}, {[4-CNPy] = 0.0225 M and at 10.0 °C}. [b] [$CF_3CH_2Co(Hdmg)_2MeOH$] = 2 × 10^{-3}, [NH_2Py] = 0.08 M, {[Py], [4-CNPy] = 0.16 M}, and at 40.0 °C. [c] [$CF_3CH_2Co(Hdmg)_2H_2O$] = 2 × 10^{-3}, [Py] and [4-CNPy] = 0.08 M, pH = 8, at 40.0 °C and I = 0.1 M $NaClO_4$.

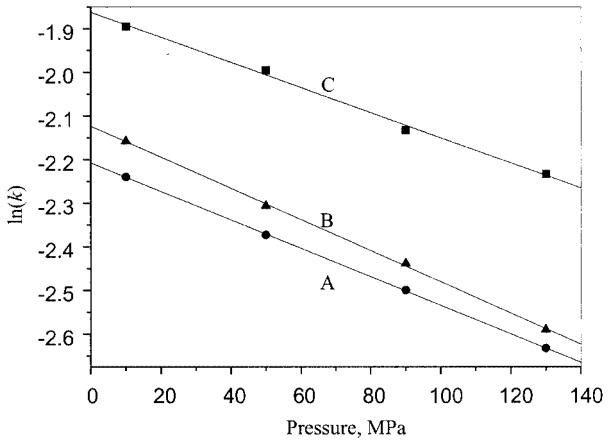

Figure 4. Plots of ln(k) versus pressure for the reaction between *trans*-$(CF_3CH_2)Co(Hdmg)_2(MeOH)$ and L, where L = Py (A), 4-CNPy (B) and 4-NH_2Py (C). Experimental conditions: [Co^{III}] = 2 × 10^{-3} M, [NH_2Py] = 0.08 M, [Py] and [4-CNPy] = 0.16 M, at 40.0 °C

be 1.49 × 10^4 (isopropyl), 1.17 × 10^3 (ethyl), 1.16 × 10^2 (methyl), 1.22 × 10^3 (phenylethyl), 1.64 × 10^2 (3-cyanopropyl), 1.65 × 10^2 (2-methoxyethyl), 2.34 × 10^1 (1-propenyl), 4.2 (iodomethyl), 3.17 × 10^{-1} (2,2,2-trifluoroethyl), 1.06 × 10^{-1} (chloromethyl), and 5.59 × 10^{-2} (cyanomethyl) $M^{-1}\ s^{-1}$ at 25 °C, respectively.[36] The second-order rate constants for substitution of methanol by pyridine in the complex *trans*-$(RSO_2)Co(Hdmg)_2(MeOH)$ were found to be 4.79 ± 0.01 and 3.56 ± 0.11 $M^{-1}\ s^{-1}$ for R = *p*-tolyl and methyl, respectively. Substitution of the solvent by pyridine in the complex $(CH_3C_6H_4SO_2)Co(Hdmg)_2S$ does have an effect on the second-order rate constants, which were found to be 1.12 × 10^{-1}, 4.79 × 10^{-2}, and 4.16 × 10^{-3} $M^{-1}\ s^{-1}$ for S = EtOH, MeOH, and H_2O, respectively.[37]

Ligand-substitution reactions of *trans*-$RCo(Hdmg)_2H_2O$, for R = $PhCH_2$ by Py and 4-CNPy in methanol, and also for R = CF_3CH_2 by 4-CNPy in H_2O and MeOH, are characterised by a linear dependence of the observed pseudo first-order rate constant on the concentration of the entering nucleophile as shown in Figures 3 and S3. In terms of the suggested dissociative interchange mechanism, this means that precursor formation is weak and does not show up in the kinetic data even at high concentrations of the entering ligand. The curvature observed in the nucleophile concentration dependence of k_{obs} for the substitution reactions of *trans*-$RCo(Hdmg)_2(H_2O)$ (R = $PhCH_2$ and CF_3CH_2) by 4-NH_2Py and Py suggests that an interchange mechanism involving a rapid pre-association of the complex with the incoming ligand is operating. The precursor-formation constant decreases when the electron donor ability of the alkyl group in the *trans* position is increased. It was found that the precursor-formation constants for the substitution of MeOH by 4-NH_2Py are 0.35 and 0.54 M^{-1} at 25.0 °C for R = $PhCH_2$ and CF_3CH_2, respectively. It is also apparent that the precursor-formation constant depends on the nature of the nucleophile. The π-electron density on the Py ring increases in the order 4-CNPy < Py < 4-NH_2Py,[38] which is also the order of increasing tendency for precursor formation.

It is generally known from the literature that a system must be sufficiently electron-rich in order that bonding through the π-electrons of pyridine can occur.[39] This π-interaction results in the effective binding of the nucleophile close to the metal centre during precursor formation, which is followed by an interchange of ligands controlled by

breakage of the Co−OH_2 bond by an I_d mechanism.[25] The pre-equilibrium constants for the reaction of $[MeCo\{(DO)(DOH)pn\}H_2O]^+$ with L = imidazole, benzylamine, Py and 4-MePy at 25 °C were found to be 0.26, 0.12, 1.00, and 1.81 M^{-1}, respectively.[15] The pre-equilibrium constants for the reaction of aquacobalamin with Py, 4-MePy, and 2,4-DMePy were found to be 1.1, 2.5, and 4.9 M^{-1}, respectively.[25]

By way of comparison, the lability of *trans*-$RRh(Hdmg)_2(H_2O)$ is affected by the steric and electronic effects of the alkyl group R, and in all cases the reaction rate is almost independent of the nucleophilicity of the incoming ligand.[40,41] There is a definite trend in the $\Delta V^{\neq}$ data: the values are significantly positive for the faster substitution reactions (R = CH_3) but significantly negative for the slower substitution reactions (R = CF_3CH_2).[42] This trend correlates well with the *trans*-influence of the R groups in the ground state, as observed for a series of pyridine (py) complexes: the Rh−Py bond length decreases in the order CH_3 [2.220(3) Å] > $ClCH_2$ [2.178(3) Å] > CF_3CH_2 [2.145(3) Å].[40,41] A similar trend is expected for the Rh−O bond in the corresponding aqua complexes: faster reactions are thus associated with the stronger *trans* influence of the methyl group, and slower reactions with the weaker *trans* influence of $ClCH_2$ and CF_3CH_2. Furthermore, the nature of the R group directly determines the substitution mechanism. The strong donor properties of CH_3 result in a dissociative substitution process (I_d), characterised by the significantly positive $\Delta V^{\neq}$ value, whereas the weaker donor properties of CF_3CH_2 favour a more associative substitution mechanism (I_a), as indicated by the significantly negative value of $\Delta V^{\neq}$.[42] Thus, in the transition state the degree of bond breakage (Rh−OH_2) and bond formation (Rh−L) is controlled by the donor properties of R.

The $\Delta H^{\neq}$ values for substitution reactions of *trans*-$RCo(Hdmg)_2(H_2O)$ (for R = $PhCH_2$ and CF_3CH_2) by pyridine derivatives in H_2O and methanol are relatively independent of the nature of the incoming ligand. It is expected that the reactions involve a dissociative activation process, since the ligands are loosely bound in the transition state. The activation enthalpy for the substitution reaction with R = CF_3CH_2 is higher than for R = $PhCH_2$ due to the strong Co−OH_2 bond in the ground state. Hence, $\Delta H^{\neq}$ values appear to be affected by both the electron-withdrawing and steric effects of the R group. The influence of these factors on $\Delta S^{\neq}$, however, cannot be rationalised. The entropy values should be slightly more positive since the transition state should be less ordered than the initial state, owing to the relief of steric strain. The organocobaloximes are about 10^5 times more labile than the corresponding nitro and iodo-aqua complexes. This very high rate enhancement is due to both the decrease in the activation enthalpy and the increase in the activation entropy.[43]

The values of $\Delta V^{\neq}$ obtained for R = CF_3CH_2 in methanol were found to be +7.5, +8.6, and +9.4 $cm^3\ mol^{-1}$, respectively. The values of $\Delta V^{\neq}$ for substitution of the solvent by pyridine derivatives (4-NH_2Py, Py, and 4-CNPy) in the complex *trans*-$(PhCH_2)Co(Hdmg)_2(H_2O)$ were found to be +9.8, +10.3 and +13 $cm^3\ mol^{-1}$, respectively. This is consistent with an enhanced dissociative (limiting D) character in the mechanism on going from the CF_3CH_2 derivative to the $PhCH_2$ derivative. Interestingly, $\Delta V^{\neq}$ for substitution of H_2O by Py and 4-CNPy (R = CH_2CF_3 in H_2O) were found to be +5.7 and +7.4 $cm^3\ mol^{-1}$, respectively. In these cases the small positive values of $\Delta V^{\neq}$ suggest that the mechanism is of an I_d nature. Thus the substitution mechanism changes from limiting D to I_d along the series from R = $PhCH_2$ to R = CF_3CH_2, on decreasing the basicity of the nucleophiles, and on changing the solvent from MeOH to H_2O. This mechanistic changeover is clearly seen in the size of $\Delta V^{\neq}$, and can be directly correlated with the donor properties of R, which in turn control the magnitude of the rate constants. The greater donating properties of $PhCH_2$ result in a limiting dissociative process as characterized by the significantly positive $\Delta V^{\neq}$. Similarly, the weaker donor properties of CF_3CH_2 favour more a dissociative interchange mechanism, as shown by the $\Delta V^{\neq}$ data. The activation parameters for substitution of aquacobalamin by thiourea, substituted thiourea and pyridine for the forward and reverse reactions conclusively confirm that the mechanism of the substitution is a dissociative interchange. For instance, the volumes of activation for both the forward and reversible reactions have values between +6 and +10 $cm^3\ mol^{-1}$.[16,17]

We conclude that all the available data underline the operation of a limiting dissociative (D) mechanism for substitution of methanol by 4-CNPy when R = $PhCH_2$. However, when R = CF_3CH_2, the mechanism is I_d for substitution of the solvent by 4-CNPy in methanol or H_2O. The non-linear concentration dependence must therefore be due to the operation of an I_d mechanism, and involve the formation of a precursor complex. The strong precursor formation is ascribed to an interaction of the π system of the pyridine ligand with the coordination sphere of the complex. This π interaction results in the effective binding of the entering nucleophile close to the metal centre during precursor formation, which is followed by an interchange of ligands controlled by the breakage of the Co−solvent bond by an I_d mechanism.

Experimental Section

Materials: All chemicals were of p. a. grade and used as received. 4-Aminopyridine and 4-cyanopyridine were purchased from Acros, tricine buffer from Sigma and pyridine from Baker. Ultra pure water was used in the kinetic measurements. *trans*-$RCo(Hdmg)_2H_2O$ (R = CF_3CH_2, $PhCH_2$) were prepared as previously reported.[44] Because alkyl cobaloximes are light sensitive, their solutions were prepared and handled away from light.

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 and Hewlett Packard 8452A 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 entering nucleophile concentration was in at least a tenfold excess. Measurements at high pressure were carried out using a home-made high pressure stopped-flow unit.[45] Kinetic data were analyzed with the OLIS KINFIT program. All instruments used were thermostatted to the desired temperature (± 0.1 °C).

Acknowledgments

The authors gratefully acknowledge financial support from CNR (Rome), MIUR (Rome), PRIN No. MMO3185591, the Deutsche Forschungsgemeinschaft and the Max-Buchner Research Foundation (to R. v. E.).

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Received October 14, 2003

