shows the 1:3:3:1 quartet resonance (J_{HF} = 2 Hz) for the hydride proton which is ascribable to the through-space coupling with the nearest three equivalent ^{19}F nuclei. However, it is worth pointing out that each of the two pathways shown in Figure 1 has its own energy barrier for the equilibration. Let us refer to the rotational barrier as A which is to be overcome when the wedge-type orientation of the two cyclopentadienyl groups is maintained. A stereochemically nonrigid molecule would prefer to proceed along the alternative path, the polytopal rearrangement with barrier B; this molecule when it comes to a top of barrier B will witness an elevation of barrier A due to the increase in steric crowding at the quasisquare-planar transition state.

The energy barrier of *ca.* 17 kcal mol^{-1} suggests the possibility of separating the conformers. The configurational stability of $Cp_2MoH(R)$ is remarkable in view of the stereochemical nonrigidity[51] or the lability[52–54] of the group VIII metal–hydride complexes. A chiral pseudotetrahedral complex, *e.g.*, (π-C_5H_5)(π-C_5H_4X)MoH(R), if it were prepared, should in principle be resolvable into optical isomers as was the case for, *e.g.*, $[CpMn(CO)(NO)(PPh_3)]^+$.[55,56]

Acknowledgments. We wish to acknowledge experimental assistance of Mr. H. Minamida and Mr. J. Izawa. Appreciation is also due to Mr. Y. Terawaki for the nmr spectra and to Professor T. Fueno and Dr. O. Kazimoto for the computer program.

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Coenzyme B$_{12}$ Model Studies. Equilibria and Kinetics of Axial Ligation of Methylaquocobaloxime by Thiols[1,2]

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Abstract: The reactions of thiols with methylaquocobaloxime have been shown to involve only axial ligation and not cleavage of the carbon–cobalt bond at 25°, ionic strength 1.0 *M*, and pH values less than 13. The rate constants for ligation by neutral thiol are twofold greater than those for thiolate anion. Mechanisms which account for the apparent reactivity of neutral thiols on the basis of general or specific catalysis by protons of the attack by thiolate anions on methylaquocobaloxime have been ruled out by (i) calculation of rate constants which are greater than the diffusion-controlled limit, (ii) structure–reactivity correlations, and (iii) the similarities of equilibrium and kinetic constants for ligation by neutral thiol and an *S*-methyl sulfide. The small effects of variations in thiolate anion basicity on the rate and equilibrium constants for ligation reactions of methylaquocobaloxime may be due to contributions to the stabilization of transition states and thiol-liganded products by π bonding between the cobalt and sulfur atoms. The data are consistent with a detailed mechanism for ligation which is SN1 in nature.

The similarities of numerous chemical and physical properties of cobaloximes with those of various derivatives of coenzyme B$_{12}$ have recently been emphasized, especially by Schrauzer and coworkers.[4–14]

The cobaloximes are octahedral cobalt complexes with a planar ligand field (Figure 1) provided by two bidentate dimethylglyoxime anion ligands, and in at least one case the glyoxime nitrogens and the cobalt atom have been shown to be coplanar by X-ray crystallography.[15] A variety of alkylcobaloximes have been formed, isolated, and characterized, and either organic or inorganic neutral and anionic Lewis bases may act as axial ligands.

Several papers dealing with the ligand-substitution reactions of cobaloximes[16–19] and cobalamins[20–23]

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(2) Abbreviations: Bicine, *N*,*N*-bis(2-hydroxyethyl)glycine; EDTA, ethylenediaminetetraacetic acid; HEPES, *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid; MA, mercaptoacetic acid; ME, 2-mercaptoethanol; $Me(D_2H_2)HOH$, methylaquocobaloxime; MMA, methyl mercaptoacetate; py, pyridine; SMME, *S*-methyl-2-mercaptoethanol.

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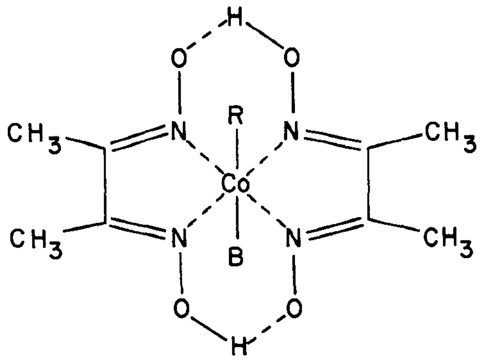

Figure 1. Cobaloxime, a bis(dimethylglyoximato)cobalt complex.

have appeared, but no systematic study of structure–reactivity correlations has been made nor have thiol ligands been studied in detail.

Kinetic and equilibrium studies of axial ligation in methylcobaloximes (Figure 1, R = CH_3) by thiols

$$\mathrm{Me(D_2H_2)HOH} + \begin{bmatrix} \mathrm{L^-} \\ \mathrm{LH} \end{bmatrix} \underset{k_{-f}}{\overset{k_f}{\rightleftarrows}} \begin{bmatrix} \mathrm{Me(D_2H_2)L^-} \\ \mathrm{Me(D_2H_2)LH} \end{bmatrix} + \mathrm{HOH} \quad (1)$$

where L^- and LH are the ligands, are of biological interest, since sulfur ligands have been implicated in biologically active forms of cobalamins.[10,24,25] In addition, many of the B_{12}-requiring enzymes contain essential sulfhydryl groups which may be important for binding and/or activation of the B_{12} moiety.[26]

It had been our original intent to study methyl transfer from methylcobaloximes to thiols, a reaction which was reported by Schrauzer and Windgassen[9] and which might serve as a model for the B_{12} dependent N_5-methyl tetrahydrofolate–homocysteine transmethylase reaction. However, the carbon–cobalt bond remains intact under the conditions employed in the present work, and the reaction of methylaquocobaloxime with thiol involves only axial ligation. Studies on the mechanism of ligation and thermodynamic stabilities of various alkyl–cobalt complexes are the subjects of this paper.

Experimental Section

Materials. Methylaquocobaloxime was synthesized as described by Schrauzer and Windgassen.[9] *Anal.* (Huffman Laboratories) Calcd for $C_9H_{19}O_5N_4Co$: C, 33.55; H, 5.94; N, 17.39. Found: C, 33.21; H, 5.91; N, 17.79.

Methylcobaloximes and their solutions were handled in dim light in order to prevent photolytic cleavage of the carbon–cobalt bond. Thiols and SMME were redistilled and stored under nitrogen. Buffer components, inorganic salts, and EDTA were reagent grade and used without further purification. Stock solutions of thiol and methylaquocobaloxime were made fresh daily. Deionized water of greater than 5 × 10^5 ohms cm specific resistance was used.

Anaerobic conditions were attained by bubbling nitrogen, scrubbed *via* a vanadium oxide train,[27] through solutions for 30 min in tubes or cuvettes sealed with silicon rubber stoppers.

Product Identification. Gas chromatographic analyses were performed on a Varian Aerograph Series 2100 gas chromatograph.

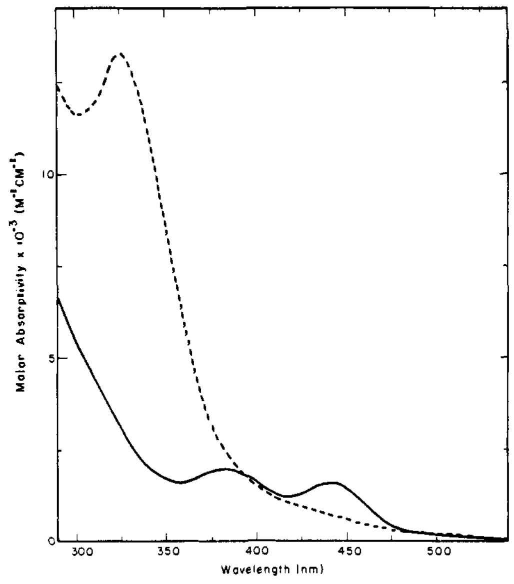

Figure 2. Spectra of $Me(D_2H_2)HOH$ (———) and $Me(D_2H_2)SR^-$ (- - - - -). Below 380 nm [complex] = 5.0 × 10^{-5} *M*, [MA] = 5 × 10^{-4} *M*; above 380 nm [complex] = 5.0 × 10^{-4} *M*, [MA] = 2.5 × 10^{-3} *M*. Carbonate buffer, 65% free base, pH 10.2. Product formation was >98% in both samples. *Note:* thiolate anion begins to absorb at 300 nm.

Methane was analyzed on a 6 ft × 0.125 in. column of Porapak Q[5] and had a retention time of 60 sec at 50°, He flow rate 60 ml/min.

SMME was analyzed on a column of 20% 1,2,3-tris(2-cyanoethoxy)propane on 65 mesh Chromosorb P[28] and had a retention time of 23.3 min at 130°, He flow rate 50 ml/min. Samples for gas chromatographic analysis were withdrawn with a 10-μl Hamilton syringe introduced through the silicon stopper. Photolysis experiments were carried out by irradiating quartz cuvettes or small test tubes containing anaerobic solutions of methylaquocobaloxime with a Sylvania CZA 500-W projector lamp at a distance of 34 cm.

Kinetic Measurements. Kinetic runs were made under pseudo-first-order conditions with ligand concentration in at least a tenfold excess over methylaquocobaloxime concentration. Unit ionic strength was maintained with KCl. Reaction mixtures and concentrated alkaline stock solutions of thiol contained 10^{-4} *M* EDTA to retard thiol oxidation. Thiol solutions were adjusted to the desired pH with KOH when necessary to prevent alteration of the pH of reaction mixtures, and, with EDTA present, proved to be stable by the criteria of reproducibility of rate measurements and uv absorbance of thiolate anion for the duration of the experiments. The pH was maintained with 0.1 *M* phosphate, HEPES, borate, carbonate, or Bicine buffers or KOH. Reaction progress was monitored by measurements of the change in absorbance upon addition of methylaquocobaloxime to reaction mixtures containing ligand in the thermostated cell compartment of a Coleman-Hitachi 124 double-beam spectrophotometer at 25 ± 0.1°. Suitable wavelengths for reaction progress measurements were determined by difference spectra between the reactants and products (split compartment quartz mixing cells, Pyrocell) on a Cary 14 recording spectrophotometer (Figure 2). Reactions which were too rapid to follow by conventional techniques were studied with a Gilford 2000, a stopped-flow mixing apparatus, and a storage oscilloscope for recording the absorbance changes. The methods of data analysis to obtain first-order rate constants (k_{obsd}) have been described.[29] Second-order rate constants, k_f, for ligation of methylaquocobaloxime (eq 1) were obtained from the slopes of graphs of k_{obsd} *vs.* ligand concentration by the least-squares method: nonzero ordinate intercepts of such plots, when present, gave values for the reverse rate constant, k_{-f}, according to

$$k_{obsd} = k_f[L] + k_{-f} \qquad (2)$$

Rate constants for ligand dissociation from $Me(D_2H_2)L^-$ were also obtained from the change in absorbance at suitable wavelengths

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of a solution of $Me(D_2H_2)L^-$ (generated *in situ*) following a 1:2 dilution and associated pH jump on a Durrum-Gibson stopped-flow spectrophotometer or following a 1:40 dilution in a dilution stopped flow mixing apparatus. Under these conditions the complexes are unstable and dissociate.

Measurements of pH were made on reaction mixtures at 25 ± 0.1° with a Radiometer Model 25 SE pH meter equipped with Radiometer combined glass electrodes GK2302 C and GK2302 B. Only the latter electrode and exclusively potassium salts were utilized at pH values above 12. The electrodes were standardized with Beckman Standard Buffers at pH 4, 7, and 10, and with 0.1 *N* NaOH (pH 12.86 at 25°, corrected for 0.1 *M* sodium ion effect on the B electrode).[30]

Equilibrium Measurements. The proton dissociation constants of $Me(D_2H_2)HOH$ and MA were determined by spectrophotometric titration at 455 and 242 nm, respectively, on a Zeiss PMQ II or Gilford 2000 spectrophotometer equipped with thermostated cell blocks maintained at 25 ± 0.1°, as described in detail elsewhere.[29] Spectrophotometric titration data were fit graphically to the equation

$$\mathrm{pH} = \mathrm{p}K' + \log[\alpha/(1 - \alpha)] \tag{3a}$$

where α is the fraction as the free base species

$$\alpha = (A_x - A_a)/(A_b - A_a) \tag{3b}$$

and A_a, A_b, and A_x are the absorbance values of solutions of the acid, conjugate base, and mixtures of the two forms at a given pH value, respectively. Since the basic end point was unavailable for the titration of $Me(D_2H_2)HOH$ due to the instability of this complex at high pH, the data were analyzed utilizing[31]

$$(A_x - A_a) = (A_b - A_a) - (A_x - A_b)[H^+]/K' \tag{4}$$

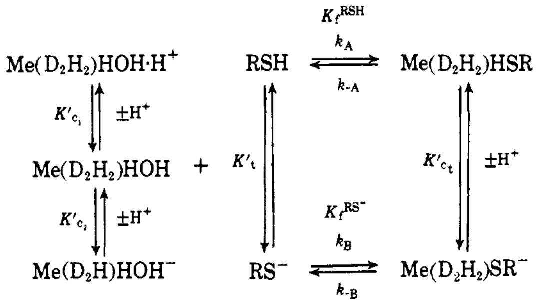
where K' is the proton dissociation constant and the other symbols are defined above. The value of A_b obtained from eq 4 was used to fit the data to eq 3a, since the latter method provides a less biased weighting of the data.

Apparent equilibrium constants for the formation of methylcobaloxime adducts from $Me(D_2H_2)HOH$ and RSH or $RSCH_3$

$$K_f^{app} = \{[Me(D_2H_2)L^-] + [Me(D_2H_2)LH]\}/[Me(D_2H_2)HOH]\{[L^-] + [LH]\} \tag{5}$$

(see Scheme I) were determined by two methods. In method I,

Scheme I



equilibrium constants for the formation of $Me(D_2H_2)L^-$ were determined spectrophotometrically from the change in absorbance at equilibrium at 325 nm for thiols (or 305 and 315 nm for SMME) at various ligand concentrations and pH values. The data at a given pH were analyzed with

$$OD = OD_i - (\Delta\epsilon[Me(D_2H_2)HOH][L]_{free})/([L]_{free} + 1/K_f^{app}) \tag{6a}$$

(where OD_i is the absorbance of $Me(D_2H_2)HOH$ in the absence of added ligand and $\Delta\epsilon$ is the difference between the extinction coefficient of $Me(D_2H_2)HOH$ and that of $Me(D_2H_2)L^-$) and a computer program by a nonlinear least-squares method. In method II the apparent equilibrium constants were obtained from kinetic data for ligand association and dissociation

$$K_f^{app} = k_f/k_{-f} \tag{6b}$$

Results

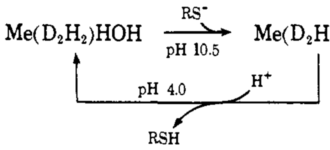
Product Analysis. Gas chromatographic analysis of reaction mixtures containing 10^{-3} *M* $Me(D_2H_2)HOH$ and a tenfold or greater excess of ME at pH 8.22, 9.74, or 10.83, following equilibration for 30 min in the presence or absence of air, revealed no detectable SMME, and as little as 10% methyl transfer could easily have been detected as SMME in a 2-μl sample. Furthermore, similar reaction mixtures at pH 9.5 (whether aerobic or anaerobic) provided no significant amounts of methane (even 5% reductive cleavage could easily have been detected as methane in a 2-μl sample).

The reaction of 10^{-3} *M* $Me(D_2H_2)HOH$ with tenfold or greater excess of dithiothreitol at pH 9.9 or 5.0 failed to produce significant amounts of methane over the course of several hours of reaction in the dark.

Finally, 10^{-3} *M* $Me(D_2H_2)HOH$ was shown to liberate similar amounts of methane upon anaerobic photolysis for 1 hr before and after reaction with a tenfold excess of ME (pH 9.44) or dithiothreitol (pH 9.9 and 5.0) for 30 min, indicating that the methyl group remains intact on the cobalt complex after reaction with ME or dithiothreitol.

We conclude that the reductive cleavage by dithiols and methyl transfer to thiols reported by Schrauzer and coworkers[9,10] are at best minor side reactions under the conditions employed in the present study as described above for the gas chromatographic experiments. The methyl transfer to thiols reported by Schrauzer and Windgassen[9] was carried out at a higher pH (0.4 *N* NaOH) than any of the work reported in this paper. We have noticed time-dependent changes in the uv and visible spectra of $Me(D_2H_2)HOH$ at pH values >13.5 that indicate an instability of the complex at high alkalinity and may complicate the interpretation of the results of Schrauzer and Windgassen.

Evidence for axial ligation by thiols has been obtained from cyclic reactions



(7)

in which the regeneration of methylaquocobaloxime was demonstrated spectrophotometrically.

Proton Dissociation Constants of Cationic and Neutral Methylaquocobaloxime. The pK' value for $Me(D_2H_2)HOH$ was obtained by spectrophotometric titration at 455 nm (Figure 3). The *solid line* was calculated from eq 3a and 3b, the value for A_b obtained from eq 4, and the value $\mathrm{p}K'_{c_2} = 12.68$. At low pH, spectral shifts occur indicative of a protonation of $Me(D_2H_2)HOH$ to form a net cationic species (Scheme I), and the pK'_{c_1} value obtained by spectrophotometric titration and eq 4 is about 0.25.[32]

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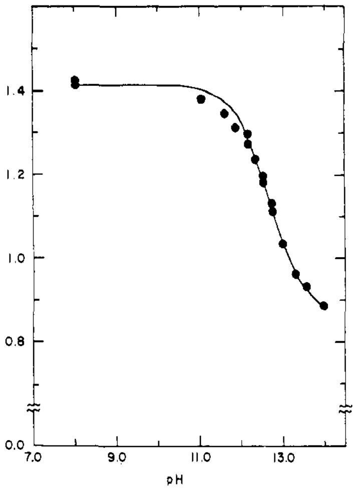

Figure 3. Spectrophotometric titration of $Me(D_2H_2)HOH$ at 455 nm, 25°, ionic strength = 1.0 *M*. The solid line was calculated using $pK'_{c_2} = 12.68$, $A_a = 1.416$, $A_b = 0.859$, and eq 3a and 3b.

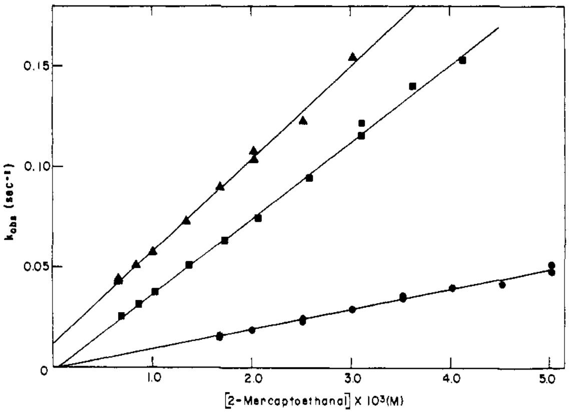

Figure 4. Effect of thiol concentration on the rate of ligation of 6.67×10^{-5} *M* $Me(D_2H_2)HOH$ by 2-mercaptoethanol, 25°, ionic strength 1.0 *M*: (▲) pH 7.72, in 0.1 *M* HEPES (64% free base), slope = 46.2 M^{-1} sec^{-1}; (■) pH 9.54, in 0.1 *M* borate (65% free base), slope = 38.7 M^{-1} sec^{-1}; (●) pH 12.92, in 0.1 *N* KOH, slope = 9.73 M^{-1} sec^{-1}. The solid lines are calculated from the least-squares slopes and intercepts.

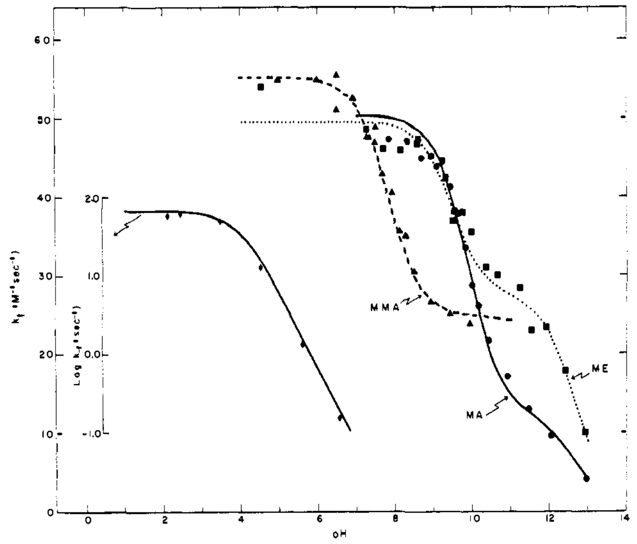

Figure 5. Dependence on pH of the second-order rate constants for formation of $Me(D_2H_2)HSR$ and $Me(D_2H_2)SR^-$ from $Me(D_2H_2)$-HOH and RSH, 25°, ionic strength 1.0 *M*: (●) MA (——), (■) ME (· · · ·), (▲) MMA (- - -). The lines were calculated from eq 10a and the values of the constants in Table I. Inset: Dependence on pH of the first-order rate constants, k_{-f}, for the dissociation of ME from $Me(D_2H_2)ME$. The solid line is calculated from eq 8 and 10a, and $K_f^{app} = k_f/k_{-f}$.

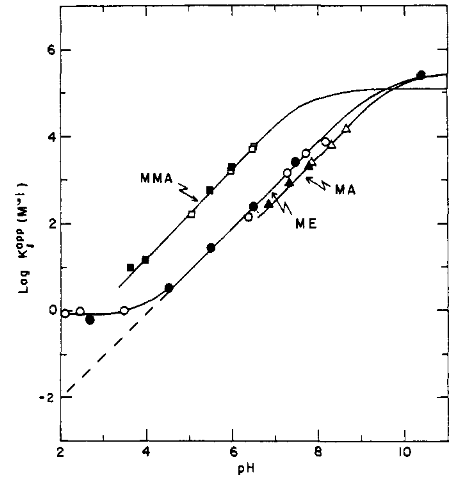

Figure 6. Dependence on pH of the apparent equilibrium constant for ligation of $Me(D_2H_2)HOH$ by RSH, 25°, ionic strength 1.0 *M*: (○) ME, (□) MMA, (△), MA. Solid symbols are spectrophotometric determinations (method I), open symbols are kinetic determinations (method II). The solid lines are calculated from eq 8 and the values for the constants in Table I. The dashed line represents the calculated dependence of K_f^{app} on pH for ME based upon thiolate anion as the sole liganding species.

Reactions of Ligands with Methylaquocobaloxime. Kinetics. The ligation reactions of $Me(D_2H_2)HOH$ in excess ligand were first order with respect to $Me(D_2H_2)$-HOH concentration. No buffer catalysis was detectable with phosphate, borate, Bicine, or acetate buffers at concentrations up to 0.5 *M*. Plots of the pseudo-first-order rate constants (k_{obsd}) for ligation with $Me(D_2H_2)HOH$ *vs.* thiol concentration at a given pH were linear up to 0.2 *M* and indicate that the reactions were also first order with respect to ligand concentration (Figure 4). The pH dependence of the apparent second-order rate constants for ligation (k_f, eq 1), obtained from the slopes of graphs similar to Figure 4, shows an inflection point for each of the thiols at the p*K'* value of the thiol, with a further decrease in rate above pH 10.5 (Figure 5) that is attributed to ionization of $Me(D_2H_2)HOH$ ($pK'_{c_2} = 12.68$). At sufficiently low pH, the graphs of k_{obsd} against ligand concentration had nonzero ordinate intercepts at [ligand] → 0, which indicate significant contributions from reverse rate constants (k_{-f}). Values of k_{-f} obtained from such plots or from independent measurements of $Me(D_2H_2)L^-$ decomposition were used to calculate the values of the apparent equilibrium constants, $K_f^{app} = k_f/k_{-f}$ and agree satisfactorily with equilibrium measurements obtained by method I (see below and Figure 6).

Equilibria. The pH dependence of the apparent equilibrium constants for ligation, K_f^{app}, from pH 4 to 10.5 is consistent with the designation that thiolate anion is the sole liganding species (Figure 6). However, from pH 2.0 to 3.5 the apparent equilibrium constants for ligation by ME become pH independent, which is a reflection of the pH independence of the rate constants for complex formation and decomposition, k_f and k_{-f}, in this pH range (Figure 5 and eq 1).

Table I. Summary of the Kinetic and Equilibrium Constants for Ligation Reactions of Methylaquocobaloxime, 25°, Ionic Strength 1.0 *M*

	Ligand			
Constant	Methyl mercaptoacetate	2-Mercaptoethanol	Mercaptoacetate	*S*-Methyl-2-mercaptoethanol
pK'_t	7.83[a]	9.51[a]	9.90[b]	
$K_f^{RS^-}$, M^{-1} [c]	$1.17 \pm 0.06 \times 10^5$	$2.04 \pm 0.14 \times 10^5$	$2.73 \pm 0.22 \times 10^5$	
K_f^{RSH}, M^{-1} [c]		0.736		88.8
pK'_{c_t}		4.00		
k_A, M^{-1} sec^{-1} [d]	55.2 ± 1.1	49.6 ± 1.3	50.4 ± 0.6	96.8 ± 18.8[e]
k_{-A}, sec^{-1}		67.3[f]		1.09 ± 0.25
k_B, M^{-1} sec^{-1} [d]	24.2 ± 2.5	27.3 ± 2.8	12.8 ± 1.2	
k_{-B}, sec^{-1} [g]	2.11×10^{-4}	1.14×10^{-4}	4.51×10^{-5}	
k_H, M^{-2} sec^{-1} [h]	3.73×10^9	1.16×10^{11}	4.00×10^{11}	

[a] G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966). [b] This work. [c] Calculated as described in text. [d] From the least-squares fit of the data in Figure 5 (corrected for cobaloxime ionization, pK'_{c_2}) to eq 10a. [e] From the measured values of K_f^{RSH} and k_A and $k_{-A} = k_A K_f^{RSH}$. [f] From $k_{-A} = k_A K_f^{RSH}$. [g] From $k_{-B} = k_B K_f^{RS^-}$. [h] From $k_H = k_A/K'_t$.

The upward deviation of up to 10^2 in K_f^{app} greater than that expected for the ligation by thiolate anion alone (Figure 6, *dashed line*) indicates that ligation by neutral thiol also occurs (Scheme I), but that the liganding affinity of thiolate anions exceeds that of neutral thiol by about 10^5 (Table I). The apparent equilibrium constants for ligation determined kinetically (Figure 6, open symbols) under conditions in which the solvent composition was not altered significantly agree satisfactorily with data (Figure 6, solid symbols) obtained from equilibrium absorbance measurements (method I) which required concentrations of ME up to 5.0 *M*. Furthermore, formation of $Me(D_2H_2)CH_3SR$ from SMME, a compound similar to neutral thiol, and methylaquocobaloxime (Table I) indicates that mercaptide ion formation is *not* a prerequisite for ligation. The pH dependence of the apparent equilibrium constants for complex formation is described by

$$K_f^{app} = K^{RSH}(1 - \alpha_t) + K^{RS^-}\alpha_t \qquad (8)$$

where α_t is the fraction of thiol as the thiolate anion, $K^{RSH} = [Me(D_2H_2)HSR]/[Me(D_2H_2)HOH][RSH]$, and $K^{RS^-} = [Me(D_2H_2)SR^-]/[Me(D_2H_2)HOH][RS^-]$. The *solid lines* in Figure 6 are based upon the equilibrium constants in Table I and eq 8 except that the first term on the right-hand side of eq 8 is negligible for MMA and MA in the pH region studied.[34]

Discussion

Product Identification. The absence of carbon–cobalt bond cleavage upon reaction of methylaquocobaloxime with ME is indicated by the inability to detect significant amounts of SMME, the nucleophilic displacement product, or methane, the reductive cleavage product, by gas chromatographic analysis. We were not able to demonstrate the generation of methane by reaction of $Me(D_2H_2)HOH$ with dithiothreitol as reported by Sibert and Schrauzer.[10] However, our effects to duplicate the conditions of these authors was limited by the sparseness of experimental detail contained in their short communication. Since the generation of methane by anaerobic photolysis of $Me(D_2H_2)HOH$ was unaffected by prior equilibration with ME or dithiothreitol, we can state with confidence that under the conditions employed in the present work nucleophilic and reductive cleavage mechanisms for carbon–cobalt bond cleavage are, at best, minor pathways.[34a]

Equilibrium Constants for the Reactions of Methylaquocobaloxime with Ligands. The dependence of the equilibrium constants for ligation of methylaquocobaloxime by thiolate anions, $K_f^{RS^-}$, and 4-substituted pyridines (K_f, in 50% aqueous DMSO)[35] upon the pK' values of the conjugate acid of the ligands (Figure 7) indicates that the equilibrium constants for ligation by thiolate anions are considerably larger than those for the substituted pyridines, but that the dependence of the equilibrium constants upon pK' value is smaller for the thiolate anions ($\beta = 0.18 \pm 0.01$) than for the 4-substituted pyridines ($\beta = 0.29 \pm 0.02$). The greater affinity of thiolate anions than of pyridines for methylaquocobaloxime is consistent with the observations of Crumbliss and Wilmarth[18] and Ludwick and Brown[17] that $Me(D_2H_2)$ behaves as a soft or class b acid.[36]

The extremely low affinity of RSH for $Me(D_2H_2)$-HOH as compared to RS^- and the decrease in pK' value for proton dissociation from the sulfur atom in $Me(D_2H_2)HSR$ of about 5.5 units (Table I) are similar reflections of the relative instability of the S-protonated liganded species. Although a more detailed analysis of these data will be deferred at present, the order of affinity of the various ligands under consideration is HOH < RSH < $RSCH_3$ < x-py < RS^- (Table I and Figure 7) under the experimental conditions considered in this study.

Kinetics of the Reaction of Methylaquocobaloxime with Thiols. The reaction of $Me(D_2H_2)HOH$ with thiols characteristically shows a decrease in rate above pH 10.5 (Figure 5) which is attributed to the loss of a proton from $Me(D_2H_2)HOH$ ($pK'_{c_2} = 12.68$, 25°, ionic strength 1.0 *M*) to form an unreactive anionic species (Scheme I). Randall and Alberty[20] have previously attributed the decrease in the rate of ligation on aquocobalamin

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[34] For MMA and MA, the equilibrium constant measurements for ligand substitution of methylaquocobaloxime were not extended to pH values low enough for the formation $Me(D_2H_2)HSR$ or $Me(D_2H_2)$-SCH_2COOH^- or prototropic tautomers thereof to make significant contributions to the apparent equilibrium constant, K_f^{app}.

[34a] NOTE ADDED IN PROOF. Methyl transfer from methylcobalamin to thiols, reported by Schrauzer and coworkers,[9,10] has been shown to occur *via* a free-radical mechanism only in the presence of oxygen and catalytic amounts of reduced B_{12r} and *not* by nucleophilic displacement [G. Agnes, H. A. O. Hill, J. M. Pratt, S. C. Ridsdale, F. S. Kennedy, and R. J. P. Williams, *Biochem. Biophys. Acta*, **252**, 207 (1971)].

[35] L. L. Ingraham, personal communication.

[36] F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York, N. Y., 1967.

above pH 6 to the loss of a proton from aquocobalamin to form the unreactive hydroxocobalamin. A pK'_{c_2} value of 12.58 for Me(D_2H_2)HOH at 10° and unit ionic strength can be calculated from the data of Crumbliss and Wilmarth.[18]

The pH-rate profiles for the ligation reactions of thiols with methylaquocobaloxime (Figure 5) are sigmoid curves with inflection points at the pK' values of the respective thiols, and indicate an apparent two-fold greater nucleophilic reactivity of neutral thiol than of thiolate anion. Similar observations of increased reactivities of conjugate acids of ligands have been reported by Hague and Halpern[16] for the anation of aquonitritocobaloxime by nitrous acid

$$\mathrm{Co(D_2H_2)(NO_2)HOH} + \begin{bmatrix}\mathrm{HNO_2}\\ \mathrm{NO_2^-}\end{bmatrix} \longrightarrow \mathrm{Co(D_2H_2)(NO_2)_2^-} + \begin{bmatrix}\mathrm{H_3O^+}\\ \mathrm{H_2O}\end{bmatrix} \quad (9)$$

and by Margerum and Simandi[37] for the reaction of HCN and CN^- with $Ni^{II}(EDTA)^{2-}$ to form $Ni^{II}(EDTA)(CN)^{3-}$. In the latter case, the decreased reactivity of the anionic ligand compared to the neutral ligand was attributed to electrostatic repulsion between anionic ligand and the dianionic complex. If the reactions of neutral thiols and thiolate anions with Me(D_2H_2)HOH are formulated similarly, the rate law of eq 10a applies in which k_A and k_B are the rate constants for neutral thiols and their conjugate bases, respectively, and α_t and α_{cob} are the fraction of total thiol and methylaquocobaloxime as the conjugate base species, respectively.

$$k_f = \{k_A(1 - \alpha_t) + k_B\alpha_t\}[\mathrm{RSH}]_{tot}(1 - \alpha_{cob}) \quad (10a)$$

However, since the methylaquocobaloxime complex used in the present study is neutral, that the thiolate anion would be less reactive on electrostatic grounds seems implausible and consideration must be given to the kinetically indistinguishable mechanism represented by the rate law with respect to total thiol of eq 10b, in which the first term

$$k_f = \{k_H a_{H^+} + k_B\}[\mathrm{RSH}]_{tot}\alpha_t(1 - \alpha_{cob}) \quad (10b)$$

(k_H) represents solvated proton catalyzed and the second term (k_B) represents solvent-catalyzed or uncatalyzed attack of thiolate anion on methylaquocobaloxime. Since no evidence was found for catalysis by acids other than solvated proton, it seems most plausible to formulate the mechanism of the solvated proton catalyzed pathway as specific acid catalysis

$$\text{rate} = k_H'[\mathrm{Me(D_2H_2)HOH\cdot H^+}][\mathrm{RS^-}] + k_B[\mathrm{Me(D_2H_2)HOH}][\mathrm{RS^-}] \quad (10c)$$

where $k_H' = k_H K'_{c_1}$ rather than general acid catalysis. Since there are spectral shifts at pH <1 indicative of protonation of Me(D_2H_2)HOH in acid to yield cationic species (pK'_{c_1} ~ 0.25), the mechanism of eq 10c appears, at first, plausible. However, the mechanisms of eq 10b and 10c can be ruled out in favor of that of 10a on the following three grounds. First, using the approximate pK'_{c_1} value of 0.25 for the proton dissociation from the conjugate acid of Me(D_2H_2)HOH, the specific rate constants for the reaction of thiolate anions with cationic methylaquocobaloxime (k'_H, eq 10c) can be calculated to be 2.10 × 10^9, 6.25 × 10^{10}, and 2.25 × 10^{11} M^{-1} sec^{-1} for MMA, ME, and MA, respectively, and for the latter two compounds the rate constants for ligation are greater than the diffusion-controlled limit.[38] For general acid catalysis by the solvated proton, eq 10b, the specific rate constants k_H (Table I) also exceed the diffusion-controlled limit, and it does not appear possible to break up k_H into elementary steps whose rates would be less than the diffusion controlled limit. Second, when the rate constants for the net monocationic transition states of eq 10b and 10c (k_H and k_H' Table I and above) for these thiols are compared with the rate constants for uncatalyzed attack (k_B Table I), k_H and k_H' show far greater variation with thiolate anion basicity than does k_B. Partial or complete proton donation to methylaquocobaloxime would be expected to create a more reactive species and on this basis be associated with a pathway which is less discriminating toward the incoming ligands than the pathway with a net neutral transition state. The experimental observations formulated in terms of eq 10b and 10c are in contrast to this expectation (Table I), since the Brønsted β values for logarithmic plots of k_H, k_H', and k_B *vs.* pK' value for the conjugate acid of the ligands are approximately 1.0, 1.0, and 0.0, respectively. Third, the neutral thiol analog, SMME, reacts with Me(D_2H_2)HOH at pH-independent rates which are within twofold of the values of k_A (Table I) calculated for neutral thiol according to eq 10a and provides evidence that neutral thiol can act as a liganding reactant in this system.

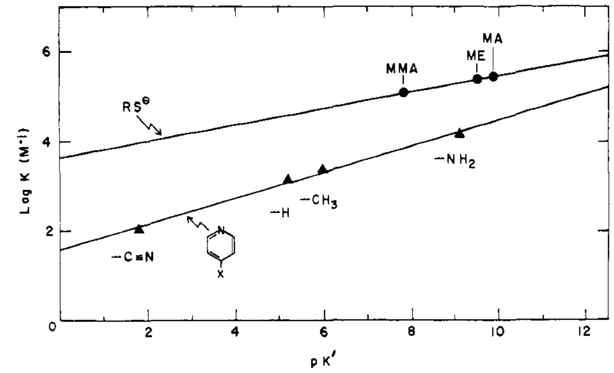

Figure 7. Dependence of the equilibrium constant for ligation on the proton dissociation constant of the conjugate acid of the ligand: (●) K^{RS^-} = [Me(D_2H_2)SR$^-$] [Me(D_2H_2)HOH][RS$^-$], slope = 0.18 ± 0.01; (▲) K_f = [Me(D_2H_2)x-py]/[Me(D_2H_2)HOH][x-py], slope = 0.29 ± 0.02 (50% aqueous DMSO).

The Mechanism of Ligation Reactions of Me(D_2H_2)HOH. The first-order kinetic dependence on incoming ligand concentration for the ligation reactions is accounted for in each of the following detailed mechanistic schemes (for simplicity, the ligation reactions have been taken to have proceeded to completion):[39] (1) an SN2 mechanism (eq 11a and 11b) for which the rate law of eq 10a applies

$$\mathrm{Me(D_2H_2)HOH + RSH \rightleftarrows Me(D_2H_2)HSR + HOH} \quad (11a)$$

$$\mathrm{Me(D_2H_2)HOH + RS^- \rightleftarrows Me(D_2H_2)SR^- + HOH} \quad (11b)$$

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[37] D. W. Margerum and L. I. Simandi, *Proc. Int. Conf. Coord. Chem., 9th*, 371 (1966).

[38] (a) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964); (b) M. Eigen, G. G. Hammes, and K. Kustin, *J. Amer. Chem. Soc.*, **82**, 3482 (1960).

[39] C. H. Langford and M. P. Johnson, *ibid.*, **86**, 229 (1964).

(2) an outer-sphere complexation mechanism (equivalent to an I_d process in the terminology of Langford and Gray[40]), eq 12a, 12b, and 13, where rapid equilibration of the outer-sphere complexation steps has been assumed

$$\mathrm{Me(D_2H_2)HOH + RSH} \xrightarrow{K_{os}^{\mathrm{RSH}}} \underset{\mathrm{III}}{[\mathrm{Me(D_2H_2)HOH\cdots HSR}]} \xrightarrow{k_x} \mathrm{Me(D_2H_2)HSR + HOH} \quad (12a)$$

$$\mathrm{Me(D_2H_2)HOH + RS^-} \xrightarrow{K_{os}^{\mathrm{RS}^-}} \underset{\mathrm{IV}}{[\mathrm{Me(D_2H_2)HOH\cdots SR}]^-} \xrightarrow{k_y} \mathrm{Me(D_2H_2)SR^- + HOH} \quad (12b)$$

$$\mathrm{Me(D_2H_2)HSR} \underset{fast}{\overset{\mp\mathrm{H}^+}{\rightleftarrows}} \mathrm{Me(D_2H_2)SR^-} \quad (13)$$

and the rate laws of eq 14a and 14b apply

$$\text{rate} = k_x[\mathrm{III}] = k_xK_{os}^{\mathrm{RSH}}[\mathrm{Me(D_2H_2)HOH}][\mathrm{RSH}] \quad (14a)$$

$$\text{rate} = k_y[\mathrm{IV}] = k_yK_{os}^{\mathrm{RS}^-}[\mathrm{Me(D_2H_2)HOH}][\mathrm{RS^-}] \quad (14b)$$

and (3) an SN1 mechanism (eq 15, 16a, and 16b)

$$\mathrm{Me(D_2H_2)HOH} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{\mathrm{V}}{\mathrm{Me(D_2H_2)}} + \mathrm{HOH} \quad (15)$$

$$\mathrm{Me(D_2H_2) + RSH} \xrightarrow{k_2^{\mathrm{RSH}}} \mathrm{Me(D_2H_2)HSR} \quad (16a)$$

$$\mathrm{Me(D_2H_2) + RS^-} \xrightarrow{k_2^{\mathrm{RS}^-}} \mathrm{Me(D_2H_2)SR^-} \quad (16b)$$

for which the rate law of eq 17a, derived by the application of the steady-state assumption to the pentavalent cobalt intermediate (V) of eq 15, applies

$$\text{rate} = k_1[\mathrm{Me(D_2H_2)HOH}]/\{1 + k_{-1}[\mathrm{HOH}]/(k_2^{\mathrm{RS}^-}[\mathrm{RS^-}] + k_2^{\mathrm{RSH}}[\mathrm{RSH}])\} \quad (17a)$$

Under the conditions in which $(k_2^{\mathrm{RS}^-}[\mathrm{RS^-}] + k_2^{\mathrm{RSH}}\cdot[\mathrm{RSH}]) \ll k_{-1}[\mathrm{HOH}]$, the rate law reduces to

$$\text{rate} = \{k_1(k_2^{\mathrm{RS}^-}[\mathrm{RS^-}] + k_2^{\mathrm{RSH}}[\mathrm{RSH}])[\mathrm{Me(D_2H_2)HOH}]\}/k_{-1}[\mathrm{HOH}] \quad (17b)$$

with a first-order dependence of the rate on the concentration of incoming ligand.

As noted, the rate constants for ligation by $\mathrm{RS^-}$ and RSH are quite insensitive to the pK' of the thiol (Table I). Although an SN2 mechanism might be expected to exhibit a relatively large dependence on the nature of the incoming ligand,[40] there is sufficient exception to this generalization to disfavor the application of this criterion to the determination of mechanism. Nevertheless, there is little evidence to indicate that ligation reactions of $\mathrm{Co^{III}}$ complexes proceed *via* SN2 mechanisms.[40]

The I_d mechanism (eq 12a and 12b) predicts an insensitivity of the rates of ligation to the nature of the incoming ligand.[40] This insensitivity is indeed found within both the series of thiolate anion ligands (k_B) and the series of neutral thiol ligands (k_A, Table I). However, the twofold increase in rate for neutral thiol over thiolate anion ligation of $\mathrm{Me(D_2H_2)HOH}$ is not expected, nor can it be explained by this simple mechanism. This rate enhancement can, however, be accounted for by modifying the mechanism for ligation by thiolate anion (eq 12b) to include an outer sphere–inner sphere proton transfer as shown in

$$\begin{tikzcd}
\mathrm{Me(D_2H_2)HOH + RS^-} \arrow[r, shift left, "K_{os}^{\mathrm{RS}^-}"] & {[\mathrm{Me(D_2H_2)HOH\cdots SR}]^-} \arrow[l, shift left] \arrow[dl, shift left, "K_z = K'_{c2}/K'_t"] & \\
\underset{\mathrm{VI}}{[\mathrm{Me(D_2H_2)OH\cdots HSR}]^-} \arrow[ur, shift left] \arrow[r, "k_z"] & \mathrm{Me(D_2H_2)HSR + OH^-} & (18)
\end{tikzcd}$$

for which the rate law of eq 19 applies.

$$\text{rate} = k_z[\mathrm{VI}] = (k_zK_{os}^{\mathrm{RS}^-}K'_{c2}/K'_t)[Me(D_2H_2)HOH][RS^-] \quad (19)$$

In this case the greater reactivity of neutral thiol over thiolate anion can be accounted for in terms of the more difficult displacement of hydroxide from VI (eq 18) than of water from III (eq 12a). However, the modified mechanism for thiolate anion substitution (eq 18) predicts a large dependence of the rate of ligation on thiolate anion basicity due to the dependence of the outer sphere–inner sphere proton-transfer equilibrium ($K_z = K'_{c2}/K'_t$) on thiolate basicity (K'_t). A similar explanation has been offered for the anation of $\mathrm{Fe(H_2O)_6}^{3+}$ by anions of weak acids when the rate constants are calculated according to the mechanism of eq 18.[41–43] However, the rate constant for anation by thiolate anion, k_B, shows little, if any, dependence on thiolate anion basicity (Table I), and the small deviation in k_B for MA is in the opposite direction to that expected from the rate law (eq 19) for the mechanism of eq 18.

We favor, at present, the SN1 mechanism of eq 15, 16a, and 16b, despite our inability to demonstrate the definitive mechanistic criterion, namely, saturation of rate with respect to incoming ligand concentration. Nevertheless, there is substantial evidence that Co(III) complexes capable of stabilizing carbon–cobalt bonds are stable enough to exist as pentacoordinate species (*cf.* ref 36). For example, Schrauzer and Windgassen[4] have prepared the pentacoordinate species $\mathrm{Me(D_2H_2)}$ (eq 15) by dehydration of $\mathrm{Me(D_2H_2)HOH}$ in benzene. Although Ludwick and Brown[17] have proposed a dimeric structure for $\mathrm{Me(D_2H_2)}$ in solution at low temperature and in nonaqueous solvent, the conditions of the present experiments are probably sufficiently different to make such structural considerations difficult to relate to the present work. Crystalline pentacoordinate complexes of the alkylcobalt derivatives of cobalt bis(salicylaldehyde)ethylenediamine and cobalt-bis(acetylacetone)ethylenediamine have also been prepared by Costa and coworkers,[44,45] and the crystal structure has been determined for the pentacoordinate

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[40] C. H. Langford and H. B. Gray, "Ligand Substitution Processes," W. A. Benjamin, New York, N. Y., 1965.

[41] M. Eigen in "Advances in the Chemistry of the Coordination Compounds," S. Kirschner, Ed., Macmillan, New York, N. Y., 1961, p 371.

[42] H. Wendt and H. Strehlow, *Z. Elektrochem.*, **66**, 228 (1962).

[43] D. Seewald and N. Sutin, *Inorg. Chem.*, **2**, 643 (1963).

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[45] G. Costa, G. Mestroni, G. Tauzher, and L. Stefani, *ibid.*, **6**, 181 (1966).

methyl derivative of the latter group of complexes.[46] Furthermore, Costa and coworkers[47] have demonstrated independence of rate with respect to incoming ligand concentration for anation reactions of alkylaquo-1,3-bis(biacetylmonooximimino)propanatocobalt monocation (a complex quite similar to the alkylcobaloximes) in a solvent of 1% water in acetone which has been interpreted in terms of a limiting SN1 mechanism. Finally, the extensive work of Hill and coworkers has provided evidence for the existence of pentacoordinate species among the alkylcobinamides and alkylcobalamins from the temperature dependence of uv, visible, and pmr spectra,[48] and from correlation of similar studies plus CD spectra with data on the thermodynamics of ligand substitution of numerous cobalt–corrin complexes.[49,50]

It may well be impossible to demonstrate the kinetic criterion for the SN1 mechanism since the rate for the dissociation of water from Me(D_2H_2)HOH (k_1, eq 15) may be extremely fast, causing the rates of ligation to become experimentally inaccessible before saturation can be achieved. Furthermore, the clear possibility exists that at room temperature the cobalt complex may exist predominately as the pentacoordinate Me(D_2H_2) species, in which case the reaction with thiols may be better described as ligand addition rather than substitution (eq 16a and 16b). In support of this possibility, Hill and coworkers[48] estimated that methylcobinamide exists 90% as the pentacoordinate species in water at 20°.

If either the SN1 mechanism of ligation (eq 15, 16a, and 16b) or the bimolecular mechanism of ligand addition to Me(D_2H_2) (eq 16a and 16b) is indeed applicable, then the greater reactivity of neutral thiol over thiolate anion in this system may be attributed to the importance of π bonding in the transition states for reactions 16a and 16b. The neutral ligands, RSH and $RSCH_3$, would be expected to act as better π acceptors than thiolate anion,[51] and although the stabilities of the complexes formed from the former compounds are far lower, the rate constants for ligand substitution are greater. A significant contribution of π bonding to the transition states for these reactions would also provide an explanation for the almost total lack of dependence of substitution rate on thiolate anion basicity, since an increase in basicity would be expected to make a thiolate anion a better σ donor, but, compensatingly, a poorer π acceptor. A similar involvement of π bonding in the ground state for the thiolate anion complexes might also explain the observed increase in the equilibrium constants for ligation by thiolate anions compared to substituted pyridines, as well as the decrease in sensitivity of the equilibrium constants to ligand basicity for the thiolate anions ($\beta = 0.18 \pm 0.01$) as opposed to substituted pyridines ($\beta = 0.29 \pm 0.02$) (Figure 7).

Further work is in progress in an attempt to substantiate the proposed SN1 mechanism for ligation reactions of Me(D_2H_2)HOH and to assess the relative importance of π bonding in trans-liganded complexes containing alkylcobalt bonds.

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Effect of Steric Hindrance on the Structure of Transition States[1,2]

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Abstract: From chlorine isotope effects in the Menshutkin reactions of triethylamine ($k^{35}/k^{37} = 1.00640 \pm 0.00009$) and quinuclidine ($1.00709 \pm 0.00011$) with methyl chloride in 1,2-dimethoxyethane solution at 25°, steric strain evidently *decreases* during passage through the transition states for these reactions, thereby causing the former reaction to have the earlier (more reactant-like) transition state. This is attributed to relatively rapid motion of the hydrogens on the flattening methyl at the transition state. Analogies to oxonium, carbonium, and enolate salt formation are noted.

No definitive information has been published concerning the effect of purely *steric* structural changes of reactants on the structure of transition states, although several rules for predicting the effect of predominantly *electronic* changes on transition-state geometry have been proposed and experimentally tested.[4–10]

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(2) For further details, including raw kinetic and mass spectral data, see N. D. Hershey, Ph.D. Thesis, Massachusetts Institute of Technology, Jan 1971, pp 3, 14–62, and ref 3.

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