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Coenzyme B₁₂ Model Studies: Thermodynamics and Kinetics of Axial Ligation of Substituted Alkyl(aquo)cobaloximes by Dimethoxyethylamine^{1,2}

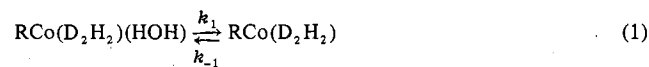
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The kinetics, equilibria, and thermodynamics of the axial ligation of a series of substituted alkyl(aquo)cobaloximes by dimethoxyethylamine (DEA) have been measured in aqueous solution, ionic strength 1.0 M, at 25.0 °C, and in some cases over the temperature range 5–45 °C. Equilibrium constants for proton dissociation of axial water are also reported for several previously unreported alkyl(aquo)cobaloximes. Free-energy correlations of the equilibrium constants for DEA ligation (K_l), the equilibrium constants for OH⁻ ligation (K_l^{OH}), and the enthalpy (ΔH_l^\ddagger) and entropy (ΔS_l^\ddagger) of DEA ligation with the Taft polar-substituent constant, σ^* , for the cobalt-bound alkyl groups are all distinctly nonlinear. These results are interpreted in terms of a mechanism for axial ligand substitution involving a preequilibrium dissociation of axial water to form a pentacoordinate alkylcobaloxime, followed by addition of the incoming ligand to this pentacoordinate species. Nonlinear least-squares analysis of these nonlinear free-energy correlations allows determination of the slope and intercept parameters for the hexacoordinate-pentacoordinate equilibrium constant (K_{cw}). Based on these considerations, the kinetics of these axial ligation reactions are interpreted in terms of an S_N1_{lim} mechanism, and the calculated values of K_{cw} allow estimation of the second-order rate constants for addition of the incoming ligand to the pentacoordinate intermediate (k_2). Free-energy correlations for k_2 for DEA and pyridine are linear, show the expected trans influence ($\rho^*_{k_2} = +1.17$ for DEA and +1.13 for pyridine), and lead to the conclusion that the transition state for these axial ligation reactions is "early", with bond formation only about 20% complete.

Introduction

In an earlier report,³ one of us, as well as others, presented data supporting the hypothesis that the neutral alkyl(aquo)cobaloximes⁴ exist in aqueous solution as an equilibrium mixture of two thermodynamically distinct forms: hexacoordinate alkyl(aquo)cobaloxime and a stable pentacoordinate species (or solvate, thereof) formed by loss of axially coordinated water:

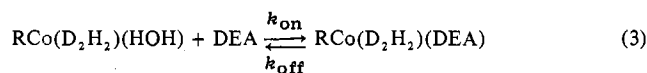


$$K_{\text{cw}} = [\text{RCo}(\text{D}_2\text{H}_2)] / [\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})] = k_1/k_{-1} \quad (2)$$

Support of this hypothesis came from temperature dependence of the electronic spectra of several representative alkyl(aquo)cobaloximes, analysis of the effects of electronic inductive abilities of the organic substituents on the electronic spectra of the alkyl(aquo)cobaloximes, and, most importantly, observation of nonlinear free-energy correlations for the substitution of axial ligands OH⁻ and pyridine for water in a series of substituted alkyl(aquo)cobaloximes.

The present paper reports our continued study of this system in which a series of extremely precise measurements of

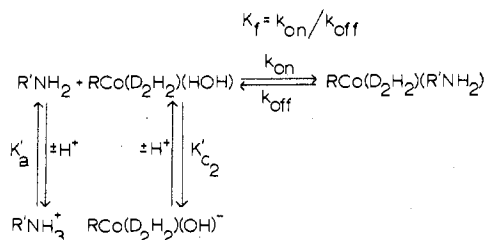
equilibrium 3 for displacement of axial water by a primary amine (DEA)² have been made in order to provide a set of



binding data sufficiently numerous and of sufficient precision to allow a statistical test of the necessity of correlating the data with a nonlinear function of an electron-inductive parameter (σ^*)⁵ for the cobalt-bound organic group. This set of data has also allowed a quantitative assessment of the importance of steric effects of the organic group on the equilibrium of eq 3. In addition, microcalorimetry, temperature-dependent equilibrium measurements, and kinetic measurements have been carried out in order to provide additional insight to the mechanism of this ligand-substitution process.

Substitution reactions of alkylcobaloximes and related organocobalt complexes have been extensively studied in recent years.^{6–15} A few calorimetric measurements on the interaction of methylcobaloxime with several ligands¹⁶ and for ligation reactions of aquocobalamin¹⁷ have also been reported. Only in noncoordinating solvents has it been possible to obtain hard kinetic evidence for a purely dissociative (D or S_N1_{lim}) mechanism.^{11b,12b,14,15} Although several authors^{10,15} feel that

Scheme I



the problem of intimate mechanism of these reactions in coordinating solvents is too difficult to approach, we believe that the present data lend support to a purely dissociative mechanism for the reaction of eq 3 in water.

Experimental Section

Materials. Alkyl halides, dimethylglyoxime, cobaltous chloride, cobaltous acetate, sodium borohydride, sodium hydroxide, methanol, buffer components, and inorganic salts were obtained in the highest purity commercially available and used without further purification.

Alkyl(aquo)cobaloximes were prepared either by the previously described modification³ of the procedure of Schrauzer¹⁸ (via the $\text{RCo}(\text{D}_2\text{H}_2)(\text{S}(\text{CH}_3)_2)$ complexes) or directly by the procedure suggested by Crumbliss and Gaus.¹⁹ All product complexes migrated as a single spot on silica gel thin layers in at least two different solvents and gave ¹H NMR spectra consistent with the proposed structures and free from spurious peaks and satisfactory elemental analyses (Galbraith Laboratories, Knoxville, Tenn.). Elemental analyses of previously unreported compounds were submitted to the referees.

Dimethoxyethylamine (Adlrich) was dried over type 4A molecular sieves, redistilled monthly under argon, and stored in the dark over type 4A molecular sieves under argon. Glass-distilled deionized water was used throughout, and ionic strength was maintained at 1.0 M with KCl.

Methods. All work with the alkylcobaloximes was performed in dim light, and solutions were covered with aluminum foil whenever possible.

UV and visible spectra were recorded on a Cary 14 recording spectrophotometer. pH measurements were made with a Radiometer PHM-64 pH meter and a Radiometer GK-2322C combined electrode for pH < 12 or a Radiometer GK-2302B combined electrode for pH ≥ 12. For ligation equilibrium, kinetic, and thermodynamic measurements at 25.0 °C, pH measurements were made at room temperature (24 ± 1 °C). For spectrophotometric and potentiometric titrations at 25.0 °C and equilibrium measurements at other temperatures, all samples, standards, electrodes, and rinse water were incubated at the measurement temperature. Electrodes were standardized at three pH values as described previously.^{6a}

Equilibrium Measurements. Values for the pK'_a of the conjugate acid of DEA (Scheme I) were obtained by potentiometric titration at 5.0 ± 0.1, 15.2 ± 0.1, 25.1 ± 0.1, 35.0 ± 0.1, and 45.0 ± 0.1 °C. Samples (5 mL) contained 0.02 M DEA, various amounts of HCl, and sufficient KCl for an ionic strength of 1.0 M. Values of pK'_a were obtained by a linear least-squares fit of the data to eq 4, derived

$$\text{pH} = \text{pK}'_a + \log (\alpha_{\text{R}'\text{NH}_2} / (1 - \alpha_{\text{R}'\text{NH}_2})) \quad (4)$$

from eq 5, where $\alpha_{\text{R}'\text{NH}_2}$ is the fraction of total amine present as the

$$K'_a = [\text{R}'\text{NH}_2] [\text{H}^+] / [\text{R}'\text{NH}_3^+] \quad (5)$$

free base (or unprotonated) species in any sample (eq 6).

$$\alpha_{\text{R}'\text{NH}_2} = [\text{R}'\text{NH}_2] / ([\text{R}'\text{NH}_2] + [\text{R}'\text{NH}_3^+]) \quad (6)$$

Apparent equilibrium constants (K'_f values, see eq 7) for formation

$$K'_f = [\text{RCo}(\text{D}_2\text{H}_2)(\text{NH}_2\text{R}') / [\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})] ([\text{R}'\text{NH}_2] + [\text{R}'\text{NH}_3^+]) \quad (7)$$

of the DEA adducts of the alkylcobaloximes (Scheme I) were determined by spectrophotometric measurements at the wavelength of maximum spectral change (generally 445–460 nm; see ref 3 and 6b) of solutions (3 mL) containing $\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})$ (generally from 5.0×10^{-4} M to 1.0×10^{-3} M), an appropriate buffer (0.1 M), varying concentrations of DEA, and KCl to ionic strength 1.0 M on a Gilford

Model 250 spectrophotometer, with its cell block maintained at the appropriate temperature (±0.1 °C). Solutions were allowed to temperature-equilibrate in the spectrophotometer cell block for at least 15 min prior to addition of cobaloxime. Final absorbance readings were taken after equilibrium was established as indicated by the time independence of the readings. This procedure was modified for $\text{R} = \text{C}_6\text{H}_5$, for which solutions containing ca. 2.50×10^{-4} M cobaloxime, total volume 15 mL, were incubated in foil-covered culture tubes for 3 h ($>7 \times T_{1/2}$ for ligand dissociation), and absorbances were determined on a Cary 14 spectrophotometer in 5-cm path-length cells.

For such experimental setups, at a given pH, eq 8 applies where

$$\Delta A = \Delta A_{\text{max}} [L]_f / (1/K'_f + [L]_f) \quad (8)$$

ΔA is the difference in absorbance between solutions containing cobaloxime and primary amine (L, in eq 8) and solutions containing only cobaloxime at the same concentration, ΔA_{max} is the maximal absorbance change thus obtainable at high $[L]$, and $[L]_f$ is the equilibrium concentration of amine distributed over both ionization states. The data were analyzed by a least-squares fit to the rearranged form of (8) to give eq 9. $[L]_f$ is calculated from eq 10 using the

$$\Delta A = \Delta A_{\text{max}} - \Delta A / K'_f [L]_f \quad (9)$$

$$[L]_f = [L]_{\text{tot}} - C_T \Delta A / \Delta A_{\text{max}} \quad (10)$$

measured value of ΔA_{max} , where $[L]_{\text{tot}}$ is the total concentration of added amine and C_T is the total concentration of cobaloxime. Values of K'_f were obtained from the least-squares slopes of eq 9.

The values for the equilibrium constants for axial ligation with respect to unprotonated amine (eq 11) were calculated from the

$$K_f = [\text{RCo}(\text{D}_2\text{H}_2)(\text{NH}_2\text{R}') / [\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})] [\text{R}'\text{NH}_2]$$

relation $K_f = K'_f / \alpha_{\text{R}'\text{NH}_2}$, where $\alpha_{\text{R}'\text{NH}_2}$ (defined in eq 6) was calculated from eq 12, which was derived from (5) and (6). At least two such

$$\alpha_{\text{R}'\text{NH}_2} = K'_a / (K'_a + [\text{H}^+]) \quad (12)$$

determinations were made for each alkylcobaloxime: one at $\text{pH} \rightarrow \text{pK}'_{\text{c}2} - 2$ (Scheme I), where, generally, $\alpha_{\text{R}'\text{NH}_2} \geq 0.90$, in order to avoid formation of the species $\text{RCo}(\text{D}_2\text{H}_2)(\text{OH})^-$, and one at pH ca. 8.8, where $\alpha_{\text{R}'\text{NH}_2} = \text{ca. } 0.50$. The only exceptions were for $\text{R} = \text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2$ and $\text{CH}_3\text{OOCCH}_2\text{CH}_2$, for which the alkylcobaloximes were insufficiently stable at $\text{pH} > 10$ to permit such measurements. In these cases, multiple determinations were made at pH ca. 8.8.

Spectrophotometric determinations of the values of $\text{pK}'_{\text{c}2}$ (Scheme I) for the alkylcobaloximes were performed similarly, using the method described in detail for $\text{R} = \text{CH}_3$ (ref 6a).

Kinetic Measurements. The second-order rate constant for ligation of DEA to the alkylcobaloximes (k_{on} , Scheme I) was determined from absorbance measurements at the same wavelength used for K'_f determinations under pseudo-first-order conditions with DEA in at least 10-fold excess over cobaloxime concentration for all complexes with $\sigma_{\text{R}}^* \geq 0.31$. Reactions were initiated by addition of a small volume of alkylcobaloxime solution in methanol to cuvettes containing buffer (0.1 M), KCl, and DEA in the thermostated (25.0 ± 0.1 °C) cell compartment of a Gilford Model 250 spectrophotometer. Absorbance measurements were recorded continuously for at least six half-times. First-order rate constants (k_{obsd}) were obtained by least-squares fits of the data to eq 13, where A_t is the absorbance at time t and A_∞ is $\ln (A_t - A_\infty) = k_{\text{obsd}} t \quad (13)$

the final absorbance. Second-order rate constants, k_{on} , at a given pH, were obtained from the slopes of least-squares fits of the data to eq 14, where $[\text{DEA}]_{\text{tot}}$ is the total concentration of DEA present,

$$k_{\text{obsd}} = k_{\text{on}}' [\text{DEA}]_{\text{tot}} + k_{\text{off}} \quad (14)$$

distributed over both ionization states. Values for k_{on} , the second-order ligation rate constant with respect to free base amine, were then calculated from $k_{\text{on}} = k_{\text{on}}' / \alpha_{\text{R}'\text{NH}_2}$, where $\alpha_{\text{R}'\text{NH}_2}$ is defined above. As for the equilibrium measurements, generally two determinations were made for each alkylcobaloxime: one at $\text{pH} \rightarrow \text{pK}'_{\text{c}2} - 2$ (and $\alpha_{\text{R}'\text{NH}_2} \geq 0.90$) and one at pH ca. 8.8 ($\alpha_{\text{R}'\text{NH}_2} \sim 0.50$), except for $\text{R} = \text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2$ and $\text{CH}_3\text{OOCCH}_2\text{CH}_2$ for which multiple determinations were made at pH 8.8. For all complexes with $\sigma_{\text{R}}^* <$

0.31, where the forward rates of ligation were too fast to be measured by this technique, values were calculated from $k_{on} = k_{off}K_f$, where k_{off} was measured as below.

Ligand dissociation rate constants, k_{off} (Scheme I), were measured spectrophotometrically by addition of a small volume of a solution containing preformed $\text{RCo}(\text{D}_2\text{H}_2)(\text{DEA})$ (generally, ca. 0.02 M $\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})$ plus ca. 0.04 M DEA, in methanol) to cuvettes containing either phosphate buffer (pH ca. 6.5) or acetate buffer (pH ca. 5.5) and KCl, in the thermostated (25.0 ± 0.1 °C) cell compartment of a Gilford Model 250 spectrophotometer. Absorbance was continuously monitored at the same wavelength used for K_f and k_{on} measurements. Triplicate measurements were made at each pH, and first-order rate constants, k_{off} , were determined as above (eq 13). In all cases, calculations using $K_f' = \alpha_{\text{R}^-\text{NH}_2}K_f$ showed that ligand dissociation proceeded to $\geq 99\%$ completion at both pHs. In no case did the rate constants obtained at pH 5.5 differ significantly from those obtained at pH 6.5, and all plots of eq 13 were satisfactorily linear (correlation coefficients ≥ 0.998). All six determinations were averaged to obtain a final value of k_{off} . For $\text{R} = \text{CF}_3\text{CH}_2$ and $\text{CH}_3\text{OOCCH}_2$, where the half-time for ligand dissociation exceeded 20 h, the reactions were not followed to completion. Instead, observations were made over at least three half-times, and the rate constants were obtained by the method of Guggenheim.²⁰ Where both k_{on} and k_{off} could be measured, $0.31 \leq \sigma^*_\text{R} \leq 0.60$, an additional value of K_f was calculated from $K_f = k_{on}/k_{off}$ and was averaged with the spectrophotometric values.

Thermodynamic Measurements. The enthalpy of ligation of DEA to the alkylcobaloximes was measured by titration calorimetry using a Tronac 450-4 Isoparabol calorimeter. The system consists of a constant delivery rate microburet (1 mL/153.11 s) and a reaction vessel (50 mL Dewar flask), both immersed in a thermostated bath (25.00 ± 0.01 °C). For each determination two solutions were prepared: a ligand solution containing sufficient DEA such that the ligation equilibrium would proceed to $\geq 99\%$ completion (as calculated from the measured values of K_f above), 0.10 M buffer (only for experiments conducted at $\text{pH} \leq \text{p}K'_2 - 2$; for experiments at pH ca. 8.8, DEA itself provided the necessary buffering action), and KCl to ionic strength 1.0 M, in 5% methanol and a blank solution identical with the ligand solution but containing no DEA. A cobaloxime solution was prepared volumetrically from alkylcobaloxime using the blank solution as solvent (0.01–0.05 M, depending on the solubility of the cobaloxime). Most determinations consisted of four runs: (A) heat of reaction, (B) heat of dilution of alkylcobaloxime, (C) heat of dilution of DEA, and (D) correction for temperature difference, if any, between the buret and the Dewar. Each run consisted of three sequential 100-s additions of buret solution to the reaction vessel (approximate volume delivered = 0.65 mL/addition) with calibration heats taken before and after each addition. For runs A and B, cobaloxime solution was placed in the buret, while for C and D the buret contained blank solution. For runs A and C, the reaction vessel contained ligand solution, while for B and D it contained blank solution. Observed enthalpies of addition at 25.00 ± 0.01 °C were obtained by linear least-squares fits of observed enthalpies for each addition²¹ vs. reaction vessel temperature as measured thermoelectrically (corresponding to extrapolation or interpolation of observed enthalpies of addition to bath temperature, i.e., 25.00 ± 0.01 °C). The enthalpy of formation of the DEA complex, ΔH_f , was then calculated using eq 15, where

$$\Delta H_f = \Delta H_A - \Delta H_B - \Delta H_C + \Delta H_D \quad (15)$$

ΔH_A etc. are the observed enthalpies of addition at bath temperature for the four runs. Generally, two separate determinations, one at pH ca. $\text{p}K'_2 - 2$ and one at ca. pH 8.9, were performed. In some cases, where the enthalpy of dilution of alkylcobaloxime (run B) proved extremely small in the first determination ($\leq 2\%$ of ΔH_A), the second determination omitted runs B and D, but runs A and C consisted of five sequential additions (of length 20, 40, 60, 80, and 100 s). Values of ΔH_f for $\text{R} = \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$ and C_6H_5 could not be determined in this manner due to the low solubility of these complexes. From the measured enthalpies of formation and calculated values of the free energy of formation (from measured values of K_f), values of the entropy of formation of the DEA complexes, ΔS_f , were calculated.

For $\text{R} = (\text{CH}_3\text{CH}_2)_2\text{CH}$, CH_3CH_2 , and $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$, values for the enthalpy and entropy of formation of the DEA complexes were obtained from the temperature dependence of the values for K_f for these complexes. Determinations were made at ca. 5, 15, 25, 35, and

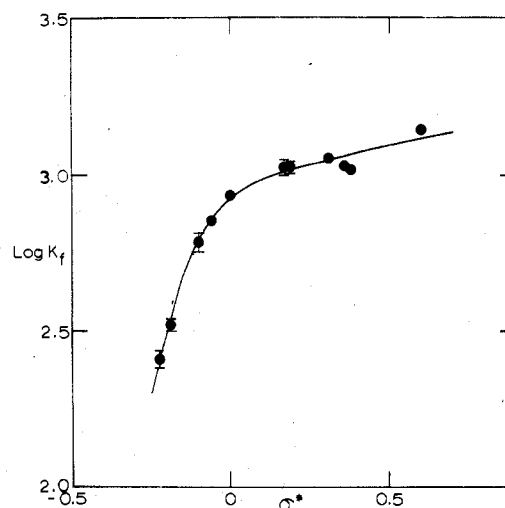


Figure 1. Dependence of $\log K_f$ for the formation of DEA complexes of the alkylcobaloximes on the polar substituent constant (σ^*). The solid line is calculated from eq 26 and the least-squares parameters $\rho^*_{K_{cw}} = -5.58 \pm 0.95$, $\log K^{\circ}_{cw} = -0.88 \pm 0.26$, $\rho^*_{K_L} = 5.81 \pm 1.02$, and $\log K^{\circ}_L = 3.86 \pm 0.23$. Standard deviations fall within the symbols unless otherwise depicted.

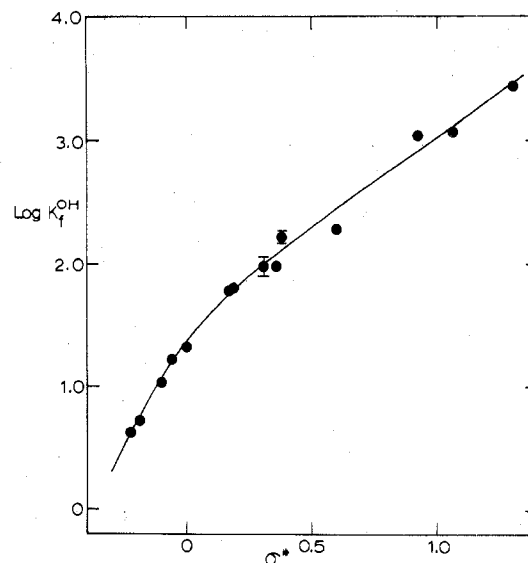
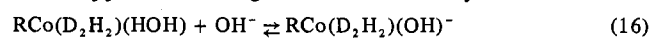


Figure 2. Dependence of $\log K_f^{\text{OH}}$ for formation of alkyl(hydroxo)cobaloximes on the polar substituent constant, σ^* . K_f^{OH} is calculated from eq 18, and the values of $\text{p}K'_2$ in Table I and ref 3. The solid line is calculated from eq 30 and the least-squares parameters $\rho^*_{K_{cw}} = -3.33 \pm 1.21$, $\log K^{\circ}_{cw} = -0.24 \pm 0.36$, $\rho^*_{K_{\text{OH}}} = 4.82 \pm 1.28$, and $\log K^{\circ}_{\text{OH}} = 1.80 \pm 0.27$. Standard deviations fall within the symbols unless otherwise depicted.

45 °C, except for $\text{R} = (\text{CH}_3\text{CH}_2)_2\text{CH}$ which was not sufficiently stable at 45 °C to allow a determination. Linear least-squares fits of $\ln K_f$ vs. $1/T$ (K) provided values of ΔH_f (from the slope) and ΔS_f (from the intercept). These values were averaged with those obtained from the calorimetry work.

Results

Equilibrium Measurements. Values for the equilibrium constants, K_f (Scheme I), for the binding of DEA to 11 alkylcobaloximes are listed in Table I. Figure 1 shows a plot of $\log K_f$ vs. σ^* for these alkylcobaloximes. Figure 2 shows a plot of $\log K_f^{\text{OH}}$ vs. σ^* for 14 alkylcobaloximes, where K_f^{OH} is the apparent binding constant for the hydroxide ion:



$$K_f^{\text{OH}} = \frac{[\text{RCo}(\text{D}_2\text{H}_2)(\text{OH})^-]}{[\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})][\text{OH}^-]} \quad (17)$$

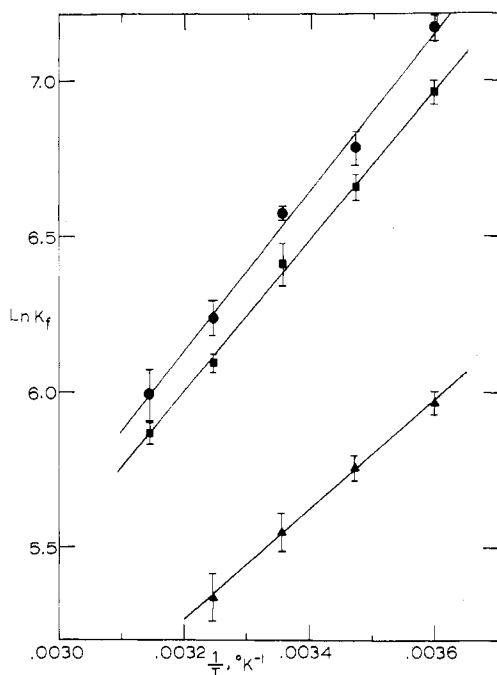


Figure 3. Dependence of $\ln K_f$ for the formation of DEA complexes of three alkylcobaloximes on the reciprocal of absolute temperature. $R = C_6H_5CH_2CH_2$ (\bullet), slope = 2570 ± 110 K, intercept = -2.08 ± 0.36 ; $R = CH_3CH_2$ (\blacksquare), slope = 2430 ± 60 K, intercept = -1.76 ± 0.21 ; $R = (CH_3CH_2)_2CH$ (\blacktriangle), slope = 1790 ± 40 K, intercept = -0.475 ± 0.140 . Error bars represent ± 1 standard deviation.

which is related to K'_c (Scheme I) by, and has been calculated from, eq 18, using $K_w = 10^{-14}$ at 25.0 °C. Note that, despite

$$K_f^{OH} = K'_c / K_w \quad (18)$$

some scatter, both of these free-energy correlations are distinctly nonlinear and that each is adequately predicted by the calculated solid lines (see below).

Values for pK'_a for DEA (Scheme I) at various temperatures were as follows: 5.0 °C, $9.52 \pm .01$; 15.2, $9.17 \pm .01$; 25.1, $8.86 \pm .01$; 35.0, $8.62 \pm .01$; 45.0, $8.41 \pm .01$. A plot (not shown) of $\ln K'_a$ vs. $1/T$ provided values for the enthalpy and entropy of deprotonation of DEA ($\Delta H = 11.3 \pm 0.4$ kcal/mol and $\Delta S = -2.86 \pm 1.39$ eu from the least-squares slope and intercept, respectively), in good agreement with such values for other primary amines.²³

Values for the equilibrium constant, K_f , at various temperatures for $R = (CH_3CH_2)_2CH$, CH_3CH_2 , and $C_6H_5CH_2CH_2$ are listed in Table II. Figure 3 shows plots of $\ln K_f$ vs. $1/T$ for these three complexes from which values for the enthalpy and entropy of DEA complexation were obtained (see Experimental Section).

Calorimetry. Values for the enthalpy (ΔH_f) and entropy (ΔS_f) of formation of the DEA complexes of nine alkylcobaloximes from calorimetry measurements are given in Table III, along with the values determined from the temperature dependence of K_f (Table II and Figure 3). Agreement between duplicate calorimetric measurements, as well as between calorimetric and temperature dependence determinations, is generally quite good. Note, however, that the entropy values have much higher relative uncertainties than the enthalpy values due to the method of calculation of the former (Table III, footnote b).

Figure 4 shows a plot of the enthalpies and entropies of formation of the DEA complexes vs. σ^* for the nine alkylcobaloximes in Table III. Clearly, these correlations for the enthalpies and entropies are distinctly nonlinear, despite considerable scatter and large relative uncertainty for some

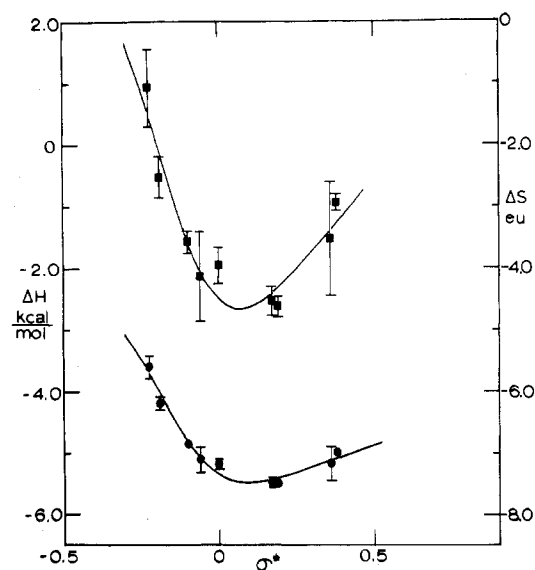


Figure 4. Dependence of ΔH_f (\bullet) and ΔS_f (\blacksquare) for the formation of DEA complexes of the alkylcobaloximes on the polar substituent constant (σ^*). The solid lines are calculated from eq 38 and 39 and the values of the ten parameters given in Table V. Error bars represent ± 1 standard deviation and fall within the symbol where not shown.

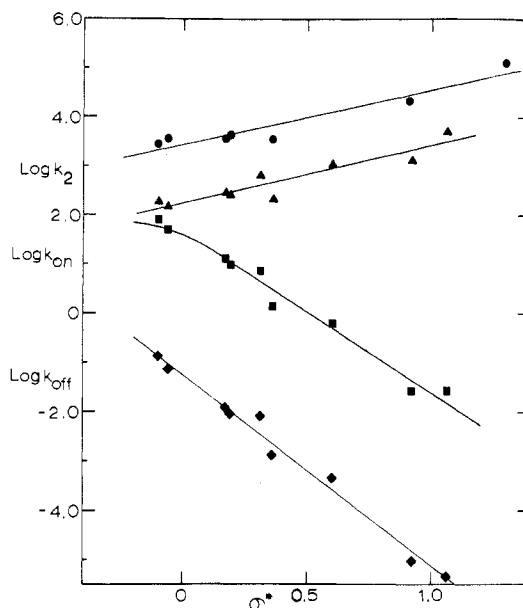


Figure 5. Dependence of $\log k_2$ for pyridine (\bullet), $\log k_2$ for DEA (\blacktriangle), $\log k_{on}$ for DEA (\blacksquare), and $\log k_{off}$ for DEA (\blacklozenge) for the formation and dissociation of complexes of the alkylcobaloximes on the polar substituent constant, σ^* . The upper two and bottom most solid lines are linear least-squares regression lines omitting data for $\sigma^* = 0$ ($R = CH_3$) and $\sigma^* = +0.38$ ($R = CH_3OOCCH_2CH_2$). The solid, curved line is calculated from eq 45 and the values of the parameters listed in Table V.

of the latter values. Note that the data for both of these correlations are well fit by the calculated solid lines (see below).

Kinetics. Rate constants for the formation (k_{on}) and dissociation (k_{off}) of the DEA complexes of 11 alkylcobaloximes are given in Table IV. Figure 5 shows plots of $\log k_{on}$ and $\log k_{off}$ vs. σ^* , as well as $\log k_2$ for DEA and pyridine (see below) vs. σ^* . In all these correlations, the data for $R = CH_3$ and $CH_3OOCCH_2CH_2$ ($\sigma^* = 0.0$ and 0.38 , respectively) deviate badly from the lines determined by the remaining data for reasons which are unknown. Consequently, these points have been omitted from further analysis.

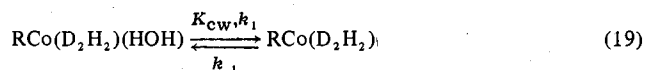
Table I. Equilibrium Constants for Formation of DEA Complexes of Alkylcobaloximes in Aqueous Solution (25.0 °C, Ionic Strength 1.0 M)

R	σ^{*a}	pH	α_{DEA}^b	K_f^c, M^{-1}	K_f^d, M^{-1}	K_f^e, M^{-1}	K_f^f, M^{-1}	$\text{p}K'_{c_2}$	K_{cw}^g
$(\text{CH}_3\text{CH}_2)_2\text{CH}$	-0.225	10.48 ± 0.02	0.977 ± 0.001	251 ± 28	257 ± 29		257 ± 16	13.38 ± 0.02	2.8
		8.84 ± 0.01	0.488 ± 0.009	125 ± 5	256 ± 12				
$(\text{CH}_3)_2\text{CH}$	-0.19	10.67 ± 0.03	0.985 ± 0.001	338 ± 23	343 ± 23		331 ± 15	13.28 ± 0.02 ⁿ	2.0
		8.83 ± 0.02	0.483 ± 0.013	154 ± 9	319 ± 20				
CH_3CH_2	-0.10	10.67 ± 0.02	0.986 ± 0.001	595 ± 56	604 ± 57		608 ± 42	12.97 ± 0.02 ⁿ	7.7 × 10 ⁻¹
		8.71 ± 0.02	0.415 ± 0.013	254 ± 25	612 ± 63				
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$	-0.06 ^h	10.69 ± 0.01	0.985 ± 0.001	706 ± 16	717 ± 16		714 ± 19	12.78 ± 0.02 ⁿ	5.1 × 10 ⁻¹
		8.71 ± 0.02	0.415 ± 0.013	295 ± 11	711 ± 34				
CH_3	0.00	10.54 ± 0.08	0.980 ± 0.004 ⁱ	835 ± 37 ⁱ	852 ± 38 ⁱ	866 ± 24 ⁱ	861 ± 20 ⁱ	12.68 ± 0.02 ⁿ	2.8 × 10 ⁻¹
		8.68 ± 0.01	0.398 ± 0.009 ⁱ	344 ± 14 ⁱ	864 ± 40 ⁱ				
$\text{NCCH}_2\text{CH}_2\text{CH}_2$	+0.17 ^j	10.22 ± 0.02	0.958 ± 0.002	1020 ± 80	1060 ± 80		1060 ± 60	12.22 ± 0.02 ⁿ	4.8 × 10 ⁻²
		8.71 ± 0.02	0.415 ± 0.013	442 ± 37	1060 ± 100				
$\text{CH}_3\text{OCH}_2\text{CH}_2$	+0.19 ^k	10.12 ± 0.02	0.948 ± 0.003	995 ± 72	1050 ± 80		1060 ± 50	12.19 ± 0.02 ⁿ	3.9 × 10 ⁻²
		8.87 ± 0.01	0.506 ± 0.008	536 ± 27	1060 ± 60				
$\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2$	+0.31 ^l	8.90 ± 0.01	0.523 ± 0.009	594 ± 49	1140 ± 100	905 ± 26	1130 ± 40	12.02 ± 0.08	1.1 × 10 ⁻²
		8.86 ± 0.01	0.500 ± 0.008	594 ± 47	1190 ± 100				
$\text{CH}_3\text{CH}=\text{CH}$	+0.36	9.97 ± 0.02	0.928 ± 0.003	986 ± 89	1060 ± 100	1040 ± 30	1070 ± 40	12.02 ± 0.01 ⁿ	6.8 × 10 ⁻³
		8.82 ± 0.02	0.477 ± 0.013	523 ± 32	1100 ± 70				
$\text{CH}_3\text{OOCCH}_2\text{CH}_2$	+0.38 ^m	8.85 ± 0.01	0.494 ± 0.008	514 ± 13	1040 ± 30	950 ± 40	1040 ± 30	11.78 ± 0.05	5.5 × 10 ⁻³
		8.85 ± 0.01	0.494 ± 0.008	558 ± 40	1130 ± 80				
C_6H_5	+0.60	9.57 ± 0.01	0.837 ± 0.004	1200 ± 60	1430 ± 70	1370 ± 50	1390 ± 30	11.72 ± 0.03	5.7 × 10 ⁻⁴
		8.83 ± 0.01	0.483 ± 0.008	662 ± 25	1370 ± 60				

^a See ref 5. ^b Calculated from eq 12 using $\text{p}K'_a = 8.86 \pm 0.01$ at 25.0 °C. ^c Spectrophotometric determinations; see Experimental Section. ^d Calculated from $K_f = K'_f/\alpha_{\text{DEA}}$. ^e Calculated from $K_f = k_{\text{on}}/k_{\text{off}}$ (Scheme 1). ^f Average value from d and e. ^g Calculated from eq 25 and parameter values in Table V. ^h Calculated from $\sigma^* = 6.23\sigma^i$, see ref 22. ⁱ Values recalculated from ref 6b using $\text{p}K'_a = 8.86$ for DEA at 25.0 °C. ^j Calculated from $\sigma^*(\text{NCCH}_2\text{CH}_2\text{CH}_2) = \sigma^*(\text{NCCH}_2)/(2.76)^2$. ^k Calculated from $\sigma^*(\text{CH}_3\text{OCH}_2\text{CH}_2) = \sigma^*(\text{CH}_3\text{OCH}_2)/2.76$. ^l Calculated from $\sigma^*(\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2) = \sigma^*(\text{C}_6\text{H}_5\text{OCH}_2)/2.76$. ^m Calculated from $\sigma^*(\text{CH}_3\text{OOCCH}_2\text{CH}_2) = \sigma^*(\text{CH}_3\text{OOCCH}_2)/2.76$; $\sigma^* = 6.23\sigma^i$; see ref 22. ⁿ Ref 3.

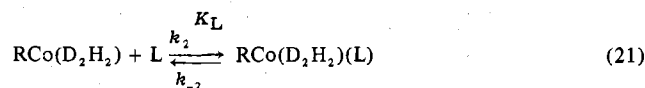
Discussion

Equilibrium. As shown in a previous report,³ the nonlinear free-energy relationships for ligand-exchange equilibrium for alkylcobaloximes can be interpreted in terms of a preequilibrium mechanism in which the equilibrium dissociation of axial water, to form a pentacoordinate species (eq 19 and 20),



$$K_{\text{cw}} = [\text{RCo}(\text{D}_2\text{H}_2)] / [\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})] = k_1/k_{-1} \quad (20)$$

is followed by association of the incoming ligand (eq 21 and 22). Hence, the apparent equilibrium constant for ligand



$$K_L = [\text{RCo}(\text{D}_2\text{H}_2)(\text{L})] / [\text{RCo}(\text{D}_2\text{H}_2)] [\text{L}] = k_2/k_{-2} \quad (22)$$

substitution, K_f , is given by eq 23a and b. Assuming that both

$$K_f = [\text{RCo}(\text{D}_2\text{H}_2)(\text{L})] / ([\text{RCo}(\text{D}_2\text{H}_2)] + [\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})]) [\text{L}] \quad (23a)$$

$$K_f = K_L(K_{\text{cw}}/(K_{\text{cw}} + 1)) \quad (23b)$$

K_L and K_{cw} are linearly correlated with the Taft polar substituent parameter, σ^* ,²⁴

$$\log K_L = \rho^*_{K_L} \sigma^* + \log K^{\circ}_{K_L} \quad (24)$$

$$\log K_{\text{cw}} = \rho^*_{K_{\text{cw}}} \sigma^* + \log K^{\circ}_{K_{\text{cw}}} \quad (25)$$

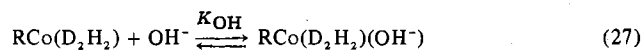
then the dependence of $\log K_f$ on σ^* is given by eq 26. The

$$\log K_f = \rho^*_{K_f} \sigma^* + \log K^{\circ}_{K_f} - \log(1 + 10^{-(\rho^*_{K_{\text{cw}}} \sigma^* + \log K^{\circ}_{K_{\text{cw}}})}) \quad (26)$$

data for K_f for DEA (Table I) have thus been fit to the four-parameter eq 26 by a nonlinear least-squares routine utilizing a mixed Hartley²⁷-Marquardt²⁸ algorithm to yield values for $\rho^*_{K_f}$ and $\log K^{\circ}_{K_f}$ (listed in Table V), $\rho^*_{K_{\text{cw}}} = -5.58$

± 0.95 , and $\log K^{\circ}_{\text{cw}} = -0.88 \pm 0.26$. The solid line in Figure 1 is calculated from these parameters and eq 26 and represents a very good fit of a clearly nonlinear correlation.

The axial water proton dissociation of the alkyl(aquo)cobaloximes, $\text{p}K'_{c_2}$ (Scheme I, Table I), can be treated in a similar manner since it is thermodynamically equivalent to displacement of axial water by a hydroxide ion. Hence, the preequilibrium dissociation of axial water (eq 19 and 20) is followed by association of hydroxide ion:



$$K_{\text{OH}} = [\text{RCo}(\text{D}_2\text{H}_2)(\text{OH}^-)] / [\text{RCo}(\text{D}_2\text{H}_2)] [\text{OH}^-] \quad (28)$$

The apparent binding constant, K_f^{OH} , for hydroxide ion (eq 16 and 17) is given by eq 29, and the dependence of $\log K_f^{\text{OH}}$

$$K_f^{\text{OH}} = K_{\text{OH}}(K_{\text{cw}}/(K_{\text{cw}} + 1)) \quad (29)$$

on σ^* is given by eq 30. Again, the values of $\log K_f^{\text{OH}}$

$$\log K_f^{\text{OH}} = \rho^*_{K_{\text{OH}}} \sigma^* + \log K^{\circ}_{K_{\text{OH}}} - \log(1 + 10^{-(\rho^*_{K_{\text{cw}}} \sigma^* + \log K^{\circ}_{K_{\text{cw}}})}) \quad (30)$$

(calculated from eq 18, values of $\text{p}K_{c_2}$ listed in Table I, and some additional values taken from ref 3) have been fit to eq 30 using a nonlinear least-squares routine to yield the values of $\rho^*_{K_{\text{OH}}}$ and $\log K^{\circ}_{K_{\text{OH}}}$ listed in Table V, $\rho^*_{K_{\text{cw}}} = -3.35 \pm 1.21$, and $\log K^{\circ}_{\text{cw}} = -0.24 \pm 0.36$. The solid line in Figure 2 is calculated from these parameters and eq 30.

In order to obtain the best available estimates of the parameters $\rho^*_{K_{\text{cw}}}$ and $\log K^{\circ}_{\text{cw}}$, the values from the above two correlations were averaged to give the values listed in Table V. Table I (last column) lists the best estimates of K_{cw} for 11 alkylcobaloximes calculated from eq 25 and these average parameter values in Table V.

These results show that the model of eq 19–22 provides an adequate description of the nonlinear free-energy correlations for the formation of alkylcobaloxime adducts in aqueous solution.

Table II. Equilibrium Constants for Formation of DEA Complexes of Alkylcobaloximes at Various Temperatures in Aqueous Solution (Ionic Strength 1.0 M)

R	T, °C	pH	α_{DEA}^a	$K_f',^b \text{ M}^{-1}$	$K_f,^c \text{ M}^{-1}$
(CH ₃ CH ₂) ₂ CH	5.0 ± 0.2	9.74 ± 0.02	0.624 ± 0.012	244 ± 18	390 ± 14
	15.1 ± 0.1	9.51 ± 0.02	0.686 ± 0.011	217 ± 9	316 ± 13
	25.0 ± 0.1				257 ± 16 ^d
	35.0 ± 0.1	8.93 ± 0.07	0.671 ± 0.036	139 ± 8	208 ± 16
CH ₃ CH ₂	5.0 ± 0.1	9.53 ± 0.01	0.506 ± 0.008	533 ± 19	1050 ± 40
	15.0 ± 0.1	9.33 ± 0.02	0.585 ± 0.013	454 ± 17	777 ± 33
	25.0 ± 0.1				608 ± 42 ^d
	35.0 ± 0.1	8.61 ± 0.01	0.494 ± 0.008	219 ± 5	443 ± 13
C ₆ H ₅ CH ₂ CH ₂	45.0 ± 0.1	8.45 ± 0.01	0.523 ± 0.008	185 ± 6	354 ± 12
	5.1 ± 0.1	9.53 ± 0.02	0.506 ± 0.013	657 ± 23	1300 ± 60
	15.0 ± 0.1	9.29 ± 0.02	0.569 ± 0.013	501 ± 25	882 ± 48
	25.0 ± 0.1				714 ± 19 ^d
	35.1 ± 0.1	8.63 ± 0.02	0.506 ± 0.013	259 ± 13	512 ± 29
	45.1 ± 0.1	8.43 ± 0.02	0.512 ± 0.013	205 ± 17	400 ± 34

^a Calculated from eq 12 using pK_a' for the appropriate temperature. ^b Spectrophotometric determination; see Experimental Section. ^c Calculated from $K_f = K_f' / \alpha_{\text{DEA}}$. ^d Average value at 25.0 °C from Table I.

Table III. Enthalpies and Entropies of Formation of DEA Complexes of the Alkylcobaloximes in Aqueous Solution (25.0 °C, Ionic Strength 1.0 M)

R	σ^{*a}	Microcalorimetry			Temperature dependence of K_f			
		pH	$\Delta H_f,^c \text{ kcal/mol}$	$\Delta S_f,^b \text{ eu}$	$\Delta H_f,^c \text{ kcal/mol}$	$\Delta S_f,^d \text{ eu}$	$\Delta H_f,^e \text{ kcal/mol}$	$\Delta S_f,^e \text{ eu}$
(CH ₃ CH ₂) ₂ CH	-0.225	10.62	-3.64 ± 0.36	-1.20 ± 1.21	-3.56 ± 0.08	-0.94 ± 0.28	-3.60 ± 0.18	-1.07 ± 0.62
(CH ₃) ₂ CH	-0.19	10.52	-4.08 ± 0.15	-2.15 ± 0.51			-4.19 ± 0.10	-2.52 ± 0.34
		10.54	-4.30 ± 0.13	-2.89 ± 0.45				
CH ₃ CH ₂	-0.10	10.46	-4.83 ± 0.04	-3.48 ± 0.20	-4.82 ± 0.12	-3.50 ± 0.42	-4.86 ± 0.05	-3.58 ± 0.18
		8.92	-4.92 ± 0.07	-3.76 ± 0.27				
C ₆ H ₅ CH ₂ CH ₂	-0.06 ^f				-5.10 ± 0.21	-4.13 ± 0.72	-5.10 ± 0.21	-4.13 ± 0.72
		CH ₃	0.00	10.52	-5.10 ± 0.12	-3.69 ± 0.42		-5.18 ± 0.08
NCCH ₂ CH ₂ CH ₂	+0.17 ^g	8.90	-5.26 ± 0.12	-4.22 ± 0.39				
		10.19	-5.44 ± 0.09	-4.43 ± 0.32			-5.47 ± 0.07	-4.53 ± 0.23
CH ₃ OCH ₂ CH ₂	+0.19 ^h	8.86	-5.50 ± 0.10	-4.62 ± 0.34				
		10.15	-5.53 ± 0.06	-4.70 ± 0.23			-5.50 ± 0.04	-4.62 ± 0.16
CH ₃ CH=CH	+0.36	8.85	-5.47 ± 0.06	-4.53 ± 0.23				
		10.02	-5.12 ± 0.50	-3.36 ± 1.68			-5.17 ± 0.27	-3.53 ± 0.92
CH ₃ OOCCH ₂ CH ₂	+0.38 ⁱ	8.90	-5.22 ± 0.22	-3.69 ± 0.74				
		8.94	-5.02 ± 0.06	-3.05 ± 0.21			-4.99 ± 0.04	-2.94 ± 0.13
		8.90	-4.95 ± 0.04	-2.82 ± 0.15				

^a See ref 5. ^b Calculated from $\Delta S_f = (\Delta H_f - \Delta G_f)/T$ and $\Delta G_f = -RT \ln K_f$. ^c Calculated from the least-squares slopes of plots of $\ln K_f$ vs. $1/T$ (Figure 3). ^d Calculated from the least-squares intercepts of plots of $\ln K_f$ vs. $1/T$ (Figure 3). ^e Unweighted average of all determinations. ^f See footnote h, Table I. ^g See footnote j, Table I. ^h See footnote k, Table I. ⁱ See footnote m, Table I.

Thermodynamics. The nonlinear correlations of ΔH_f and ΔS_f for DEA complex formation with σ^* (Figure 4) are also adequately explained by the model of eq 19–22. Thus, if ΔH_{cw} and ΔS_{cw} represent the enthalpy and entropy of axial water dissociation (eq 19) and ΔH_L and ΔS_L represent the enthalpy and entropy of association of DEA to the pentacoordinate alkylcobaloxime species (eq 21), then the enthalpy and entropy of formation of the DEA complexes are given by eq 31 and 32, respectively, where the term $1/(1 + K_{\text{cw}})$ represents the fraction of alkylcobaloxime as the hexacoordinate aquo species at 25 °C, i.e.,

$$1/(1 + K_{\text{cw}}) =$$

$$\frac{[\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})]/([\text{RCo}(\text{D}_2\text{H}_2)(\text{HOH})] + [\text{RCo}(\text{D}_2\text{H}_2)]}{(33)}$$

Again, if the individual enthalpies and entropies are linearly correlated with the Taft σ^* parameter (eq 34–37), then eq 25

$$\Delta H_L = \rho^* \Delta H_L \sigma^* + \Delta H_L^\circ \quad (34)$$

$$\Delta H_{\text{cw}} = \rho^* \Delta H_{\text{cw}} \sigma^* + \Delta H_{\text{cw}}^\circ \quad (35)$$

$$\Delta S_L = \rho^* \Delta S_L \sigma^* + \Delta S_L^\circ \quad (36)$$

$$\Delta S_{\text{cw}} = \rho^* \Delta S_{\text{cw}} \sigma^* + \Delta S_{\text{cw}}^\circ \quad (37)$$

and 34–37 can be substituted into eq 31 and 32 to provide eq 38 and 39, which describe the dependence of ΔH_f and ΔS_f on

$$\Delta H_f = \rho^* \Delta H_L \sigma^* + \Delta H_L^\circ + (1/(1 + 10^{(\rho^* K_{\text{cw}} \sigma^* + \log K_{\text{cw}}^\circ)}))(\rho^* \Delta H_{\text{cw}} \sigma^* + \Delta H_{\text{cw}}^\circ) \quad (38)$$

$$\Delta S_f = \rho^* \Delta S_L \sigma^* + \Delta S_L^\circ + (1/(1 + 10^{(\rho^* K_{\text{cw}} \sigma^* + \log K_{\text{cw}}^\circ)}))(\rho^* \Delta S_{\text{cw}} \sigma^* + \Delta S_{\text{cw}}^\circ) \quad (39)$$

σ^* , respectively. Since only nine points were available for each correlation, no attempt was made to fit the six-parameter eq 38 and 39 directly. Instead, the average values for $\rho^* K_{\text{cw}}$ and $\log K_{\text{cw}}^\circ$ (Table V) obtained from the fits of the $\log K_f$ and $\log K_f^{\text{OH}}$ correlations to eq 26 and 30, respectively, were substituted into eq 38 and 39 to provide the simplified eq 40 and 41. The thermodynamic data in Table III were then fit

$$\Delta H_f = \rho^* \Delta H_L \sigma^* + \Delta H_L^\circ + (1/(1 + 10^{(-4.47 \sigma^* - 0.56)}))(\rho^* \Delta H_{\text{cw}} \sigma^* + \Delta H_{\text{cw}}^\circ) \quad (40)$$

$$\Delta S_f = \rho^* \Delta S_L \sigma^* + \Delta S_L^\circ + (1/(1 + 10^{(-4.47 \sigma^* - 0.56)}))(\rho^* \Delta S_{\text{cw}} \sigma^* + \Delta S_{\text{cw}}^\circ) \quad (41)$$

to the four-parameter eq 40 and 41 by the least-squares technique to provide the values for the eight parameters listed in Table V. The *solid lines* in Figure 4 have been calculated from these parameters and eq 40 and 41, and they clearly represent adequate descriptions of the nonlinear behavior of both correlations.

Table IV. Rate Constants for Formation and Dissociation of DEA Complexes of Alkylcobaloximes in Aqueous Solution (25.0 °C, Ionic Strength 1.0 M)

R	σ^* ^a	pH	ϵ_{DEA}^b	$k_{\text{on}}^{\prime,c} \text{ M}^{-1} \text{ s}^{-1}$	$k_{\text{on}}^d \text{ M}^{-1} \text{ s}^{-1}$	$k_{\text{on}}^e \text{ M}^{-1} \text{ s}^{-1}$	$k_{\text{on}}^f \text{ M}^{-1} \text{ s}^{-1}$	$k_{\text{off}}^g \text{ s}^{-1}$
CH ₃ CH ₂	-0.10							1.33 ± 0.05 × 10 ⁻¹
C ₆ H ₅ CH ₂ CH ₂	-0.06 ^h							7.15 ± 0.14 × 10 ⁻²
CH ₃	0.0							5.91 ± 0.14 × 10 ⁻³ⁱ
NCCH ₂ CH ₂ CH ₂	+0.17 ^j							1.23 ± 0.02 × 10 ⁻²
CH ₃ OCH ₂ CH ₂	+0.19 ^k							8.87 ± 0.37 × 10 ⁻³
C ₆ H ₅ OCH ₂ CH ₂	+0.31 ^l							8.00 ± 0.20 × 10 ⁻³
CH ₃ CH=CH	+0.36	8.89 ± 0.01	0.517 ± 0.010	3.65 ± 0.02	7.06 ± 0.15	7.24 ± 0.10	8.09 ± 0.64 × 10 ¹	1.33 ± 0.04 × 10 ⁻³
CH ₃ OOCCH ₂ CH ₂	+0.38 ^m	8.80 ± 0.01	0.465 ± 0.008	3.45 ± 0.03	7.42 ± 0.14	1.38 ± 0.02	5.11 ± 0.17 × 10 ¹	1.21 ± 0.05 × 10 ⁻²
C ₆ H ₅	+0.60	9.98 ± 0.01	0.929 ± 0.002	1.23 ± 0.01	1.32 ± 0.01		5.09 ± 0.17 ^j	4.54 ± 0.13 × 10 ⁻⁴
CF ₃ CH ₂	+0.92	8.82 ± 0.01	0.477 ± 0.008	6.85 ± 0.07 × 10 ⁻¹	1.44 ± 0.03	1.15 ± 0.03 × 10 ¹	1.30 ± 0.08 × 10 ¹	9.49 ± 0.13 × 10 ⁻⁶
CH ₃ OOCCH ₂	+1.06 ⁿ	8.67 ± 0.01	0.392 ± 0.008	4.64 ± 0.13	1.18 ± 0.04 × 10 ¹	6.21 ± 0.15 × 10 ⁻¹	9.40 ± 0.59	4.57 ± 0.03 × 10 ⁻⁶
		8.82 ± 0.01	0.477 ± 0.008	5.29 ± 0.15	1.11 ± 0.04 × 10 ¹	2.69 ± 0.09 × 10 ⁻²		
		9.62 ± 0.02	0.852 ± 0.007	5.11 ± 0.06 × 10 ⁻¹	6.00 ± 0.08 × 10 ⁻¹	2.71 ± 0.10 × 10 ⁻²		
		8.83 ± 0.01	0.483 ± 0.008	3.10 ± 0.11 × 10 ⁻¹	6.41 ± 0.28 × 10 ⁻¹			
		8.95 ± 0.02	0.569 ± 0.016	1.53 ± 0.03 × 10 ⁻²	2.69 ± 0.09 × 10 ⁻²			
		8.90 ± 0.01	0.523 ± 0.006	1.41 ± 0.07 × 10 ⁻²	2.70 ± 0.14 × 10 ⁻²			
		8.83 ± 0.01	0.483 ± 0.008	1.32 ± 0.07 × 10 ⁻²	2.73 ± 0.14 × 10 ⁻²			

^a See ref 5. ^b Calculated from eq 12 using $\text{p}K_a' = 8.86 \pm 0.01$ at 25.0 °C. ^c Least-squares slope of plots of k_{obsd} vs. $[\text{DEA}]_{\text{tot}}$, eq 14. ^d Calculated from $k_{\text{on}} = k_{\text{on}}^{\prime}/\epsilon_{\text{DEA}}$. ^e Average of two values from *d*. ^f Calculated from $k_{\text{on}} = K_{\text{off}}K_f$. ^g Average of six values. ^h See footnote *h*, Table I. ⁱ Taken, or recalculated, from ref 6b using $\text{p}K_a = 8.86$ for DEA at 25.0 °C. ^j See footnote *j*, Table I. ^k See footnote *k*, Table I. ^l See footnote *l*, Table I. ^m See footnote *m*, Table I. ⁿ Calculated from $\sigma^* = 6.23\sigma^{\dagger}$, see ref 22.

Table V. Linear Free-Energy Correlations with Polar Substituent Constants (σ^*) for Equilibria and Kinetics of Axial Ligation Reactions of Alkylcobaloximes^a

Reaction ^b	Slope (ρ^*)	Intercept	
		Value	Term
K_L	5.81 ± 1.02	3.86 ± 0.23	$\log K_{\text{L}}^{\text{O}}$
K_{OH}	4.82 ± 1.28	1.80 ± 0.27	$\log K_{\text{OH}}^{\text{O}}$
K_{ew}	-4.47 ± 0.77 ^c	-0.56 ± 0.22 ^d	$\log K_{\text{ew}}^{\text{O}}$
ΔH_L	-4.0	-3.7	ΔH_L^{O}
ΔH_{ew}	5.9	-2.1	$\Delta H_{\text{ew}}^{\text{O}}$
ΔS_L	-4.5	-0.5	ΔS_L^{O}
ΔS_{ew}	10.7	-5.2	$\Delta S_{\text{ew}}^{\text{O}}$
k_2 (DEA)	1.17 ± 0.18	2.25 ± 0.10	$\log k_2^{\text{O}}$ (DEA)
k_{off} (DEA)	-3.87 ± 0.18	-1.26 ± 0.10	$\log k_{\text{off}}^{\text{O}}$ (DEA)
k_2 (py)	1.13 ± 0.16	3.43 ± 0.10	$\log k_2^{\text{O}}$ (py)
k_{off} (py)	-4.13 ± 0.28 ^e	0.08 ± 0.16 ^e	$\log k_{\text{off}}^{\text{O}}$ (py)

^a 25.0 °C, ionic strength 1.0 M. ^b The reaction constants are defined by Scheme 1 and eq 16, 17, 19-22, and 27-29. ^c Average of two values, -3.35 ± 1.21 and -5.58 ± 0.95; see text. ^d Average of two values, -0.24 ± 0.36 and -0.88 ± 0.26; see text. ^e Taken from ref 3.

It must be noted that due to the limited amount of data and the scatter in the data, the eight parameters of eq 40 and 41 are rather poorly determined, precluding any detailed discussion of their significance. However, the signs and magnitudes of the slope parameters are certainly consistent with the expected behavior of the individual reaction steps, eq 19 and 21, as correlated by eq 34-37.

In order to assess the applicability of the foregoing analysis, it is important to justify the assumptions of linearity implicit in eq 24, 25, and 34-37. Of the 14 free-energy correlations presented in this and the previous report,³ six do not depend on the preequilibrium of eq 19 and are expected to be linear. Application of Taft's *f* statistic^{29,30} shows that four of these relationships ($\log k_{\text{off}}$ for DEA (below), $\log k_{\text{off}}$, $\log K_f'$, and $\text{p}K_{\text{c-L}}$ for pyridine (ref 3); $f = 0.08, 0.11, 0.09$, and 0.10 , respectively) are well-correlated by linear functions.³⁰ The remaining two, ($\log k_{\text{on}}'$ and $\log k_{\text{off}}$ for pyridine³) were less well-correlated ($f = 0.13$ and 0.24 , respectively) since only five points were available. Furthermore, for the data in Figures 1, 2, and 4 ($\log K_f$, $\log K_f^{\text{OH}}$, ΔH_f , and ΔS_f), calculation of the *f* statistic for both linear and the nonlinear correlations shown in the figures ($f = 0.55, 0.16, 0.62$, and 0.78 for linear correlations and $f = 0.08, 0.07, 0.14$, and 0.25 for nonlinear correlations, respectively) shows that a great improvement in correlation is obtained by use of the nonlinear functions.

It is also important to address the question of the steric influence of R on the observed binding data. We have attempted to see if steric effects could be the cause of the observed nonlinearities by application of the modified Taft equation^{5,31} (eq 42), in which δ represents the susceptibility

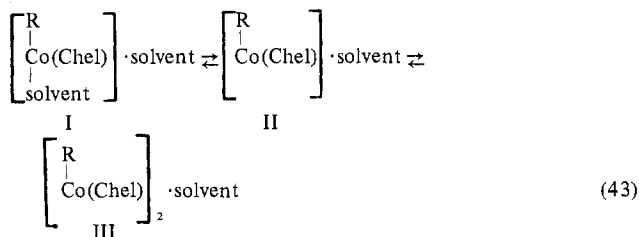
$$\log(K/K_0) = \rho^*\sigma^* + \delta E_s \quad (42)$$

of the reaction to steric effects and E_s is a substituent steric parameter. Using the E_s values compiled by Unger and Hansch,³² we have correlated our data to eq 42 via the least-squares method to obtain values of $f = 0.31, 0.19, 0.42$, and 0.54 for K_f , K_f^{OH} , ΔH_f , and ΔS_f , respectively. Clearly, eq 42 is much less successful than our treatment at correlating these data. Furthermore, even if one is willing to accept the rather poor precision of the correlations of K_f and K_f^{OH} to eq 42, the results ($\rho^* = 0.98$ and $\delta = 0.16$ for K_f , $\rho^* = 1.86$ and $\delta = 0.05$ for K_f^{OH}) show that the steric effect, if real, is minimal.³³ These results make it highly unlikely that steric effects can account for the observed nonlinearities, or, for that matter, that they are very important in this reaction series.

The Model. The above analysis, taken together with spectrophotometric evidence presented in an earlier report,³ is consistent with the existence of two thermodynamically

distinct, but interconvertible, species of alkylcobaloxime in aqueous solution. However, none of these data sheds any light on the nature of these two species. Clearly, one of these must be a solvate of the conventional hexacoordinate octahedral alkyl(aquo)cobaloxime for which there is ample structural evidence in the solid state.³⁶ We believe that the most likely assignment for the second species is a solvate of pentacoordinate alkylcobaloxime (as in eq 19) in which axially coordinated water has been lost from the inner coordination sphere. There is considerable support in the literature for such an assignment in the form of evidence for the occurrence of pentacoordinate alkyl-cobalt complexes among several other B₁₂ model chelate systems.³⁷⁻⁴¹ More recently, Ogoshi et al.⁴² have synthesized a series of alkylcobalt octaethylporphyrins which were found to be pentacoordinate in both solution and the solid state. Similarly, Hill and co-workers⁴³⁻⁴⁶ have published considerable evidence for the existence of two interconvertible species of alkylcobalt corrins. More recently, Hogenkamp et al.⁴⁷ presented ¹³C NMR evidence for a temperature-dependent equilibrium between two species for several alkylcobalamins and methyl(aquo)cobinamide. Although these authors prefer to explain their results in terms of a temperature-dependent conformational equilibrium involving the corrin ring and/or the acetamide side chains, their observations are also consistent with the equilibrium formation of pentacoordinate alkylcobalt corrin species. Furthermore, it seems unlikely in the cobaloxime system and other simple model chelates that a change in conformation (say from octahedral to square bipyramidal with concomitant displacement of cobalt from the equatorial ligand plane) would proceed without loss of the sixth ligand.^{37,48}

It should also be noted that the elegant work of T. L. Brown and co-workers,¹¹ showing that the "ligandless" alkylcobaloximes (i.e., those with no sixth ligand, readily prepared by warming the alkyl(aquo)cobaloximes in vacuo) are dimers both in noncoordinating solvents and probably in the solid state, does not constitute evidence against the existence of stable pentacoordinate alkylcobaloximes in aqueous solution. Clearly, the situation of such dehydrated alkylcobaloximes in solution is as described in eq 43, in which solvated hexacoordinate



species with solvent in the inner coordination sphere (I) are in equilibrium with solvated pentacoordinate species (II) and solvated dimers (III). Brown's work shows that, in noncoordinating solvents in which species I is precluded, the solvation of the potential pentacoordinate species is insufficient to compensate for the free energy of formation of dimers, and hence no evidence of monovalent pentacoordinate species is found. However, in water, where the formation of dimers has been previously excluded,³ solvation of the pentacoordinate species may well be extensive enough to permit substantial equilibrium formation of species II. Hence we conclude that the most reasonable assignments for the two interconvertible thermodynamically distinct species of alkylcobaloxime in aqueous solution are species I and II in eq 43.

Recent arguments⁴⁹ against the existence of the equilibrium of eq 19, based on the strong acid nature of the RCo(D₂H₂) metal center, ignore the fact that oxygen donors are known to have anomalously low affinity to this center.⁵⁰ As our data show (above and ref 3) the affinities of DEA and pyridine for

the RCo(D₂H₂) centers exceed those for hydroxide ion by anywhere from 2- to 100-fold, despite the fact that hydroxide ion is many orders of magnitude more basic (toward the proton) than either DEA or pyridine. For the electron-donating RCo(D₂H₂) centers only, hydroxide affinities are about 50-fold lower than DEA affinities and 90-fold lower than pyridine affinities. Considering the fact that HOH is some 17 orders of magnitude less basic than hydroxide ion, the values for K_{cw} (eq 19 and 20) derived herein and listed in Table I do not seem unreasonable.

Kinetics and Mechanism. If the above analysis is correct, then axial ligand substitution of the alkyl(aquo)cobaloximes in aqueous solution should proceed via a purely dissociative or S_N1_{lim} mechanism. Kinetic evidence has been presented for such an assignment for the ligand-substitution reactions of alkyl(ligand)cobaloximes in chloroform¹⁵ and for alkyl(aquo)-1,3-bis(biacetyl monoximimino)propanecobalt monoocations in 1% aqueous solution.^{9a}

Applying the model of eq 19 and 21, as shown in a previous report,³ the forward rate constant for ligand substitution, k_{on}, is given by eq 44, and the dependence of log k_{on} on σ* is given

$$k_{\text{on}} = k_2(K_{\text{cw}}/(K_{\text{cw}} + 1)) \quad (44)$$

by eq 45, which is obtained by substitution of eq 25 and 46

$$\log k_{\text{on}} = \rho^*_{k_2} \sigma^* + \log k_2^\circ - \log (1 + 10^{-(\rho^*_{K_{\text{cw}}} \sigma^* + \log K_{\text{cw}})}) \quad (45)$$

$$\log k_2 = \rho^*_{k_2} \sigma^* + \log k_2^\circ \quad (46)$$

into eq 44. Figure 5 shows plots of log k₂ vs. σ* for DEA and pyridine, where k₂ has been calculated from eq 44 using values of k_{on} in Table IV for DEA and from ref 3 for pyridine, calculated values of K_{cw} from eq 25, and the parameters listed in Table V. Both plots are reasonably linear, giving rise to the least-squares slope and intercept parameters listed in Table V. Figure 5 also shows a plot of log k_{on} for DEA vs. σ*. The solid line through these data has been calculated from eq 45 and the parameters listed in Table V and represents a reasonable fit of the data. Also shown in Figure 5 is a plot of log k_{off} vs. σ* and its least-squares regression line, giving rise to the k_{off} slope and intercept parameters in Table V.

As seen in Table V, ρ*_{k₂} values for DEA and pyridine are quite similar, although the log k₂[°] values show that transition states involving pyridine are considerably more stable than those involving the primary amine, presumably due to considerable metal-ligand π donation in the former case (see ref 6b, and references cited therein). Consistent with these observations, the ρ*_{k_{off}} values for the two ligands are also nearly identical, while log k_{off}[°] values again show the pyridine transition states to be more stable. Furthermore, we note that a high degree of internal consistency of the complete kinetic and equilibrium analysis is indicated by the fact that for DEA ρ*_{k₂} - ρ*_{k_{off}} (1.17 ± 0.18 - (-3.87 ± 0.18) = 5.04 ± 0.36) does not differ significantly from ρ*_{K_L} (5.81 ± 1.02). Finally, from the relatively small dependence of k₂ on σ* for DEA compared to the dependence of K_L on σ* (ρ*_{k₂} = 1.17 ± 0.18 while ρ*_{K_L} = 5.81 ± 1.02), we conclude that a relatively "early" transition state, in which bond formation is only some 20% complete, occurs in these ligand-substitution reactions.

Registry No. (CH₃CH₂)₂CHCo(D₂H₂)(DEA), 64413-50-9; (CH₃)₂CHCo(D₂H₂)(DEA), 64413-54-3; CH₃CH₂Co(D₂H₂)(DEA), 64413-53-2; C₆H₅CH₂CH₂Co(D₂H₂)(DEA), 64413-52-1; CH₃Co(D₂H₂)(DEA), 64413-59-8; NCCH₂CH₂CH₂Co(D₂H₂)(DEA), 64413-58-7; CH₃OCH₂CH₂Co(D₂H₂)(DEA), 64413-66-7; C₆H₅OCH₂CH₂Co(D₂H₂)(DEA), 64413-65-6; CH₃CH=CHCo(D₂H₂)(DEA), 64413-64-5; CH₃OOCCH₂CH₂Co(D₂H₂)(DEA), 64413-63-4; C₆H₅Co(D₂H₂)(DEA), 64413-62-3; CF₃CH₂Co-

(D₂H₂)(DEA), 64413-61-2; CH₃OOCCH₂Co(D₂H₂)(DEA), 64413-60-1.

References and Notes

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- (2) Abbreviations: RCo(D₂H₂)(HOH), substituted alkyl(aquo)bis(dimethylglyoximate)cobalt = alkyl(aquo)cobaloxime; DEA, dimethoxyethylamine = aminoacetaldehyde dimethyl acetal.
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Template Condensations: Metal-Ion-Directed Syntheses of Macrocyclic Complexes from 2,3-Butanedione Dihydrazone and Aldehydes or Ketones

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The metal-directed condensation of 2,3-butanedione dihydrazone with formaldehyde yields metal complexes of the 14-membered macrocyclic ligand, C₁₀H₂₀N₈, with M = Fe(II), Co(II), Ni(II), or Cu(II). Other aldehydes and ketones, as well as acetals and ketals, condense similarly to give related macrocyclic ligands. The hydrazones of the α -diimine functions have the anti-anti configuration yielding a macrocyclic species with D_{2h} symmetry. Six-coordinate diamagnetic Fe(II) complexes have been obtained with a variety of axial substituents (pyridine, imidazole, ammonia, thiocyanate, and acetonitrile). The Ni(II) complex is diamagnetic and four-coordinate, the Co(II) and Cu(II) complexes exhibit only weak interactions with axial ligands. Oxidation of the Co(II) complex with dioxygen under acidic conditions in acetonitrile yields the Co(III) complex, [Co(C₁₀H₂₀N₈)(CH₃CN)₂](ClO₄)₃. The physical and chemical properties of the complexes are compared with other closely related macrocyclic complexes.

Introduction

Most macrocyclic ligand complexes are best prepared with the aid of metal ions as "templates" to direct the steric course of the condensation reactions which ultimately end with ring closure.¹⁻³ However, important nontemplate syntheses have been developed for a number of important macrocyclic lig-

ands.⁴⁻⁷ This paper reports the formation and characterization of octaazabis(α -diimine) macrocyclic complexes of Fe(II), Co(II), Co(III), Ni(II), and Cu(II) from the template condensation of 2,3-butanedione dihydrazone with aldehydes and ketones.

A wide variety of amines, both "free" and coordinated, are known to react with aldehydes to form more complicated amine ligands. The products of these reactions can be of many

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