

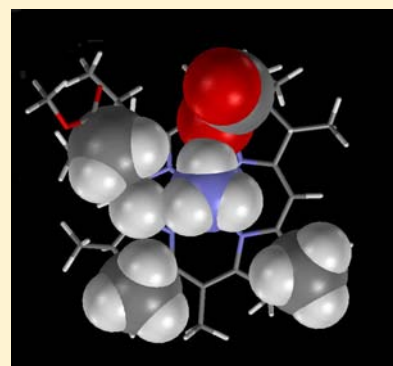
Probing the Nature of the Co(III) Ion in Corrins: Comparison of Reactions of Aquacyanocobyrinic Acid Heptamethyl Ester and Aquacyano-Stable Yellow Cobyrinic Acid Hexamethyl Ester with Neutral N-Donor Ligands

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S Supporting Information

ABSTRACT: Equilibrium constants ($\log K$) for substitution of coordinated H_2O in aquacyanocobyrinic acid heptamethyl ester (aquacyanocobester, ACCBs) and aquacyano-stable yellow cobyrinic acid hexamethyl ester (aquacyano-stable yellow cobester, ACSYCbs), in which oxidation of the C5 carbon of the corrin interrupts the normal delocalized system of corrins, by neutral N-donor ligands (ammonia, ethanolamine, 2-methoxyethylamine, *N*-methylimidazole, and 4-methylpyridine) have been determined spectrophotometrically as a function of temperature. $\log K$ values increase with the basicity of the ligand, but a strong compensation effect between ΔH and ΔS values causes a leveling effect. The aliphatic amines with a harder donor atom produce ΔH values that are more negative in their reactions with ACSYCbs than with ACCBs, while the softer, aromatic N donors produce more negative ΔH values with ACCBs than with ACSYCbs. Molecular modeling (DFT, M06L/SVP, and a quantum theory of atoms in molecules analysis of the electron density) shows that complexes of the aliphatic amines with SYCbs produce shorter and stronger Co–N bonds with less ionic character than the Co–N bonds of these ligands with the cobester. Conversely, the Co–N bond to the aromatic N donors is shorter, stronger, and somewhat less ionic in the complexes of the cobester than in those of the SYCbs. Therefore, the distinction between the harder Co(III) in ACSYCbs and softer Co(III) in ACCBs, reported previously for anionic ligands, is maintained for neutral N-donor ligands.



1. INTRODUCTION

An intriguing aspect of the inorganic chemistry of cobalt corrins (derivatives of vitamin B_{12} , Figure 1) is the lability of Co(III) (for example, see refs 1–17). The approximate lability ratio of Co(III) toward axial ligand substitution in corrin, porphyrin, cobaloxime, and tetra-ammine systems is $10^9:10^6:10^4:1$,^{14,18} thus, the extent of unsaturation of the equatorial ligand seems to be an important factor in determining the lability of the axial coordination site. We suggested that this kinetic cis effect is the consequence of the delocalization of electron density between the equatorial ligands and the metal, making the metal softer and imparting to it a more labile Co(II)-like character.^{14,18,19}

As part of our investigations of this aspect of B_{12} chemistry we have been interested for some time in the cis effect of the corrin macrocycle. It is well established that the electronic spectra of the cobalamins are dominated by $\pi \rightarrow \pi^*$ transitions of the corrin ring^{20–23} and that the spectra are heavily dependent on the identity of the axial ligand;^{19,22,24} there is therefore electronic communication between the axial and equatorial ligands. We have shown that the C10–Cl bond length in X-10–ClCbs, in which the C10 H is replaced by Cl, depends strongly on the polarizability of the axial ligand, X.¹⁴ We have also shown that substitution of the C10 H by an

electron-withdrawing group such as NO deactivates the axial coordination site toward ligand substitution.²⁵ This all indicates that the chemistry of the axial coordination site of Co(III) can be controlled and modified by the electronic structure of the corrin ring.

To further examine this, we recently prepared and fully characterized^{1,17} a derivative of the hexamethyl ester of cobyrinic acid, (5*R*,6*R*)-Co α ,Co β -dicyano-5,6-dihydro-5-hydroxy-hexamethylcob(III)yrinate-*c*,6-lactone (which we refer to as a “stable yellow cobester”, DCSYCbs, Figure 1), originally reported by others,^{26,27} from the corresponding dicyanocobyrinic acid heptamethyl ester, Co α ,Co β -dicyano-heptamethylcob(III)yrinate (DCCbs, Figure 1), in which the 13-atom, 14 π -e⁻ delocalized system of normal corrins is interrupted by oxidation of the C5 carbon, leading to a 10 π -e⁻ system between N21 and N24 and an isolated double bond between N21 and C4. We showed from a variety of spectroscopic data and DFT calculations that the diminished conjugation of the corrin in DCSYCbs increases the hardness of Co(III) in the corrin. We prepared the corresponding aquacyano complexes of the

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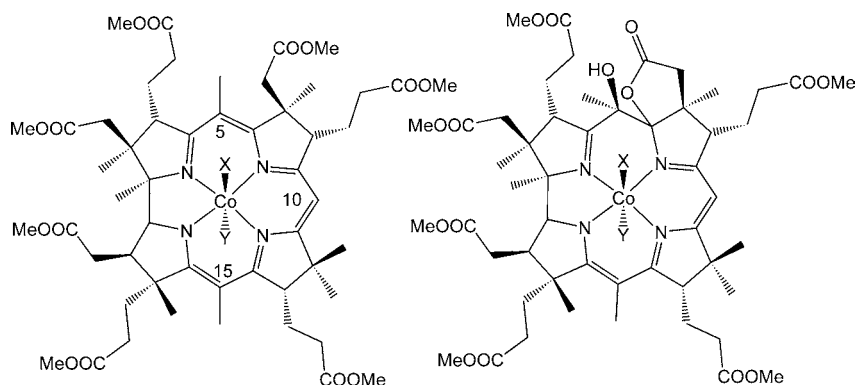


Figure 1. Structure of, left, the dicyano ($X = Y = \text{CN}^-$) and aquacyano ($X = \text{H}_2\text{O}$, $Y = \text{CN}^-$ or $X = \text{CN}^-$, $Y = \text{H}_2\text{O}$) cobester. Latter exists in solution as a mixture of two interconverting diastereomers. Corresponding stable yellow cobesters, right, have an interrupted conjugation between C5 and C6. Lactone bridges C6 and C7 and is directed toward the upper (β) face of the corrin.¹

cobester and the stable yellow cobester, ACCbs and ACSYCbs, and showed that they exist as a mixture of interconverting diastereomers (i.e., $\alpha\text{-H}_2\text{O}, \beta\text{-CN}^-$ and $\alpha\text{-CN}^-, \beta\text{-H}_2\text{O}$ cobester and $\alpha\text{-H}_2\text{O}, \beta\text{-CN}^-$ and $\alpha\text{-CN}^-, \beta\text{-H}_2\text{O}$ stable yellow cobester) which can therefore not be isolated.¹⁷ We compared the thermodynamics (with the anionic ligands N_3^- , NO_2^- , CN^- , SO_3^{2-}) and kinetics (with CN^-) of the substitution of H_2O .¹⁷ We found that the ligands with a harder donor atom (N in N_3^- and NO_2^-) produce ΔH values that are more negative in their reactions with ACSYCbs than with ACCbs. If the ligand has a softer donor (C in CN^- , S in SO_3^{2-}) then ΔH is less positive, or more negative, for reactions with ACCbs than with ACSYCbs. Thus, the softer metal in ACCbs has a preference for softer ligands and the harder metal in ACSYCbs for the harder ligands.

There is a significant increase in inertness of Co(III) on decreasing the extent of the conjugation of the corrin ligand. ACCbs is more labile than ACSYCbs toward substitution of H_2O by CN^- with ΔH^\ddagger smaller by some 12 kJ mol^{-1} . We interpreted this as arising from an earlier transition state in which bonding between the softer metal of ACCbs and the ligand is greater than in ACSYCbs with its harder metal center.

Our comparison of the thermodynamics of H_2O substitution on ACCbs and ACSYCbs was limited to anionic ligands. In this paper we turn our attention to neutral N-donor ligands, including an imidazole (*N*-methyl imidazole, NMeIm), four pyridines, (pyridine, Py; 4-methyl pyridine, 4MePy; 4-methoxypyridine, 4MeOPy; dimethylaminopyridine, DMAP), and four primary amines (NH_3 , ethanolamine (NH_2EtOH), 2-methoxyethylamine (MeOEtNH_2), and 2,2,2-trifluoroethylamine ($\text{CF}_3\text{CH}_2\text{NH}_2$)). Reactions with hydroxylamine, methoxylamine, methylamine, and 2-chloroethylamine were also investigated; these proved to be problematic, for reasons discussed.

2. EXPERIMENTAL SECTION

2.1. Instrumentation. UV–vis spectra were recorded in 10 mm quartz cuvettes on a Cary 1E or Cary 300 UV–visible spectrophotometer. The temperature of the cell block was maintained ($\pm 0.1 \text{ }^\circ\text{C}$) by a water-circulating bath or with a Peltier device. pH was measured using a Metrohm 720 or 827 pH meter with a Unitrode or Biotrode electrode calibrated at pH 7.00 and 9.00 with standard buffers.

2.2. Reagents. *Co* α ,*Co* β -dicyano-heptamethylcob(III)yrinate (dicyanocobester, DCCbs, Figure 1A) and its aquacyano form, ACCbs, and (*5R,6R*)-*Co* α ,*Co* β -dicyano-5,6-dihydro-5-hydroxyhexamethylcob(III)yrinate-*c*,6-lactone (dicyano-stable yellow cobester,

DCSYCbs, and its aquacyano form, ACSYCbs) were prepared as previously described.¹ NH_4Cl (Merck), NH_2EtOH , $\text{NH}_2\text{EtOH}\cdot\text{HCl}$, $\text{NH}_2\text{EtOCH}_3$, CH_3NH_2 40% solution in H_2O , $\text{CH}_3\text{NH}_2\cdot\text{HCl}$, NMeIm, 4MePy, 4MeOPy, hydroxylamine·HCl, sodium bicarbonate, and sodium carbonate (all Sigma Aldrich), $\text{CF}_3\text{CH}_2\text{NH}_2\cdot\text{HCl}$, 2-chloroethylamine·HCl, Py, DMAP, and *O*-methoxylamine·HCl (Aldrich), and sodium dihydrogen phosphate and disodium hydrogen phosphate (Saarchem, Unilab) were used as received. Water was purified using a Millipore RO unit and further purified using a Millipore Milli-Q unit ($18 \text{ M}\Omega \text{ cm}$).

It was difficult to determine the acid dissociation constant of coordinated H_2O in the cobesters because of competing hydrolysis of the ester moieties.¹ A reasonable value was obtained for ACCbs ($\text{p}K_a = 10.56 \pm 0.08$ at $25.0 \text{ }^\circ\text{C}$, see below) as ester hydrolysis only sets in above ca. pH 11. The value for ACSYCbs is probably lower, but in that case hydrolysis is rapid and occurs above ca. 10.5. As the pH at which equilibrium constants were determined was between 9 and 9.2, correction for hydrolysis of coordinated H_2O in either ACCbs or ACSYCbs is unnecessary. The values of the $\text{p}K_a$ s of the conjugate acids of the ligands were from the NIST database.²⁸

2.3. Methods. The acid dissociation constant of ACCbs was determined using UV–vis spectroscopy. ACCbs was dissolved in a multicomponent buffer²⁹ ($\mu = 0.1 \text{ M}$, Na_2SO_4) in an external 50 mL thermostatted cell. pH was adjusted by adding negligible volumes of 8 M NaOH between pH 5.5 and 11.5 while the solution was pumped through a flow cell housed in the thermostatted cell compartment of a Cary 3E UV–vis spectrophotometer. The dependence of the absorbance at 354 nm was fitted using standard nonlinear least-squares methods employing a Newton–Raphson procedure (Figure S1, Supporting Information).

The concentrations of the cobesters and stable yellow cobesters in solution were determined by addition of excess KCN to give DCCbs ($\epsilon_{368} 3.0 \times 10^{-4} \text{ L mol}^{-1} \text{ cm}^{-1}$)³⁰ and DCSYCbs ($\epsilon_{484} 1.0 \times 10^{-4} \text{ L mol}^{-1} \text{ cm}^{-1}$),²⁶ respectively.

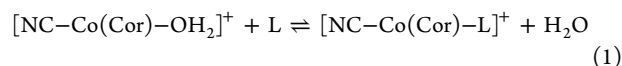
The equilibrium constants for coordination of the ligands by ACCbs and ACSYCbs (eq 1) were determined by addition of between 8 and 15 aliquots of a stock solution of the appropriate ligand to a 20–70 μM solution of the cobalt corrin contained in a 10 mm path length cuvette housed in the thermostatted cell block of a UV–vis spectrophotometer. All absorbance readings were corrected for dilution. Solutions were buffered with carbonate (pH 9) or phosphate (pH 7) at an ionic strength $\mu = 0.10 \text{ M}$. Stock solutions of NH_3 and NH_2EtOH were prepared from NH_4Cl and $\text{NH}_2\text{EtOH}\cdot\text{HCl}$, respectively, and adjusted to pH 9 by addition of NaOH. The stock solution of NH_2EtOMe was adjusted to pH 9 by addition of HCl. For titrations of ACCbs and ACSYCbs with NH_3 , NH_2EtOH , and NH_2EtOMe , the ionic strength in the cell increased to 0.22–0.28 M and 0.30–0.67, respectively. Stock solutions of NMeIm, 4MePy, and 4MeOPy for reaction with ACCbs were prepared by dissolving the ligand in buffer; neat NMeIm and 4MePy were used for titrations with ACSYCbs. Reactions of all ligands were “instantaneous”, except that

Table 1. Equilibrium Constants for Substitution of Coordinated H₂O in ACCbs and ACSYCbs^a

ligand	ACCbs					ACSYCbs				
	T/°C	log K	ΔH/kJ mol ⁻¹	ΔS/J K ⁻¹ mol ⁻¹	log K ₂₅ ^b	T/°C	log K	ΔH/kJ mol ⁻¹	ΔS/J K ⁻¹ mol ⁻¹	log K ₂₅ ^b
NH ₃	10.0	3.22(7)	-41(1)	-85(2)	2.75	10.0	3.30(4)	-46(2)	-98(7)	2.94
	15.0	3.08(5)				15.0	3.18(12)			
	20.0	2.95(7)				20.0	3.02(14)			
	25.0	2.84(6)				25.0	2.86(5)			
	30.0 ^c	2.71(3)				30.0 ^c	2.78(15)			
NH ₂ EtOH	9.9	2.04(23)	-24(2)	-44(7)	1.91	10.0	2.18(7)	-79(3)	-23(9)	1.52
	16.7	2.00(13)				15.0	1.96(16)			
	23.2	1.89(13)				17.5	1.84(16)			
	32.0	1.74(16)				20.0	1.75(7)			
	37.4	1.69(10)				25.0	1.44(12)			
NH ₂ EtOMe	11.0	2.40(10)	-51(2)	-136(8)	1.84	10.0	2.28(35)	-53(4)	-145(15)	1.70
	17.5	2.15(8)				17.5	1.92(10)			
	25.0	1.89(9)				25.0	1.59(30)			
	32.5	1.68(10)				32.5	1.48(13)			
	40.0	1.52(7)				40.0	1.27(12)			
NMeIm	9.9	4.43(4)	-23(1)	5(4)	4.29	9.9	1.31(29)	23(3)	107(11)	1.56
	16.7	4.32(3)				17.1	1.47(33)			
	23.2	4.21(3)				19.5	1.49(15)			
	32.0	4.16(6)				24.4	1.52(15)			
	37.4	4.05(4)				31.5	1.64(33)			
4MePy	10.0	3.62(3)	-29(2)	-33(8)	3.36	10.0	0.37(16)	5(1)	24(2)	0.38
	17.5	3.53(2)				17.5	0.40(9)			
	25.0	3.41(3)				25.0	0.41(22)			
	32.5	3.22(2)				32.5 ^c	0.44(23)			
	40.0	3.14(2)								
4MeOPy	10.0	3.54(4)	-25(1)	-19(3)	3.33	See text				
	17.5	3.45(3)								
	25.0	3.32(3)								
	32.5	3.23(3)								
	40.0	3.11(3)								
CF ₃ CH ₂ NH ₂	25.0				0.4 ^d	25.0				<-2 ^d
NH ₂ OCH ₃	25.0				1.93(3)	25.0				see text

^aThese values have been corrected for the pK_a of the conjugate acid of the ligand. Correction for the pK_a of coordinated H₂O is probably unnecessary (see text). ^bInterpolated value of log K at 25 °C from the values of ΔH and ΔS. ^cUnstable at 40 °C. ^dEstimated; see text.

between ACSYCbs and 4MePy, which was allowed to stand for ~1 h before taking readings.



$$K = [\text{NC-Co}(\text{Cor})-\text{L}]^+ / [\text{NC-Co}(\text{Cor})-\text{OH}_2]^+ \cdot [\text{L}]$$

$$[\text{L}]_{\text{neutral}} = [\text{L}]_{\text{total}} / (1 + 10^{\text{p}K_{\text{a}} - \text{pH}}) \quad (2)$$

In eq 1, L specifically refers to the neutral or unprotonated N donor available for coordination to the metal center; this will depend on the pH of the solution (eq 2) where pK_a refers to the acid dissociation constant of the conjugate acid of the ligand. pH was measured at the start and end of each titration, and the average pH value was used for this pH correction. Equilibrium constants reported have therefore been corrected for the effect of pH.

As we mentioned above and discussed elsewhere,¹⁷ both ACCbs and ACSYCbs exist in solution as an equilibrium mixture of two diastereomers. They are expected to have similar, but not identical, equilibrium constants (log K, eq 1) for replacement of coordinated H₂O by L. Spectrophotometric determination of log K will therefore show a wavelength dependence, which is a function of the relative extinction coefficients of the two diastereomers at the monitoring wavelength.³¹ As we did before,¹⁷ we determined log K at every 1 or 2

nm between about 320 and 570 nm, excluding wavelengths (such as those close to isosbestic points) where the absorbance change was small and where the decrease in the signal-to-noise ratio makes values of log K unreliable. Typically, we only used wavelengths where the correlation coefficient of the nonlinear fit to the binding isotherm (see below) was >0.97. K was then found from a weighted average, weighted by the reciprocal of the variance, 1/σ², where the standard deviation σ = (standard error of the fit)/n^{1/2} for n data points in the titration.

For cases where log K is relatively small (log K < 4), absorbance data were fitted using standard nonlinear least-squares methods to a simple binding isotherm (eq 3) as objective function, with A₀, A₁, and K as the parameters to be optimized and where [L] refers specifically to neutral, unprotonated L (eq 2). A₀ and A₁ are the absorbance values at λ corresponding to 0 and 100% complex formation, respectively.

$$A_{\lambda} = (A_0 + KA_1[\text{L}]) / (1 + K[\text{L}]) \quad (3)$$

When log K is relatively large (>4), the implicit assumption in eq 3 that [L]_{free} ≈ [L]_{neutral} will not be true as a non-negligible fraction of L will be complexed to the metal ion. In such cases [L]_{free} is given by a quadratic expression,³² only one root of which (eq 4) has physical meaning and where [M]_{total} is the total metal ion concentration.

$$[L]_{\text{free}} = \frac{-a_2 \pm \sqrt{a_2^2 - 4a_1a_3}}{2a_1}$$

$$a_1 = K; a_2 = 1 + K[M]_{\text{total}} - K[L]_{\text{neutral}}; a_3 = -[L]_{\text{neutral}} \quad (4)$$

Values of K were determined as a function of temperature between 10 and 40 °C. Values of ΔH and ΔS were determined from the slope and intercept, respectively, of weighted linear least-squares van't Hoff plots of $\ln K$ against $1/T$.

2.4. Computational Methods. Density functional theory (DFT) calculations were carried out using the Gaussian 09³³ suite of programs. Models used for calculation of the structure of the ammine, imidazole, NH_2EtOH , and 4MePy adducts of ACSYCbs were based on the crystal structure of dicyano-SYCbs¹ after suitable editing. For all calculations, the b , d , e , f , and g methyl-ester side chains were replaced by methyl groups while the a side chain was left in place. Since no crystal structures are available for any of the compounds of interest, the β -axial ligand in the crystal structure of dicyano-SYCbs¹ was replaced by the appropriate ligand as follows. The NH_3 adduct was modeled by replacing the $\beta\text{-CN}^-$ ligand with NH_3 . The lowest energy conformation of the imidazole moiety relative to the corrin ring was determined by rotating the $\text{Co-N}_{\text{imidazole}}$ bond through 360° in 5° increments in both the positive and the negative directions using the semiempirical PM6 method.³⁴ The 4MePy ligand was positioned such that its orientation relative to the corrin ring was the same as that for imidazole. The NH_2EtOH ligand was positioned over the southeastern quadrant of the corrin ring when viewed from above; this is known to be an energy-minimum conformation for many cobalamin derivatives.³⁵ Models used for calculation of the structure of the ammine, imidazole, NH_2EtOH , and 4MePy adducts of the cobester were based on the crystal structure³⁶ of ImCbl^+ after suitable editing. For all calculations, the b , d , e , f , and g amide side chains were replaced by methyl groups while the a and c side chains were left in place and converted into methyl esters. The α -axial dimethylbenzimidazole ligand was replaced with CN^- and the imidazole β axial ligand with the appropriate ligand. The 4MePy ligand was positioned such that its orientation relative to the corrin ring was the same as that for imidazole. Once again, the NH_2EtOH ligand was positioned over the southeastern quadrant of the corrin ring when viewed from above. Geometry optimizations were performed using the M06L density functional³⁷ and the SVP³⁸ basis set in combination with the SVP density fitting basis set.^{39,40} (M06L was chosen to allow us to take advantage of the performance gains afforded using the density fitting approximation.^{41,42}) Convergence criteria for SCF calculations and geometry optimizations were Gaussian 09 default values. The topological properties of the electron density (ρ) were obtained using Bader's Quantum Theory of Atoms in Molecules (QTAIM) approach⁴³ as implemented in AIMALL.⁴⁴

Values of $\log P$, the water-octanol partition coefficient, were estimated using ChemDraw Ultra.⁴⁵

3. RESULTS

Examples of the absorbance changes accompanying replacement of coordinated H_2O in ACCbs and ACSYCbs are shown in Figure S2, Supporting Information. The spectroscopic changes for ACSYCbs are significantly smaller and span a narrower useable wavelength range than for ACCbs; this results in somewhat larger errors in $\log K$ values. An example of the fits of the data to eq 3 is shown in Figure S3, Supporting Information. Typically, about 150 wavelengths were used per titration with ACCbs and about 100 wavelengths with ACSYCbs to obtain weighted $\log K$ average values. These are listed in Table 1. Examples of van't Hoff plots obtained for the data in this work are shown in Figure S4, Supporting Information.

Reaction of NH_2OH with ACCbs at 25 °C, $\text{pH} = 9$, rapidly produces a species with a band at around 460 nm which is

indicative of formation of a stable yellow corrinoid; thus, it appears that NH_2OH does not merely coordinate the metal ion but acts as a reductant as well. There is a report of a similar reaction between NH_2OH and B_{12a} itself;⁴⁶ in that case, by working rapidly at $\text{pH} 7$, the reduction reaction was sufficiently slow to allow for an estimation of $\log K$. When we performed the reaction at $\text{pH} 6$ we did indeed observe spectral changes clearly indicative of ligand coordination (the γ band shifted from 354 to 359 nm, gaining 6% in intensity; the D/E band shifted from 406 to 419 nm; and the $\alpha\beta$ bands shifted from 497 and 526 to 515 and 547 nm, respectively), but over the course of 15 min the spectrum underwent a blue shift with an increase in intensity at 460 nm, indicative of attack on the corrin ring. Hence, reductive attack on the corrin prevented a reliable determination of the $\log K$ value.

Reaction of NH_2OCH_3 with ACCbs proceeded smoothly at $\text{pH} 9.2$ with well-defined isosbestic points and $\log K$ at 25.0 °C = 1.93(3). However, reaction between NH_2OCH_3 and ACSYCbs at $\text{pH} 9.2$ and 7.0 gave complex spectral changes (Figure S5, Supporting Information). It appears that two different ligands coordinate the metal center, and there is a slow loss of intensity of the entire spectrum, consistent with destruction of the chromophore. It has recently been reported that in a free radical mechanism $[\text{Fe}^{\text{II}}(\text{CN})_5\text{H}_2\text{O}]^{3-}$ catalyzes the disproportionation of methoxylamine to NH_3 , N_2 , and CH_3OH by initially coordinating the amine and then promoting homolysis of the N-O bond.⁴⁷ We tentatively suggest by analogy that NH_2OCH_3 coordinates to ACSYCbs, which catalyzes its disproportionation, leading to at least some formation of the NH_3 complex (Figure S6, Supporting Information). The radical nature of the reaction presumably is responsible for the spectral bleaching. Because of the intractability of the reaction of CH_3ONH_2 with ACSYCbs, we only determined $\log K$ for its reaction with ACCbs at 25 °C.

Reaction of trifluoroethylamine, $\text{CF}_3\text{CH}_2\text{NH}_2$, with ACCbs at $\text{pH} 6.8$ first proceeded smoothly with good isosbestic points, but this was followed by a slow loss of intensity over the entire spectrum (Figure S7, Supporting Information). Even though the end point for the titration could not be determined, an approximate pH -independent value for $\log K$ of 0.4 could be obtained from a plot⁴⁸ of A_{357} vs $(A_0 - A_{357})/[L]$ (eq 5), where the monitoring wavelength of 357 nm is the maximum of the γ band of the product and A_0 , A_1 , and L are defined as in eq 3. The plot gives a straight line with slope = $1/K$ and intercept = A_1 ; the value of K was then corrected for pH using eq 2.

$$A_{357} = (A_0 - A_{357})/(K[L]) + A_1 \quad (5)$$

For ACSYCbs at the same pH only the slow loss of intensity of the spectrum was observed (Figure S7, Supporting Information). For 0.16 M $\text{CF}_3\text{CH}_2\text{NH}_2$, the decrease in intensity was sufficiently slow to show that no coordination had occurred. Assuming that 5% coordination of $\text{CF}_3\text{CH}_2\text{NH}_2$ should be detected and correcting for pH , a $\log K$ value of <-2 is estimated.

Reaction of 2-chloroethylamine, $\text{ClCH}_2\text{CH}_2\text{NH}_2$ (0.15 M), with ACSYCbs at $\text{pH} 9$ was slow; it proceeded for ~ 90 min with good isosbestic points and then reversed itself over ~ 15 h. At the same time the pH dropped from 9.00, immediately after addition of $\text{ClCH}_2\text{CH}_2\text{NH}_2$, to 6.99, presumably from slow release of HCl during coordination of $\text{ClCH}_2\text{CH}_2\text{NH}_2$.

Methylamine, CH_3NH_2 (pK_a of its conjugate acid = 10.65²⁸), is more than an order of magnitude more basic than NH_3 and any of the other amines studied. ACSYCbs becomes

increasingly unstable with increasing basicity (see above). Attempts to react ACSYCbs with CH_3NH_2 or $\text{CH}_3\text{NH}_2\cdot\text{HCl}$ in pH 9 carbonate buffer at an ionic strength $\mu = 0.10$ M, where $\sim 2\%$ CH_3NH_2 is present, were unsuccessful because large amounts of CH_3NH_2 (~ 0.8 M for $\text{CH}_3\text{NH}_2\cdot\text{HCl}$ and ~ 0.2 M for CH_3NH_2) were needed to drive the reaction to completion and the buffer capacity was insufficient to maintain a constant pH. Increasing the buffer capacity by increasing the ionic strength of the carbonate buffer to $\mu = 0.50$ M still gave rise to unacceptable changes in pH: a decrease of 0.65 log units for $\text{CH}_3\text{NH}_2\cdot\text{HCl}$ and an increase of 0.53 for CH_3NH_2 . Reaction of ACSYCbs with CH_3NH_2 in pH 9 carbonate buffer, at ionic strength $\mu = 0.50$ M (Figure S8, Supporting Information), showed a good isosbestic point at 460 nm up to a pH of 9.2, but at pH values greater than 9.35 a progressive shift of this isosbestic point was observed, consistent with increasing hydrolysis of the ester moieties of ACSYCbs.

It has been reported that coordination of Py by ACCbs occurs with $\log K = 2.19^{49}$ and that coordination of dimethylaminopyridine (DMAP) by ACCbi occurs with $\log K = 4.75^{49}$. When ACSYCbs was reacted with 0.52 M Py at pH 9.2, no reaction was observed. Further addition of Py resulted in turbidity of the solution. Assuming that 5% coordination of Py should be detected, a $\log K$ value of < -1 is estimated. Both DMAP and 4MeOPy react with ACSYCbs extremely slowly. When ACSYCbs was reacted with 0.062 M DMAP and 0.79 M 4MeOPy, respectively, at pH 9.2 the reaction was still proceeding after 24 h for DMAP and 48 h for 4MeOPy. This made it impractical to determine $\log K$ for the equilibria of ACSYCbs with DMAP and 4MeOPy.

4. DISCUSSION

Values of $\log K$ ($T = 25$ °C, eq 2) for substitution of axially coordinated H_2O in ACCbs, interpolated from the van't Hoff plots where values as a function of temperature are available, or from a determination at 25 °C only (Table 1) for the ligands studied vary in the order $L = \text{NMeIm}$ (4.29) $>$ 4-MePy (3.36) \approx 4-MeOPy (3.33) $>$ NH_3 (2.75) $>$ NH_2OCH_3 (1.93) \approx NH_2EtOH (1.91) $>$ $\text{NH}_2\text{EtOCH}_3$ (1.84) $>$ $\text{CF}_3\text{CH}_2\text{NH}_2$ (0.4). For ACSYCbs, $L = \text{NH}_3$ (2.94) $>$ $\text{NH}_2\text{EtOCH}_3$ (1.70) $>$ NMeIm (1.56) \approx NH_2EtOH (1.52) $>$ 4MePy (0.38) $>$ $\text{CF}_3\text{CH}_2\text{NH}_2$ (< -2) (Table 1). Listed in Table 2 for purposes of comparison and discussion are the $\log K$ values from Table 1, $\log K$ values for ACCbs obtained by others,^{5,49–51} as well as available values for the related aquacyanocobinamide (ACCbi).

The values of $\log K$ for coordination of a given ligand by ACSYCbs are generally lower than those for its coordination by ACCbs, except for NH_3 where the converse is true ($\log K = 2.75$ and 2.94, respectively). The ligands fall into two classes: those with an aromatic N donor (the pyridines and the azoles) and those with an aliphatic N donor. The value of $\log K$ clearly increases with the basicity of the aromatic N donor, but that dependence is much less pronounced in the case of the aliphatic N-donor ligands (Figure 2).

One of the limitations of comparing equilibrium constants at a single temperature is that there is often a compensation effect between ΔH and ΔS for the reaction; this has a leveling off effect on $\log K$ values.¹⁷ Figure S9, Supporting Information, shows that a strong correlation does indeed exist, and that as ΔH becomes more negative, so does ΔS .

For the ligand substitution reactions of ACCbs, all ligands have relatively large and negative ΔH values and large and negative ΔS values, except for NMeIm, where ΔS is close to

Table 2. Equilibrium Constants for Substitution of Coordinated H_2O Trans to CN^- in Co(III) Corrins

	ligand (L)	ligand ^a $\text{p}K_a^{28}$	$\log K^a$		
			ACCbs	ACSYCbs	ACCbi ^b
1	Py	5.24	2.19 ⁴⁹	$< -1^c$	2.3 ⁵⁰
2	4MePy	6.05	3.36	0.38	3.1 ⁵⁰
3	4MeOPy	6.47	3.33		
4	Imidazole	7.00	3.95 ⁴⁹		4.15 ⁵¹
5	N-MeIm	7.10	4.29	1.56	4.3 ⁵²
6	DMAP ^d	9.58			4.75 ⁵⁰
7	NH_2OCH_3	4.62	1.93		
8	$\text{CF}_3\text{CH}_2\text{NH}_2$	5.84	0.4	$< -2^c$	0.78 ⁵⁰
9	NH_2EtBr	8.5	2.25 ⁴⁹		2.5 ⁵⁰
10	NH_3	9.25	2.75	2.94	3.15 ⁵⁰
11	NH_2EtOH	9.52	1.91	1.52	
12	$\text{NH}_2\text{EtOCH}_3$	9.68	1.84	1.74	
13	CH_3NH_2	10.65			3.4 ⁵

^a $\text{p}K_a$ of the ligand's conjugate acid. ^bACCbi = aquacyanocobinamide. ^cEstimated; see text. ^d4-Dimethylamino-pyridine

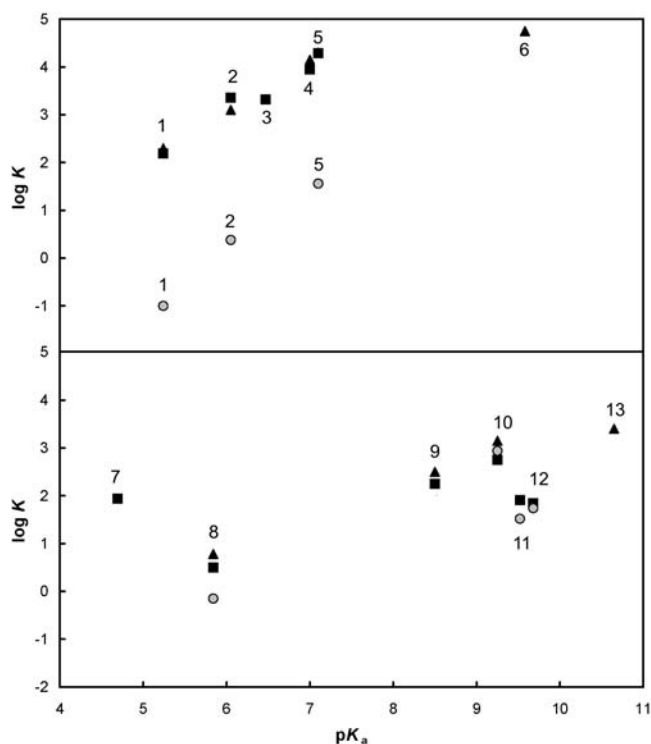


Figure 2. Dependence of $\log K$ for substitution of H_2O trans to CN^- by aromatic amines (top) and aliphatic amines (bottom) on the basicity of the ligand. Values given are for ACCbs (■), ACCbi (▲), and ACSYCbs (○). Ligands are identified by the numbering given in Table 2.

zero; thus, the reactions are enthalpically driven. For ACSYCbs, the aliphatic N-donor ligands, with a harder donor atom, NH_3 , NH_2EtOH , and $\text{NH}_2\text{EtOCH}_3$, also have large and negative ΔH and ΔS values. In contrast, the aromatic N donors, with a softer donor atom, NMeIm and 4MePy, have positive ΔH and ΔS values, and the reactions are entropically driven.

Values of ΔS for reactions in solution are not always easy to interpret. Substitution of H_2O in ACCbs and ACSYCbs by neutral ligands (L) should not give rise to significant changes in solvation of the complexes, as both $[\text{NC}-\text{Co}(\text{Cor})-\text{OH}_2]^+$

Table 3. Axial Bond Lengths and Topological Properties of the Electron Density at Their Bond Critical Points of Models of the Cobester and Stable Yellow Cobester with Axial Ligand L^a

L	Co–L /Å	$\rho(\text{Co–L})$	$ V/G$	Co–CN /Å	$\rho(\text{Co–CN})$	$ V/G$	log K	ΔH /kJ mol ⁻¹	ΔS /J K ⁻¹ mol ⁻¹
ACCBs									
NH ₃	2.112	0.06455	0.99112	1.852	0.13453	1.43234	2.75	-41	-85
NH ₂ EtOH	2.139	0.06185	0.99402	1.854	0.13399	1.42918	1.90	-24	-44
imidazole	2.089	0.06634	0.98828	1.855	0.13368	1.42904	4.29	-23	5
4MePy	2.128	0.06201	0.98330	1.855	0.13377	1.43132	3.39	-29	-33
ACSYCBs									
NH ₃	2.088	0.06921	1.00424	1.856	0.13279	1.41187	2.94	-46	-98
NH ₂ EtOH	2.119	0.06544	1.00119	1.859	0.13178	1.40691	1.52	-79	-236
imidazole	2.141	0.05927	0.97785	1.848	0.13517	1.42504	1.56	23	107
4MePy	2.188	0.05467	0.97668	1.849	0.13508	1.42628	0.38	5	24

^aThe electron density ρ (in au) at the bond critical point is a measure of the strength of the bond;^{53–55} 1 au of $\rho = 6.7483 \text{ e } \text{Å}^{-3}$. The ratio of the potential V and kinetic G energy densities at the bond critical point can be used to characterize a bond. For covalent interactions $|V/G| > 2$; for ionic interactions, $|V/G| < 1$; interactions of intermediate character have $1 < |V/G| < 2$.⁵⁶ The values V and G are in au (1 au = 627.5095 kcal mol⁻¹).

and $[\text{NC–Co}(\text{Cor})\text{–L}]^+$ have the same charge, unlike for anionic ligands where charge neutralization occurs in the product. For all the charged ligands previously studied entropy increases,¹⁷ as expected, presumably as a result of less solvent ordering on product formation. Solvent effects on the neutral ligands appear not to be important since the more hydrophilic ligands (NH₃, log $P = -1.32$; NH₂EtOH, -1.30 ; NH₂EtOCH₃, -0.67),⁴⁵ which should be more solvated than the more hydrophobic ligands (NMeIm, log $P = -0.03$; 4MePy, 1.14), give rise to negative ΔS values, the opposite of what would have been expected, as loss of solvated water from the ligand on coordination should proceed with $\Delta S > 0$.

For the aliphatic amines, reactions with ACSYCBs produce more negative ΔH values than for ACCBs but for the two softer ligands, NMeIm and 4MePy, the opposite is the case. DFT models of the structure of the β -L, α -CN⁻ isomers of the cobester and the stable yellow cobester, L = NH₃, NH₂EtOH, imidazole, and 4MePy (imidazole rather than N-MeIm was used for simplicity; substitution on N_δ has little effect on the donor properties of N_ω, pK_a = 7.00 and 7.10, respectively), were examined. They are illustrated in Figure S10, Supporting Information, and the results are given in Table 3.

The presence of a lactone in the stable yellow cobester certainly increases the steric crowding of the β face, and there is a close contact between an H on the ligand and the lactone O (Figure S10, Supporting Information). This, however, does not appear to unduly influence the ability of the metal to coordinate the ligand. For example, modeling shows that the Co–N ligand to NH₂EtOH, which gives the closest steric contact with the lactone, is shorter in its complex with the stable yellow cobester than with the cobester itself (Table 3). Therefore, electronic factors appear to override these steric factors.

The NH₃ and NH₂EtOH complexes of the stable yellow cobester have shorter and stronger (larger ρ values) Co–N bonds than those of the cobester. These stronger bonds have less ionic character (although the difference is very small) and cause a small elongation of the trans Co–CN bond. By contrast, the Co–N bond to the aromatic N donors is shorter, stronger, and somewhat less ionic in the complexes of the cobester than in those of the stable yellow cobester. The modeling therefore rationalizes the experimental ΔH values and suggests that the reason why reactions of the aliphatic amines with ACSYCBs produce more negative ΔH values than the reactions with ACCBs is a greater affinity of the metal for the harder N-donor ligand which leads to a shorter Co–N bond.

Conversely Co(III) in the cobester rather than in the stable yellow cobester has greater affinity for the two softer aromatic N-donor ligands and results in shorter Co–N bonds. Therefore, the distinction between the harder Co(III) in ACSYCBs and softer Co(III) in ACCBs, seen for anionic ligands,¹⁷ is maintained for neutral N-donor ligands.

■ ASSOCIATED CONTENT

📄 Supporting Information

Spectrophotometric titration of ACCBs between pH 5.5 and 11.5; examples of the spectroscopic changes accompanying the displacement of H₂O by NH₃ in ACCBs and ACSYCBs, their fits to a binding isotherm, and van't Hoff plots; spectrophotometric changes on titration of ACSYCBs with NH₂EtOH, NH₂OCH₃, CF₃CH₂NH₂, and CH₃NH₂; correlation between ΔH and ΔS for the ligand substitution reactions of coordinated H₂O in ACCBs; and illustrations of DFT models of the cobester and the stable yellow cobester with various ligands. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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