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Substituent effect analysis in organocobalt corrinoids: binding constants for cyanide, azide and the pendent 5,6-dimethylbenzimidazole nucleotide

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Abstract

Binding constants for cyanide ion to eight alkylcobinamides (including four β-alkylcobinamides in which the organic ligand is in the 'upper' axial ligand position and four α-alkylcobinamides in which the organic ligand is in the 'lower' axial ligand position) have been determined. Unlike all other alkylcobinamides investigated, which undergo rapid cyanolysis to form dicyanocobinamide in the dark, these eight complexes were sufficiently stable towards cleavage by cyanide to permit accurate measurement of the binding constants. The values obtained vary by 6.4×10^4-fold from 4.33 M^{-1} for β-ethylcobinamide to 2.79×10^5 M^{-1} for β-cyanomethylcobinamide. In contrast, these alkylcobinamides are stable in the presence of excess azide ion, but bind this ligand much more weakly, the binding constants varying from <1 M^{-1} for β-ethylcobinamide to 15.8 M^{-1} for β-cyanomethylcobinamide. A multiparameter substituent effect equation, including inductive, resonance and steric terms, has been successfully used to correlate the intramolecular equilibrium constants for the coordination of the pendent 5,6-dimethylbenzimidazole nucleotide to the metal atom in a series of ten alkylcobalamins. The significance of this correlation with respect to similar correlations recently obtained for alkylcobaloximes is discussed.

Introduction

Recent work [1, 2] on substituent effect analysis in organocobaloximes** has led to substantial progress in understanding substituent effects in complexes of the type $YCH_2Co(D_2H_2)L$†, where Y is the substituent, by application of multiparameter substituent effect equations [3, 4]. We have recently correlated a wide variety of kinetic, equilibrium and spectroscopic properties of $YCH_2Co(D_2H_2)L$ complexes via eqn. (1), where Q_Y is the correlatable property, σ_I, σ_R and σ_S are inductive,

$$Q_Y=\rho_I\sigma_I+\rho_R\sigma_R+\rho_S\sigma_S+C \qquad (1)$$

resonance and steric substituent constants for the substituent, Y, respectively, ρ_I, ρ_R and ρ_S represent the sensitivity of the property under investigation to inductive, resonance and steric effects, respectively, and C is a constant [2]. Thus, the equilibrium constants for cyanide ion ligation to $YCH_2Co(D_2H_2)OH_2$ complexes [2], pK_as for axial water ionization and pyridine ligation for these complexes [5, 6], rate constants for the dissociation of pyridine [5], 4-cyanopyridine [1] and 4-methoxyaniline [1] from $YCH_2Co(D_2H_2)L$ complexes, pK_as for equatorial ligand ionization from $YCH_2Co(D_2H_2)py$ complexes [5], and ^{13}C and ^{15}N NMR chemical shifts of $YCH_2Co(D_2H_2)^{13}C^{15}N^-$ complexes [2] and the cyano bridged dimeric [7, 8] $YCH_2Co(D_2H_2)^{13}C^{15}NCo(D_2H_2)CH_2Y^-$ complexes [2] have been successfully correlated via eqn. (1). In all such successful correlations, the 'resonance' effect (i.e. ρ_R) has been found to be of comparable magnitude to the inductive effect of Y (i.e. ρ_I). This important 'resonance' effect has been attributed to the significance of hyperconjugation in these complexes. Hyperconjugation, in the form of $\sigma\rightarrow\pi$ conjugation (or exalted hyperconjugation [9]) had previously been found to be

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**Cobaloximes are bis(dimethylglyoximato)cobalt complexes.

†Abbreviations: $RCo(D_2H_2)L$ = alkyl(ligand)cobaloxime = alkyl(ligand)bis(dimethylglyoximato)cobalt(III); α-RCbi = α-alkylcob(III)inamide (the organic ligand is in the 'lower' axial ligand position); β-RCbi = β-alkylcob(III)inamide (the organic ligand is in the 'upper' axial ligand position); α-RCbl = α-alkylcob(III)alamin (the organic ligand is in the 'lower' axial ligand position); β-RCbl = β-alkylcob(III)alamin (the organic ligand is in the 'upper' axial ligand position); α-CN-β-(H_2O)Cbi = α-cyano-β-aquacob(III)inamide; α-H_2O-β-(CN)Cbi = α-aqua-β-cyanocob(III)inamide; AdoCbl = β-5′-deoxyadenosylcobalamin; $(CN)_2$Cbl = dicyanocobalamin; α- or β-R(CN)Cbi = α- or β-alkyl(cyano)cobinamide; α- or β-$R(N_3)$Cbi = α- or β-alkyl(azido)cobinamide; α-ribazole = 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole; HEPES, *N*-2-hydroxyethylpiperazine-*N*′-2-ethane sulfonic acid; BICINE, *N*,*N*-bis(2-hydroxyethyl)glycine.

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responsible [9] for the organometallic 'β effect', including the weak acidity of 1-carboxyalkylcobaloximes [9, 10] and carboxymethylcobalt corrinoids [11, 12], the low carbonyl stretching vibration of formylmethylcobaloximes [13], the upfield shift of the aldehyde ^{1}H NMR resonance of formylmethylcobalamin [14], and the anomalous ^{19}F NMR chemical shifts of p-fluorobenzylcobaloximes [15–17]. In all of these cases, the organic ligand possesses a low lying π system involving the β atom, thus permitting $\sigma \rightarrow \pi$ conjugation. The successful application of eqn. (1) to $YCH_2Co(D_2H_2)L$ complexes not possessing such low-lying π systems, and the importance of the 'resonance' effect in such complexes, suggests that hyperconjugation is a more general phenomenon in such complexes and that delocalization involving Y can occur either via donation (eqn. (2)) or withdrawal (eqn. (3)) of electron density by Y.

$$Y\text{-}CH_2\text{-}Co(D_2H_2)L \longleftrightarrow \overset{\delta+}{Y}{=}CH_2\text{---}\overset{\delta-}{C}o(D_2H_2)L \qquad (2)$$

$$Y\text{-}CH_2\text{-}Co(D_2H_2)L \longleftrightarrow \overset{\delta-}{Y}{=}CH_2\text{---}\overset{\delta+}{C}o(D_2H_2)L \qquad (3)$$

Steric effects (i.e. ρ_S) in $YCH_2Co(D_2H_2)L$ complexes were found to be relatively small, but inclusion of the steric term in the multiparameter substituent effect equation generally improved correlations significantly [2]. Somewhat surprisingly, even binding of the small, linear cyanide ion to $YCH_2Co(D_2H_2)OH_2$ complexes was subject to a small, but highly significant steric effect. Since the known influence of sterically bulky organic ligands on cobaloxime geometry [18] is unlikely to influence the binding of cyanide, this effect was interpreted to indicate an indirect transmission of steric effects, i.e. a sterically induced reduction of Co–C overlap resulting in a decrease in the inductive effect of Y.

Recently, we have also reported [19–24] that the reductive alkylation of Co(III) cobinamides and Co(III) cobalamins with alkyl halides results in the formation of pairs of diastereomeric α- and β-alkylcobinamides (RCbis) and α- and β-alkylcobalamins (RCbls) in which the organic ligand is in the 'lower' or 'upper' axial ligand position (Fig. 1), as had previously been described by Friedrich and co-workers for methylcobalt corrinoids [25–30], and, more recently, for (2-oxo-1,3-dioxolan-4-yl)-cobalamin by Alelyunas *et al.* [31]. While the α diastereomers of RCbi and RCBl complexes have been well characterized, there is little data in the literature comparing the chemical properties of pairs of α and β diastereomers [32] and few binding constants have been reported for exogenous ligands to α-RCbis or α-RCbls [31, 32]. We have consequently undertaken a study of the binding of cyanide ion and azide ion to α- and β-YCH_2Cbis to provide such data and to attempt to use eqn. (1) to correlate trends in such data with the properties of the substituent, Y. While neither the binding constants for cyanide or azide provided data sets suitable for use with eqn. (1), unimolecular equilibrium constants for the intramolecular binding of the pendent 5,6-dimethylbenzimidazole nucleotide ligand of β-YCH_2Cbls (Fig. 1) have been found to correlate reasonably well via eqn. (1).

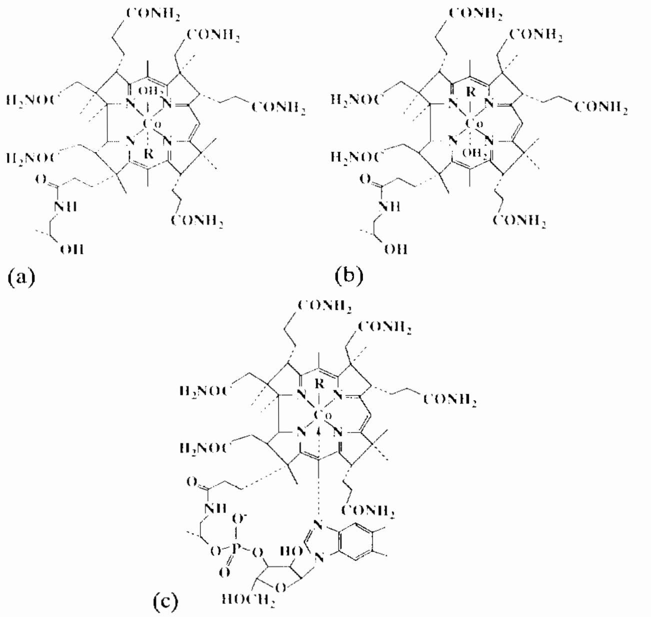


Fig. 1. (a) Structure of an α-alkylcobinamide in which the organic ligand is in the 'lower' axial ligand position. (b) Structure of a β-alkylcobinamide in which the organic ligand is in the 'upper' axial ligand position. (c) Structure of the base-on form of a β-alkylcobalamin.

Experimental

Factor B (a mixture of the diastereomeric α-CN-β-(H_2O)Cbi and α-H_2O-β-(CN)Cbi) was prepared by a modification [33] of the procedure of Renz [34]. Previously reported compounds (β-CH_3CH_2Cbi, β-CH_3Cbi, β-$^-OOCCH_2$Cbi, α-CF_2HCbi and α- and β-$NCCH_2$Cbi) were synthesized and purified as described elsewhere [20, 35]. α- and β-$ClCH_2$Cbi were obtained by reductive alkylation of Factor B with zinc/10% acetic acid in 50% methanol (vol./vol.) using a 100-fold excess of dichloromethane as alkylating agent. The reaction mixture contained roughly equal amounts of each diastereomer in *c.* 40% total yield. The disastereomers were separated by semi-preparative HPLC as described elsewhere [19, 20, 22]. The UV–Vis spectra (λ (log ϵ), α-$ClCH_2$Cbi, 480 (4.12), 406(sh) (3.84), 326 (4.38), β-$ClCH_2$Cbi, 458 (4.02), 398 (3.88), 350 (sh) (4.12), 320 (4.34)) displayed the typical red shift (here, 22 nm) of the longest wavelength (or α) band of the α diastereomer compared to the β diastereomer as has been observed for most pairs of α- and β-R Cbis [20]. The diastereomeric $ClCH_2Cbis$ were further characterized by FAB-MS (*m/e*, calc, 1039.6, α-$ClCH_2Cbi$, 1039.0, β-$ClCH_2Cbi$, 1038.4), conducted as described previously [22]. As has been observed for other RCbis [19, 22, 36], the parent ion in positive ion FAB-MS is pentacoordinate and occurs at $M^+ - H_2O$. The diastereomeric α- and β-$BrCH_2Cbis$ were similarly prepared (using a 300-fold excess of dibromomethane as alkylating agent) and characterized (UV–Vis, λ (log ϵ), α-$BrCH_2Cbi$, 461 (4.01), 376 (4.01), β-$BrCH_2Cbi$, 460 (4.18), 402 (4.10). 351 (4.36), FAB-MS, *m/e*, calc, 1084.1, α-$BrCH_2Cbi$, 1085.1, β-$BrCH_2Cbi$, 1083.7). In this case, the red shift of the longest wavelength band of the α diastereomer is essentially absent as previously observed for α- and β-CF_3Cbi [20].

β-$ClCH_2Cbl$ was obtained by reductive alkylation of aquacobalamin with $NaBH_4$ in 50% methanol (vol./vol.) with a 100-fold excess of dichloromethane. Under these (i.e. neutral) conditions, only the β diastereomer is obtained [20, 21]. The product was shown to undergo the typical base-on/base-off equilibrium [33] by UV–Vis spectroscopy (λ (log ϵ), pH 7.03, 523 (3.98), 465 (sh) (3.77), 410 (3.68), 351 (4.27), pH 0.03, 453 (3.98), 405 (sh) (3.83), 350 (4.24), 325 (4.24)). The value for the pK_a ($pK_{base\text{-}off}$) was determined spectrophotometrically [33] at 503 nm to be 2.54 ± 0.01. The FAB-MS parent ion (calc. 1379.8, obs. 1380.2) occurred at MH^+ as previously observed for other β-RCbls [19, 22].

Electronic spectra and single wavelength absorbance measurements were made on a Cary 219 recording spectrophotometer thermostatted at 25.0 ± 0.1 °C. Apparent formation constants for the cyanide and azide complexes of the RCbis were determined spectrophotometrically as described previously [37]. Complex formation was monitored at visible wavelengths between 488 and 590 nm. In the case of α-CF_2HCbi and CN^-, duplicate measurements were made (at each of 5 pHs) at 372 and 488 nm and the resulting formation constants were averaged. Samples contained RCbi ($3.0\text{–}7.5 \times 10^{-5}$ M), KCN or KN_3 at various concentrations, acetate, phosphate, HEPES or BICINE buffers (0.05–0.1 M) or KOH, as needed, to maintain pH (5.6 to 12.4), and KCl (ionic strength 1.0 M). Samples were incubated at 25.0 ± 0.1 °C for 30 min prior to addition of RCbi. Absorbance changes due to complexation were complete as soon as the first measurement could be made. Sample pH was measured (after absorbance measurements) using a Radiometer PHM 84 pH meter and a Radiometer GK23023 type C combined electrode.

Results and discussion

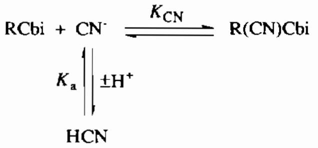
Formation constants for the alkyl(cyano)cobinamides

A number of alkylcobalt corrinoids are known to be labile toward dealkylation by cyanide in the dark, including AdoCbl and other 5′-deoxyadenosylcobalt corrinoids [38–40], carbomethoxymethyl- [41, 42] and carbomethoxyethylcobalamin [41], 2-cyanoethylcobalamin [41], trimethylaminoethylcobalamin [43], and trifluoromethyl- and difluorochloromethylcobalamin [44]. We have now also found that α- and β-CF_3Cbi, α- and β-CF_3CH_2Cbi, β-$ClCH_2Cbi$ and β-$BrCH_2Cbi$ undergo rapid cyanolysis in the dark to yield $(CN)_2Cbi$. We have also found that even in total darkness, all RCbis tested undergo slow cyanolysis to yield $(CN)_2Cbi$. However, for a number of complexes, including β-CH_3CH_2Cbi, β-CH_3Cbi, α-$BrCH_2Cbi$, α-$ClCH_2Cbi$, β-$^-OOCCH_2Cbi$, α-CF_2HCbi, and α- and β-$NCCH_2Cbi$, this cyanolysis was sufficiently slow to permit determination of R(CN)Cbi formation constants, since the establishment of the ligand exchange equilibrium was essentially complete upon mixing.

Apparent formation constants for the R(CN)Cbis, eqn. (4), where $[CN]_T$ is the total concentration of

$$K_{CN}{}^{app} = [R(CN)Cbi]/[RCbi][CN]_T \tag{4}$$

cyanide species (i.e. $[CN]_T = [CN^-] + [HCN]$), were found to be pH-dependent, in general, due to the ionization of HCN (Scheme 1, $pK_a = 9.04$ [45]). From the equilibria in Scheme 1 and the law of mass action, eqn. (5) showing the dependence of $K_{CN}{}^{app}$ on hydrogen ion concentration, may be readily derived.



Scheme 1.

$$K_{CN}{}^{app} = K_a K_{CN}/([H^+] + K_a) \tag{5}$$

For complexes such as α- and β-$NCCH_2Cbi$, for which the value of K_{CN} was quite large (*vide infra*), only the limiting behavior for $[H^+] \gg K_a$, eqn. (6), could be observed (Fig. 2). For a number of other RCbis

$$\lim_{[H^+] \gg K_a} K_{CN}{}^{app} = K_a K_{CN}/[H^+] \tag{6}$$

(including β-CH_3CH_2Cbi, α-$BrCH_2Cbi$, α-$ClCH_2Cbi$ and β-$^-OOCCH_2Cbi$), for which the value of K_{CN} was fairly small, only the pH-independent behavior for $[H^+] \ll K_a$ (eqn. (7)) was readily demonstrable (Fig. 2). However, for α-CF_2HCbi, the complete range of anticipated

$$\lim_{[H^+] \to 0} K_{CN}{}^{app} = K_{CN} \tag{7}$$

pH-dependence (eqn. (5)), including the linear dependence on $1/[H^+]$ at $[H^+] \gg K_a$ and the approach to 'saturation' at $[H^+] \ll K_a$ could be demonstrated (Fig. 2). Thus, for each measurement of $K_{CN}{}^{app}$, a value of

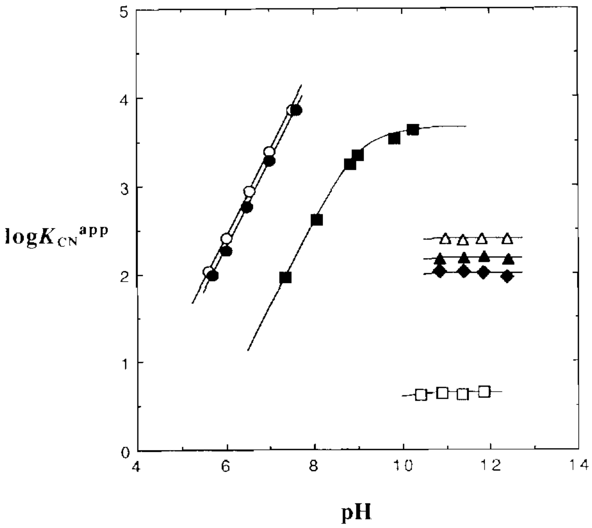


Fig. 2. Plots of the logarithm of the apparent binding constants for cyanide ion to the RCbis, K_{CN}^{app} (eqn. (4)) vs. pH (○) β-$NCCH_2Cbi$, (●) α-$NCCH_2Cbi$, (■) α-CF_2HCbi, (△) β-$^{-}OOCCH_2Cbi$, (▲) α-$ClCH_2Cbi$, (◆) α-$BrCH_2Cbi$, (□) β-CH_3CH_2Cbi. The solid lines were calculated from eqn. (5), the values of K_{CN} given in Table 1, and $pK_a = 9.04$ for HCN (ref. 45).

TABLE 1. Formation constants for the alkyl(cyano)- and alkyl(azido)cobinamides[a]

RCbi	K_{CN} (M^{-1})[b]	K_{N_3} (M^{-1})[c]	K_{CN}/K_{N_3}
β-CH_3CH_2Cbi	$4.33 \pm 0.16 \times 10^0$	< 1.0	< 4.3
β-CH_3Cbi	$8.41 \pm 0.26 \times 10^1$	3.50 ± 0.18[e]	24.0
β-$BrCH_2Cbi$	[f]	3.99 ± 0.21	
α-$BrCH_2Cbi$	$9.98 \pm 0.33 \times 10^1$	2.11 ± 0.13	47.3
β-$ClCH_2Cbi$	[f]	4.19 ± 0.29	
α-$ClCH_2Cbi$	$1.50 \pm 0.03 \times 10^2$	3.84 ± 0.12	39.0
β-$^{-}OOCCH_2Cbi$	$2.50 \pm 0.14 \times 10^2$	4.93 ± 0.29	39.1
α-CF_2HCbi	$4.56 \pm 0.24 \times 10^3$	4.94 ± 0.17	923
β-$NCCH_2Cbi$	$2.79 \pm 0.12 \times 10^5$	15.8 ± 0.7[g]	17660
α-$NCCH_2Cbi$	$2.10 \pm 0.09 \times 10^5$	10.0 ± 0.3	21000

[a] 25.0 ± 0.1 °C, ionic strength 1.0 M (KCl). [b] Scheme 1. Average of 4–6 determinations at several pHs, calculated from eqn. (5) and the pK_a of HCN (9.04, ref. 45). [c] Determined at pH 8.14, except as noted. [d] Binding was detected spectrophotometrically but was too weak to be quantitated. [e] Lit. 4.17 ± 0.09 M^{-1} (ref. 46). [f] Decomposes to $(CN)_2Cbi$ in the dark. [g] Average of four determinations at various pHs > 8.1. The individual values were pH independent.

K_{CN} could be calculated from eqn. (5) using the measured pH and K_a for HCN, and these values were averaged to obtain the estimates of K_{CN} summarized in Table 1. The failure to observe any positive deviation of K_{CN}^{app} from the strictly linear decrease with pH for α- and β-$NCCH_2Cbi$ (Fig. 2) suggests that any binding of HCN itself must be quite weak indeed. Assuming an undetected 10% deviation for β-$NCCH_2Cbi$ at the lowest pH for which K_{CN}^{app} could be measured, an upper limit of *c.* 5 M^{-1} could be set for the binding constant for HCN. Thus, the affinity of this RCbi for HCN must be at least 1.8×10^{-5}-fold lower than its affinity for CN^-.

The values of K_{CN} (Scheme 1) listed in Table 1 can be seen to increase markedly in the order $R = CH_3CH_2 < CH_3 < {}^{-}OOCCH_2 < NCCH_2$ for the β diastereomers and $BrCH_2 < ClCH_2 < CF_2H < NCCH_2$ for the α diastereomers with a net variation of 6.4×10^4 across the complete series. Values of K_{CN} were determinable for both members of a pair of diastereomers only for $R = NCCH_2$, for which the β diastereomer has a 33% higher affinity for cyanide than the α diastereomer, the ratio $K_{CN}^{\beta}/K_{CN}^{\alpha}$ being 1.33 ± 0.08. Unfortunately, the lability of many RCbis towards cyanolysis in the dark limits the K_{CN} data to only 8 values, 4 α-RCbis and 4 β-RCbis. Thus, neither data set provides sufficient data for correlation via eqn. (1).

Formation constants for the alkyl(azido)cobinamides

A weak binding of azide ion (eqn. (8)) to two RCbis (β-$C_6H_5CH_2Cbi$ and β-CH_3Cbi) has previously been observed [46]. The current work provides 9 values

$$RCbi + N_3^- \overset{K_{N_3}}{\rightleftharpoons} R(N_3)Cbi \qquad (8)$$

of K_{N_3} determined spectrophotometrically at wavelengths between 540 and 590 nm (Table 1). The anticipated pH-independence for $K_{N_3}^{app}$ above neutral pH (pK_a for HN_3 is 4.41 [47]) was demonstrated by four determinations of $K_{N_3}^{app}$ for β-$NCCH_2Cbi$ between pH 8.14 and 9.61. The values showed no trend and the average value was 15.8 ± 0.7 M^{-1}. All other values of K_{N_3} were determined at pH 8.14. For β-CH_3CH_2Cbi, although binding of azide could be detected spectrophotometrically, the binding constant was too small to be measured accurately (i.e. $K_{N_3} < 1$ M^{-1}).

The values of K_{N_3} determined (Table 1) permit further comparisons of the relative affinity of a pair of diastereomeric RCbis for an exogeneous ligand. Thus, for $R = ClCH_2$, $BrCH_2$ and $NCCH_2$, the ratio $K_{N_3}^{\beta}/K_{N_3}^{\alpha}$ is

TABLE 2. Values for the formation constants of selected alkyl(pyridine)-, alkyl(hydroxo)- and alkyl(cyano)cobaloximes[a]

R	K_{py} (M^{-1})[b]	K_{OH} (M^{-1})[c]	K_{CN} (M^{-1})[d]	K_{CN}/K_{py}
CH_3CH_2	7.85×10^2	1.07×10^1	4.74×10^7	6.04×10^4
$C_6H_5CH_2$	1.37×10^3	1.66×10^1	6.29×10^7	4.59×10^4
CH_3	2.15×10^3	2.09×10^1	1.06×10^8	4.93×10^4
$ClCH_2$	2.29×10^3	1.12×10^2	6.64×10^8	2.81×10^5
ICH_2	2.64×10^3	1.90×10^2	1.36×10^9	5.15×10^5
CF_3	2.69×10^3	1.10×10^3	1.15×10^{10}	4.28×10^6

[a] 25.0 ± 0.1 °C, ionic strength 1.0 M (KCl). [b] Ref. 5. [c] Calculated from the reported pK_as for axial water ligand ionization in the $RCo(D_2H_2)OH_2$ complexes (refs. 5 and 6). [d] Ref. 2.

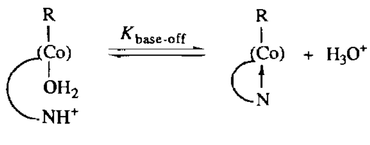
1.09 ± 0.08, 1.42 ± 0.12 and 1.58 ± 0.08, respectively. In each case, there is a slightly greater affinity for the ligand when the *trans* alkyl group is in the β axial ligand position, as was seen for the affinity of $NCCH_2$Cbis for cyanide.

The measured values of K_{N_3} (Table 1) vary from <1 to 15.8 M^{-1}, a surprisingly small variation of only $>c$. 16-fold, compared to the 6.4×10^4-fold range of K_{CN} values for a similar set of complexes. Omitting β-CH_3CH_2Cbi, for which a value of K_{N_3} could not be accurately determined, the values of K_{N_3} vary by only 7.5-fold while those of K_{CN} vary by 2.5×10^3-fold. Thus, K_{CN} is some 3.3×10^2 to 4.0×10^3-fold more sensitive to variations in R than is K_{N_3}. A similar, but less striking, 'leveling' effect can be seen from a comparison of the binding constants for pyridine (K_{py}), hydroxide ion (K_{OH}) and cyanide ion (K_{CN}) for $RCo(D_2H_2)OH_2$ complexes (Table 2). For each R, the formation constants increase in the order $K_{OH} < K_{py} \ll K_{CN}$, but K_{CN} exceeds K_{py} by 4.6×10^4 to 4.3×10^6-fold. The range of binding constants across the series of complexes is only 3.4-fold for pyridine, but rises to 102-fold for OH^- and to 242-fold for CN^-. Thus, K_{CN} is 71 times as sensitive to R as K_{py}, a trend in the same direction, but 4.6 to 56-fold smaller, than that seen in the RCbis. Thus, the magnitude of the 'leveling' effect of the binding of azide relative to cyanide in the RCbis is surprisingly large.

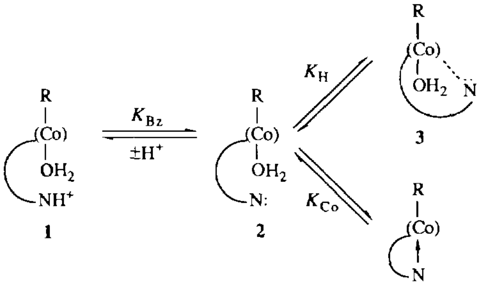
The stability of the $R(N_3)$Cbi complexes, in contrast to the lability of many R(CN)Cbis in the presence of excess cyanide, potentially makes it possible to determine many values of K_{N_3}. However, the very small range of the K_{N_3} values does not provide a data set suitable for testing the applicability of eqn. (1) to alkylcobalt corrinoids. Thus, an excellent correlation of a data set with so little variability would not inspire confidence in the predictive ability of eqn. (1). Similarly, the failure of eqn. (1) to correlate such relatively constant K_{N_3} values well would be neither surprising, nor an indication of the inappropriateness of such a substituent effect analysis for RCbis [3].

Correlation of the intramolecular binding constants for the pendent dimethylbenzimidazole ligand of alkylcobalamins

In order to attempt to determine the applicability of eqn. (1) to the properties of organocobalt corrinoids, we have consequently turned to the equilibria associated with the base-on/base-off reactions of alkylcobalamins (eqn. (9)). From previous work on the thermodynamics of the association of the pendent 5,6-dimethylbenzimidazole nucleotide in RCbls [11, 22, 33, 35, 46, 48], 21 values of $pK_{base\text{-}off}$ (eqn. (9)) are available for compounds of the type YCH_2Cbl. As discussed in detail elsewhere [35], the overall equilibrium of eqn. (9) consists of the components shown in Scheme 2.



(9)



Scheme 2.

The ionization of the protonated, base-off species, **1**, leads to the base-off, but benzimidazole deprotonated species, **2**. The value of pK_{Bz} for this ionization may be accurately taken as the pK_a for the conjugate base of the detached nucleoside, α-ribazole ($pK_a = 5.56$ at 25 °C, ionic strength 1.0 M [33]). Following dissociation of the proton, the benzimidazole moiety may either coordinate to the metal (to form the base-on species, **4**), or hydrogen bond to a side chain amide NH to form the so-called 'tuck-in' species, **3**. There is now overwhelming evidence that base-off but benzimidazole deprotonated cobalamins form such a 'tuck-in' species [23, 35, 49, 50], and that the hydrogen bond donor is the g side chain amide, at least for $(CN)_2$Cbl [49, 50]. From Scheme 2 and the law of mass action, eqn. (10) may be derived [35] for $K_{base\text{-}off}$ (eqn. (9)). Thus, K_{Co}, the intrinsic intramolecular equilibrium constant for

$$K_{base\text{-}off} = (1 + K_H + K_{Co})K_{Bz} \tag{10}$$

coordination of the free base axial nucleotide, may be calculated from the rearranged eqn. (11). The value of K_H (Scheme 2) has been measured for base-off β-CH_3Cbl ($K_H = 4.07$) and is very similar to the

$$K_{Co} = (K_{base\text{-}off}/K_{Bz}) - K_H - 1 \tag{11}$$

measured value for base-off β-$^-OOCCH_2$Cbl ($K_H = 3.29$) [35]. These values are quite small compared to $K_{base\text{-}off}/K_{Bz}$ (eqn. (11)) for almost all β-RCbls indicating that the competition for species **2** (Scheme 2) between formation of the 'tuck-in' species and formation of the base-on species greatly favors the latter, and that the complication of K_H has a minor effect on the calculated values of K_{Co}. We have consequently used $K_H = 4.07$ for the calculation of K_{Co} [35].

We have now attempted to correlate values of K_{Co} calculated in this manner via eqn. (1). Of the 21 values of $pK_{base\text{-}off}$ available for complexes of the type YCH_2Cbl, σ_I and σ_R values are available, from the extensive

TABLE 3. Values of $pK_{\text{base-off}}$, K_{Co}, and inductive, resonance and steric substituent constants for YCH_2Cbls used in the correlation via eqn. (1)

Y	$pK_{\text{base-off}}$[a]	K_{Co}[b]	σ_I[c]	σ_R[c]	$E_s^{(Y)}$[d]
C_6H_5	4.47[e]	7.90×10^0	0.12	−0.17	−3.80
CH_3	4.16[f]	2.00×10^1	−0.01	−0.16	−1.24
CH_3CH_2	4.10[g]	2.37×10^1	−0.01	−0.14	−1.31
$C_6H_5OCH_2$	3.53[h]	1.02×10^2	0.12	−0.11	−1.86
$HOCH_2$	3.43[h]	1.30×10^2	0.11	−0.15	−1.21
CH_3OCH_2	3.25[h]	1.99×10^2	0.11	−0.10	−1.55
H	2.90[f]	4.52×10^2	0	0	0
CF_3	2.60[g]	9.23×10^2	0.40	0.15	−2.40
Cl	2.54[i]	1.04×10^3	0.47	−0.21	−0.97
NC	1.81[j]	5.62×10^3	0.63	0.08	−0.51

[a] Equation (9). Values from references as noted. [b] Calculated from eqn. (11) (based on Scheme 2) using 5.56 for pK_{Bz} (ref. 33) and 4.07 for K_H (ref. 35), except for $R=C_6H_5CH_2$ (see ref. 46). [c] Taken from ref. 4. [d] Taft steric substituent constant for Y [51] taken from ref. 52. [e] Ref. 46. [f] Ref. 35. [g] Ref. 33. [h] Ref. 22. [i] This work. [j] Ref. 48.

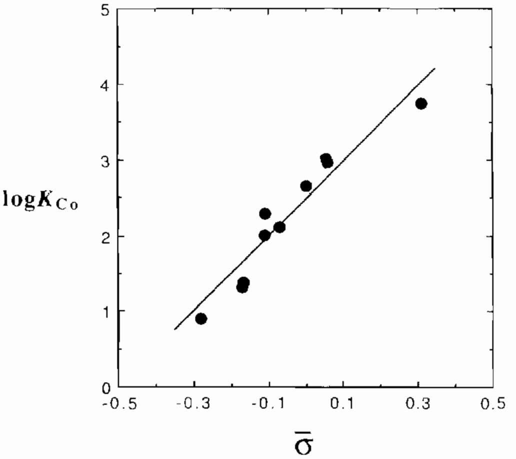


Fig. 3. Plot of log K_{Co} (Scheme 2) vs. $\bar{\sigma}$ (eqn. (13)) for the YCH_2Cbls, according to eqn. (12). The values of K_{Co} (Table 3) were calculated from eqn. (12) as described in the text. The solid line is the calculated correlation line (eqns. (12)–(16)), $\bar{\rho}=4.97$, $C=2.48$.

listings of Charton [4], for only 14. Using as the steric substituent constant, σ_S, Taft's [51] E_s constants [52], Dubois' E_s' constants [53, 54], or Charton's ν constants [55, 56], correlations were attempted using all four sets of σ_R constants (σ_R, $\sigma_R{}^{\circ}$, $\sigma_R{}^{-}$ and $\sigma_R{}^{+}$ [4]) as well as all three steric substituent constants for either Y or YCH_2 [2]. The best correlation was obtained using the $\sigma_R{}^{+}$ resonance substituent constant, and the Taft E_s steric substituent constant for the substituent Y. The data and substituent constants for the 10 compounds for which all three substituent constants were available are shown in Table 3. This is a reasonable data set for correlation via eqn. (1) as the values of K_{Co} vary by nearly three orders of magnitude across the series, and there is also a fairly good range of all three substituent constants for the Ys represented. The correlation obtained is reasonable good ($r^2=0.93$), although not as good as the best correlations previously obtained for $YCH_2Co(D_2H_2)L$ complexes. The parameter values (eqn. (1)) obtained were $\rho_I=2.49$, $\rho_R=2.09$, $\rho_S=0.39$ and $C=2.48$. As discussed previously [2], such correlations may be visualized using the two-dimensional transformation shown in eqn. (12), where $\bar{\rho}$ and $\bar{\sigma}$ are defined in eqns. (13)–(16). The plot of eqn. (12) for the data in Table 3 is shown in Fig. 3.

$$Q_Y=\bar{\rho}\bar{\sigma}+C \tag{12}$$

$$\bar{\sigma}=(\sigma_I+\lambda_1\sigma_R+\lambda_2\sigma_S)/(1+|\lambda_1|+|\lambda_2|) \tag{13}$$

$$\bar{\rho}=\rho_I(1+|\lambda_1|+|\lambda_2|) \tag{14}$$

$$\lambda_1=\rho_R/\rho_I \tag{15}$$

$$\lambda_2=\rho_S/\rho_I \tag{16}$$

The results of this correlation are quite interesting. The signs of the ρ values are all as expected, i.e. K_{Co} is increased by increasing inductive and 'resonance' (i.e. hyperconjugative) withdrawal by Y, but decreased by increasing steric bulk of Y. The relative importance of 'resonance' and inductive effects (i.e. $\lambda_1=0.84$, eqn. (15)) is similar to that found for a number of correlations of axial ligand exchange equilibria and kinetics for $YCH_2Co(D_2H_2)L$ complexes [2]. This suggests that hyperconjugation is about as important in RCbls as it is in $RCo(D_2H_2)L$ complexes. Furthermore, the resonance substituent constant giving the best correlation, $\sigma_R{}^{+}$, is applicable to reactions in which the reaction center is strongly resonance withdrawing [3]. This seems appropriate for the RCbls in which the metal center is cationic. Finally, the magnitude of ρ_S is not much different from that obtained from correlation of formation constants of $YCH_2Co(D_2H_2)L$ complexes [2], suggesting that steric effects are not much more important in the ligation of the 5,6-dimethylbenzimidazole ligand in RCbls than they are in ligand binding to the simpler cobaloximes. Further work is in progress to obtain additional data sets for alkylcobalt corrinoids for which correlations via eqn. (1) may be attempted.

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References

1 L. G. Marzilli, F. Bayo, M. F. Summers, L. B. Thomas, E. Zangrando, N. Bresciani-Pahor, M. Mari and L. Randaccio, *J. Am. Chem. Soc., 109* (1987) 6045.
2 K. L. Brown and S. Satyanarayana, *J. Am. Chem. Soc., 114* (1992) 5674.
3 S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem., 10* (1973) 1.
4 M. Charton, *Prog. Phys. Org. Chem., 13* (1981) 119.
5 K. L. Brown, D. Lyles, M. Penkovici and R. G. Kallen, *J. Am. Chem. Soc., 97* (1975) 7338.
6 K. L. Brown and A. W. Awtry, *Inorg. Chem., 17* (1978) 111.
7 A. L. Crumbliss and P. L. Gaus, *Inorg. Nucl. Chem. Lett., 10* (1974) 485.
8 P. L. Gaus and A. L. Crumbliss, *Inorg. Chem., 15* (1976) 2080.
9 K. L. Brown and E. Zahonyi-Budo, *J. Am. Chem. Soc., 104* (1982) 4117, and refs. therein.
10 K. L. Brown and E. Zahonyi-Budo, *Inorg. Chem., 20* (1981) 1264.
11 K. L. Brown, J. M. Hakimi and Y.-J. Huang, *Inorg. Chim. Acta, 106* (1985) 123.
12 T. E. Walker, H. P. C. Hogenkamp, T. E. Needham and N. A. Matwiyoff, *J. Chem. Soc., Chem. Commun.,* (1974) 85.
13 R. B. Silverman and D. Dolphin, *J. Am. Chem. Soc., 96* (1974) 7094.
14 R. B. Silverman and D. Dolphin, *J. Am. Chem. Soc., 98* (1976) 4633.
15 D. Dodd, M. D. Johnson and C. W. Fong, *J. Chem. Soc., Dalton Trans.,* (1974) 58.
16 C. Bied-Charreton, A. Gaudemer, C. A. Chapman, D. Dodd, B. D. Gupta, M. D. Johnson, B. C. Lockman and B. Septe, *J. Chem. Soc., Dalton Trans.,* (1978) 1807.
17 K. L. Brown and L.-Y. Lu, *Inorg. Chem., 20* (1981) 4178.
18 N. Bresicani-Pahor, M. Forcolin, L. G. Marzilli, L. Randaccio, M. F. Summers and P. J. Toscano, *Coord. Chem. Rev., 63* (1985) 1.
19 K. L. Brown and D. R. Evans, *Inorg. Chem., 29* (1990) 2559.
20 K. L. Brown, X. Zou and L. Salmon, *Inorg. Chem., 30* (1991) 1949.
21 K. L. Brown and X. Zou, *Inorg. Chem., 30* (1991) 4191.
22 K. L. Brown, L. Salmon and J. A. Kirby, *Organometallics, 11* (1992) 422.
23 K. L. Brown and D. R. Evans, *Inorg. Chim. Acta, 197* (1992) 101.
24 K. L. Brown and X. Zou, *Inorg.Chem., 31* (1992) 2541.
25 W. Friedrich and J. P. Nordmeyer, *Z. Naturforsch., Teil B, 23* (1968) 1119.
26 W. Friedrich and R. Messerschmidt, *Z. Naturforsch., Teil B, 24* (1969) 465.
27 W. Friedrich and J. P. Nordmeyer, *Z. Naturforsch., Teil B, 24* (1969) 588.
28 W. Friedrich and R. Messerschmidt, *Z. Naturforsch., Teil B, 25* (1970) 972.
29 W. Friedrich and M. Moskophidis, *Z. Naturforsch., Teil B, 25* (1970) 979.
30 M. Moskophidis, C. M. Klotz and W. Friedrich, *Z. Naturforsch., Teil C, 31* (1976) 255.
31 Y. W. Alelyunas, P. E. Fleming, R. G. Finke, T. G. Pagano and L. G. Marzilli, *J. Am. Chem. Soc., 113* (1991) 3781.
32 K. L. Brown, X. Zou, M. Richardson and W. P. Henry, *Inorg. Chem., 30* (1991) 4834.
33 K. L. Brown, J. M. Hakimi, D. M. Nuss, Y. D. Montejano and D. W. Jacobson, *Inorg. Chem., 23* (1984) 1463.
34 P. Renz, *Methods Enzymol., 18C* (1971) 82.
35 K. L. Brown and S. Peck-Siler, *Inorg. Chem., 27* (1988) 3548.
36 B. P. Hay and R. G. Finke, *J. Am. Chem. Soc., 109* (1987) 8012.
37 K. L. Brown, *Inorg. Chim. Acta, 37* (1979) L513.
38 A. W. Johnson and N. Shaw, *J. Chem. Soc.,* (1962) 4608.
39 H. P. C. Hogenkamp, *Ann. N. Y. Acad. Sci., 112* (1964) 552.
40 H. P. C. Hogenkamp and T. G. Oikawa, *J. Biol. Chem., 139* (1964) 1911.
41 H. P. C. Hogenkamp, J. E. Rush and C. A. Swenson, *J. Biol. Chem., 240* (1965) 3641.
42 W. W. Reenstra, R. H. Abeles and W. P. Jencks, *J. Am. Chem. Soc., 104* (1982) 1016.
43 H. P. C. Hogenkamp, *Fed. Proc., 25* (1966) 1623.
44 M. W. Penley, D. G. Brown and J. M. Wood, *Biochemistry, 9* (1970) 4302.
45 W. W. Reenstra and W. P. Jencks, *J. Am. Chem. Soc., 101* (1979) 5780.
46 K. L. Brown and H. B. Brooks, *Inorg. Chem., 30* (1991) 3420.
47 K. L. Brown and M. Ngamelue, *J. Organomet. Chem., 243* (1983) 339.
48 K. L. Brown and J. M. Hakimi, *Inorg. Chem., 23* (1984) 1756.
49 K. L. Brown, H. B. Brooks, X. Zou, M. Victor, A. Ray and R. Timkovich, *Inorg. Chem., 29* (1990) 4841.
50 K. L. Brown, H. B. Brooks, B. D. Gupta, M. Victor, H. M. Marques, D. C. Scooby, W. J. Goux and R. Timkovich, *Inorg. Chem., 30* (1991) 3430.
51 R. W. Taft, Jr., in M. S. Newman (ed.), *Steric Effects in Organic Chemistry,* Wiley, New York, 1965, p. 556.
52 S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem., 12* (1976) 91.
53 J. A. MacPhee, A. Panaye and J.-E. Dubois, *Tetrahedron, 24* (1978) 3553.
54 A. Panaye, J. A. MacPhee and J.-E. Dubois, *Tetrahedron, 36* (1980) 759.
55 M. Charton, *J. Am. Chem. Soc., 97* (1975) 1552.
56 M. Charton, *J. Org. Chem., 41* (1976) 2217.