Relative Importance of the Inductive and Steric Effects of Alkyl Groups (R) in Understanding the Nature of the Co^{III}–C Bond in Alkyl Cobaloximes, and Comments on Related Alkyl Cobalamins

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We have shown that multiple regression analyses involving Taft's polar substituent constant, σ^*, and Dubois' steric parameter, E'_s, can satisfactorily ($r^2 \geqslant 0.9$) explain the properties of alkyl cobaloximes (R = alkyl) and alkyl cobalamins related to the effects of the R groups. The properties studied are the redox potential of the Co^{III}–Co^{IV} couple, Co→C charge transfer energy, *trans* influence and *trans* effect of R in alkyl cobaloximes, and *trans* influence of R in alkyl cobalamins. From these studies, it is concluded that the Co^{III}–R bond strength decreases with decrease in $(\sigma^* + \lambda E'_s)$ where λ is the mixing coefficient. As indicated by the values obtained, the steric demand of the corrin moiety is found to be an order of magnitude higher than that of dimethylglyoximate. Such semi-quantitative estimation is the first of its kind. The *trans* influence of R is found to be just opposite to the general observation for this static phenomenon and is designated as a special feature of the Co^{III}–R bond.

The most enigmatic feature of the organo derivatives of vitamin B_{12} is the cobalt(III)–carbon bond, and, consequently, it has been the focal point of continuous research on B_{12}-coenzyme and related systems.[1–4] In a previous paper we examined the kinetics of the formation of this bond from the cobalt(I) complexes,[1] here we investigate its nature.

In a variety of experiments on alkyl cobalamins (R = alkyl) and their models it has always been felt that steric factors (of R as well as of the equatorial ligand framework around the Co^{III} centre) play a significant role in the energetics of the metal–carbon bond.[2–4] Recent theoretical calculations on model systems also support this view.[5] However, in only one report has this been shown explicitly, by correlating the solution kinetics of the spontaneous dissociation of R, from four alkyl cobalamins, with Taft's steric factor, E_s, associated with an R group.[6] An attempt[7] has been made to incorporate steric effects indirectly through correlating the number of substituents on the co-ordinated carbon atom to the Co^{III}–C bond lengths in the pyridine (py) adducts of three alkyl cobaloximes {$[CoR(Hdmg)_2(py)]$; Hdmg = dimethylglyoximate anion}.†

Although it is generally well understood that the steric effects of R alone cannot explain the phenomena related to the properties of R, surprisingly to our knowledge, there is so far only one successful report[8] of multiple regression analysis using Taft's polar substituent parameter σ^* (to include the inductive effect exerted by an R group)[9] together with Taft's E_s to correlate the photolysis of Co^{III}–R bonds in several alkyl cobalamins. However, a few unsuccessful attempts at such multiple regression analysis have been described.[10,11] Here we analyse the various data available in the literature, which is lacking in systematic studies on this subject, using multiple regression to assess the relative importance of the inductive and steric effects of an R group in understanding the nature of the Co^{III}–R bond. We have found it preferable to use Dubois' steric parameter[12] E'_s, since this has been shown elsewhere[13] to represent the bulkiness of an alkyl group more effectively than Taft's E_s scale. In the Table the values for σ^* and E'_s for the various alkyl groups studied are given.

Statistical Technique

A physical observable P is related to σ^* and E'_s through equation (1) where ρ^* and ρ^s are the regression coefficients of σ^* and E'_s, respectively, and P_0 is the value of P when $\rho^*\sigma^* + \rho^s E'_s = 0$. Since both σ^* and E'_s are dimensionless in our analyses, we can write the above equation as in equation (2).

$$P = P_0 + \rho^*\sigma^* + \rho^s E'_s \qquad (1)$$

$$P = P_0 + \rho^*[\sigma^* + (\rho^s/\rho^*)E'_s] \qquad (2)$$

Substituting λ for ρ^s/ρ^*, the mixing coefficient, we rewrite (2) as shown in equation (3). Thus the multiple regression (1) reduces to a simple linear regression given by equation (4), where P has to be fitted with a single parameter, σ^s_λ, whose composition is $(\sigma^* + \lambda E'_s)$. Equation (4) helps us represent the simultaneous variation of P with σ^* and E'_s by a two-dimensional plot of P *versus* σ^s_λ. It should be noted that our approach differs slightly from that of Taft[14] for the graphical presentation of such variation.

$$P = P_0 + \rho^*(\sigma^* + \lambda E'_s) \qquad (3)$$

$$P = P_0 + \rho^*\sigma^s_\lambda \qquad (4)$$

In our analyses, we have used r^2, the coefficient of determination (square of the correlation coefficient, r), as a measure of the goodness of fit, since of all the statistical tests known only this one has direct significance.[15] For example, in our case $100r^2$ gives the percentage of the variation in P that can be attributed to the variation in σ^s_λ. Incidentally, Taft's f parameter, which represents an arbitrary test, is related to r^2 by equation (5).

$$r^2 + f^2 = 1 \qquad (5)$$

Here we shall accept a value of r^2 greater than 0.90 to yield a reasonably good correlation, which means more than 90% of the variation of P is explained. This would mean $f < 0.32$ using Taft's parameter.

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† However, considerable efforts have been made to examine the steric effects exerted by the axial ligand in the model complexes of alkyl cobalamins; especially using the 'cone angle' of phosphines (see refs. 2 and 4 for details).

Table. Taft's polar substituent constant σ^* and Dubois' steric parameter E'_s for the various organo groups (R) involved in the present studies

	R	σ^{*a}	$-E'^{\,b}_s$
1	CF_3	2.55	0.78
2	CF_2H	2.05	0.32
3	CH_2CN	1.30	0.89
4	CCPh	1.35	1.97
5	CH_2Cl	1.05	0.18
6	CH_2Br	1.00	0.24
7	CH_2I	0.85	0.30
8	Ph	0.60	2.31
9	CH_2CH_2OPh	0.31	0.31^c
10	$CH_3O_2C(CH_2)_2$	0.26^d	0.31^c
11	CH_2Ph	0.215	0.39
12	CH_2CH_2OMe	0.19	0.31^c
13	$(CH_2)_3CN$	0.17^e	0.31^c
14	CH_2CH_2Ph	0.08^f	0.35
15	CH_3	0.00	0.00
16	CH_2CH_3	−0.100	0.08
17	$CH_2CH_2CH_3$	−0.115	0.31
18	$(CH_2)_3CH_3$	−0.130	0.31
19	CH_2CHMe_2	−0.125	0.93
20	*cyclo*-C_6H_{11}	−0.150	0.69
21	$CH(CH_3)_2$	−0.190	0.48
22	*cyclo*-C_5H_9	−0.200	0.41
23	$CH(CH_3)C_2H_5$	−0.210	1.00
24	$CH_2C(CH_3)_3$	−0.165	1.63
25	$CH(C_2H_5)_2$	−0.225	2.00

[a] Values from ref. 9 unless otherwise specified. [b] Values from ref. 12 unless otherwise specified. [c] Estimated; a survey of the E'_s data in ref. 12 shows that the steric parameters for the mono-substituted ethyl groups (at β position) are levelled to −0.31. For examples, see propyl and butyl groups in this table. For comparison, see also CH_2CH_2Ph (11). [d] $\sigma^*(10) = \sigma^*(CH_2CO_2CH_3)/2.79 = \sigma_I(CO_2CH_3)/(0.45 \times 2.79)$, $\sigma_I(CO_2CH_3) = 0.32$ [from M. Charton, *Prog. Phys. Org. Chem.*, 1981, **13**, 146]. [e] $\sigma^*(13) = \sigma^*(CH_2CN)/(2.79)^2$. [f] $\sigma^*(14) = \sigma^*(CH_2Ph)/2.79$.

Results and Discussion

Alkyl Cobaloximes.—Alkyl cobaloximes $[CoR(Hdmg)_2L]$; L = a monodentate ligand, are considered to be very good models[1–4] of alkyl cobalamins and various studies on them constitute the bulk of studies on model compounds. First we examine the nature of the Co^{III}–C bond in these model complexes.

Co^{III}–C *bond strength order.* To find out the Co^{III}–C bond strength order in alkyl cobaloximes, the variation of the redox potentials ($E_{\frac{1}{2}}$) of the Co^{III}–Co^{IV} couple in several $[CoR(Hdmg)_2(H_2O)]$ complexes[16] with σ^* and E'_s was studied. A mixing coefficient (λ) of 0.090 gives a very good correlation (r^2, 0.937; *f*, 0.252; Figure 1). Since $E_{\frac{1}{2}}$ decreases with decreasing σ^s_λ, the thermodynamic stability of the Co^{III} species decreases and that of the corresponding Co^{IV} one increases (*i.e.* the process $Co^{IV} + e \rightleftharpoons Co^{III}$ becomes less facile thermodynamically). If the changes in other factors (*e.g.* solvation of the ions) along the series are assumed, reasonably, to be less important, the trend in $E_{\frac{1}{2}}$ essentially reflects the difference between the Co^{III}–R and Co^{IV}–R bond strengths; the factor which largely controls the thermodynamic stabilities of the Co^{III} and the corresponding Co^{IV} species. This indicates that while Co^{IV} is an electrophile, the Co^{III} centre in the alkyl cobaloximes is a nucleophile. Consequently a more electron releasing R group (σ^* more negative) forms a weaker bond with the nucleophile Co^{III} and the steric factor associated with R facilitates this weakening further. Since λ is positive, the inductive and steric effects of R act in the same direction.

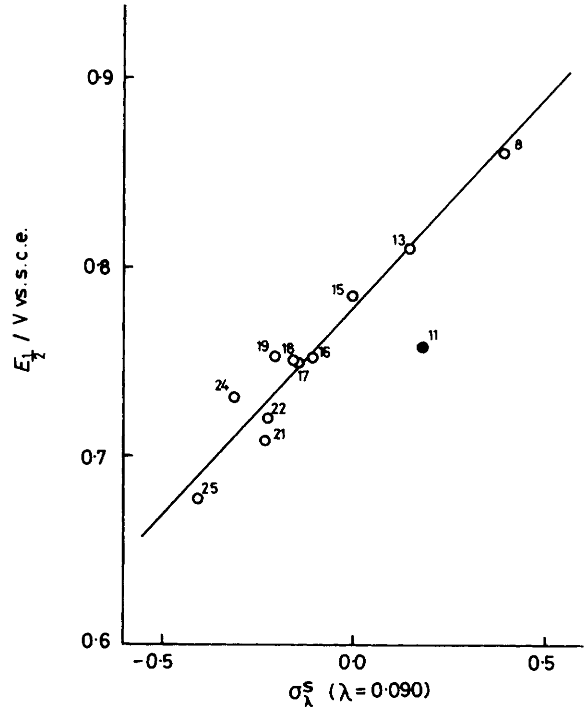


Figure 1. Variation of the redox potential $E_{\frac{1}{2}}$ (in V *vs.* saturated calomel electrode) of the Co^{III}–Co^{IV} couple in $[CoR(Hdmg)_2(H_2O)]$ with $\sigma^* + 0.090E'_s$. For identification of the R group given by the numbers, see the Table. The point corresponding to the benzyl group (11, ●) was not used for the least-squares fit. $E_{\frac{1}{2}}$ data from ref. 16

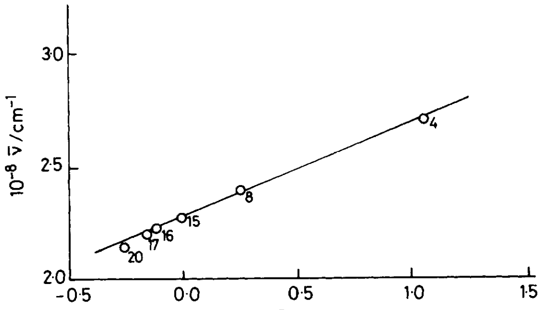


Figure 2. Variation of the charge transfer energy $\bar{\nu}$ (in cm^{-1}) in $[CoR(Hdmg)(py)]$ with $\sigma^* + 0.148E'_s$. For identification of R group, see the Table. Data for $\bar{\nu}$ from ref. 17

The derived bond strength order is supported by the observed variation of the Co→C charge transfer energy ($\bar{\nu}$) with σ^* and E'_s (λ, 0.148; r^2, 0.995; *f*, 0.071; Figure 2) in several $[CoR(Hdmg)(py)]$ complexes.[17] In Figure 2, $\bar{\nu}$ increases with the increase in σ^s_λ, *i.e.*, with the Co–R bond strength. A stronger bond implies that the carbon-based orbital in question increases in energy with respect to the cobalt one, as expected from simple molecular orbital (m.o.) theory.

The trans *influence and* trans *effect of* R. To examine the nature of the *trans* influence, a static phenomenon,[18] we have studied the equilibrium binding constants (K_f) of dimethoxyethylamine (dea) in various $[CoR(Hdmg)_2(dea)]$ complexes.[11] In Figure 3 (λ, 0.133; r^2, 0.953; *f*, 0.216) we find that the weaker the Co^{III}–R bond (lower value of σ^s_λ), the lower is the value of the formation constant. This is opposite to the trend expected from

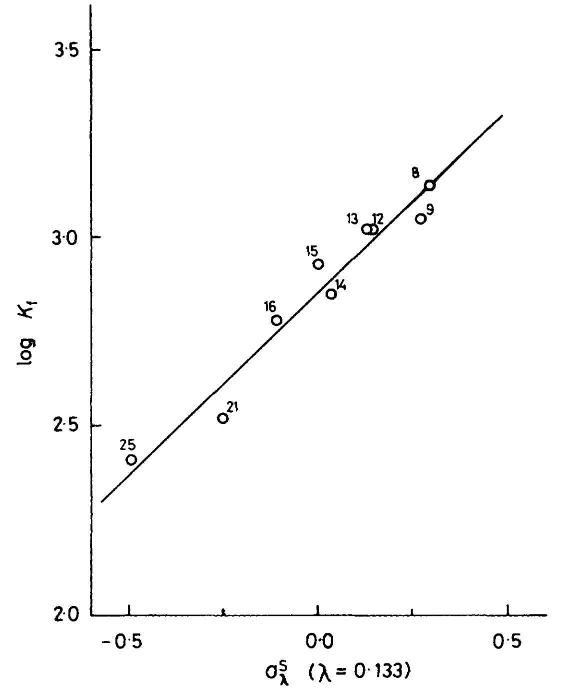


Figure 3. Variation of the equilibrium binding constant (K_f) of dea in $[CoR(Hdmg)_2(dea)]$ with $\sigma^* + 0.133E'_s$. For identification of the R group, see the Table. Data for K_f from ref. 11

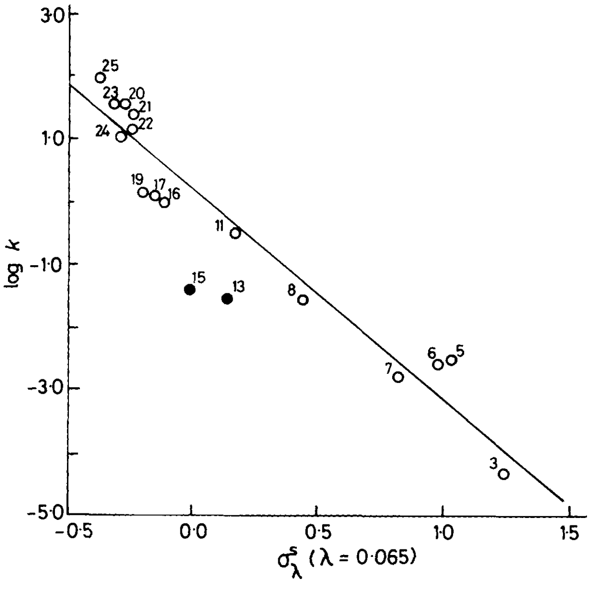


Figure 4. Variation of the pseudo-first-order rate constant (k) for the dissociation of $[CoR(Hdmg)_2(py\text{-}CN\text{-}4)]$ with $\sigma^* + 0.065E'_s$. For identification of the R group, see the Table. The points (●) corresponding to 13 and 15 were not used for the least-squares fit. Data for k from ref. 4

the usual idea of *trans* influence.[18] Previously Marzilli and coworkers[4] have also observed that in alkyl cobaloximes a weak axial bond leads to a weak *trans* bond. However, here we try to put forward an explanation for our specific case. Since the amine is basically a nucleophile, it forms a stronger bond (larger K_f) with Co^{III} when it is depleted of electrons by a more electron withdrawing R group (σ^* more positive). Here the steric factor of R again acts in the same direction, probably by pushing the equatorial ligand framework towards the amine to weaken the Co^{III}–N bond more. It should be noted that Brown and Awtrey[11] attempted such multiple regression for log K_f with much less success by using Taft's steric parameters (r^2, 0.904; f, 0.31).

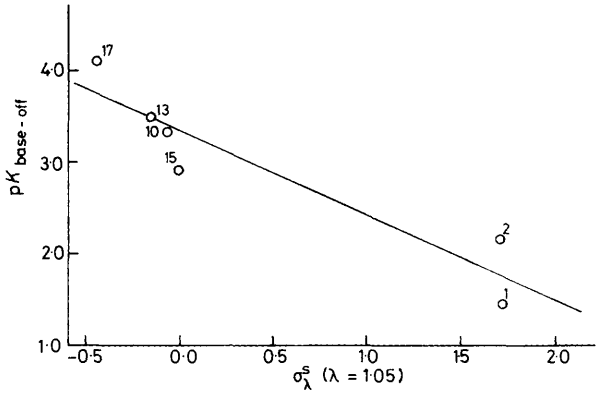
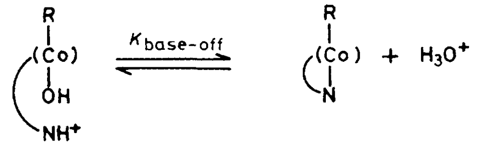


Figure 5. Variation of $K_{base\text{-}off}$ for the equilibrium binding of the benzimidazole in alkyl aquacobalamins [equation (6)] with $\sigma^* + 1.05E'_s$. For identification of the R group, see the Table. Data for $K_{base\text{-}off}$ from ref. 8

The *trans* effect, a kinetic phenomenon,[18] of R is exemplified by the variation of the pseudo-first-order rate constant (k) for the dissociation of the base from several $[CoR(Hdmg)_2(py\text{-}CN\text{-}4)]$ complexes (see Table 41 in ref. 4), shown in Figure 4 (λ, 0.065; r^2, 0.937; f, 0.252). This supports the earlier viewpoint that a strong axial Co^{III}–R bond leads to a strong *trans* bond, at least, for a base. Since a more positive value of σ^s_λ leads to a stronger Co^{III}–R bond, it also gives rise to a stronger Co^{III}–py bond causing its dissociation to be more difficult (lower k). But the correlation is very interesting with regard to pyridine. This implies that py seeks electrons in the transition state, which is lowered in energy by the availability of electrons. Such a tendency for py is, however, not new (see Figure 3 in ref. 19 for example).

Alkyl Cobalamins.—Alkyl cobalamins have not been studied systematically. The available data, which are few, permit us only to examine the observed *trans* influence of R in reaction (6) where $K_{base\text{-}off}$ is the equilibrium binding constant for the benzimidazole group.[8] For five R groups, a mixing coefficient of



(6)

1.050 yields an 87.7% correlation (r^2, 0.877; f, 0.351) of p$K_{base\text{-}off}$ with σ^* and E'_s (Figure 5). Though the correlation is only satisfactory, it follows the same trend as observed in the cobaloximes (Figure 3).

However, it should be mentioned that the R groups are known to undergo steric distortions in the alkyl cobalamins[20] because of the high steric demand of the corrin ring. Consequently Dubois' steric parameters may not adequately describe their bulk in alkyl cobalamins. This may be one of the reasons for the lower value of r^2 (poorer fit) in Figure 5.

Conclusions

We conclude that the Co^{III}–C bond strength increases with the increase in σ^s_λ; the inductive and the steric effects of R act in the same direction. Compared with the inductive effect, the magnitude of the steric effect operating in the cobaloximes is only 10.90 (± 3.31)% (from the values of λ from Figures 1—4) while that in the cobalamins is an order of magnitude higher (105% from Figure 5). This result is not unexpected since the steric demand of the corrin moiety is much more than that of dimethylglyoximate. Such a semi-quantitative demonstration of the relative steric effects in cobaloximes and cobalamins is the first of its kind. As observed by other workers[4] the *trans* influence of the R groups defies the general notion of *trans* influence. We note that this is a very special feature of the Co^{III}–R bond.

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