DALTON

Factors affecting the rate of ligand substitution reactions of aquacobalamin (vitamin B_{12a}) ‡

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The ligand substitution reactions of co-ordinated H_2O in aquacobalamin (vitamin B_{12}) by OCN^-, SCN^-, $SeCN^-$, NO_2^-, $S_2O_3^{2-}$ and N_3^- in a $NaNO_3$ medium, in contrast to an earlier report on some of these ligands in a KCl medium, proceeded too rapidly for saturation kinetics to be observed. The discrepancy, as suggested previously, is due to formation of a significant fraction of the more substitution-inert chloro complex in a KCl medium. Second-order rate constants, corrected for pH effects, for the reactions have been determined as a function of temperature, from which activation parameters were calculated. The identity of the donor atom of the ambidentate ligands in the rate-determining processes, k_{II}, is considered and correlations found between $\Delta H^\ddagger_{k_{\text{II}}}$, the enthalpy of activation, and $\Delta S^\ddagger_{k_{\text{II}}}$, the entropy of activation, respectively, the Mulliken population on the donor atom, and the energy of the highest occupied molecular orbital (HOMO) with σ symmetry. The parameters $\Delta H^\ddagger_{k_{\text{II}}}$ is strongly dependent on the HOMO energy, and more weakly dependent on the electron density on the donor atom, while the converse is true for $\Delta S^\ddagger_{k_{\text{II}}}$.

Aquacobalamin (vitamin B_{12a}, Fig. 1) contains an axially co-ordinated water molecule which is readily replaced by a wide range of exogenous ligands from solution. The reactions are surprisingly fast for Co^{III} and attest to the *cis* labilising effect of the delocalised π-electron system of the corrin ring. Randall and Alberty[1,2] and subsequently Thusius[3] reported that the rate constants, k, for substitution of co-ordinated H_2O by a variety of incoming ligands, L, varied by about two orders of magnitude, while the equilibrium constants, K, for these reactions varied by over eleven orders of magnitude. Since there is also a linear relationship between log k and log K, this led to the view that the reactions proceed by a strictly dissociative (D) mechanism.[4–8] However, it had been pointed out[2] that, because of the significantly slower rate of substitution of H_2O by imidazole compared to N_3^- and NCO^-, the reaction was unlikely to involve unimolecular release of water from Co^{III} followed by fast binding of the incoming ligand. Reenstra and Jencks,[9] in an insightful analysis of the mechanistic course of reactions in solution proceeding through dissociative activation, suggested that in *aqueous* solutions a D mechanism is most unlikely because of the short lifetime of the five-co-ordinate intermediate. Evidence began to mount against a purely D mechanism. The transition state for substitution of H_2O by CN^- is enthalpically stabilised by 25 kJ mol^{-1} relative to that for substitution by HCN,[10] the rate of substitution by substituted imidazoles depends linearly on the K_a of the entering ligand,[11] and the activation parameters for substitution of H_2O by primary amines[12] and small anionic and neutral ligands (SCN^-, $S_2O_3^{2-}$, NO_2^-, CN^-, HCN, N_3^-, HN_3, SO_3^{2-}, HSO_3^-)[13,14] depend on the nature of the incoming ligand. These observations are inconsistent with a strictly D mechanism.

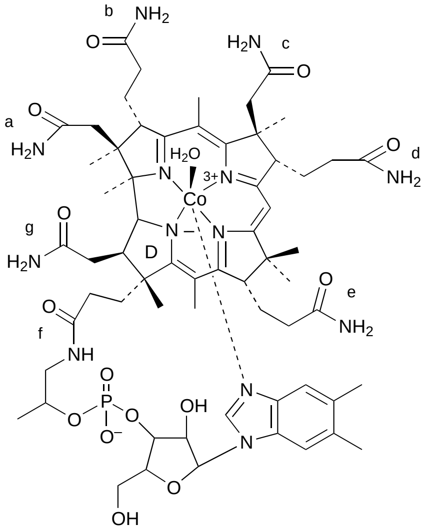

Fig. 1 Aquacobalamin (vitamin B_{12a}), in which Co^{III} is co-ordinated in the equatorial plane by corrin. The axial ligand on the lower (α) face is 5,6-dimethylbenzimidazole (dmbzim), and that on the upper (β) face is H_2O

After a report[8] that when L = pyridine a plot of the observed rate constant against ligand concentration showed saturation behaviour and reached a limiting rate constant at high (>0.5 mol dm^{-3}) ligand concentrations, the most convincing evidence against a limiting D mechanism was obtained. It was shown[15] that the limiting rate constant depends on the identity of the incoming ligand; this is conclusive evidence that a D mechanism is not operative. A similar conclusion was arrived at for substitution of H_2O in aquacyanocobinamide.[16] The mechanism of these ligand substitution reactions is therefore best described as an interchange mechanism proceeding through dissociative activation (I_d) [equations (1) and (2)], and the

$$\text{dmbzim–Co–OH}_2 + \text{L} \xrightleftharpoons{K} \{\text{H}_2\text{O}\cdots\text{dmbzim–Co}\cdots\text{L}\} \quad (1)$$

$$\{\text{H}_2\text{O}\cdots\text{dmbzim–Co}\cdots\text{L}\} \xrightleftharpoons[k_{-4}]{k_4} \text{dmbzim–Co–L} + \text{H}_2\text{O} \quad (2)$$

saturating rate constant, k_{sat}, is related to the microscopic rate

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‡ Supplementary data available (No. SUP 57278, 8 pp.): primary kinetic data. See Instructions for Authors, *J. Chem. Soc.*, *Dalton Trans.*, 1997, Issue 1.

Non-SI units employed: cal = 4.184 J, eV ≈ 1.60 × 10^{-19} J.

constants by equation (3) (assuming the reverse rate constant, k_{-4}, is insignificantly small).

$$k_{obs} = \frac{k_4K[L]}{1 + K[L]} \qquad (3)$$

In a subsequent report,[17] the dependence of the saturation rate constant on the nature of the incoming ligand was demonstrated for a series of small anionic ligands (I^-, $S_2O_3^{2-}$ NO_2^-, SCN^- and N_3^-). We showed that for these the enthalpy of activation, $\Delta H^{\ddagger}_{k_4}$, of the interchange reaction, k_4, is correlated with the Mulliken population of the donor atom of the entering ligand (as determined by semiempirical molecular orbital calculations using the PM3[18,19] model) if we assume that the donor atom in the transition state with anionic ligands capable of forming linkage isomers is the donor atom with the larger electron density. No correlation was found between the Mulliken population and the activation parameters for N-donor ligands such as pyridines and imidazoles; the activation parameters for these species correlated instead with the steric demands of the ligand as quantified by the cone angle subtended by the ligand at the metal ion. It therefore appears that steric demands can override the electronic effects.

A potential problem with these suggestions has now emerged. The ionic strength adjustor used in all these studies was KCl, because it is UV-transparent (unlike NO_3^-), allows standard combination glass electrodes to be used for the measurement of pH (unlike ClO_4^-), and little spectroscopic evidence was found for the binding of Cl^- to Co^{III}.[10,17] A recent report[20] has shown that at high chloride concentrations there is significant retardation of reaction rates, which must be due to the formation of the more substitution-inert chloro complex; K for formation of chlorocobalamin was measured to be 0.8 dm^3 mol^{-1}. Although this finding does not invalidate the conclusions reached concerning the mechanism of the ligand substitution reactions of aquacobalamin (there is now general agreement that they proceed through an interchange mechanism under dissociative activation) it certainly brings into question any conclusions based upon the absolute values of the rate constants and their activation parameters. We have therefore reconsidered our previous suggestions concerning the identification of the reacting atom of an entering ambidentate ligand, and report on our findings here.

Experimental

Hydroxocobalamin (>99% pure, HPLC) was from Roussel; $Na_2S_2O_3$, NaSCN, $NaNO_2$ (Saarchem, S. Africa), NaOCN (Fluka), NaN_3 (Riedel-de-Haën) and KSeCN (Sigma) of the highest purity available were used as received. Water was purified in a Millipore RO unit and further purified by passage through a Millipore MilliQ system (18 MΩ cm). Preliminary spectroscopic investigations were carried out on a Cary 3E UV/VIS spectrometer. All reactions were studied under pseudo-first-order conditions with B_{12a} concentrations of between 50 and 80 μmol dm^{-3} buffered with 0.1 mol dm^{-3} 2-(*N*-cyclohexylamino)ethane sulfonic acid (CHES) at *ca.* pH 9. The total ionic strength was adjusted to 2.2 mol dm^{-3} with $NaNO_3$. No spectroscopic evidence was found for co-ordination of Co^{III} by NO_3^-. Ligand solutions were also buffered with ches and the pH and ionic strength were adjusted to the same values as for the B_{12a} solutions. The kinetics of the reactions was monitored at around 375 nm (where the absorbance due to NO_3^- is negligible) by mixing equal volumes (0.1 cm^3) of the two solutions using a Hi-Tech SF51 stopped-flow spectrometer (cell pathlength 1.00 cm) interfaced through a DAS-50 A/D board with a personal computer. The observed pseudo-first-order rate constants, k_I^{obs}, were found by fitting the absorbance *vs.* time trace by an equation of the form $A_1 \exp(-k_I^{obs}t) + A_2$ as objective function, A_1, A_2 and k_I^{obs} as variable parameters, using non-linear least-squares methods and a Newton–Raphson procedure. Since hydroxocobalamin is inert to substitution[9,10,14,21] values of k_I^{obs} were converted into pH-independent values, k_1, using equation (4), where K_{Co} is the acid dissociation constant

$$k_I = k_I^{obs}(1 + K_{Co}/[H^+]) \qquad (4)$$

for co-ordinated H_2O in B_{12a} [corrected for its temperature variation, pK_{Co} 8.09 (25 °C), $I = 0.5$ mol dm^{-3}, $NaNO_3$; $\Delta H = 36.0 \pm 1.9$ kJ mol^{-1}, $\Delta S = -34 \pm 6$ J K^{-1} mol^{-1}].[22] The temperature of the system was maintained (±0.1 °C) with a water-circulating bath. The pH of solutions was measured with a Metrohm 605 pH meter and a 6.021 00.100 combination glass electrode calibrated against standard buffers, all maintained at the appropriate temperature with a water-circulating bath.

Molecular orbital calculations were performed using HYPERCHEM V. 4.5.[23] After molecular building, the species were geometry-optimised initially by semiempirical molecular orbital calculations using the PM3 model;[18,19] this was followed by full geometry optimisation using an *ab initio* method at the Hartree–Fock level of theory with the STO-6G* minimal basis set,[24] the Raffenetti integral format,[25] a self-consistent field (SCF) convergence limit of 10^{-5} kcal mol^{-1}, and an energy convergence criterion of 0.01 kcal mol^{-1} for the root-mean-square gradient. More sophisticated basis sets such as split-valence or polarised basis sets could not be used because of lack of parameters for Se.

Results and Discussion

We previously noted[17] that the reactions between small anionic ligands and B_{12a} proceed rapidly and just show saturation behaviour at high (>*ca.* 0.5 mol dm^{-3}) ligand concentration. We have now found, in agreement with the report of van Eldik and co-workers,[20] that on substituting Cl^- with non-co-ordinating NO_3^- as ionic strength adjustor the reactions are significantly more rapid. We agree with the suggestion[20] that this is a consequence of the co-ordination of Cl^- by Co^{III}, and that chlorocobalamin is more inert than aquacobalamin towards substitution. In the absence of Cl^-, we find the reactions are so fast that curvature from linearity of a plot of k_I^{obs} against ligand concentration is not observable with the instrumentation available, despite conducting the reactions in alkaline solution (pH 8.5–9.5) where a substantial fraction of the cobalamin is present as the inert hydroxo complex. Saturation rate constants are therefore not available, and only the second-order rate constants, k_{II}, obtained from the slopes of plots of k_I^{obs} against ligand concentration, could be determined. This second-order rate constant is composite and is related to the equilibrium and rate constants of equations (1) and (2) by (5), assuming k_{-4} is insignificantly

$$k_{II} = k_4K \qquad (5)$$

small. Measured values of k_{II} are listed in Table 1 (the primary kinetic data are listed in SUP 57278); for example, plots of $L = NO_2^-$ are shown in Fig. 2(*a*). The activation parameters (also listed in Table 1) for the reactions were determined by plotting ln ($k_{II}h/k_BT$), where h and k_B are the Planck and Boltzmann constants, respectively, against T^{-1}. Fig. 2(*b*) is an example of such a plot for $L = NO_2^-$.

We have previously noted[17] that the enthalpies and entropies of activation for the saturating rate constant, k_4, $\Delta H^{\ddagger}_{k_4}$ and $\Delta S^{\ddagger}_{k_4}$, are strongly correlated ($R^2 = 0.92$) and compensate each other; as $\Delta H^{\ddagger}_{k_4}$ increases and the reaction becomes enthalpically less favoured, there is a compensating increase in $\Delta S^{\ddagger}_{k_4}$ and the reaction becomes entropically more favoured. Owing to this effect, the similarity of rate constants at a single temperature cannot be used as the basis for assigning a D mechanism to a series of reactions. A variety of explanations for these compensating effects may be possible. Our interpretation was in terms of the fundamental steps of an I_d mechanism. The onset

Table 1 Rate constants * and activation parameters for the reaction of aquacobalamin with various small anionic ligands ($I = 2.2$ mol dm^{-3}, KNO_3)

Ligand, L	T/°C	k_{II}/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}_{k_{II}}$/kJ mol^{-1}	$\Delta S^{\ddagger}_{k_{II}}$/J K^{-1} mol^{-1}
NO_2^-	5.0	10.179(1)		
	15.0	36.202(3)		
	25.0	99.82(4)		
	35.0	249.2(2)	73(3)	37(9)
NCO^-	15.0	74.6(4)		
	25.0	234.4(4)		
	35.0	648(4)	77(1)	60(4)
N_3^-	5.0	58.18(1)		
	15.0	173.1(1)		
	25.0	415.8(4)		
	35.0	1192(1)	68(2)	34(8)
$S_2O_3^{2-}$	5.0	4.112(1)		
	15.0	12.00(1)		
	25.0	42.75(3)		
	35.0	143.73(1)	82(4)	63(12)
SCN^-	5.0	8.30(3)		
	15.0	430.4(4)		
	25.0	1319(5)		
	35.0	3200(40)	68(3)	42(10)
$SeCN^-$	5.0	160.89(3)		
	15.0	522.9(2)		
	25.0	1376.9(4)		
	35.0	3799(2)	72(1)	57(5)

* Corrected for inert hydroxocobalamin [equation (3) of the text]; each reported value is the average (standard deviation) of five or six determinations.

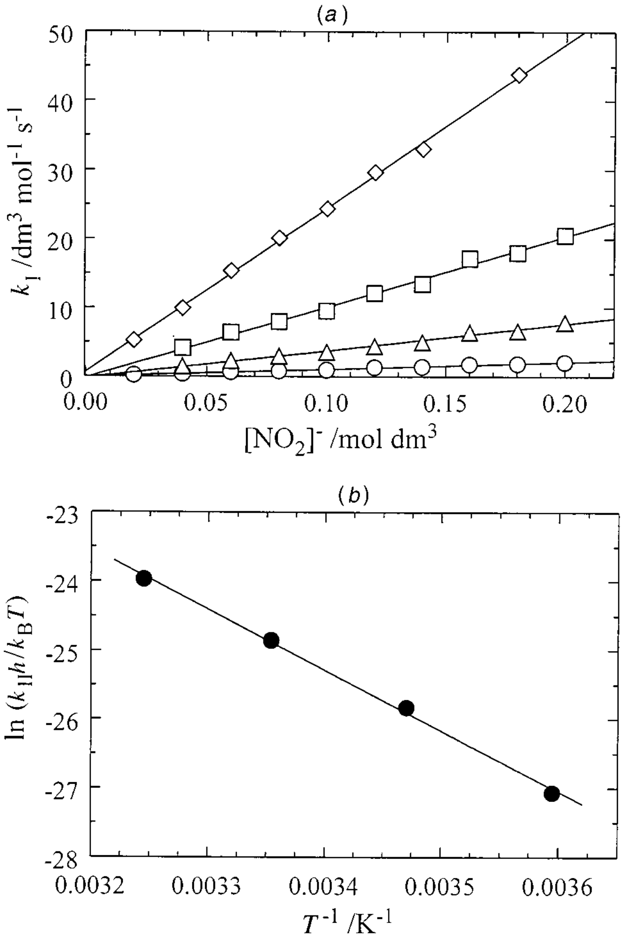

Fig. 2 Dependence of (*a*) the pseudo-first-order rate constant k_I on ligand concentration and temperature (○, 5; △, 15; □, 25; ◇, 35 °C), $I = 2.2$ mol dm^{-3} and (*b*) of the second-order rate constant, k_{II}, on temperature for substitution of H_2O in aquacobalamin by NO_2^-

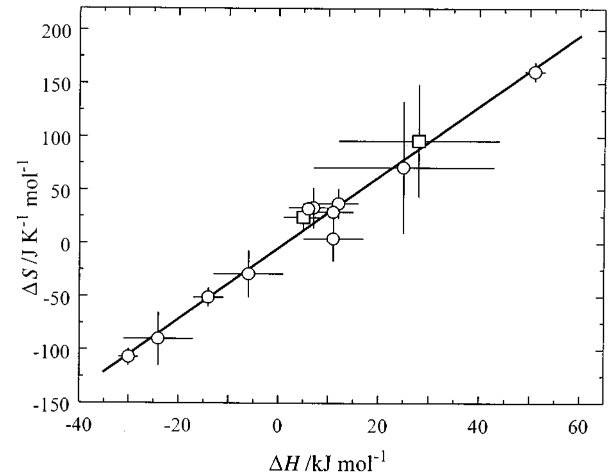

Fig. 3 Correlation of the enthalpy and entropy of formation of the precursor complex between entering L and aquacobalamin in aqueous solution (Table 2). The values have been calculated from the reported temperature dependence of K [equation (2)] in refs. 15 and 17 (○) and in ref. 26 (□)

of bond formation between L and the metal will compensate for bond breaking between the metal and H_2O; $\Delta S^{\ddagger}_{k_4}$ would be large and negative due to loss of freedom of the incoming L while $\Delta H^{\ddagger}_{k_4}$ would be small; conversely, a large value of $\Delta H^{\ddagger}_{k_4}$ necessitates a more positive value for $\Delta S^{\ddagger}_{k_4}$ as bond breaking between Co and O is the major process in the transition state.

It is perhaps not surprising to find now that the correlation between $\Delta H^{\ddagger}_{k_{II}}$ and $\Delta S^{\ddagger}_{k_{II}}$ for the k_{II} values reported here is much weaker ($R^2 = 0.63$). Since k_{II} is a composite rate constant [equation (5)], it follows that $\Delta H^{\ddagger}_{k_{II}} = \Delta H_K + \Delta H^{\ddagger}_{k_4}$ and $\Delta S^{\ddagger}_{k_{II}} = \Delta S_K + \Delta S^{\ddagger}_{k_4}$. The values of ΔH_K and Δs_K for a number of ligands can be determined from data which have been reported previously. From the reported temperature dependence of K, we have calculated the values of ΔH_K and ΔS_K from plots of ln K against T^{-1}, and these are listed in Table 2. Although the uncertainty in many of the values is large [the determination of K is from the initial slope (which is equal to k_4K) of a plot of k_{obs} against [L], and hence requires k_4 to be known], the values describe a good straight line ($R^2 = 0.98$) as shown in Fig. 3, and a compensating effect exists between ΔH_K and ΔS_K, as expected for weak associations in solution.[27]

Table 2 Thermodynamic parameters for the formation of an outer-sphere complex between aquacobalamin and an incoming ligand, L, from solution

Ligand, L	K^{25a}/dm^3 mol^{-1}	ΔH_K/kJ mol^{-1}	ΔS_K/J K^{-1} mol^{-1}	Ref.
NH_2OH	0.3	51 ± 2	161 ± 9	15
Methyl glycinate	0.7	12 ± 4	37 ± 14	15
Imidazole	0.6	−14 ± 3	−51 ± 9	15
Histamine	0.5	−30 ± 2	−107 ± 8	15
Pyridine	3.1	7 ± 5	33 ± 19	15
4-Methylpyridine	4.2	6 ± 1	32 ± 3	15
Pyridine	0^b	−15 ± 7	−297 ± 24	27
4-Methylpyridine	2.4	5 ± 4	24 ± 13	27
3-Acetylpyridine	1.3	28 ± 16	96 ± 53	27
$S_2O_3^{2-}$	0.0	11 ± 6	4 ± 21	17
N_3^-	0.3	−24 ± 7	−90 ± 25	17
SCN^-	0.3	−6 ± 7	−29 ± 22	17
NO_2^-	0.4	11 ± 4	29 ± 11	17
I^-	0.2	25 ± 18	71 ± 82	17

^{a} At 25 °C, calculated from the values of ΔH_K and ΔS_K. ^{b} The experimentally determined value reported at 25 °C is 1.1 ± 0.2 dm^3 mol^{-1}.

Attempts have been made to rationalise the nature of the outer-sphere or precursor complex formed between aquacobalamin and incoming L;[26] it was suggested that the complex was formed by π–π interactions between the corrin ring (or functional groups on the corrin, presumably the amide side-chains) and L. However, as we now report, the precursor complex is formed with anions, a primary amine, two imidazoles, and three pyridines, with thermodynamic parameters that span a wide range of values, and in no apparent order (Fig. 3). It is therefore difficult to rationalise the nature of the precursor complex. An electrostatic interaction between an anionic species and the residual +2 charge at the metal centre (the negative charge on the phosphate is some 9 Å away) is certainly expected when L is anionic; but histamine (imidazole-4-ethanamine), which is cationic below pH 10, also forms a complex, as does imidazole itself, the pyridines, and hydroxylamine. It seems likely that hydrogen bonding between the upwardly projecting acetamide side-chains, *a*, *c*, and *g*, and L, as we have previously suggested,[12] plays an important role. Although the formation of π–π complexes between the 14-electron aromatic system of the corrin ring and a planar ligand such as a pyridine or an imidazole is possible in principle, it is most unlikely in our view because of the crowded nature of the corrin ring (unlike a porphyrin ring, for example, where the existence of such complexes are well established[28]) with its upwardly projecting sentinel groups [the *a* and *c* side chains, methyl C(46), methyl C(54), and the *g* side-chain].[29] The nature of the precursor complex has not yet been adequately established; it is unlikely to involve only one type of interaction and electrostatic, hydrogen bonding, and hydrophobic interactions are all likely to contribute to its formation.

Weak interactions in solution (those for which the enthalpic change is significantly lower than the enthalpy of a typical covalent bond) are characterised by such compensating effects.[26] An increasingly favourable enthalpic effect is offset by an increasingly adverse entropic effect, a consequence of the loss of degrees of freedom as the associating entities are constrained within the complex. Within the framework of an I_d mechanism, where there is, albeit small, not negligible, nucleophilic participation of L in the transition state (the energetics of the process are largely dominated by the rupture of the Co–O bond) one might therefore expect an inverse relationship between the activation enthalpy, $\Delta H^{\ddagger}_{k_4}$, of the k_4 step [equation (2)] and ΔH_K of the K step [equation (1)]; the greater the enthalpic stabilisation of the precursor complex, the greater the enthalpy of activation of the subsequent interchange step would be since attainment of the transition state would require a (positive) enthalpy contribution to disrupting the intermolecular interactions (hydrogen bonding, electrostatic, hydrophobic, for example) responsible for formation of the precursor complex. The limited data available do indeed show just this inverse relationship (Fig. 4). Since $\Delta H^{\ddagger}_{k_4}$ and $\Delta S^{\ddagger}_{k_4}$, and ΔH_K and ΔS_K, respectively, are correlated, there is also a correlation between $\Delta S^{\ddagger}_{k_4}$ and ΔS_K (not shown). The effect is to level off the values of $\Delta H^{\ddagger}_{k_{\mathrm{II}}}$ and $\Delta S^{\ddagger}_{k_{\mathrm{II}}}$ and explains why the numerical ranges of these parameters (and in particular $\Delta H^{\ddagger}_{k_{\mathrm{II}}}$) are rather small (Table 1).

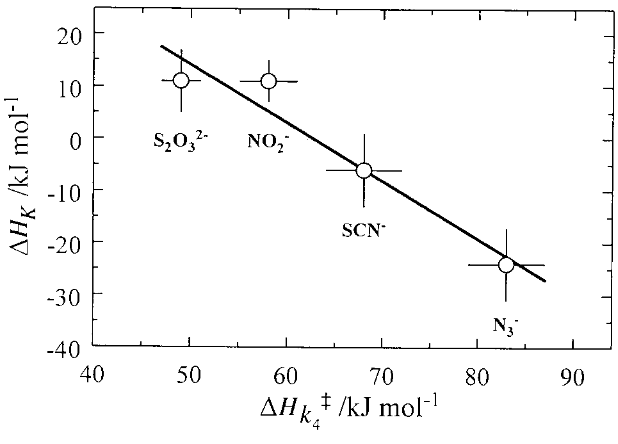

Fig. 4 Inverse correlation of the enthalpy change, ΔH_K, for formation of the precursor complex [equation (1)] and the enthalpy of activation, $\Delta H^{\ddagger}_{k_4}$, for the ligand interchange reaction [equation (2)]. Data from ref. 17

Of the six ligands studied, all except N_3^- are potentially ambidentate towards Co^{III} in aquacobalamin. The donor atom of a ligand depends on a number of factors,[30] including the nature of the metal ion, the presence of other ligands, and even whether the complex is in the solid state or in solution. Furthermore, the donor atom in the transition state of the reaction need not necessarily be the same as that in the final product.

We conducted a search of the Cambridge Structural Database (CSD) and found that whether thiocyanate is N or S bound depends largely on the nature of the metal ion. As expected,[31] N tends to bond to harder metal ions while S bonds to softer ones; the preferred mode of bonding of SCN^- has been used as a gauge of the hardness or softness of a metal centre.[32] Steric factors can perturb this general pattern[31] because S-bound thiocyanate requires the ligand to bind in an bent fashion (the M–S–C angle is usually between 95 and 115°), whereas in N-bound thiocyanates the ligand is virtually linear (the M–N–C angle is close to 180°);[33] thus in [Pd(Et$_4$trien)(NCS)]X (Et$_4$trien = 1,1,7,7-tetraethyldiethylenetriamine, X = PF_6^- or BPh_4^-), thiocyanate is N-bound because of the steric demands of the substituted diene ligand. Tuan *et al.*[34] performed molecular orbital calculations on SCN^- in an endeav-

Table 3 Mulliken populations of the donor atoms, and symmetry and energy of the highest occupied MO with σ symmetry of the investigated ligands as determined by an *ab initio* molecular orbital method using a minimal STO-6G* basis set

Ligand	Donor atom	Mulliken population	Frontier orbital	
			Symmetry	Energy/eV
$S_2O_3^{2-}$	S	6.6475	a_1	6.071
	O	6.5389		
SCN^-	S	6.4572	σ^+	−3.447
	N	5.4714		
NO_2^-	N	5.2981	a_1	−3.933
	O	6.3509		
NCO^-	N	5.5538	σ^+	−2.997
	O	6.5105		
$SeCN^-$	Se	6.6671	σ^+	−5.233
	N	5.3771		
N_3^-	N	5.4727	σ_u^+	−3.892

our to determine which of the two atoms would bond preferentially to a given metal ion. It was shown that, since S is less electronegative than N, the amplitude of the frontier orbitals is larger on S than on N, suggesting (other factors being equal) a preference for S-bonded complexes. Iron(III) and cobalt(III), centres in complexes in which the equatorial ligand contains a π-delocalised electron system tend to prefer the softer S atom in their complexes with SCN^-; examples include (phthalocyaninato)(pyridine)thiocyanatocobalt,[35] (2,3,9,10-tetramethyl-1,4,8, 11-tetraazacyclotetradeca-1,3,8,10-tetraene)-dithiocyanoto ironn(III) hexafluorophosphate and a range of cobaloximes.[37] Pratt,[38] quoting a personal communication with Dorothy Hodgkin, reports that in the solid state SCN^- is S-bound to Co^{III} in the cobalamins. The π-electron system of the corrin ring can control and modulate the electronic properties of the metal ion, and Co^{III} is considerably more labile in the cobalamins than in many of its complexes because of the conferring of partial Co^{II}-like character on the metal ion by the equatorial ligand.[22]

Although Co^{III} is expected to be reasonably soft in aquacobalamin, this does not preclude the reaction preceding initially through N, and the immediate kinetic and final thermodynamic products may differ. Biphasic kinetics have previously been noted for the reaction of both SCN^- and $S_2O_3^{2-}$ with B_{12a} at high ligand concentrations;[17] at the much lower concentrations used in the present study we only observed simple exponential kinetics after monitoring the reaction with both stopped-flow (2 ms $\leqslant t \leqslant$ 500 s) and conventional ($t \geqslant$ 50 s) spectroscopic methods. Thusius[3] observed that a rapidly established equilibrium exists in solutions of thiocyanate and cobalamin, and attributed this to linkage isomerism. Similar effects have been reported for reactions between SCN^- and cobalt(III) porphyrins.[39]

The co-ordination chemistry of $SeCN^-$ is very similar to that of SCN^-.[31] A search of the CSD revealed the expected pattern of Se binding to softer, and N binding to harder, metal ions although $SeCN^-$, presumably because of the softer nature of Se compared to S, is more resistant to having this trend affected by steric effects. Thus $[Pd\{Ph_2P(CH_2)_nPPh_2\}X_2]$ (n = 1–3, X = $SeCN^-$) contain only Se-bound $SeCN^-$, but the analogous SCN^- complexes contain at least one N-bound ligand.[40] As expected, therefore, $SeCN^-$ binds to Co^{III} through Se both in the cobaloximes[41] and in the cobalamins as shown by both UV/VIS spectroscopy[42] and X-ray diffraction structure determination.[43]

As previously reported,[33] and confirmed by a search of the CSD, all complexes of monodentate cyanate have the ligand binding through N. This is as expected from Tuan and Hoffman's molecular orbital calculations[44] which show N to be less electronegative than O, and the spatial extensions of the orbitals on N always larger than on O. Nevertheless, we have found that when the absorbance of a solution containing B_{12a} and cyanate is monitored the spectrum changes slowly with time. The bands undergo a red-shift (for example, the γ band shifts from 357.8 to 360.9 nm), and the intensity of the γ and increases by 27%. Since the spectra of N-donor complexes of cobalt(III) cobalamins (such as the ammonia, pyridine and imidazole complexes, for example) have UV/VIS spectra in which the band positions are at longer wavelength than those of O-donor complexes (such as complexes with H_2O and acetate), we attribute these slow changes ($t_{\frac{1}{2}} \approx$ 30 min in 50 mmol dm^{-3} NCO^-, at which concentration there is no evidence for conversion into the dicyanato complex for which there is kinetic evidence at high ligand concentrations) to the isomerisation from the kinetically favoured O-bound to the thermodynamically favoured N-bound species.

We have also observed previously biphasic kinetics in the reaction of $S_2O_3^{2-}$ with B_{12a},[17] and attributed this to formation of a minor O-bound component, before isomerisation to the expected S-bound species. We found no evidence of isomerisation in the present investigation.

Whether NO_2^- is N- or O-bound in the nitrocobalamin complex is unknown. When $[Co(NH_3)_5(OH_2)]^{3+}$ reacts with HNO_2 the O-bound complex rearranges to the stable N-bound complex in an intramolecular process;[45] it has been suggested[46] that this reactivity pattern arises because of the smaller steric demands of the nitrito compared to the nitro complex. The reaction of B_{12a} with NO_2^- exhibited simple monophasic kinetics and we assume the final product to be the N-bound species.

We have sought correlations between $\Delta H^\ddagger_{k_{II}}$, $\Delta S^\ddagger_{k_{II}}$, and parameters determined from molecular orbital calculations. If we assume that, in the microscopic processes which determine the magnitude of the activation parameters of k_{II}, SCN^- reacts through N rather than S, NO_2^- reacts through N, NCO^- reacts through O, $S_2O_3^{2-}$ reacts through S, and $SeCN^-$ reacts through Se, then a plot of $\Delta H^\ddagger_{k_{II}}$ against the Mulliken population of the donor atom, and the energy of the highest occupied molecular orbital with σ symmetry, is a reasonable surface (Fig. 5). The predicted values of $\Delta H^\ddagger_{k_{II}}$ (Table 4) are all within, or close to, the uncertainties in the experimental determinations. Hence, although the adjusted R^2 value is relatively modest (0.80), this is a consequence of the fairly small numerical range spanned by the $\Delta H^\ddagger_{k_{II}}$ values; the f statistic of 6.3 means there is only an 8% chance that the observed correlation is due to random chance. A stronger correlation with $\Delta S^\ddagger_{k_{II}}$ is observed (R^2 = 0.95), presumably because of the larger numerical range of this parameter. Again, the predicted values of $\Delta S^\ddagger_{k_{II}}$ are all within the error in the experimental data. Using any other donor atom for any of the ligands (for example, assuming S rather than N is the donor atom in SCN^-) leads to very much weaker correlations (R^2 = 0.65 and 0.78 for the correlations of Mulliken population and orbital energy with $\Delta H^\ddagger_{k_{II}}$ and $\Delta S^\ddagger_{k_{II}}$, respectively).

The reaction of SCN^- through N rather than S is surprising as S is softer, has the higher Mulliken population, and the frontier molecular orbitals have larger amplitude on this atom. The reason is unlikely to be steric as both $SeCN^-$ and OCN^- react through Se and O, respectively. Since the final thiocyanate complex is almost certainly S-bound, and we found no evidence for isomerism, we must assume that isomerisation occurs very rapidly. The reaction with OCN^- through O is also surprising, but in this case there is clear kinetic evidence of a subsequent isomerisation to the expected N-bound complex. The other four ligands react as expected.

If the correlation shown in Fig. 5 are not fortuitous (and the statistical evidence would indicate they are not), then $\Delta H^\ddagger_{k_{II}}$ is strongly dependent on the energy of the highest occupied molecular orbital of σ symmetry, and more weakly dependent on the electron density on the donor atom; the converse is true

Table 4 Statistics of the correlation between $\Delta H^{\ddagger}_{k_{II}}$ and $\Delta S^{\ddagger}_{k_{II}}$, the Mulliken population of the donor atom, and the energy of the highest occupied molecular orbital with σ symmetry

(*a*) Correlations with $\Delta H^{\ddagger}_{k_{II}}$ [a]

Coefficient		*t* Statistic	% Confidence[b]
a_1	3.7 (2.1)	2.55	96
a_2	0.85 (33)	1.74	90
a_3	53 (13)	4.07	98
R^2	0.81		
f Static	6.30		
% Confidence[c]	92		

	$\Delta H^{\ddagger}_{k_{II}}$/kJ mol^{-1}		
Ligand L	obs.	predicted	obs − predicted
$S_2O_3^{2-}$	82(4)	82	0
SCN^-	68(3)	70	−2
NO_2^-	73(3)	69	4
NCO^-	77(1)	75	2
$SeCN^-$	72(1)	73	−1
N_3^-	68(2)	70	−2

(*b*) Correlations with $\Delta S^{\ddagger}_{k_{II}}$ [a]

Coefficient		*t* Statistic	% Confidence[b]
a_1	17.4 (2.6)	6.60	99.6
a_2	0.64(41)	1.57	89
a_3	−54(16)	−3.40	98
R^2	0.95		
f Statistic	26.6		
% Confidence[c]	99		

	$\Delta S^{\ddagger}_{k_{II}}$/JK^{-1} mol^{-1}		
Ligand, L	obs.	predicted	obs. − predicted
$S_2O_3^{2-}$	63(12)	64	−1
SCN^-	42(10)	39	3
NO_2^-	37(9)	36	1
NCO^-	60(4)	57	3
$SeCN^-$	57(5)	59	−2
N_3^-	34(8)	39	−5

[a] For equations of the form $\Delta H^{\ddagger}$ (or $\Delta S^{\ddagger}$) $= a_1 \times$ Mulliken population on donor atom $+ a_2 \times$ molecular orbital energy $+ a_3$. Values in parentheses are standard errors. [b] The percentage confidence (based on a single-tailed test) in the significance of the variable in predicting the value of $\Delta H^{\ddagger}_{k_{II}}$ or $\Delta S^{\ddagger}_{k_{II}}$. [c] The percentage confidence, based on the *f* statistic (single-tailed test), that the observed correlation is *not* due to random chance.

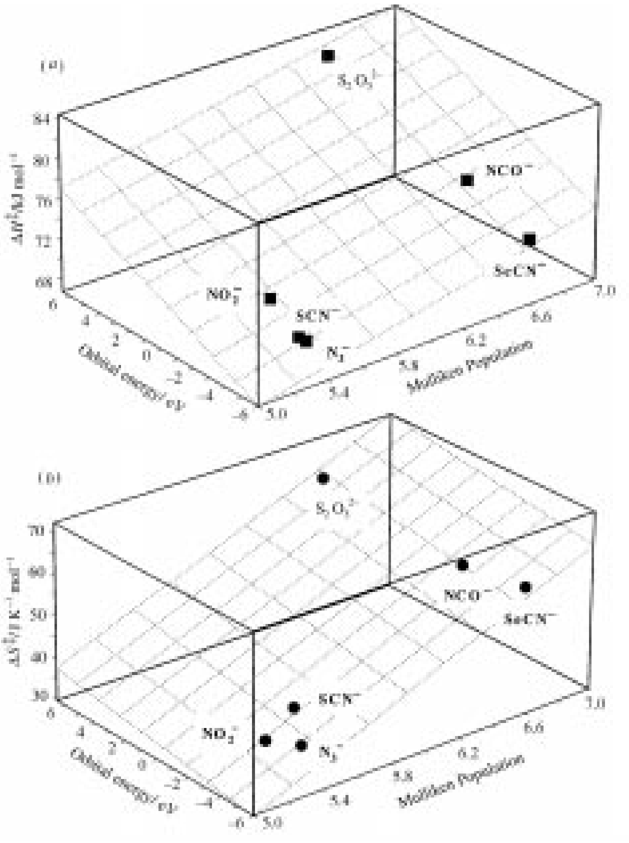

Fig. 5 Correlations between (*a*) $\Delta H^{\ddagger}_{k_{II}}$ and (*b*) $\Delta S^{\ddagger}_{k_{II}}$ and the Mulliken population on the donor atom and the energy of the highest occupied molecular orbital of the ligand, L, with σ symmetry

for $\Delta S^{\ddagger}_{k_{II}}$. Since $\Delta H^{\ddagger}_{k_{II}}$ and $\Delta S^{\ddagger}_{k_{II}}$ are composite functions, and are the results of the interplay between $\Delta H^{\ddagger}_{k_4}$ and ΔH_K, and between $\Delta S^{\ddagger}_{k_4}$ and ΔS_K, respectively, a rationalisation of these observations on the microscopic level is unlikely to be fruitful, and we would merely suggest this sort of study as an empirical method for probing the course of reactions with ambidentate ligands.

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