# Binding of Cyanoferrates to Cobaloximes and Cobalamins: an EHMO Study

A. F. CUTHBERTSON, C. GLIDEWELL*, A. R. BUTLER and A. S. McINTOSH
*Chemistry Department, University of St. Andrews, St. Andrews, Fife KY16 9ST, U.K.*
(Received May 30, 1986)

## Abstract

The binding of nitroprusside, $[Fe(CN)_5NO]^{2-}$, and hexacyanoferrate(II) to methylcobaloxime, and to a cobalt corrin, has been analysed by means of extended Hückel calculations. The binding of $[Fe(CN)_5NO]^{2-}$ to the cobalt atom in methylcobaloxime can occur in three isomeric configurations, of which the most stable involves the axial cyano ligand in a Fe–C–N–Co bridge, and the least stable involves the nitrosyl ligand in a Fe–N–O–Co bridge. The binding of both cyanoferrates involves primarily a $\sigma$ orbital largely localised as a lone pair on a cyano nitrogen and the vacant $d_{z^2}$ orbital of cobalt: $\pi$ interactions involving cobalt d-orbitals and the $\pi$ orbitals of the cyano ligands are of negligible importance.

## Introduction

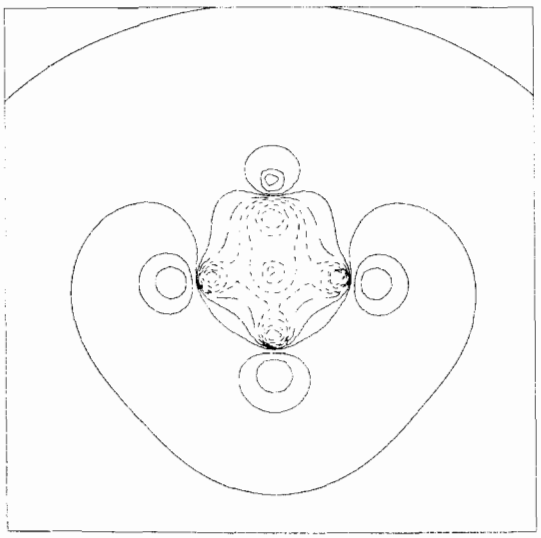
Sodium nitroprusside, $Na_2[Fe(CN)_5NO]\cdot 2H_2O$, is a powerful hypotensive agent which has been widely used in the treatment of severe hypertension, in the management of myocardial infarction, and in the induction of surgical hypotension [1–4]. However, there have been a number of reports [5] that the nitroprusside ion is metabolized in the red blood cells, with rapid release of cyanide into the bloodstream. As a possible antidote to potential cyanide poisoning induced by the administration of nitroprusside, the use of aquocobalamin, Vitamin $B_{12a}$, has been suggested [6, 7]: (this material is often referred to as hydroxocobalamin, but its $pK_a$ is 8.1 [8], and hence at physiological pH it is primarily in the aquo form).

Following experiments [9] which showed that aquocobalamin significantly influences the pharmacokinetics of the hypotensive action of nitroprusside, and suggested the possibility that aquocobalamin might interact with nitroprusside, rather than simply acting as a means of removing free cyanide (as cyanocobalamin, Vitamin $B_{12}$), we undertook a $^{13}C$ NMR study [10] of the interactions between aquocobalamin and nitroprusside, using highly enriched $Na_2[Fe(^{13}CN)_5NO]\cdot 2H_2O$. The results of the NMR study [10] may be summarised as follows: (i) in an equimolar mixture, at concentrations of *ca.* $5 \times 10^{-3}$ mol $dm^{-3}$, nitroprusside and aquocobalamin are entirely in the form of a 1:1 adduct, in which the nitrogen of the axial cyano ligand of $[Fe(CN)_5NO]^{2-}$ has displaced the aquo ligand from cobalt; (ii) at molar ratios of cobalamin:nitroprusside of 5:1 or greater, all of the nitroprusside is in the form of a 2:1 complex in which a pair of *trans* equatorial cyano ligands are bound to the cobalt atom of two cobalamin fragments (at intermediate concentration ratios, mixtures of these two complexes, or of the 1:1 complex and free nitroprusside are observed); (iii) the nitrosyl ligand in $[Fe(CN)_5NO]^{2-}$ is not involved in the binding to cobalt, nor is it essential for such binding since hexacyanoferrate(II), $[Fe(CN)_6]^{4-}$, forms entirely similar complexes; and (iv) the binding of cyanoferrate to cobalt via a FeCNCo bridge is not specific to aquocobalamin, as similar complexes are formed with aquomethylcobaloxime, $CH_3Co(dmg)_2H_2O$ (dmg = dimethylglyoxime). For the cobalamin, the binding at cobalt was proved by *inter alia* the observation that no change occurred in the $^{13}C$ spectrum of the cyanoferrates when the sixth ligation site at cobalt was blocked by cyanide (for which the stability constant $K = 1.2 \times 10^{14}$ $dm^3$ $mol^{-1}$ [11]); for the cobaloxime, such binding at cobalt was demonstrated by direct observation of the $^{59}Co$ resonance.

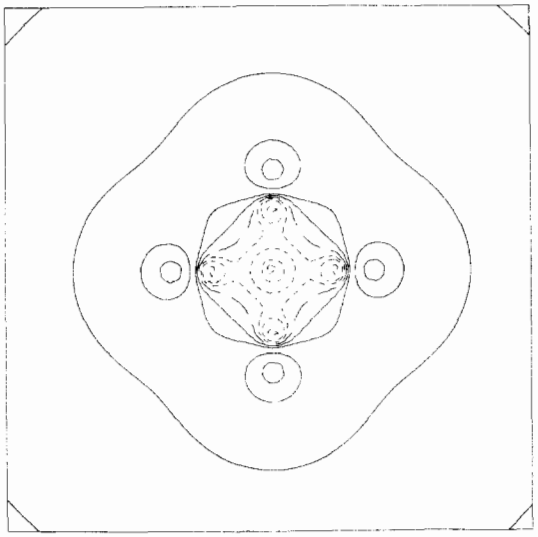
In the present paper we present the results of a computational study of the interaction of two cyanoferrates, $[Fe(CN)_5NO]^{2-}$ and $[Fe(CN)_6]^{4-}$ with both aquomethylcobaloxime and with a cobalt corrin model for aquocobalamin which sheds light on the following questions concerning complex formation: (i) the geometry of the FeCNCo bridge; (ii) the relative energies of the possible isomeric forms of the nitroprusside isomers; (iii) the nature of the bonding in the complexes, especially the orbital interactions involved; (iv) the greater stability of the cobalamin complexes compared with the cobaloxime complexes.

*Author to whom correspondence should be addressed.

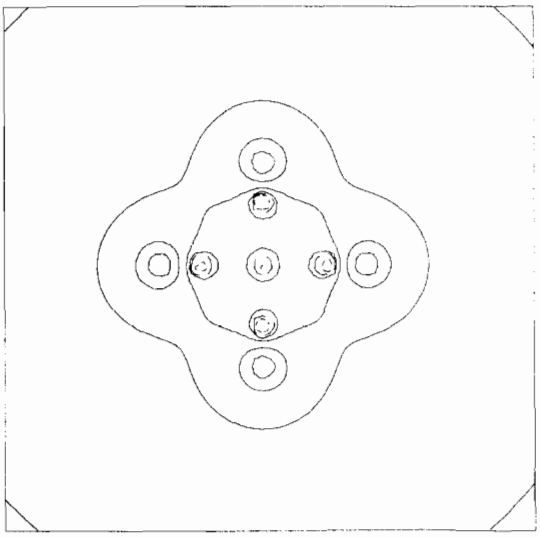
0020-1693/87/$3.50



(a)



(b)



(c)

Fig. 1. (a) Electrostatic potential in $\sigma_v$ plane of $[Fe(CN)_5NO]^{2-}$. (b) Electrostatic potential in equatorial plane of $[Fe(CN)_5NO]^{2-}$. (c) Electrostatic potential in $\sigma_h$ plane of $[Fe(CN)_6]^{4-}$. For $[Fe(CN)_5NO]^{2-}$, successive contours represent −1.0, −0.5, −0.2, −0.1, 0.0, +0.1, +0.2, +0.5, and +1.0 a.u.; for $[Fe(CN)_6]^{4-}$, successive contours represent −2.0, −1.0, −0.5, −0.2, 0.0, and +0.5 a.u. (—— negative; – – – zero; ------ positive).

## Calculations

All molecular-orbital calculations were made with the extended Hückel method [12, 13], using published atomic parameters [14]. Structure data were taken from X-ray studies [15–17]. Electrostatic potentials were calculated and plotted [18] using the net atomic charges taken from the extended Hückel calculations.

## Results

*Nitroprusside and Hexacyanoferrate(II)*

In the nitroprusside anion, $[Fe(CN)_5NO]^{2-}$, the HOMO is calculated to be the $d_{xy}$ orbital, at −12.79 eV, closely followed at −12.95 eV by the equatorial $\sigma$(FeCN) combination of type E in $C_{4v}$ symmetry: the equatorial $\sigma$(FeCN) levels of types $A_1$ and $B_1$ lie at −13.95 eV and −13.76 eV respectively. The $d_{yz}$ and $d_{zx}$ orbitals are at −13.12 eV, while the axial $\sigma$(FeCN) and $\pi$(CN) levels which turn out to be the most important in binding to cobalt (see below) are at −13.33 eV and −14.49 eV respectively. The LUMO in nitroprusside is calculated to be the $\pi^*$(NO) orbitals, at −10.01 eV, for which the coefficients indicate fairly strong localisation on the nitrogen atom, as expected for an anti-bonding orbital: next above the LUMO amongst the virtual orbitals is the axial $\pi^*$(CN) at −8.45 eV.

The nitrogen atoms of the cyano-ligands are calculated to be the most negatively charged: the axial

cyano nitrogen carries a charge of −1.07e, and the equatorial nitrogen slightly less, −0.98e. In contrast, the terminal oxygen atom of the nitrosyl ligand carries a charge of only −0.42e. Hence it is to be expected that electrophilic reagents will interact primarily, if not exclusively, at the terminal atoms of the cyano ligands, with perhaps a marginal preference for the axial site over the equatorial. On the other hand the nitrogen atom of the nitrosyl ligand bears the highest positive charge, +0.72e, of any atom in the nitroprusside anion (the equatorial carbons bear charges of +0.46e, and the axial carbon +0.51e).

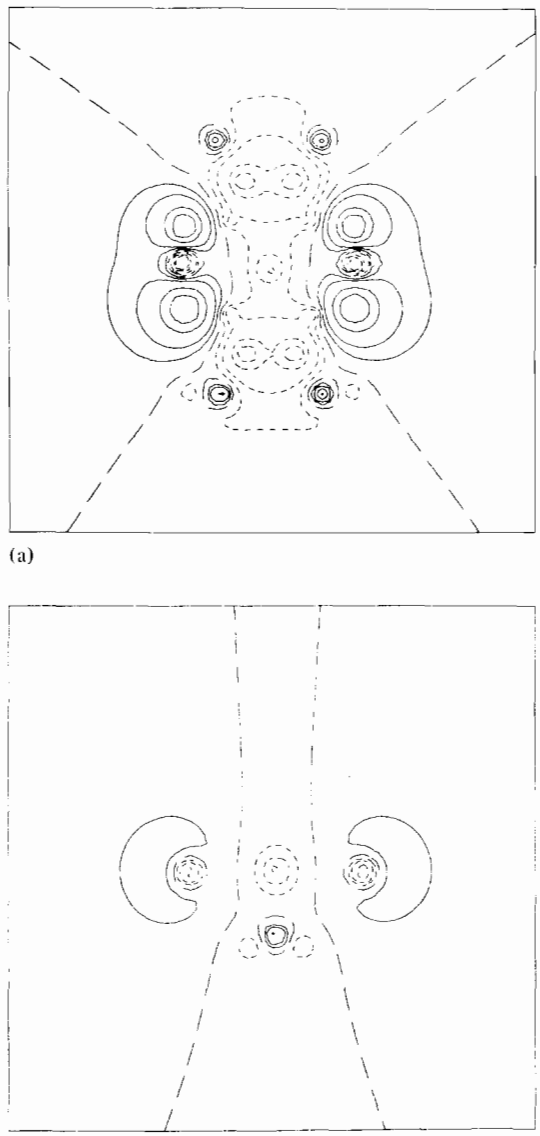
These results indicate that nucleophilic reagents are expected to attack, whether in orbital-controlled or in charge-controlled reactions, exclusively at the nitrosyl nitrogen, as observed [19–22].

In hexacyanoferrate(II), of $Q_h$ symmetry, the HOMO at −12.83 eV is calculated to comprise the $d_{xy}$, $d_{yz}$, and $d_{zx}$ orbitals, of symmetry class $T_{2g}$. Next below these lie the $T_{1u}$, $E_g$, and $A_{1g}$ combinations of the $\sigma$(FeCN) orbitals, at −13.04 eV, −13.91 eV, and −14.12 eV respectively. Immediately above the large HOMO–LUMO gap are the four sets of $\pi^*$(CN) orbitals, respectively of symmetry classes $T_{2u}$, $T_{1u}$, $T_{2g}$, and $T_{1g}$, at −8.32, −8.16, −7.89 and −7.54 eV. The nitrogen atoms bear a charge of −1.15e, and the carbons +0.44e.

In Fig. 1 we present sectional plots of the electrostatic potentials around these two anions, $[Fe(CN)_5NO]^{2-}$ and $[Fe(CN)_6]^{4-}$. In Fig. 1a, the plot represents a section in one of the $\sigma_v$ planes, to include the axial nitrosyl, the axial cyanide, and two of the equatorial cyanides. Figure 1b represents an alternative section through the equatorial plane. Figure 1c represents a section in one of the $\sigma_h$ planes of $[Fe(CN)_6]^{4-}$, to include iron and four coplanar ligands. The dominant feature in Fig. 1a is the very electrophilic reactive site at the nitrosyl ligand, whereas the potential sections shown in Figs. 1b and 1c are comparatively featureless. It should be noted that different contours have been chosen for Figs. 1b and 1c such that the second contour in $[Fe(CN)_6]^{4-}$ corresponds in electrostatic potential to the first contour in $[Fe(CN)_5NO]^{2-}$: this difference in scaling is due primarily to the difference in overall charge between the two anions. In every section, the nucleophilic sites of reaction are seen to be the peripheral nitrogens of the cyanide ligands.

*Aquomethylcobaloxime and Methylcobaloxime*

For $CH_3Co(dmg)_2H_2O$ (dmg ≡ monoanion of dimethylglyoxime (butane-2,3-dionedioxime)), atomic coordinates were taken from the X-ray analysis [17]: identical coordinates were used throughout for the $CH_3Co(dmg)_2$ portion, regardless of the axial ligand. In $CH_3Co(dmg)_2$, containing a five coordinate cobalt(III) in an approximately square-pyramidal environment, the LUMO may be described approximately as cobalt $3d_{z^2}$, with some admixture of $4p_z$, to provide an axial orbital directed towards the vacant site. The first two occupied orbitals, at −12.26 eV and −12.68 eV are $d_{zx}$ and $d_{yz}$ respectively (the molecule is oriented so that the $Co(dmg)_2$ fragment lies in the $xy$ plane such that the $y$ axis bisects the central C–C bond of each dmg ligand). The only important interaction between $CH_3Co(dmg)_2$ and a water molecule involves a p orbital on the oxygen of water and cobalt $3d_{z^2}$. In Fig. 2, we present two sections of the electrostatic potential around $CH_3Co(dmg)_2$, taken in the $xy$ and $zx$ planes.



(a)

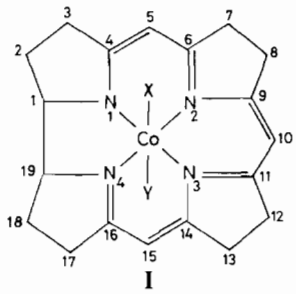
(b)

Fig. 2. (a) Electrostatic potential of $CH_3Co(dmg)_2$ in the $xy$ plane. (b) Electrostatic potential of $CH_3Co(dmg)_2$ in the $zx$ plane. Successive contours represent −1.0, −0.5, −0.2, −0.1, 0.0, +0.1, +0.2, +0.5, and +1.0 a.u. (hatching as in Fig. 1).

The *xy* section, as well as showing clearly the asymmetric O–H···O bonds [17], indicates a large positive region, attractive to incoming nucleophiles, centred on the cobalt, but extending across the dmg ligands: the *zx* section, however, as well as showing the methyl ligand directly bound to cobalt, indicates the rather narrow potential channel down which an incoming nucleophile is expected to approach the coordinatively unsaturated electrophilic centre at cobalt.

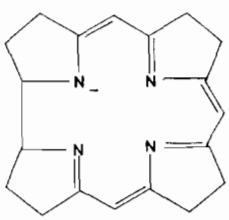
*Cobalt Corrin Models*

For the sake of computational economy, the corrinoid structure of vitamin $B_{12}$ [16, 23] was substantially simplified in the present work. While the macrocyclic skeleton was retained, in the proper oxidation level, so that the $B_{12}$ chromophore is unchanged, all substituents on the macrocycle were replaced by hydrogen: of the two axial ligands, one is to be reserved for either cyanide or a cyanoferrate, while a range of different substituens were investigated at the second axial site. The system thus investigated is shown at **I**

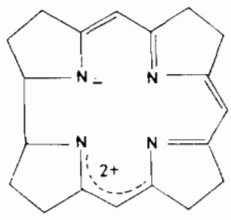



**I**

First a series of derivatives was investigated having no substituent X, where Y was a series of simple ligands. When Y was a good $\sigma$ donor, the cobalt was calculated to be $d^6$ Co(III); the LUMO in these complexes was the $d_{z^2}$ orbital and the HOMO a delocalised $\pi$ orbital concentrated substantially in the $C_{14}$–$C_{15}$–$C_{16}$–$N_4$–$C_{19}$ fragment, and bonding between $C_{14}$ and $C_{15}$ and between $C_{16}$ and $N_4$, but otherwise antibonding. However when Y was a poor $\sigma$ donor/good $\pi$ donor, or was absent entirely, the $d_{z^2}$ orbital was at a lower energy than the delocalised $\pi$ orbital, so that the $\pi$ was then the LUMO and $d_{z^2}$ the HOMO, corresponding to a $d^8$ Co(I) system in which the macrocyclic ligand had undergone a two-electron oxidation, from **II** to **III**.




**II**




**III**

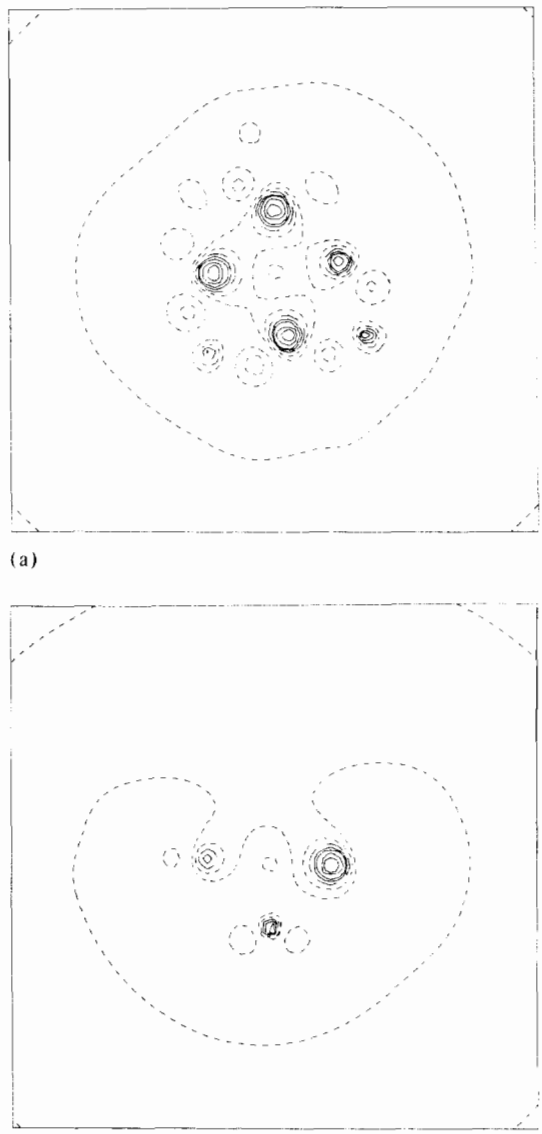



Fig. 3. (a) Electrostatic potential of (I, Y = $NH_3$) in $CoN_4$ plane. (b) Electrostatic potential of (I, Y = $NH_3$) perpendicular to $CoN_4$ plane. Contours and hatching as in Fig. 2.

The system was calculated to be Co(I) when Y was absent, or was $H_2O$ or $NH_2^-$; but to be Co(III) when Y was $NH_3$, $CH_3^-$, or $CN^-$. Hence, there is a requirement for a good $\sigma$ donor as one of the axial ligands in order to preserve the oxidation state of cobalt as Co(III): without such a $\sigma$ donor, an internal redox reaction between Co(III) and the $\pi$ electron-rich macrocycle is likely to occur. In the $d^6$ examples, the net charge on cobalt is always positive, ranging from +0.03e when $Y = CH_3^-$ to +0.36 e when $Y = CN^-$: in the $d^8$ cases, this charge is always negative, ranging from –0.43 e when $Y = NH_2^-$ to –0.66 e when $Y = H_2O$.

It is of some interest that the $\sigma$-donor order deduced from the ligands Y studied here is $H_2O < NH_2^- < NH_3 < CH_3^- \sim CN^-$: *i.e.* the cyano ligand, commonly thought of as a powerful $\pi$-acceptor, is here acting primarily as a powerful $\sigma$-donor. A recent *ab initio* study of $[Co(CN)_6]^{3-}$ and $[Co(CN)_5OH]^{3-}$ concluded [24] that the principal difference between $CN^-$ and $OH^-$ acting as ligands towards Co(III) arose from their $\sigma$-donor capacity rather than from their $\pi$-donor/acceptor properties.

In Fig. 3, we show sections of the electrostatic potential for the cobalt corrin model having Y = $NH_3$, taken in Fig. 3a through the best plane through the cobalt atom and the four nitrogen atoms and perpendicular to this in Fig. 3b: the irregular contours in Fig. 3a are partly a reflection of the deviations of the macrocycle from planarity [16], as the peripheral carbon and hydrogen atoms exhibit differing deviations from the plane chosen for the section. The electrostatic potential in the $CoN_4$ plane, in contrast to that of the cobaloxime $CH_3$-$Co(dmg)_2$, is dominated by the uniformly positive residual charges on the peripheral atoms of the macrocycle. Figure 3b shows clearly the electrophilic site. Whereas $CH_3Co(dmg)_2$ (Fig. 2) exhibits substantial negative regions around the oxygen atoms, the only negative regions in Fig. 3 are those in the immediate vicinity of the ligating nitrogens, and the quasi-aromatic type carbons, C5, C10, and C15: on the other hand, in $CH_3Co(dmg)_2$ the nitrogen atoms all bear a net positive residual charge, consequent upon their being bound to oxygen.

*The Methylcobaloxime–Nitroprusside Complex*

When making calculations on the interaction between methylcobaloxime and nitroprusside it was assumed that the structure of the methylcobaloxime fragment was unchanged from that in the aquo complex [17], and that the bond lengths in the nitroprusside fragment were unchanged from the free ion values [15], although with all interbond angles around iron set at 90°. Further the Fe–X–Y–Co bridge was assumed to be linear: the modest deviations from linearity of the Co–C–N–Co bridges in the isomeric compounds $(NH_3)_5CoNCCo(CN)_5$ [25] and $(NH_3)_5CoCNCo(CN)_5$ [26] were regarded [25, 26] as the result of forces exterior to the bridges, rather than as resulting fron ay factor intrinsic to the bridges.

Subject to these assumptions, three isomeric forms were investigated, having the nitroprusside bound to cobalt via axial cyanide, equatorial cyanide, and nitrosyl ligands respectively. All three isomers showed clear energy minima as the distance Y–Co was varied. For the axial and equatorial cyano ligands binding to cobalt, the N–Co distances corresponding to the energy minima were 1.80 Å and 1.82 Å respectively, while for the nitrosyl ligand binding to cobalt, the O–Co distance for minimum energy was 1.65 Å.

The energy differences between the isomers, taking the axial cyano isomer as zero, are for the equatorial cyano isomer, +1.9 kJ $mol^{-1}$, and for the nitrosyl isomer, +22.2 kJ $mol^{-1}$; so that the preference found experimentally [10] for axial binding in a complex of 1:1 stoichiometry is only very slight. Comparison of the energy, at the minimum, for the axial cyano isomer of the 1:1 complex with the energies of its two components, methylcobaloxime and nitroprusside, shows that the interaction energy, equivalent to the axial N–Co bond energy term, is 235 kJ $mol^{-1}$. It must be noted however that this value refers to isolated species, and does not take any account of solvation effects. On the other hand, it is probable that the relative energies calculated for the isomeric forms are reasonably accurate, since solvation effects are expected to be similar for all three isomers.

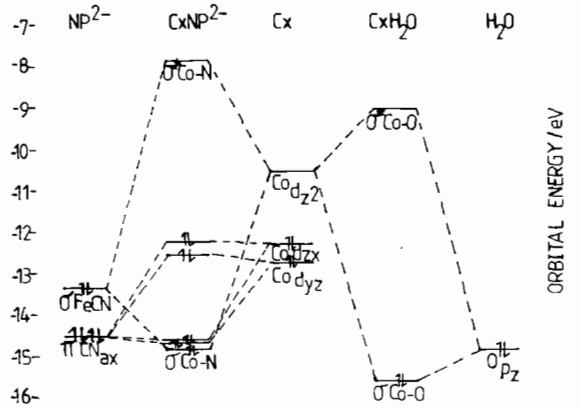



Fig. 4. Important orbital interactions between $CH_3Co(dmg)_2$ (Cx) and $[Fe(CN)_5]^{2-}$($NP^{2-}$) or $H_2O$.

The principal orbital interactions within the 1:1 complex of methyl–cobaloxime and nitroprusside are summarised in Fig. 4 for the axial isomer. there is a very strong $\sigma$ interaction between the axial $\sigma$-(FeCN) orbital in $[Fe(CN)_5NO]^{2-}$ (which approximates to a nitrogen lone pair) and the cobalt $d_{z^2}$ orbital, together with a very small $\pi$ interaction involving the axial $\pi$(CN) orbitals of nitroprusside and the cobalt $d_{yz}$ and $d_{zx}$ orbitals, all of which are occupied. Neither in this complex nor in the very simple model *trans*-$[(ON)Fe^{II}H_4CNCo^{III}H_5]^{4-}$ is there any interaction between the occupied cobalt $d_{yz}$ and $d_{zx}$, and the unoccupied $\pi^*$(CN) orbitals of the axial cyano ligand. Such $\pi$ back-bonding from the electrophile to the ligand $\pi^*$ orbitals is not necessary for the stabilisation of cyano-bridged complexes of type M–C–N–E (where E represents an electrophile), since cyanoferrates readily bind through nitrogen to simple electrophiles including

$BF_3$ [27–29] and $H^+$ [29, 30]. Structural evidence in the two linkage isomers of $(NH_3)_5Co(CN)Co(CN)_5$ [25, 26] indicates that even when the appropriate orbitals are present, the $\pi$ back-bonding interaction appears to be negligible in the Co–NC bond, as calculated here, although significant in the Co–CN bonds.

*The Methylcobaloxime–Hexacyanoferrate(II) Complex*

This 1:1 complex is very similar to cyanide bound isomers of the nitroprusside complex with methylcobaloxime. The minimum energy occurs at a N–Co distance of 1.83 Å, where the interaction energy (N–Co bond energy) is 174 kJ $mol^{-1}$, less by some 60 kJ $mol^{-1}$ than the interaction energy in the nitroprusside complex. Further comparison may be made by inspecting the corresponding axial N–Co overlap populations. In the hexacyanoferrate-(II) complex, this is 0.297, compared with 0.309 for the nitroprusside complex (axial isomer): for binding of nitroprusside via the nitrosyl ligand, the corresponding O–Co overlap population is only 0.257. Thus the calculations point to rather weaker binding of hexacyanoferrate(II) compared with nitroprusside, entirely consistent with the experimental observations [10].

*The Cobalt Corrin–Nitroprusside Complex*

The interaction between the cobalt corrin model **I** ($Y = NH_3$) and nitroprusside was studied as a function of the axial N–Co distance, subject to essentially the same constraints as employed in the methylcobaloxime system. For the sake of computational economy, only the axial isomer of nitroprusside was studied. The energy minimum for the 1:1 complex was located at a Co–N distance of 1.75 Å rather shorter than in the cobaloxime, corresponding to an interaction energy of 288 kJ $mol^{-1}$, substantially higher than for the cobaloxime: the orbital interactions involved are very similar to those in the simpler cobaloxime model, but the key N–Co overlap population is 0.347 in the corrin system, compared with only 0.309 in the cobaloxime. Thus, upon all three criteria of bond length, bond strength, and orbital overlap, the interaction of nitroprusside is calculated to be much stronger with the cobalt corrin (**I**, $Y = NH_3$) than with a cobaloxime.

## Discussion

For the binding both of $[Fe(CN)_5NO]^{2-}$ and of $[Fe(CN)_6]^{4-}$ to methylcobaloxime, the Co–NC distances corresponding to the energy minima are significantly longer than the isomeric M–CN distances: this, and the absence of any $\pi$-bonding between cobalt and the bridging cyano ligand, are in agreement with experimental results [25, 26] on the isomeric $\mu$-cyano complexes $(NH_3)_5Co(CN)Co(CN)_5$.

The results for the axially and equatorially bound complexes of $[Fe(CN)_5NO]^{2-}$ with methylcobaloxime indicate only a small energetic advantage for the axial isomer, but a significant disadvantage for the nitrosyl bound isomer. In 2:1 complexes [10], both steric and electrostatic considerations require the two cobalts to be bound to a pair of *trans* ligands in a cyanoferrate. The additional binding energy resulting from complexation of the cyanoferrate to a second cobalt species overcomes the small preference for axial binding, and thus the 2:1 complexes of nitroprusside involve [10] a *trans* pair of equatorial cyanide ligands.

Although in complexes of $[Fe(CN)_5NO]^{2-}$ there is preference, albeit small, for binding at the axial cyanide, in the $[Fe(CN)_6]^{4-}$ complexes all the ligand sites yield complexes of identical energy. Consequently, there is in these complexes no thermodynamic impediment to migration of the cobalt species from one cyano ligand to another. Such fluxional behaviour in the case of $[Fe(CN)_6]^{4-}$ could explain why the $^{13}C$ NMR observed [10] in the $[Fe(CN)_6]^{4-}$ cobalamin system contain broad unresolved resonances from which no coupling data could be derived, whereas in the analogous $[Fe(CN)_5NO]^{2-}$ system, very sharp, well-resolved first-order spectra were always obtained [10].

The interaction of $[Fe(CN)_5NO]^{2-}$ was calculated to be much stronger with the cobalt corrin (**I**, $Y = NH_3$) than with $CH_3Co(dmg)_2$: this reproduces the experimental findings [10] that nitroprusside forms far stabler complexes with cobalamin than with $CH_3Co(dmg)_2$. Although all these cobalt species contain Co(III), in $CH_3Co(dmg)_2$ the cobalt is bound to two uninegative $(dmg)^-$ ligands and to a negative $(CH_3)^-$ axial ligand: in both aquocobalamin and (**I**, $Y = NH_3$) the axial ligand is neutral (either a benzimidazole or $NH_3$ respectively) and the macrocyclic ligand is only uninegative. Hence, on these grounds alone, the cobalt in $CH_3Co(dmg)_2$ is expected to be rather less electrophilic than that in **I** or in a natural cobalamin. Nonetheless, the binding of $[Fe(CN)_5NO]^{2-}$ to $CH_3Co(dmg)_2$ demonstrates that such complex formation is not a unique property of cobalamins.

The known chemistry of the $[Fe(CN)_5NO]^{2-}$ anion [19–22, 31–35] points to the nitrosyl ligand as being the crucial site in the physiological activity [1–4] of nitroprusside. If this is indeed so, then the formation of 1:1 complexes with cobalamins will not impair the accessibility to the nitrosyl ligand of external nucleophiles, such as those in potential receptors: on the other hand, in 2:1 complexes with cobalamins, the nitrosyl

ligand is effectively masked by the corrin macrocycles. If however, the nitroprusside anion requires access from the bloodstream (the normal site for infusion) to its receptor via a specific ion channel through a membrane (e.g. the chloride channel) then even 1:1 complex formation will hamper such access.

## Acknowledgements

We thank the National Foundation for Cancer Research (U.S.A.) and the Rollo Trust (U.K.) for financial support.

## References

1 T. H. Taylor, M. Styles and A. J. Lamming, *Br. J. Anaesth., 42,* 859 (1970).
2 D. J. Ahearn and C. E. Grim, *Arch. Intern. Med., 133,* 187 (1974).
3 K. Chatterjee, H. J. C. Swan, V. S. Kaushik, G. Jobin, P. Magnusson and J. S. Forrester, *Circulation, 53,* 797 (1976).
4 J. H. Tinker and J. D. Michenfelder, *Anesthesiology, 45,* 340 (1976).
5 (a) A. J. Merrifield and M. D. Blundell, *Br. J. Anaesth., 46,* 324 (1974); (b) R. P. Smith and H. Kruszyna, *J. Pharmacol. Exp. Ther., 191,* 557 (1974); (c) S. Nakamura, T. Shin, Y. Hirokata and A. Shigematsu, *Br. J. Anaesth., 49,* 1239 (1977).
6 M. A. Posner, R. E. Tobey and H. McElroy, *Anesthesiology, 44,* 157 (1976).
7 J. E. Cottrell, P. Casthely, J. D. Brodie, K. Patel, A. Klein and H. Turndorf, *N. Engl. J. Med., 298,* 809 (1978).
8 W. W. Reenstra and W. P. Jencks, *J. Am. Chem. Soc., 101,* 5780 (1979).
9 D. Hewick, A. R. Butler, C. Glidewell and A. S. McIntosh, *J. Pharm. Pharmacol.,* in press.
10 A. R. Butler, C. Glidewell, A. S. McIntosh, D. Reed and I. H. Sadler, *Inorg. Chem., 25,* 970 (1986).
11 D. Lexa, J. M. Savéant and J. Zickler, *J. Am. Chem. Soc., 102,* 2654 (1980).
12 R. Hoffmann, *J. Chem. Phys., 39,* 1397 (1963).
13 J. Howell, A. Rossi, D. Wallace, K. Haraki and R. Hoffmann, *QCPE, 12,* 344 (1980).
14 (a) P. Kubáček, R. Hoffmann and Z. Havlas, *Organometallics, 1,* 180 (1982); (b) T. A. Albright, R. Hoffmann, J. C. Thibeault and D. L. Thorn, *J. Am. Chem. Soc., 101,* 3801 (1979); (c) T. Hughbanks and R. Hoffmann, *J. Am. Chem. Soc., 105,* 3528 (1983); (d) K. I. Goldberg, D. M. Hoffman and R. Hoffmann, *Inorg. Chem., 21,* 3863 (1982); (e) S. D. Wijeyesekera and R. Hoffmann, *Inorg. Chem., 22,* 3287 (1983).
15 P. T. Manoharan and W. C. Hamilton, *Inorg. Chem., 2,* 1043 (1963).
16 P. G. Lenhert, *Proc. Roy. Soc., A303,* 45 (1968).
17 D. L. McFadden and A. T. McPhail, *J. Chem. Soc., Dalton Trans.,* 363 (1974).
18 A. F. Cuthbertson, unpublished work.
19 J. H. Swinehart, *Coord. Chem. Rev., 2,* 385 (1967).
20 J. A. McCleverty, *Chem. Rev., 79,* 53 (1979).
21 A. R. Butler, C. Glidewell, J. Reglinski and A. Waddon, *J. Chem. Res. (S) 279,* (M) 2768 (1984).
22 A. R. Butler, C. Glidewell, V. Chaipanich and J. McGinnis, *J. Chem. Soc., Perkin, 2,* 7 (1986).
23 P. G. Lenhert and D. C. Hodgkin, *Nature, 192,* 937 (1961).
24 L. G. Vanquickenborne, M. Hendrickx, I. Hyla-Kryspin and L. Haspeslagh, *Inorg. Chem., 25,* 885 (1986).
25 B.-C. Wang, W. P. Schaefer and R. E. Marsh, *Inorg. Chem., 10,* 1492 (1971).
26 F. R. Fronczek and W. P. Schaefer, *Inorg. Chem., 13,* 727 (1974).
27 D. F. Shriver, *J. Am. Chem. Soc., 85,* 1405 (1963).
28 D. F. Shriver and J. Posner, *J. Am. Chem. Soc., 88,* 1672 (1966).
29 D. Hall, J. H. Slater, B. W. Fitzsimmons and K. Wade, *J. Chem. Soc. A,* 800 (1971).
30 R. J. Gillespie and R. Hulme, *J. Chem. Soc., Dalton Trans.,* 1261 (1973).
31 S. K. Wolfe and J. H. Swinehart, *Inorg. Chem., 14,* 1049 (1975).
32 W. I. K. Bisset, M. G. Burdon, A. R. Butler, C. Glidewell and J. Reglinski, *J. Chem. Res.,* (S) 299, (M) 3501 (1981).
33 P. J. Morando, E. B. Borghi, L. M. de Schteinhart and M. A. Blesa, *J. Chem. Soc., Dalton Trans.,* 435 (1981).
34 W. P. Arnold, D. E. Longnecker and R. M. Epstein, *Anesthesiology, 61,* 254 (1984).
35 K. Antal, I. Bányai and M. T. Beck, *J. Chem. Soc., Dalton Trans.,* 1191 (1985).