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Vitamin B_{12} Coenzyme Models: Perspectives on Recent Developments in the Chemistry of the Cobaloximes and Related Models

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Vitamin B_{12} Coenzyme Models : Perspectives on Recent Developments in The Chemistry of the Cobaloximes and Related Models

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Discoveries on B_{12} models made since 1989 are assessed in the light of the advances in structural and spectroscopic methodologies. Further studies emanating in part from these advances have confirmed, often definitively, previously identified principles describing the properties of the classic simple models (cobaloximes and iminocobaloximes) and have established some new principles defining the properties of the axial Co-C and Co-N bonds; the latter are clearly relevant to enzymatic processes. Some new simple models have been proposed and studied in relation to the classic ones and to the more complicated natural cobalamins. In several cases, the influence of the steric and electronic factors have been established, sometimes in semi-quantitative terms, also with the help of studies on the rhodium analogues of cobaloximes. New spectroscopic techniques have been introduced, which have been found useful in the study of the natural cobalamins. Recent structural analyses of the binding site in some B_{12}-based enzymes have shown that the B_{12} cofactors bind in the base-off form, with displacement of the benzimidazole residue from cobalt and coordination of a histidine residue of the protein chain. Such observations have stimulated new experiments aimed at defining the mechanism of the Co-C homolytic cleavage in isomerases and mutases or at testing the recently proposed mechanism for the Co-C heterolytic cleavage in methionine synthase. As a consequence, the information now available on models and on cobalamins (e.g., on the nature of the Co-S bond) is much

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broader in scope, and these advances have prompted this new analysis of models. The experimental aspects have advanced much more quickly than our theoretical understanding, and hence further calculations, possibly based on more sophisticated approaches, are clearly required.

Keywords: *vitamin B_{12}; B_{12} coenzymes; B_{12} models; Co-C homolysis; Co-C heterolysis; electronic factors; steric factors; structure property relationship; rhodoximes*

1. INTRODUCTION

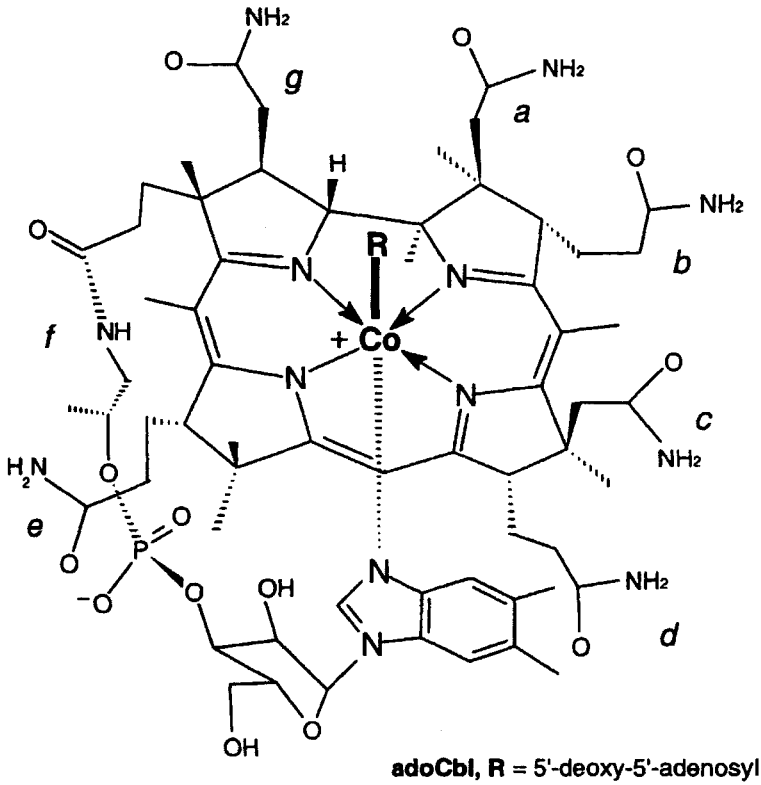
The aim of the present review is to cover the gap since the chemistry of simple B_{12} models was last assessed in depth in 1989. The last ten years have seen numerous developments in the model chemistry stimulated by the recent structural analyses of a few B_{12}-based enzymes. This article will outline some new lines of research with model compounds.

2. THE VITAMIN B_{12} ENZYMES

The B_{12}-based enzymes are the only ones thus far known whose cofactors contain a metal-carbon bond. These coenzymes belong to the corrinoid cobalt series of complexes, the so-called vitamin B_{12} family. Their often unique properties arise from the special interactions between the bound metal and the macrocyclic ligands. An important point to be stressed is that their basic reactivity and functions are not greatly altered in the protein-bound state, but merely modulated to operate optimally under physiological conditions. For this reason, simple models have been proposed and, in some respect, have been found useful in understanding[1] some basic features of the more complex bio-systems, thereby providing clues into the elusive mechanisms of B_{12} dependent enzymatic processes.[2] An understanding of the properties of corrinoid complexes might not only be beneficial for elucidating these natural processes, but this knowledge could also be profitably exploited in the other fields of chemistry, in medicine, and in environmental protection.[2]

The known B_{12} cofactors are alkylcobalamins, (RCbl), consisting of a cobalt corrinoid with a pendant nucleotide (with different purine base), which occupies five coordination sites of an octahedral Co(III), the sixth position being occupied by the R group or by a CN ligand in the cyanocobalamin, vitamin B_{12} itself (Scheme 1).[3] The latter is not a biologically

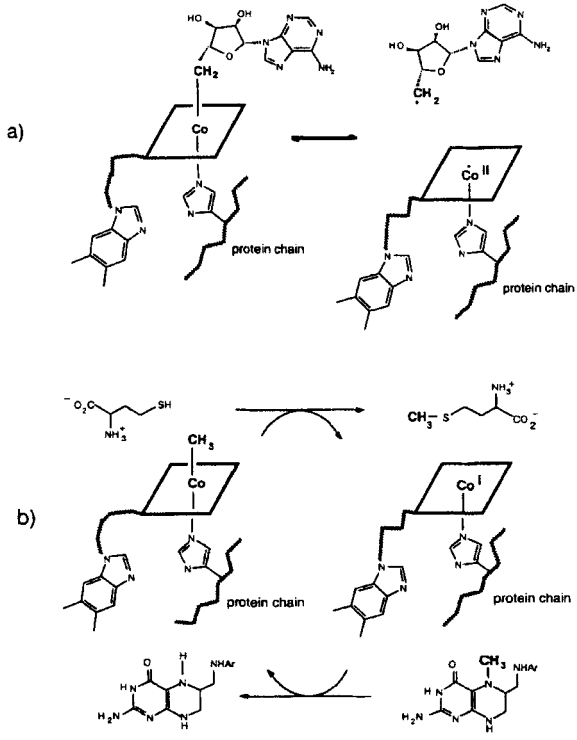
active species, whereas the two cofactors have R = methyl (methylcobalamin, MeCbl) and 5′-deoxy-5′-adenosyl (B_{12} coenzyme, adoCbl), respectively. From the chemical point of view, alkylcobalamins are stable, acid resistant, but thermo- and photo-labile organocobalt complexes.[4]



SCHEME 1

All of the currently known reactions of B_{12}-dependent enzymes involve the making and breaking of the Co-C bond.[5] adoCbl is the cofactor in isomerase and mutase enzymes, which catalyze the intramolecular 1,2-shift of a hydrogen and an electronegative X group. An example is methylmalonyl-coenzymeA mutase, which isomerizes

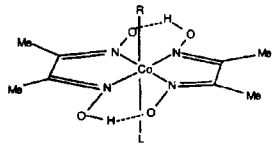
reversibly the methylmalonyl group to the succinyl group.[6] The rearrangement proceeds through a stepwise process initiated by the key homolysis step of the Co-C bond (Scheme 2a), with formation of two radicals, cob(II)alamin (B_{12r}) and adenosyl. The former is a relatively long-lived species, while the latter rapidly abstracts an H atom from the substrate. The Co-C cleavage is believed to be the only step in which the metal center is involved, apart from the recombination of the Co-C bond at the end of the catalytic cycle.[5] adoCbl has also been found to be the cofactor of the ribonucleotide reductase, which catalyzes the conversion of nucleoside di- and tri-phosphates to deoxy analogues in some bacteria. A mechanism different from that operating in mutases and isomerases has been proposed, which involves the generation of an aminoacid thiyl radical, but initiated by the homolysis of the Co-ado bond, as above.[7]



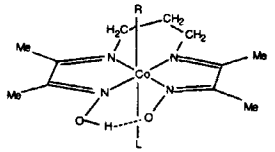
SCHEME 2

The MeCbl-based enzymes (methyltransferases) catalyze the transfer of methyl groups from an N or O atom to cob(I)alamin (to form MeCbl) for onward transmission to an S atom, as in methionine synthase. The overall mechanistic scheme requires a reversible heterolytic cleavage of the Co-Me bond (Scheme 2b) in the methyl carbocation and the strongly nucleophilic cob(I)alamin species.[8] MeCbl also plays a metabolic role in the organometallic pathway of carbon dioxide fixation in several anaerobic aceto-bacteria, as well as in the reverse pathway, which results in formation of methane from acetic acid.[9]

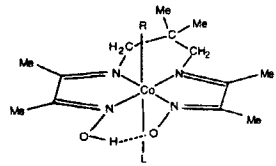
Before 1994, due to the lack of structural information on coenzyme-enzyme binding, most hypotheses concerning such enzymatic mechanisms, particularly for hydrolysis, were based essentially on a wide-ranging and in-depth study on the simple models, LCo(chel)R (L is a neutral base and R an alkyl group, axially coordinated and chel the equatorial ligand)[1] (Scheme 3) and on cobalamins.[1, 10, 11]



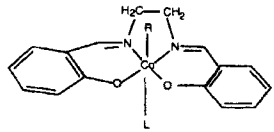
$LCo(DH)_2R$



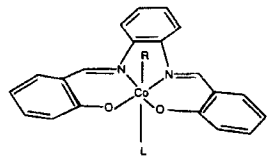
$[LCo((DO)(DOH)pn)R]^+$



$[LCo((DO)(DOH)Me_2pn)R]^+$



LCo (salen) R



LCo (saloph) R

SCHEME 3

Since the pioneering work of D. Hodgkin on cyanocobalamin, crystal structures of cobalamins, in contrast with those of the simple models, were not accurate enough for even a basic discussion,[12] and only recently have a few structures of cobalamins been reported with an accuracy similar to that of high resolution small molecules.[13] Structural investigations were also complicated by some EXAFS measurements in solution,[14] whose results contrasted, in some instances, with the crystallographic and thermodynamic[1c] ones. However, accurate crystallographic data available, on cobalamins suggest[13b] that the structural effects of changes in R are similar to those found in cobaloximes and, sometimes, can be related to their chemical behavior. Therefore, model studies have furnished some insight into the factors affecting the homolysis and have allowed in-depth analysis of the variations in geometry of the R-Co-L fragment[1] (in terms of the electronic and steric properties of the R and L groups), as well as rationalization of the relationships between solution behavior and structure.[15] On the basis of these observations, some mechanisms (unfortunately none conclusive) for homolytic cleavage in adoCbl have been proposed.[4,16] More importantly, model studies have suggested that the ligand *trans* to adenosyl in cobalamins should play a crucial role in the enormous enhancement (about 12 orders of magnitude) of the homolysis rate in the enzyme with respect to the free coenzyme.[5] The recent X-ray crystal structure of adoCbl-dependent methylmalonyl-CoA mutase[17] and ESR spectroscopy measurements[18]have launched a new era in coenzyme B_{12} bioinorganic chemistry. Specifically, the structure of the enzyme indicates that the *Co is not bound to the appended 5,6-dimethylbenzimidazole nucleotide, but is instead coordinated to a histidine residue of the protein chain.* However, the adenosyl residue was not found in the structurally characterized enzyme, suggesting that the metal is essentially present as pentacoordinated Co(II). This histidine coordination to Co was also found in the structure of the MeCbl bound domain of the methionine synthase.[19] However, recent results strongly suggest that the benzimidazole residue is still coordinated to Co in dioldehydrase.[20] The involvement of not only the axial Co-C bond properties, but also those of the axial Co-N bond in the enormous enhancement of the rate homolysis was suggested by studies on simple models.[16]

Much less attention has been devoted to the heterolytic Co-C cleavage and to the transfer of a methyl group to thiolates,[9] but some studies on simple models[21] and isolated cobalamins[22] have recently appeared. In

fact, the chemistry which underlies the mechanism of the *multipurpose* enzyme methionine synthase is very exciting, requiring cobalt to assume different oxidation states (from +1 to +3) and different coordination numbers.[23] The methionine synthase mechanism, which involves transfer of the methyl carbocation from MeCbl to a thiolate, and the proposed mechanisms for ribonucleotide reductase[7] have prompted preliminary studies on the Co-S bond.[22] Furthermore, recent results on the reaction of cyanide with MeCbl suggest the existence of weak bonding interactions between corrinoids and charged species which influence the alkylcorrinoid behavior.[24] However, at the present time it is not clear how the cobalamin molecule is involved in such interactions.

Therefore, some problems related to the enzymic action of the B_{12} system remain. The above hypothesis emerged from previous work, concerning the Co-C homolytic cleavage, requires verification, in view of the indications furnished by the more recent work on the B_{12}-dependent enzymes.[17–19] Thus, explanations are needed to rationalize why adoCbl enzymes operate through a homolytic process, whereas the MeCbl enzymes operate through a heterolytic mechanism.

3. COBALOXIMES, IMINOCOBALOXIMES (COSTA MODEL) AND COBALIMINES (SCHIFF BASES)

Previous studies on cobaloximes and iminocobaloximes (Costa models), which provided a considerable amount of structural, spectroscopic, thermodynamic, and kinetic data for a wide variety of R and L ligands, have been reviewed,[1] together with the relatively fewer investigations of cobalimines (Schiff base complexes).[1c] At that time, the trends in these properties as a function of the steric and electronic properties of the axial ligands R and L were qualitatively interpreted.[15] The weakening of the Co-C bond (steric *cis* influence), as measured by a lengthening of up to 0.2 Å going from Me to adamantyl, and by a decrease in bond dissociation energies of up to about 50 kJ/mol, on going from Me to CH(Me)Ph, was essentially related to the increase in bulk of R, which sterically interacts with the DH ligands. The weakening of the L bonding to Co (electronic *trans* effect and influence) has been attributed to the R electron-donating ability, but also to the bulk of R, which through a bending of the $(DH)_2$ moiety towards L, lengthens the Co-L bond (steric *trans* influence). When R varied from electron-withdrawing lig-

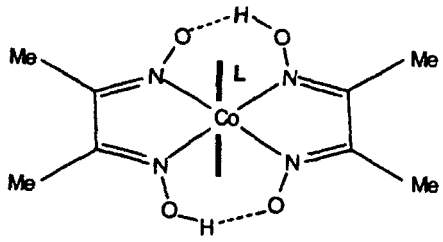
ands, such as CH(CN)Cl, to electron-donating ones, such as i-Pr,[1] bond lengthening up to about 0.2 Å and an increase of several orders of magnitude in the log *k* for the L displacement were found. Analogously, an increase in the bulk of L determines the lengthening of the Co-L bond (steric *cis* influence) and the observed increase of two orders of magnitude of the log *k* (steric *cis* effect). Available data at that time gave rise to the suspicion that the Co-R bond, especially with bulky R ligands, can be lengthened by an increase in the bulk of L (steric *trans* influence). On the other hand, the response of the Co-C bond to variations in the electronic properties of the alkyl group was not clear.[1c] A similar situation existed in the case of iminocobaloximes and cobalimines.[1c] Furthermore, the evidence was compelling that many of the chemical properties related to the axial fragment, such as the geometry, the kinetics, and the spectroscopic behavior, are significantly affected by the change in the equatorial ligand (*cis* effect and *cis* influence). Thus, the dissociation rates of (3,5-lutidine)Co(saloph)R were found to be ten orders of magnitude larger than those in the cobaloxime analogues.[1a] In complexes containing planar N-donor ligands, such as py or 1,5,6-trimethylbenzimidazole (Me_3Bzm), the orientation of these ligands was always found to be close to that of type A in cobaloximes and to that of type B in iminocobaloximes (Scheme 4). However, for the less bulky imidazole ligands both orientations were found, but the orientation A corresponded to shorter Co-N axial distances.[1c]

In the intervening period, several additional papers have appeared that have not only furnished further insight into the above features,[25–45] but have also revealed new and interesting features related to the Co-C bond in these systems,[46–53] Finally, after the first attempts,[15] the quantitation of the relationships between structure and property was analyzed more deeply.[54–59] Previous theoretical calculations (limited to analysis of the conformational changes about the Co axial bonds in cobaloximes,[60a–c] or more simple metallorganic complexes[60d] and cobalamin[61]) were extended further.[62]

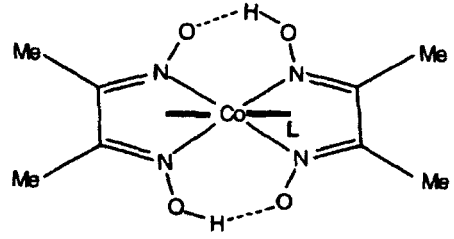
3.1 Cobaloximes and iminocobaloximes

The additional work carried out on simple models after 1989 concerned mainly the synthesis, IR-Raman and NMR spectroscopy, and crystallography of many new cobaloximes and iminocobaloximes with several R

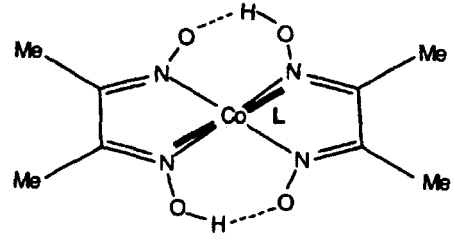
a) orientation A



b) orientation B



c) orientation C



SCHEME 4

and L axial ligands. Recently, molecular mechanics (MM) calculations have also been performed.[43–45] A new synthetic route to organoimine-cobaloximes, which cannot be prepared by the method usually employed for analogous cobaloximes, was described.[41] All the experimental data reported in references 25–59 should be added to those previously reported in Tables 11–14, 19, 20 and 41 of reference la and in Tables 3, 4 and 6 of reference 1c. Relevant results are summarized in the following paragraphs.

3.1.1. On the nature of the R-Co-L axial fragment

The influence of the orientation of planar L ligand with respect to the equatorial moiety on the Co-L distance has been definitely established.[28,41,52] An orientation close to A (Scheme 4a) is typical of cobaloximes with L = py and Me_3Bzm, whereas orientations close to B (Scheme 4b) are found in iminocobaloximes. However, cobaloximes with the less bulky imidazole-type ligands exhibit both orientations. MM calculations[43,45] have suggested that the observed lengthening of the Co-L distance of 0.03–0.04 Å in orientation B is due to steric interaction between the L and equatorial ligands. In particular, it appears that the Co-N axial bond increases with an increase in the strain energy when the torsional angle around this bond, φ, is varied from 0° (orientation A) to 90° (orientation B). When L is varied, the torsional barrier about φ increases in the order imidazole (Im) = 1-methylimidazole (1-MeIm) < py ~ 1,2-dimethylimidazole (1,2-Me_2Im) ~ Me_3Bzm < 6-Cl-purine < 2-NH_2-py (N-endo-coordinated). MM calculations have further suggested a slight lengthening of the *trans* Co-C bond in orientation B when R = ribosyl.[45] This agrees with the observation[41] that, for several R groups, this bond appears to be slightly shorter in cobaloximes (L in orientation close to A) than in iminocobaloximes (L in orientation close to B). More interestingly, methylcobaloximes exhibit $\nu_{Co\text{-}Me}$ stretching frequencies, both in solution and in the solid state, ~6 cm^{-1} higher than those in methyl iminocobaloximes (*vide infra*).[48] This was attributed to the steric effect of L in the latter compounds, which in orientation B bends the equatorial ligand towards Me; this distortion in turn lengthens the Co-Me bond.[48] The φ/Co-L distance correlation is particularly apparent when the $[NO_2Co(DH)_2NO_2]^-$ structure[63] is compared with that of *trans*-dinitro-2,2′-(1,3-diaminopropane)-bis(2-methyl-3-butanone)dioximato,[64] whose equatorial ligand is similar to that of iminocobaloximes. In the latter, the two nitro groups are perpendicular to each other, with Co-NO_2 distances of 1.937(3) Å (φ ~ 0°) and 1.984(3) Å (φ ~ 90°), respectively. In the former the nitro groups are approximately coplanar (φ ~ 0°) with nearly equal Co-NO_2 distances of 1.944(3) and 1.945(3) Å, respectively. It is likely that the steric interaction of the nitro groups with the more crowded equatorial moiety, as compared with that in cobaloxime, should be responsible for such difference.

It is well established[65] that the strength of the Co-C bond in cobaloximes is also influenced by the basicity of the *trans* L ligand. In fact, in

the series (4-X-py)$Co(DH)_2$[Ph(Me)CH], the Co-C bond dissociation energy (BDE) was found to increase linearly with the pKa of the sterically invariant 4-substituted pyridines. The trend was ascribed to the stabilization of the Co-C bond by more basic *trans* ligands (electronic *trans* influence).[65] However, Halpern *et al.*[32] have found that the BDE in the *endo* coordinated 2-NH_2-py analogue is significantly smaller than that expected on the basis of its pKa. This finding was attributed to the steric interaction of the 2-NH_2-py ligand with the equatorial moiety, which lengthens the Co-N bond (steric *trans* influence), so that it becomes a poorer electron donor and, hence, weakens the *trans* Co-C bond.[32] Such an interpretation is based on the abnormally long Co-N(*endo*) bond (2.194(4) Å) in (2-NH_2-py)$Co(DH)_2$(i-Pr),[66] as compared with that of 2.099(2) Å reported for py$Co(DH)_2$(i-Pr).[1a] This finding was suggested to have implications in the mechanism of the Co-C homolysis in the enzyme, since a strained Co-N (axial) bond should favor the homolysis, in addition to the steric lengthening of the Co-C bond in the active site.[16] In fact, the weakening of the Co-C bond, due to the bulk of the R (steric *cis* influence) was well established in simple models by BDE and crystallographic measurements.[1] Furthermore, evidence has already been reported that the bulk of L (steric *trans* influence) could lengthen the Co-C bond.[1] The steric *trans* influence in cobaloximes has been definitely established[34, 37] on the basis of data in Table I, where the Co-C distances, the dihedral angles between the two DH units (α) and the displacement of Co out of the four-N equatorial donor plane (*d*) are given for the two series of L$Co(DH)_2$Me and L$Co(DH)_2$adam, (adam = adamantyl) with several L ligands of different bulk. Analysis of these data has shown that Co-C bond lengths of bulkier alkyl groups are more sensitive to the steric *trans* influence, whereas α and *d* respond essentially to the difference in bulk between the two axial ligands. The data in Table I do make it appear that this is an appropriate model for the "trigger mechanism" proposed for the activation of the Co-C bond toward homolysis in the B_{12} enzymes.[16]

In the previous analysis of all cobaloxime data,[1c] it was hypothesized that the Co-alkyl distance could also be influenced by the σ-donating ability of the alkyl group itself. However, this could not be definitely established as data available at that time referred essentially to bulky groups, and the effect of the steric *cis* influence could have masked electronic influences. Since then a number of papers on fluoroalkylcobaloximes[27, 31, 33, 38] have clearly shown that the strong

electron-withdrawing ability of the R group induces a shortening of the Co-C bond, in spite of the R bulkiness. Data collected in Table II show that, upon "fluorination of the alkyl group", the Co coordination polyhedron becomes compressed along the axial direction ("inverse" *trans* influence[58]). The steric and electronic properties of R exert opposite influences on the Co-C distance, such that they may compensate in the enormously bulky perfluoro-i-propyl (i-FPr) ligand, for which the Co-C distance is nearly the same as that in the i-Pr analogue. However, the α and *d* values (Table II) still reflect the difference in bulk between the axial ligands.[31] Importantly, kinetic measurements of the L displacement in $LCo(DH)_2$(i-FPr) allow for the first time detection of a measurable steric *trans* effect for L ligand substitution in organocobaloximes.[33] It was also found that $^{19}F(CF_3)$ chemical shifts were largely independent of any electronic influence, if steric parameters of L were kept constant, such as in 3- and 4-substituted py or anilines. On the contrary, ^{19}F(Co-CF) chemical shifts show a linear correlation with pK_a's or Hammett constants for sterically similar L ligands.[33] On the other hand, the structural influence of non-bulky, but strongly σ–donating CH_2OMe group, has very recently been analyzed in cobaloximes[43] and iminocobaloximes.[41]A strong *trans* influence, similar to that of i-Pr, has been confirmed. In addition, Co-CH_2OMe distances of up to 2.065(5) Å long were found, which are close and sometimes even longer that those of the ethyl analogues.[1] The trends in the ^{13}C chemical shifts of the benzimidazole nuclei, with varying R, have been reported for both classes of complexes.[39,41,43] These trends have been interpreted in terms of electronic and steric interactions between the axial and equatorial ligands.[41]

A previous NMR study[53a] on cyano cobalt corrins, based on ^{13}C and ^{15}N resonances, was extended to a series of 17 cyanocobaloximes with several *trans* neutral N-donor ligands.[53b] As the *trans* ligand was varied, an inverse dependence of the ^{15}N chemical shift on the ^{13}C shift was observed, and for 14 of the complexes an excellent linear correlation was found. This result in combination with the observation that trends in the individual chemical shifts and in ν_{CN} vary linearly with the basicity of the N-donor ligands, was interpreted to suggest the existence of a significant Co to CN π-bonding according to the following resonance structures:

$$Co - C \equiv N \longleftrightarrow Co^+ = C = N^-$$

TABLE I Co-C distances (Å), α(°) and *d* (Å) values for adamantyl- and methylcobaloximes with different L ligands.[a] The positive sign of α and *d* indicates bending toward R and displacement toward L and *vice versa*

L	*adamantyl*			*methyl*		
	Co-C	α	*d*	*Co-C*	α	*d*
H_2O	2.129(3)	-15.8	–0.093	1.990(5)	–4.6	–0.002
1-Me-Im[b]	2.154(5)	–9.7	–0.057	1.980(4)	+4.1	+0.050
NH_2Ph	2.159(4)	–10.0	–0.065	1.992(2)	+3.8	+0.035
Py[c]	2.160(4)	–10.6	–0.047	1.998(2)	+1.6	+0.054
Me_3Bzm	2.179(6)	–7.5	–0.027	1.989(2)	+3.0	+0.056
$P(i\text{-}PrO)_3$	2.199(6)	–7.3	–0.006			
$P(MeO)_3$	2.214(3)	–7.2	–0.015	2.01(1)	+10.2	+0.093
PPh_2Et[d]	2.217(7)	–3.2	–0.011	2.026(6)	+11.2	+0.111

[a]Ref.37.
[b]Ref. 52 for the methyl derivative. The 1-MeIm ligand has the orientation B (see Scheme 4).
[c]For the adamantyl derivative L= 4-Me_2N-Py.
[d]For the methyl derivative L= PPh_3.

The recent accurate structural re-determination of CN-Cbl, carried out in our laboratory, indicated that the Co-C and the C-N distances are significantly shorter and longer, respectively, than the analogous distances in cyanocobaloximes, suggesting that the π-bonding, if any, could be more enhanced in cobalamins.[13b]

The Co coordination distances in a series of aquaiminocobaloximes, with R = CH_2CF_3, CH_2CO_2Me, Me, CH_2Ph, i-Pr and i-Bu, were determined by the EXAFS technique.[40] The equatorial Co-N distances were found to be similar in all the complexes studied and close to those obtained by X-ray crystallography for R = Me, CH_2Ph, i-Pr.[1c] Unexpectedly, the Co-C distances appeared to increase with the Taft σ^* constant, but not with the bulk of R (Table III), leading to the conclusion that the Co-C distances in aqua derivatives do not depend on the R bulkiness, which is in contrast with previous findings in other B_{12} model series.[1c] Even more unexpectedly, the Co-OH_2 distances *trans* to good electron-donating groups (Me, i-Pr) were found to be shorter than those *trans* to electron-withdrawing groups (CH_2CF_3, CH_2CO_2Me) (Table III). However, the results of the subsequent crystallographic characterization of the CH_2CF_3 and CH_2CO_2Me derivatives[42] contradict these EXAFS-based

trends, indicating that the aqua derivatives behave in the same manner as the analogous alkyliminocobaloxime series with other L ligands and as the alkylcobaloxime series with several L ligands.[1c]

TABLE II Axial distances (Å), α(°) and *d* (Å) values LCo(chel)R with Me, Et and i-Pr and variously fluorinated alkyl groups. The positive sign of α and *d* indicates bending toward R and displacement toward L and *vice versa*. Data are from ref. 38 if not otherwise stated

R/L	*Co-C*	*Co-L*	α	*d*
	chel = $(DH)_2$			
Me/py	1.998(5)	2.068(3)	+1.6	+0.054.
CF_3/py	1.949(4)	2.043(39	−3.0	+0.022
Me/1,2-Me_2Im	1.989(2)	2.060(2)	+4.7	+0.060
CHF_2/1,2-Me_2Im	1.948(5)	2.090(2)	+2.1	+0.033
Et/py	2.035(5)	2.081(3)	+5.8	+0.050
CH_2CF_3/py	2.010(3)	2.041(4)	−1.2	+0.007
CF_2CHF_2/py	1.997(6)	2.036(4)	−9.5	−0.031
i-Pr/py	2.085(3)	2.099(3)	+3.6	+0.022
$CF(CF_3)_2$/py	2.084(5)	2.037(3)	−10.3	−0.076
Et/PPh_3[a]	2.045(5)	2.415(1)	+1.4	+0.060
CH_2CF_3/ PPh_3[a]	2.036(3)	2.383(1)	+1.7	+0.040
	chel = (DO)(DOH)pn			
Et/H_2O	2.020(3)	2.109(2)	−9.3	−0.030
CH_2CF_3/H_2O[b]	1.989(3)	2.062(2)		
Et/NH_2Ph	2.030(4)	2.174(3)	−7.1	+0.006
CH_2CF_3/NH_2Ph	2.009(2)	2.130(2)	−5.6	+0.011
Et/Me_3Bzm	2.039(4)	2.105(3)	+16.7	+0.096
CH_2CF_3/ Me_3Bzm	2.026(4)	2.060(3)	+16.6	+0.060
	chel = saloph[c]			
Et/py	2.042(6)	2.214(4)	−25.4	+0.030
CH_2CF_3/py	1.99(1)	2.126(9)	+17.0	+0.050

a. Data from Ref. 1a.
b. Data from Ref. 42.
c. Ref. 1c.

TABLE III Comparison of Co-C and Co-O axial distances (Å) determined by XRD and EXAFS and relative differences Δ (Å) in $\{RCo[(DO)(DOH)pn](H_2O)\}^+$ Cations. Data are from Ref. 42

	Co-C			*Co-O*		
	XRD	*EXAFS*	Δ	*XRD*	*EXAFS*	Δ
Me	1.977(4)	2.041(7)	–0.064	2.103(3)	2.127	–0.024
CH_2CF_3	1.989(3)	2.067(10)	–0.078	2.062(2)	2.219	–0.157
CH_2CO_2Me	2.015(3)	2.056(9)	–0.041	2.024(2)	2.206	–0.182
Et	2.020(3)			2.109(2)		
CH_2Ph	2.052(2)	2.040(8)	0.012	2.099(1)	2.102	–0.003
i-Pr	2.055(5)	2.021(10)	0.034	2.138(3)	2.160	–0.022
	2.090(3)		0.069	2.128(2)		–0.032

3.1.2. Molecular mechanics calculations

In spite of the abundance of experimental data available for vitamin B_{12} models, only recently have MM calculations been reported.[43–45] As an extension of this approach to a small number of cobalamins,[67,68] Brown *et al.* have derived[44] a force field (FF) for modeling organo- and non-organocobaloximes, based on a set of experimental structures with the R factor < 10%. This FF reproduces the experimental bond lengths and angles of the equatorial moiety with an accuracy better than 0.01 Å and 2°, respectively. However, in the case of the axial ligands the agreement was poorer. The FF was applied to reproduce the geometry of $(H_2O)Co(DH)_2$(n-Pr) and of its inclusion compound with α-cyclodextrin (α–cd).[49] Bond lengths and angles were satisfactorily reproduced, except for the C_α -C_β distance and the Co-C_α-C_β angle of the n-Pr group (*vide infra*). Furthermore, a significant difference between the experimental and calculated structures of the inclusion compound was detected in the position of the cobaloxime moiety with respect to α-cd. Such a discrepancy was attributed to the H-bond interactions between the two moieties of the inclusion compound, which were not taken into account in the FF used.[44] Finally, the FF was also applied to alkylcobalamins, already examined with MM calculations,[69] essentially confirming the conclusions previ-

ously reached. In another study, the FF parameters were derived by optimization of seven cobaloximes and iminocobaloximes with R = Cl, Me, CH_2OMe and L = py and Me_3Bzm.[43] Calculated and experimental bond lengths and angles differed by less than 0.06 Å and 5°, respectively. However, this agreement was reached by the adjustment of some FF parameters, namely an approximately 10% reduction of the Van der Waals parameters for the N donors and C(sp^2) atoms linked to the latter. In order to reproduce the dependence of the geometric features on *trans* influence, different FF parameters for the Co-L bonds were used in the case of weak (Cl) and strong (Me, CH_2OMe) *trans*-influencing ligands.

A new approach[45] to the derivation of a FF for modeling alkylcobaloximes was devised in order to systematically take into account the variations in the geometry of the axial fragment, which, due to the electronic properties of the R group, are considered to be responsible for the significant variations in the Co-L (*trans* influence) and Co-R distances (*cf.* Section 3.1.1). The unstrained bonding constants involving the axial bonds were assumed to be a linear function of the electronic charge of R, calculated by the ZINDO method. The coefficient of the two linear relationships, together with the other FF parameters for the Co coordination, were optimized in order to reproduce the experimental geometry of 52 alkylcobaloximes, with crystallographic R factors of less than 0.08. Introduction of this correction (step 2) improves significantly the agreement between calculated and experimental data with respect to step 1, in which the electronic contribution was not included. The axial distances calculated in the two steps and the experimental values are compared in Table IV for some alkylcobaloximes with L = 1,2-Me_2Im).

In order to check the conformational behavior of the axial ligands, this FF field was also used to calculate plots of strain energy as a function of the torsional angles about the Co-N (φ) and Co-C (ϕ) bonds for $LCo(DH)_2$(ribosyl) derivatives. When L = Me_3Bzm, the plot is characterized by steep, high energy barrier of approximately 10 kcal/mol at $\varphi = 90°$ against a minimum at $\varphi = 0°$, whereas the barrier relative to ϕ is smoother, with a height of ~2 kcal/mol. When L = imidazole, the energies of both these barriers were significantly lower, in spite of the fact that the Co-N distance is shorter than that in Me_3Bzm. Comparison of the calculated geometries of the axial fragment of the molecule at the highest and lowest conformational energies indicates a similar lengthening (~0.02 Å) of the Co-C bond at the highest energy, but a more marked increase of the Co-N distance in the Me_3Bzm derivative (0.06 Å

vs. 0.03 Å). The derived FF was also used to calculate the energy for the Co-N rotational barrier for the *endo* coordinated 2-NH_2-py in (2-NH_2-py)Co$(DH)_2$Me. The energy was calculated to be 10 kcal/mol, which compares well with the experimental values derived from dynamic and saturation ^{1}H NMR analysis. These varied in the range 9.2–13.1 kcal/mol for R$Co(DH)_2$(2-NH_2-py) with R = i-Pr, Et, neo-pentyl, CH_2Br $CH_2C(Me)(CO_2Et)$, CH_2CN, CH_2NO_2.[70]

TABLE IV Observed and calculated Co-C and Co-N bond distances [Å] for R$Co(DH)_2$(1,2-Me_2Im), after the first and second step of the force field parameter optimization process. Data are from Ref. 55

R		*obs*	*step 2*	*step 1*
CCl_2CN	Co-C	2.046	2.060	2.115
	Co-N	2.024	2.011	2.108
CH_2NO_2	Co-C	1.999	1.991	2.030
	Co-N	2.048	2.018	2.090
CH_2CN	Co-C	2.018	2.004	2.031
	Co-N	2.050	2.050	2.090
CH_2CH_2CN	Co-C	2.023	2.035	2.038
	Co-N	2.083	2.088	2.094
Me	Co-C	2.001	1.996	1.999
	Co-N	2.085	2.078	2.086
i-Pr	Co-C	2.095	2.084	2.079
	Co-N	2.121	2.114	2.103

3.1.3. New spectroscopic tools for the analysis of the Co-C bond

Ten years ago, Marzilli, Yu and coworkers described[46] the first application of near infrared excited Fourier transform Raman (Near IR-FT Raman) spectroscopy to study photolabile methylcobaloximes. By this technique, which uses the near IR excitation at 1064 nm, the fluorescence interference and the Co-C bond photolysis which precluded measurement with other spectroscopic techniques are avoided.[71] The $\nu_{Co\text{-}Me}$ stretching mode was assigned to a very intense and sharp Raman line at 504 cm^{-1} for py$Co(DH)_2CH_3$ in chloroform solution which shifted to 477 cm^{-1} for py$Co(DH)_2CD_3$.[46] In the solid state the frequency increased to 522 cm^{-1}.

$\nu_{Co\text{-}Me}$ frequencies at ~500 cm^{-1} were then assigned in several methylcobaloximes with different L ligands in chloroform solution and in the solid state. They are given in Table V, together with the corresponding Co-Me distances. Comparison of spectroscopic data in solution and in the solid state indicates the existence of conformational differences in the two cases.[46] Furthermore, comparison with crystallographic data shows that, when L is an N-donor ligand, the $\nu_{Co\text{-}Me}$ frequencies are higher and the Co-C bond lengths are shorter than those obtained for P-donor ligands. A similar trend is apparent in iminocobaloximes[48] (Table V). This observation appears to support the conclusion, based on the crystallographic data of Table I, that the ground state *trans* influence of the L ligand is essentially steric. The apparent conflict between this conclusion and BDE results (*cf.* Section 3.1.1),[32] which indicate that electronic *trans* influence of L may be reconciled by the observation that BDE depends on the ground and the product states, whereas FT-Raman and distances probe only the ground state properties of a molecule. This technique was also used to measure the $\nu_{Co\text{-}Me}$ frequency in crystals of MeCbl.[73] The value of 500 cm^{-1} is very close to those found in the models. However, other Co-alkyl stretches in cobalamins have escaped detection with this technique, and only recently has the resonance Raman (RR) technique permitted ready assignment of the Co-C stretching frequencies at 506, 471 and 443/429 cm^{-1} for Me-, Et- and ado-Cbl, respectively.[74] This trend is consistent with the previously described steric *cis* influence in the simple models (*cf.* Section 3.1.1). In order to obtain further insight into the biological role of replacing dimethylbenzimidazole with imidazole or imidazolate,[24] the effect of this replacement on the properties of the cofactor was studied by FT- Raman spectroscopy.[73] This study suggested that replacement in MeCbl and in methylcobinamides does not involve the ground state species. These studies provide important control for the investigation in vitamin B_{12}- dependent enzymes.[2] In fact, a band at 429 cm^{-1} was assigned for the first time in a protein, namely a methylated corrinoid/iron sulfur protein.[75] The value, lower than that found in the isolated MeCbl, strongly suggests a weaker Co-Me bond in the protein.

Correlations between the Co-C distances and $\nu_{Co\text{-}Me}$ frequencies have been found in other simple B_{12} models.[48] In fact, both respond slightly, but significantly, to the orientation of the planar L ligand (*cf.* Section 3.1.1) and to changes of the equatorial ligand[48] (Table V) (steric *trans* influence). However, they respond strongly to the larger variations in the electronic properties of the *trans* ligand. Thus, $\nu_{Co\text{-}Me}$ frequencies in

XCo[(DO)(DOH)pn]Me with X= Cl, 3,5-Me_2PhS, Me are 505, 496 and 455 cm^{-1}, respectively.[48] Correspondingly, the Co-C bonds in Me[Co(DO)(DOH)pn]Me (2.045 (8) and 2.049(8) Å),[76] the longest Co-Me distances so far reported, are significantly longer than the Co-Me bond *trans* to weak donor ligands (Table V).

TABLE V Comparison between solid state $\nu_{Co\text{-}Me}$ frequencies (cm^{-1}) and Co-Me distances (Å) in some $LCo(DH)_2CH_3$ complexes. Frequency values in solution ($CHCl_3$) for $LCo(DH)_2CH_3$ and $\{L^{-n}Co[(DO)(DOH)pn]\ CH_3\}^{(1+n)+}$ complexes are also reported

	(DH)$_2$			*(DO)(DOH)pn*	
	$\nu_{Co\text{-}Me}$[a] *solid state*	$\nu_{Co\text{-}Me}$[a] *solution*	*Co-Me*[b]	$\nu_{Co\text{-}Me}$[c] *solution*	*Co-Me*[b]
L					
Cl				505	
Py	522	504	1.998(5)	497	2.003(3)
1-MeIm	520	508	1.980(4)[d]	503	2.001(3)
$PhNH_2$	510	502	1.992(2)		2.011(3)
$P(OMe)_3$	510		2.01(1)		2.021(5)
$P(c\text{-}Hex)_3$	505	481	2.016(5)		
3,5-Me_2PhS^-				496	
PMe_3	498	495	2.015(3)	487	
PPh_3	491	487	2.026(6)		2.018(5)
CD_3				455	2.047(8)[e]

a. Ref. 47.
b. Ref. 1.
c. Ref. 48.
d. Ref. 52.
e. Ref. 76.

High resolution one bond $^{13}C\text{-}^1H$ coupling constants, $^1J_{C\text{-}H}$, have been determined, by a new sensitive reverse detection method (JHMQC), for Me_3Bzm C atom in the series $Me_3BzmCo(DH)_2R$

(R = Cl, CH_2NO_2, Me, Et, adam).[50a] In terms of the assessment of the electronic properties of the metal center, $^1J_{C\text{-}H}$ values appear to be more reliable parameters than the traditionally used ^{13}C shifts, especially for carbons close to the metal center. In fact, previous studies of ^{13}C shifts in cobaloximes indicated the magnetic anisotropy influence of the metal on the ligand nuclei close to it. Therefore, to minimize this through-space effect, only chemical shifts of metal remote carbons (*e.g.* the γ-carbon in pyridine cobaloximes) were used to assess the trans influence,[15] although it was suggested that other factors may contribute to the observed shift.[54] Unlike ^{13}C shifts, $^1J_{C\text{-}H}$ constants reflect through-bond influences in relative isolation from the through-space effects.[50a] These constants have been obtained for a large series of cobaloximes (with L = Me_3Bzm and 1-MeIm) and analyzed as function of a new set of parameters, the *t* scores, derived by Randaccio *et al.*[57] through the application of the principal component analysis to a large set of cobaloximes properties (*cf.* paragraph 3.1.5). The *t* scores were found to be a valuable set of parameters for interpreting such spectroscopic data. In fact, their use allowed the identification of steric effects on the ^{13}C shifts and $^1J_{C\text{-}H}$ constants for the bulky lopsided Me_3Bzm ligand, but not for the 1-MeIm one.[52] The intraligand $^1J_{C\text{-}H}$ values for close-in N_2CH carbons of Me_3Bzm and 1-MeIm were found to reflect the ligand-to-metal binding even better than ^{13}C shifts of carbons remote from the metal center, suggesting that their use holds promise in metallobiochemistry.[52]

Derivation of coupling constants for several $(PR_3)Co(DH)_2Me$ complexes (18 phosphines and 3 phosphites, with different pK_a and bulk) has further supported the structural and FT-Raman results, which suggested that the ground state properties of the Co-Me bond are only slightly affected by the change of the *trans* neutral ligand.[50b] In fact, regression analysis showed that $^1J_{C\text{-}H}$ values of the Co-Me moiety correlate well with the pK's of non-bulky phosphines. Inclusion into the regression of a steric term (cone angle) allowed simultaneous fits of all PR_3 ligands, including the bulky ones.[50b] The $\delta^{59}Co$ and $^1J_{Co\text{-}P}$ values for a series of $(PPh_3)Co(DH)_2R$ complexes were also reported.[50c]

3.1.4. Inclusion compounds of alkylcobaloximes with cyclodextrins

Recently, the interesting propensity of alkylcobaloximes to form inclusion compounds with cyclodextrins (cd) has been described.[49,51] Sev-

eral 1:1 α–cd/[$(H_2O)Co(DH)_2R$] inclusion compounds, with R = n-Pr, n-Bu, n-pentyl and i-Bu, were synthesized and characterized by ^1H NMR spectra and X-ray crystallography in the case of R = n-Pr.[49] The crystal structure analysis of the latter revealed that the equatorial moiety of the cobaloxime is located near the widest opening of the truncated cone-shaped α-cd and the n-Pr group protrudes inside the hydrophobic cavity. Upon inclusion, the cobaloxime was reported to undergo conformational changes with respect to the isolated species, although some changes are highly questionable, such as a lengthening of the n-Pr C_α-C_β bond by 0.16 Å. The stability of the inclusion compounds, as measured by the formation constant, depends on R in the following order : n-pentyl >> n-Bu > n-Pr > i-Bu. Thus, both the length and the size of the R group affect stability. The crystal structures of the $(H_2O)Co(DH)_2$(i-Bu) inclusion compounds with α- and β-cd have also been reported.[51] Structural results showed that in both cases the inclusion of the n-Bu derivative occurs in a similar way to that of the i-Pr analogue. However, because of the different size of the cavity, distortions induced by inclusion in α-cd are somewhat different from those in β-cd. The most significant differences between the free and the *included* cobaloxime relate to the α angle, the displacement *d* and the Co-OH_2 distance (from 0.02 to 0.10 Å). No variation in the Co-C bond length is observed in any case, suggesting that the Co-R fragment is *soaked* within the cd cavity with stretching of the Co-O bond, but not of the Co-C bond. This finding indicates that such inclusion compounds could be a model for the displacement of the benzimidazole residue from Co in the binding of B_{12} coenzymes to the apoenzyme and, thus, could be of interest in developing artificial enzymes, modeling the B_{12}-based ones.[51] These studies appear to have prompted some preliminary work on inclusion compounds between α-cd and a long-chain alkylcobalamin, from which the first B_{12}-rotaxane characterized by spectroscopic techniques could be obtained.[77]

3.1.5. Quantitation of the relationships between structure and property

As pointed out at beginning of Section 3, the qualitative interpretation of the mutual influences among the ligands was fairly straightforward. However, the quantitative rationalization of those influences was more intriguing. In a first approach,[15a] it was assumed that, in the series

$pyCo(DH)_2R$, the values of the differences in ^{13}C NMR chemical shift of γ-C(py) with respect to the methyl derivative, EP, were a measure of the electronic influence of the *trans* R ligand. In fact, when the Co-N axial distances and log *k*'s for the displacement reaction of py are plotted against EP, fairly linear relationships are found.[15a] Such an approach has the advantage that it can be applied to any alkyl R group, but it does not allow the quantitation of the influence of the bulk of the R ligand. Furthermore, once more data became available, it was shown[55] that the linear regressions improved when restricted only to CH_2Y groups (Y with small bulk), with the other bulky R groups are all above the best line, thereby suggesting (*vide infra*) that steric factors play an appreciable role.[55] A similar attempt using single scale sets of organic substituent constants met with limited success.[15b] This led to attempts to describe the cobaloxime properties as a linear function of the electronic and steric constants derived from organic chemistry.[54] However this model suffered from outlying data.

A quite different approach,[15c] successfully applied to series of the type $LCo(DH)_2CH_2Y$, was based on the classical dual substituent parameter equation:

$$Q_Y - Q_H = a_I \Delta\sigma_I + a_R \Delta\sigma_R \qquad (1)$$

where Q_Y and Q_H are the examined properties for CH_2Y and methyl derivatives, respectively, and a_I and a_R represent the relative contributions of inductive and resonance effects. $\Delta\sigma_I$ and $\Delta\sigma_R$ are the literature inductive and resonance parameters re-normalized to $\sigma_I = \sigma_R = 0$ for Y = Me and not Y = H. The parameter modification and the exclusion of steric contributions were criticized, and the modified equation (2) was proposed:[56]

$$Q_Y = a_I\sigma_I + a_R\sigma_R + a_S\sigma_S + C \qquad (2)$$

where σ_S a is the steric parameter for the Y group, derived from organic chemistry, and a_I, a_R and a_S are the relative contributions of the inductive, resonance and steric effects, respectively. Equation 2 was applied to interpret satisfactorily not only solution and solid state properties of cobaloximes,[56] but also some solution properties of cobalamins.[78] Unfortunately, this kind of approach, which has the advantage of transferring to organometallic chemistry substituent constants from organic chemistry without any further assumption, is limited to CH_2Y alkyl groups.

This unsatisfactory situation necessitated a different methodology, one able to extract and to rationalize the most important counteracting or superimposing factors, some steric, the others electronic, by a statistical treatment. Therefore, the well-known method[79] based on the "multicomponent" analysis, namely the Principal Component Analysis (PCA), was applied to analyze the large number of data on cobaloximes.[57] PCA allows investigation of the relationships between a set of variables in a class of compounds and enables the identification of the descriptors relevant to the problem. These descriptors, the so-called scores, can be related to the nature of the R groups and interpreted as a measure of some of their chemical properties. Five experimental quantities of 23 $pyCo(DH)_2R$ cobaloximes, with the R groups indicated in Table VI, i.e. the Co-C and Co-N axial distances, displacements *d* of Co out of the coordination plane, log *k*'s for the displacement reaction of py, and γ-^{13}C(py) shifts were analyzed. A three-component PCA model, based on t_1, t_2, and $t_3$scores, is significant according to the cross validation criterion[79] and accounts for 95% of the variance (82% with t_1 and t_2) of the data set. The scores for each R group (Table VI) have been interpreted and discussed in terms of the electronic and steric properties of the R groups. t_1 values increase with the increase of the electron-donating ability of groups substituting the H methyl atoms. t_2 scores follow the increase in bulk of R. t_3 is interpreted as a measure of the angular distortions at C_α. The three-component model was applied to interpret kinetic, spectroscopic, structural, and thermodynamic data of several series of alkylcobaloximes and alkyliminocobaloximes, with different L ligands,[57] by using the equation:

$$Q_L = a_0 + a_1 t_1 + a_2 t_2 + a_3 t_3 \qquad (3)$$

where Q_L is the analyzed property in the series with a given L ligand and a_i represents the contribution of the t_i parameter. The t_1 and t_2 parameters are the predominant descriptors of most of the properties. In fact, log *k* and Co-L distances are essentially dependent upon t_1, displacements *d* upon t_2 and chemical shifts upon t_1 and t_2, while the Co-C distances depend upon all the scores. Particularly, the latter finding represents the first attempt to rationalize quantitatively the variation observed in Co-C bond lengths as the R properties vary. Thus, the bond lengthens with an increase in bulk and σ-donor ability of R and shortens when the Co-C-Y angle increases. This may be relevant to the understanding of the mechanism of the Co-C bond homolysis occurring in the

biological processes which involve the B_{12} coenzyme. Application of scores to alkylcobalamins is limited by the small number of data in the available series.

TABLE VI Values of the scores obtained by PCA.[a]

R	t_1	t_2	t_3	R	t_1	t_2	t_3
CHClCN	−2.50	0.62	0.17	CH_3	0.10	−1.91	0.07
CF_3	−2.48	−0.57	−1.11	CH_2Ph	0.71	−0.77	1.00
CH_2NO_2	−2.47	−0.56	0.49	$CH_2CMe(COOCH_2Me)_2$	0.89	0.36	−0.41
CH_2CN	−2.14	−0.35	1.03	$CH(CH_3)COOCH_3$	1.09	0.56	0.67
CF_2CHF_2	−1.97	0.87	−0.75	CH_2CH_3	1.10	−1.35	0.24
$CF(CF_3)_2$	−1.65	3.08	−0.03	$CH_2Si(CH_3)_3$	1.17	−0.41	−0.66
$CH(CN)CH_2CN$	−1.57	0.96	0.79	CH_2OCH_3	1.55	−1.71	−0.13
$CHCl_2$	−1.34	0.19	−0.70	$CH_2C(CH_3)_3$	1.64	−0.09	−0.14
CH_2CF_3	−1.31	−0.20	−0.03	$CH(CH_3)_2$	2.19	0.00	0.10
$CH(CN)CH_3$	−0.66	0.54	0.24	c-C_6H_{11}	2.26	0.87	−0.65
CH_2CH_2CN	−0.22	−0.77	−0.15	adamantyl	3.69	2.20	0.30
ribosyl	0.05	−1.11	−0.16	CH_2Cl[b]	−0.85	−1.10	−0.90

[a]Ref. 57.
[b]The scores have been calculated from experimental data using the appropriate equations given inTables VI–VIII of Ref. 57.

The PCA method was applied by Burgi *et al.*[58] to deeply analyze the structural behavior of several alkylcobaloximes. No significant correlation between the equatorial moiety deformations and changes in the axial bond lengths was apparent. This analysis confirmed the previous suggestion[38] that electron-withdrawing R groups shorten and electron-donating R groups lengthen simultaneously the two axial bonds (inverse *trans* influence), but to a different extent, as suggested by equation 3, where t_1, t_2 and t_3 contribute to define the Co-C bond length, whereas only t_1 contribute to the Co-L bond length.

The interpretation of cobaloxime physico-chemical properties in terms of steric and electronic influences was criticized by Drago,[59] who instead used the electrostatic-covalent (E-C) model. For a series of

measurements, restricted to substituent changes in a series of compounds, this approach is based on the following equation:

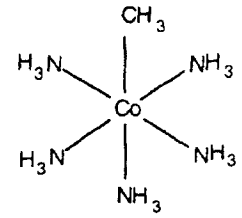
$$\Delta\chi^X = d^E\Delta E^X + d^C\Delta C^X + \Delta\chi^H \qquad (4)$$

where Δ^H is the measurement of the parent H compound, $\Delta\chi^X$ the measurement of the X (R for alkyl) substituted derivative and ΔE^X and ΔC^X are the changes in the E and C values caused by the substituent. The d^E and d^C terms represent the relative contributions of the variations in the electrostatic and covalent term, respectively, due to the substitution of H by X. The analysis, based on equation 4, led to the proposal of a greatly diminished role of steric effects. In fact, according to Drago, "compared with the emphasis on steric effects in the literature explanation of this (cobaloxime) chemistry, these effects are seen to be minimal, when a proper estimate of the covalency is made".[59] The tendency of Co to undergo electrostatic interaction with L is decreased and its tendency for covalency in the interaction is increased by an increase in the electron-donating ability of R. Furthermore, the deviations found by this analysis in free energy rate and equilibrium constant correlations are assumed to be caused by an entropic effect associated with the rotational freedom of X, which does not affect distance and electrochemical correlations. This approach was applied not only to alkyl derivatives, but also to non-organometallic cobaloximes. However, it should be noted that the data analyzed did not include the R groups with the most positive values of t_1 and t_2, namely the very bulky R groups.

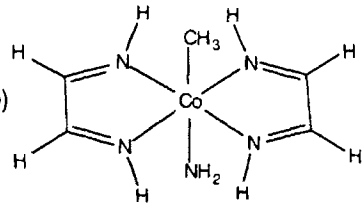
3.1.6. Theoretical studies of the electronic structure of alkylcobaloximes

Since the pioneering work on the electronic structure of the Co-C bond in cobaloximes and cobalamins,[60a] only a few papers have appeared.[60b,c–62] Previous theoretical calculations have focused on factors which enhance the Co-C homolysis and model systems with increasing complexity (Scheme 5) were studied. Treatment of model 5a by the PRDDO (Partial Retention of Diatomic Differential Overlap) method suggested that the Co-C distance is not affected by changes in the electronic nature of the *trans* ligand. This study concluded that the Co-C experimental lengthening is more likely due to steric interactions and that a weakening of that bond may be determined by the deviation of the C-Co-N(eq) angle from 90°, as measured by the tilt angle (*vide*

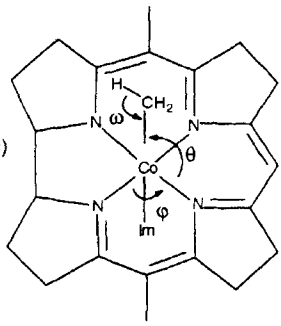
a)



b)

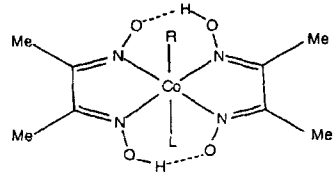


c)



Im = imidazole

d)



R = Me, i-Pr, 5'-deoxy-5'-adenosyl

L = NH_3, py, 2-NH_2-py, 5,6-dimethylbenzimidazole

SCHEME 5

infra).[60b] On the other hand, calculations carried out on model 5b by the Extended Hückel MO method[60c] suggested that a necessary component of the Co-C homolysis is the weakening of the *trans* Co-N bond. The Fenske-Hall method was used to study model 5c, exemplifying the cobalt(III) corrin nucleus, and the influence of the structural deformations on the Co-C bond strength was considered.[61] This approach suggested that deformations of θ and ω (scheme 5c) greatly labilize the bond. The lengthening of the Co-Im bond has a minor effect and, finally, variation in the torsional angle about the Co-N(ax) bond, φ, has no direct influence. The PRDDO method was then applied to model 5d, which takes into account the "full" structure of several alkylcobaloximes with different L and R ligands, in order to determine which factors may contribute to structural changes in the equatorial and axial moieties, when the bulkiness and the σ-donor ability of the axial ligands is varied.[62a] Theoretical calculations agree with experimental findings[1a] that the geometry of the equatorial moiety is scarcely affected by variations of the axial ligands and that the α and *d* values respond essentially to differences in bulk between the latter. Furthermore, the Co-C and Co-N(ax) bonds are both lengthened in the derivatives in which the axial ligands are bulky, in agreement with experimental data of Table II. Analogously, theoretical calculations agree with the crystallographic results that an increase in the N(ax) donor basicity has no effect on the Co-C bond, which also appears to be scarcely affected by changes in the σ-donor character of the alkyl group itself (*cf.* Section 3.1.5). For $(Me_3Bzm)Co(DH)_2Me$, orientation B ($\varphi = 90°$) (Scheme 4) was found to be energetically less favored than orientation A by 10 kcal/mol, and to correspond to a lengthening of the Co-N(ax) bond from 2.04 to 2.10 Å. However, no marked change in the Co-C distance was apparent.[62a] Interestingly, the latter figures are equal to those obtained[45] for the same compound by MM calculations, using the FF modified to include electronic effects (*cf.* Section 3.1.2). However, the calculated difference in strain energy between the two conformers (A and B) was significantly lower (5.0 kcal/mol).

Surprisingly, no appreciable *trans* influence of R was apparent in Co-N(ax) calculated distances. The calculated Co-C bond length was found to increase in the order i-Pr (2.04 Å) < Me (2.05 Å) < ado (2.07 Å), which is different from the experimental sequence, Me (1.998 Å) < ribosyl (2.025 Å) < i-Pr (2.085 Å), where ribosyl is the ado moiety lacking the terminal adenine base.[25] Similar results were obtained from

PRDDO calculations on model 5c, with the axial methyl group replaced by the 5′-deoxy-5′–adenosyl group.[62b] The Co-N(ax) distances, for R = Me, i-Pr and ado, are calculated to be significantly longer than the analogous distances in cobaloximes,[62c] in agreement with crystallographic evidence.[1c] However, as before the trend of the Co-N(ax) with R was not reproduced. On these grounds, the authors concluded that the structural features of the axial fragment are dictated primarily by steric interactions. This conclusion appears to be in conflict with crystallographic results, reported in Table II, which indicate that for electron-withdrawing groups, such as fluoroalkyls, both the axial bonds are shortened with respect to those of the less bulky parent alkyls. Analogously, this contrasts with the enormous lengthening of the Co-N bond, *trans* to the CH_2OMe group, which has a small bulk.[41,43] The theoretical calculations, sometimes reaching conclusions in conflict with experiments, are limited and require further work and perhaps more sophisticated *ab initio* approaches. Possibly, the application of methods based on density functional theory[80] should allow a much better understanding of the nature of the changes observed in the ground state properties of these systems.

4. RHODOXIMES, THE RHODIUM ANALOGUES OF COBALOXIMES

Early studies on the cobaloxime analogues, rhodoximes, which have Rh in place of Co, showed several chemical similarities with cobaloximes.[81] Stable organometallic $LRh(DH)_2R$ species have been obtained[81] and characterized in solution.[82] The observation that the Rh analogue of adoCbl is a B_{12} coenzyme inhibitor in *E. coli*[83] has prompted further studies on alkylrhodoximes.[84–96]

4.1 Similarities and differences between rhodoximes and cobaloximes : interpretation of the rhodoxime properties in terms of t scores

Several structural, physico-chemical and reactivity properties of alkylrhodoximes parallel those of alkylcobaloximes.[84–96] For example, the Rh-C bond has been found to be more stable than the Co-C bond toward homolysis.[87] In addition, although the hexacoordination is more favored

with respect to pentacoordination in both rhodoximes and cobaloximes,[92] this situation is more enhanced in the former.

These studies were carried out in order to obtain more insight into the factors affecting the metal-carbon bond. In fact, the change in the size and electronic properties of the metal center could give further information about the factors affecting the metal-carbon bond. Particularly, in relation to the steric/electronic contribution in defining the Co-C distance, the axial distances in rhodoximes would be expected to be longer than those in cobaloximes, owing to the larger ionic radius of Rh(III) than Co(III). Consequently, the steric interaction between R and the equatorial moiety should be partially or totally relieved, as suggested[85] by the comparison of $Ph_3PM(DH)_2Cl$ structures with M = Rh[97] and Co:[98] the Co-Cl and Rh-Cl distances are 2.287(2) and 2.381 (1) Å, whereas the Co-P and Rh-P ones are found to be 2.330(2) and 2.327(1) Å, respectively. Experimental data were obtained mostly by crystallographic,[85–92,94] NMR spectroscopy,[86, 92, 93, 95, 96] and kinetic[84–86] studies of several series of alkylrhodoximes with different L ligands, including some halorhodoximes (R = halide). The linear regressions between the properties when R is varied are summarized in Table VII.

TABLE VII Correlations between alkylrhodoxime properties. The errors of the equation coefficients are given in parentheses. Processed data are from Refs. 85,86, 93–95

Equation	r^a	n^b
$\delta^{103}Rh\ (PPh_3) = -378(181) + 1.26(9)\bullet\ \delta^{103}Rh(PMe_3)$	0.984	8
$\delta^{103}Rh\ (PPh_3) = 73(227) + 0.79(9)\bullet\ \delta^{103}Rh(py)$	0.948	11
$^1J_{Rh\text{-}C}\ (PPh_3) = -1.8(9) + 1.17(4)\bullet{}^1J_{Rh\text{-}C}\ (PMe_3)$	0.996	9
$^1J_{Rh\text{-}C}\ (PPh_3) = -0.3(1.8) + 0.86(7)\bullet{}^1J_{Rh\text{-}C}\ (py)$	0.980	8
$^1J_{Rh\text{-}P}\ (PPh_3) = -0.69(9) + 1.7(1)\bullet{}^1J_{Rh\text{-}P}\ (PMe_3)$	0.985	9
$^1J_{Rh\text{-}P}\ (PPh_3) = 25(1) + 5.5(2)\bullet{}^1J_{Rh\text{-}N}\ (py)$	0.997	8
$^1J_{Rh\text{-}P}\ (PPh_3)^c = 1116(74) - 428(31)\bullet d_{Rh\text{-}P}\ (PPh_3)$	0.997	8
$^1J_{Rh\text{-}N}\ (py)^d = 150(23) - 0.65(10)\bullet d_{Rh\text{-}N(ax)}\ (py)$	0.961	5

a. Correlation factor.
b. Number of observables.
c. R= Cl is included.
d. R= Cl and I are included.

The statistical analysis of data indicates:

a) no linear correlation binds δ^{103}Rh, $^1J_{Rh\text{-}C}$ and $^1J_{Rh\text{-}P}$, in each series;

b) δ^{103}Rh does not correlate with the axial distances and $^1J_{Rh\text{-}C}$ does not correlate with Rh-C bond lengths;

c) the coupling constants, $^1J_{Rh\text{-}L}$, correlate with the Co-L distances with an inverse dependence, as already observed for L = PPh_3[93];

d) the trend of each property with R is similar when the L ligand is varied. As can be seen from the slope of the relationships reported in Table VIII, it appears that the influence of changes in R on δ^{103}Rh and $^1J_{Rh\text{-}C}$ increases in the order py > PPh_3 > PMe_3, whereas for $^1J_{Rh\text{-}L}$ the order is PPh_3 > PMe_3 >> py. Similar excellent linear relationships were found for Co-N(ax), Co-C, log *k*and δ^{13}C shifts in cobaloximes when L was varied.[15, 55]

TABLE VIII Dependence on t_1, t_2 and t_3 of structural, spectroscopic and kinetic properties of alkylrhodoximes with L = PPh_3, PMe_3, py. The scores which gives the predominant contribution is in bold character. Processed data are from Refs. 85,86, 93–95

Property	*scores*[a]	a_1/a_2	a_1/a_3	a_2/a_3	*r*[b]	*n*[c]
δ^{103}Rh (py)	$-t_1$, **$+t_2$**, $-t_3$	–0.54	0.73	–1.4	0.980	7
$^1J_{Rh\text{-}C}$ (py)	$-t_1$, $+t_2$, **$-t_3$**	–0.63	0.25	–0.39	0.949	7
$d_{Rh\text{-}C}$ (py)	**$+t_1$**, $+t_2$, $-t_3$	1.52	–1.1	–0.71	0.999	6
logk (py)	**$+t_1$**, $-t_2$	–3.1	–	–	0.998	6
δ^{103}Rh (PPh_3)[d]	**+t2**,$-t_3$	–	–	–1.6	0.840	10
$^1J_{Rh\text{-}C}$ (PPh_3)	$-t_1$, **$-t_3$**	–	0.30	–	0.903	8
$^1J_{Rh\text{-}P}$ (PPh_3)[e]	**$-t_1$**, $+t_3$		–2.1		0.931	10

a. The predominant score is indicated in bold.
b. Correlation factor.
c. Number of observables.
d. The regression for δ^{59}Co (PPh_3)[50c] gave a_2/a_3 = 2.1 (r = 0.995, n = 6).
e. The regression analysis for $^1J_{Co\text{-}P}(PPh_3)$[50c] gave a_1/a_3 = –0.92 (r = 0.955, n = 6).

In this article, I take the opportunity to analyze these series of data in terms of the t_1, t_2 and t_3 scores (Table VIII). This analysis indicates that (i)

δ^{103}Rh chemical shifts are affected predominantly by t_2, *i. e* by steric interactions, as previously suggested,[95] and to a minor extent by t_3; (ii) the $^1J_{Rh\text{-}C}$ coupling constants are affected predominantly by t_3 with a contribution from t_1; (iii) the $^1J_{Rh\text{-}P}$ coupling constant is affected by t_1 with a contribution from t_3; (iv) the log *k* values depend essentially upon t_1 and the Rh-C distances upon t_1, t_2 and t_3. Since the coupling constants $^1J_{Rh\text{-}L}$ correlate linearly with the Rh-L distances and since the analogous Co-L distances in cobaloximes depend essentially on t_1, one can conclude that the Rh-P and Rh-N(ax) distances, which cannot be analyzed by scores because of the limited data available, are essentially affected by t_1. In fact, the regression analysis between Rh-py distances against t_1, restricted to R = CH_2CF_3, CH_2Cl, Et, i-Pr, gave an r value of 0.96.

The regressions given in Table VIII for L = PPh_3 are not as good as those for L = py. A likely reason for this is that the application of the scores, derived for N-donor ligands with relatively small bulk, such as py, cannot take into account the significantly larger bulk of the phosphine and, possibly, their σ-donating ability. Therefore, the extension of the previous PCA analysis[57] to complexes containing other L ligands is desirable, so that also the scores related to the electronic and steric properties of L can be derived and, hence, include a larger number of examined complexes.

Due to the larger size of the Rh center in comparison with cobaloximes, the expected relief of the steric interactions between R and the equatorial moiety is indicated by the slope of 0.50 for the linear regression between the Rh-C and Co-C distances (Table IX). This is also supported by the analysis of the Rh-C distances, based on the scores, which gives a_1/a_2 and a_1/a_3 ratios of 1.5 and 1.1, respectively. These ratios should be compared with those of 0.90, and 0.55, respectively, obtained for the corresponding cobaloximes.[57] The steric term, related to t_2, is much less important in determining log *k* (Table VIII) and, in fact, a slope close to unity is obtained when log *k* (Rh) is plotted against log *k* (Co) for pyridine derivatives (Table IX).

The successful application of scores to rhodoximes further supports them as a valuable set of parameters for interpreting the ground state and, possibly, kinetic properties, and demonstrates their more general applicability to complexes containing metal centers different from cobalt.

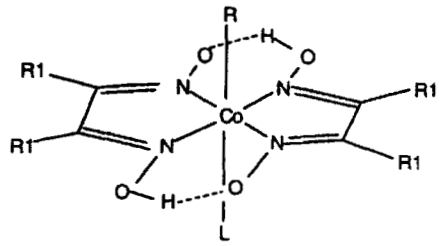
TABLE IX Comparison of kinetic, structural and spectroscopic properties of alkylrhodoximes (data from Refs. 93–95) with the corresponding properties of alkylcobaloximes (data from Refs. 1, 45c, 50c and 108)

Equation	r^a	n^b
log *k* (Rh, py) = –038(14) + 1.14(7)•logk (Co, 4-CN-py)	0.990	6
$d_{Rh\text{-}C}$ (py) = 1.07(12) + 0.50(6)• $d_{Co\text{-}C}$ (py)	0.973	6
δ^{103}Rh (py) = 1092(308) + 0.39(8)•δ^{59}Co (py)	0.903	7
δ^{103}Rh (PPh_3) = 430(312) + 0.44(8)•δ^{59}Co (py)	0.908	8
δ^{103}Rh (PPh_3) = 663(709) + 0.48(24)•δ^{59}Co (PPh_3)	0.717	6
$J_{Rh\text{-}P}$ (PPh_3) = 12(14) + 0.35(7)•$J_{Co\text{-}P}$ (PPh_3)	0.934	6

a. Correlation factor.
b. Number of observables.

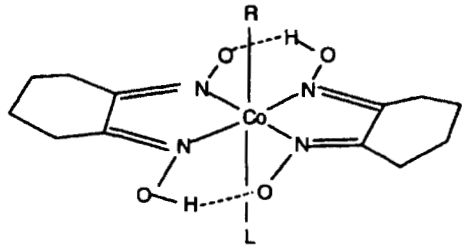
5. MODIFIED COBALOXIMES AND IMINOCOBALOXIMES

Cobaloximes and iminocobaloximes with a modified equatorial moiety have been synthesized and studied in order to try to model more successfully some specific properties of the B_{12} coenzyme, such as the reversible Co-C homolysis when it binds the apoenzyme[99] or the interaction of the corrin side chains with the axial ligands.[100] Modifications of the equatorial moiety have been carried out in several ways, so that the electronic properties of the Co center and the bulk of the equatorial ligand side chains are altered. Sketches of the modified models so far reported are shown in Scheme 6. They can be grouped in the following classes : a) those derived from cobaloximes by the formal substitution of the side oxime methyl groups with H[1c] or larger alkyl groups (Scheme 6a-c);[101–106] b) those derived from cobaloximes by substituting one or two H's of the oxime bridges with either BF_2[107–111] or BPh_2 groups[100, 108, 111–113] (Scheme 6d-f) or from iminocobaloximes by substitution of the H oxime bridge by a BF_2 (Scheme 6g):[108, 114] for the latter some Rh derivatives are also reported;[115] c) those derived formally from iminocobaloximes, where a pendant py is attached covalently at the 2-position by a one-methylene link to the central C atom of the propylene chain (Scheme 6h);[116, 117]d) the new class of B_{12} models (Scheme 6i-l) characterized by a highly distorted coordination around Co;[118, 119] e) those derived from cobaloximes, in which the Co-bond

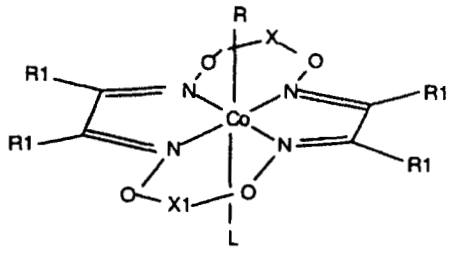


a) $LCo(GH)_2R$, R1 = H

b) $LCo(DPH)_2R$, R1 = Ph



c) $LCo(DCH)_2R$

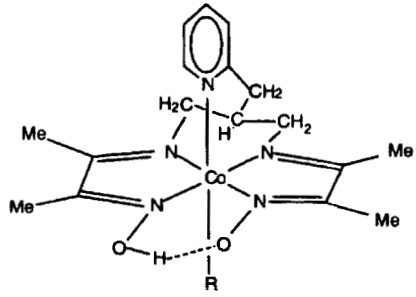


d) $LCo(DBF_2)_2R$, X = X1 = BF_2

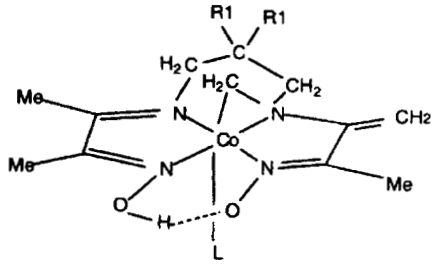
e) $LCo[(DBPh_2)_2]R$, X = X1 = BPh_2

f) $LCo[(DH)(DBPh_2)]R$, X = H, X1 = BPh_2

g) $LCo[(DO)(DBF_2)]R$, $O_2X = (CH_2)_3$, X1= BPh_2

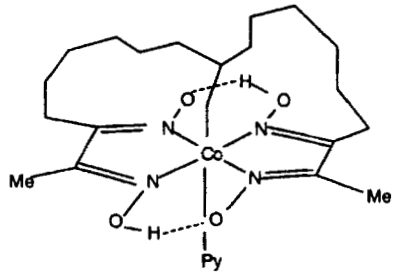


h) $[RCo(C1py)]^+$



i) $[LCo(N\text{-}CH_2\text{-}CHEL)]^+$, R1 = H

l) $[LCo(N\text{-}CH_2\text{-}Me_2\ pn\text{-}CHEL]^+$, R1 = Me



m)

SCHEME 6

methylene is covalently attached to the equatorial moiety by two hexamethylene bridges (Scheme 6m).[120] Recently, attempts have been made to improve the latter model by introducing a binding site for the substrate.[99, 121]

5.1 Derivatives with dioxime side groups different from methyl group

Several organocobalt complexes of group a) have been synthesized and studied by NMR, IR and UV-vis spectroscopies. The order of the *cis* influences on the axial bonds is DPH > DCH > DH (Scheme 6), which is the opposite of the order of the C=N and N-O stretching frequencies.[101-104] Some of these modified cobaloximes have been structurally characterized,[101–103] and comparison of the geometry of the equatorial moiety indicated that lateral compression and the bending α angle are related to the steric bulk of the dioxime substituents (Scheme 6 a-c). As already shown by the comparison of DH and GH (Scheme 6) derivatives,[1c] no significant variation in the coordination geometry can be detected.[106] The compression occurs in the direction perpendicular to the oxime bridges. Gupta and Qanungo have also reported dinuclear alkyl derivatives, where the metal centers are bridged either by a bidentate neutral ligand,[105] such as pyrazine, or by a polymethylene bridge.[104b] The latter complexes, of the form py(chel)Co$(CH_2)_n$Co(chel)py, with chel = $(DH)_2$, $(DPH)_2$ and n = 3–6, have been prepared and characterized by ^{1}H NMR spectroscopy. Another example of a dinuclear complex was reported and characterized in solution and in the solid state by Marzilli *et al.*:[114] the two metal centers in Me$(DBF_2)_2$Co(Im^-)Co$(DBF_2)_2$Me are bridged in the axial position by the imidazolate ligand, Im^-, with relatively short Co-N axial distances as compared to those involving the neutral imidazole.

5.2 H oxime bridge-substituted cobaloximes

Substitution of the oxime bridges induces more remarkable changes in the structure and properties of the complexes belonging to groups b) (Scheme 6 d-g), which exhibit some interesting new properties with respect to the parent cobaloximes. The intense blue pentacoordinate compound, [py$Co(DBF_2)_2$]NH_4, is the only example of a Co(I) complex, with such an equatorial ligand structurally characterized thus

far.[109] The complex anion exhibits a remarkable shortening of about 0.03 Å of the Co-N equatorial distances (mean 1.839(4) Å), with respect to the hexacoordinate Co(III) analogues (*vide infra*) and of 0.04 Å with respect to the hexacoordinate $(MeOH)_2Co(II)(DBF_2)_2$. In addition, significant variations in the geometry of the equatorial moiety with respect to that of the Co(II) complex and a substantial Co displacement, *d*, of 0.26 Å toward py (Co-py = 2.019(3) Å), were observed and attributed to the larger size of the low-valent metal ion.[109] However, the lengthening of the C-N bonds and the shortening of the C-C bonds in $(DBF_2)_2$ unit could suggest an increase in the electron delocalization over the equatorial moiety with respect to Co(II) and Co(III) analogues. The py orientation A, unusual for oxime bridge substituted cobaloximes (*vide infra*), forces the two BF_2 units to be displaced both below the equatorial plane and away from py. The geometrical features of this Co(I) complex could be of interest in the study of the mechanism of the heterolytic cleavage of the Co-Me bond in methionine synthase.[23] Furthermore, some $[LCo(DBF_2)_2R]$ complexes have been shown[110] to be able to transfer the alkyl group to $Ni(tmc)(CF_3SO_3^-)$ (tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazocycle-tetradecane), with a rate increasing in the R order : Me < Et <i-Pr. This reaction has been proposed to be the first model of a methyl group transfer from MeCbl to the Ni-containing enzyme carbon monoxide dehydrogenase during the acetyl coenzyme A synthesis.[110]

As mentioned at the beginning of this section, substitution of the oxime bridge results in changes in the electronic properties of Co and in the geometry of the equatorial moiety. The Co-L distance is also influenced, whereas the axial Co-C bond appears to be less affected. For a given R group, $E_{1/2}$ values for the Co(III)/Co(II) ($E_{1/2}(I)$) and for Co(II)/Co(I) ($E_{1/2}(II)$) electron transfers are remarkably shifted toward less negative values (increasing electron affinity) in the order $(DH)_2 << (DO)(DOH)pn < (DBF_2)_2 < (DO)(DBF_2)$, when $L = H_2O$[108] (Table X). The corresponding trend in $\delta^{59}Co$ values is in the order $(DBF_2)_2 < (DH)_2 < (DO)(DBF_2) \leq (DO)(DOH)pn$, as shown in Table X. The Co-N equatorial distances, in both $(DBF_2)_2$ and $(DBPh_2)_2$ derivatives, shorten by about 0.03 Å with respect to cobaloximes. In complexes where the two bridges are different, such as iminocobaloximes and complexes of Scheme 6f-g, the chemically equivalent Co-N distances are very similar and close to those found in the complexes with two equal bridges (Table X). In each chel series, when the R group changes

(R = Me, Et, n-Pr, i-Pr and benzyl), the plots of $E_{1/2}(I)$ against $\delta^{59}Co$ showed a similar behavior, which reflects a similar sensitivity of these properties to changes in R. $E_{1/2}(II)$ is less sensitive to changes in R, but the trend of the plot against $\delta^{59}Co$ is still similar in all the chel series. Relatively strong electron donor ligands such as py shift $E_{1/2}(I)$ to more negative values and increase the shielding of the ^{59}Co nucleus. The 1-MeIm ligand causes the most negative value of $E_{1/2}(I)$ and the largest shielding.[108] The axial distances in LCo(chel)Me complexes for several chel and L ligands are given in Table XI. As noted above, the Co-L distances are lengthened with respect to cobaloximes, while the Co-Me distances appear to be almost insensitive to chel. The lengthening of the Co-OH_2 distance can be ascribed to the electronic influence of the chel ligand, whereas the length of the Co-N distances in Table XI appear to be related to the orientation of the planar ligand L. In fact, independently of chel, orientation A corresponds to shorter Co-L distances (*cf.* Section 3). It should be noted that one of the imidazole derivatives exhibits the C orientation, intermediate between A and B (Scheme 4), which corresponds to a longer Co-N axial bond, in agreement with MM calculations.[45]

TABLE X Mean Co-N_{eq} chemically equivalent equatorial distances, $E_{1/2}(I)$, $E_{1/2}(II)$ and $\delta^{59}Co$ in the MeCo(chel) moiety. Data are from Refs. 1, 110–112, 114

	$(DH)_2$	*(DO)(DOH)pn*	*$(DBF_2)_2$*	*(DO)(DBF_2)*	*$(DBPh_2)_2$*	*(DH)$(DBPh_2)$*
Co-N_{eq}/Å	1.8901(9)	1.880(9)	1.864(9)	1.886[a]	1.865(7)	1.869(8)
		1.912(8)				1.878(8)
$E_{1/2}(I)$/ V	−1.361	−0.861	−0.819	−0.631		
$E_{1/2}(II)$/ V	−1.60	−1.08	−1.04	−0.85		
$\delta^{59}Co$/ppm	4156	4630	3888	4588		

a. Mean of the four non-equivalent distances.

TABLE XI Axial distances (Å) in some LCo(chel)Me derivatives. Data are from Refs. 1, 110–112, 114, if not otherwise stated. The orientations A, B and C are also indicated for L planar ligands (Scheme 4)

Chel / L		*H_2O*	*1-MeIm*	*Im*	*py*
$(DH)_2$	Co-C	1.990(5)	2.009(7)	1.985(3)	1.998(5)
	Co-L	2.058(3)	2.058(5), **B**	2.019(3), **A**	2.068(3), **A**
(DO)(DOH)pn	Co-C	1.997(4)	2.001(3)	1.991(5)	2.003(3)
	Co-L	2.103(3)	2.042(2), **B**	2.032(3), **B**	2.106(3), **B**
$(DH)(DBPh_2)$	Co-C	–	2.00(1)	–	2.00(1)[a]
	Co-L		2.014(9), **A**	–	2.082(9), **A**[a]
$(DO)(DBF_2)$	Co-C		2.015(6)		
	Co-L		2.043(5), **B**		
$(DBF_2)_2$	Co-C	2.000(6)	–	2.003(2)	2.007(8)
	Co-L	2.127(4)	–	2.053(2), **C**	2.119(4), **B**
$(DBPh_2)_2$	Co-C		2.021(8)		
	Co-L		2.068(7), **B**		

a. Unpublished result.

TABLE XII Relevant distances (Å) and angles (°), involving Co in $LCo[(N\text{-}CH_2\text{-}Chel)]^+$ and in $\{LCo[(DO)(DOH)pn]Me\}^+$ cations

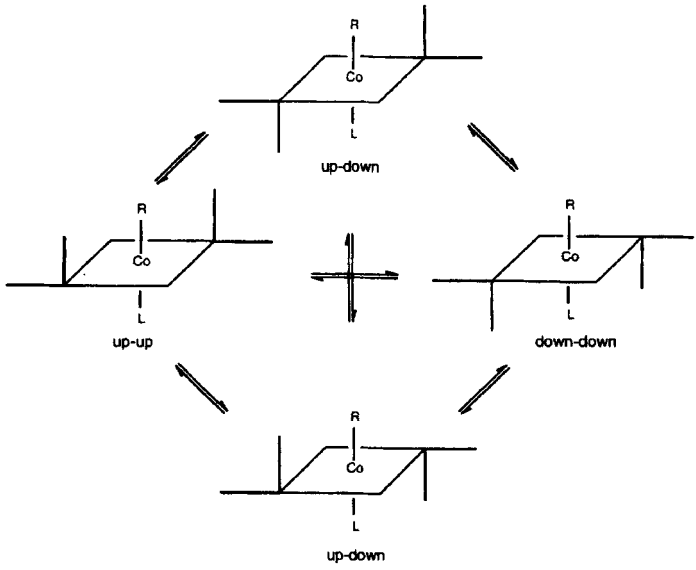
L	*Me_3Bzm*	*1-MeIm*	*py*
$LCo[(N\text{-}CH_2\text{-}Chel)]^+$ [a]			
Co-C	1.913(7)	1.932(59)	1.927(5)
Co-N_{ax}	2.052(5)	2.036(49)	2.068(5)
Co-N_{eq} (sp^3)	1.968(5)	1.938(4)	1.943(5)
N_{ax}-Co-C	155.0(2)	148.4(2)	159.9(2)
N_{eq}-Co-C	43.6(3)	43.7(2)	43.8(2)
$\{LCo[(DO)(DOH)pn]Me\}^+$ [b]			
Co-C	2.011(3)	2.001(3) [c]	2.003(3)
Co-N_{ax}	2.100(3)	2.042(2) [c]	2.106(3)
Co-N_{eq}(sp^3)	1.909(3)	1.914(2) [c]	1.918(3)
N_{ax}-Co-C	177.4(1)	179.2(1) [c]	178.9(1)
N_{eq}-Co-C	87.6(1)	87.5(1) [c]	87.2(1)

a. Refs. 118 and 119.
b. Ref. 1c.
c. Ref. 28.

5.3 The interaction between the axial ligands and the equatorial ligand side groups

The interactions of axial ligands with equatorial ligand side groups have been studied in the case of the $LCo(DBPh_2)R$ derivatives by means of X-ray crystallography and NMR spectroscopy. [100, 111, 113] As shown by the extensive work of Stynes *et al.*[122] on the analogous $LFe(II)(DBPh_2)L'$ complexes, the π-π interactions between the axial ligands and the equatorial ligand side groups, *i.e.* phenyls, control the conformation assumed by the equatorial moiety in systems with a high degree of geometrical complementarity. For diphenylborylated cobaloximes it was shown that they may assume different fast inter-converting conformations (Scheme 7) in solution, depending on the interaction between the BPh_2 phenyls and the axial ligands. For L = 1-MeIm the up-down conformation is preferred both in solution and in the solid state when R = Me,[100, 111–113] but when the R bulk increases, the down-down conformation, where both the axial phenyl groups face the imidazole ligand (Scheme 7) becomes important.[115] This result suggested that for axial ligands with poor complementarity with the host (equatorial moiety), steric effects (steric *trans* influence) play an important role. In fact, for L = MeCN, the up-down conformation is found in the solid state for R = Me; however, when R = n-Pr or trans-β-styryl, the down-down conformation is preferred in the solid state.[113] Thus, the favored conformation is determined by the difference in bulk between the axial ligands. However, when L = tetracyanoethylene (TCNE) and R = Me, the down-down conformation is found in the solid state since the π-π interactions between the good acceptor TCNE and the side phenyls become the conformational driving force.[113] The predominance of the π–π interactions is also indicated by the orientation of TCNE with respect to the equatorial moiety, *i.e* B (Scheme 4, in which the H of the oxime bridges is substituted by BPh_2) which facilitates efficient alignment with the side Ph groups. These findings agree with the conclusion of Stynes[122] that the electronic interactions vary from repulsive for the electron-rich 1-MeIm to strongly attractive for TCNE, the MeCN being in an intermediate position, possibly closer to 1-MeIm.

Addition in MeOH solution of boronic acids, containing donor groups in the side phenyls, such as 3-pyridylboronic acid, resulted in formation of polynuclear complexes. The synthesis and the structure of $MeCoDH[DB(OMe)(3\text{-}Py)]_2$ has been reported,[112] where the pyridyl

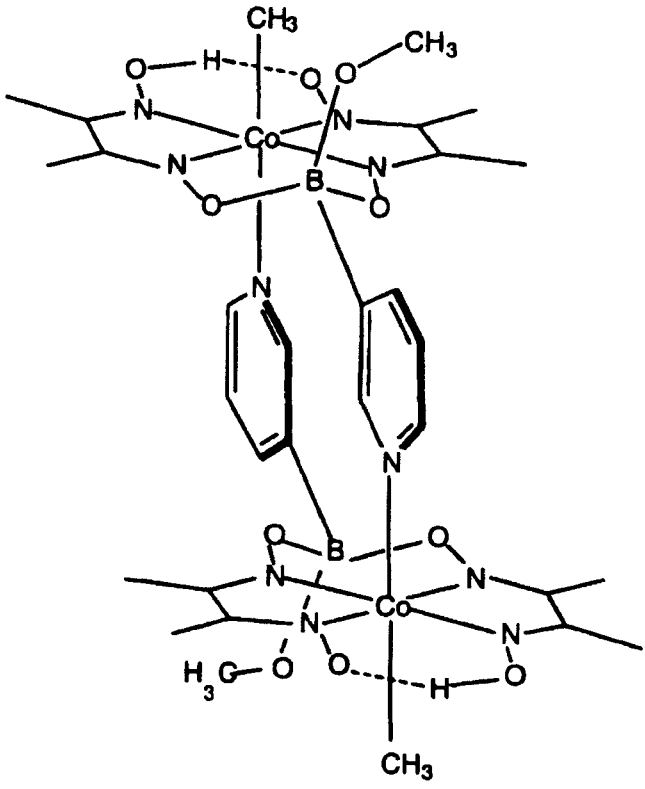


SCHEME 7

group of the equatorial ligand of one unit coordinates axially the Co center of the other one to give the dinuclear species shown in Scheme 8. The formation of the OMe group bonded to B suggests that the hydroxo group of the boronic acid is an additional site to which another arm can be attached in order to obtain a multinuclear assembly of the basic constituents.[112]

5.4 B_{12} models containing pentadentate iminoxime ligands

Two new types of synthetic organocobalt model were discovered by Marzilli and coworkers.[116–119] One of these, the lariat-type model of Scheme 6h, combines the corrin-like feature of iminocobaloximes with an appended axial base. The methylene link forces the pyridyl residue to assume the A orientation, unusual for pyridine iminocobaloximes, with a consequent shortening of the Co-N axial distance and a decrease in the α bending for C1-py derivatives with respect to the parent iminocobalo-



SCHEME 8

xime complexes.[116, 117] The somewhat fixed pyridyl moiety cannot rotate about the Co-N axial bond, thereby allowing assessment of the relative contribution of anisotropic and electronic effects on ^{1}H and ^{13}C NMR shifts of the pendant residue, which cannot be determined when py is freely rotating.[117] Thus it was found that the pyridyl β- and γ-C signals respond to the trans axial ligand R, including potential π-bonding,[53b] when R = CN. It was also found that the values of Co(III)/Co(II) redox couple correlate well with those of the analogous cobalamins, for several R ligands (R = H_2O, Cl, CN, *neo*-pentyl and Me). This is

because of the better electrochemical reversibility in C1-py complexes with respect to cobaloximes and iminocobaloximes, probably due to the fixed pendant grouping.[116] The near unity slope of the linear regression (r = 0.981) indicates that the reduction process is influenced by R in the same way for the two series of complexes.

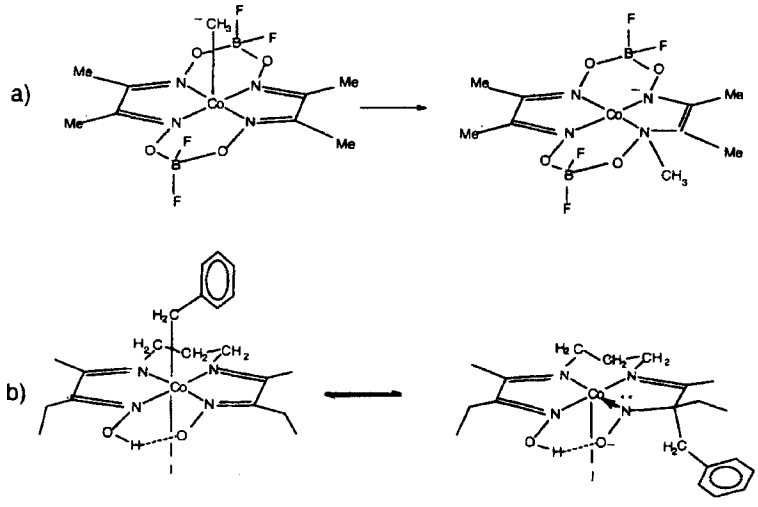
More recently, during attempts to prepare new organoiminocobaloximes, the treatment of MeCo[(DO)(DOH)pn]CH_2X^+ (X = halogen) with bases afforded a major product with some striking NMR spectral features. The crystallographic analysis showed that the complex has the structure of Scheme 6i (L = py), characterized by a rare Co-C-N three-membered ring, a highly distorted coordination about Co, and the dehydrogenation of the starting C-Me grouping to the $C{=}CH_2$ one.[118] The distortion is concentrated in the Co-C and Co-$N_{eq}(sp^3)$ linkages, with a C-Co-N angle of 43.7°. The analogous derivatives with L = 1-MeIm and Me_3Bzm were fully characterized and the closely related complex, shown in the Scheme 6l (L = 1-MeIm), was prepared.[119] A similar complex was also obtained starting from the lariat-type complex of Scheme 6h.[119] Selected bond lengths and angles, involving Co in LCo[(N-CH_2-Chel)]$^+$ cations with L = Me_3Bzm, 1-MeIm and py, are given in Table XII, where they are compared with the corresponding ones in the analogous iminocobaloximes. In the LCo[(N-CH_2-Chel)]$^+$ cations, the Co-C bond lengths are very similar. However, in spite of the large distortion in the three-membered metallocycle, they are significantly shorter (by ~0.1 Å) than those in the iminocobaloxime analogues. The values of the axial Co-N distances, as compared to those of iminocobaloximes, suggest that the axial CH_2 group exerts a *trans* influence smaller than that of a Me group, even if the Co-CH_2 distance is shorter than the Co-Me distance. However, it is not clear whether the large deviation from the ideal value of 180° of the axial fragment may reduce the potential σ donating ability of CH_2. Comparison of the Co-N axial distances for L = Me_3Bzm, 1-MeIm and py indicates that the shortest distance is found for the 1-MeIm derivative, as found in cobaloximes and iminocobaloximes. The overall geometric evidence allows one to clearly distinguish that the bulk of 1-MeIm is smaller than that of Me_3Bzm. Qualitative observations[118] suggested that the short Co-C bond corresponds to a greater stability towards homolysis with respect to iminocobaloximes, in spite of the N_{eq}-Co-C angle (the tilt angle θ of Scheme 5c) of 44°, being dramatically smaller than that of about 90° in the parent complex. Theoretical

calculations have suggested[61] that values of up to 60° (with ω = 109.5°, Scheme 5c) prompts a decrease in the Co-C overlap population of 27%, whereas with a concurrent deformation of ω to 125°, the overlap population decreases by 84%. The behavior of $LCo[(N\text{-}CH_2\text{-}Chel)]^+$ agrees with theoretical calculations, which suggest that ω deformation is more likely to be an important way of the Co-C weakening in B_{12} reactions than θ deformation.[118] At pH 13, the three-membered metallocycle opens and the iminocobaloxime is restored as the $(1\text{-MeIm})_2Co[(DO)(DOH)pn]^+$ cation.[119]

In the past, modifications of the equatorial ligand have been observed in organocobaloxime-type complexes as a consequence of the Co-C cleavage and migration of the alkyl group, although there was uncertainty about the site of migration.[123] Since then, more precise information was obtained.[124, 125] By addition of $NaBH_4$ to $LCo(DBF_2)_2R$ (R = Me, Pr, CH_2Ph and L = py, H_2O), a deep blue diamagnetic solution, indicating formation of a Co(I) species, was obtained. For R = Me, NMR spectra were interpreted as indicating a new Co(I) complex with a modified macrocycle, formed by migration of the axial methyl group to one of the equatorial N donor (Scheme 9a).[124] Other experiments, carried out by Finke and coworkers,[125] showed that photolysis of the iminocobaloximes, on the left side of Scheme 9b, gives the cobalt-to-carbon alkyl rearrangement product, where the benzyl group migrates to the oxime C atom bearing the side Et substituent. The rearrangement was shown to be reversible, and the complex on the right side of Scheme 9b was characterized by X-ray crystallography.[124b] Reduction by $NaBH_4$ of one of the four oxime groups to the imino function was also reported in rhodoximes with phosphines of small bulk.[89]

6. CONCLUSIONS

Thirty years since their discovery as model of the B_{12} coenzyme, alkylcobaloximes have become a classic topic at the interface of organometallic and bioinorganic chemistry, such that their synthesis and basic reactivity have been suggested as subjects for student high level courses. In fact, a recent paper published in the *Journal of Chemical Education*,[126] has presented a demonstration of "*umpolung*" in the reactivity of an organocobaloxime. Although the main interest has been concentrated on the properties, which model the cobalamin family, it is well



SCHEME 9

known that they have also interesting applications as catalysts[127] and as templates[128] in organic reactions.

The relative ease of their synthesis and characterization has allowed (and will allow) knowledge of an incredible number of complexes with a large variety of axial ligands to be obtained and, hence, data with an approximate continuity in the variation of the properties is available. For this reason, alkylcobaloximes probably represent a unique class of compounds in organometallic and coordination chemistry, one in which a systematic analysis of the structure-properties relationships has been performed. On the other hand, they have furnished useful indications concerning the Co-C homolysis mechanism in the B_{12} coenzyme, revealing that the factors affecting not only the Co-C bond but also the *trans* Co-N bond are important in defining homolysis conditions.

For many other problems raised by the recent results obtained from B_{12}-based protein studies, simple models may play a role in the future. For example, the expected increase in the so far limited number of investigations on the Co-S bond properties in simple models, parallel to those in cobalamins, could give insight into the complex mechanism of

the methionine synthase as well as on the nature of the less studied heterolytic cleavage of the Co-Me bond.[23] At the present time, the limited understanding of the functions of this multipurpose enzyme will require investigation of the relationships among the Co(I), Co(II) and Co(III) species involved and their coordination states to determine which factors govern the redox, ion, and radical transfer processes.

Another question needs to be answered : which factors determine the different behavior of MeCbl and adoCbl in the Co-C cleavage?

Certainly, studies on simple models, such as those described in this review, will continue to complement those on the more complex cobalamins and B_{12}-based proteins.[129]

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