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MECHANISTIC ASPECTS OF COENZYME B_{12}-DEPENDENT REARRANGEMENTS. ORGANOMETALLICS AS FREE RADICAL PRECURSORS

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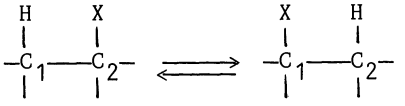
Abstract - The mechanistic aspects of coenzyme B_{12}-dependent rearrangements are discussed. At the present stage it appears that the principal, if not the only, role of coenzyme B_{12} is to serve as the precursor for an organic free radical, generated by homolytic dissociation of the cobalt-carbon bond, which triggers the substrate rearrangement. The determination of cobalt-alkyl bond dissociation energies in organocobalt compounds related to coenzyme B_{12}, and the electronic and structural factors that influence such bond dissociation energies, are discussed. An analogy is developed between the role of coenzyme B_{12} in biological systems as a reversible "free radical carrier" and the role of hemes as reversible dioxygen carriers.

INTRODUCTION

Coenzyme B_{12} (5'-deoxyadenosylcobalamin, abbreviated RCH_2-B_{12}), whose structure is depicted in Fig. 1, serves as a cofactor for a variety of enzymatic reactions, a common feature of which involves the 1,2-interchange of a hydrogen atom and another group (X = OH, NH_2, $CH(NH_2)COOH$, $C(=CH_2)COOH$, etc.) on adjacent carbon atoms according to eq. 1 (Ref. 1-3). A specific example of such a reaction is the deamination of ethanolamine catalyzed by ethanolamine ammonia lyase according to eq. 2 (Ref. 4).



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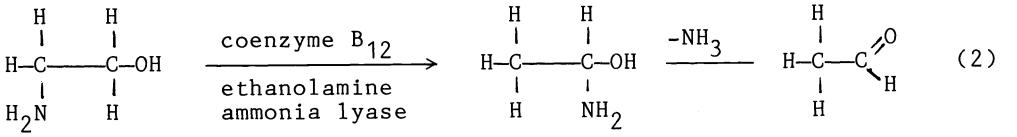

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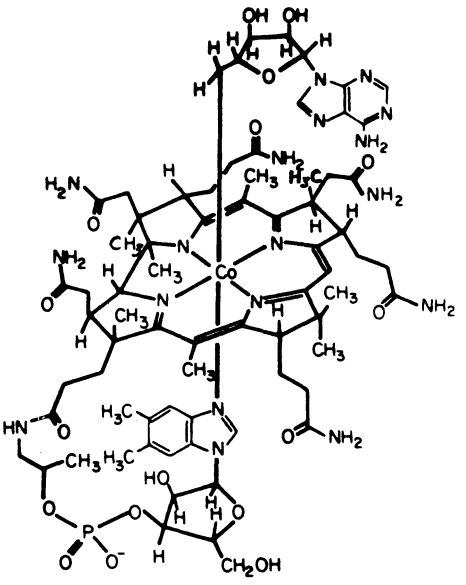


Fig. 1. Coenzyme B_{12}

A widely accepted mechanism of such coenzyme B_{12}-dependent rearrangments, supported by a variety of studies on the enzymatic processes as well as on model systems, is depicted by eq. 3 and 4 (Ref. 1-3).

$$RCH_2\text{-}B_{12} \underset{}{\overset{\text{enzyme}}{\rightleftharpoons}} RCH_2^{\cdot} + B_{12_r} \qquad (3)$$

$$\text{-}C_1(H)(X)\text{-}C_2\text{-} \xrightarrow[(-RCH_3)]{RCH_2^{\cdot}} \left[\text{-}C_1(\cdot)(X)\text{-}C_2\text{-}\right] \longrightarrow \left[\text{-}C_1(X)(\cdot)\text{-}C_2\text{-}\right] \xrightarrow[(-RCH_2^{\cdot})]{RCH_3} \text{-}C_1(X)(H)\text{-}C_2\text{-} \qquad (4)$$

This mechanism encompasses the following sequence of steps: (i) enzyme-induced homolytic dissociation of the cobalt-carbon bond to generate cob(II)-alamin (i.e., vitamin B_{12r}) and a 5'-deoxyadenosyl radical (abbreviated $CHR_2^{\cdot}$), (ii) H-atom abstraction from the substrate to generate a substrate radical and 5'-deoxyadenosine (RCH_3), (iii) rearrangement of the resulting substrate radical (through a mechanism that is not fully understood and that probably differs from substrate to substrate) and (iv) abstraction of an H-atom from RCH_3 by the rearranged radical to complete the rearrangement reaction.

While the possible involvement of the cobalt complex in the substrate radical rearrangement step has been suggested, the evidence for this is inconclusive. At this stage it appears that the principal, if not only, role of the organo-metallic cofactor (i.e., of coenzyme B_{12}) in these reactions is to serve as a precursor for an organic free radical.

Model system studies have played, and promise to continue to play, several important roles in the study and understanding of such coenzyme B_{12}-dependent rearrangements, notably (Ref. 1):

1. In the development of methods of determining cobalt-alkyl bond dissociation energies, including that of coenzyme B_{12}, and in the eludication of

the factors that influence such bond dissociation energies and that may contribute to the weakening and dissociation of the cobalt-carbon bond under the conditions of the enzymatic reactions.

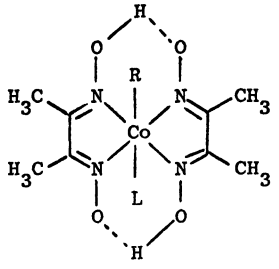
2. In achieving an understanding of the mechanisms of rearrangement of the substrate radical intermediates.

The present paper is concerned particularly with the first of the above themes.

DETERMINATION OF COBALT-ALKYL BOND DISSOCIATION ENERGIES

The role of coenzyme B_{12}, encompassed by the mechanistic interpretation of eq. 3 and 4, implies a very weak cobalt-carbon bond. A troublesome feature of this interpretation has been the absence of direct supporting evidence that the cobalt-carbon bond in coenzyme B_{12} (whose dissociation energy has not yet been determined) is sufficiently weak, that facile homolysis under the mild conditions of the enzymatic reactions is a plausible process. Indeed, hardly any cobalt-alkyl (or other transition metal-alkyl) bond dissociation energies were known reliably, nor were general methods for the determination of such bond dissociation energies (defined as the enthalpies of the process depicted by eq. 5) available, until quite recently (Ref. 5). Accordingly, as detailed below, we have undertaken the development of such methods and have successfully applied them to the determination of cobalt-alkyl bond dissociation energies of organocobalt compounds related to coenzyme B_{12}, notably alkyl-bis(dimethylglyoximato)cobalt(III) compounds (1, abbreviated [R-Co(DH)$_2$L], where DH_2 = dimethylglyoxime) and alkyl(N,N'-disalicyclidene-o-phenylenediamine)cobalt(III) compounds (2, abbreviated [R-Co(Saloph)L] or Co-R). Both classes of compounds have been widely invoked in a variety of contexts as coenzyme B_{12} analogues (Ref. 1).

$$L_nM\text{-}R \longrightarrow L_nM^{\cdot} + R^{\cdot} \qquad (5)$$



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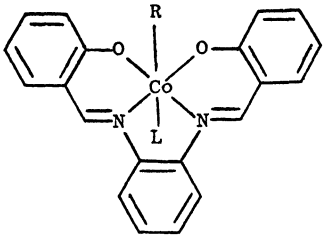

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Equilibrium Method

We have found that for certain organocobalt compounds, exemplified by [(py)(DH)$_2$Co-CH(CH$_3$)C$_6$H$_5$] (py = pyridine) decomposition according to eq. 6 attains a measurable equilibrium under mild conditions (10°-40°C in solvents such as acetone or toluene) permitting the spectrophotometric determination of the equilibrium constant K_6 (1.3 x 10^{-5} $M^{3/2}$ at 25°C) (Ref. 6). The temperature-dependence of K_6 yields the corresponding values of ΔH°_6 (22.1 kcal/mol) and ΔS°_6 (+52 cal/mol°K).

$$[(py)(DH)_2Co^{III}\text{-}CH(CH_3)C_6H_5] \rightleftharpoons [(py)(DH)_2Co^{II}] + C_6H_5CH{=}CH_2 + \tfrac{1}{2}H_2 \qquad (6)$$

$$K_6 = \frac{[(py)(DH_2)Co^{II}][C_6H_5CH=CH_2][H_2]^{\frac{1}{2}}}{[(py)(DH)_2Co^{III}\text{-}CH(CH_3)C_6H_5]} \quad (7)$$

Using available data for the heats of formation of $C_6H_5CH=CH_2$ [$\Delta H°_f$ (25°C) = 35.2 kcal/mol] (Ref. 7) and of the $C_6H_5\dot{C}HCH_3$ radical [$\Delta H°_f$ (25°C) = 33 kcal/mol], (Ref. 8) the cobalt-carbon bond dissociation energy of $[(py)(DH)_2\text{-}Co\text{-}CH(CH_3)C_6H_5]$ (i.e., $\Delta H°$ for eq. 9) can be deduced to be 19.9 kcal/mol using the following thermochemical cycle:

	$\Delta H°$(kcal/mol)	
$[(py)(DH)_2Co^{III}\text{-}CH(CH_3)C_6H_5] \rightleftharpoons [(py)(DH)_2Co^{II}] + C_6H_5CH=CH_2 + \frac{1}{2}H_2$	22.1	(6)
$C_6H_5CH=CH_2 + \frac{1}{2}H_2 \rightleftharpoons C_6H_5\dot{C}HCH_3$	-2.2	(8)
$[(py)(DH)_2Co^{III}\text{-}CH(CH_3)C_6H_5] \rightleftharpoons [(py)(DH)_2Co^{II}] + C_6H_5\dot{C}HCH_3$	19.9	(9)

It should be noted that this determination of the cobalt-carbon bond dissociation energy rests entirely upon thermodynamic considerations and is independent of the mechanism of reaction 6.

Values of the thermodynamic parameters and Co-C bond dissociation energies for various $[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]$ compounds, containing different axial ligands L, determined by this procedure, are listed in Table 1 (Ref. 9).

TABLE 1. Equilibrium and kinetic data for the decomposition of some $[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]$ compounds in acetone according to Eq. 6 (Ref. 9)

L	10^6K_6(25°C) $M^{3/2}$	$\Delta H°_6$ kcal/mol	$\Delta S°_6$ cal/mol°K	$D_{Co\text{-}R}$ kcal/mol	10^4k_6(25°C) sec^{-1}	$\Delta H^‡_6$ kcal/mol	$\Delta S^‡_6$ cal/mol°K
4-NH_2-Pyridine	5.5	23.4	54.3	21.2	4.0	23.1	3.8
4-CH_3-Pyridine	13.6	22.3	52.5	20.1	6.0	21.8	0.9
Pyridine	19.5	21.7	52.2	19.5	7.3	21.6	-0.2
4-CN-Pyridine	47.2	20.1	47.5	17.9	13.1	20.1	-3.9
Imidazole	4.0	23.0	52.5	20.8	1.7	23.0	1.9

Kinetic Method

The systems just described also provide a test of the validity of the kinetic approach to the determination of bond dissociation energies. Although the Co-C bond dissociation energies listed in Table 1 were deduced by a method that does not depend on the mechanism of reaction 6, a plausible mechanism encompasses the sequence of steps depicted by eq. 10-12, the rate-determining step being the homolysis of the Co-C bond. Kinetic measurements confirmed that these decomposition reactions obey first order kinetics, i.e., $-d[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]/dt = k_6[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]$, and yielded the values of $\Delta H^‡_6$ and $\Delta S^‡_6$ listed in Table 1. The finding that the values of $\Delta H^‡_6$ are consistently about 2 kcal/mol higher than the corresponding Co-R bond dissociation energies lends strong support to this mechanistic interpretation

and implies that measurements of $\Delta H^{\ddagger}$ for reactions analogous to eq. 6 (or other reactions whose rates are determined by Co-C bond homolysis) can be used to deduce the corresponding Co-C bond dissociation energies in cases where the reactions do not achieve measurable equilibria.

$$[L(DH)_2Co\text{-}CH(CH_3)C_6H_5] \xrightarrow{k_6} [L(DH)_2Co^{II}] + CH_3\dot{C}HC_6H_5 \quad (10)$$

$$[L(DH)_2Co^{II}] + CH_3\dot{C}HC_6H_5 \xrightarrow{fast} [L(DH)_2Co^{III}\text{-}H] + C_6H_5CH{=}CH_2 \quad (11)$$

$$[L(DH)_2Co^{III}\text{-}H] \xrightarrow{fast} [L(DH)_2Co^{II}] + \tfrac{1}{2}H_2 \quad (12)$$

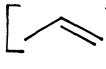
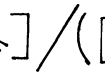
Results of such kinetic measurements on other $[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]$ compounds, notably containing tertiary phosphine axial ligands, are listed in Table 2 (Ref. 11).

TABLE 2. Effect of axial ligands on the kinetics of decomposition of $[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]$ compounds in acetone according to eq. 6 (Ref. 10)

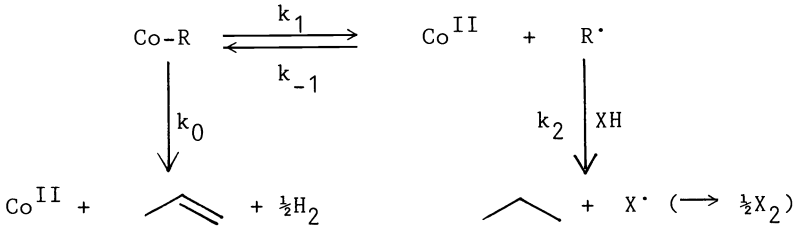
L	Cone Angle deg.	10^3k_6(25°C) sec^{-1}	$\Delta H_6^{\ddagger}$ kcal/mol	$\Delta S_6^{\ddagger}$ cal/mol°K	$D_{Co\text{-}R}$ kcal/mol
$P(CH_3)_2C_6H_5$	122	0.10	25.9	10.5	24
$P(CH_2CH_2CN)_3$	132	3.1	22.1	4.5	20
$P(n\text{-}C_4H_9)_3$	132	1.2	22.8	5.1	21
$P(CH_3)(C_6H_5)_2$	136	1.4	-	-	-
$P(C_2H_5)(C_6H_5)_2$	140	3.3	21.3	1.9	19
$P(C_6H_5)_3$	145	19.2	19.3	-1.4	17
$P(cyclo\text{-}C_6H_{11})_3$	170	480	-	-	-

The kinetic approach also has been applied to the determination of cobalt-alkyl bond energies in some organocobalt Schiff base compounds, [R-Co(Saloph)L] (2, abbreviated Co-R, L = pyridine) (Ref. 11). Such compounds were found to undergo thermal decomposition at conveniently measurable rates in pyridine solution at temperatures below 100°C in the presence of efficient radical traps such as the hydrogen donor, $n\text{-}C_8H_{17}SH$ (abbreviated XH). When R = n-propyl or isopropyl (i.e., an alkyl containing a β-hydrogen atom) the reaction yielded a misture of propene and propane, exhibiting the kinetics (eq. 13) and product distribution (eq. 14) corresponding to Scheme I where CoR = $(py)(Saloph)Co\text{-}C_3H_7$ and $Co^{II} = (py)(Saloph)Co^{II}$ (Ref. 11).

$$\frac{-d\ln[CoR]}{dt} = k_{obsd} = k_0 + \frac{k_1k_2[XH]}{k_{-1}[Co^{II}] + k_2[XH]} \quad (13)$$

$$\left[\text{  }\right] \Big/ \left(\left[\text{  }\right] + \left[\text{}\right]\right) = k_0/k_{obsd} \quad (14)$$

Scheme I



The probable mechanism of the olefin-elimination step corresponding to k_0 is that depicted by eq. 15, i.e., β-hydrogen transfer between the $C_3H_7\cdot$, Co^{II} geminate radical pair, followed by rapid decomposition of the resulting cobalt-hydride. Such β-hydrogen abstraction has been shown to be fast in closely related systems and, in one case, to occur within the cage lifetime of such a radical pair (Ref. 12). In any event, since k_0 is small compared with k_1 (in no case greater than ca 3%) its interpretation does not seriously affect the interpretation of the major k_1-derived radical pathway. For R = neopentyl or benzyl (i.e., lacking a β-hydrogen atom) the olefin-producing path was absent. Accordingly, the organic products were exclusively neopentane and toluene, and the kinetics conformed to eq. 13 with $k_0 = 0$.

$$[Co\text{-}C_3H_7] \longrightarrow \overline{[Co^{II}],C_3H_7\cdot} \longrightarrow C_3H_6 + [CoH] \longrightarrow C_3H_6 + [Co^{II}] + \tfrac{1}{2}H_2 \qquad (15)$$

The results of these kinetic measurements are summarized in Table 3 (Ref. 11) together with the Co-R bond dissociation energies (D_{Co-R}), deduced from $\Delta H_1^{\ddagger}$ on the assumption that recombination of Co^{II} and R· is diffusion controlled, i.e., that $\Delta H_{-1}^{\ddagger} \sim 2$ kcal/mol, hence $D_{Co-R} \sim \Delta H_1^{\ddagger} - 2$ kcal/mol.

All the Co-alkyl bond dissociation energies determined in these studies, both for $[R\text{-}Co(DH)_2L]$ compounds (Tables 1 and 2) and [R-Co(Saloph)L] compounds (Table 3), lie in the range 17-25 kcal/mol. Comparable values have recently been estimated for some alkylcobalamins by a similar kinetic procedure (Ref. 13). These values lie in an appropriately low range to be consistent with, and supportive of, the proposed role of Co-C bond homolysis in coenzyme B_{12}-promoted reactions according to eq. 3 and 4. Co-C bond homolysis probably also is involved in other reactions of organocobalt compounds, for example the photochemical or thermal insertion of O_2 according to eq. 16 (Refs. 14 and 15).

$$L_nCo\text{-}C \underset{}{\overset{h\nu \text{ or } \Delta}{\rightleftharpoons}} L_nCo^{II} + R\cdot \xrightarrow{O_2} L_nCo^{II} + RO_2\cdot \longrightarrow L_nCo\text{-}OO\text{-}R \qquad (16)$$

TABLE 3. Kinetic data for the decomposition of some [R-Co(Saloph)L] compounds according to Scheme I (Ref. 11)

R	k_0(70°C) sec^{-1}	$\Delta H_0^{\ddagger}$ kcal/mol	$\Delta S_0^{\ddagger}$ cal/mol°K	k_1(70°C) sec^{-1}	$\Delta H_1^{\ddagger}$ kcal/mol	$\Delta S_1^{\ddagger}$ cal/mol°K	$(k_{-1}/k_2)_{70°C}$	D_{Co-R} kcal/mol
$-CH_2CH_2CH_3$	1.0×10^{-5}	23.4	-15.1	4.7×10^{-4}	27.1	2.6	10	25
$-CH_2(CH_3)_2$	1.9×10^{-3}	19.8	-15.5	5.7×10^{-2}	21.8	-2.9	93	20
$-CH_2C(CH_3)_3$	-	-	-	3.4×10^{-2}	20.3	-6.2	8	18
$-CH_2C_6H_5$	-	-	-	1.2×10^{-2}	23.6	1.3	70	22

EFFECTS OF ELECTRONIC AND STERIC PARAMETERS ON COBALT-ALKYL BOND DISSOCIATION ENERGIES

The Co-C bond dissociation energies listed in Table 1 span the range 17.9 to 21.2 kcal/mol. For the series of complexes containing p-substituted pyridines as the axial ligands, for which the steric influences presumably are constant, the Co-C bond dissociation energy increases with the basicity of the axial ligand L according to the trend depicted in Figure 2. This is not unexpected since dissociation of the Co-C bond according to eq. 9 involves a decrease in the formal oxidation state of cobalt from +3 to +2. By favoring the higher oxidation state more basic ligands should, accordingly, stabilize the organocobalt compound and reduce the driving force for Co-C bond homolysis. Analogous reasoning has been invoked to explain the increase in reactivity of $Co^{II}(DH)_2L$ complexes toward organic halides with increasing basicity of L (Ref. 16).

The influence of steric factors on Co-C bond dissociation energies is illustrated in Table 2 and Fig. 3. When L is a tertiary phosphine ligand the value of k_6 was found to increase markedly (and the value of $\Delta H_6^{\ddagger}$, and hence of D_{Co-R}, to decrease correspondingly) with the cone angle (Ref. 17) of L, e.g., from 1.0×10^{-4} sec^{-1} at 25°C ($\Delta H_6^{\ddagger}$ = 26 kcal/mol, $D_{Co-R} \sim$ 24 kcal/mol) for L = dimethylphenylphosphine (cone angle 122°), through 1.9×10^{-2} sec^{-1} ($\Delta H_6^{\ddagger}$ = 19 kcal/mol, $D_{Co-R} \sim$ 17 kcal/mol) for L = triphenylphosphine (cone angle 145°) to ca 1.5 sec^{-1} for L = tricyclohexylphosphine (cone angle 170°).

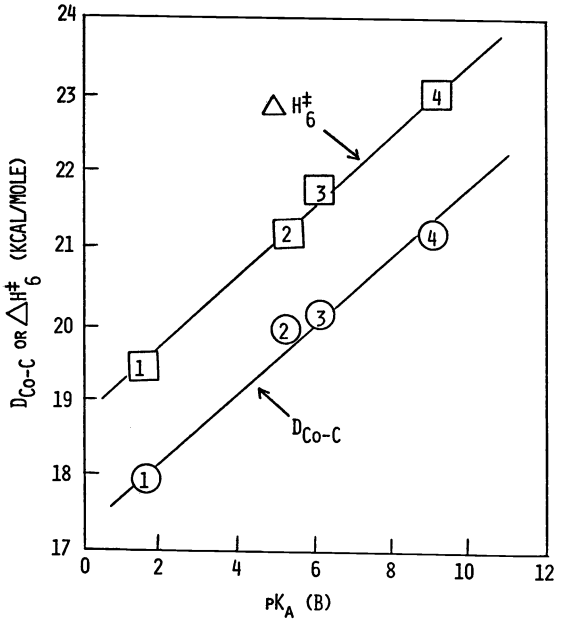


Fig. 2. Dependence of D_{Co-C} and $\Delta H_6^{\ddagger}$ on pK_a of L. B: 1, 4-CN-pyridine; 2, pyridine; 3, 4-CH_3-pyridine; 4, 4-NH_2-pyridine.

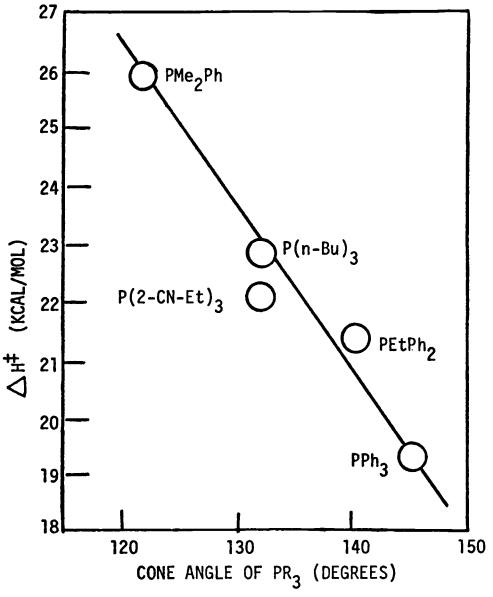


Fig. 3. Effect of the cone angle of the axial phosphine ligand (L) on $\Delta H_6^{\ddagger}$ for the decomposition of $[L(DH)_2Co\text{-}CH(CH_3)C_6H_5]$ (data from Table 2).

Marked steric influences also are apparent in the trend of D_{Co-R} bond dissociation energies of (py)(Saloph)Co-R compounds listed in Table 3. These D_{Co-R} values span the range 18-25 kcal/mol. While the trend, in part (e.g., n-propyl > benzyl), parallels that for other alkyl bond dissociation energies (e.g., R-H), the low values of D_{Co-R} for isopropyl and neopentyl, compared with benzyl, attest to the importance of steric effects in such cobalt complexes. In this context our results suggest that neopentyl is at least as sterically demanding as isopropyl.

The influence of steric factors also is reflected in the results of structural studies on $[L(DH)_2Co\text{-}R]$ compounds. Such results, summarized in Table 4, reveal significant lengthening of the Co-C bond (as well as other distortions reflecting steric hindrance) with increasing steric bulk of either the R or L group (Ref. 18).

TABLE 4. Selected Co-C and Co-L bond lengths in $[L(DH)_2Co-R]$ compounds (Ref. 18)

R	L	Co-C (Å)	Co-L (Å)
CH_3	H_2O	1.990	2.058
"	Pyridine	1.998	2.068
"	$P(CH_3)_3$	2.015	2.294
"	$P(C_6H_5)_3$	2.026	2.418
$CH_2C(CH_3)_3$	H_2O	2.044	2.056
"	Pyridine	2.060	2.081
"	$P(CH_3)_3$	2.084	2.316
"	$P(C_6H_5)_3$	2.118	2.460

COMPARISON OF DIFFERENT ORGANOCOBALT COMPOUNDS AND EXTENSION TO ORGANOCOBALAMINS

The approaches described above have not been applied successfully to the determination of cobalt-carbon bond dissociation energies in cobalamins, although the prospects of accomplishing this would appear to be promising. Nevertheless, some inferences about cobalt-carbon bond dissociation energies in cobalamins can be drawn from the results obtained on other organocobalt compounds. Comparisons of the redox properties of various cobalt complexes, and of the reactivities of various cobalt(II) complexes (including vitamin B_{12r}) toward organic halides suggests that cobalamins fall somewhere between the dimethylglyoxime and Schiff base cobalt complexes discussed in this paper (Ref. 1). Comparison of the corresponding Co-H bond dissociation energies suggests a similar trend, as does comparison of the stabilities of the corresponding cobalt-benzyl compounds (benzyl cobalamin being significantly less stable than the $Co(DH)_2$-benzyl analogues) (Ref. 1). On the basis of such comparisons it seems likely that the 5'-deoxyadenosyl-cobalt bond dissociation energy in coenzyme B_{12} is in the range of cobalt-alkyl bond dissociation energies that we have determined for model compounds, notably of the Co(Saloph)-R compounds, i.e., 18-25 kcal/mol.

FACTORS CONTRIBUTING TO COBALT-CARBON BOND WEAKENING AND DISSOCIATION

Possible causes of enzyme-induced cobalt-carbon bond weakening and bond dissociation include: (1) axial ligand substitution, i.e., displacement of the 5,6-dimethylbenzimidazole ligand of coenzyme B_{12} by another ligand (e.g., a sulfur-bonded cysteine residue) which weakens the cobalt-carbon bond through electronic or steric influences, (2) oxidation or reduction of the coenzyme which has been shown to induce cobalt-carbon bond dissociation in model organocobalt compounds (Ref. 1) and (3) conformational distortion of the corrin ring resulting in sterically unfavorable bending of the latter upward toward the 5'-deoxyadenosyl group. The influences of steric factors on cobalt-carbon bond dissociation energies identified in the studies described in this paper, as well as other lines of evidence, favor the last of the above interpretations (Ref. 1).

COMPARISONS WITH THE REVERSIBLE BINDING OF DIOXYGEN

The weakness of the cobalt-carbon bonds in coenzyme B_{12} and related organocobalt compounds (collectively denoted as $[L_5Co^{III}R^-]$) permits homolytic dissociation of such bonds to occur under mild conditions (below 100°C).

Because recombination of the resulting cobalt(II) complex and free radical generally is rapid such dissociation processes, depicted by eq. 17, are readily reversible. Such processes also can be described as (inner sphere) redox changes and, as already noted, the influence of electronic factors on cobalt-carbon bond dissociation energies (Table 1 and Fig. 2) can be interpreted in terms of the accompanying changes in the oxidation state of the cobalt (eq. 17).

$$[L_5Co^{III}R^-] \rightleftharpoons [L_5Co^{II}] + R^\cdot \qquad (17)$$

There is at least a formal parallel between the process depcited by eq. 17 and the reversible binding of dioxygen by cobalt or iron complexes (e.g., myoglobin) in accord with eq. 18 and 19.

$$[L_5Co^{III}O_2^-] \rightleftharpoons [L_5Co^{II}] + O_2 \qquad (18)$$

$$[L_5Fe^{III}O_2^-] \rightleftharpoons [L_5Fe^{II}] + O_2 \qquad (19)$$

This parallel is quite far-reaching and is reflected in trends in the dependence of $Co-O_2$ (and presumably $Fe-O_2$) bond dissociation free energies and enthalpies on electronic factors that parallel those of Co-R bond dissociation trends (Table 5 and Fig. 4) (Refs. 19 and 20). Indeed, typical $Co-O_2$ bond dissociation energies in such reversible oxygen carriers lie in the same range (10-20 kcal/mol) as the values of the Co-R bond dissociation energies that we have determined.

In the light of these considerations it is not unreasonable to describe the role of coenzyme B_{12} in biological systems as that of a "reversible free radical carrier" analogous to the role of myoglobin or hemoglobin as a "reversible oxygen carrier." Thus, coenzyme B_{12} fulfills its biochemical role by serving as a "free radical reservoir," from which (5'-deoxyadenosyl) free-radicals are reversibly released under mild conditions, just as oxyhemoglobin serves as a reservoir for the storage and reversible release of dioxygen. Significant questions, in this context, relate to the alternative choices of cobalt and iron, as well as of the corrin and porphyrin ligand systems, for these two parallel functions.

TABLE 5. Effect of axial ligands (L) on the reversible binding of O_2 to protophorphyrin IX dimethyl ester cobalt(II) [LCo^{II}(P)] and N,N'-ethylenebis(benzoylacetiminato)cobalt(II) [LCo^{II}(benacen)] in toluene

Co Complex	L	pK_a of L	Log K_{O_2} mm^{-1}	$\Delta H°$ kcal/mol	$\Delta S°$ cal/mol°K	Ref
[LCo^{II}(P)]	4-CN-Py	1.8	-3.8 (-45°C)	-	-	19
"	Py	5.2	-2.84 "	-9.2	-53	19
"	4-t-Bu-Py	6.0	-2.77 "	-9.8	-56	19
"	4-NH_2-Py	9.1	-2.05 "	-9.9	-53	19
[LCo^{II}(Benacen)]	4-CN-Py	1.8	-2.68 (-21°C)	-16.9	-77	20
"	Py	5.2	-2.03 "	-16.6	-75	20
"	3,4-$(CH_3)_2$Py	6.4	-1.66 "	-16.8	-75	20

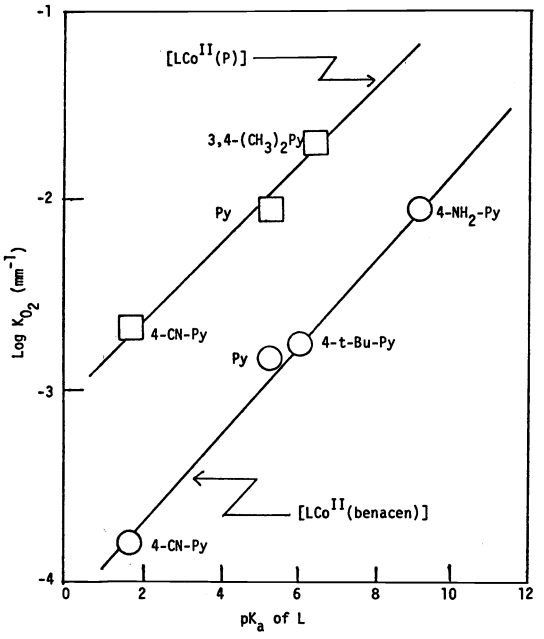


Fig. 4. Effect of axial ligands (L) on the reversible binding of O_2 to protoporphyrin IX ester cobalt (II) [$LCo^{II}(P)$] and N,N'-ethylene-bis(benzoylacetiminato)-cobalt (II) [LCo^{II}(benacen)] in toluene.

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