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Coenzyme B₁₂ Co-C Bond Homolysis: Insights from Qualitative Molecular Orbital Theory

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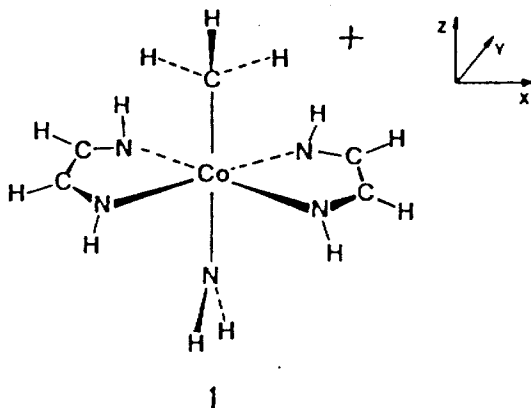
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From extensive investigations into the factors which influence Co-C bond cleavage in coenzyme B₁₂,¹ a few features are now well established: (i) the enzymatic cleavage is homolytic; (ii) the measured dissociation energy is ca. 25-30 kcal/mol;^{1b,d} (iii) this energy increases with increasing basicity of the trans ligand in relevant organocobalt compounds.^{1b} Many structures of such compounds with different substituents at both the axial carbon and nitrogen ligating atoms have shown that in some cases the Co-C and Co-N bonds can elongate by >0.1 Å from unstrained values (Co-C ≈ 2.00, Co-N ≈ 2.10 Å).² This elongation is evidence for the dependence of bond length on steric effects and on the trans influence. Approximate ab initio studies of geometrical deformations introduced in a model system did not reveal the existence of any major electronic effect.³

Herein we outline some insights, based on qualitative MO and perturbation theories,⁴ into the Co-C dissociation process. The shortcomings of EHMO⁵ in providing correct bond distances do not obscure the essential effects which our study illustrates. The model employed, **1**, contains simplified ligands, especially for the corrin.



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(1) (a) The most comprehensive review articles are in: B₁₂; Dolphin, D., Ed.; Wiley-Interscience: New York, 1982. See: (b) Halpern, J. *Science (Washington, D.C.)* 1985, 227, 69. (c) Finke, R. G.; Schiraldi, D. A.; Mayer, B. J. *Coord. Chem. Rev.* 1984, 54, 1. Reference 2 for recent reviews. (d) Hay, B. P.; Finke, R. G. *J. Am. Chem. Soc.* 1986, 108, 4820.

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(6) In B₁₂ the coordination environment of the metal is not perfectly octahedral and the four equatorial ligands are not all equivalent. The NH₂ group simulates the two-electron σ-donor function of benzimidazole as well as some of its π-donor character.

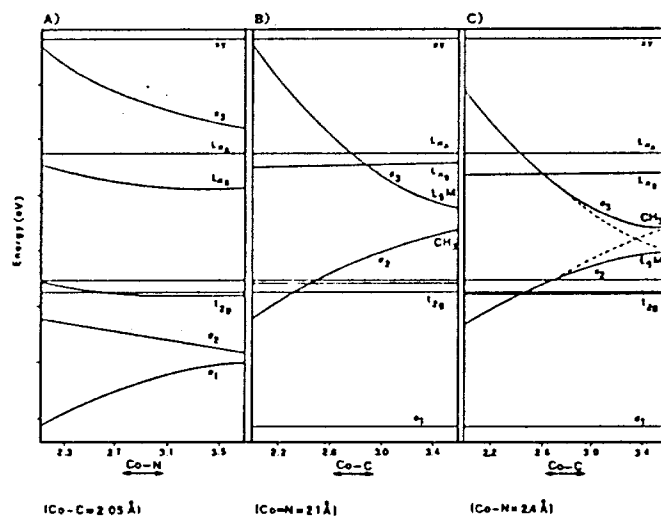
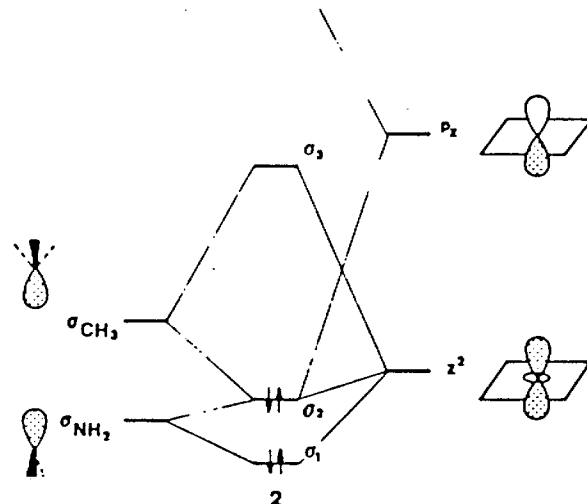


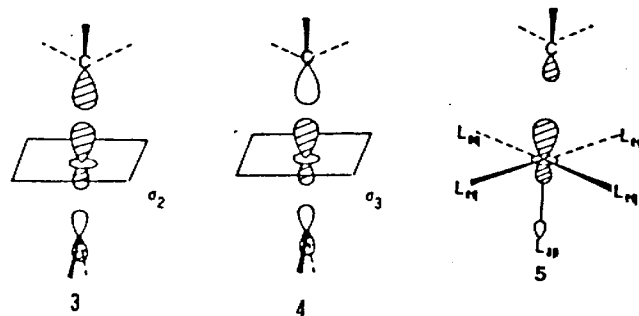
Figure 1. Evolution of MOs for the model [(NH₂)Co(HN=CH-CH=NH)₂Co(CH₃)]⁺: (A) the Co-N (amido group) bond is elongated with Co-C fixed at 2.05 Å; (B) the Co-C bond is elongated with Co-N fixed at 2.1 Å; (C) the Co-C bond is elongated with Co-N fixed at 2.4 Å.

However, our interest focuses on the axial interactions along N-Co-C as illustrated in **2**.⁷ The metal atom in the square plane



contributes with two fundamental levels: i.e., almost pure z^2 and p_z orbitals. The groups NH₂ and CH₃ each utilize a σ hybrid. For electronegativity reasons, σ(NH₂) lies below σ(CH₃), which is closer to z^2 .

Of the four MOs, the two lower ones (σ₁ and σ₂) are populated. An oversimplified view of the nature of σ₁ and σ₂ is to equate them with the bonding combinations $z^2-\sigma(\text{NH}_2)$ and $p_z-\sigma(\text{CH}_3)$, respectively. Actually, second-order perturbations complicate the composition of σ₂, **3**. Both the metal z^2 and σ(NH₂) levels are



(7) As found by others,⁸ we observe that the important axial MOs are perturbed by p combinations of the conjugated equatorial ligands (the corrinoid ring in coenzyme B₁₂). However, the perturbation does not alter other important features and may be disregarded as a first approximation.

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mixing in an antibonding manner. In essence σ_2 has Co-C bonding and Co-N antibonding character. Finally σ_3 , 4, is both Co-C and Co-N antibonding. This latter MO may be also viewed as one member of the e_g set (z^2 and xy) of an octahedral complex.

In Figure 1A, the effects of Co-N bond elongation on the σ levels (Co-C maintained at 2.05 Å) are easily understood. In the lower energy region, below the populated octahedral t_{2g} set, σ_1 rises due to the loss of M-N bonding whereas σ_2 falls slowly because of its partial M-N σ^* character. For the same reason σ_3 also falls. The other e_g level (xy) is unaffected. Finally, two π^* combinations of the equatorial ligands,⁹ located between t_{2g} and e_g , are unimportant for our considerations. What matters is that the total energy variation¹⁰ is not large since σ_1 and σ_2 have opposite behavior and lie below the frontier region. In agreement with more sophisticated calculations,³ a Co-N elongation from 2.1 to 2.4 Å costs only 6-8 kcal/mol. In terms of the σ interaction between the combining fragments L_3M^{11} and CH_3 ,¹² 5, the larger the p_z - z^2 mixing at the metal atom, the more developed is the σ lobe of L_3M and the better is the overlap with $\sigma(CH_3)$. The pd hybridization in L_3M increases with the amount of antibonding introduced by the axial ligand.⁹ In the present case it depends on the relative position of the amide group and on its strength as a base, in agreement with point iii above.

Next the Co-C bond is elongated with Co-N set at 2.1 Å (Figure 1B). The level σ_1 , Co-N bonding, is hardly affected, whereas σ_2 destabilizes because it loses Co-C bonding energy. The Co-C antibonding σ_3 MO stabilizes.¹³ When the Co and C atoms are definitely separated (Co-C > 3.6 Å), the MOs σ_2 and σ_3 coincide with the CH_3 and L_3M lobes which combine in 5. In other words, σ_2 and σ_3 correlate with the methyl and pd metal hybrids, respectively. As a consequence, the two Co-C bonding electrons in σ_2 become more and more localized in the methyl group. Were the process not obstructed by a significant energy increase (mainly that lost by the two electrons in σ_2), the Co-C cleavage would be heterolytic with formation of a methyl anion and a square-pyramidal d^6 metal complex.

As mentioned, the hybridization and energy of the L_3M σ orbital are strongly dependent on the position of the trans axial ligand. It may happen that for a certain Co-N elongation the final relative positions of σ_2 and σ_3 levels are reversed. Figure 1C shows the evolution of the MOs for the Co-C elongation, with Co-N fixed at 2.4 Å. Apparently, the solid lines behave similarly to Figure 1B but the smoothness of the σ_2 and σ_3 curves hides an essential feature: namely, a strongly avoided crossing region. According to electron transfer reaction theory,¹⁴ this region accounts for the possibility of promoting a *sudden electron jump*. In other words, rather than having an ionic separation of the fragments (CH_3^- and L_3Co^{III}), the system may convert into a radical pair (CH_3^0 and L_3Co^{II}). In order to switch character the two levels, σ_2 and σ_3 must intermix. A Mulliken analysis of the atomic charges confirms that a major variation is associated with the dashed lines region. In fact, for the diamagnetic ground-state model with short Co-C and Co-N bonds, the charge of the carbon atom is somewhat negative and that of the metal slightly positive. As the Co-C bond lengthens, the carbon atom becomes smoothly more negative and the cobalt atom more positive. However, for a stretched Co-N bond (e.g., 2.4 Å), the carbon becomes more positive and the metal negative due to a progressively larger metal character in the doubly populated σ_2 orbital.

The mono-electronic wavefunctions in EHMO are inadequate in evaluating reliable energetics associated with the *sudden electron jump*. The energy of the diradical system is computed to be about 60-70 kcal/mol higher than that of the diamagnetic octahedral structure. However, in response to changes in relevant interelectronic effects, it may be profitable to promote an electron in a higher level so that the total energy loss is compensated. The process is probably analogous to the dissociation of Na-Cl into Na and Cl atoms.¹⁵

In conclusion, we have gained some idea of the conditions required for Co-C homolysis in coenzyme B₁₂. A weakening of the trans Co-N bond forces the carbon and metal orbitals to mix at nonbonding distances and is the necessary step for the genesis of the alkyl radical. The energetics required for such a Co-N weakening are low and the activation may be provided by minor conformational rearrangements introduced by the binding of coenzyme to apoenzyme or the binding of substrate to holoenzyme.¹

Acknowledgment. L.G.M. thanks the NIH for support through Grant GM 29225.

(15) An MO treatment also leads to the wrong products (Na^+ and Cl^- ions) but the problem is solved at the VB level by mixing ionic and covalent contributions to the wavefunction.¹²

Probing the Binding Site of Bacteriorhodopsin with a Fluorescent Chromophore

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The discovery of bacteriorhodopsin (bR), the protein pigment of the purple membrane of the halophilic microorganism *Halo-bacterium halobium*,¹ had a significant impact on the field of bioenergetics and on the study of visual photochemistry.² It was found that photobiological activity of bR is due to a pigment consisting of a retinal (all-trans) chromophore covalently bound to a protein through a protonated Schiff base.

Electrostatic interactions in the binding site of bacteriorhodopsin play an important role in its function and properties. Its red-shifted absorption (relative to a protonated Schiff base in methanol solution) was attributed in part to a weaker interaction between the positively charged Schiff base nitrogen and its counteranion³ and to electrostatic interaction of the retinal polyene with a dipole introduced by the protein in the vicinity of the β -ionone ring.^{3d,4} The electrostatic interaction may also play a role in catalyzing the thermal isomerization of all-trans to 13-cis-bR in the dark adaption reaction and in the thermal isomerization of the M_{412} intermediate.⁵ In addition, it was proposed⁶ that the reduction

* Incumbent of the Morris and Ida Wolf Career Development Chair.

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(9) The levels are largely in-phase (S) and out-of-phase (A) combinations of a π^* orbital of the ligand $HN=CH-CH=NH$.

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