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

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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 EHMO[5] 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.

(2) Bresciani-Pahor, N.; Forcolin, M.; Marzilli, L. G.; Randaccio, L.; Summers, M. F.; Toscano, P. J. *Coord. Chem. Rev.* **1985**, *63*, 1. Marzilli, L. G.; Summers, M. F.; Bresciani-Pahor, N.; Zangrando, E.; Charland, J.-P.; Randaccio, L. *J. Am. Chem. Soc.* **1985**, *107*, 6880.

(3) Christianson, D. W.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1985**, *107*, 2682.

(4) The most recent and comprehensive summary of qualitative MO theory, with special emphasis on transition-metal elements, is in: Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley-Interscience: New York, 1985.

(5) Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397. Hoffmann, R.; Lipscomb, W. H. *Ibid.* **1962**, *36*, 1379, 3489; **1962**, *37*, 2872.

(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

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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 (σ_1 and σ_2) are populated. An oversimplified view of the nature of σ_1 and σ_2 is to equate them with the bonding combinations z^2–σ(NH₂) and p_z–σ(CH₃), respectively. Actually, second-order perturbations complicate the composition of σ_2, **3**. Both the metal z^2 and σ(NH₂) levels are

3   **4**   **5**

(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.

(8) Salem, L.; Eisenstein, O.; Anh, N. T.; Burgi, H. B.; Devaquet, A.; Segal, A.; Veillard, A. *Nouv. J. Chim.* **1977**, *1*, 335.

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 variation[10] 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_5M[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_5M and the better is the overlap with $\sigma(CH_3)$. The pd hybridization in L_5M 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_5M 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_5M 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_5Co^{III}), the system may convert into a radical pair (CH_3^0 and L_5Co^{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 monoelectronic 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 B_{12}. 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]

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(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 *Halobacterium 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 counteranion[3] 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 proposed[6] that the reduction

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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 $HN=CH-CH=NH$.

(10) The EHMO method assigns an absolute energy minimum at Co–C and Co–N distances both equal to 2.0 Å.

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(12) Gimarc, B. M. In *Molecular Structure and Bonding*; Academic: New York, 1979.

(13) Crossings of σ_2 and σ_3 with t_{2g} and ligand π^* levels have no major consequences.

(14) The argument is exhaustively treated in the textbook: Salem, L. *Electrons in Chemical Reactions: First Principles*; Wiley-Interscience: New York, 1982. For a more specific theoretical treatment of electron-transfer reactions concerning metal elements, see: (a) Burdett, J. K. *Inorg. Chem.* **1978**, *17*, 2537. (b) Burdett, J. K. *Comments Inorg., Chem.* **1981**, *1*, 85.

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