Spin-Pairing Model of Dioxygen Binding and Its Application to Various Transition-Metal Systems as well as Hemoglobin Cooperativity

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Understanding the various ways to activate dioxygen with metal-containing systems is one of the most important challenges in chemistry. The findings have implications in the areas of improving commercial oxidations,[1] overcoming the inefficiency of the oxygen electrode in fuel cells,[2a,b] and understanding the oxidation processes that occur in biological systems.[3a,b] Determining the factors that influence the strength of the metal–dioxygen interaction and electronic nature of the bound dioxygen will be essential to acquire the full understanding necessary to solve these problems.

Systematic approaches to dioxygen activation by metals require insight about the electronic nature of the bound O_2 fragment. The cobalt(II) adducts of dioxygen are particularly well suited for an investigation of electronic structure because they possess at least one unpaired electron, making them ideal for EPR studies. Accordingly, these systems have been the most extensively studied and provide us with the greatest amount of information regarding the metal–dioxygen interaction. Three different types of geometries have been discovered to date for cobalt–dioxygen compounds, the end-on bonded (A),[4] bridged (B),[4] and ring-bonded mode (C)[5] shown.[6]
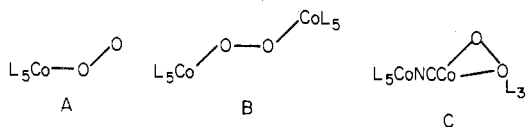
Our main concern will be with the formulation of a spin-pairing model to describe the bonding in complexes of type A. The extension of this model to accommodate systems with the structures shown in B and C will also be discussed briefly.

Though this topic of dioxygen bonding has been thoroughly studied and reviewed,[4,7–12] many significant questions remain. For example, what factors govern the metal–dioxygen bond strength? What properties of the metal determine the extent of electron transfer and the nucleophilicity of the bound O_2? What factors determine the geometry that is obtained when dioxygen coordinates to metals? Finally, what influence do these geometric and electronic variations have on the re-

Table I

α	β	nature of O_2 adduct	ET^a	ψ_1
0	1	Co-O_2^-	1.0	100% O_2
$2^{1/2}/2$	$2^{1/2}/2$	Co-O_2	0	50% Co, 50% O_2
1	0	Co-O_2^+	−1.0	100% Co

^{a} $ET \approx 2(1 - \alpha^2) - 1$. Note that the unpaired electron will reside in the O_2-based MO regardless of the extent of electron transfer (e.g., the value of α).

activity of the bound O–O? The spin-pairing model provides a basis for understanding and predicting answers to these questions.

The Spin-Pairing Model

The spin-pairing model of binding dioxygen to metals can be viewed as a typical free-radical reaction in which metal spins pair up with either one or two of the unpaired π^* electrons of dioxygen. This description is similar to that proposed by Wayland et al.[13a,b] to explain observations pertinent to the coordination of diatomic molecules, e.g., CO, NO, and O_2. The case of five-coordinate cobalt(II) complexes is illustrated in Figure 1.

One of the two π^* orbitals of O_2 overlaps with the a_1 (d_{z^2}) orbital of cobalt(II) to form a σ bonding molecular orbital ψ_1 containing two electrons, while the corresponding σ^* antibonding molecular orbital, ψ_3, is empty. The second π^* orbital of O_2 is orthogonal to d_{z^2}. Since there are no other unpaired metal eletrons in the system and π-back bonding is small (vide infra), ψ_2 remains essentially oxygen based and contains the unpaired electron. Neglecting, for convenience, the d-orbital

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(2) (a) Damjanovic, A. *Mod. Aspects Electrochem.* 1969, 5, 369. (b) Appleby, A. J. *Ibid.* 1974, 9, 369.
(3) (a) Kahn, M. T.; Martell, A. E. "Homogeneous Catalysis by Metal Complexes"; Academic Press: New York, 1974. (b) Hayaishi, O. "Molecular Mechanisms of Oxygen Activation"; Academic Press: New York, 1974.
(4) Valentine, J. S. *Chem. Rev.* 1973, 73, 235, and references therein.
(5) Halpern, J.; Goodall, B. L.; Khare, G. P.; Liu, H. S.; Pluth, J. J. *J. Am. Chem. Soc.*, 1975, 97, 2301.
(6) In these systems L can be monodentate or the subscript suitably adjusted for multidentate ligands. L can also represent different ligands in the same complex. Since some L groups are ionic, charges have not been indicated on the above species but are readily figured out for any specific system.
(7) Henrici-Olive, G.; Olive, S. *Angew. Chem., Int. Ed. Engl.* 1974, 13, 29.
(8) Basolo, F.; Hoffman, B.; Ibers, J. *Acc. Chem. Res.* 1975, 8, 384.
(9) Vaska, L. *Acc. Chem. Res.* 1976, 9, 175.
(10) McLendon, G.; Martell, A. E. *Coord. Chem. Rev.* 1976, 19, 1.
(11) Collman, J. P. *Acc. Chem. Res.* 1977, 10, 265.
(12) Jones, R. D.; Summerville, D. A.; Basolo, F. *Chem. Rev.* 1979, 79, 139.
(13) (a) Wayland, B. B.; Minkiewiez, J. V.; Abd-Elmageed, M. E. *J. Am. Chem. Soc.* 1974, 96, 2795. (b) Wayland, B. B.; Abd-Elmageed, M. E. *Ibid.* 1974, 96, 9809.

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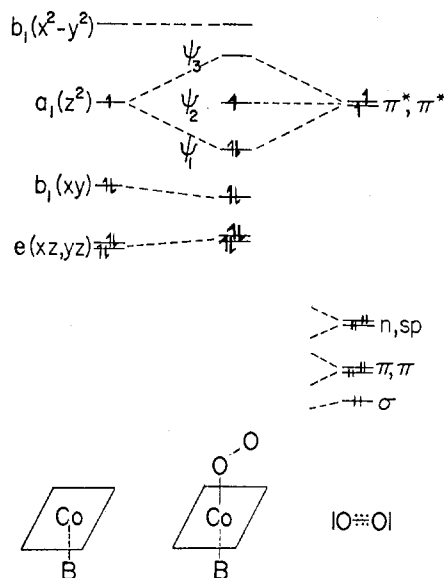
Figure 1. Molecular orbital diagram for the dioxygen adduct of Co(II). One electron from one O_2 π^* orbital spin pairs with one unpaired electron from Co(II) to form the ψ_1 molecular orbital; the remaining unpaired electron is in an O_2 π^* orbital.

mixing and minor overlap with other orbitals, ψ_1, ψ_2, and ψ_3 have the form

$$\psi_3 = \beta(d_{z^2}) - \alpha(\pi_1{}^*)$$

$$\psi_2 = \pi_2{}^*(a2p_1 + b2p_2), \; \beta = (1 - \alpha^2)^{1/2}$$

$$\psi_1 = \alpha(d_{z^2}) + \beta(\pi_1{}^*)$$

In this model, the nature of the bound dioxygen is seen to be related to the coefficients of molecular orbital ψ_1 which does not contain the unpaired electron. The various charges that can be accommodated on the bound O_2 by this model are indicated in Table I where it is shown that O_2, $O_2{}^{\delta+}$, or $O_2{}^{\delta-}$ situations could exist.

The formulation of this model is a direct result of our reanalysis of the EPR spectra of the O_2 adducts.[14] The [17]O anisotropic hyperfine coupling constant indicates that one unpaired electron in this system resides in a molecular orbital composed essentially of oxygen p orbitals (the π^* orbitals of O_2). The oxygens are shown to be nonequivalent, possessing 60 and 40% spin densities on the terminal and middle oxygens, respectively. This is consistent with the molecular orbital model shown in Figure 1. We emphasize that, contrary to earlier claims[15] that these results provide confirmation of an ionically bound superoxide ion, the fact that the unpaired electron is on O_2 provides no information about the charge on the bound O_2.

With the unpaired electron in the system residing essentially on O_2, one might ask how the cobalt hyperfine coupling arises. If one interprets the cobalt hyperfine as arising from a direct delocalization of the electron onto cobalt, a summation of the anisotropic [17]O and Co hyperfine coupling constants would indicate more than one unpaired electron in the system, even though only one exists. An indirect, rather than direct, mechanism must lead to negative spin density on the metal center. The spin polarization of the paired

electrons in ψ_1 by the one unpaired electron in ψ_2 produces negative spin density at the cobalt nucleus, and this accounts for the cobalt hyperfine coupling observed in the EPR. The pronounced variation in the cobalt hyperfine coupling constant in a series of O_2 adducts[14] indicates extensive variation in the cobalt contribution to ψ_2 and thus in the nature of the bound O_2. In a subsequent section we shall indicate how an analysis of the cobalt hyperfine coupling constant permits *an estimate* of the partial charge on the bound O_2 fragment.

Consistency of the Spin-Pairing Model with Experimental Observations

Several physical methods have been used to elucidate the nature of end-on cobalt–dioxygen binding. X-ray results were used to formulate the complexes as a species containing an ionically bound superoxide ion, $Co^{III}O_2{}^-$. This conclusion was based on a comparison[16a,b] of the O–O distance in the O_2 adduct (1.24 and 1.26 Å) with that in the free O_2 (1.21 Å) and in the ionic potassium superoxide salt (1.28 Å).[17a] A reevaluation[17b,c] of the original data for the KO_2 system shows that the O–O distance falls in the range 1.32–1.35 Å. The ionic sodium superoxide with a reported[18a,b] distance of 1.33 Å was not compared. Inferences of the electronic nature of materials from bond distances are known historically to be extremely risky when good model compounds are not available for interpolation purposes. For example, the O–O distance to be expected for a coordinated singlet or neutral triplet O_2 molecule with possible metal-to-ligand π back-bonding cannot be predicted from the structure of free O_2. With two antibonding electrons, a slight weakening of the σ bond could result in an appreciable increase in the O–O distance upon coordination even if electron transfer from the metal did not occur.

Infrared spectroscopy has proved to be of considerable utility in distinguishing geometries of type A dioxygen adducts from B or C.[19] Unfortunately, the similarity in the O–O stretching vibration of the type A dioxygen adducts with that of potassium superoxide again was interpreted as support for an ionic superoxide formulation of the adducts. Once again this conclusion is suspect because in order to gauge the extent of electron transfer from infrared evidence, one would need to interpolate the measured value between that for an established neutral coordinated dioxygen and an ionically coordinated superoxide ion. For end-on binding to various complexes, the values of ν_{O-O} are relatively insensitive to the metal, the ligand field strength, and the strength of dioxygen binding (see Table II).

The conclusion from the infrared experiments is that either the electron transfer into the O_2 is similar in all instances (and thought by many to be nearly complete)

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(15) Getz, D.; Melamud, E.; Silver, B. L.; Dori, Z. *J. Am. Chem. Soc.* **1975**, *97*, 3846, and references therein.

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Table II
Vibrational Frequencies of Dioxygen Complexes

compound	$\nu_{16_{O_2}}$, cm^{-1}	ref
HO_2	1138	a
$Li[O_2^-]^j$	1097	b
$K[O_2^-]$	1146	c
$Rb[O_2^-]$	1141	c
$Cs[O_2^-]^j$	1115	b
$Co(acacen)py \cdot O_2$	1123	d
$CO(acacen)(CH_3\text{-}py)O_2$	1195	d
$Co(TpivPP)(1\text{-MeIm})O_2$	1150	e
$Hb(deutCo)O_2$	1105	f
$Hb(deutFe)O_2$	1106	f
HbO_2	1107	g
MbO_2	1103	h
$Fe(TpivPP)(1\text{-MeIm})O_2$	1159	e
$Cr(TPP)(py)O_2$	1142	i

[a] See ref 21. [b] Andrews, L. In "Cryochemistry"; Moskovits, M., Ozin, G. R., Eds.; John Wiley: New York, 1976. [c] Blunt, F. J.; Hendra, P. J.; Mackenzie, J. R. *Chem. Commun.* 1969, 278. [d] Crumbliss, D. L.; Basolo, F. *J. Am. Chem. Soc.* 1970, 92, 55. [e] Collman, J. P.; Brauman, J. I.; Halbert, T. R.; Suslick, K. S. *Proc. Natl. Acad. Sci. U.S.A.* 1976, 73, 3333. [f] Maxwell, J. C.; Caughey, W. S. *Biochem. Biophys. Res. Commun.* 1974, 60, 1309. [g] Barlow, C. H.; Maxwell, J. C. Wallace, W. J.; Caughey, W. S. *Ibid.* 1973, 55, 91. [h] Maxwell, J. C.; Volpe, J. A.; Barlow, C. H.; Caughey, W. S. *Ibid.* 1974, 58, 166. [i] Cheung, S. K.; Grimes, C. J.; Wong, J.; Reed, C. A. *J. Am. Chem. Soc.* 1976, 98, 5028. [j] Values in argon matrices. Acacen, *N,N'*-ethylenebis(acetylacetoniminato); TPP, *meso*-tetraphenylporphyrinato; deut, deuteroporphyrinato; 1-MeIm, 1-methylimidazole; TpivPP, $\alpha,\alpha,\alpha,\alpha$-tetrakis(pivalamidophenyl)porphyrinato ("picket fence" porphyrin).

or else the O–O stretching vibration is insensitive to the variation in electron transfer in these adducts. The assumption of nearly constant electron transfer is at odds with an EPR study (vide infra), indicating that the amount of electron transfer varies extensively with ligand variations. It is also in conflict with molecular orbital results[20a-g] that indicate more extensive electron transfer into O–O by a cobalt(II) complex than by the analogous iron(II) complex. If the bound dioxygen is neutral in the iron complexes, as has been proposed by several recent molecular orbital calculations, ν_{O-O} is nearly the same for a neutral bound dioxygen as it is for the ionic superoxide ion (1145 cm^{-1}). The hypothesis that the O–O stretching frequency is insensitive to the nature of the metal–oxygen bond receives strong support from evaluation of reported[21a,b] infrared matrix isolation frequencies of HO_2 and its isotopic variants. The Lewis acidity of a bare proton and the covalency expected in the O–H bond preclude viewing the O–O fragment in HO_2 as an ionic superoxide. The O–O stretching frequency in HO_2 corrected for OH coupling occurs at 1138 cm^{-1}, even lower than that usually quoted for O_2^-. Not only do the infrared spectra not support previous conclusions of extensive electron transfer into metal–dioxygen, but they provide no information about the extent of electron transfer in the metal–dioxygen adducts. Thus, neither the infrared nor the X-ray

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(21) (a) Blint, R. J.; Newton, M. D. *J. Chem. Phys.* 1973, 59, 6220. (b) Jacox, M. E.; Milligan, D. E. *J. Mol. Spectrosc.* 1977, 42, 495.

Table III
Electron Transfer in Some O_2 Adducts
of Cobalt(II) Complexes

compound[a]	ET[b]	donor set
$Co(acacen) \cdot H_2O \cdot O_2$	0.1	
$Co(X\text{-SalDAPE}) \cdot O_2$, X = 5-H	0.2	N_2O_3
5-OMe	0.3	
5-Br	0.3	
$Co(acacen) \cdot py \cdot O_2$ [c]	0.4	
$Co(salen) \cdot py \cdot O_2$	0.5	N_3O_2
$Co(SMDPT) \cdot O_2$	0.5	
$Co(DPGB)_2 \cdot HMPA \cdot O_2$ [d]	0.7	N_4O
$Co(DPGB)_2 \cdot acetone \cdot O_2$ [d]	0.8	
$Co(PPIXDME)(py)O_2$	0.5	
$Co(p\text{-OCH}_3TPP) \cdot py \cdot O_2$ [c]	0.6	
$Co(p\text{-OCH}_3TPP)(1\text{-MeIm})O_2$	0.5	N_5
$Co(DMGH) \cdot py \cdot O_2$ [d]	0.7	
$Co(DPGB)_2 \cdot CH_3CN \cdot O_2$ [d]	0.8	

[a] Abbreviations: salen, *N,N'*-ethylenebis(salicylidenimine); SMDPT, bis(salicylidene-γ-iminopropyl)methylamine; DMGH, dimethylglyoxime; DPGB, BF$_2$-capped diphenylglyoxime; X-SalDAPE, bis(salicylidene)diaminopropyl ether; *p*-OCH$_3$TPP, *p*-methoxyphenyl-*meso*-tetraphenylporphyrin; PPIXDME, protoporphyrin IX dimethyl ester; HMPA, hexamethylphosphoramide; py, pyridine. [b] Electron transfer from Co(II) to O_2. The results are semiquantitative but trends are accurate. See ref 14. [c] MO calculations on these systems agree with our ET values.[20b] [d] The high ET values for the oxime donors is expected since oximes generate about the same ligand field strenghts as cyano compounds.[23a]

diffraction results are inconsistent with the spin-pairing model.

There are two sets of experiments whose results correlate very well with the spin pairing model: (1) the interpretation of the variation in the cobalt hyperfine coupling costant in a series of adducts; and (2) the enthalpies of adduct formation with axial base variation. We shall consider these next.

The spin-pairing model predicts that as the donor strength of the ligands around cobalt increases (e.g., ligand field plus spherical field strength), the metal orbital is raised in energy relative to the π^* orbitals of O_2 and the complex becomes more O_2^- in character, i.e., β increases. There are, of course, many complex, subtle electronic changes[22] (for example, d-orbital mixing and a varying 4s orbital contribution) that can cause minor reversals in this predicted trend. However, the gross effect is clearly manifested by the data in Table III. In general nitrogen donors have higher ligand field strength than oxygen donors. Accordingly, a N_2O_3 donor set gives rise to electron-transfer values of 0.1 e$^-$ to 0.3 e$^-$, a N_3O_2 set from 0.4 e$^-$ to 0.5 e$^-$, or for the N_5 set, from 0.5 e$^-$ to 0.8 e$^-$. When the very strong glyoximate donor ligand[23a] is employed, ET values of 0.7 e$^-$ to 0.8 e$^-$ occur in both the N_4O and N_5 donor sets. Minor reversals are noted in some systems; for example, in the Co(PPIXDME) series[23b] the ET values of 0.5, 0.5 and 0.4 for the bases DMA, py, and 1MeIm do not parallel the donor strengths. Acetone and HMPA behave similarly toward Co(DPGB)$_2$. These minor trends are not understood, though it is clear that both the cis and trans ligands to dioxygen influence the ET values.

(22) Chien, J. C. W.; Dickinson, C. L. *Proc. Natl. Acad. Sci. U.S.A.* 1972, 69, 2783. Jörin, E.; Schweiger, A.; Gunthard, Hs. H. *Chem. Phys.*, 1979, 61, 228.
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Table IV

base	$-\Delta H^\circ$ 1:1, kcal mol^{-1}	$-\Delta H_{O_2}$, kcal mol^{-1}
N-MeIm	9.6	10.0 (0.2)^a
pyridine	8.9	8.0 (0.4)
hexamethylphos- phoramide (HMPA)	8.9	8.9 (0.2)
N,N-dimethyl- acetamide (DMA)	7.4	6.6 (0.7)
tetrahydro- thiophene (THTP)	6.0	7.6 (0.6)

^{a} Numbers in parentheses are error limits. $-\Delta H^\circ$ 1:1, enthalpy of formation of 5-coordinate base adduct. $-\Delta H_{O_2}$, of 6-coordinate dioxygen adduct.

The magnitude of the cobalt contribution to ψ_1 has been evaluated by calculating a McConnell type of scaling factor[24] to convert the anisotropic cobalt hyperfine coupling constant to fraction cobalt(II) character in ψ_1. From this, the oxygen coefficient (β) is determined for the ψ_1 MO and converted into the extent of electron transfer, ET, into the bound O_2.[25] A list of adducts studied to date is given in Table III. The trend observed in the ET values spans a range of electron transfer to oxygen of 0.1 to 0.8 electron. These values are consistent with the trend expected on the basis of the influence of the change in ligand field strengths on the spin-pairing model.

The enthalpies of dioxygen binding (Table IV) have been found[23b] to parallel the strength of axial base coordination in a series of five-coordinate cobalt(II) protoporphyrin IX dimethyl ester [Co(por)] complexes. As the axial base interaction increases in a series of complexes, the d_{z^2} orbital is driven higher in energy relative to the oxygen π^* orbital. The higher the initial energy of the d_{z^2} electron in the five-coordinate adduct, the more it is stabilized upon forming the O_2 adduct.

The results of several reported molecular orbital calculations at various levels of approximation[20a] are in agreement with the spin-pairing model. In particular, one report[20b] is a recent INDO–UHF calculation on Co(acacen)NH$_3$O$_2$. Within the calculation, O_2 adduct formation is shown to be consistent with a spin-pairing interaction of one unpaired O_2 electron and one on cobalt. The delocalization of the unpaired electron over O_2 agrees well with the ^{17}O hyperfine results: 0.38 and 0.61 electron on the middle and terminal oxygen π^* orbital. The calculated spin densities of cobalt $3d_{z^2}$ and 4s are negative, as predicted in the EPR analysis[14] based on polarization arguments. The very small calculated spin densities in d_{xz} and d_{yz} confirm our claim that little unpaired electron spin is delocalized from ψ_2 to metal π orbitals. Finally, the amount of electron transfer from cobalt to O_2 is calculated to be 0.3, compared to our upper limit of 0.4 estimated from the EPR analysis of Co(acacen)pyO$_2$.

Spin-Pairing Predictions Regarding Cobalt–Dioxygen Complexes

In the previous section we presented a rationale based on the spin-pairing model for increased dioxygen–metal
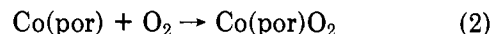
interaction with increased axial base, B, strength in a series of B·Co(por)–O$_2$ adducts. The thermodynamic data were incorporated into the E and C equation[23b]

$$-\Delta H = E_A E_B + C_A C_B$$

so that enthalpies of dioxygen adduct formation can be predicted for any of the 51 bases whose E_B and C_B parameters have been reported. Values of $E_A = 7.3$ and $C_A = 1.2$ were found for the Co(por)O$_2$ Lewis acid, enabling one to calculate $-\Delta H$ for the reaction

$$\text{Co(por)O}_2 + \text{B} \rightarrow \text{BCo(por)O}_2 \qquad (1)$$

The enthalpy for the reaction

$$\text{Co(por)} + \text{O}_2 \rightarrow \text{Co(por)O}_2 \qquad (2)$$

has the value -1.5 kcal mol^{-1}. An enthalpy for the reaction

$$\text{Co(por)} + \text{B} \rightarrow \text{Co(por)B} \qquad (3)$$
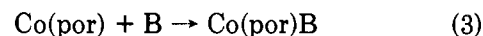
can be predicted by using reported E_B and C_B values with $E_A = 4.44$ and $C_A = 0.58$ for the Lewis acid Co(por). Adding eq 1 and 2, subtracting eq 3, and doing likewise with the enthalpy values produce the equation and the enthalpy for

$$\text{Co(por)B} + \text{O}_2 \rightarrow \text{Co(por)B·O}_2$$
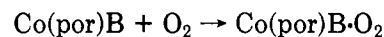
Thus our understanding of the factors influencing O_2 binding to this porphyrin has progressed to the point where they can be quantitatively predicted from the base E_B and C_B properties. The treatment would not work for bases in which there are steric effects involved in the cobalt–base interaction or those in which the ligand has π-acceptor properties. The predictability of the behavior of the 1-methylimidazole system with the E and C approach clearly indicates that contrary to previous literature reports[26,27] π effects do not account for the strong dioxygen binding properties of this axial base.

Comparison of the E and C values of Co(por)O$_2$ with Co(por) indicates that O_2 coordination has increased both the C_A and E_A values of the cobalt center. This is expected when metal electron density is transferred into the O_2. Since the oxygen binding enthalpies fit the E and C equation, the amount of transfer of electron density into the O_2 upon base coordination must parallel the base strength if there is a significant enthalpic stabilization from this effect. It has been shown[28] that contributions to the enthalpy that are proportional to base strength can be incorporated into the acid E and C numbers.

The axial base variation in the porphyrin series is expected to have the most pronounced influence on the d_{z^2} orbital energies accounting for the simple interpretation of the binding trends in terms of the spin-pairing models. It would be improper to extrapolate these conclusions directly to the lower symmetry complexes which arise from equatorial base variation, for example, to compare porphyrins with Schiff base complexes.

(24) McConnell, H. M.; Chestnut, D. B. *J. Chem. Phys.* 1958, *28*, 107.
(25) The reported electron-transfer values are semiquantitative. They are upper limits of the extent of electron transfer. The reader is urged to read the original paper (ref 23) for a full explanation of how these values are obtained.

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Table V
Enthalpies of O_2 Adduct Formation

compound	pH	$-\Delta H^\circ$, kcal mol^{-1}	ref
hemoglobins (Hb)			
OxHb[a]	6.8	9.7	d
OxHb[a]	9.5	13.6	d
horse Hb[a]	~9.5	13.4	e, f
human Hb[a]	~9.5	13.8	e, f
mouse Hb	~9.5	13.1	g
chironomus Hb			
meso	7.0	7-10	h
deutero	7.0	9.5	h
proto	7.0	13.2	h
CoHb			
meso	7.0	8.0	i
deutero	7.0	7.5	i
proto	7.0	10.7	i
myoglobins			
sperm whale Mb			
meso	7.0	12.6	j
deutero	7.0	8.9	j
proto	7.0	14.9	j
CoMb			
meso	7.0	10.3	i
deutero	7.0	10.3	i
proto	7.0	11.9	i
proto	6.9	13.3	k
Fe(TpivPP)(1-MeIm)	7.0	15.6	l
Co(TpivPP)(1-MeIm)	7.0	12.2[b]	l
Co(PPIXDME)(1-MeIm)	7.0	9.6	m

[a] An average of reported values. [b] In toluene solution. [c] Solid state. [d] Roughton, F. J. W. *J. Biol. Chem.* **1935**, *29*, 2604 and **1936**, *30*, 2117. [e] Dill, D. B. (1939). Quoted by: Wyman, J. *Adv. Protein Chem.* **1948**, *4*, 469. [f] Antonini, E.; Wyman, J.; Brunor, M.; Fronticelli, C.; Bucci, E.; Rossi Fanelli, A. *J. Biol. Chem.* **1965**, *240*, 1096. [g] Smith, D. B.; Brunori, M.; Antonini, E.; Wyman, J. *Arch. Biochem. Biophys.* **1966**, *113*, 725. [h] Antonini, E.; Brunori, M. "Hemoglobin and Myoglobin in Their Reaction with Ligands"; North-Holland Publishing Co.: Amsterdam, 1971. [i] Yonetani, T.; Yamamoto, H.; Woodrow, G. V., III. *J. Biol. Chem.* **1974**, *249*, 682. [j] Rossi Fanelli, A.; Antonini, E. *Arch. Biochem. Biophys.* **1957**, *73*, 243. [k] Collman, J. P.; Brauman, J. I.; Suslick, K. S. *J. Am. Chem. Soc.* **1975**, *97*, 7185. [l] Spilburg, C. A.; Hoffman, B. M.; Petering, D. H. *J. Biol. Chem.* **1972**, *247*, 4219. [m] See ref 23.

Experiments are under way to determine the influence of these changes.

Extreme caution must be exercised when comparing the $-\Delta H_{O_2}$ of porphyrin adducts to their biological analogues (see Table V).

The data for the hemoglobin systems exhibit a pronounced pH dependence that is referred to as the Bohr effect. This behavior illustrates the difficulty of obtaining information about the metal–dioxygen bond strengths in such complex systems. Many effects can contribute to the measured enthalpies. The variation found in the oxygen binding affinities for meso, deutero, and proto hemoglobins is considerably larger than that expected for a metal substituent effect arising from these substitutions on the porphyrin. Substitution of iron by cobalt in myoglobins results in a 2.3 kcal mol^{-1} decrease for the meso protein, a 1.4 kcal mol^{-1} increase for the deutero protein, and a 3.0 or 1.6 kcal mol^{-1} decrease for the proto protein compared to the iron system. Understanding the energetics of these biological systems is far from complete.

As more electron density is transferred into O_2, the bound dioxygen is expected (on the basis of the spin-

pairing model) to become a better nucleophile. Attempts to gain experimental confirmation of the trend in this property have been hampered by the difficulty in finding reactions that can be demonstrated to involve coordinated O_2. A recent[29] result from our laboratory shows that trifluoroethanol can hydrogen bond to a dioxygen molecule coordinated to CoSMDPT. The hydrogen-bonding enthalpy for this interaction is about 6.6 kcal mol^{-1}. This chemical behavior is consistent with the spin-pairing model view of the nature of the bound O_2. The hydrogen bonding has implications with regard to the larger ΔH values observed for CoMb and Co-(TpivPP)(1-MeIm) compared to Co(PPIXDME)(1-MeIm). Hydrogen bonding of the bound O_2 to acid groups in the protein or pickets could enhance the enthalpy of dioxygen binding in the former systems.

The combination of a Co–O_2 adduct with a second cobalt complex to form type B complexes can be considered to involve a reaction of coordinated dioxygen. The same type of spin-pairing interaction described in Figure 1 occurs with the second cobalt and the odd electron in ψ_2 of the 1:1 adduct forming a diamagnetic 2:1 adduct (type B). Thermodynamics for the second step are not available but are needed for an understanding of the factors influencing the reactivity of the bound O_2 in the 1:1 adduct.

Prior to recent research from our laboratory, all of the reported dioxygen adducts of cobalt(II) contained six-coordinate cobalt. The spin-pairing model would predict that as long as the energy of the metal orbital containing the odd electron had the appropriate energy a reversible dioxygen adduct would form for various metal coordination numbers. The following reaction leading to a five-coordinate dioxygen adduct has been reported.[30]

$$Co(P)_3(CN)_2 + O_2 \rightarrow Co(P)_2(CN)_2O_2 + P$$
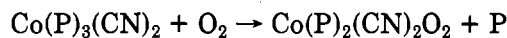
P is tertiary phosphine. EPR has been used to establish this as a type A adduct. If the complex were a six-coordinate, type C dioxygen adduct, the unpaired electron in this system would have to be contained in a molecular orbital that is essentially metal based. One would have to promote an electron into $d_{x^2-y^2}$ from, e.g., the d_{xz} or d_{yz} or d_{xy} set. Pairing up two of these spins with the two on dioxygen to form a type C complex would leave the unpaired electron in a metal orbital. EPR rules out this possibility. Evidently, not enough energy is gained by spin pairing the second unpaired electron of dioxygen with cobalt to unpair the electrons in the metal via promotion to the $d_{x^2-y^2}$ orbital.

These results are interesting in the context of those reported by Halpern et al.[5] When oxygen was bubbled through a benzene solution of Co(PMe$_2$Ph)$_3$(CN)$_2$ for 8 h, diamagnetic Co$_2$(PMe$_2$Ph)$_5$(CN)$_4$O$_2$ was crystallized out as a solid by the addition of hexane. A single-crystal X-ray structure indicated that both of the oxygen atoms coordinated to the metal in a ring-bonded type of interaction. It was proposed that electron transfer occurred from one cobalt to the one containing O_2 to produce the formal structure
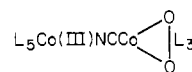
(29) Drago, R. S., Cannady, P., Leslie, K. *J. Am. Chem. Soc.*, in press.
(30) Drago, R. S., Stahlbush, J. R., Kitko, D. J., Breese, J. *J. Am. Chem. Soc.* **1980**, *102*, 1884.

x^2-y^2 ——

z^2

xy

xz,yz

π^*

O_2

$-Cr-$
B

O_2

(A)

π^*

O_2

Mn
(MnTPP)

Mn

O_2

(B)

x^2-y^2
z^2

xy
xz, yz
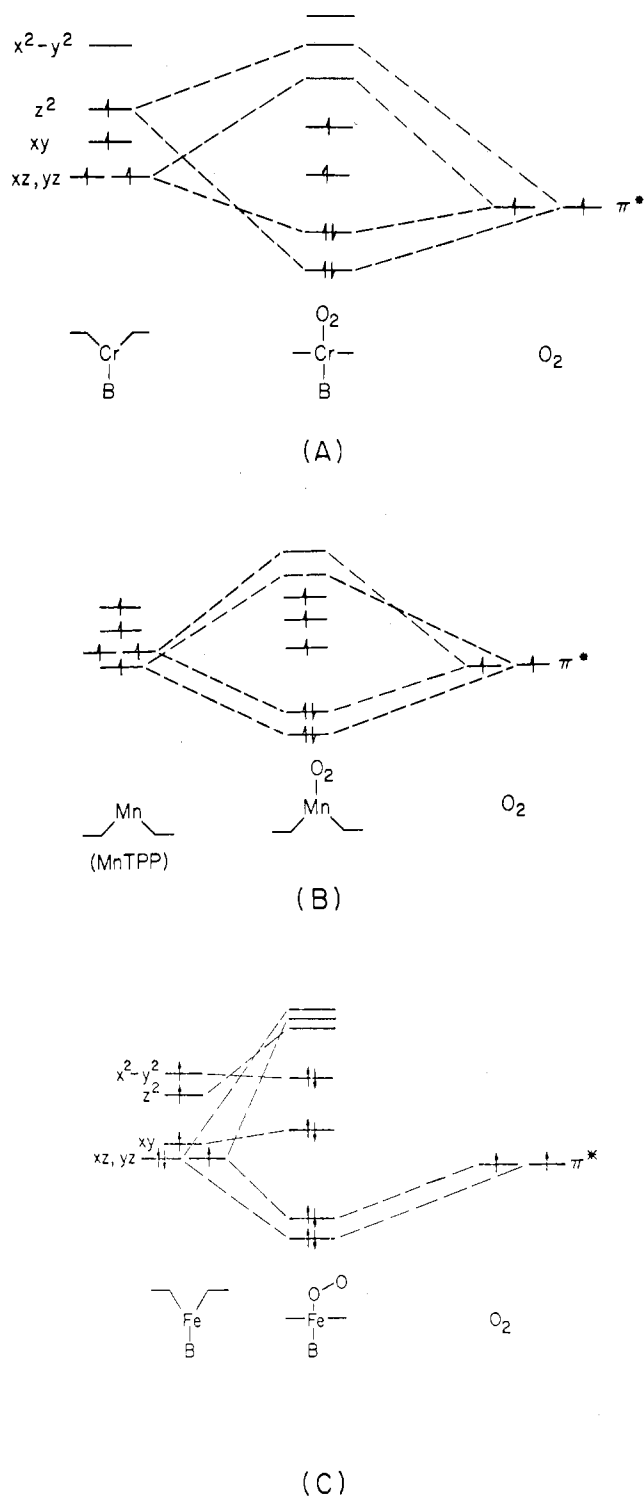
π^*

Fe
B

$-Fe-$
B

O_2

(C)

Figure 2. Molecular orbital diagram for O_2 adducts of Cr(II), Mn(II), and Fe(II) showing spin pairing upon adduct formation.

where L = CN or phosphines. A five-coordinate intermediate similar to that identified in our study was proposed to react in a slow second step with another $Co(CN)_2(PMePh)_3$ molecule to form the bimetallomer. It is possible that the ground state of this bimetallomer could be described by the electronic configuration discussed above that arises by promotion of an electron out of the $d_{xz}d_{yz}$ set, producing $d_{xy}^2d_{xz}^2d_{yz}^1d_{z^2}^1d_{x^2-y^2}^1$. A spin-pairing interaction of the two orthogonal π^* electrons of O_2 with those in d_{z^2} and $d_{x^2-y^2}$ would lead to a ring-bonded dioxygen adduct with an unpaired electron in an essentially metal orbital. In the bimetallomer the

unpaired electrons on the two cobalt centers could be antiferromagnetically coupled to produce a diamagnetic product. If this were the case, we might have expected that the 1:1 O_2 adduct would be ring bonded with the unpaired electron on the metal. The fact that the 1:1 adduct is coordinatively unsaturated with the unpaired spin on O_2 would support the electron-transfer step proposed.[5] It would then appear that a d^8 configuration (or as in the bimetallomer an electron-transfer step to provide this configuration) is the requirement for obtaining the type C, ring-bonded mode of dioxygen bonding. Nevertheless, the antiferromagnetically coupled model described above cannot be eliminated, for this additional interaction could provide the energy necessary to achieve the electron promotion described above. It is clear, however, that a vacant coordination position in a four-coordinate Co(II) complex capable of binding O_2 is not a sufficient requirement for type C bonding.

Application of the Model to Other First-Row Transition-Metal Ion Complexes

In using the spin-pairing model on other transition-metal systems, the key feature is that the metals have one or more unpaired electron(s) in d orbitals with high enough energy to spin-pair with the electrons in the oxygen antibonding orbitals. We saw in the cobalt(II) adducts of O_2 that this type of interaction left one unpaired spin on dioxygen by using the only unpaired electron in the cobalt(II) complex for dioxygen bonding. In the O_2 adducts of iron(II), chromium(II), and manganese(II) there are enough unpaired electrons in metal orbitals to permit spin pairing with both π^* electrons of O_2.

We can propose a simplified MO scheme that permits prediction of the magnetic properties of the dioxygen adducts of these metals. Molecular orbital calculations show much more extensive mixing of the orbitals than is presented here, but this description should suffice to provide a working model of the essential nature of the interaction. A description of the iron complex will be presented first.

Square-planar, four-coordinate iron(II) complexes are generally low or intermediate spin. Coordination of an axial base leads to a high-spin complex in the systems which reportedly pick up O_2 reversibly after base coordination. A low-spin O_2 adduct results as shown (see Figure 2c). The d_{z^2} orbital in the O_2 adduct would be driven higher in energy via the stronger interaction of O_2 with this orbital, accounting for the diamagnetic O_2 adducts observed in the reversible iron(II) system reported to date.[31a,b] The model predicts that a paramagnetic O_2 adduct of iron(II) could result by employing a ligand field that led to a decreased $d_{x^2-y^2}$ and d_{z^2} separation in the adduct. A weak interaction with O_2 could also lower the $d_{xz}-O_2$ or $d_{yz}-O_2$ antibonding orbitals to a place where it becomes populated and a paramagnetic adduct would result.[32] Thus the spin-

(31) (a) Pauling, L.; Coryell, C. D. *Proc. Natl. Acad. Sci. U.S.A.* **1936**, *22*, 210. (b) Collman, J. P.; Brauman, J. I.; Rose, E.; Suslick, K. S. *Ibid.* **1978**, *75*, 1052.

pairing model leads to a prediction of a paramagnetic dioxygen adduct of iron(II) in which the unpaired spin is contained in essentially metal-based orbitals. The recent report[33a,b] of a thermally populated paramagnetic state of hemoglobin is readily accommodated by these considerations, but the absence of a contact-shifted NMR in this system is surprising.

Similar application of the model describes the reported O_2 adducts of Cr(II) (see Figure 2A). The Cr–O_2 adduct contains two metal-based unpaired electrons[34] after the spin-pairing interaction of two metal electrons of the d^4 configuration with both of the $O_2 \pi^*$ electrons. In a lower symmetry ligand field of appropriate strength, a diamagnetic adduct would be conceivable.

The magnetic properties[35a] of the reported O_2 adducts of Mn(II) are also consistent with the predictions of the spin-pairing model (see Figure 2B). It is not known whether this adduct is a type A or type C complex, but in either instance an adduct with three metal-based, unpaired electrons is predicted.[35b] Again by properly adjusting the ligand-field differences of coordinated groups, a low-spin O_2 adduct with one metal-based unpaired electron could result. Thus the spin-pairing model we propose can account for the electronic structure of a wide variety of O_2 adducts.

Since the essential spin pairing of metal orbital electrons with antibonding orbitals of dioxygen is involved in the binding of oxygen to cobalt(II) and iron(II), the spin-pairing model suggests that the effects of axial base variation on the d-orbital energies will result in the same trends in dioxygen binding strengths in the iron(II) system as were observed in the cobalt(II) protoporphyrin IX dimethyl ester adducts. These considerations have implications regarding the mechanism of cooperativity in the hemoglobin system.[23]

The Spin-Pairing Model and the Cooperativity of Hemoglobin

To a first approximation, the spin-pairing model predicts that dioxygen binding will become weaker as

Figure 3. (A) corresponds to the T state. Longer Fe–histidyl and Fe–O_2 bonds denote a weaker O_2 adduct. (B) corresponds to the R state. A stronger, high-affinity, Fe–O_2 interaction occurs, denoted by a shorter Fe–O_2 bond.

Figure 4. Schematic diagram for hemoglobin conformation change. (A) and (B) correspond to the heme units depicted in Figure 3A,B.

the strength of the axial base bond to a metal becomes weaker. This relationship suggests a potential-energy storing model for cooperativity. Hemoglobin has two different quaternary structures: the R state, whose O_2 affinity is essentially that of the isolated subunits, and the T state, whose O_2 affinity is diminished. In the five-coordinate deoxy T form, the iron is displaced out of the plane toward the coordinated (proximal) histidine. For a protein in the T state, movement of the proximal histidine toward the iron cannot be accomplished without a change in protein conformation.[36] As shown by the enthalpies of oxygenation of cobalt(II) protoporphyrin IX dimethyl ester and as predicted by the spin-pairing model, a weakened proximal imidazole–iron interaction will lower the oxygen binding affinity. Evidence suggests that the deoxy T form does not have this constraint present.[37a,b] The restraint may be introduced upon oxygenation of the iron in the T form. This could result from a bond lengthening or a bent metal–nitrogen bond preventing direct overlap of the nitrogen with the iron d_{z^2} orbital (see Figure 3). A comparison of the E and C values of Co(por)O_2 with Co(por) indicates that the former is nearly twice as good a Lewis acid as the latter and shorter metal–base distances are expected toward the stronger acid. Thus, by analogy with the cobalt system, the metal–proximal imidazole distance would be expected to shorten upon oxygenation of the iron, and inhibition of this shortening by the protein would weaken the dioxygen binding affinity. This proposal is consistent with the results[37a] of EXAFS experiments that show very small

(32) Our orbital diagram contains some features of reported MO schemes (see ref 20g), but is modified slightly. The $X\alpha$ scheme empties both $d_{x^2-y^2}$ and d_{z^2} and pairs up electrons in the antibonding d_{xz}–O_2 molecular orbital. This is unsatisfactory for several reasons. A 14 kcal mol^{-1} bonding interaction of O_2 with a metal should lead to a larger separation of the bonding and antibonding molecular orbitals than the d-orbital separations observed from crystal-field effects. Furthermore, population of the antibonding d_{xz}–O_2 orbital would lead to a net iron–oxygen bond order of one. The cobalt–oxygen bond would be expected to be stronger than the iron–oxygen bond for this orbital sequence because of this antibonding interaction. This does not agree with experimental results that show more negative enthalpies of O_2 binding and shorter metal–oxygen bond distances in the iron complexes.[9] It is difficult to assess the relative energies $d_{x^2-y^2}$ and d_{z^2} as reflected by our alternation in their positions in various articles. Mixing of the 4s and d orbitals[22] with d_{z^2} further complicates the problem.

(33) (a) Cerdonio, M.; Congiu-Castellano, A.; Mogno, F.; Pispisa, B.; Romani, G. L.; Vitale, S. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 398. (b) Cerdonio, M.; Congiu-Castellano, A.; Calabrese, L.; Morant, S.; Pispisa, B.; Vitale, S. *Ibid.* **1978**, *75*, 4916.

(34) Cheung, S. K.; Crimes, C. J.; Wong, J.; Reed, C. A. *J. Am. Chem. Soc.* **1976**, *98*, 5028.

(35) (a) Hoffman, B. M.; Weschler, C. J.; Basolo, F. *J. Am. Chem. Soc.* **1976**, *98*, 5473. (b) Dedieu, A.; Rohmer, M. M. *Ibid.* **1977**, *99*, 8050. The authors in (a) concluded that Mn–O_2 is a type C adduct. Results of ab initio calculations (b) indicate that a type A adduct should be significantly more stable then the type C conformation. These authors (b) predict a $(O_2\pi)^2(O_2\pi)^1(d_{xy})^2(d_{yz})^1(d_{xz})^1$ ground state that is inconsistent with the ^{17}O EPR results.[35a] A better basis set and CI is not expected to enhance the stability of the type C over the type A adduct,[35b] but it could lead to a ground-state configuration with three metal-based unpaired electrons. An end-on bonded dioxygen is consistent with the EPR results. Based on the above considerations we have chosen the energy level scheme in Figure 2B.
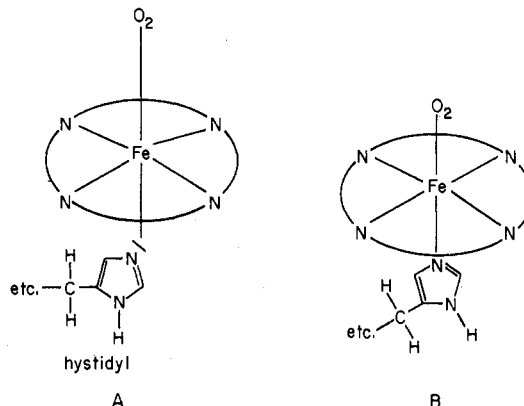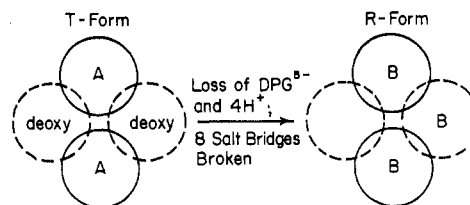
(36) Perutz, M. F. *Br. Med. Bull.* **1976**, *32*, 195. *Annu. Rev. Biochem.* **1979**, *48*, 327, and references therein.

(37) (a) Eisenberger, P.; Shulman, R. G.; Kincaid, B. M.; Brown, G. S.; Ogawa, S. *Nature (London)* **1978**, *274*, 30, and references therein. (b) Kincaid, J.; Stein, P.; Spiro, T. G. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 549.

changes in the iron–porphyrin distances upon oxygenation. Similar iron–porphyrin bond lengths (within 0.02 Å) were found in low-affinity deoxy-HbA and high-affinity deoxy-Hb Kempsey, indicating that the restraint in the T form is introduced upon oxygenation. This is further supported by resonance Raman results[37b] of Fe–N(axial) bond length changes for T and R Hb Kempsey which account for no more than 0.2 kcal mol^{-1} for heme.

A weakened iron–proximal histidine interaction results in weaker iron–nitrogen and metal–dioxygen bonds in the T form than they would be in the absence of the restraint. In this manner, coordination of dioxygen stores potential energy in the system that could be released if the iron–nitrogen restraint were removed by a protein conformational change. Not enough energy for the protein change is generated upon binding the first dioxygen. Multiples of this potential energy are stored on binding the second and third dioxygens. Note that potential energy is stored from a stronger metal–base interaction as well as a stronger dioxygen interaction for each bound oxygen. Upon coordination of the third dioxygen more than enough potential energy is available in the system from the increased iron–nitrogen and iron–O$_2$ bond strengths that would exist in the R form to effect the endothermic T to R protein transformation. Addition of the fourth dioxygen is expected to be the most exothermic of all the O$_2$ binding steps (see Figure 4) because the O$_2$ coordinates to an iron in the R form.

In this model, all of the structural changes in the iron relative to the porphyrin are similar in Hb to those observed in systems not exhibiting cooperativity; hence, the proximal imidazole interaction is the key to cooperativity. An energy balance to account for the 3.5 kcal mol^{-1} difference in the O$_2$ binding affinity of high- and low-affinity forms is difficult. If the T to R protein transformation is endothermic, this energy plus the 3.5 kcal mol^{-1} is distributed over the 3 metal–oxygen, 3 iron–proximal imidazole, and 12 iron–porphyrin nitro-

gen interactions in the O$_2$ adduct.

The decreased extent of cooperativity found in CoHb relative to Hb does not provide any insight regarding cooperativity.[38a–c] In view of the preceding discussion, we see that the problem is very complex. The potential energy gained and stored upon oxygen complexation would depend on the relative cobalt–base or iron–base bond energies as well as on the sensitivity of the dioxygen–iron or –cobalt bond strengths to coordinated axial base strength.

Clearly, two features of the cooperativity model have fallen into place. First, the affinity of the Hb is dependent on the Fe–histidyl bond strength. We favor the bending of the Fe–N(axial) bond in the oxygenated T form arising from restraint of the histidine residue by the globin. Nonbonded contacts between the proximal histine and the heme have been suggested[39a–c] as providing a mechanism for cooperativity. The excellent fit of the cobalt porphyrin oxygen binding enthalpies to our *E* and *C* equation suggests that steric effects are not operative in this system. Furthermore, it is difficult to see how the protein conformation can cause the heme unit to be domed toward the proximal histidine in one state and not the other. The configurational changes about the iron are expected to be the same upon oxygenation of the T and R forms of the protein unless restraint in the histidine–iron interaction is operative.

The second salient feature of cooperativity is that most of the potential-energy difference between the two quaternary deoxy states arises from hydrogen-bonding interactions in the protein and not from the heme unit. The subtle geometrical changes about the iron that occur upon oxygenation are insignificant relative to the changes in the globin.

(38) (a) Hoffman, B. M.; Diemente, D. L.; Basolo, F. *J. Am. Chem. Soc.*, 1970, *92*, 55. (b) Schiedt, W. R.; Dwyer, P. N.; Madera, P. *Ibid.* 1974, *96*, 4815. (c) Little, R. G.; Ibers, J. A. *Ibid.* 1974, *96*, 4452.

(39) (a) Warshel, A. *Proc. Natl. Acad. Sci. U.S.A.* 1977, *74*, 1789. (b) Hopfield, J. J. *J. Mol. Biol.* 1973, *77*, 207. (c) Gelin, B. R.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* 1977, *74*, 801.

Optical Molecular Dephasing: Principles of and Probings by Coherent Laser Spectroscopy

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Coherent laser spectroscopy of large molecules is a new and challenging area of study. The strength of this type of optical spectroscopy is that it can probe important dynamical molecular processes that are not

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amenable to conventional methods such as absorption and emission spectroscopy. One such dynamical process is optical dephasing.

When a laser interacts with an ensemble of molecules, under certain conditions, one can create a coherent linear combination of ground and excited molecular wave functions. This coherent state, or what is sometimes called a pure state, possesses a definite phase relationship between the wave function of the ground