

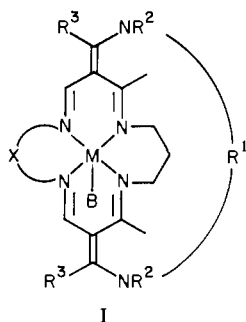
Reversible Dioxygen Binding by a Totally Synthetic Non-Porphyrin Macrocyclic Iron(II) Complex Containing a Persistent Void

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Although the functioning of iron in a variety of heme proteins is accompanied by formation of characterizable O₂ adducts (e.g., cytochrome P450, cytochrome *c* oxidase, hemoglobin, myoglobin), it has not yet been possible to demonstrate reversible formation of such adducts, under comparable conditions, with completely synthetic iron complexes (synthetic porphyrins do form such adducts, *vide infra*). In order to understand the more complex functions of iron in heme proteins, it is necessary to understand the O₂ adducts. Our recent synthetic and structural work on transition-metal complexes containing persistent voids (lacunar complexes, structure I)^{1,2} has been focused, over the short range,



toward the coordination of small molecules within the void in a manner reminiscent of that occurring in natural systems. Such cobalt(II)-dioxygen^{3,4} and iron(II)-carbon monoxide⁵ systems have been discussed earlier. Here we report the development of a specific lacunar complex of iron(II) that binds O₂ reversibly.

The lacunar ligands are characterized by great flexibility in design. The chelating macrocycle can be changed in size (X), while the bridge (R¹) and the substituents on the bridge nitrogens (R²) and the vinyl groups (R³) are easily varied. This synthetic flexibility allows the O₂ affinity of the cobalt complex to be controlled over a range⁴ of at least 10⁵ torr⁻¹. Values in the high part of the range may be as great or greater than those of natural iron-containing hemoglobin and myoglobin.⁴ The same relationships have been demonstrated for the reaction between carbon monoxide and the corresponding iron(II) complexes and it is the iron complexes that present the greater challenge.

Elegant studies on modified porphyrin complexes⁶⁻⁸ have identified the deleterious processes that must be inhibited in order to facilitate reversible O₂ binding to iron(II). The lacunar ligands were designed to avoid these processes. However, in the design of totally synthetic non-porphyrin heme protein models such as the lacunar complexes, one must answer the additional question—"given that the destructive processes can be controlled, what are the basic requirements that must be met so that an iron(II) atom can combine reversibly with dioxygen?". Vogt et

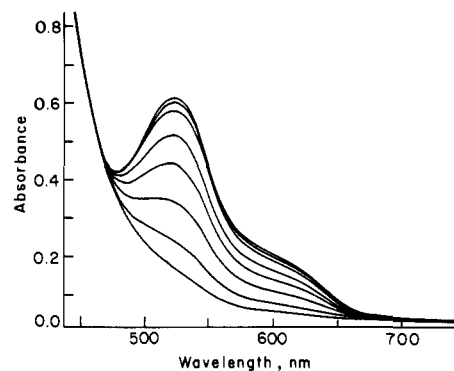


Figure 1. Electronic spectral changes accompanying formation of the O₂ adduct of complex I (M = Fe^{II}, X = (CH₂)₃, R¹ = *m*-xylyl, R² = R³ = CH₃, B = pyridine), 1.96 × 10⁻⁴ M in 4:1 (v/v) acetone:pyridine solution at -41.5 °C. Maxima at 523 nm (ε 3200 M⁻¹ cm⁻¹) and 619 nm (ε 950 M⁻¹ cm⁻¹) are due to the O₂ adduct.

al.⁹ suggested that there is a critical range of redox potentials within which the appropriate metal ion couple must fall. If the divalent iron is too easily oxidized, irreversible electron transfer will occur. At the other extreme, no interaction will occur between O₂ and Fe²⁺. The ligands of structure I were chosen for these studies because early preliminary results^{10,11} showed *E*_{1/2} for the Fe²⁺/Fe³⁺ couple very close to those of hemoglobin and myoglobin.

Although initial studies showed discouragingly rapid irreversible reactions between the lacunar iron(II) complexes and O₂, the studies with the Co-O₂ and Fe-CO systems have provided the basis for selecting structural modifications that do produce the desired reversible process. The most revealing result is the exceptionally large O₂ affinities that are attainable with cobalt complexes. In general,¹² iron(II) species interact with O₂ something like 100 times more strongly than do the corresponding cobalt(II) species; e.g., CoMb (sperm whale) *K*_{O₂} = 0.03 torr⁻¹ and FeMb (sperm whale) *K*_{O₂} = 2.0 torr⁻¹ at 20 °C. Since the lacunar cobalt complexes have, by far, the greatest O₂ affinities known among cobalt-O₂ adducts of the Pauling type,¹² the corresponding iron(II) complexes should have phenomenal O₂ affinities. Now it is also true that iron serves to activate O₂ in many heme proteins, and it might be expected that the reactivity of O₂ bound to iron would increase along with an increase in iron-O₂ interaction. Consequently, lacunar ligands having structural parameters that weaken the O₂ affinity of the cobalt(II) complex are expected to give reversible O₂ binding to iron(II). On this basis, structure I with M = Fe^{II}, R¹ = *m*-xylyl, R² = CH₃, R³ = CH₃, and X = (CH₂)₃ was chosen for detailed study; this is the ligand L in the following discussion.¹³

Deep red crystals of [Fe(L)Cl]PF₆ were prepared as previously described,⁵ and the solution behavior of the complex was investigated. In the nonaqueous solvents acetone and acetonitrile, the chloride remains coordinated even in the presence of 20% pyridine or 1-methylimidazole, as indicated by electronic spectra and electrochemical results.¹⁴ However, the addition of only 1% water

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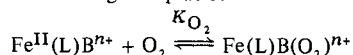
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Table I. Oxygen Binding Constants for Reversible Oxygen Adducts of lacunar-Fe^{II}(L)Bⁿ⁺ at -41.5 °C^a

| B | solvent | K_{O_2} , torr ⁻¹ b |
|----------|--------------------------|----------------------------------|
| pyridine | acetone/py/water = 3/1/1 | 0.16 ± 0.01 |
| chloride | acetone/py = 4/1 | 0.015 ± 0.003 |
| pyridine | acetone/py = 4/1 | 0.08 ± 0.01 |
| 1-MeIm | acetone/MeIm = 4/1 | 1.7 ± 0.2 |

^a K_{O_2} defined according to equation^b O_2 , average of values at four wavelengths across the spectrum using nonlinear least-squares fit to absorbance data.⁴

is sufficient to facilitate complete conversion to the 5-coordinate neutral base derivative (electronic spectrum identical with that of the complex prepared independently from the CO complex⁵). The water is apparently necessary to solvate the chloride, thereby assisting its displacement by neutral base. The resulting 5-coordinate complexes are high spin ($\mu_{\text{eff}} \sim 5.2\text{--}5.4 \beta$) and very sensitive to oxygen in solution.

Cooling solutions of the complex Fe(L)B²⁺ (B is pyridine or 1-methylimidazole) to -35 °C in a combination of acetone/water/axial base as solvent produces a system that reacts with O₂ in a fully reversible manner. Gas uptake measurements¹⁵ at -35.7 °C in pyridine solvent show that 1.0 ± 0.1 mol of O₂ is absorbed per mol of Fe(II); the resulting O₂ adduct is ESR silent. Visible spectral changes in a mixed solvent (Figure 1, see caption) show the reversibility of the O₂ reaction. The two spectral maxima, in the 500–650-nm region, associated with the O₂ adduct, increase in intensity as the partial pressure of O₂ is increased and the isosbestic point at 462 nm remains sharp. Following exposure to 1 atm of O₂, the system may be quantitatively reversed by flushing with N₂ to regenerate the original spectrum while retaining the sharp isosbestic point at 462 nm. This, of course, strongly supports the conclusion that reversible oxygenation is occurring.

A close parallel in qualitative spectral behavior further supports the presence of an O₂ adduct. The visible spectrum of the O₂-saturated solution of Fe(L)py²⁺ shows absorption maxima at 523 and 610 nm. These bear a striking similarity to the bands observed at 541 and 577 nm for oxyhemoglobin.¹⁶

Equilibrium constants for oxygen binding by the lacunar complexes Fe(L)Bⁿ⁺ have been estimated at -41.5 °C and are presented in Table I. The trends in values are very much as anticipated, with the progression increasing for axial bases in the sequence Cl < py < 1-MeIm. This parallels the behavior of the cobalt complexes¹⁷ and modified porphyrin complexes.¹⁸ The presence of water in the mixed solvent increases the O₂ affinity, as was found for the lacunar cobalt(II) derivatives.⁴ Comparison of the values of K_{O_2} for the iron complexes with those for the corresponding cobalt complexes shows that the O₂ adducts of iron are stronger by the expected factor.

At higher temperatures, for example at 20 °C, the O₂ complexes are unstable, rapidly producing iron(III)-containing species. The mode of irreversible oxidation is itself a fascinating problem in the fundamental chemistry of iron-dioxygen systems. Preliminary results indicate that the synthetic systems react in accord with a superoxide mechanism similar to that proposed for the auto-oxidation of Hb and Mb.¹⁹ The thorough understanding of this process is essential to further refinements in the design of synthetic iron(II)-oxygen carriers and our studies are continuing.

The series of iron complexes of general structure I offer the exciting possibility of producing totally synthetic, non-porphyrin

iron containing heme protein analogues capable of closely mimicking biological functions. The susceptibility of structure I toward systematic variation fosters the belief that further rational structure changes will lead to greater success in controlling Fe-O₂ systems. Prior to the studies reported here the only unchallenged example of a non-porphyrin iron O₂-carrying complex was that reported in 1973 by Baldwin and Huff.²⁰ That complex only attained reversibility at -85 °C while suffering irreversible oxidation at -50 °C in toluene/pyridine.

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Isotope Enrichment by Photolysis on Ordered Surfaces

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Recent reports of Turro¹ and other^{2,3} have verified that under some conditions there exists an unusually large ratio of the rate of reaction of ¹²C vs. ¹³C compounds when compared to the ratio expected from the ordinary "mass" isotope effect. The so-called magnetic isotope effect³ appears to be responsible whereby a reaction producing triplet biradicals as intermediates (e.g., Scheme I) reverts more frequently back to the starting compound when the odd electron density is on ¹³C than on ¹²C.

Turro has demonstrated that in order to observe substantial ¹³C enrichment in the photolysis of dibenzyl ketone (DBK), the triplet diradicaloid arising from photolysis must be constrained within a cage long enough for electron nuclear hyperfine coupling to take place between an unpaired electron and a magnetic nucleus (¹³C). The hyperfine coupling (hfc) induces singlet-triplet mixing in the radical pair (k_{ST}) followed by release of energy as the singlet radical pair undergoes bond reformation. Apparently in solution the weak solvent cage provides little resistance to the rapid diffusional separation of the radicals (k_{escape}). Thus the reaction in solutions, including viscous solutions, forms escape products which do not exhibit the effects of hfc. However, a dramatic isotope effect, which is apparently due to the differences in the nuclear magnetic moments rather than the masses of ¹³C and ¹²C, was observed when DBK was photolyzed in micellar cages in solution. The "restricted dimensionality" of the micelles holds the triplet radical pairs sufficiently long for hfc to cause intersystem crossing, thus recycling predominantly ¹³C back to the starting material.

Clearly, it would be worthwhile to optimize the "magnetic isotope effect" to give ¹³C enrichments that are as high as possible. Unfortunately, it is not possible to systematically alter the size, interior viscosity, and similar properties of a micelle⁴ to optimize the effect by "moving" the reflecting boundaries closer together

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