The Phenomenon of 'Dioxygen Protection' during Autoxidation of a Lacunar Macrobicyclic Iron(II) Reversible Dioxygen Carrier. An Outer-sphere Autoxidation Mechanism

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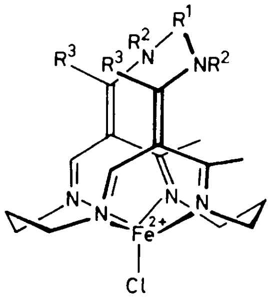
The autoxidation kinetics of an iron(II) complex which is a dioxygen carrier and which contains a sizeable protected cavity around one axial co-ordination site of the metal ion display a maximum in rate at *ca.* 1 Torr of dioxygen pressure at 0 °C and this unusual behaviour is interpreted as evidence for an outer-sphere oxidation mechanism involving hexaco-ordinated iron(II) species.

The intimate autoxidation mechanism of reversible iron(II) dioxygen carriers is a subject of acute importance, particularly in biochemistry. Hemoglobin, for instance, is known to suffer autoxidation in functioning erythrocytes.[1] Yet, despite the fundamental nature of the autoxidation of such species, very little kinetic or mechanistic information on the process is available.[2] While extensive use has been made of synthetic porphyrin complexes of iron(II) to model reversible dioxygen carrying behaviour,[3] these same complexes have not been used to model the complex mode of autoxidation which is com-



(1)

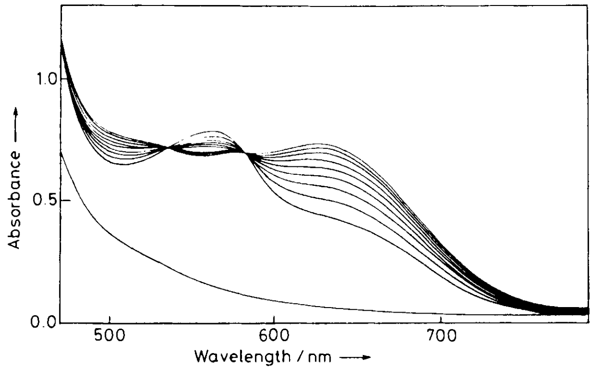


Figure 1. Visible spectral changes accompanying autoxidation of (**1**; $R^1 = [CH_2]_5$, R^2 = Me, R^3 = Ph). $P(O_2)$ = 6.2 Torr, $[Fe^{II}] = 2.5 \times 10^{-4}$ M, μ = 0.5 M (KNO_3), T = 0.0 °C in 311APW. Plots are 350 s apart and the peak at 640 nm is growing.

petitive with the reversible dioxygen-binding reaction in these and natural systems. We now report the first such mechanistic study of autoxidation of a synthetic, non-porphyrin dioxygen carrier which shows some remarkable similarities to the mechanism of hemoglobin and myoglobin oxidation recently proposed by Caughey.[2] As a consequence this synthetic complex and its congeners[4] may provide simple model systems for complex biological autoxidation phenomena.

The crystalline, purple iron(II) complex (**1**: $R^1 = [CH_2]_5$, R^2 = Me, R^3 = Ph) was prepared as previously described.[4] Dissolution in acetone–pyridine–water (3 : 1 : 1 v/v; 311APW) causes replacement of the chloro ligand by pyridine to generate a high-spin five-co-ordinate complex in a yellow-red solution.[4] In non-aqueous solvents the chloro ligand remains co-ordinated, solutions again being yellow-orange with high-spin five-co-ordinate iron(II) present and $E_{\frac{1}{2}}$ (acetonitrile soln., *vs.* Ag°/Ag^+, 0.1 M, in acetonitrile reference) for the reversible $Fe^{II}/^{III}$ couple = −0.31 V.[4] In dry pyridine at 0.0 °C a 2.5×10^{-4} M solution of the complex will reversibly bind dioxygen, as judged spectrophotometrically, with $K(O_2)$ = *ca.* 0.01 ± 0.002 $Torr^{-1}$ and very little evidence for irreversible autoxidation processes.

In 311APW (μ = 0.05 M, KNO_3) at 0.0 °C the complex undergoes irreversible autoxidation competitively with reversible dioxygen binding and the kinetics of this process display a unique dependence on dioxygen pressure. Good isosbestic behaviour accompanies the autoxidation (Figure 1), and the process, monitored at 640 nm, is rigorously first order in total iron(II) concentration over >3 half-lives. Observed rate constants derived from such data are plotted in Figure 2 as a function of the partial pressure of dioxygen and the data are tabulated in Table 1. Clearly, the autoxidation reaction proceeds with its maximum rate at $P(O_2)$ = *ca.* 1 Torr and at higher O_2 pressures the rate slows until at 760 Torr the reaction is some 75 times slower than at its maximum. E.s.r. spectra of an autoxidized solution show that all the products lie in the slow-spin iron(III) region (*g ca.* 2) which is tentatively proposed to arise from six-co-ordinate iron(III) species.[4,5]

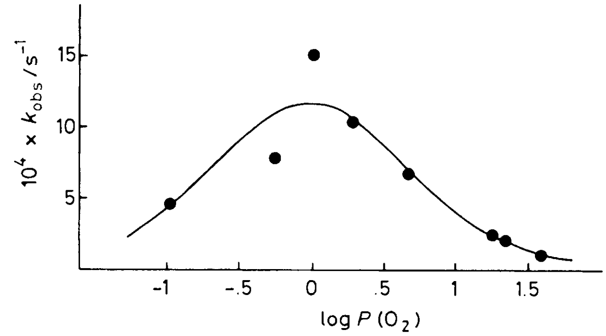


Figure 2. Plot of log $P(O_2)$ *vs.* k_{obs} for autoxidation of (**1**; $R^1 = [CH_2]_5$, R^2 = Me, R^3 = Ph) in 311APW at 0.0 °C (μ = 0.05 M, KNO_3).

Table 1. Observed first-order rate constants of the autoxidation of (**1**; $R^1 = [CH_2]_5$, R^2 = Me, R^3 = Ph) in 311APW,[a] T = 0.0 °C, μ = 0.05 M (KNO_3).

$P(O_2)$/Torr	$10^4\, k_{obs}/s^{-1}$	Half-life, $t_{\frac{1}{2}}$/s
0.11	4.6 ± 0.4	1480
0.59	7.7 ± 0.6	900
1.1	15 ± 3	450
1.9	10.2 ± 0.8	680
4.6	6.4 ± 0.4	1080
18.7	2.6 ± 0.2	2665
25.9	2.0 ± 0.2	3490
38.0	1.2 ± 0.2	5590
760.0	0.20 ± 0.05	34000

[a] Acetone–pyridine–water (3 : 1 : 1 v/v).

Clearly, increased dioxygen pressures (above *ca.* 1 Torr) appear to protect the iron(II) complex from the autoxidation. Such 'dioxygen protection' behaviour has been noted in porphyrin systems where it arises from the necessity of having both oxygenated and deoxy iron(II) species present simultaneously so that they can combine in a bimolecular fashion to give a μ-peroxo-dimeric species[6] in the rate-determining step. The rate law for such a process is of the form rate = $kK_0[Fe^{II}]^2[O_2]/(1+K_0[O_2])^2$ and, while predicting dioxygen protection at high $[O_2]$, also predicts second-order dependence on iron(II) concentration. This latter point is inconsistent with the present data as is the idea of μ-peroxo-dimer formation in these protected structures (**1**). An alternative mechanism explaining the observations must involve the deoxy iron(II) five-co-ordinate complex reacting with something other than O_2 in a rate-determining step prior to autoxidation. Such a scheme is provided by equations (1)—(3), where L represents the lacunar

$$Fe^{II}L(py) + O_2 \overset{K_0}{\rightleftharpoons} Fe^{II}L(py)O_2 \qquad (1)$$

$$Fe^{II}L(py) + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Fe^{II}L(py)S \qquad (2)$$

$$Fe^{II}L(py)S + O_2 \xrightarrow{k_2} Fe^{III}L(py)S + O_2^- \qquad (3)$$

macrobicyclic ligand, py is pyridine axial base, and S represents some solvent component capable of co-ordinating to the metal centre within the lacuna. Applying the steady-state approximation to the concentration of the six-co-ordinate $Fe^{II}L(py)S$ gives a rate law (4), where $[Fe^{II}]$ represents the

$$k_{obs} = \frac{k_1(k_2/k_{-1})[S][O_2]}{(k_2/k_{-1})K_0[O_2]^2 + \{(k_2/k_{-1}) + K_0\}[O_2] + 1} \qquad (4)$$

total iron(II) concentration as $Fe^{II}L(py)$ and $Fe^{II}L(py)O_2$. The data have been fitted to the rate law by an iterative least-squares technique (Figure 2), correlation coefficient 0.99177. The kinetic parameters have been extracted by the Newton–Raphson method, yielding the following values: $K_0 = 0.47$ Torr^{-1}; $k_2/k_{-1} = 2.4$ Torr^{-1}; $k_1[S] = 2.4 \times 10^{-3}$ s^{-1}. Confidence in the interpretation is also gained from the agreement between the calculated and observed values for the oxygen pressure at which the maximum rate occurs. Differentiation of the rate law shows that the rate should reach a maximum value when $[O_2] = (k_{-1}/k_2K_0)^{\frac{1}{2}}$. The calculated value for this quantity is 0.94 Torr while the experimental value is approximately 1 Torr.

The scheme postulated, equations (1)—(3), in order to explain the observed kinetics implies several fundamentally new reactivities for synthetic iron(II) complexes. (i) The dioxygen adduct $Fe^{II}L(py)O_2$ is not involved in the primary route to autoxidized species. In fact this entity is a relatively stable component of the system and so is responsible for the observed dioxygen protection. (ii) The lacunar complex is capable of accepting a sixth ligand S within the cavity of the molecule and that sixth ligand promotes the autoxidation. (iii) The autoxidation proceeds *via* an outer-sphere electron transfer from the hexaco-ordinate metal centre to dioxygen generating the superoxo radical (solution pH *ca.* 10)[4] as a primary product. [Superoxide will rapidly go on to oxidize further iron(II) centres in this medium as previously noted.[7]]

The nature of S in equations (2) and (3) is of interest since for S to promote autoxidation it should be a strong σ electron donor, and preferably anionic, in order to shift $E_{\frac{1}{2}}$ for the iron(II)/(III) couple more negative. This will facilitate the outer-sphere electron transfer step (3) from iron(II) to dioxygen. The prime candidate for S in 311APW is, therefore, hydroxide ion since, not only is it anionic, but it is also small enough to fit within the cavity of structure (**1**). (Molecular models show that pyridine is much too large to be accommodated in this manner.) That small anions can occupy the cavity is demonstrated by the fact that addition of CN^-, NCS^-, or N_3^- to 311APW solutions of this complex in the absence of O_2 generates deeply purple solutions showing the typical $M \rightarrow \pi^*$ charge transfer of a six-co-ordinate low-spin iron(II) species at *ca.* 500 nm.[8] Interestingly these solutions with NCS^- and N_3^- are reversibly thermochroic, turning yellow on heating, indicative of a 5- to 6-co-ordinate equilibrium occurring in solution.

The autoxidation mechanism postulated, equations (1)—(3), is quite unlike that which we have recently proposed for iron(II) complexes (**1**) where $R^1 = [CH_2]_3$ or $C_6H_4(CH_2\text{–})_2$, $R^2 = R^3 = Me$. Despite the homologous similarities of the present system to these latter two {complexes with $R^1 = [CH_2]_3$ or m-$C_6H_4(CH_2\text{–})_2$ (*m*-xylylene) autoxidize *via* outer-sphere oxidation of the 5-co-ordinate deoxy species $Fe^{II}L(py)$[7,9]} a fundamental difference in mechanism arises because of the ability of the present $R^1 = [CH_2]_5$ complex to accommodate S inside the lacuna whereas the other two complexes cannot. The outer-sphere oxidation of the six-co-ordination material appears to be a more facile process than equivalent oxidation of the five-co-ordinate species, which is consistent with S moving $E_{\frac{1}{2}}$ for the iron(II)/(III) couple more negative.

The present scheme, equations (1)—(3), is essentially identical to that recently proposed by Caughey to explain the complex dioxygen and anion dependence of the autoxidation of hemoglobin and myoglobin.[2] Consequently, the present iron species is found to provide an excellent model for the complex autoxidation chemistry of the natural dioxygen carriers. Further continuing investigations of the autoxidation process with this complex and its congeners (**1**) will, we hope, provide additional data relevant to both the synthetic and natural systems.

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