The Mechanism of Oxidation of Alkanes by Peroxo Complexes of Iron Porphyrins in the Presence of Acylating Agents: a Model for Activation of O_2 by Cytochrome P-450

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A new model for cytochrome P-450 oxidation of alkanes, which imitates the process of O_2 activation by cytochrome P-450, involving the formation of iron porphyrin peroxo complexes in the presence of acylating agents is proposed.

The problem of dioxygen activation occupies a central place in the study of the mechanism of oxidation by cytochrome P-450.[1] Although no active intermediate for cytochrome P-450 has been observed, recent work[2] has shown that a high valent oxo-complex of Fe-porphyrin, $[(porph)FeO]^+$,† can react with the substrate. In model studies the reactive species has been characterized as an oxo-iron(IV)–porphyrin cation-radical $[(porph)Fe^{IV}{=}O]^+$.[3,4]

Direct evidence for formation of this intermediate from molecular oxygen has not yet been obtained. Sligar and coworkers obtained evidence for acylation and O–O bond cleavage in the P-450–$^{18}O_2$–dihydrolipoic acid system using an isotopic labelling method.[5]

Previously we have reported the formation of Fe–porphyrin dioxygen complexes from O_2^- and hemes.[6] These have since been assigned peroxo complex structures.[7,8] These complexes possess only weak oxidative capability but the addition of the acylating agent RCOX (X = RCO_2 or Cl) activates them towards alkane and alkene oxidation.[8,9] This paper presents the results of our investigations of the mechanism of this new reaction and shows its similarity to that of the enzymatic oxidation of alkanes. The addition of Fe^{III}(tpp)Cl (0.76×10^{-2} M) to a solution of KO_2–18-crown-6 (3.1×10^{-2} M) in benzene results in the formation of $Fe^{III}(tpp)(O_2^{2-})$ {subsequently referred to as $[Fe(tpp)O_2]^-$} ($\lambda_{max.}$ 438, 566, and 610 nm, g = 7.6, 4.2, and 1.99).[8] Addition of an equal volume of acetic anhydride (1.0×10^{-2} M) in C_6H_{12} to $[Fe(tpp)O_2]^-$ leads to the formation of $C_6H_{11}OH$ (0.45×10^{-3} M) and $C_6H_{10}O$ (0.30×10^{-3} M), as determined by g.l.c. When the reaction is carried out in the presence of triethylamine and *in vacuo* to exclude O_2 only the alcohol is formed.‡

An intermediate is obtained in the interaction of $[Fe(tpp)O_2]^-$ with Ac_2O in toluene at −70 °C ($\lambda_{max.}$ 421, 505, 574, 650, and 699 nm; g = 5.9) and is assigned the peroxyacetate complex structure (tpp)Fe^{III}OOAc. This complex is also obtained from the reaction of (tpp)FeCl with peroxyacetic acid in the presence of Et_3N. At −50 °C cyclohexane oxidation occurs with this peroxyacetate complex. The e.s.r. signal with g = 5.9 diminishes and a broad band centred at 650 nm, typical of a porphyrin π-cation-radical, appears in the visible spectrum.

In the case of tetramesitylporphyrin iron, Fe(tmp), the corresponding peroxyacetate complex with $\lambda_{max.}$ 418, 500, 568, 633, and 654 nm is formed by the interaction of $[Fe(tmp)O_2]^-$ ($\lambda_{max.}$ 435, 571, and 637 nm) with Ac_2O in toluene at −70 °C. This complex, when heated to −45 °C, is converted into a new intermediate with $\lambda_{max.}$ 420 and 635 nm (toluene : acetonitrile 1 : 4), which is apparently identical to the $[(tmp)Fe^{IV}{=}O]^+$ complex ($\lambda_{max.}$ 406 and 645 nm in dichloromethane–methanol) obtained by Groves and coworkers in the reaction of Fe(tmp)Cl and *m*-chloroperoxybenzoic acid.[4] Thus, the formation of the FeO intermediate from a dioxygen precursor may be described by equation (1).

$$[(porph)FeO_2]^- \xrightarrow[-X^-]{RCOX} (porph)FeOOC(O)R \downarrow -RCOO^- \rightarrow [(porph)FeO]^+ \quad (1)$$

Further evidence for this intermediate being responsible for the oxidation of alkanes in our system is as follows. First, there is retention of configuration (60—70%) in the oxidation of *cis*- and *trans*-dimethylcyclohexane; exclusive alcohol formation suggests oxoligand insertion into the C–H bond, equation (2).

$$[(porph)FeO]^+ + RH \rightarrow [(porph)Fe]^+ + ROH \quad (2)$$

Secondly, in the reaction of $[Fe(tpp)O_2]^-$ (1.0×10^{-2} M) with Ac_2O in CH_2Cl_2–MeOH–C_6H_{12} (10 : 2 : 1) in the presence of $H_2{}^{18}O$ (0.4 M) at −50 °C, the mass spectrum of the cyclohexanol produced indicates 70 ± 10% ^{18}O incorporation into the alcohol. Thus, the oxygen of the hydroxylating species is exchangeable with $H_2{}^{18}O$ added, which indicates FeO participation. Thirdly, the kinetic isotope effect in the oxidation of anisole and [*Me*-$^2H_3$]anisole (k_H/k_D 7.0 ± 0.5) is close to that for oxidation with Fe(tpp)Cl–PhIO and cytochrome P-450[10] and characteristic of alkane oxidation by metal oxocomplexes.[11]

Confirmation of the active species in oxidation of alkanes in the $[Fe(porph)O_2]^-$–Ac_2O system was obtained by studies on the site selectivity of isopentane and n-hexane oxidation (Table 1). There is a change in regioselectivity; decreased attack at the most inaccessible C–H bonds, relative to primary C–H bonds, is observed with the sterically hindered tetramesitylporphyrin. As far as we are aware this is the first observation of steric hindrance in selective oxidations on the terminal carbon atom in alkanes.§ The regioselectivities of hexane oxidation in the Fe(tpp)Cl–PhIO (C-3 : C-2 : C-1 = 100 : 110 : 1) and $[Fe(tpp)O_2]^-$–Ac_2O systems in benzene become approximately the same (C-3 : C-2 : C-1 = 7 : 8 : 1) after the addition of acetic acid to the former system owing to

Table 1. The regioselectivity in isopentane and hexane hydroxylation by peroxocomplexes of tetraphenyl- and tetramesitylporphyrinatoiron in the presence of acetic anhydride.

	Selectivity per H atom					
	Isopentane			Hexane		
Porphyrin	Tertiary	Secondary	Primary	C-3	C-2	C-1
tpp	40	12	1	10	10	1
tmp	16	6	1	3	7	1

† Abbreviations: porph, porphyrin; tpp, tetraphenylporphyrin; tmp, tetramesitylporphyrin dianions.

‡ The reaction of hydrocarbon oxidation catalysed by free superoxide in the presence of acylating agents also takes place but occurs *via* a free radical mechanism.

§ The change of regioselectivity at the (ω − 1) position in heptane oxidation (D. Mansuy, J. P. Bartoli, and M. Momenteau, *Tetrahedron Lett.*, 1982, **23**, 2781) has been observed when using sterically hindered porphyrins.

the transformation of the μ-peroxodimer into an oxoiron complex.[4]

The mono-oxygenase reaction of alkane oxidation in the Fe(tpp)Cl–Ac_2O–O_2 system using an electrode as the source of electrons is also possible. In the oxidation of cyclohexane, cyclohexanol is formed in 7% electrochemical yield. The number of catalytic cycles on the heme is *ca.* 100. In the hydroxylation of dimethylcyclohexane, retention of configuration is observed at the asymmetric carbon atom. In the oxidation of hexane, the change of selectivity to the preferred ω and ω−1 hydroxylation is similar to that observed in the cytochrome P-450 dependent enzymatic system.[12]

This work has thus shown that for the activation of O_2 participation of an acylating agent is necessary for the effective heterolytic cleavage of the O–O bond. Evidently, this is a complete analogue of the activation of O_2 by cytochrome $P\text{-}450_{CAM}$ (CAM = camphor hydroxylase).[5] The proposed chemical system is at present the best model of cytochrome P-450.

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