Oxidation of Aldehydes by an Iron(III) Porphyrin Complex–*m*-Chloroperbenzoic Acid System

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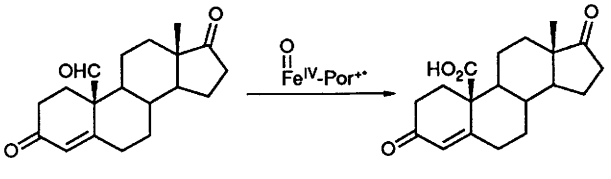
Oxidation of aldehydes by an iron(III) porphyrin complex–*m*-chloroperbenzoic acid system has been found to yield the carboxylic acids in good yields; a direct hydrogen abstraction mechanism is suggested based on kinetic studies.

While the oxidation of androstene-3,17,19-trione (**1**) to the corresponding 2β-hydroxide by aromatase cytochrome P-450 has been proposed in estrogen biosynthesis,[1] we have previously shown that (**1**) is readily oxidized to the carboxylic acid (**2**) by an oxo-ferryl porphyrin cation radical species,[2] a model complex of the active species responsible for oxidations by cytochrome P-450[3] (Scheme 1). Exclusive formation of (**2**) is a clear indication that aldehyde oxidation is a favourable process relative to α,β-unsaturated ketone epoxidation. We now report that aldehyde oxidation by a model system of cytochrome P-450 proceeds to yield the carboxylic acids in good yields, epoxidation of terminal alkenes competing with the aldehyde oxidation.

In a typical reaction, an aldehyde (0.25—0.5 mmol) and Fe^{III}(pfpp)Cl [3 nmol; pfpp = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin] in 5 ml of CH_2Cl_2 was cooled to −78 °C, and 0.1 mmol of purified *m*CPBA (*m*-chloroperbenzoic acid) was introduced under a continuous N_2 flow. The consumption of aldehyde and formation of carboxylic acid were monitored at the same time by GLC (Shimadzu capillary column; HiCap-CBP1, 25 m). The oxidation was usually completed in 30 min and yields were calculated based on *m*CPBA employed. As shown in Table 1, alkyl and aromatic aldehydes were oxidized to the carboxylic acids in good yields. When *trans*-cinnamaldehyde was employed, *trans*-cinnamic acid was obtained as the sole product (Table 1). On the other hand, the oxidation of undec-10-enal afforded a mixture of the acid and the epoxide in yields of 48 and 36%, respectively (run 5). These results suggest that the rate of aldehyde oxidation is close to that of terminal alkene epoxidation. Thus, preferable formation of epoxides was observed in the competitive oxidations of 2-phenylpropionaldehyde with more reactive alkenes such as α-methylstyrene and cyclo-octene[4] (runs 6 and 7).

Recent studies on cytochrome P-450-promoted oxidations indicate that there are two general mechanistic pathways, *i.e.*, a hydrogen abstraction mechanism in alkane hydroxylation[5] and involvement of a one-electron transfer process in many oxidations such as epoxidation,[6] *S*-oxidation,[7] and *N*-dealkylation reactions.[8] To understand the oxidation mechanism of aldehydes, we have examined the deuterium isotope effect and competitive oxidations of substituted benzaldehydes.

In the competitive oxidation experiments, a mixture of several *para*- and *meta*-substituted benzaldehydes was oxidized with Fe^{III}(pfpp)Cl/*m*CPBA at −78 °C and relative oxidation rates were determined by comparison of d[aldehyde]/d*t* (relative rate, *p*-MeO : 3.15, *p*-Me : 1.81, H : 1, *p*-Cl: 0.92, *m*-NO_2: 0.57, *p*-NO_2: 0.44); good correlation with Hammett σ^+ ($\rho = -0.53$, $r = 0.981$) was observed. While



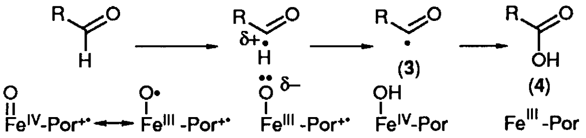
(**1**) (**2**)

Scheme 1

Table 1. Oxidation of aldehydes with Fe^{III}(pfpp)(Cl)/*m*CPBA system.[a]

Run	Substrate	Product(s) (% yield)[b]
1	PhCH(Me)CHO	PhCH(Me)CO_2H (98)
2	*p*-MeC_6H_4CHO	*p*-$MeC_6H_4CO_2H$ (100)
3	*p*-$NO_2C_6H_4CHO$	*p*-$NO_2C_6H_4CO_2H$ (50)
4	*trans*-PhCH=CHCHO	*trans*-PhCH=$CHCO_2H$ (85)
5	CH_2=CH$[CH_2]_8$CHO	CH_2=CH$[CH_2]_8CO_2H$ (48) $\overline{OCH_2C}H[CH_2]_8CHO$ (36)
6[c]	PhCH(Me)CHO + cyclo-octene	PhCH(Me)CO_2H (trace) cyclo-octene oxide (84)
7[c]	PhCH(Me)CHO + PhCMe=CH_2	PhCH(Me)CO_2H (4) $Ph\overline{CMeCH_2O}$ (49)

[a] All reactions were carried out in CH_2Cl_2 at −78 °C under N_2. [b] Yields were determined by GLC based on *m*CPBA used. [c] Mixture of alkene and aldehyde (1 : 1) was oxidized.



Scheme 2

Table 2. Oxidation of 2-phenylpropionaldehyde with *m*CPBA catalysed by Fe^{III}-porphyrins.

Catalyst	Products (%)[a]	Carboxylic acid : decarbonylated product(s)
Fe^{III}(pfpp)(Cl)	PhCH(Me)CO_2H (98) PhCH(OH)Me (trace)	~100 : 0
Fe^{III}(dcpp)(Cl)[b]	PhCH(Me)CO_2H (85) PhCH(OH)Me (4) + PhEt (trace)	21 : 1
Fe^{III}(tmp)(Cl)[b]	PhCH(Me)CO_2H (59) PhCH(OH)Me_2 (3) + PhEt (1.5)	13 : 1

[a] Yields were determined by GLC based on *m*CPBA employed. [b] tdcpp = 5,10,15,20-tetrakis(2,6-dichlorophenyl) porphyrin; tmp = 5,10,15,20-tetramesitylporphyrin.

correlation of oxidation rates with Hammett σ^+ was also reported for alkene oxidations catalysed by Fe^{III} porphyrins,[4d,6a,d] similar ρ values (usually less than 1) were commonly observed for benzylic hydrogen abstractions from alkylbenzenes and benzaldehyde by electron-deficient radicals such as Cl$^•$ and peroxyl.[9]

To study isotope effects, a mixture of *p*-MeC_6H_4CHO and *p*-MeC_6H_4CDO (43 : 57) was oxidized by adding 0.19 equivalent of *m*CPBA. After the reaction, 81% of the aldehydes remained unchanged and 94% (based on the consumed aldehydes) formation of toluic acid was observed by GLC. The ratio of *p*-MeC_6H_4CHO and *p*-MeC_6H_4CDO in the recovered aldehyde was measured by ^1H NMR spectroscopy (Bruker, 200 MHz) to be 39 : 61. Accordingly, k_H/k_D for the oxidation was calculated to be 1.99. In the oxidation of *p*-chlorobenzaldehyde, an isotope effect of 1.46 was obtained. These values are also close to those observed in reactions of toluene and isobutene (tertiary position) with Cl$^•$,[10] and of benzaldehyde with the trichloromethyl radical,[9c] respectively.

These results support the rate-determining step of aldehyde oxidation with oxo-ferryl cation radical species being similar to the reactions of alkylbenzenes and benzaldehyde with electron-deficient radicals as shown in Scheme 2.[9,10]

Once the acyl radical (**3**) is formed in the oxidation, decarbonylation of the acyl radical could compete with the carboxylic acid formation if the oxygen rebound process, (**3**)→(**4**), is slow. For example, the decarbonylation rate constants of $PhCH_2CO^•$ and PhCH(Me)CO$^•$ were reported to be 10^6—10^7/s.[11] In the oxidation of 2-phenylpropionaldehyde with Fe^{III}(pfpp)(Cl)/*m*CPBA traces of 1-phenylethanol were formed. Thus, less reactive Fe porphyrin complexes,[12] Fe^{III}(dcpp)(Cl) and Fe^{III}(tmp)(Cl), were also employed as the oxidation catalyst to compare the oxygen rebound and decarbonylation reactions. As shown in Table 2, less reactive Fe porphyrins gave lower yields of the carboxylic acid with relatively greater amounts of decarbonylated products.

In conclusion, the oxidation of aldehydes with oxo-ferryl porphyrin cation radical complexes gave the carboxylic acids in good yields *via* a direct hydrogen abstraction mechanism. Further, the relative reactivity of aldehydes and alkenes with the oxo complex is as follows; cyclo-octene, styrene > aldehyde ≈ terminal alkene > α,β-unsaturated ketone (aldehyde).

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References

1 J. Fishman and M. S. Raju, *J. Biol. Chem.*, 1981, **256**, 4472.

2 Y. Watanabe and Y. Ishimura, *J. Am. Chem. Soc.*, 1989, **111**, 8047. Our results are consistent with the recent proposal by Stevenson *et al.*: D. E. Stevenson, J. N. Wright, and M. Akhtar, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2043.

3 The oxo-ferryl porphyrin cation radical (O=Fe^{IV}-Por$^{+•}$) is equivalent to an $(FeO)^{3+}$ species; R. E. White and M. J. Coon, *Annu. Rev. Biochem.*, 1980, **50**, 315; J. T. Groves, R. C. Haushalter, M. Nakamura, T. E. Nemo, and B. J. Evans, *J. Am. Chem. Soc.*, 1981, **103**, 2884; T. J. McMurry and J. T. Groves, in 'Cytochrome P-450: Structure, Mechanism and Biochemistry,' ed. P. R. Ortiz de Montellano, Plenum, New York, 1986, Ch. 1.

4 (a) J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, 1983, **105**, 5786; (b) I. Tabushi and A. Yazaki, *ibid.*, 1981, **103**, 7371; (c) E. Guilment, and B. Meunier, *Nouv. J. Chim.*, 1982, **6**, 511; (d) J. R. Lindsay Smith and P. R. Sleath, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1009; (e) B. De Poorter and B. Meunier, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1735.

5 J. T. Groves, G. A. McClusky, R. E. White, and M. J. Coon, *Biochem. Biophys. Res. Commun.*, 1978, **81**, 154; J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, 1983, **105**, 6243.

6 J. T. Groves and Y. Watanabe, *J. Am. Chem. Soc.*, 1986, **108**, 507; T. G. Traylor and A. R. Miksztal, *ibid.*, 1987, **109**, 2770; 1989, **111**, 7443; T. G. Traylor, T. Nakano, B. E. Dunlap, P. S. Traylor, and D. Dolphin, *ibid.*, 1986, **108**, 2782; J. M. Garrison, D. Ostovic, and T. C. Bruice, *ibid.*, 1989, **111**, 4960.

7 Y. Watanabe, T. Iyanagi, and S. Oae, *Tetrahedron Lett.*, 1982, **23**, 533.

8 G. T. Miwa, J. S. Walsh, and A. Y. H. Lu, *J. Biol. Chem.*, 1984, **259**, 3000; R. P. Hanzlik and R. H. Tullman, *J. Am. Chem. Soc.*, 1982, **104**, 2048; T. L. Macdonald, K. Zirvi, L. T. Burka, P. Peyman, and F. P. Guengerich, *ibid.*, 1982, **104**, 2050.

9 (a) G. A. Russell, in 'Free Radicals,' ed. J. K. Kochi, vol. 1, Wiley, New York, 1973, ch. 7; (b) C. Walling and E. A. McElhill, *J. Am. Chem. Soc.*, 1951, **73**, 2927; (c) K. H. Lee, *Tetrahedron*, 1968, **24**, 4793; 1970, **26**, 2041, 1503.

10 G. Chiltz, R. Eckling, P. Goldfinger, G. Huybrechts, H. S. Johnston, L. Meyers, and G. Verbeke, *J. Chem. Phys.*, 1963, **38**, 1053; G. A. Russell, *J. Am. Chem. Soc.*, 1958, **80**, 5002; K. Wiberg and L. H. Slaugh, *ibid.*, 1958, **80**, 3033; H. C. Brown and G. A. Russell, *ibid.*, 1952, **74**, 3995.

11 L. Lunazzi, K. U. Ingold, and J. C. Scaiano, *J. Phys. Chem.*, 1983, **87**, 529; M. J. Perkins and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1974, 297; N. J. Turro, I. R. Gould, and B. H. Baretz, *J. Phys. Chem.*, 1983, **87**, 531.

12 P. S. Traylor, D. Dolphin, and T. G. Traylor, *J. Chem. Soc., Chem. Commun.*, 1984, 279; B. De Poorter and B. Meunier, *Tetrahedron Lett.*, 1984, **25**, 1895; M. J. Nappa and C. A. Tolman, *Inorg. Chem.*, 1985, **24**, 4711; T. G. Traylor and A. R. Miksztal, *J. Am. Chem. Soc.*, 1989, **111**, 7443.