

The Oxidation of Organic Compounds with Iodosylbenzene catalysed by Tetra(4-*N*-methylpyridyl)porphyrinatoiron(III) Pentacation: A Polar Model System for the Cytochrome P450 Dependent Mono-oxygenases

John R. Lindsay Smith* and David N. Mortimer

Department of Chemistry, University of York, York YO1 5DD, U.K.

Replacing the tetraphenylporphyrinatoiron(III) chloride (Fe^{III}TPPCL) catalyst, in Groves' model system (Fe^{III}TPPCL-PhIO) for cytochrome P450 mono-oxygenases, with tetra(4-*N*-methylpyridyl)porphyrinatoiron(III) pentacation allows oxidations to be carried out in protic and dipolar aprotic solvents without significantly altering the mechanisms of the reactions.

The report by Groves and his co-workers¹ that many of the oxidations of cytochrome P450 mono-oxygenases can be brought about by iodosylbenzene in the presence of tetraphenylporphyrinatoiron(III) chloride (Fe^{III}TPPCL) has stimulated research into the oxidations catalysed by this and by related metalloporphyrins.² This, in turn, has led to the development of several metalloporphyrin catalysed systems, as models for the cytochrome P450 mono-oxygenases^{2,3} and these systems have been used to oxidise a wide range of organic compounds. A common feature of these chemical systems is that the oxidations take place in the presence of a metalloporphyrin dissolved in a low polarity solvent, typically dichloromethane, benzene, or chlorobenzene. However, the oxidation mixtures are not homogeneous. Iodosylbenzene, a mono-oxygen donor used in many studies, is only poorly soluble in most organic solvents⁴ and aqueous hypochlorite, another oxidant, has to be transported into the organic medium by phase-transfer catalysis.^{3a,c} We report here how with the polar iron porphyrin, tetra(4-*N*-methylpyridyl)porphyrinatoiron(III) pentacation (Fe^{III}TMPyP) as

catalyst the oxidation of organic compounds with iodosylbenzene can be carried out in protic and dipolar aprotic solvents. With methanol, in which iodosylbenzene is readily soluble,⁴ the reaction mixtures are homogeneous.

The epoxidations of alkenes with the Fe^{III}TMPyP-PhIO-methanol and with the Fe^{III}TPPCL-PhIO-dichloromethane systems show very similar stereoelectronic requirements (Table 1) and both systems give stereospecifically the *syn*-addition product. The oxidations with Fe^{III}TMPyP can also be carried out in water but the epoxide yields are lowered by the poor water solubility of the substrates and allylic oxidation becomes a significant side reaction.

The Fe^{III}TMPyP-PhIO system hydroxylates cyclohexane to cyclohexanol in low yield (1% based on oxidant in MeCN and 0.1% in MeOH, with solvent:substrate:oxidant in molar proportions 2000:20:1). The analogous reaction with Groves' system gives yields of 5–10% (CH₂Cl₂)⁵ and 30% (C₆H₆).^{5b} Data from competitive oxidations of cyclohexane and [²H₁₂]cyclohexane in acetonitrile, methanol, or dimethylformamide show that the alkane hydroxylation has a large

Table 1. The reactivities of aliphatic alkenes, relative to cyclohexene, towards epoxidation with iodosylbenzene catalysed by Fe^{III}TMPyP in methanol or acetonitrile and by Fe^{III}TPPCL in dichloromethane.^a

Substrate	Product (yield, %) ^b	Reactivity relative to cyclohexene	
		Fe ^{III} TMPyP ^c	Fe ^{III} TPPCL ^d
2,3-Dimethylbut-2-ene	2,3-Epoxy-2,3-dimethylbutane (95)	8	10
1-Methylcyclohexene	1,2-Epoxy-1-methylcyclohexane (55)	4	4
<i>cis</i> -4-Methylpent-2-ene	<i>cis</i> -2,3-Epoxy-4-methylpentane (55)	2.2	1.5
Cyclohexene	Epoxycyclohexane (30)	1.0	1.0
<i>trans</i> -4-Methylpent-2-ene	<i>trans</i> -2,3-Epoxy-4-methylpentane (20)	0.2	0.1

^a Data obtained from competition experiments with molar ratio of each substrate to oxidant and to catalyst, 200:10:1, respectively.

^b Typical yields, based on PhIO, from reactions in MeOH. ^c Relative reactivities were unchanged when reactions were carried out under nitrogen. ^d Ref. 2d.

Table 2. Kinetic isotope effects in oxidations with iodobenzene catalysed by Fe^{III}TMPyP or by Fe^{III}TPPCL.

Oxidising System	Kinetic isotope effects (k_H/k_D)			
	C ₆ H ₁₂ , ^a C ₆ D ₁₂ Intermolecular	PhOCH ₃ , ^b PhOCD ₃ Intermolecular	PhCH ₂ NMe ₂ , PhCD ₂ NMe ₂ Intermolecular	PhCH ₂ N(Me)CD ₂ Ph, ^a Intramolecular
Fe ^{III} TPPCL-PhIO-C ₆ H ₆	7.0 ± 0.1 ^c	9 ± 3 ^d	1.3 ± 0.1 ^a	3.0 ± 0.2
Fe ^{III} TMPyP-PhIO-MeCN	7.0 ± 1.0 ^e	5.5 ± 1	1.3 ± 0.1 ^f	6.0 ± 1.0 ^g

^a Measured by g.c.-mass spectroscopy. ^b Calculated from relative yields of phenol and 2-methoxyphenol (ref. 6). ^c Ref. 7; Groves and Nemo (ref. 5a) report a value $k_H/k_D = 12.9 \pm 1.0$ for oxidation in CH₂Cl₂. ^d Solvent CH₂Cl₂ (ref. 6). ^e The same value was obtained in MeOH and Me₂NCHO. ^f Each substrate was oxidised in competition with 4-chloro-*N,N*-dimethylbenzylamine. ^g Solvent water.

primary kinetic isotope effect, in agreement with the values from this oxidation by Groves' system (Table 2) and by cytochrome P450 from liver microsomal systems ($k_H/k_D = 7.0-8.6$).⁸

The similarity between oxidations catalysed by the two porphyrins and the lack of sensitivity of their reactions to solvent changes is also apparent from kinetic isotope effects in oxidative *O*- and *N*-dealkylations. Table 2 shows that with each of the metalloporphyrin systems the demethylation of anisole occurs *via* a rate-determining methoxy C-H bond breakage.⁶ However, with tertiary amines, which are oxidised in high yield (> 80% based on oxidant), inter- and intramolecular kinetic isotope effects reveal⁹ that dealkylation occurs by a rate-determining electron-transfer (small k_H/k_D) followed by a product-determining proton loss (medium-large k_H/k_D). The Hammett ρ values from the relative rates of oxidation of 3- and 4-substituted *N,N*-dimethylbenzylamines with each iron porphyrin catalyst (Fe^{III}TPPCL-PhIO-C₆H₆, $\rho = -0.41 \pm 0.02$ and Fe^{III}TMPyP-PhIO-Me₂NCHO, $\rho = -0.73 \pm 0.08$) are in agreement with the latter mechanism.

We conclude that the use of Fe^{III}TMPyP as a catalyst extends the range of suitable solvents for the metalloporphyrin model systems without significantly altering the mechanism of the oxidations.

One of us (D. N. M.) thanks the S.E.R.C. for a research studentship.

Received, 6th December 1984; Com. 1723

References

- J. T. Groves, T. E. Nemo, and R. S. Myers, *J. Am. Chem. Soc.*, 1979, **101**, 1032.
- (a) J. T. Groves and W. J. Kruper, *J. Am. Chem. Soc.*, 1979, **101**, 7613; (b) A. Gold, W. Ivey, and M. Bowen, *J. Chem. Soc., Chem. Commun.*, 1981, 293; (c) D. Mansuy, J-F. Bartoli, and M. Momenteau, *Tetrahedron Lett.*, 1982, **23**, 2731; (d) J. R. Lindsay Smith and P. R. Sleath, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1009; (e) J. A. Smegal and C. L. Hill, *J. Am. Chem. Soc.*, 1983, **105**, 3515; (f) J. T. Groves and R. S. Myers, *ibid.*, 1983, **105**, 579.
- (a) E. Guilmet and B. Meunier, *Tetrahedron Lett.*, 1981, **21**, 4449; (b) I. Tabushi and A. Yazaki, *J. Am. Chem. Soc.*, 1981, **103**, 7371; (c) D. Mansuy, M. Fontecave, and J-F. Bartoli, *J. Chem. Soc., Chem. Commun.*, 1983, 253; (d) A. W. van der Made, J. W. H. Smeets, R. J. M. Nolte, and W. Drenth, *ibid.*, 1983, 1204; (e) J. P. Collman, J. I. Brauman, B. Meunier, S. A. Raybuck, and T. Kodadek, *Proc. Natl. Acad. Sci. USA*, 1984, **81**, 3245; (f) P. S. Traylor, D. Dolphin, and T. G. Traylor, *J. Chem. Soc., Chem. Commun.*, 1984, 279; (g) M. F. Powell, E. F. Pai, and T. C. Bruice, *J. Am. Chem. Soc.*, 1984, **106**, 3277; (h) A. M. Khenkin and A. A. Shteinman, *J. Chem. Soc., Chem. Commun.*, 1984, 1219.
- B. C. Schardt and C. L. Hill, *Inorg. Chem.*, 1983, **22**, 1563.
- (a) J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, 1983, **105**, 6243; (b) J. R. Lindsay Smith, M. W. Nee, J. B. Noar, and T. C. Bruice, *J. Chem. Soc., Perkin Trans. 2*, 1984, 255.
- J. R. Lindsay Smith and P. R. Sleath, *J. Chem. Soc., Perkin Trans. 2*, 1983, 621.
- E. Bergström and J. R. Lindsay Smith, unpublished observations.
- V. Ullrich, data presented at the Priestley Conference, Birmingham, U.K., 1980.
- J. R. Lindsay Smith and D. N. Mortimer, *J. Chem. Soc., Chem. Commun.*, 1985, 64.