Sterically Protected Hemins with Electronegative Substituents: Efficient Catalysts for Hydroxylation and Epoxidation

Patricia S. Traylor,*[a] David Dolphin,[b] and Teddy G. Traylor[c]

[a] *Department of Chemistry, University of San Diego, San Diego, California 92110, U.S.A.*
[b] *Department of Chemistry, University of British Columbia, Vancouver, B.C., Canada*
[c] *Department of Chemistry, University of California, San Diego, La Jolla, California 92093, U.S.A.*

Meso-tetra(2,6-dichlorophenyl)porphinatoiron(III) chloride and meso-tetra(pentachlorophenyl)porphinatoiron(III) chloride, which resist μ-oxo dimer formation and oxidative destruction, are found to be unusually efficient catalysts for high-turnover, high-yield alkene epoxidation and alkane hydroxylation.

The cytochromes P-450 are postulated to catalyse hydroxylation of alkanes and epoxidation of alkenes through high-valent iron porphyrin intermediates.[1] Attempts to mimic the catalytic action by using metalloporphyrins oxidized with peracids or iodosylbenzene have produced unstable intermediates capable of oxidizing alkanes and alkenes.[2a] Typical turnover numbers reported for epoxidations have been around 10,[2b] and for hydroxylations even lower.[3] Extensive and rapid metalloporphyrin destruction attenuates catalytic activity, such destruction being especially rapid in the absence of oxidizable substrates.

Recent studies indicate that the prevention of the formation of μ-oxo dimers[4,5] (by steric hindrance), or the introduction of electron-withdrawing substituents [*e.g.* as in meso-tetra-(pentafluorophenyl)porphinatoiron(III) chloride][6] increases catalytic capability by decreasing the rate of oxidative destruction of hemin. We have synthesized two tetraphenylhemins combining both of these features, namely, 5,10,15,20-tetra(2,6-dichlorophenyl)porphinatoiron(III) chloride (TDCPPFeCl) and 5,10,15,20-tetra(pentachlorophenyl)-porphinatoiron(III) chloride (TPCPPFeCl). These compounds are capable of effectively catalysing oxidations at room temperature without being extensively destroyed.

The precursor porphins were synthesized by the Rothe-

Table 1. Epoxidation and hydroxylation catalysed by TDCPPFeCl in CH_2Cl_2 at room temperature.

Substrate	Oxidant[a]	[TDCPP]/M	Yield[b]/%	Turnover[c]
Norbornene	C_6F_5IO	4×10^{-4}	70	900
Norbornene	C_6F_5IO	3.3×10^{-5}	85[d] (9)[e]	10000
Norbornene	PhIO–HOAc[f]	4×10^{-4}	30[d]	300
Cyclohexane[g]	C_6F_5IO	5×10^{-4}	45[h] (4)[i]	440
Cyclohexane[j]	C_6F_5IO	8×10^{-4}	73[h] (1.2)[i]	45
Norbornane	C_6F_5IO	8×10^{-4}	50[k]	170

[a] The characteristics of these two new oxidizing agents will be described elsewhere. [b] Based on the molar ratio of oxidation product to iodopentafluorobenzene or iodobenzene. [c] Ratio of moles of product to moles of TDCPPFeCl used. (Turnover = yield/100 × [R–IO]/[TDCPPFeCl].) None of these reactions resulted in complete bleaching of TDCPPFeCl. [d] Epoxynorbornene. [e] This product which slightly precedes epoxynorbornene in g.l.c. was not identified. [f] All of the iodosylbenzene dissolved in a few seconds. [g] Mole ratio of cyclohexane : oxidant 7 : 1. [h] Cyclohexanol. [i] Cyclohexanone. [j] Mole ratio of cyclohexane : oxidant 40 : 1. [k] 2-Norborneol, isomers not determined, mole ratio of norbornane : oxidant 18 : 1.

mund method,[7] using 2,4,6-collidine instead of pyridine, followed by demetallation. The substitution for pyridine was crucial for the successful synthesis of TPCPP and improved the yield of TDCPP. Purification by dry chromatography (grade I neutral alumina) and crystallization (CH_2Cl_2–C_6H_{14} or $CHCl_3$–C_7H_{16}) yielded products whose visible spectra were virtually identical to those reported for TDCPP by Kim *et al.*[8] and for TPCPP by Longo *et al.*[9] except that the peaks at 644 and 663 nm, respectively, were absent in our purified porphins.

Both porphins were converted into hemin chlorides by the method of Kobayashi[10] (TDCPPFeCl, λ_{max} 643, 578, and 507 nm and a split Soret at 414 and 360 nm; TPCPPFeCl, λ_{max} 638, 572, and 505 nm and a split Soret at 418 and 355 nm). On shaking a CH_2Cl_2 solution of each hemin chloride with NaOH (aq.) or during chromatography on neutral alumina each chloride was converted into a species showing absorption peaks at *ca.* 574 and 413 nm. This type of spectrum is characteristic of hemin hydroxide[11] rather than the μ-oxo dimer.[10] We therefore conclude that these hemin chlorides, like the tetramesitylporphinatoiron(III) chloride, are too sterically hindered to form the dimer compound.

The following experiments demonstrate the remarkable stability of these novel hemin chlorides toward oxidative destruction. Iodosylbenzene suspended in CH_2Cl_2 containing a spectroscopic concentration of TDCPPFeCl was left at room temperature for 1 h. This resulted in a decreased and broadened Soret absorption. Subsequent reduction with an excess of hydroquinone produced a spectrum indicating that most of the porphyrin was recovered. In another experiment, a spectroscopic concentration of TDCPPFeCl in CH_2Cl_2 was treated with *ca.* 10^{-3} M *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature. A significant decrease in the Soret absorption at 415 nm was observed after 30 min, at which time an excess of norbornene was added. When left for 8 days, 83% of the original Soret peak, slightly shifted to 418 nm, was recovered. Sufficient *N*-methylimidazole to produce the bis *N*-methylimidazole complex was then added and measurement of the resultant Soret peak at 417 nm indicated a 69% recovery of the original hemin. The same experiment with TPCPPFeCl gave rise to only a 7% decrease in Soret absorption when left at room temperature for 3 h. The parent compound, tetraphenylporphinatoiron(III) chloride (TPPFeCl), was instantly bleached under these conditions.

TDCPPFeCl is also a very good catalyst for epoxidation and hydroxylation as shown in Table 1. In a typical experiment iodosylpentafluorobenzene (20 mg)[12] was suspended in a solution of norbornene (49 mg) in CH_2Cl_2 (100 μl); no reaction occurred. When a solution of TDCPPFeCl (5×10^{-6} mmol in 5 μl CH_2Cl_2) was added, the suspension dissolved within 20 min. At this time, spectroscopic examination of a small aliquot indicated little hemin loss. However, an 85% yield of epoxynorbornene, based on concomitant production of iodopentafluorobenzene, was detected. This yield indicates epoxidation of 10 000 norbornene molecules for each molecule of TDCPPFeCl catalyst.

Since TDCPPFeCl is not destroyed under the epoxidation conditions cited in Table 1, these turnover numbers are clearly minimal and can easily be increased. Comparison of the two experiments involving oxidation of cyclohexane reveals that increasing the ratio of substrate hydrocarbon to oxidant increases the yield of the primary product, cyclohexanol, and decreases overoxidation to cyclohexanone. The high yield of cyclohexanol accompanied by only a small amount of cyclohexanone indicates that this hemin catalyses hydroxylation with a specificity approaching that of the cytochromes P-450.

The high turnover, the virtual absence of by-products under certain conditions, and the stability of the hemin make this a practical catalyst for syntheses and a suitable system with which to investigate the details of the mechanisms of hemin-catalysed epoxidation and hydroxylation reactions.[4]

The authors are grateful to J. Marsters for synthesizing the pentafluoroiodosylbenzene, and M. Goldberg and T. Leung for experimental assistance. This research was supported by a National Science Foundation grant (T. G. T.), a Fogarty International Center Fellowship (T. G. T.), and a National Institutes of Health grant (D. D.).

Received, 31st October 1983; Com. 1417

References

1 R. E. White and M. J. Coon, *Annu. Rev. Biochem.*, 1980, **49**, 315.
2 (a) J. T. Groves, T. E. Nemo, and R. S. Myers, *J. Am. Chem. Soc.*, 1979, **101**, 1032; (b) J. T. Groves and T. E. Nemo, *ibid.*, 1983, **105**, 5786.
3 J. T. Groves, W. J. Kruper, Jr., and R. C. Haushalter, *J. Am. Chem. Soc.*, 1980, **102**, 6375.
4 J. T. Groves, R. C. Haushalter, M. Nakamura, T. E. Nemo, and B. J. Evans, *J. Am. Chem. Soc.*, 1981, **103**, 2884.
5 J. T. Groves, S. Krishnan, G. E. Avaria, and T. E. Nemo, *Adv. Chem. Ser.*, 1980, **191**, 277.
6 C. K. Chang and F. Ebina, *J. Chem. Soc., Chem. Commun.*, 1981, 778.
7 G. M. Badger, R. A. Jones, and R. L. Laslett, *Aust. J. Chem.*, 1964, **17**, 1028.
8 J. B. Kim, J. J. Leonard, and F. R. Longo, *J. Am. Chem. Soc.*, 1972, **94**, 3986.
9 F. R. Longo, M. G. Finarelli, and J. B. Kim, *J. Heterocycl. Chem.*, 1969, **6**, 927.
10 H. Kobayashi, T. Higuchi, Y. Kaizu, H. Osada, and M. Aoki, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3137.
11 R.-J. Cheng, L. Latos-Grazynsky, and A. L. Balch, *J. Am. Chem. Soc.*, 1982, **21**, 2412.
12 M. Schmeisser, K. Dahmen, and P. Sartori, *Chem. Ber.*, 1967, **100**, 1633.