Pergamon

*Tetrahedron Letters*, Vol. 37, No. 7, pp. 1091-1094, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02312-7

# Oxidation of Isosafrole by Sodium Hypochlorite Catalysed by Manganese Porphyrins: Unusual Competition between Epoxidation and O-Dealkylation

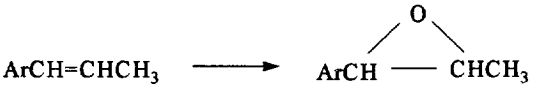
Luisella Bocchio Chiavetto, Gianfranco Guglielmetti, Cecilia Querci, and Marco Ricci*

EniChem, Istituto G. Donegani, 28100 Novara, Italy

**Abstract**: isosafrole (**1a**) and isoeugenol methyl ether (**1b**), two closely related substrates, behave very differently when subjected to manganese porphyrins catalysed epoxidation by sodium hypochlorite. A possible explanation is given, in terms of an unusual competition between the epoxidation and the O-dealkylation of the -$OCH_2O$- moiety.

During the last 15 years, metalloporphinates have been shown to be excellent models for cytochrome P-450[1] and peroxidases[2] enzymes and particularly to be very effective catalysts for the epoxidation of olefins[1], C-H hydroxylation[1], and O-demethylation.[2] Usually, however, these reactions proceed at very different rates, the epoxidation being, by far, more efficient than the others.

Within a research aimed to envisage new, efficient syntheses of α-methyldopa, one of the most important antihypertensive agents,[3] we examined the epoxidation of isosafrole **1a** and of some related olefins (isoeugenol methyl ether, **1b**, and β-asarone, **1c**) by sodium hypochlorite catalysed by manganese porphyrins.




**1 a-c** **2 a-c**

| 1,2 | Ar |
|---|---|
| **a** | 3,4-$(OCH_2O)C_6H_3$ |
| **b** | 3,4-$(CH_3O)_2C_6H_3$ |
| **c** | 2,4,5-$(CH_3O)_3C_6H_2$ |

We now report that, surprisingly, the results of the oxidation of these substrates are quite different and strongly depend upon the catalyst used We also attempt to explain these findings with the occurrence of an unusual competition between double bond epoxidation and O-dealkylation of the methylenedioxy (-$OCH_2O$-) group.

All reactions were performed under phase-transfer conditions by dissolving the Mn-TPP[4] (6 μmol) or Mn-TDCPP[4] (5 μmol), 4-methylpyridine (0.2 mmol), benzyldimethylhexadecylammonium chloride (10 μmol),

and the substrate (1 mmol) in 2.5 mL of dichloromethane. Then NaOCl (6% aqueous solution, 4 mol per mol of alkene) was added and the reaction was initiated by vigorous stirring at room temperature. After the required time the aqueous and the organic layers were separated. The latter was analysed by g.l.c. with n-decane or n-dodecane as an internal standard. Some significant results are reported in Table 1.

**Table 1.** Oxidation of Olefins **1a-c** by Sodium Hypochlorite Catalysed by Mn-Porphinates.[a]

| Substrate | Catalyst | Time, min | Substrate conversion, % | Epoxide and yield, % | |
|---|---|---|---|---|---|
| Isosafrole, **1a** | none | 120 | [b] | **2a** | 0 |
| | Mn-TPP | 60 | 84 | | 33 |
| | Mn-TDCPP | 60 | 72[c] | | 0 |
| Isoeugenol methyl ether, **1b** | none | 120 | [b] | **2b** | 0 |
| | Mn-TPP | 60 | 100 | | >95 |
| | Mn-TPP | 60 | 94 | | 39[d] |
| | Mn-TDCPP | 60 | 100 | | 72 |
| β-Asarone, **1c** | Mn-TPP | 60 | 100 | **2c** | >95 |
| | Mn-TDCPP | 60 | 100 | | >95 |

[a] Conditions as described in the text. [b] Not determined. [c] 100% NaOCl conversion. [d] Mixture of isoeugenol methyl ether (0,5 mmol) and 1,2-methylenedioxybenzene (0,5 mmol) as substrate.

Epoxides **2a-c**[5] turned out to be extremely acid sensitive. So, a different oxidant, magnesium monoperoxyphthalate (a very efficient oxygen donor in oxidations catalysed by manganese porphinates[6]) was too acidic to allow to detect any epoxide at the end of the reactions. With sodium hypochlorite as the oxygen donor and Mn-TPP as the catalyst, however, isoeugenol methyl ether and β-asarone afforded the corresponding epoxides **2b-c** with excellent yields and selectivities, while the oxidation of isosafrole afforded **2a** in much lower yield, most of the substrate having been transformed into an insoluble, polymeric material.

It seemed likely that this peculiar behaviour of isosafrole could be due to the presence of the methlylenedioxy ($-OCH_2O-$) moiety. So, in view of the interest of the reactions of cytochrome P-450 with this functional group,[7] we investigated its behaviour under our reaction conditions using 1,2-methylenedioxybenzene as the substrate.

As a matter of fact, 1,2-methylenedioxybenzene was oxidised (39% conversion within 60 min), affording

a complex mixture of products, including pyrocatechol (*ca.* 1%, determined by HPLC and confirmed by MS; pyrocatechol was very quickly consumed under the reaction conditions) and carbonate ion. Neither manganese-carbene[7] complexes nor pyrocatechol carbonate could be detected in the reaction mixture and, apparently, no polymerization occurred. Moreover, the oxidation of a 1:1 mixture of isoeugenol methyl ether and 1,2-methylenedioxybenzene gave only low (39%) epoxide yield, while substantial amounts of polymeric materials also formed.

These results suggest the occurrence, in the reaction of isosafrole, of a competition between the epoxidation of the double bond and the oxidation of the $-OCH_2O-$ group. Consistently with this view, it was not possible to improve the yield of isosafrole epoxidation by using an usually better catalyst, such as Mn-TDCPP, since it speeded up both the double bond epoxidation and the $-OCH_2O-$ oxidation. Particularly, only a 72% conversion of the substrate could be achieved (Table 1) but, nevertheless, at the end of the reaction, neither the epoxide nor any unreacted oxidant were detected, thus confirming consumption of the latter in a competitive oxidation.

On the other hand, epoxides **2b** and **2c** could be obtained in satisfactory yields, without extensive cleavage of methoxy groups, thus indicating that these groups are poorly reactive under the reaction conditions.

Electron-rich aromatic substrates are known to be oxidised to quinones by synthetic metalloporphinates[2] via a well-documented, peroxidase-type O-demethylation initiated by a one-electron oxidation with formation of an aryl radical cation.[8] According to this mechanism, the observed polymeric material could be formed from polymerization of quinone or intermediate semi-quinone compounds.[2a] Some difficulties, however, arise to explain the observed reactivity difference between the $-OCH_2O-$ and $-OCH_3$ groups.[9]

An alternative mechanism might involve a P-450-type O-demethylation[8] via hydroxylation of the $CH_2$ group, followed by hydrolytic release of a $C_1$ fragment with formation of diphenolic compounds which, reacting with the epoxide, could transform it into the polymeric material. In this case, the observed selectivity would be a consequence of the low reactivity of the $CH_3$ compared with the $CH_2$ groups in oxidations catalysed by synthetic metalloporphinates.[6b]

These results appear of some interest for two different reasons. On one hand, surprisingly poor selectivities have to be expected in metalloporphyrins catalysed epoxidations of $-OCH_2O-$ substituted olefins. On the other hand, O-dealkylation of aryl alkyl ethers is a well documented reaction of cytochrome P-450 and peroxidases;[1,8] the $-OCH_2O-$ substitution greatly enhances it, thus allowing to extend the scope of using metalloporphinates as models for heme-containing enzymes.

## REFERENCES AND NOTES


1. Montanari, F.; Casella, L. Eds. *Metalloporphyrins Catalyzed Oxidations*; Kluwer Academic: Dordrecht, 1994.
2. (a) Labat, G.; Seris, J.L.; Meunier, B. *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1471; (b) Artaud, I.; Ben Aziza, K.; Chopard, C.; Mansuy, D *J. Chem. Soc., Chem. Commun.* **1991**, 31; (c) Higuchi, T.; Satake, C.; Hirobe, M. *J. Am. Chem. Soc.* **1995**, 117, 8879.

3. Kleemann, A.; Engel, J. *Pharmazeutische Wirkstoffe. Synthesen, Patente, Anwendungen* (2nd ed.); Thieme: Stuttgart, 1982. α-Methyldopa is usually prepared from 1-[3,4-(methylenedioxy)phenyl]- or 1-(3,4-dimethoxyphenyl)-2-propanones, readily obtained by oxidation of the corresponding olefins (ArCH=CHMe) with peracetic or performic acids, followed by an acid promoted rearrangement: Kojima, A.; Katagami, T.; Okubo, I. *Japan. Kokai* 74 100044 (1974) to Mitsui Pharmaceuticals, Inc. and Mitsui Toatsu Chemicals, Inc.; *Chem. Abstr.* **1975**, 82, 72640.
4. Mn-TPP: *meso*-tetraphenylporphinatomanganese(III) chloride; Mn-TDCPP: *meso*-tetrakis-(2,6-dichlorophenyl)porphinatomanganese(III) acetate.
5. Olefins **1a-c** have been purchased (Aldrich) as mixtures of cis and trans isomers. So, epoxides **2a-c** have also been obtained as mixtures of cis and trans isomers and characterized by their $^1$H-NMR and MS spectra in comparison with authentical sample prepared according to Mann, J.; Wilde, P. D.; Finch, M.W. *Tetrahedron* **1987**, 43, 5431.
6. (a) Querci, C.; Ricci, M. *J. Chem. Soc., Chem. Commun.* **1989**, 889; (b) Querci, C.; Ricci, M. *Tetrahedron Lett.* **1990**, 31, 1779.
7. Mansuy, D.; Mahy, J. P. in ref. 1; pp. 187-192.
8. Meunier, B. N- and O-Demethylations catalyzed by peroxidases in Peroxidases in Chemistry and Biology, Everse, J.; Everse, K.E.; Grisham, M.B. Eds.; CRC Press: Boca Raton, 1991, vol. 2, pp. 210-214.
9. Ionization potential of 1,2-dimethoxybenzene (8.17 eV) is very close to, and even lower than, that of 1,2-methylenedioxybenzene (8.21 eV): Anderson, G.M.; Kollman, P.A.; Domelsmith, L.N.; Houk, K.N. *J. Am. Chem. Soc.* **1979**, 101, 2344. Although ionization potentials of substrates **1a-c** could not be found in the literature, preliminary semiempirical AMPAC-MOPAC calculations with full geometry optimization suggest that also **1a** and **1b** have very close ionization potentials: Ranghino, G.; Ricci, M. unpublished results.

(*Received in UK* 28 *July* 1995; *revised* 6 *December* 1995; *accepted 7 December* 1995)