First Example of a Chloroperoxidase-type Chlorination of Dimedone using a Supported Manganese Porphyrin Catalyst

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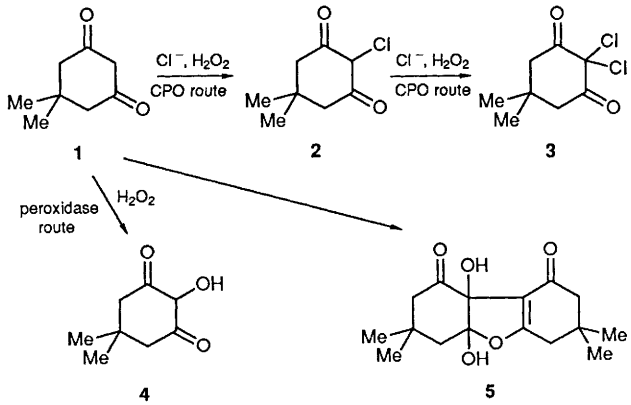
Chloroperoxidase can be mimicked by a supported manganese porphyrin catalyst; besides the oxidative chlorination product of dimedone, the usual substrate for chloroperoxidase, another oxidation product corresponding to a peroxidase pathway is also observed.

Chloroperoxidase, CPO, has been isolated from *Caldariomyces fumago*.[1] This enzyme catalyses the oxidative halogenation of the biosynthetic precursor of caldariomycine, 1,3-dihydroxy-2,2-dichlorocyclopentane.[2] Besides its peroxidase and catalase activity, chloroperoxidase is mainly able to create carbon–halogen bonds on β-diketone substrates from Cl^-, Br^- or I^- ions using H_2O_2 as co-factor at acidic pH, according to eqn. 1. Oxidative iodination or bromination reactions can be catalysed by horseradish peroxidase, but only chloroperoxidase can perform chlorinations.[3]

$$A\text{–}H + Cl^- + H^+ + H_2O_2 \xrightarrow[pH\,3\text{–}5]{CPO} A\text{–}Cl + 2\,H_2O \qquad (1)$$

More recent studies indicate that CPO is also a catalyst for *N*-dealkylation of amines,[4] alkene epoxidation[5] and oxygenation of sulphides to sulphoxides.[6] Chloroperoxidase has the same prosthetic group as cytochrome P-450, an iron-protoporphyrin IX with a cysteinato proximal ligand.[7]

During the last decades, many different models based on metalloporphyrins have been proposed for cytochrome P-450,[8] peroxidases[9] and catalase,[10] but chloroperoxidase models have been less documented. Only one article described the metalloporphyrin-mediated chlorination of chlorodimedone **2** to dichlorodimedone **3** by $NaClO_2$, which mimicks the second possible step in the oxidative chlorination by CPO (see Scheme 1).[11] The association $NaClO_2$–iron porphyrin generates *in situ* HOCl, which is known to



Scheme 1

Table 1 H_2O_2–Cl^- Oxidation of dimedone **1** catalysed by soluble or supported iron or manganese complexes[a]

Run	Catalyst	pH	Conversion of **1** (%)	Yield of **2** (%)	Yield of **4** (%)	**4**:**2** Ratio
1	FeTPPS	3.0	42	n.s.[b]	35	—
2	FeTPPS-Am	3.0	50	2	28	14
3	FeTPPS-Am	6.0	48	1	20	20
4	FeTMPS-PVP	6.0	45	1	32	32
5	FeTMPS-Am/Imid	3.0	58	n.s.	46	—
6	FeTMPS-PVP/Imid	3.0	90	n.s.	60	—
7	FeTMPS-PVP/Imid	6.0	77	n.s.	36	—
8	MnTMPS-PVP/Imid	3.0	71	9	26	2.9
9	[c]	3.0	65(42)[d]	5(7)[d]	22(19)[d]	4.4(3)[d]
10	MnTMPS-PVP	3.0	60	15	29	1.9

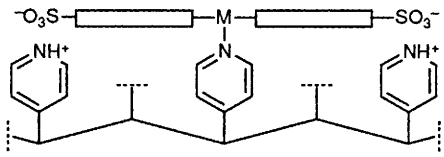
[a] All indicated conversion and yields correspond to the same reaction time 1 h at room temperature. For additional experimental details, see text. [b] Not significant. [c] Same conditions as for run 8, but with only 5 equiv. of hydrogen peroxide with respect to the catalyst. [d] Data obtained for the third run performed with the same supported manganese catalyst.

reproduce the main features of CPO-catalysed chlorinations.[12]

Here, we report the catalytic activity of supported manganese porphyrin complexes in the oxidative chlorination of dimedone and the influence of different factors (nature of the central metal, ligand and the reaction medium).

Two different categories of metalloporphyrins have been used: (i) a soluble iron porphyrin FeTPPS† or (ii) supported iron or manganese porphyrins, FeTMPS-Am, FeTMPS-PVP‡ and the MnTMPS-PVP (see Scheme 2). Dimedone and two oxidation products, chlorodimedone, **2**, and hydroxydimedone, **4**,¶ were monitored by HPLC using a C_{18}-Bondapak column (detection at 280 nm; eluent: methanol–10 mM ammonium acetate, 50:50, v/v acidified to pH 4.5 by acetic acid; flow rate: 1 ml min^{-1}). No other oxidation products were detected by this method, suggesting that they are high molecular weight compounds.

The Table 1 data were obtained under the following conditions: to 20 μmol of dimedone (500 μl of a 40 mM acetonitrile solution of **1**), 2 μmol of catalyst (for supported catalysts, these 2 μmol were immobilized onto 100 mg of resin), 1 ml of a buffer solution (0.1 M citrate–phosphate buffer for experiments at pH 3.0 or 0.5 M phosphate buffer at pH 6.0) and 200 μmol of sodium chloride were added 200 μmol of H_2O_2 in 500 μl of buffer (this solution was prepared from a 8.6 M Merck H_2O_2 solution, *ca.* 30 wt. % in water). For runs 5 to 10, imidazole (100 μmol) was added before the addition of hydrogen peroxide. Reactions were performed at room temperature under air atmosphere. No dimedone conversion was observed in control experiments in which the metalloporphyrin catalyst was omitted.



Scheme 2

Table 1 data indicate that iron porphyrin complexes, in solution or immobilized on a support, are unable to catalyse the formation of chlorodimedone (runs 1 to 7). The main oxidation product is **4**, which can be considered as a compound resulting from a 'peroxidase pathway' (the same compound can be obtained using horseradish peroxidase as catalyst). The most efficient iron catalyst is FeTMPS-PVP in the presence of imidazole: 90% of dimedone is converted in one hour, which corresponds to nine catalytic cycles per hour (run 6).

The other iron complexes, FeTPPS or FeTMPS-Am, which cannot take advantage of a proximal effect from a nitrogen-containing ligand, are less efficient catalysts: conversions are ranging from 42 to 50%. Only a small amount of chlorodimedone was detected in runs 2, 3 and 4. However, the situation is modified when the supported manganese catalyst MnTMPS-PVP is used (runs 8 to 10). Thus, by merely changing the porphyrin metal from iron to manganese it is possible to obtain a catalytic system able to produce the chloroperoxidase oxidation compound of dimedone. The dimedone conversion rates are similar to those obtained with iron catalysts (60 to 71% within one hour; conversion completion is observed by increasing the reaction time), but the key point is the significative formation of chlorodimedone **2** besides hydroxydimedone **4**. It must be pointed out that no dichlorodimedone **3** was detected in the reaction mixture, thus suggesting that no free hypochlorous acid was present. This latter chlorination agent is the active species in the $NaClO_2$ chlorination of monochlorodimedone catalysed by haemins.[11]

The ratio 4:2 is lower in the absence of imidazole (2.9 in run 8 compared with 1.9 in run 10). In addition, run 9[d] shows that

† Abbreviations used: TPPS stands for *meso*-tetrakis(4-sulphonatophenyl)porphyrinato ligand, TMPS for *meso*-tetrakis(3,5-disulphonatomesityl)porphyrinato, -Am for Amberlite® IRA 900 and -PVP for a reticulated polyvinylpyridinium polymer.

‡ FeTMPS-Am and FeTMPS-PVP correspond to the immobilisation of FeTMPS§ onto Amberlite® IRA 900 (Am) or polyvinylpyridinium polymer (PVP), respectively. For a recent use of sulphonated metalloporphyrins immobilised on ion-exchange resins, see reference 13. In the case of PVP supported catalyst, a pyridine from the support is acting as axial ligand. This type of supported catalyst was characterised by reflectance UV–VIS data and elemental analyses.

§ Sulphonated porphyrin ligands were prepared according to the initial work-up published by Srivastava and Tsutsui.[14]

¶ This compound, hydroxydimedone, actually exists in solution as a stable enol form: 2,3-dihydroxy-5,5-dimethyl-2-cyclohexen-1-one.[15] This compound can also be prepared by oxidation of dimedone (350 mmol) with FeTPPS (3.5 μmol) in the presence of hydrogen peroxide (75 mmol). **4** has been identified by NMR, IR and UV–VIS spectroscopy.[15] It must be noted that compound **4** has the same retention time as that of a dimer **5** in the HPLC conditions used to monitor the catalytic dimedone oxidation. **4** and **5** were separated on a phenyl-Bondapak column (eluent: methanol–water: 50:50, v/v). This yellow compound was previously obtained in the oxidation of dimedone by hydrogen peroxide in basic conditions.[16] An authentic sample of **5** was prepared by oxidizing **1** by horseradish peroxidase in the presence of H_2O_2 (50 mg of **1** were oxidized by 1 mg of peroxidase in 5 ml of phosphate buffer at pH 6.0). **4** and **5** were characterised by use of ^1H NMR, IR, UV–VIS and MS data.

this CPO model is only partially destroyed during the catalytic oxidative chlorination. In a third run with the same manganese catalyst, 64% of the initial activity is observed. We are presently studying the mechanistic aspects of this biomimetic chlorination reaction.

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