Oxidation of tertiary diaryl alcohols catalyzed by a water-soluble metalloporphyrin: C_{aliph}–C_{aliph} *versus* C_{aliph}–C_{Ar} bond cleavage

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In water and at room temperature, tertiary diaryl alcohols were easily cleaved by monopersulfate oxidation using a water-soluble metalloporphyrin catalyst to give mainly aryl methyl ketones and to a lower extent diaryl ketones, probably resulting from a β-fragmentation of the diarylethoxy radical $Ar_2MeC–O·$; a small amount of unexpected ester derivatives was also detected indicating at least one alternative pathway.

As a part of our mechanistic studies on C–H bond oxidation catalyzed by water-soluble metalloporphyrins,[1–3] we wished to determine how the oxidation of some intermediate tertiary alcohols can give ketones through cleavage of a C–C bond. In addition, little is known about oxidative C–C bond cleavage by biomimetic catalysts, whereas this is a key step in the degradation of the lateral chain of cholesterol by cytochrome P-450.[4] Tertiary alcohols are usually resistant to oxidation and their oxidative conversion generally requires a sufficient intrinsic reactivity and the use of strong oxidants (*e.g.* concentrated H_2O_2 in sulfuric acid,[5] chromium(VI)[6] or cerium(IV)[7] reagents). We chose to develop this study on the two diarylmethyl alcohols 4-(1-hydroxy-1-phenylethyl)benzoic acid **1**§ and 1,1-diphenylethanol, using $KHSO_5$ as oxidant (hydrogen peroxide was also tested in similar conditions but proved to be inactive) and Mn-TMPyP¶ as catalyst. This water-soluble metalloporphyrin is well-known for its efficiency in epoxidation,[8] hydroxylation[2,3] or peroxidasic oxidation[9] reactions in aqueous media. The reaction products were identified by HPLC co-injection of authentic samples, and by NMR and GC–MS analyses of the product mixtures.

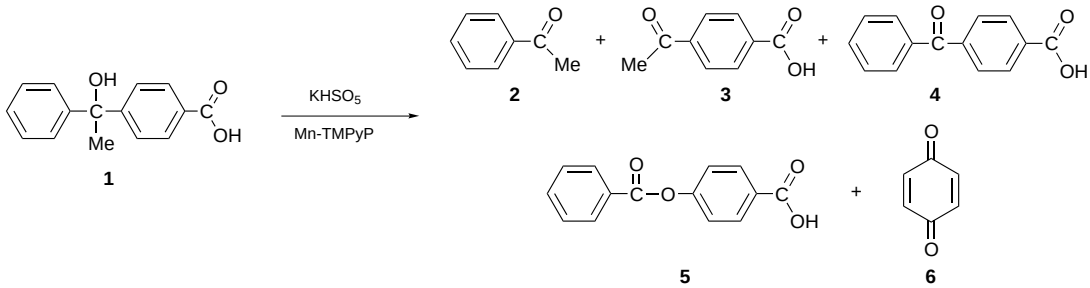
Among the compounds produced by the oxidation of **1**, two resulted from the loss of one of the two aromatic rings (**2**, **3**), two others from the loss of the methyl group (**4**, **5**) and the last one (**6**) was identified as benzoquinone (Scheme 1). Conversion and product yields are given in Table 1. More than 90% of the starting material was converted in 10 min at room temperature, with only 2% of catalyst (introduced in five consecutive additions). Such levels of conversion could not be obtained under similar conditions with cerium(IV) salts, which are well-known for their ability to oxidize some tertiary alcohols,[7] even in acetonitrile–water at reflux and/or raising the concentrations of substrate and oxidant by a factor of 100. The pool **2** + **3** + **4** + **5** represented about 50% yield (or 56% yield with respect to the starting material converted). Relative yields of ketones **2**, **3** and **4** show that cleavage of the C_{aliph}–C_{Ar} bond (with release of a phenyl or a carboxyphenyl group) occurred more than 10 times faster than that of C_{aliph}–C_{aliph} bond (with release of a methyl group). The relative scission of phenyl and 4-carboxyphenyl groups differed only by a factor of 2 (ratio **2**/**3** ≈ 2). Thus the relative rates of cleavage with formation of **2**, **3** and **4** were in the ratios 35 : 17.5 : 1.

These results are reminiscent of the oxidative cleavage of some tertiary alcohols by cerium(IV) salts in aqueous acetonitrile at reflux,[7] where *tert*-butyl, benzyl and allyl radicals were shown to be cleaved rapidly from the appropriate alcohol (the relative rates of formation of the *tert*-butyl : benzyl : allyl radicals were 20–63 : 4.4 : 1). In the present case, the formation of the ketones **2**–**4** suggests a mechanism involving the formation of a diarylethoxyl radical intermediate (Scheme 2) which is cleaved by β-fragmentation to give the three different ketones **2**, **3** and **4** and carboxyphenyl (route a), phenyl (route b) or methyl (route c) radicals. The diarylethoxyl radical could be formed from **1** in two steps by e^- loss followed by H^+ abstraction, or directly by H· abstraction. Benzoquinone **6** might be an end-product deriving from one or both aryl radicals

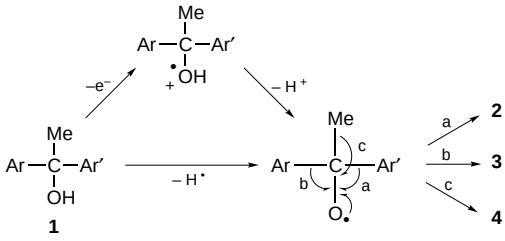
Table 1 Yields of products obtained from oxidation of **1** catalyzed by Mn-TMPyP[a]

Products	Yield (%)[b]	Selectivity (%)[c]
2	27.9 ± 1.1	31.3 ± 0.7
3	14.0 ± 0.5	14.0 ± 0.4
4	0.8 ± 0.1	0.9 ± 0.1
5	7.7 ± 0.3	10.6 ± 0.3
6	9.2 ± 0.4	8.7 ± 0.2
Conversion (%)	90.5 ± 4.0	

[a] The reaction medium (1 ml of acetonitrile–water, 1 : 9) contained 66 mM phosphate buffer, pH 5 and 500 μM **1** (introduced as a 25 mM solution in acetonitrile) and 200 μM of *p*-diacetylbenzene as internal standard; [$KHSO_5$] was 10 mM, and [Mn-TMPyP] was 10 μM (introduced in five consecutive 2 nmol additions, every 2 min; the first addition initiated the reaction). The reaction was monitored by HPLC using a Nucleosil C18 10 μm column and 65 or 75% aqueous acetonitrile containing 0.1 M triethylammonium acetate as eluent (flow rate: 1 ml min^{-1}); the detection was performed at 240 nm and experimental errors were obtained from three independent experiments. [b] Yields were calculated after 10 min of reaction at room temperature. [c] Selectivity is defined as the ratio of product yield divided by substrate conversion.



Scheme 1



Scheme 2 β-Fragmentation of a possible alkoxyl radical intermediate (Ar = phenyl and Ar′ = *p*-carboxyphenyl)

resulting from the β-scission (routes a, b), since we checked that phenol, benzoic acid and *p*-hydroxybenzoic acid, three putative evolution products of the released aryl radicals, could be quickly oxidized to **6** by the catalytic system. With this substrate, aryl (phenyl or carboxyphenyl) rather than methyl is lost, yielding acetophenone rather than benzophenone derivatives. This direction of cleavage differs from investigations on the decomposition of cumyloxyl radical[10,11] and from our recent results on oxidation of 4-(1-hydroxy-1-methylethyl)benzoic acid[3] where the loss of methyl is predominant. A plausible explanation of this special behaviour could be a combination of resonance stabilization of the resulting radicals (methyl less stable than aryl) and of the enhanced stability of acetophenone compared to acetone[10] or to benzophenone derivatives.

In the course of catalytic oxidation of **1**, the unexpected product **5** was detected. It was identified as benzoyloxybenzoic acid by MS and NMR analyses of a collected sample, and by comparison of its chromatographic behaviour with that of an authentic sample.§ Product **5** represented only about 8% yield when 10% acetonitrile was used in the reaction medium but this yield was increased up to 18% when the amount of acetonitrile was raised to 30%. At the same time, the yields of all other identified products were slightly lowered. Furthermore, the formation of **5** was dependent on oxygen concentration (yield of **5** was 1.5% under nitrogen and 7.5% under oxygen atmosphere, under experimental conditions slightly different from that of Table 1), while the formation of all the other products did not significantly depend on the atmospheric composition. It is also remarkable that the isomeric compound monophenyl terephthalate was not detected. A conceivable pathway to afford the ester **5** would be a Baeyer–Villiger oxidation of benzoylbenzoic acid (which is effectively produced in the reaction, product **4**) but this assumption can be discarded since, in a control experiment, we showed that benzoylbenzoic acid was stable under the catalytic oxidation conditions used. The results clearly demonstrate that pathway for formation of **5** is different from that of the other products **2**–**4** and **6** and, especially, that dioxygen probably plays a crucial role. The exact mechanism explaining the formation of this unexpected reaction product, which needs the cleavage of two C–C bonds, is presently unknown.

Similar experiments as with **1** were performed with 1,1-diphenylethanol. Here also, results show a high conversion of the substrate (more than 75%) and, while they are in qualitative agreement with the above data concerning the oxidation of **1** (oxidation products from 1,1-diphenylethanol were: acetophenone, benzophenone, *p*-benzoquinone and phenyl benzoate), the quantitative results differ significantly. Especially, the yield of phenyl benzoate was very low (about 1–2%), indicating that the carboxylic group present in **1** presumably plays a crucial role in orienting the reaction towards the ester **5**.

In summary, a highly efficient oxidative cleavage of a tertiary diaryl alcohol has been observed. Scission of the C_{aliph}–C_{Ar} bond occurred preferentially compared to the C_{aliph}–C_{Aliph} bond, yielding mainly acetophenone derivatives through a probable β-fragmentation mechanism. The presence of an ester derivative whose formation is oxygen dependent indicates that an alternative pathway is involved. An overall comprehensive mechanism of this oxidative cleavage reaction is presently under investigation using isotopic labelling experiments.

Footnotes and References

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§ Compound **1** was synthesized from benzoylbenzoic acid **4** and methylmagnesium bromide according to ref. 13, and 4-benzoyloxybenzoic acid **5** was obtained by esterification of benzoyl chloride with 4-hydroxybenzoic acid.
¶ Mn-TMPyP denotes the pentaacetate of the diaqua-manganese(III) derivative of *meso*-tetrakis(1-methylpyridinium-4-yl)porphyrin, and was prepared according to ref. 12.

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