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Oxidation of α-Alkylbenzyl Alcohols Catalysed by 5,10,15,20-Tetrakis(pentafluorophenyl)porphyrin Iron(III) Chloride. Competition between C-H and C-C Bond Cleavage

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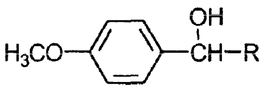
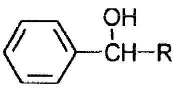
Abstract: *The iodosylbenzene promoted oxidation of a number of α-alkylbenzyl alcohols catalysed by 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin iron(III) chloride (Fe(III)TPFPPCl) leads to the formation of C-H and C-C bond cleavage products, aryl ketones and benzaldehydes, respectively. It is suggested that the C-H bond cleavage path occurs through a hydrogen atom transfer (HAT) mechanism, whereas C-C bond cleavage products derive from the decomposition of an intermediate complex formed between the iron oxo complex and the alcohol.* © 1998 Elsevier Science Ltd. All rights reserved.

Mechanistic studies concerning the oxidation of organic compounds catalysed by metalloporphyrins raise continuous interest, as these reactions mimic those induced by cytochrome P-450.[1] However, the most attention has so far been devoted to the hydroxylation of hydrocarbons[2] and the epoxidation of alkenes,[3] whereas no mechanistic information is available on another important process like the oxidation of alcohols.

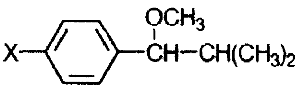
Recently, however, Meunier and his associates investigated the oxidation of tertiary diaryl alcohols catalysed by water soluble iron porphyrins. They observed exclusive C-C bond cleavage, as expected, and suggested that alkoxyl radicals might be the key intermediates in the oxidative process.[4] We wish now to report on our own study of the oxidation of secondary α-alkylbenzyl alcohols where C-H and C-C bond cleavage can compete. Namely, we present results concerning the oxidation of alcohols **1**-**7** by iodosylbenzene, catalysed by 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin iron(III) chloride, abbreviated as Fe(III)TPFPPCl. For comparison also the methyl ethers **8** and **9** have been investigated. This study is also of interest in the light of our previous investigation concerning the oxidation of α-alkylbenzyl alcohols catalysed by cytochrome P-450.[5]



1: R = CH_3
2: R = CH_2CH_3
3: R = $CH(CH_3)_2$
4: R = $C(CH_3)_3$
5: R = $CH_2C_6H_5$



6: R = $CH(CH_3)_2$
7: R = $C(CH_3)_3$



8: X = OCH_3
9: X = H

The oxidations were carried out in CH_2Cl_2 at room temperature under an argon atmosphere, using a 100:50:1

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substrate/oxidant/catalyst ratio. The results of the products analysis, reported in Table 1, show that the reaction of the alcohol **1** (R = CH_3) leads to the formation of the corresponding ketone, whereas with all other alcohols a mixture of ketone and benzaldehyde is formed. No benzaldehyde was obtained in the reactions of the ethers **8** and **9**, but ketones were observed along with other products.[6] Clearly, the formation of the ketone can be ascribed to the breaking of the C-H bond in the substrate, whereas the formation of benzaldehyde indicates cleavage of the C-C bond. Thus, alcohol **1** undergoes exclusively C-H bond cleavage, whereas with alcohols **2**-**7** there is substantial competition between C-H and C-C bond cleavage.

Very likely, the formation of the ketone from the alcohol should involve a hydrogen atom transfer (HAT) from the substrate to the iron-oxo complex suggested to be the active oxidant in these reactions (Scheme 1, structure **10**, where P represents the porphyrin), as proposed for the hydroxylation of alkanes and alkylaromatics.[1d,2] A carbon radical forms, which undergoes oxygen rebound to form the hydrated ketone (Scheme 1, path **a**). An electron transfer (ET) mechanism can be excluded since competitive experiments showed that **3** and **6** react with Fe(III)TPFPPCl at approximately the same rate,[7] in spite of the fact that **3** (bearing a 4-methoxy group on the ring) should be much more easily oxidisable than **6**.

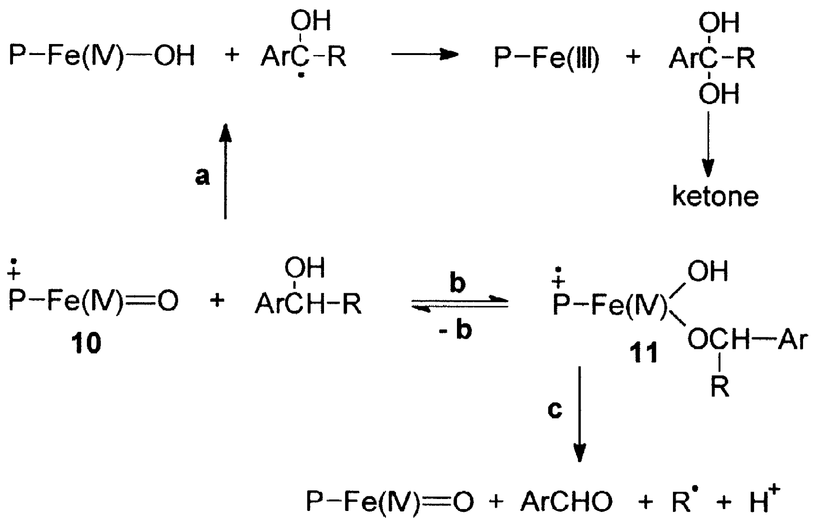
More difficult is to envisage a mechanism able to explain the path leading to C-C bond cleavage products. Accordingly, the dependence of the aldehyde/ketone molar ratio (A/K), which represents the relative weight of the two pathways, on the nature of R is quite complex, no regular trend being observed. Particularly, the dependence of this ratio on the strength of the scissible C-C bond is quite intriguing. Thus, the A/K ratio increases on going from **1** (R = Me) to **2** (R = Et), as expected; however, it decreases on going from **6** (R = *i*Pr) to **7** (R = *t*Bu), when the contrary would have been expected on the basis of the C-C bond dissociation energies.[8] Likewise, also not in line with expectations is the observation of similar A/K ratios for **3** (R = *i*Pr) and **4** (R = *t*Bu).

Table 1. Product distribution[a] and total yield[b] for the oxidation of alcohols **1**-**7** (ArCH(OH)R) with the system PhIO/Fe(III)TPFPPCl in CH_2Cl_2[c].

compd	Ar	R	aldehyde (%)	ketone (%)	yield (%)
1	4-MeOPh	CH_3	-	> 99	23
2	4-MeOPh	CH_2CH_3	35	65	40
3	4-MeOPh	$CH(CH_3)_2$	75	25	47
4	4-MeOPh	$C(CH_3)_3$	73	27	36
5	4-MeOPh	CH_2Ph	83	17	55
6	Ph	$CH(CH_3)_2$	87	13	80
7	Ph	$C(CH_3)_3$	56	44	49

[a] Average of two or three experiments. The error is ±10 % of the reported value. [b] Referred to the oxidant. [c] The reactions were performed at room temperature under an argon atmosphere in 4 ml of anhydrous CH_2Cl_2 thoroughly purged with argon using a 100:50:1 substrate/oxidant/catalyst ratio. A solution containing 5×10^{-4} mol of substrate, 2.5×10^{-4} mol of PhIO and 5×10^{-6} mol of Fe(III)TPFPPCl was magnetically stirred for 3 hours. 1-2 ml of a 0.05 M solution of $Na_2S_2O_5$ were then added, the solution was stirred for about 10 minutes and an internal standard was added. The organic phase was collected and directly analysed by GLC (comparison with authentic samples). Blank reactions without catalyst were performed for all substrates and negligible amounts of oxidation products were detected.

These data clearly indicate that in the transition state of the pathway leading to C-C bond cleavage the energetics associated to this cleavage do not play a fundamental role. A possible explanation is that an intermediate complex (**11**) is first reversibly formed between the oxo complex radical cation and the alcohol, which then decomposes to the fragmentation products as shown in Scheme 1, paths **b**, **- b** and **c**.



Scheme 1

Consistent with this mechanism is the observation that no fragmentation products but only the expected ketones are formed in the reactions of the methyl ethers of **3** and **6** (substrates **8** and **9**), clearly indicating that the presence of the OH group, which may form the complex, is required for the occurrence of the fragmentation reaction. Moreover, it should also be mentioned that the formation of an intermediate complex has been proposed for the enzymatic[10] and biomimetic[11] oxidations of 1,2-diols leading to C-C bond cleavage products as well as for the oxidative fragmentation of α-alkylbenzyl alcohols promoted by Ce(IV).[12,13]

According to the mechanism shown in Scheme 1, the irregular dependence of the competition between the two pathways on the nature of the R group becomes understandable since it will be related to the influence exerted by R on as many as 4 rate constants (k_a, k_b, k_{-b}, k_c). The direction of this influence is therefore not easily predictable mainly because opposite effects may balance with one another . Only when R is Me a quite clear situation holds: k_c is so slow (it would lead to the methyl radical, which is by far the most unstable carbon radical)[9] that only C-H bond cleavage is observed.

Finally, it is interesting to note that the above results are significantly different from those observed in the oxidation of α-alkylbenzyl alcohols catalysed by cytochrome P-450. Accordingly, it was found that the microsomal oxidation of **3** and **4**, involves exclusively C-H bond cleavage, since the only observed products were the corresponding ketones.[5] It appears that the presence of a single OH group is not sufficient to promote the enzymatic C-C bond cleavage. In this respect, it can be noted that two hydroxylations to form an 1,2-diol appear necessary for the cholesterol side-chain C-C bond cleavage induced by biosynthetic P-450 enzymes.[10]

Acknowledgements. Thanks are due to the Ministry for University and Technological Research (MURST) and to the National Research Council (CNR) for financial support.

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6. In the case of compounds **8** and **9**, no fragmentation products were detected but only the ketone and the corresponding alcohol (presumably formed by side-chain O-demethylation of the substrate), together with small amounts of ring oxygenated products. On the basis of the absence of benzaldehyde in the reaction mixture it can be excluded that the ketone derives by oxidation of the first formed alcohol.
7. In the competitive experiment, 2.5×10^{-4} mol of **3** and 2.6×10^{-4} mol of **6** were allowed to react under the experimental conditions described in Table 1. This reaction yielded: 4.3×10^{-5} mol of 4MeOPhCHO and 2.8×10^{-5} mol of $4MeOPhCOCH(CH_3)_2$ (total amount of products from **3**: 7.1×10^{-5} mol), 5.7×10^{-5} mol of PhCHO and 5.4×10^{-6} mol of $PhCOCH(CH_3)_2$ (total amount of products from **6**: 6.2×10^{-5} mol).
8. The BDE (kcal mol^{-1}) are 71.3 for $C_6H_5CH_2$-$CH(CH_3)_2$ and 69.6 for $C_6H_5CH_2$-$C(CH_3)_3$.[9] A larger difference can be expected with a tertiary benzylic carbon.
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13. A reaction of $P^{+\cdot}Fe(IV)=O$ with the alcoholic OH group forming an alkoxyl radical which undergoes a β-fragmentation reaction, as suggested by Meunier for the biomimetic oxidation of tertiary alcohols, might also explain the formation of C-C bond cleavage products. However, we feel that this possibility is unlikely in the case of secondary alcohols as the O-H bond dissociation energy is much higher than that of a benzylic C-H bond.