# The NIH Shift of Deuterium during the Oxidation of Aromatic Compounds by Iron Perchlorate and Hydrogen Peroxide in Acetonitrile

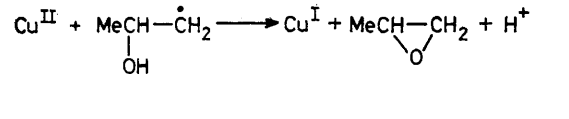
By LAURENCE CASTLE and JOHN R. LINDSAY SMITH*
(*Department of Chemistry, The University, York* YO1 5DD)

*Summary* The oxidations of five deuteriated aromatic compounds by iron perchlorate and hydrogen peroxide in acetonitrile show large values of the NIH shift and the mechanism of these reactions is discussed in terms of a free radical process.

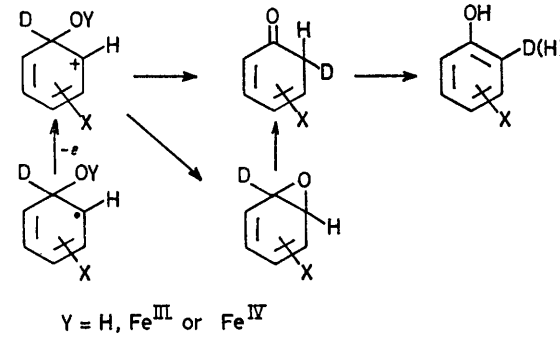
THE oxidation of β-hydroxyalkyl radicals to epoxides by copper(II)[1] (equation 1) has prompted us to re-examine[2] the oxidation of aromatic compounds by iron(II) salts and hydrogen peroxide (Fenton's reagent) and, in particular, the possibility of oxidising hydroxycyclohexadienyl radicals to phenols *via* arene oxides and/or cyclohexadienyl cations (equation 2).

We find that aromatic compounds can be oxidised to phenols and quinones by iron salts and hydrogen peroxide in acetonitrile.[3] More importantly, we report here the large values for the NIH shift of deuterium in the oxidation of a selection of deuteriated aromatic substrates (Table), and the implications these results have on the mechanism of hydroxylation by cytochrome P-450 dependent monooxygenases.

The NIH shifts of deuterium in the oxidation of the isomeric monodeuteriochlorobenzenes and 1,4-dideuterionaphthalene are comparable with the values obtained from the liver microsomal hydroxylations of these substrates;[4] however, the value for 4-deuterioanisole is a little smaller than the corresponding shift from enzymatic hydroxylation.[5] The exclusion of dioxygen from the oxidation system has no effect on these results.



(1)



(2)

Since 4-methoxyphenol and 1-naphthol are rapidly converted into 1,4-quinones in the oxidising system, the

NIH shift values for the deuteriated anisole and naphthalene were measured in the 1,4-quinones. We confirmed that the second oxidation of the phenols to 1,4-quinones does not result in a shift of deuterium by showing that [2,4-$^2H_2$]-1-naphthol is oxidised to [2-$^2$H]-1,4-naphthoquinone, with no [2,3-$^2H_2$]-1,4-naphthoquinone, by iron(II) perchlorate and hydrogen peroxide in acetonitrile.

TABLE. The NIH shift of deuterium in the oxidation of some deuteriated aromatic compounds by iron perchlorates and hydrogen peroxide in acetonitrile[a]

| Substrate (% deuterium) | Iron perchlorate | Product[b] | NIH Shift /%[c] |
|---|---|---|---|
| [2-$^2$H]Chlorobenzene (95·8) | $Fe^{II}$ | 2-Chlorophenol[d] | 32 |
| [3-$^2$H]Chlorobenzene (94·8) | $Fe^{II}$ | 3-Chlorophenol[d] | 14 |
| [4-$^2$H]Chlorobenzene (92·5) | $Fe^{II}$ | 4-Chlorophenol[d] | 54 |
| [4-$^2$H]Anisole (87·4) | $Fe^{II}$ | 1,4-Benzoquinone | 30[e] |
| [4-$^2$H]Anisole (87·4) | $Fe^{III}$ | 1,4-Benzoquinone | 28[e] |
| [1,4-$^2H_2$]Naphthalene ($^2H_2$, 95·3; $^2$H, 4·2) | $Fe^{II}$ | 1,4-Naphthoquinone | 68 |

[a] $H_2O_2$ (0·88 mmol) in MeCN was added to substrate (0·46—0·92 mmol) and iron perchlorate (1·25 mmol) in MeCN. [b] Product examined for shift of deuterium. [c] Measured by mass spectrometry. [d] Methylated and measured as methoxychlorobenzene. [e] Measured by mass spectrometry on quinone and on Diels–Alder adduct of quinone with cyclopentadiene.

We can exclude a peroxocarboximidic acid, generated *in situ* either from acetonitrile and hydrogen peroxide alone[6] or by catalysis with iron salts, as the attacking species for the following reasons. (i) There was a total lack of oxidation of the aromatic compounds in the absence of the iron salts. The epoxidation of alkenes by nitriles and hydrogen peroxide requires long reaction times and a basic hydroxylic solvent: in the absence of base little reaction occurs.[6,7]† (ii) Yamamoto and Kimura[9] have recently shown that an iron(III)–hydrogen peroxide system in acetonitrile epoxides alkenes not in the stereospecific manner expected of a peroxocarboximidic acid but by a two-step non-stereospecific process.

We conclude that these oxygenations do not proceed *via* the direct insertion of oxygen into the aromatic rings, by either a singlet oxenoid species or a peroxoacid, to give arene oxides[10] with subsequent isomerism to phenols. Nor is it likely that the phenols arise by insertion of an oxygen atom into aromatic C–H bonds, by a singlet or triplet oxenoid species, for such a process would not show a large value for the NIH shift.[11] We believe that the active oxidant behaves as a radical, possibly the hydroxyl radical, an iron derivative of the hydroxyl radical such as $FeO^{3+}$ or $FeO^{2+}$, or a triplet oxenoid species, and that the initially formed radical adduct with the aromatic compound is rapidly oxidised to a cyclohexadienyl cation which gives a phenol with a large value for the NIH shift (equation 2). The involvement of an arene oxide in such a process cannot be excluded. It is noteworthy that iron(III) is a very much stronger oxidant in acetonitrile than in water[12] which may account for the relative unimportance of this oxidation of hydroxycyclohexadienyl radicals in an aqueous Fenton's system.[2]

The results above, together with those of other workers,[3,9] show clearly that iron salts with hydrogen peroxide in acetonitrile have many of the characteristics expected of a model for cytochrome P-450 dependent mono-oxygenases and appear to resemble closely the hydroperoxide oxidations catalysed by cytochrome P-450.[13] Further they lend weight to the view that biological hydroxylations may occur by radical processes rather than by a direct oxygen insertion mechanism.

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† Recently some more reactive peroxocarboximidic acids have been prepared from cyanates, isocyanates (J. Rebek, S. Wolf, and A. Mossman, *J. Org. Chem.*, 1978, **43**, 180), and carbodi-imides (ref. 8) and some of these have been shown to epoxidise aromatic compounds directly (ref. 8).

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