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Radicals formed by Ultraviolet Irradiation of Substituted 4-Chlorophenols

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Aqueous alkaline solutions (pH 8) of (**I**) 2-methyl-4-chlorophenol, (**II**) 2-cyclohexyl-4-chlorophenol, (**III**) 2-benzyl-4-chlorophenol, (**IV**) 2,2′-methylene-bis-(4-chlorophenol), (**V**) 2-methoxy-4-chlorophenol, have been irradiated *in situ* with u.v. light and studied by electron spin resonance spectroscopy with a view to investigating further the free radicals formed by photoallergens with this basic chemical structure. Radical species were observed in all cases within minutes of irradiation. The radical spectra were interpreted and assigned as arising from substituted semiquinone radical anions, showing the initial replacement of the 4-chloro group with OH to give the corresponding hydroquinones. In the presence of oxygen, the hydroquinones are oxidised to the corresponding semiquinone radicals. There was no direct evidence of the presence of initial carbon-centred aryl radicals formed by the loss of chlorine; radicals of this type were, however, demonstrated by spin-trapping experiments using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO).

Photoallergy can be caused by many compounds, but specifically by compounds such as chlorophenols, which contain a photolabile carbon–chlorine bond. Fentichlor and bithionol are two such 2-substituted 4-chlorophenols and cause photoallergic response. On irradiation with u.v. light they interact with the skin *via* a free-radical mechanism to cause photodermatitis.[1, 2]

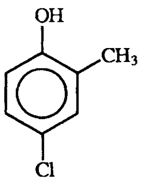
E.s.r. studies of both compounds have been carried out by ourselves[3] and Li and Chignell.[4] We have found that irradiation of these compounds in aerated aqueous alkaline solutions (pH 8) yields relatively stable free radicals. In order to investigate further free radicals formed by photoallergens with this basic structure we have extended the study to related 4-chlorophenols such as 2-methyl-4-chlorophenol (**Ia**), 3-methyl-4-chlorophenol (**Ib**), 2-cyclohexyl-4-chlorophenol (**II**), 2 benzyl-4-chlorophenol (**III**), 2,2′-methylene bis-(4-chlorophenol) (**IV**) and 2-methoxy-4-chlorophenol (**V**). The compounds, on u.v. irradiation in alkaline solution, not only form relatively stable radicals that can be detected directly by e.s.r. but unstable radicals that can be trapped in the presence of 5,5-dimethylpyrroline *N*-oxide (DMPO).

Experimental

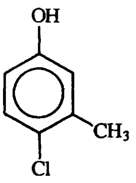
Materials

Compounds **Ia**, **Ib**, **II**, **III**, **IV** and **V** were obtained from Lancaster Synthesis UK and used without further purification.

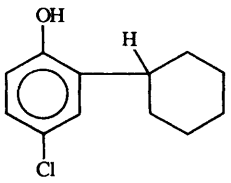
The spin trap DMPO (Aldrich) was filtered with charcoal under nitrogen before use to remove any impurities.



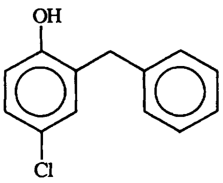
Ia



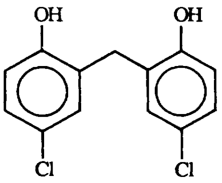
Ib



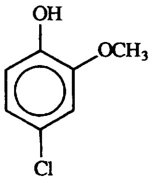
II



III



IV



V

Procedure

Aqueous solutions were prepared from stock solutions of the chlorophenols in ethanol (0.05 g in 2 cm^3) by adding five drops of this stock solution to distilled water (3 cm^3). The solutions were made alkaline by the addition of 0.1 mol dm^{-3} sodium hydroxide and the pH was adjusted as desired. Spin-trapping experiments were prepared by adding DMPO (0.001 g in 1 cm^3) to aqueous solutions of the respective 4-chlorophenol under nitrogen and in air. E.s.r. measurements were made with a Varian E3 spectrometer. Samples were irradiated *in situ* in the cavity of the spectrometer using either a Bausch and Lomb 150 W xenon lamp or a medium-pressure mercury lamp. No differences were observed in the radicals produced by either lamp.

Results and Discussion

The e.s.r. spectra of radicals obtained on irradiation of compounds **Ia**, **Ib**, **II**, **III** and **IV** are shown in fig. 1–4, respectively, together with their computer-simulated spectra based on coupling constants given in table 1.

E.S.R. Spectra from Ia and Ib

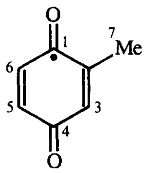
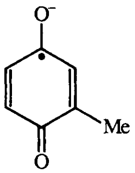
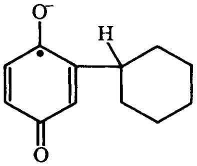
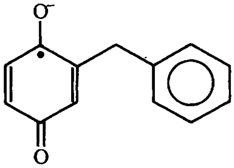
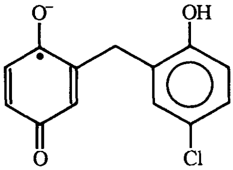
Irradiation of both these chlorophenols in alkaline solution (pH 8) gave the same e.s.r. spectra [fig. 1(*a*)] consisting of a triplet of doublets split further into a quartet. The hyperfine coupling constants have been assigned on the basis of the work of Pedersen.[5]

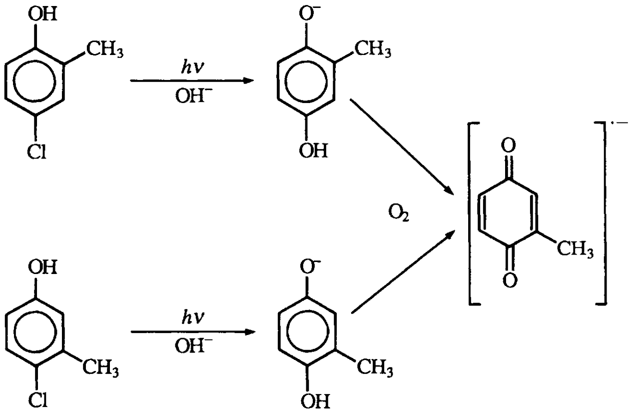
The fact that the spectra are identical means that the same radical is produced in both systems. This shows that on irradiation the chlorine atom is replaced with an OH group to yield the corresponding dihydroxybenzene. Continued irradiation would then in the presence of oxygen lead to the formation of the same methyl benzosemiquinone radical (see scheme 1). This is consistent with the method of formation of the primary radical in the fentichlor system.[3]

E.S.R. Spectrum from II

The spectrum [fig. 2(*a*)] can be interpreted in terms of a triplet split into two doublets. When compared with the spectrum of the radical from **Ia** and **Ib** it can be seen that the splitting due to the methyl group of 2.10 G has been replaced by a splitting of 1.17 G

Table 1. Hyperfine coupling constants and their assignment

radical	splitting/G			
	3	5	6	7
 **Ia**  **Ib**	1.75	2.42	2.30	2.10
 **II**	1.60	2.50		1.17
 **III**	1.85	2.40		1.65
 **IV**	1.80	2.40		1.95



Scheme 1.

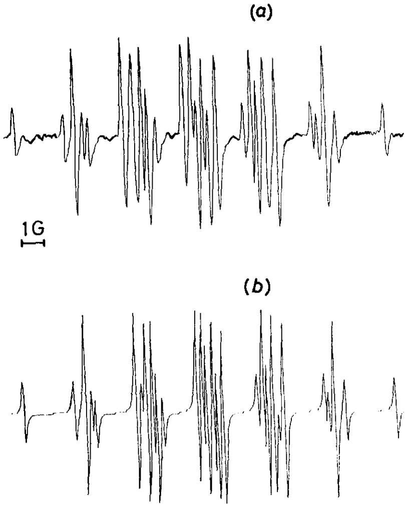


Fig. 1. (*a*) E.s.r. spectrum obtained on u.v. irradiation of **Ia** or **Ib** in alkaline solution (pH 8) at room temperature. (*b*) Computer simulation of (*a*).

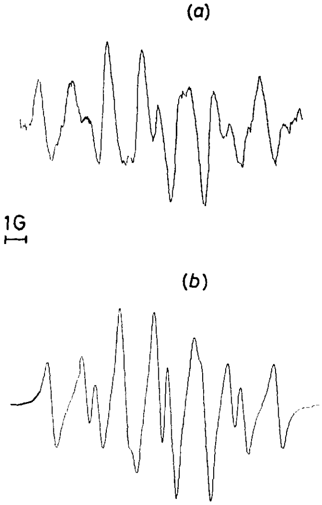


Fig. 2. (*a*) E.s.r. spectrum obtained on u.v. irradiation of **II** in alkaline solution (pH 8) at room temperature. (*b*) Computer simulation of (*a*).

from the cyclohexyl hydrogen. The protons in the 5 and 6 position on the benzosemiquinone ring have become equivalent. Not surprisingly, no interaction was observed with the other hydrogens of the cyclohexyl moiety.

E.S.R. Spectrum from III

The spectrum [fig. 3(*a*)] consists of a triplet split into a triplet and a further doublet, the bridge CH_2 position is larger than the proton on the cyclohexyl ring in the radical of **III** and smaller than the methyl protons in the radical of **I**. Again positions 5 and 6 of the

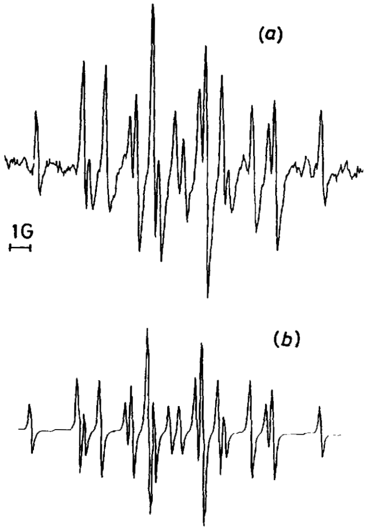


Fig. 3. (*a*) E.s.r. spectrum obtained on u.v. irradiation of **III** in alkaline solution (pH 8) at room temperature. (*b*) Computer simulation of (*a*).

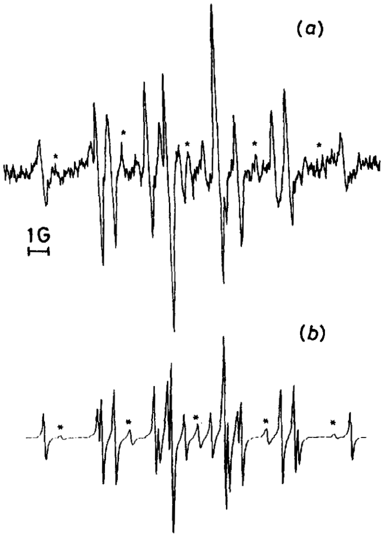


Fig. 4. (*a*) E.s.r. spectrum obtained on u.v. irradiation of **IV** in alkaline solution (pH 8) at room temperature. (*b*) Computer simulation of (*a*).

benzosemiquinone ring are equivalent. No other splitting was observed, suggesting that the electron is not delocalised onto the phenyl ring of the benzyl group.

E.S.R. Spectrum from IV

A similar spectrum [fig. 4(*a*)] to that of the radical from **III** was obtained, the main difference being the increase in the hyperfine coupling of the bridge CH_2 group. Again no evidence for delocalisation on to the other ring was observed. However, it is now apparent that a small concentration of another species is present [lines marked * in fig. 4(*a*)]. This can be interpreted as a 1:4:6:4:1 quintet with a coupling of $a_H = 2.35$ G. This radical is formed by cleavage of the C—CH$_2$ bond followed by hydrogen abstraction from water which, on further oxidation, gives the benzosemiquinone radical. A similar effect was observed on irradiation of the photoallergen fentichlor,[3] where this radical appeared after prolonged irradiation [tertiary species ref. (3), $a_H = 2.37$ G].

Irradiation of these compounds (pH 8) leads in the main to only one species, *i.e.* the substituted benzosemiquinone radical. This does not, however, undergo further oxidation and nucleophilic attack by OH^- to give rise to a secondary radical of a substituted hydroxybenzosemiquinone type as found in the fentichlor/bithionol system [secondary species, ref. (3)]. This we feel can only be attributed to the presence of the sulphur atom in these compounds.

Note that the coupling constant for one hydrogen attached to the substituent in the 2 position of the semiquinone is 1.17 G, for two hydrogens in this position is 1.65 G and for three hydrogens is 2.10 G.

E.S.R. Spectrum from V

On irradiation of **V** the production of radicals was much more difficult to achieve. This may be due to the fact that an oxygen atom is now attached to the 2 position. Only a weak, badly resolved spectrum was obtained which was analysed giving a triplet of triplets 3.5 and 1.0 G. This cannot be accommodated in terms of the parent molecule, and might be due to a radical of a product of oxidation.

Irradiation of Compounds I–IV in the Presence of DMPO

When compounds I–IV were irradiated in aqueous solution in the presence of the spin trap DMPO spin adducts were observed in each case. The e.s.r. spectra obtained were complex and consisted of at least three species, which varied in concentration from compound to compound and on the degree of oxygenation of the solution. The spectra could be interpreted as an aryl adduct of DMPO (nitrogen triplet of 15.6 ± 0.1 G and a large doublet of 23.5 ± 0.5 G), an OH radical adduct. [a_N(triplet) = a_H(doublet) = 14.9 G] and an H-atom adduct. [a_N(triplet) = 16.7 G, a_H(triplet) = 22.4 G]. If the solution were out-gassed with nitrogen, the spectra due to the aryl adduct increased in intensity while the other two decreased. The spectra are similar to those obtained by Li and Chignell[4] for the photolysis of fentichlor and bithionol, and the e.s.r. parameters assigned to the aryl radical are close to those of the phenyl adduct of DMPO observed by Hill and Thornalley.[6] This is consistent with the fact that upon irradiation aryl radicals are formed, possibly by removal of the chlorine atom in the 4 position.

Conclusion

The results show that on u.v. irradiation at pH 8, compounds **Ia**, **Ib**, **II**, **III** and **IV** give relatively stable substituted benzosemiquinone radicals. These compounds have a substituted carbon moiety as opposed to a substituted sulphur group. Both types of compounds initially behave in the same way, *i.e.* breaking of the photolabile C—Cl bond and subsequently, in the presence of oxygen, forming a semiquinone-type radical. They differ, however, in that the compounds containing the sulphur group (fentichlor and bithionol) undergo nucleophilic attack by OH^- to give a secondary 4-hydroxy benzosemiquinone-type radical [see ref. (3)]. These compounds on prolonged irradiation give the benzoquinone radical formed by cleavage of the C—S bond and subsequent hydrogen abstraction from the solvent. This radical is observed only from compound **IV**.

The spin-trapping technique shows that on irradiation the compounds undergo photo-dehalogenation to form the corresponding aryl radical. These aryl radicals, because of their high degree of reactivity, can abstract hydrogen from suitable donors, such that *in vivo* these radicals may initiate lipid peroxidation and oxidize glutathione *etc*. The subsequent radicals formed could react with the aryl radicals to form covalent compounds which could act as allergens and cause an allergic response.

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