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Oxidation of 2,6-Dimethoxyphenol with 2,6-Di-*tert*-butyl-4-propionylphenoxy Radical. Evidence for the Formation of an Intermediate "Radical Pair"

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In the title reaction an intermediate is formed which is stable at temperatures below −10 °C. It gives no EPR signal. Warming leads to the formation of coerulignone and poly-2,6-dimethoxyphenylene oxide. Acid hydrolysis at low temperatures leads to cross-coupled products. The results are discussed in terms of a two-stage reaction mechanism for the formation of a bond between two phenoxy radicals.

Oxidative coupling is an important reaction in the metabolism of phenolic compounds and it may also become a useful synthetic method if the mechanism and the rules governing the course of these reactions were better known. One current theory for the coupling reaction assumes that a phenolate ion is oxidized to a free phenoxy radical.[1] This radical then reacts rapidly with other radicals under kinetic control. It also assumes that coupling occurs at the positions of highest density of the unpaired electron, except where there is steric hindrance of approach.[1] In many cases, however, these basic assumptions are insufficient for explaining the structures and yields of the products of oxidative coupling of phenols. Kinetic and steric evidence[2–5] suggests that the formation of a bond between two phenoxy radicals is a two-stage process. In the first stage the aromatic systems are brought face to face, interaction between the two half filled HOMO's providing an orientation effect and partial bonding (for benzyl radicals, theoretical calculations suggest[6] that such a configuration is stabilized to an extent of approximately 92 kJ/mol compared with the radicals at infinite separation). The second stage is the formation of a carbon–carbon or carbon–oxygen bond. The resulting cyclohexadienone then reacts further irreversibly giving stable products.

In the coupling reaction between 2,6-dimethoxyphenol (*1*–H) and 2,6-di-*tert*-butyl-4-propionylphenoxy radical (*2*) a system has been encountered

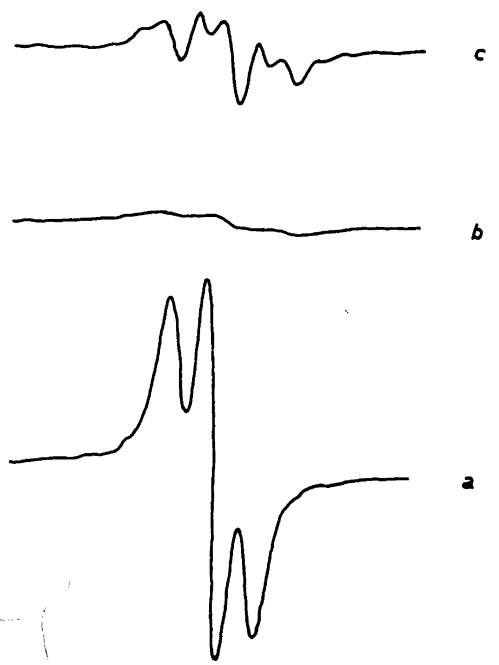

Fig. 1. EPR signals from the solution of radical *2* in 1,2-dimethoxyethane at −10 °C (a), after addition of half the equivalent amount of *1*–H (b) and when the temperature of the resulting solution was allowed to rise to −4 °C (c).

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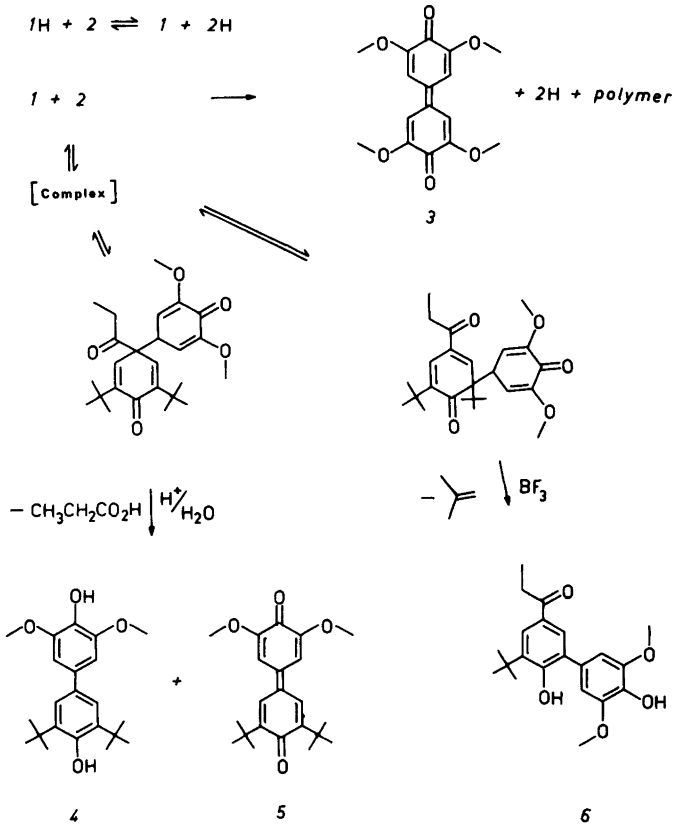

Scheme 1.

which clearly demonstrates the existence of intermediate equilibria in the formation of coupling products. This allows some conclusions to be drawn concerning the structure and stability of a metastable intermediate which can be formulated as a radical pair or charge transfer complex.[4,5]

RESULTS

When a solution of 2,6-dimethoxyphenol (*1* – H) was added to a cold (below – 10 °C) solution of the free radical *2*, the blue colour due to radical disappeared when exactly half the equivalent amount of *1* – H had been added. At this point the solution gives no detectable EPR signal (Fig. 1). When this solution is treated in different ways, different coupling products are obtained.

Heat. When the temperature of the EPR-cavity was raised to – 4 °C an EPR signal began to appear. At the same time a dark violet precipitate of *3* (coerulignone) was formed. The yield of *3* after heating briefly to 50 °C was 45 – 50 %. By evaporating the solution to a small volume an amorphous precipitate (*ca.* 50 %) could be isolated. Its NMR spectrum was identical with that of a polyphenylene oxide polymer obtained by oxidation of *1* – H with silver oxide.[7] No coupling products between *2* and *1* were found.

Aqueous acid. If a few drops of 2 M hydrochloric acid was added to the original solution at – 10 °C, no diphenoquinone precipitated when the solution was warmed to room temperature. GLC analysis showed that propionic acid was formed. The main product isolated by TLC was the *p-p*-coupled biphenyl *4* together with its oxidation product, the diphenoquinone *5*.

Boron trifluoride. When the cold solution was treated with boron trifluoride etherate instead of

the aqueous acid no propionic acid was detected. The only coupling product isolated in this case was the *o*–*p*-coupled biphenyl *6*.

DISCUSSION

The disappearance of the EPR signal and colour associated with the free radical when half the equivalent amount of phenol was added shows that one mol of *2* oxidized phenol *1* – H to a radical which in turn combined with a second mol of *2*. The fact that the reaction can go in different directions from this point indicates the existence of an equilibrium between at least two different cyclohexadienones. Depending on whether the acid treatment is done in the absence or presence of nucleophile either the tertiary butyl group or the propionyl side chain is split off giving a stable biphenyl compound. Heating the mixture without the addition of acid regenerates the free radicals (EPR signal) and the less sterically hindered radical couples with itself to form, after oxidation by *2*, the diphenoquinone *3* and polymer. Since the equilibrium between the cyclohexadienones (see Scheme 1) does not involve free phenoxy radicals, the most plausible explanation is that the two radicals combine to form a "radical pair" before forming a normal bond. The fact that most phenolic couplings proceed under kinetic control is explained by the irreversibility of the final stabilization step. The product composition in oxidative coupling of phenols is then governed by the steric requirements of the "radical pair" and by the relative rates of the irreversible steps leading to each product.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. EPR spectra were run on a Varian E-4, NMR spectra on a Varian A-60 and high resolution mass spectra on an AEI MS 902. GLC: Perkin Elmer 990, column 2 m, outer diameter 3 mm, stationary phase 10 % Carbowax 20M/terephthalic acid, carrier gas N_2 30 ml/min, column temperature 125 °C, detector FID.

2,6-Dimethoxyphenol (*1* – H) was purchased from Aldrich Co.

2,6-Di-tert-*butyl-4-propionylphenoxy radical* (2) was prepared using a published procedure.[8]

The coupling reactions were carried out in dry 1,2-dimethoxyethane. In a typical run, 200 mg radical *2* was dissolved in 2 ml solvent agitated by a stream of dry nitrogen. Half a mol of phenol *1* – H (58.9 mg) in 2 ml solvent was added dropwise to discharge the blue colour of the radical.

Heat treatment. The solution was kept at 50 °C for 40 min and the precipitated diphenoquinone filtered off (26.1 mg). The filtrate was evaporated to a small volume and the residue triturated with diethyl ether to yield a white amorphous material which was insoluble in ether (10.7 mg). The NMR spectrum (in $CDCl_3$) was identical to that of poly-2,6-dimethoxyphenylene oxide prepared by oxidation of *1* – H with silver oxide.[7] Separation of the ether soluble material on preparative TLC gave 18.0 mg of material, which according to its NMR spectrum was a lower molecular weight polyphenylene oxide, and 175 mg 2,6-di-*tert*-butyl-4-propionylphenol (*2* – H).

Treatment with aqueous acid. The reaction vessel was transferred to a dry ice bath at −30 °C. After half an hour 2 drops of dilute (2 M) hydrochloric acid were added and the solution left overnight in the ice bath. Next day 13 mg of yellow crystals could be filtered off which were identified as 2,6-dimethoxy-*p*-benzoquinone. The solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution and water, dried and evaporated. The residue was chromatographed on a preparative thin–layer plate and eluted with cyclohexane–ethyl acetate (1:1). The main fraction, apart from *2* – H, was 118 mg of a mixture of biphenyl *4* and diphenoquinone *5*. The structure was determined after reduction of the mixture with sodium borohydride and acetylation. The monoacetate of *4* gave colourless crystals (ethyl acetate) m.p. 123–124 °C. MS [IP 70 eV, ion source 90 °C; *m/e* (% rel.int.)]: 400 (25, M), 358 (100, M – CH_2CO), 343 (11), Mol. wt., obs. 400.2254, calc. for $C_{24}H_{32}O_5$ 400.2245.

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.49 (18 H, s), 2.36 (3 H, s), 3.88 (6 H, s), 5.29 (1 H, s), 6.75 (2 H, s), 7.34 (2 H, s).

Treatment with boron trifluoride–diethyl etherate. The treatment is carried out as in the preceding experiment with a few drops of boron trifluoride diethyl etherate instead of aqueous hydrochloric acid. Working up as above gave, apart from *2* – H and traces of *4* and *5*, 53.7 mg of 2,4′-dihydroxy-3-*tert*-butyl-3′,5′-dimethoxy-5-propionyl-1,1′-biphenyl (*6*), m.p. 102 °C. MS [IP 70 eV, ion source 140 °C; *m/e* > 5 % (rel. int.)]: 358 (34, M), 343 (19, M – CH_3), 329 (100), 163 (12), 158 (9), 139 (42), 135 (8), 125 (6), 119 (5), 115 (6), 109 (7), 107 (8), 93 (10), 91 (16), 79 (15), 77 (15), 65 (13), 57 (55), 55 (9), 51 (11). Mol wt., obs. 358.1860, calc. for $C_{21}H_{26}O_5$ 358.1780. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.12 (t, 3H), 1.47 (s, 9H), 2.83 (q, 2H, J = 7 Hz), 3.80 (s, 6H), 6.6–7.6 (m, 6H).

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REFERENCES

1. Musso, H. In Taylor, W. I. and Battersby, A. R., Eds., *Oxidative Coupling of Phenols*, Dekker, New York 1967.
2. Mahoney, L. R. and Da Rooge, M. A. *J. Am. Chem. Soc. 97* (1975) 4722.
3. Williams, D. J. and Kreilick, R. *J. Am. Chem. Soc. 90* (1968) 2775.
4. Sarkanen, K. V. and Wallis, A. F. A. *J. Chem. Soc. Perkin Trans. 1* (1973) 1869.
5. Anderson, R. A., Dalgleish, D. T., Nonhebel, D. C. and Pauson, P. L. *J. Chem. Research (S)* (1977) 12; *J. Chem. Research (M)* (1977) 201.
6. Zahradnik, R. and Cársky, P. *Prog. Phys. Org. Chem. 10* (1973) 327.
7. Savolainen, A. *Diss.*, Helsinki 1970.
8. Brunow, G. *Acta Chem. Scand. 23* (1969) 2537.

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