Orientation and Relative Rate in the Isopropylation of 2-Methyl-1,4-benzoquinone

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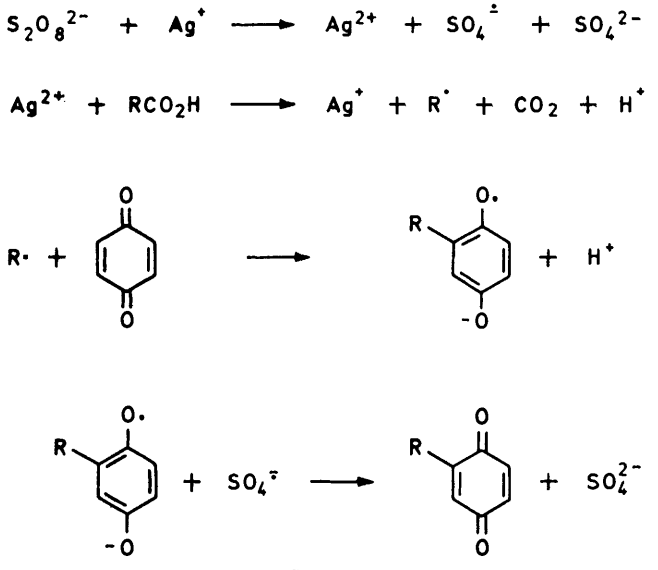
The orientation and relative rate in the alkylation of 2-methyl-1,4-benzoquinone (1) with isopropyl radicals has been measured. The value of the relative rate accounts well for the large amounts of di- and poly-alkylated products obtained in radical alkylation of quinones in homogeneous systems.

THE reaction of quinones with nucleophilic radicals generated in the silver ion catalysed oxidation of carboxylic acids with peroxydisulphate offers a convenient route to alkyl-[1-4] and alkoxycarbonyl-substituted [5] quinones. The reaction is believed to proceed according to the Scheme.[1,6]



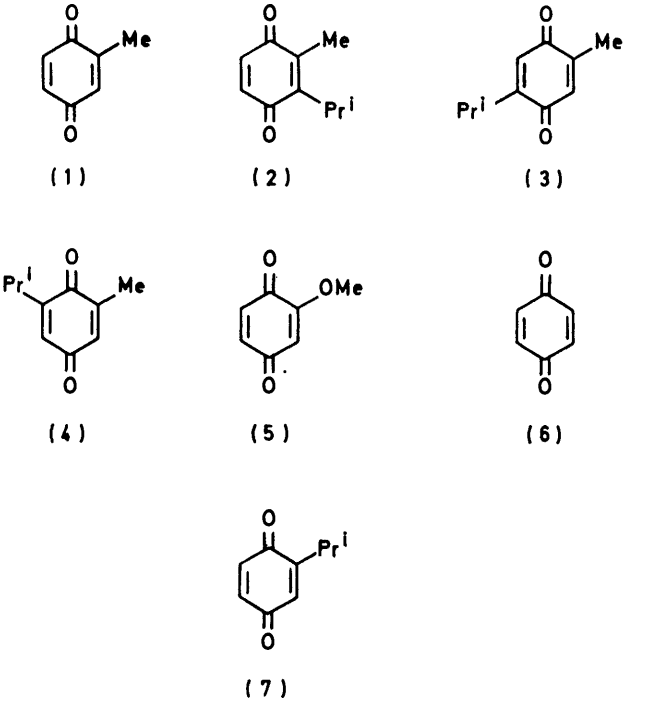
SCHEME

In these reactions, di- or poly-substitution is a potential problem, which, in the case of the alkoxycarbonylation reaction, has not yet been solved. Thus, if more than one free position in the quinone is available for substitution, di- or poly-alkoxycarbonylation prevails even when high quinone : radical ratios are used.[5] Apparently and not surprisingly, an alkoxycarbonyl substituent strongly activates the quinone nucleus towards further attack by the nucleophilic alkoxycarbonyl radical. In the alkylation reaction this difficulty can usually be circumvented by adjusting the reaction medium so that the monoalkylated quinone separates during the reaction, thus protecting it against further alkylation. In homogeneous systems, however, di- and poly-alkylation has proved to be a serious problem [7] even though the introduction of an alkyl substituent is expected to deactivate the quinone nucleus towards nucleophilic radicals. Rembaum and Szwarc [8] have measured the relative affinities of a series of quinones towards methyl radicals, but the products were not analysed, leaving some uncertainty as to the fate of the methyl radicals. Hence, relative rates of radical alkylation within systems where the reaction course is known in greater detail, become of interest.

In the present work, the relative reactivity of a typical alkyl-substituted quinone, 2-methyl-1,4-benzoquinone (1), towards a typical nucleophilic radical, isopropyl, has been determined by the competition technique. In addition, the isomer distribution of this reaction has been determined.

RESULTS AND DISCUSSION

In water, 2-methyl-1,4-benzoquinone (1) is isopropylated according to the Scheme in high yield, calculated on the amount of peroxydisulphate used, to give a mixture of the 3-, 5-, and 6-isopropyl derivatives (2)—(4) without the formation of appreciable amounts of dialkylated or other byproducts (see Experimental section). From this mixture, the individual components (2)—(4) could be isolated by liquid chromatography, and their structures were assigned on the basis of their mass spectra, ^{1}H n.m.r. spectra, and com-



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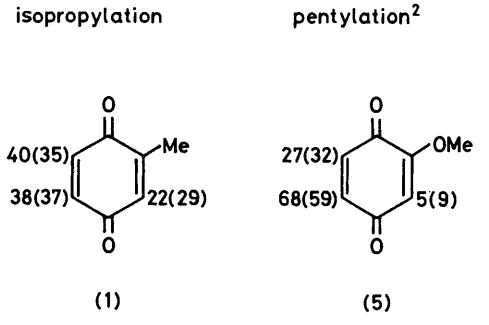
parison with authentic samples of (3) and (4). In the mass spectrum the cleavage of two C–C bonds leading to the fragments *m/e* 82 and 54 in (2) and 96 and 68 in (3) and (4) was of diagnostic value,[9] whereas in the ^{1}H n.m.r. spectrum (see Experimental section) the presence of allylic couplings between alkyl and ring protons in (3) and (4) but not in (2) as well as couplings between the two ring protons in (2) and (4) but not in (3) strongly supports the assignment.

The isomer ratio was determined from the reaction employing 0.3 equivalents of peroxydisulphate at 63 °C, but the dependance of the isomer ratio on the stage of conversion was found to be insignificant. The reaction mixture was analysed by g.l.c. comparing it with standard mixtures made up from the pure components in ratios deviating less than 10% from the actual value. Average isomer ratios from three independent experiments are found in the Table.

Isomer ratio (%) of products from isopropylation of (1)

(2)	(3)	(4)
24 ± 1	38 ± 1	40 ± 0.5

Perhaps the most surprising feature is the small, but apparently significantly higher abundance of (4) compared with (3), also seen when comparing the ^{1}H n.m.r. spectrum of the mixture with the spectra of the standard mixtures. Attempted correlation of the substitution pattern with the spin densities in the anion radical of (1) as a consequence of the nucleophilic character of the isopropyl radical,[10] does not predict this effect. Qualitatively, however, this model predicts the substitution pattern quite well both in this and another case of known isomer distribution, pentylation of 2-methoxy-1,4-benzoquinone (5) [2] (see Figure), and at present no better model seems available.



(1) (5)

Comparison of isomer ratios in radical alkylation with the spin density in the radical anion of the parent quinone (numbers in parentheses) recalculated into percentages for comparison [11,12]

The relative rate of isopropylation of (1) and 1,4-benzoquinone (6) was determined by carrying out the same reaction on equimolar mixtures of (1) and (6), and measuring the molar ratio A between 2-isopropyl-1,4-benzoquinone (7) and the sum of (2)—(4) by g.l.c. using standard mixtures as before. Values of A from three independent experiments were 0.546, 0.524, and 0.535. These values do not represent the relative rate due to the high conversion (30% if the reaction is quantitative) necessary for experimental reasons. From equations (1)

$$-\mathrm{d}[(1)]/\mathrm{d}t = k_2[\text{isopropyl}][(1)] \quad (1)$$

$$-\mathrm{d}[(6)]/\mathrm{d}t = k_2[\text{isopropyl}][(6)] \quad (2)$$

$$\text{relative rate} = k_1/k_2 = \ln\left[\frac{\text{amount of (6)}}{5.00}\right] \Big/ \ln\left[\frac{\text{amount of (1)}}{5.00}\right] \quad (3)$$

and (2), (3) is derived by division, integration, and conversion of concentrations to total amounts, using $[(1)]_0 = [(6)]_0 = 5.00$ mmol at the start of the reaction.

A lower limit for the relative rate is thus obtained by inserting the lowest value of A (0.524) in equation (3) assuming a quantitative reaction. This leads to a value of 0.461. As an upper limit, the highest value of A (0.546) can be used without correction for the effects of conversion, *i.e.* representing the highest possible deviation from a quantitative reaction. The relative rate is then given as 0.50 ± 0.05. The small difference in reactivity between (1) and (6) clearly illustrates the polyalkylation problem and the value is in qualitative agreement with the methyl affinity ratio 0.66 ± 0.05 found by Rembaum and Szwarc, the lower value for the isopropyl radical possibly, at least in part, reflecting the larger steric requirements of this radical.

EXPERIMENTAL

Instrumentation.—M.p.s were determined on a Reichert hot stage apparatus and are uncorrected. ^{1}H N.m.r. spectra were recorded on a Varian EM 360 or a HX 270, mass spectra on a Micromass 7070 F instrument. G.l.c. was done on a Hewlett–Packard 5700 A instrument equipped with flame ionisation detector, sample splitter, and a 3 370 electronic integrator. The column was a 35 m long capillary column with Apiezon L as stationary phase. Liquid chromatography was done on Merck pre-packed silica gel columns using an LKB-uvicord III detector operating at 344 nm. The eluant was 9% ether in pentane.

Materials.—1,4-Benzoquinone (6) (Fluka Purum grade) was crystallized from heptane, m.p. 111—113°. 2-Methyl-1,4-benzoquinone (1) was prepared from the hydroquinone by the method of Billmann *et al.*[13] and was crystallized twice from hexane, m.p. 66.5—67°.

2-Isopropyl-1,4-benzoquinone (7) was prepared according to Jacobsen and Torssell [1] and recrystallized from methanol and pentane respectively, m.p. 35.5—36.5° (lit.,[14] 34—36°). 5-Isopropyl-2-methyl-1,4-benzoquinone (3) was prepared according to Henderson and Boyd [15] and recrystallized from aqueous methanol and pentane respectively, m.p. 44—45° (lit.,[15] 45.5°), isomer-free by g.l.c. and liquid chromatography, δ (C_6D_6; 270 MHz) 0.97 (6 H, d, J 6.9 Hz), 1.72 (3 H, d, J 1.6 Hz), 3.02 (1 H, d heptet, J 6.9, 1.2 Hz), 6.22 (1 H, q, J 1.6 Hz), and 6.39 (1 H, d, J 1.2 Hz), *m/e* 164 (100%), 149 (35), 136 (29), 121 (36), 108 (10), 96 (8), 93 (32), and 68 (17).

6-Isopropyl-2-methyl-1,4-benzoquinone (4) —To 5-isopropyl-3-methylphenol (15 g, 0 1 mol) in trifluoroacetic acid (40 ml) and tetrahydrofuran (10 ml) was added 25% hydrogen peroxide (40 ml) keeping the temperature at 20°. The mixture, which gradually turned dark, was stirred

until it became light orange (18 h), neutralized with solid $NaHCO_3$, and extracted with ether. The ether phase was washed with 5% K_2CO_3 until the washings were no longer violet, dried, and evaporated to give almost pure (4) (8.1 g, 49%). For the preparation of standard mixtures a sample was distilled through an efficient column and a centre cut boiling at 56—56.5° and 0.6 mmHg was collected, yellow *oil*, $n_D^{26.5}$ 1.514 2, isomer-free by g.l.c. and liquid chromatography, δ (C_6D_6; 270 MHz) 0.95 (6 H, d, *J* 6.9 Hz), 1.72 (3 H, d, *J* 1.5 Hz), 2.98 (1 H, d heptet, *J* 6.9, 1.2 Hz), 6.24 (1 H, dq, *J* 2.7, 1.5 Hz), and 6.39 (1 H, dd, *J* 2.7 1.2 Hz), *m/e* 164 (28%), 149 (17), 136 (87), 121 (100), 108 (17), 96 (17), 93 (74), and 68 (28) (Found: C, 73.1; H, 7.45. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.35%).

Isopropylation of (1).—*Isolation of products.* The isopropylation of (1) by the method of Jacobsen and Torssell [1] using one equivalent of ammonium peroxydisulphate yielded a crude product which by liquid chromatography gave fractions 1—4. Fractions 1 and 2 (1.5%) were tentatively identified as the 3,5- and 2,6-di-isopropyl derivatives from their similar 60 MHz ^1H n.m.r. spectra, δ ($CDCl_3$) 1.13 (6 H, d, *J* 7 Hz), 1.27 (6 H, d, *J* 7 Hz), 2.03 (3 H, s), 3.1 (2 H, m), and 6.43 (1 H, d, *J ca.* 1 Hz). Fraction 3 (87%) was a mixture of (2)—(4) which on repeated liquid chromatography could be isolated as pure compounds, each of which was isomer-free by g.l.c. and liquid chromatography. Compounds (3) and (4) prepared in this way were identical (n.m.r., m.s., m.p., and g.l.c.) with authentic samples. *2-Isopropyl-3-methyl-1,4-benzoquinone* (2) gave yellow needles, m.p. 65—65.5°, δ (C_6D_6; 270 MHz) 1.27 (6 H, d, *J* 7.1 Hz), 1.86 (3 H, s), 2.91 (1 H, heptet, *J* 7.1 Hz), and 6.18 and 6.24 (2 H, AB, *J* 9.9 Hz), *m/e* 164.084 (100%) ($C_{10}H_{12}O_2$ requires 164.084), 149 (35), 136 (55), 121 (63), 108 (9), 82 (26), and 54 (25).

Isomer ratio and relative rate. Product ratios were determined by comparison with standard mixtures as described in the text. For each product mixture, three standard mixtures were made, and the product mixture was analysed three times alternating with the standard mixtures. Under these conditions, the reproducibility of the electronic integration of each peak as well as the sum of integrations of the peaks from (2)—(4) was better than 1%.

Isomer ratio. To a vigorously stirred mixture of (1) (1.22 g, 10 mmol), silver nitrate (0.5 g) (Merck analytical grade), and isobutyric acid (0.88 g, 10 mmol) (Fluka Purum grade) in water (40.0 ml) kept at 63 ± 1° was added a solution of ammonium peroxydisulphate (Fluka Puriss grade) (0.684 g, 3.00 mmol) in water (4 ml) during 40 min. After a further 5 min stirring the mixture was extracted with ether (2 × 30 ml). The ether phase was washed with 10% $NaHCO_3$ (20 ml), dried, and concentrated *in vacuo* at 20° to 2 ml. This mixture was used immediately for g.l.c. analysis.

Relative rate. The above reaction was repeated using a mixture of (1) (0.611 g, 5.00 mmol) and (6) (0.541 g, 5.00 mmol) instead of 10.0 mmol of (1). Work-up as before gave an ether solution (2 ml), which was used immediately for g.l.c. analysis.

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