# The *ortho*:*para* Ratio in the Bromination of Phenol. Evidence for a Co-ordination Effect

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Bromination of phenol with bromine has been studied in various solvents in the presence of an epoxide as a hydrobromic acid scavenger. From the observed dependence of the orientation of products upon the nature of the electrophile, solvent, phenol, epoxide, and hydrobromic acid concentrations, a mechanism is proposed wherein at very low hydrobromic acid concentrations and in solvents with a small tendency to form hydrogen bonds with phenol, molecular bromine makes a kinetically controlled attack upon phenol to give an *o*-quinonoid intermediate rather than a *p*-quinonoid one. At higher concentrations of acid the *o*-quinonoid intermediate is rapidly isomerized to the more stable *p*-quinonoid form. This mechanism is confirmed by the similar behaviour of 2,4,6-trimethyl-phenol. In solvents which can form hydrogen bonds with phenol and hence probably inhibit sterically *ortho*-attack by the electrophile, the *p*-quinonoid intermediate is the predominant product. The same is true if bromination is carried out at higher concentrations of phenol and epoxide. Bromination in the presence of epoxide represents a useful and simple method of preparing *o*- or *p*-bromophenols.

THE factors which govern the *ortho* : *para* ratio in the electrophilic substitution of phenols are not well understood. In some cases there is evidence for steric hindrance of *ortho*-substitution,[1-6] while in others interaction between the substituent and the electrophile facilitates *ortho*-substitution.[7-10] The nature of electrophile is also important. The excess of *ortho*-substitution is different in chlorination[9] than in bromination of phenol.† In the preceding paper, we showed that preferential *ortho*- or *para*-bromination of phenol can be simply achieved by using as brominating reagents bromocyclohexadienones or *N*-bromosuccinimide (NBS). The peculiar brominating properties of these reagents could be due to a fast reaction which occurs with HBr or HCl to give low equilibrium bromine or BrCl concentrations. Thus simultaneously these reagents act as
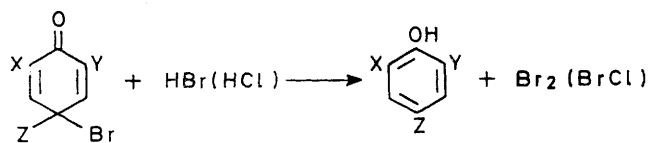
X = Y = Z = Br or Cl

efficient hydracid scavengers,[11,12] and this effect is responsible for the observed orientation. The halogenation of phenol by molecular bromine is shown in the Scheme.

If the concentration of HBr is not negligible, as in bromination with molecular bromine, the *ortho*-dienone would rearrange to the more stable *para*-isomer, to give finally *p*-bromophenol. Moreover if an acid scavenger is present (*e.g.* in bromination with bromocyclohexadienones or NBS), the rate of rearrangement slows down

and *o*-bromophenol can be obtained as a major product. The formation of the *ortho*-isomer is probably easier than

SCHEME
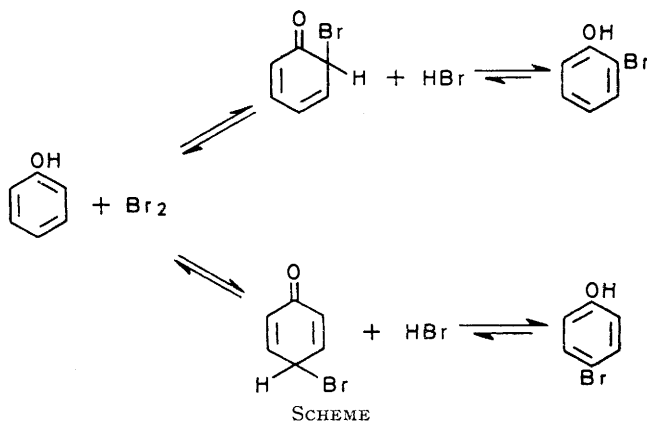
that of the corresponding *para*-derivative because of the possibility of a cyclic six-membered transition state (I) being formed.

(I)
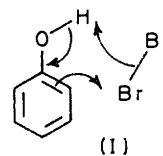
If the considerations on bromination with bromocyclohexadienones or NBS are valid, they can also be applied to bromination with molecular bromine, giving rise to both synthetic and mechanistic implications. In fact both the *o*- and *p*-quinonoid intermediates are

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† See refs. 1—4 in the preceding paper.

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vinylogues of α-bromo-ketones, and the interconversion of the two forms, through reduction to the starting phenol, can be influenced by acids. The factors which could influence the stability of halogenocyclohexa-dienone intermediates have been studied by other authors.[13,14] Recently it was shown [15] that p-bromo-phenols can disproportionate in the presence of hydro-bromic acid. The o-bromophenols disproportionate more slowly than the $para$-isomers, because of the presence of hydrogen bonds between the phenolic OH and the halogen in the $ortho$-position. Hydracids facilitate interconversion of the two quinonoid forms by a ' push and pull ' mechanism ($cf.$ the reduction of
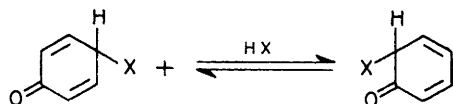
α-bromo-ketones by HBr, in which both the ' push ' and the ' pull ' provided by HBr are needed [16]).

Therefore the rate of rearrangement of the o- to the p-quinonoid form would be influenced not only by the relative C–X strength in the cyclohexadienone inter-mediates but also by the relative nucleophilicity of bromide or chloride ions in HX.[17] In other words the rearrangement of an o-chlorodienone would be slower than the corresponding bromo-analogue. Using this concept one can explain the difference in the isomer distribution between the chlorination [9] and the bromin-ation [18] of phenol in, for example, carbon tetrachloride.

In order to verify the validity of these ideas, we have examined the factors (acid formation, solvent, nature of the electrophile, concentration of the reactants) which could influence the formation and stability of the o- and p-quinonoid intermediates, and hence the observed isomer distribution, in the halogenation of phenol with molecular halogen.

RESULTS AND DISCUSSION

Hydracids.—When the chlorination (or bromination) of phenol was carried out in the presence of a suitable hydracid scavenger (*e.g.* an epoxide) an almost com-pletely *ortho*-halogenated product was obtained. The reagent used was molecular halogen in the presence of cyclohexene oxide in chlorinated solvents. The results are reported in Table 1 which also contains those for the same conditions but in the absence of the epoxide. Interestingly, even with stoicheiometric amounts of the reagents, only monobrominated phenol in high yield was isolated in the presence of epoxide.

The *ortho* : *para* ratio was not influenced by adding variable amounts of tetraethylammonium bromide or photochemical or radical initiators such as azobisiso-

butyronitrile. This removes the possibility that a large proportion of the *ortho*-isomer can arise from a free radical reaction between bromine and phenoxyl radical. The influence of hydrobromic acid on the stability of the cyclohexadienone intermediates was demonstrated by

TABLE 1

Bromination of phenol with bromine with (1) [a] and without (2) [b] added cyclohexene oxide at 25°

		Orientation (%)	
Solvent		o	p
Carbon tetrachloride	(1)	96	4
	(2)	11	89
Chloroform	(1)	76	24
	(2)	8	92
Methylene chloride	(1)	44	56
	(2)	6	94
Acetonitrile	(1)	30	70
	(2)	3	97
Acetic acid	(1)	11	89
	(2) [c]	4	96

[a] Slow addition (30 min) of bromine (0·1 ml, 1 mol. equiv.) in solvent (5 ml) to phenol (0·2 g, 1 mol. equiv.) dissolved in the same solvent (10 ml) containing cyclohexene oxide (0·32 g, 1·5 mol. equiv.). [b] Slow addition of bromine (0·1M, 1 mol. equiv.) in solvent (5 ml) to phenol (0·2 g, 1·5 mol. equiv.) dissolved in the same solvent (10 ml). [c] Ref. 27.

the bromination of 2,4,6-trimethylphenol which reacts with bromine alone to give the fairly stable, known 4-bromo-2,4,6-trimethylcyclohexa-2,5-dienone (II).[19]

(II)   (III)
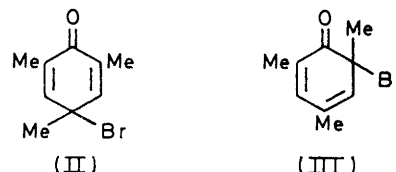
Notwithstanding the steric hindrance of the two o-methyl substituents, the same reaction carried out in carbon tetrachloride in the presence of cyclohexene oxide, gives besides the dienone (II) some *ortho*-isomer (III) which was not isolated but characterized by its u.v. spectrum, which has a maximum at an appreciably higher wavelength [14,20] than that of the isomer (II). When gaseous HBr was added to a carbon tetrachloride solution of (II) and (III), the u.v. spectrum rapidly changed to give the spectrum of (II). The preferential *ortho*-bromination of phenol in the presence of epoxide cannot be ascribed to the formation of a complex between bromine and the scavenger. The u.v. spectrum provides no evidence for such a complex. Moreover it is known [21] that the complex between bromine and dioxan *para*-brominates phenol exclusively.

Nature of the Electrophile.—Contrary to the results obtained with molecular bromine, bromination of phenol in carbon tetrachloride with BrCl, obtained by mixing

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equimolar amounts of bromine and chlorine, gives 58 o- and 42% p-bromophenol. In this case, since the chloride ion in HX is a weaker nucleophile than bromide ion, the rearrangement of the initially formed o-bromo-dienone is slower and hence more ortho-brominated product can be isolated.

Solvent Effects.—As reported in Table 1, for bromin-ation in the presence of epoxide the orientation of pro-ducts is dramatically influenced by the solvent. The ortho-content reaches its highest value in dry carbon tetra-chloride and its lowest in acetonitrile and glacial acetic acid. These results may be explained either by the formation of hydrogen bonds between the phenol OH and the solvent,[22] which hinders the ortho-approach of the electrophile, or by the slower reaction of HBr with the scavenger, which allows the isomerization of the o-dienone to the para-isomer. In the light of the results obtained with variable amounts of the reactants we favour the former hypothesis.

Concentration of Reactants.—It is known that in 'inert solvents' such as carbon tetrachloride, phenol can form strong intermolecular hydrogen bonds with acceptors such as nitriles,[23] ethers,[24] and other com-pounds. Moreover in not very dilute solutions, phenols are self-associated.[25] The u.v. and i.r. spectra of phenol in carbon tetrachloride change with the concentration of phenol and with the addition of variable amounts of cyclohexene oxide. This phenomenon, which is due to the formation of intermolecular hydrogen bonds, in-fluences the orientation of products (Table 2). The

TABLE 2

Bromination of phenol with various concentrations of reagents at 24°, [Bromine] 0·138M

		Orientation (%)	
[Phenol]/M	[Epoxide]/M	o	p
0·142	0·218	93	7
0·142	1·31	61	39
0·142	2·61	43	57
0·142	4·62	10	90
0·355	0·218	72	28
0·710	0·218	46	54
1·42	0·218	18	82

inversion of orientation with increasing concentrations of phenol or epoxides is further evidence for the import-ance of cyclic co-ordination effects on orientation.* Therefore, despite the fact that the p-quinonoid form is more stable than the corresponding o-quinonoid [26] and hence more important in the valence bond description of the transition state for substitution, the unstable o-dienones are the kinetically controlled products.

* Preliminary kinetic experiments on the bromination of phenol in the presence of epoxide at 0° show that in carbon tetra-chloride, where third-order kinetics obtain [19] (k 3·7 × 10⁻³ l² mol⁻² s⁻¹) in the absence of epoxide, show that the reaction of equimolar amounts of phenol and epoxide (2 × 10⁻³M each) and bromine (10⁻³M) gives a second-order rate constant (k 2·78 l mol⁻¹ s⁻¹) and the rate of the reaction decreases upon increasing the epoxide concentration.

[22] V. S. Karpinskii and V. D. Lyashenko, *J. Gen. Chem. U.S.S.R.*, 1962, **32**, 3922.

[23] A. Allerhand and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1963, **85**, 866.

From the results we can suggest an explanation for this phenomenon at least for the weakly polar solvents in which the Wheland type para-intermediates are but little solvated. In these phenol can react via a cyclic six-membered transition state.[9] Also, since the break-ing of the O–H and Br–Br bonds are both rate deter-mining,[27] there is mutual assistance in breaking these bonds in the dienone (II), i.e. the OH proton acts as an electrophile on the negatively polarized end of the bonded halogen molecule which in turn acts as a nucleo-phile on the OH proton as predicted by the theory of the halogenation of benzene derivatives in weakly polar solvents.[28]

In conclusion while some aspects of the suggested mechanism are not fully understood, the importance of hydracids and the solvent in favouring ortho-substitution of phenols, permit a simple solution to the problem of directive effects in the bromination of the phenols and avoids the use of more complex reactions.

EXPERIMENTAL

Materials.—Phenol, 2,4,6-trimethylphenol, and cyclo-hexene oxide were redistilled commercial samples. The solvents were purified by standard procedures.

Bromination of Phenol.—The conditions for the bromin-ation of phenol with bromine are reported in Table 1. The isomer composition obtained for various conditions was determined directly from the reaction mixture by g.l.c., using a 6 ft column packed with silicone SE 30 on Chromo-sorb AW DMCS 60—80. A calibration curve of peak height against composition was constructed by using mixtures of authentic o- and p-bromophenol. Only peaks due to monobrominated products are present in chromato-grams of reactions performed in the presence of epoxide together with peaks for unchanged epoxide and cyclo-hexane bromohydrin. The yields of isolated monobromo-phenols determined by preparative t.l.c. on silica gel (eluant chloroform) were >95%. The composition of product mixtures does not change with time.

Bromination of Phenol with BrCl.—To phenol (2 g, 1 mol. equiv.) dissolved in dry CCl₄ (100 ml) was added during 30 min a solution of BrCl (50 ml, 1 mol. equiv.), obtained by mixing immediately before use 0·5 and 0·44 mol of bromine and liquefied chlorine respectively, with stirring at 25° in CCl₄. G.l.c. analysis showed for this solution peaks due only to o- (58) and p-bromophenol (42%).

Bromination of 2,4,6-Trimethylphenol.—(a) *In acetic acid.* To the phenol (2 g, 1 mol. equiv.) dissolved in glacial acetic acid (30 ml) containing anhydrous sodium acetate (1·81 g, 1·5 mol. equiv.) was added dropwise with stirring at room temperature bromine (0·75 ml, 1 mol. equiv.) in glacial acetic acid (20 ml). This solution was poured into ice–water and extracted with hexane (30 ml). The washed and

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[26] W. A. Waters, *Trans. Faraday Soc.*, 1941, **37**, 745; *J. Chem. Soc.*, 1948, 722.

[27] P. B. D. de la Mare, O. M. H. El Dusouqui, J. G. Tillett, and N. Zeltner, *J. Chem. Soc.*, 1964, 5306; P. B. D. de la Mare and O. M. H. El Dusouqui. *J. Chem. Soc. (B)*, 1967, 251.

[28] L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.*, 1957, **86**, 5169, and references therein.

dried hexane solution was stored in a refrigerator overnight to give crystals of 4-bromo-2,4,6-trimethylcyclohexa-2,5-dienone, m.p. 27—30° (lit.,[28] 27—28°), $\lambda_{max.}$ (CCl$_4$) 265 nm, $\nu_{max.}$ (CCl$_4$) 1640 and 1670 cm^{-1}.

(b) *In* CCl$_4$. The phenol, bromine (0·047M each), and cyclohexene oxide (0·07M) were dissolved in dry CCl$_4$ (30 ml) at room temperature. After 10 min the i.r. spectrum of the solution showed bands at 1640 and 1670 cm^{-1} and the u.v. spectrum showed two bands at 347 and 265 nm. The band at higher wavelength is due [14,20] to 6-bromo-2,4,6-trimethylcyclohexa-2,5-dienone. The intensity of this band decreased with time with a corresponding increase in the band at 265 nm due to the p-dienone derivative. The rearrangement was very fast if traces of gaseous HBr were added. Several attempts to isolate the o-dienone failed, and even after very fast evaporation of the solvent, the oily residue obtained rapidly decomposes.