Orientation in the Chlorination of Phenol and of Anisole with Sodium and t-Butyl Hypochlorites in Various Solvents

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The effects of several factors on orientation in the chlorination of phenol and of anisole have been studied. The *ortho/para* ratio in the chlorination of phenol with aqueous NaOCl increases with increasing pH (0.64 at pH 4.0 and 4.3 at pH 10.0), whereas the ratio in the chlorination of anisole is almost constant (0.63—0.66) at pH 4.0—10.0. In chlorination with t-butyl hypochlorite, phenol gives an *ortho/para* ratio of 0.61 in methanol and 0.20 in acetonitrile, whereas anhydrous sodium phenoxide gives 1.23 in methanol and 2.54 in acetonitrile. The chlorination temperature and the concentration of phenol in hydroxylic solvents have virtually no effect on the *ortho/para* ratio. On the basis of these observations and literature information, the mechanism of reaction is discussed.

The chlorination of phenols can be performed with a variety of chlorinating agents such as Cl_2, Cl_2O, SO_2Cl_2, NaOCl, Bu^tOCl, *etc.* The *ortho/para* ratio is largely dependent on the chlorinating agents and the conditions. For example, the chlorination of phenol with Cl_2 in CCl_4 gives an *ortho/para* ratio of 2.85, whereas a similar reaction with Bu^tOCl in CCl_4 gives an *ortho/para* ratio of 1.04;[1] the ratio also depends on the concentration of phenol.[2] However, only a few studies on the factors influencing orientation have been reported. We have examined the effects of pH, solvent, temperature, and concentration on orientation in the chlorination of phenol and of anisole with NaOCl in aqueous buffers and with Bu^tOCl in methanol and acetonitrile, in an attempt to elucidate the chlorination mechanism.

Results and Discussion

Effect of pH of Aqueous Solution.—Phenol is rapidly chlorinated with an equimolar quantity of NaOCl in aqueous solution to give *o*- and *p*-chlorophenols; di- and tri-chlorophenols are formed in the presence of an excess of NaOCl. The chlorination was conducted at various pH values and the compositions of the mixtures of *o*- and *p*-chlorophenols obtained are listed in Table 1(a).

The *o*/*p* ratio increases from 0.64 at pH 4.0 to 4.3 at pH 10.0. The latter value (4.3, *i.e.* 81% *ortho*) is close to that (4.18; 80.7%) reported by Harvey and Norman[1] for aqueous NaOCl. Chlorination in acidic solution was always accompanied by production of brown tarry material, with a resulting decrease in chlorination yield. Treatment of authentic *o*- and *p*-chlorophenol with hypochlorite gave a similar tar, probably by the oxidation with hypochlorite. The rates for this reaction of *o*- and *p*-chlorophenol were similar; thus the *o*/*p* ratio shown in Table 1 is considered to be little affected by the production of this tarry material.

The observed acidity effect may be explained in two ways: (i) by the dissociation of phenol ($PhOH \rightleftharpoons PhO^- + H^+$) ($pK_a$ 9.98 at 20 °C); (ii) by the dissociation of hypochlorous acid ($HOCl \rightleftharpoons OCl^- + H^+$) ($pK_a$ 7.3 at 25 °C). However, the *o*/*p* ratio changes more with pH in the range 8.5—10.0 than in the range 7.0—8.5; thus the dissociation of phenol rather than of HOCl appears to be the factor affecting the *o*/*p* ratio.

Table 1. Effect of pH on the yields of products in the chlorination of phenol and of anisole with aqueous buffered NaOCl at 20 °C[a]

(a) Phenol

pH	o-ClC_6H_4-OH (%)	p-ClC_6H_4-OH (%)	PhOH (%)	$Cl_2C_6H_4$ (%)	*o*/*p*
4.0	8.4	13.2	51.0	3	0.64
7.0	14.0	7.6	50.8	13	1.8
8.5	29.6	10.6	26.6	24	2.8
10.0	50.0	11.6	12.6	17	4.3

(b) Anisole

pH	o-ClC_6H_4OMe (%)	p-ClC_6H_4OMe (%)	PhOMe (%)	*o*/*p*
4.0	33.0	50.1	7.5	0.66
7.0	23.6	37.3	29.0	0.63
10.0	34.3	54.8	1.0	0.63

[a] Initial concentrations: $[substrate]_0 = [NaOCl]_0 = 0.01$M. Analysed by g.l.c. after complete consumption (iodometry) of NaOCl.

Anisole is chlorinated with NaOCl in the same aqueous buffers, but it cannot dissociate to give an anion. It reacts rapidly with aqueous NaOCl at 20 °C to give *o*- and *p*-chlorophenols in a ratio which varies little with pH (0.63—0.66 in the pH range 4.0—10.0) [Table 1(b)]. Thus the orientation in the chlorination of anisole is independent of the acidity of solution; *i.e.* the dissociation of HOCl has no effect. This confirms that the observed pH effect with phenol is caused by the ionisation of PhOH. The phenoxide ion should not be chlorinated by OCl^- because of the high energy of the doubly charged intermediate O^{2-} and electrostatic repulsion between PhO^- and OCl^-.

Chlorination of Anhydrous Sodium Phenoxide with t-Butyl Hypochlorite.—In our preliminary experiments, the observed orientation in chlorination of phenol was not altered when the reagent was changed from NaOCl to Bu^tOCl in aqueous solutions at pH 7 and 11. To avoid the formation of tar and hydrolysis of Bu^tOCl, anhydrous PhONa was prepared and chlorinated with Bu^tOCl in methanol and in acetonitrile.

The results are shown in Table 2 along with the data for the chlorination of undissociated phenol. The chlorination of PhONa in methanol gave an *o*/*p* ratio of 1.23 and that for undissociated PhOH gave an *o*/*p* ratio of 0.54. In acetonitrile, the ratio was 2.54 for PhONa and 0.20 for PhOH. Thus

Table 2. Product composition in the chlorination of phenol and of anhydrous sodium phenoxide with Bu^{t}OCl at 20 °C[a]

Substrate	Solvent	Yields of chlorophenols *ortho* (%)	Yields of chlorophenols *para* (%)	*o*/*p*
PhOH	MeOH	28.9	53.5	0.54
PhONa	MeOH	9.6	7.8	1.23
PhOH	MeCN	12.7	62.5	0.21
PhONa	MeCN	31.2	12.3	2.54

[a] Initial concentrations: $[\text{substrate}]_0 = [\text{Bu}^t\text{OCl}]_0 = 0.01\text{M}$.

Table 3. Solvent effect on *ortho*/*para* ratio for the chlorination of phenol and anisole at 25 °C.[a] Initial concentrations: 0.02M-PhOH, PhOMe, and Bu^{t}OCl

Solvent	*o*/*p* of ClC_6H_4OH	*o*/*p* of ClC_6H_4OMe
MeCN	0.26	0.17
Bu^{t}OH	0.33	0.19
MeOH	0.61	0.36
$HCONMe_2$	0.61	0.10
CCl_4	5.7	0.37
Hexane	6.1	0.32

[a] Analysed by g.l.c. after complete consumption (iodometry) of Bu^{t}OCl.

phenoxide ion directs strongly *ortho*, expecially in acetonitrile which cannot hydrogen bond with PhO^-.

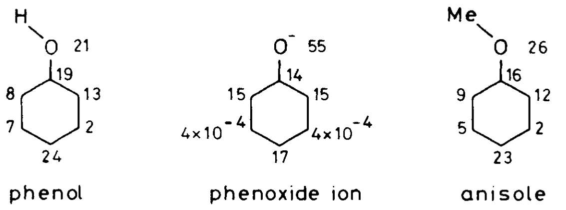
Concentration and Solvent Effects.—The *o*/*p* ratio for the chlorination of phenol with Bu^{t}OCl in CCl_4 decreases with increasing phenol concentration; *e.g.* an *o*/*p* ratio of 3 in 5% CCl_4 solution decreased to 0.64 in neat (molten) phenol.[2] We conducted the chlorination of phenol with Bu^{t}OCl in a variety of dilute solutions. The observed *o*/*p* ratio was high in non-polar solvents, *e.g.* 5.7 in CCl_4 and 6.1 in hexane as shown in Table 3. On the other hand, the chlorination in hydroxylic solvents showed no effect of concentration on orientation; *i.e.* an *o*/*p* ratio of 0.61 in 0.02M- and 0.65 in 1.0M-methanol.

As shown in Table 3, phenol is *ortho*-orienting in non-polar solvents, especially at high dilution, whilst anisole is *para*-orienting, irrespective of the polarity of solvent. These facts imply that undissociated phenol in dilute non-polar solvents is chlorinated mostly (85%) at the *ortho*-position *via* a hydrogen-bonded transition state, while solvated phenol in polar solvents and associated phenol at high concentration tend to favour *para*-chlorination, owing probably to steric hindrance by solvation around the OH group as suggested by Watson[2] and by Campbell.[3] Analogous steric hindrance with hydrogen-bonding solvents resulting in *C*-alkylation rather than *O*-alkylation has been observed in the alkylation of phenol derivatives.[4]

Temperature Effect.—If the orientation were related to the thermodynamic stability of products, it would depend on the temperature; the temperature effect was examined at −20 to 60 °C in methanol using Bu^{t}OCl. The *o*/*p* ratio observed was 0.63, independendent of temperature and therefore of stability of products.

Electron Densities.—Orientation may depend on electron densities of reactive sites in substrates, if steric and solvation effects are negligible. The frontier and π-electron densities of phenol, phenoxide ion, and anisole calculated by the STO-3G molecular orbital method are shown in the Figure.* The frontier electron densities, which are more appropriate, would

(a) Frontier electron densities[a]



(b) π – Electron densities

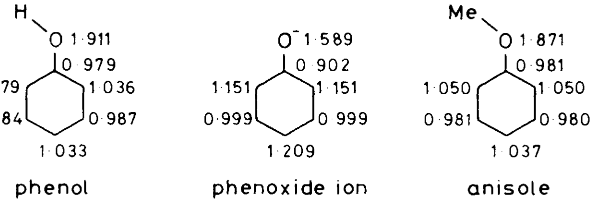
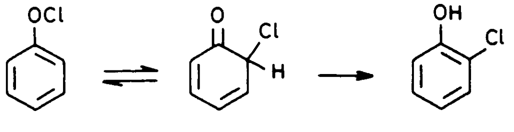


Figure. Frontier and π-electron densities calculated by the STO-3G molecular orbital method

[a] Expressed as (AO-coefft.)^2 × 100.

$$\text{Ph–O}^- + \text{HOCl (or Bu}^t\text{OCl)} \longrightarrow \text{Ph–O–Cl} + \text{HO}^-\text{(or Bu}^t\text{O}^-\text{)} \quad \text{(1)(a}$$



(1)(b)

direct the orientation of electrophilic attack in the order *para* > *ortho* ∼ oxygen ≫ *meta* for phenol, O^- > *ortho* > *para* ≫ *meta* for phenoxide ion, and *para* > *ortho* ≫ *meta* for anisole.

Mechanism.—Thus far two reasons have been considered for the occurrence of the *ortho* preference in phenol halogenation: (a) a hydrogen-bonded transition state involving phenolic OH and halogenation agents;[5] and (b) formation of phenyl hypochlorite (PhOCl) followed by the migration of halogenium ion to the neighbouring *ortho*-position.[6,7]

The scheme involving hydrogen bonding (a)[5] is acceptable for phenol in dilute solutions of non-polar solvents, but is less probable in solvents which associate with the phenolic OH group: there is no apparent reason why the attacking HOCl or Bu^{t}OCl should make preferential hydrogen bonds with the phenolic OH by thrusting the surrounding solvent molecules aside. Also, this mechanism cannot explain our observation that the chlorination of dry PhONa with Bu^{t}OCl, in which no hydrogen bonding is conceivable, gives a high *o*/*p* ratio (>2).

The mechanism involving PhOCl[6] shown in equation (1)(b) is attractive in view of the frontier electron densities; *ie*.. the highest negative charge at O^- would favour attack of electrophilic Cl of HOCl or Bu^{t}OCl. Further, analogous electrophilic substitutions at O or N followed by rearrangement to a ring carbon atom are known in the acylation of phenol *via* a

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* A similar calculation for π-electron densities has been reported and gives similar results: J. A. Pople, W. J. Hehre, and L. Radom, *J. Am. Chem. Soc.*, 1972, **94**, 1496. However, data for PhO^- are unavailable.

phenyl ester,[8] the nitrosation of phenol,[9] the chlorination of aniline,[10] the sulphonation of aniline,[11] the diazo coupling of aniline,[12] *etc*. Some of these intermediates have actually been isolated, and their rearrangement to the *ortho* and *para*-positions observed. 2,4,6-Tribromophenyl hypochlorite has been isolated in the reaction of 2,4,6-tribromophenol with HOCl; here there is no *ortho*-position for the migration of chlorine.[13]

However, we could not confirm the intermediacy of ArOCl from a study of the n.m.r. behaviour of phenol derivatives (*e.g*. 2,4-dibromophenol) towards $\mathrm{Bu^tOCl}$ in CCl_4.

In view of the n.m.r. behaviour and our inability to isolate unsubstituted PhOCl, it is presumably very unstable as in the case of PhOOH, and its concentration should be too low for detection even if it is present. This means that equation (1)(a) is practically irreversible and a study on PhOCl would be difficult at normal temperatures.

Anisole, on the other hand, exhibits the frontier electron density order *para* > *ortho* and has no dissociating or hydrogen-bonding proton. Therefore, it is predominantly chlorinated at the *para*-position irrespective of pH, solvent, and even chlorinating agent.[14]

Experimental

Materials.—Phenol (m.p. 36.0—37.0 °C), *o*-chlorophenol (b.p. 175 °C), and *p*-chlorophenol (m.p. 41.0—42.5 °C) were of reagent grade. t-Butyl hypochlorite was prepared by the normal method.[15] Aqueous sodium hypochlorite was prepared by introducing gaseous chlorine into ice-cooled aqueous 3M-NaOH until iodometry of the solution showed that a *ca*. 1.5M-NaOCl solution had been obtained. The solution can be stored in a refrigerator with little change in concentration for several months. Buffer solutions were prepared by mixing 0.02M-solutions of phosphoric, boric, and acetic acids with an appropriate amount of 0.20M-NaOH (Britton–Robinson buffer solution). Organic solvents used were purified by fractionation.

Analysis.—G.l.c. analyses of phenol and chlorophenols were carried out with a Yanagimoto G 180 gas chromatograph (column packed with 20% Carbowax 20M operating at 160—220 °C with a N_2 flow rate of 15 ml min^{-1} and *p*-cresol as internal standard). Products from anisole were analysed similarly by g.l.c. at 100—150 °C

Chlorination of Phenol with Aqueous NaOCl.—Chlorination of aqueous 10.0mM-phenol (100 ml) was performed in aqueous buffers of pH 4.0—10.0 at 20 °C by adding an equimolar amount of buffered 10mM-NaOCl (100 ml). After the consumption of NaOCl, *p*-cresol was added as an internal standard, and the products were analysed by g.l.c. The concentration effect was examined by analogous chlorinations using 2.0mM- and 50mM-phenol.

Chlorination of Anisole with Aqueous NaOCl.—Chlorination of aqueous 10.0mM-anisole (100 ml) was carried out essentially as for phenol.

Chlorination of Phenol with t-Butyl Hypochlorite.—Chlorination of 10mM-phenol in methanol (100 ml) or acetonitrile (100 ml) was performed at 20 °C by adding equimolar $\mathrm{Bu^tOCl}$. The chlorination was completed (iodometry) after 1 h and the product mixture was analysed. When CCl_4 or hexane was used as the solvent, a longer reaction time (*ca*. 1 day) was necessary for completion of chlorination. The effect of temperature on the chlorination of phenol with $\mathrm{Bu^tOCl}$ in methanol was studied at −20 and 60 °C.

Chlorination of Sodium Phenoxide with $\mathrm{Bu^tOCl}$.—Anhydrous sodium phenoxide was prepared as follows. A methanolic solution (150 ml) of phenol (94 g) was added with stirring to a solution of NaOH (40 g) in methanol–water (17 : 3 v/v; 100 ml) at 20 °C. The solvent was evaporated off, and remaining traces of solvent and free phenol were removed at 80 °C under vacuum (5 mmHg) for 2 h.[1] The product was stirred in a desiccator under $CaCl_2$ and N_2. Anhydrous sodium phenoxide thus obtained was dissolved in methanol or acetonitrile and the 20mM-solution (50 ml) was mixed with an equimolar $\mathrm{Bu^tOCl}$ solution (50 ml) at 20 °C. After completion of the chlorination, the mixture was acidified with aqueous 4M-HCl and concentrated to *ca*. 10 ml. The products were extracted with dichloromethane and analysed by g.l.c. as above.

Chlorination of o- *and* p-*Chlorophenol*.—Aqueous 20mM-*o*- or *p*-chlorophenol was added to 0.5 equiv. of NaOCl in aqueous buffer. Work-up and analysis were as above.

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