BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 39 1961—1967 (1966)

The Oxygen Exchange Reaction of Phenol in Acidic Media[1)]

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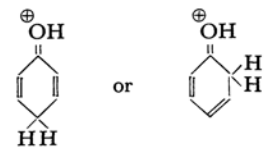
(Received December 15, 1965)

The acid-catalyzed oxygen exchange reaction to a number of phenolic compounds that is, phenol, *o*- *m*- and *p*-hydroxy phenols, α- and β-naphthols, *o*- *m*- and *p*-nitrophenols, *o*- *m*- and *p*-aminophenols, *o*- and *p*-bromophenols, 2, 4, 6-tribromophenol, *o*- *m*- and *p*-cresols and 2, 4, 6-trimethylphenol, plus quinone for comparison with ^{18}O-enriched water was carried out under various conditions. A plot of the log k_x/k_h line against Hammett σ-constants in the substituted phenols gave a fairly good correlation line ($\rho=0.47$) except in the cases of *p*-bromophenol and *p*-aminophenol. The mechanism of these reactions has been discussed.

During the course of our study of the acid-catalyzed hydrolysis of phenyl benzenesulfonate with concentrated hydrochloric acid in ^{18}O-enriched water, we found that the phenol recovered was always incorporated with an excess of ^{18}O and that the amount of ^{18}O incorporation increased with prolonged heating.[2)] We have suggested that, in a strong acidic medium and at a high temperature, such as 180°C, phenol readily accepts a proton at either the *p*- or *o*- position to form a quasi-stable incipient carbonium ion intermediate (A) in which the original hydroxyl function acquires more of a carbonyl character, and hence the oxygen exchange is facilitated.



(A)

Gold and Satchell have proposed that phenolic compounds usually accept one proton at either the *o*- and *p*-position in a strong acidic medium to form the σ-complexes of the corresponding conjugate acids.[3)] Such a σ-complex has been shown by NMR and ultraviolet spectroscopic studies[4)] to exist in an appreciable concentration in the cases of phloroglucinol and its alkyl ethers. However,

1) The Reactions of Phenols and Phenolic Esters, Paper VII
2) a) S. Oae, T. Fukumoto and R. Kiritani, This Bulletin, **36**, 346 (1963); b) S. Oae and R. Kiritani, ibid., **37**, 770 (1964).
3) V. Gold and D. P. N. Satchell., *J. Chem. Soc.*, **1955**, 3619.
4) A. J. Kresge, G. W. Barry, K. R. Charles and Y. Chiany, *J. Am. Chem. Soc.*, **84**, 4343 (1962).

the ultraviolet spectra of phenol itself in concentrated sulfuric acid indicates that the major species is the oxygen-protonated phenol, while the so-called σ-complex is of only minor importance.[5]

Although the equilibrium concentration of such a σ-complex of phenol would be quite low around room temperature, it would definitely be increased at an elevated temperature. Moreover, even though its concentration would be low, the ring protonation is undoubtedly a very facile equilibrium reaction in view of the rapid hydrogen exchange reaction of phenol in strong acidic media; it would also be very important in the present oxygen exchange reaction. The ring protonation at the *o*- and *p*-positions to form the σ-complex causes the hydroxy group to acquire something of a carbonyl character, thus making the subsequent acid-catalyzed oxygen-isotopic exchange with ^{18}O-enriched water very facile. Incidentally, the carbonyl group of ketone or aldehyde is known to undergo very facile oxygen isotopic exchange with that of water in both acidic and alkaline media.[6] The overall picture of the reaction process is quite analogous to that of Bucherer-type reaction of naphthols. Naphthols, known to have something of a carbonyl character, undergo facile nucleophilic replacement reactions. Namely, β-naphthol is known to react with such nucleophilic reagents as sulfurous acid[7] and thioglycolic acid.[8] Here again these reactions are believed to proceed by the attack of the nucleophile at the carbonyl carbon of the quasi keto-form intermediate, formed by the ring protonation at either the *o*- or the *p*-position.

Therefore, the oxygen exchange reaction of phenol can best be understood when one assumes a mechanism involving a prior ring protonation and the subsequent nucleophilic attack of water at the carbonyl carbon. However, this somewhat unfamiliar idea has to be tested with more investigations in view of the fact that, although the hydroxylic proton of phenol has been shown to undergo a very facile D–H exchange in both acidic and alkaline aqueous media,[9] the oxygen exchange of the hydroxyl group with solvent water itself has been believed not to occur, even in a strong acidic medium.

This work was undertaken in order to determine the most suitable reaction conditions of oxygen exchange and in order to clarify the mechanism by examining the effect of the substituent on the rate of oxygen exchange.

Results and Discussion

The oxygen exchange reaction was tested at first under conditions similar to those used for the acid-catalyzed hydrolyses of phenyl benzenesulfonate[2] and *p*-nitrophenyl benzenesulfonate.[10] Phenol and 10 N hydrochloric acid, prepared by dissolving hydrogen chloride gas in ^{18}O-enriched water, were sealed in a glass tube, and the tube was heated under the conditions listed in Table I. The same procedure was also used for the solution 4.8 N hydrochloric acid. In a separate experiment, a mixture containing the same reactants was refluxed. The products, labeled phenols, were then recovered and subjected to ^{18}O analysis by the usual method.[11] The reaction conditions and the results are shown in Table I.

The phenols recovered were always incorporated with an excess of ^{18}O when the exchange reactions were carried out at 180°C in a sealed tube, the amount of ^{18}O incorporation increasing with an increase in the duration of heating. Since the reaction conditions used in this work were rather drastic, one might expect some possible rearrangement products from the phenols used. However, it was found that all the phenols used in this work, except for the isomeric nitrophenols, were recovered in almost quantitative yields. The purities of these recovered phenols were checked by infrared, ultraviolet and gas chromatographic analyses, and by the fractional recrystallization of the ester derived from the phenols, no rearranged phenol was detected from any of the phenols applied. Even in the case of the isomeric nitrophenols, where some severe decompositions were observed, the recovered phenols were identical to the starting phenols, although the yields of the recovered phenols were low. The change in the concentration of hydrochloric acid from 10 N to 4.8 N did not affect the extent of ^{18}O incorporation. However, both at 110°C in a sealed tube and under a reflux, no oxygen exchange was observed, even after 24 hr. These results can be explained by assuming either an increased concentration of the intermediate (A) at high temperatures, or an increased rate of the nucleophilic attack of water, or both.

The contribution of the quinoid structure A would be greater for the oxygen exchange of β-naphthol and related compounds than for that of phenol. Therefore, the oxygen exchange reactions of catechol, resorcinol, hydroquinone, quinone and both α- and β-naphthols were next investigated. The procedures for the preparation of the reaction mixtures and the reaction conditions were similar

5) E. M. Arnett and C. Y. Wu, ibid., **82**, 5660 (1960).
6) a) M. Cohn and H. C. Urey, ibid., **60**, 679 (1938); b) J. N. E. Day, *Science Progress*, **34**, 47 (1939).
7) See the Bucherer Reaction in "Organic Reaction," Vol. I, John Wiley & Sons, New York, N. Y. (1942), p. 105.
8) F. M. Furman, J. H. Thelin, D. W. Hein and W. B. Hardy, *J. Am. Chem. Soc.*, **82**, 1450 (1960).
9) a) C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, **1936**, 1637; b) M. Koizumi and T. Titani, This Bulletin, **13**, 681 (1938); c) M. Koizumi, ibid., **14**, 353 (1939).
10) S. Oae and R. Kiritani, ibid., **38**, 765 (1965).
11) S. Oae, T. Kitao and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3359 (1962).

Table I. Oxygen exchange reaction of phenol

Reaction condition			^{18}O Atom% of		Exchange %
Concn. of HCl N	Time hr.	Temp. °C	Eq. HCl soln.	Recovered product	
10	3	180	0.77	0.33	22.8
10	5	180	0.8	0.37	28.3
10	12	180	0.77	0.55	61.4
10	24	180	0.77	0.73	93.0
4.8	6	180	0.77	0.39	33.3
10	6	110	0.77	0.20	0
10	24	110	0.77	0.21	0
10	6	Reflux	0.77	0.20	0

Table II. Oxygen exchange reaction of related phenols

Compound	Reaction condition		^{18}O Atom % of		Exchange %
	Time hr.	Temp. °C	Eq. 10 N soln.	Product	
Hydroxy phenols					
o-	6	180	0.74	0.37	31.5
	24	110	0.74	0.21	0
m-	6	180	0.77	0.53	57.9
	24	110	1.5	0.59	30.0
p-	6	180	0.74	0.50	55.6
	24	110	1.58	0.43	16.7
Quinone	6	180	0.74	0.52	59.3
	24	180	0.74	0.62	77.8
	24	110	1.5	0.58	29.2
Naphthols					
α-	6	180	0.77	0.54	59.7
	24	180	0.74	0.53	61.1
	24	110	1.5	0.74	41.5
β-	6	180	0.77	0.56	63.2
	24	180	0.74	0.56	66.7
	24	110	0.77	0.40	35.1

to those described in connection with the oxygen exchange of phenol (Table I). The results are shown in Table II.

Unlike the cases of monobasic phenols, the oxygen exchange of dibasic phenol listed in Table II took place not only at 180°C, but also at 110°C, except for the case of *o*-hydroxyphenol (catechol). The very facile oxygen exchange of both α- and β-naphthols is evident from their higher amounts of oxygen exchange, about 40%, even at 110°C. Here, the mechanism involving the quasi-quinoid intermediates appears to fit the experimental observations. It is interesting to note that the amount of ^{18}O incorporation was higher with resorcinol than those of the other *o*- and *p*-isomers. The same trend was observed in the cases of isomeric aminophenols.

We next carried out a series of experiments in the hope of obtaining more concrete information on the nature of this exchange reaction through comparing the substituent effects on the oxygen exchanges. This exchange reaction is considered to fall in the category of aromatic nucleophilic displacement reactions; it is also considered generally that the rate-determining step would be the addition of solvent water to the phenolic carbon. An important question is whether or not the quinoid structure A described before is well developed before the rate-determining step. If the hydroxyl group acquires a distinct carbonyl character before the actual oxygen-exchange reaction, the substituent effect represented by Hammett σ-values should nicely fit, just as in the cases of nucleophilic attack on a carbonyl carbon.

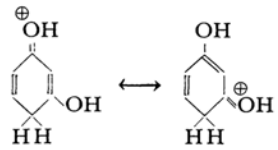
A similar substituent effect would be expected when the quinoid structure makes no contribution, with little assistance of ring protonation, and when the reaction proceeds directly through the nucleophilic attack on the aromatic carbon. However, in the latter case a strong electron-withdrawing substituent, such as the nitro group, would facilitate the exchange, especially by resonance, more than what may be expected from the σ- constant, and the substituent effect would be better expressed by σ^--constants. Furthermore, an important difference would be expected between the effects of *m*- and either the *o*- or *p*-OH and the NH_2 group. Ring protonation to form the quinoid structures would be favored for *m*-OH and *m*-NH_2 phenols because of the contribution of the following

TABLE III. OXYGEN EXCHANGE REACTION OF SUBSTITUTED PHENOLS

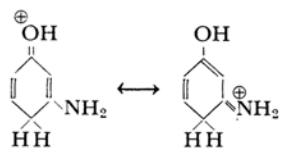
Compound	Reaction condition Time, hr.	^{18}O Atom % of Eq. HCl soln.	^{18}O Atom % of Product	Exchange %
Nitrophenols				
o-	6	1.58	0.21	0
	24	1.58	0.21	0
m-	6	1.58	0.23 (0.30)	7.2
	24	1.58	0.24 (0.32)	8.7
p-	6	1.58	0.40 (0.80)	43.5
	24	1.58	0.37 (0.72)	37.7
Nitrobenzene	24	1.58	0.20	0
Aminophenols				
o-	6	0.74	0.21	0
	24	0.74	0.22	0
m-	6	0.74	0.41	38.9
	24	0.74	0.42	40.0
p-	6	0.74	0.24	7.4
	24	0.74	0.27	13.0
Bromophenols				
o-	6	0.74	0.32	22.2
	24	0.74	0.42	40.7
p-	6	0.77	0.30	17.5
	24	0.77	0.45	43.9
2,4,6-Tri-	6	0.77	0.21	0
	24	0.77	0.21	0
Cresols				
o-	6	0.77	0.26	10.5
	24	0.77	0.38	31.6
m-	6	0.77	0.30	17.5
	24	0.77	0.45	43.9
p-	6	0.77	0.26	10.5
	24	0.77	0.45	43.9
2,4,6-Tri-	6	0.77	0.22	0
	24	0.77	0.24	7.4

Reaction temp. 180°C.

Numerical values in parentheses represent the ^{18}O concentration of phenolic oxygen calculated from the concentration of whole molecule by neglecting the ^{18}O exchange of nitro group.



IIa IIb



IIIa IIIb

resonance structures (IIa, IIb, IIIa, IIIb). Such a stabilization of quinoid structure is not expected for the corresponding *o*- and *p*-isomers. On the other hand, amino phenol is considered to be equilibrating with its *N*-protonated conjugate acid, and the *p*-ammonio group would strongly hinder the protonation at the same *p*-position, while the *m*-ammonio group would not much obstruct the protonation to the hydroxyl group at either the *o*- or the *p*-position. Both free amino and ammonio groups which are equilibrating thus favor the quinoid structure for the *m*-isomer much more than for the *p*-isomer. The same conclusions may be drawn for the hydroxyl group.

The results of the oxygen exchange reactions of isomeric nitrophenols, aminophenols, bromophenols and cresols are shown in Table III. The oxygen exchanges for cresol and bromophenol were the same or slightly less than that for unsubstituted phenol. Marked differences were observed for isomeric amino and nitro phenols. *p*-Nitrophenol showed an unusually high extent of oxygen exchange as compared to its *o*- and *m*-isomers, whereas the oxygen exchange of *m*-aminophenol was far greater than those of the *o*- and *p*-isomers. The same trend as in aminophenols, although less marked was observed for hydroxyphenols (Table II). Another remarkable observation is that practically no oxygen exchange takes place for *o*-isomers of amino-, hydroxy- and nitrophenol. Steric hindrance alone cannot explain such results, since the oxygen exchange was observed for *o*-cresol and *o*-bromophenols, although such exchange was smaller

than in the corresponding *m*- and *p*-isomers. Another responsible factor for the remarkable retardation of the ^{18}O exchange would be the intramolecular hydrogen bondings, which are expected for the former three phenols and which would stabilize the ground states much more than the transition states of the former three phenols.

Competitive Reaction—As is indicated in the runs of *p*-nitrophenol in Table III, the percentage of oxygen exchange was greater here despite the shorter reaction time. Since the reaction temperature was high and since the reactions were carried out in a sealed tube in an electric furnace, it was difficult to maintain the same reaction conditions. Therefore, we have carried out competitive reactions in order to eliminate other complicating factors and obtain at least a semi-quantitative measure of the relative reactivities of the isomeric phenols.

The reaction conditions and the procedures were essentially the same as those described above. A mixture of equimolar amounts of the unsubstituted reference phenol and a substituted phenol was sealed with a large excess of ^{18}O-enriched 10 N hydrochloric acid. The reaction products were then separated into phenol and substituted phenol by a combination of distillation, recrystallization and gas chromatography. The relative reactivity, k_x/k_h, was calculated using Eq. 3:

$$\frac{dX_t}{dt} k_x(X_\infty - X_t) \quad [H_2{}^{18}O] \tag{1}$$

$$\frac{dh_t}{dt} k_h(X_\infty - h_t) \quad [H_2{}^{18}O] \tag{2}$$

$$k_x/k_h = \log \frac{(X_\infty - X_0)}{(X_\infty - X_t)} \Big/ \log \frac{(X_\infty - h_0)}{(X_\infty - h_t)} \tag{3}$$

X_∞ : Calculated ^{18}O-atom% of the reaction mixture at equilibrium

X_t : Observed ^{18}O-atom% of the substituted phenol at the time *t*.

h_t : Observed ^{18}O-atom% of the unsubstituted phenol at the time *t*.

X_0 : Initial ^{18}O-atom% of substituted phenol ($t=0$).

h_0 : Initial ^{18}O-atom% of unsubstituted phenol ($t=0$).

Since Eq. 3 is derived from Eqs. 1 and 2, neglecting the reverse reaction, the k_x/k_h value depends on the extent of oxygen exchange; for more precise values, extrapolation to zero-time values is desirable. For a more precise ^{18}O-analysis, it is desirable that the atom % of the ^{18}O-enriched water be as high as possible. However, we had access to ^{18}O-enriched water of only 1.5% ^{18}O enrichment in the present work. Therefore, the values of k_x/k_h are unavoidably crude. In spite of these limitations, the two values of k_x/k_h for each isomer at different times were close to each other and, hence, may be used as reactivity measures of the isomeric phenols. The trends in Table IV are similar to those found in Table III. *m*-Aminophenol and *p*-nitrophenol are about three times more reactive than unsubstituted phenol. Methyl and bromo-substituents slightly decrease the reactivity, while *p*-aminophenol again shows an unusually low reactivity.

A plot of log k_x/k_h against Hammett σ-constants did not give a good correlation curve for isomeric methyl, bromo and *p*-nitro groups. Since aminophenol is considered to be an equilibrium mixture of free amino and ammonio species, it is difficult to assign any substituent constant to this group.

Table IV. Competitive reaction of phenol with related phenols

Compound	mol. $\times 10^{-3}$	Reaction time hr.	^{18}O Atom % X_∞	h_t	X_t	k_x/k_h	log k_x/k_h
Aminophenol	7.33		1.533				
m-		4		0.50	0.87	2.760	0.441
		4		0.647	1.139	2.999	0.477
p-		7		0.816	0.395	0.268	−0.572
		8		0.786	0.497	0.250	−0.602
Nitrophenol	5.75		1.537				
p-		4		0.617	1.197	3.928	0.594
Cresol	7.39		1.532				
o-		4		0.440	0.272	0.569	
		8		0.783	0.319	0.308	
m-		4		0.619	0.606	0.971	−0.013
		8		0.726	0.66	0.869	−0.061
p-		4		0.462	0.416	0.879	−0.056
		8		0.583	0.565	0.959	−0.018
Bromophenol	4.62		1.540				
o-		8		0.545	0.491	0.874	
		24		1.074	0.931	0.733	
		25		0.936	0.848	0.835	
p-		8		0.578	0.532	0.896	−0.048

X_∞: ^{18}O Atom % of each compound when exchange reaction was taken place completely.

However, if the substituent constant of the trimethyl ammonio group, 0.904 for m-$\overset{\oplus}{N}(CH_3)_3$, is taken as the constant for m-$\overset{\oplus}{N}H_3$, and if $\sigma_p^-(=1.27)$ is used for p-nitrophenol, a fairly good correlation line ($\rho=0.47$) is obtained, as is shown in Fig. 1, although p-nitrophenol, p-bromophenol and, especially, p-aminophenol still greatly deviate from this line.

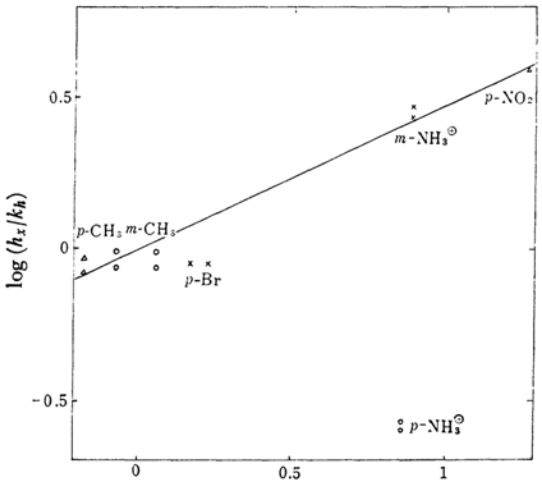
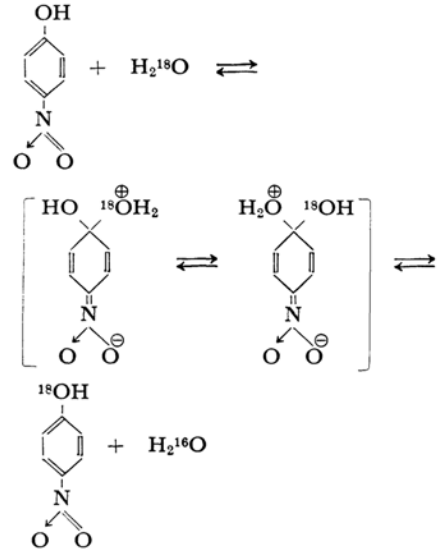


Fig. 1

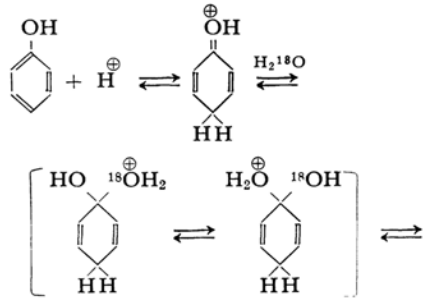
A self-consistent explanation of all the above results is not easy. However, there are a few points of interest worthy of attention. The ρ value was found to be substantially smaller than that expected from ordinary aromatic nucleophilic substitutions. We believe that it is by no means a ρ value for a simple aromatic nucleophilic substitution, but a value that results from two succesive reactions with two different ρ values opposite in sign, i. e., the prior equilibrium reaction of protonation and the subsequent aromatic nucleophilic reaction. The small ρ value with a positive sign may indicate that the electronic effect of the substituent operates more at the second step, namely, the aromatic nucleophilic substitution, than at the prior protonation equilibrium reaction. The correlation of the reactivity of p-nitrophenol by the σ^--constant seems to indicate that the mechanism of the oxygen exchange of this phenol is different from those of the other phenols, as has been discussed before, the ring protonation to form the intermediate of the quinoid structure is not necessary, and the reaction may well proceed through direct nucleophilic displacement due to the strong electron-withdrawing ability of the p-nitro group (Eq. 4). This is consistent with our previous observations that the acid-catalyzed hydrolysis of p-nitrophenyl benzenesulfonate under strong acidic conditions proceeds partly through the fission of the phenolic C–O bond, while the hydrolysis of the unsubstituted phenyl benzenesulfonate proceeds by the fission of the S–O bond and practically no phenolic C–O bond fission was detected. The mechanism of the oxygen exchange of the other isomers seems to be better explained by assuming the quinoid structure A as the pre-equilibrium species which participates in the rate-determining step.

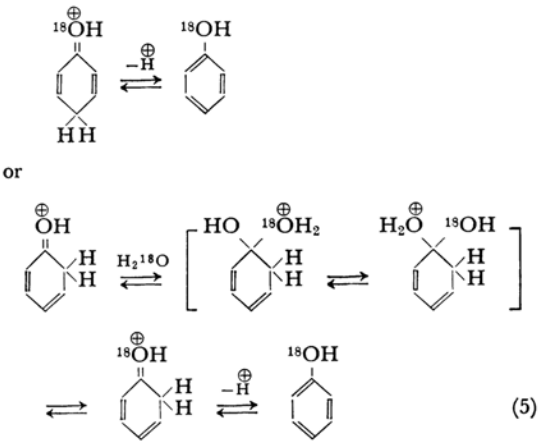


(4)

Only this mechanisms seems capable of explaining the large rate differences between p- and m-aminophenol presented before, irrespective of whether the contributing species is a free amino group or a protonated ammonio group. The usual unreactivity of p-aminophenol is undoubtedly due to the low concentration of the incipient quinoid intermediate A formed in the unfavored equilibrium of protonation, because the electron-withdrawing inductive effect of the ammonium group serves to deactivate the benzene ring for an electrophilic attack. The decreased reactivity of bromophenols is probably also due to the decreased concentration of the incipient intermediate A formed in the pre-equilibrium protonation, since the bromo group is known to deactivate the benzene ring for an electrophilic attack due to its strong electron-withdrawing inductive effect.

In conclusion, the mechanism involving the quinoid intermediate may be summarized as in Eq. 5:





or

(5)

Experimental

The Oxygen Exchange Reaction of Substituted Phenols.—a) In a sealed tube, in 10 N hydrochloric acid: A phenol (1 g.) and 5 ml. of ^{18}O-enriched aqueous 10 N hydrochloric acid were sealed in a tube and heated at 110°C or 180°C for a suitable time. Then the sealed tube was broken, and all the contents except resorcinol, quinone and aminophenols were extracted with ether. The ether layer was dried over calcium chloride and concentrated, and the residue was treated in the following manner: Phenol was purified by distillation under reduced pressure or by reaction with bromine to give 2, 4, 6-tribromophenol, m. p. 96°C; catechol was recrystallized from alcohol, m. p. 105°C; hydroquinone was recrystallized from alcohol, m. p. 170—171°C; α-naphthol was purified by sublimation, m. p. 96°C; β-naphthol was purified by sublimation, m. p. 122—123°C; nitrophenols were purified by recrystallization or sublimation—*o*-nitrophenol (m. p. 44—45°C), *m*-nitrophenol (m. p. 97°C) and *p*-nitrophenol (m. p. 113—114°C); bromophenols were purified by distillation—*o*-bromophenol (b. p. 194°C) and *p*-bromophenol (b. p. 238°C, 92°C/24 mmHg); 2, 4, 6-tribromophenol was purified by sublimation, m. p. 96°C; and 2, 4, 6-trimethylphenol was recrystallized from ethanol, m. p. 75°C. Both resorcinol and quinone, after they had been subjected to the ^{18}O exchange experiments, were separated from the sealed tubes and collected by filtration. Resorcinol was purified by sublimation (m. p. 110—111°C), while quinone was recrystallized from alcohol, m. p. 115°C.

The aminophenols which separated as hydrochloride after the evaporation of the water from the reaction mixture were collected and recrystallized from water. The ammonium salts were neutralized with aqueous sodium hydroxide, and the free aminophenols which precipitated were filtered and recrystallized from ethanol—*o*-aminophenol (m. p. 170—174°C), *m*-aminophenol (m. p. 122—123°C) and *p*-aminophenol (m. p. 188°C). The reaction mixtures for isomeric cresols were separated into two layers. The upper, oily layer was distilled under reduced pressure, thus producing *o*-cresol (b. p. 191—192°C), *m*-cresol (b. p. 202°C) and *p*-cresol (b. p. 202°C).

Other Conditions for the ^{18}O Exchange.—b) In 4.8 N hydrochloric acid: The procedures were the same as in a).

c) Under reflux: The same reaction mixture of phenol and 10 N hydrochloric acid as was used in the above experiments was placed in a 20 ml. flask and refluxed for 6 hr. The procedure of the separation of phenol was the same as that described above.

All the results described in above (a), b) and c)) are shown in Tables, I, II and III.

When nitrobenzene was treated by the same procedure as in the reaction of nitrophenols, it was verified that the oxygen exchange of the nitro group did not take place.

Competitive Reactions.—a) Aminophenol: Phenol (0.800 g. (8.5×10^{-3} mol.)), *m*- or *p*-aminophenol (0.800 g. (7.33×10^{-3} mol.)) and 10 N hydrochloric acid containing excess ^{18}O (8.000 g. (0.444 mol.)) were sealed in a tube. The sealed tubes were then heated at 180°C for 4, 7 or 8 hr. The entire contents were extracted with ether and treated as above. Phenol was obtained from the ether layer, and aminophenol, from the aqueous layer.

b) *p*-Nitrophenol: Phenol (0.800 g. (8.5×10^{-3} mol.)), *p*-nitrophenol (0.800 g. (5.75×10^{-3} mol.)) and 10 N hydrochloric acid containing excess ^{18}O (8.000 g. (0.444 mol.)) were sealed in a tube. The sealed tubes were then heated at 180°C for 2 or 4 hr. The entire contents were extracted with ether, and the ether layer was dried over calcium chloride. The ether extract was then put into a sublimation apparatus to which a trap cooled with dry ice - acetone had been joined. When the sublimation apparatus was heated in vacuo, purified *p*-nitrophenol in the sublimation apparatus and phenol in the trap were simultaneously obtained.

c) Cresol: Phenol (0.800 g. (8.5×10^{-3} mol.), *o*- *m*- or *p*-cresol (0.800 g. (7.39×10^{-3} mol.)) and 10 N hydrochloric acid containing excess ^{18}O (8.000 g. (0.444 mol.)) were sealed in a tube. The sealed tubes were then heated at 180°C for 4 or 8 hr. The entire contents were extracted with ether, and the ether extracts were distilled. The distilled mixture was then separated to phenol and cresol by gas chromatography, using a 2 m. column of silicone 550, with nitrogen as the carrier gas (10—13 cc./min.), with a temperature of 160°C, and with a sensibility of 1.

d) Bromophenol: Phenol (0.800 g. (8.5×10^{-3} mol.)), *o*- or *p*-bromophenol (0.800 g. (4.62×10^{-3} mol.)) and 10 N hydrochloric acid containing excess ^{18}O (8.000 g. (0.444 mol.)) were sealed in a tube. The sealed tubes were then heated at 180°C for 8, 24 or 25 hr., and the entire contents were treated by the same procedure as was used for cresol.

All the phenols thus separated were subjected to ^{18}O analysis, and the k_x/k_h value was calculated according to Eqs. 1—3.