The Nucleophilic Replacement of the Phenolic Hydroxy Group by the Mercapto Group in Acidic Media*

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During our study of the acid-catalyzed hydrolysis of phenyl benzenesulfonate with concentrated hydrochloric acid in ^{18}O-enriched water, we have found that the phenol recovered is always incorporated with an excess of ^{18}O when the hydrolysis is carried out at 180°C in a sealed tube, and also that the amount of ^{18}O incorporation increases as the heating prolonged.[1] Even in the case of *p*-nitrophenyl benzenesulfonate, it has been shown that the *p*-nitrophenol recovered is incorporated with an excess of ^{18}O only at the phenolic oxygen.[2]

We have suggested that, in a strong acidic medium, phenol readily accepts a proton at either the ortho- or para-position, thus forming a quasi-stable incipient carbonium ion intermediate in which the original hydroxyl function acquires more of a carbonyl character and, hence, facilitates the oxygen exchange with ^{18}O-enriched water.[1,3]

Meanwhile, it has been known that carbonyl group of either ketone or aldehyde undergoes a very facile oxygen isotopic exchange in both acidic and alkaline aqueous media.[4] Therefore, it is not very surprising that a phenolic hydroxy group undergoes a nucleophilic replacement with ^{18}O-enriched water, when the phenolic hydroxy group acquires a rather carbonyl character. In fact, β-naphthol, which is known to have some carbonyl character, has been known to react with nucleophilic reagents, such as sulfurous acid[5] and thioglycolic acid,[6] to replace the phenolic hydroxyl group and form β-naphthyl sulfonic acid and thioglycolic acid respectively.

If the oxygen isotopic exchange of the phenolic hydroxy group in acidic media takes place by means of the nucleophilic attack of the water molecule, phenols in general would react better with other nucleophiles, such as alcohols and mercaptans, under the same conditions as those in which the oxygen exchange takes place. Indeed, we have isolated the corresponding ethers or sulfides by adding alcohols or mercaptans to the reaction mixture of phenol with hydrochloric acid and heating the mixtures at 180°C for a few days in a sealed tube.

The present work was designed to investigate in detail the nature of the reaction by which sulfides are formed from mercaptans and phenols in the presence of a strong acid.

Results and Discussion

We have proposed that the acid-catalyzed oxygen exchange reaction of phenol above 180°C in a sealed tube proceeds through the "quasi-stable quinoid intermediate"[1] with a proton attached to either the ortho- or para-position, and that the quinoid intermediate, which has a substantially long life, is attacked by water molecule on the quasi-carbonyl carbon in the succeeding step, thus causing the remarkable oxygen isotopic exchange. The essential feature of this mechanism is identical to that of any of the known nucleophilic replacements involving a carbonyl carbon. Therefore, one would expect that other nucleophiles would also undergo similar nucleophilic replacements.

Our first choice of nucleophilic reagents were mercaptans, since the thiol group has been known to be strong nucleophiles and quite stable in strong acidic media. Accordingly, under the conditions in which the oxygen isotopic exchange takes place, thiol may be expected to replace the phenolic hydroxy group. The results of rough kinetic experiments of the phenolic oxygen exchange carried out in strong acidic media enriched with ^{18}O-water are shown in Table I.

Phenol was then heated in sealed tubes at 180°C and 110°C with various mercaptans for a long time in the presence of hydrochloric acid. Indeed, when heated at 180°C for some hours, at which the oxygen exchange occurs, and the mercaptans, i. e., *n*-butylmercaptan,

* Reactions of Phenols and Phenolic Esters. VI., previous papers, D. R. Christman and S. Oae, *Chem. & Ind.*, 1959, 1251 and Refs. 1, 2 and 3.

1) S. Oae, T. Fukumoto and R. Kiritani, This Bulletin, 36, 346 (1963).

2) S. Oae and R. Kiritani, ibid., 38, 765 (1965).

3) S. Oae and R. Kiritani, ibid., 37, 770 (1964).

4) a) M. Cohn and H. C. Urey, *J. Am. Chem. Soc.*, 60, 679 (1938); b) J. N. E. Day, *Science Progress*, 34, 47 (1939).

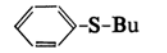
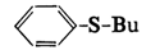
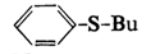
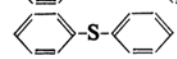
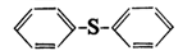
5) See Bucherer Reaction in "Organic Reaction," Vol. I, John Wiley & Sons, New York (1942), p. 105.

6) F. M. Furman, J. H. Thelin, D. W. Hein and W. B. Hardy, *J. Am. Chem. Soc.*, 82, 1450 (1960).

TABLE I. OXYGEN EXCHANGE REACTION OF PHENOL IN 10 N HYDROCHLORIC ACID

Reaction condition		^{18}O Atom. % of		Exchange
Time, hr.	Temp., °C	aq. HCl soln.	Product	%
5	180 in a sealed tube	0.8	0.37	28.3
12	180 in a sealed tube	0.77	0.55	61.4
24	180 in a sealed tube	0.77	0.73	93.0
24	110 in a sealed tube	0.77	0.21	0
6	Reflux	0.77	0.20	0

TABLE II. THE REACTION OF PHENOL WITH MERCAPTAN

Reactant	Reaction condition			Product	
Mercaptan	Mole ratio*	Time, hr.	Temp., °C	Sulfide	Yield, %
n-Butylmercaptan	a	48	180		31
	b	48	180		22.0
	b	24	180		Trace
	a	48	110	None	None
	a	48	Reflux	None	None
Benzylmercaptan	a	48	180		43.4
Thiophenol	a	72	180		26.7
	a	119	180		32.2

* Mole ratio; phenol: mercaptan, a; 1:5, b; 1:1.

benzylmercaptan and thiophenol, were all found to react with phenol and to give the corresponding sulfides; on the other hand, no reaction took place under milder conditions, such as heating at 110°C, at which no oxygen exchange occurs. The phenyl sulfides obtained are shown in Table II, together with the yields.

When the three marcaptans were allowed to react with phenol at 180°C, the corresponding sulfides were obtained in considerable yields. The yields of sulfides increased with prolonged heating. It appears that the ease of sulfide formation is also related to the nucleophilicity of the mercaptan used. The *n*-butyl phenyl sulfide was identified by comparing it with an authentic sample, while the other sulfides were identified on the basis of their elemental analyses and their infrared spectra. The reaction appears to involve the attack of the thiol group on the 1-carbon of phenol, which is presumably protonated at either the ortho- or the para-position. This is analogous to the mechanism suggested for the acid-catalyzed phenolic oxygen exchange reaction involving nucleophilic substitution at the C-1 position, as is shown in Fig. 1.

Meanwhile, one may postulate another alternative pathway, i.e., one that involves the nucleophilic addition of the thiol group at one of the ortho-positions or at the para-position

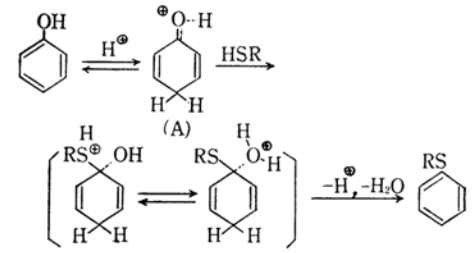


Fig. 1.

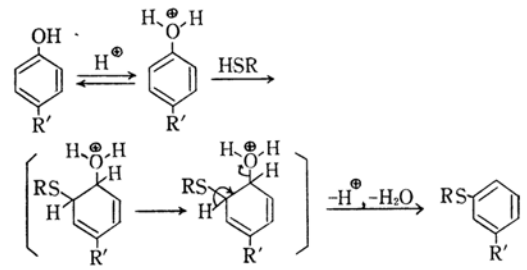


Fig. 2.

of phenol, followed by the elimination of water, as is shown below (in Fig. 2).

Recently Mc. Arnett and Wu,[7] in their study of the pK_a's of the oxonium ions of phenol

7) E. Mc. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, **82**, 5660 (1960).

Table III. Oxygen exchange reaction of cresols

Compound	Reaction time hr.	^{18}O Atom. % of aq. HCl soln.	^{18}O Atom. % of Product	Exchange %
o-Cresol	24	0.77	0.37	31.6
m-Cresol	24	0.77	0.45	43.9
p-Cresol	24	0.77	0.45	43.9

and various phenyl ethers under normal conditions, have suggested that the primary site of protonation in the phenolic compound is the oxygen. If this is the case, even at a higher temperature, the oxonium group would induce the nucleophilic attack at either the ortho- or para-position, as in the case of the Bamberger reaction.[8] In this case, one would expect to get a rearranged product. This mechanism was, however, contradicted by the reaction with *p*-substituted phenol. Namely, when *p*-cresol was allowed to react with *n*-butyl mercaptan in the presence of hydrochloric acid at 180°C for 48 hr. in a sealed tube, *p*-tolyl *n*-butyl sulfide was obtained in a 14% yield, while no *m*-tolyl *n*-butyl sulfide was obtained, as Table IV shows. The identification was made by comparing the infrared absorption spectrum with that of an authentic sample of *p*-tolyl *n*-butyl sulfide.

In separate experiments, *o*-, *m*- and *p*-cresols were subjected to the oxygen exchange reaction at 180°C in the same acidic medium, they were found to exchange their respective phenolic oxygen with ^{18}O of the medium, as is shown in Table III.

Here, one finds that the same amount of ^{18}O exchange occurred in both *m*- and *p*-cresols, whereas the amount of ^{18}O exchange of *o*-isomer was a little less, probably due to a small steric hindrance by the *o*-methyl group. These results, together with the formation of the sulfide, strongly suggest that the reaction involves the nucleophilic attack at the phenolic carbon rather than at the ortho-position of phenol.

Another possible path would be the aromatic S_N2-type reaction involving the nucleophilic replacement of the hydroxy group by thiol, as is shown in Fig. 3.

In this case, when the bond-forming is the controlling stage, electron-withdrawing substituents will enhance the reactivity, whereas if the reaction is controlled by the bond-fission stage, electron-releasing substituents will accelerate the reaction. However, in both oxygen exchange reaction and sulfide formation, the substitution of any group at the ring carbon usually retards the reactions. Furthermore, one would anticipate that the reaction would

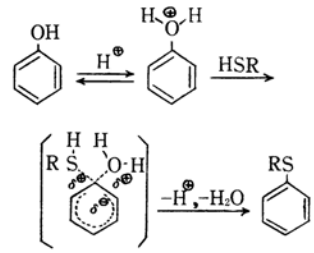


Fig. 3.

be more facile with a better leaving group, such as benzenesulfonate, instead of the hydroxy group. However, neither phenyl benzenesulfonate nor *p*-nitrophenyl benzenesulfonate undergoes any facile hydrolyses, nor do their hydrolyses proceed via Ar-oxygen cleavage, while there was no formation of the sulfides between these compounds and *n*-butyl mercaptan under similar reaction conditions. These results clearly disfavor the aromatic S_N2-type mechanism and favor the first one, since any substituent would destroy the symmetry of the protonated species and decrease the lifetime of the intermediate incipient carbonium ion (A),* thus effecting less change in the nucleophilic attack at the phenolic carbon, which will presumably assume a quasi-carbonyl character; moreover, the replacement of phenolic hydrogen by the benzenesulfonyl group will destroy the phenolic hydroxyl group, which is essential for the nucleophilic replacement via the incipient carbonium ion (A). As a corollary deduction from this mechanism, one may expect a more facile nucleophilic replacement with phenols with a more carbonyl character. In fact, naphthols were found to give naphthyl *n*-butyl sulfides in better yields in the acid-catalyzed reaction with *n*-butyl mercaptan, as Table IV shows.

The formation of β-naphthyl sulfide was noticed earlier by Furman et al.,[6] when β-naphthol was heated at 110—120°C with various mercaptans for 16 hr. in the presence of and also without any solvent. They have also proposed a similar reaction mechanism analogous to the Bucherer reaction involving the

8) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, London (1953).

* Carbonium ion (A):

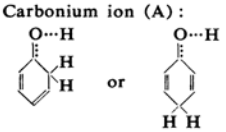
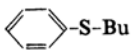
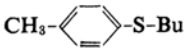
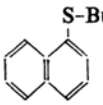
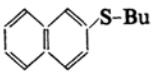


TABLE IV. THE REACTION OF *n*-BUTYLMERCAPTAN WITH *p*-CRESOL, *α*-, *β*-NAPHTHOLS

Reactant Phenol	Reaction condition			Product	
	Mole ratio*	Time, hr.	Temp., °C	Sulfide	Yield, %
Phenol	b	48	180		22.0
p-Cresol	b	48	180		14.0
α-Naphthol	a	52	180		69.5
β-Naphthol	b	48	180		55.4

* Mole ratio; phenol : mercaptan, a; 1 : 5, b; 1 : 1.

attack of the mercaptan on the carbonium ion derived from *β*-naphthol by the protonation of the hydroxy group.

Experimental

Phenyl *n*-Butyl Sulfide. — A mixture of phenol (0.94 g., 0.01 mol.), *n*-butyl mercaptan (4.5 g., 0.05 mol.) and 12 N hydrochloric acid (1 ml.) was sealed in a tube and then heated at 180°C for 48 hr. The sealed tube was then broken, the unreacted *n*-butyl mercaptan was distilled off under reduced pressure, and the residue was extracted with ether. The ether layer was treated with an aqueous sodium hydroxide solution to remove the unchanged phenol, and the two layers were separated. The ether layer was washed with dilute hydrochloric acid, and then with water, and dried. Distillation gave 0.52 g. of phenyl *n*-butyl sulfide in a 31% yield. The infrared spectra is completely in agreement with that of an authentic sample. Found: C, 72.35; H, 8.43%, n_D^{20} 1.5426, b. p. 75°C/1 mmHg. Meanwhile, when the same reaction mixture was heated in a sealed tube at 110°C for 48 hr. and treated as above, no sulfide was obtained.

In a separated experiment, a mixture of phenol (0.94 g., 0.01 mol.), *n*-butyl mercaptan (0.9 g., 0.01 mol.) and 12 N hydrochloric acid (1 ml.) was heated at 180°C for 48 hr. in a sealed tube; 0.37 g. of phenyl *n*-butyl sulfide was thereby obtained (yield 22%). However, when the same mixture was heated at 180°C for 24 hr. in a sealed tube, only a trace amount of phenyl *n*-butyl sulfide was obtained. The sulfide was found to be identical with an authentic sample in infrared spectra. Meanwhile, an authenthic sample of phenyl *n*-butyl sulfide was prepared by reacting diazotized aniline with sodium *n*-butyl mercaptide in over a 90% yield; b. p. 83°C/2 mmHg.

Phenyl Benzyl Sulfide. — A mixture of phenol (0.94 g., 0.01 mol.), benzyl mercaptan (6.2 g., 0.05 mol.) and 12 N hydrochloric acid (1 ml.) was sealed in a tube and heated at 180°C for 48 hr. The sealed tube was then broken, and two layers were separated. The upper, yellow layer neutralized with an aqueous sodium hydroxide solution, dried, and then distilled under reduced pressure. Two and six-tenths grams of phenyl benzyl sulfide was obtained (yield 43.4%); b. p. 118°C/3.5 mmHg. Found: C, 77.92; H, 6.00%, n_D^{20} 1.6083. From the lower layer 2 g. of dibenzyl disulfide was obtained; m. p. 71°C.

Diphenyl Sulfide.—A mixture of phenol (0.94 g., 0.01 mol.), thiophenol (5.5 g., 0.05 mol.) and 12 N hydrochloric acid (1 ml.) was sealed in a tube and heated at 180°C for 72 hr. The sealed tube was then treated as has been described in the case of phenyl *n*-butyl sulfide. Diphenyl sulfide (0.5 g., 26.7% yield) was obtained, together with 0.3 g. of diphenyl disulfide. Found: C, 77.18; H, 5.38%, n_D^{20} 1.6298, b. p. 113°C/1 mmHg.

In a separate experiment, the same mixture was heated at 180°C for 119 hr., 0.6 g. of diphenyl sulfide was thereby obtained (yield 32.2%).

***p*-Tolyl *n*-Butyl Sulfide.**—A mixture of *p*-cresol (1.08 g., 0.01 mol.), *n*-butyl mercaptan (1 g., 0.011 mol.) and 12 N hydrochloric acid (2 ml.) was sealed in a tube and heated at 180°C for 48 hr. The sealed tube was then broken, and two layers were separated. The lower layer consisted of hydrochloric acid and was discarded. The upper layer was treated as has been described above, thereby removing the unreacted *p*-cresol and *n*-butyl mercaptan. Then the product was collected by distillation in vacuo. *p*-Tolyl *n*-butyl sulfide (0.7 g.) was obtained in a yield of 14%. The product was identified with that of the authentic sample by comparing their infrared spectra. Found: C, 73.19; H, 8.85%, n_D^{20} 1.5397, b. p. 92—94°C/2 mmHg. An authentic sample of *p*-tolyl *n*-butyl sulfide was prepared by reacting diazotized *p*-toluidine with *n*-butyl mercaptan; 95% yield; b. p. 90°C/2 mmHg.

***β*-Naphthyl *n*-Butyl Sulfide.** — A mixture of *β*-naphthol (4.3 g., 0.03 mol.), *n*-butyl mercaptan (2.7 g., 0.03 mol.) and 12 N hydrochloric acid (2 ml.) was sealed in a tube and heated at 180°C for 48 hr. The sealed tube was then broken, and the entire contents were treated as has been described in the case of phenyl *n*-butyl sulfide. When the ether extract was distilled, 3.6 g. of *β*-naphthyl *n*-butyl sulfide was obtained (yield 55.4%). Found: C, 77.57; H, 7.40%, n_D^{20} 1.6229, b. p. 130—135°C/2 mmHg.

***α*-Naphthyl *n*-Butyl Sulfide.** — A mixture of *α*-naphthol (1.44 g., 0.01 mol.), *n*-butyl mercaptan (4.5 g., 0.05 mol.) and 12 N hydrochloric acid (1

ml.) was sealed in a tube and heated at 180°C for 52 hr. The entire contents in the sealed tube were then treated as has been described above. When the ether extract was distilled, 1.9 g. of α-naphthyl *n*-butyl sulfide was obtained (yield 69.5%). Found: C, 77.77; H, 7.19%, n_D^{20} 1.6190, b. p. 140—142°C/2.5 mmHg.

Benzenesulfonate.—Phenyl benzenesulfonate (2.34 g., 0.01 mol.) was sealed in a tube with *n*-butyl mercaptan (4.5 g., 0.05 mol.) and 12 N hydrochloric acid (1 ml.). The mixture was then kept at 180°C for 48 hr. The entire contents in the sealed tube were treated as has been described above. The reactants, phenyl benzenesulfonate and *n*-butyl mercaptan, were recovered quantitatively. Also when *p*-nitrophenyl benzenesulfonate (2.79 g., 0.01 mol.) was treated by a procedure similar to that used for phenyl benzenesulfonate, no reaction products were obtained.

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