The Nucleophilic Substitution of a Phenolic Hydroxy Group in Acidic Media

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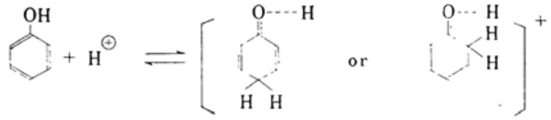
During our study of the acid-catalyzed hydrolysis of phenyl benzenesulfonate with concentrated hydrochloric acid in ^{18}O-enriched water, we have found that the phenol recovered was always incorporated with an excess of ^{18}O and also, that the amount of ^{18}O incorporation increased with prolonged heating.[1] We then suggested that, in a strong acidic medium, phenol readily accepts a proton at either the para- or ortho-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 facilitates the oxygen exchange with ^{18}O-enriched water.



A

We have now extended this remarkable oxygen exchange reaction to a number of phenolic compounds. The conditions used for this reaction were: temperature, 180°C; medium, 10 N hydrochloric acid in $H_2{}^{18}O$, enriched with 0.77 atom % ^{18}O; time, 6 hr. and 24 hr. Resorcinol, and both α- and β-naphthols, which are known to have some carbonyl character, were found to exchange their oxygen atoms substantially in 6 hr. and completely in 24 hr.; the oxygen exchange occured substantially with the ease of ^{18}O incorporation, falling in the order of phenol, *p*-nitrophenol, *p*-cresol, *m*-aminophenol, and *p*-bromophenol, while with tri-substituted phenols, such as 2, 4, 6-trimethylphenol and 2, 4, 6-tribromophenol, very little oxygen exchange took place, even under heating for 24 hr. In order for phenol to get a successful oxygen exchange, perhaps the incipient intermediate A should have a substantially long life. The substitution of electronegative groups at either the ortho- or para-position or at both will discourage the electrophilic addition of proton to form a quasi-stable intermediate A, while the substitutions at both ortho- and para-positions, even with electron-releasing alkyl groups such as in 2, 4, 6-trimethylphenol, will give an unstable unsymmetrical intermediate which may not have a life sufficiently long enough to exchange its oxygen.

Other alternative pathways would be aromatic nucleophilic substitution and that involving incipient aromatic carbonium ions. Aromatic nucleophilic substitution is known to be facilitated by substituting electron-withdrawing groups at either ortho- or para-positions or at both. In this case, however, the substitution of an electron-withdrawing group failed to increase the ^{18}O exchange. Meanwhile, the formation of aromatic carbonium ions would be facilitated by electron-donating substituents at ortho- and/or para-positions, but this trend was not observed in this ^{18}O exchange.

As an extension of this ^{18}O exchange experiment, it was expected that the phenolic hydroxyl group would be replaced by more nucleophilic reagents, such as alcohols and mercaptans. Indeed, when about five equivalent moles of ethanol was added in the reaction mixture of phenol and hydrochloric acid used for the ^{18}O exchange experiment and the mixture was heated in an ampoule at 180°C for two days, phenetole was obtained in a yield exceeding 60%. Naphthols and *p*-cresol also gave the corresponding ethyl ethers in good yields in the same procedures. When *n*-butylmercaptan was used instead of ethanol, phenolic oxygen was replaced by an *n*-butylmercapto group under the same reaction conditions. Thus, from phenol, *p*-cresol and both α- and β-naphthols, the corresponding *n*-butylsulfides of phenyl, *p*-tolyl and α- and β-naphthyl were obtained in good yields, recovering some unreacted starting materials.

Although β-naphthol has been known to react with nucleophilic reagents such as sulfurous acid[2] and thioglycolic acid[3] replacing the phenolic hydroxyl group forming β-naphthyl sulfonic acid and thioglycolic acid, our

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

[2] See Bucherer Reaction in "Organic Reaction," Vol. I, John Wiley & Sons, Inc., New York. p. 105.

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

results are the first general examples in which the phenolic hydroxyl group is replaced by nucleophilic reagents. We believe that this procedure will serve as a general method of substituting the phenolic hydroxyl group with other nucleophilic reagents; further work is in progress here.

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