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The Alkaline Hydrolysis of Halophenols[*1]

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The mechanism of both the alkaline fusion and the alkaline hydrolysis of halophenols has been investigated. In case of alkaline fusion, the product identified is resorcinol, the formation of which has been found to proceed through the benzyne intermediate. While the alkaline hydrolysis of halophenols gives different ratio of dihydroxyphenol and phenol by changing the mole ratio of halophenol to alkali, by utilizing ^{14}C tracer experiment and substituted halophenol, the mechanism of the formation of both products has been revealed to proceed by way of the direct substitution of halide with hydroxide. Copper compounds are found to be effective in this reaction.

The aqueous alkaline hydrolysis of halobenzenes has been shown to proceed by way of benzyne mechanism, though it gives somewhat different results depending upon the reaction temperatures, halogen species and the concentration of alkali applied.[1] Whereas, the alkaline hydrolysis of halobenzenes activated with nitro or sulfone group, has been demonstrated to proceed through an S_N2 type substitution on carbon atom bearing halogen atom.[2] Although the alkaline hydrolysis of halophenols apparently gives several unusual products, for example, phenol which cannot possibly be obtained through either the benzyne process or the concerted S_N2 route alone, this process is patented as one of promising methods of preparing dihydroxyphenols, such as catechol.[3] However, the mechanism of this reaction has been completely unkown. Apparently the reaction carried out with molten alkali at high temperature proceeds through a different route from that performed in aqueous alkali at a moderately low temperature. Usually, the treatment of molten alkali on halophenols gives rearranged dihydroxy-benzene, for

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[*1] Phenol and Phenolic Esters. XVII.

1) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 1458 (1957); A. Lüttringhaus and D. Ambros, *Chem. Ber.*, **89**, 463 (1956).

2) S. Oae and Y. H. Khim, This Bulletin, **40**, 1716 (1967).

3) German Pat. 1040563 (*Chem. Abstr.*, **55**, 10391g (1961)); Brit. Pat. 834254 (*Chem. Abstr.*, **54**, 20986d (1960)).

example, resorcinol from *o*-chlorophenol, suggesting that the reaction proceeds through the route involving benzyne formation. While, the aqueous alkali gives unrearranged products, catechol from *o*-chlorophenol and the reaction can be interpreted as an aromatic S_N2 types subtitution, no clear cut mechanism has yet been suggested. The remarkable feature of this aqueous alkaline hydrolysis of the halophenol is that the reaction is catalyzed by heavy metals or metal ions such as copper. This paper will describe the preliminary results of our investigation and the implication on the mechanism of these reactions.

Results and Discussion

The Alkaline Fusion of Halophenols. The reactions of halophenols with molten alkali have been known to give phenol, dihydroxybenzene and unidentified products.[4] Usually, the yield of dihydroxybenzene by alkaline fusion is not as good as that of the aqueous alkaline hydrolysis of halophenols; usually yielding the product in less than 20%. Meoreover dihydroxybenzene obtained by this alkaline fusion is rearranged products; for example, the only isolable product in the alkaline fusion of both *o*- and *p*-chlorophenols is resorcinol.

One possibility is that resorcinol may be formed by way of the incipient formation of benzyne as an intermediate (Eq. (1)). Another conceivable mechanism may be the route involving the prior formation of phenol, followed by the oxidation of it to resorcinol (Eq. (2)), since it has been known that resorcinol can be prepared from the reaction of phenol with molten alkali.[5] The mechanisms may be illustrated as shown below.

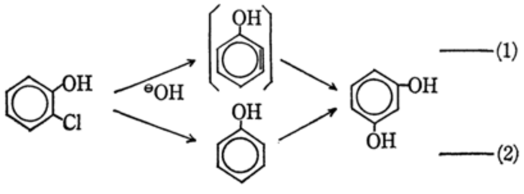
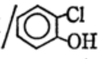


Fig. 1. Mechanism of the formation of resorcinol.

The choice between these two possible mechanisms can be readily made by means of ^{14}C tracer experiment using ^{14}C labeled phenol. Providing that the reaction would proceed through "benzyne route," resorcinol obtained would not have any ^{14}C activity, whereas if phenol would be the initial intermediate the original ^{14}C activity should be found in resorcinol. Accordingly *o*- or *p*-chlorophenol was mixed with the ^{14}C labeled phenol and the mixture was reacted with molten alkali for several hours and the resulting resorcinol was converted to its tribromide. From the activity measurement of the tribromoresorcinol obtained from the reaction was found to contain no ^{14}C activity. The ^{14}C tracer experiment reveals very clearly that "benzyne route" is considered to be the only plausible pathway for the alkaline fusion of halophenols.[2]

The Aqueous Alkaline Hydrolysis of Halophenols. The reaction is usually carried out in a copper tube which is placed in an autoclave kept at a temperature between 160—200°C for 4—6 hr. The reaction can also be carried out in a glass sealed tube containing a catalytic amount of a copper compound. After the reaction, the products were isolated as usual and identified by comparing their bp, mp, infrared spectra and gas-chromatographic behaviors with those of the authentic samples. The reaction has following few characteristic features. a) The main products are phenol and catechol but the product ratio changes by the change of the mole ratio of alkali to halophenol. The products and their yields are shown in Table 1. b) The relative ease of the halide-displacement in the halophenols appears to be in the following sequence $o > p \gg m$. Although there is no detailed kinetic study available, *o*-chlorophenol appears to undergo the most facile reaction to afford the products under the reaction conditions. Under the same conditions, however, only a small amount of phenol can be detected through gas chromatography from the reaction of *p*-chlorophenol. *m*-Chlorophenol apparently do not react and can be recovered almost quantitatively. c) The reaction has been known to be facilitated by copper catalysts. Moreover, under the reaction condition of hydrolysis in which the formation of phenol is favorable, the reaction is catalyzed only by copper and no other metal exhibit any effective catalytic activity. Among the following metal compounds tested for catalyst only copper compounds showed noticeable activities; Cu^0(Cu-tube), Cu^{1+}(Cu_2O), Cu^{2+}(CuO, $CuSO_4$); Ag^{+1}($AgNO_3$); Hg^{2+}($Hg(CN)_2$, $HgCl_2$); Fe^{2+} ($FeCl_2$), Fe^{3+}($FeCl_3$); Ni^{2+}($Ni(NO_3)_2$). Based on these observations one can construct the mechanisms of the hydrolysis reactions, especially of the formations of the two major products, *i. e.*,

TABLE 1. THE YIELDS OF PHENOL AND CATECHOL

NaOH/ Mole ratio	Products		
	Phenol (%)	Catechol (%)	Residue (%)
1	56	trace	44
1.5	25	15	50
2	trace	58	42

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[4] H. E. Fierz-David and G. Stamm, *Helv. Chim. Acta*, **25**, 256 (1942).

[5] J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **46**, 304 (1950).

phenol and catechol.

Mechanism of the Formation of Phenol. The yield of phenol was found to reach the maximum value when the reaction was carried out with 1:1 mole ratio of alkali to *o*-halophenol. The probable mechanism can be illustrated in Fig. 2.

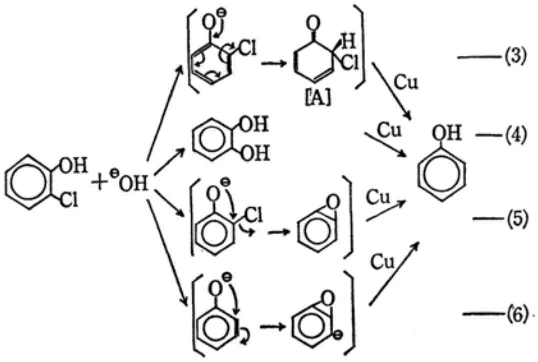

Fig. 2. Mechanism of the formation of phenol.

The Eq. (3), tentatively called as direct chlorine substitution, involves the initial formation of phenoxy anion followed by prototropy to form an intermediate (A) from which chlorine is abstracted by copper metal to produce phenol. Equation (4) demands that phenol is formed by way of the initial formation of catechol. This mechanism is also possible because catechol is always formed even when the concentration of alkali is relatively low. Equations (5) and (6) involve the incipient formation of the intermediate epoxy compound from which phenol is to be formed. The choice between the mechanisms, namely Eq. (3) and those (5) or (6) can be achieved by using a suitably substituted halophenol such as 2-bromo-4-methylphenol. Equation (3) will require cresol obtained from 2-bromo-4-methyl phenol to be *p*-cresol alone, whereas according to Eq. (5) or (6) both *m*- and *p*-cresols should be formed. When 2-bromo-4-methylphenol was actually subjected to the hydrolysis with an equal mole of alkali, phenolic products obtained in 35% yield contained phenol (5%) and *p*-cresol (30%), but no *m*-cresol. Since *m*- and *p*-cresols have characteristically different IR absorption spectra, their absence is readily confirmed. Consequently Eqs. (5) and (6), *i. e.*, the oxygen migration mechanism, can now be ruled out. Since no phenol formation was observed when catechol was treated under the same condition that applied to the hydrolysis, Eq. (4) can also be eliminated. Thus the phenol formation is considered to follow Eq. (3).

Now a question arises why *o*-halophenol is especially so reactive, since a similar mechainsm can be applied to *p*-halophenol which does not produce phenol so readily. The reason is probably illustrated by a complex formation between copper and *o*-halophenol at the transition state especially with *o*-hydroxyl group and halogen as shown below and the formation of such a complex may decrease the activation energy of the reaction. Moreover, the change of product ratio by changing the amount of alkali to *o*-halophenol can be explained by such a complex formation. Namely, when an excess amount of alkali to halophenol is used, hydroxide anion attacks preferentially the *o*-carbon atom bearing halogen atom, since carbon-halogen bond is probably loosen by such a complex formation, thus catechol is produced as a main product. While, in case of an equimolar amount of alkali, only halogen is abstracted by copper giving rise to phenol.

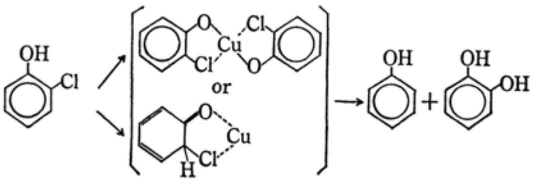

Fig. 3. Complex formation.

The Mechanism of the Formation of Catechol. The formation of catechol is also interesting in connection with the phenol formation, because copper catalyst is also necessary in this reaction.

Among several mechanisms conceivable, the one involving the initial benzyne formation followed by the epoxy intermediate formation can be ruled out from the afore-mentioned experiment using 2-bromo-4-methylphenol. While it is considered that the formation of catechol may be achieved by the direct nucleophilic substitution of chlorine by hydroxy group, there is another possibility, namely, the process involving the initial formation of phenol which is then oxidized to catechol in the presence of copper catalyst. The two mechanisms are depicted as shown below.

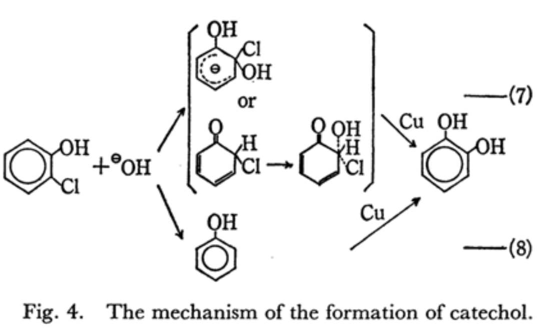

Fig. 4. The mechanism of the formation of catechol.

In order to make a choice between the two mechanisms, we have carried out a ^{14}C-tracer experiment using a small amount of ^{14}C-labeled phenol mixed with *o*-chlorophenol. If the reaction proceeds according to Eq. (8), the catechol obtained should have ^{14}C activity, whereas according to the

Eq. (7), catechol should have no ^{14}C activity. Our result revealed that less than 2% of the original ^{14}C activity was found in catechol. Moreover, from this experiment we have found that more than 95% of phenol was recovered unchanged. Therefore Eq. (8) can be eliminated. Thus the formation of resorcinol is considered to proceed through the direct nucleophilic substitution of chlorine by hydroxide, probably assisted by copper ion which acts as a Lewis acid.

Experimental

The Alkaline Fusion of *p*-Chlorophenol Mixed with ^{14}C Labeled Phenol. The experimental condition was same as that Fierz-David described. A mixture of sodium *p*-chlorophenolate (3 g) and sodium phenolate-^{14}C (0.5 g) was reacted in a nickel muffle heated in a silicone oil bath, the temperature of which was kept at 300°C for 5 hr. After the reaction, the vessel was cooled and the products were dissolved into a large amount of water To this aqueous solution was added bromine water. Solid precipitates were collected and dried. The yellow colored solid was extracted with *n*-hexane. The hexane solution was cooled with ice-bath. Crystalline precipitates were collected, recrystallized from *n*-hexane and then sublimed. Colorless needles were obtained, mp 104—106°C, and ^{14}C activities were measured by a liquid scintillation counter. The specific activities were: phenol, 9.2×10^4 dpm/mmol (as tribromide); resorcinol, 2.2×10^3 dpm/mmol (as tribromide).

The Aqueous Alkaline Hydrolysis of *o*-Halophenols. A typical example of the experiments are the following. *o*-Chlorophenol (commercially available, 1 g) was dissolved in 3 m*l* of water containing 0.4 g of sodium hydroxide and the whole mixture was placed in an ampoule. To this solution was added 1% of cuprous oxide. The ampoule was sealed and heated in an autoclave at a temperature between 180—200°C for 4 hr. After cooling the ampoule was broken and the mixture was filtered to remove polymeric substance and the catalyst. The filtrate was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was dried over magnesium sulfate. After ether was removed, the residue was distilled and product (0.4 g, bp 160—180°C) was obtained. Among the products identified were phenol and a small amount of recovered *o*-chlorophenol. The yield of phenol was 56%.

Similar experiments were carried out by changing catalyst, alkali concentration and halophenols. The results are summarized in Table 1.

2-Bromo-4-methylphenol. The titled phenol was prepared from *p*-cresol and bromine in carbon tetrachloride solution in 66% yield. The alkaline hydrolysis of 2-bromo-4-methylphenol (3 g) gave 1.1 g of liquid products (bp 160—200°C) among which were isolated *ca.* 1.5% of phenol and *p*-cresol (33%). The identification of these phenols was made by IR and gas chromatography.

The Reaction of Catechol with Alkali. A mixture of 1.0 g and 10 m*l* of 10% aqueous sodium hydroxide was sealed into a glass ampoule and was heated in an autoclave for 3 hr at 200°C. The isolation of products were performed similarly. Catechol was recovered in 50% yield but no phenol was isolated.

The Alkaline Hydrolysis of *o*-Chlorophenol and Phenol-1-^{14}C. *o*-Chlorophenol (2.62 g) and phenol-1-^{14}C (0.5 g) prepared from aniline-1-^{14}C was treated as similarly. After the reaction, catechol obtained was purified by sublimation, yield 58%, mp 104—106°C. ^{14}C activity was measured by a liquid scintillation counter. Sp. activity: Phenol-1-^{14}C (as tribromide), 1.12×10^5 dpm/mmol. Catechol, 1.36×10^3 dpm/mmol. Thus, 1.2% of the original ^{14}C activity was incorporated in catechol.

Recovery Test of Phenol-1-^{14}C. Phenol-1-^{14}C (0.41 g) was dissolved into 1 m*l* of 20% aqueous sodium hydroxide solution containing Cu_2O. The mixture was heated for 4 hr at 170—180°C. After the reaction was added 430 mg of the authentic phenol. The phenol recovered was converted to the tribromide and ^{14}C activities of the initial and the recovered tribromophenol were measured by a liquid scintillation counter. The ^{14}C activities are 4.19×10^4 dpm/mmol for the initial phenol and 2.02×10^4 dpm/mmol for the recovered phenol.

Thus, by means of the isotope dilution method, 95% of phenol was found to be recovered under the alkaline hydrolysis.