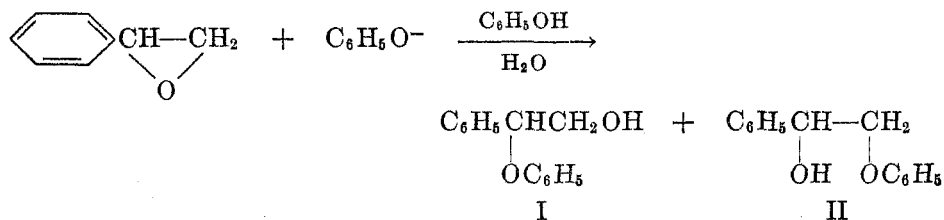


THE EFFECT OF SOLVENT AND TEMPERATURE ON THE BASE-CATALYZED REACTION OF STYRENE OXIDE WITH PHENOL

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The base-catalyzed³ reaction of styrene oxide with phenol is known (1) to proceed largely as shown:



In the presence of water and excess phenol this reaction can produce about three parts of the primary alcohol (I) for each part of secondary alcohol (II). However, when the water is replaced by dioxane, nearly equal parts of the two alcohols can be formed. As was pointed out (1), the reaction medium affects the course of the ring-opening reaction in some manner. The present work is concerned with an investigation of the role of the solvent in this reaction.

It is becoming evident that the primary alcohol (I) is formed by a unimolecular mechanism. Thus, the base-catalyzed reaction (2) of styrene oxide with excess 2-naphthol in water gives large amounts of a phenol-alcohol, 2-(2-hydroxy-1-naphthyl)-2-phenylethanol, and a minor amount of the ether-alcohol corresponding to I; in dioxane, both of the isomeric ether-alcohols are formed in nearly equal amounts and much less of the phenol-alcohol is produced. Also, none of the isomeric phenol-alcohol, formed by the alternate opening of the ring, is found. It is believed that the nuclear alkylation, and probably the formation of the ether-primary alcohol, proceeds by a different mechanism than obtains in the formation of the ether-secondary alcohol since the latter is the expected product from a S_N2 reaction (8). The acid-catalyzed reaction of styrene oxide with phenol

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² This paper is based on part of the M.S. thesis (August, 1950) of Mr. Homer R. Williams whose present address is Stanford University, Department of Chemistry, Palo Alto, California.

³ Although the authors feel that the reaction of an olefin oxide with phenoxide ion is not properly described as base-catalyzed, this term is commonly used with reference to the bimolecular reaction between an olefin oxide and an alcohol or phenol when carried out with the addition of base to convert at least part of the hydroxylic compound into its anion, which is the reacting species (8). Therefore, this usage is continued in the present paper except that, in certain instances, we point up the belief that the use of styrene oxide and sodium phenoxide does not lead to the bimolecular reaction usually associated with these conditions.

and with 2-naphthol (3) gives products that are almost exclusively the result of ring opening at the *alpha* carbon.

A cogent argument in favor of a unimolecular mechanism is provided by the results from the base-catalyzed reaction of *p*-nitrostyrene oxide with phenol (4). Under the same conditions used with styrene oxide, *p*-nitrostyrene oxide and phenol interact to form a mixture of ether-alcohols about two-thirds of which is the secondary alcohol. Now, if the formation of the primary alcohol proceeds by a bimolecular mechanism, then the effect of the nitro group in *p*-nitrostyrene oxide ought to be similar to that shown in the bimolecular reaction of the nitrobenzyl chlorides with potassium iodide in acetone. Conant, Kirner, and Hussey (5) have shown that the nitrobenzyl chlorides are more reactive than benzyl chloride in this S_N2 reaction. On this basis it might be assumed that with *p*-nitrostyrene oxide a bimolecular route to the primary alcohol would be favored and consequently relatively more of the primary alcohol would be formed than with styrene oxide. Actually the opposite is the observed result. On the other hand, Olivier (6) has reported that the solvolysis of benzyl chloride, which is a unimolecular reaction (7), is considerably faster than the solvolysis of the nitrobenzyl chlorides. Thus, as might be predicted, with the nitrobenzyl chlorides the nitro group increases the rate of a bimolecular reaction and decreases the rate of a unimolecular reaction relative to benzyl chloride. Therefore, it seems reasonable to conclude that in the styrene oxides, the ring-opening reaction to form the primary alcohol, either acid-catalyzed or "base-catalyzed", is unimolecular. The secondary alcohol is presumed to be formed by a bimolecular mechanism (8); the steric effect of the phenyl group prevents this route to the primary alcohol (4).

Since, in the base-catalyzed reaction of styrene oxide with phenol (1) and with 2-naphthol (2), the change of solvent from water to dioxane favors the formation of the secondary alcohol, the role of the dioxane must be to decrease the relative rate of the unimolecular reaction. In order to get more evidence on this point, the base-catalyzed reaction was run in the presence of several different solvents with the results shown in Table I

It was our conjecture that the data in Table I reflected the influence of the hydroxylic components on the course of the reaction between styrene oxide and the phenoxide ion. Furthermore, these data were viewed with the implication that hydrogen bonding was occurring between the oxide and the hydroxylic components and that this intermediate state was energetically more disposed to follow a course leading to I than to II. On this basis the results in Table I are entirely reasonable.

That hydroxylic compounds form hydrogen bonds with olefin oxides (13, 16) and other cyclic ethers has been reported (9-17). The ethylenimines have also been discussed (18) relative to their reaction by way of an intermediate involving hydrogen bonds. In considering the data in Table I it is important to bear in mind that excess phenol was present in most of the runs, so actually a composite effect of excess phenol and added solvent was being observed in these instances. Of the hydroxylic components in the reaction mixture, free phenol would have

the greatest capacity for forming hydrogen bonds with the oxide and, therefore, of greatest influence in promoting the formation of I relative to II. In the presence of ethers, such as dioxane and tetrahydrofuran, the free phenol would be expected to be distributed, as hydrogen-bonded complexes, between the oxide and the ether (11-14, 17); apparently there was relatively diminished hydrogen bonding with the oxide since the isomeric mixture of I and II was low in I. In the alcohols the distribution of the free phenol between the alcohol and the oxide (12, 13, 19, 20) might be expected to lead to a higher proportion of I as compared to that in the ethers, while in nitrobenzene (12), toluene, and thiophene essen-

TABLE I
THE EFFECT OF SOLVENT ON THE COMPOSITION OF THE MIXTURE OF ISOMERS^a

SOLVENT	TIME, HR.	TEMP., °C.	YIELD OF MIXTURE, I + II, %	I IN MIXTURE, %
Tetrahydrofuran, 75 cc plus methanol, 3.2 g. (0.1 mole).....	22	70	41 ^{b, c}	28
Tetrahydrofuran, 25 cc.....	3	93	81	43
Dioxane, 25 cc.....	3	100	77	47
Acetal, 25 cc.....	3	100	65	55
Ethanol, 25 cc.....	3	94	84	57
Allyl alcohol, 25 cc.....	3	100	80	64
Methanol, 25 cc.....	3	70	85 ^d	69
Nitrobenzene, ^e 25 cc.....	3	100	56	71
Toluene, ^e 25 cc.....	3	100	70	72
Thiophene, ^e 25 cc.....	3	94	61	73
Water, 7.5 cc.....	1	100	80	77
Phenol, ^f 14.1 g.....	3	100	50	88

^a Reactants: styrene oxide (0.05 mole), added over a three-minute period and phenol (0.15 mole); sodium (0.05 mole) with non-aqueous solvents; sodium hydroxide (0.05 mole) with water as the solvent. These were all one-phase reactions except as noted. ^b Reactants: styrene oxide (0.05 mole); phenol (0.1 mole); sodium (0.1 mole). ^c *Anal.* Calc'd for C₁₄H₁₄O₂: C, 78.48; H, 6.59. Found: C, 78.44; H, 6.58. ^d *Anal.* Calc'd for C₁₄H₁₄O₂: C, 78.48; H, 6.59. Found C, 78.90; H, 6.27. ^e Some sodium phenoxide remained undissolved. ^f This amount was in addition to the quantity present in all runs.

tially all of the excess phenol would be available for hydrogen bonding with the oxide. In water, and more so in phenol, the higher concentration of the free phenol would favor hydrogen bond formation with the oxide. When the amount and concentration of the hydroxylic components were held to a near minimum, as was done in the first run recorded in Table I, the relative amount of II in the mixture of products was greatest. It was possible to change the content of I in the product from 28% to 88% by increasing the probability for the formation of hydrogen bonds with the oxide oxygen. These results show that a statement merely designating the reaction of styrene oxide as base-catalyzed is insufficiently accurate to define the nature of the products that might be formed.

The data that follow lend support to this concept of the presence and the effect of hydrogen bonding between the hydroxylic components and the oxide.

In order to show further that the excess phenol in the foregoing experiments might be influencing the course of the reaction, several runs were repeated except that the excess phenol was added slowly with the styrene oxide to a solution of sodium phenoxide in the solvent. This procedure reduced the concentration of free phenol present at the time the oxide was undergoing reaction with phenoxide ion. A comparison of these results, Table II, with those in Table I showed that this reduction in the amount of free phenol did indeed decrease the ratio of the primary alcohol (I) to the secondary alcohol (II). This evidence indicated again that two different mechanisms could be responsible for the formation of I and II and that free phenol might favor the mechanism leading to I.

From the data in Table II it appeared that the rate of the reaction was slower in the non-hydroxylic solvents. Additional data, which are shown in Table III,

TABLE II
THE EFFECT OF EXCESS PHENOL ON THE COMPOSITION OF THE MIXTURE OF ISOMERS^a

SOLVENT	ADDITION TIME, HR.	TOTAL REACTION TIME, HR.	TEMP., °C.	YIELD OF MIXTURE, I + II, %	I IN MIXTURE, %
Tetrahydrofuran, 25 cc.....	2.5	5.5	74-90	50 ^b	34
Dioxane, 20 cc.....	36.0	44.0	100	59 ^b	38
Dioxane, 20 cc.....	1.75	3.75	100	30 ^b	38
Ethanol, 25 cc.....	20.0	21.0	70	89	49
Methanol, 25 cc.....	20.0	21.0	70	79	63
Water, 7.5 cc.....	1.0	2.0	100	70	67

^a Reactants: styrene oxide (0.05 mole) and phenol (0.1 mole); sodium (0.05 mole) with non-aqueous solvents; sodium hydroxide (0.05 mole) with water as the solvent. One-half of the phenol was added with the styrene oxide over the stated period to the solution of the remaining phenol as sodium phenoxide. When dioxane was the solvent, an additional 10 cc. of dioxane was added with the oxide-phenol mixture. ^b Some styrene oxide was recovered.

made this phenomenon more explicit. The rate was found to increase as the capacity for the formation of hydrogen bonds with the oxide was augmented. Furthermore, the ratio of the isomers formed was nearly constant at different degrees of conversion in the same solvent, showing that neither alcohol was being preferentially consumed in any side reaction and that reaction time had no effect on the ratio of I to II. In excess phenol as the solvent the yield of ether-alcohols was relatively low because of a competing reaction involving nuclear attack to give phenol-alcohols and perhaps other products (3). Two isomeric phenol-alcohols, both formed by the opening of the oxide ring at the *alpha* carbon atom, were isolated and identified. This type of nuclear attack is much more pronounced with 2-naphthol (2). These data also showed that the rate of the uncatalyzed reaction in excess phenol was nearly the same as that of the so-called base-catalyzed reaction in excess phenol.

Since the formation of hydrogen bonds appeared to be a rather definite factor in determining the direction of ring opening, the study now turned to an in-

TABLE III
THE EFFECT OF SOLVENT ON THE RATE OF THE BASE-CATALYZED REACTION OF
STYRENE OXIDE WITH PHENOL^a

SOLVENT	TIME, HOURS	YIELD OF MIXTURE, I + II, %	I IN MIXTURE, %
Dioxane	7.0	33	65
	14.0	52	61
	22.0	64	61
	48.0	79	61
	90.0	88	61
Ethanol	0.75	31	67
	1.5	51	70
	3.0	71	67
	14.0	87	65
Methanol	0.75	39	71
	1.5	57	72
	3.0	86	72
	14.0	84	71
Phenol ^b	0.185	26	93
	0.37	34	94
	0.75	46	94
	1.5	39	95
	14.0	43	93 ^c
Phenol (uncatalyzed)	0.37	31	89
	2.5	37	89

^a Reactants: styrene oxide (0.05 mole), phenol (0.15 mole), and sodium (0.025 mole). The reaction was conducted in 25 cc. of solvent, or in 26 g. of additional phenol when the latter was employed as the solvent. The styrene oxide was added over a one-minute period to the mixture at 72°. ^b The low yields in this series resulted from side reactions leading to alkali-soluble products. ^c In addition to the isomeric ether-alcohols, products from nuclear attack were also isolated. The yields were: 2-(2-hydroxyphenyl)-2-phenylethanol, 0.4 g. (3.7%) and 2-(4-hydroxyphenyl)-2-phenylethanol, 0.9 g. (8.4%).

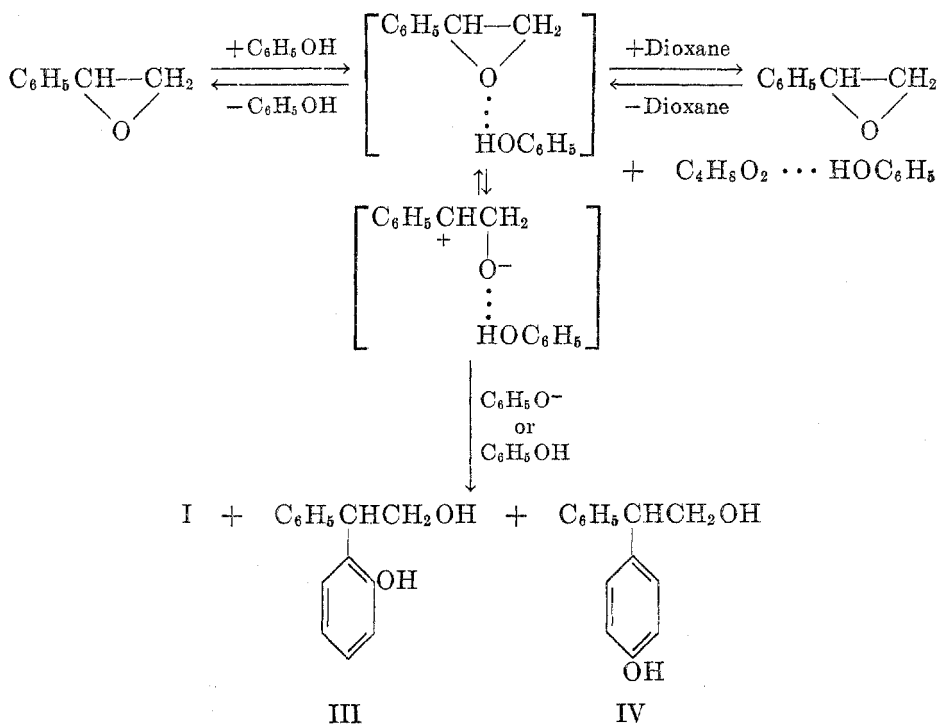
TABLE IV
THE EFFECT OF TEMPERATURE ON THE COMPOSITION OF THE MIXTURE OF ISOMERS^a

SOLVENT	TIME, HR.	TEMP., °C.	YIELD OF MIXTURE, I + II, %	I IN MIXTURE, %
Methanol, 25 cc.....	40.0	22	44 ^b	80
Methanol, 25 cc.....	3.0	74	84	68
Water, 7.5 cc.....	72.0	0	13 ^b	92
Water, 7.5 cc.....	4.5	70	81	82
Water, 7.5 cc.....	1.0	100	80	77
Phenol, 14.1 g.....	60.0	24	44	92
Phenol, 14.1 g.....	3.5	70	54	89
Phenol, 14.1 g.....	3.0	100	50	88
Phenol, 14.1 g.....	0.5	138	59	79
Phenol, 14.1 g.....	0.25	190	74	66

^a Reactants: styrene oxide (0.05 mole) and phenol (0.15 mole); sodium (0.05 mole) with non-aqueous solvents; sodium hydroxide (0.05 mole) with water as the solvent. When phenol was used as the solvent, the amount stated in the table above was in addition to that present in all of the runs. The styrene oxide was added over a three-minute period. ^b Some unreacted styrene oxide was recovered. ^c Some sodium phenoxide remained undissolved.

vestigation of temperature effects. From the foregoing data it would be predicted that at higher temperatures, because the formation of hydrogen bonds between the hydroxylic components and the oxide would be retarded (10, 15), the amount of II in the product ought to be relatively greater. Conversely, at lower temperatures the formation of I ought to be favored. As shown in Table IV, the observed results were in complete agreement with this prediction.

On the basis of the foregoing data the base-catalyzed reaction of styrene oxide with phenol, in the presence of only excess free phenol, is construed to be described to a degree by the sequence shown. The action of dioxane is also indicated.



The base-catalyzed reaction, in the presence of *sufficient* excess phenol but no other added solvent, appears to be predominantly the unimolecular type, that is, the rate is independent of phenoxide ion concentration. The phenol can assist the rate-determining unimolecular ring opening (20), and the carbonium ion is solvated and also stabilized by resonance, which is the factor that directs the ring opening. This carbonium ion reacts with phenoxide ion, or with phenol (3), to produce the primary alcohol (I) and the two isomeric phenol-alcohols (III and IV). Only a small amount, if any, of the secondary alcohol (II) is formed. Under these conditions this "base-catalyzed" reaction is similar to the acid-catalyzed reaction (3). Any change that diminishes the effective concentration of free phenol, or any change that otherwise prevents or retards the formation of the hydrogen-bonded complex with the oxide, will correspondingly favor the

slower bimolecular reaction leading to the secondary alcohol (II), which presumably could become the sole isomer formed. The effect of dioxane or tetrahydrofuran on the rate and course of the reaction is a case in point. Also, the base-catalyzed reaction of styrene oxide in excess phenol at higher temperatures, as shown in Table IV, exhibits a shift from the unimolecular to the bimolecular mechanism, because the hydrogen bond becomes less stable as the temperature is raised (10, 15). One consequence of this shift is a higher yield of ether-alcohols and less nuclear attack. Such a shift is also characterized by an increase in the ratio of II to I in the mixture of ether-alcohols.

It is possible that methanol or ethanol, for example, can form hydrogen bonds with the oxide and thereby increase the rate of the bimolecular reaction (20) as well as induce the ring opening to proceed unimolecularly. That methanol might be able to induce the unimolecular reaction is evidenced by the finding that the base-catalyzed reaction of styrene oxide with methanol produces appreciable quantities of the primary alcohol (21).

With *p*-nitrostyrene oxide there should be less and weaker hydrogen bond formation than with styrene oxide between the oxide and excess phenol since the nitro group would tend to withdraw electrons from the oxide oxygen (13, 14). This, coupled with the reduced stabilization of the carbonium ion resulting from the unimolecular ring opening, could account for the formation of the relatively large amount of secondary alcohol from *p*-nitrostyrene oxide (4).

EXPERIMENTAL⁴

General procedure. The base-catalyzed reactions were conducted in a three-neck reaction flask, which was equipped with a stirrer, dropping-funnel, and reflux condenser. Temperatures were maintained constant over long periods by using a large Dewar vessel as a water-bath, heat being supplied by steam or a heating element.

The phenol was dissolved in aqueous sodium hydroxide or, with non-aqueous solvents, sodium was added to the phenol and solvent, or to the phenol only. The mixture was then brought to the desired temperature, and the styrene oxide, n_D^{20} 1.5353, was added over the period indicated in the Tables. The solvents used were C.P. anhydrous commercial products or, as with dioxane and tetrahydrofuran, were refluxed over sodium metal and then distilled.

At the end of the reaction the mixture was poured onto ice and water containing a slight excess of sodium hydroxide over that calculated to react with the free phenol initially present. The isolation of the ether-alcohols and the determination of the composition of the isomeric mixture followed previous procedures (1).

Isolation of the phenol-alcohols (III and IV). In only one experiment was an attempt made to isolate and identify any alkali-soluble products that might have been formed. In this instance, a run in excess phenol as explained in Table III, the alkali-soluble mixture remaining after removal of the ether-alcohols was slowly acidified with conc'd hydrochloric acid. The insoluble material was taken up in ether, washed with a saturated sodium bicarbonate solution and water respectively, and the ether and phenol removed by distillation. The residue was then distilled in a modified Claisen flask to give one fraction weighing 2.56 g., b.p. 165–200° (1 mm.) and a second fraction weighing 1.68 g., b.p. 200–215° (1 mm.). A saturated solution in toluene was made from each fraction. The first,

⁴ All melting and boiling points are uncorrected. Microanalyses are by Mr. Joseph Pirie of this Department.

lower-boiling fraction deposited 0.4 g. (3.7%) of 2-(2-hydroxyphenyl)-2-phenylethanol (III), m.p. 71–74°, and the second fraction gave 0.9 g. (8.4%) of crude 2-(4-hydroxyphenyl)-2-phenylethanol (IV), m.p. 88–90°. Identification was accomplished by mixture melting point determinations with authentic compounds (3).

SUMMARY

The base-catalyzed reaction of styrene oxide with phenol was shown to give different ratios of primary alcohol to secondary alcohol when the reaction environment and temperature were varied. Nearly exclusive formation of the primary alcohol and the incidence of nuclear attack to give phenol-alcohols were observed when only excess phenol was the solvent; other conditions were found that led predominantly to the secondary alcohol. This behavior is discussed in terms of a unimolecular ring opening, which is thought to be induced by a hydrogen-bonded complex between the oxide and hydroxylic components in the reaction mixture and to lead to the primary alcohol.

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