

236–238°. A sample for analysis was precipitated from a dimethylformamide solution with the addition of ethanol and ether; m.p. 240–243°, $[\alpha]^{25D} -19.6^\circ$ (c 0.96, dimethylformamide).

Anal. Calcd. for $C_{37}H_{54}N_8O_{10}$: C, 57.5; H, 7.07; N, 14.5. Found: C, 57.2; H, 7.18; N, 14.3.

N-Carbobenzoxy-L-seryl-L-leucyl-L-tyrosyl-L-glutamyl-L-leucyl-L-benzyl-L-glutamyl-L-asparaginyl-L-tyrosyl-S-p-nitrobenzyl-L-cysteinyl-L-asparagine p-Nitrobenzyl Ester Tetrahydrate.—N-Carbobenzoxy- γ -benzyl-L-glutamyl-L-asparaginyl-L-tyrosyl-S-p-nitrobenzyl-L-cysteinyl-L-asparagine p-nitrobenzyl ester (3.25 g.) was dissolved in 2 N HBr in acetic acid (60 ml.). After 1 hour at room temperature, dry ether (500 ml.) was added and the precipitated product was isolated and reprecipitated from methanol-ether. To a cold solution of this product in dimethylformamide (50 ml.) and triethylamine (0.45 ml.) was added N-carbobenzoxy-L-seryl-L-leucyl-L-tyrosyl-L-glutamyl-L-leucine azide prepared as noted: N-carbobenzoxy-L-seryl-L-leucyl-L-tyrosyl-L-glutamyl-L-leucine hydrazide (2.2 g.) was dissolved in a mixture of dimethylformamide (15 ml.), acetic acid (30 ml.) and 1 N HCl (80 ml.); the solution was cooled in an ice-bath and sodium nitrite (0.2 g.) in water (5 ml.) was added; the mixture was kept at 0° for 20 minutes and ice-cold water (50 ml.) was added; the precipitated solid was isolated by filtration, washed with ice-cold water, 1 N HCl and water and dried *in vacuo* for 30 minutes over phosphorus pentoxide at a temperature of 0°; this

azide was then added to the solution of the amino component prepared as described above. The reaction mixture was kept at 5° for 24 hours and at room temperature for 1 hour and then poured into ice-cold 1 N HCl (200 ml.). The precipitated product was collected by filtration and washed with water, 1 N NH_4OH and water again; wt. 2 g. (40%), m.p. 228–230° dec. A sample for analysis was reprecipitated from dimethylformamide-water; m.p. 231–233° dec., $[\alpha]^{25D} -36.3^\circ$ (c 1.1, dimethylformamide).

Anal. Calcd. for $C_{88}H_{101}N_{15}O_{26} \cdot 4H_2O$: C, 55.0; H, 6.06; N, 11.6. Found: C, 54.7; H, 6.06; N, 12.1.

Amino acid analysis of an acid hydrolysate by a Beckman-Spinco analyzer gave the expected amino acid composition as discussed previously. For paper chromatography and enzymatic analysis a sample of the protected decapeptide was decarboxylated on exposure to HBr in nitromethane; R_f (hydrobromide) 0.53; single ninhydrin, methionine and tyrosine positive spot and single spot as revealed by ultraviolet quenching. The decarboxylated decapeptide was completely digested by LAP as demonstrated by paper chromatography of the digest.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, IND.]

Solvation as a Factor in the Alkylation of Ambident Anions: The Importance of the Hydrogen Bonding Capacity of the Solvent^{1,2}

BY NATHAN KORNBLOM, PAUL J. BERRIGAN³ AND WILLIAM J. LE NOBLE

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When solutions of the salts of phenol or *p*-alkylphenols in a wide variety of solvents are alkylated with allyl or benzyl halides the ether (oxygen alkylation) is the sole product. However, when these reactions are conducted in water, phenol or fluorinated alcohols, substantial amounts of *o*- and *p*-alkylated products result. Neither carbon nor oxygen alkylation is a carbonium ion process but, rather, these are second-order nucleophilic displacements. An explanation for the fact that water, phenol and fluorinated alcohols foster carbon alkylation, which invokes their strong hydrogen bonding capabilities, is proposed.

Introduction

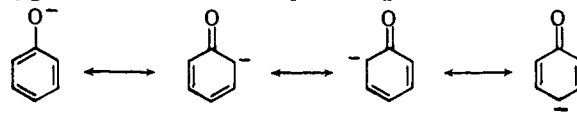
As part of a study of the factors which control the reactions of ambident anions,⁴ *i.e.*, anions possessing capability for covalent bond formation at either of two alternative positions, the role of the solvent has been investigated. The present paper describes experiments which employ salts of phenol and *p*-cresol and the one immediately following⁵ deals with the alkylation of β -naphthoxide salts. These studies clearly demonstrate that the solvent in which an ambident anion reaction is conducted may well decide the reaction course. As an example, when sodium β -naphthoxide is treated with benzyl bromide in dimethyl sulfoxide solution a 95% yield of benzyl β -naphthyl ether results, but in trifluoroethanol the major product is 1-benzyl-2-naphthol (85% yield).

In order to account for the ability of solvents to control the course of ambident anion alkylations we invoke two properties of solvents: their capacity for solvating ions and their dielectric constants. In so doing, we hark back to Hammett⁶ who, in 1940, pointed out that solvents which are effective at dissolving salts have two attributes: (1) a high dielectric constant and,

(2) a considerable tendency on the part of the solvent molecules to attach themselves to ions, *i.e.*, to solvate them. In particular, Hammett noted that such solvation often depends upon hydrogen bonding between the solvent molecules and the unshared electrons of the anion of the salt.

In the interest of orderly development, the present paper pays particular attention to the hydrogen bonding capacity of the solvent while the one which follows emphasizes the role of the dielectric factor. But in order to provide perspective it should be stated at the outset that, in our view, when an ambident anion reaction is conducted in protic solvents the free energies of the two possible transition states are influenced by a combination of the hydrogen bonding and dielectric factors. In aprotic solvents the dielectric factor and whatever capability the solvent molecules possess for solvating ions combine to influence the free energies of the two possible transition states. It is now clear, especially because of studies by Zook⁷ and by Zaugg,⁸ that aprotic solvents may possess significant capabilities for solvating cations; the consequences of cationic solvation for the reactions of ambident anions are discussed in the second of these two papers.⁵

The phenoxide ion is capable of bond formation at oxygen or at the *ortho* and *para* ring carbon atoms



(1) Paper V in the series, "The Chemistry of Ambident Anions." A preliminary account of this work appeared in *J. Am. Chem. Soc.*, **82**, 1257 (1960).

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(3) Predoctoral fellow 1957–1960, CF-7406-C2, National Cancer Institute, Public Health Service.

(4) N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(5) N. Kornblum, R. Seltzer and P. Haberfeld, *ibid.*, **85**, 1148 (1963).

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 39.

(7) H. D. Zook and T. J. Russo, *J. Am. Chem. Soc.*, **82**, 1258 (1960); H. D. Zook and W. L. Gumby, *ibid.*, **82**, 1386 (1960).

(8) H. E. Zaugg, B. W. Horrom and S. Borgwardt, *ibid.*, **82**, 2895 (1960); H. E. Zaugg, *ibid.*, **82**, 2903 (1960); **83**, 837 (1961).

TABLE I
 SOLVENTS IN WHICH THE HOMOGENEOUS ALKYLATION OF PHENOLIC SALTS RESULTS IN OXYGEN ALKYLATION^a

| Solvent | Salt | Alkylating agent | Yield of ether, % | | |
|-------------------------------------|---|---|-------------------------------|------------------------|-----|
| | | | Isolated | By V.P.C. ^b | |
| <i>t</i> -Butyl alcohol | Sodium phenoxide | Allyl bromide | | 100 | |
| | Diethyl ether | Sodium <i>p</i> - <i>t</i> -octylphenoxide | Allyl bromide ^{c,d} | 99 | |
| | Dimethylformamide | Sodium phenoxide | Allyl chloride | | 100 |
| Dioxane | Potassium phenoxide | Allyl bromide | 91 | | |
| | | Benzyl chloride | | 100 | |
| | | Allyl chloride | | 100 | |
| | Sodium phenoxide | Allyl chloride | | 100 | |
| | | Allyl bromide | 93 | | |
| | | Benzyl chloride | | 100 | |
| Ethanol | Sodium phenoxide | Allyl chloride | 99 | | |
| Ethylene glycol dimethyl ether | Sodium phenoxide | Allyl chloride | | 100 | |
| | | Allyl bromide | | 100 | |
| | | Benzyl chloride | | 100 | |
| | Potassium phenoxide | Allyl bromide ^{c,d} | 99 | | |
| | | Allyl bromide | | 100 | |
| | | Sodium <i>p</i> - <i>t</i> -octylphenoxide | Allyl bromide ^{c,d} | 98 | |
| | | Potassium <i>p</i> - <i>t</i> -octylphenoxide | Benzyl bromide ^{c,d} | 97 | |
| Methanol | Sodium phenoxide | Allyl chloride | | 100 | |
| | | Allyl bromide | 96 | | |
| | | Benzyl chloride | | 100 | |
| | Potassium phenoxide | Benzyl chloride | | 100 | |
| | | Sodium phenoxide | Allyl bromide | 93 | |
| | | Benzyl chloride | | 100 | |
| 1-Propanol | Sodium phenoxide | Allyl bromide ^e | 94 | | |
| | | Benzyl bromide ^e | 96 | | |
| | | Allyl chloride | 96 | | |
| Tetraethylene glycol dimethyl ether | Sodium phenoxide | Allyl bromide | 94 | | |
| | | Benzyl chloride | | 100 | |
| | Sodium phenoxide | Allyl chloride | 96 | | |
| | | Allyl bromide | 94 | | |
| Tetrahydrofuran | Sodium phenoxide | Benzyl chloride | | 100 | |
| | | Allyl bromide | 92 | | |
| | Lithium phenoxide | Allyl bromide | 97 | | |
| | | Potassium <i>p</i> - <i>t</i> -octylphenoxide | Allyl chloride ^d | 97 | |
| Toluene | Potassium <i>p</i> - <i>t</i> -octylphenoxide | Benzyl chloride ^d | 97 | | |

^a All reactions conducted at 27° except when otherwise noted. ^b The analyses for ethers and for carbon-alkylated phenols are by vapor phase chromatography of the crude reaction product which is isolated in 90–100% yield. The only alkylated product detected in this way is the corresponding allyl (or benzyl) ether. It was demonstrated that the procedure employed could readily have detected 0.5% of carbon-alkylated phenol. ^c At 35°. ^d Ref. 9. ^e A. P. Lurie, Ph.D. Thesis, Purdue University, 1958. In these experiments and those of ref. 9, analysis by vapor phase chromatography was not employed.

A recent paper⁹ described the alkylation of phenolic salts with allyl and benzyl halides. It was shown that when the salts of phenols are alkylated *in solution* only oxygen alkylation occurs; it was also established that the truly heterogeneous reaction¹⁰ (*i.e.*, the reaction at the crystal surface) gives exclusively carbon alkylation and that the carbon alkylation thus achieved takes place solely at the *ortho* position.¹¹

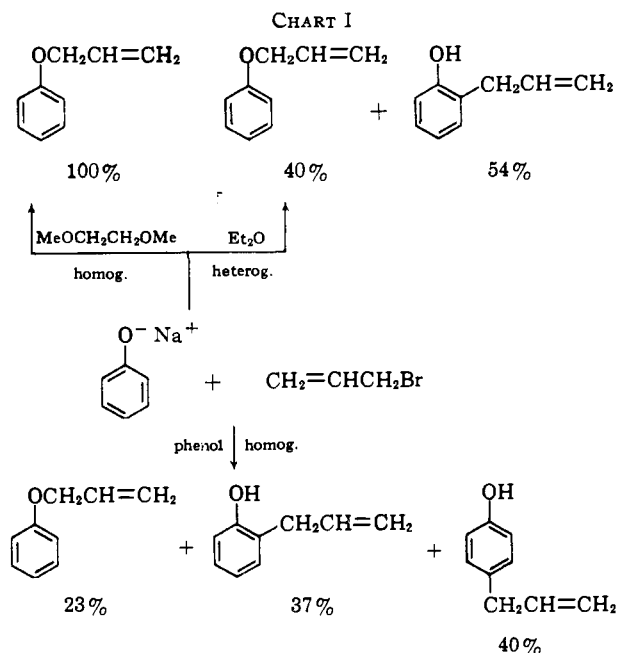
It has now been found that, in certain solvents, *solutions* of phenolic salts react to give much carbon alkylation; furthermore, in contrast to the heterogeneous process, carbon alkylation takes place at both the *ortho* and *para* positions. These solvents are water, phenol and fluorinated alcohols. Chart I illustrates the importance of the medium in which a phenolic salt is alkylated.

The significance of the fact that reactions conducted in water, phenol and fluorinated alcohols give carbon alkylation becomes apparent by comparison with the results summarized in Table I. There it will be seen

(9) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).

(10) Regrettably, there appears to be some misunderstanding as to what is meant by "the truly heterogeneous reaction" and "heterogeneity." These terms refer to a reaction on the surface of a crystalline salt. It is especially important to recognize that the presence of a crystalline salt, *e.g.*, sodium phenoxide, in a reaction mixture does not ensure that any part of the reaction will occur at the crystal surface. For, as we have already pointed out,⁹ the heterogeneous process must compete with the homogeneous process. Thus, the presence of the crystalline salt in a reaction mixture is a *necessary but not a sufficient condition* for "heterogeneity," *i.e.*, for "the truly heterogeneous reaction."

(11) Other factors which favor carbon alkylation are discussed in ref. 9. Also see N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961); N. Kornblum, P. Pink and K. V. Yorka, *ibid.*, **83**, 2779 (1961); N. Kornblum and P. Pink, *Tetrahedron*, in press.



that numerous experiments conducted in a wide variety of solvents lead, in every case, to an essentially quantitative yield of ether. As a check on the validity of the analytical method (vapor phase chromatography), in sixteen of the experiments the products were isolated; invariably the yields of pure ethers fell in the range 91–

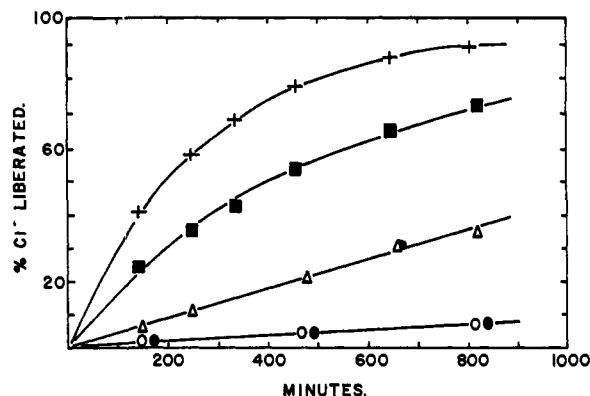


Fig. 1.—Rates of reaction of allyl chloride (0.0275 *M*) at 27.5°: ●, in pure water; ○, in 0.0715 *M* aqueous KClO_4 ; △, in 0.0813 *M* aqueous NaOH solution; ■, in 0.049 *M* aqueous sodium phenoxide solution; +, in 0.098 *M* aqueous sodium phenoxide solution.

99% and there was no evidence of carbon-alkylated phenols (Table I).^{11a}

The results of alkylations conducted in water, phenol and fluorinated alcohols are presented in Table II. The large amount of carbon alkylation¹² observed is in sharp contrast to the results obtained in the solvents of Table I.

TABLE II
SOLVENTS IN WHICH THE HOMOGENEOUS ALKYLATION OF PHENOLIC SALTS RESULTS IN BOTH CARBON AND OXYGEN ALKYLATION^a

| Solvent | Salt | Alkylating agent | Yield, % | |
|---------------------|----------------------------|------------------|-----------------|---------------------------|
| | | | o-alkylation | c-alkylation ^b |
| Water | Sodium phenoxide | Allyl chloride | 49 | 41 |
| | | Allyl bromide | 51 | 38 |
| | | Benzyl chloride | 65 | 24 |
| | Sodium <i>p</i> -cresoxide | Allyl chloride | 67 | 25 |
| | | Allyl bromide | 58 | 30 |
| | | Benzyl chloride | 22 ^d | 78 ^a |
| Phenol ^c | Sodium phenoxide | Allyl chloride | 23 ^d | 77 ^d |
| | | Allyl bromide | 22 | 69 |
| | | Benzyl chloride | 30 ^d | 70 ^d |
| | Potassium phenoxide | Allyl chloride | 58 | 37 |
| | | Allyl bromide | 37 | 42 |
| | | Benzyl chloride | 62 | 26 |

^a All reactions conducted at 27° except when otherwise noted. ^b This includes dialkylated products derived from further alkylation of *o*- and *p*-alkylated phenols. No dialkylation occurs when phenol is the solvent. ^c At 43°. ^d By vapor phase chromatography.

The possibility that the carbon-alkylated phenols produced by conducting these reactions in water, phenol and fluorinated alcohols derive from a carbonium ion process has to be considered, especially since it is known that carbon alkylation, both *ortho* and *para*, occurs when carbonium ions react with phenoxide ions.¹³ This possibility is rejected for several reasons.

(11a) NOTE ADDED IN PROOF.—Using still more sensitive techniques, H. J. Taylor has now demonstrated that traces of carbon alkylated products are formed in THF and in ethylene glycol dimethyl ether.

(12) After the completion of this work we became aware of several reports of carbon alkylation of phenoxides in water. (a) Allyl chloride with sodium phenoxide in water at 38–40° gives both *o*- and *p*-carbon alkylation products (isolated in low yield) [I. L. Kotlyarevskii and T. G. Sheshmakova, *Tr. Vost.-Sibirsk. Filiala, Akad. Nauk S.S.S.R., Ser. Khim.*, No. 4, 32–36 (1956); C. A., 51, 14593 (1957)]. (b) 1,1,1-Trichloropropene-2 and 1,1,2-trichloropropene-2 with sodium phenoxide in water give *p*-carbon alkylation in an unspecified yield [I. L. Kotlyarevskii and A. I. Korbukh, *Tr. Vost.-Sibirsk. Filiala, Akad. Nauk S.S.S.R., Ser. Khim.*, No. 4, 26–31 (1956); C. A., 51, 14594 (1957)]. (c) Allyl chloride and sodium *m*-cresoxide in water gives both *o*- and *p*-carbon alkylation in unstated yield [I. L. Kotlyarevskii, A. A. Samorlova and N. I. Shergina, *Izvest. Sibir. Otdel. Akad. Nauk S.S.S.R.*, No. 6, 54–58 (1958); C. A., 54, 6607 (1960)].

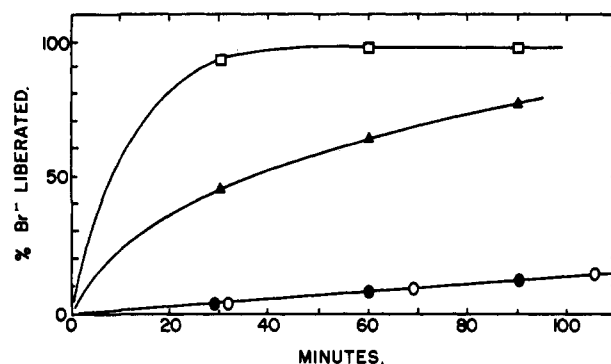


Fig. 2.—Rates of reaction of allyl bromide (0.0259 *M*) at 27.5°: ●, in pure water; ○, in 0.075 *M* aqueous $\text{Mg}(\text{ClO}_4)_2$; ▲, in 0.065 *M* aqueous sodium phenoxide solution; □, in 0.195 *M* aqueous sodium phenoxide solution.

In pure water the rate of the reaction between allyl chloride and sodium phenoxide exhibits a clear dependence on phenoxide concentration (Fig. 1), a dependence that is also observed in reactions employing allyl bromide (Fig. 2). Furthermore, it is clear that this dependence of rate on sodium phenoxide concentration is not a salt effect (*cf.* Fig. 1 and 2). Although the data of Fig. 1 and 2 leave no doubt that the rate depends on phenoxide concentration, they do not establish that the kinetics are clearly first-order in phenoxide. Actually, really precise kinetic data are difficult to obtain because of the circumstance that, while the system allyl chloride, sodium phenoxide and water is initially homogeneous, the products of the reaction, allyl phenyl ether and allyl phenols, almost immediately form a second liquid phase and this extracts allyl chloride from the aqueous layer; as a consequence, the second-order rate constant decreases with time (Table VI). Attempts to prevent development of a second phase by adding organic solvents to the water (up to 25%) were unsuccessful. By graphic extrapolation of the data of Table VI, an initial second-order rate constant of $9 \pm 2 \times 10^{-2}$ l. mole⁻¹ min.⁻¹ over a twenty-six fold change in initial phenoxide concentration was obtained.

The reaction of allyl chloride with sodium hydroxide in water, unlike the corresponding reaction with sodium phenoxide, remains homogeneous and, when followed to 25% reaction, yields a precise second-order rate constant of $3.47 \pm 0.18 \times 10^{-3}$ l. mole⁻¹ min.⁻¹ over a twenty-fold change in initial hydroxide concentration. The fact that this reaction of hydroxide ion, here a poorer nucleophile than phenoxide ion (*cf.* Fig. 1), is unmistakably first-order in hydroxide and first order in allyl chloride provides further support for the view that the reaction of allyl chloride with phenoxide is also a second-order nucleophilic displacement.

The view that the reactions of allyl and benzyl halides with aqueous solutions of sodium phenoxide are $\text{S}_{\text{N}}2$ processes is confirmed by product analysis. If these reactions proceeded *via* carbonium ions, then the halides would in large part be converted to the alcohols.¹⁴ Actually, when allyl chloride, allyl bromide and benzyl chloride are treated with sodium phenoxide in pure water, 85%, 87% and 87%, respectively, of the alkyl groups are accounted for as alkylation products of the phenoxide ion. Also an aqueous solution of sodium *p*-cresoxide, on treatment with allyl chloride or bromide,

(13) Unpublished work by Dr. R. B. Smyth, Purdue University; *cf.* footnote 27 in ref. 9.

(14) Thus, when *t*-butyl chloride is solvolyzed in 70% acetone–30% water containing sodium phenoxide, only 4% of the *t*-butyl carbonium ions are accounted for as phenyl *t*-butyl ether and *t*-butylated phenols. Indeed, even with trityl chloride in 70% acetone–30% H_2O , only 51% of the trityl carbonium ions end up reacting with phenoxide ions.¹⁴

gives a 90% or an 89% yield, respectively, of the alkylation products of the *p*-cresoxide ion. It is clear, then, that the reactions of allyl and benzyl halides with aqueous solutions of phenolic salts are not carbonium ion processes.¹⁵

In molten phenol the reaction of sodium phenoxide with alkyl halides shows a rate dependence on phenoxide concentration which is much too large to be a salt effect (*cf.* Table III). In light of this dependence, alkylations conducted in molten phenol are reasonably looked upon as second order nucleophilic displacements.

TABLE III
RATES OF REACTION IN MOLTEN PHENOL AT 43°

| Reactants ^a | Time, hr. | Reaction, % |
|------------------------|-----------|-------------|
| Allyl chloride | 18.0 | 4 |
| + LiClO ₄ | 17.8 | 8 |
| + sodium phenoxide | 17.5 | 48 |
| Allyl chloride | 24.3 | 5 |
| + LiClO ₄ | 24.0 | 12 |
| + sodium phenoxide | 23.8 | 59 |
| Benzyl chloride | 18.75 | 38 |
| + LiClO ₄ | 19.25 | 46 |
| + sodium phenoxide | 18.25 | 83 |
| Benzyl chloride | 20.0 | 43 |
| + LiClO ₄ | 20.5 | 50 |
| + sodium phenoxide | 21.0 | 88 |

^a All reactions at initial concn. of 0.225 molar.

The reactions of allyl chloride and benzyl chloride with sodium phenoxide in trifluoroethanol also proceed at rates clearly dependent on the phenoxide concentration, and again this is not due to a salt effect (Table IV). As would be expected for a non-carbonium ion

TABLE IV
RATES OF REACTION IN TRIFLUOROETHANOL AT 27.5°

| Reactants ^a | Time, hr. | Reaction, % |
|------------------------|-----------|-------------|
| Allyl chloride | 45 | 0.8 |
| + LiClO ₄ | 45 | 0.9 |
| + sodium phenoxide | 44 | 12 |
| Allyl chloride | 237 | 1.3 |
| + LiClO ₄ | 237 | 1.5 |
| + sodium phenoxide | 237 | 31 |
| Benzyl chloride | 5.0 | 0.5 |
| + LiClO ₄ | 4.75 | 0.6 |
| + sodium phenoxide | 4.50 | 10.5 |
| Benzyl chloride | 44.00 | 1.1 |
| + LiClO ₄ | 43.75 | 1.5 |
| + sodium phenoxide | 43.50 | 63.3 |

^a All reactants at initial concn. of 0.225 molar.

process, from 77% to 89% of the alkyl halide employed is isolated as an alkylation product of the phenoxide ion.¹⁶

(15) The essentially quantitative accounting for allyl and benzyl halides as products of phenoxide alkylation also rules out the possibility that hydroxide ions derived from hydrolysis of phenoxide ions are reacting with the halides. This is not surprising, since at the initial concentration of phenoxide employed (1.5 molar) only about 1% of the phenoxide is hydrolyzed. Also, because excess phenoxide is used, at the conclusion of the reaction the solution is 0.10 to 0.15 molar in phenoxide and this is only hydrolyzed to the extent of 2 to 3%. Furthermore, as can be seen from Fig. 1, phenoxide is a better nucleophile than hydroxide in these reactions.

(16) In fluorinated alcohols the reaction of phenoxide ion with the solvent must be considered, *e.g.*, $C_6H_5O^- + CF_3CH_2OH \rightleftharpoons C_6H_5OH + CF_3CH_2O^-$. The possible significance of such equilibria may be appreciated from the K_a 's (in water) of phenol, 1.0×10^{-10} , trifluoroethanol, 4.3×10^{-12} , and 2,2,3,3-tetrafluoropropanol, 4.6×10^{-12} . [P. Donner and J. Hildebrand, *J. Am. Chem. Soc.*, **74**, 2824 (1952); P. Ballinger and F. Long, *ibid.*, **81**, 1050 (1959); R. N. Hazeldine, *J. Chem. Soc.*, 175B (1953)]. While it is not possible to calculate from this information the percentage alcoholysis in these fluorinated alcohols, it is probable that a significant fraction of the phenoxide ion has reacted with trifluoroethanol to give phenol and $CF_3CH_2O^-$. Nonetheless, the excellent yields of alkylation products of the

The full significance of these findings becomes apparent when it is recognized that the examples of carbon alkylation herein described are not unique in being second-order processes; the purely oxygen alkylation reactions of sodium phenoxide with allyl bromide in methanol and in ethanol are also second order¹⁷ and there can be little doubt that this is true of the other instances of purely oxygen alkylation recorded in Table I. Thus, the incorporation of different solvent molecules into an otherwise identically constituted activated complex produces a profound change in the reaction course. It is proposed that the transition states of reactions conducted in water, phenol and fluorinated alcohols are significantly different from those of reactions carried out in the solvents of Table I because of (1) *selective solvation* of the phenoxide anion and (2) enhanced solvation of the leaving group of the alkylating agent,¹⁸ and that these two effects, *operating jointly*, produce the observed differences in reaction course.

By "selective solvation" we mean that when an anion such as the phenoxide ion is dissolved in water, phenol and fluorinated alcohols, substances which are unusually effective at forming hydrogen bonds,¹⁹ the oxygen of the phenoxide ion is so intensely solvated that the availability of the oxygen for nucleophilic displacement is greatly decreased; as a consequence, displacements employing the otherwise unfavored *ortho* and *para* carbon atoms can compete successfully.^{20,21}

Support for the concept of selective solvation comes from studies of the displacement of halogen from alkyl halides by iodide and bromide ions in acetone solution; the rates of such reactions are known to be significantly decreased by the addition of small amounts of water,²²⁻²⁴ phenol²⁴ and ethanol.²⁴ Cavell,²³ who studied

phenoxide ion (*vide supra*) show that fluorinated alkoxide ions produced in equilibria such as the foregoing do not compete effectively with phenoxide ions for the alkyl halide. This is consistent with the fact that fluoroalkoxide ions are known to be very weak nucleophiles toward alkyl halides [A. Henne and M. Smook, *J. Am. Chem. Soc.*, **72**, 4378 (1950); F. L. Scott, *Chem. Ind. (London)*, 224 (1959)]. The possibility that phenol produced by solvolysis of phenoxide ion is responsible for the selective solvation (*vide infra*) cannot be dismissed; however, it seems unreasonable to assign the role of innocent bystander to the fluorinated alcohols.

(17) K. Lauer and H. Shingu, *Ber.*, **69**, 2731 (1936).

(18) The consequences of enhanced solvation of the leaving group will be discussed in a subsequent paper.

(19) L. M. Mukherjee and E. Grunwald, *J. Phys. Chem.*, **62**, 1311 (1958); H. C. Eckstrom, J. E. Berger and L. R. Dawson, *ibid.*, **64**, 1458 (1960).

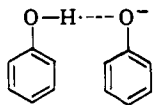
(20) Simultaneous with our Communication¹ describing these results and the concept of selective solvation, H. D. Zook and T. J. Russo [*J. Am. Chem. Soc.*, **82**, 1258 (1960)] reported that ethylation of sodiodiphenylacetophenone in the dimethyl ether of diethylene glycol occurs almost exclusively at the oxygen atom to give the enol ether 1,2,2-triphenyl-1-ethoxyethene. However, in *t*-butyl alcohol, carbon alkylation to give α , α -diphenylbutyrophenone occurs to the extent of 25%. Zook and Russo ascribe this difference to "specific solvation," by which they presumably mean the same thing as selective solvation. We prefer the term "selective solvation" because it emphasizes the idea that the phenoxide ion is more intensely solvated at oxygen than anywhere else. Then, too, "specific solvation" has been used to describe solvation of symmetrical systems, *e.g.*, the solvation of chlorine atoms by aromatic hydrocarbons [R. F. Hudson, *Proc. Chem. Soc.*, 258 (1957)]; the solvation of iodide ions by water, phenol and ethanol [S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens and J. S. Gall, *Tetrahedron Letters*, No. 9, 29 (1960)]; and the solvation of sodium ions by DMF, DMSO and pyridine N-oxide [H. E. Zaugg, B. W. Horrom and S. Borgwardt, *J. Am. Chem. Soc.*, **82**, 2895 (1960)]. It is noteworthy that the ambident anion studied by Zook and Russo has its reaction path altered by *t*-butyl alcohol, a solvent which is not able to cause the phenoxide ion to undergo carbon alkylation (Table I). Clearly the system studied by Zook and Russo is more delicately balanced than the phenoxide ion. Another ambident anion which responds more readily than phenoxide ion to solvent changes is the β -naphthoxide ion.⁵

(21) Since the publication of the Communications by Zook and Russo²⁰ and ourselves,¹ R. Barner and H. Schmid [*Helv. Chim. Acta*, **43**, 1393 (1960)] also have reported that the reaction of sodium phenoxide with allyl bromide in aqueous alcohol, aqueous dioxane or water gives, in addition to the ether, *o*- and *p*-allylphenol, and have presented a discussion of their findings.

(22) L. J. LeRoux and S. Sugden, *J. Chem. Soc.*, 1279 (1939).

(23) E. A. S. Cavell, *ibid.*, 4217 (1958); also see E. A. S. Cavell and J. A. Speed, *ibid.*, 226 (1961).

the retarding effect of small amounts of water on the rate at which iodide ions react with *n*-butyl bromide in acetone, has postulated that a specific interaction between iodide ion and water, productive of the entity $(I, H_2O)^-$, occurs, and that it is less reactive than I^- . Similarly, Leary and Kahn²⁴ have attributed the retarding effect of added water, phenol and ethanol on the isotopic exchange between potassium iodide and benzyl iodide in acetone to hydrogen bonding of iodide ion by these hydroxylic compounds; hydrogen-bonded iodide ion is taken to be much less reactive than iodide ion solvated by acetone. It is also of interest that the existence of phenoxide ion hydrogen-bonded to phenol



has been postulated to account for anomalous behavior at or near the half-neutralization point in non-aqueous titrations and that the isolation and characterization of such a phenolic half-salt derived from 4-formamido-3,4-xyleneol has been reported.²⁵

In summary, it is clear that selective solvation plays a significant role in controlling the course of ambident anion alkylations. This, aside from its intrinsic interest, may be turned to good account. For, in contrast to non-ambident systems, we deal here with changes not only of rate but also of product distribution and so are provided with a new and simple probe for investigating solvent effects in organic reactions.

Experimental²⁶

The phenol employed was Dow U.S.P., free of any inhibitor. This was distilled *in vacuo* to remove traces of water.²⁷ The CF_3CH_2OH (Pennsalt) and $HCF_2CF_2CH_2OH$ (du Pont) were allowed to stand over sodium carbonate, then over anhydrous magnesium sulfate and, finally, rectified; n_D^{20} 1.2917 and 1.3204, respectively.²⁸ The diethyl ether used was Mallinckrodt anhydrous grade. Dioxane was purified by the method of Hess and Frahm²⁹; tetrahydrofuran was distilled from KOH pellets. The ethylene glycol dimethyl ether was dried over CaH_2 and distilled from $LiAlH_4$. All the other organic solvents were purified by distillation from CaH_2 . The halides were redistilled from CaH_2 : allyl chloride, n_D^{20} 1.4154; allyl bromide, n_D^{20} 1.4655; benzyl chloride, n_D^{20} 1.5415.

Sodium phenoxide was made in two ways: (1) by the method reported previously⁹ and (2) by the procedure of Vogel.³⁰ In the latter procedure, to a suspension of 24 g. (1.0 mole) of sodium hydride in 50 ml. of tetrahydrofuran was slowly added, with cooling in an ice-bath, a solution of 33 g. (0.35 mole) of phenol in 100 ml. of tetrahydrofuran. When addition was complete, the ice-bath was removed and the mixture stirred overnight. The resulting mixture was filtered in a dry nitrogen atmosphere and the filtrate was added to 2 l. of petroleum ether (b.p. 65–67°). This produced a white precipitate which was filtered, washed with five 100-ml. portions of petroleum ether (b.p. 65–67°), and dried overnight in a desiccator at 1 mm. The yield was 36 g. (88%).

Anal. Calcd. for C_6H_5ONa : neut. equiv., 116.1. Found: neut. equiv., 116.3, 115.8.

Potassium phenoxide was prepared as described by Kornblum and Lurie.⁹ Here, as with the other salts, each batch was used only if it gave a satisfactory analysis.

Lithium Phenoxide.—To a suspension of 15 g. (2.2 moles) of lithium hydride in 50 ml. of tetrahydrofuran was added slowly, with cooling (ice-bath), a solution of 65.8 g. (0.70 mole) of phenol in 150 ml. of tetrahydrofuran. After addition was complete the ice-bath was removed and the mixture was stirred for an

additional 6 hours after which it was filtered in a dry-box. The filtrate was evaporated at room temperature and 40 mm. and, finally, at 1 mm. at 100° for 48 hours. The yield was 67 g. (95%) of a white powder.

Anal. Calcd. for C_6H_5OLi : Li, 6.94; neut. equiv., 100.0. Found: Li, 7.29, 7.31; neut. equiv., 102.0.

Alkylations were conducted under nitrogen. For those reactions in which water was the solvent, agitation was provided by tumbling. Rates of reaction were followed by one of three procedures. (1) The consumption of phenoxide salt as determined by titrating an aliquot in water with standard hydrochloric acid to a brom thymol blue end-point; (2) where the alkali metal halide formed remained in solution, an aliquot was titrated potentiometrically for chloride ion with standard silver nitrate; (3) in a few instances unreacted halide was determined according to the method of Schwenk, Papa and Ginsberg.³¹

Allyl Bromide with Sodium Phenoxide in Dimethylformamide at 27°.—This exemplifies the procedure used in those cases listed in Table I wherein allyl phenyl ether was isolated. To 18.6 g. (0.16 mole) of sodium phenoxide dissolved in 200 ml. of DMF at 27° was added, over a 10-minute period with stirring, 19.4 g. (0.16 mole) of allyl bromide; reaction was complete after 5 hours. The product was added to 300 ml. of water, made acidic with 10% hydrochloric acid, and extracted with ten 30-ml. portions of benzene. The benzene solution was extracted with six 30-ml. portions of 10% aqueous sodium hydroxide, washed with water and dried (solution I). The alkaline washings were combined, layered with benzene and acidified at 0–10°; the aqueous phase was repeatedly extracted with benzene and the extracts were dried over anhydrous magnesium sulfate. On removal of the solvent no residue remained. When solution I was distilled, 19.5 g. (91% yield) of pure allyl phenyl ether was obtained, b.p. 73–75° (7 mm.), n_D^{20} 1.5206, lit.³² n_D^{20} 1.5208. The infrared spectrum of this product was identical with that of an authentic sample of allyl phenyl ether.

Benzyl Chloride with Sodium Phenoxide in Dimethylformamide at 27°.—This illustrates the procedure used in those instances in which the alkylation product was determined by V.P.C. analysis (Table I). To a solution of 4.65 g. (0.04 mole) of sodium phenoxide in 30 ml. of DMF was added 5.06 g. (0.04 mole) of benzyl chloride after which the solution was made up to 50 ml. with DMF. The rate of reaction was followed by titration of 2-ml. aliquots for unreacted phenoxide with hydrochloric acid; after 3 hours the reaction was complete. The product was added to 200 ml. of water, made acidic with 10% hydrochloric acid and extracted with eight 50-ml. portions of benzene. The benzene solution was washed with four 50-ml. portions of water, dried over anhydrous magnesium sulfate and then the solvent was removed *in vacuo*. The 7.50 g. of solid residue (99% allowing for 4% loss in aliquots following the rate) was found by V.P.C. analysis to be benzyl phenyl ether free of either *o*- or *p*-benzylphenol. It was demonstrated that under these conditions 1% of *o*-benzylphenol in benzyl phenyl ether gives a distinct *o*-benzylphenol peak and that even as little as 0.5% would have been detected.

(A) Allyl Bromide and Sodium Phenoxide in Water at 27°.—Phenol (30.1 g., 0.32 mole) was added to 12.8 g. (0.32 mole) of sodium hydroxide in 200 ml. of water. The resulting solution was protected by a nitrogen atmosphere and to it was added 36.3 g. (0.30 mole) of allyl bromide; the two-liquid phase system was agitated by tumbling. The reaction was complete after 2 days, at which time the product was made acidic with 10% hydrochloric acid and extracted with three 75-ml. portions of benzene. The aqueous phase was saturated with sodium chloride and continuously extracted with benzene for 48 hours. The combined benzene solutions were extracted with eight 50-ml. portions of 10% aq. sodium hydroxide, with five 50-ml. portions of Claisen potash³³ (the last two extracts were not cloudy after acidification), washed with water and dried over anhydrous magnesium sulfate (solution I). The combined alkaline extracts were layered with benzene and acidified with 18% aq. hydrochloric acid at 0–15°. The aqueous phase was extracted with three 75-ml. portions of benzene and then continuously extracted with benzene for 48 hours. The combined benzene solutions were dried over anhydrous magnesium sulfate (solution II).

Distillation of solution I gave 18.78 g. of allyl phenyl ether, b.p. 97–99° (31 mm.), n_D^{20} 1.5208–1.5210.

Anal. Calcd. for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.38; H, 7.37.

In addition, 1.79 g. of higher boiling material, b.p. 104–112° (10 mm.), n_D^{20} 1.5239–1.5300, was obtained. This, by vapor phase chromatography (V.P.C.), was shown to be a mixture of the allyl ethers of *o*- and *p*-allylphenols (26% allyl ether of *o*-allylphenol and 76% allyl ether of *p*-allylphenol).

(31) E. Schwenk, D. Papa and H. Ginsberg, *Anal. Chem.*, **15**, 576 (1943).

(32) C. D. Hurd and L. Schmerling, *J. Am. Chem. Soc.*, **59**, 108 (1937); E. M. Filachione, J. H. Lengel and W. P. Ratchford, *ibid.*, **73**, 839 (1950).

(33) L. Claisen, *Ann.*, **418**, 96 (1919).

(24) J. A. Leary and M. Kahn, *J. Am. Chem. Soc.*, **81**, 4173 (1959).

(25) A. T. Shulgin and H. O. Kerlinger, *J. Org. Chem.*, **26**, 2037 (1960).

(26) Analyses are by Dr. C. S. Yeh, Mrs. B. Groten and Mrs. V. Kebly, Purdue University, and Galbraith Microanalytical Laboratories, Knoxville, Tenn. The infrared absorption spectra were determined by Mrs. W. Dilling on Perkin-Elmer models 21 and 221 spectrophotometers.

(27) It is a pleasure to acknowledge our indebtedness to the Dow Chemical Co. for a generous gift of phenol.

(28) We thank Pennsalt Chemicals Corp. and the Organic Chemicals Department of the du Pont Co. for very substantial gifts of these alcohols.

(29) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(30) C. Vogel, Ph.D. Thesis, Purdue University, June, 1960.

Anal. Calcd. for $C_{12}H_{16}O$: C, 82.83; H, 8.10. Found: C, 82.63; H, 8.35.

Solution II was separated into four fractions by distillation: fraction 1, 8.63 g., b.p. 79–105° (8 mm.), which by V.P.C. was shown to consist of 47% phenol, 34% *o*-allylphenol and 19% *p*-allylphenol; fraction 2, 6.78 g., b.p. 105–112° (8 mm.), which by V.P.C. analysis was 29% *o*-allylphenol and 71% *p*-allylphenol. Fraction 2 was analyzed.

Anal. Calcd. for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.32; H, 7.44.

Fraction 3, 1.25 g., b.p. 112–116° (8 mm.), which by V.P.C. analysis was 83% *p*-allylphenol and 17% of a mixture of 2,6- and 2,4-diallylphenol; fraction 4, 1.30 g., b.p. >117° (8 mm.), which by V.P.C. analysis was 39% *p*-allylphenol and 61% of a mixture of 2,6- and 2,4-diallylphenol. When 3.10 g. of fraction 2 was chromatographed on silica gel, eluting with benzene and then with 1:1 benzene-methanol, 0.80 g. of *o*-allylphenol (26% of fraction 2) was isolated, n_D^{20} 1.5466; lit. values, n_D^{20} 1.5450,³² n_D^{20} 1.5461⁹; its infrared spectrum was identical with that of an authentic sample⁹ and lastly, it has the composition of *o*-allylphenol.

Anal. Calcd. for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.54; H, 7.30.

In addition, 1.98 g. (64% of fraction 2) of *p*-allylphenol was isolated, n_D^{20} 1.5451, lit. value³⁴ n_D^{20} 1.5448. *Anal.* Calcd. for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.50; H, 7.59. This, by the method of Brewster and Ciotti,³⁵ was converted into the 3,5-dinitrobenzoate of *p*-allylphenol which, when recrystallized from aqueous acetone, has m.p. 103.5–104° (94% yield), lit. m.p.³⁴ 103.5–104.5°.

When 0.80 g. of fraction 4 was chromatographed on silica gel, 0.45 g. of 2,4-diallylphenol was obtained. *Anal.* Calcd. for $C_{12}H_{16}O$: C, 82.83; H, 8.10. Found: C, 82.82; H, 7.94. This gave a phenylurethan in ca. 80% yield, m.p. 87.5–88°, lit. m.p.³³ 88–88.5°. *Anal.* Calcd. for $C_{12}H_{16}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.76; H, 6.54; N, 5.03.

It will be seen, then, that 0.320 – 0.043 = 0.277 mole of phenoxide reacted with allyl bromide and of this 0.140 mole was converted to allyl phenyl ether. Therefore, 51% of the phenoxide underwent oxygen alkylation. The carbon alkylation products obtained were *o*- and *p*-allylphenol, diallylphenols and the allyl ethers of *o*- and *p*-allylphenol; the total number of moles of these products isolated is 0.104; that is, 38% carbon alkylation. *p*-Alkylation of the phenoxide ion takes place ca. 1.9 times as often as *o*-alkylation.

Allyl chloride was treated with sodium phenoxide in water at 27° as in A.

(B) Benzyl Chloride with Sodium Phenoxide in Water at 27°.—As in the allyl bromide experiment, 0.32 mole of sodium phenoxide in water was treated with 38.0 g. (0.30 mole) of benzyl chloride. After 20 days of tumbling the two-phase system was worked up as usual, except that the phenolic material which dissolved in 10% aqueous sodium hydroxide was not combined with the phenolics which required Claisen potash to be extracted.

Distillation of the neutral fraction gave 33.05 g. (0.178 mole) of benzyl phenyl ether, b.p. 105–108° (1 mm.), m.p. 39°, lit.³⁶ m.p. 39°. *Anal.* Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.62; H, 6.35. In addition, 1.70 g. of a higher boiling liquid, b.p. 130° (1 mm.), which has the composition and an infrared spectrum consistent with that of a mixture of the benzyl ethers of *o*- and *p*-benzylphenol, was obtained. *Anal.* Calcd. for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.83, 87.61; H, 6.71, 6.82.

From the phenolic material extracted by 10% aqueous alkali there was isolated, by distillation, 4.13 g. of phenol, b.p. 71–75° (9 mm.), m.p. 40–41°, and 10.62 g., b.p. 116–126° (1 mm.), of a material which by V.P.C. analysis was 38% *o*-benzylphenol and 62% *p*-benzylphenol. Three grams of this material was chromatographed on silica gel using benzene as the eluent; this gave 1.18 g. of *o*-benzylphenol, m.p. 53–54°.³⁷

Anal. Calcd. for $C_{12}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.76; H, 6.48. The 3,5-dinitrobenzoate of *o*-benzylphenol, after recrystallization from aqueous acetone, melted at 158.5–159°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 63.44; H, 3.73; N, 7.41. Found: C, 63.51; H, 3.90; N, 7.10.

Following the *o*-benzylphenol, the silica gel column yielded 1.97 g. of *p*-benzylphenol when eluted with methanol; m.p. 83.5–84.0°, lit.³⁸ m.p. 83–84°. *Anal.* Calcd. for $C_{12}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.73; H, 6.58. The 3,5-dinitrobenzoate melts at 117.5–118°.

(34) S. Palkin and P. Wells, *J. Am. Chem. Soc.*, **55**, 1556 (1933).

(35) J. Brewster and C. Ciotti, *ibid.*, **77**, 6214 (1955).

(36) S. G. Powell and R. Adams, *ibid.*, **42**, 646 (1920); W. Short and M. Stewart, *J. Chem. Soc.*, 553 (1929).

(37) *o*-Benzylphenol exists in two forms, a stable form melting at 52° and a labile form melting at 21°; L. Claisen, *Ann.*, **442**, 240 (1925).

(38) K. Clemmensen, *Ber.*, **47**, 682 (1914).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.23; H, 3.94; N, 7.23.

The phenolic material, insoluble in 10% aqueous alkali but soluble in Claisen potash, weighed 1.75 g. This viscous yellow liquid had an infrared spectrum with a large number of peaks, every one of which is present in the spectrum of 2,4- or 2,6-dibenzylphenol. Unfortunately, this sample was accidentally lost. However, there can be little doubt that it was, in essence, a mixture of the 2,4- and the 2,6-dibenzylphenols. Since this material represents only 2% of the product, this assignment, if incorrect, cannot significantly affect the conclusion concerning the proportion of carbon alkylation. Thus, there was observed 24% C- and 65% O-alkylation. The *para/ortho* ratio is ca. 1.6.

(C) Allyl Chloride and Sodium *p*-Cresoxide in Water at 27°.—Sodium hydroxide (11.2 g., 0.28 mole) was dissolved in 180 ml. of water and in this 30.3 g. (0.28 mole) of *p*-cresol was dissolved under a nitrogen atmosphere. Allyl chloride (19.7 g., 0.258 mole) was added and the two-phase system agitated by tumbling. The reaction was complete after 10 days. The reaction mixture was worked up as in the alkylation of phenoxide. The neutral, solvent-free fraction weighed 24.88 g. and by V.P.C. analysis was found to be 96% allyl cresyl ether and 4% the allyl ether of 2-allyl-4-cresol.

The phenolic fraction weighed 12.46 g.; on chromatographing 3.0 g. on silica gel and eluting with benzene the following were isolated: (a) A liquid (0.14 g.) whose infrared spectrum is entirely consistent with that expected from 2,6-diallyl-4-cresol. *Anal.* Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.71; H, 8.44. This phenol gave a 3,5-dinitrobenzoate, m.p. 87.5–88°. *Anal.* Calcd. for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.34; H, 5.08; N, 7.24.

(b) 2-Allyl-4-cresol (1.89 g.), n_D^{20} 1.5396; lit. n_D^{20} 1.5350,³⁹ n_D^{16} 1.5424,⁴⁰ n_D^{15} 1.5425,⁴¹ n_D^{20} 1.5405.⁴² *Anal.* Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.16; H, 8.21. The phenylurethan melted at 67–68°, lit.⁴³ m.p. 68°. *Anal.* Calcd. for $C_7H_7O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.59; H, 6.51; N, 5.30. Following this, the silica gel column was eluted with benzene-methanol (1:1), whereupon 0.95 g. of *p*-cresol was recovered.

Thus, there was observed 25% C-alkylation and 67% O-alkylation.

Allyl bromide was treated with sodium *p*-cresoxide in water at 27° as in C.

Allyl chloride was treated with sodium phenoxide in 2,2,3,3-tetrafluoropropanol-1 at 27° as in D.

Allyl Bromide and Sodium Phenoxide in 2,2,2-Trifluoroethanol at 27°: as in D.

(D) Benzyl Chloride and Sodium Phenoxide in 2,2,2-Trifluoroethanol at 27°.—To a solution of 23.2 g. (0.20 mole) of sodium phenoxide in 200 ml. of trifluoroethanol, 24.0 g. (0.19 mole) of benzyl chloride was added and then the volume was adjusted to 250 ml. with trifluoroethanol. After 15 days the reaction mixture was worked up in the usual way. The neutral fraction weighed 21.90 g. On molecular distillation (<0.01 mm.) of 13.20 g., benzyl phenyl ether (10.16 g.), m.p. 36–39°, was isolated; 1.80 g. of material did not distill. When 1.15 g. of this residue was chromatographed on silica gel, using benzene-petroleum ether for elution, 0.28 g. of the benzyl ether of *o*-benzylphenol (infrared spectrum identical with that of an authentic sample) was obtained; following this, 0.79 g. of the benzyl ether of 4-benzylphenol was isolated, m.p. and mixture m.p. 48–49°, lit.³⁶ m.p. 49.5°.

The phenolic material soluble in 10% aqueous alkali weighed 8.90 g. Distillation at 10 mm. of 7.45 g. of this liquid gave 4.12 g. of phenol, b.p. 72–74°, m.p. 36–39°, and a 3.0-g. residue which, by V.P.C. analysis, was 60% *o*-benzylphenol and 40% *p*-benzylphenol. The phenolic material which required Claisen potash for extraction weighed 2.20 g.; when 1.20 g. was chromatographed on silica gel using benzene as the eluent, 0.14 g. of 2,6-dibenzylphenol and 1.06 g. of 2,4-dibenzylphenol were obtained; these had infrared spectra identical with the spectra of authentic samples. Thus, 26% C- and 62% O-alkylation was evident.

(E) Allyl Bromide and Sodium Phenoxide in Phenol at 43°.—Sodium phenoxide (4.90 g., 0.0422 mole) was dissolved in 95.1 g. of phenol at 43°. Thirty grams of this solution was placed in a glass tube and, after cooling to 0°, 1.45 g. (0.012 mole) of allyl bromide was introduced; the tube was then sealed and maintained at 43° for 10 days. On cooling the product was poured into 50 ml. of water, acidified with 10% hydrochloric acid and extracted with six 50-ml. portions of benzene. The benzene solution was dried over anhydrous magnesium sulfate

(39) C. D. Hurd and W. A. Yarnall, *J. Am. Chem. Soc.*, **59**, 1687 (1937).

(40) L. Claisen, *Ann.*, **401**, 44 (1913).

(41) K. von Auwers, *ibid.*, **422**, 174 (1921).

(42) V. I. Pansevich-Kolyada and Z. B. Idelchik, *J. Gen. Chem. U.S.S.R.*, **25**, 2177 (1955) (Eng. Translation).

(43) A. J. Hill and L. E. Graf, *J. Am. Chem. Soc.*, **37**, 1845 (1915).

and then the solvent was removed *in vacuo*. V.P.C. analysis of the residue, including comparisons with known mixtures of phenol, allyl phenyl ether and *o*- and *p*-allylphenols, showed 37% *o*- and 40% *p*-allylphenol and 23% allyl phenyl ether, indicating 77% C- and 23% O-alkylation.

Allyl chloride and sodium phenoxide in phenol at 43° was carried out as in E.

(F) Benzyl Chloride and Sodium Phenoxide in Phenol at 43°.—(a) To 30 g. of a phenol solution containing 1.63 g. (0.014 mole) of sodium phenoxide was added 1.52 g. (0.0212 mole) of benzyl chloride as described above. After 12 days at 43° the sealed tube was opened and the reaction product worked up in the usual way; V.P.C. analysis, including comparison with synthetic mixtures, showed 35% *o*-benzylphenol, 37% *p*-benzylphenol and 28% benzyl phenyl ether; 72% C- and 28% O-alkylation.

(b) The validity of the V.P.C. procedure was demonstrated in a preparative scale experiment: 19.5 g. (0.168 mole) of sodium phenoxide was dissolved in 380.5 g. of phenol at 43° and 20.3 g. (0.160 mole) of benzyl chloride was added. After 16 days at 43° most of the phenol was removed at 1 mm. pressure and a temperature below 80°, and the residue was added to 150 ml. of water and acidified with 10% hydrochloric acid. The product was then worked up in the usual way. The neutral fraction consisted of 6.40 g. of benzyl phenyl ether, m.p. 39° and mixture m.p. 39° with an authentic sample. The phenolic fraction weighed 20.71 g.; when 3.00 g. was chromatographed on silica gel (benzene eluent), clean separation into *o*-benzylphenol (1.42 g., m.p. and mixture m.p. 52–53°) and *p*-benzylphenol (1.53 g., m.p. 82–84°, mixture m.p. 82–84°) took place, demonstrating 69% C-alkylation and 22% O-alkylation.

Benzyl chloride was treated with potassium phenoxide in phenol at 43° as in part a of F.

Rate of Hydrolysis of Allyl Chloride at 27.5°.—An aqueous allyl chloride solution was prepared by shaking allyl chloride with distilled water at 27.5° for a few minutes and then allowing the two-phase system to settle for 20 minutes. The clear aqueous phase was then delivered into 50-ml. volumetric flasks to the mark, the remaining volume filled with glass beads, and the flasks stoppered with rubber serum bottle caps. After holding in a thermostated bath at 27.5°, an aliquot was removed, acidified with 10% aq. nitric acid, and extracted with benzene; the benzene solution was washed with water and the combined aqueous solutions were titrated potentiometrically with standard silver nitrate. In this way the amount of allyl chloride which hydrolyzed was determined. To determine the initial concentration of allyl chloride, another aliquot of the aq. allyl chloride solution was treated with Raney nickel alloy to convert the organic halogen into halide ion⁴¹ and then the chloride ion was titrated potentiometrically. In three runs, 1.60 g. (0.01 mole) of lithium perchlorate trihydrate was added to the 50-ml. flask prior to introducing the aqueous allyl chloride solution. Table V gives the results.

Rate of Reaction of Allyl Chloride with Sodium Phenoxide in Water at 27.5°.—Sodium phenoxide was weighed into five volumetric flasks in such an amount that on dilution to 100 ml. with the aq. allyl chloride solution, the concentrations of sodium phenoxide were 0.0100, 0.0306, 0.0521, 0.1061 and 0.2600 molar. These solutions were kept at 27.5° and the rate of reaction followed by potentiometrically titrating 5-ml. aliquots for the chloride ion liberated. In calculating for the second-order rate constants, the concurrent solvolysis of allyl chloride was taken into account.⁴⁴ These rate constants (Table VI)

(44) For this, and other details, the doctoral dissertation of P. J. Berrigan should be consulted.

TABLE V

KINETICS OF HYDROLYSIS OF ALLYL CHLORIDE AT 27.5°

| Time, min. | Molar concn. of allyl chloride | | 10 ⁴ k ₁ , min. ⁻¹ ^b |
|------------|--------------------------------|--------------------|--|
| | Initial | At time t | |
| 590 | 0.0364 | 0.0342 | 1.08 |
| 2945 | .0352 | .0256 | 1.09 |
| 2980 | .0271 | .0197 ^a | 1.07 |
| 3010 | .0279 | .0202 | 1.07 |
| 4265 | .0295 | .0192 ^a | 1.02 |
| 4380 | .0291 | .0181 ^a | 1.08 |
| 4940 | .0296 | .0174 | 1.08 |

^a In 0.40 M aqueous lithium perchlorate solution. ^b Average $k_1 = 1.07 \pm 0.01 \times 10^{-4} \text{ min.}^{-1}$.

were plotted *vs.* the time interval in which they were determined and from this series of curves an initial second-order rate constant, $9 \pm 2 \times 10^{-2} \text{ l. mole}^{-1} \text{ min.}^{-1}$, was extrapolated.

Rate of Reaction of Allyl Chloride with Sodium Phenoxide in Phenol at 43°.—To two tubes each containing 11.0 g. of phenol at 0° was added 0.190 g. (0.0025 mole) of allyl chloride (0.225 molal). Similarly, 0.190 g. of allyl chloride was added to two tubes each containing 11.0 g. of a 0.225 molal solution of sodium phenoxide in phenol and to two tubes each containing 11.0 g. of a 0.225 molal solution of anhydrous lithium perchlorate in phenol. These tubes were sealed at 0°, quickly brought to 43° and the resulting clear solutions maintained at 43°. After the time intervals given in Table III the tubes were opened and the chloride ion determined.

TABLE VI

ALLYL CHLORIDE AND SODIUM PHENOXIDE IN WATER AT 27.5°
[Allyl chloride]₀ = 0.042 M

| Time, min. | [Phenoxide] ₀ , M | 10 ⁴ k ₁ , l. mole ⁻¹ min. ⁻¹ | | | | |
|------------|------------------------------|---|--------|--------|--------|--------|
| | | 0.0100 | 0.0306 | 0.0521 | 0.1061 | 0.2600 |
| 30 | | 10.7 | 11.3 | 7.50 | 5.45 | 5.38 |
| 68 | | 8.36 | 6.10 | 5.37 | 4.12 | 4.93 |
| 100 | | 7.82 | 5.20 | 4.27 | 3.93 | 4.60 |
| 140 | | 6.60 | 5.27 | 4.30 | 3.85 | 4.71 |
| 187 | | 5.30 | 4.34 | 3.76 | 3.65 | 4.17 |
| 361 | | | 4.12 | 3.76 | 3.51 | 2.69 |

The data for benzyl chloride (Table III) were obtained in the same way.

Rate of Reaction of Allyl Chloride with Sodium Phenoxide in Trifluoroethanol at 27.5°.—To two tubes each containing 10 ml. of trifluoroethanol at 0° was added 0.172 g. (0.00225 mole) of allyl chloride. Similarly, 0.172 g. of allyl chloride was added to two tubes each containing 10 ml. of a 0.225 M solution of sodium phenoxide in trifluoroethanol, and to two tubes each containing 10 ml. of a 0.225 M solution of anhydrous lithium perchlorate in trifluoroethanol. The tubes were sealed at 0° and then brought to 27.5°. After the time intervals noted in Table IV, the chloride ion produced was determined.

The results recorded in Table IV for benzyl chloride were similarly obtained.