

Mechanism of Bimolecular Nucleophilic Substitution. Part 9.¹ Stereochemical Course of *ortho*-Alkylation of Phenoxide Ion with Optically Active Alkyl Halides under S_N2 Reaction Conditions

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The rate, product distribution, and stereochemical course for reactions of sodium phenoxide with 1-phenylethyl chloride and butyl bromide, respectively in acetone and in 2,2,2-trifluoroethanol at 100.0°, have been investigated as a function of phenoxide concentration. Alkylation with both halides obeys second-order kinetics. The rate constants increase at lower phenoxide concentrations, indicating that dissociated phenoxide ion has higher nucleophilic reactivity than the ion-pair or higher aggregates. The results of product analyses for the reactions at various phenoxide concentrations reveal that the dissociated phenoxide ion does not afford the *C*- but solely the *O*-alkyl derivative, where the ion-pair can give rise to both *C*- and *O*-alkyl derivatives. Alkylations with optically active 1-phenylethyl chloride and [1-²H]butyl bromide show that *O*- and *para*-alkylation (one of the possible *C*-alkylations) proceed with complete inversion of configuration, whereas the *ortho*-alkyl derivatives possess inverted configurations but accompanied by considerable (30–70%) racemization, despite their formation under S_N2 reaction conditions. This is explained by *ortho*-alkylation proceeding partly by front-side attack of the phenoxide ion-pair, probably *via* a cyclic six-membered transition state. The possibility of a correlation between the mechanism of this sterically unexpected bimolecular *ortho*-alkylation and Snee's ion-pair mechanism, proposed for bimolecular S_N reactions, is discussed.

It has been known for a long time that S_N2 type displacement proceeds with Walden inversion; for the reactions of various optically active secondary,² and even primary,³ alkyl halides, one-to-one correlation of inversion with S_N2 type displacement has been demonstrated. However, as regards ambident anion reaction with optically active alkyl halides, there have heretofore been reported two examples with stereochemical courses which cannot

† In ref. 4 no description of the comparison of the net steric course (%) of *O*- and *C*-alkylation is given.

¹ Part 8, K. Okamoto, S. Fukui, I. Nitta, and H. Shingu, *Bull. Chem. Soc. Japan*, 1967, **40**, 2354.

² (a) E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1935, 1525; (b) S. H. Harvey, P. A. T. Hoye, E. D. Hughes, and C. K. Ingold, *ibid.*, 1960, 800; (c) H. M. R. Hoffmann and E. D. Hughes, *ibid.*, 1964, 1252.

be explained by the general principle of Walden inversion in the S_N2 reaction.

First, Hart and Eleuterio⁴ reported on the results of alkylation with inversion of some phenols with optically active 1-phenylethyl chloride in acetone in the presence of potassium carbonate.† When we calculated the net steric course (%) from their data using the maximum rotations for the respective alkyl derivatives,^{4,5} we confirmed that *O*-alkylation of the phenoxide, *p*-cresoxide, and 2,6-xyleneoxide ions proceeds with almost

³ A. Streitwieser, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 1117.

⁴ H. Hart and H. S. Eleuterio, *J. Amer. Chem. Soc.*, 1954, **76**, 516.

⁵ K. Okamoto, H. Yamada, I. Nitta, and H. Shingu, *Bull. Chem. Soc. Japan*, 1966, **39**, 299.

complete inversion, whereas *C*-alkylation of *p*-cresoxide and 2,6-xylenoxide anions is accompanied by considerable racemization.* These racemizations strongly suggest that the *C*-alkylation of these phenoxide ions might partly include a retentive course other than usual S_N2 pathway proceeding with inversion.

Secondly, Suama *et al.*⁵ reported the unexpected result that β -dicarbonyl anions in dimethyl sulphoxide attack optically active 1-methylpropyl bromide with retention of configuration during *C*-alkylation; they suggested that *C*-alkylation is not a simple S_N2 reaction but some

tration of phenoxide ion for each solvent are illustrated in Figure 1; the plots are linear with a negative slope at lower phenoxide concentrations. At higher concentrations ($>0.01M$), however, the curves become flat suggesting that aggregates are important at those concentrations. The values of the ion-pair dissociation constant (K) and the limiting equivalent conductance (λ_0), calculated by the method of Fuoss and Kraus,⁷ are also presented in Table 1. Although calculated dissociation constants decrease in the order tetrahydrofuran (THF) $>$ acetone $>$ water $>$ 2,2,2-trifluoroethanol (TFE), it is obvious for each solvent that at the concentrations ($>0.100M$), at which the product

TABLE 1
Measured specific conductance (κ) equivalent conductance (λ), limiting equivalent conductance (λ_0), and ion-pair dissociation constant (K) of sodium phenoxide at 25.0°

Solvent	$K/\text{mol l}^{-1}$ ^a	[NaOPh]/M	$\kappa/\text{mho cm}^{-1}$	$\lambda/\text{mho cm}^2 \text{mol}^{-1}$	$\lambda_0/\text{mho cm}^2 \text{mol}^{-1}$
H_2O	5.62×10^{-14}	9.05×10^{-1}	3.70×10^{-2}	4.09×10	2.1×10^8
		1.78×10^{-6}	6.03×10^{-5}	3.39×10^4	
CF_3CH_2OH	2.56×10^{-14}	1.57	7.06×10^{-2}	4.50×10	1.4×10^8
		1.05×10^{-8}	8.80×10^{-6}	8.38×10^5	
Acetone	6.42×10^{-19}	1.50×10^{-3}	3.21×10^{-5}	2.12×10	1.1×10^8
		2.50×10^{-7}	4.52×10^{-7}	1.83×10^3	
THF	2.17×10^{-22}	1.00×10^{-1}	6.50×10^{-7}	6.50×10^{-3}	1.0×10^7
		1.00×10^{-7}	4.40×10^{-8}	4.40×10^2	

^a Accurate to within $\pm 10\%$.

front-side attack of the ambident anion must have occurred.

Since these observations merely concerned product analysis and lacked confirmation of the mechanism, we decided to obtain information which would contribute to the interpretation of this discrepancy between the stereochemical course for *O*- and *C*-alkylation. Using the key ambident ion, the configurationally rigid phenoxide ion, the kinetics, product distribution, and stereochemical course for reactions with optically active 1-phenylethyl chloride and [1-²H]butyl bromide were examined under conditions where the reactions proceed strictly by a bimolecular mechanism.

RESULTS

Dissociation Constants of Sodium Phenoxide in Several Protic and Aprotic Solvents.—Since it is known that ionic nucleophiles react with alkyl halides not only as the dissociated ion but also in the form of the ion-pair or higher aggregates, it is necessary for consideration of the mechanism to examine the extent of dissociation of the ion-pair at concentrations and temperatures at which the reaction proceeds,⁶ prior to the product and kinetic studies. For this purpose conductometry of solutions containing various concentrations of sodium phenoxide at 25° was carried out. Although the actual reaction temperature was higher than 25°, it was expected that the magnitude of the dissociation constants at higher temperature would not deviate significantly from those at 25°.† Measured specific conductances (κ) and equivalent conductances (λ) in several solvents are given in Table 1. Plots of $\log \lambda$ against \log concen-

* In the case of phenoxide ion Hart and Eleuterio⁴ did not separate the *ortho*- and *para*-alkyl derivatives, so that the steric course was not established.

† It is known that the magnitude of the dissociation constants for various quaternary ammonium salts^{7a,b} and hexachloroantimonates^{7b,c} change by two or three times over a temperature range of ca. 70°.

analyses were conducted, most ($>99.9\%$) sodium phenoxide exists in the form of the ion-pair or higher aggregates.

Alkylation of Sodium Phenoxide with 1-Phenylethyl Chloride.—(A) *Product distribution.* Hart and Eleuterio⁴ carried out the alkylation of phenol with 1-phenylethyl chloride in acetone containing suspended potassium carbonate; they did not isolate *ortho*- and *para*-alkylated

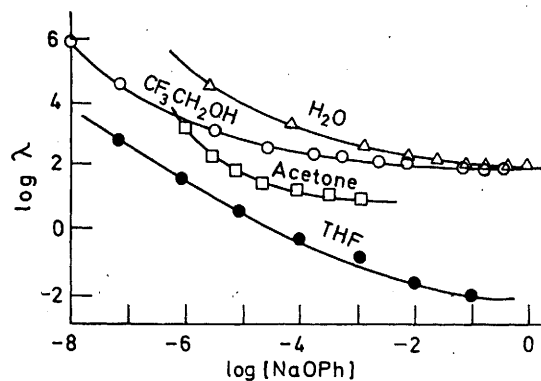


FIGURE 1 Effect of sodium phenoxide concentration on the equivalent conductance (λ) in various solvents at 25.0°

phenols separately. We followed their experiment under modified conditions, using sodium phenoxide instead of phenol and potassium carbonate in an ampoule at 100.0° and isolated *o*- and *p*-1-phenylethylphenol by column chromatography and then preparative t.l.c. The product distributions were determined by g.l.c. in separate runs with various phenoxide concentrations. The results are illustrated in Figure 2.

⁶ For recent model studies, see S. G. Smith and D. V. Milligan, *J. Amer. Chem. Soc.*, 1968, **90**, 2393; P. Beronius and L. Pataki, *ibid.*, 1970, **92**, 4518.

⁷ R. M. Fuoss and C. A. Kraus, *J. Amer. Chem. Soc.*, 1933, **55**, 476.

The product distribution of the *C*-alkyl derivatives (alkylated phenols) decreases with decrease in the phenoxide concentrations and approaches zero at zero concentration upon graphical extrapolation, whereas the product distribution of the *O*-alkyl derivative (the phenyl ether) reaches

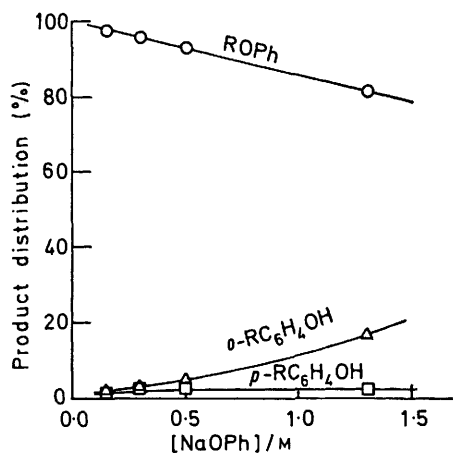


FIGURE 2 Effect of sodium phenoxide concentration on the product distributions in the reaction of 1-phenylethyl chloride in acetone at 100.0°

almost 100% at lower phenoxide concentrations (see also Table 6).

From the change in product distribution, it is concluded that in this reaction the dissociated phenoxide ion affords only the *O*-derivative, whereas the ion-pair gives rise to both *O*- and *C*-derivatives.

(B) *Rate of alkylation.* Titrimetric rate constants for runs with various concentrations of sodium phenoxide in acetone at 100.0° were measured by use of the Volhard method; the second-order plot exhibited an upward drift during the run especially after 50% conversion. The integrated second-order rate constants increase to about three times the initial rate constant by the end of the reaction. After each run we found *ca.* 0.07M-diacetone alcohol in the reaction mixture. This alcohol seems to be produced from solvent acetone by self-condensation in the presence of higher concentrations of sodium phenoxide. In a separate run with initially added diacetone alcohol (0.05M) the initial rate constant increased *ca.* 2.6 fold. Therefore, it is probable that the increase in the integrated second-order rate constant is primarily due to acceleration by diacetone alcohol concomitantly produced from acetone as the reaction progresses. On the basis of these observations, the initial rate constant, calculated graphically from the second-order plots at <50% conversion, was considered as the intrinsic second-order rate constant not affected in the presence of diacetone alcohol; the results are tabulated in Table 7 (see Experimental section). The graphical presentation in Figure 3 indicates that at concentrations >0.3M-sodium phenoxide k_2 is virtually constant and corresponds to the rate constant for the phenoxide ion-pair, whereas at lower concentrations the rate constant increases reflect the higher reactivity of the dissociated phenoxide ion.

(C) *Stereochemical course.* The products from optically active 1-phenylethyl chloride were isolated, purified, and subjected to measurements of rotation. The net steric courses for the products were calculated by the use of

maximum rotations in Table 2; the results are summarized in Table 3.

TABLE 2
Maximum rotation (°) of (*R*)-1-phenylethyl and (*R*)-[1-²H]butyl derivatives

	ROH	RCI	RBr
1-Phenylethyl	+45.7 ^a	+129 ^b	
[1- ² H]Butyl	+0.185 ^e		+0.57 ^f
	ROPh	<i>o</i> -RC ₆ H ₄ OH	<i>p</i> -RC ₆ H ₄ OH
1-Phenylethyl	-37.4 ^c	+25.2 ^d	-13.4 ^d
[1- ² H]Butyl	-1.87 ^g		

^a α_D (neat, 1 dm).¹⁷ ^b α_D (neat, 1 dm), calculated from +45.7° for ROH at 125°. ^c $[\alpha]_D$ (benzene).¹⁵ ^d $[\alpha]_D$ (benzene); previous values (+27.85° and -10.26°, respectively¹⁵) were redetermined by the use of a chemical method. ^e α_D (neat, 1 dm).¹⁹ ^f α_D (neat, 1 dm).¹⁸ ^g $[\alpha]_D$ (ethanol).

The stereochemical courses for phenyl ether and *para*-alkyl formation are almost completely (95–100%) inverted, whereas the *ortho*-alkyl derivative is formed with 70–53% inversion of configuration. In view of the slight (1–2%) racemization of the unchanged chloride and the almost complete inversion of the *O*- and *para*-derivatives, the substantial (30–47%) racemization for *ortho*-alkylation is obviously not due to racemization of unchanged chloride. On the basis of this stereochemical result along with the trend observed in the rate measurements and product analyses, it is most probable that the dissociated phenoxide ion gives completely inverted *O*-derivative, whereas the phenoxide ion-pair can give rise to retained *C*-derivative (*o*-1-phenylethylphenol) besides the usual inverted product.

Alkylation of Sodium Phenoxide with Butyl Bromide.—(A) *Product distribution.* Butyl bromide was selected as a

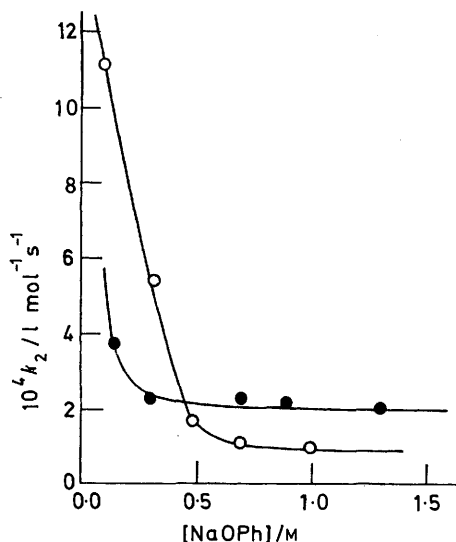


FIGURE 3 Effect of sodium phenoxide concentration on the titrimetric rate constant in the reactions of 1-phenylethyl chloride in acetone (●) and of butyl bromide in 2,2,2-trifluoroethanol (○) at 100.0°

substrate which reacts with a nucleophile by a typical S_N2 mechanism; as a solvent in which *C*-alkylation of the ambident ion proceeds with ease, TFE was chosen.⁸ Prior to the kinetic and stereochemical studies, the yield of the *C*-derivative from the phenoxide ion was examined for

⁸ N. Kornblum, R. Seltzer, and P. Haberfeld, *J. Amer. Chem. Soc.*, 1963, **85**, 1148.

the reaction at various sodium phenoxide concentrations at 100.0° by the use of g.l.c. analysis. The results are in Table 4 along with the yield of *O*-derivative (butyl phenyl ether).

Under these reaction conditions the yield of *C*-derivatives (*o*- and *p*-butylphenol) are low (0.1–2.8%). However, the possibility that the *C*-derivatives are produced by a mechanism other than S_N2 can be eliminated on the basis of the following facts. (a) In each run even a trace of butyl 2,2,2-trifluoroethyl ether was not detected by the g.l.c. analysis. This indicates that sodium phenoxide does not react with TFE to afford sodium 2,2,2-trifluoroethoxide and phenol, and consequently there is no chance of the formation

analysis. The disappearance of phenoxide was followed titrimetrically and the second-order plot gave a straight line to at least 70% reaction. The results as a function of phenoxide concentrations are illustrated in Figure 3 (see also Table 8).

In a fashion similar to the results for 1-phenylethyl chloride, the rate constant increases with decrease in the concentration of the phenoxide ion, reflecting an increase in the concentration of the more reactive dissociated ion in the reaction medium.

(C) *Stereochemical course*. Sodium phenoxide was subjected to alkylation with optically active [$1-^2H$]butyl bromide in TFE at 100.0° for 20 h. The products were

TABLE 3

Net steric course of alkylation in the reaction of sodium phenoxide with 1-phenylethyl chloride in acetone at 100.0°

[RCl]/M { α_D (°)} ^a	[NaOPh]/ M	t/h	RCl recovered		Net steric course (%) {[α_D] (°)} ^b		
			Recovery (%) { α_D (°)} ^a	Racemiz- ation (%)	Ether	<i>o</i> -Phenol ^c	<i>p</i> -Phenol ^c
0.100 {−28.6}	0.502	44			101.2 ± 2.4 inv. {−8.4 ± 0.2}	62.9 ± 2.8 inv. {+3.52 ± 0.16}	
0.200 {+49.0}	1.301	24			100.0 ± 1.4 inv. {+14.2 ± 0.2}	53.2 ± 2.1 inv. {−5.09 ± 0.20}	
0.200 {−37.6}	1.297	0.75	9.7 {−37.1}	1.3	99.2 ± 0.9 inv. {−10.8 ± 0.1}		
0.800 {−54.25}	0.726	5 ^d	71.6 {−53.05}	2.2	100.3 ± 0.3 inv. {−15.8 ± 0.04}	70.1 ± 1.8 inv. {+7.43 ± 0.19}	95.2 ± 7.3 inv. {−5.37 ± 0.41}

^a Neat, 1 dm, accurate to within ±0.6%. ^b In benzene. ^c *C*-alkylated products. ^d At reflux temperature.

TABLE 4

Product yields as a function of phenoxide concentration for the reaction of sodium phenoxide with butyl bromide in 2,2,2-trifluoroethanol at 100.0°

[RBr]/M	[NaOPh]/N	[PhOH]/M	[H ₂ O]/M	t/h	Yield (%) ^a		
					Ether	<i>o</i> -RC ₆ H ₄ OH	<i>p</i> -RC ₆ H ₄ OH
0.100				44	0.00 ^a	0.00 ^a	0.00 ^a
0.078	0.101			44	73.4	2.01	0.13
0.074	0.302			44	74.1	2.08	0.11
0.077	0.501			44	72.5	2.31	0.23
0.076	0.688			44	72.5	2.80	0.45
0.106	0.241	0.010		22	64.8	0.00	0.00
0.102	0.241	0.020		22	63.9	0.00	0.00
0.100	0.100		0.101	22	63.3	0.00	0.00
0.100	0.100		0.211	22	66.5	0.00	0.00
0.100	0.500 ^b			20	70.1	1.5	0.15
0.100	0.500 ^c			20	86.8	1.5	0.39

^a No butyl 2,2,2-trifluoroethyl ether was detected by the use of g.l.c. analysis. ^b Under illumination. ^c In an evacuated tube.

of the 2,2,2-trifluoroethyl ether from butyl bromide and the ethoxide and of the formation of the *C*-derivatives from butyl bromide and phenol. Also, though phenol may be produced in small amount in TFE accidentally contaminated with water, the possibility of formation of *C*-derivatives from phenol can be eliminated, since reactions carried out in the presence of added phenol (0.1–0.2M) no longer gave rise to *C*-compounds (Table 4). (b) Even when the reaction was conducted in an evacuated ampoule or under illumination, no appreciable increase in the yield of the *C*-compound was observed within experimental error (Table 4). In addition, it has recently been claimed^{9c} that phenyl radical gives rise merely to the *O*-derivative in the S_{RN} reaction of iodobenzene with phenoxide anion. Thus, there is no need to invoke a mechanism involving the butyl radical and the phenoxide anion, *i.e.*, the S_{RN} mechanism,⁹ to explain the formation of *C*-derivative.

(B) *Rate of alkylation*. The rate measurements were conducted under conditions identical to those for product

isolated by column chromatography, and the optical rotation of [$1-^2H$]butyl phenyl ether was determined polarimetrically. The optical purity was calculated from the maximum rotation (Table 2) determined from the results of chemical conversion of [$1-^2H$]butyl bromide to the phenyl ether under strict S_N2 conditions (see Experimental section). The *C*-derivatives, owing to their very small rotations and low yields, were converted to methyl [$2-^2H$]pentanoate by permanganate oxidation and by the subsequent methylation with diazomethane. The optical purities of the esters were then determined by the use of 1H n.m.r. shift reagent method with tris[3-trifluoroacetyl-(+)-camphorato]europium(III). The results are in Table 5 along with calculated net steric courses.

O-Alkylation proceeds with complete inversion as

⁹ (a) C. Kerber, G. W. Urry, and N. Kornblum, *J. Amer. Chem. Soc.*, 1964, **86**, 3904; (b) J. K. Kim and J. F. Bunett, *ibid.*, 1970, **92**, 7463; (c) S. Rajan and P. Sridaran, *Tetrahedron Letters*, 1977, 2177.

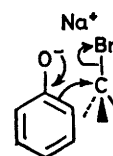
expected for a typical S_N2 reaction, whereas the inverted *ortho*-derivative is accompanied by appreciable amounts (70%) of racemization. The steric course for the formation of the *para*-compound seems to be complete inversion, although the comparatively large error in the measurement of the optical purity makes this result less unambiguous. These trends in stereochemical course of alkylation with butyl bromide are compatible with those for 1-phenylethyl chloride, and suggest that the phenoxide ion-pair can afford in part the *ortho*-alkyl derivative with retention of configuration.

DISCUSSION

The features for phenoxide alkylation common to both 1-phenylethyl chloride and butyl bromide can be summarized as follows.

- (A) Alkylation of the phenoxide ion for both systems takes place by a bimolecular displacement mechanism.
 (B) The dissociated phenoxide ion does not afford

cyclic six-membered transition state as the explanation for the formation of the *ortho*-compounds.^{8,10} However, they have not considered the configurational problem. Thus, the substantial racemization observed only in the case of bimolecular *ortho*-alkylation allows us to contend



SCHEME

that this cyclic transition state results from front-side attack on a saturated carbon atom, a retentive S_N2 reaction,¹¹ in part, if not in whole, though complete one-to-one correspondence of the cyclic transition state with front-side attack has not been established.

TABLE 5

Net steric course of alkylation in the reaction of sodium phenoxide with [1-³H]butyl bromide in 2,2,2-trifluoroethanol at 100.0°

[RBr]/M { α_D (°)} ^a	[NaOPh]/M	t/h	Net steric course (%) { $[\alpha]_D$ (°)} ^b		
			Ether	<i>o</i> -Phenol ^c	<i>p</i> -Phenol ^c
0.196 {−0.136 ± 0.004}	0.717	20	100.3 ± 0.9 inv. {−0.448 ± 0.004}	30.2 ± 3.2 inv.	90.5 ± 11 inv.

^a Neat, 1 dm. ^b In ethanol. ^c C-Alkylated products; calculated from the optical purities of methyl [2-³H]pentanoate, derived from the C-alkyl derivatives (see text).

alkylphenols but solely the alkyl phenyl ether, whereas the ion-pair or higher aggregates can give rise to both the C- and O-derivatives. This correlation of the formation of C-derivative with the ion-pair reaction has heretofore been known in alkylation with the other ambident ions.⁶ (C) O-Alkylation of the phenoxide ion proceeds with complete inversion, whether the phenoxide reacts in the form of the ion-pair or of the dissociated ion. From this stereochemical result and the bimolecular kinetics it is concluded that the O-alkylation proceeds by a typical S_N2 mechanism. (D) *para*-Alkylation of the phenoxide ion-pair affords the *para*-alkylphenol with almost completely inverted configuration, most probably by an S_N2 mechanism. (E) *ortho*-Alkylation of the phenoxide ion-pair takes place with inversion of configuration accompanied by considerable racemization, although alkylation proceeds by a bimolecular mechanism.

The fact that the *ortho*-alkylation of the phenoxide ion-pair proceeds with considerable racemization provides support for the view that a retentive displacement, front-side attack by the phenoxide ion-pair, is taking place competitively with the usual S_N2 inversion mechanism. Several investigators have proposed a

* In the case of the secondary system, we reported,¹³ prior to Sneen's proposal,¹² that diphenylmethyl halide reacts with hindered phenoxides in acetonitrile by a second-order mechanism but the substrate reacts *via* an ion-pair intermediate, *i.e.*, an Arrhenius-type intermediate, in the S_N1 mechanism.

¹⁰ C. K. Ingold, *Ann. Reports*, 1926, 142; D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, 1958, **80**, 1391.

Another point of interest as regards front-side attack of the phenoxide ion-pair may be a correlation of this sterically unexpected *ortho*-alkylation with Sneen's ion-pair mechanism for a bimolecular displacement reaction.¹² Sneen has proposed that S_N2 -type substitution proceeds through an ion-pair intermediate but that the total rate can be expressed as a second-order reaction, provided that the rate-limiting step is not the first ionization but the reaction of the ion-pair with a nucleophile. The generality of Sneen's ion-pair mechanism would be difficult to prove in the case of a primary system* and is still under debate.¹⁴ If this *ortho*-alkylation is taking place by Sneen's mechanism, front-side attack by the phenoxide ion-pair *via* a four-centre transition state may be possible. However, this is less attractive because it has been proved that in phenolysis^{5,15} the phenoxide ion (most probably the ion-pair) prefers back- to front-side attack on the S_N1 ion pair intermediate.

Experiments for further correlation between this bimolecular retentive *ortho*-alkylation of the phenoxide

¹¹ To date, only one example of the retentive S_N2 reaction has been claimed for a bromocyclopropane derivative, H. Yamaguchi, K. Kawada, T. Okamoto, E. Egert, H. J. Lindner, M. Braun, R. Dammann, M. Liesner, H. Neumann, and D. Seebach, *Chem. Ber.*, 1976, **109**, 1589.

¹² R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, 1966, **88**, 2593; 1969, **91**, 362.

¹³ K. Okamoto, Y. Matsui, and H. Shingu, *Bull. Chem. Soc. Japan*, 1965, **38**, 1844.

¹⁴ For a recent discussion, see D. J. McLennan, *Accounts Chem. Res.*, 1976, **9**, 281.

¹⁵ K. Okamoto, T. Kinoshita, Y. Takemura, and H. Yoneda, *J.C.S. Perkin II*, 1975, 1426.

ion-pair and Snee's mechanism^{12,13} are in progress in the case of the 2-norbornyl system.

EXPERIMENTAL

¹H N.m.r. spectra were obtained on Hitachi R-24 60 MHz and Varian HA-100D 100 MHz spectrometers in CCl₄ with tetramethylsilane as internal standard. I.r. spectra were recorded on a Hitachi 215 i.r. spectrophotometer. G.l.c. was performed with a Hitachi 023-6003 gas chromatograph with a thermal conductivity detector using a 3 mm stainless steel column. Optical rotations were recorded on a JASCO DIP-SL polarimeter using a cell with pathlength 1 dm. Microanalyses were performed by the Elemental Analysis Centre, Kyoto University. Products were identified by comparison of their n.m.r. and i.r. spectra and g.l.c. retention times with those of authentic samples.

Materials.—The resolution of 1-phenylethanol was performed by the Pope-Peachey method.¹⁶ Optically active and racemic 1-phenylethyl chlorides were prepared by reactions of 1-phenylethanol with thionyl chloride in the manner previously reported⁵ or with phosphoryl chloride in pyridine.¹⁷ (S)-(-)-[1-²H]Butyl bromide [α_D^{23} -0.214 ± 0.008° (neat, 1 dm)], was prepared by the reaction of phosphorus tribromide with (R)-(+)-[1-²H]butan-1-ol,¹⁸ [α_D^{24} +0.160 ± 0.004° (neat, 1 dm)], which had been synthesized by an asymmetric reduction of butyraldehyde by 2-[2-²H]bornyloxymagnesium bromide.¹⁹

Sodium phenoxide was prepared by refluxing a toluene solution of phenol with sodium metal under dry nitrogen in the dark and was immediately purified by digesting with dry benzene three times; the purity determined by titration was >99.9%.

1-Butyl 2,2,2-trifluoroethyl ether was synthesized by the reaction of 1-butyl bromide with sodium 2,2,2-trifluoroethoxide prepared from 2,2,2-trifluoroethanol and sodium metal in DMF *in situ*.

Other organic reagents were dried and fractionated prior to use.

Conductance Measurements.—Conductance of the solutions containing various concentrations of sodium phenoxide was measured with a TOA Electronics M-6A conductometer. The conductance cell, a TOA CG-2001 PL cell, had a cell constant of 0.099 00 cm⁻¹ and a volume of 15 ml, required to cover the electrodes. The cell was immersed into a water-bath thermostatted at 25.0 ± 0.1°. Measured specific conductance (κ) and equivalent conductance (λ) in several solvents are tabulated for the representative values in Table 1.

Synthesis of Optically Active [1-²H]Butyl Phenyl Ether.—A solution of (S)-(-)-[1-²H]butyl bromide [0.624 g; $\alpha_D^{21.0}$ -0.080 ± 0.006° (neat, 1 dm)], in anhydrous DMF (100 ml) containing sodium phenoxide (0.200M) was prepared under dry nitrogen and was maintained at 25.0° for 21 h. After work-up preparative t.l.c. (silica gel) of the residual oil gave (R)-(-)-[1-²H]butyl phenyl ether {0.513 g; [$\alpha_D^{20.5}$ -0.263 ± 0.004° (*c* 27.0, ethanol)]; the structure was assigned on the basis of spectral data and elemental composition (Table 9). A duplicate run of the bromide [$\alpha_D^{26.6}$ -0.042° (neat, 1 dm)] with sodium phenoxide (0.300M) gave

¹⁶ S. H. Wilen, R. Davidson, R. Spector, and H. Steffanou, *Chem. Comm.*, 1969, 603.

¹⁷ A. Streitwieser, jun., and L. Reif, *J. Amer. Chem. Soc.*, 1964, **86**, 1988.

the phenyl ether (64.7%), { $[\alpha_D^{29.5}$ -0.137° (*c* 7.30, ethanol)}. The optical rotation ratio (3.28 ± 0.05) of the phenyl ether and the bromide is virtually constant in spite of variation in the concentration of added sodium phenoxide.

Determination of Product Distribution.—(A) *Reactions of 1-phenylethyl chloride.* According to the previously reported procedure,²⁰ product distributions for reactions of 1-phenylethyl chloride with sodium phenoxide were assayed by g.l.c. by the use of diphenyl ether as internal standard. The results are summarized in Table 6.

TABLE 6

Product distributions as a function of phenoxide concentration for the reaction of sodium phenoxide with 1-phenylethyl chloride in acetone at 100.0° for 24 h

[RCI]/ M	[NaOPh]/ M	Product distribution (%) ^a		
		Ether	<i>o</i> -RC ₆ H ₄ OH	<i>p</i> -RC ₆ H ₄ OH
0.100	0.150	97.7	1.0	1.3
0.100	0.298	95.5	2.5	2.0
0.200	0.499	93.1	4.5	2.4
0.200	1.301	81.0	17.2	1.8

^a Total yields were 66.1—87.7%.

(B) *Reactions of butyl bromide.* Product distributions for reactions of butyl bromide with sodium phenoxide were analysed by g.l.c. by the use of a Hitachi Golay column Q-45 at 170° and *t*-butylbenzene as internal standard in the manner previously described.²⁰ The results are summarized in Table 6.

Rate Measurements.—(A) *Reactions of 1-phenylethyl chloride.* The usual sealed ampoule (4 ml) technique was employed. The reactions were followed by the Volhard titration method. The rate data are in Table 7.

TABLE 7

Initial rate constants as a function of phenoxide concentration for the reaction of sodium phenoxide with 1-phenylethyl chloride in acetone at 100.0°

[RCI]/M	[NaOPh]/M	10 ⁴ <i>k</i> ₂ /l mol ⁻¹ s ⁻¹ ^a
0.099	0.149	3.77
0.200	0.301	2.27
0.200	0.700	2.29
0.200	0.898	2.10
0.200	1.299	2.01

^a Accurate to within ±3%.

TABLE 8

Rate constants as a function of phenoxide concentration for the reaction of sodium phenoxide with butyl bromide in 2,2,2-trifluoroethanol at 100.0°

[RBr]/M	[NaOPh]/M	10 ⁴ <i>k</i> ₂ /l mol ⁻¹ s ⁻¹ ^a
0.100	0.101	11.1
0.100	0.314	5.40
0.117	0.487	1.65
0.103	0.690	1.11
0.101	1.020	1.01

^a Accurate to within ±1%.

(B) *Reactions of butyl bromide.* Rate measurements for reactions of butyl bromide with sodium phenoxide were

¹⁸ V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1966, **88**, 3595.

¹⁹ A. Streitwieser, jun., J. R. Wolfe, jun., and W. D. Schaeffer, *Tetrahedron*, 1959, **6**, 338.

²⁰ K. Okamoto and T. Kinoshita, *Bull. Chem. Soc. Japan*, 1972, **45**, 2802.

carried out by the sealed ampoule (1 ml) technique and by titration with 0.01 N-HCl by the use of lacmoid as an indicator. The rate data are summarized in Table 8.

Isolation of Products.—(A) *Reactions of 1-phenylethyl chloride.* The usual procedure¹⁵ was employed; a typical run is as follows. A solution of (*R*)-(+)-1-phenylethyl chloride [2.812 g; $\alpha_D^{21.2} + 49.0 \pm 0.3^\circ$ (neat, 1 dm)], and

The *o*-butylphenol was subjected to permanganate oxidation in acetone^{4,20} to give [2-²H]pentanoic acid (0.0363 g), subsequently converted into methyl [2-²H]pentanoate (0.289 g) by diazomethane prior to n.m.r. analysis. The *p*-butylphenol afforded the deuteriated ester (0.0181 g) in the same manner. The products were identified by their spectral data and elemental composition (Table 9).

TABLE 9
B.p.s, spectral data, and elemental compositions of [1-²H]butyl derivatives

B.p. (°C)	ROPh	<i>o</i> -RC ₆ H ₄ OH	<i>p</i> -RC ₆ H ₄ OH	RCO ₂ H	RCO ₂ Me
	76—80 at 4 mmHg	82—86 at 4 mmHg	88—92 at 4 mmHg	187—189	73—80 at 6 mmHg
	$\nu_{\max.}/\text{cm}^{-1}$ ^a				
$\nu_{\text{C-H}}$	2 950 1 430	2 960 1 450	2 960 1 460	2 960 1 410	2 950 1 430 1 360
$\nu_{\text{arom.ring}}$	1 600 1 500	1 600 1 510	1 610 1 520		
$\nu_{\text{O-H}}$		3 620	3 450	3 200—2 500	
$\nu_{\text{C-O-C}}$	1 230				
$\nu_{\text{C=O}}$				1 710	1 740
	δ ^a				
Methyl H	0.97 (t)	0.95 (t)	0.90 (t)	0.92 (t)	0.93 (t) 3.65 (s)
Methylene H	1.20—1.90 (4 H, m) 3.93 (1 H, t)	1.30—1.90 (4 H, m) 2.55 (1 H, t)	1.30—1.85 (4 H, m) 2.45 (1 H, t)	1.18—1.65 (4 H, m) 2.15 (1 H, t)	1.15—1.85 (4 H, m) 2.30 (1 H, t)
Ring H	6.75—7.35 (5 H, m)	6.50—7.15 (4 H, m)	6.55—7.05 (4 H, m)		
OH		4.80 (s)	5.40 (s)	11.75 (s)	
	Elemental composition				
Calc. C (%)	79.45	79.45	79.45	58.25	61.5
Found C (%)	79.25	79.2	79.55	58.45	61.65
Calc. ¹ H + ² H (%)	10.0	10.0	10.0	10.75	11.15
Found ¹ H + ² H (%)	10.05	10.0	10.25	10.9	11.15

^a In CCl₄.

TABLE 10
Determination of optical purity of methyl [2-²H]pentanoate converted from [1-²H]butylphenols by ¹H n.m.r. spectroscopy^a using the Eu(facac)₃^b shift reagent technique

[1- ² H]Butylphenol	Proton ^c	Shifts for enantiomers (p.p.m.) ^d	Peak area ratio ^e	Optical purity (%)	
				Mean value ^f	
<i>ortho</i>	2-H (t)	2.02; 1.99	1.1 ₆ : 1.0 ₀	7.4	7.2 ± 0.8
<i>para</i>	2-H (t)	2.30; 2.26	1.6 ₀ : 1.0 ₀	23	22 ± 3

^a Taken with a 100 MHz n.m.r. instrument. ^b Tris[3-trifluoroacetyl-(+)-camphorato]europium(III), 0.1M; the methyl ester molar ratios were 0.5. ^c ν 6.6 Hz. ^d Downfield shift from the original proton (δ 2.30) for each enantiomers (see text). ^e Mean value for the triplet peak. ^f Of duplicate measurements.

sodium phenoxide (1.300N) in dry acetone (100 ml) was kept at 100.0° for 24 h. After work-up, (*S*)-(+)-1-phenylethyl phenyl ether {1.277 g; $[\alpha]_D^{19.6} + 14.2 \pm 0.2^\circ$ (*c* 2.29, benzene)}, and (*S*)-(–)-*o*-1-phenylethylphenol {0.252 g; $[\alpha]_D^{22.0} - 5.09 \pm 0.20^\circ$ (*c* 1.98, benzene)}, were obtained. The results are summarised in Table 3.

(B) *Reaction of [1-²H]butyl bromide.* A solution of (*S*)-(–)-[1-²H]butyl bromide [8.28 g; $\alpha_D^{24.5} - 0.136^\circ$ (neat, 1 dm)] and sodium phenoxide (0.717M) in 2,2,2-trifluoroethanol (300 ml) was kept at 100.0° for 20 h. After the usual work-up (*R*)-(–)-[1-²H]butyl phenyl ether {2.918 g; $[\alpha]_D^{17.5} - 0.448^\circ$ (*c* 27.90, ethanol)}, *o*-[1-²H]butylphenol (0.230 g), and *p*-[1-²H]butylphenol (0.0382 g) were obtained.

The optical purity of methyl [2-²H]pentanoate was determined by the previous ¹H n.m.r. shift reagent method¹⁵ by the use of tris[3-trifluoroacetyl-(+)-camphorato]europium(III) as shift reagent. The results are summarized in Table 10.

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