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Kinetic Studies of Solvolysis. XI.* The Steric Course of the Phenolyses of Optically Active α-Phenylethyl Chloride in Mixtures of Various Phenols and Organic Solvents—A Mechanism for the S_N1 Reaction with a Net Retention of Configuration

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The S_N1 phenolyses of optically active α-phenylethyl chloride in binary mixtures of organic solvents and certain substituted phenols (i. e., phenol, *p*-cresol, *p*-chloro- and *p*-nitro-phenol) proceed in the presence of aniline and of triethylamine to give the corresponding α-phenylethyl substituted-phenyl ethers with a predominantly-retained configuration. In binary mixtures of benzene and various phenols, the extents of retention for the ethers are slightly reduced at the higher base concentrations. However, in binary solvents of acetonitrile and certain phenols, the optical purities of the ethers with retained configurations decrease continuously with the base concentrations, while at the higher concentrations ($\sim$0.4 M) the steric courses change to the inverted course. The *C*-alkylated (α-phenylethylated) derivatives of these phenols, isolated along with the phenyl ethers, have inverted configurations, irrespective of the configurations of the corresponding phenyl ethers. These results are all consistent with a mechanism in which a molecule of the phenol reacts with the S_N1 ion-pair intermediate of the phenolysis to give a phenyl ether with a retained configuration, probably by S_Ni-like four-center substitution, whereas the reaction of a phenoxide anion with the S_N1 intermediate proceeds predominantly by the Walden inversion mechanism yielding a phenyl ether and α-phenylethylated phenols with inverted configurations.

It has been demonstrated in the literature that the S_N1 solvolyses of optically active α-phenylethyl chloride ordinarily proceed with a net inversion of the configuration in methanol,[1] ethanol,[1] aqueous acetone[1] and acetic acid[2]. The results[3] in our laboratories have also revealed that a net inversion is standard for the α-phenylethyl system in S_N1 solvolyses in such solvents as cyclohexanol, formic acid, trifluoroacetic acid and pivalic acid. In contrast to these facts, however, we found[4] that the S_N1 phenolysis of optically-active α-phenylethyl chloride in a phenol-benzene mixture gave α-phenylethyl phenyl ether with a net retention of the configuration in the presence of a base such as aniline. In this earlier investigation, it was not clear whether the retention of the configuration was a result typical of all phenolyses in the substituted phenols, nor was it clear which nucleophile (a phenoxide anion or a phenol molecule) was responsible for this unordinary steric course.

In this paper we wish to report on the results of studies undertaken in order to answer the above questions. It will be shown that the S_N1 phenolyses of optically active α-phenylethyl chloride in various

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* Presented at the 15th Organic Reaction Mechanism Symposium of the Chemical Society of Japan, Nagoya, October, 1964. Part X of this series: K. Okamoto, Y. Matsui and H. Shingu, This Bulletin, **38**, 1844 (1965).

[1] E. D. Hughes, C. K. Ingold and A. D. Scott, *J. Chem. Soc.*, **1937**, 1201.

[2] J. Steigman and L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 2536 (1937).

[3] K. Okamoto and Y. Matsui, unpublished data.

[4] K. Okamoto, K. Takeuchi and H. Shingu, This Bulletin, **35**, 525 (1962).

TABLE I. EFFECT OF NATURE OF ORGANIC SOLVENT IN PHENOL-ORGANIC SOLVENT MIXTURES ON STERIC COURSE OF PHENOLYSIS OF OPTICALLY ACTIVE α-PHENYLETHYL CHLORIDE IN THE PRESENCE OF ANILINE AT 40.0°C

Run. No.	Org. solvent	Phenol a) M	Aniline M	RCl M	RCl b) α_D	ROC_6H_5 c) α_D	Net steric course d)	k_t min^{-1}
25	Cyclohexane	4.71 e)	0.256	0.088	−47.8°	+3.67°	20.6% ret.	7.45×10^{-2}
20	Anisole	6.11 f)	0.200	0.096	−48.1°	+5.45°	30.4% ret.	4.11×10^{-2}
83	Benzene	4.71	0.243	0.076	+41.02°	−5.36°	35.0% ret.	3.13×10^{-2}
85	Acetonitrile	4.71	0.248	0.076	+41.02°	−6.46°	42.2% ret.	2.42×10^{-3}
84	Acetone	4.71	0.246	0.076	+41.02°	−7.84°	51.2% ret.	4.13×10^{-4}

a) Calculated from composition (by weight) and density (at 40.0°C) of the mixture.
b) Rotations of starting α-phenylethyl chloride, taken neat, $l=1$ dm.
c) Rotations of α-phenylethyl phenyl ether, taken neat, $l=1$ dm.
d) Calculated taking into account lack of optical purity of starting chloride; the rotations of the optically pure materials are taken to be 125° (H. M. R. Hoffmann and E. D. Hughes, *J. Chem. Soc.*, **1964**, 1244) for α-phenylethyl chloride and 46.6° for α-phenylethyl phenyl ether; reported value, 41.1°,11) for the ether was recalculated on the basis of the new value for the maximum rotation for the chloride (H. and H., loc. cit.).
e) Phenol-cyclohexane mixture (1 : 1 by weight).
f) Phenol-anisole mixture (1 : 1 by weight).

substituted phenols, i. e., *p*-cresol, *p*-chlorophenol, and *p*-nitrophenol, yielded the corresponding α-phenylethyl substituted-phenyl ether with a predominantly retained configuration, and that this retention of configuration is caused by the attack, probably of the four-center type, of the undissociated molecules of the phenols on the S_N1 ion-pair intermediate, whereas the ambident phenoxide anions react with the S_N1 intermediate by the Walden-inversion mechanism to yield the corresponding ethers and α-phenylethylphenols with an inverted configuration.

Part I. The Steric Course of Phenyl Ether Formation in the S_N1 Phenolyses of Optically Active α-Phenylethyl Chloride

The Effect of the Nature of the Organic Solvent on the Steric Course of the Formation of α-Phenylethyl Phenyl Ether from Optically Active α-Phenylethyl Chloride. — Optically active α-phenylethyl chloride was subjected to phenolysis in phenol-organic solvent mixtures (about 1 : 1 by weight). The reactions were carried out in the presence of aniline as a base at 40.0°C for ten half-lives. The half-life for each reaction was estimated from the results of the kinetic runs carried out at 40.0°C under conditions similar to those used in the product studies. α-Phenylethyl phenyl ether was isolated by chromatography on silica gel or basic alumina.

Table I compares the effect of the organic solvent variation on the stereochemical outcome of phenolysis. In all runs, α-phenylethyl phenyl ether had a retained configuration, accompanied by 50 to 80% racemization.

It has been postulated that the retained steric course in the decomposition of secondary aliphatic chlorosulfites is due to the back-side participation of the solvents, such as ethers or alkyl halides, in a positive center of the ion-pair intermediate of this reaction.5) An examination of the data in Table I, however, reveals that there can be hardly any specific relationship between the nucleophilic coordination power of these organic solvents and the extent of the net retention of the configuration. Therefore, the organic solvent molecule seems to play no primary rôle in the retention of the configuration; rather, the presence of the compound "phenol," i. e., a phenol molecule, a phenoxide anion, or an ion-pair of the phenoxide ion, seems to control the net steric course.

Furthermore, in those runs carried out in similar phenol concentrations there is a clear trend toward a larger racemization of the product ether with higher phenolysis rates (Table I). This trend may be explained if one assumes that the higher rates are responsible for the looser ion-pair intermediates, which in turn result in a larger racemization of the ether so formed.

The Effect of the Composition of Phenol-Organic Solvent Mixtures on the Steric Course of the Formation of α-Phenylethyl Phenyl Ether from Optically Active α-Phenylethyl Chloride.—In order to obtain further evidence for the essential rôle of phenol in the retention of the configuration, phenolyses of α-phenylethyl chloride were carried out in phenol-benzene and the phenol-acetonitrile mixtures with various phenol concentrations. As is shown by the degree of the retention of the configuration of α-phenylethyl phenyl ether (Table II), the higher concentration of phenol is not a necessary condition for the retention of the steric course. In fact, in a phenol-acetonitrile mixture with such a small concentration as 0.55 M of phenol in the

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5) E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **74**, 308 (1952); C. E. Boozer and E. S. Lewis, ibid., **75**, 3182 (1953).

TABLE II. EFFECT OF THE COMPOSITION OF PHENOL-ORGANIC SOLVENT MIXTURES ON THE STERIC COURSE OF PHENOLYSIS OF OPTICALLY ACTIVE α-PHENYLETHYL CHLORIDE AT 40.0°C

Run. No.	Phenol[a) M	Base M	RCl M	RCl[b) α_D	ROC_6H_5[c) α_D	Net steric course[d)	k_t min^{-1}
			Organic solvent, benzene; Base, aniline				
92	11.2[e)	0.248	0.076	−43.49°	+6.34°	39.1% ret.	—
83	4.71	0.243	0.076	+41.02°	−5.36°	35.1% ret.	3.18×10^{-2}
91	2.26	0.245	0.078	−43.49°	+5.64°	34.8% ret.	4.29×10^{-2}
			Organic solvent, acetonitrile; Base, triethylamine				
90	11.2[e)	0.176	0.076	+42.89°	−5.36°	33.5% ret.	—
	4.73	0.175	0.070			30.5% ret.[f)	1.42×10^{-3}[g)
67[h)	1.61	0.175	0.075	+54.13°	−4.95°	24.5% ret.	4.20×10^{-2}
88[i)	0.55	0.165	0.084	+41.13°	−3.71°	24.1% ret.	2.97×10^{-3}

a), b), c) and d) See foot notes a), b), c) and d), Table I.
e) 100% Phenol.
f) Interpolated from data cited in Table III.
g) Initial concentration of triethylamine was 0.424 M.
h) Carried out at 90.5°C.
i) Carried out at 111°C.

presence of 0.165 M triethylamine, the extent of retention for α-phenylethyl phenyl ether still amounts to 24.1%, in spite of the fact that the reaction was carried out at a rather higher temperature because of the low rate in the solvent ranges with such low phenol concentrations. This is another support for the conclusion in the preceding section, i. e., the primary rôle of the compound "phenol" in the steric course with a net retention of the configuration.

The Effect of the Base Concentration on the Steric Course of the Formation of α-Phenylethyl Phenyl Ether from α-Phenylethyl Chloride in *p*-Substituted Phenol-Organic Solvent Mixtures.—In order to differentiate the rôles of a phenol molecule and a phenoxide anion (or ion-pair) on the steric course of the phenyl ether formation, the effect of the base concentration on the extent of the retention of the configuration of α-phenylethyl *p*-substituted-phenyl ether was examined in mixtures of various *p*-substituted phenols and benzene (or acetonitrile). The results are illustrated in Fig. 1 and in Table IV (see Experimental Section).

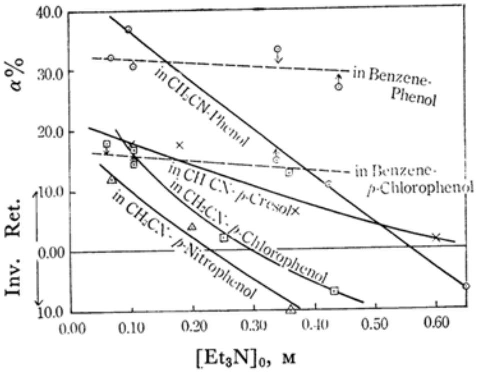


Fig. 1. Effect of base concentration on the steric course for the formation of α-phenylethyl *p*-substituted-phenyl ethers optically active α-phenylethyl chloride in *p*-substituted phenol-organic solvent mixtures (1 : 1 by weight).

In a benzene-phenol mixture (1 : 1 by weight) the extent of retention of α-phenylethyl phenyl ether shows a slight trend towards lower optical purities at higher triethylamine concentrations; this trend becomes more pronounced in an acetonitrile - phenol mixture (1 : 1 by weight). Finally, the run carried out in the presence of 0.65 M triethylamine afforded α-phenylethyl phenyl ether with an "inverted" configuration.

Similarly, in a *p*-chlorophenol - acetonitrile mixture (1 : 1 by weight), the net steric course of *p*-chlorophenolysis changes from a 37% retention to a 6.5% inversion as the concentration of triethylamine is increased from 0.1 to 0.6 M ,whereas in a benzene - *p*-chlorophenol mixture (1 : 1 by weight) the extent of retention of α-phenylethyl *p*-chlorophenyl ether does not show such a large decrease in optical purities as in the mixtures of acetonitrile - *p*-chlorophenol.

Similar trends are also observed in *p*-cresolysis and in *p*-nitrophenolysis in mixtures of these phenols and acetonitrile (1 : 1 by weight).

These results suggest that the reactions of the phenoxide anions of various phenols (or the triethylammonium salt of these phenols) with the S_N1 intermediate proceed predominantly with an inversion of the configuration. Accordingly, it may be concluded that the reaction of these undissociated phenol molecules with the intermediate is responsible for the retention of the configuration.

The most probable course for the retention of the configuration caused by the reaction of a phenol molecule and the S_N1 ion-pair intermediate would be a four-center reaction, such as the one depicted below:

TABLE III. STERIC COURSE OF *C*-ALKYLATION IN PHENOLYSIS OF α-PHENYLETHYL CHLORIDE IN *p*-SUBSTITUTED PHENOL-ORGANIC SOLVENT MIXTURES (1 : 1 BY WEIGHT) AT 40.0°C

Run No.	*p*-Substituted phenol	Et_3N M	RCl M	RCl[a] α_D	*p*-Substituted-*o*-α-phenylethylphenol[b]		Net steric course[c]	
					$[\alpha]_D$ (temp., °C; *c*)	Yield %	Alkylation on carbon	Alkylation on oxygen[d]
					Organic solvent, benzene			
97	Phenol	0.408	0.175	+54.66°	ortho-isomer −4.65° (16.6; neat)	14.8	38.1% inv.	31.0% ret.
					para-isomer +1.845°(21.5; 30.4)	13.3	41.2% inv.	
70	*p*-Chlorophenol	0.106	0.084	−54.3°	+4.94° (30.3; 1.82)	16.5	25.4% inv.	14.7% ret.
					Organic solvent, acetonitrile			
53	Phenol	0.340	0.071	+29.5°	−5.38° (19.0; 39.4)[e]	19.4[e]	86.7%[f] inv.	14.9% ret.
52	Phenol	0.650	0.130	+29.5°	−3.16° (19.0; 76.4)[g]	21.4[g]	57.9%[f] inv.	6.5% inv.
59	*p*-Cresol	0.182	0.075	−50.2°	−4.43° (21.2; 31.3)	23.3	64.5% inv.	17.7% ret.
56	*p*-Cresol	0.370	0.075	+16.4°	+1.43° (20.2; 31.4)	24.9	64.0% inv.	6.9% ret.
57	*p*-Chlorophenol	0.249	0.074	−52.0°	−6.28° (25.3; 11.0)	6.4	33.8% inv.	2.1% ret.
58	*p*-Chlorophenol	0.429	0.073	−52.0°	−11.8° (26.3; 14.8)	11.5	63.4% inv.	7.3% inv.

a) Rotations of starting α-phenylethyl chloride, taken neat, calcd. for l=1 dm.

b) Specific rotations of *p*-substituted-*o*-α-phenylethylphenol, taken in benzene.

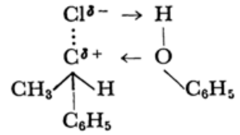
c) See foot note d), Table I; rotations (neat, l=1 dm.) for optically pure materials are taken to be 27.85° for *o*-α-phenylethylphenol (see text), 10.26° for *p*-α-phenylethylphenol (see text), 17.1° for *o*-α-phenylethyl-*p*-cresol,[7] and 44.7° for *o*-α-phenylethyl-*p*-chlorophenol (calculated from the results[13] of the S_N2 reaction between optically active α-phenylethyl chloride and potassium *p*-chlorophenoxide in acetone, assuming the same optical purities for the *O*-alkylated and the *C*-alkylated product.

d) See the 7th column, Table III, except the runs 97 and 70.

e) For the mixture of ortho-isomer (90%) and para-isomer (10%).

f) Calculated for the mixture, assuming the same optical purities for the ortho and the para isomer.

g) For the mixture of ortho-isomer (79%) and para-isomer (21%).



Considering that in relatively non-polar benzene-phenol mixtures the base concentration has not so much effect on the optical purities of the ethers as in polar acetonitrile-phenol mixtures, we may suggest that the more effective reaction species in the inversion of configuration would not be triethylammonium phenoxide (an ion-pair) but, rather, a phenoxide anion (a dissociated anion).

The Determination of the Configurations and Maximum Rotations of α-Phenylethyl *p*-Chlorophenyl Ether and α-Phenylethyl *p*-Nitrophenyl Ether.—In order to establish the configuration and the maximum rotation of α-phenylethyl *p*-chlorophenyl ether, a dioxan solution of α-phenylethyl chloride, ($[\alpha]_D^{16}$ −35.4° (benzene)) and sodium *p*-chlorophenoxide was refluxed for 6.5 hr.; this gave α-phenylethyl *p*-chlorophenyl ether ($[\alpha]_D^{15}$ −5.80° (benzene)) and unchanged α-phenylethyl chloride ($[\alpha]_D^{15}$ −35.7° benzene)). From these results of the S_N2 reaction, the maximum rotation, $[\alpha]_D$ in benzene, for R-α-phenylethyl *p*-chlorophenyl ether was estimated to be −22.40° (see Experimental Section).

In order to determine the configuration and the maximum rotation of α-phenylethyl *p*-nitrophenyl ether, a dimethyl sulfoxide solution of *p*-nitrobromobenzene and potassium α-phenylethoxide, which afforded α-phenylethyl alcohol (α_D^{24} +15.6° (l=1 dm., neat)) after hydrolysis, was maintained at 40.0°C for 17 hr. After the usual treatment, the reaction mixture afforded α-phenylethyl *p*-nitrophenyl ether ($[\alpha]_D^{26}$ +15.3° (benzene)) and unchanged potassium α-phenylethoxide, recovered as α-phenylethyl alcohol with α_D^{26} +13.4° (l=1 dm., neat). Assuming that the optical activity of potassium α-phenylethoxide decreases linearly during the reaction, we took the arithmetic mean of the rotations before and after the reaction as the rotation of the α-phenylethoxide in the course of the reaction. The estimated maximum rotation of R-α-phenylethyl *p*-nitrophenyl ether amounted to +46.6° (see Experimental Section).

Part II. The Steric Course of α-Phenylethylphenol Formation in the S_N1 Phenolyses of Optically Active α-Phenylethyl Chloride

The Steric Course of Various α-Phenylethylphenol Formations in *p*-Substituted Phenol - Organic Solvent Mixtures (1 : 1 by Weight).—The phenoxide anion, as an ambident

TABLE IV. EFFECT OF BASE CONCENTRATION ON PHENOLYSES OF OPTICALLY ACTIVE α-PHENYLETHYL CHLORIDE IN p-SUBSTITUTED PHENOL-ORGANIC SOLVENT MIXTURES (1 : 1 BY WEIGHT)

Run No.	p-Substituted phenol	Et_3N M	RCl M	RCl[a] α_D	ROR'[b] α_D or $[\alpha]_D$ (temp., °C; c)	Net steric course[c]	k_t min^{-1}
			Organic solvent, benzene; temp. 25.0°C				
45	Phenol	0.071	0.072	−32.4°	+3.90°	32.2% ret.	—
69	Phenol	0.107	0.075	−54.3°	+6.22°	30.8% ret.	1.68×10^{-2}
49	Phenol	0.293	0.073	+27.1°	−3.38°	33.4% ret.	—
48	Phenol	0.446	0.090	+42.1°	−4.30°	27.4% ret.	1.44×10^{-2}
43	p-Chlorophenol	0.061	0.066	−44.9°	+1.47° (15.6; 22.1)	18.3% ret.	—
70	p-Chlorophenol	0.106	0.084	−54.3°	+1.43° (30.3; 32.5)	14.7% ret.	3.38×10^{-2}
41	p-Chlorophenol	0.361	0.123	−44.9°	+1.03° (14.7; 11.9)	12.8% ret.	2.81×10^{-2}
			Organic solvent, acetonitrile; temp. 40.0°C				
50	Phenol	0.100	0.073	+27.1°	−3.74°	37.0% ret.	—
53	Phenol	0.340	0.071	+29.5°	−1.64°	14.9% ret.	—
51	Phenol	0.424	0.143	+27.1°	−1.10°	10.9% ret.	1.42×10^{-3}
52	Phenol	0.650	0.130	+29.5°	+0.71°	6.5% inv.	1.06×10^{-3}
55	p-Cresol	0.103	0.075	+16.4°	−0.47° (21.5; 46.8)	17.5% ret.	8.18×10^{-4}
59	p-Cresol	0.182	0.075	−50.2°	+1.45° (22.0; 46.2)	17.6% ret.	—
56	p-Cresol	0.370	0.075	+16.9°	−0.18° (21.5; 37.9)	6.5% ret.	—
60	p-Cresol	0.595	0.076	+24.6°	−0.065°(22.3; 46.2)	1.6% ret.	6.76×10^{-4}
54	p-Chlorophenol	0.105	0.076	+16.5°	−0.50° (27.5; 49.4)	16.9% ret.	—
57	p-Chlorophenol	0.249	0.074	−52.0°	+0.20° (22.0; 41.1)	2.1% ret.	7.06×10^{-4}
58	p-Chlorophenol	0.429	0.073	−52.0°	−0.68° (23.5; 44.0)	7.3% inv.	6.53×10^{-4}
40	p-Nitrophenol	0.071	0.061	+43.8°	+1.97° (23.6; 27.9)	12.1% ret.	6.58×10^{-2}
38	p-Nitrophenol	0.198	0.100	+43.8°	+0.63° (15.2; 3.2)	3.9% ret.	—
46	p-Nitrophenol	0.358	0.143	+42.1°	−1.55° (17.2; 6.3)	9.9% inv.	6.47×10^{-2}

a) Rotations of starting α-phenylethyl chloride, taken neat, calculated for l=1 dm.

b) Rotations of p-subsituted-phenyl α-phenylethyl ether, taken neat (calcd. for l=1 dm.) or in benzene.

c) See foot note d) Table I; the specific rotations (in benzene) of optically pure materials are taken to be −22.40° for R-α-phenylethyl p-chlorophenyl ether (see text), 46.6° for R-α-phenylethyl p-nitrophenyl ether (see text), 20.4° for S-α-phenylethyl p-cresyl ether. Reported value for the p-cresyl ether, 18°,[11] was recalculated on the basis of the new value for the maximum rotation of the chloride (see Table I, foot note d)).

ion,[6] reacts bimolecularly in acetone with α-phenylethyl chloride to afford not only α-phenylethyl phenyl ether but also o- or p-phenylethylphenol (C-alkylation products).[7] Accordingly, the S_N1 intermediate formed from α-phenylethyl chloride should also react with the phenoxide anion to give C-alkylation products as well as O-alkylation products (α-phenylethyl phenyl ethers). In this case, it may be anticipated that C- and O-alkylation will both have the same steric outcome, because both reactions proceed by the anion transfer mechanism. Regarding the steric course of such O-alkylation of the phenoxide anion, we concluded in the preceding part that the reaction proceeds with an inversion of the configuration with respect to α-phenylethyl chloride. Therefore, we can expect to obtain inverted α-phenylethylphenols also in the C-alkylation of the phenoxide anion by the S_N1 reaction.

The possibility of the concomitant C-alkylation of the phenol molecule by the S_N1 intermediate can be eliminated because its rate is slower[4] than the rate for the phenoxide anion.

Thus, we isolated the C-alkylated phenols in several runs carried out in the presence of a base. The yields and net steric courses of the C-alkylation are summarized in Table III. For purposes of comparison, the net steric courses of the O-alkylations are also illustrated in that table.

As expected, in all runs carried out for ten half-lives, the C-alkylated phenols, i. e. α-phenylethylphenol (the ortho and the para isomer), o-α-phenylethyl-p-cresol and o-α-phenylethyl-p-chlorophenol, had rotations which demonstrated that the C-alkylation process involved a predominant inversion of the configuration.

The Determination of the Configuration and the Maximum Rotation for p-α-Phenylethylphenol.—In order to determine the configuration and the maximum specific rotation for p-α-phenylethylphenol, the permanganate oxidation[7] of optically active p-α-phenylethylphenol ($[\alpha]^{21.5}_D$ +1.845° (benzene)) was conducted in acetone.

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[6] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, ibid., 77, 6269 (1955).

[7] H. Hart and H. S. Eleuterio, ibid., 76, 516 (1954).

From the specific rotation of the α-phenylpropionic acid so obtained ($[\alpha]_D^{23.1}$ +14.57°), the maximum rotation of *p*-s-α-phenylethylphenol was estimated to be +10.26° (benzene). Using this value for the optically-pure para isomer and the value, −24.8°, estimated for the mixture of optically pure *o*- and *p*-s-α-phenylethylphenol (92 : 8),[7] the specific rotation for the pure ortho isomer was evaluated as −27.85° (s-configuration).

Experimental[8]

Materials.—The preparations of racemic and optically active α-phenylethyl chloride followed previous practice.[9] All the reagents employed were of a reagent-grade quality, and all were purified by fractional distillation except *p*-nitrophenol (commercial material, m. p. 111—114°C); acetone, b. p. 55.0—56.0°C; acetonitrile, b. p. 82.0—83.0°C; anisole, b. p. 152.0°C; benzene, b. p. 79.5—80.0°C; *p*-chlorophenol, b. p. 110—116°C/32 mmHg, m. p. 42.5—43.5°C; *p*-cresol, 99.5—102.0°C/24 mmHg; phenol, b. p. 180—181°C; aniline, b. p. 182—183°C; triethylamine, b. p. 89.3°C.

Kinetic Measurements.—The previous procedure[10] was followed. For the runs measured at 25.0±0.05°C, 1-cc. aliquots were removed at intervals from 20 cc. of the reaction mixture placed in a glass-stoppered flask. For the runs at 40.0±0.05°C, the usual sealed-ampoule (1 cc.) technique was employed. The diminution of base concentrations was followed by titration with standard perchloric acid in acetic acid, using crystal violet as an indicator. The phenol concentrations at the reaction temperature were calculated from the weight compositions and the densities of the phenol-organic solvent mixtures. All the rate data were treated graphically by a plot of log $a/(a-x)$ against the time. In each case the reaction was followed to at least 80% conversion and a smooth linear relationship was obtained. Infinity titers were determined after at least ten half-lives and gave reproducible results. These results are summarized in Tables I, II and IV.

The Isolation of the Reaction Products (General Procedure).—In a 100-cc. ampoule or a 100-cc. glass-stoppered round-bottomed flask, there were placed ca. 100 cc. of a mixture of a phenol, an organic solvent and the calculated amount of base (triethylamine or aniline). The concentration of the base was determined by titration of a 1-cc. aliquot (see Kinetic Measurement section). Finally, 1-cc. (0.00757 mol.) of optically active α-phenylethyl chloride was added. The sealed tube or the flask was then placed in a constant-temperature bath for at least ten half-lives. To the reaction mixture, 100 cc. of benzene was added; then the benzene solution was washed with three 70 cc.-portions of 10% aqueous sodium chloride, three 100 cc.-portions of 10% aqueous sodium hydroxide, and several 70 cc.-portions of 10% aqueous sodium chloride. After being dried with magnesium sulfate, the benzene solution was distilled and the residual oil was chromatographed over 25 g. of basic alumina. The *n*-hexane fractions afforded α-phenylethyl phenyl ether, whereas various α-phenylethyl substituted-phenyl ethers were obtained from the *n*-hexane - benzene (1 : 1 by volume) eluent. In the run in which aniline was used as the base, an excess of aniline was recovered from the benzene fractions. Various α-phenylethylphenols were obtained from the ethanol fractions. The phenyl ethers so obtained were used for the measurement of the rotation after structural verification by means of a comparison of the infrared spectrum with that of an authentic sample. Some of the ethers were sent for microanalysis. The *C*-alkylation products were distilled under reduced pressure, and the rotations of the distillates were taken in a benzene solution. These phenols were identified by infrared spectra and by microanalyses. The ortho and para compositions of α-phenylethylphenol were estimated by using the infrared spectrum of the mixture. Some of the mixtures were separated by chromatography on silica gel. The results are summarized in Tables I—IV. The details of the experimental procedure for representative runs are cited below.

The Phenolysis of Optically Active α-Phenylethyl Chloride in a Phenol-Acetonitrile (1 : 1 by Weight) Mixture (Run 53).—In a 100-cc. ampoule, 100 cc. of a mixture of phenol-acetonitrile (1 : 1 by weight), 5.00 cc. of triethylamine (0.340 mol./l.), and 1.00 cc. (0.00757 mol.) of α-phenylethyl chloride (b. p. 45—46°C/1mmHg, $\alpha_D^{15.5}$ +14.75±0.01°, 0.5 dm., neat) were placed. The ampoule was then sealed and maintained at 40.0°C for 46 hr. After the treatment mentioned above, 1.26 g. of an oily material was chromatographed over 25.0 g. of basic alumina. *n*-Hexane - benzene (1 : 1 by volume) eluent left 0.900 g. (60.1% yield, based on the starting chloride) of α-phenylethyl phenyl ether. M. p. 34.0—35.3°C (Lit. m. p. 38—39°C[11]) (Found: C, 85.09; H, 7.32. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12%); λ_{max}^{neat} 8.07 μ; $\alpha_D^{15.5}$ −0.82±0.01°, 0.5 dm., neat. The ethanol (99%) fractions afforded 0.291 g. of a pale yellow oil, which was then distilled under reduced pressure to give 0.85 g. (5.67% yield) of a mixture of *o*- and *p*-α-phenylethylphenol; b. p. 110—115°C (bath, 0.3 mmHg) (Found: C, 83.17; H, 7.30. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12%); $[\alpha]_D^{25.5}$ −5.38±0.33°, benzene, *c* 39.4. The ratio between the *o*- and the *p*-α-phenylethylphenol in the mixture was estimated to be 90 : 10 by infrared analysis. The characteristic bands used for the analysis were 6.62 and 6.72 μ.

The *p*-Cresolysis of Optically Active α-Phenylethyl Chloride in a Mixture of *p*-Cresol and Acetonitrile (1 : 1 by Weight) (Run 59).—Into a 100-cc. ampoule, 100 cc. of a mixture of *p*-cresol and acetonitrile (1 : 1 by weight), 2.60 cc. of triethylamine (0.182 M), and 1.00 cc. (0.00757 mol.) of α-phenylethyl chloride (b. p. 45—46°C/1 mmHg, $\alpha_D^{25.5}$ −25.11±0.015°, 0.5 dm., neat) were placed; the ampoule was sealed. After the mixture had been maintained for 65.7 hr. 40.8°C and subsequent usual treatment, 1.312 g. of an oily material was chromatographed over 25.0 g. of basic alumina. The *n*-hexane - benzene (1 : 1 by volume) eluent left 0.905 g. (56.4% of the starting chloride) of α-phenylethyl *p*-cresyl ether; m. p. 54.0—56.0°C

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[8] All melting points are uncorrected. The microanalyses were performed by the Microanalytical Center, Kyoto University, Kyoto. The infrared spectra were obtained from a Shimadzu model IR-27 spectrometer. Optical rotations were measured with a Zeiss-Winkel "Kreispolarimeter 0.01°."

[9] K. Okamoto, K. Takeuchi and H. Shingu, This Bulletin, **34**, 1137 (1961).

[10] K. Okamoto and H. Shingu, ibid., **34**, 1131 (1961).

[11] H. Hart and H. S. Eleuterio, *J. Am. Chem. Soc.*, **76**, 519 (1954).

54.0—56.0°C (Lit. m. p. 49—50°C[11]); (Found; C, 85.02; H, 7.84. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60%); $\lambda_{max}^{CCl_4}$ 8.07 μ; $[\alpha]_D^{22.0}$ +1.45±0.11° (benzene, *c* 46.16). A pale yellow oily material (0.905 g.), obtained from ethanol fractions, was distilled in vacuo giving 0.295 g. (18.4% yield) of *o*-α-phenylethyl-*p*-cresol; b. p. 125°C (bath, 0.2 mmHg.) (Lit. b. p. 175—177°C/13 mmHg[12]); (Found: C, 84.09; H, 7.90. Calcd. for $C_{15}H_{16}O$: C, 84.87 H, 7.60%); $[\alpha]_D^{21.2}$ −4.43±0.39° (benzene, *c* 31.34); λ_{max}^{neat} 2.82 and 2.96 μ.

The *p*-Chlorophenolysis of Optically-Active α-Phenylethyl Chloride in a Mixture of *p*-Chlorophenol and Acetonitrile (1 : 1) by Weight (Run 57). — A reaction mixture was prepared from 100 cc. of a mixture of *p*-chlorophenol and acetonitrile (1 : 1 by weight), 3.75 cc. of triethylamine (0.249 M; determined by titration), and 1.00 cc. (0.00757 mol.) of α-phenylethyl chloride (b. p. 45—46°C/1 mmHg, α_D^{18} −26.01±0.015°, 0.5 dm., neat.). A part (10 cc.) of the mixture was pipetted out for the rate measurement. The remaining part was sealed into a 100-cc. ampoule and kept at 40.0°C for 90.8 hr. After the usual treatment, 1.086 g. of white crystals was chromatographed over 25.0 g. of basic alumina. The *n*-hexane - benzene (1 : 1 by volume) fractions gave 0.879 g. (56.5% of the starting chloride) of α-phenylethyl *p*-chlorophenyl ether; m. p. 65—67.6°C (Lit. m. p. 66.4—67.0°C[13]); (Found: C, 72.01; H, 5.52. Calcd. for $C_{14}H_{13}OCl$: C, 72.26; H, 5.63%); $\lambda_{max}^{CCl_4}$ 8.07 μ; $[\alpha]_D^{22}$ +0.195±0.15° (benzene, *c* 41.08). An oily material (0.112 g.), obtained from ethanol fractions, was distilled in vacuo to give 0.0805 g. (a 5.7% yield) of *o*-(α-phenylethyl)-*p*-chlorophenol, b. p. 120°C (bath temp., 0.1 mmHg) (Lit. b. p. 155°C/2 mmHg[13]); (Found: C, 72.30; H, 6.38. Calcd. for $C_{14}H_{13}OCl$: C, 72.26; H, 5.63%); $[\alpha]_D^{25.8}$ −6.28±0.46° (benzene, *c* 10.98); λ_{max}^{neat} 2.85 and 2.96 μ.

The *p*-Nitrophenolysis of Optically Active α-Phenylethyl Chloride in a Mixture of *p*-Nitrophenol and Acetonitrile (1 : 1 by Weight) (Run 46).—A mixture of 49.97 g. of *p*-nitrophenol, 49.89 g. of acetonitrile, and 3.75 g. of triethylamine (0.358 M, as determined by titration) was prepared. To 100 cc. of the mixture there was added 2.00 cc. (0.0150 mol.) of α-phenylethyl chloride (b. p. 43—47°C/2 mmHg; $\alpha_D^{17.0}$ +21.07°, 0.5 dm., neat). From the reaction mixture so prepared, 8 cc. of an aliquot was removed for the rate measurement; the remaining mixture was sealed into an 100-cc. ampoule and kept at 40.0°C for 54 hr. To the reaction mixture were added 150 cc. of benzene and 150 cc. of 10% aqueous sodium hydroxide. The crystals of sodium *p*-nitrophenoxide, which precipitated in an aqueous layer, were filtered off; then the benzene solution was treated in the usual manner described above. Benzene was distilled off from the dried benzene solution, and the residue was distilled in vacuo to give 1.35 g. (37% yield, based on the chloride) of α-phenylethyl *p*-nitrophenyl ether; b. p. 122—124°C/0.1 mmHg; $[\alpha]_D^{17.2}$ −1.55±0.04° (benzene, *c* 6.29); (Found: C, 69.92; H, 5.47. Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39%). For the authentic sample, see below.

Optically Active α-Phenylethyl *p*-Nitrophenyl Ether from Optically Active Potassium α-Phenylethoxide and *p*-Bromonitrobenzene.—Potassium α-phenylethoxide was prepared in 50 cc. of *t*-butanol (b. p. 81.8°C) from 5.10 g. (0.042 mol.) of α-phenylethyl alcohol (b. p. 68.5°C/5 mmHg, $\alpha_D^{22.3}$ +9.995°, 0.5 dm., neat) and potassium *t*-butoxide, which had been prepared by the addition of 1.41 g. (0.036 g.-atom) of potassium to *t*-butanol. After the distillation of the *t*-butanol, the excess α-phenylethyl alcohol was evaporated in vacuo, leaving 5.95 g. (0.036 mol.) of crude potassium α-phenylethoxide.

The optical purity of the potassium α-phenylethoxide was determined by the measurement of that of the recovered α-phenylethyl alcohol after the hydrolysis. A part (1.53 g.) of the potassium α-phenylethoxide was hydrolysed by the addition of 10 cc. of water; the alcohol was extracted with ether, and the oily material obtained after the evaporation of the ether was chromatographed over 25 g. of basic alumina. Ether fractions afforded 0.226 g. of acetophenone (identity established by a study of the infrared spectrum), and the ethanol fractions gave 0.574 g. of a yellow oil, which was distilled in vacuo to yield 0.4373 g. of α-phenylethyl alcohol, b. p. 75°C/6 mmHg, $\alpha_D^{24.4}$ +7.78±0.02° (0.5 dm., neat), identified by a study of the infrared spectrum.

To the solution of the optically active potassium α-phenylethoxide (1.60 g.) in dimethyl sulfoxide (50 cc., b. p. 81.0°C/2 mmHg.), 1.80 g. (0.00892 mol.) of *p*-bromonitrobenzene (m. p. 117—120°C) was added. After 17 hr. at 40.0°C under a nitrogen atmosphere, 40 cc. of ether was added to the black reaction mixture; the mixture was then washed with 50 cc. of 10% aqueous sodium chloride. The ether solution was dried with magnesium sulfate and evaporated under reduced pressure to give a black viscous mass, which was then extracted with *n*-hexane. The aqueous layer was extracted with *n*-hexane, and the combined *n*-hexane extracts were dried with magnesium sulfate and evaporated in vacuo to yield 1.4023 g. of an oil containing yellow crystals. The mixture was chromatographed over 25 g. of basic alumina. The first half of the *n*-hexane - benzene fractions gave 0.5108 g. of *p*-bromonitrobenzene (m. p. 111—119°C), while the second half afforded 0.1475 g. of α-phenylethyl *p*-nitrophenyl ether, m. p. 65.5—67.0°C; $[\alpha]_D^{25.9}$ +15.28 ±0.43° (benzene, *c* 14.22); $\lambda_{max}^{CCl_4}$ 7.97 μ.

Found: C, 68.70; H, 5.41. Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39%.

The ether fractions afforded 0.013 g. of an oil, while the ether-ethanol (1 : 1 by volume) fractions gave 0.2527 g. of an oil. The combined oily materials were distilled under reduced pressure to give 0.1369 g. of α-phenylethyl alcohol, b. p. 58.0°C/2 mmHg, $\alpha_D^{25.6}$ +6.70±0.104° (0.5 dm., neat). From these results, the maximum specific rotation of α-phenylethyl *p*-nitrophenyl ether has been estimated to be as follows: $15.28\times44.2/(7.78\times6.70)=46.6°$ (benzene) (see text).

Optically Active α-Phenylethyl *p*-Chlorophenyl Ether from Sodium *p*-Chlorophenoxide and Optically Active α-Phenylethyl Chloride. — To ethanolic sodium ethoxide, prepared from 0.33 g. (0.0147 g.-atom) of metallic sodium and 25 cc. of 99% ethanol, there was added 1.92 g. (0.0149 mol.) of *p*-chlorophenol; the solution was then evaporated in

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[12] Ng. Ph. Buu-Hoi, H. Le Bihan and F. Binon, *J. Org. Chem.*, **17**, 246 (1952).

[13] H. Hart, W. L. Spliethoff and H. S. Eleuterio, *J. Am. Chem. Soc.*, **76**, 4547 (1954).

vacuo to give white crystalls of sodium *p*-chlorophenoxide. A solution of sodium *p*-chlorophenoxide was prepared by refluxing a mixture of the chlorophenoxide crystals so prepared and 88 cc. of dioxan (b. p. 101.0—102.0°C). α-Phenylethyl chloride (1.00 cc., 0.00760 mol., b. p. 45—46°C/1 mmHg), $\alpha_D^{16.6}$ $-16.20°$ (0.5 dm., neat), $[\alpha]_D^{16.0}$ $-35.43°$ (benzene, *c* 6.833) was then added to the solution, and the mixture was refluxed for 6.3 hr. The reaction mixture was concentrated, and, after the addition of 80 cc. of benzene, the solution was washed with 120 cc. of 10% aqueous sodium chloride, two 50-cc. portions of aqueous sodium hydroxide, and seven 50-cc. portions of 10% aqueous sodium chloride. The benzene layer was dried with magnesium sulfate and evaporated under reduced pressure to give an oily material, which was distilled in vacuo to afford 0.40 g., of α-phenylethyl chloride (b. p. 35—37°C/0.5—0.8 mmHg, $[\alpha]_D^{15.2}$ $-35.7°$, benzene, *c* 13.78) and 0.30 g. of an oil (b. p. 105—120°C/0.7—1.0 mmHg.). The redistillation of the oil afforded 0.20 g. of *p*-chlorophenyl α-phenylethyl ether, b. p. 130—140°C (bath temp., 0.5 mmHg); $[\alpha]_D^{15.2}$ $-5.80\pm0.06°$, benzene, *c* 17.23; m. p. 64.0—65.5°C (99% ethanol) (lit. m. p. 66.4—67.0°C[13]); (Found: C, 72.01; H, 5.52. Calcd. for $C_{14}H_{13}OCl$: C, 72.25; H, 5.63%); $\lambda_{max}^{CCl_4}$ 48.07 μ. The maximum specific rotation of α-phenylethyl *p*-chlorophenyl ether was estimated to be as follows: $(5.80\times125)/(16.20\times2)=22.40°$ (benzene) (see text).

The Phenolysis of Optically Active α-Phenylethyl Chloride in a Phenol Benzene Mixture (1 : 1 by Weight) (Run 97).—A triethylamine solution (0.408 M) in a phenol-benzene mixture was prepared from 11.4 cc. of triethylamine and 190 cc. of a mixture of benzene and phenol (1 : 1 by weight). After the solution had been kept in a 200-cc. round-bottomed flask at 40.0°C for 0.5 hr., 5.06 g. of α-phenylethyl chloride ($\alpha_D^{17.8}$ $+27.33°$, 0.5 dm., neat) was added to the solution. After a 3 hr. reaction and the subsequent addition of 200 cc. of benzene, the benzene solution was washed with two 50-cc. portions of 10% aqueous sodium hydroxide, and ten 100-cc. portions of 10% aqueous sodium hydroxide, and ten 100-cc. portions of 10% aqueous sodium chloride, and then dried with magnesium sulfate. After the concentration of the solution, 7.4 g. of a yellow-brown oil was chromatrographed over 70 g. of silica-gel (Nakarai, No. F 1, 100—200 mesh). The column was eluted with *n*-hexane-benzene (1 : 1 by volume) and then with benzene, 45-cc. portions being taken. Fractions 1—6, using *n*-hexane-benzene, gave 4.204 g. of α-phenylethyl ether, m. p. 30.0—31.5°C, $\alpha_D^{16.6}$ $-2.325°$ (0.5 dm., neat); λ_{max}^{neat} 8.07 μ, while fractions 8—15, using benzene, gave 0.980 g. of *o*-(α-phenylethyl)-phenol, b. p. 130—131°C/2 mmHg (Lit. b. p. 127—127.5°C/0.9 mmHg[14]); n_D^{30} 1.5850 (Lit.[14] n_D^{20} 1.5923); $\alpha_D^{16.6}$ $-2.325°$ (0.5 dm. neat); λ_{max}^{neat} 2.34 μ; (Found: C, 84.26; H, 7.14. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12%) and fractions 19—52, using benzene, afforded 0.914 g. of *p*-(α-phenylethyl)-phenol, m. p. 49.0-51.0°C (Lit. m. p. 56.0—56.3°C[14]); $[\alpha]_D^{21.5}$ $+1.845\pm0.07°$ (benzene, C 30.37); $\lambda_{max}^{CCl_4}$ 2.73 and 2.99μ; (Found: C, 84.84; H, 6.88. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12%). An intermediate fraction, 7, using benzene, 10.6 mg. of a mixture of α-phenylethyl phenyl ether and *o*-(α-phenylethyl)-phenol, and the other intermediate fractions, 16—18, afforded 39.6 mg. of a mixture of *o*- and *p*-(α-phenylethyl)-phenol. On the basis of the infrared spectra, the intermediate fractions were estimated to be 1 : 1 mixtures of the relevant two components. The total analysis was 4.209 g. (62.5% of the chloride) of α-phenylethyl phenyl ether; 1.054 g. (14.8% yield) of *o*-(α-phenylethyl)-phenol, and 0.934 g. (13.3% yield) of *p*-(α-phenylethyl)-phenol.

The Oxidation of Optically Active *p*-(α-Phenylethyl)-Phenol to α-Phenylpropionic Acid.—Optically active *p*-(α-phenylethyl)-phenol was oxidized according to the procedure of Hart and Eleuterio.[7] To a solution of 0.6722 g. (0.00339 mol.) of *p*-(α-phenylethyl)-phenol, obtained in the run 97 ($[\alpha]_D^{21.5}$ $+1.845°$, benzene, *c* 30.37), in 200 cc. of acetone, there was added 4.1 g. of potassium permanganate in 200 cc. of water at 13—15.5°C for 25 min. The mixture was then stirred for 1.8 hr. and acidified with 6 N sulfuric acid, and the precipitated manganese dioxide was destroyed with sodium bisulfite. The mixture was extracted with 10% sodium bicarbonate (four 50-cc. portions), and the extracts were acidified with 90-cc. of 6 N hydrochloric acid and extracted with four 50-cc. portions of benzene. The benzene solution was dried with magnesium sulfate, after the solvent had been removed, it was distilled in vacuo to give 96.8 mg. (19.0% yield) of α-phenyl-propionic acid, b. p. 120°C (bath temp., 0.2 mmHg) (Lit. b. p. 145—148°C/15 mmHg[7]); n_D^{20} 1.5239; neut. equiv. 151.4 (Calcd. 150); $[\alpha]_D^{23.1}$ $+14.57°$ (ethanol, *c* 14.46). Since this reaction does not involve the asymmetric carbon atom, the configurations of α-phenylpropionic acid and *p*-(α-phenylethyl)-phenol should be identical. Thus, the specific rotation of optically pure *p*-(s-α-phenylethyl)-phenol may be estimated to be $+10.26°$ (in benzene) (Lit. $[\alpha]_D$ $+7.78°$, benzene[15]) on the basis of the value for optically pure s-α-phenylpropionic acid, $+81.1°$ (in ethanol).[7]

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[14] H. Hart, *Anal. Chem.*, **24**, 1500 (1952).

[15] R. H. Pickard and W. O. Littlebury, *J. Chem. Soc.*, **89**, 467 (1906).