

SOLVENT MOLECULES AND CARBOCATION INTERMEDIATES IN SOLVOLYSES

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Abstract — Electrophilic or hydrogen bonding assistance of hydroxylic molecules can be verified by the rate acceleration in S_N1 acetolysis of 1-phenylethyl chloride, by retentive outcomes of the substitution products in the reaction of an optically active trifluoroacetate in benzene, and by kinetic partial resolution of 1-phenylethyl chloride in optically active carboxylic acid solvents. Nucleophilic solvation of carbocation intermediates is another driving force for S_N1 ionization and can be verified by rear-side shielding of the intermediate by nitriles and hindered phenols in the solvolyses in these solvents. As a solvolysis solvent, phenol has an amphiphilic, i.e. electro- and nucleo-philic, driving force, which has been proved by stereochemical outcomes of phenolyses of 1-phenylethyl systems with various leaving groups and by those of competitive methanolysis and phenolysis of optically active 1-phenylethyl chloride. There are two types of phenolysis pathways for simple alkyl and aralkyl systems; both of them afford retained phenyl ether from optically active substrate in the presence of a base. One type has single ion-pair intermediate, while the other has two. In the latter most of the phenolysis products are derived from the second intermediate. The number of intermediates has been determined by use of Winstein's k_p - k_t plot against concentration of added salt, such as LiOPh, NaOPh, 2,6-di-tert-butyl-4-methylpyridinium phenoxide, LiClO₄, and Bu₄NClO₄. Examination of the steric outcomes of three products, ROPh, o- and p-RC₆H₄OH, suggests a variety of ion-pair structures, including four-center quadrupole and rear-side shielded ion-pair, as the first and second intermediates, respectively, in phenolyses. The usefulness of the methanol perturbation method for examination of the intermediate structure has been elucidated in the retentive phenolysis of 1-p-anisyl-2,2-dimethylpropyl p-nitrobenzoate.

INTRODUCTION

The intermediacy of the carbocation in the solvolyses of alkyl and aralkyl halides was suggested in the mid 1920's (Ref. 1). Ten years later the mechanism was designated as S_N1 by Ingold, and a free carbocation was suggested as the intermediate (Ref. 2). In 1940 the role of solvent molecules in carbocation formation was first described by Hammett, and the reaction was depicted as polymolecular solvolysis (Ref. 3). He pointed out the incipient solvation of the leaving group ion in the transition state as the driving force of the solvolytic reaction. Eighteen years later Winstein presented irrefutable experimental evidence for two kinetically distinguishable ion-pairs as the successive intermediates (Ref. 4), and since then the ion-pairing and ion-pair return has been shown to be of critical importance in every solvolysis. Although many experimental methods have been designed and refined, they have mostly been used to add detailed and additional examples to Winstein's mechanistic scheme, and mechanistic interpretation of solvolytic displacement has not changed much in principle. Reviews of some of the developments have recently been published (Ref. 5).

Despite such a long history some problems of importance still remain, mainly because of the experimental difficulty of direct observation of carbocation intermediates with a very short life in a very low concentration. Hence microscopic features of ionization, especially, the role of solvent molecule as an electrophilic (electron-accepting) and a nucleophilic (electron-donating) molecule have not been entirely disclosed. The structure of ion-pair intermediates has also been a subject for debate, although Winstein's intimate and solvent-separated ion-pair theory has prevailed. In addition, the molecularity of solvent in connection with "borderline case" solvolysis is still open for future study (Ref. 6).

Phenol has remained relatively unfamiliar among the traditional solvolysis solvents. However, it has high ionizing power (*vide infra*) and low polarity, and has three reaction centers towards the carbocation intermediate. In addition, phenolysis generally gives the phenyl ether with predominantly retained configuration, starting from optically active substrates which do

not have any group imposing configurational restriction (*vide infra*). Because of these unique features, phenolysis is expected to afford insight, more detailed and perhaps more essential as compared with any other solvolysis solvent, into ambiguous parts of the mechanistic problems.

The current state of recognition of the ionization mechanism and of the structural variation of the carbocation intermediate is the subject of this presentation. Following descriptions of the role of solvent in ionization and of the unique features of phenol solvent, the structure of the ion-pair intermediate will be discussed mainly on the basis of our phenolysis studies.

SOLVOLYSIS SOLVENT AS ELECTROPHILE — ELECTROPHILIC SOLVATION OF LEAVING GROUP

Hammett pointed out in 1940 that soft electrophiles such as Ag^+ and Hg^{2+} catalyse solvolyses of some alkyl halides (Refs. 3 & 7). He also pointed out that small amounts of water or other hydroxylic molecules can catalyse ethanolysis like metallic electrophilic catalysts do. Thus there have been many reports of electrophilic catalysis of the hydroxylic molecules on the leaving group of the substrate (Table 1).

Table 1. Acceleration of $\text{S}_{\text{N}}1$ Solvolysis Rate by Hydroxylic Molecules.

Substrate	Solvent	Added Hydroxylic Molecules (Refs.)
t-butyl bromide	nitromethane (25°C)	PhOH > H ₂ O > EtOH (Gelles, ⁸ Pocker ⁹)
t-butyl bromide	nitromethane (25°C)	PhOH (p-NO ₂ > H > p-Me) (Pocker ⁹)
t-butyl bromide	HOAc-CCl ₄ (70°C)	PhOH (p-NO ₂ > p-Cl > H > o-NO ₂) (Okamoto ¹⁰)
benzhydryl chloride	EtOH (25°C)	H ₂ O (Farinacci, ¹¹ Ward, ¹ Norris ¹²)
p-MeO-benzhydryl chloride	nitrobenzene (25°C)	MeOH (Bartlett ¹³)
triphenylmethyl chloride	benzene (25°C)	Benzyl-OH (p-NO ₂ > H > Me) (Hawthorn ¹⁴)
triphenylmethyl chloride	benzene (25°C)	MeOH, PhOH (Swain ¹⁵)
triphenylmethyl chloride	CCl ₄ (20°C)	EtOH (Hudson ¹⁶)

Phenol is one of the most powerful catalysts among these hydroxylic molecules, and solvation of the leaving group ion by the hydrogen bonding should be essential for catalysis. This is clearly shown in Fig. 1, where o-nitrophenol with the hydroxy group blocked by intramolecular hydrogen bonding, gives very little acceleration on the acetolysis rate of t-butyl bromide in a mixture of acetic acid and carbontetrachloride (1:3 v/v), whereas p-nitrophenol exhibits the largest acceleration of the acetolysis rate (Ref. 10).

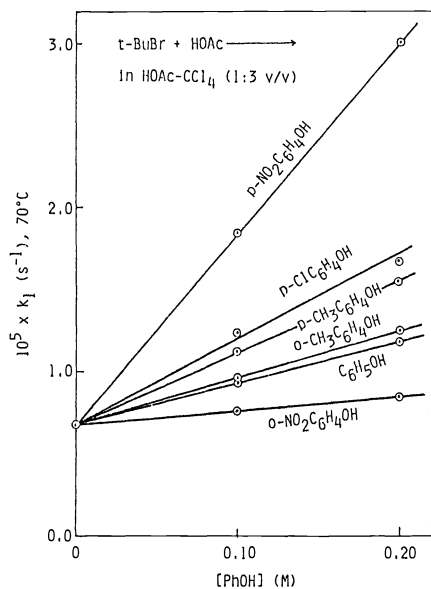
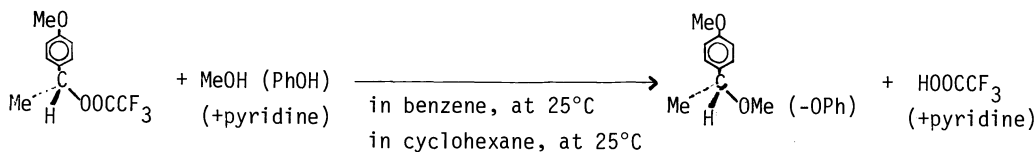


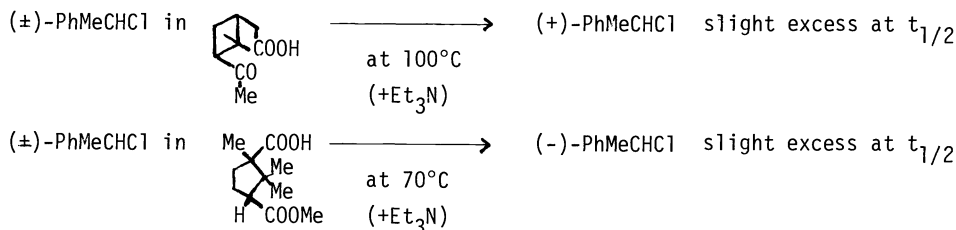
Fig. 1. Acceleration of acetolysis rate of tert-butyl bromide by phenols.

Specific anion solvation by a hydroxylic molecule was also demonstrated by a stereochemical study of the reaction of 1-(p-methoxyphenyl)ethyl trifluoroacetate with a small amount of methanol or phenol in benzene or cyclohexane solvent (Ref. 17). In these reactions the substrate gave the methyl ether or the phenyl ether with partially retained (predominantly racemized) configuration, and the reactions obeyed second-order kinetics. These results may be explained by the intermolecular $\text{S}_{\text{N}}1$ reaction pathway (Scheme 1). Thus the electrophilic or hydrogen bonding propensity of methanol or phenol to the leaving group of the substrate would be the driving force to afford the retentive product.

If the interaction between the substrate and a hydroxylic solvent were specific to cause such an $\text{S}_{\text{N}}1$ type interaction, the solvolyses of anti-podonic substrates in an optically active solvent may proceed with rates which are different from each other. In turn, when the solvolysis of racemic substrate is carried out in an optically active hydroxylic solvent, unchanged substrate reclaimed at a half-life might exhibit optical activity, although slight. It was confirmed in the solvolysis of racemic 1-phenylethyl chloride in pinonic acid or in monomethyl ester of camphoric acid that the chloride recovered at



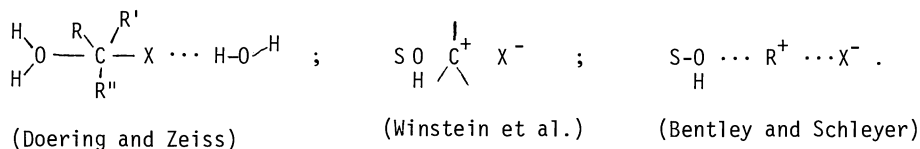
half-life showed a small amount of optical activity (Ref. 18), in other words, the chloride underwent partial kinetic resolution at the half-life (Scheme 2).



These electrophilic solvations should be estimated partly by the empirical Grunwald-Winstein Y parameter for the ionizing power of solvolytic solvents (Ref. 19) and Gutmann's Acceptor Number (AN) for the acceptor property of solvolytic solvents (Ref. 20).

SOLVOLYSIS SOLVENT AS NUCLEOPHILE — NUCLEOPHILIC SOLVATION OF CARBOCATION

Nucleophilically solvated ion-pair intermediates have been discussed by Doering and Zeiss (Ref. 21), Winstein and co-workers (Ref. 22), and Bentley and Schleyer (Ref. 6a) (Scheme 3).



Chemical evidence of the cation solvation in the ion-pair by acetone (Ref. 23) and by dibutyl ether (Ref. 24) has also been reported. In addition, stereochemical evidence for nucleophilic intervention of nitriles such as fumaronitrile, malononitrile, acetonitrile, and acrylonitrile on the ion-pair intermediate was demonstrated in the S_N1 butyrolisis (Ref. 25) and S_N1 hydrolysis (Ref. 26) of optically active 1-phenylethyl chloride.

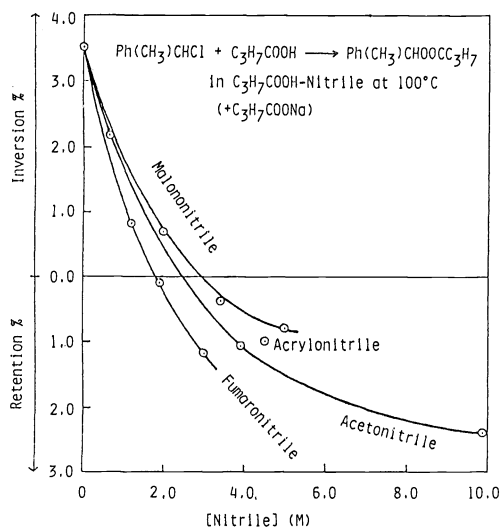
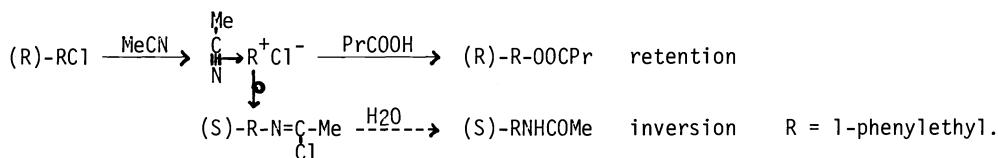


Fig. 2. Stereochemical course of butyrolisis of 1-phenylethyl chloride in the presence of nitriles.

As shown in Fig. 2 and Scheme 4, the stereochemical course for the formation of 1-phenylethyl butyrate turns out from the usual inversion (with predominant racemization) to retention (with predominant racemization) with an increase in the nitrile concentration in butyric acid solvent. Furthermore, the by-product after work-up with water, *N*-1-phenylethylacetamide in the case of acetonitrile, exhibits inversion (with predominant racemization) even when retained butyrate is produced.

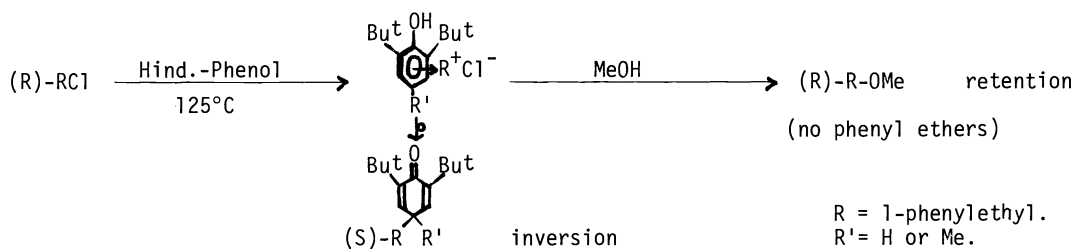
Similar nitrile solvation has been proposed in the hydrolysis of optically active 1-phenylethyl chloride in acrylonitrile-water mixture (97:3 w/w). Thus the hydrolysis product, 1-phenylethanol, was obtained with retention of configuration, although accompanied by predominant racemization (Ref. 26).

A phenol molecule has a hydroxyl group as its electrophilic part and reacts as a powerful hydrogen bonding catalyst for solvolysis (Table 1 & Fig. 1). However, it has a



Scheme 4.

6π electron system on the ring and may play the role of electron donor as does acetonitrile. Thus a hindered phenol, 2,6-di-*tert*-butylphenol or 2,6-di-*tert*-butyl-4-methylphenol, may behave as an electron donor or a rear-side shielder, due to the blocking of the electrophilic part. In fact, the methanolysis of optically active 1-phenylethyl chloride proceeds to give the methyl ether a partially retained configuration when it is carried out in a mixture of methanol and the hindered phenols (0.5:99.5 w/w). In addition, the phenolysis product, 4-(1-phenylethyl)-2,6-di-*tert*-butyl-2,5-cyclohexadienone or 4-methyl-4-(1-phenylethyl)-2,6-di-*tert*-butyl-2,5-cyclohexadienone, exhibits inversion with racemization in the stereochemical outcome (Ref. 27)(Scheme 5).



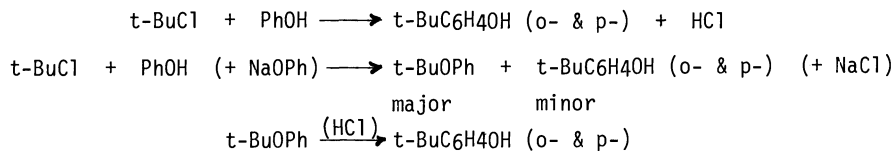
Scheme 5.

In a similar fashion to the case of anion solvation, the cation solvation of nitriles or hindered phenols should be estimated by Gutmann's Donor Number (DN) (Ref. 28), by Bentley-Schleyer's N parameter for solvent nucleophilicity (Ref. 6), and also in some cases by Grunwald-Winstein's Y parameter (Ref. 19).

In addition to these specific solvations of anion or cation, electrostatic solvation which is estimated from a macroscopic dielectric constant should be one of the primary controlling factors of the driving force for the ionization, especially in solvents with higher dielectric constants (Ref. 29).

PHENOL AS A SOLVOLYSIS SOLVENT — COMPARISON WITH OTHER SOLVOLYSIS SOLVENTS

Although Hammett clearly designated phenol as a solvolytic solvent in 1940 (Ref. 3) and since then a few reports have demonstrated the catalysis of phenol in solvolyses (Refs. 8, 9, 10, & 15), search for a model phenolysis in phenolic solvent was first started in our laboratories in 1949 (Ref. 30). In that year Hart and Simons reported that *tert*-butyl chloride can alkylate phenol without any catalyst to give *tert*-butylphenols (Ref. 31). When the rate of this reaction was investigated in our laboratories in the presence of sodium phenoxide, it was revealed that phenolysis proceeds by the S_N1 mechanism and that the main product is not *tert*-butylphenols but *tert*-butyl phenyl ether (Ref. 30). In addition, it was demonstrated that the phenyl ether undergoes rapid rearrangement with HCl to give *tert*-butylphenols in the absence of the base, sodium phenoxide (Refs. 30 & 32)(Scheme 6).



Scheme 6.

Phenol has a dielectric constant of 9.78 at 60°C, a little higher than that of acetic acid (6.15 at 25°C). The Grunwald-Winstein Y value (1.77), extrapolated from the data of Ref. 29, resembles those of formic acid (2.05) and 50% aqueous ethanol (1.655), and is much higher than acetic acid (-1.64) (Ref. 33). The Bentley-Schleyer N value (-3.23, 50°C) is lower than those of acetic acid (-2.05) and 2,2,2-trifluoroethanol (-2.78), and much less than those of typical nucleophilic solvents such as 80% aqueous ethanol (0.00), methanol (0.01), and water (-0.26). Therefore, phenol can be classified as a typical solvolysis solvent with high ioni-

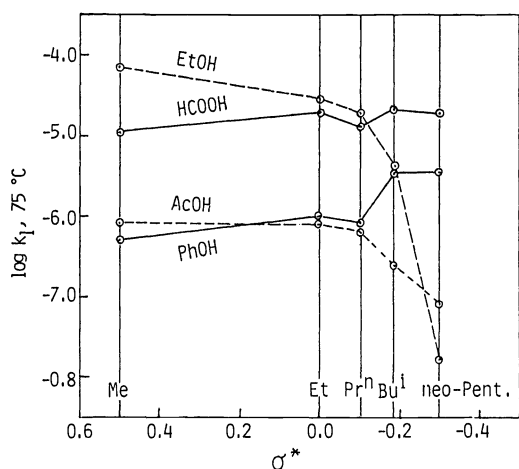


Fig. 3. $\log k_1$ vs σ^* plots for β -methylated primary alkyl tosylates in various solvents.

zing power and low polarity and nucleophilicity.

The phenolysis rate sequence of some primary alkyl tosylates increases with increasing β -substitution in the alkyl moiety (Me < Et \sim n-Pr < iso-Bu < neo-Pent), and closely resembles the formolysis sequence of corresponding tosylates. The similarity of both solvents is shown in the $\log k_1$ vs Taft's σ^* plot for these primary alkyl tosylates (Fig. 3), indicating the high ionizing power of phenol solvent like formic acid (Ref. 33).

In addition, the phenolysis rate sequence for *p*-substituted-1-phenyl-1-methylethyl *p*-nitrobenzoates (*p*-NO₂ < *m*-Cl < H < *p*-Me < *p*-MeO) obeys Brown-Okamoto's $\rho\sigma^+$ relation and the ρ value (-4.61) resembles those of the hydrolysis in 70% aqueous acetone (-3.74) and the hydrolysis of the corresponding chlorides in 90% aqueous acetone (-4.54) (Ref. 33). This also demonstrates the high ionizing power of phenol solvent.

PHENOL AS A SOLVENT FOR RETENTIVE SOLVOLYSIS

In 1962 we reported that the phenolysis of optically active 1-phenylethyl chloride proceeds with predominant retention of configuration to yield the phenyl ether in the presence of added aniline in phenol-benzene (1:1 w/w) solvent (Ref. 34). This was the first example which demonstrated that S_N1 solvolysis of the substrate without configurational restriction does not always proceed to yield a net inverted product, although the inversive product still prevails in organic chemistry textbooks. Thereafter it was revealed in our laboratories that for many secondary and tertiary substrates without a neighboring group imposing configurational restrictions (Table 2) phenolysis proceeds in various mixed solvents to afford the phenyl ether with predominant, in some cases more than 90%, retention of configuration, so long as a base was added as the neutralizing agent (Ref. 35). Thus, 1-(*p*-nitrophenyl)ethyl *p*-nitrobenzoate (Ref. 36), 2,2-dimethyl-1-phenylpropyl and 2,2-dimethyl-1-(*p*-nitrophenyl)propyl *p*-nitrobenzoates (Ref. 35) yield corresponding phenyl ethers with predominant retention (90 - 97%) in phenolyses in pure phenol solvent with added bases. From this specific feature of the stereochemical course we anticipated that this solvent would shed light on some still ambiguous aspects of ionization and of product formation stage of solvolysis.

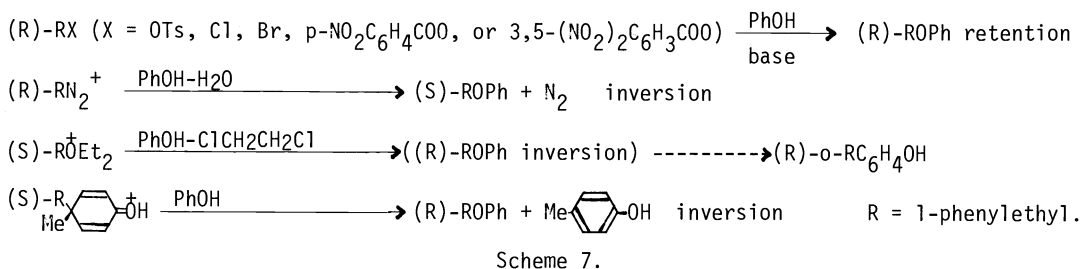
Table 2. Optically Active Secondary and Tertiary Substrates Which Yield Phenyl Ethers with Retained Configuration in Various Phenolic Solvents.

YC ₆ H ₄ (Me)CHX	X = Cl, Br, <i>p</i> -NO ₂ C ₆ H ₄ COO, 3,5-(NO ₂) ₂ C ₆ H ₃ COO, OTs, or CF ₃ COO. Y = <i>p</i> -NO ₂ , H, or <i>p</i> -MeO.
YC ₆ H ₄ (R)CHX	X = Cl, <i>p</i> -NO ₂ C ₆ H ₄ COO, or CF ₃ COO. Y = <i>p</i> -NO ₂ , H, or <i>p</i> -MeO. R = Et, iso-Pr, or <i>t</i> -Bu.
(Et)(Me)(i-Hex)CX	X = Cl or CF ₃ COO.
(Et)(Me)(Ph)CX	X = <i>p</i> -NO ₂ C ₆ H ₄ COO.
(Ph)(<i>p</i> -ClC ₆ H ₄)CHX	X = <i>p</i> -NO ₂ C ₆ H ₄ COO.
Added Base	Aniline, Et ₃ N, NaOPh, LiOPh, Urea, or 2,6-di- <i>t</i> -Bu-4-Me-pyridine.
Solvent	Phenol, Phenol-Benzene, Phenol-Acetonitrile, Phenol-Acetone, Phenol-Toluene, Phenol-Cyclohexane, 2,6-di- <i>i</i> -Pr-C ₆ H ₃ OH, 2,6-di-Me-C ₆ H ₃ OH, or <i>p</i> -Cresol

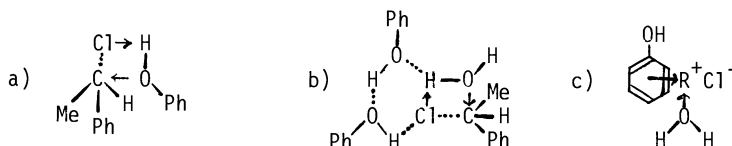
In view of the amphiphilic role of phenol molecule both as an electrophile and as a nucleophile (*vide supra*), the retentive function of phenol may be ascribed to its front-side attack, like S_N1 reaction, and also to its rear-side shielding ability, as seen in 2,6-di-*tert*-butyl-phenol solvent (Scheme 5).

An example which indicates the close relation between hydrogen bonding and retentive phenoly-

sis has been seen in the stereochemical outcome of the phenyl ether formation from 1-phenylethyl system with various leaving groups. When the leaving group is OTs, Cl, Br, p-nitrobenzoate, or 3,5-dinitrobenzoate, the phenyl ether exhibits 2 - 28% retention of configuration. In contrast, 1-phenylethyl system with positively-charged leaving group (a protonated cyclohexadienone, N_2^+ , or Et_2O^+) gives 8 - 13% inverted phenyl ether. Provided that the phenolyses proceed via a single ion-pair intermediate (*vide infra*), the formation of retained phenyl ether can be explained by intermolecular S_Ni -like transition state (or intermediate) formed by the substrate and the phenol molecule. On the other hand, the positively charged substrate should not have hydrogen bonding with the phenol molecule, and consequently should not yield the retentive phenyl ether either (Ref. 37)(Schemes 7 & 8a).



The stereochemical course of competitive phenolysis and hydrolysis (or methanolysis) provides another interesting aspect when considering retentive function of the phenol molecule in phenolysis. Thus 1-phenylethyl chloride yields not only retained phenyl ether, but also retained alcohol (or methyl ether), when competitive solvolyses are carried out in phenol-water (or phenol-methanol) mixtures in the presence of triethylamine (Figs. 4 & 5)(Refs. 38 & 39). Since the hydrolysis or methanolysis of 1-phenylethyl chloride usually proceeds with inversion of configuration, these results may be elucidated by an S_Ni -like attack of water or methanol, which is hydrogen-bonded with phenol via a cyclic transition state (Scheme 8b) or by a front-side attack of water or methanol to a rear-side shielded ion-pair as shown in Schemes 4 and 5 (Scheme 8c). In order to distinguish between these possibilities we need more information on the detailed structure of and also the number of ion-pair intermediates in these 1-phenylethyl chloride solvolyses.



Scheme 8.

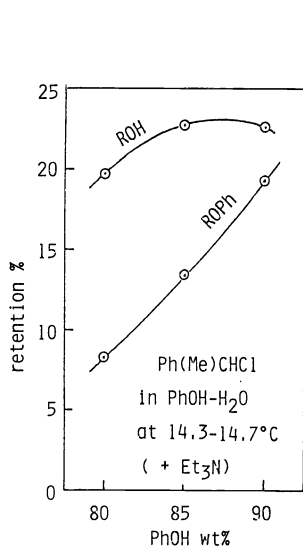


Fig. 4. Stereochemical course for solvolysis products in phenol-water mixtures.

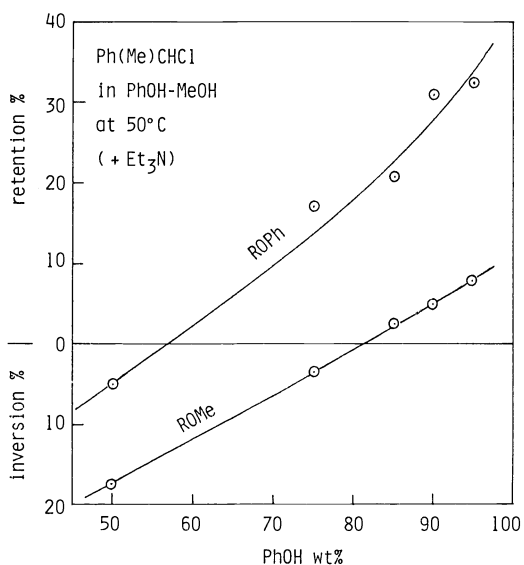
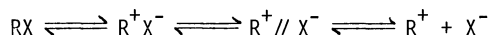


Fig. 5. Stereochemical course for solvolysis products in phenol-methanol mixtures.

THE NUMBER AND STABILITY OF CARBOCATION INTERMEDIATE

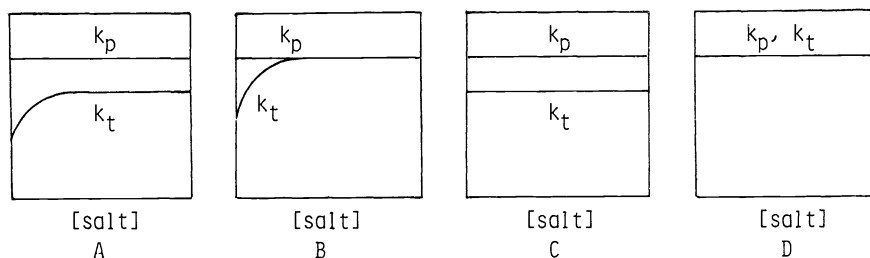
In view of the recent recognition of multiple intermediates in solvolysis (Ref. 5) we need to know how many intermediates exist in each solvolysis, before we consider the ion-pair structure. As a tool for determining the presence of multiple intermediates a method of k_p (polarimetric rate constant) and k_t (titrimetric rate constant) profile against the concentration of added salt was first explored by Winstein and his co-workers, and this was successfully applied to the acetolysis of *threo*-2-*p*-anisyl-1-methylpropyl brosylate (Ref. 4). They claimed that there are two kinetically distinguishable ion-pair intermediates, intimate and solvent-separated, and that solvolysis proceeds further to the dissociated free ion (Scheme 9).



Scheme 9.

Although this solvolysis scheme has been widely applied to many solvolyses, especially to acetolysis, the example which actually presents experimental evidence for the presence of multiple intermediate has not often been reported except by Winstein (Ref. 4) and us (Refs. 35 & 36).

When one measures k_p and k_t at variable concentrations of added salt for the optically active substrate and subsequently plots the k_p and k_t against the salt concentration, one would generally obtain four patterns of k_p - k_t profile, A - D (Ref. 35)(Fig. 6), providing that there is no general salt effect.

Fig. 6. Patterns of salt effect on k_p and k_t .

Winstein and his co-workers presented the examples for pattern A (Ref. 4) and B (Ref. 40) in the acetolysis of some aralkyl tosylates. In the phenolyses of some secondary aralkyl *p*-nitrobenzoates we present all examples for patterns A, B, C, and D in Table 3.

Table 3. The k_p - k_t Patterns for Phenolyses of Some Secondary Aralkyl Systems.

Substrate	Added salt	Pattern	Substrate	Added salt	Pattern
<chem>MeO-C6H4-C(Bu^t)H-OPNB</chem>	<chem>NaOPh</chem> , ³⁵ <chem>LiOPh</chem> ⁴²	A	<chem>MeO-C6H4-C(Me)H-OPNB</chem>	<chem>NaOPh</chem> ³⁶	A
<chem>MeO-C6H4-C(Bu^t)H-OPNB</chem>	<chem>Bu4NClO4</chem> ⁴²	A			
<chem>H-C6H4-C(Bu^t)H-OPNB</chem>	<chem>NaOPh</chem> ³⁵	B			
<chem>H-C6H4-C(Bu^t)H-OPNB</chem>	<chem>Bu4NClO4</chem> ⁴²	C	<chem>H-C6H4-C(Me)H-OPNB</chem>	<chem>NaOPh</chem> ³⁶	C
<chem>O2N-C6H4-C(Bu^t)H-OPNB</chem>	<chem>NaOPh</chem> ³⁵	D	<chem>O2N-C6H4-C(Me)H-OPNB</chem>	<chem>NaOPh</chem> ³⁶	D

OPNB = *p*-nitrobenzoate.

A common feature of patterns A and B is seen in the special salt effect on k_t , which was first found in acetolysis by Winstein and his co-workers (Ref. 41). The special salt effect indicates that the added salt scavenges an ion-pair intermediate making the rate of ion-pair return negligibly low as compared with the rate of product formation. However, it is important to recognize that the number of intermediates cannot be determined from just the k_t profile. Only when k_t profile is compared with the k_p profile, can the number of intermediates be determined. For example, a single intermediate reacting with added salt can be suggested from the coincidence of the k_p and k_t lines at higher salt concentrations in pattern B. Similarly in pattern A the k_p and k_t lines do not coincide with each other even at higher salt concentrations, indicating that only the second ion-pair intermediate is scavenged by the added salt. Consequently the solvolysis which exhibits the k_p - k_t pattern A proceeds via two successive intermediates.

In the phenolysis of aralkyl *p*-nitrobenzoate the corresponding phenyl ether and alkylated phenols (*o*- and *p*-) are found in the products, and their composition would be affected by the added salt such as sodium phenoxide or tetrabutylammonium perchlorate. It is anticipated that

when the composition is plotted against the concentration of added salt, a pattern similar to special salt effect on k_t would be observed, provided that most of product is derived from the ion-pair scavenged by added salt at higher salt concentrations. In fact, in the phenolyses of 1-p-anisyl-2,2-dimethylpropyl p-nitrobenzoate a composition pattern similar to special salt effect on k_t has been observed for both added sodium phenoxide and tetrabutylammonium perchlorate (Ref. 42)(Figs. 7 & 8). A similar composition pattern against added sodium phenoxide has been observed in the phenolysis of 2,2-dimethyl-1-phenylpropyl p-nitrobenzoate which exhibits the k_p - k_t pattern B (Table 3)(Ref. 42).

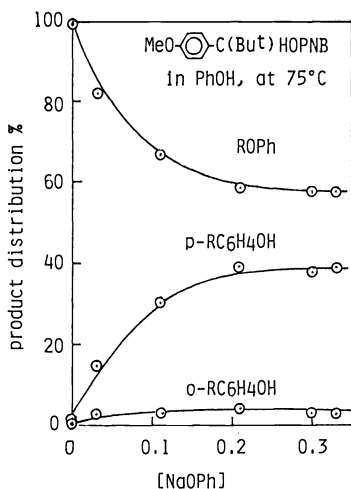


Fig. 7. Product distribution in the phenolysis of 1-p-anisyl-2,2-dimethylpropyl p-nitrobenzoate in the presence of added sodium phenoxide.

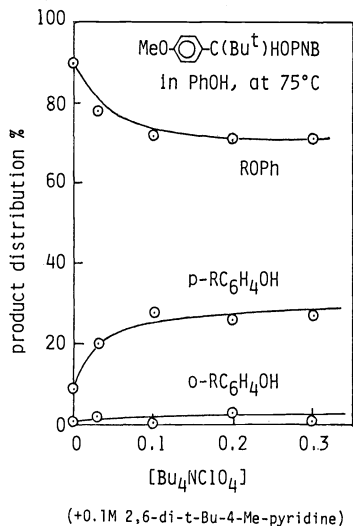


Fig. 8. Product distribution in the phenolysis of 1-p-anisyl-2,2-dimethylpropyl p-nitrobenzoate in the presence of added tetrabutylammonium perchlorate.

Provided that no general salt effect is observed, in patterns C and D the added salt does not exhibit an increase in k_t and k_p , most probably indicating that the salt virtually does not react with the intermediate, but the solvent molecule alone reacts with reactive first intermediate. Furthermore, in pattern C the first intermediate reacts partly with the solvent molecule, but it partly returns to the substrate, whereas in pattern D all of the first intermediate is scavenged by the solvent molecule.

In fact, 2,2-dimethyl-1-phenylpropyl and 1-phenylethyl p-nitrobenzoates undergo Pattern C phenolysis in the presence of tetrabutylammonium perchlorate and sodium phenoxide, respectively (Table 3). However, p-nitro-derivatives of these substrates, which should give a relatively less stable and short-lived ion-pair intermediate, show a coincidence of k_p and k_t in the whole range of concentration of added sodium phenoxide, pattern D (Table 3). In the phenolysis of 2,2-dimethyl-1-phenylpropyl p-nitrobenzoate, added perchlorate is less nucleophilic than sodium phenoxide. This is reflected in the changeover of the pattern from B to C (Table 3).

When a series of the p-substituents, p-MeO, H, and p-NO₂, is compared, there appears to be a general trend showing more formation of the second intermediate as the stability of the intermediate increases.

STRUCTURE AND REACTIVITY OF THE FIRST ION-PAIR INTERMEDIATE

Although intimate or contact ion-pairs provide a reasonable explanation for the structure of the first intermediate in acetolysis, phenolysis, and other solvolysis, stereochemical examinations of the structure of the first intermediate have been undertaken in relatively few solvolyses. Thus, Hammett found that the acetolysis of optically active 1-phenylethyl chloride yields the acetate with net inverted configuration (Ref. 43), and this was explained by a contact ion-pair. However, a k_p - k_t examination to determine the precise number of acetolysis intermediates was not carried out.

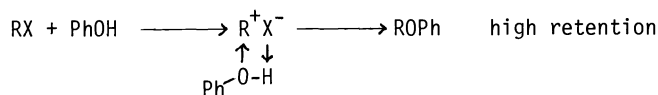
Among our k_p - k_t studies there are several phenolyses which clearly proceed via only a single intermediate alone, most probably a contact ion-pair in such a low dielectric media (Table 4). For simple alkyl and aralkyl systems, which have no group imposing configurational restriction or neighboring group participation, inversion plus racemization has so far been recognized as a predominant steric course, but it is shown in Table 4 that in phenolyses of aralkyl systems retention plus racemization is common.

Table 4. Predominant Stereochemical Course of Phenolyses with a Single Ion-Pair Intermediate.

Substrate	Steric Course	$k_p-k_t^a)$	Substrate	Steric Course	$k_p-k_t^a)$
2-Octyl tosylate	inversion	B^{44}	$\text{MeO-C}_6\text{H}_4\text{-C}(\text{Bu}t)\text{H-O}_2\text{CCF}_3$	retention	B^{35}
$\text{Ph}(\text{Me})\text{CH-OPNB}$	retention	C^{36}	$\text{H-C}_6\text{H}_4\text{-C}(\text{Bu}t)\text{H-OPNB}$	high retention	C^{35}
$\text{O}_2\text{N-C}_6\text{H}_4\text{-C}(\text{Me})\text{H-OPNB}$	high retention	D^{36}	$\text{O}_2\text{N-C}_6\text{H}_4\text{-C}(\text{Bu}t)\text{H-OPNB}$	high retention	D^{35}

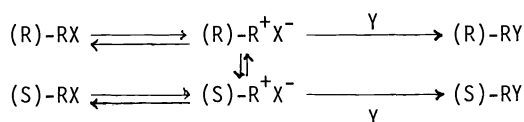
a) The pattern of salt effect on k_p and k_t (Fig. 6).

In view of such retentive examples of phenolyses with a single intermediate, and of intermolecular $\text{S}_{\text{N}}1$ type phenolysis (Scheme 1), the single intermediate may include a phenol molecule making a quadrupole (Scheme 10). The carbenium carbon is not free but has weak interaction with the leaving group anion, hence the ion-pair as it is initially formed from the asymmetric substrate must also be asymmetric.



Scheme 10.

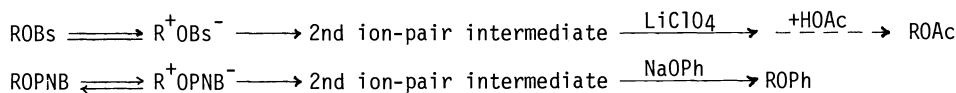
Conventional rear-side attack on the asymmetric carbenium carbon can lead to an inverse product, and this reaction pathway can compensate for the front-side attack and lead to racemization. However, another reaction pathway such as internal rotation in the asymmetric ion-pair can also cause racemization in the final product. This reaction pathway cannot be eliminated especially in a more stable and long-lived ion-pair, which may proceed further to the second ion-pair intermediate (Refs. 34, 38b, 45 & 46) (Scheme 11).



Scheme 11.

STRUCTURE AND REACTIVITY OF THE SECOND ION-PAIR INTERMEDIATE

There are a few examples which indicate the existence of second ion-pair intermediate on the basis of k_p-k_t measurement. Thus, as mentioned above, 25 years ago Winstein and his co-workers first found the k_p-k_t pattern A (Fig. 6) in the acetolysis of threo-2-p-anisyl-1-methylpropyl brosylate, and they claimed that the added lithium perchlorate scavenges the second ion-pair intermediate, eliminating the external return (Ref. 4) (Scheme 12). We also found a similar pattern A in the phenolyses of 1-p-anisyl-2,2-dimethylpropyl and 1-p-anisylethyl p-nitrobenzoates in the presence of added sodium phenoxide (Refs. 35 & 36) and tetrabutylammonium perchlorate (Ref. 42) (Scheme 12 and Table 5).



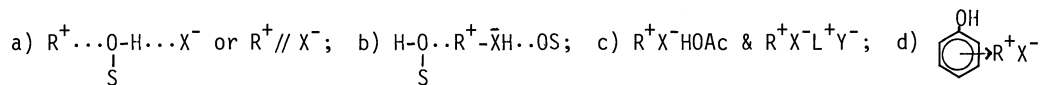
Scheme 12.

Table 5. Predominant Stereochemical Course of Solvolyses with the Second Ion-pair Intermediate.

Substrate	Solvent	Added Salt	Steric Course	$k_p-k_t^a)$
$\text{MeO-C}_6\text{H}_4\text{-C}(\text{Me})\text{H-C}(\text{Me})\text{H-OBs}$ (threo-)	HOAc	LiClO_4^4	high retention	A
$\text{MeO-C}_6\text{H}_4\text{-C}(\text{Bu}t)\text{H-OPNB}$	PhOH	$\text{LiOPh}^{4,2}$ $\text{NaOPh}^{3,5}$ $\text{Bu}_4\text{NClO}_4^{4,2}$	low retention	A
$\text{MeO-C}_6\text{H}_4\text{-C}(\text{Me})\text{H-OPNB}$	PhOH	$\text{NaOPh}^{3,6}$	low retention	A

a) The pattern of salt effect on k_p and k_t (Fig. 6).

Various types of the second ion-pair intermediate have been proposed: a) Winstein's solvent-separate ion-pair, $\text{R}^+//\text{X}^-$ (Refs. 4 & 3c), b) Dannenberg's cation-anion stabilized intermediate (Ref. 47), c) Topsom's quadruplet (Ref. 48), and d) a rear-side shielded ion-pair (Refs. 5e, 26, & 27) (Scheme 13).



Scheme 13.

Unfortunately, we have no other examples for which we can really examine the reality of the postulated structures a)-d) as the second intermediate, except those cited in Table 5. For example, the acetolysis of 1-methyl-2-phenylethyl tosylate, which was used by Dannenberg and his co-workers for consideration of the second intermediate (Ref. 47) has not been examined for the salt effect pattern on both k_p and k_t . Besides, we can assume the k_p - k_t for this tosylate to be B (Fig. 6), in other words, to show a single ion-pair intermediate, because even 2-p-anisyl-1-methylethyl tosylate, which gives a more stable ion-pair intermediate, exhibits pattern B, a case of a single ion-pair intermediate, in acetolysis (Ref. 40).

By the same token, the acetolysis of 2-p-anisyl-1-methylethyl tosylate, for which Winstein and his co-workers found the induced common ion depression as compelling evidence for the solvent-separated ion-pair (Ref. 49), exhibits pattern B, *i.e.*, only single ion-pair as the intermediate. Similarly, the acetolysis of cholesteryl tosylate, for which Topsom proposed a quadruplet as the second intermediate (Ref. 48), has not been examined for the number of intermediates by the k_p - k_t method.

As regards the detailed structure of the second intermediate, the case of phenolysis of 1-p-anisyl-2,2-dimethylpropyl p-nitrobenzoate, with added sodium phenoxide, lithium phenoxide, 2,6-di-tert-butyl-4-methylpyridinium phenoxide, lithium perchlorate, and tetrabutylammonium perchlorate, is instructive. In order to neutralize the liberated acid, phenolyses with the perchlorates were carried out in the presence of 2,6-di-tert-butyl-4-methylpyridinium phenoxide. All of these phenolyses exhibit the pattern A (Fig. 6) and the product distribution affords a pattern similar to the special salt effect (Figs. 7 & 8). Consequently, it is evident that almost all of the products are derived from the second intermediate at higher concentrations of the added salt.

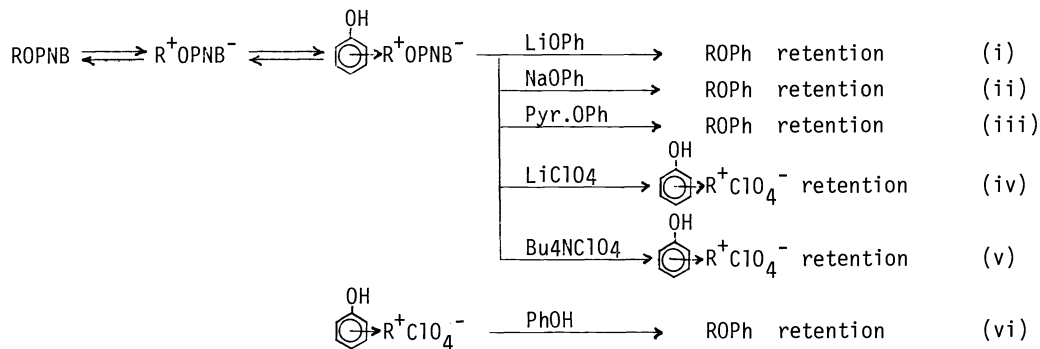
The stereochemical results (Table 6) and the composition (Figs. 7 & 8) can be explained by a rear-side shielded ion-pair intermediate (Scheme 13), composed of a phenol molecule and the contact ion-pair. Possible reaction pathways for the formation of the phenyl ether are shown in Scheme 14, (i) - (vi).

Table 6. Stereochemical Course for the Products of Phenolysis of 1-p-Anisyl-2,2-dimethylpropyl p-nitrobenzoate at 75°C (Ref. 42)

Salt	LiOPh	NaOPh	Pyr.OPh ^{a)}	LiClO ₄ ^{b)}	Bu ₄ NC10 ₄ ^{b)}
ROPh	1.7% retention	4.2-4.5% retention	1.2% retention	1.5% retention	0.8% retention
o-RC ₆ H ₄ OH	0.8% inversion	4.0-4.8% retention	? % retention	3.0% inversion	2.7% retention
p-RC ₆ H ₄ OH	0.4% inversion	3-4% retention	2.2% retention	0.1% retention	1.8% retention

a) 2,6-di-tert-butyl-4-methylpyridinium phenoxide, added as the correspondig pyridine.

b) 0.1 M 2,6-di-tert-butyl-4-methylpyridine was added as the neutralizing agent.



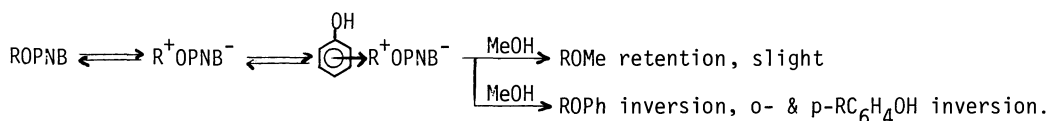
Scheme 14.

The reaction path for the formation of retentive phenyl ether in the presence of the perchlorates leaves other possibilities open for discussion. Thus, this would also be elucidated by the solvent-separated ion-pair instead of the pathways (iv), (v), and (vi) (Scheme 14). However, when one assumes a solvent-separated ion-pair as the second intermediate, the formation of retained phenyl ether even in the presence of the phenoxides is difficult to explain as

the solvent-(or phenol-)separated ion-pair can be attacked by the more nucleophilic phenoxides from the rear-side to give inverted phenyl ether.

The stereochemical outcomes in the presence of added methanol afford other interesting information in the discussion of second ion-pair intermediates. Thus, when 3 wt% of methanol was added in the phenolysis of 1-p-anisyl-2,2-dimethylpropyl p-nitrobenzoate, the methyl ether, which was obtained in compensation of decrease in the phenyl ether yield, exhibited a slightly retained configuration. In contrast, the phenyl ether exhibited a definite inversion of configuration. In this phenolysis 2,6-di-tert-butyl-4-methylpyridine was added to neutralize the liberated p-nitrobenzoic acid (Ref. 50).

Since addition of tetrabutylammonium perchlorate to this phenolysis medium disclosed the k_p - k_t pattern A (Fig. 6), indicating the existence of the second ion-pair intermediate, it is conceivable that these ethers are derived from the second intermediate. Providing a reaction pathway where more nucleophilic methanol can react with the proton of the phenol shielding the rear-side of the contact ion-pair, the formation of inverted, otherwise retained, phenyl ether can be rationalized by the collapse of rear-side phenol by methanol (Scheme 15). In view of the large ionizing power of phenol as compared with methanol, and of the low concentration of added methanol, methanol-separated ion-pair as the second intermediate, or methanol-sorting by the contact ion-pair would not be a practical model.



Scheme 15.

Obviously, these explanations apply only to the predominant pathways among all those leading to the final, optically active products. The fact that all the products suffer significant racemization (Table 6) indicates a relatively long life of the contact ion-pair, leading to its self-racemization as shown in Scheme 11.

CONCLUDING REMARKS

Despite these detailed investigations we do not believe the details can be regarded as settled, since some important matters as yet remain unsolved. For example, most of solvolysis studies in the literature lacks determination of the number of intermediates according to the tool of k_p - k_t profile. Phenolysis studies of simple aralkyl systems have disclosed that solvolysis does not always proceed with inversion of configuration but sometimes proceed with retention of configuration even when the substrate has no group with configurational restriction, e.g., neighboring group participation. Three phenolysis products exhibit a variety of steric outcomes by perturbation of added salts and methanol. Hence phenol is a promising solvent for studies of ion-pair structures as we have recognized various types of intermediates other than intimate and solvent-separated ion-pairs.

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