Effect of the Leaving Group and Solvent in Nucleophilic Aliphatic Substitutions Promoted by Quaternary Onium Salts

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Rates of nucleophilic substitutions by N_3^- and SCN^- (as hexadecyltributylphosphonium salts) in a series of *n*-octyl derivatives ($C_8H_{17}X$, X = Cl, Br, I, OTos, OMes) have been measured in different solvents (MeOH, Me_2SO, PhCl, cyclohexane). Nucleofugacity scales are as follows: OTos > I > OMes ≳ Br ≫ Cl in MeOH; I > Br > OTos > OMes > Cl in Me_2SO; I > OTos ≃ Br > OMes ≫ Cl in PhCl; OTos > OMes > I > Br ≫ Cl in cyclohexane. In the case of the methanesulfonic group, reaction rates progressively increase as the polarity and polarizability of the medium diminish: the highest rates are observed in cyclohexane, with 732- and 33-fold enhancements for MeOH and Me_2SO, respectively, with N_3^-, and 22- and 14-fold enhancements with SCN^-. In the case of halo derivatives the highest rates are observed in Me_2SO with enhancements up to three orders of magnitude with respect to MeOH. The rate ratios in Me_2SO and MeOH, expressed as log k_{Me_2SO}/k_{MeOH} are OMes (1.3), OTos (1.7), Cl (2.2), Br (2.4), I (2.9); they show the anionic nature of the activated complexes and reflect an increasing polarizability (hence an increasing solvation by Me_2SO) of the activated complexes on transfer from mesilate to iodide according to the reported sequence. In cyclohexane any appreciable solvation of the entering group and of the activated complex can be excluded. Therefore, the observed rates should reflect, better than in any other solvent, not only the intrinsic nucleophilicity of the entering group but also the intrinsic nucleofugacity of the leaving group. Rate variations observed in the nonprotic solvents are discussed on the basis of differences of solvation of the activated complex as a function of its polarizability and of that of the solvent.

The enormous body of work on solvent effects in anion-promoted reactions almost entirely concerns high-polarity media, namely, protic and dipolar aprotic solvents.[1-3] Under these conditions, solvation totally obscures the intrinsic reactivities of nucleophiles and substrates, which are typically shown in the gas phase. By using ammonium and phosphonium quaternary salts, it is possible to work in solvents of low polarity and/or polarizability, such as aliphatic and aromatic hydrocarbons. This narrows the gap between reactions carried out in gas phase and in solution, due to the low interaction between anion and quaternary onium cation and to the very limited solvation of the anion in nonpolar media.

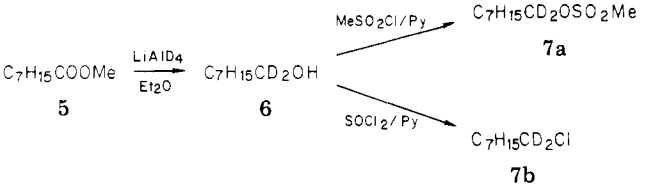
By the same token, nucleofugacity of the leaving groups may also be dramatically affected by moving from polar to nonpolar media.

In previous papers[4-7] we found that, in the displacement of the methanesulfonic group in *n*-octyl methanesulfonate (**1a**) by the anions of quaternary phosphonium salts Q^+Y^- (Y = Cl, Br, I, SCN, N_3, CN), reaction rates increase by decreasing the polarity of the solvents in the order $k_{MeOH} < k_{Me_2SO} < k_{PhCl} < k_{cyclohexane}$. Differences were the highest for anions with localized and/or less polarizable charge (e.g., Cl^-, Br^-, N_3^-, CN^-). Whereas specific solvation of the nucleophile by hydrogen bonding accounts for the low reactivities in methanol, it is more difficult to explain the reactivity sequence in the other solvents. It seemed especially important to know if the solvent dependence found in nucleophilic substitutions of methanesulfonic group in **1a** is peculiar to this group, or is common to some or all of the other leaving groups. For this reason we have measured the rates of nucleophilic substitutions in a series of *n*-octyl derivatives (chloride, bromide, iodide, and tosylate, **1b–e**). The solvents used were MeOH, Me_2SO, PhCl, and cyclohexane, representative of polar–protic, dipolar–aprotic, fairly polar and polarizable, and nonpolar and nonpolarizable solvents, respectively.

Results

The nucleophiles examined were N_3^- and SCN^- as hexadecyltributylphosphonium salts (**2a,b**); with the latter anion the study was limited to iodo and tosyl derivatives (**1d,e**, reaction 1). As for methanesulfonate (**1a**),[4,5] kinetics

Scheme I



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$$n\text{-}C_8H_{17}X + C_{16}H_{33}P^+Bu_3Y^- \rightarrow n\text{-}C_8H_{17}Y + C_{16}H_{33}P^+Bu_3X^- \quad (1)$$

1a, X = $MeSO_3$; **b**, X = Cl; **c**, X = Br; **d**, X = I; **e**, X = *p*-$MeC_6H_4SO_3$

2a, Y = N_3; **b**, Y = SCN; **c**, Y = $MeSO_3$

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were performed at 60 °C, with comparable concentrations of substrates **1b–e** [(2–8) × 10^{-2} M] and quaternary salts **2a,b** [(2–4) × 10^{-2} M]. Reactions rates were measured titrimetrically, following the disappearance of the nucleophile for **1e** and the appearance of halide ion for **1b–d**. Under these conditions, reaction 1 followed second-order kinetic equation 2 up to at least 3 half-lives.

$$\text{rate} = k[\text{substrate}][Q^+Y^-] \quad (2)$$

† Deceased on January 7, 1983.

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Table I. Second-Order Rate Constants for Nucleophilic Substitutions in *n*-Octyl Derivatives (n-$C_8H_{17}X$, X = Cl, Br, I, OTos, OMes) by $C_{16}H_{33}P^+Bu_3N_3^-$ in Various Solvents at 60 °C

solvent	10^2k,[a-c] M^{-1} s^{-1}				
	Cl	Br	I	OTos	OMes
MeOH	0.0013 (1)	0.053 (41)	0.14 (108)	0.22 (169)	0.060 (46)
Me_2SO	0.23[d] (1)	21.8 (95)	126 (548)	12.3 (54)	1.35[e] (5.9)
PhCl	0.064[f] (1)	9.32 (146)	46.2 (722)	9.4 (147)	7.04[g] (110)
cyclohexane	0.059 (1)	10.6 (180)	39.5 (670)	49.2 (834)	43.9 (744)

[a] [Substrate] = (2-8) × 10^{-2} M; [$C_{16}H_{33}P^+Bu_3N_3^-$] = (2-4) × 10^{-2} M. [b] The rate constants are computer generated by using a least-squares analysis and are the average of at least three runs. [c] Relative rates in parentheses. [d] The α-deuterium isotope effect $(k_{2H}/k_{2D})_\alpha$ is 0.991, evaluated from k_{2H} = 0.234 and k_{2D} = 0.236 × 10^{-2} M^{-1} s^{-1}. [e] $(k_{2H}/k_{2D})_\alpha$ = 1.013, from k_{2H} = 1.35 and k_{2D} = 1.33 × 10^{-2} M^{-1} s^{-1}. [f] $(k_{2H}/k_{2D})_\alpha$ = 1.034, from k_{2H} = 0.0642 and k_{2D} = 0.0621 × 10^{-2} M^{-1} s^{-1}. [g] $(k_{2H}/k_{2D})_\alpha$ = 1.006, from k_{2H} = 7.04 and k_{2D} = 7.00 × 10^{-2} M^{-1} s^{-1}.

Table II. Second-Order Rate Constants for Nucleophilic Substitutions in *n*-Octyl Derivatives (n-$C_8H_{17}X$, X = I, OTos, OMes) by $C_{16}H_{33}P^+Bu_3SCN^-$ in Various Solvents at 60 °C

solvent	10^2k,[a-c] M^{-1} s^{-1}		
	I	OTos	OMes
MeOH	0.054 (3.2)	0.012 (0.7)	0.017 (1)
Me_2SO	1.97 (73)	0.12 (4.4)	0.027 (1)
PhCl	1.26 (17)	0.11 (1.5)	0.075 (1)
cyclohexane	1.15 (3.0)	0.56 (1.5)	0.38 (1)

[a] [Substrate] = (2-8) × 10^{-2}M; [$C_{16}H_{33}P^+Bu_3SCN^-$] = (2-4) × 10^{-2}M. [b] The rate constants are computer generated by using the least-squares analysis and are the average of at least three runs. [c] Relative rates are in parentheses.

Table III. Activation Parameters[a] for Nucleophilic Substitutions in *n*-Octyl Derivatives ($C_8H_{17}X$, X = Br, OMes, OTos) by $C_{16}H_{33}P^+Bu_3N_3^-$ [b]

X	parameter	MeOH	Me_2SO	PhCl	cyclohexane
Br	E_a[c]	18.2	12.9	18.3	16.6
	ΔS^*_{60}[d]	−21.0	−24.9	−10.6	−15.2
OTos	E_a[c]	22.5	20.7	19.2	13.7
	ΔS^*_{60}[d]	−5.4	−2.6	−7.6	−21.3
OMes	E_a[c]	15.0	16.5	18.6	18.0
	ΔS^*_{60}[d]	−30.0	−19.7	−10.1	−8.4

[a] From measurements at 40, 50, and 60 °C. [b] For reaction conditions see footnote *a* of Table I. [c] All E_a are in units of kcal/mol. [d] All ΔS^* are in units of cal K^{-1} mol^{-1}.

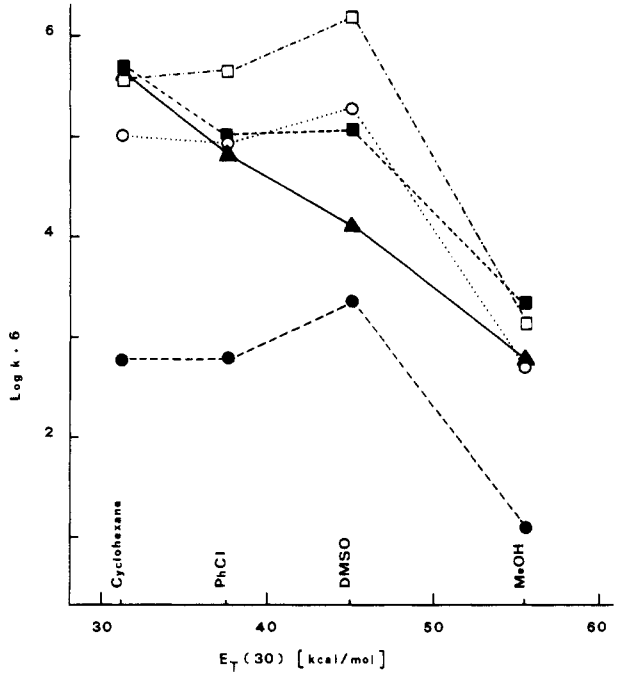

Figure 1. Effect of the solvent polarity, log k vs. $E_T(30)$, for nucleophilic substitutions in n-octyl derivatives, n-$C_8H_{17}X$ [X = Cl (●), Br (○), I (□), OTos (■), OMes (▲)] by $C_{16}H_{33}P^+Bu_3N_3^-$ at 60 °C. For reaction conditions see footnote a of Table I.

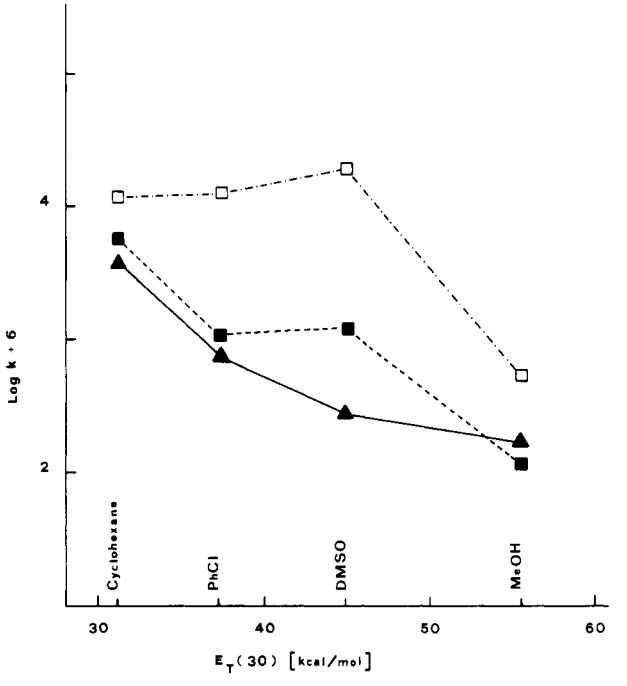

Figure 2. Effect of the solvent polarity, log k vs. $E_T(30)$, for nucleophilic substitutions in n-octyl derivatives n-$C_8H_{17}H_{17}X$ [X = I (□), OTos (■), OMes (▲)] by $C_{16}H_{33}P^+SCN^-$ at 60 °C. For reaction conditions see footnote a of Table II.

In the case of octyl methanesulfonate and octyl chloride, reaction rates were measured also on 1,1-d_2 derivatives **7a,b** which were obtained via $LiAlD_4$ reduction of the methyl octanoate (**5**) to give labeled octyl alcohol **6** and subsequent conversion of **6** into methanesulfonate **7a** and chloride **7b** (Scheme I).

Second-order rate constants are reported in Tables I and II; activation parameters for nucleophilic substitutions by N_3^- on **1a,c,e** measured at 40, 50, and 60 °C are reported in Table III. Effects of the solvent polarity[3] on the second-order rate constants (log k vs. E_T) are reported in Figures 1 and 2.

Discussion

The influence of the solvent on the reaction rates is strictly related to the nature of the leaving group (Tables I and II, Figures 1 and 2). As already shown,[4,5] in the case of the methanesulfonic group reaction rates progressively increase as the polarity and polarizability of the medium decrease; thus the highest rates are observed in cyclo-

hexane with 732- and 33-fold enhancements for MeOH and Me_2SO, respectively, with N_3^-, and 22- and 14-fold enhancements with SCN^- (Tables I and II, Figures 1 and 2). The situation is completely different in the case of halides **1b–d** for which the highest rates are observed in Me_2SO.

Tosylate **1e** represents a somewhat intermediate case, since after the strong rate increase on passing from methanol to Me_2SO, rate values remain roughly constant in chlorobenzene and increase another 5–6-fold in cyclohexane. As a consequence, the reactivity scales as a function of the leaving group in the examined solvents are as follows: OTos > I > OMes ≳ Br ≫ Cl in MeOH; I > Br > OTos > OMes > Cl in Me_2SO; I > OTos ≃ Br > OMes ≫ Cl in PhCl; OTos > OMes > I > Br ≫ Cl in cyclohexane.

In anion-promoted nucleophilic aliphatic substitutions the medium has only a small effect on the free energy of neutral substrates, whereas it is well-known[1-3] that it plays a substantial role both in anion and activated complex stabilization.

As already reported.[1,3] the anionic activated complexes, $[YRX^-]^‡$, should behave like large polarizable anions and, therefore, should be better solvated in polarizable solvents such as dipolar aprotic than in protic solvents. At the same time anions such as N_3^- are substantially destabilized on transfer from MeOH to Me_2SO. The rate ratios found in the two solvents, expressed as log k_{Me_2SO}/k_{MeOH}, are OMes (1.3), OTos (1.7), Cl (2.2), Br (2.4), and I (2.9). They show the anionic nature of the activated complexes and strictly reflect the values reported for similar reactions between N_3^- and CH_3X, measured in DMF and MeOH, in which log k_{DMF}/k_{MeOH} values are OTos (2.0), Cl (3.3), Br (3.9), and I (4.6).[1b,3]

The sequence (OMes < OTos < Cl < Br < I) is that expected for an increasing polarizability of the anionic activated complex $[N_3RX^-]^‡$; it reflects the increasing stabilization of the latter in the polarizable Me_2SO.[8] On transfer from Me_2SO to nonpolar, nonpolarizable cyclohexane it can be assumed that there is no appreciable solvation of the entering group or of the anionic activated complex. Therefore the observed rates should reflect, better than in any other solvent, not only the intrinsic nucleophilicity of the entering group but also the intrinsic nucleofugacity of the leaving group. The latter, in the case of N_3^- as the entering group, is therefore OTos > OMes > I > Br ≫ Cl (Table I, Figure 1).

The relative influence of the anion and activated complex solvation is made evident by comparing the variation of reactivity of mesilate **1a** with that of the other substrates, in particular the halides **1b–d**. In the case of scarcely polarizable mesilate **1a**, solvation of the activated complex is small in Me_2SO (the lowest value of log k_{Me_2SO}/k_{MeOH}; see above); it should be progressively less important on passing to chlorobenzene and then to cyclohexane; therefore, rate constants observed with this leaving group should best reflect the extent of solvation of the entering nucleophile. This also means that in Me_2SO N_3^-, although largely destabilized with respect to MeOH, is still appreciably solvated (33 times less reactive than in cyclohexane; see above). In the halides **1b–d** this solvation of the nucleophile is accompanied by a substantial solvation of the activated complex (the highest values of log k_{Me_2SO}/k_{MeOH}). The relative stabilization of the transition state is progressively lost on trasfer to chlorobenzene and then to cyclohexane. Therefore, unlike mesylate, the observed rates diminish on passing from Me_2SO to the two less polar solvents (Table I, Figure 1).[10]

The higher reactivity of tosyl derivative **1e** compared to mesyl derivative **1a**, observed in all solvents, likely derives from the delocalization of the incipient negative charge of the transition state by the aromatic ring.

Also, the reactivity sequence of the three halides is the same for all the solvents, as expected on the basis of their bond energies.

The activation parameters (Table II) for reaction with N_3^- in the examined solvents cannot be correctly interpreted for **1a,c,e**, due to the lack of knowledge about the contribution of solvation free energies of the nucleophiles, substrates, and transition state. However, the case of mesyl derivative **1a** is interesting, in which a steady increase of reaction rates on transfer from MeOH to Me_2SO, PhCl, and cyclohexane corresponds to an analogous increase of activation energy and to a similar notable decrease of negative activation entropy.

When the entering nucleophile is SCN^-, the observed behavior as a function of the leaving group is similar to that observed for N_3^-, although the range of reactivity variations is narrower (Table II, Figure 2). Lower sensitivity of the more polarizable SCN^- to the solvents is consistent with a number of well-known examples in the literature.[1b,11-13]

The data as a whole indicate that in aliphatic nucleophilic substitutions carried on in aprotic nonpolar solvents the nucleofugacity scales are largely modified with respect to those observed in protic and in dipolar aprotic solvents. In every case the reactivities in non polar solvents are comparable or even higher than those found in dipolar aprotic solvents.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian EM-390 90-MHz spectrometer with tetramethylsilane as an internal standard. Potentiometric titrations were performed with a Metrohm Titroprocessor E636 by using silver and calomel electrodes, the latter isolated with a potassium sulfate bridge. GC data were obtained on a Varian 3700 gas chromatograph equipped with a 3% Carbowax 20M on Chromosorb W column and were evaluated with a Varian data system, Model 401, by the internal standard method.

Materials and Solvents. *n*-Octyl chloride, bromide, and iodide (**1b–d**) were AnalaR grade commercial products and were purified by vacuum distillation before use. *n*-Octyl *p*-tosylate [**1e**: bp 164–166 °C (0.01 mm); n^{21}_D 1.4957] was prepared according to the literature[14] (lit.[15] n^{20}_D 1.4933). *n*-Octyl methanesulfonate (**1a**: bp 112–114 °C (2 mm); n^{20}_D 1.4398] was obtained by following a reported procedure [lit.[16] bp 110–114 °C (2 mm); n^{20}_D 1.4392].

(8) It may be observed that the lower reactivity increases found for tosylate **1e** and mesylate **1a** should correspond to a larger localization of negative charge with respect to halides **1b–d** due to the more advanced C–X bond-breaking in the transition state. Indeed, it has been observed that those reactions possesing the tightest activated complex, in which therefore bonds with entering and leaving groups have the highest covalent character, are also those in which the greatest rate increases on transfer from protic to dipolar aprotic solvents are observed.[1b,3] The comparison between the reaction rates of 1,1-d_2 substrates **7a** and **7b** and of the corresponding nondeuterated analogues **1a** and **1b** in Me_2SO and PhCl show in every case a very small secondary isotope effect ($k_H/k_D \approx 1$). This agrees with an S_N2 mechanism without substantial C–X bond breaking in the transition state.[9]

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(10) It is likely that this approach is a simplification of the problem. Indeed, if the factors involved are only those discussed above, a different behavior for the three halides should be expected, and the curves for I, Br, and Cl should not be parallel as they are (Figure 1). We thank a referee for this observation.

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1,1-Dideuterio-*n*-octyl Alcohol (6). To a stirred suspension of 4.2 g (0.1 mol) of lithium aluminum deuteride in dry THF (150 mL) under nitrogen was added a solution of 15.8 g (0.1 mol) of commercial methyl octanoate (**5**) in dry THF (30 mL) during 30 min. After an additional 4 h of reflux, the mixture was cooled with ice bath and treated cautiously with THF/water (1:1 v/v mixture, 50 mL) and then with water (50 mL). It was poured into chilled water (100 mL), and 10% sulfuric acid (300 mL) was added. The mixture was extracted with ether (2 × 150 mL). The combined ether layers were washed with water and evaporated after being dried (Na_2SO_4) to afford 13 g (98.5%) of 1,1-dideuterio-*n*-octyl alcohol (**6**) (deuterium content >95%, by NMR analysis). The latter when assayed by GC showed >98% purity and was used without further purification for subsequent reactions: NMR ($CDCl_3$) δ 0.9 (3 H, t), 1.1–2.0 (12 H, m), 1.7 (1H, s).

1,1-Dideuterio-*n*-octyl methanesulfonate [**7a**: bp 95–96 °C (0.05 mm); n^{20}_D 1.4403] was obtained from **6** with the previously described procedure[16] for unlabeled derivative **1a**: NMR ($CDCl_3$) δ 0.9 (3 H, t), 1.1–1.9 (12 H, m), 3.0 (3 H, s). 1,1-Dideuterio-*n*-octyl chloride [**7b**: bp 179–181 °C (760 mm); n^{20}_D 1.4298] was prepared from **6** by following a reported procedure[17] for unlabeled derivative **1b** [lit.[17] bp 181.5 °C (765 mm); n^{20}_D 1.4306]. Quaternary phosphonium salts **2a,b** were obtained from the corresponding hexadecyltributylphosphonium methanesulfonate (**2c**) by exchange with the appropriate anion.[4,5]

Commercial methanol, Me_2SO, chlorobenzene, and cyclohexane were carefully purified and dried by standard methods[4] and stored under nitrogen over molecular sieves. In all cases Karl Fishcher analyses showed a water content of ≤50 ppm.

Kinetic Measurements. At zero time a standardized solution (20 mL) of substrate [(10–40) × 10^{-2} M] was added to a standardized solution (80 mL) of quaternary salt [(2.5–5) × 10^{-2} M] in a 100-mL flask thermostated at 60 ± 0.1 °C. Samples (2–5 mL), withdrawn periodically, were quenched in ice-cold MeOH (50 mL) and analyzed by potentiometric titration with 0.01 N silver nitrate. The unreacted nucleophile was determined in the case of methanesulfonate **1a** or tosylate **1e**. When the leaving group was the halogen, the halide ion formed during the reaction was evaluated in the presence of 3 mL of 6 M HNO_3. The second-order rate constants were evaluated by using a least-squares analysis computer program, as previously described.[4]

Registry No. **1a**, 16156-52-8; **1b**, 111-85-3; **1c**, 111-83-1; **1d**, 629-27-6; **1e**, 3386-35-4; **2a**, 66997-37-3; **2b**, 67047-78-3; **2c**, 86471-19-4; **5**, 111-11-5; **6**, 78510-02-8; **7a**, 86471-18-3; **7b**, 86471-20-7; D_2, 7782-39-0.

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Reaction of (Acyloxy)alkyl α-Halides with Phenols: Effect of Nucleofugicity and Nucleophilicity on Product Distribution

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The product distribution obtained from the reaction of (acyloxy)alkyl α-halides (**1** or **5**) with phenols was found to depend on the nucleophilicity of the phenol, the nucleofugicity of the leaving group, and the ability of the electrophile to stabilize a carbenium ion. More nucleophilic phenols tended to give more acylation while better leaving groups and more stable incipient carbenium ions in the electrophile tended to favor the formation of alkylated products. In addition, the reaction of methanol with **1a** was found to give a mixture of acylated and alkylated products (40:60). Thus, a general trend for all the nucleophiles for which information is available suggests that better nucleophiles undergo relatively more acylation and that poorer nucleophiles undergo more alkylation. These results are suggested to be consistent with the observations of Westaway on the effect of leaving group nucleofugicity and nucleophilicity of the nucleophile on bond lengths in the S_N2 transition state. Facile rearrangements of acylated to alkylated products and of one alkylated product to another caused by the phenolate anion were also observed in the 3-phenoxy-1(3*H*)-iosbenzofuranone–phenyl 2-formylbenzoate series.

A recent study of the effect of the nucleophilicity of the amine and the nucleofugicity of the leaving group on the product distribution obtained from the alkylation reaction of amines with (acyloxy)alkyl α-halides (**1** or **5**)[1] revealed two interesting trends. First, better nucleophiles tended to undergo acylation (reaction at the acyl carbon atom) upon reaction with the α-chlorides while poorer nucleophiles tended to undergo alkylation (reaction at the alkyl α-halide carbon atom). Second, the extent of alkylation of the more nucleophilic amines was increased by using a better leaving group in the electrophile, i.e., an α-iodide. These trends were rationalized in terms of looser (good nucleophile–poor leaving group) and tighter (poorer nucleophile–better leaving group) transition states.[2] However, the fact that it was necessary to use amines with significant structural differences in order to obtain the desired range of nucleophilicites made it desirable to obtain collaborative evidence from another series of nucleophiles. Phenol nucleophiles represent an attractive series in that regard. Nucleophilicities can be varied over several orders of magnitude by changing the 4-substituent from nitro to methoxy[3] without affecting the steric requirements of the nucleophile.

In addition, the products of the alkylation reaction of phenols with (acyloxy)alkyl α-halides [(acyloxy)alkyl α-ethers (**4** and **7**)] represent an important class of derivatives of phenols because they have the potential to serve as protecting groups in synthetic reactions or as prodrug

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