5c was obtained. In this case however a pH of 6 rather than 8 was maintained since a trial run at the higher pH showed that much **3** as well as **7** was obtained under the latter condition. Imidazole (2.0 g, 0.0294 mol) was dissolved in 60 mL of water in a 500-mL Erlenmeyer flask equipped with a mechanical stirrer and the pH adjusted to 6 with 1 M hydrochloric acid. After the solution was cooled to 0 °C, 10.6 g (0.0655 mol) of DEP in 60 mL of benzene was added in a slow stream with stirring. The reaction mixture was then maintained at pH 6 by addition of 1 M sodium hydroxide and at 0 °C while being stirred over 1 h. The benzene layer was then separated from the aqueous which was extracted further with two 20-mL portions of benzene. The combined benzene solutions were dried over sodium sulfate, filtered, and evaporated to dryness. The oily residue was distilled under vacuum in a short-path apparatus, yielding **7** (45%): bp 107 °C (0.1 torr); IR (neat) 3075, 2900, 2875, 1705, 1605 cm^{-1}; UV (MeCN) λ_{max} 240 nm (ϵ 6600); NMR (C^2HCl_3) δ 6.60 (s, 1, HCO), 6.20 (s, 2, CH=), 4.20 (q, $J = 7.0$ Hz, 4, $-CO_2CH_2-$), 3.73 (q, $J = 6.5$ Hz, 2, $-O-CH_2-$), 1.29 (t, $J = 7.0$ Hz, 6, $-CO_2CH_2CH_3$), 1.18 (t, $J = 6.5$ Hz, 3, $-OCH_2CH_3$); mass spectrum, *m/e* (relative intensity, %) 258 (4, M^+), 213 (23), 140 (38), 97 (16), 95 (17), 69 (35), 68 (100). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.14; H, 7.04; N, 10.85. Found: C, 51.46; H, 6.94; N, 11.00.

Methyl 2,4-Bis(carbethoxyamino)-5-(*N*-formylcarbethoxyamino)pent-4-enoate (13) and Methyl 2,5-Bis(carbethoxyamino)-4-(*N*-formylcarbethoxyamino)pent-4-enoate (14). These compounds were prepared from histidine methyl ester and DEP in the same way as the imidazole analogue **3** (method i). The reaction was followed spectrophotometrically by taking aliquots for absorbance measurement (after dilution) at 222 nm. When maximal absorbance was achieved, the reaction mixture was extracted with chloroform. Evaporation of the dried chloroform extracts yielded an oil whose NMR spectrum indicated the presence of a histidine derivative and of two formyl compounds. Chromatography on silica gel in 9/1 methylene chloride/ethyl acetate yielded 34% of a 40/60 mixture of **13** and **14** as a viscous oil. The properties of this mixture were as follows: IR (neat) 3270, 2940, 1685 (br), 772 cm^{-1}; NMR δ 9.17, 9.11 (s, 1, CHO, **13**, **14**), 6.75 (d, $J \simeq 9$ Hz, NH—*CH*=, **14**), 6.2 (br s, 1, NH, **13**, **14**), 5.53 (s, 1, >N—CH=, **13**), 4.37 (q, 2, $N(CHO)CO_2CH_2CH_3$, **13**, **14**), 4.13 (q, 4, $NHCO_2CH_2CH_3$, **13**, **14**), 3.76, 3.68 (s, 3, CO_2CH_3, **13**, **14**), 3.2–2.5 (m, 2, CH_2—CH, **13**, **14**), 1.37 (t, 3, $N(CHO)CO_2CH_2CH_3$, **13**, **14**), 1.25 (t, 6, $NHCO_2CH_2CH_3$, **13**, **14**); mass spectrum, *m/e* (relative intensity, %) 403 (4, M^+), 375 (5), 314 (4), 286 (50), 243 (100), 215 (78), 169 (42). Anal. Calcd for $C_{16}H_{25}N_3O_9$: C, 47.64, H, 6.25; N, 10.42. Found: C, 47.78; H, 6.40; N, 10.24.

Reactions of DEP with Imidazole and Histidine Derivatives in Dilute Aqueous Solution. Typically these were studied spectrophotometrically in reaction mixtures containing the imidazole derivative (0.01–0.1 mM) in an appropriate buffer solution. Reactions were initiated by addition of a small aliquot of DEP in acetonitrile solution to the aqueous solution in a thermostated cuvette. The change in spectrum with time was then monitored. Yields of imidazole cleavage products obtained from reactions studied as above were determined by the amount of **4** produced, as follows. After the DEP reaction was judged complete by the absence of further spectral change, an aliquot of 3.24 M Tris solution was added to the reaction mixture, giving a final solution containing 0.2 M Tris at a pH between 8 and 10. Under these conditions all **3** is converted into **4** and all *N*-carbethoxyimidazole back to imidazole. The total extent of imidazole cleavage that had occurred could then be determined by the remaining absorbance at 234 nm, a measure of **4** concentration.

Acknowledgment is made to Wesleyan University and to the National Institutes of Health for support of this research.

Mechanism of Reactions of *N*-(Methoxymethyl)-*N*,*N*-dimethylanilinium Ions with Nucleophilic Reagents[1]

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Abstract: The prediction that the oxocarbonium ion derived from formaldehyde should have a "lifetime" of $\sim 10^{-15}$ s that gives rise to an enforced preassociation or concerted reaction mechanism has been tested by examining the reactions of *N*-(methoxymethyl)-*N*,*N*-dimethylanilinium ions in water in the presence of added nucleophilic reagents. These compounds undergo well-behaved second-order reactions with nucleophiles and give the amount of substitution product that is expected from the rate increase in the presence of nucleophile. Structure–reactivity correlations exhibit behavior intermediate between that expected for S_N2 (Swain–Scott) and carbonium ion (N^+) reactions. The small values of $s = 0.3$ and $\beta_{nuc} = 0.14$ and large values of $\beta_{lg} = -0.7$ to -0.9 indicate a transition state that can be described either as an open transition state for S_N2 displacement or as an oxocarbonium ion that is stabilized by weak interactions with the entering and leaving groups. Secondary α-deuterium isotope effects for the second-order reactions range from $(k_H/k_D)/D = 0.99$ for fluoride ion to 1.18 for iodide ion. Solvolysis and the second-order reaction with *n*-propylamine exhibit values of $\Delta S^{\ddagger} = -1.2$ and -2.1 cal K^{-1} mol^{-1}, respectively, and display similar changes in rate in mixed water–alcohol solvents. It is suggested that the lifetime of the carbonium ion species in the presence of nucleophiles is so short that the reaction mechanism must be concerted.

We have been interested in the extent to which reaction mechanisms, and transitions between reaction mechanisms, are determined by the lifetimes of species that might exist as intermediates in the reaction. A knowledge of these lifetimes provides a relatively simple approach to the vexing problem of the nature and meaning of "borderline", "intermediate", "merging", and "solvent-assisted" mechanisms.[2-7]

The cleavage of a series of substituted acetophenone ketals has been shown to proceed through oxocarbonium ion intermediates with significant lifetimes by trapping these intermediates with sulfite dianion; the rate of ketal cleavage is independent of sulfite concentration.[8] Such a stepwise mechanism and the absence of a second-order reaction with nucleophilic reagents are charac-

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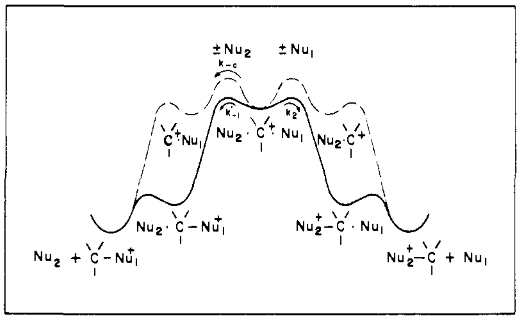
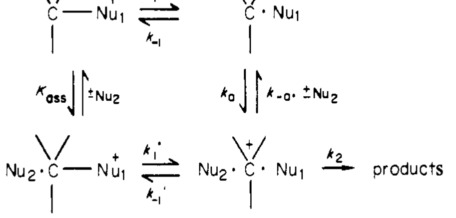


Figure 1. Reaction coordinate diagram to show why the preassociation mechanism (solid line) is preferred to the fully stepwise mechanism of eq 1 (dashed line) when the carbonium ion collapses to reactants (k_{-1}') faster than a nucleophile, Nu_2, diffuses away from it (k_{-a}).

teristic of ketals and acetals.[9] The lifetimes of the carbonium ion intermediates were found to be in the range 10^{-7}–10^{-9} s from the ratio of the rate constants for their reactions with sulfite and water and an estimated rate constant of 5×10^9 M^{-1} s^{-1} for the reaction with sulfite, which was shown to be diffusion controlled.[8] These lifetimes are in agreement with direct measurements of the rate constants for hydration of the oxocarbonium ions in strong acid solutions.[10] By extrapolating a correlation of the rate constants for the addition of water with those for addition of sulfite to the corresponding carbonyl compounds, we estimated the lifetimes in water of the oxocarbonium ion formed from formaldehyde derivatives to be on the order of 10^{-15} s. Such a "lifetime" is shorter than a vibration frequency and does not correspond to a species that has a meaningful existence. It was predicted, therefore, that reactions that would be expected to generate the formaldehyde oxocarbonium ion in water would certainly not proceed through a free, solvent-equilibrated intermediate and might well proceed through a concerted reaction mechanism with no intermediate at all.[8]

Two paths for the formation of a carbonium ion that will react with solvent or an added nucleophilic reagent, Nu_2, are shown in eq 1. The upper path involves bond cleavage (k_1) followed by encounter with Nu_2 (k_a), and the lower path involves a preassociation mechanism in which an encounter complex with Nu_2 is formed before the bond cleavage step (k_1'). The favored path in this scheme is determined by the lifetime of the carbonium ion intermediate.[8,11] When the carbonium ion and the leaving group Nu_1 collapse back to reactants (k_{-1}', eq 1) faster than the carbonium ion and the acceptor (Nu_2) diffuse apart from each other (k_{-a}), the lowest energy pathway for cleavage of the C–Nu_1 bond in this scheme is through an enforced preassociation mechanism (K_{ass} and k_1').



(1)

The reason for this is illustrated in Figure 1. When the barrier for collapse of the intermediate $Nu_2 \cdot R^+ \cdot Nu_1$ to reactants ($k_{-1}' \simeq k_{-1}$) is smaller than that for diffusion away of Nu_2 (k_{-a}), the lowest energy pathway for both the breakdown and the formation of this intermediate species will be through the preassociation pathway with the initial formation of the encounter complex $Nu_2 \cdot R{-}Nu_1^+$. If there is sufficient development of positive charge in the transition state and steric factors are not too unfavorable, the electron pair of Nu_2 is likely to interact weakly with this developing charge to stabilize the transition state. If Nu_2 is solvent, this represents "solvent assistance"; if it is some other nucleophilic reagent, it represents a second-order nucleophilic reaction. If the intermediate is still less stable, so that there is no barrier for its breakdown to reactants or for its reaction with Nu_2, the intermediate does not exist; we will define this as a concerted reaction mechanism because the reaction cannot proceed through a stepwise mechanism.[2] Part or all of this sequence of mechanisms is followed for general acid–base catalyzed, carbanion, ligand-exchange, and other carbonium ion reactions.[8,11,12]

When the reaction with the acceptor, k_2, is faster than the collapse to reactants, k_{-1}', the bond cleavage step, k_1', is rate limiting for the preassociation mechanism; when reaction with Nu_2 is slower than with Nu_1, k_2 becomes rate limiting. When k_2 becomes still slower, as in an unreactive or weakly nucleophilic solvent, a point can be reached at which all other steps become relatively fast and the reaction can occur through other pathways. A fully stepwise mechanism through a free, diffusionally equilibrated carbonium ion will be favored for a stable carbonium ion because diffusion away of Nu_1 and Nu_2 will become faster than bond-forming steps. In an unreactive solvent the reaction through a free carbonium ion must always be the lowest energy pathway at sufficiently low concentration of the reactants because the Gibbs free energy will always become lower for the free ion (because of the unfavorable entropy for complex formation with Nu_1 and Nu_2).

The roles of possible intermediates and of solvent assistance in displacement and solvolysis reactions have been the subject of extensive examination and discussion.[2-7] Bordwell and Schleyer and their colleagues, for example, have recently discussed the "S_N2 (intermediate)" mechanism for reactions which proceed through a "nucleophilically solvated intimate ion pair" or "ion sandwich" and have summarized evidence for a progressive increase in nucleophilic assistance with decreasing carbocation stability in solvolysis reactions.[5,7] The S_N2 (intermediate) mechanism corresponds to a preassociation mechanism in which the intermediate has a lifetime longer than a vibration frequency and is formed through a transition state that is stabilized by Nu_2; however, reactions that have no such stabilization and concerted reactions, in which the intermediate does not have a significant lifetime, can also occur through preassociation mechanisms. The point that we wish to emphasize here is the role of the lifetime of possible intermediate species and, in particular, the relationship of this lifetime to the time required for diffusion away of Nu_2, in determining the mechanism that will be followed in a particular solvent or with different Nu_1 and Nu_2.

The fact that the hydrolysis of glycosides is even slower than that of formaldehyde acetals suggests that the oxocarbonium "intermediate" in glycoside hydrolysis is even less stable than that derived from formaldehyde, so that glycoside solvolysis should proceed through a preassociation or concerted mechanism. Evidence supporting this conclusion for the solvolysis of a series of glucose derivatives in trifluoroethanol–ethanol mixtures has been reported recently.[12]

It has been generally believed that the solvolysis of formaldehyde derivatives proceeds through an oxocarbonium ion intermediate or at least a transition state that closely resembles an oxocarbonium ion.[13-16] The solvolysis of methoxymethyl chloride (chloromethyl

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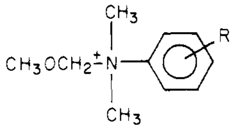
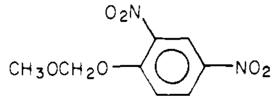
methyl ether) in a series of mixed solvents follows a Grunwald–Winstein parameter of m = 1.0–1.1, the same as for *tert*-butyl chloride, and exhibits a secondary α-deuterium isotope effect of k_H/k_D = 1.24 (per deuterium atom).[15] The importance of electron donation from the oxygen atom is shown by the rapid rate of the solvolysis reaction, which has been estimated to be some 10^{13} faster than that of 1-propyl chloride and is even 5×10^6 faster than that of *tert*-butyl chloride,[14] by the ρ value of −3.0 for the acid-catalyzed hydrolysis of $ArOCH_2OAc$[16] and by ρ^* values of −3 and −3.4 for the acid-catalyzed hydrolysis of $ROCH_2OAr$ and $ROCH_2OAc$, respectively.[17] The acidity dependence of the rate of hydrolysis of formaldehyde acetals has been interpreted as evidence for an A1 mechanism with a weakly solvated transition state.[18] A decrease in the hydrolysis rate of ethylal in the presence of increasing concentrations of ethanol has been interpreted in terms of partitioning of an oxocarbonium ion intermediate between reaction with water and ethanol,[18b] but a similar or identical result would be expected for a bimolecular reaction with the protonated acetal from the decrease in water concentration. On the other hand, the rate of ethanolysis of methoxymethyl chloride is increased in the presence of ethoxide ion, and it has been suggested that the reaction is bimolecular, with a second-order rate constant that is 10^5 larger than that for the reaction of ethoxide ion with methyl chloride and a transition state that closely resembles an oxocarbonium ion.[14]

In order to test the prediction that formaldehyde derivatives would react through a preassociation or concerted mechanism that is enforced by the lifetime of $\leq 10^{-15}$ s for an oxocarbonium ion "intermediate", rather than through a free, diffusionally equilibrated oxocarbonium ion, and to determine whether the transition state for cleavage of methoxymethyl derivatives is sufficiently electrophilic to be stabilized by added nucleophilic reagents, we have examined the reactions of a series of compounds, **1**, with substituted dimethylanilines as the leaving groups in aqueous solution in the presence and absence of added nucleophiles. This series of compounds and an aqueous solvent were chosen in order to avoid possible difficulties in interpretation from the formation of ion pairs.



1a, R = H
b, R = *p*-Br
c, R = *m*-NO$_2$
d, R = *p*-CN



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While this work was in progress, Craze, Kirby, and Osborne reported similar experiments on the closely related compound (methoxymethoxy)-2,4-dinitrobenzene (**2**).[19] This compound undergoes second-order reactions with a number of added nucleophilic reagents that exhibit secondary α-deuterium isotope effects in the range k_H/k_D = 1.05–1.16. Although the possibility of reaction with a reversibly formed ion pair was not excluded, the authors favored an interpretation in terms of an S_N2 reaction with weak bonding to the nucleophile and leaving group in the transition state because the reaction does not follow the N^+ scale for reactions of carbonium ions,[20] the same conclusion has been reached from the work reported here. It has been believed that second-order S_N2 reactions exhibit α-secondary deuterium isotope effects of ≤1.06 and that this isotope effect could be used to distinguish S_N2 and S_N1 reaction mechanisms, but there are several other reactions, including solvent-assisted solvolyses and second-order reactions, that exhibit secondary isotope effects larger than 1.06.[7,21,22]

Experimental Section

Materials. Organic reagents were obtained commercially and were purified by recrystallization, distillation or sublimation. Sodium tetrafluoroborate was recrystallized from methanol and other inorganic reagents were used as received. Solutions of sodium perchlorate were prepared by neutralizing solutions of perchloric acid of known concentration.

N-(Methoxymethyl)-*N*,*N*-dimethylanilinium salts were prepared from the reaction of chloromethyl methyl ether and ring-substituted *N*,*N*-dimethylanilines under anhydrous conditions. The reactions were ordinarily carried out in dry acetonitrile saturated with sodium tetrafluoroborate, which brought about precipitation of the liberated chloride ion as sodium chloride and prevented reversal of the reaction.

The synthesis of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*p*-bromoanilinium perchlorate is described to illustrate the procedure. Chloromethyl methyl ether (1.0 mL) (caution, carcinogen) was added to *p*-bromo-*N*,*N*-dimethylaniline (2.4 g) in 5 mL of dry acetonitrile that had been saturated with sodium tetrafluoroborate and flushed with nitrogen in a 15-mL conical centrifuge tube fitted with a rubber serum cap. After 30 min on a vortex mixer in the presence of excess solid sodium tetrafluoroborate, the tube was centrifuged briefly and the supernatant fluid was transferred to another tube. A crystalline product was obtained upon evaporating the acetonitrile under a stream of dry nitrogen; it was washed with dry ether and dried under a stream of nitrogen. Proton NMR of this material in CD_3CN gave δ 7.8 (4 H, m), 5.00 (2 H, s), 3.54 (6 H, s), and 3.50 (3 H, s) (δ is downfield from tetramethylsilane), and a small peak at δ 3.3 (s), suggesting ~5% contamination with *p*-bromo-*N*,*N*-dimethylaniline. A small amount of solid was dissolved in the minimum amount of 70% perchloric acid (caution), and water was added slowly to precipitate the perchlorate salt. Two recrystallizations by this procedure gave white flakes, mp 85–85.5 °C. Anal. Calcd for $C_{10}H_{15}NO_5BrCl$: C, 34.82; H, 4.35; N, 4.07. Found: C, 34.87; H, 4.32; N, 4.06 (Galbraith Laboratories, Inc.). The corresponding dideuterio compound was synthesized by the same procedure from $ClCD_2OCH_3$[15] for the determination of secondary α-deuterium isotope effects.

_N_-(Methoxymethyl)-_N_,_N_-dimethyl-_m_-nitroanilinium perchlorate was prepared by the same procedure; mp 99–100 °C. Anal. Calcd for $C_{10}H_{15}N_2O_7Cl$: C, 38.63; H, 4.83; N, 8.98. Found: C, 38.69, H, 4.82; N, 8.93.

_N_-(Methoxymethyl)-_N_,_N_-dimethyl-_p_-cyanoanilinium tetrafluoroborate was prepared as described above and was used without further purification. *N*-(Methoxymethyl)-*N*,*N*-dimethylanilinium tetrafluoroborate gave an oil by this procedure and was prepared immediately before use by mixing equimolar amounts of dry *N*,*N*-dimethylaniline and chloromethyl methyl ether at room temperature, from which the solid product precipitated after 5–10 min. The product was washed with ether, dissolved in water, brought to pH 7, and extracted with ether to remove any remaining *N*,*N*-dimethylaniline. Aliquots of this solution were used directly to initiate kinetic experiments.

Kinetics. Rate constants were determined spectrophotometrically by following the appearance of the *N*,*N*-dimethylaniline product at 252 nm (unsubstituted), 254 nm (*p*-bromoaniline), 248 or 400 nm (*m*-nitroaniline), and 297 nm (p-cyanoaniline), using 1-cm quartz cuvettes and a thermostated cell compartment. Reactions were initiated by adding aliquots of freshly prepared aqueous stock solutions of the anilinium salt to a cuvette containing a temperature-equilibrated solution of the other reactants. Aqueous reaction mixtures also contained 0.002 M ethylenediaminetetraacetate. Nucleophilic reagents were present in large excess and pseudo-first-order rate constants were calculated from the slopes of semilogarithmic plots of $(A_\infty - A)$ against time by using a final absorbance, A_∞, measured after 10 half-times. In almost every case the reactions followed first-order kinetics for >5 half-times. Some reactions of the unsubstituted compound **1a** were followed by measurements of initial rates, by using an end point that was determined from a parallel run with *n*-propylamine. Rate constants determined by this method were found to agree with those obtained from measurements of the entire reaction in several instances. Secondary α-deuterium isotope effects were determined from at least six pairs of rate measurements in which the protium and deuterium compounds reacted with identical solutions of nucleophilic reagents in the same spectrophotometer at the same time.

Product Analysis. Formaldehyde formation was determined by the method of Georgia and Morales.[23] *N*-(Methoxymethyl)trimethyl-

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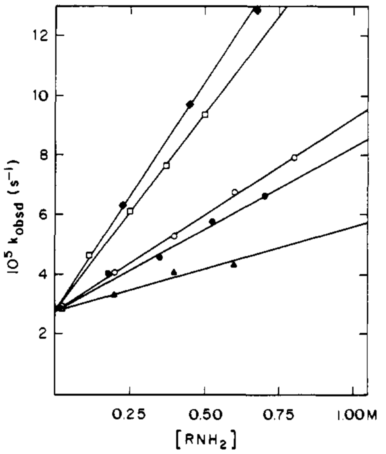
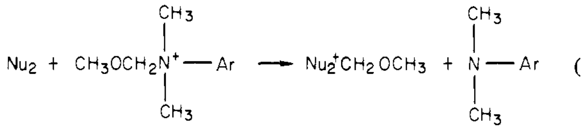


Figure 2. Pseudo-first-order rate constants for the reactions of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*p*-bromanilinium ion (**1b**) with primary amines at 25 °C, ionic strength 1.0 M (KCl): *n*-propylamine, ■; methoxyethylamine, □; hydroxylamine, ○; 1,1-dimethylethylenediamine, ●; methoxyamine, ▲.

ammonium ion was identified as a product of the reaction of 1.6 M trimethylamine in 3 mL of deuterium oxide with 400 mg of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium perchlorate after the mixture was shaken for 90 min. After extraction of *N*,*N*-dimethyl-*m*-nitroaniline with cyclohexane the remaining solution was concentrated by evaporation and taken up in CD_3CN. The NMR spectrum gave bands identical with those of *N*-(methoxymethyl)trimethylammonium chloride (prepared from trimethylamine and chloromethyl methyl ether in CD_3CN) and trimethylamine; no bands indicating the formation of other products were observed. The ultraviolet spectra of the reaction products were shown to be identical with those of the expected *N*,*N*,-dimethylanilines; the yield of the dimethylaniline product was shown to be quantitative for reactions of **1b** and **1c**.

Results

N-(Methoxymethyl)-*N*,*N*-dimethylanilinium ions (**1**) were found to react with added amines and other nucleophilic reagents, Nu_2, in aqueous solution according to eq 2. The pseudo-first-order



$$Nu_2 + CH_3OCH_2\overset{CH_3}{\underset{CH_3}{N^+}}\text{—Ar} \longrightarrow Nu_2^+CH_2OCH_3 + \overset{CH_3}{\underset{CH_3}{N}}\text{—Ar} \quad (2)$$

rate constants for reactions in the presence of a large excess of the nucleophilic reagent were determined spectrophotometrically by measuring the appearance of the aniline product. These rate constants, k_{obsd}, increase with increasing concentration and basicity of added amines, as illustrated for reactions of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion in Figure 2. Second-order rate constants for the reactions of **1** with a series of primary, secondary, and tertiary amines and other nucleophiles, including several substituted dimethylanilines as leaving groups, were obtained from the slopes of similar plots and are summarized in Table I. In addition, the rate constants for reactions of the para cyano compound (**1d**) with propylamine and with water were found to be 575 × 10^{-5} M^{-1} s^{-1} and 0.0039/55.5 = 7.0 × 10^{-5} M^{-1} s^{-1}, respectively. Rate constants for reactions of dimethylanilines could not be measured in water because of their low solubility; measurements for the reaction with the para nitro compound (**1c**) in methanol gave values of 10^5k_N = 210, 590, and 2190 M^{-1} s^{-1} for *p*-bromo-*N*,*N*-dimethylaniline, *N*,*N*-dimethylaniline, and *n*-propylamine, respectively (25 °C, no added salt). The solvent deuterium isotope effect for the hydrolysis of **1c** was found to be k_{HOH}/k_{DOD} = 1.07 (ionic strength 1.0 M ($NaClO_4$), 25 °C). The same isotope effect was found in the presence of four concentrations of sodium acetate up to 1.6 M (1.0–1.2 M $NaClO_4$, 25 °C) and the hydrolysis and reaction with n-propylamine of **1b** gave values of k_{HOH}/k_{DOD} = 1.07 and 0.94, respectively (ionic strength 1.0 M (KCl), 25 °C).

Table I. Second-Order Rate Constants for the Reactions of $XPhN^+(CH_3)_2CH_2OCH_3$ with Nucleophilic Reagents[a]

nucleophile	pK_a	10^5k_N,[b] M^{-1} s^{-1}, for H = H	*p*-Br	*m*-NO_2
methoxyamine	4.60[c]	...	2.67[d]	21.0[e]
N,*O*-dimethylhydroxylamine	4.75[f]	...	...	59.8[d]
hydroxylamine	6.17[g]	1.17[h]	6.45[d]	49.2[e]
1,1-dimethylethylenediamine	6.93[i]	...	5.53[j]	...
N,*N*-dimethylethylenediamine	6.90[i]	1.62[j]	...	74.0[j]
2-cyanoethylamine	8.20[i]	1.95[h]	6.43[d]	76.4[d]
morpholine	8.82[k]			196[d]
diallylamine	9.29[l]	...	...	191[m]
2-methoxyethylamine	9.72[g]	3.74[h]	12.9[e]	177[e]
n-propylamine	10.89[g]	3.53[h]	14.4[e]	184[h]
dimethylamine	10.64[l]	...	...	493[e]
triethylenediamine	9.22[n]			875[d,o]
quinuclidine	11.55[i]	...	...	841[m]
nicotinamide	3.40[l]			146[d,p]
pyridine	5.17[l]			207[d,p]
4-dimethylaminopyridine	9.8[q]			311[d,p]
aniline	4.60[l]			320[d,p]
acetate ion	4.76[l]		1.1[h]	
acetohydroxamate ion	9.40[l]		48[r]	
hydroxide ion	15.7		11.4	
water[s]	−1.7	0.0088	0.051	1.32
p*K* $ArNMe_2H^+$ [t]		5.07	4.23	2.63

[a] In water at 25 °C, ionic strength maintained at 1.0 M with potassium chloride. [b] Second-order rate constants were determined from plots of four values of k_{obsd} (s^{-1}) against the concentration of free amine. [c] do Amaral, L.; Koehler, K.; Bartenback, D.; Pletcher, T.; Cordes, E. H. *J. Am. Chem. Soc.* 1967, *89*, 3537–3545. [d] Buffer 80% base. [e] Buffer 50% base. [f] Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* 1957, *79*, 796–800. [g] Jencks, W. P.; Gilchrist, M. *Ibid.* 1968, *90*, 2622–2637. [h] Buffer 90% base. [i] Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* 1972, *94*, 8818–8827. [j] Buffer 87.5% base. [k] Page, M. I.; Jencks, W. P. *Ibid.* 1972, *94*, 8828–8838. [l] Jencks, W. P.; Regenstein, J. In "Handbook of Biochemistry", 2nd ed.; Sober, H. A., Ed., Chemical Rubber Co.: Cleveland, Ohio, 1970; pp J-150–189. Not at ionic strength 1.0 M. [m] Buffer 40% base. [n] Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* 1969, *91*, 6353–6361. [o] Not statistically corrected. [p] Ionic strength maintained at 1.0 M with $NaClO_4$. [q] Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* 1977, *99*, 6970–6980. [r] Buffer 60% base. [s] k_{solv}/55.5 M. [t] Fickling, M. M.; Fischer, A.; Mann, B. R.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* 1959, *81*, 4226–4230.

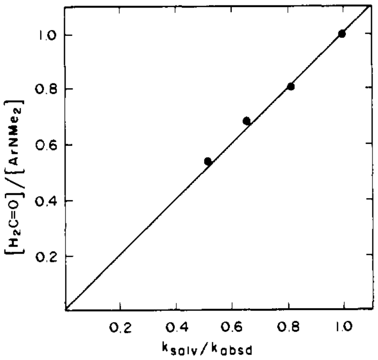


Figure 3. Comparison of product and rate constant ratios for the reaction of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion (**1c**) with triethylenediamine at 25 °C and ionic strength 1.0 M (KCl). The ordinate describes the fraction of the total reaction products as formaldehyde, and the abscissa gives the ratio of the rate constant for hydrolysis to the observed rate constant in the presence of different concentrations of amine.

Figure 3 shows that the fraction of the total reaction of **1c** that gives formaldehyde as product is within experimental error identical with the ratio of the rate constant for solvolysis, in the absence of nucleophile, to the observed rate constant in the

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Table II. Dependence on Temperature of the Rate Constants for Solvolysis and the Reaction with *n*-Propylamine of $m\text{-}NO_2PhN^+(CH_3)_2CH_2OCH_3$[a]

temp, °C	$10^4 k_N$,[b] $M^{-1}\ s^{-1}$	$10^4 k_{solv}$, s^{-1}
11.4	3.45	1.05
18.0	8.10	2.90
25.0	18.4	7.4
30.0	32.0	13.8
34.3	52.0	21.5
39.2	96.1	36.0

[a] In water at ionic strength 1.0 M, maintained with potassium chloride. [b] From four point plots of k_{obsd} (s^{-1}) against free *n*-propylamine concentration, based on experiments in *n*-propylamine buffers, 90% base.

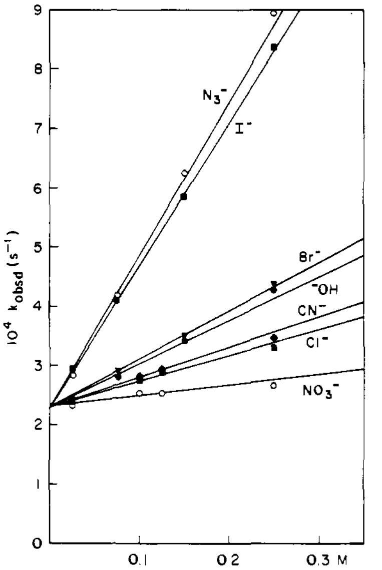

Figure 4. Pseudo-first-order rate constants for the reactions of *N*-(methoxymethyl)-*N*-*N*-dimethyl-*m*-nitroanilinium ion (**1c**) with anionic nucleophiles at 25 °C, ionic strength 1.0 M ($NaClO_4$).

presence of a series of different concentrations of triethylenediamine; i.e., the amount of product that is formed from the nucleophile is accounted for by the rate increase that is caused by the nucleophile, and there is no trapping of any free intermediate by the nucleophile to give product. Analysis by NMR of the products from the reaction of trimethylamine with **1c** showed transfer of the methoxymethyl group to trimethylamine to give $CH_3OCH_2N(CH_3)_3^+$, as expected for reaction at the formaldehyde carbon atom. This product, with a basic amine as the leaving group, is stable under the conditions of these experiments.

The dependence on temperature of the second-order rate constants for the reaction with *n*-propylamine and the first-order rate constants for the solvolysis of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion (Table II) gives values of $\Delta H^{\ddagger} = 20.5$ and 21.3 kcal mol^{-1} for the second-order and solvolysis reactions, respectively. The value of $\Delta S^{\ddagger}$ for the nucleophilic reaction is −2.1 cal K^{-1} mol^{-1} and for the solvolysis reaction $\Delta S^{\ddagger} = -1.2$ or −9.2 kcal K^{-1} mol^{-1}, depending on whether the rate constants are expressed as first-order rate constants for solvolysis or second-order rate constants for reaction with water, respectively.

The second-order reactions of anionic nucleophilic reagents with the meta nitro compound (**1c**) at ionic strength 1.0 M, maintained with sodium perchlorate, are illustrated in Figure 4. Second-order rate constants for reactions of anionic nucleophiles and of water with this compound and with the corresponding dideuterio compound are given in Table III, along with the secondary α-deuterium isotope effects per deuterium atom. Replicate determinations of the isotope effect showed good agreement, almost always within <2%.

Table III. Second-Order Rate Constants and α-Deuterium Kinetic Isotope Effects for Reactions of Nucleophiles with $m\text{-}NO_2PhN^+(CH_3)_2CH_2OCH_3$ and $m\text{-}NO_2PhN^+(CH_3)_2CD_2OCH_3$[a]

	$10^5 k_N$, $M^{-1}\ s^{-1}$		
nucleophile	$-CH_2-$	$-CD_2-$	k_H/k_D[b]
I^-	278	200	1.18
Br^-	85.9	63.4	1.16
Cl^-	39.6	31.0	1.13
F^-	14.1	14.3	.99
HO^-	90.6	79.1	1.07
PhO^-	237	204	1.08
AcO^-	24.0	21.1	1.07
NC^-	52.0	44.6	1.08
$CH_3(CH_2)_2NH_2$	196	169	1.08
$NC(CH_2)_2NH_2$	78.4	68.5	1.07
$HO(CH_2)_2S^-$ [c]	751	578	1.14
$CH_3O_2CCH_2S^-$ [c]	1140	882	1.14
N_3^-	278[d]		
NO_3^-	9.52[d]		
H_2O	0.434[e]	0.353[e]	1.11

[a] In water at 25 °C, ionic strength 1.0 M maintained with sodium perchlorate. Second-order rate constants were determined from linear plots of >6 values of k_{obsd} (s^{-1}) against nucleophile concentration. The solutions were unbuffered, unless otherwise noted, and contained 2×10^{-3} M Na_2EDTA. [b] Per deuterium atom, $k_H/k_D = [k_{H(obsd)}/k_{D(obsd)}]^{1/2}$. [c] Self-buffered; acid:base = 1:1. [d] Based on four values of k_{obsd}. [e] $k_{solv}/55.5$ M.

Table IV. Solvent Effects on Reactions of $m\text{-}NO_2PhN^+(CH_3)_2OCH_3$ at 25 °C

aqueous solvent	$10^4 k_{solv}$, s^{-1}	$10^4 k_N$-(n-$PrNH_2$), $M^{-1}\ s^{-1}$
water	2.4[a]	19.6[a]
ethanol, *X* = 0.2	14.8	
dimethylformamide, *X* = 0.2	29.6	
dimethyl sulfoxide, *X* = 0.2	22.2	
dioxane, *X* = 0.2	30.8	
hexamethylphosphoramide, *X* = 0.2[b]	153	
50% (v/v)	29.4	74
1 M H_2O	219	605

[a] Ionic strength 1.0 M ($NaClO_4$). [b] 70% (v/v).

Solvolysis of the meta nitro compound (**1c**) exhibits a negative salt effect with values of $10^4\ k_{solv}$ = 4.2, 2.8, and 2.4 s^{-1} in water, 1 M $NaBF_4$, and 1 M $NaClO_4$, respectively, at 25 °C. Plots of k_{obsd} against the concentration of salts containing nucleophilic anions show downward curvature for halides, which presumably also represents a negative salt effect, but upward curvature for potassium hydroxide. However, the plots are linear up to 0.25 M salt when the ionic strength is maintained at 1.0 M with $NaClO_4$, the conditions used for determination of second-order rate constants (Figure 4). The similar second-order rate constants for the reaction with *n*-propylamine of 1.84×10^{-3} and 1.96×10^{-3} $M^{-1}\ s^{-1}$ in the presence of 1 M KCl and 1 M $NaClO_4$, respectively (Tables I and III), show that specific salt effects do not have a large influence on the rate constants for nucleophilic reactions. Solvolysis of the uncharged substrate (methoxymethoxy)-2,4-dinitrobenzene (**2**) shows a much smaller negative salt effect in the presence of sodium perchlorate and exhibits upward curvature in plots of k_{obsd} against the concentration of nucleophilic salts.[19]

Rate constants for solvolysis and for the second-order reaction with *n*-propylamine of **1c** exhibit similar increases with increasing alcohol concentration in the range 50–90% ethanol/water (v/v) and in 100% methanol but decrease with increasing concentration of trifluoroethanol in the range 60–100%. The results are plotted in Figure 5 as a function of the *Y* values for these solvents.[7,24] The

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(24) Based on *Y* values for the solvolysis of *tert*-butyl chloride.[7] The lines have slopes of $m = 0.6$ (k_N) and 1.0 (k_{solv}) for TFE–H_2O. *Y* values based on the solvolysis of 2-adamantyl tosylate[7] give values for k_N of $m = -0.34$ (EtOH–H_2O) and 1.6 (TFE–H_2O) and for k_{solv} of $m = -0.30$ (EtOH–H_2O) and 3.0 (TFE–H_2O).

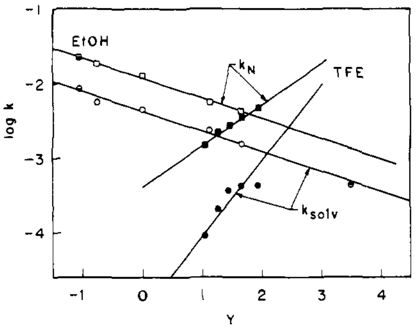


Figure 5. First-order rate constants for solvolysis, k_{solv} (circles), and second-order rate constants for the reaction with *n*-propylamine, k_N (squares) of **1c** in ethanol–water (50–90%, open symbols), methanol (◘, ◒), water (◓), and trifluoroethanol–water (60–90%, closed symbols), as a function of *Y*.[23]

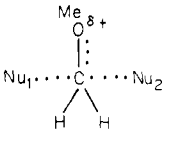
rate of solvolysis also increases upon addition of aprotic solvents to water, and there are similar increases in the rates of solvolysis and the second-order reaction with *n*-propylamine in the presence of hexamethylphosphoramide (Table IV). The amount of reaction with the organic cosolvent in the solvolysis reactions is not known.

Discussion

The prediction that the short lifetime of the oxocarbonium ion "intermediate" formed from formaldehyde derivatives will lead to an enforced preassociation mechanism for reactions of these derivatives is supported by the results reported here and by the data published previously by Craze, Kirby, and Osborne.[19] The reactions are well-behaved second-order nucleophilic displacements, although they display some of the characteristics that are expected for S_N1 reactions. They are "borderline" reactions, but we believe that there is a real line on the border and the mechanism is on the bimolecular substitution side of this line. The preassociation mechanism requires that the entering nucleophilic reagent be present at the time that the bond to the leaving group is broken and the observation of second-order reactions with nucleophiles means that the oxocarbonium ion species has become so unstable and electrophilic that the transition state is stabilized by the incoming nucleophile. When the oxocarbonium ion is more stable, there is no such stabilization of the transition state by nucleophiles, as in the solvolysis of 2-(3,4-dinitrophenoxy)tetrahydropyran.[19] Although the possibility of a small dip near the center of the reaction coordinate–energy profile[2] cannot be rigorously excluded, the evidence suggests than in this reaction the carbonium ion has become so unstable that it does not exist, there is only one barrier along the reaction coordinate (aside from diffusion steps), and the reaction is truly concerted with a single, symmetrical transition state when the attacking and leaving groups are similar.

The bimolecular nature of the displacement reactions is shown most directly by the dependence of the observed pseudo-first-order rate constants on the concentration of the nucleophilic reagent, which is present in large excess (Figures 2 and 4), and by the correlation of the observed rate increase in the presence of added nucleophile with the amount of product formed from the nucleophile (Figure 3); there is no product formed from the trapping of any intermediate that would react with water in the absence of an added nucleophile. The reactions do not represent attack of nucleophiles on an ion pair because cleavage of the C–N bond of **1** does not give an ion pair; in any case ion pairs have little or no stability in water.

Structure–Reactivity Relationships. The effects of changing structure of the entering and leaving groups on the second-order rate constants show that reactions of **1** proceed through an "exploded" transition state, **3**, that can be described either an as unusually open transition state for an S_N2 displacement reaction or as an oxocarbonium ion that is stabilized by weak interactions with a nucleophilic and a nucleofugic reagent, depending on one's taste.



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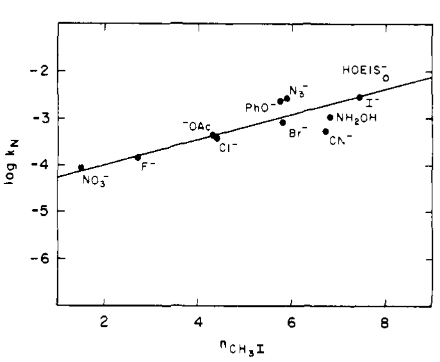

Figure 6. Swain–Scott correlation of the second-order rate constants for reactions of *N*-(methoxymethyl)-*N*,*N*-dimethyl-*m*-nitroanilinium ion (**1c**). The values of *n* are based on reactions of methyl iodide in methanol; an estimated value of $n = 8.0$ for HS^- is used for $HOEtS^-$.[25]

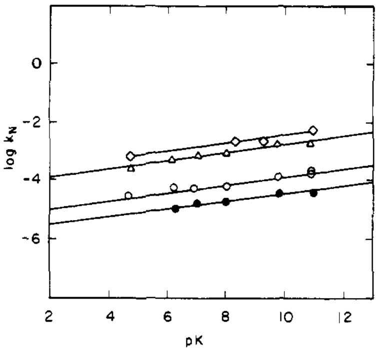

Figure 7. The dependence on basicity of the rate constants for reactions of primary aliphatic amines with the meta nitro (△), para bromo (○), and unsubstituted (●) derivatives of **1**. Rate constants for reactions of secondary amines with the meta nitro compound are indicated by (◇).

The second-order rate constants for reactions of the meta nitro derivative of **1** give a value of $s = 0.28$ in a Swain–Scott correlation based on nucleophilic constants for reactions of methyl iodide in methanol[25] (Figure 6). Slopes of $s = 0.31$ and 0.43 were obtained from a smaller number of nucleophilic constants for reactions of anions with methyl iodide and methyl bromide, respectively, in water,[26] and a slope of 0.35 was obtained from a plot against Ritchie's N^+ parameter for reactions with carbonium ions,[20] which gives somewhat more scatter of the points (not shown); the former values may be compared with the value of $s = 0.2$–0.3 for reactions of (methoxymethoxy)-2,4-dinitrobenzene.[19] Thus, these reactions are approximately one-third as sensitive to the nature of the entering nucleophile as the reference reactions of nucleophiles with methyl halides and carbonium ions. A similar value of $s = 0.43$ has been found for the reactions of ethyl diazoacetate with halide ions.[27]

The deviant points in the Swain–Scott correlation of Figure 6, especially that for N_3^-, give a better fit to the N^+ scale and the rate constants follow the order $N_3^- > HO^- > CN^-$, which is the same as that of the N^+ scale but opposite to that for S_N2 reactions with methyl halides.[20,25,26] We conclude that the sensitivity of the reaction to the nucleophilicity of the attacking group is small and contains components that are characteristic of both S_N2 and carbonium ion reactions; we suspect that a correlation giving approximately equal weight to contributions from each scale

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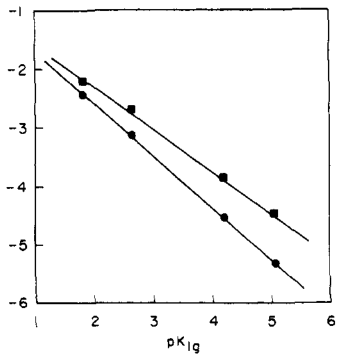

Figure 8. Dependence on the pK_a of the leaving dimethylaniline of the rate constants for reactions of ring-substituted *N*-(methoxymethyl)-*N*-*N*-dimethylanilinium ions with water (●) and with *n*-propylamine (■).

would describe the data well, but too few reagents are presently represented on both scales to test this notion.

A small amount of bond formation in the transition state is also shown by the small dependence on the basicity of the attacking amine, with a slope of $\beta_{nuc} = 0.14$ in a correlation of log *k* with p*K* for a series of aliphatic amines (Figure 7). Secondary and tertiary amines are about twofold more reactive than primary amines (Figure 7, top line; Table I). This slope is smaller than the slopes of $\beta_{nuc} = 0.21$ for the reaction of a series of 30 substituted quinuclidines with methyl iodide in methanol[28] and $\beta_{nuc} = 0.36$ for the reaction of amines with (*p*-nitrophenyl)dimethylsulfonium ion in acetonitrile.[29] A large amount of bond cleavage in the transition state is indicated by the slopes of $\beta_{lg} = -0.89$ and -0.70 for reactions of **1** with water and *n*-propylamine, respectively, in a plot of log *k* against pK_a of the leaving dimethylaniline (Figure 8).

The open nature of the transition state is shown dramatically by a comparison of the small difference of only threefold in the rate constants for the reaction of **1c** with fluoride and chloride ions with the difference of $>3 \times 10^6$-fold for chloride and fluoride ions as leaving groups in the reactions of the corresponding halomethyl methyl ethers with water.[30]

The parallel lines in Figure 7 show no indication of a change in the amounts of bond formation and bond cleavage in the transition state with changing structure of the reactants over a range of 6 p*K* units for the attacking amines and >3 p*K* units for the leaving amines. Thus, there is no detectable "Hammond effect" and the interaction coefficient $p_{xy} = \delta\beta_{nuc}/\delta pK_{lg} = \delta\beta_{lg}/\delta pK_{nuc}$ is small or zero. There is a more negative value of β_{lg} for the attack of water than for attack of amines (Figure 8), but this is probably a consequence of the different attacking atom[31] rather than a difference in nucleophilicity in view of the small difference between the rate constants for reaction of water and of amines. The larger secondary α-deuterium isotope effect (Table III) is consistent with the larger amount of bond cleavage that is indicated by the more negative β_{lg} for the water reaction.

The rate constants for reactions of water, acetate ion, and hydroxide ion with the meta nitro compound (**1c**) fall below the line for the reactions of amines by factors of 9.3, 1.3, and 11, respectively. This indicates that oxygen nucleophiles follow a reactivity series that is not very different from that for amines and that the hydrolysis reaction with water can be accounted for by the same second-order reaction mechanism that is followed by other nucleophiles; i.e., there is no evidence for any additional reaction mechanism such as S_N1 solvolysis that causes an increased rate for the hydrolysis reaction above that expected for a bimolecular reaction with water.

The rate constant for the reaction of acetohydroxamate ion, an "α-effect" compound,[32] falls above the line of $\beta_{nuc} = 0.12$ that fits the data for the reactions of hydroxide ion, acetate ion, and water with the para bromo compound (**1b**) by a factor of 20. However, hydroxylamine and methoxyamine, which are also "α-effect" compounds, show no enhanced reactivity compared with other primary amines (Table I). This is consistent with the conclusion that the "α effect" represents at least two different phenomena.[32] Hydroxylamine and methoxyamine also show no enhanced reactivity toward methyl iodide.[35]

Kirby and co-workers observed a slope of $\beta_{nuc} = \sim 0.5$ for the reaction of oxyanion nucleophiles with (methoxymethoxy)-2,4-dinitrobenzene with a positive deviation of 100-fold for hydroperoxide anion, another "α-effect" compound; they found a negative deviation of ~20-fold for the rate constant of the reaction with water.[19] It is of interest that the rate constant of 2×10^{-4} s^{-1} for the solvolysis of this compound at 30 °C[19] is similar to the rate constant of 0.5×10^{-4} s^{-1} for the expulsion of a dimethylaniline of p*K* = 4 (this rate constant is based on the observed rate constant for solvolysis of the meta nitro compound **1c** at 30 °C (Table II), corrected to $pK_{lg} = 4.0$ by using $\beta_{lg} = -0.89$). This suggests that the leaving group abilities of oxygen anions and nitrogen are very similar for compounds of a given basicity in this system.

The product of the second-order reaction of **1c** with chloride ion is chloromethyl methyl ether, which undergoes rapid hydrolysis in water.[15] Thus, this reaction is an example of nucleophilic catalysis of hydrolysis, and the same is presumably true of the reactions with bromide and iodide ions. The existence of second-order reactions with halide ions means that a second-order reaction of halomethyl methyl ethers with amines in the reverse direction must also exist, from the principle of microscopic reversibility.

Thermodynamic Activation Parameters and the Effects of Solvents and Salts. The entropies of activation for solvolysis and for the second-order reaction with *n*-propylamine of **1c** are very similar, -1.2 and -2.1 cal K^{-1} mol^{-1}, respectively; if the first-order rate constant for solvolysis is divided by 55 M to convert it into a second-order rate constant the value of $\Delta S^{\ddagger}$ is -9.2 cal K^{-1} mol^{-1}. The small negative values of $\Delta S^{\ddagger}$ are consistent with transition states for the reactions with both water and *n*-propylamine that include the entering nucleophilic reagent but have only a weak interaction of the central carbon atom with the entering and leaving groups (**3**). If the solvolysis reaction were unimolecular, it would be expected to exhibit a positive value of $\Delta S^{\ddagger}$, similar to the value of $\Delta S^{\ddagger} = +15.7$ cal K^{-1} mol^{-1} for the solvolysis of *tert*-butyldimethylsulfonium ion at 25 °C.[34] The second-order reaction of hydroxide ion with (*p*-chlorophenyl)dimethylsulfonium ion at 78.8 °C has a negative value of $\Delta S^{\ddagger} = -5$ cal K^{-1} mol^{-1}.[29] Values of $\Delta S^{\ddagger}$ that are based on the same standard states are actually more negative for the reaction of **1c** with water than with propylamine, instead of the more positive values that would be expected for a monomolecular reaction.[34] The values of $\Delta S^{\ddagger}$ for (methoxymethoxy)-2,4-dinitrobenzene are slightly more negative, -6.7 cal K^{-1} mol^{-1} for solvolysis and -9 ± 2 cal K^{-1} mol^{-1} for the second-order reaction with iodide ion.[19]

The rate constants for solvolysis and for the second-order reactions of *n*-propylamine with **1c** increase with increasing ethanol concentration and decrease with increasing trifluoroethanol concentration (Figure 5). Aprotic solvents cause larger increases in the rate of both reactions (Table IV). The similar dependence on solvent of the rate constants for solvolysis and for the nucleophilic reaction with propylamine suggests that the *predominant* effect of the solvents reflects changes in the relative stabilities of the reactants and transition state, rather than changes in the nucleophilicity of the solvent. The similar behavior is consistent

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with the same mechanism for both reactions.

The increased rate in the presence of organic cosolvents (except for trifluoroethanol) is in the expected direction for going from the localized charge of the starting material to the more dispersed charge of the transition JA9M9C Strifluoro It is in the opposite direction to the solvent effect for the solvolysis of an uncharged alkyl halide and corresponds to negative Grunwald-Winstein coefficients[36] of $m = -0.30$ for both the solvolysis and the *n*-propylamine reactions. The favorable effect of ethanol on the rates of *both* the solvolysis and second-order nucleophilic reactions is ~3 times larger than on the solvolysis of *tert*-butyldimethylsulfonium ion.[37] This suggests that the effect arises primarily from destabilization of the localized charge of **1** in the presence of organic solvents and that solvation is more important for the charge of the relatively small nitrogen cation of **1**. The rate constants for the solvolysis of triethyloxonium ion[38] and for the reactions of **1** in aqueous ethanol and trifluoroethanol show a fair correlation with slopes of 0.75 and 0.42 for log k_{solv} and log k_{N}, respectively. The low nucleophilicity of trifluoroethanol probably contributes to the sharp decrease in the solvolysis rate of both compounds in the presence of this solvent, and the smaller decrease with **1** is consistent with the small amount of bond formation in the transition state that is indicated by the small values of s and β_{nuc}. The decreases in both k_{solv} and k_{N} with increasing trifluoroethanol concentration might be accounted for by hydrogen bonding of the relatively acidic trifluoroethanol molecule to the nucleophilic reagent, thereby decreasing the availability of the electron pair for nucleophilic reaction with **1**[28] (the data in Figure 5 are for 60–90% trifluoroethanol, and there is only a small decrease in the solvolysis rate between 0 and 60% trifluoroethanol).

The negative salt effect on the solvolysis reaction is in the expected direction for delocalization of the charge of **1** in transition state **3**. Since sodium perchlorate is known to stabilize carbonium ions,[39] the observed decrease in the rate is consistent with transition state **3**, in which a water molecule rather than an ion is interacting with the central carbon atom in the transition state.

Deuterium Isotope Effects. The secondary isotope effects for deuterium substitution on the formaldehyde carbon atom (Table III), range from $k_{\text{H}}/k_{\text{D}} = 0.99$ for the reaction with fluoride ion to 1.18 for iodide ion (the isotope effect is expressed per deuterium atom). In the halide series the isotope effect increases with increasing polarizability, size, and reactivity and with decreasing electronegativity of the nucleophile. A large isotope effect of $k_{\text{H}}/k_{\text{D}} = 1.14$ is also observed for the large, polarizable thiol anions, and there are smaller isotope effects of 1.07–1.08 for the "harder" amine and oxyanion nucleophiles; the reaction with water has an intermediate value of $k_{\text{H}}/k_{\text{D}} = 1.11$.

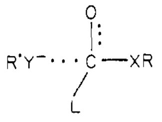
These results establish that large secondary α-deuterium isotope effects can occur in reactions that are cleanly second order and in which there are no uncertainties arising from the possibility of reactions with ion pairs. This confirms and extends the results and conclusions of Kirby and co-workers for reactions of (methoxymethoxy)-2,4-dinitrobenzene, of Westaway for reactions of PhS^- with $\text{PhCH}_2\text{N(CH}_3)_2\text{Ar}^+$ in dimethylformamide, of Hayami et al. for isotopic chloride exchange of chloromethyl aryl ethers in acetonitrile, and of Ferraz, Bull, and Cordes for reactions of nicotinamide nucleotides with hydroxide ion.[19,21,22] Similar isotope effects were found for formaldehyde derivatives with 2,4-dinitrophenolate anion as the leaving group in the reactions with water, an amine, and iodide ion, but a larger value of $k_{\text{H}}/k_{\text{D}} = 1.15$ was observed for the reaction with acetate ion.[19]

The large isotope effects provide additional support for an open, "exploded" transition state for at least some of the second-order reactions (**3**), with a large amount of carbonium ion character and freedom for bending motions of the C–H bonds of the formaldehyde moiety. The differences in the isotope effects provide additional evidence that there is significant interaction of the nucleophilic reagent with the formaldehyde carbon atom in the transition state. If the reactions proceeded by some mechanism that involved only C–N cleavage or the formation of an amine–carbonium ion complex in the rate-limiting step, the same secondary isotope effect would be observed for all nucleophiles.

The large variations in the secondary isotope effects with different nucleophiles suggest that there are large differences in the freedom of vibrations, especially bending vibrations, of the C–H bonds in the different transition states. The results are consistent with the hypothesis that large, "soft", polarizable nucleophiles such as I^- and RS^-, which show the largest isotope effects, can provide electrons to overlap with and stabilize the developing electron deficiency of the central carbon atom from a greater distance than can smaller nucleophilic atoms.[40]

The order in the halide series follows the trend of equilibrium isotope effects that were calculated by Buddenbaum and Shiner, which appear to be correlated with the electronegativity and bond strength of substituents on the carbon atom,[41] but it is unlikely that the observed large differences in isotope effects could be accounted for by such bond strength effects in view of the very small amount of bond formation in the transition state that is indicated by the low s and β_{nuc} coefficients. The observed range of kinetic isotope effects from $k_{\text{H}}/k_{\text{D}} = 0.99$ to 1.18, in fact, is twice as large as the range of equilibrium isotope effects of $K_{\text{H}}/K_{\text{D}} = 0.98$–1.09 that were calculated from the fractionation factors for exchange of deuterium between $\text{DCH}_2\text{NH}_3^+$ and XCH_3.[41] The large differences in the isotope effects cannot be accounted for by a "Hammond effect" because the range of reactivity of different nucleophiles is only 20-fold in the series F^- to I^-. The secondary isotope effect[15] of $k_{\text{H}}/k_{\text{D}} = 1.24 \pm 0.08$ suggests a somewhat later transition state for the solvolysis of methoxymethyl chloride in 2-propanol.

Pohl and Hupe have shown that the secondary α-deuterium isotope effect for the attack of oxyanions on formate esters and thiol esters, LCOXR, is $k_{\text{D}}/k_{\text{H}} = 1.22$, whereas the isotope effect for the attack of thiol anions on the same esters is $k_{\text{D}}/k_{\text{H}} = 1.01$.[42] Although these effects appear to be different from those for reactions with **1**, they represent the same phenomenon and can be explained in the same way. The large isotope effect for oxyanion attack means that the reaction behaves *as if* there is significant conversion of the sp^2 carbon atom of the ester to sp^3 character as the new bond forms in transition state **4**, whereas



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the nucleophilic interaction with thiol anions in the transition state occurs without significant perturbation of the sp^2 character of the ester, as measured by isotope effects. This is the same behavior that is observed in the reactions of **1**, which go from an sp^3 hybridization in the starting material to an sp^2-like transition state that shows little perturbation by an attacking thiol anion.

Rate constants for the addition of ROH, amines, and HO^- to ferrocenyl-stabilized carbocations show secondary α-deuterium isotope effects of $k_{\text{H}}/k_{\text{D}} = 0.9$, 0.96, and 1.0, respectively, which have been interpreted as evidence for progressively earlier transition states for attack of the nucleophile in this series.[43] The opposite order is observed for the secondary isotope effects on the reactions of HOH and HO^- with **1**, and this order might be

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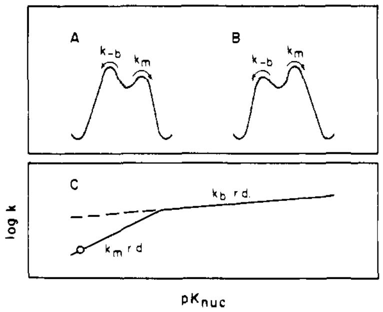


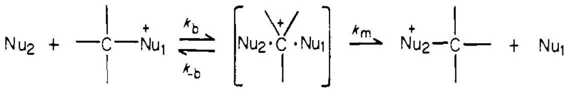
Figure 9. Reaction coordinate diagram for (A) rate-limiting bond breaking ($k_m > k_{-b}$) and (B) rate-limiting bond making ($k_{-b} > k_m$) in the mechanism of eq 3. As the nucleophile becomes weaker, there will be a change in the rate-limiting step from k_b to k_m (C).

interpreted as evidence for a later transition state for the hydroxide ion reaction. However, the data in Table III suggest that it is premature to interpret secondary isotope effects in terms of early or late transition states when there are different atoms or charges on the attacking nucleophiles.

The *solvent* deuterium isotope effect of $k_{HOH}/k_{DOD} = 1.07$ for solvolysis is in the range of reported values for S_N2 reactions of methyl derivatives with water and is smaller than the values of $k_{HOH}/k_{DOD} = 1.2–1.4$ for S_N1 reactions.[44] The solvent isotope effects near 1.0 for the reactions with acetate and *n*-propylamine are consistent with second-order nucleophilic displacement reactions; intramolecular reactions of methylsulfonium ions with ROH, which are subject to general base catalysis, exhibit isotope effects of $k_{HOH}/k_{DOD} = 1.28–1.37$.[45]

Is There an Intermediate? The results establish that the reactions of **1** with nucleophilic reagents proceed through a preassociation mechanism that is enforced by the short lifetime or nonexistence of an oxocarbonium ion "intermediate", and that the rate-limiting transition state is stablized by interaction with nucleophilic reagents. The question remains whether the reaction passes through an unstable intermediate, as shown in Figure 1, or whether the "intermediate" is so unstable that there is no barrier for its formation or its breakdown so that the reaction is forced to proceed through a concerted mechanism.

If the reaction does proceed through an intermediate, it can be described by eq 3 (omitting the preassociation steps), and, if



$$Nu_2 + -C-\overset{+}{N}u_1 \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} [Nu_2\cdot\overset{+}{C}\cdot Nu_1] \xrightarrow{k_m} \overset{+}{N}u_2-C- + Nu_1 \quad (3)$$

the entering and leaving groups are significantly different, either the bond-breaking step (k_b) or the bond-making step (k_m) will be rate limiting. When the entering group is a better nucleophile than the leaving group so that $k_m > k_{-b}$, the bond-breaking step (k_b) will be rate limiting, and when the leaving group is a better nucleophile so that $k_{-b} > k_m$, the bond-making step (k_m) will be rate limiting, as illustrated in Figure 9A,B, respectively.

It might be thought that the reaction proceeds by rate-limiting attack of the nucleophile on a reversibly formed encounter complex or ion-dipole complex of the carbonium ion and the leaving group[4] (eq 3, $k_{-b} > k_m$, or eq 1, upper path). Such a mechanism might account for the different reactivities and secondary isotope effects of different nucleophilic reagents. This kind of mechanism is excluded by the following:

(1) The attacking amines are up to 10^8 more basic than the leaving *N,N*-dimethyl-*m*-nitroaniline, so that the intermediate is expected to react with the attacking amine faster than with the leaving group ($k_m > k_b$) and the rate-limiting step must be k_b not k_m (Figure 9A).

(2) Except for water and methoxyamine, all of the nucleophilic reagents examined for which values of N^+ are available[20,46] are stronger nucleophiles toward carbonium ions than aniline, so that it is expected that $k_m > k_{-b}$ and k_b would be rate limiting, as in (1). Approximately half of them have larger Swain–Scott nucleophilicity parameters, *n*.[25,26]

(3) In order to confirm that there is no special property of *N,N*-dimethylanilines that causes an anomalously high nucleophilic reactivity, we measured their nucleophilic reactivity toward **1c** directly in methanol and found it to be less than that of *n*-propylamine, confirming the conclusions of (1) and (2) above.

(4) (a) The reactions do not represent rate-limiting diffusion-controlled reactions with an ion-dipole complex (k_a, eq 1) because different rate constants and secondary isotope effects are observed for different nucleophiles. The absence of a secondary α-deuterium isotope effect for the reaction with fluoride ion is additional evidence against a diffusion-controlled reaction with a carbonium ion leaving group complex. (b) The reactions do not represent activation-limited second-order reactions of Nu_2 with such a complex (k_2, eq 1) because if there is a large enough activation barrier for bond formation with Nu_2 to be rate limiting, there must be a similar activation barrier for the reaction of Nu_1. Under these conditions all diffusion steps would be fast, Nu_1 would diffuse away before Nu_2 could react, and the reaction would involve a solvent-equilibrated carbonium ion intermediate not a second-order nucleophilic reaction. (c) They do not represent second-order nucleophilic reactions with a "sticky" ion-dipole complex because if the carbonium ion forms such sticky complexes with Nu_2 and Nu_1, the resulting low values of k_{-a} for their separation would provide an even stronger requirement for an enforced preassociation mechanism (eq 1, Figure 1). If the transition state is close to symmetrical and has stabilizing interactions with both the attacking and leaving groups, it is identical with **3**.

The reactions with most nucleophiles must, therefore, proceed either through a fully concerted mechanism or through the stepwise mechanism of eq 2 with bond-breaking (k_b) rate limiting. If bond-breaking is rate limiting, there is still a significant interaction with the entering group as well as the leaving group in the transition state,[5,7] as shown by the different reactivities and secondary deuterium isotope effects that are observed with the different nucleophiles. The transition state, therefore, must be qualitatively similar to that of an S_N2 displacement reaction.

The estimated rate constant of $\sim 10^{15}$ s^{-1} for reaction of the oxocarbonium ion "intermediate" with water[8] is crude, but the reaction with strong nucleophiles should be much faster. The "rate constants" for reactions with thiol anions in an encounter pair are $\sim 10^{23}$ s^{-1}, from the ratio of the rate constants for reactions of water and thiol anions with carbonium ions.[20,46] Neither of these rate constants corresponds to a significant activation barrier. The absence of a barrier for this step means that there is no intermediate along the reaction coordinate and the reaction must be concerted, not stepwise.

Finally, if there is an intermediate, the transition states of the two steps must be asymmetrical and different and there must be a change in rate-limiting step from rate-limiting bond cleavage with strong nucleophiles (Figure 9A) to rate-limiting bond making with weak nucleophiles (Figure 9B). The values of β_{nuc} and β_{lg} indicate that there is some interaction of the central atom with both the attacking and leaving groups in the transition state and are consistent with a symmetrical transition state but do not exclude a small amount of asymmetry. The data show no evidence for the break in structure–reactivity correlations that is required by a change in rate-limiting step from k_b to k_m (Figure 9C). The Swain–Scott correlation appears to be linear with no indication of a break for weak nucleophiles such as F^-, Cl^-, AcO^-, and NO_3^-, that have *n* values well below the value of $n = 5.7$ for aniline (Figure 6). The nucleophilicity of *m*-nitroaniline is expected to be only $\sim$2-fold smaller than that of aniline, from the value of

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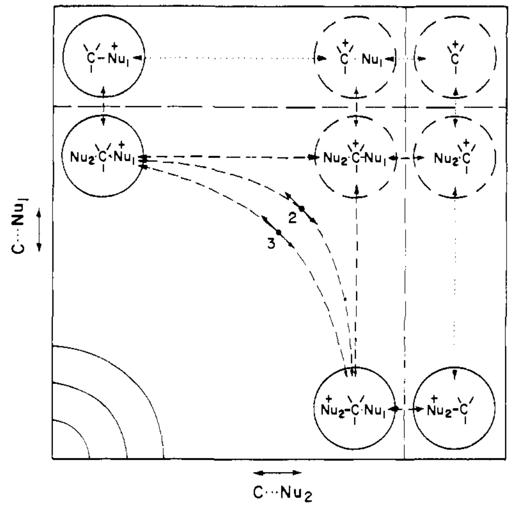

Figure 10. Reaction coordinate diagram for nucleophilic substitution on carbon with wings for the transport steps. The contour lines are omitted except for the lower left corner.

$\beta_{nuc} = 0.14$. Water is 10^4 less reactive toward carbonium ions than aniline[20] so that the attack step would become rate limiting for the water reaction if the reaction were stepwise. However, the rate constants for the reactions of **1b** and **1c** with water, acetate ion, and hydroxide ion are all slightly below those for amines of comparable p*K* and are consistent with a correlation with $\beta_{nuc} = 0.12$; the negative deviation from the line for amines is no larger for water than for hydroxide ion. These results suggest a concerted reaction mechanism with a single transition state that does not vary appreciably in structure as long as the nucleophilic atom remains constant.

The single, symmetrical transition state of a concerted reaction would be expected to involve more bond formation with the attacking nucleophile than the first transition state of a stepwise preassociation mechanism with an intermediate (Figure 9A), in which the entering reagent might participate only as a weakly involved spectator. This provides a possible reason, in addition to steric effects, that nucleophilic participation is small or absent in reactions in which the intermediate has a significant lifetime.[19]

Conclusions

The reaction coordinate–energy diagram of Figure 10, which has wings added to describe diffusional steps,[3,44,47–49] provides a convenient way to illustrate our conclusions. The diagram is drawn with the carbon–nucleophile bond order along the abscissa, the carbon–leaving group bond order on the ordinate, and Gibbs energy in the third dimension, in accordance with the usual convention for such diagrams; most of the energy contour lines are omitted for clarity. A fully stepwise reaction with a solvent-equilibrated carbonium ion intermediate proceeds through the pathway on the outside of the diagram (dotted lines), and a classical concerted S_N2 displacement reaction proceeds through the innermost pathway (dashed lines, pathway 3).

Substitution of oxygen for CH_2 in the β-position of **5** enormously

$CH_3YCH_2N_1^+$ $CH_3YCH_2^+$

5a, Y = CH_2 **6**

b, Y = O

stabilizes the cation **6** so that the energy of the upper right corner of the diagram is lowered. The reaction coordinate for the S_N2 reaction of **5a** will then slide downhill in a perpendicular direction toward this structure,[47–49] and the transition state will increasingly resemble **6**, with decreased bond making and increased bond breaking. If Y = N, the reaction will be likely to proceed around the outer part of the diagram through a free carbonium ion intermediate.

Two clear-cut, qualitative distinctions among mechanisms can be made: (1) Whether the reaction proceeds through a free, diffusionally equilibrated intermediate; i.e. whether it proceeds through an inside or an outside pathway in the diagram of Figure 10. The inside pathways involved preassociation of the reactants. (2) Whether or not it proceeds through an intermediate that has a significant barrier for collapse to both products and reactants; i.e., whether the intermediate exists in a potential well surrounded by a ridge, as indicated by the dashed circle of Figure 10.

The estimated lifetimes of the carbonium ion species and the experimental data reported here lead to the conclusion that reactions of **1** with nucleophilic reagents in water proceed through the inner part of the diagram by an enforced preassociation mechanism, as indicated by the dashed line of pathway 2 in Figure 10. This mechanism differs qualitatively from the fully stepwise mechanism around the outside of the diagram but differs only quantitatively from a classical S_N2 mechanism. We might say that the carbonium ion structure has become stable enough that the reaction would dearly love to proceed through an intermediate with the structure, $Nu_2R^+{\cdot}Nu_1$, and we cannot disprove this possibility directly. However, the evidence strongly suggests that this intermediate is so unstable that it does not represent a significant dip in the energy surface, so that the reaction proceeds through a transition state that closely resembles this structure. This transition state is symmetrical for closely similar entering and leaving groups and describes a concerted reaction mechanism. We do not wish to speculate at this time on the nature of any possible coupling between the motions of the attacking and leaving groups in the transition state.

If the lifetime of the "intermediate" formed from **1** is so short that a concerted mechanism is enforced, it is certain that displacement reactions of methyl derivatives, which would give a much less stable carbonium ion, are also concerted.[7,50] It appears probable to us that many carbocations, such as those derived from secondary aliphatic carbon derivatives, have no barrier for collapse back to reactants and represent transition states rather than intermediates, so that many (or even most) reactions that are thought to proceed through intimate ion pairs,[4,6] "nucleophilically solvated ion pairs",[7] or "ion sandwich" intermediates[5] actually proceed through concerted mechanisms. It is even possible that scrambling of labeled oxygen atoms in carboxylate and tosylate leaving groups to give rearranged reactants[51] may occur by a concerted mechanism, in the sense that no intermediate species is formed along the reaction coordinate that has a significant barrier for collapse back to starting material. The solvolysis of methoxymethyl chloride is faster than that of *tert*-butyl chloride[14] by a factor of 5×10^6, so that even the *tert*-butyl cation may be too unstable to exist in the presence of a nucleophilic solvent; there is some evidence that the relatively unstable transition state for the solvolysis of *tert*-butyl chloride is stabilized by "solvent assistance", despite the unfavorable steric effect of the *tert*-butyl groups.[52] The available data appear to be consistent with the hypothesis that all solvolysis and substitution reactions at saturated carbon that proceed through S_N2 displacement mechanisms do so simply because the intermediate in the alternative S_N1 mechanism is too unstable to exist.

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