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Cation-Anion Combination Reactions. 18. Reactions of Nucleophiles with an Ion Pair

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Abstract: The reactions of an intramolecular ion pair, Phenol Red Dimethyl Ether (4′,4″-dimethoxytritylium-2-sulfonate), with nucleophiles have been studied and compared with analogous reactions of a sterically similar unpaired cation, DAMS (4′,4″-dimethoxy-2-(methylsulfonyl)tritylium ion), all in aqueous slution. Reactions of a few nucleophiles with a formally dinegatively charged electrophile, Bromphenol Blue (3′,3″,5′,5″-tetrabromo-4′,4″-dioxidotritylium-2-sulfonate), have also been studied. The relative reactivities of neutral, anionic, and dianionic nucleophiles are the same toward Phenol Red Dimethyl Ether and DAMS and are qualitatively the same toward Bromphenol Blue. The effects of the negatively charged sulfonate group on equilibria and spectral properties of the triarylmethyl cation are also quite small. The data show clearly that ion-paired carbon cations behave very much the same as unpaired cations in reactions with nucleophiles, at least in aqueous solution.

Introduction

Although ion pairs have been implicated as intermediates in many reactions,[1] the very nature of the rapid equilibria with higher aggregates and free ions makes it very difficult to determine reaction characteristics of such species. The carbon cation-anion pairs, implicated in many solvolysis reactions, have been of particular interest to us in connection with our studies of the reactions of nucleophiles with various electrophilic reagents.[2] Specifically, we would like to know if orders of nucleophilic reactivity toward ion pairs might differ from those toward free cations and provide some rationalization of variations of trapping ratios found in solvolysis reactions.[3,4]

We have, therefore, prepared the intramolecular ion pair, Phenol Red Dimethyl Ether, whose structure is shown in Figure 1, and studied reactions of a wide variety of nucleophiles with this molecule in aqueous solution. We anticipated that the rather large ortho-sulfonate group might give appreciable steric effects on some of the reactions which might mask any other effects. In order to allow clear interpretation of results, we have prepared a sterically similar cation, DAMS (structure in Figure 1), in which the sulfonate group is replaced by an ortho-methylsulfone group, and studied reactions of the same nucleophiles with this cation. We have also found that Bromphenol Blue (structure in Figure 1), a formally dinegatively charged electrophile, reacts with some nucleophiles in aqueous solution and have been able to measure rates of some of these reactions.

Experimental Section

Syntheses. Phenol Red Dimethyl Ether was prepared from Phenol Red by a slight modification of the method reported by Orndorff.[5] Phenol Red (3 g) was dissolved in 100 mL of anhydrous methanol to which was added 5 mL of concentrated HCl. The mixture was refluxed overnight. When the mixture was cooled to ca. −20 °C, crystals formed which were removed by filtration, washed with water, and recrystallized from glacial acetic acid until the apparent molar absorptivity of the compound in 0.1 M $HClO_4$ at 510 nm was unchanged by further crystallization. The ^1H NMR (Me_2SO-d_6) showed: δ 3.8 (s, 6 H), 6.8-8.2 (m, 12 H). Anal. Calcd for $C_{21}H_{18}O_5S$: C, 65.95; H, 4.74, S, 8.38. Found: C, 65.98; H, 4.76; S, 8.36. Melting point: 180.5-181.0 °C, uncorrected.

Bromphenol Blue was prepared as described by Acree.[6] The cream colored crystals were recrystallized from acetic acid-acetone to constancy of the molar absorptivity of the compound in pH 6.58 (phosphate buffer) aqueous solution at 591 nm. Anal. Calcd for $C_{19}H_{10}O_5SBr_4$: C, 34.06; H, 1.50; S, 4.80. Found: C, 33.93, H, 1.55; S, 4.89.

DAMS Carbinol was prepared by the Grignard reaction of *p*-bromoanisole with methyl 2-thiomethylbenzoate, followed by oxidation of the thiomethyl group with *m*-chloroperbenzoic acid. Methyl 2-thiomethylbenzoate was prepared as described by Friedlaender[7] and was recrystallized from petroleum ether. The Grignard reaction was then carried out as follows. Five drops of *p*-bromoanisole and 2 drops of methyl iodide were added to a flask containing 0.5 g of magnesium turnings in 15 mL of tetrahydrofuran. The mixture was refluxed for a few minutes until reaction commenced and then 3.0 g of *p*-bromoanisole in 8 mL of tetrahydrofuran was added dropwise over the period of 1 h. The mixture was refluxed an additional hour, cooled to 0 °C, and then transferred by means of a gas-tight syringe to a flask containing 1.46 g of methyl 2-thiomethylbenzoate in tetrahydrofuran. The reaction mixture was allowed to warm slowly to room temperature and stand for 1.5 h. Saturated ammonium chloride solution (100 mL) was added and the mixture then extracted with three 50-mL portions of ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and then chromatographed on basic alumina (8:2 hexane-methylene chloride eluant) to yield 1.7 g (60%) of a viscous product. ^1H NMR ($CDCl_3$): δ 2.2 (s, 3 H), 3.6 (s, 6 H), 5.7 (s, 1 H), 6.6-7.2 (m, 12 H).

The entire yield of the above reaction was dissolved in 25 mL of methylene chloride and added dropwise to a cold solution of 2.5 g of *m*-chloroperbenzoic acid (2.3 equiv) in 50 mL of methylene chloride. The reaction mixture was allowed to come to room temperature and stand for 4 h. The mixture was then washed with successive portions of 5% $NaHSO_3$, 5% $NaHCO_3$, and water and then dried over $MgSO_4$. Evaporation of the solvent yielded a solid product which was recrystallized three times from hexane to give pale yellow needles, mp 174.5-175.0 °C, uncorrected. ^1H NMR ($CDCl_3$): δ 2.8 (s, 3 H), 3.8 (s, 6 H), 6.4 (s, 1 H), 6.6-7.5 (m, 12 H). Anal. Calcd for $C_{22}H_{22}O_5S$: C, 66.32; H, 5.56; S, 8.05. Found: C, 66.30; H, 5.56; S, 8.01.

Rate and Equilibrium Studies. Materials. Water used for all solutions was house-distilled water which was redistilled from basic permanganate under nitrogen and stored under nitrogen. In runs where possible oxidation was anticipated, the water was further degassed with a stream of nitrogen for 30 min prior to use. Stock sodium hydroxide solutions were prepared from J. T. Baker Dilut-It concentrates, standardized by titration of potassium hydrogen phthalate, and stored in polyethylene bottles. Stock solutions of perchloric acid were prepared by dilution of standardized (by NaOH titration) 70% $HClO_4$. Sodium azide was purified by dissolving in hot water, filtering, and precipitating with ethanol. Methoxylamine was prepared from the HCl salt by neutralization of the salt in aqueous solution followed by fractional distillation and then a second distillation of the free base from KOH pellets under nitrogen. Triethylamine and *n*-propylamine were distilled from KOH pellets under nitrogen. Hydrazine monohydrochloride was recrystallized from ethanol-water and dried in a vacuum desiccator. Dabco was recrystallized

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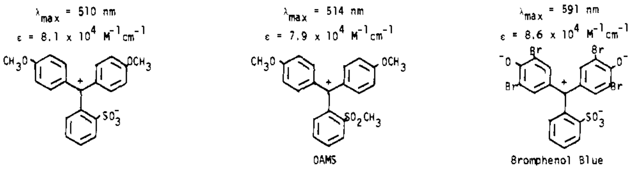


Figure 1. Structures of electrophiles studied. Chemical Abstracts has supplied nomenclature 4′,4″-dimethoxytritylium-2-sulfonate, 4′,4″-dimethoxy2-(methylsulfonyl)tritylium ion, and 3′,3″,5′,5″-tetrabromo-4′,4″-dioxidotritylium-2-sulfonate for the structures from left to right.

from hexane. Mercaptoethanol was distilled under a nitrogen pressure of 9mmHg immediately prior to use. Hydrogen peroxide stock solutions, ca. 0.1 M, were prepared from 30% reagent and were standardized by titration with $KMnO_4$, which had, in turn, been standardized against ferrous ion. All other materials were reagent grade products used without further purification.

Instrumentation. UV-vis spectra were recorded on a Cary Model 14 spectrophotometer. A Gilford Model 240 spectrophotometer equipped with a thermostated cell holder (regulation to ±0.1 °C) was used for kinetic studies where the reactions had half-lives of greater than ca. 1 min.

pH measurements were made by using a Beckman Model 1019 pH meter equipped with a Corning triple-purpose glass electrode and a saturated calomel reference electrode. The meter was standardized by standard buffers within 2 pH units of the range to be measured before each measurement.

Reactions with half-lives less than ca. 1 min were followed by use of a stop-flow spectrophotometer constructed so that solutions contact only glass, quartz, and Teflon. Most experiments utilized single wavelength measurements obtained by use of a Bausch & Lomb Model 33-86-25-02 monochromator with high-intensity source and an EMI photomultiplier detector. The output from the photomultiplier is passed to an emitter-follower, and data are collected with a Nicolet Model 1090A digital oscilloscope. The digital oscilloscope is interfaced with a Nova 3/12 computer for data treatment and hard copy.

Where possible, at least one experiment for each electrophile-nucleophile reaction was carried out by using rapid-scanning stop-flow spectrophotometry. The light source used in this instrument is an Oriel Model 6310 deuterium lamp. After passage through the stop-flow observation chamber (2-cm length, $^1/_{16}$-in. diameter), the light beam is conducted by a quartz fiber bundle to the entrance slit of a J-Y Optical Systems Model UFS-200 Spectrograph which spreads the spectrum onto a Reticon Model RL 256EC/17 photodiode array mounted $^1/_2$ in. outside the exit port of the spectrograph. The diode array may be positioned horizontally to receive any 300-nm "window" within the 220–800-nm range of the light source. the analogue output from the Reticon device is fed to an A/D converter interfaced to the Nova 3/12 computer, and the data are stored on a 10 Mbyte hard disk. The computer is interfaced to the Reticon device controls to set scan time, repetition time, etc. Immediate display of spectra is available through the interfaced digital oscilloscope mentioned above, and hard copy spectra are made by use of a Hewlett-Packard 7221A digital plotter. Auxiliary programs allow calculation of rate constants from any specified wavelength of the spectra, generation of theoretical spectra, etc.

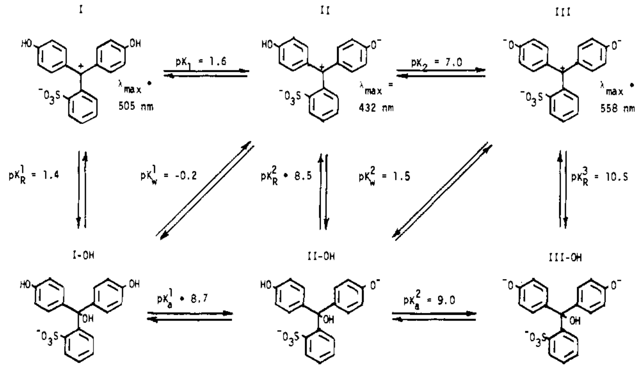
In practice, reasonable spectra anywhere within the 230–700-nm range can be obtained in 8 ms by averaging at least four scans. Generally, 64 complete spectra are obtained in a single stop-flow run, and averaging of each spectrum is attained by repeating the run four times.

Preparation of Solutions. Stock solutions of the dyes were prepared by weighing ca. 3–7 mg of the appropriate compound on a Cahn Electrobalance and dissolving the sample in either 5.0 or 10.0 mL of acetonitrile (for DAMS and Phenol Red Dimethyl Ether) or ethanol (for Bromphenol Blue) in a volumetric flask to give a final concentration of ca. 1×10^{-3}/M.

For stop-flow runs, 0.50 mL of the stock solution of the dye was added to a 50.0-mL volumetric flask containing $HClO_4$ (0.10 M for Phenol Red Dimethyl Ether, 0.20 M for DAMS) and enough $NaClO_4$ to produce an ionic strength in the final reaction solutions of 0.50 M. The solutions of nucleophiles were prepared with enough of the basic form of the nucleophile or of an added buffer to neutralize the acid in the dye solution and still maintain at least a 1000-fold excess of the minor buffer component over the concentrations of the electrophile in the mixed solutions.

For slower reactions, mostly those of Bromphenol Blue, solutions of the nucleophiles were prepared, placed in a 1.0-cm spectrophotometer cuvette, and allowed to reach thermostat temperature in the spectrophotometer. A 0.030-mL portion of the electrophile solution was then introduced either by means of a gas-tight syringe and micropipet or by "plumpers" (Calbiochem).

Scheme I. Ionization Equilibria for Phenol Red



The acidic solutions of Phenol Red Dimethyl Ether were used within 1 h of preparation, and those of DAMS were used within 5 min of preparation because of the decomposition of these dyes in acidic solution.

Decomposition of Phenol Red Dimethyl Ether in Acidic Solution. A study of the decomposition of Phenol Red Dimethyl Ether in 0.10 M $HClO_4$ with 0.40 M $NaClO_4$ was made as follows. The solution of the dye was prepared as described above. At various time intervals, aliquots of the solution were removed and the spectrum of the acidic solution was recorded. A second aliquot of the solution was made basic by addition of NaOH to give a final hydroxide concentration of 0.05 M. The spectrum of this basic solution was then recorded.

Analysis of the above spectra was greatly aided by observations of the pH dependence of the spectrum of solutions of Phenol Red. A stock solution of Phenol Red, prepared as above, was quantitatively diluted with various aqueous buffers. Spectra were obtained for solutions with 0.10 M $HClO_4$, pH 2.0, pH 3.0, pH 4.6, and 0.05 M NaOH. The equilibria shown in Scheme I are analogous to those which we have previously studied for amino-substituted triarylmethyl cations,[9a] and the data treatment is also analagous.

pK_R Determinations.[9c] The spectra of Phenol Red Dimethyl Ether and of DAMS in solutions of varying $HClO_4$ concentrations were obtained. The variation of absorbance at the wavelength of maximum absorbance of the dye was fitted to the equation: $pK_R = H_R - \log [(A^0 - A)/A]$ by iterative adjustment of pK_R and A^0. Values of H_R were taken from the literature.[8]

The pK_R of Bromphenol Blue was determined from measurements at a pH of 11.0 (borate buffer, 0.50 M ionic strength with $NaClO_4$). The absorbance of the solution at 591 nm reached a constant value after 5 weeks, and the pK_R was calculated from the initial and final absorbances.

Rate Constant Determinations. All reactions were studied under pseudo-first-order conditions with nucleophile in large excess. Ionic strength was 0.50 M and temperature was 25.0 ± 0.1 °C for all runs. The disappearance of absorbance at the wavelength of maximum absorbance of the dye was followed, and rate constants were calculated by the nonlinear least-squares procedure described in earlier papers.[2]

Second-order rate constants were calculated by weighted least-squares treatment of first-order rate constants vs. concentrations of nucleophiles. At least a tenfold variation in nucleophile concentration was used in each case.

The general experimental conditions used for each reaction are summarized in Table I, and derived rate and equilibrium constants are reported in Table II.

Results

Structures of Reactant Electrophiles and pK_R Determinations.[9c] The spectral characteristics and the acidity dependences of these characteristics of solutions of Phenol Red Dimethyl Ether and of DAMS cation are those typical of triarylmethyl cations. For Phenol Red Dimethyl Ether, acidic solutions show an absorbance maximum at 510 nm, and this absorbance decreases with increasing H_R[9c] in accordance with conversion of the zwitterionic form shown in Figure 1 to the corresponding carbinol. Measurements at a series of $HClO_4$ concentrations establish a pK_R value of 1.17 and a molar absorptivity of 8.1×10^4 M^{-1} cm^{-1} at

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[9] (a) C. D. Ritchie, D. J. Wright, D.-S. Huang, and A. Kamego, *J. Am. Chem. Soc.*, **97**, 1163 (1975); (b) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955). (c) K_R is the equilibrium constant for reaction of cation with water to form carbinol plus proton; H_R is the acidity function pertinent to this equilibrium.

Table I. Summary of Experimental Conditions^{a}

nucleophile	concn range, M	buffer base (ratio; concn)	rate const range, s^{-1}
Phenol Red Dimethyl Ether			
water		acetate (1:1; 0.01–0.05)	0.028 ± 0.001
water, OH^-		HPO_4^{2-} (1:1; 0.01)	0.099
OH^-	0.01–0.10	none	0.78–7.6
CN^-	0.01–0.10	PO_4^{3-} (10:1; 0.05)	0.17–1.1
CH_3ONH_2	0.0025–0.020	HPO_4^{2-} (1:1; 0.05)	0.13–0.82
	0.007–0.015	CH_3ONH_2 (3:1)	0.26–0.56
n-$PrNH_2$	0.001–0.020	*n*-$PrNH_2$ (1:2)	0.5–7.3
NH_2NH_2	0.001–0.01	Dabco (1:1; 0.05)	1.2–11.7
N_3^-	0.0007–0.010	HPO_4^{2-} (1:1; 0.05)	135.–260^{b}
SO_3^{2-}	1.7×10^{-6}–4.2×10^{-5}	acetate (1:1; 0.05)^{d}	0.07–0.94
	4.5×10^{-7}	acetate (1:10; 0.05)	0.037
HOO^-	6.3×10^{-5}–7.0×10^{-4}	OH^- (0.02)^{e}	2.7–27.3
$HOCH_2CH_2S^-$	1.1×10^{-7}–1.1×10^{-6}	acetate (1:1; 0.05)^{e}	0.09–0.58
	7.3×10^{-7}	acetate (1:1; 0.01)	0.40
DAMS Cation			
water		acetate (1:1; 0.02–0.1)	0.090 ± 0.003
water, OH^-		HPO_4^{2-} (1:1; 0.01)	0.100
		cacodylate (1:1; 0.10)	0.12
OH^-	0.01–0.10	none	4.6–45.6
CN^-	0.02–0.20	Et_3N (2:1; 0.10)	0.27
CH_3ONH_2	0.008–0.08	HPO_4^{2-} (1:1; 0.05)	0.9–8.3
n-$PrNH_2$	0.003–0.030	*n*-$PrNH_2$ (3:50 and 3:5)	6.6–60
NH_2NH_2	0.001–0.010	Dabco (1:1; 0.10)	3.4–34
N_3^-	4.5×10^{-5}–4.5×10^{-4}	HPO_4^{2-} (1:1; 0.05)	4.5–140^{b}
SO_3^{2-}	1.7×10^{-6}–1.7×10^{-5}	acetate (1:1; 0.10)^{d}	0.27–1.9
HOO^-	6.3×10^{-5}–7.0×10^{-4}	OH^- (0.01–0.02)^{e}	11–95
$HOCH_2CH_2S^-$	1.2×10^{-6}–1.2×10^{-5}	HPO_4^{2-} (1:1; 0.05)^{e}	1.9–15.
Bromphenol Blue			
OH^-	0.02–0.20	none	1.9×10^{-5}–1.9×10^{-4}
CN^-	0.01–0.10	CN^- (1:1)	7.2×10^{-7}–7.0×10^{-6}
NH_2NH_2	0.02–0.20	OH^- (0.05)	5.8×10^{-4}–5.3×10^{-3}
HOO^-	0.0003–0.003	OH^- (0.12)^{d}	1.6×10^{-3}–8.6×10^{-3}
$HOCH_2CH_2S^-$	0.10–0.40	OH^- (0.05–0.20)^{e}	$>10^{3}$ ^{c}

[a] All measurements at ionic strength of 0.5 M with $NaClO_4$ and at 25.0 °C. [b] These reactions reach an equilibrium with the rate law for second-order reversible reactions. [c] Equilibrium is established before the first observation can be made on the stop flow. [d] Solutions contained ca. 10^{-5} M hydroquinone. [e] Solutions contained ca. 10^{-7} M EDTA.

Table II. Rate Constants^{a}

nucleophile	PHRDME^{b}	DAMS cation	Bromphenol Blue
water	2.8×10^{-2} ^{c}	8.7×10^{-2} ^{d}	*e*
OH^-	7.6×10	4.5×10^{2}	8.7×10^{-4}
CN^-	1.0×10	4.4×10	7.2×10^{-5}
HOO^-	3.0×10^{4}	1.3×10^{5}	2.4
N_3^-	1.4×10^{4} ^{f}	2.7×10^{5} ^{g}	
$HOCH_2CH_2S^-$	4.8×10^{5}	1.2×10^{6}	*h*
SO_3^{2-}	2.0×10^{4}	1.0×10^{5}	
CH_3ONH_2	3.9×10	1.0×10^{2}	
n-$PrNH_2$	3.6×10^{2}	1.6×10^{3}	
NH_2NH_2	1.1×10^{3}	3.3×10^{3}	3.0×10^{-2}

[a] All measurements are for 0.50 M ionic strength with $NaClO_4$ and at 25.0 °C. Second-order rate constants are given in units of M^{-1} s^{-1} for all reactions except those of water. Water reactions rate constants are in units of s^{-1}. [b] Phenol Red Dimethyl Ether. [c] Equilibrium constant is 6.8×10^{-2} M. [d] Equilibrium constant is 6.0×10^{-1} M. [e] Equilibrium constant is 4.0×10^{-11} M. [f] The equilibrium constant is 1.9×10^{2} M^{-1}. [g] The equilibrium constant is 9.5×10^{3} M^{-1}. [h] Equilibrium constant is 0.15 M^{-1}. Equilibrium is reached too rapidly for rate measurements.

510 nm for the zwitterionic form. Analogous measurements for DAMS give $pK_R = 0.22$ and a molar absorptivity of 7.9×10^4 M^{-1} cm^{-1} at 514 nm for the cationic form.

The near identity of the molar absorptivities of DAMS cation and of Phenol Red Dimethyl Ether clearly establish that there is little, if any, of the covalent sultone at equilibrium with the zwitterionic form of Phenol Red Dimethyl Ether in aqueous solution. It is worth noting, however, that the crystals of Phenol Red Dimethyl Ether are colorless, as are solutions of the compound in acetonitrile. The covalent sultone must be the stable form in the solid and in solution in poor ion-solvating solvents.

The acidic solutions of Phenol Red Dimethyl Ether and of DAMS undergo a decomposition to be further discussed below. This decomposition limits the accuracies of the pK_R measurements to some extent and, since the rate of decomposition increases with increasing acidity, prevents the study of the more acidic solutions required for the complete conversion to the cationic forms. We estimate that the pK_R values reported for these two species are accurate to ca. ±0.1 unit.

For several purposes which will become clear in later discussion, we have also carried out some studies of the acid–base equilibria of Phenol Red. The pertinent structures and equilibria are shown in Scheme I. The various equilibrium constants shown in the scheme were calculated by using the assumption that the molar absorptivities at the wavelength of maximum absorbance are the same for forms I, II, and III, having a value of 8×10^4 M^{-1} cm^{-1}. For triarylmethyl cations in aqueous solution, the molar absorptivities are, in fact, almost invariant with structure, being 8 (±1) × 10^4 M^{-1} cm^{-1}, except for some symmetrically trisubstituted derivatives such as Crystal Violet.[9] Thus, it is unlikely that the assumed value will cause gross errors in the estimated equilibrium constants. Considering both this assumption and the limited number of measurements made, we estimate that the p*K* values are accurate to better than ±0.3 units.

Bromphenol Blue is involved in a set of acid–base equilibria completely analogous to that for Phenol Red. In 12 M H_2SO_4, Bromphenol Blue shows an absorbance maximum at 540 nm with a molar absorptivity of 7.2×10^4 M^{-1} cm^{-1}. At a pH of 2.0, the absorbance maximum is at 455 nm and the apparent molar absorptivity is 2.9×10^4 M^{-1} cm^{-1}. At pH above 7, the absorbance maximum is at 591 nm and the molar absorptivity is 8.6×10^4 M^{-1} cm^{-1}. The measurement of pK_R at a pH of 11.0 gives a value of 10.4. All of these observations are consistent with a scheme analogous to Scheme I and values of pK_1 and pK_2 slightly lower than for Phenol Red. For the present purposes, the important conclusion is that the ionized form shown in Figure 1 is the species present in the basic solutions used in the kinetic studies.

Decomposition of Acidic Solutions of DAMS and Phenol Red Dimethyl Ether. We have carried out a fairly detailed study of the decomposition of Phenol Red Dimethyl Ether in 0.1 M perchloric acid solution and have also verified that the rate of decomposition increases with increasing acid concentration as expected for the ether cleavage reaction. The final product of the reaction is Phenol Red, as verified by the spectrum obtained in basic solutions.

In acidic solution, the spectrum shows an increase in absorbance at ca. 430 nm, a decrease in absorbance at 510 nm, and, finally, a shift of the absorbance maximum to 505 nm as the decomposition proceeds. Aliquots of the acidic solution were made basic, and these solutions show absorbance at 430 nm increasing during the first 10 h and then decreasing as the absorbance of Phenol Red at 558 nm increases. Quantitative analysis of the spectra allow a molar absorptivity of 2.7×10^4 M^{-1} cm^{-1} to be assigned to the species absorbing at 430 nm in basic solutions. This species may be identified as the methyl ether of Phenol Red by comparison of spectral characteristics with those of the ionized forms of Phenol Red shown in Scheme I.

A fitting of the data to a kinetic scheme of two consecutive pseudo-first-order reactions allows estimates of the rate constants. The conversion of Phenol Red Dimethyl Ether to methyl ether occurs with a rate constant of 6.4×10^{-5} s^{-1}, and methyl ether is converted to Phenol Red with a rate constant of 8.5×10^{-6} s^{-1} in 0.10 M $HClO_4$, ionic strength 0.50 M with $NaClO_4$, at room temperature (ca. 25 °C). The smaller apparent rate constant for the second step of the reaction is expected, since only a fraction of methyl ether should be in the reactive cationic form if equilibrium constants are similar to those for analogous forms of Phenol Red shown in Scheme I. The major fraction of methyl ether should be present as the "hydrate" (form I-OH of Scheme I with a phenolic OH replaced by OCH_3) and as the zwitterionic species (form II of Scheme I with phenolic OH replaced by OCH_3).

We have not carried out detailed studies of the decomposition of DAMS solutions, but the acidic solutions show spectral changes quite similar to those of Phenol Red Dimethyl Ether. The decomposition of the acidic DAMS solutions is considerably faster than the Phenol Red Dimethyl Ether solutions.

Products of Reactions. The spectra of the reaction solutions during, and immediately following, the disappearance of the absorbance due to the reactant dyes show no formation of appreciable absorbance above 300 nm, with the specific exceptions to be discussed below. After prolonged standing (several hours to several days), the reaction solutions from Phenol Red Dimethyl Ether with amines develop strong absorbance above 600 nm. The spectra are those expected of *p*-amino-substituted triarylmethyl cations.[9a] Since this color formation is much slower than the reactions which we have followed, we have not carried out detailed studies. It seems likely that slow nucleophilic aromatic substitution occurs on the small amounts of dyes present in equilibrium with the initially formed triarylmethylamines.

As discussed above, the acidic solutions of Phenol Red Dimethyl Ether and of DAMS undergo a slow decomposition. In the short times between preparation of these solutions and their mixing with buffered solutions of nucleophiles, only a small amount (less than 20%) of the initial dye has been converted to the methyl ethers. The spectra of the solutions in the stop flow (now neutral or basic) show absorbance at 430 nm due to this decomposition product. In most of the reactions studied, the absorbance at 430 nm remains constant throughout the course of the reactions studied here, causing no problems in the rate measurements.

In those cases where strongly basic solutions are used for the reactions (hydroxide ion and amine nucleophiles), however, there is a slight increase of absorbance in the 430–480-nm range which occurs at the same rate as that of the disappearance of the dye absorbance. Using the molar absorptivity found for the monomethyl ether of Phenol Red in basic solution (2.7×10^4 M^{-1} cm^{-1}), we calculate that less than 20% of the original dye reacts to produce absorbance in this region. We believe that this increase in absorbance is due to a competing nucleophilic aromatic substitution of hydroxide or amine for the methoxyl group of the dyes. For amine substitution, producing a *p*-amino,*p*′-methoxy-substituted dye, the absorbance maximum should be close to 500 nm with a molar absorptivity of at least 5×10^4 M^{-1} cm^{-1}.[9a] With the small amounts of absorbance produced at these wavelengths, complicated by the already present methyl ether absorbance, we cannot be certain that the nucleophilic aromatic substitution by amine is occurring. The very slow color formation discussed above, however, strongly indicates such a reaction.

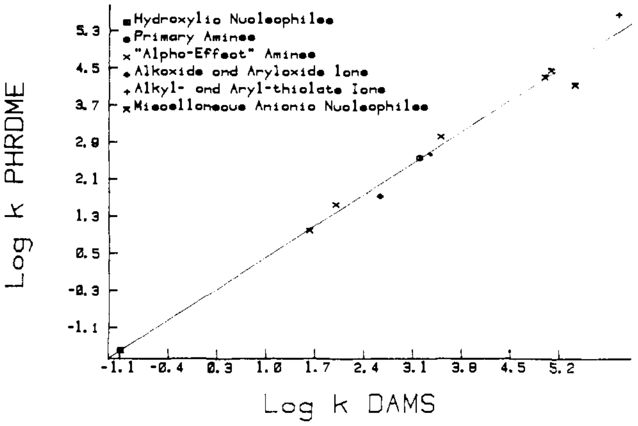

Figure 2. Reactions of nucleophiles with Phenol Red Dimethyl Ether vs. those with DAMS cation. The linear least-squares line shown is given by $\log k_{PHRDME} = 0.97 \log k_{DAMS} - 0.53$.

The data obtained indicate that these side-reactions cause errors of less than 20% in the rate constants reported in Tables I and II even in the worst cases, and that the major products are those from addition at the central carbon.

Rate Measurement. All of the reactions studied exhibit rates which are first order with respect to electrophile and first order with respect to nucleophile concentrations. The precision of the calculated second-order rate constants reported in Table II was better than ±10% in all cases. For reactions of the basic nucleophiles *n*-propylamine and hydroxide ion with Phenol Red Dimethyl Ether and with DAMS, the measured rate constants are the sums of those for the central carbon attack and the nucleophilic aromatic substitution discussed above. The rate constants for these reactions may, therefore, be as much as 20% greater than the rate constants for attack at the central carbon alone.

Discussion

Figure 2, showing a log–log plot of rate constants for reactions of nucleophiles with Phenol Red Dimethyl Ether vs. those with DAMS cation, provides a clear answer to the primary question motivating this study. The presence of the "counterion" of the Phenol Red Dimethyl Ether "ion pair" has no appreciable effect on the relative rates of reactions of nucleophiles. An excellent linear correlation of the rates of the two electrophiles is obtained by either least-squares ($r = 0.993$, root-mean-square deviation = 0.24) or unit slope (root-mean-square deviation = 0.25) relationships for all nucleophiles studied. There is no discernable pattern of deviations which might be attributed to charge type of nucleophiles.

The largest deviation (0.6 unit) from the correlation is for reactions of azide ion. Since we have previously reported that azide ion appears to be unusually unreactive toward neutral electrophiles,[10] it is of some interest to know if this deviation is significant. We believe that the plot shown in Figure 3, for reactions of tri-*p*-anisylmethyl cation[11] vs. those of Phenol Red

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[10] C. D. Ritchie and M. Sawada, *J. Am. Chem. Soc.*, **99**, 3754 (1977); C. D. Ritchie, *Pure Appl. Chem.*, **50**, 1281 (1978).

[11] K. Hillier, J. M. W. Scott, D. J. Barnes, and F. J. P. Steele, *Can. J. Chem.*, **54**, 3312 (1976).

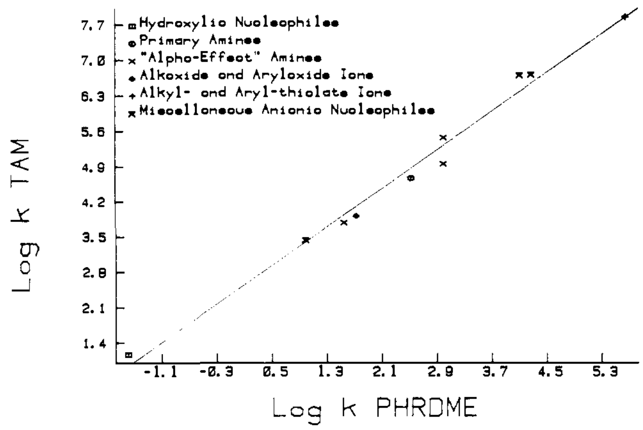


Figure 3. Reactions of nucleophiles with Phenol Red Dimethyl Ether vs. those with tri-*p*-anisylmethyl cation. The linear least-squares line shown is given by: $\log k_{\mathrm{TAM}} = 0.95 \log K_{\mathrm{PHRDME}} + 2.42$.

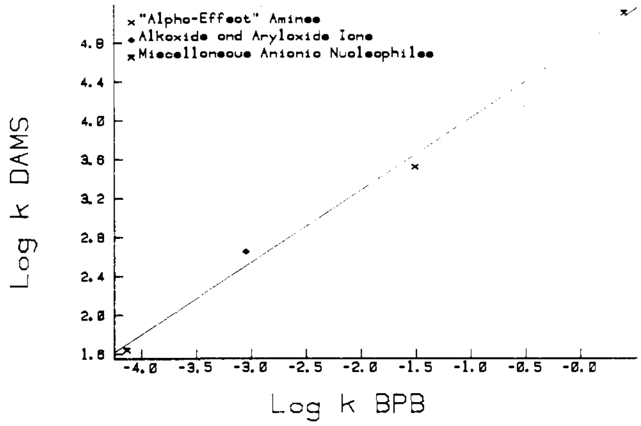


Figure 4. Reactions of nucleophiles with Bromphenol Blue vs. those with DAMS cation. The linear least-squares line shown is given by $\log k_{\mathrm{DAMS}} = 0.74 \log k_{\mathrm{BPB}} + 5.31$.

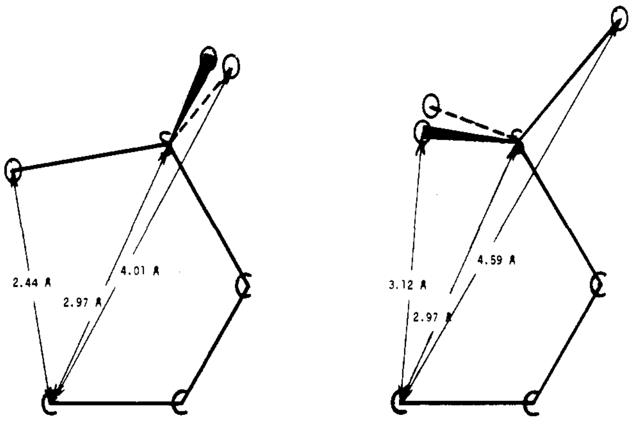
Dimethyl Ether, indicates a negative answer to this question.

The rather surprising absence of an effect of the negative charge of the sulfonate group on the relative reactivities of nucleophiles is further accentuated by the data for the reactions of Bromphenol Blue. The plot for reactions of this dinegatively charged electrophile vs. those of DAMS cation is shown in Figure 4. The neutral hydrazine nucleophile does not appear as exceptionally reactive relative to the anionic nucleophiles.

In retrospect, perhaps we should not have been surprised by this absence of electrostatic effects. In previous work,[2,10] we have commented several times on the fact that the relative reactivities of nucleophiles are generally the same toward neutral and cationic electrophiles and are not sensitive to the extent of delocalization of charge in various types of cations.

The very small effect of the negative charge of the sulfonate group on both the pK_R values and the spectral properties of the triarylmethyl cation, however, remain surprising even in retrospect. The difference in pK_R values for Phenol Red Dimethyl Ether and DAMS cation corresponds to only 1.3 kcal/mol in free energy, and the difference in wavelength of maximum absorbance is only 0.4 kcal/mol difference in excitation energy.

The long wavelength visible absorption band for triarylmethyl cations is believed to be associated with a sizable charge transfer from the central carbon to the aryl rings and conjugated para substituents.[12] We have carried out simple Hückel πMO calculations on di-*p*-anisyl, phenylmethyl cation using heteroatom parameters given by Streitwieser.[13] These calculations show a positive charge of ca. 0.7 unit on the central carbon of the ground state and a change of ca. 0.2 unit of charge on going from ground to first excited state, with small variations in these figures for various reasonable twist angles of the aryl groups.



5-e

5-s

Figure 5. Partial structure of Phenol Red Dimethyl Ether showing the distances between the central carbon and the oxygens and sulfur of the sulfonate group.

Table III. Electrostatic Energies

geometry[a]	charge distribution of group	energy[b]
5-e (SO_3^-)	S^{2+}, $3O^-$	−77.7 [e/*D*]
4-s (SO_3^-)	S^{2+}, $3O^-$	−61.5 [e/*D*]
5-e or 4-s (SO_3^-)	single charge on S–O bond projection on C–S bond	−99.6 [e/*D*]
5-s (SO_3^-)	single charge on most distant O	−72.2 [e/*D*]
5-e (CH_3SO_2)	S^{2+}, $2O^-$, CH_3 group trans	+4.7 [e/*D*]
5-s (CH_3SO_2)	S^{2+}, $2O^-$, CH_3 group trans	+10.7 [e/*D*]

[a] Geometries are shown in Figure 5. [b] Energies in units of kcal/mol are given as multiples of the ratio of charge on central carbon, e, to effective dielectric constant, *D*.

From these naive calculations, we expect a negative charge close to the central carbon to have an electrostatic effect on a process neutralizing the positive charge which is $^7/_2$ the energy effect on the excitation process. This ratio is embarassingly close to the factor of 3 observed for the pK_R process.

Although the electrostatic effect on pK_R is thus consistent with the effect on excitation energy, the magnitudes of both effects are much smaller than can easily be rationalized. We have done simple electrostatic calculations for the assumed pertinent geometries of Phenol Red Dimethyl Ether shown in Figure 5 and for several assumed charge distributions of the sulfonate and methylsulfone groups. Leaving the charge at the central carbon specified as "e" and the effective dielectric constant specified as "*D*", we obtain the energies reported in Table III. It is seen that a value of e/*D* of ca. 0.02 is required to rationalize the observed pK_R difference.

The proximity of the sulfonate group to the central carbon is such that solvent molecules certainly cannot interpose themselves between the charges. We would not expect an effective dielectric constant of greater than perhaps 4 to be applicable. Thus, the calculation would require that the charge on the central carbon is less than 0.08 unit, which appears to be unreasonably small.

The alternative to these conclusions would be to delocalize the negative charge of the sulfonate group some distance out into the solvent through hydrogen bonding. Such a situation has been suggested by Peterson[14] in a different context and is an attractive rationalization of our results.

Whatever the explanation of the small electrostatic effects observed, it is quite clear that the major effect of introducing the ortho-sulfonate group onto the di-*p*-anisyl, phenylmethyl cation is quite similar to that of introducing the ortho-methylsulfone

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(12) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists", John Wiley, New York, 1961, Chapter 8.

(13) Reference 12, p 135.

(14) P. E. Peterson and C. Dhansukh, *J. Org. Chem.*, **39**, 3684 (1974).

group and is quite likely of steric origin. The pK_R of the parent cation is −1.2; the cation has an absorbance maximum at 500 nm and reacts with water with a rate constant of 10^2 s^{-1} at 25 °C.[9b,15] The introduction of the ortho-methylsulfone group decreases the equilibrium constant for reaction with water by a factor of $10^{1.4}$, decreases the excitation energy of the cation by 2.5 kcal/mol, and decreases the rate constant for reaction with water by a factor of 10^3. It is curious, but not unprecedented, that the effect on the rate constant is larger than that on the equilibrium constant for the reaction with water.

Pertinence to Solvolysis Reaction Studies. The results presented here clearly indicate that variations in trapping ratios of solvolysis intermediates by various nucleophiles cannot be attributed to differing selectivities of ion pairs and free ions. There is, however, one point which should be made: our model ion pair is most probably similar to an "intimate" ion-pair intermediate. Although any electrostatic effect of counterion should be greater on the "intimate" than the "solvent-separated" ion pairs, there is evidence[9a,16] that the counterion of a solvent-separated ion pair can provide general-base catalysis for reaction of hydroxylic solvents. Such catalysis is usually weak compared with the "water-catalyzed" reaction[9a] and is not expected to cause large changes in rate, although observable effects on stereochemistry, for example, are expected.

We believe that the majority of the trapping results are explicable on the basis that the reactive anionic trapping nucleophile generally used in such studies reacts at diffusion-controlled rates with the highly reactive cations or ion pairs generated in solvolysis reactions. This suggestion has been implied a number of times, and the idea was cleverly used by Jencks[17] to estimate rate constants for reactions of oxocarbonium ions with water from observed trapping ratios. Rappoport[18] has pointed out that it is almost inconceivable that even the relatively stable benzhydryl cations could react with azide ion at less than diffusion-controlled rates.

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Conformational Analysis of Linear Peptides. 2. A Vapor-Pressure Osmometry Study of Self-Association in Chloroform

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Abstract: Activity coefficients, γ, and practical osmotic coefficients, ϕ, measured by vapor-pressure osmometry, are reported for biphenyl, benzoic acid, and six amino acid derivatives and peptides, all in chloroform solutions at 36 °C. Consecutive molal self-association constants are calculated from the data by attributing the osmotic nonideality to self-association. Values for the dimerization step are as follows: Ac-L-Nva-OMe, $K_2 = 1.18$ m^{-1}; Ac-L-Val-OMe, $K_2 = 1.33$ m^{-1}; and *t*-Boc-Gly-L-Val-Gyl-OMe, $K_2 = 6.59$ m^{-1}. The data for Ac-L-Val-Gly-OMe reveal a significant concentration of trimers and give values of $K_2 = 37.7$ m^{-1} and $K_3 = 1086$ m^{-2}. Comparable measurements on benzoic acid yield $K_2 = 52.4$ m^{-1} and $K_3 = 878$ m^{-2}. The temperature dependence of self-association in *t*-Boc-Gly-L-Val-Gly-OMe was measured, providing values of $\Delta H = -27$ kJ (mol dimer)$^{-1}$ and $\Delta S = -71$ J K^{-1} (mol dimer)$^{-1}$. Corollary infrared absorption data are presented as independent evidence of molecular association. Solutions of *t*-Boc-L-Val-OMe and *t*-Boc-L-Nva-OMe display osmotic nonidealties too small to attribute to self-association, as do biphenyl solutions.

Considering the importance of self-association to the question of interpreting peptide spectroscopic data, especially in relatively nonpolar solvents, little quantitative work has been reported in the literature.[3,4] We felt the present study was necessary in order to arrive at a proper interpretation of our own high-resolution ^{1}H NMR measurements on a series of linear oligopeptides in chloroform.[5] We report here the results of a vapor pressure osmometry study of Ac-L-Nva-OMe,[6] *t*-Boc-L-Nva-OMe, Ac-L-Val-OMe, *t*-Boc-L-Val-OMe, Ac-L-Val-Gly-OMe, and *t*-Boc-Gyl-L-Val-Gly-OMe.

The principles and practice of vapor-pressure osmometry have been reviewed.[7–9] A matched pair of thermistors is located in a thermally equilibrated chamber saturated with solvent vapor. A drop of pure solvent is placed on one of the thermistor beads; the other bead holds a drop of solution. Since the vapor pressure of the solvent in the drop of solution is lower than that of pure solvent, solvent vapor will condense on the solution drop at a

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(2) University of Padova.

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