observed here is quite comparable to that noted earlier in the activation volume. We therefore feel justified in concluding that the chlorine KIE supports the notion expressed earlier that the special effect of pressure on hindered Menschutkin reactions reflects the differences in position of the transition states along the reaction coordinate.

Our result is in agreement with that of Berg,[13] who deduced a similar variation in the transition state location in the methylation of 2-substituted pyridines on the basis of a selectivity relationship, and with that of Swain,[14] who found that amines and enolates have an earlier transition state than iodide as nucleophiles in their reactions with methyl chloride, but in contrast with another result by Swain:[15] the KIE in the reaction of methyl chloride with triethylamine is smaller than in the faster reaction with quinuclidine. The special explanation for this observation does evidently not apply in the reactions compared here.

Finally, it may be noted that our result is near the low end of the range of chlorine isotope effects reported so far (1.001–1.010).[16] The implication is that Menschutkin reactions have early transition states; this inference is supported by several other literature reports concerning this reaction.[17]

Acknowledgment. This work was supported by funds from the National Science Foundation. We thank Dr. Carol A. Miller for discussion regarding the statistical analysis. The mass spectrometric measurements were made on the Nuclide mass spectrometer of the Department of Chemistry, University of Wisconsin, Madison, Wis. This paper is dedicated to Professor Egbert Havinga of the Gorlaeus Laboratorium of Leiden on the occasion celebrating his attainment of emeritus status.

Note Added in Proof: Further support for transition state progression along the reaction coordinate in a Menschutkin reaction as a function of substituents has recently been claimed on the basis of ^{14}C isotope effects. [H. Yamataka and T. Ando, *J. Am. Chem. Soc.*, **101**, 266 (1979)].

Registry No.—Pyridine, 110-86-1; CH_3Cl, 108-48-5; 2,6-lutidine, 74-87-3.

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Triple Bond Participation in the Solvolysis of Soluble Sulfonates in Water and Water–Sulfuric Acid

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Received November 3, 1978

The solvolysis of a sulfonate of 6-octyn-2-ol (**1**, X = (CH_3)) with triple bond participation to give **4** and **5** (Scheme I) was reported in our laboratories in 1966,[1] following our preliminary report of triple bond participation in the solvolysis of 6-heptyn-2-yl tosylate.[2] Other types of triple bond participation were reported at approximately the same time.[3]

The reaction of **1** to give the five-membered ring ketone **5** may be considered to be the model reaction for the formation of ring D in Johnsons' spectacular steroid syntheses involving olefinic and acetylenic cyclization.[4] The triple bond "terminator" has, in fact, been a key element in several studies from the Johnson group, since other likely terminators gave complex rearrangements, presumably involving 1,2 shifts.[5]

We have now studied the reaction of Scheme I in water (containing 2% acetone) and water–sulfuric acid, using the water-soluble *p*-(trimethylammonio)benzenesulfonate **1a** (amsylate) or the *p*-(dimethylamino)benzenesulfonate **1b** (damsylate?). The use of the quaternary sulfonates has recently been introduced by Sukenik and Bergman.[6] The relative amounts of products, **4** and **5**, from triple bond participation and that, **6**, from solvent displacement are given in Table I. The results of Table I correspond to 52% cyclization in water. Increasing cyclization occurs as increasing amounts of H_2SO_4 in water are used. In 67% H_2SO_4, quantitative cyclization (>99%) is the result. The uncyclized alcohol (**6**, OR=OH) is stable under the reaction conditions.

Since previous cyclizations were conducted in relatively nonnucleophilic solvents (CH_3CO_2H, HCO_2H, and particularly CF_3CO_2H), the substantial amount of cyclization in water may appear to be surprising. However, recent advances in the understanding of solvolysis reactions[7,8] allow us to replace intuition with quantitiative estimates of the relative amounts of participation and normal solvolysis (k_Δ/k_s, Scheme I). The k_Δ and k_s processes of Scheme I may be assumed to follow eq 1 and 2, respectively.

$$\log (k_\Delta^A/k_\Delta^B) = 0.86 Y_A^B \quad (1)$$

$$\log (k_s^A/k_s^B) = 0.3 N_A^B + 0.77 Y_A^B \quad (2)$$

Here N_A^B and Y_A^B are the respective changes in nucleophilicity and ionizing power upon changing from solvent A to solvent B. Numerical values for the sensitivities to nucleo-

Table I. Ratio of Cyclization to Substitution in the Solvolysis of 6-Octyn-2-yl Sulfonates in H_2O and H_2O–H_2SO_4

amsylate[a]		damsylate[b]	
% H_2SO_4 (w/w)	product ratio (cyclic/acyclic)	% of H_2SO_4 (w/w)	product ratio (cyclic/acyclic)
0.0	1.08	14.0	0.81
0.72	1.07	31.0	1.98
18.3	1.62	43.0	4.10
45.1	5.54	50.0	8.28
55.8	13.10	56.0	13.4
		59.0	16.5
		62.0	24.1
		65.0	57.5
		67.0	115

[a] *p*-(Trimethylammonio)benzenesulfonate (trifluoromethanesulfonate salt). [b] *p*-(Dimethylamino)benzenesulfonate.

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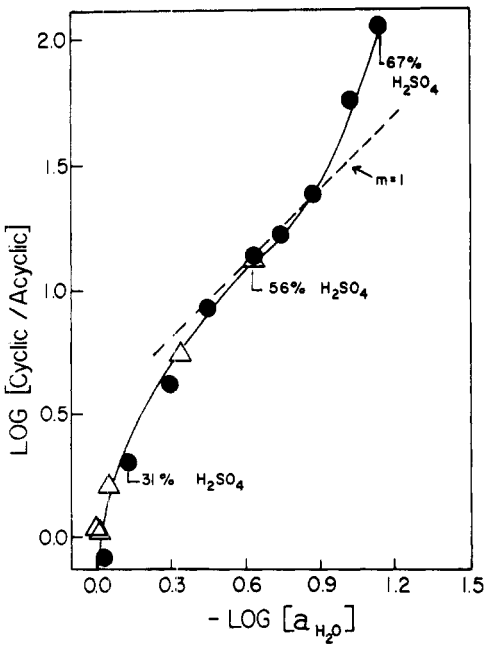


Figure 1. Plot of the logarithm of the ratio of cyclic to acylic solvolysis products (Table I) vs. the activity of water in H_2O–H_2SO_4: (△) *p*-(trimethylammonia)benzenesulfonate **1a**. (●) *p*-(dimethylamino)-benzenesulfonate **1b**.

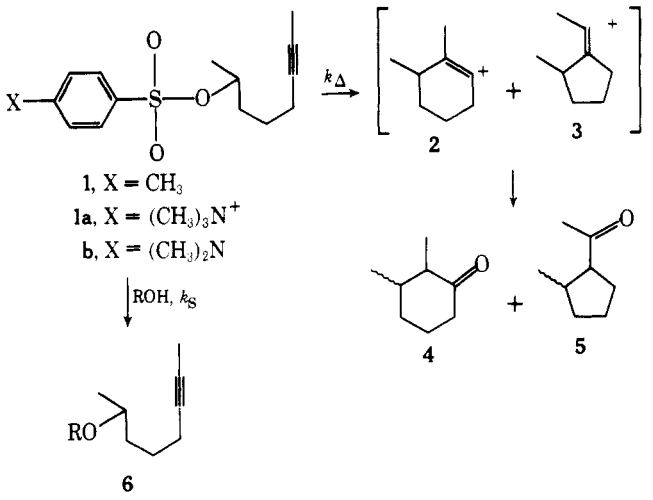
philicity and ionizing power have been chosen by comparison with model compounds. The letter designations *s* and m[8] or *l* and m[7] have been used for these parameters. Based on extrapolation of data for water–ethanol, we take Y^{H_2O} to be 2.49 and N^{H_2O} to be −0.04.

The calculated ratios of cyclization product (**4** + **5**) to substitution product (**6**) in water are 0.68 (based on data in HCO_2H)[2] or 0.61 (from data in CH_3CO_2H). The observed ratio is 1.1 close to the calculated values. Two factors might lead to gross departures from expectation in water. One is micelle formation. Sukenik and Bergman[6] state that sulfonates comparable to **1** are micellar in water, but effects upon rates and products of reactions are not discernable in their study or ours. The second factor is a possible preference for a coiled conformation of **1** in water, attributable to hydrophobic effects, as postulated for squalene in dioxane–water.[9] In practice neither of the above-mentioned special effects appears to perturb the amount of cyclization observed. Instead, the *sN* + *mY equation predicts the behavior of water as a solvent.*

Our results show that the use of water or acid-soluble sulfonates opens a window not only to phenomena in water, but also to aspects of reactions in water–H_2SO_4. It is interesting to plot (cf. Figure 1) the log of our product ratio vs. the log of the water activity, a_{H_2O}.[10] A unit slope (dotted line) is expected if k_s is proportional to a_{H_2O} and if there is no change in ionizing power over the range of H_2O–H_2SO_4 mixtures (or if the effect of changing ionizing power cancels for k_s and k_Δ). It may be seen that over parts of the concentration range, the ratio is more sensitive to the concentration of H_2SO_4 than the above-mentioned assumption predicts. In this connection we note that concentrated H_2SO_4 has been found to be a solvent of very low nucleophilicity.[11] The cost advantage of using H_2O–H_2SO_4 instead of other solvents of low nucleophilicity is so substantial that cyclizations on a preparative scale should now be considerably more attractive.

It is noteworthy that the *p*-(dimethylamino)benzenesulfonate **1b** was soluble by protonation in H_2O–H_2SO_4 and gave product ratios indistinguishable from those obtained from the less accessible *p*-(trimethylammonio) derivative (cf. Figure 1). A principal barrier to the preparation of *p*-(dimethylamino)benzenesulfonates via the sulfonyl chloride has been the lack of reproducibility and low yield of the two-phase

Scheme I



methylation of sodium *p*-(aminobenzene)sulfonate with Me_2SO_4 in the presence of NaOH–H_2O.[12] We have now accomplished this preparation by a reductive methylation procedure which makes the pure sodium salt of *p*-(dimethylamino)benzenesulfonic acid available in large quantities and high yield.

It is of interest that the dimethylamino group of *p*-(dimethylamino)benzenesulfonates is an electron-releasing substituent until it is protonated. Accordingly, these sulfonates potentially are unusually stable until they are activated in acidic solvolysis solvents. (The methyl derivative, however, gives N-methylation in the solid phase.[6b]) That formic acid is sufficient to accomplish activation of $N(CH_3)_2$ by protonation was shown by solvolysis of 6-octyn-2-yl damsylate **1b** in formic acid. The first order solvolysis, followed in an NMR probe, was faster than that of the previously studied tosylate by a factor of approximately 7.5.

Experimental Section

Sodium *p*-(Dimethylamino)benzenesulfonate. To 200 mL of H_2O, 0.4 mol of sulfanilic acid and 0.4 mol of NaOH were added with stirring. Additional water was added to increase the volume to ~400 mL. Then 80 mL of 37% aqueous formaldehyde (0.84 mol) and 2 g of 10% Pd on charcoal were added. The mixture was hydrogenated in a Parr hydrogenator for 56 h at 4 atm (absolute). Consumption of half the H_2 required 14 h. (If gray, technical sulfanilic acid was used, hydrogenation occurred only if the hydrogenation mixture was pretreated with activated charcoal.) The partially crystallized reaction product was dissolved by heating. Activated charcoal was added. Filtration using filteraid and cooling to 4 °C gave crystalline sodium *p*-(dimethylamino)benzenesulfonate, 92%, showing no impurities by ^1H NMR.

2-Oct-6-ynyl *p*-(Dimethylamino)benzenesulfonate (Damsylate). The sulfonyl chloride[6] was allowed to react with the alcohol in pyridine at approximately 4 °C for 3 days. Isolation using HCl (30 mL 12 M), ice (100 g), and ether (3 × 50 mL) gave an extract which upon concentration gave crystals, 43%: mp 56.5–57.7 °C; NMR δ 1.25 (d), 1.73 (t), 3.06 (s), 4.57 (sextuplet), 6.68 (d), 7.72 (d).

2-Oct-6-ynyl *p*-(Trimethylamino)benzenesulfonate Trifluoromethanesulfonate. The reported procedure[6b] was used. The damsylate **1b** (1g) was allowed to react for 5 h at 0 °C with methyl trifluoromethanesulfonate (400 μL) in $CHCl_3$ (10 mL). Precipitation of the product with hexane gave a solid: NMR ($CDCl_3$) δ 1.27 (d), 3.75 (s) (quaternary ammonium methyl), 4.77 (sextuplet), 7.89 (d), 8.09 (d).

Solvolyses of 6-Octyn-2-yl Damsylate and Amsylate. For the amsylate solvolyses reported in Table I 0.4 mL of acetone solution containing 0.1 g of amsylate was added to 20 mL of magnetically stirred aqueous solution at 25 °C in a 50 mL Erhlenmeyer flask. After 15 min of reaction time, the mixture was poured into a separatory funnel, diluted with 200 mL of H_2O, then extracted three times with 8-mL portions of $CHCl_3$. The $CHCl_3$ solution was dried with $MgSO_4$ and reduced to approximately 0.5 mL volume by distillation of the chloroform through a 0.5 m Vigreaux column at room temperature and approximately 120 mm Hg pressure. Then the $CHCl_3$ solution

was analyzed by gas chromatography on a 10% tris(cyanoethoxy)-propane column (80–100 mesh Chromosorb C-AW-DCMS support in a stainless steel, 2.4 mm inside diameter, 2.7 m column). Peak identifications were established as described in ref 2. The same procedure was followed for damsylate solvolyses, but only 0.06 g of damsylate was used for each solvolysis.

Registry No.—1a·trifluoromethanesulfonate, 68854-29-5; **1b**, 68854-30-8; **4**, 13395-76-1; **5**, 1601-00-9; **6**, 24395-07-1; sodium *p*-(dimethylamino)benzenesulfonate, 2244-40-8; sulfanilic acid, 121-57-3.

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Direct Fractionation Procedure, an Improved Technique for the Quantitative Isolation of Highly Purified Chromate(VI) Oxidation Products by Utilizing Porous Styrene–Divinylbenzene Copolymer Gel–Liquid Chromatography

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Received September 5, 1978

For the isolation of the products from synthetic reaction mixtures, multiple and discontinuous separation techniques such as extraction, distillation, recrystallization, or sublimation have been generally adopted. Such separation procedures are not only tedious and time consuming but also inefficient, causing a significant loss of products and in many cases leading to contamination of the products. Because each process is carried out manually, experimental results often depend heavily on the technical skill of the laboratory worker himself. Also, these methods are not generalizable, and the details of an isolation procedure must be tailored to fit the conditions met within a particular synthesis.[1]

One of the authors (Hara) has been trying to generalize and to systematize the separation procedures in organic synthesis in order to do away with tedious traditional experimental techniques.[2,3] To achieve this, a direct fractionation technique using high-performance liquid chromatography has been developed.[3] The procedure was designed to simplify and speed up isolation procedures, while providing for quantitative isolation of a highly purified product. We wish to report here an improved technique for the isolation of chromate oxidation products as an example of this scheme.

Chromate(VI) oxidation has been used very often as an important synthetic method. However, the isolation procedure used in this reaction is troublesome. Multiple extraction is required in the first stage to insure complete removal of the chromate and other polar substances. This often results in loss of products. In order to fundamentally improve the separation procedure, a single-step resolution of the polar inorganic and less polar organic substances in the chromate oxidation products has been extensively investigated. In a model experiment, the individual components of a crude reaction mixture were directly injected into a column packed with various materials and retention behaviors of the compounds were experimentally determined. A reversed phase column[4] packed with a porous styrene–divinylbenzene copolymer gel was found to exclude inorganic salts such as chromates(III and VI) by using methanol/water as an eluent. For example, the capacity factor of chromate(VI) in the case of the methanol/water (9:1 v/v) system was nearly equal to zero. On the other hand, organic compounds were retained and could be separated from each other. Retention of the solutes on the column was intensified when the water content in the mobile phase increased. The retention was also strengthened when the polarity of functional groups in the organic solutes decreased or the number of carbons in the solutes increased.[5]

These results suggest that the clean up of crude reaction mixtures and separation of the organic products can be accomplished in a single step by using liquid chromatography

Table I. Application Examples of Direct Liquid Chromatographic Isolation Procedure for Chromate(VI) Oxidation Products

ref	substrate	registry no.	reagent	methanol water (v/v)[i]	*j*	g of substrate[k]	product yield %	product yield lit. %	recovered %
6	cholesterol	57-88-5	$Na_2Cr_2O_7$, CH_3CO_2H, C_6H_6	1:0	4-choletene-3,6-dione,[c] 6.1; cholesterol, 10.3; CH_3CO_2H, 0.1	3.5	71	39–40	
7	*p*-nitrotoluene	99-99-0	CrO_3, H_2SO_4, $(CH_3CO)_2O$	4:1	*p*-nitrobenzal diacetate,[d] 5.4; *p*-nitrotoluene, 8.3	6.4	95	65–66	
8	naphthalene	91-20-3	CrO_3, CH_3CO_2H	9:1	1,4-naphthoquinone,[a,e] 3.8; naphthalene, 7.3	1.6	35	18–22	62
9	1-decanol	112-30-1	$CrO_3(C_5H_5N)_2$, CH_2Cl_2	4:1	decanal,[f] 2.5; 1-decanol, 1.9	0.5	94	63–66	
10	indene	95-13-6	$K_2Cr_2O_7$, H_2SO_4	9:1	homophthalic acid,[g] 2.5; indene, 7.8	6.3	81	66–77	
11	2-acetylfluorene[b]	781-73-7	$Na_2Cr_2O_7$, CH_3CO_2H	20:1	9-oxo-2-fluorenecarboxylic acid,[h] 1.8; 2-acetylfluorene, 2.3	5.8	78	67–74	

[a] Colorless crystals. Yellow needles were obtained in the literature.[8] [b] Starting material was synthesized from fluorene by the procedure described in "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1952, p 23. [c] Registry no. 984-84-9. [d] Registry no. 2929-91-1. [e] Registry no. 130-15-4. [f] Registry no. 112-31-2. [g] Registry no. 89-51-0. [h] Registry no. 784-50-9. [i] Solvent system for polystyrene gel LC. [j] Capacity factor of products, substrate, and medium solvent. [k] Quantity injected.

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