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THE NUCLEOPHILICITY OF AQUEOUS TRIFLUOROETHANOL

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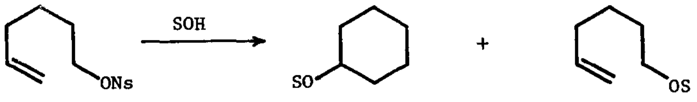
Intramolecular nucleophilic displacement reactions hold a position of great importance in synthetic and biological chemistry.[1] Recently Schleyer and his coworkers have shown that nucleophilic assistance from solvent competes strongly with other ionization processes,[2] indicating that successful intramolecular nucleophilic displacements should require the use of a solvent which is sufficiently polar to support ionic reactions, but at the same time is relatively non-nucleophilic. 2,2,2-Trifluoroethanol has been shown[3-7] to possess these characteristics; moreover, the use of aqueous trifluoroethanol also permits determination of solvolysis rates by the conductivity method.[5] We have carried out an investigation of a series of aqueous trifluoroethanol mixtures in order to determine those solvent compositions which possess the optimum combination of high ionizing power and low nucleophilicity.

Until recently the only available solvents of low nucleophilicity and high ionizing power have been those of the carboxylic acid series (i.e., formic and trifluoroacetic acids), and their acidity frequently results in undesired side reactions of the substrate or products. Aqueous trifluoroethanol is far less acidic[5] and appears to exhibit an excellent combination of high ionizing power and low nucleophilicity. This was demonstrated by Trahanovsky and Doyle[4] who found that in trifluoroethanol 5-hexenyl p-nitrobenzenesulfonate (1) undergoes intramolecular nucleophilic displacement (giving mainly 2) in 80-90% yield; in contrast acetolysis of 1 yields 3 via direct solvent displacement to the extent of 50-80%.[8]



1 2 3

We have used the analysis of Bentley, Schadt and Schleyer[9] (equation 1) to explicitly evaluate the nucleophilicities (N_{BS}) of a series of aqueous trifluoroethanol mixtures.

$$N_{BS} = \log (k^{CH_3OTs}/k_o^{CH_3OTs}) - 0.30\ Y \qquad (1)$$

Equation (1) represents a modification of Winstein's original method[10] for correlation of solvolysis rates according to equation (2). In order to assess solvent nucleophilicities

$$\log (k/k_o) = \ell\ N + m\ Y \qquad (2)$$

Bentley, Schadt and Schleyer utilized methyl tosylate as the model compound and assigned its ℓ-value (response to solvent nucleophilicity) as unity; the m-value of 0.30 is that determined from solvolysis in acetic and formic acids which appear to have very similar nucleophilicities. The Y-value (solvent ionizing power) retains its original meaning,[10] and k and k_o refer to the rate constants for solvolysis in the solvent under investigation and in 80% aqueous ethanol respectively. The rate constants for solvolysis of methyl tosylate in aqueous trifluoroethanol are listed in Table I, and the calculated values of solvent nucleophilicity are shown in Table II together with selected data from the literature.

Inspection of Table II reveals that in accord with earlier qualitative estimates[3-6] the aqueous trifluoroethanol solvents are indeed quite non-nucleophilic. While Bentley and Lacadie[7] concluded that 97 wt. % trifluoroethanol and formic acid have similar nucleophilic properties, our results show that the former is somewhat less nucleophilic. It should be noted that solvolysis rates in aqueous trifluoroethanol may be inaccurately predicted with Y-values based on t-butyl chloride.[11,12] Using Y_{Ad} (based on 1-adamantyl bromide[11]) the values of N_{BS} for the aqueous trifluoroethanol solvents would be still more negative.

Also listed in Table II are values of % Cyclization for a substrate analogous to **1** for which direct displacement (k_s) in 80% ethanol is faster than cyclization (k_Δ) by a factor of 50. Relative values of k_s and k_Δ in each solvent were calculated with eq. (2) using parameters typical of a primary substrate[9] (for k_s: $\ell = 0.85$, $m = 0.4$) and of a participating substrate[11] (for k_Δ: $\ell = 0$, $m = 0.6$). The values of % cyclization calculated using eq. (3) are in good agreement with experimental data reported for compound **1** (see footnotes to Table II).

$$\%\ \text{Cyclization} = 100\ k_\Delta/(k_s + k_\Delta) \qquad (3)$$

Table I. Solvolysis of Methyl Tosylate in Aqueous Trifluoroethanol Mixtures.[a]

Solvent[b]	Temp. (°C)	k (sec^{-1})	$\Delta H^{\dagger}$ (kcal/mol)	$\Delta S^{\dagger}$ (e.u.)
97 wt. %	124.7	$(5.38 \pm 0.50) \times 10^{-5}$	20.0	-28.5
	99.8	$(9.35 \pm 0.22) \times 10^{-6}$		
	50.0[c]	1.28×10^{-7}		
1:1 (mol/mol)[d]	99.7	$(9.32 \pm 0.30) \times 10^{-5}$	22.1	-18.2
	75.85	$(1.14 \pm 0.07) \times 10^{-5}$		
	50.0[c]	8.23×10^{-7}		
70 wt. %	99.8	$(2.59 \pm 0.03) \times 10^{-4}$	17.7	-27.9
	74.8	$(4.34 \pm 0.01) \times 10^{-5}$		
	50.0[c]	5.64×10^{-6}		
50 wt. %	99.7	$(9.61 \pm 0.16) \times 10^{-4}$	20.7	-17.2
	74.9	$(1.22 \pm 0.07) \times 10^{-4}$		
	50.0[c]	1.13×10^{-5}		

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[a] Determined conductimetrically. [b] Percentages refer to trifluoroethanol; the remainder is water. [c] Extrapolated from data at other temperatures. [d] 84.5 wt. %.

Table II. Nucleophilicities of Various Solvents.[a]

Solvent	CH_3OTs, $k_{50°}$ (sec^{-1})	N_{BS}	Y	% Cyclization[b]
80% CH_3CH_2OH[c]	2.22×10^{-5}	0.00	0.00	2
50% CH_3CH_2OH[c]	4.41×10^{-5}	-0.20	1.66	6
97 wt. % CF_3CH_2OH[d]	1.28×10^{-7}	-2.59	1.15	84[e]
1:1 (mol/mol) CF_3CH_2OH[d]	8.23×10^{-7}	-1.83	1.35	57
70 wt. % CF_3CH_2OH[d]	5.64×10^{-6}	-1.09	1.66	27
50 wt. % CF_3CH_2OH[d]	1.13×10^{-5}	-0.96	2.23	27
CH_3CO_2H[c]	6.32×10^{-8}	-2.05	-1.64	34[f]
HCO_2H[c]	8.3×10^{-7}	-2.05	2.05	74[g]

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[a] From eq. (1). [b] See text. [c] Data from ref. 9. [d] This work. [e] Cf. 78-93% cyclization in 100% CF_3CH_2OH (ref. 4). [f] Exptl. value, 20-40% (ref. 8). [g] Exptl. value, 60-73% (ref. 13).

The data indicate that cyclization yields in aqueous trifluoroethanol will be greatest when the water content of the solvent is minimized. On the other hand, solvolytic reactions can be reversible in anhydrous trifluoroethanol, and in the absence of small amounts of water deviations from limiting behavior are too large for rates to be determined conductimetrically. A non-nucleophilic medium with high ionizing power and low acidity is often required when intramolecular displacement reactions are attempted for either synthetic or mechanistic investigations. Our data shows that for such studies 97 wt. % trifluoroethanol is clearly the solvent system of choice. Table II indicates that in cases where traditional solvolysis media such as acetic acid and 80% ethanol do not afford useful amounts of cyclization, the use of aqueous trifluoroethanol can give rise to good yields of cyclic products.

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