Neighboring Group Competition Revisited: Relative Abilities of Cyclobutyl/ Cyclopentyl/Phenyl Groups To Stabilize an Electron-Deficient Carbon

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In previous solvolytic[1] investigations of neophyl-like systems, it was proposed that cycloalkyl assisted ionization occurs prior to phenyl rearrangement. By measuring the acetolysis rates of a series of [1-(*p*-X-phenyl)-cyclopropyl]carbinyl[1a] tosylates (**3**) and the acetolysis and 2,2,2-trifuoroethanolysis (TFE) rates of a series of [1-(*p*-X-phenyl)-cyclobutyl]carbinyl[1b,1c] brosylates (**4**) and [1-(*p*-X-phenyl)cyclopentyl]carbinyl[1d] tosylates (**5**), and by comparing their (k^{OMe}/k^{NO_2}) rate ratios with those of similarly substituted neophyl derivatives; we were able to propose that their solvolyses take place by a k_Δ process[1d,2] involving strong σ-participation[3] by the three-membered ring in series **3**, moderate σ-participation by the four-membered in series **4**, and weak σ-participation by the five-membered ring in series **5**.

Some time ago, it was observed[4a,b] that neophyl triflate solvolyzes slower in 70% TFE than in 97% TFE. This TFE anomaly (increasing rate with decreasing ionizing power)[5a] was attributed to enhanced ability of TFE to solvate bridged carbocation ion pairs. Elsewhere,[1b,6] on the basis of $\Delta S^\ddagger$ data[7] obtained from the solvolysis of various cycloalkylcarbinyl substrates, it was also proposed that solvolysis in TFE took place with enhanced carbocation solvation.

Prompted by these mechanistic findings, we decided to reinvestigate our assessment of the neighboring group ability of the cyclobutyl and cyclopentyl groups versus that of the phenyl group by studying the solvolysis of the neophyl-like systems **4** and **5** in 97% and 70% aqueous TFE. This paper reports the results of this study.

The data indicate that 1-phenylcyclobutylcarbinyl brosylate (**4a**) and 1-phenylcyclopentylcarbinyl tosylate (**5a**) undergo solvolysis in 97% and 70% TFE via a two-stage mechanism involving a first-formed cationic center stabilized significantly by charge delocalization into the cycloalkyl rings and a subsequent solvent-separated ion pair stabilized by charge delocalization into the phenyl ring.[1]

Table 1. Solvolysis Rate Constants Determined in This Study

compound	solvent[a]	temp, °C	k, s^{-1}
2-adamantyl-OTs (**1**)	97% TFE	30	3.3×10^{-6} [b]
	70% TFE	30	4.8×10^{-6} [b]
neophyl-OTs (**2**)	97% TFE	30	7.23×10^{-6} [c]
	70% TFE	30	5.44×10^{-6}
c-PrCarb-OPms (**3**)[d]	97% TFE	25	1.56×10^{-3} [e]
	70% TFE	25	1.9×10^{-3}
1-Ph-c-BuCarb-OBs (**4a**)[f]	100% TFE[g]	30	1.5×10^{-5} [h]
	100% TFE[g]	45	1.55×10^{-4} [h]
	70% TFE	30	1.3×10^{-5}
	70% TFE	45	1.1×10^{-4}
1-p-NO_2Ph-c-BuCarb-OBs (**4b**)[i]	100% TFE[g]	45	4.5×10^{-6} [h]
	97% TFE	55	1.7×10^{-5}
	70% TFE	45	6.22×10^{-6}
	70% TFE	55	2.4×10^{-5}
1-Ph-c-PnCarb-OTs (**5a**)[j]	97% TFE	35	1.42×10^{-5} [k]
	97% TFE	45	6.5×10^{-5} [k]
	70% TFE	35	1.42×10^{-5}
	70% TFE	45	4.6×10^{-5}
1-*m*,*m*′-CF_3Ph-c-BuCarb-OTs (**5b**)[l]	97% TFE	55	1.2×10^{-7} [k]
	97% TFE	65	3.9×10^{-7} [k]
	70% TFE	55	2.4×10^{-7}
	70% TFE	65	8.3×10^{-7}
1-*p*-anisyl-c-PnCarb-OTs (**5c**)[m]	97% TFE	30	7.6×10^{-4} [k]
	97% TFE	35	1.3×10^{-3} [k]
	70% TFE	30	4.05×10^{-4}
	70% TFE	35	6.8×10^{-4}
cyclobutylcarb-OBs (**6**)[n]	100% TFE	45	7.1×10^{-5} [o]
	70% TFE	45	1.31×10^{-4}
cyclopentylcarb-OBs (**7**)[p]	100% TFE	45	2.2×10^{-6} [o]
	70% TFE	45	4.3×10^{-6}
neopentyl-OTs (**8**)	97% TFE	45	3.4×10^{-8}
	97% TFE	55	1.25×10^{-7}
	70% TFE	45	6.0×10^{-8}
	70% TFE	55	2.1×10^{-7}

[a] Percent by weight. [b] Data taken from ref 11a. [c] Reference 14. [d] Cyclopropylcarbinyl pentamethylbenzenesulfonate. [e] Reference 8a. [f] 1-Phenylcyclobutylcarbinyl brosylate. [g] In our hands, and elsewhere (ref 25), we find little difference in rate between 100% and 97% TFE. [h] Reference 1b. [i] 1-*p*-Nitrophenylcyclobutylcarbinyl brosylate. [j] 1-Phenylcyclopentylcarbinyl tosylate. [k] Reference 1d. [l] 1-[3,5-Bis(trifluoromethyl)phenyl]cyclopentylcarbinyl tosylate. [m] 1-(*p*-Methoxyphenyl)cyclopentylcarbinyl tosylate. [n] Cyclobutylcarbinyl tosylate. [o] Reference 6. [p] Cyclopentylcarbinyl tosylate.

The synthesis of all compounds listed in Table 1 was accomplished by known procedures.[1b−d,5b,6,8] The kinetic data for all compounds studied are also listed in Table 1. Each of these esters was allowed to solvolyze in the indicated solvents, and the course of each reaction was followed by titrating the liberated arenesulfonic acid. All reactions were strictly first order in the liberated arenesulfonic acid up to at least 75% conversion[9] and furnished, within experimental error, 100% of the theoretical amount of acid present. In Table 2 we have listed the calculated k_{70TFE}/k_{97TFE} ratios for (**2**−**8**) as well as that of adamantyl tosylate, the well-accepted k_c model[10] for

(1) (a) Roberts, D. D.; Watson, T. M. *J. Org. Chem.* **1970**, *35*, 978−981. (b) Roberts, D. D. *J. Org. Chem.* **1974**, *39*, 1265−1269. (c) Roberts, D. D. *J. Org. Chem.* **1976**, *41*, 486−489. (d) Roberts, D. D.; Arant, M. E. *J. Org. Chem.* **1994**, *59*, 6464−6469.

(2) For a review of the Winstein solvolysis scheme, see: Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1−67.

(3) Stoelting, D. T.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 1695−1705.

(4) (a) Shiner, V. J., Jr.; Seib, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 862−864. (b) A later report[4c] for neophyl tosylate confirmed Shiner's finding. (c) Fujio, M.; Goto, M.; Funatsu, K.; Yoshino, T.; Saeki, Y. *Bull. Soc. Chem. Jpn.* **1992**, *65*, 46−54.

(5) (a) Which stands in sharp contrast to the linear correlation between the log *k* values for neophyl and 2-adamantyl tosylates for a range of varying acetic/formic acid mixtures and alcohol/water mixtures.[5b] (b) Roberts, D. D. *J. Org. Chem.* **1984**, *49*, 2521−2526.

(6) Roberts, D. D.; Wu, C.-H. *J. Org. Chem.* **1974**, *39*, 1570−1575.

(7) The $\Delta S^\ddagger$ values reported for the trifluoroethanolysis of cyclobutylcarbinyl and cyclopentylcarbinyl brosylates are about 10 eu more negative than the corresponding acetolysis values.

(8) (a) Roberts, D. D.; Snyder, R. C.; Jr. *J. Org. Chem.* **1979**, *44*, 2860−2863. (b) Roberts, D. D.; Snyder, R. C., Jr. *J. Org. Chem.* **1980**, *45*, 4052−4056.

(9) The neopentyl tosylate runs at 45 °C were followed up to at least 55% conversion.

(10) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5466−5475.

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Table 2. k_{70Tfe}/k_{97Tfe} Rate Ratios and Types of Rearranged Products[a]

compound	k_{70TFE}/k_{97TFE}	temp, °C	rearrangement[b]
1	1.5	30	none[c]
2	0.8	30	phenyl[d,e,f]
3	1.2	25	cyclopropyl[f,g]
4a	0.9	30	phenyl[f,h]
	0.7	45	
4b	1.4	45	phenyl[f,h]
	1.4	55	
5a	0.7	35	phenyl[i]
	0.7	45	
5b	2.0	55	cyclopentyl[i]
	2.1	65	
5c	0.5	30	phenyl[i]
	0.5	35	
6	1.8	45	cyclobutyl[j]
7	1.9	45	cyclopentyl[j]
8	1.8	45	methyl[f,k,l]
	1.7	55	

[a] Solvolysis products of all listed substrates yielded almost exclusively rearranged products. [b] Rearrangement by phenyl means that a phenyl (or aryl) group has migrated from a neighboring carbon to the reaction site carbon; rearrangement by cycloalkyl means that an alkyl ring has expanded from either a three- to a four-membered ring, or a four- to a five-membered ring, or a five- to a six-membered ring. [c] Reference 11a. [d] Reference 11b. [e] Reference 11c. [f] In acetic acid. [g] Reference 26. [h] Reference 1c. [i] Reference 1d. [j] Reference 11d. [k] Reference 11e. [l] Reference 11f.

measuring response to changing solvent ionizing power. The type of rearranged product, either cycloalkyl or phenyl, which was previously reported[1c,d,11a−f] for substrates **2**−**8** is also given in Table 2.

Discussion

On the basis[1d,12] that primary solvolysis occurs by two discrete pathways—k_s, nucleophilically solvent assisted which leads to only unrearranged products, and k_Δ, neighboring group assisted which leads to only rearranged products—the observation that all the primary substrates[13] listed in Table 2 yield almost exclusively rearranged products supports[15] a k_Δ pathway. This mechanistic speculation has been further corroborated by the linear correlation of log k_t (**3**, **6**, **7**, **8**)[5b] with log k_t (**2**) in a series of solvents and by the linear correlation of log k_t (**4**, **5**)[1b,d] with log k_t of the correspondingly substituted neophyl arenesulfonates in acetic acid and aqueous TFE.

The k_{70TFE}/k_{97TFE} ratios listed in Table 2 cover a small range but show a consistent and significant pattern. Those for neopentyl (**8**) and the cycloalkylcarbinyl compounds (**3**, **6**, **7**) respond normally to the solvent change, i.e., their rates of solvolysis increase with increasing ionizing power of the solvent. In contrast, the neophyl-like arenesulfonates (**2, 4a**, **5a**, **5c**) respond abnormally to the solvent change, i.e., their rates of solvolysis decrease with increasing ionizing power of the solvent. Among these, **5c**, the neophyl-like compound with the most highly activated phenyl group, shows the largest decrease in rate when the solvent is changed from 97% to 70% TFE. More significantly, **4b** and **5b**, the two neophyl-like substrates with highly deactivated phenyl groups, respond normally to the solvent change—a solvent response which is consistent with that of the cycloalkylcarbinyl compounds.

The solvolysis products listed in Table 2 also show a trend consistent with the k_{70TFE}/k_{97TFE} ratios. For example, the cycloalkylcarbinyl (**3**, **6**, **7**) and neopentyl arenesulfonates (**8**), which respond normally to the aqueous TFE solvent effect, yield over 99% rearranged products.[1a,d,7,11e−f] While the neophyl-like compounds (**2**, **4a**, **5a**, and **5c**), which respond abnormally to the aqueous TFE solvent effect, yield over 99% phenyl-rearranged products.[1c,d,11b,16] Interestingly, **5b**, the deactivated neophyl-like compound which shows a normal response to the aqueous TFE solvent effect, also yields exclusively ring-expanded products.[1d] Taken altogether, these results suggest that an aryl group rearrangement step accounts for the abnormal response of **4a** and **5a** to the aqueous TFE solvent effect. Equally important, the evidence, based on k^{OMe}/k^{NO_2} rate ratios[1d] and ρ^+ values,[1d] clearly demonstrates that these same solvolysis reactions (in acetic acid or TFE) undergo ionization by a k_Δ process involving σ-participation by the cycloalkyl groups in the developing carbocation center.

This somewhat complicated picture is understandable in terms of a two-step mechanistic scheme:[1b,d] (1) ionization of the arenesulfonate to a tight ion pair via a transition state, stabilized largely by σ-bond delocalization of charge into its cycloalkyl ring, and (2) dissociation of the tight ion pair to a solvent-separated ion pair. More specifically, we propose that the tight ion pair undergoes both solvent and structural rearrangement to give a solvent-separated ion pair.[10,17] Then, upon nucleophilic attack by solvent, the solvent separated ion pair yields the titrable arenesulfonic acid as well as the aryl-rearranged products.

Such a proposal, that is, solvolysis of a neophyl-like substrate via a transition state with little phenonium ion character followed by significant structural reorganization before eventual capture by solvent, explains well the solvolytic behavior of both the 1-arylcyclopropylcarbinyl and 1-arylcyclbutylcarbinyl arenesulfonates.

Given the normal solvolytic behavior of **3**, **6**, and **7** in the aqueous TFE solvents, it seems very unlikely that reduced charge delocalization into the cycloalkyl rings would account for the reverse order of solvolysis of **4a**, **5a**, and **5c** in the same two solvents. Nor does it seem likely that ion pair return[18] would be enhanced in 70% aqueous TFE over that in 97% aqueous TFE. On the other hand, it does seem likely that solvation effects upon carbocations stabilized by aryl bridging and those stabilized by the inductive effects of aliphatic substrates [such

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(12) Dukes, M. D.; Harris, J. M.; Mount, D. L. *J. Am. Chem. Soc.* **1978**, *100*, 8137−8146.

(13) 2-Adamantyl tosylate is the major exception. Also, although the solvolysis of cyclopropylcarbinyl arenesulfonates yields nonrearranged esters and alcohols as the major products, it is generally accepted that both the rate-controlling and product-determining steps occur via a σ-bond delocalization of charge into the cyclopropane ring.[14]

(14) For a review, see: Roberts, D. D. *J. Org. Chem.* **1991**, *56*, 5661−5665.

(15) See ref 1d and references therein.

(16) T.; Ishitobi, H.; Irie, T. *J. Org. Chem.* **1969**, *34*, 1086−1089.

(17) Shiner, V. J., Jr.; Imhoff, M. A. *J. Am. Chem. Soc.* **1985**, *107*, 2121−2124.

(18) (a) It is known[19] that ion pair return is higher in less aqueous trifluoroethanol solvents. (b) Kevill, D. N.; D'Sousa, M. J. *J. Phys. Org. Chem.* **1992**, *5*, 287−294. (c) Bunton, C. C.; Mhala, M. M.; Moffatt, J. R. *J. Org. Chem.* **1984**, *49*, 3684.

as 2-adamantyl tosylate (**1**)] should be different, and this difference could account for the reverse solvolysis order. That such differences in solvation effects are well-known[20] supports this speculation. Furthermore, enhanced charge delocalization in solvolysis reactions involving neighboring group participation (k_Δ processes) is known[3a,21] to be enhanced in the more strongly ionizing TFE. Thus an enhanced aryl ring rearrangement may well occur in 97% aqueous TFE relative to that in 70% aqueous TFE.

With this mechanistic analysis in mind, we interpret the TFE anomaly in terms of the importance of carbocation solvation[14,22] in the equilibrium between the first-formed intimate ion pair and the solvent-separated ion pair. Assuming that the incipient carbocation center leading to the intimate ion pair is stabilized by cycloalkyl participation, and that the transition state leading to the solvent-separated ion pair is stabilized by the rearranging aryl group, it appears likely that the equilibrium would be favored toward the rearranged product in a solvent which enhances aryl-group rearrangement. This scheme is consistent with both the TFE anomaly observed in this study and the previously reported abilities of the cyclopropyl, cyclobutyl, and cyclopentyl groups relative to that of phenyl to stabilize an electron-deficient carbon.

Experimental Section

Preparation of Arenesulfonates. All arenesulfonates were prepared by published procedure.[1b,c,5b,c,6,8] In a typical run, the appropriate arenesulfonyl chloride (35 mmol) was added all at once to a hand-stirred solution of the alcohol (30 mmol) in 40 mL of dry pyridine (spectrophotometric grade, Aldrich Chemical Co.) cooled to 0 °C. After standing for 24 h at about 5 °C, the mixture was carefully hydrolyzed by the slow addition of 20 mL of cold water, followed by acidification with cold, dilute HCl. Each of the separated esters was purified by washing several times with 50-mL portions of cold, dilute HCl and three times with 50 mL of cold water, followed by air drying. Crystallization from pentane−benzene gave the purified arrenesulfonate with melting points in agreement with literature values.[1c,d,5b,6,8]

Solvents. 97% TFE was prepared from 970 g of 2,2,2-trifluoroethanol (Aldrich Chemical Co.) and 30 g of deionized water. 70% TFE was prepared from 700 g of 2,2,2-trifluoroethanol and 300 g of deionized water.

Rate Measurements. The rates of solvolysis were measured titrimetrically. In a typical kinetic run, the requisite amount of ester was accurately weighed into a 25-mL volumetric flask,[23] and then sufficient solvent was added rapidly to give a 25-mL reaction solution volume. Reaction time commenced with the addition of half the solvent. Prior to addition, the solvent was thermostated at the run temperature in a constant-temperature bath for at least 10 min. At appropriate times, 2-mL aliquots[24] were analyzed for liberated arenesulfonic acid. The titrating solution, which was routinely restandardized, was approximately 0.02 M sodium hydroxide in 95% aqueous methanol. The indicator used was 2 drops of aqueous bromothymol blue which changed from off yellow to a bright blue color at the end point. Eight to ten titrations were carried out during a typical kinetic run.

Treatment of the Kinetic Data. First-order rate constants were calculated by using the integrated first-order equation: $k_t = 1/t \ln[mL_{final}/(mL_{final} - mL_t)]$. Multiple determinations (8−10) were made for each kinetic run which were averaged to give the reported k_t value.

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(23) For the slower runs, 2-mL aliquots were pipetted into ampules, which were then sealed, prior to immersion in the constant-temperature bath.
(24) For the faster runs, the 2-mL aliquot was quenched with 2 mL of cold ethanol.
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