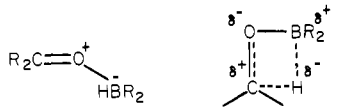

1 2

ordination between the borane and the carbonyl oxygen in the transition state (**2**), they do indicate a strong interaction between the borane and the carbonyl oxygen. It may be mentioned that BF_3 forms complexes with aldehydes.[3,13] Trialkylboranes are also reported to form complexes with aldehydes.[14]

In conclusion, while the kinetics of the reduction of aldehydes and ketones with $(9\text{-BBN})_2$ identifies the actual reducing agent as the 9-BBN monomer formed by the dissociation of the dimer, the relative rates obtained by the competitive method show that the 9-BBN monomer is coordinated with the carbonyl oxygen during reaction. Together, these two studies define the mechanistic details of this reaction.

Experimental Section

General Methods. Detailed procedures for the manipulation of boron reagents have been outlined in Chapter 9 of ref 15. Glassware, syringes, and needles were dried for several hours in an oven at 140 °C and cooled in a stream of dry nitrogen before use. Syringes were assembled while hot and cooled as assembled units in a nitrogen atmosphere. GC analyses were carried out using an HP 5750 research chromatograph. For relative reactivity measurements, 12 ft × 0.125 in. column of 10% SE-30 on 100/120 mesh Chromosorb W, protected by a short column of Theed, was used. For kinetic studies, a Miran-1A variable-filter infrared spectrometer from Wilks Scientific Corp. was used. The calculations of the kinetic data were carried out on a Hewlett-Packard 9820 calculator.

Materials. The purification of solvents was carried out as described elsewhere.[15] The aldehydes and ketones were obtained commercially and were distilled before use, after drying over Drierite. Commercial 9-BBN (aldrich) was used as received.

Kinetics Studies. The kinetics of the reduction of aldehydes and ketones were followed by monitoring the absorbance of the boron–hydrogen bridge vibration of $(9\text{-BBN})_2$ at 1570 cm^{-1} using a quantitative IR spectrometer.[1c] A typical example is given as follows. A solution of $(9\text{-BBN})_2$ in CCl_4 (0.27 M, 9.25 mL) was taken in a 50-mL reaction flask equipped with septum inlet and a connecting tube. CCl_4 (15.13 mL) was added to it and the mixture was equilibrated at 25.00 ± 0.05 °C. It was then pumped through a 0.10-mm NaCl IR cell at a rate of 4 mL/min to determine the absorbance of boron–hydrogen bridge bonds at 1570 cm^{-1}. The reaction was initiated by adding hexanal (0.62 mL) using a syringe. The initial concentrations of hexanal and $(9\text{-BBN})_2$ were 0.200 and 0.100 M, respectively. The absorbance was recorded on a chart paper. When the absorbance ceased to decrease, pure CCl_4 was pumped through the cell to determine the background absorbance. The concentrations of $(9\text{-BBN})_2$ at desired time intervals were calculated. The first-order rate constant was obtained graphically.[1c]

Relative Reactivity. The procedure to determine the relative reactivities of aldehydes and ketones toward $(9\text{-BBN})_2$ in THF at 25 °C has been described previously.[16] The substrate pairs were so chosen that their relative rates did not differ by a factor of more than 10. The relative rates obtained are listed in Table II.

Acknowledgment. We thank the National Science Foundation for Grants 76-20846 and 79-18881.

Registry No. $(9\text{-BBN})_2$, 70658-61-6; hexanal, 66-25-1; propanal, 123-38-6; 2-methylpropanal, 78-84-2; 2,2-dimethylpropanal, 630-19-3; 2-phenylpropanal, 93-53-8; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-chlorobenzaldehyde, 104-88-1; cyclohexanone, 108-94-1; 2-methylcyclohexanone, 583-60-8; cyclopentanone, 120-92-3; cycloheptanone, 502-42-1; acetone, 67-64-1; norbornanone, 497-38-1; acetophenone, 98-86-2; *p*-methylacetophenone, 122-00-9; *p*-methoxyacetophenone, 100-06-1; 2,4-dimethyl-3-pentanone, 565-80-0; *p*-tolualdehyde, 104-87-0; 2-butanone, 78-93-3; 2-heptanone, 110-43-0; 3-methyl-2-butanone, 563-80-4; benzophenone, 119-61-9; *p*-chloroacetophenone, 99-91-2; 3,3-dimethyl-2-butanone, 75-97-8; cyclooctanone, 502-49-8; camphor, 76-22-2; 3-pentanone, 96-22-0.

(13) Grinvald, A.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 94–98.
(14) Midland, M. M.; Zderić, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525–528.
(15) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975.
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Solvolysis of 1-Aryl-2,2,2-trifluoroethyl Sulfonates. Kinetic and Stereochemical Effects in the Generation of Highly Electron-Deficient Carbocations

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Abstract: Solvolysis rates of sulfonates $XC_6H_4CH(O_3SR)CF_3$ (R = *p*-Tol or CF_3) correlate with $\sigma^+(X)$ with values of ρ^+ between −6.7 and −11.9 depending upon solvent. For the tosylates the rates depend on the solvent parameter Y_{OTs} with values of m_{OTs} of 0.76 (X = *p*-MeO), 0.94 (X = *p*-Me), and 0.69 (X = H). These results are interpreted in terms of rate-limiting carbocation formation (the k_C process). Rates for $PhCH(OTf)CF_3$ (**12e**) in ten solvents gave a scattered correlation with Y_{OTs}, and optically active **12e** reacted with racemization in TFA and HFIP and significant inversion in EtOH and AcOH. These results indicate that nucleophilic solvent participation becomes important with this derivative in the more nucleophilic solvents. Deuterium isotope effects for $PhCD(OTf)CF_3$ are not a definitive criterion of mechanism but are consistent with this interpretation.

The reactivity of 1-aryl-1-methyl-2,2,2-trifluoroethyl tosylates (**1**) has been investigated by ourselves[1] and by Liu and co-workers.[2] These substrates have been found to react by rate-limiting ionization to form intermediate cations **2** and then to form mixtures of elimination products **3** and substitution products **4** (eq 1).

(1) (a) Allen, A. D.; Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1982**, *104*, 207–211. (b) Koshy, K. M., Tidwell, T. T. *Ibid.* **1980**, *102*, 1216–1218.
(2) (a) Liu, K.-T.; Kuo, M.-Y.; Sheu, C.-F. *J. Am. Chem. Soc.* **1982**, *104*, 211–215. (b) Liu, K.-T.; Sheu, C.-F. *Tetrahedron Lett.* **1980**, *21*, 4091–4094.

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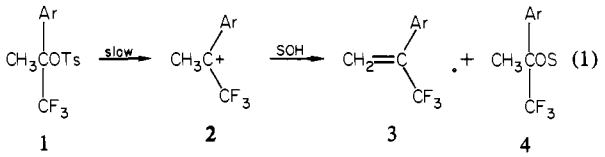
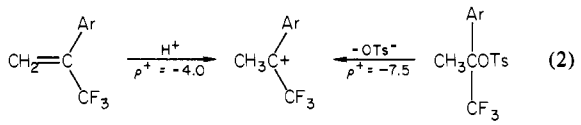


1 2 3 4

Evidence for this process includes the linear dependence of the rate of reaction with the solvent parameter Y_{OTs}[3] for Ar = Ph[1,2] and Ar = 3-ClC_6H_4,[2] m_{OTs} = 1.01 and 1.03, respectively. Other evidence for the process in eq 1 includes the dependence of the rate on the σ^+ parameters of the aryl substituents with $\rho^+ = -7.46$,[2] salt effects in 80% EtOH[1], and the secondary isotope effects $k(CH_3)/k(CD_3)$.[1] Studies of bromides $ArC(CF_3)(CH_3)Br$ confirmed these conclusions.[2]

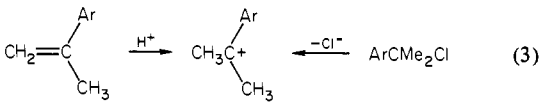
These results on solvolysis are complemented by rate studies of protonation of (α-trifluoromethyl)styrenes (eq 2).[4] It is in-



(2)

teresting that the ρ^+ values of these two reactions are rather different. This parameter measures the sensitivity of the rates to substituents, and its greater magnitude for the sulfonate solvolysis can be interpreted as indicating that there is more positive charge development on carbon in this reaction.

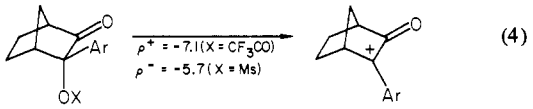
However caution is necessary in comparisons of ρ^+ values for different reactions, even those as in eq 2 that nominally lead to the same intermediate.[5] The ground states of the two reactions are obviously different, as are the reaction media (80% EtOH in the solvolysis, aqueous H_2SO_4 in the hydrations). The larger ρ^+ for the solvolysis is not unprecedented, as ρ^+ for solvolysis of cumyl chlorides is -4.54,[6a] whereas ρ^+ for H_2SO_4 protonation of α-methylstyrenes to produce the same ion (eq 3) is -2.9.[6b]



(3)

The large magnitude of the ρ^+ values for the CF_3 systems in both solvolysis and styrene protonation can be attributed to the high electron demand at the cationic center engendered by the strongly electron-withdrawing CF_3 group. Rate decelerations of the order of 10^5–10^7 for CF_3 relative to H are manifested in these reactions.[1]

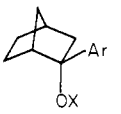
Related work on the reactivity of benzyl-type tosylates substituted with strong electron-withdrawing substitutents has been carried out by several groups. Thus Creary[7a,b] studied the systems shown in eq 4, which were interpreted as involving the cationic



(4)

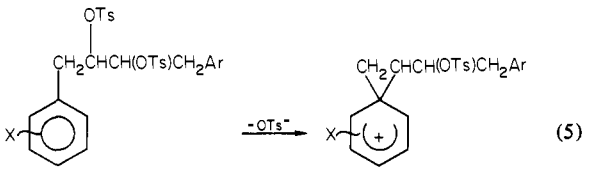
5

intermediate shown, perhaps with some positive charge delocalization onto oxygen.[7b] The large magnitude of ρ^+ noted is evidence for the high demand for stabilization by electron donation from the aryl substituents in these systems. For comparison ρ^+ in the system **6** is -3.72.[8] This demand in **5** is created by the strong electron-withdrawing character of the carbonyl group, as evidenced by the rate ratio $k(\mathbf{6})/k(\mathbf{5})(Ar = Ph) = 6 \times 10^5$.



6

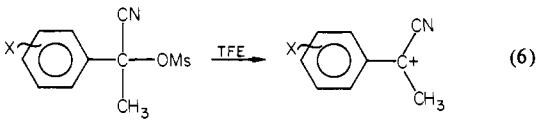
Lambert and co-workers studied the reaction shown in eq 5,[9]



(5)

in which the effect of the aryl substituents is manifested by the participation process illustrated. It was found that the presence of the nonreacting CHOTs greatly enhanced the extent of participation in comparison to a model system that lacked this group. Thus the presence of the second CHOTs group destabilized the developement of positive charge at the adjacent position and favored aryl migration to delocalize the positive charge into the aryl group.

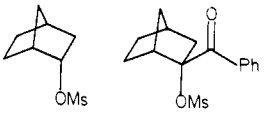
In the α-cyano benzyl system **7** a ρ^+ value of -6.70 for solvolysis in 100% trifluoroethanol (TFE) was observed by Gassman and Guggenheim (eq 6).[10] It is interesting to note that the magnitude



(6)

7

of ρ^+ for the electronically destabilized tertiary benzylic systems shown in eq 1, 4, and 6 are of comparable magnitude (-7.5, -7.1, and -6.7, respectively), even though the destabilizing influence of the CF_3, CN, and carbonyl substituents are strikingly different. Thus for the system $PhCR(OY)CH_3$ the rate ratio $k(H)/k(CF_3)$ is 2×10^5 in 100% EtOH,[1] whereas for the same substrate the ratio $k(H)/k(CN)$ is 2×10^3 in 100% TFE.[10] Furthermore the rate ratio $k(H)/k(C{=}O)$ derived from $k(\mathbf{8})/k(\mathbf{9})$ is only 10 in HOAc at 25 °C.[7c]



8 9

The studies noted above have involved reactions proceeding through carbocationic transition states that have been rendered *electron deficient* by the presence of substituents that are *destabilizing* due to their electron-withdrawing tendency.[11] With certain exceptions[7,9] these studies have dealt with tertiary systems, and the goal of the present study has been to extend the study of the destabilizing effect of the CF_3 group to secondary carbocations.

(3) (a) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667–7674. (b) Bentley, T. W.; Bowen, C. T.; Brown, H. C.; Chloupek, F. J. *J. Org. Chem.* **1981**, *46*, 38–42.

(4) Koshy, K. M.; Roy, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 357–363.

(5) The postulated variation in ρ^+ with transition-state charge development is an application of the reactivity-selectivity principle. A discussion of the difficulties in the use of this principle is given by: Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461–3480.

(6) (a) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979–4987. (b) As recalculated in ref 4.

(7) (a) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938–3945. (b) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463–2465. (c) Creary, X.; Geiger, C. C. *Ibid.* **1982**, *104*, 4151–4162.

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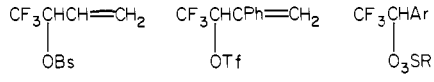
(10) Gassman, P. G.; Guggenheim, T. L. *J. Org. Chem.* **1982**, *47*, 3023–3026.

(11) For reviews of the general area of destabilized carbocations and the more restricted topic of electron-deficient carbocations see Tidwell, T. T. *Angew Chem., Int. Ed. Engl.*, in press, and Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.*, in press, respectively.

Previous studies in this area include an effort to generate the 1,1,1-trifluoro-2-propyl cation for direct observation by NMR that was unsuccessful,[12a] as was an attempt to form the same ion by solvolysis.[12b] An early effort to solvolyze the secondary system **10** bearing the CF_3 group gave no reaction,[13a] but in a more recent study of the allylic system **11** utilizing a better leaving group solvolysis kinetics were successfully measured.[13b] The success of this latter effort was a strong indication that solvolytic studies of 1-aryl-2,2,2-trifluoroethyl systems **12** would be feasible, as the cation stabilizing influence of the vinyl and phenyl groups are quite similar.[13c]



10 **11** **12**

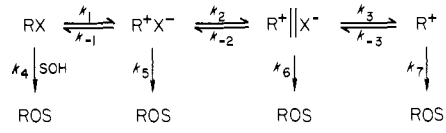
To estimate the magnitude the rates that might be anticipated in systems such as **12** in which the methyl group in the tertiary system **1** has been replaced by a hydrogen, it may be noted that in aliphatic systems $K(CH_3)/k(H)$ rate ratios of 5×10^7, 3×10^7, and 2×10^4 have been reported for the 7-norbornyl,[14a] 2-adamantyl,[14b] and 2-propyl[14c] systems, respectively. However for 1-aryl-1-ethyl systems $k(CH_3)/k(H)$ rate ratios between 1×10^3 and 7×10^3 can be calculated for three different systems,[15,16] and the relative constancy of this factor suggests it is a good standard of comparison for **1** and **12**.

An alternative reaction path that may become significant for the secondary system **12** is nucleophilic solvent displacement, which is indicated to be important in certain 1-phenylethyl systems. The α-trifluoromethyl group in S_N2 processes was examined very early by Hine and Ghirardelli,[17a] who reported the $k(CH_3)/k(CF_3)$ rate ratio of 2×10^4 shown in eq 7. Comparable results have been subsequently reported by other authors.[17]

$$RCH_2I \xrightarrow[MeOH]{PhSNa} RCH_2SPh$$

$$k(CH_3)/k(CF_3) = 2 \times 10^4 \qquad (7)$$

The system **12** is also potentially informative regarding some recent elaborations of the generally accepted theory that solvolysis reactions occur through either discrete S_N1 or S_N2 pathways, with variable involvement of ion pairs (eq 8).[18] A further distinction



(8)

is made that processes in which solvent participates in the rate-limiting step as either a nucleophile or base are classified as k_s processes, reactions in which there is rate-limiting participation of a neighboring group leading to a cationic intermediate are designated k_Δ, and reactions in which rate-limiting ionization to a cationic intermediate occurs without participation by solvent or a neighboring group are defined as k_c processes.

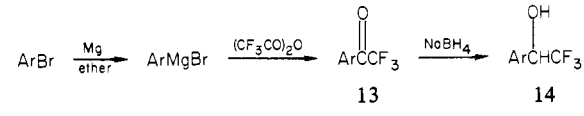
One variation on this theme is the occurrence of the "S_N2-intermediate" mechanism.[3a,19] According to this proposal there is a continuous spectrum of solvolysis mechanisms ranging from the classical S_N1 process with a distinct cationic intermediate to the S_N2 process where direct displacement by solvent leads through a single transition state to an inverted product.

In the "S_N2-intermediate" mechanism it is suggested that there also occurs in some cases an energy minimum in which one side of the cationic center is coordinated to solvent and the other side to the leaving group. The primary evidence for this proposal would appear to be the existence of a continuous range of dependences of reaction rates on solvent parameters, as measured by the parameters m_{OTs} or Q.[19b]

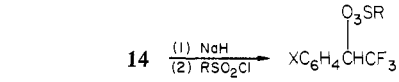
The question of the respective roles of carbocation intermediates and nucleophilic displacement reactions by solvent or added nucleophiles has also been examined by Jencks and co-workers.[20] In the case of the 1-arylethyl chlorides, which are structurally analogous to the sulfonates **12** examined here, it was proposed that in the presence of azide ion in aqueous acetonitrile or aqueous trifuoroethanol that for strongly electron-donating aryl substituents ($\sigma^+_x \leq -0.32$) that reaction occurred via carbocations, whereas for less strongly electron-donating substituents reaction with azide ion took place by an initial preassociation of the substrate and azide and that the rate-limiting step was an "enforced" S_N2 attack of azide leading directly to product. However, in the case of 1-(*p*-nitrophenyl)ethyl tosylate it was concluded "that there is little or no solvent assistance in the solvolysis of this compound".[20e]

Results

Aryl trifluoromethyl ketones **13** were in most cases prepared by the reaction of aryl Grignard reagents with trifluoroacetic anhydride and were then reduced to the known carbinols **14** by $NaBH_4$.[21] The carbinols were converted to tosylate or triflate esters **12** by reaction with NaH in ether followed by treatment with the appropriate sulfonyl chloride.[1]



13 **14**



12a-g

12a, X = *p*-MeO, R = *p*-Tol
b, X = *p*-Me, R = *p*-Tol
c, X = H, R = *p*-Tol
d, X = *p*-Br, R = *p*-Tol
12e, X = H, R = CF_3
12f, X = *p*-Br, R = CF_3
12g, X = *m*-CF_3, R = CF_3

α-Deuterated carbinol **15** was obtained by reduction of **13** (Ar = Ph) with $LiAlD_4$ and converted to triflate **12e**-*1-d* and (*R*)-(−)-**16**[22] was obtained commercially and converted to triflate

(12) (a) Olah, G. A.; Pittman, C. U., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 3310–3312. (b) Drabicky, M. J.; Myhre, P. C.; Reich, C. J.; Schmittou, E. R. *J. Org. Chem.* **1976**, *41*, 1472–1474.

(13) (a) Pegolotti, J. A.; Young, W. G. *J. Am. Chem. Soc.* **1961**, *83*, 3251–3258. (b) Gassman, P. G.; Harrington, C. K., unpublished results. Harrington, C. K. Ph.D. Thesis, The Ohio State University, 1976; Diss. Abstr. **1976**, *37*, 2248B. (c) Chwang, W. K.; Knittel, P.; Koshy, K. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1977**, *99*, 3395–3401.

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(15) $k(PhCMe_2Cl)/k(PhCHMeCl) = 1.8 \times 10^3$ in 100% EtOH at 25 °C from $k(PhCMe_2Cl)$[16a] $= 3.94 \times 10^{-4}$ s^{-1} and $k(PhCHMeCl)$[16b] $= 2.16 \times 10^{-7}$ s^{-1}. $k(p\text{-AnisCMe}_2OPNB)/k(p\text{-AnisCHMeOPNB}) = 1.1 \times 10^3$ in 70% acetone at 48 °C, from $k(p\text{-AnisCMe}_2OPNB)$[16c] $= 1.5 \times 10^{-2}$ s^{-1} and $k(p\text{-AnisCHMeOPNB})$[16d] $= 1.33 \times 10^{-5}$ s^{-1}. $k(PhCMe_2OPNB)/k(PhCHMeOPNB) = 7.0 \times 10^3$ in 70% acetone at 100 °C, from $k(PhCMe_2OPNB)$[16c] $= 1.48 \times 10^{-3}$ s^{-1} and $k(PhCHMeOPNB)$[16d] $= 2.1 \times 10^{-7}$ s^{-1}.

(16) (a) Okamoto, Y.; Inukai, T.; Brown, H. C. *J. Am. Chem. Soc.* **1958**, *80*, 4972–4976. (b) Fainberg, A. H.; Winstein, S. *Ibid.* **1957**, *79*, 1597–1602. (c) Tanida, H.; Matsumura, H. *Ibid.* **1973**, *95*, 1586–1593. (d) Goering, H. L.; Briody, R. G.; Sandrock, G. *Ibid.* **1970**, *92*, 7401–7407.

(17) (a) Hine, J.; Ghirardelli, R. G. *J. Org. Chem.* **1958**, *23*, 1550–1552. (b) McBee, E. T.; Battershell, R. D.; Braendlin, H. P. *J. Am. Chem. Soc.* **1962**, *84*, 3157–3160. (c) Bordwell, F. G.; Brannen, W. T., Jr. *Ibid.* **1964**, *86*, 4645–4650. (d) Nakai, T.; Tanaka, K.; Ishikawa, N. *J. Fluorine Chem.* **1977**, *9*, 89–93.

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(19) (a) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7658–7667. (b) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *Ibid.* **1981**, *103*, 5466–5475. (c) Bentley, T. W.; Carter, G. E. *Ibid.* **1982**, *104*, 5741–5747.

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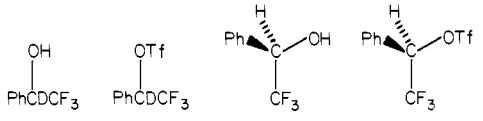
Table I. Solvolytic Rate Constants for Sulfonates $XC_6H_4CH(OTs)CF_3$ and $XC_6H_4(OTf)CF_3$

X	solvent[a]	T, °C	k,[c,d] s^{-1}	ΔH*, kcal/mol	ΔS*, eu	X	solvent[a]	T, °C	k,[c,d] s^{-1}	ΔH*, kcal/mol	ΔS*, eu
p-MeO[h]	97% HFIP	12.7	0.263	10.4	−24.7	H[h]	TFA	100.6[f,g]	3.04×10^{-4}		
		3.7	0.140					100.1[f,g]	2.98×10^{-4}		
		25.0[b]	0.583					83.3[f]	5.74×10^{-5}		
	97% TFE	34.3	0.117					72.7	2.16×10^{-5}		
		25.0	5.97×10^{-2}	14.9	−14.3			67.4[f]	1.46×10^{-5}		
		4.8	8.22×10^{-3}					25.0[b]	1.05×10^{-7}	22.5	−14.9
	70% TFE	25.0	6.18×10^{-2}				97% HFIP	130.9	8.14×10^{-5}		
	50% TFE	25.0	7.24×10^{-2}					114.6	3.39×10^{-5}		
	HCO_2H	25.0	9.34×10^{-2}					103.7	1.78×10^{-5}		
	HOAc	56.3	1.22×10^{-3}					25.0[b]	4.03×10^{-8}	16.6	−36.6
		41.2	2.44×10^{-4}				97% TFE	145.4	9.09×10^{-5}		
		25.0	4.18×10^{-5}	20.4	−10.2			130.5	3.15×10^{-5}		
	60% EtOH	56.3	7.86×10^{-2}					115.0	1.06×10^{-5}		
		41.2	2.21×10^{-2}					25.0[b]	1.48×10^{-9}	22.0	−25.2
		25.0	4.50×10^{-3}	17.2	−11.5	H[i]	TFA	37.0	6.29×10^{-3}		
	80% EtOH	56.3	2.19×10^{-2}					25.0	2.04×10^{-3}	17.3	−12.8
		41.1	6.26×10^{-3}					5.0	2.24×10^{-4}		
		25.0	1.19×10^{-3}	17.6	−12.8		97% HFIP	25.0	1.85×10^{-2}		
	100% EtOH	56.4	2.41×10^{-3}				97% TFE	25.0	1.44×10^{-3}		
		41.2	5.06×10^{-4}				70% TFE	25.0	5.11×10^{-3}		
		25.0	7.22×10^{-5}	21.2	−6.3		50% TFE	25.0	0.97×10^{-2}		
p-Me[h]	TFA	55.4	9.48×10^{-4}				HCO_2H	25.0	5.72×10^{-3}		
		41.2	2.76×10^{-4}				HOAc	25.0	5.54×10^{-6}		
		25.0	6.19×10^{-5}	16.8	−21.3		60% EtOH	25.0	2.08×10^{-3}		
	97% HFIP	55.4	6.60×10^{-4}				80% EtOH	25.0	3.88×10^{-4}		
		46.1	3.50×10^{-4}				100% EtOH	25.0	2.00×10^{-5}		
		25.0	5.66×10^{-5}	15.2	−26.9	p-Br[h]	TFA[f]	104.4	2.41×10^{-4}		
	97% TFE	72.3	1.75×10^{-4}					94.6	1.17×10^{-4}		
		62.8	7.25×10^{-5}					73.7	1.64×10^{-5}		
		44.0	1.01×10^{-5}					25.0[b]	7.41×10^{-8}	22.2	−16.5
		25.0[b]	1.10×10^{-6}	21.3	−14.2	p-Br[i]	TFA	25.0	1.53×10^{-3}		
	HOAc	130.1	2.46×10^{-4}			m-CF_3[i]	TFA[f]	91.0	4.18×10^{-4}		
		113.6	5.01×10^{-5}					76.5	1.28×10^{-4}		
		101.4[e]	1.56×10^{-5}					61.8	2.89×10^{-5}		
		25.0[b]	7.68×10^{-10}	28.1	−6.0			25.0[b]	4.89×10^{-7}	21.5	−15.2
	60% EtOH	74.6	6.63×10^{-5}								
		55.2	7.02×10^{-6}								
		25.0[b]	1.20×10^{-7}	25.6	−4.3						
	80% EtOH	106.3	2.13×10^{-4}								
		89.8	4.54×10^{-5}								
		75.4	1.05×10^{-5}								
		25.0[b]	2.10×10^{-8}	24.8	−10.3						
	100% EtOH	113.4	2.44×10^{-5}								
		104.8	9.88×10^{-6}								
		89.6	1.80×10^{-6}								
		25.0[b]	1.93×10^{-10}	29.8	−3.2						

[a] TFA is 100% CF_3CO_2H, HFIP is $(CF_3)_2CHOH$, TFE is CF_3CH_2OH. [b] Calculated from data at other temperatures. [c] At least duplicate runs in each case unless noted, ±5%. [d] Measured by UV unless noted. [e] A titrimetric run gave the identical rate constant. [f] Measured by NMR. [g] Single run only. [h] $XC_6H_4CH(OTs)CF_3$. [i] $XC_6H_4CH(OTf)CF_3$.

(*R*)-(−)-**12e**. Triflates **12e** were unstable in the absence of solvent but could be stored in ether solution.



15 12e-1-d (*R*)-(−)-16 (*R*)-(−)-12e

Solvolytic rate constants for the tosylates **12a–d** and the triflates **12e–g** in various solvents were measured by UV spectroscopy in most cases, although for a few examples the rates were also measured by NMR spectroscopy. Good agreement was found where both methods of measurement were used. These kinetic results are summarized in Table I.

Product studies for the reaction of **12a–c** and **12e** were carried out in CD_3CO_2D, CD_3CD_2OD, and CF_3CO_2H by sealing the substrate and the solvent in an NMR tube and heating the solution for a time period equivalent to 10 half-lives for solvolysis. The signal due to the methine quartet of the reactant changed to the distinctive positions of the solvolysis products $ArCH(OS)CF_3$ in every case, and no signals attributable to the alcohols **14** were observed. The products $PhCH(OCH_2CH_3)CF_3$ (**17a**) and $PhCH(O_2CCF_3)CF_3$ (**17b**) from preparative scale solvolyses of **12e** were isolated, purified, and characterized. The formation of the products $ArCH(O_2CCF_3)CF_3$ on reaction of **12d**, **12f**, and **12g** in TFA were also observed directly by NMR spectroscopy.

α-Deuterium isotope effects $k(PhCH(OTf)CF_3)/k(PhCD(OTf)CF_3)$ for **12e** and **12e-*l*-*d*** in several solvents were measured

Table II. α-Deuterium Isotope Effects in Solvolysis of $PhCH(OTf)CF_3$ (12e) and $PhCD(OTf)CF_3$ (12e-*l*-*d*) at 25 °C

solvent	k(H), s^{-1}	k(D), s^{-1}	k(H)/k(D)[a]
97% HFIP	1.85×10^{-2}	1.38×10^{-2}	1.34 ± (0.07)[b]
TFA	2.04×10^{-3}	1.62×10^{-3}	1.26 ± (0.02)[c]
97% TFE	1.44×10^{-3}	1.12×10^{-3}	1.29 ± (0.01)[c]
50% TFE	9.68×10^{-3}	7.73×10^{-3}	1.26 ± (0.05)[c]
HCO_2H	5.72×10^{-3}	4.66×10^{-3}	1.23 ± (0.00)[c]
60% EtOH	2.08×10^{-3}	1.69×10^{-3}	1.23 ± (0.00)[c]
80% EtOH	3.88×10^{-4}	3.21×10^{-4}	1.21 ± (0.01)[d]

[a] Average deviation in parentheses. [b] Average of 12 determinations. [c] Average of four determinations. [d] Average of six determinations.

(22) (a) Peters, H. M.; Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4245–4250. (b) Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1967**, *89*, 5485–5487.

Table III. Solvolysis of (*R*)-(−)-PhCH(OTf)CF_3 (12e) at 25 °C

				quenched reactions				
					% product		% opt act.	
solvent	k_α,[a] s^{-1}	k_{UV},[b] s^{-1}	k_α/k_{UV}	rxn time, s	calcd[c]	obsd[d]	calcd[e]	obsd[f]
TFA	1.5×10^{-2}	2.05×10^{-3}	7.3	120	22	15 ± 10	10	10 ± 3
				300	46	43 ± 5	1	0 ± 2
100% HFIP	8.7×10^{-2}	3.23×10^{-3}	27	40	52	25 ± 10	0	5 ± 3
				90	80	65 ± 10	0	0 ± 2
100% TFE	1.42×10^{-3}	1.16×10^{-3}	1.2					
HOAc	5.54×10^{-6}	5.15×10^{-6}	1.1					
100% EtOH	3.10×10^{-5}	2.99×10^{-5}	1.0					

[a] Polarimetric rate constant. [b] Rate constant as measured by UV spectroscopy. [c] Calculated from k_{UV}. [d] Measured by NMR spectroscopy. [e] Calculated from k_α. [f] Measured from the reactant and product isolated after quenching.

Table IV. Specific Rotations (α) of 2,2,2-Trifluoro-1-phenylethanol (16) Derivatives[a]

			PhCH-$(O_2CCF_3)CF_3$		PhCH(OAc)CF_3	
λ, nm	PhCH-$(OH)CF_3$[b]	PhCH-$(OTf)CF_3$[c]	auth[d]	product	auth[d]	product
365	−74.4	−34.4	−352	0	−330	+136
436	−49.4	−21.5	−217	0	−205	+84.6
546	−28.9	−12.1	−120	0	−114	+47.2
578	−25.4	−10.4	−105	0	−100	+41.2

[a] $(\alpha) = \alpha_{lc}^{-1}$ (deg g^{-1} mL) in CCl_4, 25 °C, 0.1-m path length. Observed rotations between −1° and −11° (±0.01°). Specific rotations ±1°. Concentrations 0.03–0.045 g/mL, except 12e, 0.01 g/mL. [b] Starting material, used to prepare 12e, and authentic 17b and 17c. [c] Crude material, see text. [d] Prepared from (*R*)-(−)-16.

at 25 °C by UV spectroscopy as reported in Table II. In each of these runs the deuterated and nondeuterated substrates were run side by side in the same sample compartment using the same batch of solvent so as to minimize differences in the reaction conditions. The rate constants for the nondeuterated substrates obtained under these conditions agreed with those reported in Table I within the experimental precision of the measurements.

The solvolysis kinetics of the optically active triflate (*R*)-(−)-**12e** were measured polarimetrically in 100% TFA, 100% HFIP, 100% TFE, HOAc, and EtOH, as reported in Table III. Additional spectrophotometric rates for racemic **12e** were measured in these same batches of solvent for comparison and are also included in Table III. For the reactions of (*R*)-(−)-**12e** in TFA and HFIP the runs were interrupted before completion and the fraction of reactant and product in the sample was determined by integration of the characteristic methine hydrogen signals due to these two species in the NMR spectra. The optical rotations of these mixtures were also measured as reported in Table III.

Samples of the reaction products PhCH$(O_2CCF_3)CF_3$ (**17b**) and PhCH(OAc)CF_3 (**17c**) from optically active **12e** were isolated after 10 half-lives for solvolysis. Samples of **17b** and **17c** were also prepared from the optically active alcohol by reaction with the acid anhydrides and pyridine and were shown to be optically stable under the solvolysis conditions. The rotations of these derivatives, as well as the starting alcohol and the unstable triflate (**12e**) are given in Table IV.

Discussion

The dependence of the reaction rates of the tosylates **12a–c** at 25 °C on the solvent ionizing power parameter Y_{OTs}[19] are shown in Figure 1. Linear correlations are drawn for **12a** (X = *p*-MeO, $m = 0.76$, $r = 0.993$), **12b** (X = *p*-Me, $m = 0.94$, $r = 0.984$), and **12c** (X = H, $m = 0.69$, $r = 0.990$). In the case of **12a** (X = *p*-MeO) the points for the reactions in AcOH and HCO_2H solvents are omitted from the correlation as the negative deviation of these points from the line shown defined by the other points suggests that in these two solvents the rates are retarded by hydrogen bonding to the acidic solvents to the MeO group. This behavior has been commonly observed for this substituent in acidic solvents.[23]

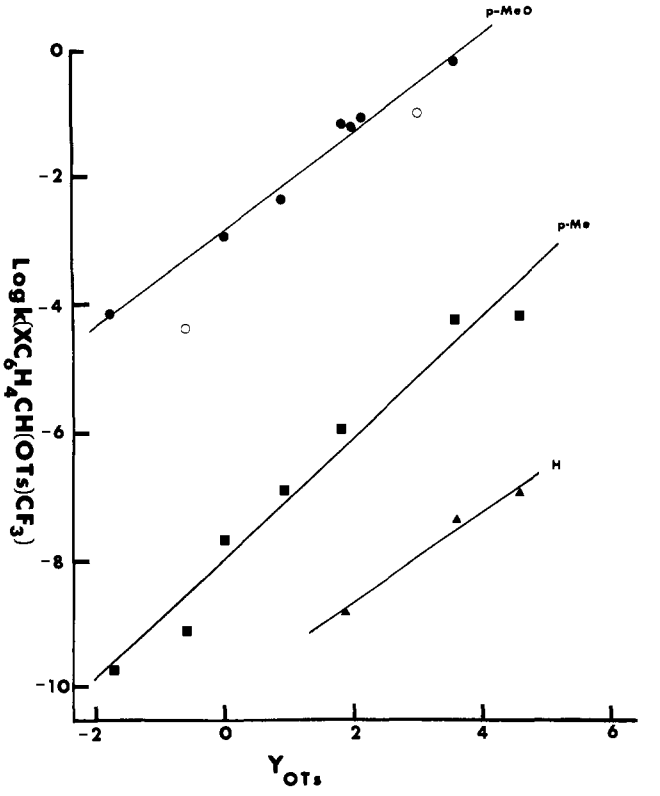


Figure 1. Rates of $XC_6H_4CH(OTs)CF_3$ at 25 °C as a function of Y_{OTs} solvent parameters (open points not included, see ref 23).

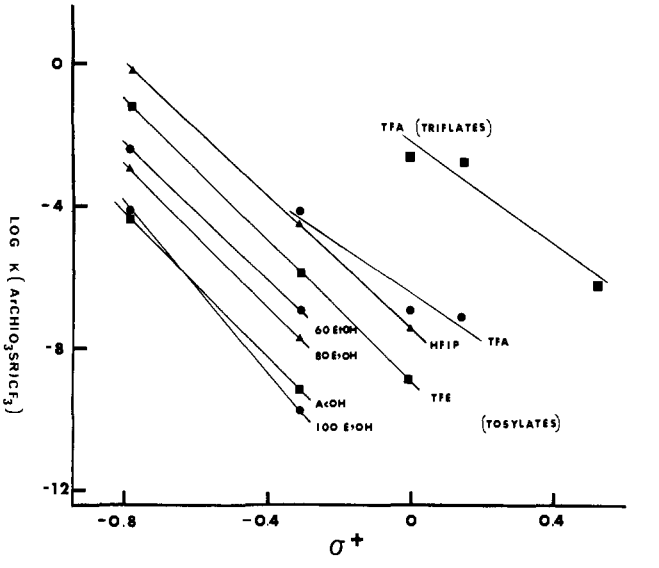
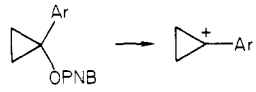


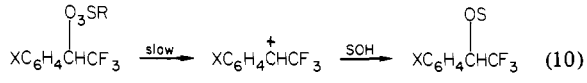
Figure 2. Correlation of rates of $XC_6H_4CH(O_3SR)CF_3$ at 25 °C with $\sigma^+(X)$ parameters.

Brown–Hammett correlations of the rates for the tosylates and triflates at 25 °C with σ^+ parameters for the aryl substituents X are shown in Figure 2: the tosylates give values of ρ^+ of −6.7 (TFA), −9.1 (97% HFIP), −9.8 (TFE), −10.1 (HOAc), −9.7 (60% EtOH), −10.1 (80% EtOH), and −11.9 (100% EtOH) and the triflates give $\rho^+ = -7.4$ (TFA). These ρ^+ values show a remarkably strong dependence of the rates on the substituents and most are greater than any of the values listed in the introduction. Besides these[2,7,10] the greatest magnitude of ρ^+ heretofore observed for a benzyl-type system was that of −7.07 for the solvolysis of 1-arylcyclopropyl tosylates (eq 9).[24] The large value of this ρ^+ was



(9)

attributed to the great destabilization of the carbocation formed due to the geometric restraints of the small ring.[24] Evidently for the tosylates **12a–c** and the triflates in TFA carbocations are also formed in the rate-limiting step (eq 10), and the rates show a very



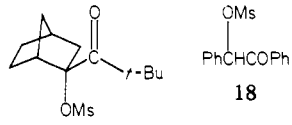
(10)

17

strong dependence upon the electron-donating ability of the substituents X because the incipient cation has been strongly destabilized by the electron deficiency created by the CF_3 group. The fact that ρ^+ is of greater magnitude in the more nucleophilic solvents is opposite what would be expected if nucleophilic solvent participation was significant, but is the behavior expected for rate-limiting carbocation formation (eq 10), where in the less ionizing solvents there would be an increased electron demand on the substituents X.

The slopes ρ^+ in TFA for either the tosylates or triflates are noticeably less than for the other solvents, and these plots also have the most scatter. The cause of the scatter is not apparent, but the triflate/tosylate rate ratios **12e/12c** and **12f/12d** are remarkably constant at 2×10^4. Converting the rate of **12g** by this factor gives a four-point line for tosylates in TFA at 25 °C with $\rho^+ = -6.8$ and $r = 0.988$. It has not yet proven feasible to obtain rate constants over a wider range of reactivities to extend the plots still further. Because of the small number of points in all of these σ^+ correlations the slopes should be interpreted with caution.

The observed values of m_{OTs} may be compared with those for the solvolyses of **1** (Ar = Ph) of 1.01,[1,2] **1** (Ar = *m*-ClC_6H_4) of 1.03,[2] **9** of 0.77,[7c] **9a** of 0.69,[7c] and **18** of 0.91.[7c] Creary and Geiger argue[7c] that despite the relatively low m_{OTs} values for **9** and **9a** that cationic intermediates are involved with these substrates with little nucleophilic solvent participation. Our results for **12a–c** support this proposal[7c] that m_{OTs} values in the range 0.6–0.9 may occur in reactions involving carbocationic intermediates.



9a

18

A factor that may affect the solvent dependence of the rates is delocalization of the positive charge onto an adjacent π system such as the aryl groups in **12a–c** and **18**, or even onto the carbonyl oxygen, as has been proposed[7] for **9**, **9a**, and **18**. Hydrogen bonding interactions of acidic solvents with the carbonyl group may affect the m_{OTs} values as well. It would appear that mechanistic assignments for reactions involving electron-deficient carbocationic species cannot rely solely on m_{OTs} values but must use other criteria as well.

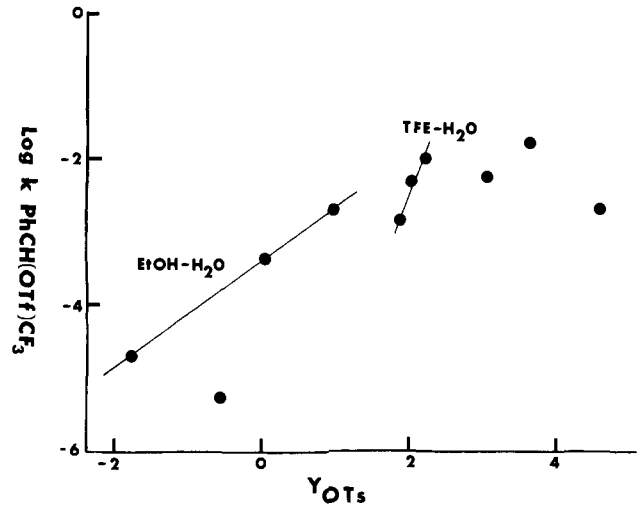


Figure 3. Rates of $PhCH(OTf)CF_3$ at 25 °C as a function of Y_{OTs} solvent parameters.

The triflate **12e** reacted at convenient rates in a variety of solvents as 25 °C. However there has been no systematic study of the dependence of triflate rates on solvents, although the evidence that is available may indicate that triflate solvolyses are affected considerably less by solvent ionizing power than are tosylate solvolyses.[25,26] A plot of the rates of triflate **12e** against the available Y_{OTs} values[3] (Figure 3) is however quite suggestive. The overall correlation leads to a low value of $m = 0.48$, but with a very poor correlation coefficient $r = 0.81$. This overall correlation is not drawn on the plot but instead distinctive subcorrelations with Y_{OTs} of the rates in aqueous TFE ($m = 2.6$, $r = 0.98$) and aqueous EtOH ($m = 0.76$, $r = 0.999$) are indicated; such subcorrelations of tosylate rates have been proposed[27] to be indicative of the intervention of solvent participation mechanisms in the more nucleophilic solvents. However until a more thorough study of the solvent dependence of triflate reactivities is available this criterion must be regarded as inconclusive in the case of **12e**.

Another mechanistic tool for the analysis of rates of secondary substrates is the α-deuterium isotope effect. Although there is considerable controversy about detailed interpretations in particular cases, there does seem to be some agreement that mechanisms involving nucleophilic solvent displacement in the rate-limiting step will have lower values of $k(H)/k(D)$ than related systems in which carbocations are formed in the rate limiting steps.[18,28] The results for **12e**-*l*–*d* are shown in Table II and are somewhat larger in the less nucleophilic solvents. However the precision of these values is not as great as is desireable, and there is forthermore a dearth of data for suitable comparative systems with deactivating electron-withdrawing α substituents or triflate leaving groups. Therefore no mechanistic conclusions from these data appear justified at the present time, although it may be noted

(23) (a) Allen, A. D.; Rosenbaum, M.; Seto, N. O. L.; Tidwell, T. T. *J. Org. Chem.* **1982**, *47*, 4234–4239. (b) Schadt, F. L., III; Lancelot, C. J.; Schleyer, P. v. P. *J. Am. Chem. Soc.* **1978**, *100*, 228–246.

(24) Brown, H. C.; Gunda Rao, C.; Ravindranathan, M. *J. Am. Chem. Soc.* **1978**, *100*, 7946–7953.

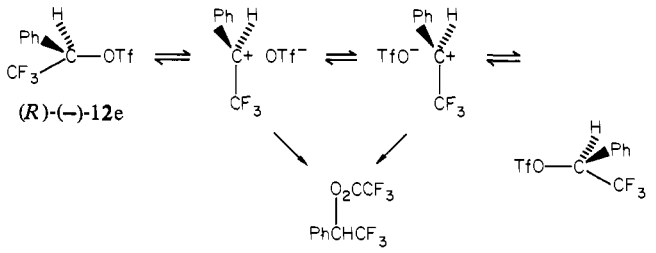
(25) The solvolysis of 2-adamantyl triflate in 80, 90, and 95% acetone at 25.4 °C gave an *m* value of 0.60 when plotted against $Y_{t\text{-BuCl}}$ values,[26a] whereas in aqueous ethanol the *m* value of 2-adamantyl tosylate plotted against $Y_{t\text{-BuCl}}$ parameters is 0.91.[26b] Even lower *m* values were found for solvolysis for cyclopropyl triflates[26a] and vinyl triflates.[26c]

(26) (a) Creary, X. *J. Am. Chem. Soc.* **1976**, *98*, 6608–6613. (b) Fry, J. L.; Lancelot, C. J.; Lam, L. K. M.; Harris, J. M.; Bingham, R. C.; Raber, D. J.; Hall, R. E.; Schleyer, P. v. R. *Ibid.* **1970**, *92*, 2538–2540. (c) Schiavelli, M. D.; Jung, D. M.; Vaden, A. K.; Stang, P. J.; Fisk, T. E.; Morrison, D. S. *J. Org. Chem.* **1981**, *46*, 92–95.

(27) (a) Raber, D. J.; Neal, W. C., Jr.; Dukes, M. D.; Harris, J. M.; Mount, D. L. *J. Am. Chem. Soc.* **1978**, *100*, 8137–8146. (b) Harris, J. M.; Mount, D. L.; Smith, M. R.; Neal, W. C., Jr.; Dukes, M. D.; Raber, D. J. *Ibid.* **1978**, *100*, 8147–8156.

(28) (a) Shiner, V. J., Jr.; Neumann, T. E.; Fisher, R. D. *J. Am. Chem. Soc.* **1982**, *104*, 354–355. (b) McLennan, D. *J. Chem. Soc. Perkin Trans. 2* **1981**, 1316–1324.

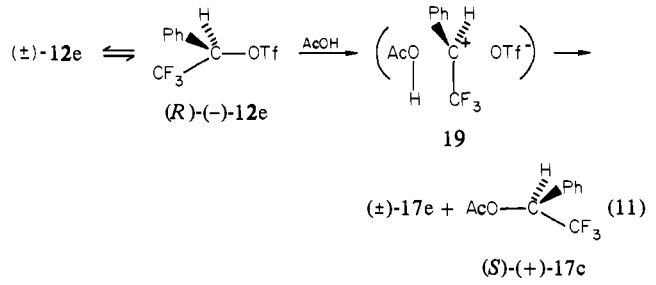
Scheme I



that these values are among the largest α-deuterium isotope effects ever reported for solvolyses.

A more reliable criterion of mechanism would appear to be the stereochemistry of the substitution, for which data for the optically active triflate (*R*)-(−)-**12e** are reported in Tables III and IV. In the strongly nucleophilic but poorly ionizing solvents HOAc and EtOH the polarimetric rate constants k_α were close to the spectrophotometric rate constants k_{UV}. Furthermore the reaction products $PhCH(OEt)CF_3$ and $PhCH(OAc)CF_3$ had strong positive rotations, whereas the precursor alcohol (*R*)-(−)-**16** and triflate (*R*)-(−)-**12e** have strong negative rotations. Unfortunately the triflate (*R*)-(−)-**12e** was unstable in an isolated state even at −10 °C so the optical purity of this material is questionable. The acetate $PhCH(OAc)CF_3$ (**17c**) isolated from solvolysis of freshly prepared (−)-**12e** was 41% inverted and 59% racemized (Table IV).

The ratio of k_α/k_{UV} for acetolysis is 1.1, so there is a small amount of racemization of (−)-**12e** by ion pair formation during reaction. Taken together the results indicate that acetolysis occurs by rate-limiting attack of solvent on covalent substrate or more probably on an ion pair that maintains a considerable degree of chirality (eq 11).



In the weakly nucleophilic but strongly ionizing solvents TFA and HFIP k_α is much greater than k_{UV}, and within the limits of the experimental measurements the reaction products are completely racemized. These observations suggest a process by which an initial ion pair is formed which undergoes competitive racemization, reformation of reactant, and formation of racemized product (Scheme I). When these reactions are stopped after partial reaction the measured rotation of the mixture of reactant and product is in quantitative agreement with the measured proportions of reactant and product in the mixture and the process of Scheme I. The occurrence of an "S_N2-intermediate" mechanism pathway can be excluded as a significant pathway in this case. The path of Scheme I predicts that considerable ^{18}O scrambling in a specifically labeled reactant triflate would occur during the course of the reaction, and such behavior has been observed in the solvolysis of certain secondary aliphatic benzenesulfonates.[29]

The rate data reported in Table I permit the calculation of a number of new $k(R = H)/k(R = CF_3)$ values for substrates $XC_6H_4CH(OTs)R$ as 4×10^3 (X = *p*-MeO, HOAc),[30] 2×10^3 (X = *p*-MeO, HCO_2H),[30a] 3×10^5 (X = *p*-Me, HOAc),[30a] and 4×10^5 (X = H, HFIP,[7c] and TFE[27b]). Previous values have been in the range 10^5–10^7 so the values for the *p*-MeO compounds are the lowest yet recorded, while the others fall in the range that has been previously observed. It is clear that these ratios are not expected to be constant because for different groups R there are different responses to both aryl substitutents and solvent ionizing power.

Comparison of the rates in different solvents for $PhCH(OTs)CF_3$ with those previously reported[1] for $PhCMe(OTs)CF_3$ permits the calculation of $k(CH_3)/k(H)$ rate ratios at 25 °C of 5×10^5 (TFA), 7×10^4 (97% HFIP), and 4×10^4 (97% TFE). Comparison of rates for *p*-TolCMe(OTs)CF_3[2] and *p*-TolCH(OTs)CF_3 in 80% EtOH at 25 °C gives another ratio $k(CH_3)/k(H)$ of 8×10^3. These values may be compared to those of 1×10^3 to 7×10^3 for benzyl systems not bearing strongly destabilizing substituents cited in the introduction.

In summary for 1-aryl-2,2,2-trifluoroethyl tosylates the *secondary* system **12** reacts by a predominant k_c route (eq 10) for the systems studied, and these show a greater dependence of rate on the aryl substituents than do the *tertiary* substrates **1**. However the effect of solvent ionizing power is less in the *secondary* substrates than for the *tertiaries*. These results may be interpreted that the increased electron demand in the *secondary* system is satisfied by increased electron delocalization onto the aryl group so that there is consequently no greater solvent effect. The triflates $ArCH(OTf)CF_3$ evidently react by the k_c route in TFA and HFIP, but in EtOH and HOAc undergo significant solvent displacement with inversion of configuration.

Experimental Section

Fluorinated solvents and reagents were obtained from Aldrich and purified as reported previously[1] with the exception of (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol ((*R*)-(−)-**16**), which was supplied by Burdick and Jackson, Inc. The known[21] carbinols **14** were obtained from the ketones **13** and converted to sulfonate esters by the general procedure described below.

In a typical example 1 g (6 mmol) of phenyl trifluoromethyl ketone (**13c**) in 10 mL of MeOH was added in one portion to a solution containing 1 g (26 mmol) of $NaBH_4$ and 2 mL of 1 N NaOH in 20 mL of MeOH in a 50-mL round-bottom flask with a magnetic stirrer. After being stirred 1 h at 25 °C, the solution was poured into 25 mL of water which was extracted three times with 15-mL portions of ether. The combined ether layers were washed with 30 mL of H_2O and then with saturated NaCl, dried over Drierite, and evaporated on the rotary evaporator. The crude product was identified by NMR spectroscopy and converted directly to the sulfonate ester.

In a dry three-neck 100-mL round-bottom flask cooled in an ice bath and equipped with a magnetic stirrer, a drying tube, and septum inlets through which a slow stream of dry nitrogen was passed was placed 0.25 g (5 mmol) of NaH (50% in mineral oil) which was then washed three times by injecting 5-mL portions of pentane by syringe and then withdrawing the pentane. The wash was repeated twice with anhydrous ether, and then 10 mL of ether was added. A solution of 0.5 g (3 mmol) of 1-phenyl-2,2,2-trifluoroethanol (**14c**) in 10 mL of ether was slowly added to the flask via a syringe, and the solution was stirred 1 h. Then 0.6 g (3 mmol) of *p*-toluenesulfonyl chloride in 10 mL of ether was added to the flask slowly via a syringe, and the mixture was stirred for 4 h. Then 20 mL of H_2O was added, the layers were separated, and the aqueous layer was extracted three times with 15-mL portions of ether. The combined ether layers were washed once with 10 mL of 5% $NaHCO_3$ and once with saturated NaCl solution. The solution was dried over Drierite, filtered by gravity, and evaporated by using the rotary evaporator. The resulting solid was recrystallized from pentane–ether at 0 °C.

The tosylates and triflates **12** were prepared by this general procedure in crude yields of 50–65%, with the properties shown.

1-(*p*-Anisyl)-2,2,2-trifluoroethyl tosylate (12a): mp 55–56 °C; NMR (CCl_4) δ 2.38 (s, 3, $CH_3C_6H_4$), 3.75 (s, 3, $CH_3OC_6H_4$), 5.50 (q, 1, J = 6 Hz, $CHCF_3$), 7.5 (m, 8 aryl H). Anal. Calcd for $C_{16}H_{15}F_3O_4S$ (mol wt 360.36): C, 53.33; H, 4.20. Found: C, 52.76; H, 4.39.

1-(*p*-Tolyl)-2,2,2-trifluoroethyl tosylate (12b): mp 81.5–82 °C; NMR (CCl_4) δ 2.33, 2.42 (each s, 3, $ArCH_3$), 5.60 (q, 1, J = 6 Hz, $CHCF_3$); 7.0–7.7 (m, 8, Ar). Anal. Calcd for $C_{16}H_{15}F_3O_3S$ (mol wt 344.36): C, 55.81; H, 4.39. Found: C, 55.62, H, 4.48.

1-Phenyl-2,2,2-trifluoroethyl tosylate (12c): mp 112–113 °C (lit.[31] 114–116 °C); NMR (CCl_4) δ 2.40 (s, 3, $ArCH_3$), 5.65 (q, 1, J = 6 Hz, $CHCF_3$), 7.1–7.8 (m, 9, Ar). Anal. Calcd for $C_{15}H_{13}F_3O_3S$ (mol wt

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330.32), C, 54.54; H, 3.97. Found: C, 54.48; H, 4.06.

1-(*p*-**Bromophenyl**)-**2,2,2-trifluoroethyl tosylate** (**12d**): mp 92–92.5 °C; NMR (CCl_4) δ 2.45 (s, 3, $ArCH_3$), 5.60 (q, 1, J = 6 Hz, $CHCF_3$), 7.5 (m, 8, Ar).

The triflates **12e**, **12f**, and **12g** were oils whose NMR spectra (CCl_4) showed the $CHCF_3$ quartet at δ 5.80, 5.74, and 5.90, respectively, and aromatic signals around δ 7.5. A correct C, H analysis was obtained for **12g**.

Products were examined by placing approximately 30 mg of tosylate or triflate in an NMR tube in 0.5 mL of the appropriate solvent and heating for 10 half-lives for solvolysis. Distinctive shifts of the $CHCF_3$ quartet (J = 6 Hz) were observed, with the following chemical shift ranges: tosylates δ 5.8–6.1, triflates δ 6.0–6.1, ethyl ethers δ 4.6–4.8, acetates δ 6.1–6.2, and trifluoroacetates δ 6.3–6.4.

The products $PhCH(OCH_2CH_3)CF_3$ (**17a**) and $PhCH(O_2CCF_3)CF_3$ (**17b**) were isolated after aqueous workup and purification by VPC (3 m × 12 mm IV-17 at 150 °C) and gave consistent NMR spectra in CCl_4 (see above) and elemental analyses: Anal. Calcd for $C_{10}H_{11}F_3O$ (**17a**; mol wt 204.20): C, 58.82; H, 5.43. Found: C, 59.14; H, 5.56. Anal. Calcd for $C_{10}H_6F_6O_2$ (**17b**; mol wt 272.16): C, 44.13; H, 2.22. Found: C, 44.03; H, 2.36. The acetate $PhCH(O_2CCH_3)CF_3$ (**17c**) has been reported previously.[22a]

Kinetics were typically measured by injecting 1.5 μL of a 0.6 M solution of the sulfonate into 1.2 mL of solvent in a 1-cm path length UV cell thermostated in the cell compartment of a Cary 118 or 210 spectrophotometer. The reactions were monitored by observing the change in the UV absorption at a position near 260 nm, which gave a maximum absorbance change for the particular sulfonate and solvent.

For runs at higher temperatures aliquots were sealed in glass ampules and withdrawn from a constant temperature bath at appropriate intervals and stored in the freezer. When all the samples had been withdrawn, the absorbances of each of the solutions were measured. An acetolysis rate for **12b** was also measured by titration and gave the same rate constant as the spectrophotometric method.

Polarimetric rates were monitored by using a Perkin-Elmer 141 polarimeter with a 1-mL water-jacketed cell with a 10.0-cm path length, which was maintained at 25.0 °C as measured with a thermocouple. The substrate (*R*)-(−)-**12e** was unstable in an isolated state so freshly prepared material was dissolved in ether to give a 0.073 M stock solution that could be stored in the freezer for months without apparent decomposition. For kinetic runs 1 mL of the stock solution was evaporated on the rotary evaporator. For rate measurements in EtOH the solvent was added to the flask, and the solution transferred to a volumetric flask that was made up to 5 mL. Rates in other solvents were more rapid so the dry triflate was quickly dissolved in 2 mL of the temperature equilibrated solvent by drawing in and out of a pipet, and the solution was promptly transferred to the cell. Mixing and transfer required 70 s, and the first reading could be made 20 s later. Typically 10–20 readings were made over at least 2 half-lives, and excellent first-order kinetics (correlation coefficients always at least 0.999) were obtained. Rates were monitored at 365, 436, and 546 nm, with no difference in measured rate constants.

Runs in TFA and HFIP were conducted in which the reaction was quenched after 1 or 2 half-lives for the UV rates by pipetting the solution into pentane and ice water and separating the pentane layer, which was washed with $NaHCO_3$ and NaCl solutions and evaporated. The product was dissolved in CCl_4 and the NMR spectrum recorded to determine the relative amounts of reactant and product from the integrals of the $PhCH(OS)CF_3$ resonances. The solution from the NMR measurement was diluted with more CCl_4 and the optical rotation measured. Control experiments in which the reactant was subjected to the workup procedure without exposure to the TFA or HFIP solvent showed that with rapid handling no change in the NMR or optical rotation was observed. The results of these experiments are given in Table III.

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Registry No. **12a**, 84877-43-0; **12b**, 84877-44-1; **12c**, 13652-13-6; **12d**, 84877-45-2; **12e**, 84877-46-3; (*R*)-(−)-**12e**, 84877-47-4; **12f**, 84877-48-5; **12g**, 84877-49-6; **13c**, 434-45-7; **14c**, 340-04-5; **17a**, 65432-43-1; **17b**, 84877-50-9; **17c**, 17659-26-6; D, 7782-39-0.

Stereochemistry of Conformationally Restricted Analogues of the Antitumor Agent ICRF-159. 2.[1] Structures of Antimetastatically Active and Inactive Isomers of a Tricyclic Analogue

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Abstract: Crystal structure determinations of antimetastatically active and inactive isomers (*cis*- and *trans*-tetrahydrodipyrazino[1,2-*a*:2′,1′-*c*]pyrazine-1,3,10,12(2*H*,4*H*,9*H*,11*H*)-tetrone) of a tricyclic analogue of the antitumor agent ICRF-159 have been carried out. Comparisons of stereochemical parameters with those of the active cis cyclopropyl derivative of ICRF-159 have allowed conclusions to be reached regarding the molecular basis for the difference in activity in the tricyclic compounds. The trans-anti-trans isomer crystallizes in two solvated forms: crystals of the trans isomer in H_2O are triclinic, space group $P\bar{1}$ with cell constants a = 11.686 Å, b = 8.168 Å, c = 6.836 Å, α = 103.63°, β = 90.23°, γ = 112.83°, and two molecules per cell; crystals of the trans isomer in $(CH_3)_2SO$ are orthorhombic, space group *Pbcn*, a = 17.80 Å, b = 8.99 Å, c = 18.20 Å, with eight molecules per cell. Both structures were elucidated; the molecular conformations in the two crystals are virtually identical. Crystals of the cis-syn-trans tricyclic isomer are triclinic, space group $P\bar{1}$, with a = 6.33 Å, b = 7.35 Å, c = 13.70 Å, α = 116.61°, β = 94.95°, γ = 105.48°, and two molecules per unit cell.

The physiological and biochemical mechanisms underlying the processes of metastasis and the sites of action and effects of antineoplastic agents on metastatic tumor development are far from being well understood. Both for development of clinically useful drugs and for mechanistic studies, production of potent antimetastatic agents with defined stereochemistries is highly desirable.

Experiments with conformationally restricted cyclopropane analogues of the cytostatic agent ICRF-159 (**1**) have indicated that the cis isomer (**3**) has antimetastatic activity while the trans

(1) For part 1, see: Hempel, A.; Camerman, N.; Camerman, A. *J. Am. Chem. Soc.* **1982**, *104*, 3456–3458.

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