Competing, k_c, Borderline, k_s, and Carbonyl Addition Processes in Solvolyses of α-Keto Mesylates and Triflates. α-Keto Cations. 5

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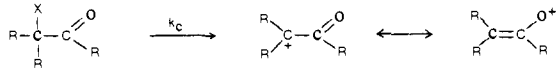
Abstract: Solvolysis studies on tertiary α-keto mesylates show quite varying responses in rate to solvent ionizing power. The *m* values are 1.01 for 2-benzoyl-2-adamantyl mesylate (**12**), 0.66 for the mesylate derivative of 2-hydroxy-2,4,4-trimethyl-3-pentanone (4), and 0.63 for the mesylate derivative of 2-hydroxy-2-methylpropiophenone (**3**). The mesylate derivative of methyl α-hydroxyisobutyrate (**5**) does not correlate well with Y_{OTs} values, but instead it gives behavior that parallels that of isopropyl tosylate. Mesylates **3–5** solvolyze giving varying ratios of elimination and substitution products at rates comparable to that of isopropyl mesylate. β-d_6 isotope effects for **3** and **4** range from 1.69 to 2.08 and are consistent with the intermediacy of α-keto cations. β-Deuterium isotope effects for **5** are quite variable (1.40–2.52) and parallel the amount of elimination product formed (22–94%). This is consistent with the intermediacy of a reversibly formed ion-pair intermediate which can suffer proton loss. However, the S_N2 (intermediate) mechanism remains a possibility in solvolyses of **5**. Mesylate **3** solvolyzed in trifluoroethanol with added triethylamine to give an alkoxyoxirane. With small amounts of added 2,6-lutidine the 1,2-elimination product was major, while with added methanesulfonic acid the rearranged trifluoroethyl ester of dimethylphenyl acetic acid was major. These variable products were interpreted in terms of competing carbonyl addition processes and processes involving the α-keto cation. Secondary triflates derived from α-hydroxypropiophenone, 2,2-dimethyl-4-hydroxy-3-pentanone, and ethyl lactate solvolyzed giving the simple substitution product. Rates parallel solvent nucleophilicity and suggest a k_s process involving negligible cationic character at the carbon α to the carbonyl group. k_Δ processes are also not involved in solvolyses of these secondary triflates.

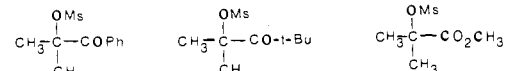
Our previous studies[1] have shown that α-keto mesylates, triflates, and trifluoroacetates can undergo solvolysis to give cationic intermediates. Many tertiary and secondary benzylic systems of type **1** reacted by k_c processes, giving discrete α-keto cations **2**.[2]



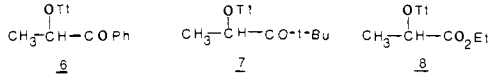
1 **2a** **2b**

The carbonyl group (relative to hydrogen) had a small or negligible rate-retarding effect on the solvolytic reactivity of these systems.[1c] This led to the suggestion that the cationic intermediate **2** can derive substantial stabilization by a conjugative interaction as in **2b**.[3]

We have previously reported[1c] a limited study of the reaction of mesylate **3** in acetic and trifluoroacetic acids. In order to more completely understand solvolytic processes in α-keto systems, a more complete study of **3** has been undertaken. The structurally related mesylates **4** and **5** have also been studied with the goal



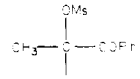
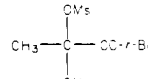
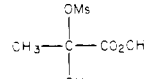
3 **4** **5**



6 **7** **8**

of generating α-keto cations. We also wanted to measure β-deuterium isotope effects in solvolyses of **3**, **4**, and **5** since this could serve as a measure of the demand for hyperconjugative stabilization in the cationic intermediate derived from these systems.[4] The solvolytic behavior of the secondary triflates **6**, **7**, and **8** has also been examined with the goal of evaluating the viability of discrete secondary α-keto cations. Reported here are the results of these studies.

Table I. Solvolysis Products from Mesylates 3, 4, and 5

mesylate	solvent	% of 9	% of 10
	HOAc	94	6
	TFE	(see Table III)	
	HCO_2H	81	19
	HFIP	97	3[a]
3	TFA	92[b]	8
	EtOH	95	5
	HOAc	100	trace[c]
	TFE	100	0
	HCO_2H	94	6
	HFIP	98	2[a]
4	TFA	97	3
	EtOH	22	78
	HOAc	70	30
	HCO_2H	39	61
	HFIP	94	6[a]
5	TFA	78	22

[a] Product is $(CH_3)_2C(OH)COR$. [b] Initial product ratio. Under the reaction conditions TFA slowly adds to 9 (R = Ph) to give 1-trifluoroacetoxy-2-methyl propiophenone, **38**. See Experimental Experimental Section. [c] Less than 1%; detected by GC.

Results and Discussion

Solvolytic Studies on 3 and 4. The structurally related mesylates **3** and **4** reacted in a variety of solvents to give the enones **9** as

(1) (a) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938–45. (b) Creary, X. *J. Am. Chem. Soc.* **1981**, *103*, 2463–5. (c) Creary, X.; Geiger, C. C. *Ibid.* **1982**, *104*, 4151–62. (d) Creary, X.; Geiger, C. C. *Ibid.* **1983**, *105*, 7123–9.

(2) For related studies in which α-keto cations have been generated, see: (a) Bégué, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207–12. (b) Takeuchi, K.; Kitagawa, T.; Okamoto, K. *Chem. Commun.* **1983**, 7. (c) Hopkinson, A. C.; Dao, L. H.; Duperrouzel, P.; Maleki, M.; Lee-Ruff, E. *Ibid.* **1983**, 727–8.

(3) A similar type of conjugative stabilization has been suggested for α-cyano cations. For leading references, see: Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279–85. This type of back-donation of carbonyl π-electrons, as a stabilization feature, was first suggested by McDonald to rationalize the apparent formation of α-keto cations from α-chloro epoxides. See: McDonald, R. N.; Steppel, R. N. *J. Am. Chem. Soc.* **1970**, *92*, 5664–70.

(4) For a discussion of β-deuterium isotope effects in solvolyses, see: (a) Shiner, V. J., Jr.; Buddenbaum, W. E.; Murr, B. L.; Lamaty, G. *J. Am. Chem. Soc.* **1968**, *90*, 418–26. (b) Fisher, R. D.; Seib, R. C.; Shiner, V. J., Jr.; Szele, I.; Tomič, M.; Sunko, D. E. *Ibid.* **1975**, *97*, 2408–12. (c) Collins, C. J.; Bowman, N. S. "Isotope Effects in Chemical Reactions"; Van Nostrand-Reinhold Co.: New York, 1970; ACS Monograph No. 167.

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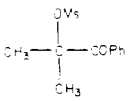
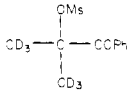
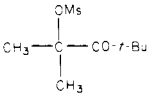
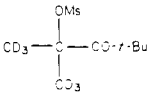
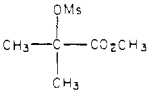
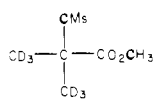
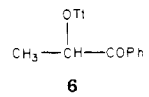
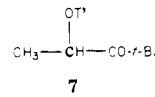
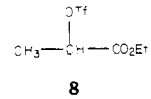
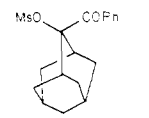
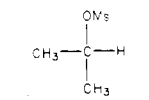
Table II. Solvolysis Rates of Mesylates and Triflates

compd	solvent[a]	temp, °C	k, s^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
 **3**	HOAc	100.0	2.34×10^{-4}	28.3	0.3
		75.0	1.44×10^{-5}		
		25.0[b]	1.30×10^{-8}		
	TFE	25.0	3.6×10^{-7} [c]		
	HCO_2H	50.0	9.21×10^{-5}	23.9	−3.2
		25.0	3.74×10^{-6}		
	HFIP	55.0	8.17×10^{-5}	23.6	−5.4
		25.0	1.93×10^{-6}		
	TFA	25.0	3.8×10^{-5}		
 **3-d_6**	HOAc	100.0	1.29×10^{-4}		
	HCO_2H	50.0	5.12×10^{-5}		
	HFIP	25.0	1.14×10^{-6}		
		55.0	4.93×10^{-5}		
 **4**	HOAc	80.0	2.53×10^{-4}	26.3	−1.0
		60.0	2.52×10^{-5}		
		25.0[b]	2.14×10^{-7}		
	EtOH	95.0	2.60×10^{-4}	26.1	−4.5
		75.0	3.17×10^{-5}		
		25.0[b]	4.87×10^{-8}		
	TFE	25.0	7.02×10^{-6}		
	HCO_2H	25.0	6.57×10^{-5}		
	HFIP	25.0	7.11×10^{-5}		
	TFA	25.0	1.1×10^{-3}		
 **4-d_6**	HOAc	80.0	1.37×10^{-4}		
	HCO_2H	25.0	3.16×10^{-5}		
	HFIP	25.0	3.46×10^{-5}		
 **5**	EtOH	120.0	3.01×10^{-4}	21.4	−20.7
		100.0	6.57×10^{-5}		
		25.0[b]	3.66×10^{-8}		
	HOAc	120.0	1.88×10^{-4}		
		110.0	7.14×10^{-5}		
		100.0	2.61×10^{-5}		
		25.0[b]	1.57×10^{-9}		
	TFE	100.0	7.16×10^{-5}	24.6	−12.1
		80.0	1.04×10^{-5}		
		25.0[b]	1.37×10^{-8}		
 **5-d_6**	EtOH	100.0	4.69×10^{-5}		
	HOAc	110.0	3.28×10^{-5}		
	HCO_2H	60.0	1.80×10^{-5}		
	HFIP	90.0	2.37×10^{-5}		
 **6**	EtOH	25.0	3.83×10^{-3}		
	HOAc	25.0	2.51×10^{-5} [d]		
	HCO_2H	25.0	6.83×10^{-5}		
	TFA	25.0	6×10^{-7} [d]		
 **7**	EtOH	25.0	2.72×10^{-3}		
	HOAc	25.0	1.22×10^{-5} [d]		
	HCO_2H	25.0	2.69×10^{-5}		
	TFA	25.0	3.7×10^{-7} [d]		
 **8**	EtOH	25.0	4.73×10^{-4}		
	HOAc	25.0	4.77×10^{-6} [d]		
	HCO_2H	25.0	8.18×10^{-6}		
	TFE	60.0	1.03×10^{-5} [d]		
	TFA	75.0	3×10^{-5} [d]		
		75.0	5×10^{-6} [d,e]		
 **12**	EtOH	80.0	1.66×10^{-4}	27.4	1.5
		60.0	1.50×10^{-5}		
		25.0[b]	1.04×10^{-7}		
	HOAc	25.0[b,f]	1.20×10^{-6}	27.3	6.1
	TFE	25.0	4.33×10^{-4}		
	HCO_2H	25.0	6.75×10^{-3}		
	HFIP	25.0	2.29×10^{-2}		
 **13-OMs**	HOAc	25.0	8×10^{-8} [g]		
	HCO_2H	25.0	2.26×10^{-5}		
	HFIP	25.0	1.29×10^{-6}		
	TFA	25.0	5.6×10^{-5}		

[a] EtOH; 0.025 M, 2,6-lutidine in ethanol. HOAc; 0.05 M NaOAc + 1% acetic anhydride in acetic acid. TFE; 0.025 M 2,6-lutidine in trifluoroethanol. HCO_2H; 0.05 M sodium formate in formic acid. HFIP; 0.05 M 2,6-lutidine in 97% hexafluoroisopropyl alcohol + 3% water (weight). TFA; 0.2 M sodium trifluoroacetate + 0.5% trifluoroacetic anhydride in trifluoroacetic acid. [b] Extrapolated from data at higher temperatures. [c] Initial rate constant with no added base. See Experimental Section. [d] Initial rate constant; rate constant decreases with time. See Experimental Section. [e] 0.04 M sodium trifluoroacetate. [f] Data from ref 1c. [g] Estimated from the tosylate rate (ref 6a) by assuming 13-OTs and 13-OMs have comparable reactivities in acetic acid.

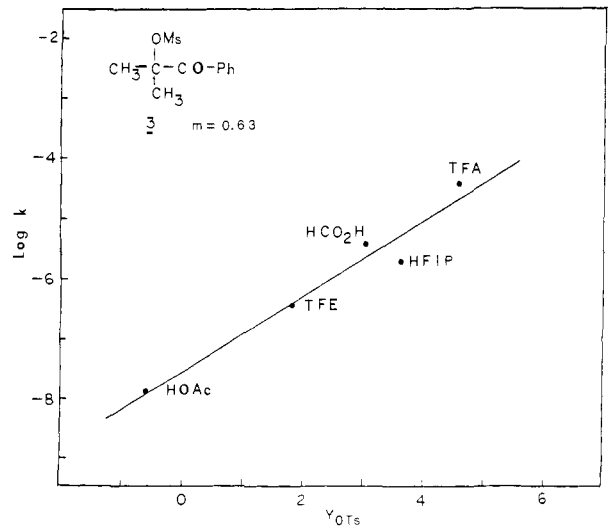


Figure 1. A plot of log k for solvolysis of **3** vs. Y_{OTs}.

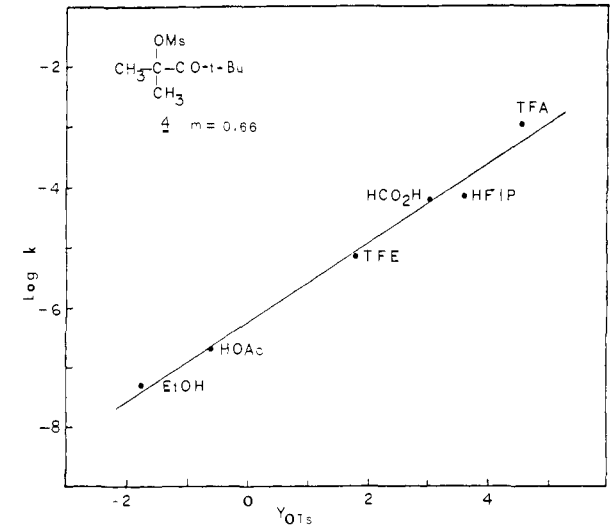


Figure 2. A plot of log k for solvolysis of **4** vs. Y_{OTs}.

the major product along with smaller amounts of the substitution product **10**. An exception is the behavior of **3** in trifluoroethanol. Details are given in Table I. Rate data for solvolyses of these mesylates are given in Table II. These data, for **3** and **4** as a

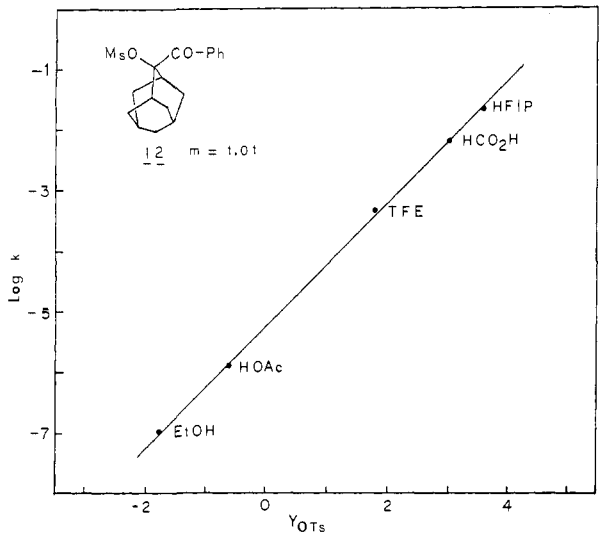
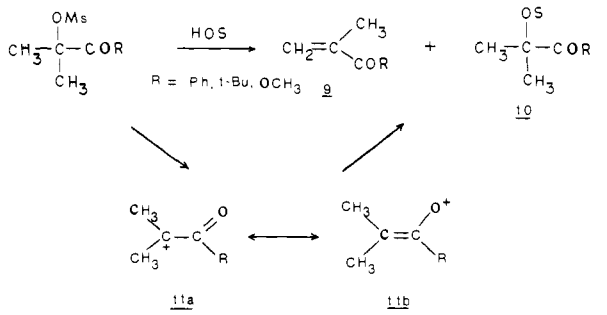


Figure 3. A plot of log k for solvolysis of **12** vs. Y_{OTs}.

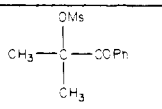
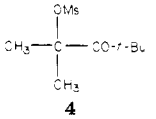
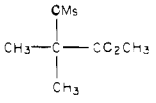
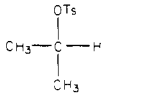
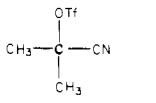
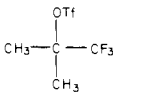
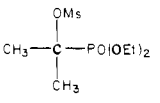
function of solvent ionizing power, Y_{OTs},[5] are presented graphically in Figures 1 and 2. The observed products and the relatively large



rate increases with solvent ionizing power are in line with the intermediacy of cations 11. However the m values of 0.63 and 0.66 are less than the defining value of 1.0 for 2-adamantyl tosylate and the value of 1.01 seen for the 2-benzoyl-2-adamantyl mesylate, **12** (Figure 3). Correlation coefficients for **3** and **4** (0.98 and 0.99) are not as high as for **12** (0.9998). Values in HFIP deviate somewhat from the line defined by the other solvents. The m values for **3** and **4** are 0.67 and 0.68, respectively, if data in HFIP are omitted from the plots. These solvent effects, although supportive of a transition state with substantial charge development, suggest the possibility of a certain degree of nucleophilic solvent involvement in formation of the cationic intermediate in the more nucleophilic solvents.[6] Solvolyses of **12**, however, appear to be limiting in all of the solvents studied.

β-Deuterium Isotope Effects in Solvolyses of 3 and 4. For further substantiation of the intermediacy of cations **11** in solvolyses of **3** and **4**, the β-d_6 isotope effect was measured. A summary of these data and related isotope effects is given in Table III. Values for mesylate **3** and **4** are variable, ranging from 1.69 to 2.08. These β-detuerium isotope effects are all in accordance with the α-keto cation intermediate **11**. Interestingly, the values are all smaller than the value of 2.12 seen for isopropyl tosylate, **13**-OTs, in trifluoroacetic acid[7] and 2.18 seen for the α-cyano triflate **14** in trifluoroethanol.[8] These latter two substrates are both considered to solvolyze via k_c processes in TFA and TFE.

Table III. Summary of β-Deuterium Isotope Effects

compd	solvent	temp, °C	k_{H_6}/k_{D_6}
 **3**	HOAc	100	1.81
	HCO_2H	50	1.80
	HFIP	25	1.69
	HFIP	55	1.66
 **4**	HOAc	80	1.85
	HCO_2H	25	2.08
	HFIP	25	2.06
 **5**	EtOH	100	1.40
	HOAc	110	2.18
	HCO_2H	60	2.00
	HFIP	90	2.52
 **13**	TFA[a]	25	2.12
	H_2O[b]	30	1.55
	97% TFE[c]	45	1.58
	TFA[g]	25	2.01–2.05
 **14**	TFE[d]	65	2.40
	TFE[d]	25	2.18
 **29**	EtOH[e]	70.5	3.73
	EtOH[e]	64	3.97
	80% EtOH[e]	55	3.78
	97% TFE[e]	64	3.73
 **32**	HOAc[f]	100	2.87
	HCO_2H[f]	90	2.73
	TFA[f]	70	2.78

[a] Reference 6. [b] Reference 33. [c] Reference 22a. [d] Reference 7. [e] Reference 17. [f] Reference 19. [g] For the naphthalene-β-sulfonate ester, see ref 37.

The implication, from comparison of the isotope effect data (in HFIP where solvolyses are undoubtedly limiting), is that there is no unusually large demand for hyperconjugative stabilization in the cationic intermediate **11**. This supports the idea of conjugative stabilization, as represented by **11b**, of the cationic intermediate by the inductively electron-withdrawing group. If the carbonyl group were only on inductively destabilizing group, then the demand for hyperconjugative stabilization in **11** would be much larger than in the isopropyl cation. A β-d_6 effect of greater than 2.12 would be expected.

Solvolysis of Mesylate 3 in Trifluoroethanol. The behavior of **3** in trifluoroethanol was a complex function of temperature, added base, or acid present in the reaction medium. Under various conditions, up to six products could be found. Details are given in Table IV. First-order plots of data obtained in trifluoroethanol with added bases (triethylamine, 2,6-lutidine, or sodium acetate added to neutralize the methanesulfonic acid released) were nonlinear, showing decreasing slopes with increasing time. In the absence of added bases, the reaction rate increased with increasing time. In the presence of triethylamine (entry 1), a new and unusual product, the epoxide **15** is the major product along with a small amount (2%) of the rearranged ester **16**. With the weaker bases, 2,6-lutidine or sodium acetate, one sees the elimination product **9** (R = Ph) as the major product, along with increased amounts of the rearranged ester **16**. At elevated temperatures, the amount of elimination product **9** further increases at the expense of the rearranged product **16**. With no added base (entries 7 and 8), the enone **9** is still the major product, but two new products, **17** and **18**, begin to appear. Finally, at room temperature, when methanesulfonic acid is added to the trifluoroethanol

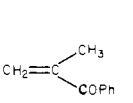
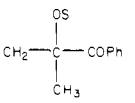
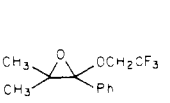
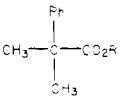
(5) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667–74.

(6) For a discussion of this mechanism, termed S_N2 (intermediate), see: (a) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7658–66. (b) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *Ibid.* **1981**, *103*, 5466–75.

(7) Streitwieser, A., Jr.; Dafforn, G. A. *Tetrahedron Lett.* **1969**, 1263–6.

(8) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 1214–6.

Table IV. Solvolysis Products from **3** in Trifluoroethanol

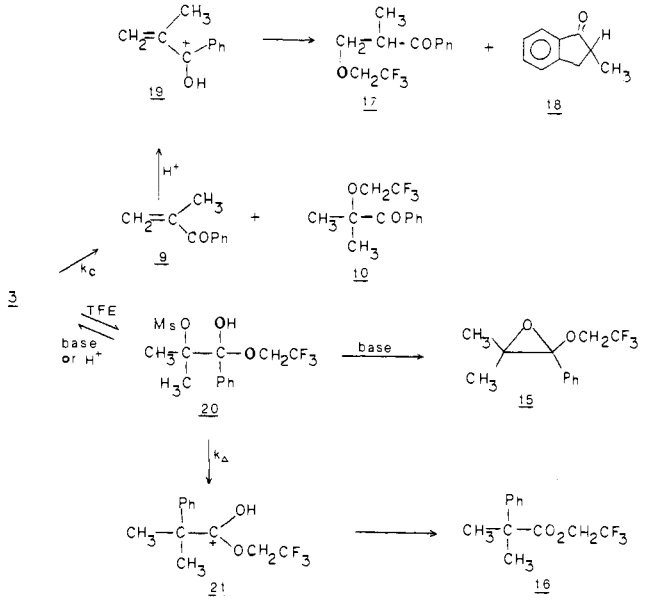
entry	conditions	 **9**	 **10**	 **15**	 **16**
1	0.15 M Et_3N (60 °C)	trace[a]	0	98	2
2	0.025 M Et_3N (60 °C)	10	0	80	10
3	0.025 M 2,6-lutidine (60 °C)	61	2	2	35
4	0.025 M 2,6-lutidine (100 °C)	96	1	0	3
5	0.05 M 2,6-lutidine (100 °C)	94	1	trace[a]	5
6	0.025 M NaOAc (65 °C)	75	2	0	23
7	no base, 0.005 M **3**	83[b]	1	0	3
8	no base, 0.022 M **3**	64[c]	2	0	9
9	0.1 M CH_3SO_3H (3 days)	11[d]	0	0	44
10	0.1 M CH_3SO_3H (17 days)	10[e]	0	0	77

[a] Detected by gas chromatography. [b] 8% of **17** and 5% of **18** also produced. [c] 16% of **17** and 9% of **18** also produced. [d] 45% unreacted **3** remained. [e] 13% of **17** also observed.

at the beginning of the solvolysis (entries 9 and 10), the rearranged ester **16** becomes the major product.

The variety of products seen in the trifluoroethanolysis of **3** is suggested to arise by the competing processes shown. Enone **9** and the substitution product **10** arise, as before, from the k_c process involving cation **11**. Ketone **17** and 2-methylindanone (**18**) are secondary products. They are derived from a methanesulfonic acid catalyzed reaction of the primary product **9** in the absence of a buffering base.[9] Carbonyl protonation followed by solvent addition to the methylene group of **19** and re-ketonization would give **17**. Intramolecular cyclization of **19** via the electron-deficient methylene carbon would lead to **18**.

The epoxide **15** is suggested to arise from a general base catalyzed addition to trifluoroethanol to the carbonyl group of **3**,[10] giving **20**, followed by intramolecular displacement of mesylate by the hydroxy group of **20**. This cyclization process is, in all



probability, also base catalyzed. Hence epoxide **15** is formed in the presence of the stronger base, triethylamine, but not to any significant extent with added 2,6-lutidine or sodium acetate. This general type of reaction has precident. Alkoxyoxiranes or products derived from these reactive epoxides can sometimes be isolated in reactions of α-halo ketones[11] or α-keto triflates[12] with alkoxide ion.

Since the addition of trifluoroethanol to the carbonyl group is general base catalyzed, there is a rate slowdown as the reaction proceeds and the buffering base is consumed. Hence first-order plots under these conditions are nonlinear. As base concentration, or base strength, is reduced, the competing k_c process becomes more important; hence increased amounts of the enone **9** are seen with 2,6-lutidine or sodium acetate as the buffering base.

The rearranged ester **16** is observed in quite variable amounts under all conditions. It is suggested to arise from solvolysis of the hemiketal **20** by a k_Δ process involving phenyl migration. Similar rearranged products have been observed by Cope,[13] Pasto,[14] and De Kimpe[11i] in the silver-assisted solvolysis of α-bromoisobutyrophenone, and a mechanism involving carbonyl addition has previously been suggested. In trifluoroethanolysis of **3** with Et_3N, virtually all of the tetrahedral adduct **20** is consumed by a base-catalyzed process leading to epoxide **15**. As Et_3N concentration decreases (entry 2) or base strength decreases (entries 3 and 6), the k_Δ process, involving phenyl migration in **20**, becomes more important. Hence the amount of **16** increases.

The formation of hemiketal **20** is also catalyzed by the methanesulfonic acid produced as the solvolysis proceeds under unbuffered conditions. Hence the apparent rate constant increases with time under unbuffered conditions.[15] The tetrahedral adduct **20** now gives the rearranged ester **16**, since there is no base to promote the epoxide-forming process. With added methanesulfonic acid (entries 9 and 10) the equilibrium between **3** and **20** is more rapidly established, resulting in the formation of the rearranged ester **16** as the major product.

The temperature effects on product distribution are probably a result of differing rate reponses for the competing cationic and carbonyl addition processes as temperature varies. The carbonyl addition sequence probably has a more negative entropy of activation than the k_c process and hence should give smaller rate increases with increasing temperature. Hence higher temperatures should favor formation of the enone **9** derived from the k_c process.

It is of interest to compare the behavior of mesylate **3** in TFE

(9) Enone **9** (R = Ph) also rearranges to **18** in the presence of $AlCl_3$. See: Combaut, G.; Giral, L. *Bull. Chim. Soc. Fr.* **1970**, 3710–4.

(10) For a discussion and leading references on general base (and general acid) catalyzed alcohol additions to carbonyl groups, see: Jencks, W. P. In "Catalysis in Chemistry and Enzymology"; McGraw-Hill, Inc.: New York, 1969; p 497.

(11) (a) Wagner, R. B.; Moore, J. A. *J. Am. Chem. Soc.* **1950**, *72*, 2884–7. (b) Stevens, C. L.; Malik, W.; Pratt, R. *Ibid.* **1950**, *72*, 4758–60. (c) Stevens, C. L.; Farkas, E. *Ibid.* **1952**, *74*, 618–20. (d) Stevens, C. L.; Weiner, M. L.; Freeman, R. C. *Ibid.* **1953**, *75*, 3977–80. (e) Loftfield, R. B.; Schaad, L. *Ibid.* **1954**, *76*, 35–7. (f) Stevens, C. L.; DeYoung, J. J. *Ibid.* **1954**, *76*, 718–20. (g) Stevens, C. L.; Weinheimer, A. J. *Ibid.* **1958**, *80*, 4072–5. (h) Karavan, V. S.; Temnikova, T. I. *J. Org. Chem. USSR* (*Engl. Transl.*) **1966**, *2*, 1399–1404, 1405–1408. (i) De Kimpe, N.; DeBuyck, L.; Verke, R.; Schamp, N. *Chem. Ber.* **1983**, *116*, 3631–6.

(12) Creary, X., Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4226–30.

(13) Cope, A. C.; Graham, E. S. *J. Am. Chem. Soc.* **1951**, *73*, 4702–6.

(14) (a) Pasto, D. J.; Sevenair, J. P. *J. Am. Chem. Soc.* **1971**, *93*, 711–6. For a related rearrangement of 1-bromocyclohexyl phenyl ketone, see: (b) Baudry, D.; Charpentier-Morize, M. *Tetrahedron Lett.* **1973**, 3013–6.

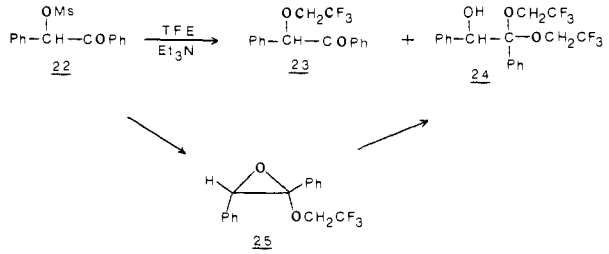
(15) The silver-assisted solvolysis of α-bromoisobutyrophenone is also acid catalyzed. See ref 14a.

Table V. Comparison of Solvolysis Rates of 3, 4, 5, and 12 at 25 °C with α-H Analogues

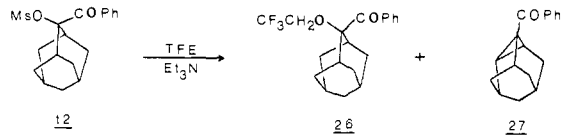
solvent	$k_3/k_{i\text{-PrOMs}}$	$k_4/k_{i\text{-PrOMs}}$	$k_5/k_{i\text{-PrOMs}}$	$k_{12}/k_{2\text{-AdOMs}}$[c]
HOAc	0.16	2.7	0.020	164[a]
HCO_2H	0.17	2.9	0.019	316[b]
TFA	0.7	20	0.006	
HFIP	1.5	55	0.024	291[b]
TFE				356[b]
EtOH				300[b]

[a] See ref 1c for data on 2-adamantyl mesylate. [b] Estimated from the tosylate rate (ref 5) assuming a mesylate/tosylate rate ratio of 1.24. See ref 1c for determination of this ratio. [c] 2-AdOMs = 2-adamantyl mesylate.

with that of mesylates **22**, **12**, and **4**. With 2,6-lutidine as the buffering base, **22** gave only the substitution product **23**, presumably via the k_c process.[1c] However, when triethylamine was present in relative high concentrations (0.15 M), the hydroxy ketal **24** (38%) was also produced along with **23** (62%). This product, **24**, is probably derived from the intermediate epoxide **25**, which does not survive the reaction conditions.



In contrast, mesylate **12** gave only the substitution product **26** and a small amount of the 1,3-elimination product **27** when either 2,6-lutidine or triethylamine was used as the buffering base. No



epoxide or epoxide-derived products were found. On trifluoroethanolysis, mesylate **4** also gave no epoxide-derived products in the presence of triethylamine. The complete dominance of the k_c process in trifluoroethanolyses of mesylates **4** and **12** is attributed to the reluctance of the more hindered carbonyl groups of these systems to form tetrahedral adducts.

Effect of the Carbonyl Group on Solvolysis Rates of Mesylates 3, 4, and 12. The data given in Table II permit comparison of the solvolysis rates of **3** and **4** with that of isopropyl mesylate, **13**-OMs. A summary of these comparisons is given in Table V. In trifluoroacetic acid and hexafluoroisopropyl alcohol, where presumably all of these solvolyses are close to limiting,[5,6a,16] the reactivity of **3** is comparable to that of isopropyl mesylate despite the electron-withdrawing benzoyl group in **3**. Mesylate **4** is substantially more reactive than isopropyl mesylate in the more highly ionizing solvents. Mesylate **12**, as previously observed,[1c] is also much more reactive than 2-adamantyl mesylate. These results are in accord with our previous observation[1c] of a negligable effect on rate (relative to hydrogen) by the formally electron-withdrawing carbonyl group. The α-keto cations **11** therefore form at rates comparable to formation rates of the isopropyl cation **28**.

As before, we suggest that the electron-withdrawing inductive

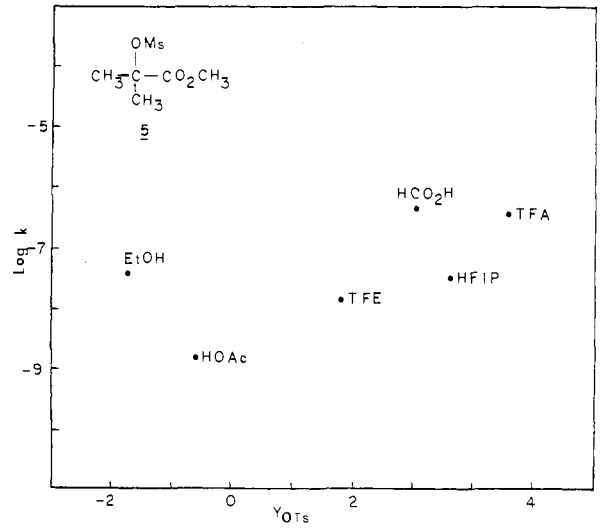


Figure 4. A plot of log k for solvolysis of **5** vs. Y_{OTs}.

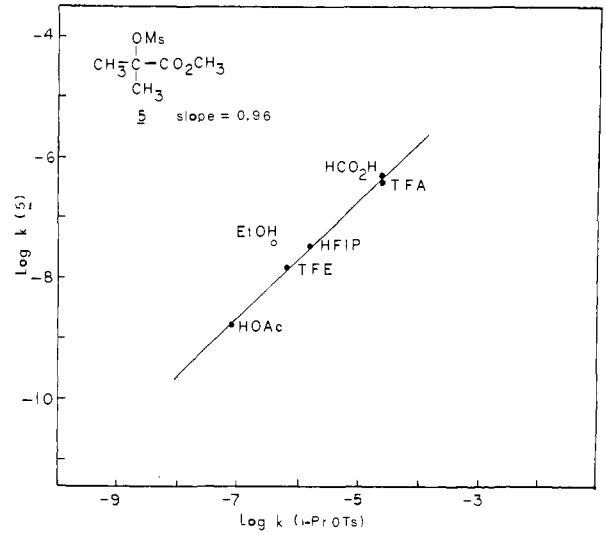


Figure 5. A plot of log k for solvolysis of **5** vs. log k for solvolysis of *i*-PrOTs.

effect of the carbonyl group in **11** is offset by a conjugative interaction as represented by **11b**. Mesylates **3**, **4**, and **12** therefore undergo quite facile solvolyses.

Solvolytic Studies on 5. Mesylate **5** reacted in a variety of solvents (Table I) to give varying amounts of methyl methacrylate (**9**, R = OCH_3) and the substitution product **10** (R = OCH_3). At first glance, one is tempted to suggest that the mechanism is similar to the solvolysis mechanism for **3** and **4**. However, the solvent effect on reaction rate contrasts with that of **3**, **4**, and **12**. The plot of log k vs. Y_{OTs} (Figure 4) is scattered.[17] Figure 5 shows a comparison of the solvent behavior of 5 with that of isopropyl tosylate.[5,6] Solvent effects are similar. The slope of the plot (excluding the data in ethanol) is 0.96 (r = 0.999).

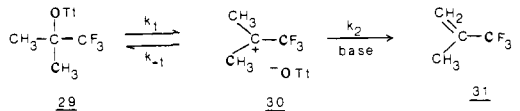
The behavior of **5** is similar to that of triflate **29**[18] which also gives a scattered Winstein–Grunwald plot. Tidwell[18] has suggested that triflate **29** undergoes solvolysis, giving exclusively the elimination product **31**, by a mechanism involving rate-limiting proton loss ($k_2 < k_{-1}$) at an ion-pair stage. This is an example of the $E2_{C^+}$ mechanism,[19,20] the cationic analgoue of the E1cb mecha-

(16) (a) Schadt, F. L.; Schleyer, P. v. R. *Tetrahedron Lett.* **1974**, 2335–8. (b) Nordlander, J. E.; Greutzmacher, R. R.; Kelly, W. J.; Jindal, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 181–5 and references therein.

(17) This behavior contrasts with that of i, which gave a resonable correlation with Y_{OTs}. The m value for i was 0.87 (vs. k_t) or 1.0 (vs. k_α). See ref

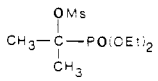
(18) Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1981**, *103*, 3863–7.

nism. The evidence for this mechanism included the lack of correlation of rate with Y_{OTs} values, the effect of added base on



29 30 31

the reaction rate, and a large β-D_6 deuterium isotope effect (k_{H_6}/k_{D_6} = 3.8) which was greater than the square of the β-D_3 isotope effect. We have recently suggested[20] that mesylate **32** also solvolyzes by a mechanism in which k_2 is important in the kinetic scheme. This type of mechanism must be considered in the solvolysis of **5**.



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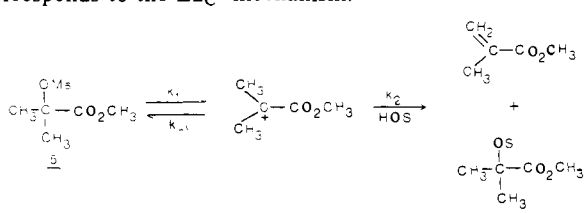
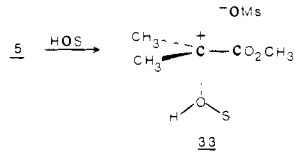
On the basis of the correlation of solvolysis rate of **5** with that of isopropyl mesylate, a similar mechanism might operate. However, the solvolysis mechanism for such substrates has been a controversial area.[6] Solvolysis rates of isopropyl tosylate respond to increasing solvent ionizing power. Rates also respond to increasing solvent nucleophilicity. It has been suggested by Sneen[21] that ion pairs are involved in solvolyses of such "border line" substrates with solvent capture and internal return processes of comparable magnitude. Shiner's[22] mechanistic scheme for solvolyses of simple secondary substrates includes all possible ion pairs as well as a variety of rate-limiting steps. If analogous reversibly formed ion pairs were involved in solvolysis of **5**, then rates could well parallel those of isopropyl tosylate. Rates of solvolysis of **5** should respond to a blend of solvent ionizing power and solvent basicity (just as isopropyl tosylate responds to solvent nucleophilicity). In the extreme where k_2 is rate limiting, this corresponds to the $E2_{C^+}$ mechanism.



5

For further insights into the solvolysis mechanism of **5** to be gained, β-D_6 deuterium isotope effects were measured (Table III). Values range from relatively small (1.40 in ethanol) to relatively large (2.52 in HFIP). these values are smaller than Tidwell's values[18] of about 3.8 seen in solvolyses of **29**, where k_2 is rate limiting, and our value[20] of 2.8 for **32**. The isotope effect for **5** in HFIP is largest and the largest amount of the elimination product **9** (94%) is seen in this solvent. In ethanol, where the isotope effect is smallest, the least elimination (22%) is seen. In other solvents the amount of elimination product **9** also parallels the β-D_6 isotope effect. These trends support the idea of k_2 being kinetically important despite the fact that the isotope effects are not of the magnitude seen for **29** and **32**.

An alternative mechanism which attempts to account for solvent effects in solvolysis of secondary substrates is due to Bentley and Schleyer.[6] This mechanism, termed S_N2 (intermediate), involves formation of a nucleophilically solvated ion pair, in which formation of this intermediate is accelerated by solvent nucleophilicity.[23] Such a mechanism accounts for the response of certain



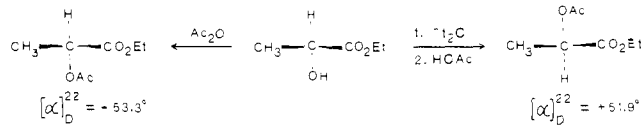
33

secondary substrates to a blend of solvent ionizing power *and* nucleophilicity. The S_N2 (intermediate) mechanism, which would involve the nucleophilically solvated ion pair **33**, would account for the correlation of rate with that of isopropyl tosylate.

While the solvent effect study is in line with the S_N2 (intermediate) mechanism, other data are not. There is no immediately apparent reason why **5** should be more susceptible to solvent nucleophilicity than **3** or **4**. In fact our subsequent data show that the analogous secondary ester **8** is less susceptible to solvent nucleophilicity than the ketones **6** and **7**. The fact that the solvents giving larger β-D_6 isotope effects also give greater amounts of elimination is also difficult to accomodate by the S_N2 (intermediate) mechanism. While this mechanism cannot be ruled out, the available data support a mechanism involving ion-pair formation where k_2 and k_{-1} can be comparable in magnitude. More information will be necessary to establish the precise nature of the ion pair(s) involves in solvolyses of **5**.

Solvolytic Studies on Triflates 6, 7, and 8. With reactivity patterns in the tertiary systems **3**, **4**, and **5** having been established, attention was next focused on the analogous secondary substrates **6**, **7**, and **8**. These triflates all gave exclusively the substitution products **34** under solvolytic conditions.[24] Examination of the data in Table II shows that reactivity follows the order **6** > **7** > **8**. Rates are faster in ethanol than in acetic acid. Rates in acetic acid are comparable to formic acid rates. Additionally, trifluoroacetolysis rates are the slowest. Strict first-order behavior was not observed in acetic and trifluoroacetic acids. The first-order rate constants were dependent on the concentration of buffering sodium acetate or sodium trifluoroacetate and hence decreased during the course of the solvolysis.

For further insights to be gained, optically active triflate **8**, prepared from (*S*)-(−)ethyl lactate, was solvolyzed in acetic acid. The acetate product had a specific rotation of +51.9 ± 0.2° while the acetate prepared by reaction of acetic anhydride with (*S*)-



(−)-ethyl lactate had a rotation of −53.3 ± 0.2°. The acetolysis product therefore has a 97.4% enantiomeric excess of the inverted product (along with a 2.6% racemization). Solvolyses in formic acid gave completely analogous results. These studies were consistent with a k_s process. The origin of the small amount of racemiziation is uncertain and may be due to slight racemization in preparation of the triflate.

The solvolytic rate behavior of the secondary triflates **6**, **7**, and **8** is also consistent with a k_s process involving negligible cationic character at the carbon α to the carbonyl group.[25] The effect

(19) Ingold, C. K. In "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell University Press: Ithica, New York, 1969; p 955.

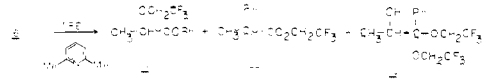
(20) For a discussion of the $E2_{c^+}$ mechanism, see: Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1983**, *105*, 2851–8. In this generalized mechanism, no attempt has been made to distinguish between intimate, solvent-separated, or other ion pairs with varying degrees of solvation. It is assumed that elimination can occur at any ion-pair stage.

(21) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46–53.

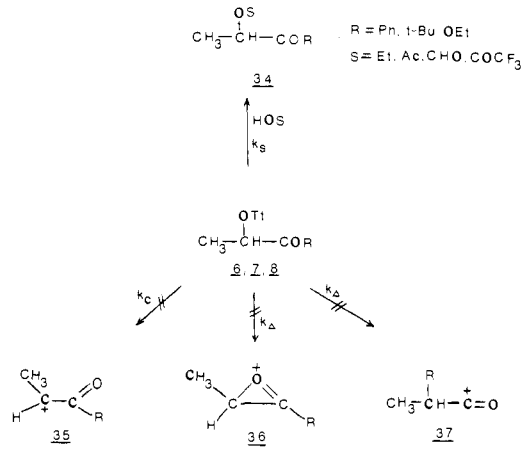
(22) (a) Shiner, Jr., V. J.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessich, M. A.; Milakofsky, L.; Rapp, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 4838–43. (b) Shiner, V. J., Jr.; Fisher, R. D.; Dowd, W. *Ibid.* **1969**, *91*, 7748–9. (c) Seib, R. C.; Shiner, V. J., Jr.; Sendijarevic, V.; Humski, K. *Ibid.* **1975**, *100*, 8133–37.

(23) The carbonyl group is known to accelerate nucleophilic attack at the α-carbon. See: Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645–50.

(24) An exception is the behavior of **6** in trifluoroethanol. With 2,6-lutidine as added base, **6** gave ii as well as iii and iv derived from base-catalyzed addition of trifluoroethanol to the carbonyl group.



of solvent on reactivity contrasts with the behavior of mesylates **3**, **4**, and **5**. Reactivity of triflates **6**, **7**, and **8** parallels solvent nucleophilicity rather than solvent ionizing power. Even in the



nonnucleophilic trifluoroacetic acid solvent, there is no evidence for cationic intermediates such as **35–37**. Solvent nucleophilicity is great enough in the solvents examined so that secondary α-keto cations **35** are not observed. Potential k_Δ processes involving carbonyl oxygen participation giving **36** or acylium ions **37** are also bypassed in favor of the nucleophilic solvolysis mechanism.

Conclusions. Mesylates **3** and **4** can solvolyze giving α-keto cation intermediates, **11**. This is supported by solvent effect and β-detuerium isotope effect studies. The β-deuterium isotope effects indicate that there is no unusually large demand for hyperconjugative stabilization in the cationic intermediates. The rate-retarding inductive effect of the carbonyl group (relative to hydrogen) in solvolyses of **3** and **4** is nil. These features support an intermediate in which carbonyl conjugation, as in **11b**, is an important feature in stabilizing the cation. In trifluoroethanol, mesylate **3** could give competing acid- or base-catalyzed solvent addition to the carbonyl group. This leads to the formation of epoxide **15** as the major product with triethylamine as a buffering base, enone **9** as the major product under more neutral conditions, and the rearranged ester **16** under acidic conditions. Solvolyses of mesylate **5** gave rate behavior similar to that of isopropyl tosylate, suggesting either the operation of the S_N2 (intermediate) mechanism or a reversibly formed ion-pair mechanism. β-Deuterium isotope effect data supported the reversibly formed ion-pair mechanism. The secondary triflates **6**, **7**, and **8** all solvolyze by a nucleophilic solvolysis mechanism, bypassing potential secondary α-keto cations **35**. The k_Δ processes, involving carbonyl participation as in **36**, or acylium ion **37**, are also bypassed in favor of the k_s process. α-Keto mesylates and triflates can therefore solvolyze over the entire spectrum of mechanisms ranging from k_s, to borderline, to k_c processes. Under appropriate conditions, with certain substrates, processes initiated by solvent addition to the carbonyl group can also compete.

Experimental Section

Gas-chromatographic analyses were carried ou on a Hewlett-Packard 5750 chromatograph with flame ionization detector and a 6-ft 5% SE-30 on Chromosorb G column. A Varian 920 chromatograph was used for sample isolation. NMR spectra were recorded on a Varian EM 390 or a Nicolet NB 300 spectrometer. Titrations were carried out on a Metrohm E57 automatic recording titrator. Optical rotations were obtained on a Rudolph Autopol III automatic polarimeter. Maximum error in observed rotation was ±0.01°.

Preparation of Mesylate 3 and 3-d_6. The preparation of **3** has been previously described.[1c] The preparation of **3**-d_6 from α-hydroxyisobutyrophenone-d_6 was identical with the preparation of **3**. The preparation of α-hydroxyisobutyrophenone-d_6 from acetone-d_6 and lithium diethyl 1-(trimethylsiloxy)-1-(phenylmethyl)phosphonate was identical to with the previously described[1c] procedure using undeuterated acetone.

Preparation of 2-Hydroxy-2,4,4-trimethyl-3-pentanone. A solution of 2.55 g of 2-cyano-2-(trimethylsiloxy)propane[26] in 15 mL of dry ether was cooled to −78 °C and 10 mL of 2.6 M *tert*-butyllithium in pentane was added dropwise. The mixture was allowed to warm to 0 °C and stirred for an additional 5 min at 0 °C. Water was added and the organic phase separated, washed with water and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed by rotary evaporator, and the residue was distilled through a short-path condenser. The imine of 2-(trimethylsiloxy)-2,4,4-trimethyl-3-pentanone (2.32 g, 66%), bp 96 °C (20 mmHg), was the product isolated. NMR ($CDCl_3$) δ 1.51 (6 H, s), 1.26 (9 H, s), 0.19 (9 H, s).

The imine (2.32 g) was dissolved in 15 mL of tetrahydrofuran (THF), and a solution of 1.45 g of H_2SO_4 in 14 mL of water was added dropwise to the stirred mixture. After being stirred for 7 h at room temperature the acid was neutralized with Na_2CO_3. The mixture was taken up into ether, and the organic phase was dried over $MgSO_4$. The solvent was removed with use of a rotary evaporator, and the solid residue was distilled through a short-path condenser with a steam line to prevent solidification of the product. The yield of 2-hydroxy-2,4,4-trimethyl-3-pentanone,[27] bp 96–98 °C (50 mmHg), mp 48–50 °C, was 1.50 g (97%). NMR ($CDCl_3$) δ 3.43 (1 H, br s), 1.44 (6 H, s), 1.28 (9 H, s).

Preparation of Mesylate 4. A solution of 1.50 g of 2-hydroxy-2,4,4-trimethyl-3-pentanone in 12 mL of CH_2Cl_2 was cooled to 0 °C, and 2.14 g of CH_3SOCl[28] was added. Triethylamine (2.6 g) was added dropwise. After the addition was complete, the mixture was stirred for 15 min at room temperature. The mixture was then taken up into ether and water. The organic phase was washed with dilute HCl and saturated NaCl solution and dried over $MgSO_4$. After solvent removal with use of a rotary evaporator the residue was distilled giving 1.84 g (86%) of the methyl sulfinate ester of 2-hydroxy-2,4,4-trimethyl-3-pentanone, bp 68–71 °C (0.3 mm Hg). NMR ($CDCl_3$) δ 2.76 (3 H, s), 1.65 (3 H, s), 1.60 (3 H, s), 1.27 (9 H, s).

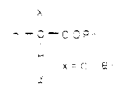
The sulfinate ester obtained above was dissolved in 15 mL of CH_2Cl_2, and 2.12 g of 85% *m*-chloroperbenzoic acid was added in one portion. The mixture was periodically cooled so that the temperature of the mixture did not exceed 30 °C. After 2 h at room temperature, the mixture was taken up into ether and washed successively with KOH in water, a KOH, NaI, $Na_2S_2O_3$ mixture in water, and a saturated NaCl solution. After being dried over $MgSO_4$, the solvent was removed with use of a rotary evaporator. The crude mesylate **4** which solidified was slurried with 5 mL of pentane and collected on a Buchner funnel and weighed 1.70 g (86%), mp 64–65 °C. NMR ($CDCl_3$) δ 3.11 (3 H, s), 1.80 (6 H, s), 1.29 (9 H, s). Anal. Calcd for $C_9H_{18}O_4S$: C, 48.63; H, 8.16. Found: C, 48.78; H, 8.43.

Preparation of Mesylate 4-d_6. The preparation of **4**-d_6, starting with acetone-d_6, was identical with the preparation of **4** from acetone.

Preparation of Mesylate 5. A solution of 3.43 g of the methyl ester of α-hydroxyisobutyric acid in 40 mL of CH_2Cl_2 and 5.13 g of Et_3N was cooled to −50 to −40 °C, and 4.58 g of mesyl chloride in 5 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to warm to 0 °C and taken up into ether, washed with water, dilute HCl, and saturated NaCl solution, and dried over $MgSO_4$. After solvent removal with use of a rotary evaporator, the residue was distilled giving 5.23 g (92%) of **5**, bp 62–65° (0.05 mm Hg). Mesylate **5**, mp 27–29 °C, solidified in the refrigerator. NMR ($CDCl_3$) δ 3.82 (3 H, s), 3.13 (3 H, s), 1.73 (6 H, s). Anal. Calcd for $C_6H_{12}O_5S$: C, 36.73; H, 6.16. Found: C, 36.59% H, 6.37.

Preparation of Methyl α-Hydroxyisobutyrate-d_6. In accordance with Baldwin's procedure,[29] a solution of 2.8 g of methyl vinyl ether in 15 mL of THF was cooled to −78 °C and 13 mL of 2.6 M *tert*-butyllithium was added dropwise. The mixture was allowed to warm to 0 °C and then recooled to −78 °C. A solution of 1.8 g of acetone-d_6 in 8 mL of THF was added, and the mixture was warmed to 0 °C. Water was added, and the mixture was taken up into ether. A drop of triethylamine was added to the organic phase which was then washed with saturated NaCl solution

(25) An analogous S_N2-type process has been suggested in the silver-assisted solvolysis of the primary substrate v. See: (a) Pasto, D. J.; Garves, K.; Serve, M. P. *J. Org. Chem.* **1967**, *32*, 778–81.



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(29) Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125–7.

and dried over $MgSO_4$. The solvent was removed with use of a rotary evaporator and the residue was distilled giving 1.91 g (56%) of 2-methoxy-3-hydroxy-3-methyl-1-butene-d_6, bp 47–49 °C (20 mmHg). NMR ($CDCl_3$) δ 4.21 (1 H, d, J = 3 Hz), 3.90 (1 H, d, J = 3 Hz), 3.60 (3 H, s), 2.21 (1 H, s, exchanges with D_2O).

A solution of 1.62 g of the enol ether obtained above, in 10 mL of methanol containing 1 drop of pyridine, was cooled to −78 °C and exhaustively ozonized (until a faint blue color appeared). The mixture was warmed to room temperature, and a solution of 0.3 g of sodium iodide and 1.8 g of sodium thiosulfate in 5 mL of water was added. The mixture was taken up into ether, and 5 mL of water was added. The aqueous phase was extracted with four additional portions of ether, and the combined ether extracts were washed with 5 mL of water and saturated NaCl solution and dried over $MgSO_4$. The solvent was removed by distillation through a Vigreux column. Distillation of the residue gave 0.88 g (53%) of methyl α-hydroxyisobutyrate-d_6, bp 45–46 °C (20 mmHg). NMR ($CDCl_3$) δ 3.81 (3 H, s), 3.15 (1 H, br s).

Preparation of Mesylate 5-d_6. The preparation of **5**-d_6 from the deuterated alcohol described above was analogous to the preparation of **5**.

Preparation of α-Hydroxypropiophenone. Lithium diisopropylamide was prepared by the addition of 10.3 mL of 1.6 M butyllithium in hexane to a solution of 1.84 g of diisopropylamine in 35 mL of tetrahydrofuran at −40 °C. The solution was cooled to −78 °C, and 5.23 g of diethyl 1-(trimethylsiloxy)-1-(phenylmethyl)phosphonate[30] was added dropwise. The solution was warmed to −60 °C for 5 min and then recooled to −100 °C in a frozen methanol–liquid N_2 slurry. A solution of 0.76 g of freshly distilled acetaldehyde in 5 mL of THF was added dropwise. The mixture was allowed to warm to 0 °C, and water was added. The mixture was transferred to a separatory funnel by using ether, washed with dilute HCl and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed with use of a rotary evaporator, and the residue was distilled through a Vigreux column to give 1.74 g of a mixture of α-hydroxypropiophenone and α-(trimethylsiloxy)propiophenone, bp 55–68 °C (0.1 mmHg).

The partially desilylated mixture obtained above (1.74 g) was dissolved in 25 mL of methanol containing 5 mg of trifluoroacetic acid. After 5 min, no α-(trimethylsiloxy)propiophenone remained as determined by GC. The solvent was removed with use of a rotary evaporator, and the residue was distilled giving 1.40 g (57%) of α-hydroxypropiophenone,[31] bp 57–58 °C (0.08 mmHg). NMR ($CDCl_3$) δ 8.2–7.9 (2 H, m), 7.8–7.3 (3 H, m), 5.18 (1 H, quintet, J = 7 Hz), 3.88 (1 H, d, J = 7 Hz), 1.44 (3 H, d, J = 7 Hz).

Preparation of Triflate 6. A solution of 1.50 g of α-hydroxypropiophenone in 20 mL of CH_2Cl_2 and 1.50 g of 2,6-lutidine was cooled to −50 °C, and 3.68 g of triflic anhydride was added dropwise. The mixture was warmed to 5 °C, taken up into ether, washed with cold water, dilute HCl solution, and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed with use of a rotary evaporator, and the residue was distilled to give 2.29 g (81%) of **6**, bp 80 °C (0.05 mmHg). The distillation was carried out as fast as possible with the aid of a heat gun since slight decomposition occurs on prolonged heating. The light yellow distillate solidified in the refrigerator and discolored on standing at room temperature. NMR ($CDCl_3$) δ 8.15–7.85 (2 H, m), 7.8–7.3 (3 H, m), 6.11 (1 H, q, J = 7 Hz), 1.72 (3 H, d, J = 7 Hz).

Triflate **6** is a potent alkylating agent and was handled with extreme caution.

Preparation of 2,2-Dimethyl-4-hydroxy-3-pentanone. A mixture of 4.11 g of ethyl lactate in 40 mL of ether was cooled to −78 °C, and 34 mL of 2.3 M *tert*-butyllithium in pentane was added dropwise. After about 7 mL was added, the temperature was lowered to −100 °C (methanol–liquid nitrogen slurry) and the remaining *tert*-butyllithium was added. After warming to −40 °C, water was added and the flask was warmed to room temperature. The organic phase was separated and dried over $MgSO_4$. After solvent removal, the residue was distilled with use of a short-path condenser. The fraction, bp 62–69 °C (20 mmHz), weighing 1.15 g, contained the desired product as well as about 10% of an impurity which was incompletely resolved by gas chromatography. This fraction was chromatographed on 25 g of silica gel and eluted with 5–10% ether in Skelly F. Initial fractions containing pure 2,2-dimethyl-4-hydroxy-3-pentanone were followed by mixtures of this product and the impurity. The solvent was removed from the chromatographed product with use of a rotary evaporator, and the residue was distilled to give 0.59 g (13%) of pure 2,2-dimethyl-4-hydroxy-3-pentanone, bp 66–67 °C (20 mmHg) [lit.[32] bp 67–69 °C (11 mmHg)]. NMR ($CDCl_3$) δ 4.60 (1 H, quintet, J = 7 Hz), 3.31 (1 H, d, J = 7 Hz), 1.32 (3 H, d, J = 7 Hz), 1.20 (9 H, s).

Preparation of Triflate 7. The preparation of **7** was analogous to the preparation of **6**. A solution of 0.577 g of 2,2-dimethyl-4-hydroxy-3-pentanone in 10 mL of CH_2Cl_2 with 0.62 g of 2,6-lutidine, on reaction with 1.56 g of triflic anhydride, gave 1.101 g (95%) of **7**, bp 69–70 °C (1.7 mmHg). NMR ($CDCl_3$) δ 5.66 (1 H, q, J = 7 Hz), 1.62 (3 H, d, J = 7 Hz), 1.25 (9 H, s).

Triflate **7** is a potent alkylating agent and was handled with extreme caution.

Preparation of Triflate 8. The preparation of **8** was analogous to the preparation of **6**. A solution of 1.5 g of ethyl lactate in 20 mL of CH_2Cl_2 with 1.77 g of 2,6-lutidine, on reaction with 4.48 g of triflic anhydride, gave 3.02 g (95%) of **8**,[33] bp 53–55°C (1.6 mmHg). NMR ($CDCl_3$) δ 5.21 (1 H, q, J = 7 Hz), 4.30 (2 H, q, J = 7 Hz), 1.67 (3 H, d, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz).

Triflate **8** is a potent alkylating agent and was handled with extreme caution.

Preparation of Mesylates 12 and 22. These mesylates were available from a previous study.[1c]

Solvolyses of Mesylates 3 and 4. General Procedures. The mesylate was dissolved in the given solvent containing a minimum of 1.2 equiv of base. The solutions were heated in sealed tubes for 10 half-lives. For solvolyses in carboxylic acid solvents, the contents of the tubes were taken up into ether and washed with water and Na_2CO_3 solution to neutralize the acid. After standard drying procedures samples of the products were isolated by preparative gas chromatography and characterized by spectral methods.

For solvolyses in alcohol solvents, most of the alcohol was removed with use of a rotary evaporator and a standard aqueous workup followed. Samples of products were isolated by preparative gas chromatography and identified by standard spectral methods. The product ratios given in Table I were determined by 300-MHz NMR analyses of reactions before aqueous workup. Acetic acid-d_4 and ethanol-d_6 were used for NMR analyses to prevent interference due to solvent signals in acetic acid and ethanol. Product ratios in Table IV were determined by 300-MHz NMR and gas chromatography. Details of specific representative solvolyses are given below.

Solvolysis of Mesylate 3 in Trifluoroethanol Containing 0.15 M Triethylamine. A solution of 149 mg of **3** in 30 mL of 0.15 triethylamine in trifluoroethanol (TFE) was kept at room temperature for 15 min and then heated at 60 °C for 125 min. The solvent was removed by rotary evaporator and the residue was taken up into ether and water. After drying the ether phase, the solvent was removed with use of a rotary evaporator and the residue was distilled through a short-path condenser to give 115 mg (76%), bp 64 °C (0.17 mm Hg), of a mixture of **15** and **16** in a 98:2 ratio as determined GC. Samples of each product were isolated by preparative gas chromatography. The 300-MHz NMR spectrum of the distilled mixture showed a trace (less than 1%) of enone **9** (R = Ph). NMR of **15** ($CDCl_3$) δ 7.58–7.35 (5 H, m), 3.92–3.76 (1 H, m), 3.74–3.59 (1 H, m), 1.591 (3 H, s), 1.045 (3 H, s). NMR of **16** ($CDCl_3$) δ 7.6–7.2 (5 H, m), 4.46 (2 H, q, J = 8 Hz), 1.63 (6 H, s).

Solvolysis of Mesylate 3 in Unbuffered TFE. A solution of 54 mg of **3** in 10 mL of TFE was heated at 100 °C for 2.5 h. The solvent was removed with use of a rotary evaporator, and a standard aqueous workup followed. Gas-chromatographic analysis showed an unresolved mixture of **9** and **16**, **10**, **17**, and **18** in a 73:2:16:9 ratio. Samples of each product were isolated by preparative gas chromatography. NMR (300 MHz) of the mixture of **9** and **16** showed a 7.7 to 1 ratio, respectively. NMR of **10** (S = CH_2CF_3) ($CDCl_3$) δ 8.216 (2 H, d, J = 7.8 Hz), 7.570 (1 H, t, J = 7.2 Hz), 7.454 (2 H, t, J = 7.6 Hz), 3.679 (2 H, d, J = 8.46 Hz), 1.597 (6 H, s). NMR of **17** ($CDCl_3$) δ 7.963 (2 H, d, J = 7.8 Hz), 7.583 (1 H, t, J = 7.5 Hz), 7.480 (2 H, t, J = 7.5 Hz), 4.03–3.70 (5 H, m), 1.218 (3 H, J = 6.89 Hz). The NMR of **18** was as previously described.[9]

Solvolysis of Mesylate 3 in TFE Containing 0.1 M Methanesulfonic Acid. A solution of 51.1 mg of mesylate **3** in 5 mL of TFE contained 46.8 mg of methanesulfonic acid. After 3 days at room temperature a 1-mL aliquot was taken up into ether and washed with Na_2CO_3 solution. After being dried over $MgSO_4$, the ether solvent was removed with use of a rotary evaporator; 300-MHz NMR analysis of the residue showed **16** and **9** in a 3.87 to 1 ratio as well as 45% unreacted mesylate **3**. After 17 days, a standard aqueous workup followed. NMR analysis showed **16**, **9**, and **17** in a 7.1:1:1.2 ratio. No unreacted **3** remained.

Solvolysis of Mesylate 3 in TFA. A solution of 26.5 mg of **3** in 0.7 mL of 0.2 M sodium trifluoroacetate in trifluoroacetic acid was monitored by 300-MHz NMR. After 12.5 h at 25 °C, the NMR showed **9** (R = Ph) and **10** (S = $COCF_3$) *in* a 92:8 ratio along with about 16%

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(31) Elphimoff-Felkin, I.; Verrier, M. *Bull. Soc. Chim. Fr.* **1967**, 1047–52.
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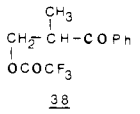
unreacted **3**. A trace of trifluoroacetate **38** was also present. After 24 h at 25 °C, about 4% of **3** remained. The amount of **38** had increased



38

to 6%. After an additional 7 days at room temperature, **9**, **10**, and **38** were present in a 59:8:33 ratio. The sample was taken up into ether, and a standard aqueous workup followed. Samples of each product were isolated by preparative gas chromatography. IR of **10** (S = $COCF_3$, R = Ph) (CCl_4) 1788, 1692 cm^{-1} (C=O). NMR of **10** ($CDCl_3$) δ 8.1–7.9 (2 H, m), 7.7–7.4 (3 H, m), 1.84 (6 H, s). IR of **38** (CCl_4) 1788, 1685 cm^{-1} (C=O). NMR of **38** ($CDCl_3$) δ 8.1–7.9 (2 H, m), 7.7–7.4 (3 H, m), 4.78 (1 H, doublet of doublets, J = 11, 8.1 Hz), 4.46 (1 H, doublet of doublets, J = 11, 5.3 Hz), 3.94 (1 H, sextet, J = 7 Hz), 1.30 (3 H, d, J = 7 Hz).

Solvolysis of Mesylate 5. General Procedures. Due to the volatility of methyl methacrylate (9, R = OCH_3), yields given in Table I were determined directly by NMR before aqueous workup. A mixture of mesylate **5** in the given solvent containing a minimum of 1.2 equiv of base was heated in a sealed NMR tube for 10 half-lives. Direct analysis of the contents of the tube was carried out by 300-MHz NMR. For the solvolysis in acetic acid, acetic acid-d_4 containing 0.1 M 2,6-lutidine was used to avoid interference due to the solvent signal and sodium acetate. The solvolysis in ethanol was carried out in ethanol-d_6. The substitution products (**10**, R = OCH_3), were characterized spectrally after isolation by preparative gas chromatography.

Solvolysis of 22 in TFE Containing 0.15 M Triethylamine. A solution of 172 mg of **22** in 25 mL of TFE containing 389 mg of triethylamine was heated at 70–72 °C for 110 min and then kept at room temperature for 12 h. The solvent was removed with use of a rotary evaporator, and a standard aqueous workup followed. After being dried over $MgSO_4$, the ether solvent was removed with use of a rotary evaporator leaving 173 mg of a mixture of **23**[1c] and **24** in a 1.6 to 1 ratio as determined by NMR. Samples of each product were isolated by preparative gas chromatography by using a 6-ft 10% XE-60 on Chromosorb column at 150 °C. The mixture was not separated by the 5% SE-30 column. NMR of **24** ($CDCl_3$) δ 7.5–6.8 (10 H, m), 5.122 (1 H, d, J = 3.8 Hz), 4.45–4.24 (2 H, m), 3.93–3.66 (2 H, m), 2.57 (1 H, d, J = 4.0 Hz).

Solvolysis of 12 in TFE Containing 0.15 M Triethylamine. A solution of 21.3 mg of mesylate **12** in 2.4 mL of TFE containing 37.5 mg of triethylamine was heated at 52–55 °C for 200 min. The TFE was removed with use of a rotary evaporator, and the residue was taken up into ether. A standard aqueous workup followed. Solvent removal with use of a rotary evaporator gave 20.1 mg of a mixture of **26** and **27**[1c] in a 9:1 ratio as determined by gas chromatography. NMR of **26** ($CDCl_3$) δ 8.02 (2 H, d, J = 7.8 Hz), 7.51 (1 H, t, J = 7.8 Hz), 7.42 (2 H, t, J = 7.8 Hz), 3.696 (2 H, q, J = 8.5 Hz), 2.53 (2 H, br s), 2.30–2.15 (2 H, m), 1.95–1.52 (10 H, m).

In a related experiment, reaction of 24.8 mg of **12** in 4.3 mL of 0.025 M 2,6-lutidine in TFE for 200 min gave 22.6 mg of a mixture containing 99% of **26** and 1% of **27**.

Solvolyses of Triflates 6, 7, and 8. General Procedure. A solution of the triflate in the solvent containing a minimum of 1.2 equiv of base was kept at a particular temperature for a minimum of 10 half-lives. For reactions in carboxylic acid solvents, the mixture was taken up into ether and washed with water and Na_2CO_3 solution. After, the mixture was dried, the ether was removed with use of a rotary evaporator and the products were characterized by standard spectral methods. For solvolyses in ethanol, the excess 2,6-lutidine was removed by extraction with aqueous HCl solution. Products were also characterized by standard spectral methods.

Acetylation of (*S*)-(−)-Ethyl Lactate. A solution of 3.0 g of (*S*)-(−)-ethyl lactate (Aldrich Chemical Co; $[\alpha]_D$ −12°, neat) in 10 mL of pyridine and 3.11 g of acetic anhydride was stirred at room temperature for 2.5 h. The mixture was taken up into ether, washed with 3 portions of water, dilute HCl solution, and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed by distillation through a Vigreux column, and the residue was distilled with use of a short path condenser. After a small forrun, 3.11 g (76%) of (*S*)-(−)-**34** (S = Ac, R = OEt), bp 83–86 °C (20 mmHg), was collected. NMR ($CDCl_3$) δ 5.08 (1 H, q, J = 7 Hz), 4.23 (2 H, q, J = 7 Hz), 2.17 (3 H, s), 1.50 (3 H, d, J = 7 Hz), 1.29 (3 H, t, J = 7 Hz). $[\alpha]^{22}_D$ −53.3° (*c* 5.6, acetone) (lit.[35] $[\alpha]^{14}_D$ −49.9°).

Formylation of *S*-(−)-Ethyl Lactate. A mixture of 17.0 g of (*S*)-(−)-ethyl lactate and 18.65 g of acetic formic anhydride[36] was heated at 52 °C for 7 h and at 45 °C for an additional 10 h. The mixture was taken up into ether, washed with two portions of water, Na_2CO_3 solution, and saturated NaCl solution, and dried over $MgSO_4$. Gas-chromatographic analysis showed about 1% unreacted ethyl lactate, 2% of **34** (S = Ac; R = OEt), along with **34** (S = CHO; R = OEt). After solvent removal by distillation through a Vigreux column, the residue was distilled through a short-path condenser giving 16.99 g of (*S*)-(−)-**34** (*S* = CHO; R = OEt), bp 72–78 °C (20 mmHg). The distillate, which contained a small amount of unreacted ethyl lactate and acetate **34**, was redistilled through a 30-cm glass-helice-packed column. An intermediate fraction, bp 75 °C (20 mmHg), was collected. Gas-chromatographic analysis showed no unreacted ethyl lactate and less than 0.4% **34** (S = Ac; R = OEt) along with **34** (S = CHO; R = OEt). NMR ($CDCl_3$) δ 8.13 (1 H, s), 5.23 (1 H, q, J = 7 Hz), 4.25 (2 H, q, J = 7 Hz), 1.54 (3 H, d, J = 7 Hz), 1.31 (3 H, t, J = 7 Hz). $[\alpha]^{22}_D$ −83.8° (*c* 5, acetone).

Solvolysis of Optically Active Triflate 8 in Acetic Acid. A solution of 2.02 g of triflate **8** (prepared from (*S*)-(−)-ethyl lactate, using the same procedure as in the preparation of inactive **8**), 1.305 g of sodium acetate, and 0.6 g of acetic anhydride in 160 mL of acetic acid was heated at 45 °C for 48 h. The mixture was diluted with 350 mL of ether and extracted with four 160-mL portions of water followed by Na_2CO_3 solution. After washing, the mixture with saturated NaCl solution, the ether phase was dried over $MgSO_4$. The solvent was removed by distillation through a Vigreux column. The residue was distilled (short-path condenser) to give 0.860 g (67%) of (+)-**34** (S = Ac; R = OEt), bp 82–85 °C (20 mmHg). Spectra were identical with those of a sample of (−)-**34** prepared as described above. $[\alpha]^{22}_D$ +51.9° (*c* 5.6, acetone).

Solvolysis of Optically Active Triflate 8 in Formic Acid. A solution of 1.95 g of triflate **8** (prepared from (*S*)-(−)-ethyl lactate) and 0.82 g of sodium formate in 120 mL of formic acid was heated at 45 °C for 33 h. The mixture was taken up into 300 mL of ether, washed with three 150-mL portions of water, Na_2CO_3 solution, and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed by distillation through a Vigreux column, and the residue was distilled through a short-path condenser. The first fraction, 0.226 g, bp 74–75 °C (20 mmHg), contained a trace of a lower boiling impurity. The second fraction, 0.506 g, bp 75 °C (20 mm Hg), was pure **34** (S = CHO; R = OEt). Spectra were identical with those of a sample of the formate ester of ethyl lactate, prepared as described above. $[\alpha]^{22}_D$ +81.2° (*c* 5, acetone).

Kinetics Procedures for Solvolyses of Mesylates and Triflates. Solvolyses of the mesylates and triflates in Table II in acetic acid containing 0.05 M sodium acetate and 1% acetic anhydride were monitored using the sealed ampule technique. Solutions of the given substrate (1.2 mL of a solution approximately 0.03 M in substrate) were sealed in tubes and immersed in a constant-temperature bath. A given times, individual tubes were quenched and opened and 1-mL aliquots were diluted in 3 mL of acetic acid and titrated potentiometrically with 0.01 M $HClO_4$ in HOAc. Infinity values were determined in duplicate after a minimum of 10 half-lives. Correlation coefficients for first-order rate constants were all greater than 0.9999 for **3**, **4**, **5**, and **12**. Maximum standard deviations were ±2% (±1% for β-deuterium isotope effect studies). First-order plots for **6**, **7**, and **8** in HOAc showed slight upward curvature over 2 half-lives. The rate constants given represent initial rates determined over approximately the first 20% reaction.

Solvolyses in formic acid were carried out in similar fashion using the sealed ampule technique in anhydrous formic acid containing 0.05 M sodium formate. At given times 1-mL aliquots were quenched in 4 mL of HOAc and titrated with 0.01 M $HClO_4$ in HOAc. For mesylate **12** (which was very reactive and dissolved slowly), a sample of **12** was partially dissolved in 0.1 mL of CH_2Cl_2. Six milliliters of formic acid was added and the mixture was shaken vigorously for 30 s and rapidly filtered (to remove undissolved **12**) through a cotton plug into a 25 °C flask. One-milliliter aliquots were quenched in 4 mL of cold acetic acid and rapidly titrated as described above. Correlation coefficients in HCO_2H were greater than 0.9999, and maximum standard deviations were ±2% (±1% for β-deuterium isotope effect studies).

Solvolyses in trifluoroethanol containing 0.025 M 2,6-lutidine were carried out (sealed ampules) by quenching 2-mL aliquots in 4 mL of HOAc and titrating potentiometrically with 0.01 M $HClO_4$ in HOAc. End points are sharper than in our previously reported[1c] method involving quenching in ethanol and titration with $HClO_4$ in ethanol. Rate data for **3** in trifluoroethanol were determined in unbuffered TFE. Two-millilter aliquots of a solution of **3** in pure TFE were quenched in 4 mL of HOAc

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and titrated with 0.002 M NaOAc in HOAc. The reaction of autocatalytic, and therefore the first-order plot is curved downward. The rate given in Table II is the initial rate determined over the first 1% reaction.

Solvolyses in ethanol containing 0.25 M 2,6-lutidine were carried out using the sealed ampule technique. Two-milliliter aliquots were added to 4 mL of HOAc and titrated with 0.01 M $HClO_4$ in HOAc. End points were sharper than when titrations were carried out in ethanol. Triflates **6–8** were quite reactive in ethanol. Therefore sealed ampules were not used. The 2-mL aliquots (withdrawn directly from a volumetric flask) were quenched in cold HOAc and titrated as rapidly as possible.

Solvolyses in hexafluoroisopropyl alcohol containing 3% (by weight) water and 0.05 M 2,6-lutidine were carried out using sealed ampules. One-milliliter aliquots were quenched in 4 mL of HOAc and titrated with 0.01 M $HClO_4$ in HOAc. Solvolysis of mesylate **12** in 97% HFIP (no base) was monitored spectrophotometrically. The kinetic run was initiated by injection of 20 μL of a solution of 8.1 mg of **12** in 1 mL of ether into 3 mL of 97% HFIP. The decrease in absorbance at 265 nm was monitored.

Solvolyses in trifluoroacetic acid, containing 0.2 M sodium trifluoroacetate and 0.5% trifluoroacetic anhydride, were monitored by NMR (90 MHz or 300 MHz). First-order plots of trifluoroacetolyses of **6**, **7**, and **8** were curved upward. Rate data given in Table II for **6** and **7** represent "initial" rate constants calculated from data over approximately 10% reaction. Maximum standard deviations in TFA for **3**, **4**, and **5** are ±7%.

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Kinetics and Mechanisms of Nucleophilic Displacement with Heterocycles as Leaving Groups. 17.[1] Solvolysis of 14-(Primary alkyl)-5,6,8,9-tetrahydro-7-phenyldibenzo[*c*,*h*]acridiniums: Rates, Identification of Products, Activation Parameters, and a General Discussion of Mechanism

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Abstract: Solvolysis rates are reported for the Me, Et, *n*-Pr, *n*-Pent, *n*-Oct, *i*-Bu, *neo*-Pent, $PhCH_2CH_2$, and $MeOCH_2CH_2$ title compounds in MeOH, EtOH, PentOH, CH_3CO_2H, and CF_3CO_2H. Rate variations with alkyl group structure are far less than the corresponding rate variations for the tosylate solvolyses, and afford no evidence for rate-enhancing participation by β-phenyl or β-methoxy groups in the acridinium solvolyses. The *n*-propyl, *n*-pentyl, and *n*-octyl title compounds solvolyze in CH_3OD and CH_3CO_2D to give mixtures of normal and rearranged products, none of which contain deuterium and which are therefore not formed via olefin intermediates. Methanolysis of the isobutyl title compounds occurs via olefin, but the acetolysis also involves an important nonolefinic pathway yielding isobutyl and *sec*-butyl acetates. Methanolysis products from the neopentyl derivative are heavily deuterated, but acetolysis yields undeuterated neopentyl acetate as well as deuterated *tert*-pentyl acetate. Product proportions calculated using GC/MS were used to deduce the fractions of reactions by various mechanistic pathways. Individual rates are calculated for solvolysis to the various unrearranged and rearranged products. They indicate that normal substitution in MeOH occurs by a classical S_N2 reaction, but that such substitution in AcOH involves ion-pair intermediates. It is concluded that such ion pairs undergo Me and H migration after the rate-determining stage, in competition with substitution. Activation parameters provide further evidence for the mechanistic paths proposed which are discussed in relation to literature data available for the corresponding tosylates.

Winstein described the solvolysis of primary systems (**1**) in terms of direct S_N2 displacement with solvent as nucleophile to yield unrearranged product (**3**) (path a of Scheme I) in competition with path b of Scheme I, a first-order anchimerically assisted heterolysis (**1** → **2**) followed by fast formation of rearranged product (**5**).[2-4] This, the so-called $k_s + k_\Delta$ theory,[4] has been supported inter alia by further work by Winstein.[5,6] However, other workers have denied the existence of anchimeric assistance by H or Me transfer and have interpreted the results in terms of paths a, c, and d of Scheme I.[7-9] In 1966, Nordlander and Schleyer[8] summarized the previous evidence for and against participation in the rate-determining stage; they concluded that none was definitive, but provided new evidence from the 1-adamantanylcarbinyl system which they (and we) consider strongly favors nonparticipation. However, the subject remains controversial; thus, in his review,[3] Harris tentatively decides in favor of the $k_s + k_\Delta$ theory, and Ando[10] and Shiner[11] have presented secondary kinetic isotope effect evidence in favor of participation in neopentyl solvolyses.

Essentially all the available work on the solvolyses of primary alkyl systems has been conducted with negatively charged leaving

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