(5) On the basis of the β-cyano effect, a rate retardation of well in excess of 10^{10} should be observed for an α-cyano effect. This is derived from the 2.8 factor for the decrease in inductive effect on addition of an insulating methylene group. An H/α-cyano ratio of $\sim 10^{11}$–10^{18} would be predicted on the basis of an inductive retardation as the only effect of the cyano function.
(6) This ratio comes from $(k_5/k_6)^{1/2}$.
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(9) Deuterium isotope effects on reactions with major S_N2 components are thought to be smaller than we have observed. For a detailed discussion and leading reference see Fisher, R. D.; Seib, R. C.; Shiner, V. J., Jr.; Szele, I.; Tomic, M.; Sunko, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 2408.
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(12) Compound **7** was prepared from cyclooctanone according to our published method: Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, 3773.
(13) It is interesting to note that **7** yields 92% 1-cyanocyclooctene as the only identifiable product from this solvolysis.
(14) The details of this comparison and of the synthesis, solvolysis, and product studies related to **9** will be forthcoming: P. G. Gassman and J. J. Talley, submitted for publication.
(15) Proctor and Gamble Fellow, 1977–1978; University of Minnesota Dissertation Fellow, 1978–1979.

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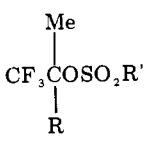
Solvolytic Reactivity of α-Trifluoromethylcarbinyl Sulfonates. Correlation of Rate Retardation by Electron-Withdrawing Substituents and Solvent Participation in Tertiary Substrates[1]

Sir:

We report here that the trifluoromethyl group is enormously deactivating relative to hydrogen as an α substituent in solvolysis reactions and that a tertiary sulfonate ester bearing this group shows evidence for strong nucleophilic solvent participation.

The rates of reaction of α-trifluoromethylcarbinyl sulfonates **1**[2] were measured in various solvents as summarized in Table I. The only product observed for **1a** was the alkene $CF_3CMe{=}CH_2$, whereas **1c** and **1d** led predominantly to the solvolysis product $CF_3CMePhOY$ and lesser amounts of alkene.[3]



	Me	R	R'
1a	CH_3	CH_3	*p*-Tol
1b	CH_3	CH_3	CH_3
1c	CH_3	Ph	*p*-Tol
1d	CD_3	Ph	*p*-Tol

The reactivities of the CF_3-substituted sulfonates **1** are greatly depressed compared with those of the corresponding hydrogen substituted compounds. Thus, rate ratios for α substituents, k_H/k_{CF_3}, are 1.1×10^5 to 2.3×10^6 from comparisons with rates for Me_2CHOTs[4,5] and derived rates for PhCHMeOTs[6] in various solvents. These ratios approach that of 10^7 which we have measured[7] for the rates of protonation of the styrenes $PhCR{=}CH_2$ in aqueous acid.

Recently substituent parameters have been derived for the influence of α substituents R in solvolysis reactions (eq 1).[8]

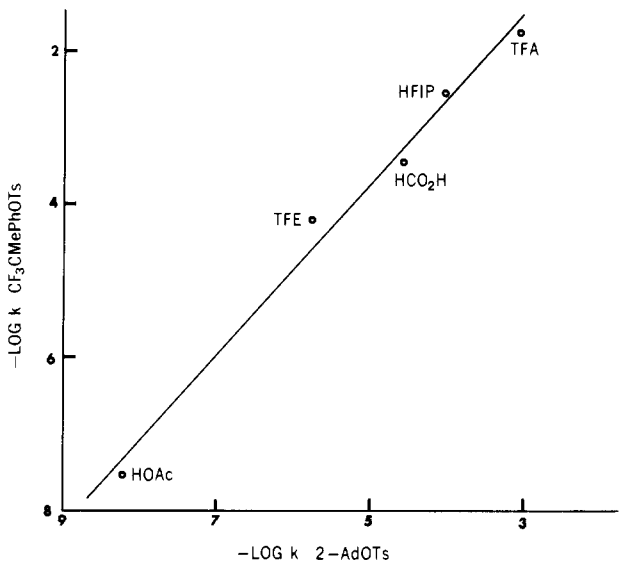
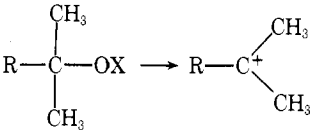


Figure 1. Comparison of the effect of solvent variation on the reactivity of $CF_3CMePhOTs$ (**1c**) and 2-adamantyl tosylate at 25 °C.



(1)

This approach was originally discussed by Traylor and Ware[8a] and has been extended by Peters[8b] and by Harris and McManus,[8c] and the designation of γ^+ for these parameters seems destined for general acceptance. Application of their treatment leads to a γ^+ parameter of 3.0 for CF_3,[9] establishing this as the most deactivating group examined by this method. For comparison, γ^+ parameters for H, Me, and Ph are 2.56, 0.63, and 0.0, respectively.

Recent studies[5a,10] of the effect of solvent on solvolytic reactivity have established that nucleophilic solvent participation is involved in some but not all secondary sulfonates[5a,10,11a,c] and may even occur in *tert*-butyl halides.[10e]

In the case of $CF_3CMePhOTs$ (**1c**) a linear free-energy relationship (Figure 1) exists for rates in various solvents compared with those for 2-adamantyl tosylate[5a] with a slope corresponding to an m_{OTs} value for **1c** of 1.11. This result indicates that **1c** reacts by rate-determining formation of a carbonium ion (k_c process) and the magnitude of m_{OTs} indicates a great demand for solvation induced by the electron-withdrawing CF_3 group. The isotope effect $k(CH_3)/k(CD_3)$ = 1.54 for **1c** is also characteristic[11] of a k_c process (cf. $k(CH_3)/k(CD_3)$ = 1.48 for 2-methyl-2-adamantyl chloride).[11b]

For **1a** and **1b**, reactivities in the more nucleophilic solvents H_2O and acetic acid are enhanced relative to trifluoroacetic acid suggesting significant nucleophilic solvent participation in the former. A quantitative measure of the degree of solvent participation,[10a] namely the ratio $[k(ROTs)/k(2\text{-AdOTs})]_{solvent}/[k(ROTs)/k(2\text{-AdOTs})]_{TFA}$, gives values for **1a** of 200 in H_2O and 4200 in acetic acid. These values are even higher than those for 2-propyl tosylate and indicate major solvent assistance in **1a**.

The reactivities of **1a–d** are interpretable in terms of the generally accepted[10] ion-pair mechanism of solvolysis:

$$CF_3CMeROTs \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CF_3CMeR^+OTs^- \xrightarrow[k_2]{YOH} \text{products} \quad (2)$$

For **1c** k_1 is rate determining, but for **1a** k_2, involving solvent assisted elimination, is evidently the slow step. Similar behavior has been suggested for *tert*-butyl halides.[10a,e]

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Table I. Solvolytic Rate Constants for Trifluoromethylcarbinyl Sulfonates $RMeC(CF_3)OSO_2R'$[a]

Me	R	R′	T, °C	solvent	k_1, s^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
CH_3	CH_3	Ts	145.2	CF_3CO_2H[b]	8.82×10^{-5}	30.2	−5.6
			130.8		2.18×10^{-5}		
			118.7		7.08×10^{-6}		
			25.0[c]		2.68×10^{-11}		
CH_3	CH_3	Ms	114.6	H_2O	3.33×10^{-5}	26.0	−12.5
			101.5		8.82×10^{-6}		
			85.3		1.93×10^{-6}		
			25.0[c]		9.22×10^{-10}		
CH_3	CH_3	Ts[d]	25.0	H_2O	1.84×10^{-9}		
CH_3	CH_3	Ts	162.6	CH_3CO_2H	1.95×10^{-5}	31.4	−8.9
			152.1		7.31×10^{-6}		
			141.8		3.05×10^{-6}		
			25.0[c]		7.36×10^{-13}		
CH_3	Ph	Ts	10.2	CF_3CO_2H[e]	3.90×10^{-3}	15.1	−15.9
			0.6		1.99×10^{-3}		
			−8.4		5.82×10^{-4}		
			25.0[c]		1.78×10^{-2}		
CH_3	Ph	Ts	78.7	CH_3CO_2H	7.37×10^{-5}	29.6	6.2
			77.4		6.21×10^{-5}		
			65.0		1.19×10^{-5}		
			61.6		7.63×10^{-6}		
			50.2		1.65×10^{-6}		
			25.0[c]		3.00×10^{-8}		
CD_3	Ph	Ts	90.7	CH_3CO_2H	1.69×10^{-4}	28.7	2.7
			77.4		4.00×10^{-5}		
			61.6		4.98×10^{-6}		
			25.0[c]		2.31×10^{-8}		
CH_3	Ph	Ts	54.8	97% CF_3CH_2OH	1.28×10^{-3}	19.6	−12.2
			45.1		5.16×10^{-4}		
			34.6		1.73×10^{-4}		
			24.8		5.63×10^{-5}		
			25.0[c]		5.87×10^{-5}		
CH_3	Ph	Ts	39.8	HCO_2H	2.33×10^{-3}	21.5	−2.1
			24.6		3.56×10^{-4}		
			9.8		5.34×10^{-5}		
			25.0[c]		3.90×10^{-4}		
CH_3	Ph	Ts	20.5	97% HFIP[f]	1.85×10^{-3}	16.6	−14.3
			9.9		6.55×10^{-4}		
			0.2		2.08×10^{-4}		
			25.0[c]		2.95×10^{-3}		

[a] Rates measured titrimetrically in duplicate except as noted with 0.012 M substrate in H_2O and 0.04 M in other solvents. [b] Measured by NMR with 0.18 M substrate and 0.20 M NaO_2CCF_3. [c] Calculated from rates at other temperatures. [d] Calculated from the rate of the methanesulfonate by the relation $k(OTs) = k(OMs) \times 2$ (ref 5a, 10f). [e] Measured by UV. [f] One run at each temperature in this solvent; HFIP is hexafluoro-2-propanol.

These results fulfill a very recent prediction[12] that substitution of the CF_3 group directly at the reactive site would provide a powerful probe of solvolytic reaction mechanisms, confirming previous indications from saturated[13] and allylic[14] secondary sulfonates bearing α-CF_3 groups and isopentenyl derivatives with allylic CF_3 groups.[15]

An independent study complementary to ours of the effects of α-cyano substituents in sulfonate solvolyses provides confirmation of the generality and value of this approach,[16a] as does a recent report of the effect of the α-keto functionality on solvolytic reactivity.[16b]

Acknowledgment. We thank the Natural Science and Engineering Research Council (NSERC) of Canada for financial support and Professor P. G. Gassman for helpful discussion of his results[16a] prior to publication.

References and Notes

(1) Presented at the 177th National Meeting of the American Chemical Society, Honolulu, April 1979; American Chemical Society: Washington, D.C., 1979; Abstracts FLUO 9.

(2) Sulfonate esters **1** were prepared by reaction of the known corresponding carbinols with NaH followed by the appropriate sulfonyl chloride or with the sulfonyl chloride and pyridine. The carbinols were obtained from reaction of the trifluoromethyl ketones with organolithium reagents as reported previously.[7]

(3) Product compositions $CF_3CMeROY$–alkene for sulfonates in different solvents were as follows: **1a** (CF_3CO_2H), <5:95; **1a** (HOAc), <5:95; **1c** (CF_3CO_2H), 95:5; **1c** (HOAc), 75:25; **1d** (HOAc), 93:7. They were determined by NMR examination of solvolysis mixtures and by VPC separation of the products.

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(6) Rates for PhCHMeOTs in other solvents were derived from reported rates in EtOH (Hoffmann, H. M. R. *J. Chem. Soc.* **1965**, 6753–6761) assuming that this tosylate would have the same response to solvent variation as others known to react by k_c mechanisms reported in ref 5a.

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(9) Derived from the relation $\log k(RCMe_2OPNB) = -4.72\gamma_R^+ - 7.14$ for rates in 80% acetone at 25 °C;[8c] $k(CF_3CMe_2OPNB)$ was obtained from the relationship $k^{PNB}_{80\%\ acetone} = (3.27 \times 10^{-11})k^{Ts}_{HOAc}$.[8b]

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(11) For S_N2-type processes β-hydrogen isotope effects CH_3/CD_3 of the order of 1.1–1.2 are normal, whereas for E2-type processes *primary* β-hydrogen effects of the order of 2–6 are to be expected. (a) Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89–110. (b) Sunko, D. E.; Szele, I.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 5000–5005. (c) Seib, R. C.; Shiner, V. J., Jr.; Sendijarević, V.; Humski, K. *Ibid.* **1978**, *100*, 8133–8137. (d) Reference 10a. (e) Cook, D.; Hutchinson, R. E. J.; MacLeod, J. K.; Parker, A. J. *J. Org. Chem.* **1974**, *39*, 534–538.
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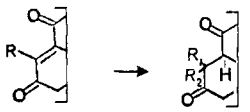
Reductive Alkylation of Enediones. 1

Sir:

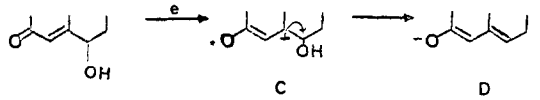
We report here on the successful application of the reductive alkylation method[1] to enedione systems, thus allowing the transformation A → B. This transformation could be very



A B

useful for the construction of polycyclic systems such as the corticosteroids and the fusidic acids which have a carbonyl function at C_{11}.

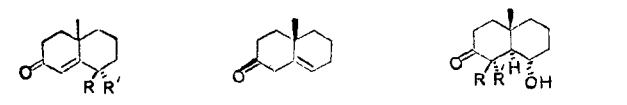
The first possibility which we envisaged involved the generation of a kinetic enolate by reduction of a γ-hydroxyenone. The process which is well known to involve loss of oxygen via the path C → D,[2] but it appeared to us likely that this loss of



C D

a hydroxyl group would be strongly conformation dependent, so that the reported results could be due to the axial nature of the hydroxyl group (better overlap for elimination).

In keeping with this view, we have now found that, in contrast to 8β-hydroxy-10-methyl-$\Delta^{1,9}$-2-octalone[3] (**1a**), mp 57–58.5 °C, which with lithium in ammonia–tetrahydrofuran afforded only the β,γ enone **2** under a variety of experimental conditions, reduction of the equatorial isomer **1b**,[3] mp 121–122 °C, furnished hydroxy ketone **3a**. Quenching the reduction mixture from **1b** with methyl iodide resulted in formation of ketones **3b** and **3c**, in 66 and 15% yields, respectively.[4]



1a R=OH, R'=H
1b R=H, R'=OH

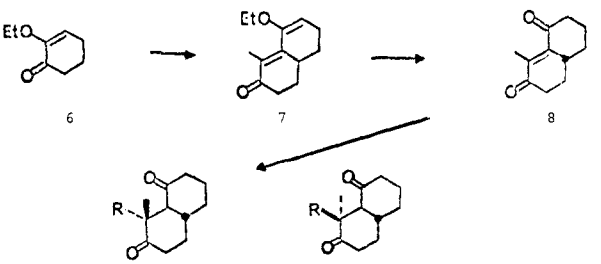
2

3a R=R'=H
3b R=H, R'=CH_3
3c R=CH_3, R'=H

4 5

Even more generally useful results were obtained from the reductive alkylation process applied to the enedione **4** (mp 70–71.5 °C, after sublimation of 70–80 °C at 0.1 mm), obtained by Jones oxidation of **1a,b**. Exposure of **4** to lithium (4 equiv) in refluxing ammonia–tetrahydrofuran (2:1), followed by quenching with methyl iodide, evaporation of ammonia, and aqueous workup, furnished three monomethylated isomers of **5**, in yields of 19, 25, and 19% after chromatographic separation on silica gel. No material derived from alkylation at the ring junction could be detected.

Extension of this sequence to bicyclic enediones unsubstituted at the ring junction could be performed in the following manner. Aprotic conjugate addition of enol ether **6** (LDA in tetrahydrofuran −78 °C) with 2-trimethylsilyl-1-penten-3-one, followed by cyclization with sodium methoxide in refluxing methanol and acid hydrolysis, furnished 1-methyl-$\Delta^{1,9}$-octalin-2,8-dione (**8**) in ~50% yield.

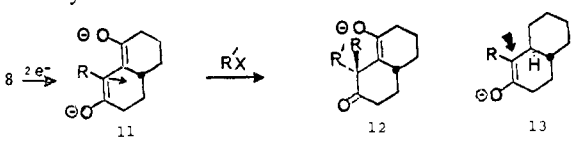


6 7 8

9a R= CD_3 9c R= CH_2Ph 10a R= CD_3
9b R= $CH_2CH{=}CH_2$ 9d R= 3,5-dimethyl-4-isoxazolylmethyl 10b R= $CH_2CH{=}CH_2$

Treatment of **8** with lithium in refluxing ammonia–tetrahydrofuran, followed by quenching with trideuteriomethyl iodide, gave, after chromatography on silica gel, a 66% yield of a mixture of the equatorially alkylated isomer **9a** and the axially alkylated isomer **10a**, in a ratio of 85:15.[5] The use of allyl bromide as alkylating agent permitted isolation of dione **9b** and dione **10b**, mp 76–77 °C, in yields of 48 and 15%, respectively, after chromatography on silica gel. The pronounced stereoselectivity of alkylation in this system, which results in the introduction of an equatorial substituent, was increased by the use of sterically more hindered alkylating agents: alkylation of **8** using benzyl bromide furnished a single dione **9c** (mp 106–107 °C after chromatography on silica gel; methyl at δ 1.40 in NMR). None of the axially alkylated dione could be detected. The use of 4-bromomethyl-3,5-dimethylisoxazole resulted in the formation of dione **9d** (mp 137 °C; methyl at δ 1.34) in 67% yield, after chromatography on silica gel.[6]

The remarkable preference of dienediolates for undergoing alkylations leading to equatorial products (**11** → **12**) is in contrast to the well-established[7] axial mode of alkylation of enolates such as **13** obtained via the reduction of the usual octalone system.



11 12 13

We suggest that this stereochemical result derives from the distortion of ring labeled B in **11** toward a half-boat to avoid the eclipsing interaction of the O^- and R substituents. The resulting rotation, shown by the arrows, results in moving R toward the center of the ring, thus exposing the α face. Whatever its exact origin, the stereoselectivity and regioselectivity of the reductive alkylation of enediones of type **8**, can be used to special advantage in the synthesis of corticosteroids, as we illustrate in the following paper.

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