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Structural and solvent effects on rates of solvolysis of secondary alkyl substrates—an update†

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ABSTRACT: Rate constants for solvolyses of secondary alkyl tosylates in fluorinated media [including hexafluoropropan-2-ol (HFIP), hexafluoroacetone sesquihydrate, and trichloromethylbis(trifluoromethyl)carbinol] are reported. Rates of solvolysis of 2-adamantyl *p*-toluenesulfonate in 97% (w/w) HFIP–water at 25 °C are neither retarded by the addition of NaOTs nor accelerated greatly by $NaClO_4$. The α-deuterium kinetic isotope effect for solvolyses of 1-(1-adamantyl)ethyl methanesulfonate in 20% acetone–water at 25 °C is 1.14. Mechanistic implications of these results are discussed. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: solvolysis; kinetics; fluorinated solvents; α-deuterium kinetic isotope effects

INTRODUCTION

Rates of solvolyses of neutral secondary substrates (R_1R_2CHX) span a huge range ($>10^{20}$), e.g. from solvolysis of bis(*p*-methoxyphenyl)chloromethane (**1**)[1] to 7-norbornyl derivatives;[2] in addition, there is a $>10^{16}$-fold dependence on the leaving group (X).[3] Rates depend primarily on the stabilization of positive charge by the R_1R_2CH unit, now supported by the link between intrinsic (gas-phase) thermodynamic stabilities of cations and solvolytic reactivity, which has recently been extended to secondary substrates.[4] Solvent effects on rates of S_N1 reactions of adamantyl tosylates (AdOTs or *p*-toluenesulfonate) in protic solvents, varying over 10^9-fold from *tert*-butanol to aqueous sulfuric acid, depend primarily on the solvent polarity or Y_{OTs} scale of solvent ionizing power.[5]

Relative rates of solvolyses of 2-propyl and 2-AdOTs (**2**) vary $>10^5$-fold, from 134 in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) to 1.1×10^{-3} in ethanol,[6] and are so strongly influenced by solvent nucleophilicity that unhindered secondary substrates react with inversion of stereochemistry by an S_N2 mechanism in more nucleophilic solvents.[6,7] In addition to typical solvolyses in ethanol, ethanol–water mixtures and acetic acid,[7] solvolysis research now includes studies of weakly nucleophilic, fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE)[1] and HFIP. Several other fluorinated alcohols have also been examined.[8] Solvent effects on solvolytic reactivity can be correlated with solvent ionizing power (Y or Y_{OTs}),[5] solvent nucleophilicity (N),[7,9] and a parameter (I) which represents solvation effects adjacent to the reaction site (often aromatic rings).[10] As multiparameter correlations require data for a diverse range of solvents, we now report new data for HFIP and exploratory kinetic studies of several other fluorinated alcohol solvents.

Direct measurements of very rapid rates of reactions of some aryl-stabilized secondary carbocations generated by flash photolysis (e.g. photoheterolysis of halides) have been made,[11] and solvolysis of **1** in TFE recently provided the first example of an S_N1 reaction in which both the formation and decomposition of a cationic intermediate could be monitored.[1] Also, lifetimes of less stable secondary cationic intermediates, such as substituted 1-phenylethyl cations, have been estimated using a trapping procedure (azide clock method).[12] However, for many solvolyses, there is only indirect evidence for the formation of a cationic intermediate. Typical, long-established, investigations of solvolytic reactions include data on product composition and stereochemistry and structural and solvent effects on rates, possibly with additional kinetic data on isotope effects, salt effects, rates of substrate racemization or ^{18}O scrambling in carboxylate or sulfonate esters.[7] Some of these studies have led to complex and controversial mechanistic interpretations, to which we now add additional data and comments.

RESULTS

Salt effects on the solvolysis of 2-AdOTs in aqueous HFIP are given in Table 1. As neither 0.03 M $LiClO_4$ nor

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Table 1. Salt effects on rate constants for solvolysis of 2-adamantyl tosylate in HFIP–water at 25 °C

Solvent (%, w/w)	Salt	[Salt] (M)	k (10^{-5} s^{-1})
97.0[a]	None		7.52 ± 0.03[b]
97.0[a]	NaOTs	0.008	7.44 ± 0.05
97.0[c]	$LiClO_4$	<0.03[d]	7.7 ± 0.1
97.0[a]	$NaClO_4$	<0.03[d]	7.8 ± 0.1
89.3[e]	None		1.88 ± 0.05
89.3[e]	$NaClO_4$	0.03	2.04 ± 0.05

[a] Monitored spectrophotometrically at least in duplicate at 24.85 ± 0.1 °C.
[b] Single conductimetric result, $10^5k = 8.69 \pm 0.02$; lit. 8.7 (Ref. 6), 7.17 (Ref. 8); spectrophotometric result, 7.97 (Ref. 13).
[c] Single measurement, monitored spectrophotometrically.
[d] Incompletely soluble.
[e] Monitored spectrophotometrically at 25.0 ± 0.05 °C.

Table 2. Rate constants for solvolysis of alkyl tosylates in HFIP and HFIP–water

	Rate constant (10^{-6} s^{-1})		
Solvent	MeOTs[a]	EtOTs[a]	Pr^{i}OTs[b]
97% HFIP[c]	6.2 ± 0.5[d]	2.93 ± 0.1	0.98 ± 0.1[e]
HFIP[f]	1.69 ± 0.23	1.87 ± 0.07	0.99 ± 0.07[g]

[a] Determined at 100.05 ± 0.05 °C by spectrophotometric analysis of quenched aliquots.
[b] Determined at 25.01 ± 0.02 °C by spectrophotometric analysis of quenched aliquots.
[c] Duplicate measurements for MeOTs and EtOTs.
[d] Literature values determined conductimetrically: 5.5 ± 0.3 (Ref. 14); 1.02 and 1.69 (5×10^{-3} M and 10^{-1} M unbuffered substrate, Ref. 8).
[e] Literature value determined conductimetrically: 1.55 (Ref. 14, extrapolated).
[f] Duplicate measurements for EtOTs, single for others; 10^{-2} M NaOAc added as buffer.
[g] In agreement with the value of 1.1 obtained by continuous spectrophotometric monitoring (Ref. 6).

Table 3. Rate constants for solvolysis in hexafluoroacetone sesquihydrate

Substrate	Monitoring	T (°C)	k (s^{-1})
2-AdOTs (**2**)	Spectrophometric[a]	25.6	$(9.8 \pm 0.1) \times 10^{-4}$
2-AdOTs (**2**)	Conductimetric[b]	25.0	$(8.93 \pm 0.03) \times 10^{-4}$
Pr^{i}OTs	Spectrophometric[b]	25.1	$(7.3 \pm 0.3) \times 10^{-6}$
Bu^{t}Cl	Conductimetric[a]	25.0	$(1.9 \pm 0.1) \times 10^{-2}$

[a] Duplicate measurements; errors shown are average deviations.
[b] Single measurements of rate constant.

$NaClO_4$ was completely soluble in 97% HFIP–water, 90% HFIP–water was also investigated. Various batches of HFIP were used to study solvolysis rates; a typical value in the presence of NaOAc buffer was $k = 1.4 \times 10^{-4}$ s^{-1}, in satisfactory agreement with our earlier data[6] ($k = 1.47 \times 10^{-4}$ s^{-1}). Inclusion of NaOAc buffer led to reliable data for solvolyses of alkyl tosylates in HFIP (Table 2), but two other buffers (2,6-lutidine and proton sponge) gave unreliable results. Results for solvolysis of MeOTs in 97% HFIP agree with our previous work,[14] and contrast with lower published values (Table 2, footnote d); rates increase on addition of water to HFIP for MeOTs and EtOTs (Table 2), but decrease for 2-AdOTs (Table 1).

Hexafluoroacetone hydrate, a 1,1-diol (i.e. a tertiary alcohol), is a low-melting solid, but solvolysis rates in hexafluoroacetone sesquihydrate [ca 95% (w/w) 1,1-diol–water)[15] at 25 °C are given in Table 3. Preliminary studies of other fluorinated tertiary alcohols were made. Perfluoro-2-methyl-2-pentanol (**3**)[16] reacted very slowly with 2-AdOTs (t >5000 min), but acetate buffers did not appear to be soluble; adequately buffered solutions containing 1–2% water gave t>7000 min. Supporting data from single spectrophotometric measurements for mixtures of **3** and HFIP gave the following results for 10^5k (s^{-1}) at 25 °C: HFIP, 13.2 ± 0.5; 51.5% (w/w) **3**–HFIP, 2.8 ± 0.2; 74.5% (w/w) **3**–HFIP, 0.70 ± 0.02; hence $k \approx 10^{-6}$ s^{-1} in 100% **3**. Conductimetric studies of 97% (w/w) **3** for *tert*-butyl bromide were inconclusive, but 1-adamantyl bromide gave $k \approx 3 \times 10^{-4}$ s^{-1} at 25 °C (but not reproducible). Other disadvantages are that **3** is toxic[16] and difficult to recycle by distillation (even from concentrated H_2SO_4) after kinetic runs.

Perfluoro-*tert*-butanol is available commercially, but is expensive, has a small liquid range (b.p. 45 °C)[16] and is fairly toxic, whereas trichlorobis(trifluoromethyl)carbinol (**4**) is less volatile and has a higher liquid range (m.p. −2 °C and b.p. 136–138 °C).[17] Various preparations of **4** were attempted (see Refs 17 and 18 and Experimental), but a very pure sample was not obtained—the product absorbed with $A > 2$ up to 325 nm (hence precluding spectrophotometric monitoring at 273 nm), and conductimetric monitoring of reactions at 25 °C buffered with acetamide gave $k \approx 3 \times 10^{-2}$ s^{-1} for Bu^{t}Cl and $k \approx 6 \times 10^{-3}$ s^{-1} for 2-AdOTs. A solution of Pr^{i}Br (0.05 M) at 100 °C, buffered with 2,6-lutidine (0.1 M), monitoring

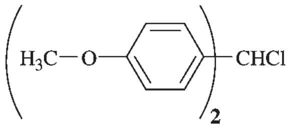
Table 4. α-Deuterium kinetic isotope effects for solvolysis of 1-(1-adamantyl)ethyl sulfonates (**5**) at 25.0 °C

Solvent	X	k_H (s^{-1})	k_D (s^{-1})	k_H/k_D
97% HFIP[a]	OTs	$(5.2 \pm 0.2) \times 10^{-3}$	$(4.8 \pm 0.3) \times 10^{-3}$	1.1 ± 0.1[b]
20% A[c]	OMs[d]	$(7.70 \pm 0.05) \times 10^{-4}$	$(6.74 \pm 0.05) \times 10^{-4}$	1.14 ± 0.02[e]

[a] Determined spectrophotometrically from five measurements for k_H and one for k_D.
[b] Value in 98% HFIP is 1.116, determined conductimetrically for the pentamethylbenzenesulfonate (Ref. 20).
[c] Determined conductimetrically in 20% (v/v) acetone–water; data quoted are for the three most reliable measurements for k_H and two for k_D.
[d] Ms = methanesulfonate.
[e] If all measurements are used (six for k_H and five for k_D), the value is 1.14 ± 0.03.

the change in the 6H doublet (isoprene is the product) by NMR, showed $k \approx 6 \times 10^{-6}\,\mathrm{s}^{-1}$ [slower than in 97% HFIP (4.5×10^{-5})];[19] as reaction of $\mathrm{Bu}^t\mathrm{Br}$ in **4** is likely to be faster than for 97% HFIP (2.2×10^{-2}),[19] the rate ratio $\mathrm{Bu}^t\mathrm{Br}/\mathrm{Pr}^i\mathrm{Br}$ (α-Me/H ratio) is likely to exceed the high value of $10^{6.2}$ for 97% HFIP.[19]

Rate constants and α-deuterium kinetic isotope effects (k_H/k_D) for solvolysis of 1-(1-adamantyl)ethyl sulfonates (**5**) in relatively polar solvents (Table 4) supplement other published studies.[20]



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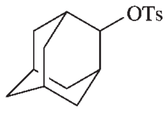

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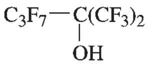

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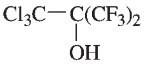
3



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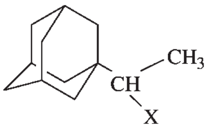

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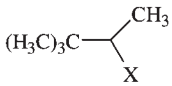

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DISCUSSION

Salt effects (Table 1) show that rates for **2** are unaffected ($\pm 2\%$) by the addition of 0.008 M tosylate anion, so the common ion effect is small or absent and the small rate acceleration in the presence of 0.03 M perchlorate appears to be a normal salt effect. The results are consistent with the accepted interpretation that products are formed by nucleophilic attack before formation of a free cation.[6] Furthermore, extrapolations of measured cation lifetimes[11] indicate that even the *tert*-butyl cation may have a lifetime shorter than the time for one bond vibration.[21] Secondary alkyl cations lacking stablizing groups such as 2-adamantyl will have shorter lifetimes; even the resonance-stabilized secondary 2-deoxyglucosyl oxacarbenium ion may not be solvent equilibrated in typical alcoholic solvolysis media.[22]

Short or negligible lifetimes of cations formed during the solvolysis of unactivated secondary substrates are probably the main factor underlying a long-running controversy:[6,20] e.g. does ^{18}O scrambling of oxygen in 'unreacted' sulfonates indicate ion pair return on the main reaction pathway[20] or a side reaction via a concerted polar mechanism?[23,24] Indirect mechanistic probes lead to different interpretations or emphases, illustrated by the results in Table 5.

Table 5. Rate ratios for 1-(1-adamantyl)ethyl (**5**)–pinacolyl (**6**) either directly observed for solvolysis (k_t) or calculated for ionization (k_1)[a] of sulfonates (X) at 25 °C

Solvent	X	$(k_5/k_6)_t$	$(k_5/k_6)_1$[a]	k_H/k_D[b]
80% (v/v) EtOH[c]	OBs	0.81	2.3[d]	1.147
97% (w/w) TFE[c]	OBs	3.8	7.7[d]	1.111
97% (w/w) TFE[e]	OTs	3.7		1.107
20% (v/v) A[f]	OMs	2.7	(2.7)[g]	1.14
97% (w/w) HFIP[h]	OTs	8.1		(1.116)[i]

[a] Ionization rates are calculated for formation of a contact ion pair.
[b] For solvolyses of 1-(1-adamantyl)ethyl sulfonates (**5**).
[c] Data from Ref. 20.
[d] From a steady-state treatment of secondary kinetic isotope effects; see Ref. 20.
[e] Data from Ref. 25; k_H/k_D refers to brosylates.
[f] Data for 20% acetone–water from Table 4 and Ref. 26.
[g] Ratio of observed rate constants, assuming negligible ion pair return for solvolyses in a highly aqueous medium (see also Refs 27 and 28).
[h] Data from Table 4 and Ref. 6.
[i] For the pentamethylbenzenesulfonate in 98% HFIP (Ref. 20).

Observed rates (k_t) for solvolysis of 1-(1-adamantyl)ethyl sulfonates (**5**) are similar to or faster than those of pinacolyl (**6**); the 10-fold variation in relative rates (Table 5) can be explained simply by the greater sensitivity of **5** to *Y*, and possibly also to a lower sensitivity to *N* (to explain the new results for 20% acetone).[25] An increased sensitivity to *Y* is often associated with a decreased sensitivity to *N*, within the S_N2–S_N1 spectrum.[6] Alternatively, results can be explained by the general model of Gregoriou and Varveri,[29] which includes the formation of an intermediate 'with extensive covalencies with the leaving group and with the incoming solvent'.

Because rapid rearrangement prevents ion pair return for solvolysis of **6**, observed rates (k_t) are equal to ionization rates (k_1); a comprehensive and complex analysis of α- and β-deuterium kinetic isotope effects, and products for solvolysis of **5** in various solvents, with a simplex optimization of 46 parameters from 86 experiments[20] gave ionization rates (k_1) up to three-fold greater than observed rates (k_t), with more ion pair return in 80% ethanol than in 97% TFE. The lower k_H/k_D for **5** (compared with 1.15 for **6** and 1.22 for **2**) was explained by a proportion of the reaction proceeding through a transition state having a rearranged structure.[20]

Both the simple and complex interpretations (see the previous two paragraphs) are in agreement that **5** can ionize up to eight times faster than **6**, but the complex interpretation does not provide insights as to why. The simple explanation[6,25,27,29] is that there are enhanced electronic effects because (i) additional carbon atoms in **5** donate electrons and (ii) contributions from nucleophilic solvation[30,31] are less in weakly nucleophilic media.

Presumably owing to changes in acidity which provide electrophilic assistance to ionization, the tertiary alcohol **4** ($\mathrm{p}K_a = 5.1$)[17] is an even more highly ionizing solvent ($Y_{OTs} \approx 5.4$), than the secondary alcohol HFIP ($\mathrm{p}K_a = 9.3$;[17] $Y_{OTs} = 3.82$)[5], continuing a trend from the primary alcohol TFE, ($\mathrm{p}K_a = 12.4$;[17] $Y_{OTs} = 1.77$).[5] Not surprisingly, the 1,1-diol HFA hydrate ($\mathrm{p}K_a = 6.6$)[32] is a more ionizing solvent ($Y_{\mathrm{OTs}} = 4.6$) than HFIP. However, rates of solvolysis of **2** in a series of primary alcohol solvents ($C_nF_{2n+1}CH_2OH$, with $n = 1$, 2, 3 and 7) are within a factor of 3,[8] in contrast to our observation that **3** ($Y_{\mathrm{OTs}} \approx 2$) is less highly ionizing than **4** ($Y_{\mathrm{OTs}} \approx 5.4$).

CONCLUSIONS

Structural effects[3,4] and solvent effects (including both electrophilic and nucleophilic solvation effects)[5] make dominant contributions to the observed rates of typical secondary solvolyses, and the nature of the initial heterolysis step may change because of nucleophilic solvent assistance or nucleophilic solvation (appropriate terminology is still under discussion[30,31]). Other effects on reactivity such as a change in rate-determining step[20] or solvation effects adjacent to the reaction site[10] are relatively small. The evidence for a mechanistic change to rate-determining separation of contact ion pairs (i.e. return from contact ion pairs)[20] relies on ambiguous ^{18}O scrambling data[23,24] and on complex interpretations of secondary deuterium kinetic isotope effects,[20] in cases where an ion pair may not survive long enough to undergo one vibration.[21]

EXPERIMENTAL

Materials. Methyl and ethyl tosylates were commercial samples (BDH) and 2-propyl and 2-adamantyl tosylates (**2**) were prepared by standard methods;[27] all were recrystallized and dried before use. 1-(1-Adamantyl)ethanol derivatives were prepared from the 1-adamantylmethyl ketone (Aldrich) using lithium aluminium hydride or deuteride, were converted to sulfonates by standard methods[27] and were recystallized from light petroleum: 1-(1-adamantyl)ethanol (m.p. 79–80 °C; lit.[33] 79.8–80.0 °C); tosylate (m.p. 122.5 °C; lit.[33] 123.0–124.2 °C); mesylate (m.p. 54–55 °C); α-D-alcohol (m.p. 77–78 °C; lit.[33] 79.5–80.3 °C), with >99.8% isotopic purity shown by mass spetrometry; α-D-tosylate (m.p. 123–124 °C; lit.[33] 123.8–124.6 °C); α-D-mesylate (m.p. 53.5–54.5 °C). The purity and structure of all samples were confirmed by ^1H NMR spectroscopy.

Sodium *p*-toluenesulfonate was prepared by neutralizing the acid with an excess of $NaHCO_3$, followed by salting out the product with NaCl and recystallizing from ethanol. Methanesulfonyl chloride was fractionally distilled from P_2O_5 (b.p. 58 °C/13 mmHg; lit.[34] 55 °C/11 mmHg). Triethylamine was heated under reflux with phthalic anhydride (1 g/30 ml) and then fractionally distilled.

HFIP, containing 0–3% water from previous studies, was recycled as follows. Addition of K_2CO_3 until alkaline (and then 20 g l^{-1} more) was followed by distillation through a Vigreux column, collecting the middle 80% fraction at 56–57 °C. This fraction was then redistilled under N_2 through a triple-pass Widmer column either from 3A molecular sieves (activated at 300 °C/1 mmHg for 2 days) or from P_2O_5 (3 g l^{-1}), collecting the middle 80% fraction (b.p. 58 °C; lit.[19] 58–59 °C). The pure solvent was stored under N_2 in the collection vessel (fitted with a tap adaptor and septum cap) and transfers were made by syringe. Binary solvents mixtures were stored in a glass-stoppered flask, sealed with Parafilm at 5 °C for up to 6 weeks; under these conditions (and in contrast to storage at room temperature), the solvent composition did not change sufficiently to affect the solvolysis rate constant for **2**.

Hexafluoroacetone sesquihydrate ($HFA \cdot 1.5H_2O$), a commercial sample (PCR), and acetone (AR grade) were used without further purification. Water was freshly distilled in an all-glass apparatus and was passed through an ion-exchange column (Amberlite MB-1) immediately prior to use.

Perfluoro-2-methylpentan-2-ol (**3**) was supplied by K. V. Scherer (b.p. 93 °C, 728 mmHg).[16] Trichloromethylbis(trifluoromethyl)carbinol (**4**) was prepared from CCl_4, BuLi and $(CF_3)_2CO$ (from HFA hydrate–H_2SO_4) in THF at -110 °C: b.p. 136–138 °C, lit.[17] 136–138 °C; yield, ca 30% maximum three (with frequent failures), lit.[17] 50%, using $(CF_3)_2CO$ or 'low yield';[18] even after three distillations the sample contained ^1H NMR signals at δ 1–3 (various signals), 6 (s) and 9 (s), possibly because of plasticizers from the PVC tubing.

Kinetic methods. Spectrophotometric measurements were made at 273 nm, using a Phillips SP1800 instrument. Kinetic runs at 25 °C were carried out directly in 1.1 ml cuvettes in a water-cooled cell block; cuvette temperatures were monitored before and after kinetic runs using a calibrated bare thermistor in a water-filled cuvette, and varied slightly with ambient temperature. Substrate concentrations were $(1\text{–}3) \times 10^{-3}$ M and [NaOAc] was ca. 10^{-2} M. The cuvette was sealed with an all-glass stopper, incorporating a sample boat containing a pre-weighed amount of substrate; the thermally equilibrated cuvette was shaken vigorously twice to dissolve the sample. Kinetic data for simple alkyl tosylates (Table 2) were obtained after reactions in thermostated baths, by analysis of quenched, sealed, 5 ml ampoules (7 × 1.5 ml, with two ampoules reserved for checking the infinity value). Rate constants were computed using LSKIN.[35]

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