Secondary and Tertiary 2-Methylbutyl Cations. 1. Trifluoroacetolysis of 3-Methyl-2-butyl Tosylate†,[1]

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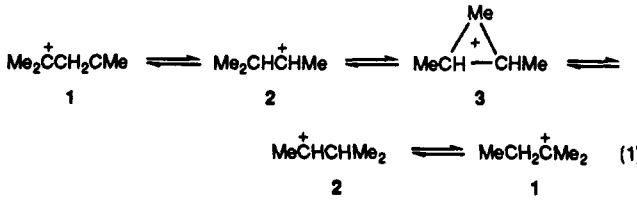
Trifluoroacetolysis rates for 3-methyl-2-butyl tosylate (**4**) and kinetic isotope effects at C(1) (k_H/k_D = 1.083 per H atom), C(2) (k_H/k_D = 1.10), and C(3) (k_H/k_D = 1.82) were determined. The products are 2-methyl-2-butyl trifluoroacetate (**5**, 98.5%) and 3-methyl-2-butyl trifluoroacetate (**6**, 1.5%). GC-MS analysis of products from labeled tosylates **4**-*1*-d_3 and **4**-*2*-*d* showed that 42% of the apparently unrearranged **6** had a methyl group shifted from the original C(3) to the original C(2), whereas 3.6% methyl shift occurred in **5**. The results do not substantiate a k_s–k_Δ competition mechanism. Instead, two carbocations, the tertiary 2-methyl-2-butyl (**1**) and the nominally secondary 3-methyl-2-butyl (**2**) intervene. The intimate structure of **2** is not established, but a symmetrical, methyl-bridged ion (**3**) does not agree with the results. A high β isotope effect does not require hydrogen assistance to ionization; ionization concerted with (assisted by) hydrogen migration is unimportant in formation of **1** (and **5**) from **4**. Instead, the reaction involves reversible formation of an intimate ion pair with subsequent rate-determining H shift (which for **2**·OTs⁻ is in competition with Me shift and ca. 25% elimination) followed by solvent capture. Methyl migration in **2** may occur in the solvent-separated ion pair; alternatively, methyl or hydrogen migration is conformationally determined. *At least* 9% of **1** is formed from **2** which has undergone methyl shift. Nucleophilic attack on **4** appears important only in strongly nucleophilic media like aqueous ethanol. The claim that nucleophilic solvent assistance is significant in solvolysis of other secondary alkyl substrates in TFA or 97% hexafluoro-2-propanol is evaluated. Such a conclusion cannot be accepted on the basis of rate correlations alone, (*i.e* without product studies to support it). The implications of our results for the trifluoroacetolysis of 2-butyl tosylate are briefly discussed.

Introduction

Some years ago one of us proposed to evaluate the energy difference between a secondary and a tertiary carbocation from the difference between the activation energy of the automerization of the 2-methyl-2-butyl cation (**1**, eq 1) and the barrier for the methyl shift in the secondary isomer, 3-methyl-2-butyl cation, **2**.[3] The former quantity had been determined by two groups from studies of the reaction of eq 1 in superacid solution;[4] a value for the latter was estimated from the energy barrier to the methyl shift reported[5] for the 2,3,3-trimethyl-2-butyl cation.[3]



The model proposed was criticized on the grounds that MINDO3 calculations had indicated that there is no energy difference between **2** and the assumed top of the barrier, **3**.[6] The criticism was accepted as valid by other workers in the field.[7] Moreover, other theoretical calculations indicated that secondary carbocations with the charge at a position adjacent to a tertiary carbon are converted to the much more stable tertiary cations by a hydride shift without an energy barrier.[8,9] From these analyses it follows that ion **2** does not exist as a true intermediate (energy minimum) among $C_5H_{11}^+$ species.

Generation of $C_5H_{11}^+$ ions from the 3-methyl-2-butyl *p*-toluenesulfonate (tosylate, **4**) in acetic acid containing sodium acetate was earlier reported by Winstein and coworkers,[10] in connection with studies of carbocationic solvolyses.[11] The reaction products at 75 °C consisted of 3-methyl-2-butyl acetate (3%), 3-methyl-1-butene (1%), *tert*-pentyl acetate (27%), 2-methyl-2-butene (54%), and 2-methyl-1-butene (15%).[10b] In another study, the olefinic products and a very small amount of tertiary ester, but no secondary ester, were obtained from the reaction at 50 °C.[12] Both reports agreed, however, in the view that most of the product was obtained from the rearranged tertiary

† Two earlier versions of this paper were dedicated when submitted to Herbert C. Brown on the occasion of his 80th birthday. That occasion was missed, but we still dedicate this work to him.

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(10) (a) Winstein, S.; Marshall, H. *J. Am. Chem. Soc.* **1952**, *74*, 1120. (b) Winstein, S.; Takahashi, *J. Tetrahedron* **1958**, *2*, 316.

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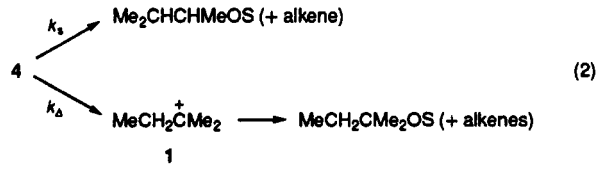
cation 1. Investigation of 3-deuterio-3-methyl-2-butyl tosylate (4-3-*d*) revealed a large kinetic isotope effect (KIE) operating in the reaction (k_H/k_D = 2.24 at 25 °C).[10b] The reaction mechanism was interpreted, therefore,[10b] as a competition between a solvent-assisted pathway (k_s, minor) forming unrearranged acetate (and terminal alkene by the related E2 mechanism) and an anchimerically assisted pathway (k_Δ) leading to tertiary ester and di- and trisubstituted alkenes (eq 2).[13] The secondary cation **2** does not intervene at all in this representation of the mechanism. Other reported data, however, are not well



(2)

accounted for by the Winstein mechanism for solvolysis (eq 2)[10] and by the representation of eq 1 resulting from the MINDO3 calculations.[6] Thus, even though the product distribution indicated the k_Δ pathway to be the major reaction course in solvolysis of **4**, no substantial rate acceleration attributable to this anchimeric assistance could be found.[10b,14] An independent mechanistic test confirmed the existence of a small nucleophilic assistance for the reaction of **4** in aqueous ethanol,[14b] but the response of rates to changes in solvent ionizing power and nucleophilicity agreed better with a k_s–k_c mechanistic model than with the k_s–k_Δ alternative.[15]

For nonsolvated cations, a study of gas-phase hydronation of 3-methyl-1-butene by the conjugate acid of xenon indicated that the 3-methyl-2-butyl cation (**2**) has a long lifetime compared with the collision frequency, and it is thermalized before isomerizing to the 2-methyl-2-butyl cation (**1**).[16] An activation energy (E_a) of 2.1 kcal/mol[17] was determined for the hydride shift converting **2** to **1**.[16]

We were intrigued by these apparently contradictory results and decided to reinvestigate the cations in a medium of low nucleophilicity and high ionizing power, trifluoroacetic acid (TFA).[18]

In their work, Winstein and Takahashi[10b] concluded that the k_s process (S_N2-type[19]) accounts for about 5% of the reaction in acetic acid. A rate study in formic acid indicated no solvent nucleophilic assistance.[20] It is noteworthy that acetic acid and formic acid have the same nucleophilicity, as measured by the *N* parameter[11f,21] (*N* = −2.05[22]), but the solvent ionizing power[11f,21] of formic acid (*Y* = 3.04[23]) is much higher than that of acetic acid (*Y* = −0.61[23]). We reckoned that in TFA (*N* = −5.55,[22] *Y* = 4.57[23]), less nucleophilic than acetic and formic acids by 3.5 orders of magnitude[24] and a much better ionizing solvent even than formic acid, the contribution of the k_s pathway to the reaction of **4** should be negligible or nonexistent.

We detail here our findings on the trifluoroacetolysis of **4** and its deuterated analogs. A study of TFA addition to the isomeric methylbutenes is presented in a separate report.[25]

Results

I. Products. The tertiary 2-methyl-2-butyl trifluoroacetate (**5**) is by far the main product of trifluoroacetolysis of **4**. Analysis by GLC, however, showed 1.5% of 3-methyl-2-butyl trifluoroacetate (**6**) in the mixture with **5**. Integration of the ^{19}F NMR spectrum of the product mixture gave a larger amount of **6** (ca. 4%), but the integration of the small peak is not reliable. That **6** was formed by solvolysis rather than by the esterification of the starting alcohol,[26] presumably existing in **4** as an impurity, was checked in two ways: First, a purified sample of **4** was divided in two inside a drybox. One half was subjected to solvolysis and the other half was recrystallized again from dry pentane, in which the alcohol is soluble, inside the drybox and then solvolyzed as well. The ratio of **5** to **6** from the two experiments was the same. In another test, solvolysis of **4** in a mixture of TFA, TFA-^{18}O, and TFA-$^{18}O_2$ (see Experimental Section) led to the same ratio of unlabled, singly labeled, and double labeled material in **5** and in **6**; **6** formed by esterification would retain the oxygen atom from the alcohol.

Unlike in the reaction in acetic acid,[10] no alkene was found among the products of solvolysis of **4** in TFA. The 1,1-disubstituted and trisubstituted alkenes would not be seen if formed, however, because they add TFA very fast;

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addition to 3-methyl-1-butene catalyzed by *p*-toluenesulfonic acid is more than three times faster than solvolysis of **4**, but in buffered TFA the latter alkene should accumulate if formed.[25]

II. Rates and Kinetic Isotope Effects. The solvolysis rates of **4** and of the deuterated tosylates **4-1-d_3**, **4-2-*d***, and **4-3-*d*** were measured in TFA containing 0.15 M potassium trifluoroacetate and a trace of TFA anhydride. The results are given in Table 1. Our measurements on **4** gave a rate constant slightly lower than the previously reported values,[14b,28] but the differences are not significant.

The large β isotope effect at C(3) is consistent with hydrogen migration concerted with ionization.[10] Alternatively, the reaction in TFA could involve a rate-determining elimination of a hydron occurring in a tight ion pair (resulting from ionization of **4**)[29] followed by fast addition of TFA to the alkene (2-methyl-2-butene). Attempts to check this possibility by measuring deuterium loss in the 2-methyl-2-butyl trifluoroacetate product (**5**) formed from **4-3-*d*** or deuterium incorporation in **5** formed from **4** in TFA-*d* were at first frustrated by fast elimination and readdition of TFA leading to extensive H/D exchange in **5**. Nevertheless, a rough assessment was made by examination of deuterium incorporation in the ethyl group of **5** isolated from the reaction of **4** in TFA-*d* after short times. A sample reacted for 234.4 s (about half of a half-life) had an isotope distribution in the fragment *m/z* 169 (7, M − methyl) 37.9% d_0, 51.5% d_1, 9.8% d_2, and 0.9% d_3. Considering that solvolysis by elimination–addition requires that the initially formed **5** be monodeuterated and then incorporate more D by exchange during the rest of the reaction time, we see that this pathway cannot be the main contributor to the mechanism. To evaluate its extent we used the observation that addition of TFA to 2-methyl-1-butene and 2-methyl-2-butene is reversible and the ratio of rate constants for proton loss from the ethyl group and from a methyl group of 1 is 9.3 ± 1.8. From the isotope content and distribution measured in **5** isolated from solvolysis of **4** in TFA-*d* after short reaction times we calculated the amount of D in the ethyl group resulting from exchange and, by difference, the proportion of ethyl groups containing D before any exchange occurred (27 ± 13%, Appendix A). This is the percentage of elimination in the tight ion pair. A different calculation gave a similar result (18%), but with higher uncertainty (Appendix B).

The β KIE at C(3) is similar in TFA and in solvents ranging from 80% ethanol to 97% hexafluoro-2-propanol (HFIP) (N = −4.27, Y = 3.61[30]).[14b,31] This feature is not expected for a competition between hydrogen participation (k_Δ) and nucleophilic solvent attack (k_s), which should lead to a high sensitivity of KIE to solvent nucleophilicity.[32] If 5% of **4** reacts by the S_N2 pathway in acetic acid, a significantly larger proportion should follow this route in 80% ethanol (N = 0.0, Y = 0.0[30]). As k_Δ has a large β KIE whereas KIE for k_s is close to 1,[32] the measured KIE for the two solvents should be sizably different. For comparison, solvolysis of 2-methyl-1-propyl trifluoromethanesulfonate (triflate), recognized as a k_s–k_Δ substrate, exhibits β KIEs of 1.208 in 80% ethanol, 1.871 in 70% trifluoroethanol (TFE), and 2.093 in 97% TFE.[33a]

Table 1. First-Order Rate Constants for Trifluoroacetolyses[a]

compd	temp, °C	$k \times 10^3$, s^{-1}	no. of runs	k_H/k_D
4	14.10	0.526	1	
	14.83	0.582	2	
	25.00	1.57 ● 0.03[b–d]	9	
4-1-d_3	25.00	1.24 ● 0.02[c]	3	1.27[e]
4-2-*d*	25.00	1.43 ± 0.01[c]	4	1.10
4-3-*d*	25.00	0.865 ± 0.008[c]	7	1.82

[a] Determined spectrophotometrically (see Experimental Section) in TFA containing 0.15 M potassium trifluoroacetate and a trace of anhydride. [b] Literature values 1.75 × 10^{-3} (ref 14b) and 1.73 × 10^{-3} (ref 28). [c] Errors are standard deviations from the average. [d] $\Delta H^\ddagger$ = 16.3 kcal/mol, $\Delta S^\ddagger$ = −16.7 cal mol^{-1} deg^{-1}; calculated with the program in ref 27. [e] 1.083 per H atom.

The α KIE in TFA (Table 1) is smaller than in more nucleophilic solvents, where it had been found to vary insignificantly with solvent, from 1.17 in acetic acid to 1.178 in 97% TFE[34] (for comparison, α KIE for 2-methyl-1-propyl triflate varies from 1.050 in 80% ethanol to 1.129 in 97% TFE[33a]). On the other hand, the β KIE for the nonmigrating hydrogens at C(1) of **4** is greater in TFA (Table 1) than in acetic acid[32] (1.27 and 1.09 per trideuteriomethyl group, respectively). The KIEs observed might suggest elimination from the intimate ion pair as the rate-determining step,[29,35] but the reactions in TFA-*d* described above indicate that this pathway is a minor reaction mechanism.[36]

III. Rearrangement of Carbon Skeleton in 5 and 6. To investigate possible rearrangements of the carbon skeleton of **4** during reaction, it is necessary to relate the position of the methyl groups in products 2-methyl-2-butyl trifluoroacetate (**5**) and 3-methyl-2-butyl trifluoroacetate (**6**) to their position in the starting material **4**. For that purpose we conducted a detailed investigation of specifically labeled **5** and **6** by GC-MS-MS,[37] which demonstrated that each position in the original molecule can be located unambiguously in the fragment ions of the products. The fragmentations particularly useful for the study presented here were those leading to ions **7** (*m/z* 169) and **8** (*m/z* 155) from **5** and **9** (*m/z* 113) and **10–12** (*m/z* 141, 142, and 143, respectively) from **6**. The GC-MS-MS analyses were conducted in both "parent" and "daughter" ion modes and showed that the species examined (**7–12**) came only from **5** and **6**, with no contribution from contaminants.[37]

The mass spectrum of the monodeuterated secondary ester obtained from the solvolysis of **4-2-*d*** (presumed to be **6**, X = D, Y = Z = H) gave a peak intensity pattern both in the region *m/z* 112–115 and in the region *m/z* 140–144

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$$CF_3COOC(CH_3)_2CHXCY_3 \rightarrow$$
5

$$CF_3COO\overset{+}{C}(CH_3)CHXCY_3 + CF_3COO\overset{+}{C}(CH_3)_2$$
7 **8**

$$CF_3COOCX(CY_3)CH(CZ_3)_2 \rightarrow CF_3O\overset{+}{C}XCY_3 +$$
6 **9**

$$CF_3COO\overset{+}{C}XCY_3 + CF_3CO\overset{+}{O}Z\dot{C}XCY_3 +$$
10 **11**

$$CF_3\overset{+}{C}(OZ)OCZXCY_3$$
12

(X, Y, Z = H or D)

different from the spectrum of the pure 6-2-*d* obtained from the corresponding alcohol and trifluoroacetic anhydride in pyridine. It could be evaluated that about 40% of deuterium had been transferred away both from **9** and from **10–12**. The same observation was made for the secondary ester from 4-*1*-d_3, which gave fragments at *m/z* 113 and 116, as well as two clusters at *m/z* 141–143 and 144–146. The ratio of the two species could be only approximately assessed from the intensities of the MS signals at *m/z* 113 (**9**-d_0) and *m/z* 116, because the latter is the sum of **9**-d_3 and of the ion $CF_3C^+(OH)(OD)$,[37] but the label content and distribution could be accurately determined from the comparison of signals for **10** (*m/z* 141) and **10**-d_3 (*m/z* 144). The measured ratio of **10**-d_0 to **10**-d_3 was 42:58.

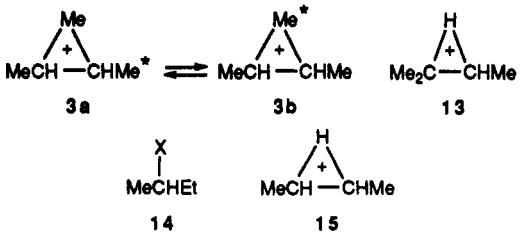
The normalized peak intensity in the *m/z* 169–172 region of the mass spectrum for the tertiary ester **5** obtained from solvolysis of 4-*1*-d_3 gave an isotope content distribution in **7** of 2.3% d_0, 0.7% d_1, 0.6% d_2, and 96.4% d_3. At the same time, the trifluoroacetate **6** prepared by the esterification of the alcohol used for making the tosylate 4-*1*-d_3 gave a peak intensity ratio *m/z* 141 to *m/z* 144 of 0.44:100, thus placing an upper limit of 0.44% for the d_0 species in ion **10**. Therefore, some of the label had migrated from C(1) to C(4) in the tertiary ion **1** by the time it was trapped by solvent. It is noteworthy that the acetone produced from oxidative degradation of 2-methyl-2-butene in the olefin mixture resulting from the acetolysis of 4-*1*-^{14}C exhibited a low level of radioactivity, indicating some transfer of label from C(1) to C(4).[12] The oxidation of the alkenes had been conducted in acid solution and the authors did not check for absence of isotope rearrangement during oxidation; nevertheless, it is surprising that most papers published afterward on solvolysis mechanisms overlooked this significant finding.

Discussion

From our results it follows that about 40% of the formally unrearranged product **6** had a methyl group shifted from the original C(3) to the original C(2) and the trifluoroacetate group attached to the original C(3). This result demonstrates not only that **2** is an intermediate in trifluoroacetolysis of **4** but that it lives long enough to undergo extensive methyl shift before being trapped by the solvent. Our results give no proof of the intimate structure[38] of the nominally secondary carbocation **2**, but the unequal distribution of label speaks against a symmetrical structure (**3**) for this intermediate.[39]

In a critique of an earlier version of this paper, however, a reviewer indicated that gas-phase calculations support **3**, not another structure as an energy minimum,[40] but the methyl groups in **3** can equilibrate rapidly over three positions (cf. **3a** ⇌ **3b**) and the 42% isotope rearrangement observed may result from incomplete equilibration. Such a mechanism requires, however, that the extent of rearrangement in 6-d_3 (from 4-*1*-d_3, determined from the loss of label in **9–12**) vary from a minimum of 50% to 67%, whereas the interchange of C(2) and C(3) likewise measured for 6-*d* from 4-*2*-*d* be constant at 50% irrespective of the extent of equilibration in the bridged ion **3**. Both predictions are at variance with the results obtained in the respective experiments.[41]

An alternative reaction scheme offered was that both **5** and **6** are formed by nucleophilic attack on a hydrogen-bridged carbocation, **13**, the latter thus being an energy minimum rather than a transition structure for the hydride shift from C-3 to C-2.[42] This representation cannot explain the large difference in the extent of skeletal rearrangement found in **5** and **6**.



Like any small number, the result for the extent of methyl migration in the tertiary ester **5** is somewhat open to question. Taking, however, that ca. 1.8% (2.3 − 0.44) of the CD_3 groups in the original 4-*1*-d_3 were present in the methyl group lost to give **7** and neglecting the isotope effect manifested in this cleavage, meaning that an equal proportion of CD_3 existed in the remaining methyl group (C(1) in **7**), it follows that 3.6% of **5** had a methyl group shifted. This rearrangement occurred most probably in the secondary cation **2** before conversion to **1** by hydride shift. Considering that **2** had undergone methyl shift to the extent of 40%, we can set a minimum limit to the amount of **1** formed from **2** at 9% (3.6/0.4).

A mechanistic description should also account for the observation that TFA addition to 3-methyl-1-butene catalyzed by toluenesulfonic acid forms in the early stages of the reaction of **4** and **5** in a ratio estimated roughly at 1:1.[25] This indicates that a significant amount of the intimate ion pair returns to **4** during solvolysis as well.[43]

(38) The electron distribution and the relative position of the nuclei (geometry) in the molecule or ion can be determined by physical measurements or ascertained computationally, but can be only inferred from rate and product studies.

(39) Interestingly, for deamination of 3-methyl-2-butylamine in acetic acid it was concluded that the "open" secondary ion is the major reaction intermediate: Silver, M. S. *J. Org. Chem.* **1963**, *28*, 1686.

(40) Disagreement with calculation results cannot by any means invalidate experimental results, but it offers a powerful incentive to check thoroughly the experiments.

(41) A more extensive rearrangement by 1,2 shifts in the protonated cyclopropane **3** would interchange the original C-2 and C-3 with the methyl carbons (not observed) and would also form upon capture by TFA 2-methyl-1-butyl and 2-pentyl trifluoroacetates (not found), in addition to **6**. This process has a high energy barrier (cf. ref 4).

(42) Preliminary *ab initio* calculations do not substantiate this assertion: Fărcaşiu, D.; Norton, S., presented at the 25th Regional Meeting of the American Chemical Society, Pittsburgh, PA, Oct 4, 1993.

(43) This test of internal return from tight ion pairs was devised by Shiner; cf. ref 29a.

Of the ion pairs which do not return, over 10% (≥9% + 1.5%) evolve as 2, undergoing partial methyl shift before being trapped by solvent or isomerizing to 1, and 25% undergo elimination to 2-methyl-2-butene (16), which adds TFA rapidly. These observations hardly accommodate the model of ionization assisted by hydrogen participation for the reaction of 4. Instead, our results demonstrate the existence of two carbocation intermediates in trifluoroacetolysis of 4. Even though the major reaction product is formed from the well-known[4,44] tertiary 2-methyl-2-butyl cation (1), the major pathway involves reversible ionization to the [2·OTs⁻] intimate ion pair. Hydrogen shift concerted with ionization, leading to 1, is at most a minor pathway.

The existence of two cations with isopentane skeleton, 1 and 2, and the existence of an energy barrier for the conversion of 2 to 1 was reported in the gas phase[16] and is now found in TFA as well. The same should hold for the ions in superacid solution, thus settling the earlier controversy.[3,6,7]

A solvolysis mechanism involving reversible dissociation to a tight ion pair followed by rate-determining conversion to solvent-separated ion pair, nucleophilic capture, or hydron loss[45] has been discussed.[29a,46] We find now that a large β KIE is produced by hydride shift (2 → 1) after ionization, a possibility not considered before.[47] The generally held view that a large β KIE is sufficient proof of β hydrogen assistance to ionization[10,32] has to be changed. Instead, the β KIE is manifested in a rate-determining hydrogen shift or elimination occurring in the tight ion pair reversibly formed from the original tosylate.[47] The large β isotope effect at C(3) is thus a composite of effects for at least two competing pathways. Such a behavior should not be expected to be limited to the 3-methyl-2-butyl system.

As for the timing of methyl shift in 2, one can argue that this automerization should occur at a stage later than the tight ion pair, otherwise more skeletal rearrangement would be seen in 5. The solvent-separated ion pair[32b] would then be the most likely intermediate to undergo methyl shift. Alternatively, the reversible ionization of 4 could occur in two conformations, one favorable to hydrogen shift and elimination, the other with the β carbon–methyl bond parallel to the empty orbital at C(2). The latter conformer undergoes methyl shift in competition with trapping by solvent and bond rotation followed by hydrogen migration. Observation of a small amount of skeletal rearrangement in the tertiary ester 5 indicates that a small part of 1 is formed from methyl-shifted 2.

The reversible formation of a tight ion pair was shown best to explain predominant racemization in the product accompanied by some racemization of the reactant in the trifluoroacetolysis of 2-butyl tosylate (14, X = OTs).[48] Ionization with hydrogen participation to form a hydrogen-bridged carbocation (15) proposed by other authors[49] could not give a simple prediction of the results.[48] Our observation of extensive return from the [2·OTs⁻] tight ion pair further supports this conclusion. Indeed, participation of the hydrogen from the tertiary carbon in 4 would be much more favored energetically than participation of a hydrogen from the (secondary) C(3) of 14. Reversible formation of a tight ion pair of very short lifetime also explains the oxygen scrambling without racemization found for the corresponding brosylate (14, X = OBs) in TFE.[50] The alternative mechanism of scrambling by a concerted (1,3-sigmatropic) shift[50] is less likely, and in any case cannot be advanced unless also observed in nonpolar solvents at the same temperature.

Even though the skeletal rearrangement observed in the secondary ester 6 proves that 6 results from the capture of a carbocation rather than from nucleophilic attack of TFA on 4, it does not allow us to establish whether the secondary ester generated in not much larger amount in acetic acid[10] is also formed through the intermediacy of the carbocation or by the S_N2 reaction. Nevertheless, the invariance of the β KIE for the migrating hydrogen with solvent could very well mean that the reaction is carbocationic, involving ions 1 and 2, in all but the strongly nucleophilic media like aqueous ethanol.

Solvolysis mechanism was rationalized[11] as an S_N1 reaction[19] for tertiary substrates in all protic media and a borderline process for secondary substrates, S_N2 in nucleophilic solvents and S_N1 in nonnucleophilic solvents with high ionizing power (anion-stabilizing solvents[51]). More recently, however, it was proposed that even tertiary substrates react with solvent assistance (S_N2) in nucleophilic media,[52,53] whereas secondary substrate are nucleophilically assisted even in TFA or HFIP.[52a] In other papers it was ascertained that secondary carbocations cannot exist as intermediates even in weakly nucleophilic media.[50] Our findings on 4 disprove both these mechanistic representations.

We have already argued that claims of S_N2 mechanism cannot be based on rate studies alone.[51,54] Thus, if solvolysis in 97% w:w HFIP (3.5:1 molar ratio HFIP to water) is, indeed, nucleophilically assisted the product

(44) Olah, G. A.; Baker, E. B.; Evans, J. C.; Tolgyesi, W. S.; McIntyre, J. S.; Bastien, I. J. *J. Am. Chem. Soc.* **1964**, *86*, 1360.

(45) Shiner, V. J., Jr.; Rapp, M. V.; Halevi, E. A.; Wolfsberg, M. *J. Am. Chem. Soc.* **1968**, *90*, 7171.

(46) (a) Seib, R. C.; Shiner, V. J., Jr.; Sendijarevic, V.; Humski, K. *J. Am. Chem. Soc.* **1978**, *100*, 8133. Shiner, V. J., Jr.; Imhoff, M. A. *J. Am. Chem. Soc.* **1985**, *107*, 2121. (b) Maskill, H.; Thompson, J. T.; Wilson, A. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1239. (c) Katritzky, A. R.; Sakizadeh, K.; Gabrielsen, B.; le Noble, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1879. Katritzky, A. R.; Schultz, H.; Lopez-Rodriguez, M. L.; Musumarra, G.; Cirma, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 73 and references therein. (d) Allen, A. D.; Kanagasabapathy, V. M.; Tidwel, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513. (e) Yamataka, H.; Tamura, S.; Hanafusa, T.; Ando, T. *J. Am. Chem. Soc.* **1985**, *107*, 5429.

(47) (a) It was argued that in some anchimerically assisted solvolyses bridging lags behind ionization: Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 381. Schleyer, P. v. R.; Bentley, T. W.; Koch, W.; Kos, A. J.; Schwarz, H. *J. Am. Chem. Soc.* **1987**, *109*, 6953. See also: ref 9b. We see in the reaction of 4 that there is no assistance and hydrogen shift is a full step behind. (b) After our first report on solvolysis of 4 (ref 1) it was disclosed that *cis*-2-methylcyclopentyl also undergoes reversible ionization upon solvolysis, followed by rate-determining hydrogen shift with a large β KIE: Imhoff, M. A.; Ragain, R. M.; Moore, K.; Shiner, V. J., Jr. *J. Org. Chem.* **1991**, *56*, 3542. Unfortunately, the authors use the term "hydrogen participation" for hydrogen migration in the step *following* the ionization.

(48) Allen, A. D.; Ambidge, I. C.; Tidwell, T. T. *J. Org. Chem.* **1983**, *48*, 4527.

(49) Dannenberg, J. J.; Goldberg, B. J.; Barton, J. K.; Dill, K.; Weinwurzel, D. H.; Longas, M. O. *J. Am. Chem. Soc.* **1981**, *103*, 7764. Dannenberg, J. J.; Barton, J. K.; Bunch, B.; Goldberg, B. J.; Kowalski, T. *J. Org. Chem.* **1983**, *48*, 4524.

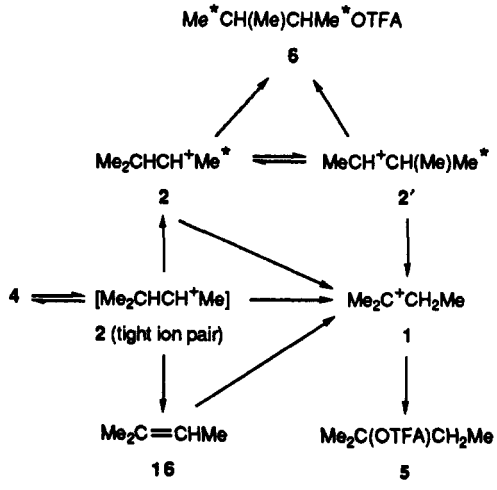
(50) Dietze, P. E.; Wojchechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240. The viewpoint that secondary carbocations (presumably their ion pairs as well) cannot exist in weakly nucleophilic solvents, expressed by the authors, is also contradicted by, among others, the papers cited in ref 46.

(51) Fărcaşiu, D. In *Nucleophilicity. Advances in Chemistry Series 215*; Harris, J. M., McManus, S. P., Eds.; American Chemical Society: Washington, DC, 1987; Chapter 20.

(52) (a) Bentley, T. W.; Bowen, C. T.; Parker, W.; Watt, C. I. F. *J. Am. Chem. Soc.* **1979**, *101*, 2486. (b) Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 5741.

(53) Kevill, D. N.; Kamil, W. A.; Anderson, S. W. *Tetrahedron Lett.* **1982**, *23*, 4635.

Scheme 1



should be the corresponding alcohol with little or no ether present (because of the very large difference in nucleophilicity between water and HFIP). Unfortunately, no product analysis was reported by the previous authors.[52,53]

The picture of the process which we can offer is shown in Scheme 1. It is a clear departure from the previously accepted model (eq 2) and it most likely applies to other solvolyses of secondary substrates previously believed to involve ionization concerted with (assisted by) hydrogen migration. For simplification only the carbocations are indicated in Scheme 1, without specifying the position of the anion.

Conclusions

1. There is no nucleophilic assistance to reaction of 4; the reaction is strictly carbocationic. It is possible that the reaction acquires an S_N2 mechanistic component only in the most nucleophilic solvents, like aqueous ethanol.

2. Two carbocations with isopentane skeleton, 1 and 2, intervene in the reaction of 4 in TFA.

3. Ionization of 4 is not concerted with (assisted by) migration of the β hydrogen. Instead, the main pathway consists of reversible dissociation to tight ion pairs of the secondary cation [2·TsO$^-$], followed by rate-determining hydrogen shift, in competition with elimination and methyl shift.

4. Extensive, but less than 50%, methyl shift occurs in 2 before trapping by solvent, and at least 9% of 1 is formed from 2 which has undergone methyl shift.

5. The structure of 2 in solution is not a symmetrical 2,3-dimethyl-1-protonated cyclopropane (3).

6. These mechanistic patterns and structural features of intermediates should not be limited to substrate 4 and carbocations 1 and 2.

Experimental Section

General Procedure. Reagent grade chemicals were used as purchased unless indicated otherwise. The glassware was dried overnight at 120 °C. GLC analyses were run at 35 °C on a 10.6 m (35 ft) × 3 mm (1/8 in.) column packed with 10% dimethylsilicone SP-2100 on 80/100 Supelcoport and at 25 °C on a 25-m silane-pretreated narrow bore capillary column coated with SP-2100. The ^{1}H NMR spectra were recorded at 60 MHz on a CW instrument and at 299.92 MHz on a pulse (FT) instrument. ^{19}F NMR spectra were obtained at 56.46 MHz (CW) and at 84.25 MHz (FT). ^{2}H NMR spectra were run at 13.69 MHz (FT). The MS, GC-MS, and GC-MS-MS experiments were described elsewhere.[37]

Trifluoroacetyl Chloride.[55] TFA (27 mL, 0.35 mol) was added during 1 h to benzoyl chloride (56 mL, 0.48 mol), at 0 °C.[56] The mixture was heated to 200 °C in 3.5 h. The product was distilled through the water-cooled reflux condenser and was collected in a dry ice trap protected from moisture by a drying tube filled half with Drierite and half with 4A molecular sieves. The acid chloride was cooled to −78 °C inside the drybox, decanted from frozen TFA (mp ca. −15 °C), and distilled slowly (40 min) on a bath warmed from −35 to 5 °C. The product collected into a Fisher-Porter tube (22.9 g, 50% yield, δ(^{19}F) −76.0) was free of TFA (δ −76.3) and of the corresponding anhydride (δ −75.7).

Preparation of TFA-^{18}O. Trifluoroacetyl chloride (18.27 g, 123 mmol) was evaporated at −20 °C from the Fisher-Porter tube and bubbled through 98% H_2O-^{18}O (2.001 g, 100 mmol), magnetically stirred in a flask provided with a dry ice condenser topped by a drying tube, and kept in a 0 °C bath, during 9 h. The flask was brought to room temperature, stirred for 30 min, capped, and transferred to the drybox. As blank experiments had shown that water conversion was occasionally incomplete, TFA anhydride (1.4 mL, 2.1 g, 10 mmol) was added to the flask and stirring was continued for 1 h. The residue (13.79 g) contained about 9.3% (molar) anhydride (^{19}F NMR). Distillation at 48 °C removed 1.4 g of volatile material and gave an acid containing a very small amount of anhydride. The product was a mixture of TFA, TFA-$^{18}O_1$, and TFA-$^{18}O_2$.

Preparation of Buffered TFA. Potassium carbonate (1.0374 g) was weighed in a 100-mL volumetric flask and freshly distilled TFA precooled to 10 °C was added slowly to the flask swirled in the 10 °C bath (frothing).[57] After half of the acid was added, the flask was brought to 25 °C, and TFA anhydride (2 mL) was added. The flask was filled to the mark with TFA and left in the drybox antechamber overnight. A separate experiment showed that water reacts rapidly with the anhydride at 0 °C; therefore this procedure gave anhydrous acid with a small amount of residual anhydride. (Karl Fischer titration gave 0.004% water.) The same procedure was used to make buffered TFA-*d* and TFA-^{18}O. To reduce losses of labeled acid with the evolving CO_2, K_2CO_3 was added to the acid frozen in dry ice and reacted slowly while the acid was thawing.

3-Methyl-2-butanol-*3-d*. This compound was prepared[14b] by deuteroboration[58] of 2-methyl-2-butene.

3-Methyl-2-butanol-*2-d*. Redistilled 3-methyl-2-butanone (4.27 g, 49.5 mmol) in anhydrous ether (25 mL) was added to $LiAlD_4$ (1.05 g, 24.9 mmol) in ether (200 mL) with magnetic stirring under nitrogen, slowly as to maintain gentle boiling. The dropping funnel was rinsed with ether (3 × 3 mL) and the flask was stoppered and stirred overnight. Water (1 mL), 15% aqueous NaOH (1 mL), and again water (3 mL) were added at 0 °C with vigorous stirring, the solid was filtered off and washed several times with ether, and the combined ether solution was concentrated on an annular column until the distillate started to contain some alcohol (1–2% in the distilling drop). The residue weighed 4.58 g, of which 3.52 g was the product (80% yield, GLC).

3-Methyl-2-butanol-*1,1,1-d*$_3$. CD_3MgI was prepared from 8.32 g of Mg (345 mmol) and 49.96 g (344.6 mmol) of CD_3I in ether (120 mL), in a dry box. Isobutyraldehyde (21.21 g, 294.2 mmol, dried on 4A molecular sieves and freshly fractionated under N_2) in 85 mL of ether was added at 0 °C (toluene–liquid N_2 bath) during 1 h (magnetic stirring); then the flask was stoppered and stirred for 70 h. Saturated aqueous NH_4Cl (80 mL) was added to the suspension at 0 °C, the clear supernatant layer was filtered, and the granular solid was washed several times with ether. The combined, pale yellow, solution was stirred for 3 h with solid sodium metabisulfite and anhydrous K_2CO_3, filtered, and concentrated on an annular column until the alcohol represented 91% of the residue (21.070 g of 23.154 g, 78.7% yield).

(54) Fărcaşiu, D.; Jähme, J.; Rüchardt, C. *J. Am. Chem. Soc.* **1985**, *107*, 5717.

(55) Henne, A. L.; Alm, R. M.; Smook, M. *J. Am. Chem. Soc.* **1948**, *70*, 1968.

(56) Brown, H. C. *J. Am. Chem. Soc.* **1938**, *60*, 1325.

(57) Compare with: Cram, D. J.; Allinger, J. *J. Am. Chem. Soc.* **1957**, *79*, 2858.

(58) Brown, H. C.; Zweifel, G. *Org. React.* **1963**, *13*, 31.

Table 2

		m/z 169				m/z 155			
run	t (s)	d_0	d_1	d_2	d_3	d_0	d_1	d_2	d_3
a	233.8	43.8	47.3	8.9		87.7	10.9	1.3	
b	234.4	37.9	51.5	9.8	0.9	86.0	12.1	1.9	
c	238.8	44.1	49.9	6.0		89.4	10.2	0.4	
average:	235.7 ± 2.6	41.9 ± 2.9	49.6 ± 1.7	8.2 ± 1.6	0.3 ± 0.4	87.7 ± 1.4	11.1 ± 0.8	1.2 ± 0.6	
d	464	31.2	50.5	16.7	1.7	81.3	15.9	2.8	
e	469	24.6	47.9	25.7	1.7	77.5	19.9	2.6	

Trifluoroacetates 5 and 6. The published procedure for such esters[54] was modified.[37a] TFA anhydride (8.9 mL, 63 mmol) was added dropwise to the alcohol (5 g, 57 mmol) in dry pyridine (10.2 mL, 126 mmol) at 0 °C, with stirring, and then maintained at 0 °C for 5 days. The ice-quenched product was extracted with isopentane, washed with 0.4 N HCl and water, and dried over Na_2SO_4 and K_2CO_3. The solvent was evaporated under low vacuum below 25 °C, giving **5** (52%) and **6** (67%), respectively, as liquids. In other batches the evaporation was conducted to about 90% concentration of ester, to avoid losses. ^1H NMR ($CDCl_3$, TMS) **5** δ 1.90 (2H, quart., J = 7 Hz), 1.57 (6H, s), 0.93 (3H, t, J = 7 Hz); **6** δ 4.93 (1H, quint., J = 6 Hz), 1.93 (1H, m, J = 6 Hz), 1.30 (3H, d, J = 6 Hz), 0.97 (6H, d, J = 6 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) **5** δ −75.1; **6** δ −75.5.

The deuterated alcohols were esterified in the same way.

3-Methyl-2-Butyl Tosylate (4).[59] *p*-Toluenesulfonyl chloride (22.75 g, 119.3 mmol, recrystallized from chloroform/ether at −78 °C, mp 67.4–68.2 °C) was slowly added to 3-methyl-2-butanol (5.25 g, 59.7 mmol) dissolved in 60 mL of pyridine (stored over CaH for drying) at −20 to −10 °C, in the drybox. (The presence of ether in the labeled alcohols did not affect the results.) The capped flask was kept at 0 °C for 26 h and worked up in the usual manner. The oil obtained was recrystallized from pentane at −78 °C in a drybox, to give 13.63 g (94%) **4**, mp 19.5–20.3 °C (lit.[10a] mp 20.1–20.8 °C). ^1H NMR: δ 7.72 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.3 Hz), 4.4 (1H, quint, J = 6.8 Hz), 2.41 (3H, s), 1.74 (1H, oct., J = 6.9 Hz), 1.15 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.9 Hz), 0.80 (3H, d, J = 6.8 Hz) (note that the methyls of the isopropyl group are nonequivalent).

The deuterated tosylates **4**-*1*-d_3, **4**-*2*-*d*, and **4**-*3*-*d*, obtained from the corresponding alcohols, gave the appropriate ^1H and ^2H NMR spectra.

Solvolysis of 4. The rates were determined spectrophotometrically,[60] following the decrease in absorbance at 273 nm. For product analysis the solution (0.15 M of **4** in buffered TFA) was quenched after 1 h at 26.5 °C in a mixture of ice and hexane (for GLC analysis), or ice and isopentane or $CFCl_3$ (for MS), neutralized with K_2CO_3 (excess) or dilute NaOH (stoichiometric), the layers were separated, and the aqueous phase was extracted twice more. The combined organic solution was dried over solid K_2CO_3. GLC analyses were run on the dilute samples. The samples for MS were concentrated on an annular column to about 10% (**5** + **6**).

Careful examination of the mass spectra of deuterated esters **5** and **6** from GC-MS experiments indicated that some isotopomer fractionation occurs on the GLC colum. Therefore, several spectra were recorded during the elution of **5** and **6**. The averaged intensities of the m/z 140–146 fragments of **6** from **4**-*1*-d_3 were 1467, 8541, 4901, 3570, 11826, 7288, and 3491. Correcting for the 2% m/z 144 found for unlabeled **6** and for 0.6% d_2 material existing in the alcohol precursor of **4**-*1*-d_3, the ratio of m/z 144 (**10**, X = H, Y =D) to m/z 141 (**10**, X = Y = H) peaks is 11725/8541 = 57.9/42.1. Likewise, the intensities of the m/z 169–172 fragments in **5** from **4**-*1*-d_3, after correction for the natural contents of carbon-13, were 19997, 6428, 5044, and 841780. (2.3:0.7:0.6:96.4).

The analysis of the product of reaction in TFA-^{18}O was best conducted by negative-ion GC-MS, looking at the CF_3COO^- fragment (m/z 113, 115, 117) for each ester (**5** and **6**). The ratio of unlabeled:monolabeled:dilabeled material was 34:48:18 for **5**, 36:47:17 for **6**.

Short-Time solvolysis of 4 in TFA-*d*. A solution of **4** (0.073 g, 0.30 mmol) in TFA-*d* (2 mL, molar ratio TFA-*d*:**4** ca. 84:1) was kept at room temperature for about 1 half-life and for half of that time. A 0.5-mL sample was removed from the flask and added to a mixture of 2 N NaOH (2 mL), hexane (0.5 mL), and ice in a separatory funnel. After shaking briefly, the hexane layer was separated and poured into a round-bottomed flask containing dry K_2CO_3 and a magnetic stirring bar. The volatile part of the mixture (product and solvent) was distilled at −5 to +5 °C under high vacuum to another flask, cooled in liquid nitrogen (bulb-to-bulb distillation). The distillate was analyzed by GLC and GC-MS. The distillation step was necessary because unreacted **4** decomposed in the injection port of the GC and led to useless chromatograms. In view of the approximate nature of the entire experiment the mass spectra were not averaged over the GLC peaks.

Appendix A

Three runs of solvolysis of **4** in TFA-*d* at about one-half of a half-life and two at about 1 half-life at room temperature (not in thermostat) were conducted. The isotope distribution in the fragments m/z 155 (**8**, M − Et) and m/z 169 (**7**, M − Me) of **5** was determined for each run (Table 2).

Ion **8** contains both methyl groups of the original **5**, whereas **7** contains the ethyl group and one of the methyl groups. Calculation of the isotope distribution in each methyl and in the ethyl group is straightforward. The sum of percentages calculated for the isotopomers of the ethyl groups was 100 ± 3; it was normalized to 100 in each case. Because the MS spectra for the three "short" runs of solvolysis in TFA-*d* gave similar values for the deuterium content, their average was used. The MS spectra for the two "long" runs were more widely diverging; an error in the reaction time or temperature might be responsible. Therefore, these two experiments were handled separately. The results were as follows:

t = 235.7 ± 2.6 s (average of "short" runs a, b, and c)

Me group 93.6 d_0, 5.9 d_1, 0.5 d_2;
Et group 46.1 d_0, 51.6 d_1, 2.3 d_2

t = 464 s (run d)

Me group 90.2 d_0, 8.8 d_1, 1.0 d_2;
Et group 34.5 d_0, 52.4 d_1, 13.1 d_2

t = 469 s (run e)

Me group 88.0 d_0, 11.3 d_1, 0.7 d_2;
Et group 27.6 d_0, 50.1 d_1, 22.2 d_2

All the deuterium present in the methyl group is incorporated by exchange after formation of ion **1**, whereas the deuterium found in the ethyl group of **5** results partly

(59) Marvel, C. S.; Sekera, V. C. *Org. Synth.* **1940**, *20*, 50.
(60) Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 2551.

from exchange and partly from addition to olefin 16 formed by elimination from the tight ion pair in Scheme 1.

The exchange can be treated as a first-order process; the loss of D in the acid was negligible (the ratio of TFA-*d* to 4 was 84 and about 1 atom of D was present in 5 at the end). The first-order rate constants for H/D exchange in a methyl group and in the ethyl group of ion 1 in TFA-*d* were determined in two experiments: (1) $k(\mathrm{Et}) = 3.01 \times 10^{-4}$, $k(\mathrm{Me}) = 4.05 \times 10^{-5}$; (2) $k(\mathrm{Et}) = 5.1 \times 10^{-4}$, $k(\mathrm{Me}) = 4.6 \times 10^{-5}\ \mathrm{s}^{-1}$.[25] The ratios of two rate constants $k(\mathrm{Et})/k(\mathrm{Me})$ were (1) 7.4 and (2) 11.1. The number of C–H bonds available for exchange (exchange sites) at two times, t_1 and t_2, are related by eq 3.

$$k = [\ln(n_1/n_2)]/(t_2 - t_1) \tag{3}$$

At $t = 0$ the number of sites available for exchange in a methyl group and the ethyl group of nondeuterated 1 were 300 and 200, respectively, both for 100 molecules. It follows immediately that

$$\ln[300/n_t(\mathrm{Me})] = [k(\mathrm{Me})/k(\mathrm{Et})]\{\ln[200/n_t(\mathrm{Et})]\} \tag{4}$$

and

$$\ln[n_t(\mathrm{Et})] = \ln 200 - [k(\mathrm{Et})/k(\mathrm{Me})]\{\ln[300/n_t(\mathrm{Me})]\} \tag{5}$$

For the ester resulting from solvolysis in TFA-*d* the number of sites available for exchange is n_0, smaller than 200 by the number of D incorporated by elimination from [2^+·OTs^-] to 16 and TFA-*d* addition (Scheme 1). Equation 5 is replaced by eq 5a:

$$\ln[n_t(\mathrm{Et})] = \ln(n_0) - [k(\mathrm{Et})/k(\mathrm{Me})]\{\ln[300/n_t(\mathrm{Me})]\} \tag{5a}$$

whence

$$\ln(n_0) = \ln[n_t(\mathrm{Et})] + [k(\mathrm{Et})/k(\mathrm{Me})]\{\ln[300/n_t(\mathrm{Me})]\} \tag{5b}$$

At $t = 235.7$ (runs a, b, and c):

$$n_t(\mathrm{Me}) = 300 - 5.9 - 2 \times 0.5 = 293.1$$

$$n_t(\mathrm{Et}) = 200 - 51.6 - 2 \times 2.3 = 143.8$$

that is, 6.9 D atoms (300 – 293.1) were introduced in the Me group by exchange in 1 and 56.2 D atoms (200 – 143.8) were introduced in the Et group by addition to 16 (Scheme 1) *and* by exchange in 1 resulting from reaction by all pathways. To calculate the extent of exchange in Et (as the number of unexchanged C–H sites, n_0) we introduced the value for $n_t(\mathrm{Me})$ and $n_t(\mathrm{Et})$ in eq 5b and obtained (1) for the rate constant ratio $[k(\mathrm{Et})/k(\mathrm{Me})]$ 7.4:

$$\ln(n_0) = \ln 143.8 + 7.4 \times \ln(300/293.1) \qquad n_0 = 170.8$$

(2) for the rate constant ratio 11.1

$$\ln(n_0) = \ln 143.8 - 11.1 \times \ln(300/293.1) \qquad n_0 = 186.2$$

The same calculation was performed for each of the two "long run" experiments: at $t = 464$ s (run d), the measured quantities

$$n_t(\mathrm{Me}) = 300 - 8.8 - 2 \times 1.0 = 289.2$$

$$n_t(\mathrm{Et}) = 200 - 52.4 - 2 \times 13.1 = 121.4$$

number of C–H existing in 5 before any exchange occurred (eq 5b):

$$(1)\ n_0 = 159.2 \qquad (2)\ n_0 = 182.3$$

At $t = 469$ s (run e), measured quantities

$$n_t(\mathrm{Me}) = 300 - 11.3 - 2 \times 0.7 = 287.3$$

$$n_t(\mathrm{Et}) = 200 - 50.1 - 2 \times 22.2 = 105.5$$

calcd from eq 5b:

$$(1)\ n_0 = 145.3 \qquad (2)\ n_0 = 170.5$$

Obviously, from elimination–addition only one D atom was introduced per molecule. The number of molecules containing D prior to exchange ($100 - n_0$) was, therefore:

(a,b,c)(1) 29.2; (a,b,c)(2) 13.8; (d)(1) 40.8;
(d)(2) 17.7; (e)(1) 54.7; (e)(2) 29.5

The statistically weighted average (giving experiments a, b, c, d, and e equal weight) is:

27.2%, S.D. = 12.6

Appendix B

This calculation does not use an independently measured rate of exchange between 5 and TFA-*d* and is, therefore, less accurate.

Considering the length of a solvolysis run in TFA-*d* as t_n, a molecule of product formed at some time t will stay in contact and be available for exchange with TFA-*d* for a period equal to $t_n - t$. For calculation, the material formed in a small interval of time, between t_{i-1} and t_i, is considered to have exchanged for an effective time (t_{eff}) measured from the middle of that interval to the end of the run (eq 6).

$$t_{\mathrm{eff}} = t_n - (t_i + t_{i-1})/2 \tag{6}$$

The amount of material formed after t_{i-1} and after t_i can be calculated from the reaction rate at 25 °C (1.57×10^{-3}). The conversion during the interval from t_{i-1} to t_i (Δconv) is then obtained by difference. If the run is divided in several small intervals (t_1, t_2, ... t_i, ... t_n), the total exchange can be approximately obtained by considering that the entire amount of product formed has exchanged for an average time calculated by eq 7:

$$t_{\mathrm{av}} = [\sum_{i=1}^{n} (\Delta\mathrm{conv} \times t_{\mathrm{eff}})]/\mathrm{convf} \tag{7}$$

where convf is the total conversion at the end of the run (after t_n). Values for a "short" run (half of a half-life, Appendix A) are given in Table 3. The length of the time intervals could be made as small as desired if the accuracy of experimental data would warrant it.

After a "long" run (ca. 467 s, Appendix A) conversion to product was 51.7%. Of this, 30.7% was formed in the first half (above) and 21.0% (51.7 – 30.7) in the second half of the run.

Ester 5 generated in the second half of the "long" run is formed with the same isotope composition as 5 formed in the first half and as 5 isolated at the end of a "short" run. For evaluation of elimination from 2, only the ethyl groups need to be considered. As calculated in Appendix A, after a "short" run the Et group is 46.1% d_0, 51.6% d_1, and 2.3% d_2.

The Et groups of 5 formed in the first half of the "long" run (30.7 mol from 100 mol of starting 4) contained at that

Table 3

	t_i (s)						
	25	50	75	115	170	230	234
conv, %	3.8	7.5	11.1	16.5	23.4	30.3	30.7
Δ conv	3.8	3.7	3.6	5.4	6.9	6.9	0.3
t_{eff}	221.5	196.5	171.5	139.0	91.5	34.0	2.0
Δ conv x t_{eff}	841.7	727.1	617.4	750.6	631.4	234.6	0.6

t_{av} = 3803.4/30.7 = 124 s

moment 30.7 × 0.461 = 14.2 d_0, 30.7 × 0.516 = 15.8 d_1, and 30.7 × 0.023 = 0.7 d_2, that is 15.8 + 2 × 0.7 = 17.2 gram atoms of D.

Likewise, **5** formed in the second half of the "long" run (21.0 mol) contained in its Et groups 21 × 0.461 = 9.7 d_0, 21 × 0.516 = 10.8 d_1, and 21 × 0.023 = 0.5 d_2 species, that is 10.8 + 2 × 0.5 = 11.8 gram atoms of D.

The total content of D in the Et groups at the end of the "long" run (t = 466.5 + 2.3 s) was found as the average of the two measurements in Appendix A: 31.1 d_0, 51.3 d_1, 17.6 d_2. For the 51.7 mol of **5** formed, we calculate 51.7 × 0.311 = 16.1 d_0, 51.7 × 0.513 = 26.5 d_1, and 51.7 × 0.176 = 9.1 d_2 species.

The D content at the end of the reaction in the Et groups of the 30.7 molecules of **5** formed at midpoint is the difference between the total content and the content in **5** formed in the second half of the run: 16.1 − 9.7 = 6.4 d_0, 26.5 − 10.8 = 15.7 d_1, and 9.1 − 0.5 = 8.6 d_2, that is 15.7 + 2 × 8.6 = 32.9 atoms gram of D. These molecules were exposed to exchange for an average time of 124 s (t_{av} above) during the first half of the run, and then for the entire second half (233 s).

Knowing that the total number of sites available for D incorporation in 30.7 mol of ethyl groups is 61.4, we can apply eq 3 (Appendix A), where n_1 = 61.4 − 17.2 = 44.2, n_2 = 61.4 − 32.9 = 28.5, t_1 = 124 s, and t_2 = 124 + 233 = 357 s. We obtain then k_{exch} = 0.00188 s^{-1}.

The D content of **5** resulting from solvolysis before any exchange had occurred is found from eq 3 between t = 0 (n_0 sites) and t_2 = 357 (n_2 = 28.5):

$$\ln(n_0) = (357 - 0)k + \ln 28.5 = 4.032 \qquad n_0 = 55.8$$

which means that 5.6 sites (61.4 − 55.8) contain deuterium at time zero. Obviously, only one position per molecule could have been deuterated then. Therefore, 5.6 out of 30.7 molecules of **5** (18.2%) contained D before undergoing any exchange.

It can be noted that the two "long" runs gave somewhat divergent results for the d_3 in the m/z 169 fragment. To assess the uncertainty of the evaluation the calculation was repeated using the results for each of these runs rather than their average. The results for the proportion of **5** deuterated at t = 0 were 2% and 31%!

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