Solvolysis of 1-(3-Noradamantyl)ethyl Sulfonates

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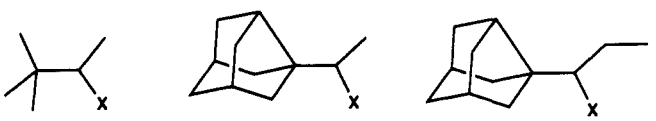
Abstract: The title esters solvolyze in aqueous ethanol (a) almost entirely to the rearranged substitution products 2-methyl-1-adamantyl alcohol and ether, (b) about 1000 times faster than unstrained analogues, (c) by a non-first-order rate law, (d) without oxygen scrambling, and (e) with production of large proportions of the rearranged tertiary 2-methyl-1-adamantyl sulfonate esters as reactive intermediates. The tertiary esters solvolyze (a) to unrearranged substitution products, (b) 2–7 times faster than the noradamantyl isomers, (c) in clean first-order reactions, and (d) with oxygen scrambling. The formation of rearranged tertiary esters as reactive intermediates in the solvolyses of the secondary esters and the oxygen scrambling during solvolysis of the tertiary esters both show that the solvolyses of the tertiary esters involve large proportions of internal return and are therefore not "k_c" processes. In addition, solvent effects on the partitioning of the tertiary ester's tight ion pair between covalent substrate and products are significant and lead to a Grunwald–Winstein m value for internal return that is about 0.5 less than that for solvent separation; this result provides an explanation for the larger-than-average m values observed for 1-adamantyl systems. The β-d_3 rate effects for solvolysis of the 1-(3-noradamantyl)ethyl esters are in the narrow range of 1.14–1.15, smaller than the value of ≈1.20 shown by 3,3-dimethyl-2-butyl sulfonates and indicative of carbon σ-participation and strong carbon hyperconjugation. Thus, the accelerated solvolysis rates, the absence of internal return, and the lowered isotope effects clearly establish this solvolysis as a k_Δ process. Plots of log k values vs Y_{OTs} for the title esters give slopes (m values) around 0.7, while the m values for the adamantyl isomers are around 1. The differences between these plots for structurally very similar reactants solvolyzing with clearly different rate-determining steps are not large and indicate the hazards in using rate correlations to establish solvolytic reaction mechanisms, especially when comparing reactants with greater structural differences. The higher homologues, 1-(3-noradamantyl)propyl sulfonate esters, were found to behave similarly.

Introduction

Some years ago it was proposed that pinacolyl (3,3-dimethyl-2-butyl) sulfonates (**1**) solvolyzed by rate-determining ionization without internal return and without participation by solvent or neighboring group.[1] Although this proposal has not met with universal acceptance,[2] we believe that the balance of the evidence strongly supports it. Recently some effort has been directed to the examination of structurally related compounds in order to probe the factors governing carbon σ-participation in the solvolysis of secondary sulfonates.[3] The aim is to establish some examples in which internal return occurs and others in which participation occurs and then to establish experimental criteria for assigning and structural criteria for predicting each type of behavior.

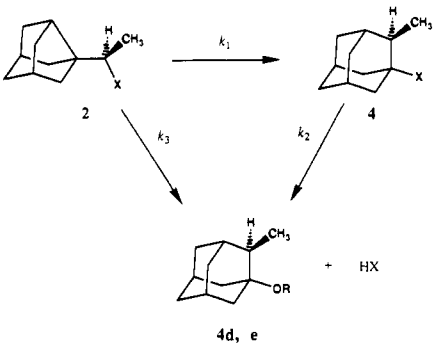
Accordingly, this paper describes research done on the solvolysis of relatives of pinacolyl sulfonates in which the γ-carbon atoms are incorporated into the noradamantyl ring system with the consequence that the Wagner–Meerwein rearrangement is accompanied by a large release of strain, which presumably promotes participation. For the case in which the γ-carbon atoms are incorporated into the relatively strain-free adamantyl ring system, which retards rearrangement, see ref 3. Comparison of these compounds with the pinacolyl example is instructive about the structural requirements for and experimental manifestations of neighboring carbon σ-participation. The structures of the secondary neopentyl-type esters that have been studied are shown below. Compounds **1a** and **1c** are pinacolyl sulfonate esters, **2a–c** are 1-(3-noradamantyl)ethyl sulfonate esters, and **3a–c** are 1-(3-noradamantyl)propyl sulfonate esters. In structures **1–3**, X = a sulfonate group: in **1a–3a**, X = OTs, *p*-toluenesulfonate; in **2b** and **3b**, X = OPms, pentamethylbenzenesulfonate (pemsylate); and in **1c** and **2c**, X = OBs, *p*-bromobenzenesulfonate.



1 **2** **3**

† This work constitutes part of the Ph.D. Thesis of D. T. Stoelting, Indiana University, 1990.

Scheme I



4d, e

Results and Discussion

A. 1-(3-Noradamantyl)ethyl Sulfonates. 1. Kinetics of Reaction. Aqueous ethanolyses of 1-(3-noradamantyl)ethyl sulfonate esters **2a** and **2b** and their α-d_1 and β-d_3 isotopomers do not follow the first-order rate law.[4] Non-first-order solvolytic behavior in some structurally related reactants has been observed by Winstein and by others[5] and attributed to rearrangement of the solvolyzing ester to an isomer of similar but different reactivity. In most cases the reactions were shown to involve ionization to the rearranged

(1) Shiner, V. J., Jr.; Fisher, R. D.; Dowd, W. *J. Am. Chem. Soc.* **1969**, *91*, 7748–7749.

(2) (a) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5466–5475. (b) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67. (c) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1974; Vol. 2, pp 247–374. (d) Bentley, T. W.; Liggero, S. H.; Imhoff, M. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 1970–1973. (e) Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89–173.

(3) Wilgis, F. P.; Neumann, T. E.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4435–4446.

(4) For the solvolysis of **2a** in 90% aqueous ethanol (90E) at 25 °C, the integrated first-order rate coefficients started at 22 × 10^{-5} s^{-1} and rose to about 33 × 10^{-5} s^{-1}.

(5) (a) Tai, J. J. Ph.D. Thesis, Indiana University, 1979. (b) Howe, R. K.; Winstein, S. *J. Org. Chem.* **1973**, *38*, 2797–2801. (c) Colter, A.; Friedrich, E. C.; Holness, N. J.; Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 378–379. (d) Meinwald, J.; Gassman, P. *J. Am. Chem. Soc.* **1963**, *85*, 57–59. (e) Winstein, S.; Fainberg, A. H. *J. Am. Chem. Soc.* **1958**, *80*, 459–465. (f) Winstein, S.; Schreiber, K. C. *J. Am. Chem. Soc.* **1952**, *74*, 2171–2178. (g) Young, W. G.; Winstein, S.; Goering, H. L. *J. Am. Chem. Soc.* **1951**, *73*, 1958–1963.

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Table I. Solvolysis Rate Constants and Winstein–Grunwald m Values of Sulfonate Esters at 25 °C

compound	k, 10^{-5} s^{-1} 80E	90E	95E	97T	m_E[a]
1-(3-noradamantyl)ethyl tosylate (**2a**)[c]	117.3	37.43	16.65		0.731
2-methyl-1-adamantyl tosylate (**4a**)	796	159.0	49.11		1.0414
1-(3-noradamantyl)propyl tosylate (**3a**)[c]	284	100	45.5		0.685
2-ethyl-1-adamantyl tosylate (**7a**)	1590	247	91		1.08
1-(3-noradamantyl)ethyl pemsylate (**2b**)[c]	19.48	6.818	3.214	1970	0.674
2-methyl-1-adamantyl pemsylate (**4b**)	91.84	20.20	6.744		0.977
1-(3-noradamantyl)propyl pemsylate (**3b**)[c]	37.97	14.45	7.26		0.619
2-ethyl-1-adamantyl pemsylate (**7b**)	147.1	34.87	12.21		0.9304
1-adamantyl tosylate	426	78.9	22.86		1.094
pinacolyl tosylate (**1a**)	0.0906	0.0206[b]	0.00701[b]	2.261	0.957
pinacolyl brosylate (**1c**)	0.6357	0.166[b]	0.0616[b]	7.98	0.873
2,2-dimethyl-3-pentyl tosylate	0.4746	0.1142[b]	0.0407[b]	19.16	0.914
2,2-dimethyl-3-pentyl brosylate	2.828	0.737[b]	0.276[b]	57.47	0.871
2,2-dimethyl-3-pentyl pemsylate	0.0583	0.0162[b]	0.006 38[b]	2.730	0.827

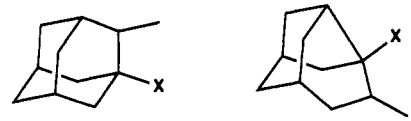
[a] Slope of the plot of log k for the ethanol–water solvents only vs Y_{OTs} values determined from the rates of solvolysis of 2-adamantyl tosylate given in ref 26. [b] Obtained by mY_{OTs} extrapolation from rate constants measured in three different solvents having compositions in the range 50E–80E.[6] [c] Rates for disappearance of reactant, which includes isomerization and solvolysis, see text.

tight ion pair formed by a 1,2 shift followed by internal return to form the covalent isomer.

Therefore, we proceeded on the assumption that during solvolysis **2a** and **2b** rearranged to their 2-methyl-1-adamantyl sulfonate isomers **4a** and **4b** and produced 2-methyl-1-adamantyl substitution products and sulfonic acid; the tertiary esters **4** further solvolyzed to 2-methyl-1-adamantyl substitution products and acid. Kinetic Scheme I incorporates this mechanistic hypothesis.

To confirm that the non-first-order behavior was caused by the isomerization of **2** to **4**, compounds **4a**, **4b**, and the 2-d_1 and methyl-d_3 isotopomers of **4b** were prepared and their solvolysis reactions examined;[7] Table I reports the hydrogen rate constants.[8] Each of these esters solvolyzed in clean first-order fashion. Kinetic data from each solvolysis of **2a** and **2b** were then analyzed with k_3 set to 0 and k_2 set to the values found independently from solvolysis of **4a** and **4b**; the error plots showed either small or no systematic trends in the resistance errors ("residuals") over the course of the reaction, confirming that the non-first-order behavior in the solvolysis of the esters **2a** and **2b** is caused by the isomerization of **2** to **4**. Table I shows that esters **2** and **4** have similar reactivities (i.e., $k_2/(k_1 + k_3) = 2$–5); since solvolyses of **4a** and **4b** show good first-order behavior, back rearrangement of **4** to **2** does not occur.

A2. Product Studies. The products of solvolysis were determined by examination of the 55.4-MHz ^{2}H NMR spectra of the spent, buffered reaction mixtures from the α-d_1 isotopomer of **2a** in 90E, 95E, 100E, and 97% aqueous trifluoroethanol (97T), **2b** in 90E, and **2c** in 90E; from the 2-d_1 isotopomer of **4b** in 90E and 97T; and from the γ-d_3 isotopomer of **4b** in 90E. The spectra show that **2** rearranges completely and gives products with the same chemical shifts and in nearly the same proportions as those produced from **4**.[9] In addition, the major product from solvolysis of **2a** in 100% ethanol buffered with 1.1 equiv of lutidine was isolated and shown by its 300-MHz ^{1}H and proton-decoupled 75-MHz ^{13}C NMR spectra to be 2-methyl-1-adamantyl ethyl ether. The 55.4-MHz ^{2}H NMR spectra were also used to observe the course of the reaction of the α-d_1 isotopomer of **2a** in 100E and to show the rise and decay of resonance peaks characteristic of the tertiary ester intermediate.[10] It was expected from product studies on the ethanolyses of the higher homologues 1-(3-noradamantyl)-2-methylpropyl pemsylate and 1-(3-noradamantyl)-2,2-dimethylpropyl pemsylate that the peak in the ^{13}C spectrum of the product mixture at δ 57.1 was probably due to the CH_2 of the ethyl group of the ethyl ether of 4-methyl-3-protoadamantanol (**5e**),[11] the other possible product from rearrangement of the 3-noradamantyl ring system. In substances **4** and **5**, X = a sulfonate group: in **4a**, X = OTs, *p*-toluenesulfonate; in **4b**, X = OPms, pentamethylbenzenesulfonate; in **4d** and **5d**, X = OH; and in **4e** and **5e**, X = OR.



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The peak height relative to that for the 1-adamantyl ether product indicated that this suspected minor product was formed in only 1.4% yield. To confirm that 3-protoadamantyl products could be formed in solvolysis, α-d_1-labeled **2a** was solvolyzed in 83% aqueous acetone, and the alcohol products, which were more easily separated by HPLC than the ethers, were examined. A small fraction which eluted just before the major product yielded a white solid, 1.5% by weight of the crude product, which the 500-MHz ^{1}H and 125-MHz ^{13}C NMR spectra indicated to be 4-methyl-3-protoadamantanol-*4-d*. Although our kinetic analysis made no allowance for the production of any 4-methyl-3-protoadamantyl pemsylate (**5b**) by internal return, the quality of the fits of the conductometric kinetic data from solvolysis of **2** indicated that no further mechanistic elaboration was required.

A3. Importance of k_3. The small systematic errors mentioned above were observed for **2b** in 80E, 90E, and 95E but not for **2a** in any solvent.[12] In 80E and 90E, these errors are caused by the influence of k_3 in the solvolysis of **2b**, but the errors observed in 95E from solvolysis of **2b** are caused by about 0.3–0.6% of pentamethylbenzenesulfonyl chloride (pemsyl chloride) impurity. We were able to fit the kinetic data of **2b** including pemsyl chloride

(6) Stoelting, D. T. Ph.D. Thesis, Indiana University, Bloomington, IN, 1990.

(7) The independent determination of k_2 is required when k_3 is small relative to k_1, because if one sets k_3 to 0 in eq 1, the equation does not change when k_2 and k_1 are interchanged.

(8) In 80E, 90, and 95E, the β-d_1 and γ-d_3 kinetic isotope effects for **4b** are 0.994 ± 0.001 and 0.968 ± 0.003, respectively.

(9) The molar reactivity ratios k_s/k_e were 2.2, 2.3, 2.4, 2.2, and 2.3 for **2a**-α-d_1, **2b**-α-d_1, **2c**-α-d, **4b**-2-d_1, **4b**-γ-d_3, respectively in 90E; 2.5 for **2a**-α-d_1 in 95E; 1.7 and 2.4 for **2a**-α-d_1 and **4b**-2-d_1, respectively, in 97T. The different values for k_s/k_e for the last two sulfonates may be due to the difference in leaving groups, to a smaller fraction of rearranging internal return, or to some other unidentified mechanistic effect; in this solvent the rates were too fast for a kinetic study. The molar reactivity ratios k_s/k_e were 2.4, 2.3, and 1.6 for **3b**-α-d_1 in 90E, 95E, and 97T, respectively.

(10) About 10 min after the time of mixing, **2a** produced **4a** and **4e** in 8% and 3% yield, respectively. Around 3.5 h later, **2a** and **4e** were present to the extent of 24% and 28%, respectively. After complete reaction, only the resonance for **4e** was apparent. Similarly, after ≈12 h, **3b** showed 31% of the intermediate ester **7b** and 44% of the product ether **7e**. After complete reaction, only the resonance for **7e** was apparent.

(11) The synthesis of 3-protoadamantanol and a study of the expected degree of difficulty in the formation of a 3-protoadamantyl cation is given in the following reference: Sosnowski, J. J.; Danaher, E. B.; Murray, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 2759–2763.

(12) k_3 was not determined in 80E because the solvolyses of the tosylate esters **2a** and **4a** were too fast; in 90E and 95E k_3 was too small, relative to k_1, to be determined accurately by our technique.

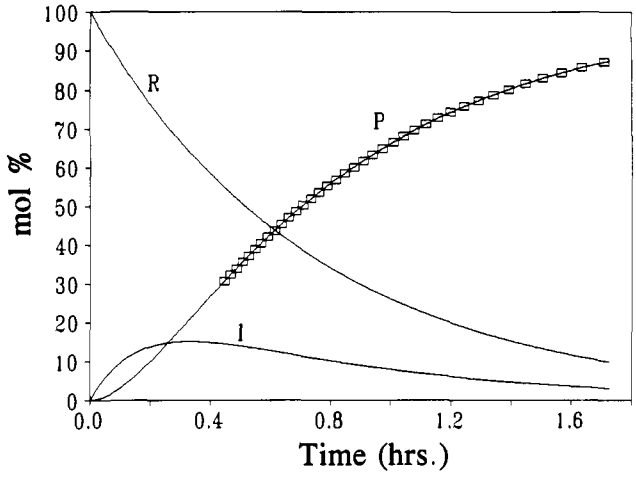

Figure 1. Solvolysis of **2a** in 90E. A typical plot showing the first-order decrease in the percent of reactant (R) remaining, the rise and decay in the yields of intermediate (I), and the non-first-order increase in the yield of product (P) over time. Each curve was calculated with the parameters which gave the best fit of the conductance data. The observed values of acid concentration are represented by a square for every eleventh conductance measurement.

in the model and found no change in the isotope effects,[13] within the limits of error. In later work (see below) a sample of the α-d_1 ester was prepared without the small trace of pemsyl chloride impurity; the serial first-order kinetic treatment of the data from solvolysis of this product gave a satisfactory fit without any observable systematic errors.

Figure 1 shows how the concentrations of **2a**, **4a**, and acid, HX, vary in 90E as a function of time. The curves in the figure were calculated using the parameters that were found to give the best fit of the data to the integrated serial first-order rate law. Experimentally determined values of acid concentration are indicated by an open square for every eleventh point only.

A4. Rate Constants and Kinetic Isotope Effects. The combined first-order rate constants for disappearance of starting ester are given in Table I.[14] The rate constants show that **2a** and **2b** are strongly accelerated over the pinacolyl analogues **1**. In 80E, **2a** reacts 1300 times faster than **1a**. Two classical criteria for a neighboring group participation mechanism are, therefore, satisfied: (1) the rate constant is large relative to that of closely related reactants which do not show neighboring group participation and (2) the products are completely rearranged. Pinacolyl sulfonates are believed to react by rate-determining ionization, without solvent participation and without internal return or neighboring group acceleration,[1,3,15] and they show β-d_3 effects in the range of 1.20–1.21. The β-d_3 KIEs for esters of **2** fall in the range of 1.14–1.15, significantly lower than those for **1**; σ-participation and/or strong hyperconjugation in rate-determining ionization acts to lower the demand of the reaction center for hyperconjugative electron release from the CH_3 or CD_3 group and, therefore, to cause the lower β-d_3 effects. Further, since the esters of **2** mainly disappear through formation of **4**, the solvent (vide infra) and isotope effects on the rate constants show that this isomerization is an ionic and not an electrocyclic process.

These β-d_3 effects can be predicted by the SBS equation, $\log(\alpha\text{-}CH_3/CD_3) = 0.02024 \log(\alpha\text{-}CH_3/H)$, which correlates the log of the β-d_3 effect with the log of the acceleration caused by the α-methyl group relative to hydrogen.[16,17] Substitution of the methyl/hydrogen rate effect observed for **2a** in 80E into the SBS equation correctly predicts the β-d_3 effect for **2** to be $\approx$1.15. In addition, the predicted β-d_3 effects for **1c** of 1.190 in 50E and 1.209 in 97T[1,18] agree fairly well with experimental values of 1.205 in 50E and 1.188 in 97T but not as well as those for **2**. The relatively small error in the prediction for **1** is probably due to the fact that the mechanisms of solvolysis of the neopentyl and pinacolyl esters are not the same. Since the β-d_3 effects are lowered relative to those for the pinacolyl analog, it is at first thought surprising that the α-d_1 effects are not also lowered proportionately. However, it is well established that π-bonding to the cationic center reduces the β-effect, which is hyperconjugative in origin; on the other hand, the α-d_1 effect is caused by the reduction in σ-bonding at the reaction center and is not reduced by increased π-bonding.[19] Thus, strain that tends to increase the C_α–C_γ and C_β–C_γ bond distances in the transition state will increase the C_α–C_β π-bonding and reduce the β- but not the α-effect. Similar bonding changes have been recently reported to occur in the 2-seco[1.1.1.1]pagodyl cation as the result of strong σ-bond hyperconjugation.[20] In this respect it is interesting that the α-d_1 effects on solvolysis rates of neopentyl triflate (1.12),[21] (1-methylcyclohexyl)methyl triflate (1.12),[22] and 3-noradamantylmethyl tresylate (1.118) are all near the same size, while that for (1-methylcyclopentyl)methyl brosylate[22] (1.10) is lower and that for 1-adamantylmethyl triflate (1.15)[23] is higher. All of these solvolyses must involve participation by neighboring C–C σ-bonds, and the α-d_1 effects must reflect the balance of changes in σ-bonding between initial and transition states.

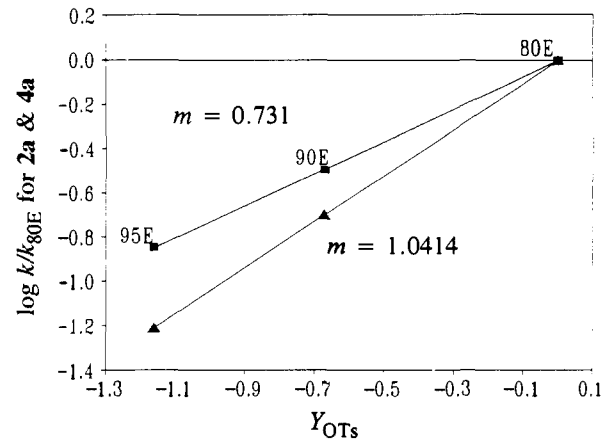

Figure 2. Winstein–Grunwald mY plots of the rate constants of **2a** (■) and **4a** (▲) versus the solvolysis rate constants of 2-adamantyl tosylate in 80E, 90E, and 95E.

A5. Winstein–Grunwald mY Plots. Table I reports the Winstein–Grunwald m values resulting from plots of the logs of the rate constants of **1**,[24] **2**, **4**, and other related sulfonate esters[25] versus the logs of the rate constants for 2-adamantyl tosylate. All of the 2-adamantyl tosylate rate constants were determined in this laboratory and are slightly different from those reported earlier which were *calculated* by extrapolation of rate constants deter-

(13) Allowing for the presence of pemsyl chloride as a reactive impurity in the reaction of **2b** in 95E did not change the isotope effects but did improve the standard deviation of the errors in those effects by a factor of 2.

(14) **2b** has α-d_1 kinetic isotope effects (KIEs) of 1.161 ± 0.002, 1.160 ± 0.002, and 1.163 ± 0.001, and β-d_3 has KIEs of 1.139 ± 0.002, 1.140 ± 0.002, and 1.145 ± 0.001 in 95E, 90E, and 80E, respectively. **2a** has α-d_1 KIEs of 1.161 ± 0.002, 1.160 ± 0.002, and 1.163 ± 0.001, and β-d_3 has KIEs of 1.146 ± 0.002 and 1.148 ± 0.002 in 95E, 90E, and 80E, respectively. **3b** has α-d_1 KIEs of 1.172 ± 0.004, 1.174 ± 0.001, and 1.1722 ± 0.0006, and β-d_3 has KIEs of 1.155 ± 0.003, 1.153 ± 0.001, and 1.1474 ± 0.0007 in 95E, 90E, and 80E, respectively.

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(16) Servis, K. L.; Borcic, S.; Sunko, D. E. *Tetrahedron* **1968**, *24*, 1247–1253.

(17) Fisher, R. D.; Seib, R. C.; Shiner, V. J., Jr.; Szele, I.; Tomic, M.; Sunko, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 2408–2413.

(18) Neopentyl brosylate rate constant in 97T was determined by Stoelting; 50E rate constant from Seib, R. C. Ph.D. Thesis, Indiana University, Bloomington, IN, 1978.

(19) Shiner, V. J., Jr.; Buddenbaum, W. E.; Murr, B. L.; Lamaty, G. *J. Am. Chem. Soc.* **1968**, *90*, 418–426.

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(21) Shiner, V. J., Jr.; Seib, R. C. *Tetrahedron Lett.* **1979**, *2*, 123–126.

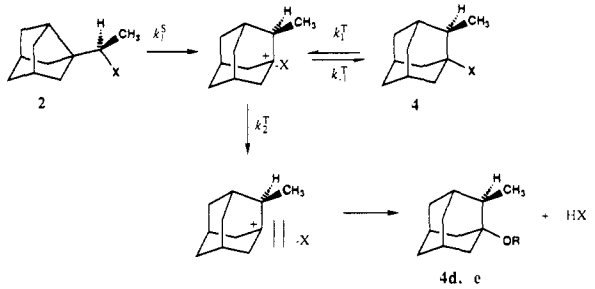
(22) Shiner, V. J., Jr.; Tai, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 436–442.

(23) Dowd, W. Ph.D. Thesis, Indiana University, 1970.

(24) Fisher, R. D. Ph.D. Thesis, Indiana University, Bloomington, IN, 1971.

(25) (a) 1-(1-Adamantyl)ethyl brosylate rate constants are taken from ref 3. (b) 2,2-Dimethylcyclopentyl brosylate rate constants are taken from ref 29.

Scheme II



mined at higher temperatures.[26] The largish m values suggest that the esters of **2** react through a highly ionized transition state.[27] Comparing m values for esters of different alcohols and the *same* leaving group, one finds that the k_Δ mechanistic example (nor-adamantylethyl, **2a**) has a smaller m value (0.731) than the k_c example (pinacolyl, **1a**, 0.936) and that the reaction involving ion-pair return (2-methyl-1-adamantyl, **4a**) has a still larger value (1.04). This is in the direction expected if m values tend to be larger for transition states having greater degrees of ionization; however, the differences are small and would not appear to provide a very reliable method of classification of these three categories of mechanisms. Figure 2 shows the Winstein–Grunwald mY plots for **2a** and **4a**.

TFE–ethanol plots have been proposed as diagnostics for mechanisms of solvolysis.[28] One useful indicator which we obtain from these plots is Δ97T,[29] the difference between the log of the rate constant found by extrapolation from aqueous ethanol and the log of the observed rate constant in 97T. The value for Δ97T for **2b** is large and negative (−0.78). Positive values of Δ97T have traditionally been interpreted to indicate that the compound under examination is more sensitive to nucleophilic attack than 2-adamantyl tosylate; this argument applied to the present example would suggest that **2b** is less sensitive to nucleophilic attack than 2-adamantyl tosylate. Since nucleophilic assistance is not expected to be important in either solvolysis, a more reasonable explanation is that trifluoroethanol (TFE) has a better ability to solvate the delocalized transition state produced upon ionization of **2b** than does aqueous ethanol.[30] Another expected cause of negative values for Δ97T arises when different leaving groups are involved in the comparison; thus, the more acidic TFE should solvate the more basic leaving group (OPms) relatively better than does ethanol. However, the Δ97T values for the tosylate and pemsylate esters of 2,2-dimethyl-3-pentanol are near 0 and −0.2, respectively, suggesting that the majority of the observed Δ97T for **2b** is due to the relatively better stabilizing effect of TFE toward the larger, delocalized carbocation. We have observed that Δ97T values are quite generally smaller or more negative for reactions involving larger or more delocalized cationic or cationic ion-pair intermediates. That is, solvolyses involving larger or more delocalized cationic intermediates are accelerated more in TFE–water solvents relative to ethanol–water solvents than solvolyses involving smaller or more localized cationic intermediates.

A6. Mechanistic Conclusions. All of the data presented above are explained by mechanistic Scheme II, for which the constants are related to those of kinetic Scheme I as shown in eqs 1, 2, and 3. Thus, k_3 is the product of the rate constant for ionization of

$$k_3 = \frac{k_1^S k_2^T}{k_{-1}^T + k_2^T} \quad (1)$$

$$k_1 = \frac{k_1^S k_{-1}^T}{k_{-1}^T + k_2^T} \quad (2)$$

$$k_2 = \frac{k_1^T k_2^T}{k_{-1}^T + k_2^T} \quad (3)$$

2 and the fraction of the rearranged tight ion pair which separates to form the solvent-separated ion pair, and k_1 is the product of the rate constant for ionization of **2** and the fraction of the rearranged tight ion pair which returns to **4**, while k_2 is the product of the rate constant for ionization of **4** and the fraction of the tight ion pair which separates to form the solvent-separated ion pair. Three more equations follow from 1, 2, and 3. Equation 4 shows

$$f_{ret} = \frac{k_{-1}^T}{k_{-1}^T + k_2^T} = \frac{k_1}{k_1 + k_3} \quad (4)$$

$$k_1^S = k_1 + k_3 \quad (5)$$

$$k_1^T = \frac{k_2}{1 - f_{ret}} \quad (6)$$

that the fraction of internal return f_{ret} is simply the ratio of the rate constant of isomerization of **2** to **4** divided by the rate constant for the disappearance of **2**; eq 5 shows that the rate constant for disappearance of **2** must equal the ionization rate constant of **2** shown in Scheme II; eq 6 shows that the ionization rate constant of **4** is equal to the solvolysis rate constant divided by 1 minus the fraction of internal return.

Values of f_{ret} for **4b**, calculated from eq 4, are 0.76 and 0.92 in 80E and 90E, respectively. The ionization rate constants k_1^T calculated from eq 6 using the latter values of internal return are $(384 \pm 40) \times 10^{-5}$ and $(243 \pm 38) \times 10^{-5}$ s^{-1}. The calculations assume, as indicated in Scheme II, that the rearranged tight ion pair from **2b** is equivalent to the ion pair from **4b**. Using the mY equation, one can extrapolate and determine the ionization rate constant for **4b** in 95E to be 173×10^{-5} s^{-1} and then, through eq 6, a value for internal return of 0.96 in that solvent.

As mentioned above, some experiments were done on **2b** which was found to contain about 1% of pemsyl chloride and some later ones were done on material from which this impurity had been removed using the technique of Schleyer and Nicholas[31] (see Experimental Section). The pure material gave error plots with no systematic trends; however, the results were generally within the limits of error of those obtained with the less pure samples. The values for the fraction of internal return in 95E, 90E, 80E were 0.92, 0.86, and 0.73, respectively, about 4–5% smaller than and just outside the error limits of those which were calculated from the results of the earlier experiments. Because of the sensitivity of the calculated ionization rate constants to fractions of internal return near 1 (eq 6), the new values for the ionization rates of **4b** are somewhat different, 88-, 150-, and 340×10^{-5} s^{-1}, for 95E, 90E, and 80E, respectively. These rate constants give an m value for ionization of 1-adamantyl pemsylate of 0.51 ± 0.01 (r = 0.999), more accurate than but still within the error limits of that previously determined (0.30 ± 0.28). The m value of only 0.51 is significantly less than that for solvolysis. This is caused

(26) The 2-adamantyl tosylate rate constants determined by us are given here in units of 10^{-8} s^{-1}: 95E, 0.1494; 90E, 0.4617; 80E, 2.167; 70E, 6.357; 60E, 16.86; 50E, 47.84; 40E, 208.9; 97T, 141.5; 70T, 221.8.

(27) It is seen for **2** and **4** that the better leaving group shows the larger m value, contrary to expectations based on the Hammond postulate;[32] for **1** the slower leaving group gives a higher m value, in accord with the Hammond postulate. However, these trends may be characteristic only of the different leaving groups being compared and not the alkyl groups; the m value for the 2,2-dimethyl-3-pentyl sulfonates in aqueous ethanol is smaller for the brosylate (0.871) than for the slower tosylate (0.914), but the even slower pemsylate (0.827) gives the smallest m value.

(28) Raber, D. J.; Neil, W. C., Jr.; Dukes, M. D.; Harris, J. M.; Mount, D. L. *J. Am. Chem. Soc.* **1978**, *100*, 8137–8146.

(29) Shiner, V. J., Jr.; Imhoff, M. A. *J. Am. Chem. Soc.* **1985**, *107*, 2121–2124.

(30) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383. These authors point out that the dipole moment of TFE (2.03 D) is only slightly larger than that of ethanol (1.7); however, unlike that of ethanol, it is strongly dependent on conformation. From the known solution dipole moment vectors of methanol (1.7 D) and 1,1,1-trifluoroethane (2.32 D) one can estimate that the anti conformation has a moment of 3.7 D, while for each of the two gauche conformations the estimated value is 1.9 D. This means that TFE alone exists mostly in the gauche conformation, but in the presence of a delocalized carbocation, TFE, unlike ethanol or water, might alter its conformation to give a dipole moment considerably larger than that of ethanol (1.7) or water (1.85).

(31) Schleyer, P. v. R.; Nicholas, R. D. *J. Am. Chem. Soc.* **1961**, *83*, 2700–2707.

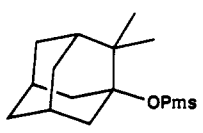
Table II. Fractions of Internal Return for the Solvolysis of Sulfonate Esters

compound	solvent	^{18}O scr value[a]	kinetic value[b]
2-methyl-1-adamantyl pemsylate (**4b**)	80E		0.76 ± 0.02
	90E		0.92 ± 0.01
	95E		0.96 ± 0.01
2-methyl-1-adamantyl pemsylate (**4b**)[c]	80E		0.72 ± 0.01
	90E		0.86 ± 0.01
	95E	0.81 ± 0.02; 0.81 ± 0.01	0.924 ± 0.002
2-ethyl-1-adamantyl pemsylate (**7b**)	80E		0.759 ± 0.008
	90E		0.914 ± 0.003
	95E		0.934 ± 0.002
2,2-dimethyl-1-adamantyl pemsylate	95E	0.89 ± 0.02	
1-(3-noradamantyl)ethyl tosylate	95E	0.0	

[a] Minimum fraction of internal return, $k_{eq}/(k_{eq} + k_t)$. [b] From eq 4. [c] Using results from **2b**, which was carefully purified to remove a trace of pemsyl chloride.

by the much larger proportion of internal return in the less aqueous solvents which lowers the solvolysis rate constants for points on the left of the plot more than those on the right. Of course, the accuracy of the determination of the slope is limited by the sensitivity of the calculated ionization rate constants to small errors in the determination of fractions of return near 1. Nevertheless, the value is reasonable and in line with expectations based upon Hammond's postulate[32] and the following consideration: the relative free energies of the isomeric transition states produced on ionization of **2b** and **4b** can be estimated from their solvolysis rate constants and the difference in strain energies of the initial states. The strain energies for the four different structures were estimated using the interactive molecular modeling program PCMODEL of Gajewski, Gilbert, and McKelvey.[33] For simplicity, the initial states were modeled as alcohols and the transition states as the corresponding cations. It was found that the strain energy for 1-(3-noradamantyl)ethanol (conformer with the C-7/C-3 bond and the C_α–O bond in an antiperiplanar arrangement) was 10.4 kcal/mol greater than that of 2-methyl-1-adamantanol, while the solvolysis rates of the pemsylates **2b** and **4b** show that the transition-state free energies are 22.7 and 21.6 kcal/mol above their respective ground states. Thus the TS for formation of the tertiary cation is estimated to be about (22.7 − 21.6 + 10.4) or 11.5 kcal/mol lower in energy than the TS for ionization of the secondary ester; the part of this due to the difference in strain between the two transition states can be estimated to be no more than 5.3 kcal/mol, the strain energy of the 1-(3-noradamantyl)ethyl cation less that of the 2-methyl-1-adamantyl cation. The balance of the calculated difference in energy between the two transition states indicates that the 2-methyl-1-adamantyl TS is electronically stabilized by at least 6.2 kcal mol^{-1} relative to the 1-(3-noradamantyl)ethyl TS.

A7. Oxygen-18 Scrambling Studies. The study of oxygen-18 scrambling in partially solvolyzed esters is a classic method[34] for the detection of internal return in solvolysis reactions.[35] Therefore, the solvolyses of **2a**, **4b**, and a close relative of **4b** (2,2-dimethyl-1-adamantyl pemsylate, **6b**), labeled with ^{18}O in the ether oxygens to the extent 26, 91, and 56%, respectively, were examined.



6

The sulfonate esters were recovered after partial solvolysis in 95E and analyzed by the NMR method of Van Etten,[36] which is based on the $^{16}O/^{18}O$ isotope effect on the chemical shift of the α-^{13}C resonance. From the mechanistic analysis given above, this technique, used previously in our laboratory,[3,37] was expected to reveal oxygen scrambling during solvolysis for **4** and **6** but not for **2**. Table II shows the results.

After approximately two half-lives, **2a** showed no scrambling of ^{18}O. After about 0.1 and 0.3 half-lives, **4a** showed 76 and 53% ^{18}O, respectively, in the ether oxygen, corresponding to a minimum fraction of internal return $k_{eq}/(k_{eq} + k_t)$ of 0.81 ± 0.02 and 0.81 ± 0.01, respectively. After 0.6 half-lives, **6**, which has been found to react only 1.89 times faster than **2b**, showed 20% ^{18}O in the ether oxygen, giving a minimum fraction of internal return of 0.89 ± 0.02. The scrambling results thus confirm that the 1-(3-noradamantyl)ethyl esters ionize without return and that 1-adamantyl esters solvolyze with large fractions of internal return. Internal return by this measure is, at minimum, approximately 81% in 95E. In other words, the ratio of internal return to solvent separation k_{-1}^T/k_2^T is at minimum 4.3 in 95E by the scrambling method; the same ratio, however, was found to be 12 by kinetic analysis. Thus, the scrambling technique *underestimates* internal return by a factor of about 2.8 ± 0.2, and recombination from the intimate ion pair favors the originally bonded oxygen over either one of the other oxygens.

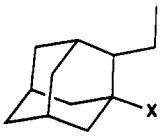
In another experiment, **2a** labeled with 50% ether ^{18}O was allowed to react in buffered 100E for 0.48 half-life before isolation of **2a**, **4a**, and the ether product. Analysis of the ^{13}C and ^1H NMR spectra of the mixture in $CDCl_3$ showed that in 100E, unscrambled **2a** rearranges to ether-^{18}O-labeled **4a** 4.6 ± 1.8 times more frequently than to sulfonyl-^{18}O-labeled **4a**. The latter analysis is based on the assumption that k_{eq}/k_t for **4a** in 100E is the same as that found for **4b** in 95E. One can then calculate that the scrambling technique for detection of internal return underestimates it by a factor of 3.7 ± 1.2, which agrees favorably with the number given in the previous paragraph. This oxygen-18 scrambling experiment also demonstrates, as do the isotope and solvent effects on the reactions of **2**, that the rearrangement does not occur through a single electrocyclic process.

A8. Conclusions from the Study of 2. In summary, the conclusions reached from this study of the solvolysis of 1-(3-noradamantyl)ethyl sulfonate esters are first, that these esters ionize with participation and/or strong hyperconjugation and without return ("k_Δ" process); second, that participation and strong hyperconjugation lowers the β-d_3 effect; third, that the solvolyses of 1-adamantyl sulfonates involve large fractions of internal return with rate-determining solvent separation; fourth, that 1-adamantyl derivatives should not be used as prototypical reference reactants for "k_c" processes which involve, as originally defined by Winstein and now generally accepted, rate-determining ionization;[38] fifth,

(32) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.
(33) Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; Liotta, D., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2.
(34) Goering, H. L.; Jones, B. E. *J. Am. Chem. Soc.* **1980**, *102*, 1628–1633.
(35) For a recent proposal that oxygen scrambling does not measure internal return from a tight ion pair, see: Dietze, Paul E.; Wojciechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240–5244. They propose a concerted 1,3-sigmatropic shift to account for scrambling in simple secondary carbon sulfonate esters because they feel tight ion pairs cannot exist in the presence of solvent and sulfonate anions. The latter reservation should not apply to our study of scrambling in the 1-adamantyl sulfonate ester, which forms a more stable carbenium cation.
(36) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252–253.
(37) Shiner, V. J., Jr.; Ensinger, M. W.; Rutkowske, R. D. *J. Am. Chem. Soc.* **1987**, *109*, 804–809.
(38) Winstein, S.; Lindegren, C. R.; Marshall, H.; Ingraham, L. L. *J. Am. Chem. Soc.* **1953**, *75*, 147–155.

that the solvolysis of pinacolyl sulfonate esters involves ionization without participation by solvent or neighboring carbon and is therefore a "k_c" process; and sixth, that those examples of solvolytic processes involving rate-determining participation, ionization, or solvent separation all give reasonably good rate correlations with Y_{OTs} with small differences in slopes.

B. 1-(3-Noradamantyl)propyl Sulfonates. 1. Kinetics of Reaction. The influence of the noradamantyl substituent group was further examined in the solvolysis of 1-(3-noradamantyl)propyl sulfonate esters **3**. The additional β-methyl group relative to **2** does not cause the solvolysis rate to become first-order in aqueous ethanol solutions at 25 °C.[39] The pemsylate ester of 2-ethyl-1-adamantanol (**7b**) was prepared, and its solvolysis was found to obey the first-order rate law. In substance **7**, X = a sulfonate group: in **7a**, X = OTs, *p*-toluenesulfonate; **7b**, X = OPms, pentamethylbenzenesulfonate; in **7d**, X = OH; and in **7e**, X = OR.



7

The rate constants for **7** are reported in Table I. The relative rates of **7** to **3** and **4** to **2** show, as expected, that the additional methyl group decreases the difference between the solvolysis rates of the rearranged and the unrearranged sulfonates, making the detection of k_3 more precise. The conductance kinetic data of each run of **3b** were successfully fit, as before, only when the program was allowed to select values for k_1 and k_3 with k_2 set to a true value found from solvolysis of **7b**. This confirms that the non-first-order behavior in the solvolysis of **3** is caused by the isomerization of **3** to **7**. Since **3b** and **7b** have similar reactivities (i.e., $k_2/(k_1 + k_3)$ values in the range of 2–4), the nicely first-order kinetics observed for **7** rules out rearrangement of **7** to **3**.

B2. Product Studies. The products of solvolysis of **3b** were determined by analysis of the 55.4-MHz ^{2}H NMR spectra of the buffered solvolysis reaction mixtures of the α-d_1 isotopomer of **3b** in 90E, 95E, 100E, and 97T; in all of these solvents only the rearranged 2-ethyl-1-adamantyl substitution products are observed.[9] Analysis of the 55.4-MHz ^{2}H NMR spectra taken during the course of the solvolysis of **3b** in 100E clearly show the rise and decay of absorption lines characteristic of the intermediate **7b**.[10] Ester **3b** was allowed to react completely in 100% ethanol buffered with lutidine. The 300-MHz ^{1}H and 75-MHz proton-decoupled ^{13}C NMR spectra were consistent with the ^{2}H NMR product analysis in indicating ethyl 2-ethyl-1-adamantyl ether to be the almost exclusive product. Again, in addition to the 1-adamantyl product the ^{13}C spectrum indicated that ethyl 4-ethyl-3-protoadamantyl ether was produced in approximately 2% yield. The solvolysis of **3b** in 82% aqueous acetone was shown to produce about 3% of the 3-protoadamantanol product, which was separated from the reaction mixture by HPLC and identified by the 500-MHz ^{1}H and the 125-MHz ^{13}C NMR spectra. Thus, both **2** and **3** produce 3-protoadamantyl substitution products in similar amounts. In fitting the conductometric kinetic data from solvolysis of **3b**, allowance for any production of 4-ethyl-3-protoadamantyl pemsylate produced by internal return was not required.

B3. Rate Constants and Kinetic Isotope Effects. The β-methyl effects on the solvolysis rates of **2** are all slightly greater than 2 and are similar to the effects observed on other solvolyses: *tert*-butyl chloride, 80E, 1.69;[40] 1-adamantyl tosylate, 80E, 1.87; **2a**, 80E, 2.4; pinacolyl tosylate, 80E, 5.2[41] (all at 25 °C). Thus the spreading of charge and the lower demand for electron donation at C_α caused by the participation mechanism for **2** leads to a β-methyl effect which is smaller than that for the pinacolyl analogue but larger than that for the tertiary isomer.

Table III. Grunwald–Winstein *m* Values of the Rate Constants for Direct Solvolysis (k_3) and Isomerization (k_1) of **2b** and **3b** and for Solvolysis and Decomposition of 1-Adamantyl Chloroformate in Aqueous Ethanol Solvent[a]

compd	*m* of k_1 or decomp	*m* of k_3 or solv
2b	0.586 ± 0.005	1.13 ± 0.01
3b	0.54 ± 0.01	1.11 ± 0.07
1-AdOCOCl	0.69 ± 0.07	0.80 ± 0.05

[a] Slopes (*m*) obtained from linear least-squares calculations on data points of log *k* for the compound and log *k* for 2-adamantyl tosylate in 80E, 90E, and 95E. 2-Adamantyl tosylate rate constants were determined in this laboratory.[26]

As is shown in Table I, the additional β-methyl group in **3** and **7** relative to **2** and **4** is associated with a decrease in the Winstein–Grunwald *m* values. The conclusions concerning the *m* values in section A.5 above apply here also in the comparison of the *m* values of **3**, **7**, and the β-methyl-substituted pinacolyl analogue 2,2-dimethyl-3-pentyl sulfonate.

The α-d_1 isotope effects[14] (1.173 ± 0.001) for **3b** are 1.2% higher than those found for 1-(3-noradamantyl)ethyl pemsylate, while the β-d_2 effects[14] (1.152 ± 0.004) are about 1% higher than the β-d_3 effects found for **2b**.[42] The larger α-d_1 effect for **3b** is probably due to the same cause referred to above for **2**, that is, to a larger degree of π- and a smaller degree of σ-bonding to the α-carbon in the transition state due to the increase in strain caused by the ethyl group. The β-d_2 effects are lowered, as expected, because of participation, and the increase is in line with the Sunko, Szele, and Hehre equation which analyses the conformation dependence of the β-deuterium isotope effect.[43]

B4. Mechanistic Conclusions. The values of k_3 were used to calculate the magnitude of internal return, given in Table II, and the ionization rate constants for 2-ethyl-1-adamantyl pemsylate. An *m* value of 0.44 ± 0.07 (r = 0.964) was calculated for the ionization rates. The somewhat poorer fit of the LFER compared to that for the lower homologue is probably the result of the sensitivity of the ionization rates to small errors when the fractions of return are large.

The sensitivities of the direct solvolysis (k_3) pathway and the isomerization (k_1) pathway to solvent ionizing power are completely different. In Table III the *m* values from a plot of log *k* versus log *k* for 2-adamantyl tosylate are given. The k_3 pathway is seen to be about twice as sensitive to ionizing power as the k_1 pathway. This results from the effect of solvent on the partitioning of the rearranged intimate ion pair between solvent separation (leading to solvolysis) and internal return. It can be shown that the difference in Winstein–Grunwald *m* values for the two pathways equals the difference in the *m* values for the rate constants for solvent separation of the tight ion pair and that for ion-pair combination to covalent sulfonate. Because the ion pairs produced by **2** and **3** are likely to be the same as or similar to those intimate ion pairs produced by the isomeric 2-alkyl-1-adamantyl pemsylate during its solvolysis, the difference in the *m* values for k_2^T and k_{-1}^T equals or nearly equals the difference in *m* values for k_3 and k_1. Thus the difference in *m* values for the rate constants k_2^T and k_{-1}^T in the solvolysis of 1-adamantyl sulfonate esters are estimated to be ≈0.56 on average. In agreement with our observations, Kevill et al. have concluded from the study of the solvolysis-decomposition of 1-adamantyl chloroformate that 1-adamantyl systems solvolyze with internal return.[44] They also

(39) In 90E the integrated first-order rate coefficients for **3b** started at about 3.7 × 10^{-5} s^{-1} and rose to about 11.3 × 10^{-5} s^{-1} during a typical kinetic experiment.

(40) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, NY, 1962; p 92.

(41) Stoelting, D. T. Ph.D. Thesis, Indiana University, Bloomington, IN, 1990.

(42) 2,2-Dimethyl-3-pentyl brosylate, a close analogue of the system under study, shows an α-d KIE of 1.165 and a β-d_2 effect of 1.24, which are, respectively, ≈0.5% and 4% larger than those for its lower homologue, the pinacolyl ester: Basinger, B. B. Ph.D. Thesis, Indiana University, Bloomington, IN, 1981.

(43) Sunko, D. E.; Szele, I.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 5000–5005. The average β-d_3 effect of 1.141 found for **2b** and an inductive effect for β-deuterium of 0.990 gives dihedral angles of 30°.

suggest that internal return in the solvolyses of 1-adamantyl systems has a low response to ionizing power because the difference in m values for k_2^T and k_{-1}^T in 1-adamantyl chloride solvolysis is predicted to be only 0.11, which is not much larger than the errors in the m values themselves. However, the intervening carbon dioxide molecule present in the decomposition of the chloroformates may influence the nature of the recombination step; in 95E, for example, only 39% of the 1-Ad$^+$X$^-$ intermediates are found to recombine to covalent substrate. We believe that the study of 1-(3-noradamantyl)ethyl sulfonate esters has provided compelling evidence, contrary to previous belief,[44] that 1-adamantyl systems ionize with rate constants that are near a factor of 2 less sensitive to ionizing power than the solvolysis rate constants.

B6. Conclusions from the Study of 3. In summary, the conclusions that we have reached from study of the solvolysis of 1-(3-noradamantyl)propyl sulfonate esters are as follows. First, these sulfonate esters ionize with participation and strong hyperconjugation. Second, this study independently confirms that solvolysis of 1-adamantyl sulfonates involves large fractions of internal return with rate-determining solvent separation. Third, solvent effects on the partitioning of the tight pair between covalent substrate and products are significant. The m value for solvent separation is about 0.5 larger than that for internal return; this provides an explanation for the larger-than-average m values observed for 1-adamantyl systems. Fourth, it is shown once again that 1-adamantyl derivatives should not be used as prototypical reference reactants for "k_c" processes defined by Winstein as rate-determining ionization.

Experimental Section

Boiling points are uncorrected. Melting points are corrected. Combustion analysis was performed by Galbraith Laboratories, Inc. NMR spectra were recorded on Varian Associates T-60, EM390, HR-220, and XL-300; Nicolet 360; and Bruker 500 spectrometers. Chemical shifts are recorded in parts per million (δ) from tetramethylsilane (TMS) for ^{1}H spectra, from $CDCl_3$ (δ 77.1) for ^{13}C spectra, and from external $CDCl_3$ in chloroform solvent for ^{2}H spectra. Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer. Gravity column chromatography was conducted with kieselgel 60 (70–230 mesh) (E. Merck no. 7734). High-performance liquid chromatography separations were performed on a Rainin HP Rabbit instrument equipped with a semipreparative 10-mm i.d. × 25-cm-*l* or preparative 21.4-mm i.d. × 25-cm-*l* prepacked silica (8 μm) gel and stainless steel column and connected to a KNAUER Differential-Refractometer and a strip-chart recorder. This Experimental Section is a shortened version of the one in ref 6.

Product Determination. The procedure utilizing ^{2}H NMR has been described in ref 37.

Conductance Kinetic Procedure. This is described in refs 45 and 46. The rate constants for the serial first-order reactions were calculated by a nonlinear, doubly-weighted, least-squares, curve-fitting program written by Stoelting in FORTRAN to run on an IBM-PC or the equivalent.[47] The program represents an adaptation of the program[45,46] for calculating first-order kinetic data. The data from reaction of 1-(3-noradamantyl)ethyl pemsylate in 95E were fit by a Simplex program[48,49] written by Stoelting in FORTRAN to run on an IBM-PC.

Solvent Preparation. The procedures employed can be found through the citations given in ref 3.

3-Acetylnoradamantane was prepared according to the published procedures.[50,51] Vacuum distillation of the crude ketone was accomplished at 1–1.5 Torr and 80–85 °C (lit.[52] bp 60–65 °C at 0.7 Torr). 60-MHz ^{1}H NMR ($CDCl_3$): δ 1.2–2.8 (m, 13 H) with maxima at 1.7, 1.8, 1.95, 2.18 (s, 3 H), 2.35, 2.65. IR (film): 2923 (s), 2871 (m), 1699 (s), 1463 (w), 1448 (w), 1428 (w), 1358 (m), 1308 (w), 1283 (w), 1243 (w), 1225 (w), 1193 (w), 1133 (w), 1103 (w), 1083 (w), 1043 (w), 963 (w), 915 (w), 865 (w), 845 (w), 778 (w) cm^{-1} (lit.[50,52] $\nu_{C=O}$: 1695 and 1697 cm^{-1}).

3-Noradamantanecarboxylic acid was prepared from 3-acetylnoradamantane according to the published procedure.[51] Mp: 106–107 °C (lit.[52] mp 108–109 °C). 60-MHz ^{1}H NMR ($CDCl_3$): δ 1.3–2.9 (m) with maxima at 1.7, 1.85, 2.01, 2.25, 2.7 (t of t, 1 H), 11.0 (s, 1 H).

3-Noradamantylmethanol and 3-Noradamantylmethanol-d_2. 3-Noradamantanecarboxylic acid was reduced with lithium aluminum hydride (LAH) or lithium aluminum deuteride (LAD) according to the published procedure.[53] Mp: 144–145 °C in a sealed capillary tube (lit.[54] mp 142–144 °C). 60-MHz ^{1}H NMR ($CDCl_3$): δ 1.4–1.8 (m, 11 H), 2.0–2.4 (m, 3 H), 3.64 (s, 2 H). The spectrum of the α-d_2 alcohol had no peak at δ 3.64.

3-Noradamantylmethyl *p*-Methylbenzenesulfonate (Tosylate) and 3-Noradamantylmethyl and 3-Noradamantylmethyl-d_2 *p*-Bromobenzenesulfonates (Brosylates). The syntheses of these compounds were accomplished by a modified Tipson procedure.[55] Mp of tosylate: 64–66 °C (lit.[54] mp 68–69 °C). Mp of brosylate: 103–103.5 °C. 90-MHz ^{1}H NMR of tosylate ($CDCl_3$): δ 1.37–2.37 (m, 13 H) with maxima at 1.58 (m, 10 H) and 2.22 (m, 3 H), 2.47 (s, 3 H), 4.05 (s, 2 H), 7.27–7.97 (AA'BB' quartet, 4 H). 60-MHz ^{1}H NMR of H brosylate ($CDCl_3$): δ 1.3–1.9 (m, 10 H) with a maximum at 1.6, 1.9–2.4 (m, 3 H) with a maximum at 2.2, 4.1 (s, 2 H), 7.5–7.9 (m, 4 H). 90-MHz ^{1}H NMR of α-d_2 brosylate ($CDCl_3$): the same as the hydrogen isotopomer except for the absence of a peak at δ 4.1.

1-(3-Noradamantyl)ethyl, 1-(3-Noradamantyl)ethyl-*1*-*d*, and 1-(3-Noradamantyl)ethyl-*2,2,2*-d_3 Brosylates, Tosylates, and Pentamethylbenzenesulfonates (Pemsylates). These sulfonate esters were made in the manner employed for the preparation of 3-noradamantylmethyl sulfonate esters from the corresponding alcohols and either *p*-bromobenzenesulfonyl chloride (brosyl chloride), *p*-methylbenzenesulfonyl chloride (tosyl chloride), or pentamethylbenzenesulfonyl chloride[56] (pemsyl chloride). Mps were recorded as follow: H pemsylate, 109–110 °C; α-d_1 pemsylate, 111–112 °C; β-d_3 pemsylate, 109–110 °C; tosylate, 80–81 °C; α-d_1 tosylate, 84–86 °C; β-d_3 tosylate, 85–87 °C. 220-MHz ^{1}H NMR of H brosylate ($CDCl_3$): δ 1.25 (d, 3 H), 1.40–1.9 (m, 10 H), 2.0–2.2 (t of t, 1 H), 2.2–2.5 (m, 2 H), 4.78 (q, 1 H), 7.73 (AA'BB' quartet, 4 H). 55.4-MHz ^{2}H NMR of α-d_1 brosylate ($CHCl_3$): δ 4.789. 300-MHz ^{1}H NMR ($CDCl_3$) of H pemsylate: δ 1.23 (d, 3 H), 1.46–1.78 (m, 10 H), 2.18–2.3 (m, 12 H) with sharp absorption peaks at 2.241 (s, 6 H), 2.28 (s, 3 H), 2.60 (s, 6 H), 4.85 (q, 1 H). 300-MHz ^{1}H NMR ($CDCl_3$) of α-d_1 pemsylate: no quartet at δ 4.85 and the doublet at δ 1.22 has become a singlet. 300-MHz ^{1}H NMR ($CDCl_3$) of β-d_3 pemsylate: singlet absorption peak at δ 4.85 and no absorption at 1.2. 300-MHz ^{1}H NMR ($CDCl_3$) of H tosylate: δ 1.2 (d, 3 H), 1.44–1.7 (m, 10 H), 2.1 (t of t, 1 H), 2.2 (m, 2 H), 2.44 (s, 3 H), 4.74 (q, 1 H), 7.3–7.85 (AA'BB' quartet, 4 H). 300-MHz ^{1}H NMR ($CDCl_3$) of α-d_1 tosylate: no quartet absorption peaks at δ 4.74 and a singlet, not a doublet, absorption at δ 1.24. 300-MHz ^{1}H NMR ($CDCl_3$) of β-d_3 tosylate: no doublet absorption peaks δ 1.24 and a singlet, not a quartet, absorption at 4.73. Removal of the small amount of pentamethylbenzenesulfonyl chloride impurity, implicated by the kinetics, was accomplished with a sample of α-d_1 pemsylate in the following manner. The α-d_1 pemsylate (270 mg) was dissolved in pyridine (10 mL). This solution was stirred for 5 min before being poured into a separatory funnel which contained cold H_2O (100 mL). The funnel was shaken well, the compound was extracted into diethyl ether (200 mL), and the diethyl ether extract was washed in succession with cold 2 N aqueous H_2SO_4, saturated sodium bicarbonate, and water. The ether extract was dried over magnesium sulfate; the drying agent was removed by suction filtration. Evaporation of the solvent left a white solid. The solid was recrystallized from petroleum ether (bp 30–60 °C, 10 mL) in the freezer to yield needle-like crystals in 33% yield (90 mg). A second crop was isolated (40 mg) to give a total yield of 48%. The 500-MHz ^{1}H and the 125-MHz ^{13}C NMR spectra of the first-crop crystals indicated excellent purity with no rearranged ester contamination.

Identification of the Solvolysis Products of 1-(3-Noradamantyl)-ethyl-*1*-*d* Tosylate in 100% Ethanol. 1-(3-Noradamantyl)ethyl-*1*-*d* tosylate (0.4997 g, 1.554 mmol) was added to a 250-mL round-bottom flask containing conductivity ethanol (100 mL) and lutidine (0.1970 g, 1.838 mmol). The tosylate was allowed to react in ethanol for 5 days and 3.85 h at room temperature, and then the solvent was removed by

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rotary evaporation under reduced pressure. The residue was taken up in diethyl ether which was then washed in succession with water (20 mL), 2 N aqueous H_2SO_4 (2 × 20 mL), and saturated aqueous $NaHCO_3$. The ether extract was dried over $MgSO_4$; the drying agent was removed by suction filtration. Evaporation of the solvent on a rotary evaporator at reduced pressure left a clear green liquid in 100% yield. The 300-MHz ^1H NMR spectrum and the 75-MHz ^{13}C NMR spectrum clearly indicated that the product is ethyl 2-methyl-1-adamantyl-*2-d* ether. 300-MHz ^1H NMR ($CDCl_3$): δ 0.966 (s, 3 H), 1.163 (t, 3 H), 1.35–1.54 (m, 2 H), 1.56–1.76 (m, 5 H), 1.78–1.94 (m, 4 H), 2.0–2.1 (m, 1 H), 2.1–2.2 (m, 1 H), 3.41 (m, 2 H). 75-MHz ^{13}C NMR ($CDCl_3$): δ 73.288, 54.131, 41.673, 40.364 (t, ^{13}C–D), 38.320, 37.343, 36.812, 36.158, 30.983, 30.491, 30.457, 16.088, 13.453.

Identification of the Solvolysis Products of 1-(3-Noradamantyl)-ethyl-*1-d* Tosylate in 83% Aqueous Acetone. 1-(3-Noradamantyl)-ethyl-*1-d* tosylate (1.19 g, 3.70 mmol) was dissolved in acetone (100 mL) containing lutidine (0.52 g), and then water (20 mL) was added. The compound was solvolyzed at room temperature (≈22 °C) for 4.80 days. After the solvolysis products were isolated in 92% yield (0.57 g), they were separated by HPLC on a preparative column with 80% hexane–20% ethyl acetate as the mobile phase. The largest peak in the chromatogram was due to 2-methyl-1-adamantanol-*2-d* which was obtained with a 65% (purified) yield (0.37 g) after HPLC separation. Besides the peak for the major product of solvolysis, there was a second much smaller peak for a compound which eluted just a little faster than the 1-adamantanol. The smaller peak (1.5% of the total area by cut-and-weigh integration) corresponded to a compound which was 2.6% of the total amount of purified product and was shown by ^1H and ^{13}C NMR to be to 4-methyl-3-protoadamantanol-*4-d*. Another compound was apparent in the ^{13}C spectrum which was probably the epimeric 3-protoadamantanol produced in one-ninth the yield of the other epimer. The 2-methyl-1-adamantanol-*2-d* data follow. 500-MHz ^1H NMR ($CDCl_3$): δ 0.982 (s, 3 H), 1.27–1.44 (m, 2 H), 1.45–1.82 (m, 9 H), 1.84–1.92 (m, 1 H), 1.98–2.14 (m, 2 H). 125-MHz ^{13}C NMR ($CDCl_3$): δ 69.855, 47.109, 44.410 (t), 38.642, 38.181, 36.967, 36.355, 31.352, 30.654, 29.929, 13.370. Mp: 208.5–209.5 °C (lit.[57] mp 206–208 °C). The 4-methyl-3-protoadamantanol-*4-d* NMR data follow. 500-MHz ^1H NMR ($CDCl_3$): δ 0.979 (s, 3 H), 1.20–1.45 (m, 6 H), 1.65–1.75 (m, 1 H), 1.75–2.03 (m, 6 H), 2.03–2.10 (m, 1 H). 125-MHz ^{13}C NMR ($CDCl_3$): δ 82.374, 45.444, 42.091, 39.552, 39.185, 37.236, 36.412, 33.381, 33.298 (t), 28.680, 15.702. 125-MHz ^{13}C NMR ($CDCl_3$) data for the minor epimeric product of 4-methyl-3-protoadamantanol-*4-d*: δ 82.2, 50.400, 42.024, 40.821, 39.068, 36.330, 35.793, 34.105, 33.343(?), 19.546. The resonance peak for the deuterated carbon is understandably not apparent, and the peak labeled with a question mark is not clearly resolved from a larger peak.

Silver pemsylate was prepared from pemsylic acid[56] by the procedure listed in ref 58.

2-Methyl-1-adamantyl, 2-methyl-1-adamantyl-*2-d*, and 2-methyl-*d*$_3$-1-adamantyl iodides were prepared using a procedure similar to that for synthesis of 1-adamantyl iodide[59] by reaction of the 1-(3-noradamantyl)ethanols in 55% aqueous hydrogen iodide (HI).

2-Methyl-1-adamantyl, 2-Methyl-1-adamantyl-*2-d*, and 2-Methyl-*d*$_3$-1-adamantyl Pemsylates and 2-Methyl-1-adamantyl Tosylate. The 2-methyl-1-adamantyl iodides were caused to react with either silver pemsylate or silver tosylate in a manner similar to that cited in ref 60. Mps were recorded as follow: H pemsylate, 179–180 °C; 2-d_1 pemsylate, 179–180 °C; γ-d_3 pemsylate, 177–178; H tosylate, 82–83.5 °C. 300-MHz ^1H NMR ($CDCl_3$) of tosylate: δ 1.04 (d, 3 H), 1.27–1.37 (m, 1 H), 1.52–2.47 (m, 16 H) with a sharp absorption peak at 2.381 (s, 3 H), 7.6 (AA′BB′ quartet, 4 H). 300-MHz ^1H NMR ($CDCl_3$) of H pemsylate: δ 1.12 (d, 3 H), 1.33–1.42 (m, 1 H), 1.58–1.7 (m, 4 H), 1.79–1.92 (m, 2 H), 2.08–2.4 (m, 16 H) with sharp signals at 2.24 (s, 6 H), 2.28 (s, 3 H), 2.60 (s, 6 H). 300-MHz ^1H NMR ($CDCl_3$) of 2-d_1 pemsylate: δ 1.12 (s, 3 H), 1.33–1.42 (m, 1 H), 1.58–1.7 (m, 4 H), 1.8–1.91 (m, 2 H), 2.06–2.36 (m, 15 H) with sharp signals at 2.24 (s, 6 H), 2.28 (s, 3 H), 2.60 (s, 6 H). 300-MHz ^1H NMR ($CDCl_3$) of γ-d_3 pemsylate: no absorption peak at δ 1.1. 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$) of tosylate: δ 143.694, 137.449, 129.542, 127.116, 95.163, 43.968, 43.912, 37.543, 37.473, 36.520, 36.383, 32.041, 31.581, 29.573, 21.657, 14.386. 125-MHz ^{13}C NMR ($CDCl_3$) of H pemsylate: δ 139.535, 137.117, 134.492, 133.930, 94.204, 44.058, 43.690, 37.532, 37.506, 36.938, 36.416, 31.905, 31.534, 29.588, 18.908, 17.663, 16.878, 14.384. 125-MHz ^{13}C NMR ($CDCl_3$) of 2-d_1 pemsylate: δ 139.520, 137.116, 134.479, 133.907, 94.128, 43.650, 43.548 (t), 37.490, 37.394, 36.928, 36.394, 31.892, 31.525, 29.576, 18.894, 17.649, 16.863, 14.261. 125-MHz ^{13}C NMR ($CDCl_3$) of γ-d_3 pemsylate: δ 139.585, 137.139, 134.539, 133.984, 94.315, 43.892, 43.720, 37.559, 37.465, 36.999, 36.452, 31.944, 31.573, 29.647, 18.962, 17.719, 16.932, 13.584 (septet).

2,2-Dimethyl-1-adamantanol. 1-(3-Noradamantyl)-1-methylethanol, prepared by treating 3-acetylnoradamantane with methylmagnesium chloride, rearranged in a solution of 58% dioxane–42% 2 N aqueous H_2SO_4. Mp: 223–225 °C in a sealed capillary (lit.[61] mp 220–222 °C). 300-MHz ^1H NMR ($CDCl_3$): δ 1.06 (s, 6 H), 2.115–1.964 (m, 6 H), 1.610–1.408 (m, 8 H). 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$): δ 71.611, 41.025, 40.486, 38.062, 32.548, 31.24, 22.647.

2,2-Dimethyl-1-adamantyl Pemsylate. This compound was made by a modified Kochi–Hammond procedure.[62] Mp: 150–152 °C. 300-MHz ^1H NMR ($CDCl_3$): δ 1.112 (s, 6 H), 1.4–1.5 (m, 2 H), 1.55–1.72 (m, 3 H), 2.0–2.1 (m, 2 H), 2.15–2.3 (m, 11 H) with sharp peaks at 2.241 (s, 6 H) and 2.27 (s, 3 H), 2.45–2.65 (m, 10 H) with a sharp peak at 2.611 (s, 6 H). 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$): δ 139.696, 136.683, 134.502, 134.426, 96.824, 42.436, 41.423, 38.742, 37.614, 32.15, 32.073, 23.43, 19.134, 17.774, 16.941.

2,2-Dimethyl-1-adamantanol-^{18}O. 2,2-Dimethyl-1-adamantyl iodide prepared by treating the alcohol with HI was caused to react in the manner of Chang and le Noble[63] to produce 2,2-dimethyl-1-adamantanol with partial ether-^{18}O incorporation.

2,2-Dimethyl-1-adamantyl Pemsylate-*ether*-^{18}O. The alcohol from the previous preparation was caused to react with pemsyl chloride in accordance with the procedure used to make the unlabeled sulfonate. The product was confirmed to be 2,2-dimethyl-1-adamantyl pemsylate by the 75-MHz ^{13}C (decoupled) NMR and 300-MHz ^1H NMR spectra in $CDCl_3$. Cut-and-weigh integration of the two peaks centered at δ 96.7 in ^{13}C NMR spectrum indicated 56.27% ether-^{18}O incorporation.

Oxygen-18 Scrambling Study of 2,2-Dimethyl-1-adamantyl Pemsylate in 95E. 2,2-Dimethyl-1-adamantyl pemsylate-*ether*-^{18}O (0.38 g, 0.93 mmol) was dissolved in chloroform (1 mL) in a round-bottom flask. A 95% aqueous ethanol solution (100 mL) containing lutidine buffer (0.0988 g) was added to the flask containing the pemsylate, and the resulting mixture was magnetically stirred for 10 min before being filtered through an HPLC nylon filter. The latter filtration took 5 min. The clear filtered solution was placed in a 25 °C oil bath for the next 45 min, at which time the flask was placed in an ice-water bath for 10 min. Next, the solution was poured into a separatory funnel which contained chloroform (200 mL), and the chloroform solution was extracted with water (2 × 200 mL). The organic extract was dried over $MgSO_4$; the drying agent was removed by suction filtration. Most of the solvent was removed under reduced pressure, and then any residual lutidine and chloroform were removed in vacuo (0.05 Torr). The solid residue was dissolved in $CDCl_3$, and the solution was filtered through an HPLC nylon filter. The filtered solution was concentrated to a volume of 0.5 mL and then placed into an NMR tube. The 300-MHz ^1H NMR spectrum indicated signals for unsolvolyzed pemsylate at δ 1.12 (s, 6 H), ethyl moiety of the ether substitution product at δ 1.113 (t, 3 H), 2,2-dimethyl-1-adamantanol substitution product at δ 1.064 (s, 6 H), 2,2-dimethyl-1-adamantyl ether substitution product at δ 1.05 (s, 6 H). Integration of the latter peaks indicated 66.25% unchanged pemsylate, 36.32% alcohol substitution, and 63.68% ether substitution. The 75-MHz ^{13}C NMR spectrum was taken by Wilgis in the manner given in his dissertation[64] and showed two signals centered at δ 96.293 due to α-^{13}C absorption of the ester; the signals of the ester occur at 96.325 ppm for the ^{13}C–^{16}O resonance peak and at 0.064 ppm upfield from the latter signal for the ^{13}C–^{18}O resonance peak. Cut-and-weigh integration of the latter two peaks indicated 20.10% ether-^{18}O pemsylate. The ratio of the equilibration rate to the solvolysis rate was calculated as log (fraction of unscrambled ester) divided by log (fraction unsolvolyzed ester).

2-Methyl-1-adamantanol-^{18}O. 2-Methyl-1-adamantyl iodide was allowed to react, in the manner described for the preparation of 2,2-dimethyl-1-adamantanol-^{18}O, to produce the desired labeled alcohol. Mp: 186–199 °C (lit.[57] mp 206–208 °C). The 75-MHz ^{13}C NMR spectrum confirmed the structure. 75-MHz ^{13}C NMR analysis of the α-carbon atom at δ 69.995 showed 89.68% ^{18}O enrichment.

2-Methyl-1-adamantyl Pemsylate-*ether*-^{18}O. This compound was made by the same method used to produce 2,2-dimethyl-1-adamantyl

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pemsylate. The 300-MHz ^{1}H NMR and 75-MHz ^{13}C (decoupled) NMR spectra of the first-crop crystals were identical, except for small peaks assignable to expected impurities, to the spectra of the unlabeled compound. The conductometrically determined solvolysis rate constant was identical, within experimental error, to the rate constant previously determined for the unlabeled material. 75-MHz ^{13}C NMR analysis of the α-carbon atom showed 91.66% ^{18}O enrichment.

Oxygen-18 Scrambling Studies of 2-Methyl-1-adamantyl Pemsylate in 95E. Experiment 1. 2-Methyl-1-adamantyl pemsylate-*ether*-^{18}O (0.40 g, 1.1 mmol) was added to 95% aqueous ethanol (100 mL) containing lutidine (0.1132 g). The mixture was sonicated (5.1 min) and then filtered (4.3 min) through a nylon HPLC filter. The clear solution was left at room temperature for another 3.2 min. The unsolvolyzed ester was recovered, in the same manner employed to isolate 2,2-dimethyl-1-adamantyl-*ether*-^{18}O pemsylate above, after partial solvolysis in 95E. The 300-MHz ^{1}H NMR spectrum indicated signals for unsolvolyzed pemsylate at δ 1.12 (d, 3 H), 2-methyl-1-adamantanol substitution product at δ 1.025 (d, 3 H), and 2-methyl-1-adamantyl ether substitution product at δ 0.966 (d, 3 H). Integration of the latter peaks indicated 93.33% unchanged pemsylate, 4.72% alcohol substitution, and 1.95% ether substitution. The 75-MHz ^{13}C NMR spectrum showed two signals centered at δ 94.145 due to α-^{13}C absorption of the ester; the signals of the ester occurred at 94.175 ppm for the ^{13}C–^{16}O resonance peak and at 0.061 ppm upfield from the latter signal for the ^{13}C–^{18}O resonance peak. Cut-and-weigh integration of the latter two peaks indicated 76.03% ether-^{18}O pemsylate. The ratio of the equilibration rate to the solvolysis rate was calculated in the manner stated in the Experimental Section for the oxygen-18 scrambling study of 2,2-dimethyl-1-adamantyl pemsylate in 95E.

Experiment 2. The second experiment was performed in the same manner as the first one except for the following modifications. The mixture was sonicated for 8 min before filtration which took 2.5 min; total reaction time including sonication and filtration was 30 min. The reaction solution was poured into a separatory funnel containing chloroform (200 mL) and water (200 mL). The 300-MHz ^{1}H NMR spectrum indicated signals for unsolvolyzed pemsylate at δ 1.12 (d, 3 H), 2-methyl-1-adamantanol substitution product at δ 1.025 (d, 3 H), and 2-methyl-1-adamantyl ether substitution product at δ 0.965 (d, 3 H). Integration of the latter peaks indicated 78.98% unchanged pemsylate, 16.08% alcohol substitution, and 4.94% ether substitution. The 75-MHz ^{13}C NMR spectrum showed two signals centered at δ 94.149 due to α-^{13}C absorption of the ester; the signals of the ester occur at 94.178 ppm for the ^{13}C–^{16}O resonance peak and at 0.058 ppm upfield from the latter signal for the ^{13}C–^{18}O resonance peak. Cut-and-weigh integration of the latter two peaks indicated 52.66% ether-^{18}O pemsylate. The ratio of the equilibration rate to the solvolysis rate was calculated in the manner stated in the Experimental Section for the oxygen-18 scrambling study of 2,2-dimethyl-1-adamantyl pemsylate in 95E.

2-[1-(3-Noradamantyl)-1-oxoethyl]dioxolane. 1-(3-Noradamantyl)-ethanone and ethylene glycol were allowed to react according to a standard procedure to form the dioxolane.[65] 60-MHz ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 3 H), 1.35–2.5 (m, 13 H), 3.95 (s, 4 H). IR (film): 2922 (s), 2867 (s), 1447 (w), 1370 (m), 1308 (m), 1290 (m), 1248 (m), 1225 (m), 1208 (s), 1170 (s), 1150 (m), 1130 (s), 1110 (s), 1087 (s), 1053 (s), 947 (m), 877 (m), 847 (w), 823 (w), 780 (w) cm^{-1}.

1-(3-Noradamantyl)ethyl Tosylate-*ether*-^{18}O, First Preparation. The tosylate was made from the alcohol by the Tipson procedure (see the preparation of 3-noradamantylmethyl tosylate). The alcohol was made by standard LAH reduction of the ketone which was enriched in ^{18}O by acid-catalyzed reaction of the dioxolane with oxygen-18-enriched water (90.97% ^{18}O) in the manner of Creary.[66] The 300-MHz ^{1}H NMR spectrum was identical to the one of the unlabeled tosylate. 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$): δ 144.253, 134.971, 129.646, 127.572, 85.161, 53.357, 45.472, 43.99, 43.648, 43.486, 41.173, 37.32, 36.957, 35.315, 21.642, 17.522. 75-MHz ^{13}C NMR analysis of the α-carbon atom showed 25.83% ^{18}O enrichment.

Oxygen-18 Scrambling Studies of 1-(3-Noradamantyl)ethyl Tosylate in 95E. Experiment 1. 1-(3-Noradamantyl)ethyl tosylate-*ether*-^{18}O (0.50 g, 1.6 mmol) from the above preparation with 25.83% ether-^{18}O incorporation was dissolved in 95% aqueous ethanol (100 mL) containing lutidine (0.1672 g) by sonication for 7 min. The reaction solution was kept at 25.000 ± 0.001 °C for ≈2.2 half-lives (2.33 h). Workup was performed in the manner used in the second ^{18}O scrambling study of 2-methyl-1-adamantyl pemsylate-*ether*-^{18}O. The 300-MHz ^{1}H NMR spectrum indicated signals for unsolvolyzed tosylate at δ 1.246 (d, 3 H), rearranged tosylate at δ 1.091, 2-methyl-1-adamantanol substitution product at δ 1.05 (d, 3 H), 2-methyl-1-adamantyl ether substitution product at δ 0.983 (d, 3 H). Integration of the latter peaks indicated 21.89% unchanged tosylate, 4.18% rearranged tosylate, 25.25% alcohol substitution, and 48.68% ether substitution. The 75-MHz ^{13}C NMR spectrum showed two signals centered at δ 84.403 due to α-^{13}C absorption of the ester; the signals of the ester occur at 84.427 ppm for ^{13}C–^{16}O resonance peak and at 0.048 ppm upfield from the latter signal for the ^{13}C–^{18}O resonance peak. Cut-and-weigh integration of the latter two peaks indicated 25.65% ether-^{18}O tosylate, and this indicated that no equilibration had occurred.

1-(3-Noradamantyl)ethanone-^{18}O, Second Preparation. 2-[1-(3-Noradamantyl)-1-oxoethyl]-dioxolane was placed into a 25-mL bantamware flask equipped with a reflux condenser along with 97% $H_2{}^{18}O$ (0.51 g). *p*-Toluenesulfonic acid (30 mg) which had been dried in a 120 °C oven overnight was added. The reaction mixture was heated at a temperature of 60–90 °C over a 4-h period. Next, the reaction flask contents were rinsed with dry diethyl ether into a separatory funnel containing anhydrous diethyl ether. The organic solution was extracted twice with saturated aqueous $NaHCO_3$ and then twice with water. The organic extract was dried over $MgSO_4$; the drying agent was removed by suction filtration. Evaporation of the diethyl ether left the ketone, which was distilled to give the crude product in 92.6% yield (3.11 g). The infrared spectrum showed a substantial amount of ^{18}O ketone along with ^{16}O ketone (≈30%). The ketone was purified by column chromatography (hexane). The infrared spectrum showed that some purification had occurred but some unchanged ketal was still present. IR (film): $\nu_{C=O}$ 1670 and 1698.

1-(3-Noradamantyl)ethanol-^{18}O, Second Preparation. The ketone (3.1 g, 0.018 65 mol) from the previous synthesis was reduced in the usual manner with LAH. The product was isolated from the reaction mixture and then purified by column chromatography on silica gel. 125-MHz ^{13}C NMR analysis of the α-carbon atom showed 50.555% ^{18}O enrichment.

1-(3-Noradamantyl)ethyl Tosylate-*ether*-^{18}O, Second Preparation. The modified Tipson procedure was employed (see the preparation of 3-noradamantylmethyl sulfonates). 125-MHz ^{13}C NMR analysis of the α-carbon atom showed 50.088% ^{18}O enrichment.

Oxygen-18 Scrambling Studies of 1-(3-Noradamantyl)ethyl Tosylate in 100E. Experiment 2. 1-(3-Noradamantyl)ethyl tosylate-*ether*-^{18}O (0.4936 g, 1.540 mmol) which had 50.088% ether-^{18}O incorporation was dissolved in ethanol (100 mL) containing lutidine (0.2084 g) by sonication for 5 min. The reaction solution was kept at 25.000 ± 0.001 °C for ≈0.48 half-lives (1.617 h). Workup was performed in the manner used in the ^{18}O scrambling study of 2,2-dimethyl-1-adamantyl pemsylate-*ether*-^{18}O. The 500-MHz ^{1}H NMR spectrum indicated signals for unsolvolyzed tosylate at δ 1.235 (d, 3 H), rearranged tosylate at δ 1.103, and 2-methyl-1-adamantyl ether substitution product at δ 0.979 (d, 3 H). Integration of these peaks indicated 71.66% unchanged tosylate, 20.83% rearranged tosylate, and 7.51% ether substitution. From these concentration data it is calculated that $k_1 + k_3 = 5.730 \times 10^{-5}$ and $k_2 = 10.2 \times 10^{-5}$. 125-MHz ^{13}C NMR spectrum showed two signals due to α-^{13}C absorption of the rearranged tosylate centered at δ 93.334; the signals of the rearranged ester occur at 93.366 ppm for the ^{13}C–^{16}O resonance peak and at 0.064 ppm upfield from the latter signal for the ^{13}C–^{18}O resonance peak. Cut-and-weigh integration of the latter two peaks indicated 25.84% ether-^{18}O tosylate. The latter NMR spectrum also showed two signals due to α-^{13}C absorption of the unrearranged tosylate centered at δ 83.792; the signals of the unrearranged ester occur at 83.817 ppm for the ^{13}C–^{16}O resonance peak and at 0.049 ppm upfield from the latter signal for the ^{13}C–^{18}O resonance peak. Cut-and-weigh integration of the latter two peaks indicated 50.05% ether-^{18}O tosylate, and this indicated that no equilibration had occurred.

Lithium 3-Noradamantanecarboxylate. This compound was prepared from 3-noradamantanecarboxylic acid in the manner described by Levine et al.[67]

2-Ethyl-2-adamantanol. This compound was prepared by the method of Landa et al.[68] Mp: 67–69 °C (lit.[68] mp 69.8–70.4 °C). 60-MHz ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3 H), 1.3–2.4 (m) with a sharp singlet at 1.4 and maxima at 1.75, 2.1, and 2.3.

1-(3-Noradamantyl)propanone. Method A. The ketone was prepared from lithium 3-noradamantylcarboxylate by the method of Levine et al.[67] **Method B.** The 2-ethyl-2-adamantanol from the above reaction was treated according to the procedure used to make 1-(3-noradamantyl)-ethanone and gave the desired ketone. 60-MHz ^{1}H NMR ($CDCl_3$): δ

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1.02 (t, 3 H), 1.32–2.8 (m) with a quartet at 2.45. IR (film): 2930 (s), 2870 (m), 1700 (s), 1461 (m), 1415 (w), 1380 (w), 1353 (m), 1321 (w), 1305 (w), 1270 (w), 1240 (w), 1220 (w), 1185 (w), 1170 (w), 1120 (m), 1103 (m), 1085 (w), 1040 (w), 970 (w), 905 (w), 880 (w), 865 (w), 845 (w), 780 (w).

1-(3-Noradamantyl)propanol. This alcohol was made by reduction of 1-(3-noradamantyl)propanone by the method employed to prepare 3-noradamantylmethanol. Mp: 64–66 °C. The 300-MHz ^{1}H and 75-MHz ^{13}C NMR spectra confirmed the structure. 300-MHz ^{1}H NMR ($CDCl_3$): δ 1.017 (t, 3 H), 1.23–1.40 (m, 1 H), 1.46–1.78 (m, 11 H), 1.82 (s, 1 H), 2.15–2.6 (m, 3 H), 3.42 (d of d, J_1 = 10.8 and J_2 = 2.1 Hz, 1 H). 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$): δ 78.514, 54.251, 45.85, 44.004, 43.657, 43.542, 41.246, 37.463, 37.386, 35.732, 26.191, 11.263.

1-(3-Noradamantyl)propanol-*1-d* and 1-(3-Noradamantyl)propanol-*2,2-d*$_2$. These alcohols were made in the usual manner by reduction of the hydrogen and β-d_2 ketones with $LiAlD_4$ and $LiAlH_4$, respectively. Mp of the α-d_1 alcohol: 69–72 °C. Before submission of a sample for combustion analysis, the alcohol was purified twice by HPLC on a preparative column (21.4-mm i.d. × 25-cm *l*) and then sublimed. One purification used 70% hexane–30% ethyl acetate to remove a more polar impurity (<1%), and the second purification used 80% hexane–20% ethyl acetate to remove a peak (<1%) with a retention time similar to that of the α-d_1 alcohol. Anal. Calcd for $C_{12}H_{19}DO$: C, 79.50; H, 11.67. Found: C, 79.70; H, 11.30. Mp of the β-d_2 alcohol: 68–71 °C. 60-MHz ^{1}H NMR ($CDCl_3$) of the β-d_2 alcohol: δ 1.0 (br s, 3 H), 1.3–2.0 (m, 11 H) with a maximum at 1.6, 2.0–2.3 (m, 3 H), 3.4 (br s, 1 H). 60-MHz ^{1}H NMR ($CDCl_3$) of the α-d_1 alcohol: δ 1.03 (distorted triplet, 3 H), 1.2–1.9 (m) with a maximum at 1.6, 2.0–2.4 (m, 3 H) with a maximum at 2.2, no resonance at 3.42.

1-(3-Noradamantyl)propyl Tosylate. This compound was made by the same procedure employed to prepare 3-noradamantylmethyl tosylate. Mp: 54–57 °C. 90-MHz ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3 H), 1.3–1.9 (m, 12 H), 2.05–2.35 (m, 3 H), 2.42 (s, 3 H), 4.75 (t, 1 H), 7.2–7.98 (AA′BB′ quartet, 4 H).

1-(3-Noradamantyl)propyl, 1-(3-Noradamantyl)propyl-*1-d*, and 1-(3-Noradamantyl)propyl-*2,2-d*$_2$ Pemsylate. This compound was made by the same modified Kochi–Hammond synthesis used to prepare 2,2-dimethyl-1-adamantyl pemsylate. Mps were recorded as follow: H pemsylate, 108–110 °C; α-d_1 pemsylate, 108–110 °C; β-d_2 pemsylate, 107–109 °C. 300-MHz ^{1}H NMR ($CDCl_3$) of the H pemsylate: 0.890 (t, 3 H), 1.4–1.8 (m, 12 H), 2.15–2.34 (m, 12 H) with sharp peaks at 2.24 (s, 6 H) and 2.275 (s, 3 H), 2.604 (s, 6 H), 4.85 (d of d, J_1 = 7.95 and J_2 = 4.35 Hz, 1 H). 300-MHz ^{1}H NMR ($CDCl_3$) of the α-d_1 pemsylate: similar to the hydrogen spectrum except there is no multiplet at δ 4.85. 300-MHz ^{1}H NMR ($CDCl_3$) of the β-d_2 pemsylate: δ 0.872 (s, 3 H), 1.4–1.8 (m, 10 H), 2.15–2.3 (m, 12 H) with sharp signals at 2.228 (s, 6 H) and 2.266 (s, 3 H), 2.600 (s, 6 H), 4.84 (s, 1 H). 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$) of the α-d_1 pemsylate: δ 139.483, 136.237, 134.505, 133.772, 90.683 (triplet), 53.439, 46.302, 44.773, 43.506, 41.849, 37.433, 37.135, 35.481, 25.2, 19.034, 17.733, 16.956, 10.881. 75-MHz ^{13}C (decoupled) NMR ($CDCl_3$) of the β-d_2 pemsylate: the changes from the spectrum of the α-d_1 compound are a quintet, not a singlet, absorption shifted upfield to δ 24.6 and a singlet, not a triplet, absorption shifted downfield to δ 90.998.

Identification of the Solvolysis Products of 1-(3-Noradamantyl)-propyl-*1-d* Pemsylate in 100% Ethanol. 1-(3-Noradamantyl)propyl-*1-d* pemsylate (0.6122 g, 1.563 mmol) was added to a 250-mL round-bottom flask containing conductivity ethanol (100 mL) and lutidine (0.2041 g, 1.905 mmol). The pemsylate was allowed to react in ethanol for 6 days and 6.72 h at room temperature, and then the solution was gently heated under reflux for ≈18 h. Isolation of the product gave a clear green liquid in 92% yield. The 300-MHz ^{1}H and 75-MHz ^{13}C NMR spectra clearly indicated that the product is mostly ethyl 2-ethyl-1-adamantyl-*2-d* ether. The impurity peak in the ^{13}C spectrum at δ 57.4 is evidence for a small (≈2% by computer integration) yield of the protoadamantyl substitution product. 300-MHz ^{1}H NMR ($CDCl_3$): δ 0.870 (t, 3 H), 1.150 (t, 3 H), 1.20–1.95 (m, 15 H), 1.98–2.08 (m, 2 H), 2.08–2.18 (m, H), 3.385 (m, 2 H). 75-MHz ^{13}C NMR ($CDCl_3$): δ 73.196, 53.953, 47.791 (t, ^{13}C–D), 41.623, 38.128, 37.462, 37.192, 30.953, 30.569, 30.396, 30.011, 18.405, 15.853, 11.897.

Identification of the Solvolysis Products of 1-(3-Noradamantyl)-propyl-*1-d* Pemsylate in 82% Aqueous Acetone. 1-(3-Noradamantyl)-propyl-*1-d* (0.75 g, 1.9 mmol) was dissolved in acetone (100 mL), and then water (22 mL) and lutidine (0.30 g) were added. The compound was solvolyzed by heating the solution under slow reflux for 25.1 h. Isolation of the solvolysis products gave a white solid in 91% yield (0.32 g). The products were separated by HPLC on a preparative column with 80% hexane–20% ethyl acetate as the mobile phase. The largest peak in the chromatogram represented 2-ethyl-1-adamantanol-*2-d*, which was obtained with an almost 100% yield (0.32 g) after HPLC separation. Besides the peak for the major product, there were two smaller peaks for compounds which eluted just a little faster than the 1-adamantanol. The two smaller peaks had relative areas of only 3% by cut-and-weigh integration. Of the two smaller peaks, the slower eluting one, which accounted for 83.4% of the combined areas, was shown by NMR to correspond to 4-ethyl-3-protoadamantanol-*4-d*. The identity of the compound which produced the smaller of the two peaks was not conclusively established, but it is probably the epimeric 3-protoadamantanol. In support of this assignment, the ^{1}H spectrum showed a triplet at δ 0.958 and the ^{13}C spectrum gave 10 resonances. The two resonances unaccounted for in the carbon spectrum are the bridgehead α-carbon and the deuterated carbon, which are undoubtedly lost in noise. The 2-ethyl-1-adamantanol-*2-d* data follow. 500-MHz ^{1}H NMR ($CDCl_3$): δ 0.868 (t, 3 H), 1.23–1.32 (m, 1 H), 1.32–1.37 (m, 1 H), 1.37–1.43 (m, 1 H), 1.47–1.63 (m, 4 H), 1.63–1.76 (m, 5 H), 1.83–1.88 (m, 1 H), 1.95–2.04 (m, 2 H), 2.07–2.12 (m, 1 H). 125-MHz ^{13}C NMR ($CDCl_3$): δ 70.200, 51.876 (t), 47.391, 39.512, 38.097, 36.913, 31.392, 30.993, 30.306, 29.982, 18.940, 12.410. Mp: 77–79 °C. The 4-ethyl-3-protoadamantanol-*4-d* NMR data follow. 500-MHz ^{1}H NMR ($CDCl_3$): δ 0.935 (t, 3 H), 1.02–1.12 (m, 1 H), 1.22–1.30 (m, 2 H), 1.34–1.45 (m, 4 H), 1.67–1.73 (m, 1 H), 1.75–1.82 (m, 1 H), 1.82–2.02 (m, 5 H), 2.03–2.13 (m, 2 H). 125-MHz ^{13}C NMR ($CDCl_3$): δ 82.323, 45.864, 42.990, 40.440 (t), 39.364, 39.241, 36.610, 34.702, 33.267, 28.477, 23.623, 11.910. 125-MHz ^{13}C NMR ($CDCl_3$) data for the minor epimeric product of 4-ethyl-3-protoadamantanol-*4-d*: δ 50.867, 42.265, 40.890, 39.265, 35.825, 34.209, 32.034, 28.578, 25.176, 13.619.

2-Ethyl-1-adamantanol was prepared in the same manner used to prepare 2,2-dimethyl-1-adamantanol. The 300-MHz ^{1}H NMR and 75-MHz ^{13}C (decoupled) NMR spectra confirmed the structure. Mp: 74–76 °C.

2-Ethyl-1-adamantyl pemsylate was prepared in the same manner used to prepare 2,2-dimethyl-1-adamantyl pemsylate. The 300-MHz ^{1}H and 75-MHz ^{13}C NMR spectra confirmed the structure. Mp: 144–150 °C. 300-MHz ^{1}H NMR ($CDCl_3$): δ 0.873 (t, 3 H), 1.3–1.48 (m, 2 H), 1.58–1.92 (m, 10 H), 1.96–2.35 (m, 13 H) with sharp peaks at 2.229 (s, 6 H) and 2.264 (s, 3 H), 2.593 (s, 6 H). 75-MHz ^{13}C NMR ($CDCl_3$): δ 139.530, 137.234, 134.515, 134.015, 94.657, 51.362, 43.898, 37.883, 37.524, 36.472, 32.612, 31.766, 31.317, 29.740, 19.583, 18.941, 17.685, 16.902, 11.99.

2-Ethyl-1-adamantyl pemsylate-*2-d* was synthesized from 2-ethyl-1-adamantanol-*2-d* which was purified by HPLC and, hence, contained no 4-ethyl-3-protoadamantanol. The alcohol was allowed to react according to the procedure employed for the preparation of 2,2-dimethyl-1-adamantyl pemsylate.

1-Adamantyl tosylate was prepared in the same manner as 2,2-dimethyl-1-adamantyl pemsylate. The NMR spectrum showed 1-adamantanol (23%) to be the only contaminant after recrystallization from hexane. 500-MHz ^{1}H NMR ($CDCl_3$): δ 1.60–1.63 (m, 6 H) with a maximum at 1.62, 2.14–2.22 (m, 9 H) with maxima at 2.15 and 2.18, 2.42 (s, 3 H), 7.53 (AA′BB′ quartet, 4 H).

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Appendix

The equation below, derived by the integrating factor method,[69] describes the time dependence of acid production in kinetic Scheme I, where t_0 is the time elapsed from 0% reaction to the first datum

$$[HX]_i = [HX]_\infty - \frac{[HX]_\infty(k_2 - k_3)e^{-(k_1 + k_3)(t_i + t_0)}}{k_2 - (k_1 + k_3)} + \frac{[HX]_\infty k_1 e^{-k_2(t_i + t_0)}}{k_2 - (k_1 + k_3)}$$

point, $[HX]_\infty$ is the acid concentration at infinite time, k_1 is the rate constant for isomerization of **2** to **4**, k_2 is the rate constant for solvolysis of **4**, and k_3 is the rate constant for direct production of acid from **2**.

A nonlinear, doubly-weighted, Lagrange multiplier, least-squares, curve-fitting program was written which selects the op-

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timum values of the parameters of this equation to fit the conductance kinetic data, i.e., the values of $[HX]_i$ and t_i. Because of interdependencies, all five parameters k_1, k_2, k_3, t_0, and $[HX]_\infty$ could not be accurately determined simultaneously; therefore, calculations were done with fixed values assigned for either one or both of k_2 and k_3. The program can also be used to calculate first-order rate coefficients where the parameters are k_3, t_0, and $[HX]_\infty$ with k_1 and k_2 set to 0.

It was determined from calculations on synthetic data generated with probable values of k_1, k_2, k_3, t_0, and $[HX]_\infty$ that, when k_3 is small but kinetically significant, setting k_2 to its true value and k_3 to 0 will result in a small systematic wave in the plot of the resistance residuals. Error plots with such systematic trends were observed for **2b** in 80E and 90E, see Figure 4 in the supplementary material. The fit of the data from **2b** in 95E as described above produced a wave in the opposite sense which was shown to be due to the presence of a fraction of 1% pemsyl chloride impurity. These data were analyzed using a Simplex algorithm, which had been developed previously in our laboratory.[48] It was applied in this case to fit conductance data from the solvolysis of a mixture of two components: the ester **2b** reacting according to the kinetic scheme described above and the chloride reacting by a simple first-order process. The number of variables derived from the least-squares treatment was reduced to four by fixing k_2 and the solvolysis rate constant for pemsyl chloride at the independently observed values and constraining k_3 by fixing f_{rel} at 0.968, the value found to give optimum fits to all kinetic runs.

Supplementary Material Available: Figures 3, 4, and 5, showing the trends in the errors in the calculated resistances ("resistance residuals") over the time span of the solvolysis of **2a** and **3b** in 90E and **2b** in 80E using the simple first-order rate law and the rate law given in the Appendix for Scheme I (4 pages). Ordering information is given on any current masthead page.

Ultrathin Monolayer Lipid Membranes from a New Family of Crown Ether-Based Bola-Amphiphiles

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Abstract: Twelve novel α,Ω-bis(*N*-azacrown ether) compounds have been prepared, characterized, and converted into a previously unknown type of niosome. Four are bis(15-crown-5) derivatives having the following spacer chains: $(CH_2)_{12}$ (**1**), $(CH_2)_{16}$ (**2**), $CO(CH_2)_{20}CO$ (**3**), and $(CH_2)_{22}$ (**4**). The eight bis(aza-18-crown-6) derivatives have the following spacers: $(CH_2)_{10}$ (**5**), $CO(CH_2)_{10}CO$ (**6**), $(CH_2)_{12}$ (**7**), $CO(CH_2)_{14}CO$ (**8**), $(CH_2)_{16}$ (**9**), $(CH_2)_{22}$ (**10**), $(CH_2)_{12}O(CH_2)_{12}$ (**11**), and $CO(CH_2)_{11}S(CH_2)_{12}S(CH_2)_{11}CO$ (**12**). Aggregation studies of **1** and **7**, employing transmission electron microscopy as well as dynamic and static light scattering, demonstrate that these compounds form a novel class of spherical monolayer lipid membrane vesicles when dispersed in water. Debye light-scattering profiles obtained from a suspension of large (≈200 nm diameter) vesicles indicate a relative refractive index near 1. Dynamic turbidimetry in acidic media on a suspension of bola-amphisomes formed from **1**, suggested that the contribution of micelle–vesicle equilibria to the bolyte aggregation state is negligible. In neutral or slightly alkaline pH at 35 °C, the vesicles grew irreversibly to yield large, probably multilamellar, aggregates. In acidic media at pH 2, the bola-amphisomes do not coalesce, even at 65 °C. On the basis of the observations presented here, bola-amphiphiles having a hydrocarbon span of 10–12 carbon atoms aggregate in aqueous media into vesicles. When the aliphatic backbone incorporates 16 or more carbon atoms, micelles are formed.

Introduction

Nearly a decade ago, Fuhrhop and co-workers reported the synthesis and self-assembly properties of several hydrophobic derivatives of succinic acid in which two polar headgroups are linked covalently by a hydrophobic, saturated hydrocarbon skeleton (Figure 1).[1] Fuhrhop called these surfactant molecules bola-amphiphiles—the name derives from the South American slingshot comprised of two leather balls attached to a string. Bolas are designed to tangle around the legs of cattle and thereby immobilize them. Their molecular counterparts (bola-amphiphiles) often remain extended when dispersed in water and form monolayer lipid membrane vesicles or *bola-amphisomes*.

The covalent chains of bola-amphisome monomers need not interdigitate in the bilayer midplane as do normal amphiphiles. A covalent span of 12 carbons affords an "ultrathin" membrane with a width of less than 20 Å compared to common biological bilayer membranes that have thicknesses ranging from about 30 to 100 Å.[2] The monomers normally involved in the formation of bilayer membranes interdigitate along the membrane's midplane.[3] When the extent of interlaminar overlap becomes small, some of the surfactant monomers protrude from the membrane and are readily exchanged by intercolloidal collisions.[4,5] This process facilitates coalescence of the vesicles to yield larger, heterogeneous, multilamellar assemblies. In the case of a covalently linked monolayer membrane, the frequency of intervesicular fusion is reduced because both vertical diffusion and intervesicular exchange of surfactant monomers are inhibited.

Covalently linked dipolar surfactants are found in the membrane of thermophilic archaebacteria (unicellular organisms that live in boiling water under conditions of high ionic strength and low pH[6]). Such bacteria maintain an intracellular pH of about 6.5 when the external pH is 1.5. Gliozzi et al.[7] isolated from the

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