A Simple Method for Determination of Solvolysis Rates by ^{1}H NMR

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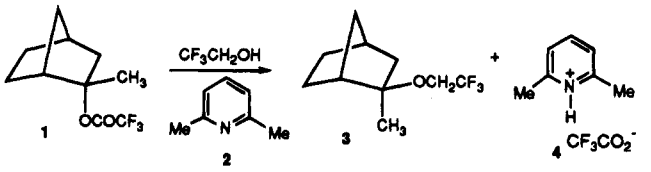
Over the years, solvolytic studies have been of primary importance in determining the properties of carbocationic intermediates.[1] Classically, rates of solvolytic displacement reactions are determined by titrimetric methods, where the acid liberated as the solvolysis proceeds is titrated with standard base. Alternatively, back titration methods can be used, where excess buffering base is added at the beginning of the reaction and the unreacted base is back titrated with standard acid.[2]

With the advent of modern instrumental methods, numerous other methods have been employed for the determination of solvolytic rates. These include spectrophotometric,[3] gas chromatographic,[4] conductometric,[5] and HPLC methods.[3b,6] NMR spectroscopic methods are also useful for the determination of solvolytic reaction rates, and we have recently reported a ^{19}F NMR method for determination of rates where the leaving group is the fluorine-containing trifluoroacetate, triflate, or triflone group.[7] In general, NMR kinetic methods depend on determination of the amount of reactant or product by integration of NMR signals as a function of time.

During the course of other studies, we had need to measure the solvolysis rate of the trifluoroacetate **1** in trifluoroethanol, a commonly used solvent (containing 2,6-lutidine as a nonnucleophilic buffering base). In the past, we have used spectrophotometric,[8] gas chromatographic,[4] and ^{19}F NMR methods[7] for determination of rates of analogous substrates. While the ^{19}F NMR method is potentially the easiest method, a drawback of this method is the need to carry out accurate integrations of covalent trifluoroacetate and trifluoroacetate anion in the presence of a large ^{19}F signal due to solvent trifluoroethanol. We now report an extremely facile and accurate method for rate determinations using ^{1}H NMR in undeuterated alcohol solvents and without the need for measurement of NMR integrals (which, in practice, can be nontrivial to determine accurately).



We have found that the reaction of **1** in trifluoroethanol can be followed by ^{1}H NMR. Even in the presence of the large solvent peak at δ 3.92, the small signals due to **1** (δ 1.572) and developing **3** (δ 1.297) can be seen if the spectrum is expanded in the appropriate regions as in Figure 1. Of more importance for rate determination, we have observed that the singlet at δ 2.504 due to the methyl groups of the buffering base, 2,6-lutidine, **2**, shifts downfield over the course of the reaction in a first-order fashion. Generally, this signal will shift downfield by about 50–60 Hz over the course of a solvolysis using typical concentrations. This is attributed to rapid proton transfer between **2** and the protonated form **4**, which increases in concentration as the solvolysis proceeds. The observed methyl group chemical shift represents an average of the amounts of **2** and **4** present. Since modern spectrometers can easily determine frequency to less than 0.1 Hz, the frequency of the 2,6-lutidine methyl singlet presents a facile probe for rate determination. Figure 2 shows a first-order kinetic plot of data determined for **1** at 25.0 °C. The correlation coefficient is 0.99999.

The linearity of Figure 1 (and other kinetic plots) implies that the chemical shift is indeed a measure of the amount of liberated acid as the reaction proceeds. This can be independently shown to be the case. A separate study shows that a plot of the chemical shift of the methyl singlet of 0.05 M 2,6-lutidine in alcohol solvents is a linear function of the amount of added CH_3SO_3H or CF_3CO_2H. After 1 equiv of acid has been added, there are no further significant changes in chemical shift. This is indicative of essentially complete deprotonation of the added acid by 2,6-lutidine, i.e., the equilibrium constant for the reaction of 2,6-lutidine with these acids is very large.

Of practical importance, using this kinetic method does *not* require the use of expensive deuterated solvents. Modern spectrometers are quite stable when run in the unlocked mode. Shimming the unlocked spectrometer is also quite simple if the spectrometer is previously shimmed using a deuterated sample (i.e., $CDCl_3$) containing the same sample volume as the solvolysis sample. Once this is done, small changes in the Z1 shim control are usually all that are necessary to obtain excellent spectra of the solvolysis mixture. Because of the large amount of signal due to the undeuterated solvent, using a pulse width of much less than 90°, or turning down the receiver gain, prevents overloading of the spectrometer. Despite the very large solvent signal, the methyl singlet due to exchanging **2** and **4** is easily discernable and the shift can be very accurately measured, if the spectrum is expanded.

This kinetic method, which is analogous to a titrimetric method, where chemical shift represents the titer, is far easier than classical titration methods. It is intrinsically more accurate (as well as easier) than NMR integration methods since the error in chemical shift determination

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(2) For a recent example of this back titration method, see: (a) Wiberg, K. B.; Shobe, D.; Nelson, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 10645. For typical examples from our laboratory of the use of titrimetric methods for determining solvolytic rate constants, see: (b) Creary, X. *J. Am. Chem. Soc.* **1984**, *106*, 5568. (c) Creary, X.; Geiger, C. *Ibid.* **1982**, *104*, 4151. (d) Creary, X.; Geiger, C.; Hilton K. *Ibid.* **1983**, *105*, 2851.

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(7) Creary, X.; Wang, Y.-X. *J. Org. Chem.* **1992**, *57*, 4761.

(8) (a) Creary, X.; Casingal, V. P.; Leahy, C. *J. Am. Chem. Soc.* **1993**, *115*, 1734. (b) Creary, X. *J. Org. Chem.* **1985**, *50*, 5080. (c) Creary, X.; Underiner, T. K. *J. Org. Chem.* **1985**, *50*, 2165.

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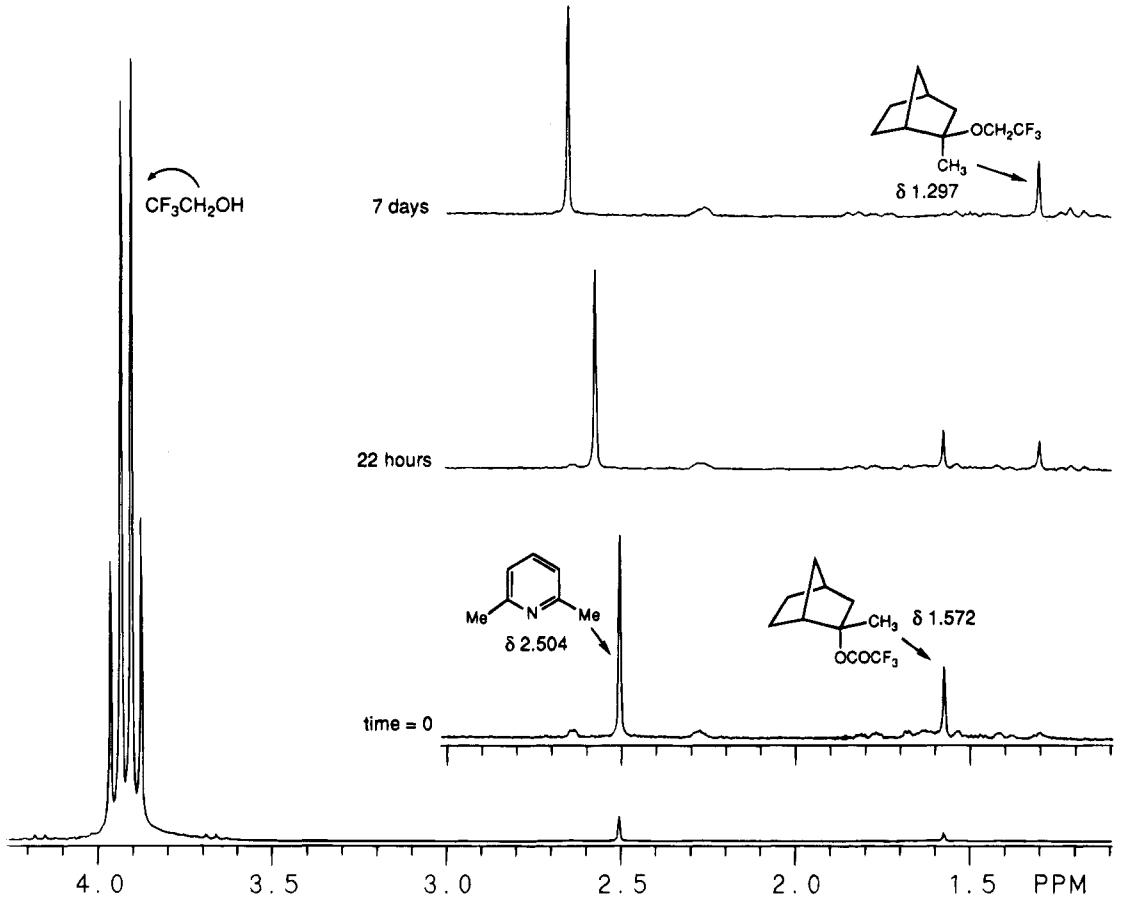
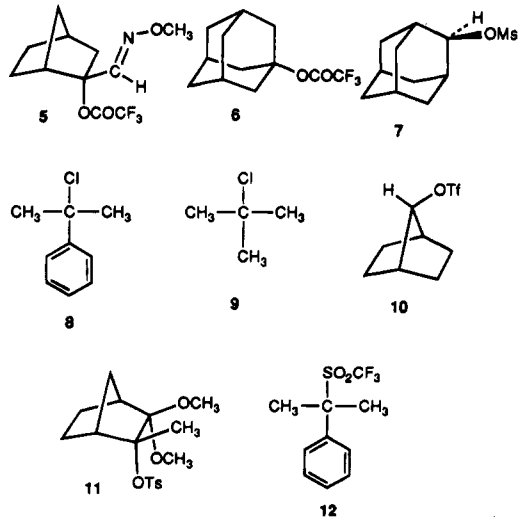


Figure 1. ^{1}H NMR spectra of **1** in trifluoroethanol containing 0.05 M 2,6-lutidine at 25 °C as a function of time.

is much less than that in determining NMR integrals. It is also applicable to solvents other than trifluoroethanol and to other leaving groups. Table 1 gives rates of solvolyses of substrates **5**–**12** in various alcohol solvents buffered with 2,6-lutidine and monitored by ^{1}H NMR. Substrates as diverse as trifluoroacetates, mesylates, chlorides, triflates, tosylates, and triflones can be monitored by this method. Rates of **8**, **9**, **10**, and **12** determined by this NMR method agree quite well with previously reported titrimetric values.



Of interest are data for 1-adamantyl trifluoroacetate, **6**, in trifluoroethanol. Our activation parameters ($\Delta H^{\ddagger}$ = 22.5 kcal/mol; $\Delta S^{\ddagger}$ = −10.5 eu) are significantly different from those reported in the literature[9] in 97% trifluoroethanol as determined by conductometric methods. Our data are much more consistent with expectations based on a k_C process. The unusual activation parameters ($\Delta H^{\ddagger}$ = 14.8 kcal/mol; $\Delta S^{\ddagger}$ = −32.8 eu) previously reported are probably due to errors in rate constants determined by the conductometric method.

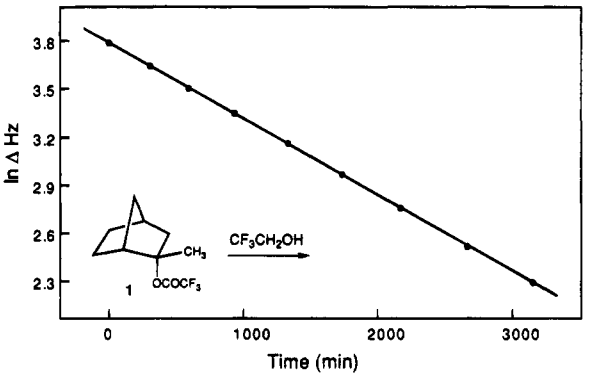


Figure 2. First-order kinetic plot for solvolysis of trifluoroacetate **1** in trifluoroethanol containing 0.05 M 2,6-lutidine as determined by ^{1}H NMR at 300 MHz. ΔHz = (shift at 100% reaction − shift at time = t).

While this NMR kinetic method is applicable to the common alcohol solvents, it fails with hexafluoroisopropyl alcohol. Apparently, 2,6-lutidine is substantially protonated in this solvent and no further downfield shifts of the methyl singlet of 2,6-lutidine are seen as solvolyses

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Table 1. Solvolysis Rates of Substrates in Various Solvents at 25.0 °C

substrate	solvent	k (s^{-1})
1	CF_3CH_2OH	7.91×10^{-6}
5	CF_3CH_2OH	5.58×10^{-5}
6	CF_3CH_2OH	1.06×10^{-6} (25 °C)
		6.85×10^{-6} (40 °C)
		2.15×10^{-5} (50 °C)
		6.51×10^{-5} (60 °C)
		1.74×10^{-4} (70 °C)
7	CF_3CH_2OH	7.46×10^{-5} (60.0 °C)
8	EtOH	3.66×10^{-4} [a]
9	CH_3OH	1.96×10^{-5} (50 °C)[b]
10	CF_3CH_2OH	4.42×10^{-5} (70 °C)[c]
11	CF_3CH_2OH	3.54×10^{-4}
12	CH_3OH	2.82×10^{-5} [d]

[a] Literature value = 3.94×10^{-4} s^{-1} (ref 14). [b] Literature value = 2.10×10^{-5} s^{-1} (ref 15). [c] Literature value = 4.74×10^{-5} s^{-1} (ref 16). [d] Literature value = 2.87×10^{-5} s^{-1} (ref 11).

of typical substrates progress. Finally, *p*-nitrobenzoate derivatives of alcohols cannot be monitored by this method. Apparently the liberated *p*-nitrobenzoic acid is not strong enough to completely protonate 2,6-lutidine under solvolysis conditions.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a General Electric GN 300 spectrometer or on a Chemagnetics A-200 spectrometer. Mass spectra were recorded on a Finnigan MAT 8430 high-resolution spectrometer. Chromatographic purifications were carried out using EM science 230–400-mesh silica gel 60. Substrates **1**,[10] **6**,[7,9] **7**,[2c] **10**,[11] and **12**[12] were available from previous studies in our laboratory.

Preparation of Trifluoroacetate 5. A solution of 570 mg of *endo*-2-hydroxybicyclo[2.2.1]heptane-2-carboxaldehyle[13] (prepared by ozonolysis of *exo*-2-vinylbicyclo[2.2.1]heptan-2-ol) in 5 mL of pyridine was cooled to 0 °C and 450 mg of methoxylamine hydrochloride was added. The mixture was stirred at room temperature for 5.5 h and then taken up into ether. The solution was washed with two portions of water and then with a dilute HCl solution. The ether extract was washed with saturated NaCl solution and then dried over $MgSO_4$. The solvent was removed using a rotary evaporator to give 637 mg (94%) of the crude oxime derivative. The oxime was further purified by chromatography on silica gel using 10% ether in hexanes to elute the oxime. ^1H NMR of *endo*-2-hydroxybicyclo[2.2.1]heptane-2-carboxaldehyle *O*-methyloxime ($CDCl_3$): δ 7.467 (s, 1 H), 3.844 (s, 3 H), 2.68 (br s, 1 H), 2.31–1.97 (m, 4 H), 1.68–1.17 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ 154.07, 77.82, 61.75, 46.65, 43.38, 37.79, 37.18, 28.77, 21.58.

A solution of 171 mg of the *O*-methyloxime derivative of *endo*-2-hydroxybicyclo[2.2.1]heptane-2-carboxaldehyle and 162 mg of 2,6-lutidine in 3 mL of ether was cooled to 0 °C and 298 mg of trifluoroacetic anhydride was added dropwise. The mixture was warmed to room temperature for 15 min and then recooled to 0 °C and a cold rapid aqueous workup followed. Cold water was added to the stirred mixture and the aqueous phase was removed via pipet. The ether solution was then extracted with dilute hydrochloric acid followed by saturated NaCl solution. The ether extract was carefully dried over $MgSO_4$ and filtered through a small amount of $MgSO_4$ in a disposable pipet. The ether was then removed using a rotary evaporator, leaving 268 mg (100%) of crude trifluoroacetate **5**, which was used directly for kinetic studies. ^1H NMR of **5** ($CDCl_3$): δ 7.549 (s, 1 H), 3.867 (s, 3 H), 2.83 (m, 1 H), 2.55–2.45 (m, 1 H), 2.34 (m, 1 H), 1.77–1.27 (m, 7 H). ^{13}C NMR ($CDCl_3$): δ 156.53 (q, J = 42 Hz), 148.72, 114.43 (q, J = 287 Hz), 90.39, 62.10, 45.08, 40.75, 36.65, 35.91, 28.43, 21.76. Exact mass calcd for $C_{11}H_{14}F_3NO_3$: 265.0926, found 265.0927.

Preparation of Tosylate 11. A solution of 899 mg of 3,3-dimethoxy-*exo*-2-methylbicyclo[2.2.1]heptan-2-ol[4a] in 7 mL of tetrahydrofuran was cooled to −78 °C and 3.35 mL of 1.6 M *n*-butyllithium in hexanes was added dropwise. The mixture was warmed to room temperature and 1.38 g of tosyl chloride was then added. After 2 h, the mixture was taken up into ether and water. The ether extract was washed with two portions of cold water and then with saturated NaCl solution. The ether phase was dried over $MgSO_4$ and the solvent was removed using a rotary evaporator. The solid residue was washed with cold pentane and the pentane was decanted, leaving tosylate **11** as a white solid, mp 88.5–89.5 °C. Removal of some of the pentane from the washing and cooling in ice led to a second crop of **11**. The yield of **11** was 1.101 g (67%). ^1H NMR of **11** ($CDCl_3$): δ 7.80 and 7.31 (AA'BB' quartet, 4 H), 3.214 (s, 3 H), 3.192 (s, 3 H), 2.61 (m, 1 H), 2.434 (s, 3 H), 2.41 (m, 1 H), 1.92 (m, 1 H), 1.75–1.35 (m, 4 H), 1.641 (s, 3 H), 1.210 (dt, J = 10.5, 1.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 143.83, 137.01, 129.59, 127.02, 106.57, 98.06, 50.91, 49.94, 49.69, 41.35, 32.99, 24.10, 21.74, 21.62, 20.81. Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11. Found: C, 59.94; H, 6.83.

Determination of Solvolysis Rates by ^1H NMR. General Procedure. A solution of 0.05 M 2,6-lutidine in the appropriate alcohol solvent was prepared and a small amount of tetramethylsilane (0.02 M) was added as an internal standard. This alcohol solution was added to the appropriate substrate such that the concentration of substrate was approximately 0.04 M and the solution was then added to an NMR tube. The solution was periodically analyzed by ^1H NMR at 200 or 300 MHz. For the slower reactions, the NMR tube was immersed in a constant temperature water bath at the appropriate temperature (±0.05 °C) between analyses. For the faster reactions (chloride **8** and tosylate **11**), the NMR tube was kept in the temperature-controlled probe at 25.0 ± 0.2 °C throughout the course of the run. For the runs at higher temperature, the NMR tube was kept in a constant temperature bath for certain time periods, withdrawn, quenched in cold water, and then rapidly analyzed by NMR at 20 °C (where the reaction rate is negligible). The NMR tube was then reheated to the appropriate temperature and the process was repeated until 8–10 measurements were obtained over approximately 2 half-lives. An "infinity" reading for all kinetic runs was recorded after 10 half-lives. First-order rate constants were calculated by standard least-squares procedures. Correlation coefficients were all greater than 0.9999. Maximum standard deviations in duplicate runs were ±2%.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **5** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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