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A Solvolysis Model for 2-Chloro-2-methyladamantane Based on the Linear Solvation Energy Approach

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Solvolysis/dehydrohalogenation rates of 2-chloro-2-methyladamantane (**CMA**) in 15 hydrogen-bond acidic and/or basic solvents are studied. The rates of reaction in these solvents have been correlated with the solvation equation developed by Kamlet, Abraham, and Taft. The linear solvation energy relationship (LSER) derived from this study is given by the following equation: $\log k = -5.409 + 2.219\pi_1^* + 2.505\alpha_1 - 1.823\beta_1$ where π_1^*, α_1, and β_1 are the solvation parameters that measure the solvent dipolarity/polarizability, hydrogen-bond acidity (electrophilicity), and hydrogen-bond basicity (nucleophilicity). A high correlation coefficient ($r = 0.996$, SD = 0.191) was achieved. The cavity term, which includes the Hildebrand parameter for solvent cohesive energy density, δ_H, was not found to be statistically significant for this reaction substrate. The resulting equation allows calculated rates of reaction in other solvents and provides insight into the reaction pathway. In a previously reported correlation for another tertiary chloride, *tert*-butyl chloride (**TBC**), the coefficients for α_1 and π_1^* are significantly larger and the coefficient for δ_H^2 is statistically significant. In addition, the coefficient for β_1 in the **TBC** correlation is positive, rather than negative, indicating that the transition states for **TBC** and **CMA** are significantly different. These results demonstrate why the uses of simple solvolytic correlation methods may be invalid even for comparisons of similar type substrates, e.g., tertiary chlorides. Also, these results provide confidence in the use of multiple linear regression analysis for predicting solvolytic rates in additional solvents.

Medium effects have an extraordinary influence on many chemical reactions. After early efforts of Berthelot and Saint-Gilles[1] (1862) and Menschutkin[2] (1890) to demonstrate that solvent media affect chemical reaction rates, many important contributions have appeared dealing with reactions induced by the solvent, i.e., solvolysis reactions.[3−11] Several studies have dealt with attempts to correlate solvolysis rates along lines proposed by Grunwald and Winstein (GW).[3] An important conclusion to be drawn from the many studies on correlation of reaction rates in pure or mixed solvents is that no single solvent parameter will satisfactorily correlate reaction rate data over a wide range of solvent types.

The inability to generalize the GW approach has attracted interest to correlations involving multiple linear regression analysis (MLRA). Koppel and Palm[12] devised the first general MLRA specifically designed for the correlation of the rate constants. In an attempt to overcome deficiencies noted earlier, Kamlet, Abraham, and Taft (KAT) and co-workers took the lead in devising a more general solvation equation which includes parameters that describe the solvent dipolarity/polarizability, hydrogen-bond acidity and basicity, and formation of a solute cavity in a solvent.[13] This treatment correlates solvent effects with some solvent-dependent property. The method continues to have wide application.[14] Of interest here is the use of this method for correlating reaction rates with solvent parameters. As applied to

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(1) (a) Berthelot, M.; Pean De Saint-Gilles, L. *Ann. Chim.* **1862**, *65*, 5. (b) Berthelot, M.; Pean De Saint-Gilles, L. *Ann. Chim.* **1862**, *66*, 5. (c) Berthelot, M.; Pean De Saint-Gilles, L. *Ann. Chim.* **1863**, *68*, 225.

(2) Menschutkin, N. A., *Z. Phys. Chem.* **1890**, *5*, 589.

(3) (a) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846. (b) Grunwald, E.; Winstein S.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700.

(4) Kosower, E. M. *An Introduction to Physical Organic Chemistry*; John Wiley and Sons: New York, 1968; pp 259−384.

(5) (a) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1982**, *104*, 5741. (b) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7658.

(6) (a) Peterson, P. E.; Kelley, R. E., Jr.; Belloli, R.; Sipp, K. A. *J. Am. Chem. Soc.* **1965**, *87*, 5169. (b) Peterson, P. E.; Vidrine, D. W.; Waller, F. J.; Henrichs, P. M.; Magaha, S.; Stevens, B. *J. Am. Chem. Soc.* **1977**, *99*, 7968.

(7) Streitweiser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill Publishing Co.: New York, 1962.

(8) Abraham, M. H. *Pure Appl. Chem.* **1985**, *57*, 1155.

(9) Kamlet, M. J.; Abboud, J. L. M.; Taft, R. W. In *Progress in Physical Organic Chemistry*; Taft, R. W., Ed.; John Wiley and Sons: New York, 1981; Vol. 13, pp 485−630.

(10) (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; Verlag Chemie: Weinheim, 1988. (b) Politzer, P.; Murray, J. S. *Quantitative Treatments of Solute/Solvent Interactions*; Elsevier: Amsterdam, 1994.

(11) (a) Parker, A. J. *Quart. Rev. (London)* **1962**, *16*, 163. (b) Parker, A. J. *J. Chem. Soc.* **1961**, 1328. (c) Parker, A. J. *Adv. Phys. Org. Chem.* **1967**, *5*, 173. (d) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

(12) Koppel, I. A.; Palm, V. A. *Org React.* **1971**, *8*, 291.

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substrate solvolysis, the linear solvation energy relationship (LSER) is shown in eq 1.

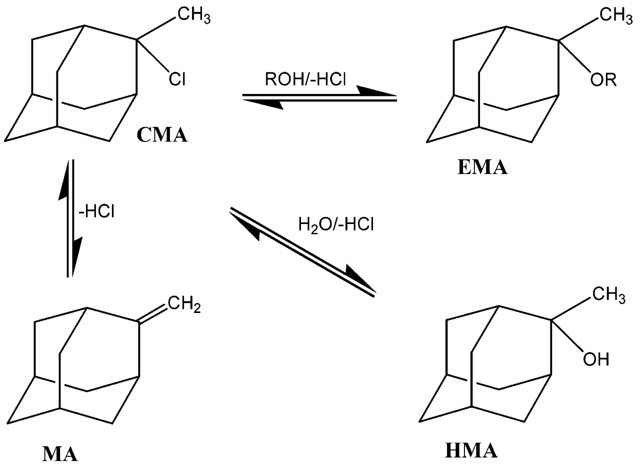
$$\log k = \log k_o + s\pi_1^* + d\delta_1 + a\alpha_1 + b\beta_1 + h\delta_H^{\,2} \qquad (1)$$

In solvation eq 1, k is the observed solvolytic rate constant. The explanatory variables are the solvent solubility parameters: π_1^* is the solvent dipolarity and polarizability; δ_1 is a polarizability correction factor which is only significant for halogenated and/or aryl solvents; α_1 is the solvent hydrogen-bond acidity; β_1 is the solvent hydrogen-bond basicity; and δ_H is the Hilderbrand solubility parameter. The term including δ_H models the formation of the solute cavity in a solvent. Log k_o is the constant resulting from the MLRA and represents the log k value for a solvent with all solubility properties equal to zero. Our interest in predicting reactivity in a wide variety of solvent types of complex substrates such as 2,2′-bischloroethyl sulfide, "mustard gas", led us to investigate MLRAs.[15]

The KAT method has been shown to provide mechanistic insight in a variety of reaction types. For example, its application to the study of the decarboxylation of benzisoxazole-3-carboxylate revealed insight regarding the relevance of catalysis in an antibody binding site.[16] These linear solvation energy relationships have also been used to study the isomerization of *cis*- to *trans*-stilbene which occurs via a photoinduced excited state.[16]

The KAT solvation equation has been applied to only a few solvolytic reactions, including the solvolysis of *tert*-butyl halides[18] and a mustard simulant, 2-phenylthioethyl naphthalenesulfonate.[19] Each study has provided indications that the method has promise for correlating reaction rates and modeling reaction pathways. However, the previous studies concluded that more reaction systems of varying types needed to be studied in order to provide a better basis to evaluate the widespread applicability of the KAT solvation equation. Because they have been so widely used in medium effects studies, the application of the KAT solvation equation to the solvolysis of 1-adamantyl chloride and bromide would be interesting. Unfortunately, 1-adamantyl halides only react to a slight extent, sometimes an immeasurably small extent, in many of the solvents required to apply solvation eq 1 and maintain statistically viable results. A similar reactant substrate that *does* react in a broad range of solvents is 2-chloro-2-methyladamantane (**CMA**). Moreover, since both **CMA** and *tert*-butyl chloride (**TBC**) are tertiary aliphatic chlorides, mechanistic similarities would be expected. This article details our application of solvation eq 1 to the solvolysis of **CMA** in a wide variety of solvents. The results are discussed in light of other available data.

SCHEME 1. Solvolysis Reaction Pathways for 2-Chloro-2-methyl-adamantane (CMA)



Results and Discussion

Previous studies by Shiner[20] and Bentley[21] and their co-workers suggested that **CMA** undergoes solvolysis in a wide variety of solvent types by either solvolytic substitution or by elimination, Scheme 1. To evaluate the KAT LSER methodology and best characterize the solvolysis of **CMA**, several solvent classes were chosen in order to provide a broad range of π_1^*, α_1, β_1, and δ_H^2 values. In Table 1 the solvents selected are listed along with their solvation parameters and log k values from rate measurements at 60 °C. The π_1^* value of the solvent greatly affects the rate for any reaction involving the formation of a dipolar transition state. Based on earlier experiences which indicate **CMA** fits this reaction category and knowing the rates of reaction of **CMA** in some highly polar solvents,[20,21] we anticipated difficulty measuring the reactivity of **CMA** in solvents with low π_1^* values.

Reactions of **CMA** in most of the pure solvents were carried out in sealed conductivity cells with platinum

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(13) (a) Taft, R. W.; Abraham, M. H.; Doherty, R. M.; Kamlet, M. J. *J. Am. Chem. Soc.* **1985**, *107*, 3105. (b) Abraham, M. H.; Grellier, P. L.; Abboud, J.-L. M.; Doherty, R. M.; Taft, R. W. *Can. J. Chem.* **1988**, *66*, 2673. (c) Kamlet, M. J. et al., *J. Org. Chem.* **1983**, *48*, 2877. (d) Kamlet, M. J.; Doherty, R. M.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *Chem Tech* **1986**, *9*, 566. (e) Abraham, M. H.; Taft, R. W.; Kamlet, M. J. *J. Org. Chem.* **1981**, *46*, 3053. (f) Abraham, M. H.; Grellier, P. L.; Nasehzadeh, A.; Walker, R. A. G. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1717.

(14) (a) Lu, J.; Brown, J. S.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2001**, 665–666. (b) Lagalante, A. F.; Bruno, T. J. *J. Phys. Chem. B* **1999**, *103*, 7319. (c) Lagalante, A. F.; Hall, R. L.; Bruno, T. J. *J. Phys. Chem. B* **1998,** 102, 660. (d) Lagalante, A. F.; Wood, C.; Clarke, A. M.; Bruno, T. J. *J. Solution Chem.* **1998**, 27, 887. Abraham, M. H.; Poole, C. F.; Poole, S. K. *J. Chromatogr. A* **1999**, *842*, 79–114. (e) Abraham, M. H.; Le, J. *J. Pharm. Sci.* **1999**, *88*, 868–880. (f) Abraham, M. H.; Chadha, H. S.; Martins, F.; Mitchell, R. C.; Bradbury, M. W.; Gratton, J. A. *Pest. Sci*. **1999**, *55*, 78–88. (g) Platts, J. A.; Abraham, M. H.; Hersey, A.; Butina, D. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 71–80.

(15) (a) McManus, S. P.; Neamati-Mazraeh, N.; Hovanes, B. A.; Paley, S. M.; Harris, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3393. (b) Harris, J. M.; Sedaghat-Herati, M.; Neamati-Mazraeh, N.; Kamlet, M. J.; Taft, R. W.; Doherty, R. M.; Abraham, M. H. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Advances in Chemistry Series No. 215; American Chemical Society: Washington, DC, 1987; pp 247–254.

(16) Grate, J. W.; McGill, R. A.; Hilvert, D. *J. Am. Chem. Soc.* **1993**, *115*, 8577–8584.

(17) McGill, R. A.; Rice, J. K.; Baronavski, A. P.; Owrutsky, J. C.; Lowrey, A. H.; Stavrev, K. K.; Tamm, T.; Zerner, M. C. *Int. J. Quantum Chem. Quantum Chem. Symp.* **1996**, *30*, 1595–1606.

(18) (a) Abraham, M. H.; Doherty, R. M.; Kamlet, M. J.; Harris, J. M.; Taft, R. W. *J. Chem. Soc., Perkin Trans. 2* **1987**, 913. (b) Abraham, M. H.; Doherty, R. M.; Kamlet, M. J.; Harris, J. M.; Taft, R. W. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1097.

(19) Harris, J. M.; Sedaghat-Herati, M. R.; McManus, S. P.; Abraham, M. H. *J. Phys. Org. Chem.* **1988**, *1*, 359.

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

(21) Bentley, T. W.; Bowen, C. T.; Parker, W.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1244.

TABLE 1. Solvation Parameters and CMA Observed and Calculated Rate Constants at 60 °C

no.	solvents	δ_1	π_1^*	α_1	β_1	δ_H^2	log k_{obs}	log k_{calc}
1	water[a]	0.00	1.09	1.17	0.18	5.490	−0.247	−0.388
2	methanol	0.00	0.60	0.93	0.62	2.052	−3.01	−2.88
3	ethanol	0.00	0.54	0.83	0.77	1.621	−3.81	−3.54
4	1-propanol	0.00	0.52	0.78	0.83	1.432	−3.85	−3.81
5	2-propanol	0.00	0.48	0.76	0.95	1.331	−3.98	−4.17
6	1-butanol	0.00	0.47	0.79	0.88	1.295	−3.77	−3.99
7	ethylene glycol	0.00	0.92	0.90	0.52	2.740	−2.31	−2.06
8	TFE[b]	0.50	0.73	1.51	0.00	1.371	−0.195	−0.007
9	HFIP[c,d]	0.50	0.65	1.96	0.00	0.893	1.18	0.943
10	nitromethane	0.00	0.85	0.22	0.25	1.585	−3.30	−3.43
11	dimethylformamide	0.00	0.88	0.00	0.69	1.389	−4.75	−4.71
12	acetonitrile	0.00	0.75	0.19	0.37	1.378	−4.04	−3.94
13	acetone	0.00	0.71	0.08	0.48	0.906	−4.46	−4.51
14	dimethyl sulfoxide	0.00	1.00	0.00	0.76	1.688	−4.46	−4.57
15	acetic acid	0.00	0.64	1.12	0.45	2.035	−2.07	−2.00
16	cyclohexane	0.00	0.00	0.00	0.00	0.980	ND[e]	−5.41

[a] Extrapolated from rates at other temperatures using rates extrapolated to pure water rates; this work. [b] 2,2,2-Trifluoroethanol. [c] Hexafluoro-2-propanol. [d] Estimated by extrapolation of rates of reaction of **CMA** in 97% (w/w) aqueous HFIP measured at other temperatures; ref 21. [e] ND = not determined.

electrodes to determine the pseudo-first-order reaction rate constants.[22] Reaction temperatures were held constant with a thermostated water bath. To provide readily measurable rates, most of the solvolytic experiments were conducted at a temperature in the range of 50−100 °C. For each solvent at each temperature, two or more rate determinations were made. If the difference between the two experimentally measured reaction rates was greater than 10% of the lower value, additional solvolytic experiments were made to improve the statistical confidence in the measured values. Correlation coefficients for all individual rate determinations were 0.995 or higher. Activation parameters were computed after obtaining average reaction rates at two or more temperatures. Measured rate constants and activation parameters are presented in Table 2.

The majority of kinetic experiments were carried out at temperatures in excess of 50 °C. However, for highly polar and hydrogen-bond acidic solvents such as ethylene glycol and trifluoroethanol (TFE), reactions were conducted at lower temperatures due to the high reactivity of **CMA** in these solvents. To improve the validity of rate comparisons, rate constants were determined at two or more temperatures near 60 °C and rate constants for solvolysis at 60 °C were calculated using the Arrhenius equation. In all solvolytic runs, 2,6-lutidine, as a molar equivalent to **CMA**, was added to scavenge the acid produced in the reaction. Without lutidine we observed considerably more scatter of the data points, which could be related to an acid-catalyzed side reaction.

Solvolysis of **CMA** in dimethylformamide (DMF) was also carried out utilizing gas chromatography (GC) to monitor the progress of the reaction. The reaction mixture, contained in a sealed vial, was sampled via a serum cap at intervals and analyzed by GC. The reaction rate was calculated by monitoring the consumption of **CMA** with respect to an internal standard, diphenyl ether. The reaction rates obtained with the GC method were in good agreement with the reaction rates obtained using the conductivity method. The GC method was also used for the solvent cyclohexane. Unfortunately, the cyclohexane reaction was found to be extremely slow even at temperatures up to 100 °C. After failing to obtain a satisfactory pseudo-first-order rate constant, the solvent was dropped from the experimental solvent set. Also, since acetolysis kinetics of **CMA** could not be satisfactorily followed conductometrically, the GC method was utilized to provide rates in the solvent acetic acid. Sodium acetate was added to buffer the acetic acid solutions although other mechanistic roles for acetate cannot be ruled out.

The rates reported for some solvents were determined from extrapolated binary solution data. The solvolysis rate in pure hexafluoro-2-propanol (HFIP) at 60 °C was estimated by extrapolation using rates measured for solvolysis of **CMA** in 97% (w/w) aqueous HFIP.[21] The rate of solvolysis of **CMA** in pure water was obtained by extrapolation of the rates obtained for solvolysis of **CMA** in a range of binary aqueous solvents. Using the Grunwald−Winstein method, estimated conductometric rates at 25 °C and 40 °C in water were obtained by extrapolating to pure water a plot of log k values versus solvent **Y** values[3,4] constructed from conductometric rate constants for solvolysis of **CMA** in binary mixtures of 40%, 50%, 60%, 70%, and 80% aqueous ethanol (v/v), Table 3. To improve confidence levels for the extrapolated value for water, a separate series of kinetic experiments in 50%, 60%, 70%, and 80% aqueous ethanol were carried out at 25 °C by monitoring the spectrophotometric absorption of methyl orange at 525 nm. The solutions were sampled at timed intervals and the data stored automatically by computer. The plot of log k versus Y values provided an extrapolated value for the solvolysis rate of **CMA** in water within 2% of the value obtained conductometrically. Similarly, the rates of solvolysis for **CMA** in 40%, 60%, and 80% aqueous acetonitrile at 25 °C, Table 3, were determined by the spectrophotometric method and plotted to determine an extrapolated rate for **CMA** in pure water at 25 °C. The extrapolated rates of solvolysis of **CMA** in pure water at 25 °C determined separately from aqueous ethanol and aqueous acetonitrile data showed good agreement. Using the extrapolated rates in pure water from the two temperatures, the rate for solvolysis of **CMA** in pure water at 60 °C, which was

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[22] Hovanes, B. A.; Harris, J. M.; McManus, S. P. *Am. Lab.* **1984**, *16*, No. 6, 22.

TABLE 2. Conductometric Rate Data for Solvolysis of 2-Chloro-2-methyladamantane in Pure Solvents

solvent	T (°C)	k (s^{-1})	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
methanol	50.0	$(3.85 \pm 0.04) \times 10^{-4}$		
	60.0	$(9.70 \pm 0.17) \times 10^{-4}$	18.8	−16.2
	65.0	$(1.47 \pm 0.04) \times 10^{-3}$		
ethanol	50.0	$(5.33 \pm 0.54) \times 10^{-5}$		
	55.1	$(9.55 \pm 0.04) \times 10^{-5}$		
	65.0	$(2.86 \pm 0.06) \times 10^{-5}$	22.9	−7.33
	70.0	$(3.91 \pm 0.07) \times 10^{-5}$		
	75.0	$(8.25 \pm 0.06) \times 10^{-4}$		
1-propanol	50.0	$(6.19 \pm 0.59) \times 10^{-5}$		
	65.0	$(2.09 \pm 0.12) \times 10^{-4}$	17.0	−25.3
	75.0	$(4.47 \pm 0.23) \times 10^{-4}$		
2-propanol	49.9	$(3.95 \pm 0.10) \times 10^{-5}$		
	59.8	$(8.90 \pm 0.01) \times 10^{-5}$	22.0	−11.0
	74.3	$(4.58 \pm 0.09) \times 10^{-4}$		
1-butanol	65.1	$(2.52 \pm 0.03) \times 10^{-4}$		
	75.0	$(5.57 \pm 0.17) \times 10^{-4}$		
	75.1	$(4.93 \pm 0.02) \times 10^{-4}$	15.8	−28.6
	85.0	$(1.04 \pm 0.01) \times 10^{-3}$		
	90.0	$(1.32 \pm 0.32) \times 10^{-3}$		
nitromethane	34.8	$(4.10 \pm 0.06) \times 10^{-5}$		
	50.1	$(2.46 \pm 0.01) \times 10^{-4}$	18.9	−17.1
	60.0	$(4.36 \pm 0.08) \times 10^{-4}$		
dimethylformamide[a]	59.9[b]	$(1.68 \pm 0.01) \times 10^{-5}$		
	69.8[b]	$(3.66 \pm 0.13) \times 10^{-5}$		
	79.4	$(9.73 \pm 0.05) \times 10^{-5}$	17.0	−29.8
	89.3	$(1.38 \pm 0.05) \times 10^{-4}$		
	95.3	$(2.26 \pm 0.06) \times 10^{-4}$		
	104.4	$(4.13 \pm 0.05) \times 10^{-4}$		
acetonitrile	56.6	$(1.00 \pm 0.01) \times 10^{-4}$		
	69.9	$(1.48 \pm 0.01) \times 10^{-4}$	15.8	−29.8
	89.9	$(7.57 \pm 0.24) \times 10^{-4}$		
DMSO	65.0	$(5.65 \pm 0.01) \times 10^{-5}$		
	79.9	$(1.97 \pm 0.01) \times 10^{-4}$	20.2	−18.7
	89.9	$(4.79 \pm 0.09) \times 10^{-4}$		
ethylene glycol	25.1	$(1.43 \pm 0.09) \times 10^{-4}$		
	34.9	$(6.07 \pm 0.05) \times 10^{-4}$	18.6	−13.6
	45.1	$(45.1 \pm 0.20) \times 10^{-3}$		
2,2,2-trifluoroethanol	25.1	$(3.94 \pm 0.47) \times 10^{-3}$		
	34.9	$(6.07 \pm 0.28) \times 10^{-3}$	14.9	−14.8
	45.1	$(1.09 \pm 0.20) \times 10^{-3}$		
acetone	80.1	$(1.23 \pm 0.24) \times 10^{-4}$		
	85.1	$(1.89 \pm 0.12) \times 10^{-4}$	16.1	−30.7
	90.0	$(4.38 \pm 0.27) \times 10^{-4}$		
	105.3	$(6.24 \pm 0.07) \times 10^{-4}$		
water[c]	25.0	$(4.73 \pm 0.09) \times 10^{-2}$		
	40.0	1.12×10^{-1}	16.2	−11.3
acetic acid[d]	40.0	$(4.73 \pm 0.09) \times 10^{-3}$		
	60.0	$(8.51 \pm 0.47) \times 10^{-3}$	5.44	−51.9

[a] Combination of rates determined by conductivity and by gas chromatography. [b] Rates determined using conductivity measurements. [c] Rates obtained by extrapolation to pure water using the Grunwald−Winstein method of rates of **CMA** in aqueous ethanol and aqueous acetonitrile (25 °C only). [d] Rates determined using gas chromatography.

TABLE 3. Rates of Solvolysis of CMA in Binary Aqueous Solvents

solvent	T (°C)	$10^4 k$, s^{-1}
100% EtOH	25	0.0245 ± 0.002
80% aq EtOH (v/v)	25	1.45 ± 0.16
70% aq EtOH (v/v)	25	3.63 ± 0.05
60% aq EtOH (v/v)	25	12.0 ± 0.7
50% aq EtOH (v/v)	25	29.5 ± 2.8
40% aq EtOH (v/v)	25	51.0 ± 3.8
100% MeCN	25	0.0309 ± 0.002
60% aq MeCN (v/v)	25	8.71 ± 0.21
40% aq MeCN (v/v)	25	32.4 ± 2.4
30% aq MeCN (v/v)	25	47.9 ± 2.9
100% EtOH	40	0.141 ± 0.012
80% aq EtOH (v/v)	40	2.45 ± 0.20
60% aq EtOH (v/v)	40	79.3 ± 1.6
50% aq EtOH (v/v)	40	113 ± 22

needed for the MLRA, was obtained by extrapolation. These estimates are shown in Table 2.

Products of Reaction of CMA in Pure Solvents. Shiner et al.[20] determined the products of solvolysis of **CMA** in 50%, 70%, and 80% aqueous ethanol finding 7%, 25%, and 33% elimination, respectively, to 2-methyleneadamantane (**MA**). 2-Hydroxy-2-methyladamantane (**HMA**) and 2-ethoxy-2-methyladamantane (**EMA**) were also products with their amounts dependent on the solvent composition. As expected, the amount of **HMA** increased with increasing water content of the solvent. Since **CMA** is sterically incapable of undergoing backside solvolytic displacement, the substitution product must form by frontside displacement, probably involving solvent-separated ion pairs.[23] We determined the products of reaction of **CMA** in some pure solvents by GC−MS analysis. As one might predict, in polar aprotic solvents, the product of elimination (**MA**) is the sole product

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[23] For example, see Adcock, W.; Trout, N. A.; Vercoe, D.; Taylor, D. K.; Shiner, V. J., Jr.; Sorensen, T. S. *J. Org. Chem.* **2003**, *68*, 5399.

TABLE 4. Regression Results for Reaction of CMA at 60 °C[a]

step	regression information	log k_0	π_1^*	α_1	β_1	δ_1	δ_H^2
1	15, all parameters	−5.374	2.084	2.409	−1.753	(0.408)	(0.039)
	T-test	0.9999	0.9772	0.9999	0.9995	0.2972	0.2057
		overall corr coefficient		0.996			
		std deviation		0.209			
2	15, exclude *h* $(d_H^2)_1$	−5.466	2.257	2.487	−1.761	(0.174)	
	T-test	1.0000	0.9998	1.0000	0.9998	0.2492	
		overall corr coefficient		0.996			
		std deviation		0.199			
3	15, exclude *h*, δ_H^2, $d\delta_1$	−5.409	2.219	2.505	−1.823		
	T-test	1.0000	0.9999	1.0000	0.9999		
		overall corr coefficient		0.996			
		std deviation		0.191			

[a] Values in parentheses are not statistically significant at 95% confidence levels.

TABLE 5. Regression Results Obtained by Sequentially and Randomly Deleting One Solvent Set at a Time[a]

step	solvent set size	log k_o	π_1^*	α_1	β_1	overall corr coeff	SD in calcd log *k* values
3	15	−5.409	2.219	2.505	−1.823	0.996	0.191
		(1.0000)	(1.0000)	(0.9999)	(1.0000)		
4	14	−5.388	2.265	2.485	−1.913	0.996	0.187
		(0.9999)	(1.0000)	(0.9999)	(1.0000)		
5	13	−5.273	2.200	2.495	−2.043	0.996	0.180
		(1.0000)	(0.9999)	(1.0000)	(1.0000)		
6	12	−5.083	2.098	2.438	−2.157	0.996	0.182
		(1.0000)	(0.9996)	(1.0000)	(0.9999)		
7	11	−4.195	1.913	2.393	−2.181	0.996	0.189
		(0.9999)	(0.9952)	(1.0000)	(0.9998)		
8	10	−4.919	1.921	2.392	−2.187	0.996	0.204
		(0.9998)	(0.9891)	(0.9999)	(0.9994)		
9[b]	14	−5.416	1.941	2.441	−1.884	0.995	0.190
		(1.0000)	(0.9986)	(1.0000)	(1.0000)		

[a] Values in parentheses indicate the calculated probability of nonrandom occurrence (T-test). [b] Obtained by excluding water from the regression analysis.

observed. Although we were unable to obtain a good rate for the solvolysis of **CMA** in cyclohexane, we determined the sole observable product of its reaction to be **MA**.

Reaction products were not determined for all of the solvents studied because the available data provided good information about the nature of the products and, to some extent, how they may have formed. Furthermore, there is no compelling evidence to indicate that the product-forming step in the reaction sequence influences the kinetics of the reaction and, hence, the application of solvation eq 1.

Application of Solvation eq 1 to CMA. The KAT solvation equation was used to correlate the solvolysis rates of **CMA** at 60 °C in pure solvents. MLRA was used to analyze the log *K* values in terms of their dependence on the solvent solubility properties. The resulting regression coefficients were considered statistically important if application of the student's T-test produced a value greater than 0.99.[13,18] In the present work, we found that coefficients either give T-tests of better than 0.99 or less than 0.70, indicating confidence levels of >99% and <70%, respectively. Therefore, decisions regarding statistical significance are not controversial. We find that only three solvent parameters are statistically significant at the 99% confidence level for the **CMA** solvolyses. Results of the multiparametric analysis are summarized in Tables 4 and 5.

We completed our analysis of the **CMA** data as follows. The first attempted MLRA, step 1, Table 4, was obtained using all 15 solvents and by including all the solvent parameters from eq 1. Notice that the coefficients for δ_1 and δ_H^2 are not statistically significant so it is reasonable to eliminate these variables from the solvation equation and repeat the MLRA. However, we do so by deleting the parameters sequentially and repeating the regression analysis. After the elimination of the term for δ_H^2 the rerun MLRA, shown in step 2, Table 4, is little changed from the result of step 1 but the overall standard deviation is slightly improved. Again the term for δ is statistically insignificant. The MLRA is again repeated after deleting δ, in step 3, Table 4. After this iteration there is little change in the magnitude of the coefficients but the regression quality was further improved. This results in eq 2:

$$\log k = -5.409 + 2.219\pi_1^* + 2.505\alpha_1 - 1.823\beta_1 \qquad (2)$$

This result is the most suitable solvation equation for modeling the solvolysis rates of **CMS** in all the solvents studied. The regression correlation coefficient is 0.996 and the standard deviation for calculated log *k* values is 0.19. Considering the magnitude of log *k* values, which include rate constants over a range of about 6 orders of magnitude, and the inherent errors associated with the experimental measurements, and the extrapolated processing of some data, the statistical quality of solvation eq 2 is excellent. The solvation rate eq 2 indicates that dipolar and hydrogen-bond acidic solvents significantly accelerate the solvolysis reaction of **CMA** whereas hydrogen-bond basic solvents retard the reaction. No significant dependence on a cavity effect is observed.

To evaluate the size and quality of the solvent set, the MLRA for solvation eq 1 was repetitively carried out by randomly deleting one solvent at a time. This process was repeated until the solvent set was reduced to 10 solvents. The resulting regression equations (steps 4−8) can be written from the data in Table 5 and indicate that there is very little change in the regression coefficients or the quality of the regression as indicated by the student T-test results, the overall correlation coefficient, and overall standard deviation. As a final test of the MLRA the data for water was excluded. Water has the largest π_1^* value and by far the largest δ_H^2 value and as a result could dominate a regression analysis. The resulting solvation equation (from data in Step 9) is again little changed from eq 2, which utilizes the full set of solvents available.

Another important factor is the choice of solvent set in the experimental design. We sought to use a wide range of solvents and solvent types to provide as wide a range in solvent−solute interactions as possible. Indeed, for statistically meaningful results, the cross correlation between the different variables, i.e., the solvent solubility parameters, must not be significant. For the full solvent set, none of the parameters are correlated with coefficients higher than 0.48. In addition, we sought to include solvents that would provide experimentally measured variables, k values, which maximized the range used in the MLRA. By the careful adoption of some rates extrapolated from those measured at other temperatures, experimental rate constants covering approximately 6 orders of magnitude were included. Ultimately, it appears that the experimental design, including the choice of solvent set, is sound and the statistical quality of the regression is excellent. Thus, a plot of experimentally determined log k and calculated log k values, using eq 2, Figure 1, illustrates the quality of the regression. As a result of the extended data set, the resulting solvation equation has provided chemically reasonable conclusions.

The resulting solvation eq 2 can now be used to calculate reaction rates for solvents that were not used and those for which it was difficult to get experimental data. The calculated rate for the solvolysis of **CMA** in cyclohexane at 60 °C gives a log k value of −5.409. This indicates that the reaction rate in this solvent is about an order of magnitude slower than the slowest reaction rate for which useful experimental data was obtained. It is perhaps, in hindsight, not surprising that during our experimental efforts to determine rate data in cyclohexane, difficulties were found in collecting reproducible or reliable data.

Mechanistic Significance of the Correlation. To place in perspective the mechanistic significance of our multiparameter correlation of **CMA**, it is useful to consider some other examples using solvation eq 1 for solvolysis studies. In fact, few examples exist, but fortunately one of them is a comprehensive solvolytic study of **TBC** at 25 °C in 21 pure solvents.[18b] The correlation for **TBC** is

$$\log k = -14.6 + 5.10\pi_1^* + 4.17\alpha_1 + 0.73\beta_1 + 0.48\delta_H^2 \quad (3)$$

Significantly, the solvolysis of **TBC** requires four parameters, whereas the solvolysis of **CMA** is correlated using only three parameters. The cavity term is not statistically significant with **CMA** while its significance is statistically justified for **TBC**. The term with δ_H^2 models any change attributed to the solvent cavity during the rate determining step of the reaction. In the solvolytic reactivity of aliphatic chlorides, the rate determining step is very likely to correspond to ionization to form the carbocation/chloride ion pair. The implication for a lack of dependence in the cavity term for the solvolysis of **CMA** is that there is no significant change in spatial size of the molecule during the rate-determining step of the reaction. This is in direct contrast to results obtained for **TBC**. Of course, upon ionization, **TBC** can lead to a flattened (planar) carbocation, something that is impossible with the rigid adamantane structure. Abraham et al.[24] have indicated that for **TBC** the minor accelerating effects of solvent cohesive energy density can be explained by the electrostriction of surrounding solvent molecules by the dipolar transition state. For **CMA** we could infer that the transition state is less dipolar reducing such effects to an inconsequential amount. Such might be the case if the **CMA** solvolysis transition state involves formation of a tight or intimate ion pair of the carbocation and chloride ion this could account for the cavity terms results. However, we will consider the possibility that the medium effects in these reactions may be temperature-dependent making a comparison of two substrates studied at different temperatures risky.

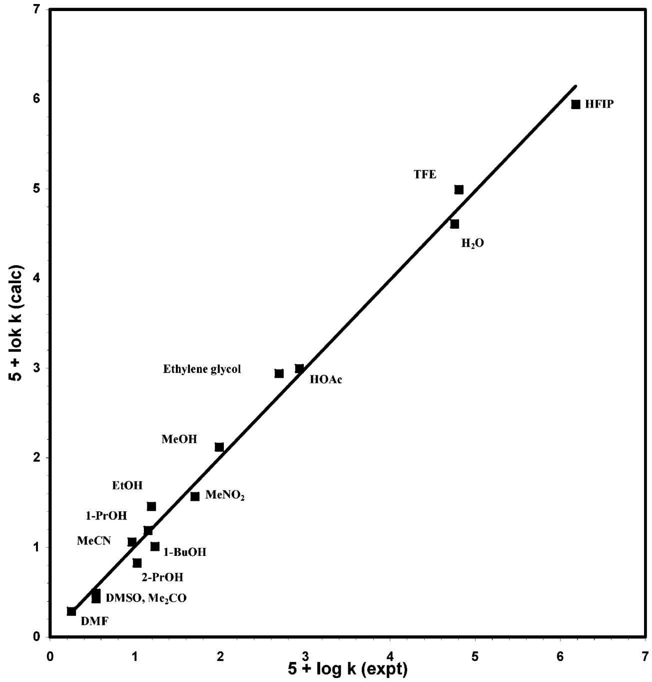

FIGURE 1. Plot of log k experimental rate constants versus log k calculated rate constants for the reaction of 2-chloro-2-methyladamantane (CMA) in aprotic and protic solvents at 60 °C; $r = 0.996$.

In general, when considering that the reaction rates for **CMA** were determined at 60 °C and those for **TBC** were determined at 25 °C it is not surprising that the rates are generally higher for **CMA** as indicated by the higher log k_o value. It is also not surprising that the

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[24] Harris, J. M. *Prog. Phys. Org Chem. Vol.* **1974**, *11*, 89−173.

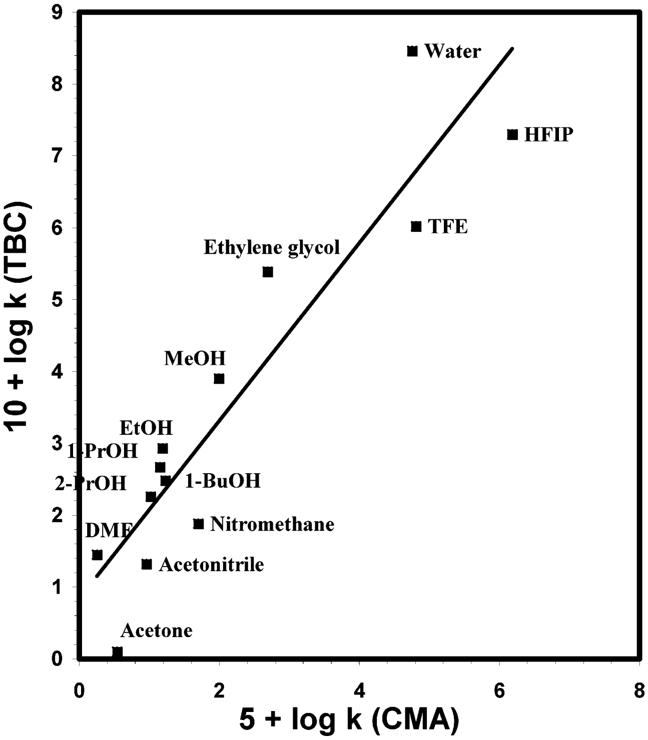


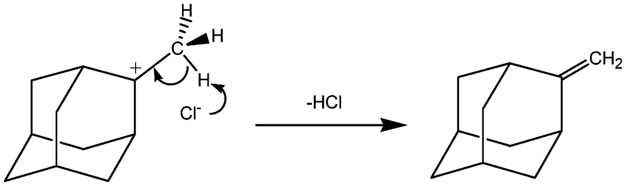
FIGURE 2. Plot of log k_{CMA} (60 °C) versus log k_{TBC} (25 °C);[17] $r = 0.924$.

dependence on the dipolarity and hydrogen-bond acidity is less because at elevated temperatures intermolecular forces are considerably reduced. However, since both the **TBC** and **CMA** correlations were highly correlated even though many rates were extrapolated from rates determined at temperatures other than 25 and 60 °C, respectively, there is no compelling evidence that a significant mechanistic change occurred with either substrate over this modest temperature range. A referee suggested extrapolation of the **CMA** data to 25 °C to allow a better comparison with TBC. While we appreciate the desire to do this, we believe that this approach would risk extrapolation errors that would potentially weaken the correlations and thus hinder the comparison.

The most significant difference between the two solvation equations, (2) and (3), is the magnitude and sign of the coefficient for the solvent hydrogen-bond basicity. This is strong evidence that the reaction pathway is markedly different for **CMA** and **TBC**. That the two alkyl chlorides indeed behave differently is simply demonstrated by the correlation of the rates of one substrate against those of the other. The least squares treatment of the correlation of log k_{TBC} versus log k_{CMA}, shown graphically in Figure 2, is relatively poor, indicative of mechanistic differences.

The relatively small a and s coefficients for solvolysis of **CMA** ($a = 2.51$ and $s = 2.22$), when compared with the corresponding coefficients for the solvolysis of **TBC** measured previously ($a = 4.17$ and $s = 5.10$), are probably not fully explained by temperature differences for the reaction data. It has been previously argued that the magnitude of the a and s coefficients for **TBC** suggests that there is significant charge separation in the transition state.[18b] The charge separation has been approximated at about 0.80−0.84 (1.0 = total separation) in polar solvents and thus the transition state species is, by this determination, highly dipolar. Assuming that the large charge separation of the transition state in **TBC** is correct, our data suggests significantly less charge development in the transition state for the solvolysis of **CMA**. In physical terms, one could suggest that, in the transition state, **CMA** appears to produce tight or intimate ion pairs while **TBC** gives either more highly disassociated (loose) ion pairs or solvent-separated ion pairs. As we discuss below, there is other data that agrees with this interpretation.

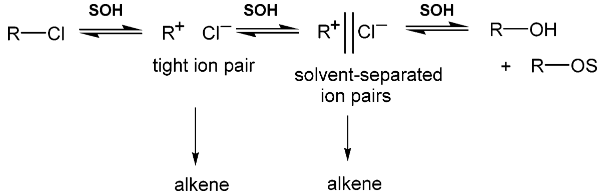
SCHEME 2. Representation of Elimination from the Tight Ion Pair



Shiner and co-workers[20] have studied **CMA** and its α and β (CD_3) deuterated derivatives in a few binary solvent mixtures including 50%, 70%, and 80% aqueous ethanol. They added the relevant data for **CMA** and its relevant analogues into a previously linear correlation found between the log k the rate effect of α-methyl substitution for α-H in carbocationic reaction processes and the logarithms of the rate effect of α-methyl deuteration. The β-d_3 isotope effect found in 50% aqueous ethanol is close to that predicted by the correlation line while the values for 70% and 80% aqueous ethanol fall off the line. Further, in 50% ethanol, **CMA** yielded only 7% elimination products, while in 70% and 80% aqueous ethanol, increasing fractions of elimination were found to be associated with increasing β-d_3 rate effects. Shiner interpreted these data as indicating that at least some fraction of the reactant substrate reacts with rate-determining elimination from a tight ion pair with the chloride ion acting as the base, as shown in Scheme 2. In their aqueous ethanol solutions the fraction proceeding by this pathway is suggested to be up to 33% of the reaction. However, their data and conclusion explicitly requires that most of the reaction is *not* proceeding by rate-limiting elimination.[20]

Our results are consistent with Shiner's conclusion that a tight ion pair is involved. It is significant to recall that our results are *inconsistent* with the involvement of solvent in a rate-limiting elimination pathway. If rate-limiting elimination were occurring, one would anticipate that solvents with enhanced basic or nucleophilic character (i.e., those with higher β values) would speed the reaction. In this scenario, a positive value for β would be expected. However, in solvation eq 2 for **CMA** the large negative coefficient for β_1 (−1.823) indicates that the rate of reaction of **CMA** *decreases* with increasing solvent hydrogen-bond basicity. This indicates that the solvent *is not* involved in a rate-limiting elimination pathway. As pointed out above, however, Shiner's conclusion was that chloride ion, and not the solvent, was acting as the base. Since the AKT correlation is focused on the various roles of the solvent, it is probable that the correlation is unable to directly elucidate the role of the chloride ion in the mechanism of the reaction.

SCHEME 3. Mechanistic Scheme for the Reaction of CMA



Bentley and co-workers[21] have studied solvolysis of CMA in 97% aq hexafluoro-2-propanol (HFIP) at various temperatures and reach conclusions totally in agreement with those drawn from our correlations. They too suggest that reaction in HFIP proceeds via the rate-determining formation of tight (contact) ion pairs. If the mechanism for solvolysis of **CMA** involves the formation of tight ion pairs, one would expect that solvents with stronger hydrogen-bond basicity would slow the reaction because the solvent could compete with the chloride ion for stabilization of the carbocation. Of course, one could argue that **CMA** could minimize the need for stabilization of the chloride ion by crossing over to a mechanism, i.e., rate-limiting elimination, where the chloride ion attacks a β-H as ionization occurs. Although solvent hydrogen-bond basicity is not indicated in the rate-determining step, the more basic solvents, by their competition with the chloride ion, may promote chloride ion-induced elimination.

Based on our data and previous studies, the reaction of **CMA** seems to follow the mechanistic scheme diagrammed in Scheme 3. The rate-determining step for the reaction of **CMA** is the first or ionization step, which leads to the formation of tight ion pairs. After the transition state is reached, other intermediates, such as solvent-separated ion pairs and free ions, may form if the particular solvent stabilizes the separated ions.

Substitution may only occur from the solvent-separated ion pairs or from free ion pairs, if they form. If SOH in Scheme 3 is a binary aqueous hydroxylic solvent, a mixture of products may form, as shown. Elimination may occur from either intermediate species with it likely occurring from the tight ion pair when solvents of low polarity are used. In nonpolar solvents like cyclohexane, very little charge development is likely and the elimination reaction may be concerted or nearly so. This suggestion is not inconsistent with our conclusion that the rate-detemining step for the solvolytic reactions studied is from the formation of a tight ion pair since the extent of carbon−chlorine bond breaking is expected and shown to be dependent on the solvent.

Since all of the solvent types chosen provide rate constants that fit solvation eq 2, we can assume that the transition-state formation is the same process being modeled for all the solvents studied. However, note that the hydroxylic solvents studied, but not the non-hydroxylic solvents, give both substitution products and the elimination product. Therefore, the products clearly occur from different intermediates and by different mechanisms. The substitution products must occur in a reaction step after the transition step since solvent insertion between the ions must occur.

Conclusions. The KAT solvation equation developed is a very powerful technique for correlating the reaction rate kinetic data obtained for the reaction of **CMA** in a wide range of solvents. With a set of fifteen solvents including protic and aprotic solvents, the overall correlation coefficient was excellent. The solvation equation for the solvolysis of **CMA** at 60 °C allows further values to be calculated for a wide variety of solvents not studied, but for which the relevant solvent parameters are available.

The KAT solvation equation provides chemical insight into the behavior of the reactant substrate, although care has to be taken in interpreting the individual regression terms. There is an obvious advantage in comparing similar substrates such as **TBC** and **CMA**, which show significant differences in their behavior from similar solvent sets. Adding additional reaction types, such as 2-adamantyl derivatives, which are thought to involve rate-limiting formation of solvent-separated ion pairs,[23] would add to the confidence of using this method mechanistically.

From our analysis of the solvolysis of **CMA** in fifteen solvents having wide ranging properties, we conclude that the solvolytic rate-determining step is the ionization step. Since there appears to be a relatively moderate amount of charge separation in the transition state, we can conclude that the principal intermediate formed is a tight or intimate ion pair. In the more polar solvents, and especially in the alcoholic solvents which are known to stabilize solvent-separated ion pairs,[24] the insertion of solvent molecules, after the transition state is reached, is anticipated. These results demonstrate why the uses of simple solvolytic correlation methods are invalid even for comparisons of tertiary chlorides. Also, these results suggest a greater reliability in the use of multiple linear regression analysis for predicting solvolytic rates in additional solvents.

Experimental Section

Reagents. All reagents and reaction solvents were purchased from standard sources. **CMA** was prepared from 2-methyl-2-adamantanol in 82% yield.[20] Recrystallization from hexane yielded pure **CMA**, mp 174−175 °C (lit.[20] 176−176.5 °C).

Solvolytic Reaction Solvents. The solvents, which were unavailable in their highest purity form, were carefully purified by distillation.[25,26] All solvents were desiccated under dry nitrogen prior to use.

Instrumentation. ^{1}H NMR spectra were obtained with an IBM 200 MHz, high-resolution NMR spectrometer. All the conductometric kinetic data were measured using an automated system consisting basically of the following components: a data acquisition unit, a microcomputer, and a conductivity bridge. Spectrophotometric data was collected using a UV−vis spectrophotometer fitted with a programmable cell changer and the associated software and a personal computer system for system control and data storage. A gas chromatograph fitted with a 25 m × 0.2 mm OV-101 column and equipped with either a flame ionization detector or a mass selective detector was used for all gas chromatographic and GC−MS measurements.

Kinetic Measurements. The kinetic data were obtained by the various methods described below. All of the kinetic runs were followed through at least one half-life and in most cases

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(25) Vogel, A. I. *Practical Organic Chemistry*; Wiley: New York, 1956.

(26) Riddick, J. A.; Toops, Jr. *Organic Solvents; Physical Properties and Methods of Purification*, 2nd ed.; Weissberger, A., Ed.;Techniques of Organic Chemistry, Vol. 7; Interscience Publishers: New York, 1955.

through more than 1.5 half-lives. The typical concentrations of reactant substrate and 2,6-lutidine were 10^{-3} M. The required amounts were weighed on a 4-figure electronic balance and the appropriate solvent was added to prepare the solutions in either 25 or 50 mL volumetric flasks. A conductivity method, previously described in detail,[22] was employed unless otherwise stated. The cells were filled until the electrodes were covered and then were sealed either by rubber caps or glass. The cells were placed in an oil bath and the leads were connected to an electrometer and the data collection system. The conductance was measured at specific times by means of a computer-actuated conductivity bridge. The conductivity data were analyzed by entering them into a computer program, **LSKIN**, to allow computation of the rate constant and to obtain calculated infinity values and correlation coefficients. The temperature of the bath was recorded for each measurement and the average temperature was computed for the run. Three or more cells were normally used to determine the rate constant at a temperature for each solvent. Multiple temperatures were used to allow computation of activation parameters and for extrapolation of rates to a single temperature for rate comparisons.

Since the conductometric method was found to be unacceptable for acetic acid solutions, a GC method was employed to follow the acetolysis of **CMA**. Aliquots of approximately 1 mL, ca. 10 M in reactant substrate, were sealed into ampules and placed in an oil bath. In the two acetolysis experiments, two different temperatures were chosen to monitor the reactions, 80 ± 0.05 °C and 100 ± 0.05 °C. The tubes were removed at timed intervals and quenched in an ice-bath. The contents of these ampules were then analyzed by GC–MS. After analysis the ampules were returned to the thermostated oil bath.

Kinetics of **CMA** in aqueous acetonitrile and aqueous ethanol solutions were determined at 25 °C using an automated spectrophotometric kinetics system previously described in detail.[27] The reactions were followed by observing the change in the methyl orange absorbance at 525 nm.

Product Analysis. Using a GC–MS with an injector temperature of 130 °C and a programmed column temperature (70–120 °C at 10°/min), the products of some of the reactions were determined using solvolytic reaction mixtures held at an appropriate temperature to provide at least five reaction half-lives. For the solvents, acetone, DMF, and cyclohexane only 2-methyleneadamantane was determined as the solvolytic product.

Acknowledgment. We gratefully acknowledge the financial support provided by the National Science Foundation (CHE-8719885) and the U.S. Army Research Office (DAAL03-92-G-0393).

JO049798L

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[27] Hovanes, B. A.; Sedaghat-Herati, M. R.; Harris, J. M.; McManus, S. P. *Am. Lab.* **1986**, *17* (3), 52.