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Evaluation of Nonlinear Ethanol-Trifluoroethanol Correlations for Mustard Chlorohydrin and Other Anchimerically Assisted Alkyl Substrates

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In an effort to understand why mustard chlorohydrin (1) gives a nonlinear plot of log k versus Y_{Cl} for solvolysis in aqueous ethanol (EtOH) and aqueous trifluoroethanol (TFE), we have constructed similar plots for several analogues. Each of the new substrates has been demonstrated to react with neighboring-group participation and to be insensitive to solvent nucleophilicity. Despite these mechanistic similarities, both linear and nonlinear plots are observed. 2-(Methylthio)ethyl chloride (2) is similar in structure to 1, without the hydroxyl group, yet both 1 and 2 give nonlinear TFE-EtOH plots; therefore, the hydroxyl group in 1 is not responsible for the nonlinear TFE-EtOH plot. The other chlorides give essentially linear correlations, although the data point for the rate in pure TFE for 2-(phenylthio)ethyl tosylate falls significantly above the line and the TFE data give a negative slope. Substrate dimerization is shown not to be a factor in the nonlinear plot of 2. Also, there is no evidence to support an earlier suggestion that neighboring-group desolvation is a factor in the nonlinear plots for 1 and 2. The nonlinear correlation with substrates 1 and 2 may be attributed to a difference in the return of free ions or ion pairs when comparing the substrates and 1-adamantyl chloride, the model for Y_{Cl}. Our previous suggestion that the TFE-EtOH correlation failure for 1 results from 1 and 1-adamantyl chloride having different sensitivities to electrophilicity is consistent with the explanation put forth here. Although we have dealt with correlation of substrates in aqueous TFE, aqueous acetone, and aqueous EtOH, these results are significant in relation to the general use of the Grunwald-Winstein equation for correlation of solvolytic rates.

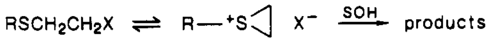
Several years ago Raber, Harris, and co-workers[1] described a method for detecting nucleophilic solvent assistance in solvolytic reactions by considering the responses of model unimolecular substrates (k_c or k_Δ reactions) and model bimolecular substrates (k_s reactions) to changes in water concentration in aqueous trifluoroethanol (TFE) and aqueous ethanol (EtOH). Their study assumed that k_c and k_Δ substrates obey the Grunwald-Winstein equation,[2-7] eq 1, and that k_s substrates obey the extended form of the equation, which applies to systems sensitive to solvent nucleophilicity,[8] eq 2.

$$\log k/k_0 = mY \qquad (1)$$

$$\log k/k_0 = mY + lN \qquad (2)$$

In the Raber-Harris method, one analyzes a plot of solvolysis rates (log k) of a substrate against those of 1-adamantyl bromide in aqueous ethanols (or acetones) and trifluoroethanols. From studies of several substrates, a single correlation line was found for substrates that react by k_c and k_Δ mechanisms, while separate aqueous ethanol and aqueous trifluoroethanol correlations were observed for k_s substrates. The method was also found to give excellent predictions for several well-understood reactions, and upon application to controversial substrates,[9] predictions were made that agreed with a large body of data. Since then the TFE-EtOH probe has been used by several groups[10] and is generally recognized as a reliable tool for detecting nucleophilic solvent participation. We now describe a general problem with this method.

Scheme I



1-3 4-6

1 and 4: R = $HOCH_2CH_2$; X = Cl
2 and 5: R = Me; X = Cl
3 and 6: R = Ph; X = Cl; OTs

Results and Discussion

Failure of the Trifluoroethanol-Ethanol Probe. Mustard chlorohydrin (1) has been considered a classic example of a substrate that undergoes hydrolysis with anchimeric assistance by sulfur, a k_Δ process, to give a cyclic sulfonium ion 4, which is rapidly hydrolyzed, Scheme I.[11] However, as we reported in a preliminary communication,[12] a plot of the rates of 1 in aqueous EtOH, aqueous acetone, and aqueous trifluoroethanol (Table I and Figure 1) by the method of Raber and Harris reveals two separate correlations. This type of plot is typical of substrates that undergo solvolysis with solvent participa-

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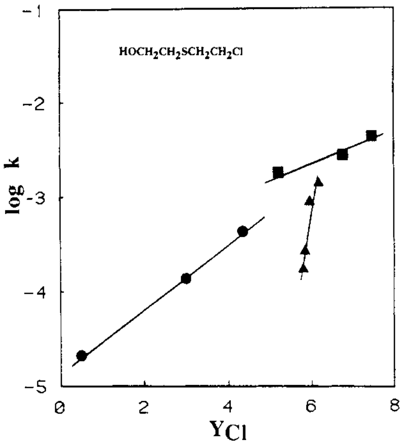

Figure 1. Plot of log *k* versus 2 + Y_{Cl} for 1 (TFE = ▲, EtOH = ●, acetones = ■).

tion. Unfortunately, the mechanistic assignment in this case is wrong. Bartlett and Swain[13] showed that highly nucleophilic anions, such as thiophosphate ion, produce no increase in the rate of chloride ion displacement from 1. Also, we have carried out extensive studies with external neutral nucleophiles (the thiourea probe) and demonstrated that external nucleophiles are not involved in the displacement of chloride from 1 (Scheme I).[14] NMR experiments on substrates specifically labeled with deuterium provide compelling evidence for the neighboring group assisted pathway. For example, upon solvolysis in aqueous acetone, the bis(dinitrophenolate), $S(CH_2CD_2ODNP)_2$, undergoes stepwise scrambling of the two deuterium labels. The process, which is readily followed by ^1H NMR, is completely consistent with cyclic sulfonium ion formation in the stepwise solvolytic displacement of each dinitrophenolate leaving group.[12]

In applying the TFE–EtOH probe to 1, care was taken to use at least some aqueous alcohol and acetone mixtures with *Y* values similar to those of the aqueous TFE's. Also, to avoid the problems that different leaving groups may introduce with these correlations,[15] Y_{Cl} values[7a] were used for Figure 1. Because the method clearly predicts the wrong mechanism for 1, we have conducted a study to uncover the cause of this disparity.

Table I. Solvolytic Rates for Selected Substrates at Designated Temperatures in Various Solvents

substrate	solvent[a,b]	temp, °C	10^4k, s^{-1}
$HOCH_2CH_2SCH_2CH_2Cl$, 1	100E	25.0	(2.09)[c,d]
	80E		1.42[d]
	60E		4.41[d]
	30A		18.2 ± 0.6
	20A		27.2 ± 0.4
	5A		42.0 ± 0.1
	100T[e]		1.70 ± 0.03
	97T		2.57 ± 0.10
	70T		8.58 ± 0.34
	50T		13.2 ± 0.1
$PhSCH_2CH_2Cl$, **3-Cl**	80E	50.1	0.741 ± 0.014
	60E		2.06 ± 0.07
	40E		8.46 ± 0.54
	97T		6.22 ± 0.52
	70T		10.6 ± 0.1
	50T		14.8 ± 0.8
$PhSCH_2CH_2OTs$, **3-OTs**	100E	25.0	0.959 ± 0.015
	80E		5.51 ± 0.01
	60E		15.2 ± 0.2
	40E		63.0[f]
	100T		101 ± 1
	97T		76.4 ± 3.9
	70T		77.1 ± 5.6
	50T		66.4 ± 8.9
$PhSeCH_2CH_2Cl$, **7**	80E	0.0	0.880[g]
	70E		1.12
	50E		3.97 ± 0.18
	40E		7.97 ± 0.03
	97T		9.43[h]
	70T		11.5 ± 0.6
$Ph_2PCH_2CH_2CH_2Cl$, 8	80E	110.0	0.36 ± 0.13
	70E		0.47 ± 0.13
	60E		1.21 ± 0.40
	50E		3.14 ± 1.9
	40E		3.95 ± 2.9
	97T		(6.58)[i]
	70T		(9.33)[j]
	50T		(8.31)[k]

[a] 50–70A = 50%–70% aqueous acetone (v/v), 50–95E = 50%–95% aqueous ethanol (v/v), 50–97T = 50%–97% aqueous trifluoroethanol (w/w), and 20–90TE = rates in mixtures of trifluoroethanol and ethanol (v/v). [b] Unless otherwise stated, Y_{Cl} and Y_{OTs} values are from ref 7. [c] Extrapolated from the nonlinear Arrhenius plot at 24.5, 53.0, 67.9, and 75.4 °C. [d] McManus, S. P.; Yorks, K.; Neamati-Nazraeh, N.; Harris, J. M. *Polym. Preprints* (*ACS Polym. Div.*) **1985**, *26*, No. 2, 265. [e] Y_{Cl} (2.79) was calculated from rates of 1-adamantyl chloride in the appropriate solvent and that in 80E (ref 7a). Rates for 1-adamantyl chloride at 25 °C were extrapolated from rates at higher temperatures. [f] Extrapolated from the rates of the *p*-methoxybenzenesulfonate (k = (4.69 ± 0.31) × 10^{-3} s^{-1}) and the benzenesulfonate (k = (1.04 ± 0.04) × 10^{-2} s^{-1}). [g] Rate from ref 25. [h] Extrapolated from rates at other temperatures: 0.3 °C, (9.43 ± 1.1) × 10^{-4}; 4.7 °C, (1.74 ± 0.1) × 10^{-3}; 9.7 °C, (4.06 ± 0.19) × 10-3; 14.7 °C, (6.45 ± 0.36) × 10^{-3}. [i] Extrapolated from rates reported in ref 26. [j] Extrapolated from rates at other temperatures: 102.9 °C, (5.22 ± 0.2) × 10^{-4}; 88.4 °C, (1.68 ± 0.01) × 10^{-4}; 78.4 °C, (6.39 ± 0.12) × 10^{-5}. [k] Extrapolated from rates at other temperatures: 103.3 °C, (4.52 ± 0.12) × 10^{-4}; 88.4 °C, (1.53 ± 0.08) × 10^{-4}; 87.7 °C, (1.49 ± 0.07) × 10^{-4}.

Four explanations for the failure of the Raber–Harris probe for 1 are proposed. First, the hydroxyl group of 1 may be affecting the solvolytic process to a different extent in aqueous EtOH and aqueous TFE. Second, dimerization of 1 may be more important in TFE or EtOH and hence could lead to a nonlinear TFE–EtOH plot. Third, the substrate and model may have different susceptibilities to electrophilicity, thus causing a poor correlation by eq 1 as the electrophilicity is varied over a wide range. Specifically, desolvation of the neighboring group may be more difficult with the highly electrophilic TFE and could lead to depressed rates in TFE. Previously[16] we have shown that 1-adamantyl chloride and 2 have different susceptibilities to electrophilicity. However, we were not able to assign the difference to any specific structural difference. The final failure mechanism we will discuss is another that could relate to the electrophilic sensitivity of the substrate. For example, there could be a difference in the degree of return from ion pairs or free ions by the model for *Y* values and the substrate being evaluated. We and others[13] have noted that hydrolysis rates of 1 are sensitive to common ion rate depression. Thus external ion return must be important if this return process or ion pair return (as yet unidentified) is solvent dependent; a nonlinear TFE–EtOH plot could result. In this article we will discuss our experiments that bear on these four possible failure mechanisms for 1.

Possible Effect of the Hydroxyl Group of 1 on the TFE–EtOH Plot. To investigate whether the hydroxyl

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Table II. Solvolytic Rates and Activation Parameters of Substrates Measured in Various Solvents at Multiple Temperatures

substrate	solvent[a,b]	temp, °C	10^4k, s^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
$MeSCH_2CH_2Cl$, **2**	50A	1.1	2.41 ± 0.10	15.3	−19.3
		24.9	22.5 ± 0.1		
		25.0	(24.3)		
		32.3	48.6 ± 0.5		
	70A	25.0	1.76 ± 0.02	16.7	−19.8
		39.9	7.04 ± 0.08		
	50E	25.0	26.7 ± 0.8		
	60E	25.0	17.1 ± 0.8		
	95E[c]	25.0	(0.290)	14.5	−30.8
		34.9	0.696 ± 0.004		
		50.8	1.93 ± 0.06		
		65.0	6.50 ± 0.05		
	50T	25.0	41.0 ± 1.1		
	70T	25.0	27.0 ± 1.4		
	97T	25.0	19.9 ± 0.4		
	100T	25.0	27.9 ± 0.8		
$PhS(CH_2)_4Cl$, **9-Cl**	70E	70.0	(3.39)	17.4	−24.1
		74.9	4.92 ± 0.10		
		84.9	10.2 ± 0.4		
	60E	64.6	3.77 ± 0.09	16.1	−26.5
		70.0	(5.60)		
		74.5	7.71 ± 0.09		
	50E	65.0	6.26 ± 0.05	14.3	−31.0
		70.0	(8.67)		
		75.0	11.9 ± 0.7		
	97T	56.0	6.59 ± 0.04	14.3	−30.0
		65.0	12.1 ± 0.3		
		70.0	(16.7)		
	70T	50.0	3.89 ± 0.08	15.1	−27.6
		60.2	8.24 ± 0.30		
		70.0	(16.3)		
	50T	60.0	12.3 ± 0.2	16.2	−23.4
		64.0	16.7 ± 2.1		
		70.0	(25.3)		

[a] 50–70A = 50%–70% aqueous acetone (v/v), 50–95E = 50%–95% aqueous ethanol (v/v), and 50–97T = 50%–97% aqueous trifluoroethanol (w/w). Rates in parentheses are extrapolated from other temperatures. [b] Unless otherwise stated, Y_{Cl} and Y_{OTs} values are from ref 7. [c] Y_{Cl} (1.57) was extrapolated from the correlation of Y versus Y_{Cl} for 60, 70, 80, and 90E.

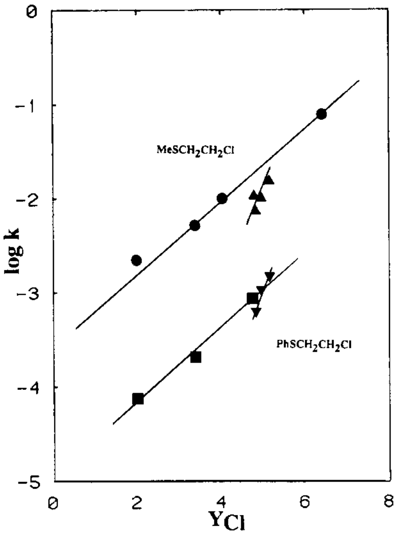
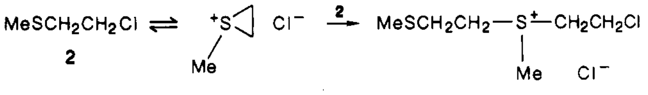


Figure 2. Plot of 0.57 log k versus 2 + Y_{Cl} for **2** (TFE = ▲, EtOH = ●) and log k versus 2 + Y_{Cl} for **3-Cl** (TFE = ▼, EtOH = ■).

group could be the cause of the nonlinear TFE–EtOH plot for **1**, we carried out kinetic studies of an analogue of **1** that lacks the hydroxyl group. Data was collected in various concentrations of aqueous EtOH and aqueous TFE for 2-(methylthio)ethyl chloride, **2** (Table II). A plot of log k versus Y_{Cl} values (Figure 2) reveals that **2** and **1** have similar responses to the TFE–EtOH probe. Although the data point for **2** in 100% TFE does not fall as far below the line as observed with **1**, clearly it and all the aqueous TFE points are below the line defined by the aqueous EtOH kinetic data. We can therefore conclude that the hydroxyl group is not the only cause of the unusual behavior of mustard chlorohydrin.

Scheme II



Dimer Formation as a Failure Mechanism. The Effect of Added Nucleophiles on Solvolytic Rate for 2. The formation of the dimer of **1** was described by Ogston[17] and by Bartlett and Swain.[13] The dimeric salt forms after a short period of storage of the neat liquid at ambient temperatures. However, Bartlett and Swain found no evidence that dimerization was a problem in acetone. Independently, Yang et al.[18] and McManus et al.[19] have recently shown that other mustard model substrates, (e.g. **2** and **3-OTs**) form dimer, some more readily than others. Dimer forms by attack of neutral sulfide on an intermediate cyclic sulfonium ion formed from another molecule, Scheme II. Yang's studies suggest that dimer forms fastest at an interface, e.g. as **2** and water are mixed.

Largely on the basis of the conclusions of Bartlett and Swain, we have previously assumed that dimerization is not important with conductimetric kinetic measurements because of the low (ca. 10^{-3} M) concentrations employed. Our recent experience[19] with **3-OTs** has caused us to reassess the propensity for dimerization of mustard models

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Table III. Effect of Concentration of 2 on First-Order Rates in 40% Aqueous Ethanol and 97% Aqueous Trifluoroethanol at 25 °C

concentration of 2,[a] mol L^{-1}	solvent	10^3k,[b] s^{-1}
1.8×10^{-4}	40% aqueous EtOH	2.50
3.62×10^{-4}		2.46
1.27×10^{-3}		2.74
1.63×10^{-3}		2.71
2.06×10^{-3}		2.52
2.39×10^{-3}		2.95
2.78×10^{-3}		2.64
3.80×10^{-3}		2.66
2.53×10^{-4}	97% aqueous TFE	1.32
5.05×10^{-4}		1.24
8.68×10^{-4}		1.45[c]
1.01×10^{-3}		1.36
1.52×10^{-3}		1.52
1.95×10^{-3}		1.72
3.79×10^{-3}		1.73[c]
3.97×10^{-3}		1.79
4.91×10^{-3}		1.76

[a] The EtOH is mixed v/v and contains 40% EtOH. The TFE is mixed w/w and contains 97% TFE. 2,6-Lutidine is added at a concentration equal to that of 2 in each case. [b] Measured conductimetrically. [c] The reference values were run simultaneously.

under kinetic conditions. From other studies we know that these dimers undergo solvolysis at rates that are significantly slower than those of the monomers.[19] However, since the dimer is a salt, it will contribute to the overall solution conductivity. These complexities make it difficult to predict the effect of dimer formation on the observed rate constant. Regardless of the effect, we assume that dimer formation *may be* more important in the poorly nucleophilic TFE solutions than in aqueous ethanol solutions. Also, since dimer formation ought to be more important at high substrate concentration, we investigated the effect of substrate concentration on the first-order rate constant.

Our first set of experiments was designed to evaluate the effect of concentration on rate. For these experiments we employed model substrate **2**, which like **1** gives a nonlinear TFE–EtOH plot (Figure 2, discussed above). In Table III are shown rates for various concentrations of **2** in 40% aqueous EtOH and 97% aqueous TFE. These solvents were chosen because they have similar Y_{Cl} values and thus provide $[k_{EW}/k_{TW}]_Y$, when expressed in the terminology of Bentley and Schleyer.[20] For our purposes here, however, we are interested in the observation that, over a wide substrate concentration range, the rate for solvolysis of **2** in 40% EtOH is constant, Table III. On the other hand, in 97% aqueous TFE, the rates vary somewhat, Table III. At low substrate concentrations (i.e. 1.01×10^{-3} M or less) the rates in TFE are constant [$(1.34 \pm 0.09) \times 10^{-3}$ s^{-1}]. Also, at concentrations between 1.95×10^{-3} M and 4.91×10^{-3} M a constant rate is obtained [$(1.75 \pm 0.03) \times 10^{-3}$ s^{-1}]. The increase in rate with concentration is not linear as it should be (at least approximately) if it is due to dimerization in solution.[14]

To verify that the variable rates of solvolysis of **2** in aqueous TFE are not due to dimer formation, we employed the thiourea probe.[14] Based on nucleophilicities determined from reaction with methyl iodide in methanol, we know that thiourea ($n = 7.27$) is a better nucleophile than **2** (n for diethyl sulfide = 5.34).[21] For our studies, we intentionally chose concentrations of thiourea that would render substrate dimerization relatively unimportant. We have earlier reported that added thiourea slightly depresses the rate of solvolysis of **2** in aqueous EtOH.[14] The data in Table IV show that *the rates of solvolysis of 2 in aqueous TFE are virtually unaffected by added thiourea.* Therefore, we can assume that dimerization of **2** is unimportant as a factor in our rate measurements and as a failure mechanism for the TFE–EtOH plots.

Table IV. The Effect of Thiourea on the Solvolysis of 2 in 97% Aqueous TFE (w/w) at 25 °C

concentration, mol L^{-1}		
substrate[a]	thiourea	10^3k, s^{-1}
$(1.01 \pm 0.5) \times 10^{-3}$[b]	0.0	1.35 ± 0.11
8.31×10^{-4}	5.0×10^{-2}	1.31
8.31×10^{-4}	1.0×10^{-1}	1.22
8.31×10^{-4}	2.0×10^{-1}	1.27

[a] 2,6-Lutidine is present in each case at a concentrations equal to 2. [b] Data from Table III.

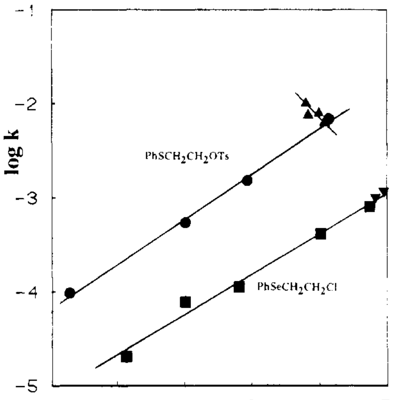

Figure 3. Plot of 2 + log k versus Y_{OTs} for **3-OTs** (TFE = ▲, EtOH = ●) and versus 2 + Y_{Cl} for **7** (TFE = ▼, EtOH = ■).

Desolvation of the Neighboring Group. Evaluation of Additional Mustard Analogues. In order to determine if neighboring group desolvation causes failure of the TFE–EtOH probe, we sought additional k_Δ substrates with neighboring oxygen, nitrogen, sulfur, selenium, and phosphorus groups since these groups should have different hydrogen-bonding requirements. We will discuss our results with the several substrates evaluated by the Raber–Harris approach.

In our characterization of the mechanism of mustard hydrolysis, we had prepared other substrates analogous to **1** and **2** (e.g. **3-Cl** and **3-OTs**).[19] There is substantial evidence that these substrates follow the same mechanistic path as **1** to give cyclic sulfonium ions, i.e. **6**, Scheme I. Rate data in various solvent mixtures for 2-(phenylthio)ethyl chloride (**3-Cl**) and 2-(phenylthio)ethyl tosylate (**3-OTs**) are given in Table I. Since the correlation coefficient is high ($r = 0.992$) for the linear least-squares treatment of the combined aqueous EtOH and aqueous TFE data for **3-Cl**, and since none of the TFE data points deviate significantly from the least-squares line (Figure 2),[22] we conclude that the TFE–EtOH plot for **3-Cl** is linear. Taken separately, however, the slope of the aqueous TFE points is different from that of the aqueous EtOH data. Nevertheless, use of the original Raber–Harris guidelines would lead one to conclude that that **3-Cl** undergoes solvolysis without backside nucleophilic solvent assistance. Of course in this case the result is completely consistent

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(20) EW is EtOH–water and TW is TFE–water. For the general use of this terminology, see ref 5 and 7b.

(21) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

(22) Young, H. D. *The Statistical Treatment of Experimental Data*; McGraw-Hill: New York, 1962.

with all of our other mechanistic indicators (e.g. thiourea probe, product studies). *Our dilemma is that the solvolysis mechanism of one mustard derivative is correctly predicted while those of two structurally related derivatives (e.g. 1 and 2) are not.*

The TFE–EtOH plot for **3-OTs** is shown in Figure 3. If we had *not* measured the rate in pure TFE, our data would have led to the conclusion that both the TFE and EtOH data points are correlated by a single line. However, we *did* measure the rate in pure TFE. Placing the point for pure TFE on the plot produces a trend that is novel; the TFE and aqueous TFE data give a negative slope! We suggest that this trend is real and may be caused by the same phenomenon that produced the nonlinear plots for **1** and **2**.

The combined results from correlation of the TFE and EtOH data of substrates **1–3** does not give us a great deal of confidence in use of the TFE–EtOH probe for these systems. Something is causing these correlations to fail to match what Raber and Harris predicted. Because we have already determined that the mustard model **2** and 1-adamantyl chloride respond differently to changes in electrophilicity,[16] desolvation of the neighboring group could account for this. However, the results discussed below do not reinforce this conclusion.

Desolvation of the Neighboring Group. Investigation of Substrates That Are Especially Susceptible to Electrophilic Solvation. To further test the desolvation mechanism, we prepared and studied several additional substrates that could conceivably suffer the same fate as **1**. Using their relative basicities as a guide, we decided that the oxygen and nitrogen analogues, $ROCH_2CH_2X$ and $R_2NCH_2CH_2X$, would provide more sensitive probes of the importance of desolvation of the neighboring group. Winstein and associates previously studied neighboring-oxygen participation by using 2-methoxyethyl tosylate and concluded that this substrate undergoes solvolysis with nucleophilic solvent assistance.[23] They also studied the branched model, $MeOCMe_2CH_2OBs$, which was assumed to be sterically protected from backside solvent assistance. Their results suggested that anchimeric assistance by the neighboring oxygen was weak but nevertheless present.

We have reinvestigated each of the above substrates and confirmed Winstein's results. The details of our studies are published elsewhere.[24] We briefly will summarize them since they bear on the mechanism under question. With the unbranched substrate, all probes suggest a k_s mechanism. In the case of the branched system, however, our evidence is consistent with neighboring-oxygen participation. In connection with the present study it is significant to note that a linear TFE–EtOH plot is observed for $MeOCMe_2CH_2OBs$. One may conclude that this result refutes the importance of neighboring-group desolvation as an important factor. This decision is not unambiguous since it is possible that the methyl groups may sterically hinder solvation of the neighboring oxygen.

We have also studied 2-bromoethyl amine, which is known to undergo anchimerically assisted loss of bromide ion to give the intermediate aziridinium ion.[11] Reproducible kinetics indicating only slight solvent dependence were obtained at 25 °C in aqueous EtOH; $k = (3.96 \pm 0.20) \times 10^{-4}\ s^{-1}$ (30% aqueous EtOH), $k = (3.51 \pm 0.16) \times 10^{-4}\ s^{-1}$ (40% aqueous EtOH), and $k = (3.36 \pm 0.07) \times 10^{-4}\ s^{-1}$ (50% aqueous EtOH). However, in pure TFE and the aqueous TFE's, initial conductance levels were too high for use of the conductance technique. Application of titrimetric procedures produced nonreproducible results. Hence we suspended further study of this substrate. One could conclude that the high conductance values noted for the amines is evidence of strong solvation or protonation of the nitrogen atom. However, without kinetic evidence of the loss of bromide ion, the case is inconclusive.

Desolvation of the Neighboring Group. Investigation of a Substrate That Is Less Susceptible to Electrophilic Solvation. Since neighboring-group desolvation should decrease in importance in going from oxygen to sulfur to selenium, we also acquired TFE-EtOH data on a selenium-containing model. McManus and Lam have previously shown that $PhSeCH_2CH_2Cl$ (**7**) undergoes solvolysis with powerful anchimeric assistance by the neighboring selenium atom, giving the cyclic selenonium ion analogous to **3-Cl**.[25] In applying the TFE–EtOH probe, the data are perfectly correlated by a single line, Figure 3. In summary, we conclude that neighboring group desolvation is *not* the key to understanding failure of the R–H probe since substrates with weakly solvated (Se) and strongly solvated (O) neighboring groups give linear plots.

Solvent-Dependent Return. Investigation of Substrates That Are Not Susceptible to Return. There is data that suggests that return to neutral substrate from the cyclic sulfonium ion is important for both **1** and **2**. Two pieces of data are especially enlightening. First, the measured conductimetric rates of both of these substrates are lower at high conversion than early in the reaction. This is consistent with Bartlett and Swain's finding of common ion rate depression for **1**. For this reason, we have recorded rates measured for 1.0–1.5 half-lives. If data for 2 or more half-lives are used, a significantly different rate constant is obtained. Also, our inability to make the chloride **2** specifically labeled with deuterium at the α-carbon[12] provides strong evidence that return occurs with both these substrates under a variety of conditions. To investigate this failure mechanism for eq 1, we sought a substrate that undergoes neighboring group assisted displacement to give a relatively stable cyclic ion, which cannot readily return to neutral starting material. Also, for eq 2 to be inapplicable, the substrate sensitivity to nucleophilicity (i.e. l in eq 2) would need to be negligible.

Neamati-Mazraeh and McManus previously published kinetic evidence supporting anchimeric assistance by the phosphorus atom in $Ph_2PCH_2CH_2CH_2Cl$ (**8**).[26] That evidence also showed that the neighboring group assisted process was superior to solvent-assisted displacement for **8**. Since phosphonium salts undergo hydrolysis by attack at phosphorus rather than by attack at carbon,[27] return from the cyclic phosphonium salt is unlikely. Thus we applied the TFE–EtOH probe to **8**. For unknown reasons, the kinetics of solvolysis of **8** in aqueous EtOH were difficult to reproduce (Table I). In an attempt to overcome the experimental problems, a large number of determinations were made. The plot of the data with error bars is shown in Figure 4. Because of the uncertainties of the data, we can only say that the plot suggests that all points *may be* correlated by one line. But more importantly, even with the spread one can conclude that the TFE data points

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[23] Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, *3*, 1.

[24] McManus, S. P.; Karaman, R. M.; Sedaghat-Herati, R.; Neamati-Mazraeh, N.; Hovanes, B. A.; Paley, M. S.; Harris, J. M. *J. Org. Chem.* **1987**, *52*, 2518.

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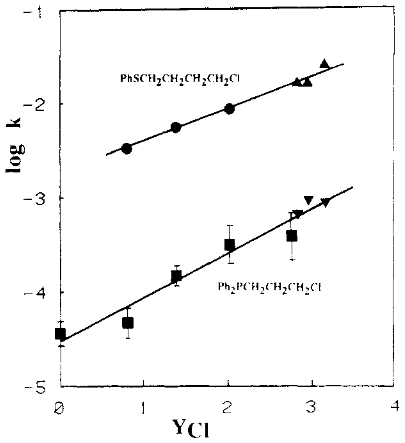
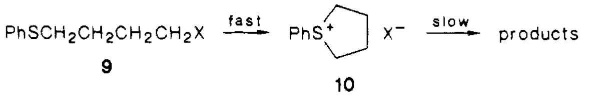


Figure 4. Plot of log *k* versus Y_{Cl} for 8 (TFE = ▲, EtOH = ●) and 1 + log *k* versus Y_{Cl} for **9-Cl** (TFE = ▼, EtOH = ■).

are not *too slow*, as would be expected for a typical nonlinear plot.

Finally, we have measured rates for 4-(phenylthio)butyl chloride, **9-Cl**, in varius concentrations of aqueous EtOH and aqueous TFE (Table II) and constructed a plot of log *k* versus Y_{Cl}, Figure 4. Unlike three-membered cyclic sulfonium ions (ethylenesulfonium ions, e.g. 4–6), five-membered cyclic sulfonium ions (e.g. tetramethylenesulfonium ions, such as **10**) are known to be rather stable to weak nucleophiles such as sulfonate anions or solvent.[28] For example, Rosnati and his co-workers recently reported that acetolysis of $PhSCH_2CH_2CH_2CD_2OTs$ (**9-*d*$_2$-OTs**) proceeds to give **10-*d*$_2$-OTs** as the only product. At 120 °C the conversion to the cyclic salt was complete in 5 min. The stability of **10** to ring-opening by the solvent is evidenced by their observation that after 85 min of heating at 120 °C, only 24% of ring-opened acetate (i.e. **9-*d*$_2$-OAc** with label scrambled) had formed; 76% of the original cyclic salt remained.[28] Therefore, **9-OTs** undergoes solvolysis by rate-limiting formation of the cyclic salt **10-OTs**. Because chloride ion is a better nucleophile than tosylate, **10-Cl** is more likely to undergo return to neutral substrate. At low substrate concentrations, however, destruction of **10** by solvent attack becomes more likely. We demonstrated that upon solvolysis in aqueous acetone, aqueous EtOH, or aqueous TFE, the solvolytic rate for **9-Cl** (at ca. 10^{-3} M) is unaffected by chloride buildup late in the reaction. Thus, we assume that, like the analogous tosylate, **9-Cl** undergoes solvolysis by rate-limiting formation of the cyclic ion, eq 3.



(3)

As shown in Figure 4, the EtOH–TFE plot for **9-Cl** is linear. This linear plot for **9** is another piece of evidence suggesting that desolvation of the neighboring group is not the cause of the nonlinear TFE–EtOH plots of **1** and **2** since all three have a neighboring sulfur group. More importantly, since return is insignificant with **9** but significant with **1** and **2**, our attention must focus on the possibility that solvent-dependent return is the cause of the nonlinear TFE–EtOH plots for **1** and **2** and the unusual slope of the plot for the tosylate **3-OTs**.

Evaluation of the Solvent Dependence of Return with Mustard Derivatives. As mentioned above, return with **1** is well documented from the studies of Bartlett and Swain. Since they found that added chloride did not affect the rate when a superior nucleophile was present, the type of return is probably from free ions.[14] We have noted above that a slight but significant rate retardation occurs with **1** and **2** as the reaction progresses. We add 2,6-lutidine to prevent acid-catalyzed processes, but this has no effect on the conversion of the cyclic sulfonium ion back to neutral chloride starting material.

To quantify the previously assumed solvent-dependent return with the β-thioethyl substrates, we needed isotopically labeled substrates. Despite use of very mild procedures,[28] we and other have found that unscrambled, deuterium-labeled **1**, **2**, or **3-Cl** is elusive.[12,29] The brosylate is available, however. Displacement of brosylate from $PhSCH_2CD_2OBs$ by strong nucleophiles, such as thiophenolate, occurs in DMSO solution almost instantly.[30] NMR shows that the product is formed without label scrambling. On the other hand, solvolysis leading to label-scrambled products occurs in DMSO with a half-life of about an hour. An attempt to use this direct substitution route to the labeled chloride failed. In reacting labeled brosylate with tetrabutylammonium chloride in DMSO we were unable to retrieve labeled **3-Cl** from solution without label scrambling.

Because the labeled chloride was unavailable, we used $PhSCH_2CD_2OBs$ (**3-*d*$_2$-OBs**) as our substrate. ^1H NMR experiments reveal that solvolysis occurs without the appearance of detectable return to label-scrambled brosylate when the solvent is 100% CD_3OD, 50% D_2O/50% CD_3COCD_3, 100% CD_3CO_2D,[29,31] or 100% CD_3SOCD_3.[30] When the spectra of the products are interpreted after more than 4 solvolytic half-lives, in each case, it is clear that the solvolysis products are completely scrambled. Therefore the experiments unambiguously reveal that solvolysis in these solvents occurs via the cyclic sulfonium ions.

When the solvolysis of **3-*d*$_2$-OBs** in pure deuterated acetone was followed by ^1H NMR, label-scrambled brosylate slowly formed. This observation allowed us to measure the solvent dependency of return for the labeled brosylate. Integration of the methylene protons of the unrearranged and rearranged brosylate provides a ratio (which changed with time) of rearranged to unrearranged brosylate. These data provide first-order rate constants for scrambling of the brosylate. At 40 °C the following brosylate scrambling rates were determined for three compositions (v/v) of acetone–water: 100% acetone, $k_{scr} = 9.55 \times 10^{-5}\ s^{-1}$; 95% acetone, $k_{scr} = 8.03 \times 10^{-5}\ s^{-1}$; and 89% acetone, $k_{scr} = 4.4 \times 10^{-4}\ s^{-1}$. As mentioned above, hydrolysis in 50% aqueous acetone occurs without scrambling of the unreacted brosylate.

In pure acetone and aqueous acetone low in water content, solvolysis is relatively slow as compared to solvent compositions containing more water because product formation occurs by water attack. To put these results on a quantitative basis, we determined the solvolytic rate constant for 89% aqueous acetone at 40 °C (by NMR, $1.4 \times 10^{-3}\ s^{-1}$, and by conductance, $8.84 \times 10^{-4}\ s^{-1}$). Although the conductance value is more accurate, either rate allows a good estimate of the ratio of hydrolysis to the rate of scrambling (ca. 2.5). In 50% aqueous acetone, the ratio is much higher, making hydrolysis the only observable process by NMR.

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[29] Rosnati, V.; Saba, A.; Angius, A.; Casarini, D. *J. Org. Chem.* **1987**, *52*, 4094.

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[31] Sedaghat-Herati, R.; McManus, S. P.; Harris, J. M., unpublished results.

Since return with **3-OBs** is solvent dependent, we conclude that return for the chloride is also solvent dependent. Assuming that return in the case of the chloride is significant in every solvent we have studied, we suggest that the failure of the Raber–Harris method for **1** and **2** may be attributed to solvent-dependent return, which is not proportional to that occurring for the model 1-adamantyl derivative. Although our hard evidence for solvent-dependent return with mustard derivatives is weak, support for the conclusion that solvent-dependent return is important is well documented for other systems. The review of ion pairs by Raber, Harris, and Schleyer[32] summarizes several studies, mostly by the Goering and Winstein groups, which relate to this phenomenon.

In light of our suggestion that solvent-dependent return is the likely cause for failure of the TFE–ETOH probe for mustard derivatives, let us summarize our view of the overall situation with these compounds. First, we previously have determined, using the Kamlet–Taft approach, that β-thioethyl chlorides have a different susceptibility to electrophilicity than 1-adamantyl chloride.[16] Sensitivity to electrophilicity for these thioethyl chlorides includes solvation of the sulfur and the leaving group whereas with the adamantyl derivative only leaving group solvation is involved. It is also important to note that the sensitivity to electrophilicity may be different between a model (1- or 2-adamantyl) and a substrate even if the leaving group is the only part of each molecule that is sensitive to electrophilicity.[16]

In the present study we have determined that the differences in susceptibility to electrophilicity is assignable to return from free ions (and possibly ion pairs) and not because of neighboring-group desolvation. Now that we have suggested a failure mechanism for the examples we have studied, we can begin to put other odd data into perspective. For example, we have recently completed a study of *exo*- and *endo*-2-norbornyl arenesulfonates and attributed the nonlinear TFE-EtOH plot for the exo tosylate to solvent dependent return.[33] Recalling the odd behavior of **3-OTs** above, the inverse slope noted for this tosylate may also be attributed to differential return between it and 2-adamantyl tosylate (the model for Y_{OTs}).

Finally, a system recently studied by Tidwell and coworkers attracted our attention. Solvolytic data in aqueous TFE and aqueous EtOH was reported for the tertiary *p*-nitrobenzoate *p*-$\mathrm{Me_2NC_6H_4C(CF_3)_2OPNB}$ (**12**), which by a variety of measures undergoes classical unimolecular solvolysis.[34] Because Y_{OPNB} values are unavailable,[35] Tidwell did not treat these data by the method of Raber and Harris. However we recall that McLennan found a good TFE–EtOH correlation when the rates of solvolysis of $\mathrm{Ph_2CHOPNB}$ were plotted versus Y_{OTs};[15] thus we have plotted the rate data for **12** against Y_{OTs}, Figure 5. We believe that the significant lack of correlation of the TFE data points with the EtOH data points cannot be attributed to the use of Y_{OTs} values. Because of the presence of the dimethylamino group, which would be highly susceptible to solvent electrophilicity, and the trifluoromethyl groups, which significantly affect the nature of the intermediate, **12** is characteristically different from 2-adamantyl tosylate. It is notable that Sunko and co-workers[36] have recently argued that H-bonding by fluorinated solvents to oxygen neighboring groups may reduce rates. In our own studies with oxygen neighboring groups,[24] we did not notice any unusual behavior. The basicity of amines, however, make them more susceptible to H-bonding problems.

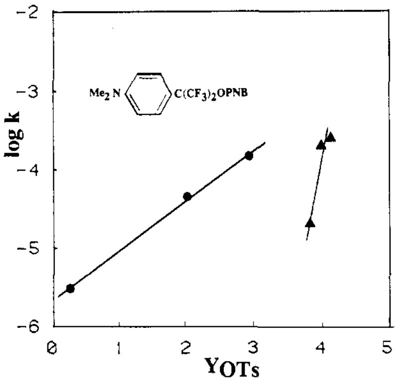

Figure 5. Plot of log *k* versus 2 + Y_{OTs} for **12** (TFE = ▲, EtOH = ●).

Appraisal of the Significance of Solvent-Dependent Return on the Use of the Trifluoroethanol–Ethanol Probe. Now that we have evidence to argue that solvent-dependent ion-pair return is causing the TFE–EtOH probe to predict the wrong mechanism for **1** and **2**, we should reassess the value of the method in general. First of all, the problem is not with the TFE–EtOH probe, it is with the Grunwald–Winstein equation in general. The TFE–EtOH probe has simply *revealed* the problem. We generalize regarding the Grunwald–Winstein equation in the next section.

There are now two problems with the TFE–EtOH probe that should be considered when using it. First, because various leaving groups have different responses to electrophilicity, one must use the same or a similar leaving group for the model as for the substrate under consideration.[15,33] Secondly, since different all-carbon substrates may show different degrees of return, one must now be concerned about the model and the substrate under question having similar or proportional amounts of return from ion pairs or free ions. Do these factors destroy the value of the probe as a mechanistic indicator. We think not. The key is that the probe is a mechanistic *indicator*. It should not be used in the absence of other data. Now, one must also consider data about ion-pair return in assessing the response of a substrate to TFE and EtOH.

It is worthwhile in light of our new knowledge about this probe to reassess data already treated. Obviously, some of the controversial systems originally treated by Raber, Harris, and co-workers need to be reassessed, but that task is outside the scope of this study. However, we would like to focus on two systems included in this study. First, we earlier mentioned that we were surprised that the TFE–EtOH probe gives a linear plot for **3-Cl** while giving a nonlinear plot for **1** and **2**. Also, we noted the negative slope for the TFE data for **3-OTs**. We can now suggest that the change in the degree of ion-pair return or return from free ions owing to a change in solvent must be different with 2-adamantyl tosylate and **3-OTs**. From the plot, Figure 3, we can conclude that return is *more* important with 2-adamantyl tosylate than it is with **3-OTs**. Also our data in Figure 1 suggests that return is *less* im-

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[35] Jursic, B.; Ladika, M.; Sunko, D. E. *Tetrahedron* **1986**, *42*, 911.

[36] We thank T. W. Bentley for pointing out ref 35 to us and for keeping us abreast of his experimental work on Y_{OPNB} measurements; personal communication to S.P.M., February and September, 1988.

portant with 1-adamantyl chloride than it is with **1** or **2**. Finally, since the points for **3-Cl** have a different slope than the aqueous EtOH points yet all points are reasonably well correlated by one line, we suggest that the return in the substrate and model are nearly proportional.

Significance of Solvent-Dependent Return to the Use of the Grunwald–Winstein Equation. The finding of solvent-dependent return in the mustard-like substrates points out a significant weakness of the Grunwald–Winstein approach to the correlation of rates. For correlation, the model substrate and the substrate under consideration either must have no return or the amount of return for the two must be related. Our studies with mustard chlorohydrin indicate that ion-pair return is not always proportional; it is substrate dependent. From the thousands of successful applications of the Grunwald–Winstein equation we can assume that appropriate proportionality is more common than uncommon. Nevertheless, with the increasing use of poorly nucleophilic but highly electrophilic solvents, one must assume that additional "poor" correlations will be observed.

It is appropriate to comment on the wide use of various leaving groups and hence various Y values. We noted above that ion-pair return is leaving-group dependent. Therefore, the various Y values are also dependent on ion-pair return (or return from free ions) in the model. This is important because we are unaware of the extent of return in most of the models used for determining Y values. For example, 2-adamantyl tosylate, the original model for Y_{OTs} values,[7b] was initially put forth as a model substrate thought to be free of return. However, Paradisi and Bunnett found that it gives ion-pair return in some solvents.[37] This return may account for the mild curvature in the plot of log k (1-adamantyl tosylate) versus log k (2-adamantyl tosylate).[38] le Noble[39] has recently described a method making quantification of ion-pair return in some substrates much easier than in the past.

Our work suggests some important considerations for those who would make use of the Grunwald–Winstein equation in the future. First, the Grunwald–Winstein equation should be used with caution if noncorrelation in solvents of low nucleophilicity is observed. Second, if a TFE–EtOH plot suggests that a substrate is a k_s substrate, a second probe such as the thiourea probe should be employed to confirm the result. Third, the determination of new Y values should be accompanied, where possible, by studies of the extent of ion-pair return in a variety of solvents. Fourth, those interested in correlation of rates should give attention to the general significance of the problem we have highlighted with this study. Finally, we encourage a continued evaluation of the new correlation approaches of Kamlet and Taft[40] and of Swain[41] to see if those approaches may have an advantage over the Winstein–Grunwald approach in treating medium effects. In particular, given the wide proliferation of Y values, we question whether electrophilic effects are properly accounted for by the Grunwald–Winstein approach.

Experimental Section

Chemicals and Analytical Procedures. Reagent-grade materials, obtained commercially (Alfa, Aldrich, Eastman, and Parish), were used as received except when procedures called for especially pure or dry reagents. Absolute ethanol was dried and distilled from magnesium. Proton NMR spectra were recorded in $\mathrm{CDCl_3}$ at 200 MHz (IBM AFT 200) and referenced to tetramethylsilane. Melting points were recorded on samples in capillary tubes and are uncorrected.

Substrates. 2-(Methylthio)ethyl and **2-(phenylthio)ethyl chlorides** were obtained commercially. The preparation of **2-(phenylthio)ethyl-*1,1*-d_2 brosylate**[29] and **2-(phenylseleno)ethyl chloride**[25] are described in other articles. **2-(Phenylthio)ethyl tosylate (4)** was prepared from commercially obtained 2-(phenylthio)ethanol by using purified tosyl chloride and the standard pyridine procedure for tosylates;[42] after crystallization from low-boiling petroleum ether at −70 °C, **4** was obtained as colorless crystals: mp 32–3 °C; NMR ($\mathrm{CDCl_3}$) δ 7.73 (d, J = 4.0 Hz, 2 H, o-$H\mathrm{ArSO_2}$), 7.30 (d, J = 4.0, 2 H, o-HArMe), 7.25 (br s, 5 H, HArS), 4.1 (t, J = 7.3 Hz, 2 H, $\mathrm{C}H_2\mathrm{O}$), 3.10 (t, J = 7.3 Hz, 2 H, $\mathrm{C}H_2\mathrm{S}$), 2.43 ppm (s, 3 H, $\mathrm{C}H_3\mathrm{Ar}$). By use of the procedure of Grim and Barth,[43] **3-(diphenylphosphino)propyl chloride (6)** was prepared as a light yellow viscous oil from commercially obtained diphenylphosphine and 1,3-dichloropropane in 85% yield: NMR ($\mathrm{CDCl_3}$) δ 7.2–7.7 (m, 10 H, ArH), 3.6 (t, 2 H, $\mathrm{C}H_2\mathrm{Cl}$), and 2.2 (m, 4 H, $\mathrm{P}CH_2\mathrm{C}H_2$). **4-(Phenylthio)butyl chloride (7)** was obtained from the reaction of reaction of thiophenol and 1,4-dichlorobutane in DMSO with 1 equiv of dimsyl.[29] The monosubstituted product was obtained upon distillation: NMR ($\mathrm{CD_3SOCD_3}$) δ 7.1–7.4 (m, 5 H, ArH), 3.66 (t, J = 6.0, 2 H, $\mathrm{C}H_2\mathrm{Cl}$), 3.00 (t, J = 6.2 Hz, 2 H, $\mathrm{C}H_2\mathrm{S}$), 1.6–1.95 ppm (m, 4 H, $\mathrm{C}CH_2\mathrm{C}H_2\mathrm{C}$).

Kinetics. Rates were determined conductimetrically by a system previously described.[44] The volume of each kinetic sample was approximately 10 mL, including solvent, substrate (ca. 10^{-3} M), and 2,6-lutidine (ca. 3×10^{-3} M). At least duplicate determinations of rates were made of samples side-by-side. In cases where duplicates failed to give agreement within ±8–10%, additional determinations were made. The rates reported are normally those determined for the first 1–1.5 half-lives. In the case of compounds **1** and **2**, in particular, rates were affected by a buildup of chloride ion. Hence a dropoff in the rate was witnessed with time.

Acknowledgement is made to the U.S. Army Research Office for (DAAG29-82-K-0181 and DAAL03-86-K-0026) and to the National Science Foundation (CHE-8719885) for financial support.

Registry No. 1, 693-30-1; **2**, 542-81-4; **3**-Cl, 5535-49-9; **3**-OTs, 116047-07-5; **7**, 50630-24-5; **8**, 57137-55-0; **9**-Cl, 14633-31-9; **12**, 101980-05-6.

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