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Hydrolysis of Mustard Derivatives. Remarkable Tosylate/Chloride and Chloride/Dinitrophenolate Rate Ratios

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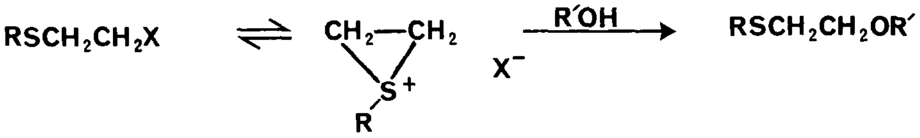
Summary: Comparisons of leaving group solvolytic rate ratios for mustard derivatives with other substrate types reveals unusual OTs/Cl and Cl/ODNP rate ratios for mustards. A very tight transition state is suggested.

Among primary alkyl chlorides, sulfur mustards show extraordinary reactivity resulting from neighboring group assistance by the beta sulfur (Scheme 1).[1-4] We recently described another significant difference between mustards and other alkyl halides: rates of solvolysis of mustard chlorohydrin (**1**) in aqueous ethanols, acetones, and trifluoroethanols cannot be satisfactorily correlated using four parameter extended Grunwald-Winstein equations.[4-8] We describe here the remarkable observation that mustard derivatives show unusually low tosylate/chloride solvolytic rate ratios but expected tosylate/dinitrophenolate rate ratios.

Scheme 1



1, R = $HOCH_2CH_2$, X = Cl
2, R = Me

Tosylates are generally regarded to be better leaving groups than chlorides.[9] Table I contains some tosylate/chloride rate ratios for primary and methyl substrates undergoing S_N2 displacement in aprotic or protic media. Although a wide variability in rate ratios is evident, even with the strong, charged sulfur nucleophiles, the tosylates maintain a significant rate advantage over the chlorides. The tosylate/chloride rate ratio for substrates undergoing solvolysis by a k_c mechanism is even higher as evidenced by the benzyl and 1-adamantyl substrates (Table II); steric factors have been shown to contribute to the ratio in the adamantyl case.[10]

In search of a mustard substrate we could study using a spectrophotometric kinetic method, we prepared the mustard tosylate $MeSCH_2CH_2OTs$ (**2-OTs**) and the mustard dinitrophenolate **2-ODNP.** We will first discuss the tosylate. Based on our knowledge of the reactivity of **2-Cl** and the tosylate/chloride rate ratios of the k_c substrates in Table II, we expected **2-OTs** to have a reactivity suitable for study in poorly ionizing media. We were surprised to find that **2-OTs** and **2-Cl** had similar reactivities in protic solvents (Table II). To determine if perhaps the benzyl system was a poor choice for assessing tosylate/chloride rate ratios of primary substrates, we studied the primary substrates *n*-butyl chloride and tosylate in 60% aq. ethanol, finding that the tosylate is by far the faster reacting primary k_s-type substrate at 25°C (Table II). Therefore, substrate **2**, a k_Δ substrate, is the anomalous one. A summary of the relative solvolytic reactivities of the mustard and *n*-butyl derivatives are shown in Table III. These comparisons allow us to establish that neighboring group assistance by the sulfur group in **1** and **2** accounts for a rate acceleration in excess of 10^6.

In addition to being suitable for spectrophotometric kinetic methods, dinitrophenolates are readily prepared from alcohols using procedures which do not favor carbocationic rearrangements.[11] Based on the comparison of 1-adamantyl tosylate/chloride (Table II) and tosylate/dinitrophenolate[11] (HOAc, 100°C, $k_{OTs}/k_{ODNP} = 8.2 \times 10^4$) rate ratios, we anticipated that **2-ODNP** would be similar in reactivity to the respective chloride. We were again surprised with the result. Relative rates for the 2,4-dinitrophenolate, *m*-nitrobenzoate, chloride, and tosylate of **2** in 50% aq. acetone at 75°C are:

2, X =	ODNP	OmNB	Cl	OTs
k_{rel} =	1	53	1.3×10^4	5.0×10^3

In this case the tosylate/dinitrophenolate ratio remained within the same order of magnitude as found with the adamantyl derivatives. The chloride/dinitrophenolate rate ratio, however, is considerably larger than anticipated. Thus, the chloride rate seems to be the anomalous one.

The factors which have been discussed as contributors to the variation in tosylate/chloride rate ratios are (i) electrophilic solvation, (ii) steric factors, and (iii) bond extension in the transition state.[12,13] The first two factors will not satisfactorily explain the results with mustard derivatives. The third factor, which has not been extensively treated in situations involving neighboring group participation, may be the key to understanding these results. If bond extension is responsible for these results, a very tight transition state is suggested. A possible complicating factor in the interpretation of these results is the internal return that is known to occur with **1-Cl**, **2-Cl**, **2-ODNP** and presumably the other derivatives.[4] We are currently studying the extent of the return in the chloride and dinitrophenolate and the possible effects of that factor on these rate ratios. We also plan to evaluate the bond extension in **2** using a Hammett approach by studying the kinetics of appropriately substituted benzenesulfonates or phenolates. The results of these studies will be reported later.

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Table I. Tosylate/Chloride Rate Ratios for Second-Order Displacement from Primary and Methyl Substrates at 25 °C.

Reaction	Solvent	k_{OTs}/k_{Cl}	Ref.
MeX + N_3^-	MeOH	631	14
	DMF	3,162	14
MeX + SCN^-	MeOH	79	14
	DMF	20	14
MeX + Cl^-	Me_2CO	180	15

Table II. Tosylate/Chloride Rate Ratios for Pseudo First-order Solvolytic Displacement Reactions at 25°C.

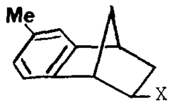
Substrate	Mechanistic Type	Solvent (v/v)	k_{OTs}/k_{Cl}	Ref.
$MeC_6H_4CH_2X$	$\underline{k}_c$	70% aq. EtOH	3.5×10^3	13
1-X-Adamantane	$\underline{k}_c$	80% aq. EtOH	4.4×10^5	16, 17
$CH_3CH_2CH_2CH_2X$	$\underline{k}_s$	60% aq. EtOH	4.4×10^3	this work
$MeSCH_2CH_2X$ (**2**)	$\underline{k}_\Delta$	60% aq. EtOH	0.42	this work
	$\underline{k}_\Delta$	50% aq. $\underline{t}$-BuOH	8.3×10^2	18

Table III. Rates of Solvolysis in 60% Aqueous Ethanol (v/v) at 25 °C.

Substrate	10^4k^a	k_{rel}
$HOCH_2CH_2SCH_2CH_2Cl$ (**1**)	4.41 ± 0.02	1.6×10^6
2-Cl	17.1 ± 0.8	6.2×10^6
2-OTs	7.11 ± 0.02	2.6×10^6
n-Butyl chloride	$(0.00000274)^b$	(1.0)
n-Butyl tosylate	$(0.0121)^c$	4.4×10^3

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[a] Rates were measured conductimetrically with 10^{-3}M 2,6-lutidine added. [b] Extrapolated from rates at higher temperatures; $k_{100.2} = 2.25 \times 10^{-5}$, $k_{107.2} = 6.38 \times 10^{-5}$, $k_{117.8} = 1.69 \times 10^{-4}$, $k_{125.0} = 4.17 \times 10^{-4}$; $\Delta H^{\neq}$ = 32.8 kcal/mol, $\Delta S^{\neq}$ = 7.83 e.u. [c] Extrapolated from rates at higher temperatures; $k_{46.0} = 1.32 \times 10^{-5}$, $k_{75.0} = 2.09 \times 10^{-4}$, $k_{84.3} = 5.22 \times 10^{-4}$, $k_{97.0} = 1.37 \times 10^{-3}$; $\Delta H^{\neq}$ = 20.8 kcal/mol, $\Delta S^{\neq}$ = -15.7 e.u.

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