

Cholesteryl Tosylate: A Solvolytic Investigation

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It is now generally recognized¹⁻⁶ that solvolysis reactions of cholesteryl arenesulfonate derivatives are assisted by homoallylic interactions.^{1a,2b,e,3b,7} In earlier papers from this laboratory,⁸ we used cholesteryl tosylate (1) as a K_{Δ} model for a Grunwald-Winstein correlation of kinetic data for the solvolysis of cyclopropylcarvinyl tosylate (2). We found such a treatment led to a dispersion of the data into two correlation lines for the solvents used in the study. We attributed this dispersion behavior of 2 to different modes of charge dispersal in its transition states for the two solvent series. Underlying this proposal, however, were the assumptions that the solvolyses of cholesteryl tosylate proceed not only via transition states with high homoallylic carbonium-ion character but also without nucleophilic solvent assistance. This paper addresses itself to testing the later assumption. Accordingly, the solvolytic behavior of cholesteryl tosylate has been investigated using two probes—the effect of varying solvent ionizing power and of added azide ion upon rate—to estimate the magnitude of nucleophilic solvent assistance.⁹

The first-order rate constants for solvolysis of cholesteryl tosylate are summarized in Table I. Reaction progress was followed by titrating the liberated *p*-toluenesulfonic acid, and strictly first-order kinetics were observed up to at least 75% conversion furnishing, within experimental error, 100% of the theoretical amount of acid present. In Table II we have listed the results obtained from correlations of the rate data, given in Table I, with Y_{OTs} values.¹⁰ The data showing effect of added azide ion upon rates of solvolysis of cholesteryl, cyclohexyl (2), and 2-adamantyl (3) tosylates are given in Table III.

The effect of solvent on the rate of reaction of a substrate has proven to be a very useful criterion for assignment of

reaction mechanism.¹¹⁻¹⁹ Therefore, we have analyzed the kinetic data of Table I in terms of a Grunwald-Winstein-type equation (1), where k refers to the solvolytic rate

$$\log k = mY_{OTs} + \log k_0 \quad (1)$$

constant in any solvent, k_0 refers to the rate constant in 80% v/v ethanol/water, and Y_{OTs} is a scale of ionizing power for tosylates.¹⁰ For comparison purposes we have carried out a similar analysis for cyclohexyl tosylate, a substrate known^{14,19} to solvolyze by a k_s process and thus sensitive to varying solvent nucleophilicity. The results are summarized in Table II.

Striking differences are obvious between the results of these two analyses: while the reaction rates of cholesteryl tosylate are correlated well against Y_{OTs} ($r = 0.98$)²⁰ over a range²³ of solvents varying in ionizing power from -2.41 (90% aqueous dioxane) to 1.83 (97% TFE), the reaction rates of cyclohexyl tosylate, as expected for a substrate sensitive to solvent nucleophilicity, are dispersed into separate correlation lines for each solvent series. These results clearly demonstrate that nucleophilic solvent assistance is not significant in the solvolysis reactions of cholesteryl tosylate.

Another noteworthy feature of Table II is the similar response of cholesteryl tosylate and the k_{Δ} substrates listed to solvent ionizing power. As can be seen, the compounds known to solvolyze with predominantly neighboring group participation,²⁴ namely, cyclopropylcarbinyl,^{8a,25a} neophyl,^{25b,26,27} pinacolyl,²⁸ and 2-*exo*-norbornyl^{29,30} tosylates, have m values in the range 0.6 to 0.8. The m

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(21) The point for acetic acid lay below the correlation line. It should be noted, however, that this displacement from the regression line is less than a factor of 3 in rate ($k_{\text{obsd}} = 5.25 \times 10^{-6}$; $k_{\text{regression}} = 1.38 \times 10^{-5}$) and therefore is too small a deviation to speculate as to why.^{16,22}

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Table I. Solvolysis Rate Constants for Cholesteryl *p*-Toluenesulfonate

solvent	<i>T</i> , °C	<i>k</i> , s ⁻¹	Δ <i>H</i> [‡] , kcal/mol	Δ <i>S</i> [‡] , eu	solvent	<i>T</i> , °C	<i>k</i> , s ⁻¹	Δ <i>H</i> [‡] , kcal/mol	Δ <i>S</i> [‡] , eu	
EtOH	25.0	4.50 × 10 ⁻⁶ ^b			75A-F ^g	40.0	(7.75 ± 0.07) × 10 ⁻⁴			
	35.0	(1.67 ± 0.05) × 10 ⁻⁵	23.3	-4.9		50.0	(1.77 ± 0.05) × 10 ⁻³			
	40.0	(3.26 ± 0.02) × 10 ⁻⁵				60.0	(3.58 ± 0.04) × 10 ⁻³			
	50.0	(1.01 ± 0.01) × 10 ⁻⁴				97TFE ^f	25.0	(6.9 ± 0.2) × 10 ⁻⁴	19.4	-8
	60.0	(3.21 ± 0.03) × 10 ⁻⁴					30.0	(1.20 ± 0.06) × 10 ⁻³		
90E-W ^c	25.0	1.3 × 10 ⁻⁵ ^b			80TFE-E ^g	40.0	(3.35 ± 0.1) × 10 ⁻³			
	30.0	(2.20 ± 0.05) × 10 ⁻⁵	22.1	-7		25.0	(5.50 ± 0.1) × 10 ⁻⁴	19.7	-7	
	35.0	(4.20 ± 0.06) × 10 ⁻⁵				30.0	(1.00 ± 0.03) × 10 ⁻³			
	40.0	(7.60 ± 0.06) × 10 ⁻⁵				35.0	(1.67 ± 0.03) × 10 ⁻³			
	50.0	(2.30 ± 0.03) × 10 ⁻⁴				90A ^h	25.0	3.2 × 10 ⁻⁶ ^b		
80E-W ^c	25.0	4.00 × 10 ⁻⁵ ^b			30.0		(5.8 ± 0.1) × 10 ⁻⁶	22.0	-10	
	30.0	(6.60 ± 0.06) × 10 ⁻⁵	19	-15	35.0		(9.9 ± 0.3) × 10 ⁻⁶			
	35.0	(1.10 ± 0.01) × 10 ⁻⁴			40.0		(1.9 ± 0.4) × 10 ⁻⁵ ^d			
	40.0	(1.9 ± 0.2) × 10 ⁻⁴ ^d			50.0		(5.8 ± 0.3) × 10 ⁻⁵ ^d			
	50.0	(5.2 ± 0.2) × 10 ⁻⁴			85A ^h	25.0	6.20 × 10 ⁻⁶ ^b			
AcOH	60.0	(1.2 ± 0.2) × 10 ⁻³				30.0	(1.09 ± 0.05) × 10 ⁻⁵	20.9	-12	
	25.0	5.50 × 10 ⁻⁶ ^b				35.0	(2.01 ± 0.04) × 10 ⁻⁵			
	30.0	(9.9 ± 0.2) × 10 ⁻⁶	22.0	-9		40.0	(3.5 ± 0.2) × 10 ⁻⁵ ^d			
	35.0	(2.00 ± 0.03) × 10 ⁻⁵				50.0	(1.0 ± 0.3) × 10 ⁻⁴ ^d			
	40.0	(3.19 ± 0.01) × 10 ⁻⁵			90D ⁱ	25.0	1.2 × 10 ⁻⁶ ^b			
50.0	(1.10 ± 0.03) × 10 ⁻⁴			30.0		(2.39 ± 0.06) × 10 ⁻⁶	26.5	+3		
65.0	(5.00 ± 0.2) × 10 ⁻⁴			35.0		(4.69 ± 0.08) × 10 ⁻⁶				
90A-F ^e	25.0	4.50 × 10 ⁻⁵ ^b				40.0	(1.0 ± 0.1) × 10 ⁻⁵ ^d			
	30.0	(8.0 ± 0.1) × 10 ⁻⁵	17.9	-18		50.0	(3.8 ± 0.2) × 10 ⁻⁵ ^d			
	35.0	(1.30 ± 0.03) × 10 ⁻⁴			90A-F ^{e,j}	25.0	2.50 × 10 ⁻⁸ ^b			
	50.0	(5.00 ± 0.05) × 10 ⁻⁴				30.0	(5.27 ± 0.04) × 10 ⁻⁸	27.6	-1	
	60.0	(1.3 ± 0.1) × 10 ⁻³				35.0	(1.10 ± 0.02) × 10 ⁻⁷			
75A-F ^e	25.0	2.00 × 10 ⁻⁴ ^b				40.0	(2.15 ± 0.01) × 10 ⁻⁷			
	30.0	(2.98 ± 0.07) × 10 ⁻⁴	16.0	-22		60.0	(3.55 ± 0.02) × 10 ⁻⁶			

^a Errors reported as 1 standard deviation from the mean. ^b Calculated from data at higher temperatures. ^c Percent by volume. For example, 90E-W means 90 volumes of ethanol plus 10 volumes of water, both at 25 °C before mixing. ^d Reference 8a. ^e Percent by volume. For example, 90A-F means 90 volumes of acetic acid plus 10 volumes of formic acid, both at the same temperature before mixing. ^f Percent by weight. 97TFE means 97 g of trifluoroethanol plus 3 g of water. ^g Percent by volume. 80TFE-E means 80 volumes of trifluoroethanol plus 20 volumes of ethanol, both at the same temperature before mixing. ^h Percent by volume. For example, 90A means 90 volumes of acetone plus 10 volumes of water, both at the same temperature when mixing. ⁱ Percent by volume. 90D means 90 volumes of dioxane plus 10 volumes of water, both at the same temperature before mixing together. ^j 2-Adamantyl *p*-toluenesulfonate.

Table II. Summary of Solvent Parameters Derived from Correlation Equations^a

compd ^b	solvents ^c	<i>m</i> values ^d	<i>r</i> ^e	<i>n</i> ^f	compd ^b	solvents ^c	<i>m</i> values ^d	<i>r</i> ^e	<i>n</i> ^f
c-PrCarb-OTs ^g	A, ^h B, ⁱ D, E	0.78 ± 0.03	0.99 ⁺	16	c-Hex-OTs ^g	A, B, ^{i,n,o} C ^{p,q}	gives A,B,C lines ^{r,s}		
neophyl-OTs ^g	A, B, ⁱ C ^{j,k}	0.66 ± 0.02	0.99 ⁺	13	cholest-OTs	A, ⁱ B, ^u C, ^v D, E	0.65 ± 0.04	0.98	12
pin-OBs ^g	A, B, ⁱ C ^l	0.74 ± 0.04	0.96	15	cholest-OTs	A, ⁱ B, ^w C, ^v D, E	0.65 ± 0.04	0.99	11
Norb-OTs ^g	A, B, ⁱ C ^m	0.84 ± 0.04	0.97	15					

^a Errors reported as standard error of the regression coefficient or of the intercept. ^b c-PrCarb-OTs = cyclopropylcarbonyl tosylate; pin-OBs = pinacolyl brosylate; Norb-OTs = 2-*exo*-norbornyl tosylate; c-Hex-OTs = cyclohexyl tosylate; cholest-OTs = cholesteryl tosylate. ^c A-series = EtOH, 90, 80, 70, 60, 50, and 40% (v/v) aqueous EtOH; B-series = AcOH, 90, 75, 50, and 25% (v/v) AcOH/HCOOH; C-series = 97, 85, and 70% (w/w) aqueous TFE; D-series = 90% and 80% (v/v) aqueous dioxane; E-series = 90% and 85% (v/v) aqueous acetone. ^d Calculated by use of eq 1: $\log k = mY_{OTs} + \log k_0$ where Y_{OTs} is based on 2-Ad-OTs.¹⁰ ^e Correlation coefficient. ^f Number of solvents. ^g Reference 25b. ^h Does not include 40% aq EtOH. ⁱ Does not include 90% (v/v) AcOH/HCOOH. ^j 70% aq TFE only. ^k Reference 31h. ^l Reference 12b. ^m Reference 12a. ⁿ Includes TFA. ^o Reference 8c. ^p Includes 50% aq TFE. ^q Reference 30. ^r Correlation coefficient = 0.34. ^s Number of solvents = 15. ^t Includes EtOH, 90, and 80% aq EtOH. ^u Includes AcOH, 90, and 75% AcOH/HCOOH. ^v Includes 97% aq TFE and 80% (v/v) TFE/EtOH. ^w Includes 90 and 75% AcOH/HCOOH.

value for cholesteryl tosylate (0.65) is within this range. This similarity in *m* values is consistent with a similarity of mechanism of 1 and the *k*_Δ substrates and the lack of dispersion is consistent with negligible nucleophilic solvent assistance.

The effect of added azide ion on rates of reaction—the azide probe³¹—has proven to be a very useful criterion for assessing the magnitude of nucleophilic solvent assistance. Accordingly, we have analyzed the kinetic data of Table

III in terms of the Winstein salt effect equation³² (2), where

$$k = k^0(1 + b[N_3^-]) \quad (2)$$

k is the observed rate constant, *k*⁰ is the rate constant in the absence of azide ion, and the value of *b* (equal to the slope of the straight line resulting from a plot of *k*/*k*⁰ vs the concentration of azide ion) indicates the magnitude of the rate enhancement produced when solvolysis is carried out in the presence of azide ion. The results are summarized in Table IV.

Again, marked differences between the solvolytic behavior of cholesteryl tosylate and cyclohexyl tosylate are observed: while the rate enhancements observed in the ethanolysis of cholesteryl tosylate in the presence of azide ion are relatively high (*b* = 24), the rate enhancements for

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Table III. Effect of Added Sodium Azide upon Solvolysis Rates of Cholesteryl, Cyclohexyl and 2-Adamantyl Tosylate

compound	solvent	conc, M	temp, °C	k_{obsd}^a (s ⁻¹)	$(k_i/k^0)^b$
Cho-OTs ^c	EtOH	0.000	50	$(1.11 \pm 0.01) \times 10^{-4}$	
		0.004	50	$(1.22 \pm 0.01) \times 10^{-4}$	1.10
		0.006	50	$(1.28 \pm 0.04) \times 10^{-4}$	1.15
		0.008	50	$(1.32 \pm 0.01) \times 10^{-4}$	1.19
		0.01	50	$(1.38 \pm 0.02) \times 10^{-4}$	1.24
c-Hex-OTs ^d	EtOH	0.00	50	$(1.40 \pm 0.01) \times 10^{-6}$	
		0.004	50	$(1.75 \pm 0.03) \times 10^{-6}$	1.25
		0.006	50	$(1.95 \pm 0.04) \times 10^{-6}$	1.39
		0.02	50	$(2.87 \pm 0.04) \times 10^{-6}$	2.05
		0.04	50	$(4.80 \pm 0.04) \times 10^{-6}$	3.43
	80E/W	0.00	60	$(5.58 \pm 0.02) \times 10^{-5}$	
		0.02	60	$(8.29 \pm 0.03) \times 10^{-5}$	1.49
		0.04	60	$(8.92 \pm 0.02) \times 10^{-5}$	1.60
		0.06	60	$(9.65 \pm 0.01) \times 10^{-5}$	1.73
		2-Ad-OTs ^e	EtOH	0.00	75
0.01	75			$(6.20 \pm 0.03) \times 10^{-7}$	1.17
0.02	75			$(7.30 \pm 0.05) \times 10^{-7}$	1.38
0.04	75			$(9.0 \pm 0.08) \times 10^{-7}$	1.70
80E/W ⁱ	0.00		75	$(1.94 \pm 0.05) \times 10^{-5}$	
	0.02		75	$(2.10 \pm 0.01) \times 10^{-5}$	1.08
	0.04		75	$(2.17 \pm 0.01) \times 10^{-5}$	1.12
	0.06		75	$(2.26 \pm 0.01) \times 10^{-5}$	1.16

^a Errors reported as 1 standard deviation from the mean. ^b Ratio of observed rate constant at some concentration of salt to observed rate constant at zero salt concentration. ^c Concentration of cholesteryl-OTs = 0.002 M. ^d Concentration of cyclohexyl-OTs = 0.01 M. ^e Compares with a value of 1.41×10^{-5} reported by Winstein (ref 39). ^f Compares with a value of 5.50×10^{-5} reported earlier by Roberts (ref 40). ^g Concentration of 2-adamantyl-OTs = 0.01 M. ^h Compares with a value of 6.28×10^{-7} reported by Kevill (ref 41). ⁱ Data taken from Table II of ref 31c.

Table IV. Summary of Parameters Derived from Salt Effect Equation^a

compd ^b	solvent	azide conc	b values ^c	r^d	% infinity titer ^e
cholest-OTs	EtOH	0.00	24	0.99	100
		0.004			100
		0.006			99
		0.008			98
		0.01			95
c-Hex-OTs	EtOH	0.00	60	0.99	100
		0.004			75
		0.006			72
		0.02			65
		0.04			46
	80E/W	0.00	6	0.99	100
		0.02			99
		0.04			89
		0.06			85
		2-Ad-OTs	EtOH	0.00	18
0.01					87
0.02					83
0.04					75
80E/W ^f	0.00		3		100
	0.02				99.9
	0.04				99.6
	0.06				99.3

^a Calculated by use of eq 2. ^b cholest-OTs = cholesteryl tosylate; c-Hex-OTs = cyclohexyl tosylate; 2-Ad-OTs = 2-adamantyl tosylate. ^c A measure of the rate enhancement produced when solvolysis is carried out in the presence of added azide ion. ^d Correlation coefficient. ^e Calculated by dividing the theoretical by the observed yield of acid. ^f Data taken from ref 31c.

cyclohexyl tosylate are 2.5 times higher ($b = 60$). Interestingly, the rate enhancements observed for the ethanolysis of 2-adamantyl tosylate in the presence of azide ion are also relatively high ($b = 18$). These higher than usual sensitivities can be accounted for in terms of the long recognized³³⁻³⁵ enhancement of salt effects upon

solvolysis rates in less polar solvents. For example, in the more polar solvent 80% aqueous ethanol, we found that the effect of added azide ion upon the rate of solvolysis of cyclohexyl tosylate is characterized by a b value of 6, one-tenth of that observed in the appreciably less polar solvent ethanol (cf. Table IV). Equally interesting, we found that the effect of added azide ion upon the rate of ethanolysis of 2-adamantyl tosylate is characterized by a b value of 18, 6 times greater than that observed^{31c} in 80% aqueous ethanol. Finally, the high values for the infinity titers of 1 listed in Table IV imply that little or no alkyl azide product was formed. These results are consistent³⁶ with negligible nucleophilic solvent assistance in the solvolysis reactions of 1.

Experimental Section

Materials. Cholesteryl tosylate (Sigma) was recrystallized from ether: mp 131.5–132.5 °C (lit.⁴² mp 131.7–132.6 °C); ¹H NMR (CDCl₃/Me₄Si) δ 2.40 (3 H, s, ArCH₃), 4.32 (1 H, heptet, $J = 5.4$ Hz, CHOTs), 5.30 (1 H, d, $J = 5.4$ Hz, vinylic), 7.32 (2 H, d, $J = 7.7$ Hz, ArH), 7.89 (2 H, d, $J = 7.7$ Hz, ArH); ¹³C NMR (CDCl₃/Me₄Si) δ 82.3, 123.4, 127.5, 129.7, 134.6, 138.8, 144.2. Cyclohexyl tosylate and 2-adamantyl tosylate were prepared as previously described.^{25b} The solvents were purified as previously described.⁴³ ¹H and ¹³C NMR spectra were obtained at 270 MHz.

Rate Measurements. The rates of solvolysis were followed titrimetrically. In a typical kinetic run, the requisite amount of ester was accurately weighed into a 25-mL volumetric flask and then sufficient solvent was added rapidly to give a 25-mL reaction solution volume.⁴⁴ Reaction time commenced with the addition of one-half the solvent. The solvent, along with the volumetric flask containing the ester, used for each kinetic run was thermostated in a constant temperature bath, maintained at the reaction temperature, at least 5 min prior to a run. At appropriate times, 2-mL aliquots were quenched, when necessary, with cold solvent and analyzed for liberated *p*-toluenesulfonic acid. The titrating solutions were as follows: for acetic acid–formic acid solvents,⁴⁶ 0.020 N sodium acetate in acetic acid; for the aqueous binary solvents, 0.017 to 0.020 N NaOH in 95% aqueous methanol. The indicators used were as follows: for acetic acid–formic acid solvents, bromophenol blue (in acetic acid), 3–4 drops; for ethanol and aqueous dioxane solvents, bromothymol blue (in water), 1–2 drops; for the other aqueous solvents and the TFE/EtOH mixture, bromophenol blue (in ethanol), 1 drop.

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(36) The established^{31c-e} argument goes as follows: azide ion is a better nucleophile than ethanol,^{37,38} hence, the lack of nucleophilic participation by azide as measured by a relatively small rate enhancement value and the absence of a significant amount of azide product implies that ethanol does not participate nucleophilically either. We concur with this argument.

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(44) The infinity titers for reactions whose half-lives were greater than 2 h and whose reaction temperatures were greater than 50 °C were obtained by the ampule technique.⁴⁵

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(46) For reactions in acetic–formic acid mixtures, it was necessary to dilute the 2-mL aliquots with 2-mL of acetic anhydride/acetic acid (75:25) to obtain a sharp end point.

Treatment of Kinetic Data. First-order rate constants were calculated by using the first-order integrated rate equation:⁴⁷ $k_t = 1/t \ln (mL_\infty / (mL_\infty - mL_t))$.⁴⁸ Multiple determinations (6-12) were made for each kinetic run. The activation parameters recorded in Table I were obtained by regression analysis⁴⁹ of \ln

(k_t/T) versus $1/T$,⁵⁰ and the m values listed in Table II and the b values listed in Table IV were also obtained by regression analysis.

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(48) The parameter mL_∞ = measured titer at 10 half-lives or theoretical titer at 100% conversion calculated from the known quantity of tosylate ester initially present in the reaction mixture; mL_t = measured titer at time t .

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(50) Reference 47b, Chapter 7.