

Registry No. D,D-2-Octyl casylate, 83200-07-1; L,D-2-octyl casylate, 83214-07-7; L,L-2-octyl casylate, 83214-08-8; D,L-2-octyl casylate, 83214-09-9.

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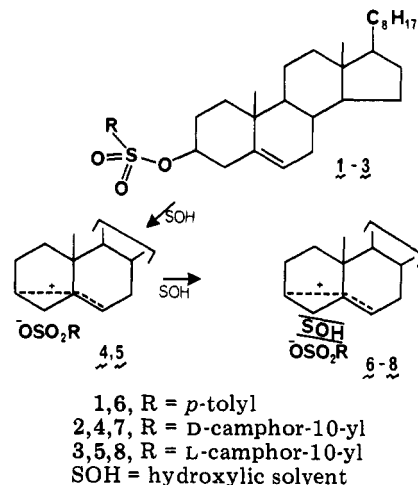
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Chiral Leaving Groups in Nucleophilic Displacement Reactions. Solvolysis of 2-Adamantyl and Cholesteryl Camphor-10-sulfonates (Casylates)

Summary: Significant rate and product differences between the 2-adamantyl D- and L-casylates upon solvolysis in aqueous L-(+)-ethyl lactate are taken as evidence of kinetic involvement of solvent-separated ion pairs involving both water and ethyl lactate.

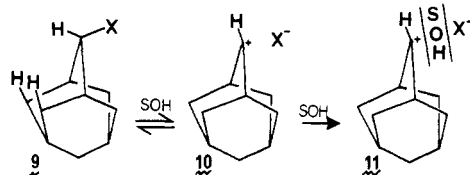
Sir: In the preceding communication¹ we showed that the diastereomeric transition states of substrates undergoing backside solvolytic displacement (a k_s process²) are very slightly different in energy. In view of efforts to utilize chiral leaving groups in asymmetric synthesis,³ the above finding suggests that steric factors alone will not suffice to provide a high enantiomeric excess. In this communication we show that large reactivity differences may occur with some substrates that undergo displacement via solvent-separated ion pair (SSIP) intermediates.

The experimental data from solvolysis of cholesteryl tosylate (1) are consistent with a mechanism involving solvolysis with π participation giving a SSIP intermediate, e.g., 6, which produces rearranged or unrearranged product.^{4,5} When cholesteryl D- and L-casylates⁶ (2 and 3) are solvolyzed in 80% aqueous ethanol (v/v), nearly identical⁷ rate constants and activation parameters are found (Table I). These data are consistent with a mechanism involving rate-determining formation of the tight ion pairs (TIPs) (4 or 5) from neutral substrate (2 or 3, respectively). If the rate-determining step were formation of the SSIPs (7 or 8) from the TIPs (4 or 5), one would expect that the diastereomeric ion pairs would provide different steric barriers for solvent insertion⁸ and, therefore, a larger



difference in rate between the isomers.

2-Adamantyl tosylate (9) is one of the very few secondary substrates known to solvolyze by a limiting (k_c) mechanism.^{9,10} Although recently debated, the rate-determining step in its solvolysis is indicated by various experimental probes to be conversion of TIPs and SSIPs^{11,12} e.g., 10 to 11. Also, for a k_c system, 9 differs from the expected by its product stereochemistry, which is net retention.¹³ It has been suggested² that because the



backside of the 2-adamantyl system is sterically hindered, the principal mode¹⁴ of solvolysis is formation and collapse by frontside attack of SSIPs. Therefore, as the solvent inserts into the TIP to form the SSIP, crowding should be important.

2-Adamantyl D- and L-casylate¹⁵ were solvolyzed in 80% aqueous L-(+)-ethyl lactate.¹⁶ Because the 2-adamantyl fragment is symmetrical, diastereomeric transition states are present only when chiral ethyl lactate is involved in the activated complex. The rate data and activation parameters (Table II) show that ethyl lactate must be involved as there is a significant difference in the ease of solvolysis of the 2-adamantyl enantiomers. Product studies provided selectivities^{10,17} (k_{ROH}/k_{H_2O}): D-casylate = 0.29, L-casylate = 0.38. On the basis of previous studies,¹⁰ the preferential reaction with water upon solvolysis of 2-adamantyl derivatives in aqueous alcohols is expected.

(1) McManus, S. P.; Roberts, F. E.; Lam, D. H.; Hovanes, B., preceding paper in this issue.

(2) Harris, J. M. *Prog. Phys. Org. Chem.* 1974, 11, 89-173.

(3) (a) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* 1983, 104, 881-884. (b) Duggan, P. G.; Murphy, W. S. *J. Chem. Soc., Perkin Trans. I* 1976, 634-638.

(4) (a) Shoppee, C. W. *J. Chem. Soc.* 1946, 1147-1150. (b) Winstein, S.; Adams, R. *J. Am. Chem. Soc.* 1948, 70, 838-842.

(5) Sunko, D. E.; Borcic, S. In "Isotope Effects in Chemical Reactions"; Collins, C. J.; Bowman, N. W., Eds.; Van Nostrand Reinhold: New York, 1970; pp 160-212.

(6) Prepared from recrystallized cholesterol, $[\alpha]^{25}_D = -37.0^\circ$ (c 4.0, $CHCl_3$), and the respective D- or L-casyl chloride (ref 1): cholesteryl D-casylate, mp 136.5-140.5, $[\alpha]^{25}_D = -2.5^\circ$ (c 4.0, $CHCl_3$); cholesteryl L-casylate, mp 136.5-137.5, $[\alpha]^{25}_D = -41.8^\circ$ (c 3.98, $CHCl_3$); each gave elemental analysis $\pm 0.3\%$ and expected IR and NMR spectra.

(7) Five different side-by-side rate measurements of the diastereomeric pairs were run at 56.2 °C. As can be seen from Table I, the averages and error limits do not overlap. Since the conductivity cells were alternated between the isomers, it is unlikely that additional determinations would serve to change anything other than our confidence level; cf. Youmans, H. L. "Statistics for Chemistry"; Charles E. Merrill: Columbus, OH, 1973.

(8) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; pp 65-68.

(9) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1981, 103, 5466-5475.

(10) Harris, J. M.; Becker, A.; Fagan, J. F.; Walden, F. A. *J. Am. Chem. Soc.* 1974, 96, 4484-4489 and references therein.

(11) Shiner, V. J.; Nollen, D. A.; Humski, K. *J. Org. Chem.* 1979, 44, 2108-2115 and references therein.

(12) Paradisi, C.; Bunnett, J. F. *J. Am. Chem. Soc.* 1981, 103, 946-948.

(13) Bone, J. A.; Whiting, M. C. *Chem. Commun.* 1970, 115.

(14) There is evidence that a second solvolysis pathway may be simultaneously active; cf. ref 11.

(15) Prepared in the normal way, ref 1; 2-adamantyl D-casylate, mp 192-194 °C, $[\alpha]^{25}_D = +69^\circ$ (c 0.96, $CHCl_3$); 2-adamantyl L-casylate, mp 193-195 °C, $[\alpha]^{25}_D = -44^\circ$ (c 1.59, $CHCl_3$); each gave elemental analysis $\pm 0.3\%$ and expected spectra.

(16) From a freshly opened bottle (Aldrich).

(17) Product analyses were performed by GLC analysis, assuming a response factor for the ether product based on comparisons with other ethers.

Table I. Solvolysis Rates of Cholesteryl D- and L-Casylate in 80% Aqueous Ethanol (v/v)

casyl-ate	T, °C	10 ⁴ k, s ⁻¹	ΔH [‡] , kcal/mol	ΔS [‡] , eu
D	25.0	0.487 ^a	22.0 ^b	-4.38 ^b
	24.2	0.442 ± 0.019		
	34.0	1.49 ± 0.10		
	45.5	5.63 ± 0.27		
	56.2	18.4 ± 0.30		
L	25.0	0.548 ^a	21.8 ^b	-5.03 ^b
	25.2	0.556 ± 0.004		
	34.6	1.81 ± 0.02		
	47.4	7.65 ± 0.09		
	56.2	19.6 ± 0.30		

^a Calculated from rates at other temperatures. ^b Based on 11 conductimetrically determined rates at the temperatures shown (*r* = 1.00).

Table II. Solvolysis Rates of 2-Adamantyl D- and L-Casylates in 80% Aqueous L(+)-Ethyl Lactate (v/v)

casyl-ate	T, °C	10 ⁴ k, s ⁻¹	ΔH [‡] , kcal/mol	ΔS [‡] , eu
D	25.0	0.00114 ^a	20.9 ^b	-20.3 ^b
	90.4	0.728 ± 0.025		
	100.4	1.92 ± 0.01		
	125.0	10.2 ± 0.010		
	25.0	0.000 098 4 ^a		
80.2	0.155 ± 0.011			
90.3	0.450 ± 0.007			
100.4	1.40 ± 0.13			
115.2	5.52 ± 0.27			

^a Calculated from rates at other temperatures. ^b Based on six conductimetrically determined rates at the temperatures shown (*r* = 0.998). ^c Based on 10 conductimetrically determined rates at the temperatures shown (*r* = 0.999).

However, since the rate studies implicate ethyl lactate involvement, the strong preference for water is surprising. Consideration of these facts prompt us to reject simple structures of these SSIPs with a single solvent molecule

between the cation and leaving group (see structure 11). Instead, a more complex ion pair involving both solvents is more satisfactory.^{18,19} In such an ion pair the ethyl lactate may be primarily involved in electrophilically solvating the leaving group, while the smaller and more nucleophilic water molecule is better able to solvate cations frontside (and backside?). While our overall view of these solvolytic processes is still somewhat rudimentary, our experiments utilizing chiral leaving groups have been helpful in confirming that SSIPs are involved in the rate-determining step in the solvolysis of 2-adamantyl substrates. Also, these studies suggest that more than one solvent molecule is involved in the SSIP.

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Registry No. 2, 83220-34-2; 3, 83289-25-2; 9, 25139-43-9; 2-adamantyl D-casylate, 83220-35-3; 2-adamantyl L-casylate, 83289-26-3; L-(+)-ethyl lactate, 687-47-8.

(18) At least two solvent molecules are suggested to separate the cation and anion; cf. Simonetta, M. "Chemical Reactivity and Reaction Pathways"; Klopman, G., Ed.; Wiley-Interscience: New York, 1974; Chapter 2. Grunwald, E., private communication See Grunwald, E.; I, T. P. *Pure Appl. Chem.* 1979, 51, 53-61 and references therein.

(19) The involvement of two solvent molecules has been suggested for *tert*-butyl chloride solvolysis in aqueous solutions; cf. Blandamer, M. J.; Burgess, J.; Duce, P. P.; Symons, M. C.; Robertson, R. E.; Scott, J. W. *M. J. Chem. Res. Synop.* 1982, 130.

(20) American Chemical Society-Petroleum Research Fund Undergraduate Scholar, 1979-1980.

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