However, the free mercaptan is unstable and cylizes spontaneously to form a sulfide lacking vinyl protons in the NMR spectrum, tentatively identified as **16**. The same overall result is achieved more efficiently by reaction of **13** with CsF/DME (89% yield of **16** after chromatography). In view of the instability of mercaptan **15**, correlation of the a and b series was performed by using Raney nickel desulfurization. Thus, treatment of either **3a** or of **16** with W-2 Raney nickel affords 5-acetoxycycloundecanone **17**[14] as the sole product. This experiment confirms the formation of a carbocyclic periphery in both a and b series ring expansions.

Work is continuing to evaluate this route to cycloundecenones in cytochalasin synthesis.

Registry No. 3a, 83076-86-2; **4**, 83076-81-7; (*E*)-**5**, 83076-82-8; **6** (isomer 1), 83076-83-9; **6** (isomer 2), 83148-35-0; **6** iodide (isomer 1), 83076-84-0; **6** iodide (isomer 2), 83076-85-1; (*E*)-**8**, 83095-35-6; (*E*)-**9**, 83076-87-3; (*E*)-**10**, 83076-88-4; (*E*)-**11**, 83076-89-5; **12**, 83076-90-8; **13**, 83076-91-9; **16**, 83076-92-0; **17**, 83076-93-1; i, 83076-94-2; ii, 83076-95-3; (*Z*)-iii, 83076-96-4; cytochalasin D, 22144-77-0; 2-ethoxybutadiene, 4747-05-1; $Me_2PhSiLi$, 3839-31-4.

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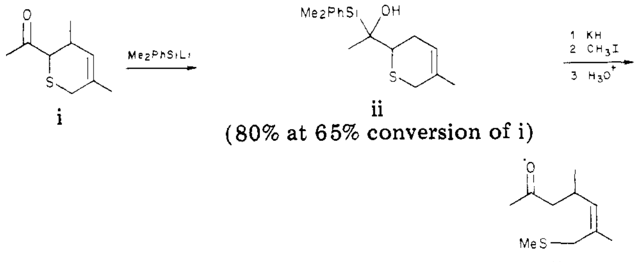
[13] (a) Analogous expulsion of an α leaving group initiated by C to O silyl migration: Corey, E. J.; Tius, M. A.; Jagabandhu, D. *J. Am. Chem. Soc.* **1980**, *102* 1742. Reich, H. J.; Kelly, M. J. *Ibid.* **1982**, *104*, 1119. (b) The analogous C–S cleavage of i[9] can be performed by using $Me_2PhSiLi$. In this case, treatment of silylcarbinol ii with KH followed by methyl iodide results in clean conversion to the acyclic sulfide iii. Use of Me_3SiLi in place of $Me_2PhSiLi$ is not satisfactory due to increased enolization.



i

ii

(80% at 65% conversion of i)

iii

(97%)

[14] Characterization of 17: IR 1720, 1705 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 4.88 (1 H, m), 2.8–2.5 (2 H, m), 2.4–2.2 (2 H, m), 2.05 (3 H, s), 1.9–1.3 (14 H, m); mass spectrum, *m/e* 226.1566 (calcd for $C_{13}H_{22}O_3$ 226.1569).

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Chiral Leaving Groups in Nucleophilic Displacement Reactions. Solvolysis of 2-Octyl Camphor-10-sulfonate (Casylate) Stereoisomers

Summary: Small kinetic differences between the diastereomeric pairs in aqueous ethanolysis of the four stereoisomeric 2-octyl casylates are consistent with a crowded S_N2 transition state.

Sir: Wilson and Cram recently showed[1] that in aromatic nucleophilic substitution a chiral leaving group may provide the driving force for asymmetric synthesis. Since the steric demands should vary with the displacement mechanism, we have studied solvolytic reactivity of some model aliphatic systems undergoing k_s, k_Δ, and k_c reactions.[2] In each case, we used the readily available (+)- or (−)-camphor-10-sulfonate ester,[3] which we call casylates, as the chiral leaving group. A second chiral component (solvent or substrate) was used to provide diastereomeric transition states for comparison. Our preliminary results show reactivity differences with diastereomers of each substrate type and interesting differences among the mechanistic classes. The reactivity of the four 2-octyl casylate stereoisomers is treated in this communication.

Table I. Solvolysis Rates of 2-Octyl Casylates

isomer	% EtOH (v/v)	T, °C	10^4k, s^{-1}	$\Delta H^‡$, kcal/mol	$\Delta S^‡$, eu
D,D	80E	25.0	6.48[a]	18.7[b]	−19.8[b]
		49.4	0.673 ± 0.025		
		56.1	1.42 ± 0.04		
		64.2	2.80 ± 0.07		
		68.8	4.20 ± 0.10		
		75.0	6.59 ± 0.22		
		85.0	12.5 ± 0.91		
L,D	80E	25.0	4.76[a]	19.7[b]	−17.0[b]
		49.4	0.619 ± 0.006		
		56.1	1.21 ± 0.01		
		56.8	1.27 ± 0.06		
		70.1	4.84 ± 0.04		
		75.0	6.65 ± 0.28		
		85.0	13.3 ± 0.22		
L,L	60E	55.0	2.66[a]	20.9	−11.4
		51.0	1.80 ± 0.01		
		64.6	6.92 ± 0.05		
	80E	56.1	1.44 ± 0.03		
	90E	55.0	0.841[a]	16.2	−28.2
		54.9	0.838 ± 0.003		
		79.2	4.95 ± 0.04		
	95E	55.0	0.726 ± 0.035		
	100E	55.0	0.491 ± 0.008		
D,L	60E	55.0	2.70[a]	20.9	−11.5
		51.0	1.80 ± 0.03		
		64.6	6.91 ± 0.03		
	80E	56.1	1.14 ± 0.01		
	90E	55.0	0.553[a]	19.4	−19.0
		54.9	0.550 ± 0.002		
		79.2	4.60 ± 0.04		
	95E	55.0	0.438 ± 0.002		
	100E	55.0	0.347 ± 0.004		

[a] Extrapolated from rates at other temperatures.
[b] From 22 separate kinetic runs at the six temperatures shown, r = 0.998.

2-Octyl substrates have long been known to follow a S_N2-like mechanism (k_s substrate)[4] in solvents of moderate nucleophilicity.[5] Multiple conductimetric rate measurements[6] of solvolytic reactions of the D- and L-2-octyl D-

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[1] Wilson, J. M.; Cram. D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881–884.

[2] Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89–173.

[3] D-(+)-Casyl chloride, mp, 66–67 °C, was prepared by the procedure of P. D. Bartlett and L. H. Knox ("Organic Syntheses"; Wiley: New York, 1973; Collect Vol. V, pp 196–198) from the optically pure acid monohydrate (Eastman or Aldrich) or was purchased from Tridom (Fluka). L-Casyl chloride, mp 66–67 °C, was prepared from the 95% optically pure ammonium salt of the L-acid (Aldrich), using the Bartlett–Knox procedure. Esters were prepared by the tosylate procedure of Schleyer (Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 1180).

[4] A variety of 2-octyl substrates have been shown to give complete inversion in a variety of solvents including ethanol and water; cf. Sukenik, C. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 6613–6623; Weiner H.; Sneen, R. A. *Ibid.* **1965**, *87*, 288–291 and references therein; also see Filippo, J. S., Jr.; Silberman, J. *Ibid.* **1981**, *103*, 5588–5590.

[5] Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67.

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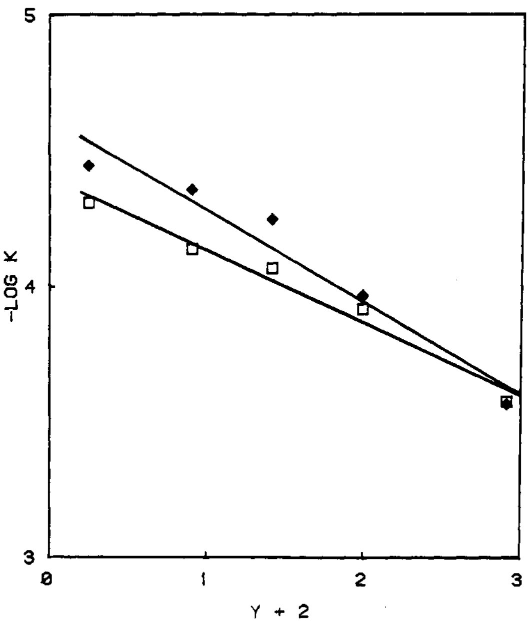


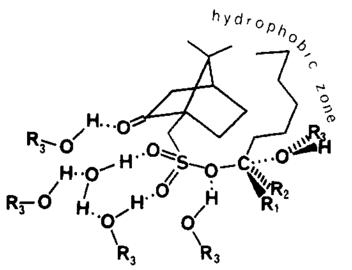
Figure 1. Grunwald-Winstein plots for the diastereomeric 2-octyl L-casylates in aqueous ethanol, (◆) = D-2-octyl L-casylate, (□) = L-2-octyl L-casylate.

casylates[7] in 80% aqueous ethanol at several temperatures have allowed determination of the reaction activation parameters with high confidence (Table I). The differences in the measured rate constant, especially at the higher temperatures, are small enough to make differences in the activation parameters almost unconvincing.[8] Hence, repeated experiments were needed to establish a suitable confidence level. To further allay doubts and for comparison with the D-casylates, the isomeric D- and L-2-octyl L-casylates were prepared and solvolyzed in a variety of solvent compositions.

In 80% aqueous ethanol, the enantiomeric pairs had different solvolysis rates when measured at 56.1 °C. The D-2-octyl D-casylate and its L,L enantiomer had measured rate constants of $(1.43 \pm 0.04)10^{-4}$ s^{-1} (six runs), while the rates measured for the L,D and D,L enantiomeric pair, in side-by-side determinations, are $(1.17 \pm 0.05)10^{-4}$ s^{-1}. A similar difference in rate constants is measured in side-by-side runs for the D,D and L,D diastereomers at 49.4 °C. (Table I). The rates of the L-casylates were determined in various concentrations of aqueous ethanol, and a Winstein-Grunwald plot was constructed for each diastereomer (Figure 1). While the slopes are obviously different (the derived **m** values are D,L = 0.34 and L,L = 0.27), each plot shows a definite curvature.

Since ethanol is more reactive toward the D, D/L, L enantiomeric pair, assuming that the ground states of the diastereomeric 2-octyl casylates are equally solvated, these data suggest that it is the ethanol reactivity that produces the rate differences observed in all solvent compositions studied. This may be because the bulkier ethanol may fit better in one of the diastereomeric transition states because of differing steric factors (e.g., see Chart I; R_1 = H or CH_3, R_2 = CH_3 or H, and R_3 = H or C_2H_5).

Chart I



Product studies[9] with 80% methanol-water, 80% ethanol-water, and 80% 2-propanol-water provide the following selectivities (k_{ROH}/k_{H_2O}):[10] methanol, 0.88; ethanol, 0.74; 2-propanol, 0.44.[11] For a series of aqueous ethanol solvents, the following selectivities were found: 60% aqueous ethanol, 1.03; 80% aqueous ethanol, 0.74, 90% aqueous ethanol, 0.65. Therefore, water, which should be the poorest nucleophile,[12,13] is the better nucleophile in all but one example (60% aqueous ethanol) and its apparent nucleophilicity increases as the solvent-ionizing power (Y) decreases. This is consistent with a crowded S_N2-like transition state[2,12] that becomes more crowded as Y decreases.

In summary, small kinetic differences are found for diastereomeric alkyl substrates undergoing solvent-assisted nucleophilic displacement. Any difference may be surprising since the nucleophilic and chiral leaving group are on opposite sides of the carbon undergoing displacement with three atoms separating the chiral centers. Nevertheless, steric differences alone would not appear to make the use of chiral leaving groups useful in S_N2-like synthetic processes. However, by maximizing the steric factors[1] and, more importantly, any electronic factors,[14] chiral leaving groups may be advantageously utilized in asymmetric synthesis. In the following communication in this issue[15] the dramatic rate difference attending the solvolysis of substrates of another mechanistic type is discussed.

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(6) McManus, S. P.; Lam, D. H. *J. Org. Chem.* **1978**, *43*, 650-651.

(7) The 2-octyl casylates were prepared as light-yellow oils with characteristic IR and NMR spectra from the appropriate sulfonyl chloride (ref 3) and the optically active alcohols (Aldrich, 90% optically pure); D-2-octyl D-casylate, $[\alpha]^{25}_D = +34.7°$ (*c* 4.03, $CHCl_3$); L,D, $[\alpha]^{25}_D = +23.8°$ (*c* 4.03, $CHCl_3$); L,L, $[\alpha]^{22}_D = -30.8°$ (*c* 4.03, $CHCl_3$); DL, $[\alpha]^{22}_D = -20.5°$ (*c* 4.10, $CHCl_3$).

(8) In the early stages of this work our claim of different activation parameters based on duplicate kinetic runs at the four higher temperatures was received with skepticism by some colleagues.

(9) Products were determined by response-calibrated GLC. Reproducibility was ca. ±5% normally; however, peak overlap and interference from lutidine (acid scavenger) limited reproducibility to ca. ±10% in some cases.

(10) Selectivity is used here as the rate ratios for attack by the nucleophiles (alcohol/water) or k_a/k_w and is determined by placing the ratio of ether and alcohol products on a molar basis; cf. Harris, J. M.; Clark, D. C.; Becker, A.; Fagan, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 4478-4484.

(11) (a) Pross, A. *Adv. Phys. Org. Chem.* **1977**, *14*, 59-132. (b) Giese, B. *Angew, Chem., Int. Ed. Engl.* **1977**, *16*, 125-136. (c) Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461-3480.

(12) McManus, S. P. *J. Org. Chem.* **1981**, *46*, 635-638.

(13) We prefer to use the term "apparent nucleophilicity" since nucleophilicity is subject to factors such as steric effects; see ref 12.

(14) (a) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375-381. (b) Duggan, P. G.; Murphy, W. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 634-638.

(15) McManus, S. P.; Safavy, K.; Roberts, F. E., following paper in this issue.

(16) (a) American Chemical Society (ACS)-Petroleum Research Fund (PRF) Undergraduate Scholar, 1979-1980. (b) ACS-PRF Undergraduate Scholar, 1977-1978. (c) ACS-PRF Undergraduate Scholar, 1980-1981.

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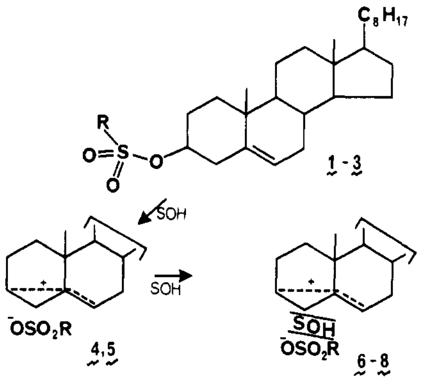
Chiral Leaving Groups in Nucleophilic Displacement Reactions. Solvolysis of 2-Adamantyl and Cholesteryl Camphor-10-sulfonates (Casylates)

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.

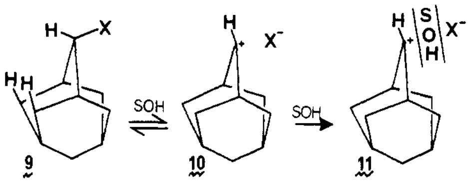
Sir: In the preceding communication[1] we showed that the diastereomeric transition states of substrates undergoing backside solvolytic displacement (a k_s process[2]) are very slightly different in energy. In view of efforts to utilize chiral leaving groups in asymmetric synthesis,[3] the above finding 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-casylates[6] (**2** and **3**) are solvolyzed in 80% aqueous ethanol (v/v), nearly identical[7] 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 insertion[8] and, therefore, a larger difference in rate between the isomers.



1,6, R = *p*-tolyl
2,4,7, R = D-camphor-10-yl
3,5,8, R = L-camphor-10-yl
SOH = hydroxylic solvent

2-Adamantyl tosylate (**9**) is one of the very few secondary substrates known to solvolyze by a limiting (k_c) mechanism.[2,9,10] 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 suggested[2] that because the backside of the 2-adamantyl system is sterically hindered, the principal mode[14] 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.



X = *p*-toluenesulfonate, SOH = hydroxylic solvent

2-Adamantyl D- and L-casylate[15] 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.

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(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. 1* **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, $[\alpha]^{25}_D = -37.0°$ (c 4.0, $CHCl_3$), and the respective D- or L-casyl chloride (ref 1): cholesteryl D-casylate, mp 136.5–140.5, $[\alpha]^{26}_D = -2.5°$ (c 4.0, $CHCl_3$); cholesteryl L-casylate, mp 136.5–137.5, $[\alpha]^{25}_D = -41.8°$ (c 3.98, $CHCl_3$); each gave elemental analysis ±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, $[\alpha]^{25}_D = +69°$ (c 0.96, $CHCl_3$); 2-adamantyl L-casylate, mp 193–195 °C, $[\alpha]^{25}_D$ $-44°$ (c 1.59, $CHCl_3$); each gave elemental analysis ±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.

0022-3263/82/1947-4388$01.25/0