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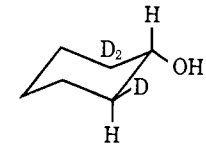
Stereochemistry of the Solvolysis of Cyclohexyl Tosylate[1]

Sir:

We wish to report that the solvolysis of cyclohexyl tosylate to give the substitution product cleanly partitions in a variety of solvents between two distinct pathways: (1) direct displacement of the leaving group to give exclusively the inverted product; (2) hydride shift to give ester at the adjacent position. No retention–racemization pathway is observed. In acetic acid[2] the reaction gives about 85% of unrearranged, inverted cyclohexyl ester, and 15% of hydride-shifted ester. In formic acid the split is about 60:40, and in trifluoroacetic acid the hydride-shift process provides at least 85% of the product.

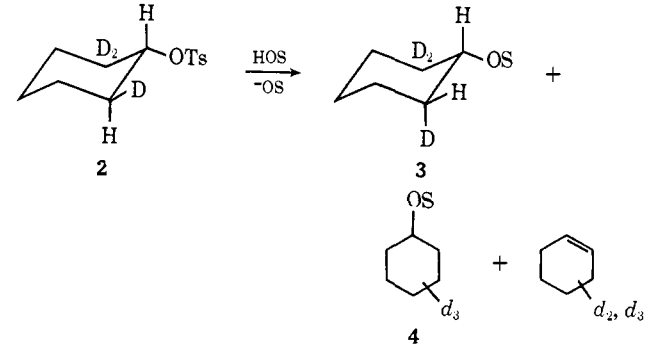
Previous stereochemical investigations of the cyclohexyl tosylate solvolysis have utilized a diastereomeric alkyl label. Thus, hydrolysis of *trans*-4-*tert*-butylcyclohexyl brosylate was found to occur with inversion, but the cis brosylate gave a mixture of retention and inversion.[3] Use of a *tert*-butyl label suffers from several serious limitations. Not only does the label distort the ground state, but, more importantly, it excludes certain transition-state geometries by steric strain. There is good evidence that the cis and trans 4-*tert*-butyl compounds solvolyze by quite different transition states.[4] Consequently, we have set out to determine the stereochemistry of the solvolysis of unsubstituted cyclohexyl tosylate,[5] since the system has no arbitrary limitations imposed on the transition state by substitution.[6]

The stereochemical label we used was a single proton vicinal to and of known relative orientation with respect to the leaving group, the remaining three vicinal protons having been replaced by deuterium (**1**). The labeling procedure was patterned after a report by Shiner and Jewett.[4] The relative orientation (trans) of the 1 and 6 protons in alcohol **1** was determined by



1

the synthetic procedure (hydroboration) and confirmed by the observed axial–axial coupling constant ($^3J_{1-6}$ = 9 Hz).[7] The alcohol was converted to the tosylate (**2**) with retention (^3J = 10.2 Hz), and this material was



2 **3** **4**

solvolyzed in the various acids.[2] The ester and cyclohexene products were separated by preparative vpc.[2,8]

After acetolysis, the 1-proton resonance of the product ester was a doublet with ^3J = 3.6 Hz, corresponding to the product with inverted stereochemistry, **3**. No retained material was observed. Computer line-shape analysis showed that the amount of material with inversion corresponded to 80–85% of the product. The remainder appeared as a broadening at the base of the peaks. Inversion has been previously observed in acyclic systems,[9] but has not heretofore been documented in an unbiased, cyclic case.[6] After formolysis, the 3.6-Hz doublet (**3**) comprised 60–65% of the product, but in trifluoroacetolysis, little or no (<15%) unrearranged product was observed. If any unrearranged trifluoroacetate-*2,2,6-d*$_3$ is formed, its stereochemistry remains undetermined because it is insufficiently abundant to be analyzed by the present methods.

In each case, the remainder of the ester product consisted not of unrearranged, retained ester but of the hydride-shifted material **4**. The amount of hydride-shifted ester was directly and independently assessed by solvolysis of cyclohexyl-*1-d* tosylate and integration of the 1-proton resonance in the product ester. In this manner, we found the proportion of hydride-shifted product to be 15–20% in acetolysis, 35–40% in formolysis, and >75% in trifluoroacetolysis. These figures accurately complement those for the unrearranged, inverted product given above.

In summary, acetolysis of cyclohexyl tosylate to form the substitution product occurs almost entirely by an

(1) This work was supported by the National Science Foundation (Grant No. GP-22942) and by the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 2970-AC4,5).

(2) The solvent was buffered with 1.1 equiv (with respect to the substrate) of the conjugate base. Cyclohexene is a major product in each solvent, but this report deals only with the substitution component of the reaction products. The elimination component will be discussed in the full paper.

(3) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955).

(4) V. J. Shiner and J. G. Jewett, *ibid.*, 87, 1382, 1383 (1965); N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968); M. Tichý, J. Hapala, and J. Sicher, *Tetrahedron Lett.*, 3739 (1969).

(5) W. H. Saunders, Jr., and K. T. Finley, *J. Amer. Chem. Soc.*, 87, 1384 (1965); J. L. Mateos, C. Percy, and H. Kwart, *Chem. Commun.*, 125 (1967); J. E. Nordlander, J. M. Blank, and S. P. Jindal, *Tetrahedron Lett.*, 3477 (1969).

(6) J. E. Nordlander and T. J. McCrary, Jr., have accomplished similar objectives by a different labeling procedure (*J. Amer. Chem. Soc.*, **94**, 5133 (1972)). We thank Professor Nordlander for making his results available to us prior to their publication.

(7) Measurements were made at −80° with deuterium decoupling and signal averaging on a Bruker HFX-10. At this temperature, ring reversal is slow and the resonance of the equatorial conformer can be observed separately from that of the axial conformer. We thank the National Science Foundation for an instrument grant that made possible the purchase of the signal-averaging equipment.

(8) Reaction conditions of time and temperature were chosen so that the cyclohexene was stable. Under more strenuous conditions, trifluoroacetic acid adds rapidly and formic acid slowly to the double bond, even with the buffer[2] present.

(9) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, 87, 287 (1965); A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, *ibid.*, 87, 2682 (1965).

inversion mechanism without rearrangement (k_s). The experiment does not differentiate between direct displacement and displacement on an intimate ion pair. Formolysis gives a mixture of inversion and hydride-shift mechanisms, and trifluoroacetolysis gives almost entirely hydride shift. It is noteworthy that no retention mechanism is observed. Cleavage of the C–OTs bond (or break-up of the ion pair) must occur with either solvent (k_s) or hydride (k_Δ) assistance. There is no evidence for a free carbonium ion (k_c) at the 1 position, even in trifluoroacetic acid. The cyclohexyl system thus stands in sharp contrast to 2-adamantyl tosylate, the solvolysis of which is now considered to be the archetypal k_c process[10] and which gives a substitution product with predominantly retained stereochemistry.[11] Flattening deformations that can accommodate the trigonal bipyramidal k_s transition state in the cyclohexyl system are structually precluded in the 2-adamantyl system.

(10) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2538 (1970).

(11) J. A. Bone and M. C. Whiting, *Chem. Commun.*, 115 (1970).

(12) (a) NDEA Fellow, 1968–1971; NASA Trainee, 1971–1972; (b) NSF Trainee, 1968–1969.

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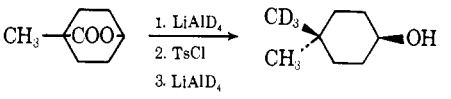
Stereochemistry and Mechanism of Acetolysis of 4,4-Dimethylcyclohexyl Tosylate

Sir:

While the solvolysis stereochemistry of a variety of conformationally fixed cyclohexyl sulfonates has been studied,[1] that of the mobile parent system has not yet been reported.[2] Such information is central to the questions of conformational reactivities and transition-state detail for this model displacement process.

Recently we presented[3] solvolysis rate data for 4,4-dimethylcyclohexyl tosylate relative to cyclohexyl tosylate, which indicated the geminate dimethyl reactant to be closely representative of the parent compound and served to rule out reaction of either substrate through a nonchair ground-state conformation. Here we report the products and stereochemistry of acetolysis of 4,4-dimethylcyclohexyl tosylate and related mechanistic observations.

Configurational analysis was based on the cis methyl-d_3 reactant, **1**, which provided for equivalent determination of both hydride-shifted and directly formed substitution products. (*Z*)-4-Methylcyclohexanol-*4-methyl-d*$_3$[4] (**2**) was synthesized from the lactone[5] **3** of (*Z*)-1-methyl-4-hydroxycyclohexanecarboxylic acid by lithium aluminum deuteride reduction, conversion[6] of the resulting diol[7] (mp 80.0–81.0°; bis-3,5-dinitrobenzoate, mp 146.0–147.0°) to the primary tosylate, and lithium aluminum deuteride reduction of the latter.



3 **2**

Acetolysis of 0.12 *M* 4,4-dimethylcyclohexyl tosylate (0.14 *M* sodium acetate, 1.0 wt% acetic anhydride) at 65° was found to produce essentially quantitatively a mixture of 83% olefin(s), 14.8% 4,4-dimethylcyclohexyl acetate, and 2.2% (13% of total acetates) 3,3-dimethylcyclohexyl acetate.[8] From 3,3-dimethylcyclohexyl tosylate[7,9] under the same conditions was obtained equally cleanly the same products in yields of 79, 2.7 (13% of total acetates), and 18.3%, respectively.

Simultaneous nmr configurational analysis of the acetates from labeled 4,4-dimethyl substrate **1** required resolution of the four ring-methyl singlets of the two unlabeled esters. This condition was not met in various solvents alone at 100 MHz, but was realized by complexation of the acetates with paramagnetic shift reagent Eu(fod)$_3$,[10] Figure 1A. From the labeled tosylate **1** only a single methyl peak was observed for each of the acetates, in both cases belonging to the position closer, *i.e.*, cis, to the complexing acetoxy group,[10,11] Figure 1B. This result corresponds to nonrearranging displacement (**4**) with complete inversion of configuration (±2%) and to hydride shift followed by solvent capture (**5**) at the face opposite the leaving group (±5%), *i.e.*, retention of configuration at the migration origin.

Further information was developed by treatment of the rate constants[3,6b] for cyclohexyl and 4,4-dimethylcyclohexyl tosylates in acetic and trifluoroacetic acids

(1) (a) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955); (b) H. L. Goering and R. L. Reeves, *ibid.*, **78**, 4931 (1956); (c) H. P. Fischer, C. A. Grob, and W. Schwarz, *Tetrahedron Lett.*, 25 (1962); (d) D. S. Noyce, B. N. Bastian, and R. S. Monson, *ibid.*, 863 (1962); (e) C. A. Grob, W. Schwarz, and H. P. Fischer, *Helv. Chim. Acta*, **47**, 1385 (1964); (f) C. W. Jefford, J. Gunsher, and B. Waegell, *Tetrahedron Lett.*, 3405 (1965); (g) C. W. Jefford, D. T. Hill, and J. Gunsher, *J. Amer. Chem. Soc.*, **89**, 6881 (1967); (h) M. A. Eakin, J. Martin, and W. Parker, *Chem. Commun.*, 298 (1968); (i) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968); (j) M. Panková, J. Sicher, M. Tichý, and M. C. Whiting, *ibid.*, 365 (1968); (k) R. Baker, J. Hudec, and K. L. Rabone, *Chem. Commun.*, 197 (1969); (l) D. S. Noyce, B. E. Johnston, and B. Weinstein, *J. Org. Chem.*, **34**, 463 (1969); (m) D. S. Noyce, B. N. Bastian, P. T. S. Lau, R. S. Monson, and B. Weinstein, *ibid.*, **34**, 1247 (1969); (n) K. Okamoto, S. Saitô, and H. Shingu, *Bull. Chem. Soc. Jap.*, **42**, 3288, 3298 (1969); (o) J. A. Bone and M. C. Whiting, *Chem. Commun.*, 115 (1970).

(2) A complementary study is reported in the accompanying communication by J. B. Lambert, G. J. Putz, and C. E. Mixan (*J. Amer. Chem. Soc.*, **94**, 5132 (1972)), to whom we are grateful for prior exchange and concurrent publication.

(3) J. E. Nordlander, J. M. Blank, and S. P. Jindal, *Tetrahedron Lett.*, 3477 (1969).

(4) Isotopic purity >99% by nmr and mass spectrometry.

(5) M. Rubin, D. Apotheker, and R. Lutmer, *Proc. Sci. Sect. Toilet Goods Ass., Suppl.*, **37**, 24 (1962); *Chem. Abstr.*, **58**, 11163h (1963).

(6) (a) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944); (b) H. C. Brown and G. Ham, *J. Amer. Chem. Soc.*, **78**, 2735 (1956).

(7) Correct elemental analyses (±0.30%) were obtained for (unlabeled) new compounds (Galbraith Laboratories, Inc.).

(8) These results confirm the mechanistic similarity of 4,4-dimethylcyclohexyl to cyclohexyl tosylate, for whose acetolysis 85% elimination at 75° and substitution with 7% hydride shift at 50° (17% at 100°) have been reported. See J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951); T. N. Shatkina, E. V. Leont'eva, and A. O. Reutov, *Dokl. Akad. Nauk SSSR*, 177, 373 (1967) (incorrectly abstracted in *Chem. Abstr.*, **68**, 86861v (1968)); see also *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2838 (1968).

(9) Mp 20–21°; prepared in the usual manner from 3,3-dimethylcyclohexanol (Chemical Samples Co.).

(10) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971) (Norell Chemical Co.).

(11) Configuration **4** was assigned from the effect of shift reagent on the acetate of **2**, while **5** conforms to results with various model compounds. See (a) G. H. Wahl, Jr., and M. R. Peterson, Jr., *Chem. Commun.*, 1167, 1584 (1970); (b) J. Briggs, F. A. Hart, and G. P. Moss, *ibid.*, 1506 (1970); (c) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970); (d) P. Belanger, C. Freppel, D. Tizane, and J. C. Richer, *Chem. Commun.*, 266 (1971); (e) *Can. J. Chem.*, **49**, 1985 (1971); (f) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971).