Bimolecular Eliminations in Conformationally Biased Systems Containing Acidic β Protons. The 2-(*p*-Tolylsulfonyl)-4-*t*-butylcyclohexyl Sulfonates[1]

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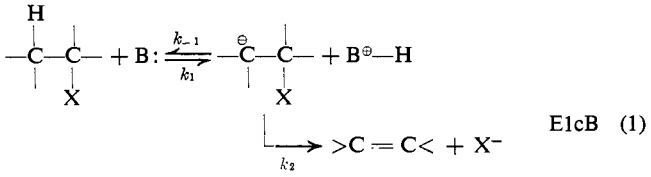
Abstract: The four possible configurational isomers of 2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanol have been synthesized. Configurational assignments to these four alcohols depend on their method of synthesis, the desulfurization of one to its corresponding 4-*t*-butylcyclohexanol, and their interrelation in ethoxide-catalyzed epimerizations. The assignments are dramatically confirmed by the nmr splitting patterns of the sulfone and sulfonate methine hydrogens of the sulfonate esters. The rates of piperidine-induced elimination from the sulfonate esters of three of these alcohols as well as the sulfonates of *cis*- and *trans*-2-*p*-tolylsulfonylcyclohexanol were determined in dimethylformamide solvent. It was found that in some cases, added piperidine hydrochloride caused a small but real rate retardation. However, deuterium exchange studies showed that this retardation is not due to reversible carbanion formation. It was further found that the rates of elimination from the different isomers are relatively insensitive to the nature of the leaving group (*p*-toluenesulfonate *vs.* methanesulfonate), the dihedral angle between the leaving group and the acidic hydrogen (of the 2-arylcyclohexyl sulfonates[17]), and even the *cis–trans* relationship between the leaving group and the acidic hydrogen (except in the cases where an *anti*-periplanar conformation is present in the ground state). All of these observations point to a mechanism in which heterolysis of the carbon–oxygen bond to the leaving group plays at most a minor role in the rate-determining step. However, it is not possible to conclude from these data that a carbanion is formed as a distinct intermediate.

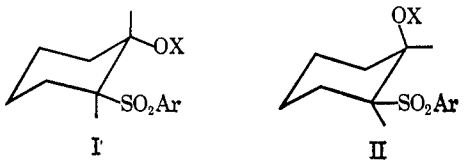
Elimination reactions involving loss of a relatively acidic proton have been the subject of considerable interest over recent years.[4] These investigations have almost invariably focused on the possibility of observing an E1cB elimination mechanism[5] and have utilized



E1cB (1)

such experimental techniques as deuterium isotope exchange,[6,7] general base catalysis[8,9] solvent effects,[10] substituent effects[10,11] (Hammett ρ values), and isotope effects.[12] With four possible exceptions[7,13] attempts to experimentally detect E1cB eliminations (*i.e.*, reactions involving initial preequilibria) in olefin-forming reactions have met with failure. These failures have alternately been rationalized by the operation of a concerted mechanism despite the acidity of the hydrogen or by loss of the proton in a slow step followed by rapid loss of the leaving group. Ingold[14] has suggested that these two possibilities may be indistinguishable; experimental challenges to this suggestion have thus far been equivocal.

One of the most extensively studied systems involving acidic β hydrogens is the 2-arylsulfonylcyclohexyl derivatives, I and II.



I II

These systems were first investigated by Bordwell and co-workers[8,15] who found that the base-induced elimination of *p*-toluenesulfonic acid from Ia (Table I) gave 2-(*p*-tolylsulfonyl)cyclohexene. Thus *cis* elimination involving the acidic C-2 proton is faster than *trans* elimination which would involve the less acidic proton on C-6. However, on the basis of their observation that the reaction exhibited general base catalysis,[8] they suggested a concerted mechanism despite the facility of the *cis* elimination. This conclusion has been challenged, principally by Goering, Relyea, and Howe,[16]

(1) Based upon dissertations submitted by M. Lynn in 1961 and T. G. Squires in 1966 to the Faculty of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Alfred P. Sloan Fellow, 1963–1967.

(3) Texaco Research Fellow, 1964–1965.

(4) For excellent reviews and general discussions on mechanisms of elimination reactions, see: J. F. Bunnett, *Angew. Chem. Intern. Ed. Engl.*, 1, 225 (1962); D. Banthorpe, "Elimination Reactions," Elsevier Publishing Co., New York, N. Y., 1963; D. J. Cram in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter VI.

(5) P. S. Skell and C. R. Hauser, *J. Am. Chem. Soc.*, 67, 1661 (1945).

(6) V. J. Shiner, Jr., and M. L. Smith, *ibid.*, 80, 4095 (1958); J. Hine, R. D. Weimer, Jr., P. B. Langford, and O. B. Ramsay, *ibid.*, 85, 3894 (1963); D. V. Banthorpe and J. H. Ridd, *Proc. Chem. Soc.*, 225 (1963); 365 (1964); A. N. Bourns and P. J. Smith, *ibid.*, 366, (1964).

(7) S. J. Cristol and D. D. Fix, *J. Am. Chem. Soc.*, 75, 2647 (1953); L. E. Erickson and R. A. Alberty, *J. Phys. Chem.*, 63, 705 (1959); J. Hine, R. Weisbock, and O. B. Ramsay, *J. Am. Chem. Soc.*, 83, 1222 (1961); Y. Iskander and Y. Riad, *J. Chem. Soc.*, 223 (1961).

(8) J. Weinstock, R. G. Pearson, and F. G. Bordwell, *J. Am. Chem. Soc.* 78, 3473 (1956).

(9) J. Hine and L. A. Kaplan, *ibid.*, 82, 2915 (1960).

(10) *Cf.* F. G. Bordwell, R. L. Arnold, and J. B. Biranowski, *J. Org. Chem.*, 28, 2496 (1963).

(11) C. H. Depuy, G. F. Morris, J. S. Smith, and R. J. Smat, *J. Am. Chem. Soc.*, 87, 2422, (1965), and references cited therein.

(12) H. Simon and G. Mullhofer, *Chem. Ber.*, 97, 2202 (1964); G. Ayrey, A. N. Bourns, and V. A. Vuas, *Can. J. Chem.* 41, 1759 (1963); W. H. Saunders, Jr., and D. H. Edison, *J. Am. Chem. Soc.*, 82, 138 (1960).

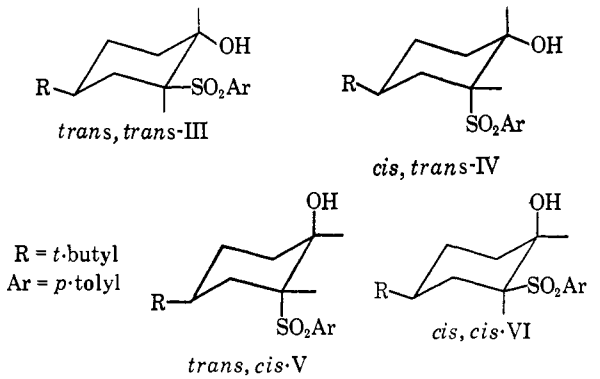
(13) These mechanistic conclusions were based on deuterium-exchange studies, a method which has recently been challenged by R. Breslow [*Tetrahedron Letters*, 399 (1964)].

(14) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 423, footnote 11.

(15) F. G. Bordwell and R. J. Kern, *J. Am. Chem. Soc.*, 77, 1141, (1955); J. Weinstock, R. G. Pearson, and F. G. Bordwell, *ibid.*, 78, 3268 (1956).

who argued that the similar rate of elimination of the cyclohexyl chloride Ib and the cyclohexyl tosylate Ia suggested a common first step, loss of the acidic proton. Similarly, this latter suggestion was challenged by Weinstock, Bernardi, and Pearson,[17] who found that the rates of base-catalyzed exchange of deuterium for hydrogen α to the sulfone in cyclohexyl *p*-tolyl sulfones occur at rates 10^{-3} to 10^{-5} as rapid as the *cis* elimination from Ia. Assuming that the inductive effect of the tosyloxy group is about the same as the chlorine atom, they concluded that the tosyloxy group could not increase the acidity of the β hydrogen enough to account for the rate of the *cis*-elimination reaction. However, after experimentally determining the inductive effects of the chloro and tosyloxy groups, Hine[18] concluded that the effect of the tosyloxy group might well have been underestimated and that the carbanion mechanism is still a real possibility. Thus, the mechanism of the reaction remains in doubt and the fundamental question revolves about the rate at which the β-hydrogen could be abstracted. The purpose of this paper is to report our attempts to determine the rate of abstraction of this proton by forcing the elimination of a sulfonic acid from a 2-arylsulfonylcyclohexyl sulfonate to proceed by an experimentally observable E1cB mechanism.

For this purpose we synthesized the isomeric 2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanols, III–VI. The notations to be used here are those described by Curtin and Harder.[19] Under this system, *trans,trans*-III is 2^t-(*p*-tolylsulfonyl)-4^t-*t*-butylcyclohexanol; *cis,trans*-IV is 2^c-(*p*-tolylsulfonyl)-4^t-*t*-butylcyclohexanol; *trans,cis*-V is 2^t-(*p*-tolylsulfonyl)-4^c-*t*-butylcyclohexanol; and *cis,cis*-VI is 2^c-(*p*-tolylsulfonyl)-4^c-*t*-butylcyclohexanol. The *trans,trans*-III, *cis,trans*-IV, etc., notations are also borrowed from Curtin and Harder.[19] In this notation, the orientation of the sulfone group relative to the hydroxyl group is first indicated followed by the orientation of the *t*-butyl group also relative to the hydroxyl group.



Our attempts to force a reversible carbanion mechanism revolved around two alternative assumptions. In our first approach, we assumed an E1cB mechanism with a rapid second step to be operating in the 2-arylsulfonylcyclohexyl tosylates and, by imposing conformational restrictions to this system, attempted to retard loss of the leaving group relative to proton abstraction from the conjugate acid of the base, *i.e.*, to increase k_{-1}/k_2 (eq 1). For example, proton abstraction from *trans,trans*-III tosylate, in which both the tosylate and aryl sulfone groups are held in the equatorial position by the bulky *t*-butyl group, would give a carbanion in which any rehybridization of the carbon toward sp^2 would cause an increase in the dihedral angle between the unshared pair of electrons and the leaving sulfonate from about 60° to a maximum of 90°, the worst possible angle for elimination.[20] This analysis also holds for *cis,trans*-IV tosylate in which the acidic proton occupies an equatorial position. The piperidine-induced elimination reaction in these systems is to be compared with that of *trans*-2-arylsulfonylcyclohexyl tosylate (Ia), originally studied by Bordwell and his group, in which proton abstraction could occur from the chair conformation with the sulfone and the sulfonate groups *trans* diaxial.[21]

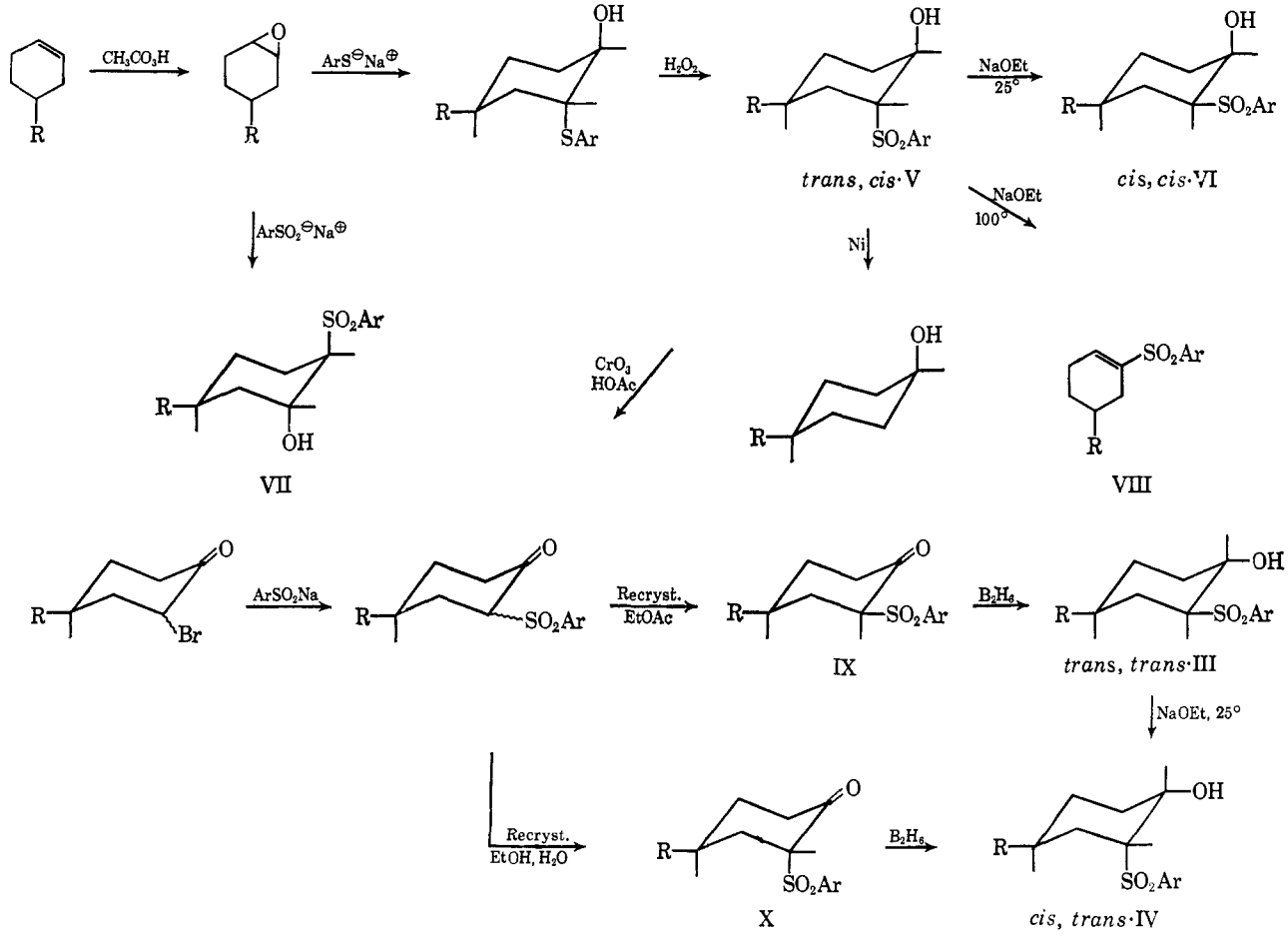
In this conformation, as in the case of *trans,cis*-V tosylate, proton abstraction would give the carbanion in which any rehybridization toward sp^2 would cause the dihedral angle between the unshared pair and the leaving group to decrease from about 60° and approach an ideal 0°.[20] In other words, we attempted to retard loss of the sulfonate relative to proton abstraction by the carbanion by holding the leaving group in a stereoelectronically unfavorable equatorial conformation. To further retard loss of the sulfonate group relative to Bordwell's system without seriously affecting and certainly without increasing the acidity of the β hydrogen, the leaving group was changed from the tosylate to the poorer leaving group, the methanesulfonate.

In the second approach to this problem, a concerted elimination was assumed for the reaction in systems Ia and b, and, again by imposing conformational restrictions, we attempted to retard this mechanism relative to the carbanion mechanism. This study focused on the *cis,trans*-IV sulfonates. In contrast to the conformationally mobile systems[8,15,16] and to the other isomers studied here, neither a concerted *cis* nor a concerted *trans* elimination is possible from a chair conformation of this system since *cis* elimination is precluded by the stereochemistry of the starting sulfonate and concerted *trans* elimination would lead to *trans*-cyclohexene. Consequently, if elimination occurs, it must either take the E1cB course or proceed through the boat conformation. If the former obtains, the leaving group is in a stereoelectronically unfavorable equatorial orientation which should improve the chances for trapping an intermediate carbanion (*vide supra*). Here again, replacing the tosylate by a methanesulfonate should influence the reaction in the direction of a reversible E1cB mechanism.

Syntheses. Syntheses of the four isomers are outlined in the flow sheet (Scheme I). *trans,cis*-V was synthesized by the oxidation of the corresponding sulfide[22] which was formed from the reaction of 4-*t*-

(16) H. L. Goering, D. L. Relyea, and K. L. Howe, *J. Am. Chem. Soc.*, **79**, 2502 (1957).
(17) J. Weinstock, J. L. Bernardi, and R. G. Pearson, *ibid.*, **80**, 4961 (1958).
(18) J. Hine and O. B. Ramsay, *ibid.*, **84**, 973 (1962).
(19) D. Y. Curtin and R. J. Harder, *ibid.*, **82**, 2357 (1960).
(20) C. H. DePuy, R. D. Thurn, and G. F. Morris, *ibid.*, **84**, 1314 (1962); C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *ibid.*, **87**, 2421 (1965).
(21) This is not, *a priori*, an unreasonable conformation for loss of a proton from Ia since the carbanion that would be forming in the transition state could allow relief of 3,5-diaxial interactions with the arylsulfone group and, in contrast to the diequatorial conformer, no eclipsing of the arylsulfonate group could come into play.
(22) (a) F. G. Bordwell and P. S. Landis, *J. Am. Chem. Soc.*, **79**, 1593 (1957). (b) For a review of the oxidation of sulfides and the use of alkali sulfinates as nucleophiles, see C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, pp 666–673.

Scheme I



butylcyclohexene oxide with the sodium salt of *p*-toluenethiol.[22a,23] The epoxide was synthesized from 4-*t*-butylcyclohexene using peracetic acid.[19,24]

Epoxidation of 4-*t*-butylcyclohexene gave a mixture of about equal amounts of the *cis*- and *trans* isomers[25] (glpc analysis). These isomers could not be separated by distillation, and since the desired sulfone was ultimately obtained from the mixture, no exhaustive attempts were made to effect this separation. Treatment of the mixture of epoxides with the sodium salt of *p*-toluenethiol led to a viscous oil that was oxidized directly with hydrogen peroxide to a mixture of sulfone alcohols from which a pure crystalline material was isolated in 35% yield. Since the starting epoxide was a mixture of *cis* and *trans* isomers and since each of the stereoisomeric epoxides has two reaction sites, four possible products could be postulated from the opening of the epoxide ring with the salt of the thiol. It was therefore impossible, *a priori*, to assign either a unique structure or configuration to the crystalline material.[26] The structure and configuration of this crystalline material were deduced in the following manner. Analyses and infrared[28] showed that it was a sulfone alcohol. Desulfurization[29,30] with Raney nickel in 75% ethanol led to *cis*-4-*t*-butylcyclohexanol.[31] This observation not only proves the gross structure for the isolated sulfone alcohol but also proves the *cis* relationship between the alcohol and the *t*-butyl group. Furthermore, if it is assumed that the sulfone alcohol is configurationally stable to the oxidation conditions, then the sulfone group and the alcohol group must be *trans* since the opening of the epoxide ring is most certainly stereospecific and *trans*. That this is a reasonable assumption will become clear in the discussion of the preparation of *cis,cis*-VI.

However, before proceeding to the synthesis of *cis,cis*-VI, there were a few interesting observations that were made in our maneuvers to obtain *trans,cis*-V that we feel warrant mentioning.

In an attempt to improve the yield of the desired sulfone alcohol, one oxidation was effected at 0°. Within a short time, a solid appeared. The infrared spectrum of this solid did not show the characteristic sulfone absorption nor did it compare with the spectrum of the starting material. Recrystallization of this solid gave a

(23) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 78 (1949).

(24) J. Sicher, F. Sipos, and M. Tichy, *Collection Czech. Chem. Commun.*, 26, 847 (1961); *Chem. Abstr.*, **55**, 164466 (1961).

(25) B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 2476 (1964).

(26) Although it was certainly most likely that the hydroxyl and the sulfone group were diaxial,[27] this assumption did not need to be invoked.

(27) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), 10, 44 (1956).

(28) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 54.

(29) R. Mozingo, D. E. Wolf, S. A. Harris, and K. J. Folkers, *J. Am. Chem. Soc.*, 65, 1013 (1943).

(30) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

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

pure material that showed a strong absorption at 9.6 μ[28] and gave a correct analysis for a sulfoxide[22b] alcohol.

Further oxidation of this material gave 92% (based on sulfoxide) of *trans,cis*-V. Attempts to isolate the other sulfoxide alcohols failed.

In another attempt to prepare *trans,cis*-V, the reaction of 4-*t*-butylcyclohexene oxide with sodium *p*-toluenesulfinate[22b] was examined. From this reaction, only one product could be isolated. The infrared spectrum of this compound showed the characteristic sulfone absorptions[28] and the elementary analysis of the compound showed that it was an isomeric *p*-tolylsulfonyl-*t*-butylcyclohexanol. Since this material is different from any of the 2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanols, this is certainly one of the 2-(*p*-tolylsulfonyl)-5-*t*-butylcyclohexanols. Furthermore, in view of Barton's[27] observations on the opening of cyclohexene oxides, it is most likely the *trans,trans* isomer. This material was not studied.

cis,cis-V was readily synthesized by treating *trans,cis*-V with sodium ethoxide in ethanol at 25°. Its formation in 50% yield (with no recovered starting material) requires an axial conformation for the aryl sulfone group in its precursor and confirms the suspected *trans* relationship between the alcohol and the sulfone groups in *trans,cis*-V.

It was interesting that, when this epimerization was attempted at 100°, there was produced only the alkene VIII which resulted from dehydration of the sulfone alcohol. This is probably the reason for the fairly low yield in the room temperature epimerizations. This dehydration is interesting since it most likely proceeds through a carbanion as evidenced by the epimerization at lower temperature.[32] Base-catalyzed dehydration of alcohols containing active hydrogens β to the hydroxyl group have ample precedence in the basic dehydrogenation of aldols.[33]

trans,trans-III and *cis,trans*-IV were obtained by the diborane reduction[34] of the corresponding isomeric sulfone ketones, *cis*- and *trans*-2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanone (IX and X). An isomeric mixture of these ketones was obtained either by oxidation of *trans,cis*-V (or *cis,cis*-VI) or by nucleophilic substitution of *p*-toluenesulfinate anion[22b] for bromide on a mixture of *cis*- and *trans*-2-bromo-4-*t*-butylcyclohexanone.[37] Recrystallization of the crude reaction mixture of isomeric sulfone ketones from ethyl acetate afforded pure IX while recrystallization of the crude product from ethanol–water afforded X. Configurational assignments of IX and X are based on configurations of their reduction products, *trans,trans*-III and *cis,trans*-IV, respectively.

The configurations of the two alcohols were established in the following manner. Elemental analyses, infrared spectra, mixture melting point data, and the mode of synthesis required them to be 2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanols and different from *trans,cis*-V and *cis,cis*-VI (thus requiring the hydroxyl group to be *trans* to the *t*-butyl group). Furthermore, one isomer could be epimerized to the other isomer with sodium ethoxide in ethanol. However the reverse was not true, and the more stable isomer could be recovered unchanged from its equilibration reaction.

On the assumption that the configuration with all three substituents *equatorial* is more stable than the one with an *axial* aryl sulfone, the isomer which was epimerized must be *cis,trans*-IV. These configurational assignments, as well as those of *trans,cis*-V and *cis,cis*-VI, were rather dramatically confirmed by the coupling patterns (*vide infra*) of the C-1 and C-2 protons in the nmr spectra of the corresponding sulfonates.

Nmr Spectra. The configurational assignments of the four alcohols III–VI were confirmed by the observed splittings[38] in the τ 4.4–5.2 and 6.3–7.2 regions in the nmr spectra of the sulfonate esters. These regions correspond to the methine protons attached to the carbons bearing sulfone and sulfonoxy groups, respectively.[39] In our discussion of the coupling patterns of the various isomers, we have initially assumed a chair conformation; that this is a valid assumption is also substantiated by the observed splittings (*vide infra*).

There are at least two factors which must be considered in correlating the splitting patterns of these two methine protons with their configuration. The gross splitting behavior is determined by the Karplus dihedral angle-coupling constant relationship.[40] Thus, vicinal diaxial couplings, involving a dihedral angle (ϕ) of 180°, should be much larger (J_{aa} = 16 cps) than couplings between vicinal equatorial protons or axial–equatorial protons in which ϕ = 60° ($J_{ee} = J_{ae}$ = 2.5 cps).

The second factor which has been found to affect coupling constants in cyclohexyl systems has been described by Williams and Bhacca[41] in their investigations of a series of steroids. These workers found that the coupling constant between vicinal equatorial and axial protons is greater when an electronegative substituent is attached to the methine carbon with the axial proton (*ca.* 5 cps) than when it is attached to the carbon with the equatorial hydrogen (*ca.* 2–3 cps). There is essentially no effect on the diequatorial coupling. This stereoelectronic effect on coupling constants has recently been substantiated and expanded in scope by Booth.[42]

The splitting patterns obtained at 60 Mc in benzene for the two relevant hydrogens of the sulfonate esters of the various *t*-butyl-substituted isomers, as well as those of the two 2-(*p*-tolylsulfonyl)cyclohexanol derivatives, Ia and IIa, are shown in Figure 1. In this figure peak positions, shown at the top of each peak, are given in τ values from an internal tetramethylsilane reference; a cps scale is shown at the bottom of each peak. Since the tosylates of two of the isomers were unavailable, the mesylates of these two isomers were used. In *cis,trans*-IV mesylate, Figure 1c, and in other mesylate deriva-

(32) However, see R. Breslow, *Tetrahedron Letters*, 349 (1964).
(33) *Cf.* C. R. Hauser and D. S. Breslow, *J. Am. Chem. Soc.*, 62, 3344 (1940).
(34) Diborane was selected as the reducing agent because we[35] had previously found that it is a relatively stereoselective reducing agent giving predominantly the equatorial alcohol, and Brown and Subba Rao[36] have reported that the sulfone group is not affected by diborane.
(35) W. M. Jones, *J. Am. Chem. Soc.*, 82, 2528 (1960).
(36) H. C. Brown and B. C. Subba Rao, *ibid.*, 82, 681 (1960).
(37) N. L. Allinger and J. Allinger, *ibid.*, 80, 5476 (1958).
(38) For a discussion of this method of configurational and conformational analysis, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77–82, 148–150.
(39) "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, Spectra no. 519 and 683.
(40) M. Karplus, *J. Am. Chem. Soc.*, 85, 2870 (1963).
(41) D. H. Williams and N. S. Bhacca, *ibid.*, 86, 2742 (1964).
(42) H. Booth, *Tetrahedron Letters*, 411 (1965).

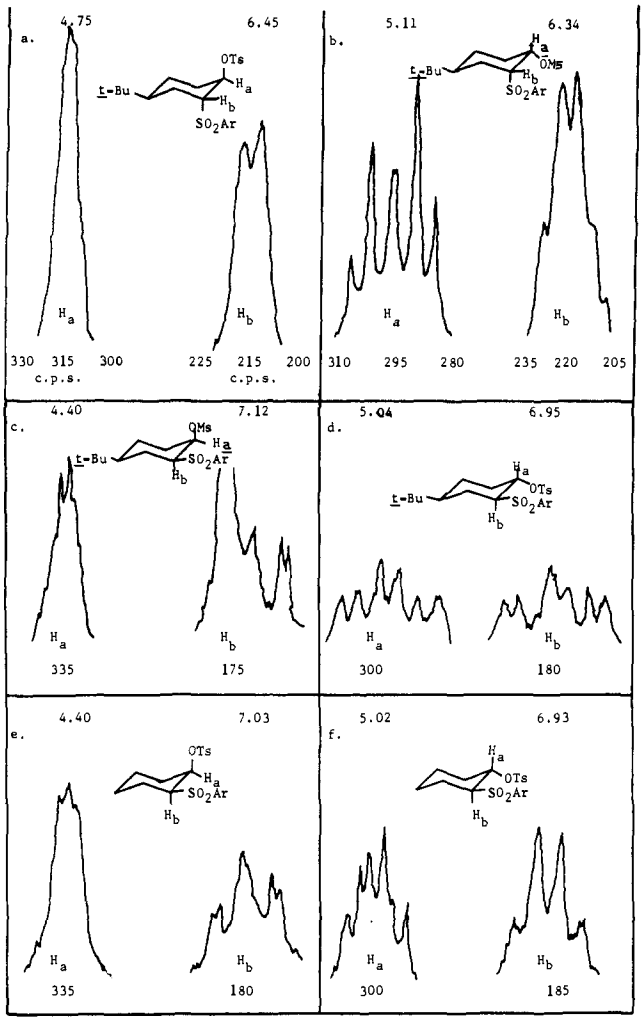


Figure 1. Splitting patterns of the sulfonate esters.

tives not shown, the H_b peak was partially obscured by the mesylate absorption.

From Figure 1 it is immediately apparent that the observed splittings in the various isomers are completely consistent with the configurations assigned in the previous section. In each case, the axial hydrogens appear as broad, strongly coupled multiplets while the equatorial protons are characterized by narrower, weakly coupled absorptions. Furthermore, these spectra present rather compelling evidence that all isomers exist predominantly in the chair conformation. This is particularly striking in the case of *trans,cis*-V tosylate. Certainly in this case, the tendency to assume some sort of boat conformation would be greater than in the other isomers since a chair conformation requires both the sulfone and tosyloxy groups to be axial. However, the weak splittings recorded in Figure 1a are incompatible with a boat conformation since any such conformation would require that the dihedral angles influencing the coupling of these methine protons approach 180°. On the other hand, these splittings do not exclude a distorted chair conformation (*vide infra*).

It is also interesting to note that the observed splittings for *cis*-2-*p*-tolylsulfonylcyclohexyl tosylate (IIa), shown in Figure 1e, militate for a large predominance of the chair conformation in which the bulkier sulfone group is equatorial and the tosylate group is axial.

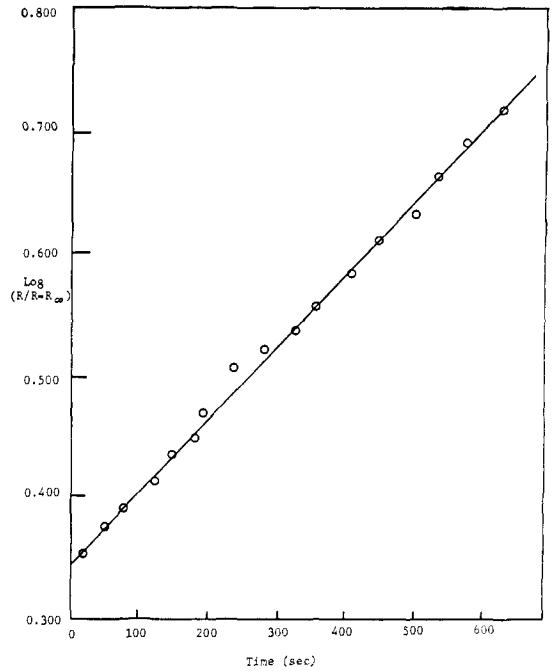


Figure 2. Pseudo-first-order plot of the data in Table II for *trans,cis*-IV mesylate.

Closer inspection of the patterns in Figure 1 reveals that the predictions of Williams and Bhacca[41] and Booth[42] are apparently valid for this system. For example, a comparison of the splittings of H_a in Figure 1a and Figure 1c shows that there are indeed additional splittings in Figure 1c which may be attributed to stronger H_a–H_b coupling in the latter case. This is also illustrated by a comparison of the H_b patterns in Figures 1a and 1b.

Finally, it should be mentioned that, in accordance with current theory,[43] the axial methine hydrogens consistently absorbed at higher field than their epimeric equatorial counterparts. In the case of *trans,cis*-V tosylate, Figure 1a, the equatorial protons, particularly H_a, appear to absorb at a position intermediate to comparable axial and equatorial protons. This shift to higher field is entirely consistent with a distortion of the normal chair conformation.

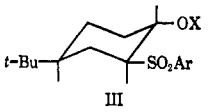
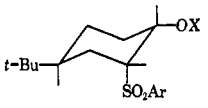
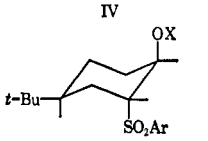
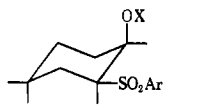
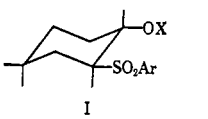
Kinetic Studies. Using the method of Weinstock, Pearson, and Bordwell,[8] the rates of the piperidine-induced eliminations were measured on the sulfonic acid esters at 30° in dimethylformide solution. Since a large excess of the amine was used, measurement of the resistance of the reaction mixture as a function of time gave pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}), obtained by plotting $\log [R/(R - R_\infty)]$ against time[44] and multiplying the slope by 2.303, were determined for the entire series. These constants, the calculated second-order rate constants (k_{calcd}), and the relative rates are given in Table I. Data obtained in a typical run are given in Table II and a plot of log $[R/(R - R_\infty)]$ *vs.* time for these data is given in Figure 2.

Since an E1cB elimination with a reversible first step (eq 1) should be retarded by the addition of a common ion, the effect of added piperidinium chloride on k_{obsd}

(43) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Ltd., Oxford, England, 1959, pp 115–119.

(44) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, pp 36–38.

Table I

		Base[a]	Salt[b]	$k_0 \times 10^4$, sec^{-1}	No. of detns	$k_{calcd} \times 10^3$	Calcd D exchange[c]
 III	a, X = $SO_2C_6H_4CH_3$	0.1983	0.005	2.53 ± 0.04	3		0.15[d]
		0.1983	0.020	2.33 ± 0.03	2	1.3	(0.04)
		0.1065	0.003	1.43 ± 0.03	2		
		0.1065	0.020	1.30	2		
	b, X = SO_2CH_3	0.1996	0.005	1.20 ± 0.008	2	0.62	0.12
		0.1996	0.020	1.12 ± 0.008	2		
 IV	b, X = SO_2CH_3	0.1996	0.005	3.81	1	1.9	0.06
		0.1996	0.020	3.69	1		
 V	a, X = $SO_2C_6H_4CH_3$	0.1983	0.005	12.4 ± 0.3	3		
		0.1983	0.020	11.8	1	6.5	0.08
		0.1065	0.003	7.06 ± 0.16	2		
		0.1065	0.020	6.60 ± 0.15	2		0.09
		0.1065	0.003[e]	7.02	1		
			0.007[e]				
	b, X = SO_2CH_3	0.1996	0.005	16.2 ± 0.2	2	8.4	0.18[d]
		0.1996	0.020	14.9 ± 0.1	2		
 II	a, X = $SO_2C_6H_4CH_3$	0.1983	0.005	150	1		
		0.1065	0.003	88.4 ± 0.8	3	79	0.00
		0.1065	0.020	88.7 ± 0.3	2		
	b, X = SO_2CH_3	0.1996	0.005	54.9 ± 0.5	2	28	0.09
		0.1996	0.020	53.5 ± 0.8	2		
 I	a, X = $SO_2C_6H_4CH_3$	0.1983	0.005	4.56 ± 0.07	2		
		0.1065	0.003	2.59	1	2.43	0.15[d]
		0.1065	0.020	2.34	1		
	b, X = SO_2CH_3	0.1996	0.005	2.90 ± 0.03	2	1.5	0.00[d]
		0.1996	0.020	2.89 ± 0.03	2		

[a] Piperidine. [b] Piperidine hydrochloride. [c] Approximate deuterium exchange was calculated on the assumption that the rate retardation results from a common ion effect (0.06 *M*) and that k_H/k_D for abstraction of a proton from piperidinium ion by carbanion is 3.5. This value was obtained from differences in zero point energy of three different stretching frequencies of the piperidinium ion. Calculated deuterium exchange is given in atom % excess deuterium in the sulfone sulfonate. [d] Atom % excess deuterium was determined for this compound by Mr. J. Nemeth of Urbana, Ill., and found to be less than 0.04%. [e] 0.003 *M* piperdine hydrochloride and 0.007 *M* sodium perchlorate.

Table II. Rate of Reaction of Piperidine with *trans,cis*-IV Mesylate in Pure DMF at 30°[a]

Time, sec	Resistance, ohms	Log $[R/(R - R_\infty)]$	Time, sec	Resistance, ohms	Log $[R/(R - R_\infty)]$
30	403	0.367	300	322	0.544
60	391	0.386	330	318	0.559
90	380	0.403	360	312	0.580
120	370	0.422	420	302	0.622
150	359	0.444	480	297	0.646
180	350	0.465	540	289	0.690
210	341	0.487	600	281	0.741
240	333	0.509	3600	230[b]	
270	328	0.525			

[a] Initial amine concentration was 0.1996 *M*; initial concentration of amine salt was 0.200 *M*; initial concentration of *trans,cis*-I mesylate was 0.0100 *M*. [b] Infinity reading. Rate constant, k_{obsd}, is 1.48×10^{-3} sec^{-1}.

was examined. The results are recorded in Table I; note that, in most cases, addition of the salt caused a small rate retardation. On the basis of these results, k_{-1}/k_2 was calculated for the various compounds and found to range from a high of about six to a low of essentially zero. Using these ratios, it was possible to calculate the corresponding amount of deuterium exchange that should occur for each compound during reaction to one half-life in the presence of added piperidinium chloride-d_2; these values are also included in Table I. For at least four compounds the predicted amount of deuterium exchange was well outside the experimental limitations[45] for actual observation. Therefore, three of these compounds, Ia, IIIa, and Vb, and others selected at random were each allowed to react to one half-life with N-deuteriopiperidine in DMF in the presence of piperidinium chloride-d_2, and the unreacted starting material was isolated, purified, and analyzed for deuterium content. In each case, it was found that the amount of excess deuterium was less than 0.04% which, in three instances, corresponds to considerably less excess deuterium than calculated from the salt effect. Owing to experimental difficulties in these analyses,[45] 0.04% excess deuterium is presumed to correspond to no deuterium incorporation.

In a final attempt to detect reversible carbanion formation, the two isomers that were anticipated to most likely eliminate *via* an E1cB mechanism (IIIb and IVb) were subjected to the following conditions. Ethanol-*d* (98%) solutions 3.0 *M* in piperidinium acetate-d_2 (in contrast to 0.06 *M* piperidinium chloride to which solubility restricted us in dimethylformamide), 0.2 *M* in piperidine, and 0.16 *M* in substrate were allowed to remain at room temperature until tlc indicated about one-half reaction.

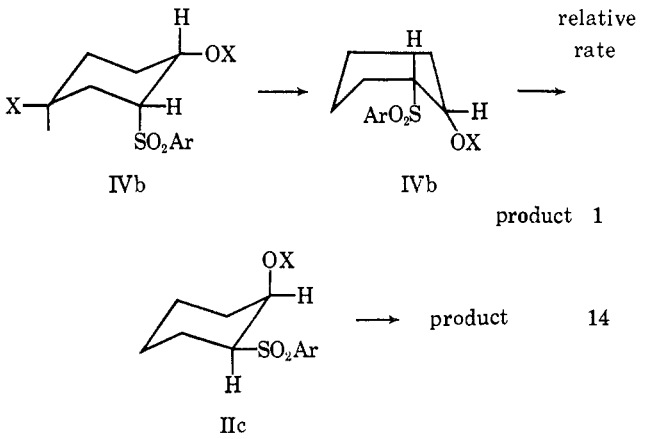
Deuterium analyses by the density method[45] showed 0.02 atom % excess deuterium in IVb and 0.06 atom % excess deuterium in IIIb. As a result of combustion difficulties, the former value must be taken as a maximum value and probably corresponds to essentially no excess deuterium. The latter value was reported as outside of experimental error (reported ±0.01% for

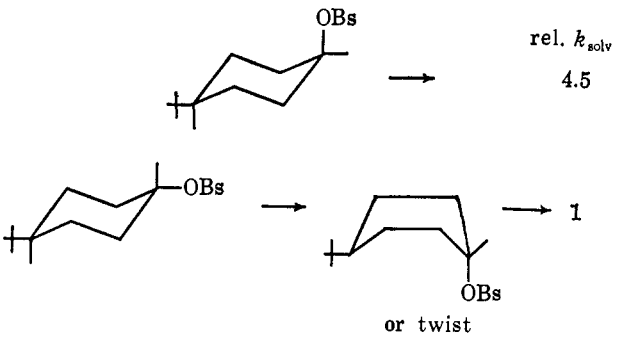
(45) Table I, footnote *d*.

this particular analysis) and may indicate a real incorporation of deuterium. Even so, this amount corresponds to only about 1.5% deuterium incorporation during the first half-life. In other words, even in the presence of a high concentration of conjugate acid, very little (if any)[46] carbanion that may have been formed could be recaptured. Finally, IVb was examined for its epimer,[47] IIIb, after nearly complete elimination in proteated alcohol with the same concentration of reagents as given above. Not the slightest trace of IIIb was detectable by tlc.

Thus, regardless of the restrictions placed on these molecules, reversible carbanion formation could not be demonstrated under any of the reaction conditions employed in this study and the apparent common ion effect in the DMF solvent system must be ascribed simply to a small negative salt effect.

Of the isomers studied, the lack of deuterium exchange and therefore exclusion of a reversible carbanion mechanism is most striking in the case of IVb since, in this case, a concerted elimination must proceed through a boat (probably a twist-boat) conformation. Intuitively, one might predict this to be a considerably less energetically favorable route than a concerted elimination from the chair isomer IIc, a prediction that is certainly not borne out by the experimental rate ratio of only 14:1 in favor of IIc. However, this prediction would necessarily be valid only if it could be assumed that the rates of elimination from IVb and IIc were directly comparable. In fact, there is recent evidence that indicates that an axial group in a chair conformation of a cyclohexane is not a good model for a pseudo-axial group in a boat conformation. Shiner and Jewett[49] found that the solvolysis of *cis*-4-*t*-butylcyclohexyl brosylate, which goes *via* the chair conformer, occurs only 4.5 times faster than the *trans* isomer which clearly showed solvolyses through the boat (*vide infra*). In other words, if it is assumed that the boat conformation of the *trans* isomer is on the order of only 4 kcal/mole higher energy than the chair conformation, then solvolysis of the brosylate group in a pseudo-axial conformation in a boat cyclohexane must occur about 150 times as rapidly as the same group in an axial conformation of a chair cyclohexane.





In light of these results, it is certainly possible that a concerted elimination from the boat conformer IVb′ could be enough faster than concerted elimination from IIc to effectively offset the rate retardation resulting from initial conversion to the boat form.

However, despite the fact that a reversible carbanion mechanism could not be detected in the kinetic runs and the rate of *trans* elimination from IVb cannot be taken as support of either a concerted or a two-step mechanism, there are trends in the kinetic data which reemphasize the fact that the rate-determining transition state in this type of system involves little (if any) breaking of the bond to the leaving group. For example, de Puy[20] has found that *trans* elimination is favored over *cis* elimination in the 2-arylcyclopentyl sulfonates by a factor of about nine, while the same ratio for the cyclohexyl system is greater than 10^4. From this he concluded that, in the cyclohexyl system, there must be a significant energy requirement to force the hydrogen and the leaving group into a conformation that would favor assistance for proton abstraction by the developing p orbital resulting from loss of the tosylate group. In the sulfone methanesulfonates reported here, the rate of *trans* elimination from IIc is only favored by factors of 3.3, 18.6, and 42 over *cis* elimination from Vb, Ic, and IIIb, respectively. In other words, the conformation requirements observed by de Puy are either small or do not come into play at all in these systems, a fact that leads to the conclusion that here there is little if any preference for a *cis*-periplanar conformation in the transition states for the *cis* eliminations. Minimal involvement of the leaving group in the transition state is further emphasized by comparing the rates of elimination of the tosylates with the methanesulfonates (Table I). Whereas the difference in solvolysis rates between methanesulfonates and tosylates is of the order of 500,[50] the *cis*-elimination rates are virtually identical, ranging from about two to less than one.

One final point that we found interesting was the fact that *cis* elimination involving an axial leaving group (V) proceeds somewhat faster (5.5–11 times) than *cis* elimination involving an equatorial leaving group (III). At first thought, this suggests some involvement of the leaving group in the rate-determining transition state. However, it is also adequately explained by a carbanion mechanism since formation of the carbanion from the diaxial isomer V would both relieve the strain of the axial aryl sulfone group and lead to a carbanion in which there is no eclipsing between the aryl sulfone and

(46) The amount of deuterium incorporation is so close to experimental error (although it is the result of duplicate analyses) that we are reluctant at this time to draw any mechanistic conclusions beyond those included in the text. However, possible incorporation of deuterium does suggest further experiments which we presently have underway.

(47) This is a possible although not probable[48] product of a reversible carbanion mechanism.

(48) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 73–84.

(49) V. J. Shiner, Jr., and J. G. Jewett, *J. Am. Chem. Soc.*, 87, 1382, 1383 (1965).

(50) E. R. Thornton, "Solvolysis Mechanisms," The Ronald Press Co., New York, N. Y., 1964, pp 164–165.

the sulfonate groups. Both of these effects would tend to accelerate formation of the carbanion of V relative to III.

In summary, the insensitivity of the rates of these reactions to the nature of the leaving group, the dihedral angle between the leaving group and the acidic hydrogen (*cf.* the 2-arylcyclohexyl sulfonates),[20] and even the *cis–trans* relationship between the leaving group and the acidic hydrogen (except in the cases where an *anti*-periplanar conformation is present in the ground-state chair) all point to a carbanion mechanism for this reaction. However, until it can be conclusively demonstrated that under reaction conditions a hydrogen α to an aryl sulfone group and β to a sulfonoxy group is acidic enough to be removed without concomitant cleavage of the carbon–oxygen bond of the sulfonoxy group, the precise mechanism of this reaction must remain in doubt. We presently have experiments underway that we hope will clarify this point.

Experimental Section

General. Melting and boiling points are uncorrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Combustion analyses for deuterium content were performed by Josef Nemeth, Urbana, Ill. Infrared spectra, using the sampling technique specified in the individual experiments, were taken with a Perkin-Elmer Model 21 spectrophotometer and with a Beckman Model IR10 spectrophotometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform (except as specified) with a Varian 4300-2 high-resolution spectrometer operating at 60 Mc. Chemical shifts are reported in τ values from an internal tetramethylsilane reference. Preparative thin layer chromatography was accomplished on 20 × 20 cm plates coated in this laboratory with 1-mm layers of Merck silica gel HF_{254} using ultraviolet detection. These plates were developed with 1:1 ether–hexane. Throughout this section *p*-toluenesulfonate and methanesulfonate derivatives of the alcohols have been referred to as tosylates and mesylates, respectively.

4-*t*-Butylcyclohexene. Method A. The olefin was prepared according to the method of Winstein and Holness.[31] From 97.3 g of 4-*t*-butylcyclohexanol (mixture of isomers) was obtained 51.6 g (60%) of the alkene, bp 65–66° (20 mm) [lit.[31] bp 65–66° (20 mm)].

Method B. Using the method of Sicher, Sipos, and Tichy,[24] 156 g of 4-*t*-butylcyclohexanol (mixture of isomers) afforded 81 g (59%) of the olefin, bp 65–66° (20 mm) [lit.[24] bp 54–55° (10 mm)].

***cis*- and *trans*-4-*t*-Butylcyclohexene Oxide.** A solution of 51.6 g (0.37 mole) of 4-*t*-butylcyclohexene in 250 ml of chloroform was cooled in an ice bath. To the stirred solution was added, dropwise over a 30-min period, 116 ml of peracetic acid[51] containing 10.3 g of sodium acetate trihydrate. After completion of the addition, the ice bath was removed and the solution was stirred for 1 hr more.

The reaction mixture was poured into 200 ml of ice water; the layers were separated, and the aqueous layer was extracted with chloroform. The combined chloroform layers were washed repeatedly with 10% sodium carbonate solution until the aqueous layer remained basic. After washing the chloroform solution with water, it was dried over sodium sulfate. Removal of the solvent and careful distillation gave 44.2 g (77%) of colorless oil, bp 74–75° (7 mm) [lit.[24] bp 78–80° (9 mm)].

Reaction of the Mixture of *cis*- and *trans*-4-*t*-Butylcyclohexene Oxide with *p*-Toluenethiol. To a stirred solution of 36.8 g (0.3 mole) of *p*-toluenethiol and 11.9 g (0.30 mole) of sodium hydroxide in 150 ml of 50% (v/v) ethanol was slowly added 44.2 g (0.28 mole) of the epoxides. Stirring was continued for 4 hr before the reaction mixture was poured into 200 ml of water. The resulting mixture was extracted repeatedly with chloroform, and the combined extracts were washed with water and dried over sodium sulfate.

The chloroform was removed under reduced pressure to give 83.8 g of a brown oil which was vacuum distilled to yield 75.0 g (95%) of the sulfide mixture, bp 164–166° (0.3 mm).

Redistillation of 61.9 g of this mixture through a 8 mm × 24 in. spinning-band column afforded 49.2 g of oily liquid, bp 159–160° (0.09 mm). The infrared spectrum of this oil (plates) indicated an isomeric mixture of 2-(*p*-tolylmercapto)-*t*-butylcyclohexanols.

2^t-(*p*-Tolylsulfonyl)-4^c-*t*-butylcyclohexanol (*trans,cis*-V). To 49.2 g (0.18 mole) of the above sulfide mixture in 100 ml of glacial acetic acid was added, dropwise with stirring, 295 ml of peracetic acid.[52,53] Stirring was continued overnight, and the resulting mixture was heated on the steam bath for 2 hr. After cooling, the reaction mixture was poured into 300 g of ice and then extracted repeatedly with chloroform. The combined extracts were washed with saturated sodium bicarbonate solution and with water before they were dried over sodium sulfate. Removal of the chloroform afforded 54.0 g of oil.

Separation of the isomers proved difficult. Finally, the oil was dissolved in 75 ml of hot cyclohexane and 5 ml of ethyl acetate was added. The solution was stored at 0°. After 5 days, crystallization was complete, and the mixture was filtered to give 8.0 g (15%) of solid material, mp 116–119°.

Recrystallization of this solid from ethyl acetate–petroleum ether (65–110°) afforded 6.8 g of the desired compound, mp 121–122°. *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44; S, 10.33. Found: C, 65.71; H, 8.42; S, 10.16. The infrared spectrum (melt) showed absorptions at 2.89 (ν_{O-H}), 7.70 (ν_{as,SO_2}), and 8.73 μ (ν_{s,SO_2}). The nmr spectrum (in τ) consisted of: an aromatic quartet centered at 2.45, the proton attached to the substituted methine at 5.60, the proton attached to the hydroxyl-substituted methine carbon between 6.50 and 6.68,[54] an aromatic methyl group at 7.59, a complex grouping of normal alicyclic protons centered at 8.32, and a *t*-butyl absorption at 9.21.

Desulfurization of *trans,cis*-V with Raney Nickel.[29,30] A solution of 0.5 g of *trans,cis*-I in 30 ml of 75% aqueous ethanol was refluxed with ~9 g of Raney nickel catalyst for 9 hr. The mixture was filtered and the filtrate extracted with pentane. A solid was filtered to give 0.2 g of starting *trans,cis*-sulfone alcohol. The pentane was removed leaving a solid. Glpc of this material showed that it was predominately *cis*-4-*t*-butylcyclohexanol contaminated with a small amount of the *trans* isomer. Sublimation of the crude solid gave pure *cis*-4-*t*-butylcyclohexanol, mp 80–82°. This was identical in every way with authentic *cis*-4-*t*-butylcyclohexanol.[31]

Glpc was effected on an 18-ft Tide detergent column (30–60 mesh, F & M Scientific Corp.) operating at 160° and 30 psi.

It was interesting that in some attempts to desulfurize this sulfone alcohol in dioxane, some epimerization of the alcohol occurred. However, in no case was *trans*-4-*t*-butylcyclohexanol the dominant product. This epimerization probably proceeds through the ketone[55] since small amounts of ketone were also detected in these desulfurizations.

Epimerization of *trans,cis*-V to 2^c-(*p*-Tolylsulfonyl)-4^c-*t*-butylcyclohexanol (*cis,cis*-VI). To 25 ml of absolute ethanol which contained 400 mg of sodium was added 1.0 g of *trans,cis*-I. The reaction mixture was allowed to remain at room temperature for 2 days. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water and then dried over sodium sulfate. The solvent was removed, leaving a yellow oil. The oil was dissolved in ethyl acetate and heated with a little Norit to remove the yellow color. From this solution was collected 0.50 g of solid, mp 130–133°; mixture melting point with *trans,cis*-V, 107–110°. Further recrystallizations from ethyl acetate afforded a material, mp 134–135°. The infrared spectrum (melt) showed characteristic sulfone and hydroxyl absorptions but differed from that of *trans,cis*-V. *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44; S, 10.33. Found: C, 65.68; H, 8.60; S, 10.43.

Reaction of *trans,cis*-V with Sodium Ethoxide at an Elevated Temperature. 1-(*p*-Tolylsulfonyl)-5-*t*-butylcyclohexene. To 25 ml of absolute ethanol was added 400 mg of sodium followed by 1.0 g (3.2 moles) of *trans,cis*-V. The solution was refluxed for 1 hr, cooled, and poured into ice-cold dilute hydrochloric acid. After extracting the resulting aqueous mixture with chloroform, the combined chloroform extracts were washed with water and then dried over sodium sulfate. Removal of the solvent afforded an oil which, when triturated with hexane, gave a solid, mp 95–96.5°.

(51) FMC Corp. (Becco), 40% minimum assay material.

(52) F. G. Bordwell, B. B. Lampert, and W. H. McKellin, *J. Am. Chem. Soc.*, 71, 1702 (1949).

(53) FMC Corp. (Becco), 40% miminum assay material was used.

(54) The exact position of this absorption was obscured by the hydroxyl absorption which occurred in the same region.

(55) *Cf.* J. A. Berson and W. M. Jones, *J. Org. Chem.*, 21, 1325 (1956), and references cited therein.

The infrared spectrum (melt) of this material indicated the presence of an olefinic linkage but showed no hydroxyl absorption. Further recrystallization from hexane afforded the pure material, mp 100–101°. *Anal.* Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27; S, 10.96. Found: C, 69.62; H, 8.06; S, 11.11.

This compound had characteristic infrared absorptions (melt) at 6.08 ($\nu_{C=C}$), 7.70 (ν_{as,SO_2}), and 8.73 μ (ν_{s,SO_2}). The nmr spectrum (in τ) showed: an aromatic quartet centered at 2.54, the vinyl proton at 3.06, an aromatic methyl absorption at 7.44, the methylene envelope centered at 8.32, and the *t*-butyl absorption at 9.16.

***cis*- and *trans*-2-Bromo-4-*t*-butylcyclohexanone.** A mixture of these ketones was prepared by the method of Allinger and Allinger.[37] Reaction of 36.5 g (0.24 mole) of 4-*t*-butylcyclohexanone with an equimolar amount of bromine afforded, after rapid vacuum distillation through a 1 × 10 cm Vigreux column, 28.5 g (51%) of an oil containing a solid, bp 82–92° (0.7 mm) [lit.[37] bp 78.5–85° (0.5 mm)]. The infrared spectrum (plates) confirmed that this was the desired isomeric mixture.

***cis*- and *trans*-2-(*p*-Tolylsulfonyl)-4-*t*-butylcyclohexanone. Method A.** The isomeric mixture (28.5 g, 0.121 mole) of 2-bromo-4-*t*-butylcyclohexanones was stirred for 9 days with 22.2 g (0.125 mole) of sodium *p*-toluenesulfinate in 70 ml of ethanol. Addition of 100 ml of water to the reaction mixture caused an oil to separate. This mixture was extracted with several portions of chloroform, and the combined extracts were washed with two portions of water and dried over sodium sulfate. Removal of the solvent afforded 35 g of oily solid which was recrystallized several times from ethyl acetate–petroleum ether (30–60°) to give 8.5 g (23%) of a single pure sulfone ketone, mp 143–144°. This isomer was assigned the *cis* configuration on the basis of its diborane reduction to *trans,trans*-III. *Anal.* Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84; S, 10.39. Found: C, 66.38; H, 7.84; S, 10.36.

Infrared absorptions[28] (melt) at 5.77 ($\nu_{C=O}$), 7.58 (ν_{as,SO_2}), and 8.71 μ (ν_{s,SO_2}) confirmed the sulfone ketone structure.

Alternate work-up of the crude product, obtained under the same reaction conditions, by two recrystallizations from ethanol–water afforded an isomeric mixture of sulfone ketones, mp 130–133°, in 47% yield. Infrared analysis of this mixture indicated that it contained ~60% of the *trans* isomer. Exhaustive recrystallization from ethanol–water gave the pure isomer, mp 127.5–128.5°. Although the infrared spectrum of this material contained characteristic sulfone and carbonyl absorptions, it was distinctly different from that of the *cis* isomer. *Anal.* Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84; S, 10.39. Found: C, 66.23; H, 7.80; S, 10.41. Since purification of the *trans* isomer was difficult, the partially purified isomeric mixture was reduced directly without extensive purification. Separation of the isomeric alcohols was accomplished quite easily.

Method B. A solution of 0.9 g of *cis,cis*-VI in 10 ml of glacial acetic acid was added to a solution of 1.0 g of chromic anhydride in 30 ml of glacial acetic acid. The mixture was allowed to remain at room temperature for 48 hr before being poured into water. The aqueous mixture was extracted with chloroform, and the chloroform extracts washed with 10% sodium bicarbonate, then water, and dried over sodium sulfate. The solvent was removed to give an oil which could be worked up as in method A to give either IX or X.

This same material was also obtained by oxidation of *trans,cis*-V with chromic anhydride in acetic acid, with chromic anhydride in pyridine,[56] and with sodium dichromate in aqueous sulfuric acid.

2^c-(*p*-Tolylsulfonyl)-4^t-*t*-butylcyclohexanol (*cis,trans*-IV). A solution of 35.3 g (0.10 mole) of an isomeric mixture (60% *trans*-X) of 2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanones in 250 ml of dry tetrahydrofuran was prepared in a cooled reaction flask equipped with a gas bubbler, a magnetic stirrer, and an outlet tube to an acetone trap. The bubbler was attached to a diborane generator,[57] and the entire apparatus was swept thoroughly with argon. Diborane was bubbled into the solution during 7 hr. After heating the generator briefly on the steam bath to remove the last traces of diborane, the entire system was again swept with argon.

The reaction mixture was poured into 500 ml of water and allowed to crystallize. Filtration afforded a gummy solid which was washed with water, dried, and triturated with petroleum ether (20–40°) to give 20 g (64%) of the crude reduction product, mp 127–145°.

Four recrystallizations from benzene afforded 12.0 g of white needles, mp 149–150.5°. *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44; S, 10.33. Found: C, 65.77; H, 8.42; S, 10.20.

The infrared spectrum (melt) was peculiar to this isomer and showed characteristic hydroxyl and sulfone absorptions at 2.84, 7.75, and 8.82 μ.

The nmr spectrum (in τ) consisted of: an aromatic quartet centered at 2.40, the hydrogen attached to the hydroxyl-substituted methine carbon at 6.18, the proton attached to the sulfone-substituted methine carbon at 6.96, the aryl-substituted methyl absorption at 7.52, the methylene envelope centered at 8.18, and a *t*-butyl absorption at 9.19.

2^t-(*p*-Tolylsulfonyl)-4^t-*t*-butylcyclohexanol (*trans,trans*-II). **Method A.** Diborane reduction of 12.0 g of pure *cis*-2-(*p*-tolylsulfonyl)-4-*t*-butylcyclohexanone under the conditions for the reduction of IX afforded 10.1 g (84%) of crude reduction product, mp 87–97°. Two recrystallizations from cyclohexane gave 6.5 g of fairly pure material, mp 105–107°, which was used directly in the preparation of sulfonate derivatives. An analytical sample, mp 115–116°, was prepared by recrystallization from ethyl acetate.

The infrared spectrum (melt) of this material was different from that of any other isomer and had characteristic absorptions at 2.82 (ν_{O-H}), 7.82 (ν_{as,SO_2}), and 8.78 μ (ν_{s,SO_2}). The nmr spectrum (in τ) consisted of: an aromatic quartet at 2.29, the hydrogen attached to the hydroxyl-substituted methine carbon at 5.94, the proton attached to the sulfone-substituted methine carbon between 6.22 and 6.31,[60] the aryl-substituted methyl absorption at 7.53, the methylene envelope centered at 8.24, and a *t*-butyl absorption at 9.15.

Method B. 2^c-(*p*-Tolylsulfonyl)-4^t-*t*-butylcyclohexanol (*cis,trans*-IV), 7 g, 0.022 mole, was stirred at room temperature for 3 days with 8.4 g (0.14 mole) of sodium ethoxide in 200 ml of absolute ethanol. The resulting deep orange reaction mixture was poured into 1 l. of ice-cold dilute hydrochloric acid and filtered to give 6.54 g (94%) of light orange solid, mp 90–102°. The infrared spectrum showed this material to be primarily *trans,trans*-III and *cis,trans*-IV in a ratio of about 2:1.

Silica gel chromatography (3:1 pentane–ether eluent) of 4.5 g of this material afforded 2.6 g of pure *trans,trans*-III, mp 114–115°, along with 1.3 g of the less stable epimer, *cis,trans*-IV.

Reaction of *trans,trans*-III with Sodium Ethoxide. To 15 ml of absolute ethanol containing 200 mg of sodium was added 0.5 g of *trans,trans*-III. This solution was allowed to remain at room temperature for 28 hr. The reaction mixture was poured into water and then worked up in the same way as the product from the epimerization of *trans,cis*-V. The infrared spectrum of the crude product, mp 110–113°, showed that starting material was recovered along with a very small amount of olefin. The crude product was recrystallized yielding only *trans,trans*-III.

2^t-(*p*-Tolylsulfinyl)-4^c-*t*-butylcyclohexanol (*trans,cis*-V). A solution of 95.7 g of the mixture of sulfides dissolved in 150 ml of glacial acetic acid was cooled in an ice bath. To the stirred mixture was added 120 ml of 30% hydrogen peroxide over a 30-min period. Stirring was continued for 6 hr after addition was completed. During this time, a white solid separated from the solution. The reaction mixture was filtered, yielding 15.5 g of material, mp 95–117°. Water was added to the filtrate and the mixture was stirred for a short time and again filtered to remove the solid that had formed. This time 103.3 g of material contaminated with acetic acid was collected. The filtrate from the second solid was extracted with chloroform, and the chloroform extracts were worked up in the usual way. When the solvent was removed, 14.3 g of oil which later soldified was collected. The infrared spectra of the three solids appeared to be similar, but there were noticeable differences in relative peak heights. However, the characteristic sulfone absorption peaks were not present in the spectrum of any of the materials.

Recrystallization of the solids from ethyl acetate–hexane mixtures produced a series of solids, each with a different melting point range. The fractions collected from the recrystallization of the second solid were typical: fraction I, 9.2 g, mp 163–167°; fraction II, 5.9 g, mp 150–161°; fraction III, 32.7 g, mp 74–135°; fraction IV, 4.0 g, mp 85–112°. The infrared spectra of these solids indicated that the sulfoxide[26] had been formed. Further

(56) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953).

(57) Diborane was generated either by dripping boron trifluoride etherate onto trimethylamineborane,[58] or by dripping a solution of sodium borohydride in diglyme into boron trifluoride etherate.[59]

(58) Callery Chemical Co., Technical Bulletin C-200, Callery, Pa., April 1, 1958.

(59) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, 22, 1135 (1957).

(60) The exact position of this absorption was obscured by the hydroxyl absorption which occurred in the same region.

recrystallizations of fraction I yielded a material, mp 173–174°. *Anal.* Calcd for $C_{17}H_{26}O_2S$: C, 69.34; H, 8.90; S, 10.89. Found: C, 69.32; H, 9.03: S, 11.03.

Futher oxidation of this material with hydrogen peroxide gave a 90% yield of *trans,cis*-V, thus proving that the sulfoxide which was isolated was 2^t-(*p*-tolylsulfinyl)-4^c-*t*-butylcyclohexanol. When the oxidation was carried out by heating on the steam bath for several hours, the yields of *trans,cis*-IV decreased, and a ketone was detected in the residue.

Attempts were made to isolate 2^t-(*p*-tolylsulfinyl)-5^t-*t*-butylcyclohexanol from fractions III and IV, but none of these attempts were successful. Further oxidation of these fractions gave low yields of *trans,cis*-V.

Reaction of the Mixture of 4-*t*-Butylcyclohexene Oxides with Sodium *p*-Toluenesulfinate. To a solution of 21.4 g of sodium *p*-toluenesulfinate in 50 ml of 50% aqueous ethanol was added a solution of 14.8 g of the *cis,trans*-epoxide mixture in 50 ml of 50% aqueous ethanol. The reaction mixture was stirred for 24 hr at room temperature, then more water was added and the mixture heated gently for 4 hr. The reaction mixture was poured into water and extracted with ether, and the ether extracts were worked up in the usual manner. The solvent was removed, leaving 21.3 g of product which was a mixture of a solid and an oil. This mixture was filtered and the solid recrystallized from an acetone–water mixture, yielding a material, mp 143–157°, whose infrared spectrum showed the characteristictic sulfone absorptions. Further recrystallizations from ethanol yielded a material, mp 164–165°. *Anal.* Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44; S, 10.33. Found: C, 65.73; H, 8.28; S, 10.38.

***trans*-2-(*p*-Tolylmercapto)cyclohexanol.** Using the method of Bordwell and Kern,[61] 25.0 g (0.26 mole) of cyclohexene oxide and an equimolar amount of *p*-toluenethiol in basic ethanol solution afforded 42.1 g (75%) of the desired compound as a light yellow oil, bp 109–110° (0.7 mm) [lit.[61] bp 116–118° (0.1 mm)].

***trans*-2-(*p*-Tolylsulfonyl)cyclohexanol.** This compound was prepared in 92% yield by peroxide oxidation of the corresponding sulfide according to the method of Bordwell and Kern.[61] It was a white solid having mp 119.5–121° (lit.[61] 121–122°).

2-(*p*-Tolylmercapto)cyclohexanone. This compound was prepared in 79% yield from 2-chlorocyclohexanone and *p*-toluenethiol using the procedure of Weinstock, Pearson, and Bordwell.[62] Purification by vacuum distillation through a 1 × 10 cm Vigreux column afforded 52.0 g of light yellow oil, bp 118–119° (0.1 mm) [lit.[42] bp 138° (0.2 mm)].

2-(*p*-Tolylsulfonyl)cyclohexanone. Hydrogen peroxide oxidation of the corresponding sulfide using the method of Weinstock, Pearson, and Bordwell[62] afforded 41.3 g (71%) of the desired sulfone ketone, mp 75–78° (lit.[62] mp 76–80°).

***cis*-2-(*p*-Tolylsulfonyl)cyclohexanol.** The stereospecific borohydride reduction of 41.3 g (0.164 mole) of 2-(*p*-tolylsulfonyl)cyclohexanone according to the procedure of Weinstock, Pearson, and Bordwell[62] afforded, after several recrystallizations from isopropyl ether and from cyclohexane, 27.0 g (65%) of the pure *cis* alcohol, mp 94.5–96° (lit.[62] mp 92–97°).

Preparation of the Sulfonate Ester Derivatives of the Alcohols. The sulfonates were all prepared by the normal Tipson procedure[63] for which the preparation of 2^t-(*p*-tolylsulfonyl)-4^c-*t*-butylcyclohexyl *p*-toluenesulfonate (*trans,cis*-IV tosylate), given below, is illustrative. Elemental analyses, infrared spectra, and nmr spectra of all previously unknown derivatives were consistent with the assigned structures and are recorded in Table III. Physical constants of previously known derivatives were in agreement with those reported. Synthetic conditions for the preparation of the sulfonates along with their melting points and yields are summarized in Table IV.

2^t-(*p*-Tolylsulfonyl)-4^c-*t*-butylcyclohexyl *p*-Toluenesulfonate (*trans,cis*-V Tosylate). A solution of 6.2 g (0.2 mole) of 2^t-(*p*-tolylsulfonyl)-4^c-*t*-butylcyclohexanol and 5.7 g (0.03 mole) of *p*-toluenesulfonyl chloride in 20 ml of dry pyridine was stirred at room temperature for 5 days. The reaction mixture was cooled to 0° and 10 ml of water was added dropwise with stirring. Sitrring was continued for 3 hr before the reaction mixture was poured into 140 ml of water. The resulting mixture was cooled overnight to complete crystallization. Filtration afforded 9.87 g of the impure tosylate, mp 114–120°. Recrystallization from 80 ml of absolute ethanol gave 8.2 g (88%) of the pure compound, mp 125–126°. *Anal.* Calcd for $C_{24}H_{32}O_5S_2$: C, 62.04; H, 6.94; S, 13.80. Found: C, 61.99; H, 7.07; S, 13.86.

Diagnostic infrared absorptions (KBr) were sulfone stretching at 7.63 and 8.77 μ and sulfonate stretching at 7.33 and 8.55 μ; there was no hydroxyl absorption. The nmr spectrum (in τ) showed: an aromatic multiplet centered at 2.54, the hydrogen attached to the tosyloxy-substituted methine carbon at 5.04, the proton attached to sulfone-substituted methine carbon at 6.58, an aryl-substituted methyl absorption at 7.56, the methylene envelope centered at 8.38, and the *t*-butyl protons at 9.04.

1-(*p*-Tolylsulfonyl)-5-*t*-butylcyclohexene. A. From *trans,cis*-IV Tosylate. A solution of 928 mg (2 mmoles) of *trans,cis*-IV tosylate and 2.80 ml (10 mmoles) of triethylamine in 25 ml of 60% aqueous dioxane was refluxed 18 hr. The reaction mixture was poured into 50 ml of water and cooled overnight. Filtration afforded, after drying, 575 mg (98.5%) of olefin, mp 100–102°. Two recrystallizations from cyclohexane gave 500 mg of pure alkenes, mp 101–102°.

Table III. Analytical Data for Previously Unreported Sulfonates

Sulfonate		Calcd, %	Found, %	Infrared absorptions,[a] μ
trans,cis-V mesylate[b]	C:	55.64	55.46	7.39, 7.63, 8.59, 8.74
	H:	7.26	7.09	
	S:	16.51	16.28	
cis,cis-VI mesylate[b]	C:	55.64	57.04[c]	7.43, 7.73, 8.58, 8.72
	H:	7.26	7.62	
	S:	16.51	15.75	
trans,trans-III mesylate[b]	C:	55.64	55.91	7.40, 7.63, 8.49, 8.73
	H:	7.26	7.23	
	S:	16.51	16.25	
cis,trans-IV mesylate[b]	C:	55.64	55.85	7.40, 7.63, 8.48, 8.73
	H:	7.26	7.11	
	S:	16.51	16.59	
trans-I mesylate[d]	C:	50.58	50.69	7.44, 7.70, 8.52, 8.73
	H:	6.06	5.98	
	S:	19.29	19.56	
cis-II mesylate[d]	C:	50.58	50.59	7.38, 7.68, 8.56, 8.70
	H:	6.06	6.01	
	S:	19.29	19.10	

[a] Potassium bromide pellet; only sulfone and sulfonate absorptions are reported. [b] $C_{18}H_{28}O_5S_2$. [c] Although this analysis was not satisfactory, all other data were consistent with the assigned structure. [d] $C_{14}H_{20}O_5S_2$.

Table IV. Conditions for Preparation of the Sulfonate Esters of the Alcohols

Sulfonate prepared	Reaction time, days; temp, °C	Recrystallization solvent	Mp, °C	Yield, %
trans,cis-V OTs[a]	5; 25	Ethanol	125–126[b]	88
trans, cis-V OMs[c]	5; 25	Benzene–petroleum ether (30–60°)	153–154	90
cis,cis-OMs	3; 25	Benzene–petroleum ether (30–60°)	166–168	90
trans,trans-OTs	5; 25	Ethanol	163–164[d]	35
trans,trans-OMs	3; 25	Benzene–petroleum ether (30–60°)	170–171	85
cis,trans-OMs	4; 25	Benzene–petroleum ether (30–60°)	130–131	88
trans-OTs	7; 25	Benzene–petroleum ether (30–60°)	111–112[e]	
trans-OMs	5; 25	Benzene–petroleum ether (30–60°)	159–160	91
cis-OTs	3; 9	Isopropyl ether	116–118[f]	46
cis-OMs	5; 0	Benzene–petroleum ether (30–60°)	178–179	89

[a] OTs = *p*-toluenesulfonate. [b] Lit.[4] 124–125°. [c] OMs = methanesulfonate. [d] Lit.[4] 164–165°. [e] Lit.[61] 111–112°. [f] Lit.[62] 121.5–124.5°.

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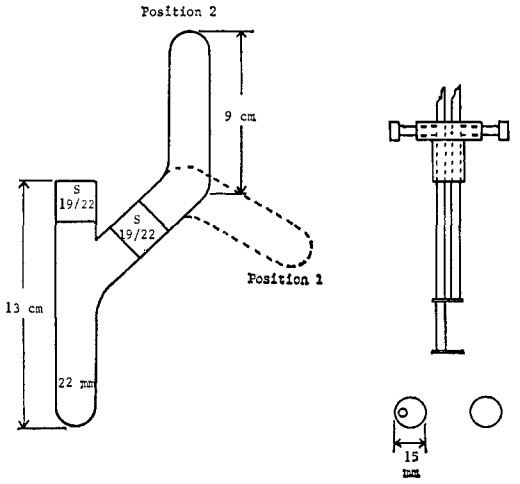

Figure 3. Drawing of the electrodes and conductance cell showing the operation of the addition tube.

B. From *trans,cis*-V Mesylate. A solution of 3.1 g (8 mmoles) of *trans,cis*-I mesylate and 2 ml (20 mmoles) of piperidine in 80 ml of N,N-dimethylformamide was sitrred at room temperature for 24 hr. The reaction mixture was poured into 600 ml of water and stored in the refrigerator overnight. The resulting solid was filtered, washed with water, and dried to give 2.34 g (100%) of the olefin, mp 101.5–103°.

1-(*p*-Tolylsulfonyl)-1-cyclohexene. A. From *cis*-II Mesylate. A solution of 1.33 g (4 mmoles) of piperidine in 40 ml of N,N-dimethylformamide was stirred at room temperature for 24 hr. The reaction mixture was poured into 300 ml of water and stored in the refrigerator overnight. The resulting precipitate was filtered, washed with water, and dried to afford 0.91 g (96%) of the olefin, mp 81–83° (lit.[13] mp 82–83°).

B. From *trans*-I Mesylate. From the reaction of 1.33 g (4 mmoles) of *trans*-I mesylate with piperidine under the conditions used for the *cis* isomer was isolated 0.99 g (94%) of the olefin, mp 80.5–83°.

Piperidinium Chloride. Anhydrous hydrogen chloride was bubbled into a solution of 10 ml (0.1 mole) of carefully redistilled Matheson Coleman and Bell piperidine in 20 ml of dry, reagent grade ether for 30 min. The resulting white solid was filtered and washed thoroughly with ether. The solid was stirred with 50 ml of ether and filtered. This process was repeated with ether, with 2:1 ether–chloroform, and finally with ether. The hydrochloride was then dried under vacuum to give 11.5 g (95%) of white powder, mp 244–245° (lit.[64] mp 242°).

Piperidinium Chloride-N,N-d_2. Several equilibrations of 13.0 g of the protium compound with deuterium oxide according to the method of Heacock and Marion[65] afforded, after thoroughly washing with ether and drying under vacuum, 12.9 g of the desired material, mp 245–247° (lit.[36] mp 247°). The infrared spectrum (Nujol mull) of the material obtained in this manner was superimposable on the reported spectrum of their compound for which they claimed at least 90% isotopic purity.

Piperidine-N-*d*. Using the method of Heacock and Marion,[65] 9.0 g (73 mmoles) of piperidinium chloride-N,N-d_2 (greater than 90% isotopically pure) was neutralized with 2 equiv of sodium deuterioxide in deuterium oxide. The resulting solution was saturated with sodium sulfate and continuously extracted with 175 ml of ether for 48 hr. Separation of the layers, removal of the ether, and careful distillation of the resulting liquid under argon through a 1 × 10 cm Vigreux column afforded 4.1 g (66%) of the pure compound, bp 105° (lit.[65] 106–108°). Again the infrared spectrum (neat) of this material was strictly comparable with that of the reported compound. The material obtained by this procedure has been shown to be greater than 90% isotopically pure.[65]

Kinectic Studies. Reagent Purification. Fisher reagent grade N,N-dimethylformamide (DMF) was purified by a modification of the method of Ferrari and Heider.[66]

DMF (1 l.) was stored under argon over 100 g of Linde Molecular Sieve 4A (MS 4A) for 48 hr. The resulting liquid was then carefully distilled under argon through a 2 × 60 cm Lackey-Ewell column, and the middle 700 ml, bp 152–152.5°, was taken and stored under argon over 70 g of MS 4A.

Similarly, 75 ml of Matheson piperidine which had been stored under argon over MS 4A was distilled under argon at atmospheric pressure through the same column. A 30-ml center fraction, bp 106°, was collected and stored under argon over MS 4A in the dark. Piperidinium chloride was purified as specified above. The sulfonate esters were recrystallized to constant melting point using the solvent systems given in Table IV.

Standard Solutions. Weighed amounts of stock piperidine and piperidinium chloride were placed in a volumetric flask and diluted to volume with stock DMF. All manipulations were carried out under an argon atomosphere, and the solutions were stored under argon. Quantities were adjusted so that these stock solutions were approximately 0.4 *M* in free piperidine and 0.01 *M* in the amine salt or, in one case, 0.2 *M* in amine and 0.005 *M* in salt. Standard solutions were prepared in quantities sufficient to run a complete series of one type of ester at one base concentration.

Kinetic Procedure and Apparatus. The procedure used was essentially that of Weinstock, Pearson, and Bordwell.[8] Resistances were measured with an Industrial Instruments, Inc., Model RC 16B1 conductivity bridge set at a frequency of 1000 cps. A 3-gal constant-temperature oil bath was maintained at 30 ± 0.02° by a Model S Sargent Thermonitor. The conductance cell and electrodes are shown in Figure 3.

In the fabrication of the electrodes, a Teflon plug was machined to the dimensions of a 19/22 standard taper male joint; the standard taper was topped by a rim 8 mm wide and 2 cm in diameter. The plug was then drilled to snugly accommodate two 4-mm glass tubes, and the rim was tapped for the retaining screws. The two platinum disks (see Figure 3) with a combined weight of ~2 g were silver soldered to two 1-cm pieces of 0.75-mm platinum wire which in turn were spot welded to two 20-cm pieces of 0.75-mm nichrome wire. Then the disks were sealed onto the bottom of two 4 × 160 mm Pyrex tubes in such a manner that the wire leads extended up through the tubes. After securing the seals with Fisher Sealit (baked 8 hr at 120°), the leads were covered to the seals with insulation. Assembly of the cell components afforded an airtight cell having a fully adjustable cell constant which could be maintained at or reset to a given value during a series of runs.

The electrodes were lightly platinized. For each different concentration of piperidine and salt, a blank was used to set the cell constant to give an optimum range of resistances for these concentrations. The retaining screws were tightened to maintain a constant electrode separation during a series of runs at the particular set of concentrations. Before each run the entire cell was rinsed with distilled water, reagent grade acetone, and methanol in that order and dried in a stream of argon. All manipulations were carried out under argon, and each kinetic run was sealed under argon.

In a typical run, 0.200 mmole of a sulfonate ester, a predetermined amount of piperidinium chloride, and 10.0 ml of stock DMF were placed in the main body of the cell. The addition tube, containing 10.0 ml of standard piperidine–piperidinium chloride solution, was attached to the cell in position 1 (see Figure 3), and the apparatus was equilibrated for 15 min in the constant temperature bath. To start a run the addition tube was rotated to position 2 as the stopwatch was started. Thorough mixing was insured by quickly rotating the entire assembly to refill the addition tube and then rotating the apparatus back to the upright position; this procedure was repeated two times. The addition tube was then replaced by a stopper. Reliable resistance readings could thus be obtained within 30 sec. Resistance readings were taken at suitable intervals, and an infinity reading was taken after the reaction mixture reached constant resistance. The infinity readings obtained in this manner corresponded to at least six half-lives. Calculations from data obtained by this procedure were made as described earlier.

Product Isolation. One of the reaction mixtures, initially containing 92.8 mg (0.200 mmole) of the tosylate, used to measure the kinetics of the reaction between *trans,cis*-V tosylate and piperidine was poured into 150 ml of water and placed in the refrigerator overnight. The resulting solid was filtered, washed with water, and dried under vacuum to give 57.5 mg (98.5%) of 1-(*p*-tolylsulfonyl)-5-*t*-butylcyclohexene, mp 102.5–104.5°.

Similar work-up of the kinetic reaction mixtures of the other sulfonates also gave greater than 88% of the olefin corresponding to loss of the proton α to the sulfone group. The purity of the

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isolated olefins was also confirmed by infrared analysis (Nujol mull) and mixture melting points.

Deuterium Exchange Studies. Standard Solutions. A standard solution of N-deuteriopiperidine and piperidinium chloride-N,N-d_2 in stock DMF was prepared in the same manner as were the solutions of the protium species. Thus 3.4457 g (0.03999 mole) of the deuterated amine and 1.1236 g (0.0010 mole) of the deuterated amine salt were weighed into a 100-ml volumetric flask which was then filled to the mark with stock DMF. The resulting solution was 0.3999 *N* in N-deuteriopiperidine and 0.0100 *N* in the deuterated amine salt.

Reactant Isolation from Half-Life Reactions. In a typical run, 163.4 mg of *trans*-I tosylate and 129 mg of piperidinium chloride-N,N-d_2 were dissolved in 10.0 ml of stock DMF and equilibrated in the constant temperature bath at 30.00 ± 0.02°. A 10.0-ml aliquot of the standard solution of the deuterated base, which had also been equilibrated at 30.00°, was added to the sulfonate solution. This gave a reaction mixture which was initially 0.02 *M* in tosylate, 0.20 *M* in N-deuteriopiperidine, and 0.06 *M* in the deuterated amine salt. After proceeding for a calculated half-life, the reaction mixture was quenched by pouring it into a mixture of 150 g of ice and 10 ml of concentrated hydrochloric acid, and the resulting mixture was stored in the refrigerator overnight. The solid which had precipitated from this mixture was filtered, washed thoroughly with water, and dried in a vacuum desiccator. Preparative thin layer chromatography of the crude mixture using the procedure described at the beginning of the Experimental Section afforded, after recrystallization from benzene–petroleum ether (30–60°), 38 mg of recovered *trans*-I tosylate, mp 111–112°, for excess deuterium analysis.[45]

Other runs were made using a similar procedure.

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Hindered Rotation in 1-Benzyl-1,2,3,4-tetrahydro-6-7-dimethoxyisoquinolines[1]

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Abstract: The conformation of several of the title compounds have been inferred from nmr data. It is shown that certain 1,2,3,4-tetrahydro-2-acetylisoquinolines substituted in the 1 position with benzyl exist as equilibrium mixtures of two conformers in nearly equal amounts. With increasing temperature the resonances for the two conformers average to a single spectrum. In the case of 1-benzyl-1,2,3,4-tetrahydro-1-acetyl-6,7-dimethoxyisoquinoline, rates of exchange due to conformer interconversion as obtained from the aromatic and acetyl line shapes are the same and both yield an activation energy of 7.8 kcal.

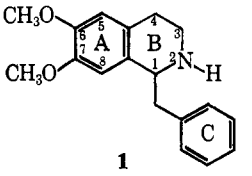
Recent empirical nmr correlations[2] of the structures of benzyl and bisbenzylisoquinoline alkaloids have, while permitting some extension to those of unknown structure, ignored possible anomalies which might arise in these structures because of steric inhibition of free rotation.[3]

In conjuction with the examination of nmr spectra of some new members of these families we felt it would be of value to examine simple cases where steric effects might be more readily observed.

Since all benzylisoquinoline alkaloids (dimerization of which produces the bisbenzylisoquinoline analogs) are substituted with oxygen-bearing moieties in the 6 and 7 positions, the parent compound chosen for this investigation was 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, **1**.[4]

Results and Discussion

Examination of the nmr spectrum of **1**, Figure 1a, indicates that ring C exists, preferentially, in that conformation which permits minimum steric interaction with ring A. Thus the aromatic hydrogens of ring A appear as a broad singlet at τ 3.39 ± 0.02 whereas the two methoxyl groups are found at the almost equivalent positions of τ 6.16 and 6.22. The spectrum of the



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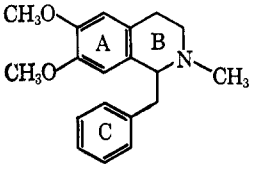
corresponding N-methyl derivative, 1-benzyl-2-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**2**,[5] (Figure 1b), however, shows that the 2-methyl group exerts a steric repulsion on ring C which is sufficient to force ring C close to ring A. Thus while the hydrogen at C_5 appears in the normal position of τ 3.43, that at C_8 is shifted upfield as a result of shielding by ring C to τ 4.01. The methoxyl group at C_7 is similarly affected,



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