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SOLVOLYSIS OF 2,2,3,4,4-PENTAMETHYLCYCLOBUTANE DERIVATIVES

Charles F. Wilcox, Jr. and Richard J. Engen
Department of Chemistry, Cornell University
Ithaca, New York

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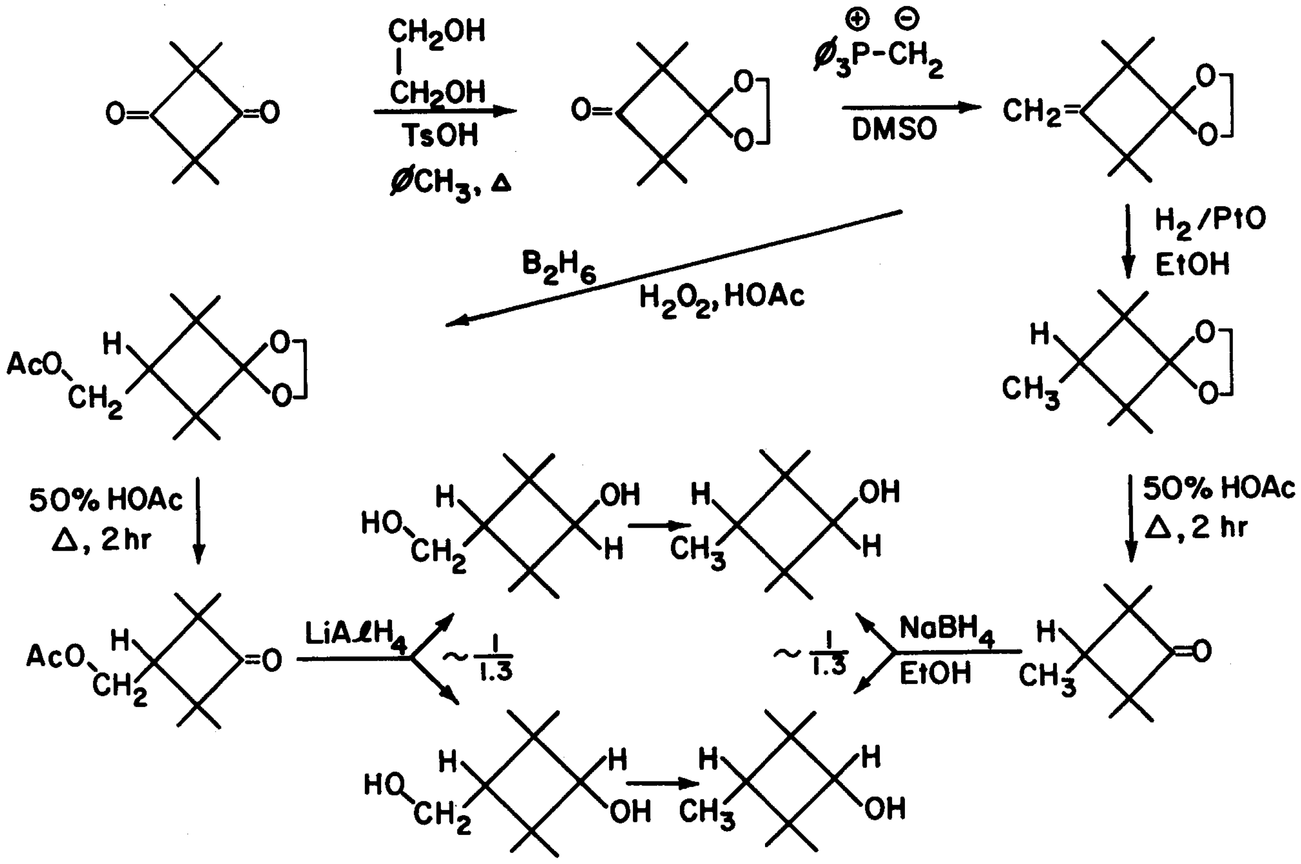
The facile acid-catalyzed cleavage of trans-2,2,4,4-tetramethylcyclobutane-1,3-diol compared to the inertness of the cis-isomer led Hasek, et al. (1) to suggest that decomposition of the trans isomer was accelerated by 1,3-hydroxyl participation. From rate and product studies of the mono- and di-p-toluenesulfonate esters of these diols as well as studies of some related esters an alternate explanation (2) in terms of carbon participation was proposed. The available evidence permitted no distinction between rapidly equilibrating classical ions and some one or more bridged ions (3). The case for carbon participation has been strengthened by similar solvolytic results in another solvent and by the very important evidence that solvolysis of the 3-d-substituted cis- and trans-tosylates did not lead to the scrambling pattern expected for a symmetrical bicyclic oxonium ion intermediate (4,5).

The large rate difference of cis-trans isomeric pairs was attributed mainly to differential steric interaction of the cis- or trans-3-hydroxyl group with the gem-dimethyls in the transition state. The rate differences of the esters with different substituents in the 3-position was attributed, in part, to inductive interaction of partial positive charge developed at C-2 or C-3 in the transition state.

One probe of the geometry of the transition state and further test of oxygen *vs.* carbon participation was to study the solvolysis of the *cis*- and *trans*-3-methyl substituted tetramethylcyclobutanol esters. It was expected that the 3-methyl group would show any effect caused by the bulk of the 3-hydroxy group while excluding the possibility of 1,3-bridging.

The required alcohols were prepared by the procedures shown below on the right of Chart I. All new compounds were characterized by micro analysis and nmr spectra. The assignment of stereochemistry of the final alcohols was based on the following permissive arguments; (a) the expectation that the *trans* alcohol would be formed in higher yield by preferential attack of hydride from the least hindered side, (b) equilibration of the alcohols led to a *cis/trans* ratio of ~1.9 favoring the di-pseudo-equatorial *cis*-alcohol, (c) the nmr spectrum of the *trans* alcohol has tertiary hydrogen absorption (multiplet) approximately 0.2 ppm downfield from the corresponding *cis* alcohol absorption as expected from the neighboring anisotropy of the flanking hydroxyl group in the *trans* isomer (6), and (d) the analogous qualitative arguments for the additional set of reactions shown on the left of Chart I. In these latter reactions the product ratio from ketone reduction was again consistent with preferential attack from the least hindered side. An attempt to observe internal hydrogen bonding in the *cis*-diol failed, presumably because of the higher energy of di-pseudo-axially disposed substituents. Further attempts to relate these two series of compounds chemically are in progress.


CH₂OH
CH₂OH
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ØCH₃, Δ
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DMSO
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B₂H₆
H₂O₂, HOAc
AcO
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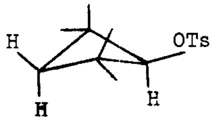
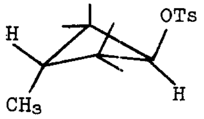
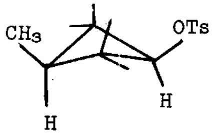
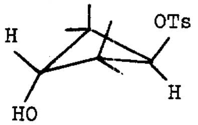
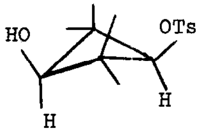
CH₃
50% HOAc
Δ, 2 hr
50% HOAc
Δ, 2hr
HO
OH
LiAℓH₄
~ 1/1.3
NaBH₄
EtOH
~ 1/1.3

CHART I

The solvolysis rates of the tosylates of the <u>cis-</u> and <u>trans</u>-3-methyl substituted alcohols in 90% acetone-water at 50° are reported in Table I along with the rates of appropriate reference compounds. Only an initial attempt has been made to

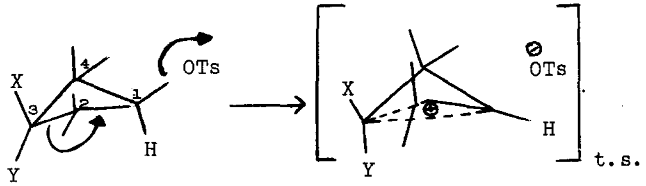
TABLE I

Rate Constants for the Solvolysis of Substituted Cyclobutyl Tosylates in 90% Acetone-Water at 50°

Compound	k_1 sec.$^{-1}$	Relative Rate
	4.6×10^{-5} (2)	1
	2.4×10^{-4}	5
	1.9×10^{-6}	0.04
	2.5×10^{-5}	0.5
	2.3×10^{-8} (7)	0.0005

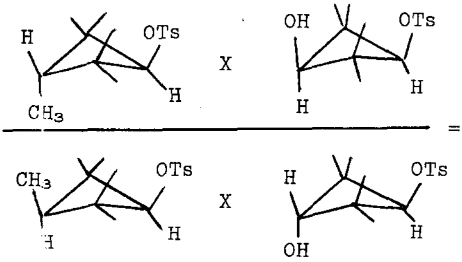
analyse the products of solvolysis of the pentamethyl esters. As with the tetramethyl reference tosylate no significant amounts of alcohols were found. Unlike the reference tosylate, however, two low-boiling materials in a ratio of close to 1:1 were found by glc for each ester. Glc of a mixture of the products from the two solvolyses gave three peaks, thereby suggesting that one common product was formed. This has been tentatively identified by infrared nmr and mass spectroscopy as 2,3,5-trimethylhexadiene, however the ultraviolet spectrum is anomalous (λmax 229mμ) if the diene chromophore is planar. The second product from the cis-methyl tosylate has a mass spectral cracking pattern and other spectral properties indicative of an unsaturated cyclic ether. Insufficient amounts of the trans-methyl tosylate products have been available for analysis.

The large rate ratio of ca. 120 between the cis- and trans-3-methyl substituted esters is consistent with the hypothesis of acceleration by participation of the C-C ring bond overlayed with steric retardations by a bulky cis substituent. The equilibration of the alcohols (cis alcohol/trans alcohol = 1.9) indicates that most of the steric retardation is associated with the transition states.

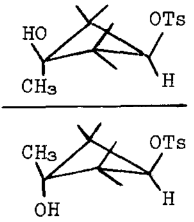


A curious aspect of the rate data is the eight-fold larger rate ratio of the 3-hydroxy esters (0.5/0.0005 = 1000) compared to the 3-methyl esters (5/0.04 = 125), particularly when a hydroxy substituent would be expected to present lesser steric requirements (8). One suggestive hypothesis would be a preferential stabilization of the cis-methyl transition state by interaction of the σ-bond between the 3-methyl and the ring with the developing vacant σ-orbit. oriented towards the departing tosylate group (9). Such stabilization amounts to highly geometry dependent C-C hyperconjugation transmitted through space. More conventional explanations in terms of some combination of entropy, solvation, dipole-dipole interactions, etc., might be possible. This aspect of the problem is being investigated both theoretically and experimentally.

It is instructive to note that the ratio of the products of the relative rates shown below is similar to the ratio of relative rates of the 3-methyl-3-hydroxy substituted esters described in the accompanying paper by Dolby and Wilkens. The similarity of



$$= \frac{5 \times 0.0005}{0.04 \times 0.5} = 0.11$$



$$= \frac{37/2800}{136/2800} = \frac{0.013}{0.048} = 0.27$$

of these ratios is even more striking when conformational equilibria are taken into account. If it is assumed that the free energy change accompanying conversion of a pseudo-equatorial substituent on a puckered cyclobutane ring into a pseudo-axial substituent is identical to that for the corresponding cyclohexane, then the distribution of each isomer between the two conformations can be calculated (10). If it is further assumed that the intrinsic ionization rate of an axial tosylate is very much less than the rate of an equatorial tosylate (Wiberg (11) in the analogous but conformationally frozen bicyclo[2.1.1] tosylates finds a rate ratio of 3×10^6) then the observed relative rates should be corrected to a common basis by dividing the rate constant by the fraction of equatorial tosylate calculated to be present. With this correction the observed rate ratios of 0.11 vs. 0.27 become 0.35 vs. 0.30. More significantly, the rate data of this paper can be used to predict the rates of the cis and trans 3-hydroxy 2,2,3,4,4-pentamethylcyclobutyl tosylates relative to the reference tetramethylcyclobutyl tosylate reported in the accompanying paper by Dolby and Wilkens. The cis isomer is calculated to have a relative rate of 0.011 compared to the observed rate of 0.013 while the trans isomer gives 0.031 calculated vs. 0.048 observed. This excellent agreement suggests that, an approximately additive free energy relation exists for these substituents and suggests that any special electronic effects would have to arise from a first order interaction (12).

Acknowledgement -- We are indebted to Professor L. L. Dolby for holding up the publication of his manuscript so that these closely related studies might appear together.

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3. See footnote 9 in ref.(2).
4. L. J. Dolby and C. Wilkins, Tetrahedron Letters, **34**, 2379(1964).
5. The scrambling result does not, of course, rigorously exclude an unsymmetrically bridged oxonium ion. However, the observation of less than 5% deuterium transfer seems inconsistent with the observed rate acceleration of 10^3.

6. A shift of 0.2 ppm downfield of the tertiary hydrogen is observed for the *trans*-tetramethylcyclobutane-1,3-diol relative to the *cis*-isomer.

7. Extrapolated rate constant from data given in ref. 2.

8. If A values (9) are used as a measure of steric requirements and a linear steric free energy relationship based on the hydroxyl ratio is assumed, a rate ratio for the methyl esters as large as *ca*. 10^6 might have been calculated.

9. R. Hoffmann (private communication) has considered the possibility of such ion stabilizing interactions as part of his analysis of carbonium ion stabilities. Extended Hückel theory calculations on one arbitrary geometry of the *cis*- and *trans*-methyl carbonium ion led to preferential stabilization of the *cis*-isomer.

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