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THE SOLVOLYSIS OF CIS AND TRANS-3-HYDROXY-2,2,3,4,4-PENTAMETHYLCYCLOBUTYL TOSYLATES (1)

Lloyd J. Dolby (2) and Charles Wilkins

Department of Chemistry, University of Oregon, Eugene, Oregon

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It has been observed that trans-2,2,4,4-tetramethylcyclobutane-1,3-diol is cleaved in acid much more rapidly than the cis-isomer (3). Moreover, the trans-monotosylate solvolyzes about 1000 times faster than the cis-monotosylate (4,5).

It has been suggested that the greater reactivity of the trans-isomer is the result of anchimeric assistance by neighboring hydroxyl (1) but several pieces of evidence from solvolysis studies argue strongly against this possibility (4,5).

In an effort to gain some insight into the cause of the difference in reactivity between the cis and trans-hydroxy tosylates we have examined the solvolysis of the cis and trans-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl tosylates. The required cis and trans-pentamethylcyclobutane-1,3-diols were prepared from a mixture of cis and trans-2,2,4,4-tetramethylcyclobutane-1,3-diol. Treatment of a mixture of the tetramethyl diols with sodium hydride in dimethylsulfoxide followed by one molar equivalent of benzyl chloride afforded a mixture of benzyl ethers which was oxidized with chromic acid in acetone. Distillation of the oxidation product afforded

3-benzyloxy-2,2,4,4-tetramethylcyclobutanone in 20% yields based on starting diol. The action of methyl lithium on 3-benzyloxytetramethyl cyclobutanone gave a mixture of the cis and trans-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl benzyl ethers which was debenzylated by the action of sodium in liquid ammonia to afford a mixture of the pentamethylcyclobutane-1,3-diols in 94% yield based on the benzyloxy ketone. The diol mixture was separated by chromatography over alumina to yield two pure 2,2,3,4,4-pentamethylcyclobutane-1,3-diols, m.p. 118-119.5°, and m.p. 98-99° in a ratio of 1/3. The higher melting isomer is tentatively assigned the trans-configuration and the lower melting compound appears to be the cis-isomer. The tosylates of these diols were prepared in the usual manner; the cis-hydroxyl tosylate showed m.p. 122.5-123° and the trans-isomer had m.p. 115-116°. The stereochemical assignments are supported by n.m.r. and infrared studies of the diols and their derived tosylates. The single ring proton of the isomeric pentamethylcyclobutane-1,3-diol is expected to appear at lower field in the trans-isomer since in this isomer it is cis to the C-3 hydroxyl group. Accordingly, the C-3 proton of trans-2,2,3,4,4-pentamethylcyclobutane-1,3-diol appears at τ 6.29 whereas the C-3 proton of the cis-isomer appears at τ 6.60, and a similar difference is observed in the hydroxy tosylates. That a ring proton is deshielded by a cis-oxygen function is demonstrated in the n.m.r. spectra of the 2,2,4,4-tetramethylcyclobutane-1,3-diols and their derivatives of known configuration. Thus the ring

protons of the trans-tetramethylcyclobutane-1,3-diol are found at τ 6.17 and those of the cis-isomer appear at τ 6.38. Similar differences of 0.17 and 0.20 p.p.m. are found for the cis and trans-2,2,4,4-tetramethylcyclobutane-1,3-diol mono and ditosylates. The shielding of the methyl groups is also affected by the relationship of the hydroxyl groups, but the chemical shifts of the methyl groups in the 2,2,4,4-tetramethylcyclobutane-1,3-diols and derivatives of known configuration did not suggest any straightforward relationalizations.

The infrared spectrum in carbon tetrachloride (ca. 10^{-2} molar) of cis-3-hydroxy-2,2,3,4,4-tetramethylcyclobutyl tosylate showed two peaks in the hydroxyl region at 3621 and 3638 cm^{-1} suggesting intramolecular hydrogen bonding. Similarly cis-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate absorbs at 3625 and 3636 cm^{-1} whereas the trans-isomers show only one peak in the hydroxyl region. The cis-diols show no evidence of intramolecular hydrogen bonding.

The solvolysis of both cis and trans-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl tosylate gives quantitative yields of the expected cleavage product, 3,3,5-trimethylhex-4-ene-2-one. The product ketone was synthesized from 2,2,4-trimethyl-3-pentenal, the cleavage product of the 2,2,4,4-tetramethylcyclobutane-1,3-diols, by the action of methyl lithium followed by chromic acid oxidation. The results of our rate studies are summarized in Table I.

It is instructive to examine the relative rates of the tetramethyl and pentamethyl cyclobutane derivatives. These data are presented in Table II.

TABLE I

Rate Constants for the Solvolysis of cis and trans-3-Hydroxy-2,2,3,4,4-pentamethylcyclobutyl Tosylate in 80% Ethanol-Water

Isomer	Temp °C	$10^5 k$ sec.$^{-1}$	$\Delta H^{\ddagger}$ kcal.	$\Delta S^{\ddagger}$ e.u.
cis	60.93	3.11±0.05		
	69.94	8.36±0.3	26.2±0.7	-0.8±2.0
	85.97	55.6±0.6		
trans	60.63	12.3±0.2	28.1	7.6
	69.94	40.0±1.5		

TABLE II (6)

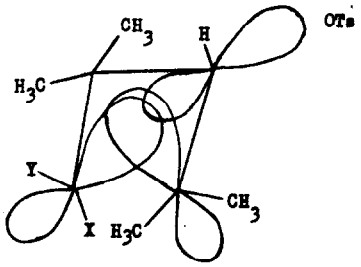
Relative Rates of Solvolysis of Substituted Cyclobutyl Tosylates in 80% Ethanol-Water at 50°

Compound	Relative Rate
2,2,4,4-Tetramethylcyclobutyl Tosylate	1
trans-3-Hydroxy-2,2,4,4-tetramethylcyclobutyl Tosylate	0.5
trans-3-Hydroxy-2,2,3,4,4-pentamethylcyclobutyl Tosylate	5×10^{-2}
cis-3-Hydroxy-2,2,3,4,4-pentamethylcyclobutyl Tosylate	1×10^{-2}
cis-Hydroxy-2,2,4,4-tetramethyl cyclobutyl Tosylate	3×10^{-4}

The striking feature of these data is that the rate difference between the cis and trans-3-hydroxy-2,2,4,4-tetramethyl cyclobutyl tosylates of over 10^3 is reduced to

less than 4 by the introduction of a methyl group at C-3. The introduction of a methyl group in the cis-series undoubtedly affects the rate of solvolysis by both an electronic and a steric effect. It seems likely that the methyl group causes additional strain in the ground state and stabilizes the transition state by an inductive effect. The sum of these effects thus causes a rate enhancement of 40. If these effects were the dominant ones in the trans-series then the trans-pentamethyl compound would be expected to react about 40 times faster than the tetramethyl compound whereas it solvolyzes more slowly by a factor of 11. Thus trans-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl tosylate solvolyzes over 400 times more slowly than might be expected and this rate retardation is clearly a special steric effect.

We would propose that this effect is a steric crowding in the transition state caused by specific directed rotations about the C-1,C-2 and C-3,C-4 bonds. This suggestion is based on the premise that the greater electron demand is at the backside of the developing carbonium ion and this is supplied by the electrons of the C-2,C-3 bond. This premise is supported by results from the solvolyses of rigid cyclobutane systems (7). This hypothesis accounts for the reduced activity of the cis-hydroxy tosylate since such a stereospecific rotation around the C-1,C-2 bond would engender a steric interaction between the cis-2-methyl substituent and the hydroxyl at C-3. In the trans-isomer the corresponding interaction would be between methyl and hydrogen. In the pentamethyl series compounds the rate



difference would be expected to be greatly diminished since the steric effects are between two methyl groups in one isomer and a methyl and hydroxyl group in the other isomer. The proposed transition state could collapse to a cyclopropylcarbinyl cation as suggested by the product from the solvolysis of 2,2,4,4-tetramethylcyclobutyl tosylate (4) or it could lead directly to the conjugate acids of the carbonyl compounds obtained from the hydroxy tosylates. Cyclopropyl carbinyl cations could be intermediates in the solvolyses of the hydroxy tosylates but the products give no evidence of their intervention (8).

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6. The relative rate of solvolysis of 2,2,4,4-tetramethylcyclobutyl tosylate was obtained from the data of Wilcox and Nealy (4). The rate constant was multiplied by 15 to correct for the change in solvent from 90% acetone-water to 80% ethanol-water. The factor of 15 is the average of the corresponding solvent effects on the solvolyses of the hydroxytetramethylcyclobutyl tosylates at 50°.

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8. Satisfactory spectrocopic and analytical data have been obtained for all new compounds described in this communication.