Tetrahedron Letters,Vol.24,No.45,pp 4959-4962,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

ACETOLYSIS AND FORMOLYSIS OF (R)-AND (S)-1-DEUTERIO-2-CYCLOPROPYLETHYL p-TOLUENESULFONATES

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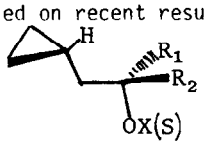
Summary: Acetolysis and formolysis of the enantiomers of 1-deuterio-2-cyclopropylethyl tosylate, 3-OTs and 4-OTs, led to 17-18% retention (cyclopropyl participation) and 82-83% inversion (nucleophilic solvent assistance) of configuration in the 2-cyclopropylethyl product.

Interest in the ability of cyclopropane as a remote neighboring group in structurally unconstrained substrates has prompted several solvolytic investigations of the 1-X or 2-X derivatives.[1-5] Based on recent results, three competing mechanisms have



X=Bs,Ts; S=solvent

1, $R_1=R_2=H$ 3, $R_1=H, R_2=D$
2, $R_1=R_2=D$ 4, $R_1=D, R_2=H$

been proposed: nucleophilic solvent displacement (k_s) to give 1-OS or 2-OS: participation by the cyclopropyl group ($k_\Delta^{c-C_3H_5}$) to yield a cyclopentyl product (with deuterium scrambled in the case of 2-X)[6] via an intramolecularly alkylated cyclopropyl intermediate which collapses to a cyclopentyl carbocation: and hydrogen participation (k_Δ^H) to obtain cyclopropylcarbinyl and/or olefinic products.[4,5] The relative contribution of each process is controlled by the nucleophilicity and ionizing power of the medium. Thus, solvolysis of 1-X in the highly nucleophilic, less ionizing ethanol[2] and acetic acid[1,2] takes place predominantly by a k_s mechanism, whereas solvolysis in the less nucleophilic, highly ionizing formic acid and particularly in 2,2,2-trifluoroethanol (TFE) proceeds by a substantial amount of $k_\Delta^{c-C_3H_5}$ in addition to k_s: k_Δ^H is also enhanced in the latter solvents.[4,5]

In the above mechanistic interpretation it was assumed that 1-OS comes predominantly from k_s. However, it is feasible that at least a portion of this product may arise from $k_\Delta^{c-C_3H_5}$ (via a bridged intermediate). We now report experimental data which differentiate quantitatively between k_s and $k_\Delta^{c-C_3H_5}$ in 1-OS. This was accomplished by solvolysis of the chiral 3-OTs and subsequent examination of the stereochemistry of the 2-cyclopropylethyl product. The results were confirmed (within experimental error) by analogous treatment of the (S)-enantiomer, 4-OTs.

Preparation of the (R)-alcohol, 3-OH, was accomplished by enzymic exchange of 1-OH using the system NAD^+/NADH-YADH/diasphorase in D_2O at 35°C, according to the method of Simon and coworkers.[7] Analogous treatment of 2-OH, using H_2O in lieu of D_2O, gave the (S)-alcohol, 4-OH. Enantiomeric purity was determined by derivitization of the alcohols with optically pure

(-)-camphanoyl chloride[8,9] and subsequent nmr analysis of the ester in the presence of $Eu(thd)_3$[10] shift reagent, according to the method by Gerlach and Zagalak.[9] Resolution of the pro-R (H_R) and pro-S (H_S) protons was optimal in this case in CS_2 solvent, and incomplete in CCl_4 or $CDCl_3$.[4,11] Product analysis revealed that the alcohol obtained from 1-OH was actually a mixture of 3-OH (47 ± 3%) and starting 1-OH (53 ± 3%), whereas the alcohol obtained from 2-OH consisted of 4-OH (16.7%), unexchanged 2-OH (78.5%), and contaminant 1-OH (4.8%),[12] as calculated from the relative nmr areas of the H_S and H_R regions of their (-)-camphanoate esters (see Table 1) in conjunction with deuterium analysis data. Incomplete enzymic exchange may be due to the low solubility of these alcohols in water.

Mixture 1-OH + 3-OH was tosylated and solvolyzed in anhydrous acetic acid[13] and in anhydrous formic acid.[14] All products were purified by VPC and analyzed as alcohols[15] after reduction of the solvolysis mixtures with $LiAlH_4$. Mixture 1-OH + 2-OH + 4-OH was

Table 1. Retention and Inversion in 2-Cyclopropylethanol

	Camphanoate Ester	% H_S	% H_R	% Retention	% Inversion
1+3	(starting material)	62.0 ± 0.7	38.0 ± 0.7		
	(after acetolysis)	41.3 ± 0.6	58.7 ± 0.6	13.8 ± 3.8	86.2 ± 6.00
	(after formolysis)	41.8 ± 0.8	58.2 ± 0.8	15.8 ± 4.7	84.2 ± 7.2
1+2+4	(starting material)	18.1 ± 2.7	81.9 ± 2.7		
	(after acetolysis)	69.6 ± 0.6	30.4 ± 0.6	19.3 ± 4.6	80.7 ± 6.7
	(after formolysis)	69.3 ± 1.3	30.7 ± 1.3	19.7 ± 4.9	80.3 ± 7.1

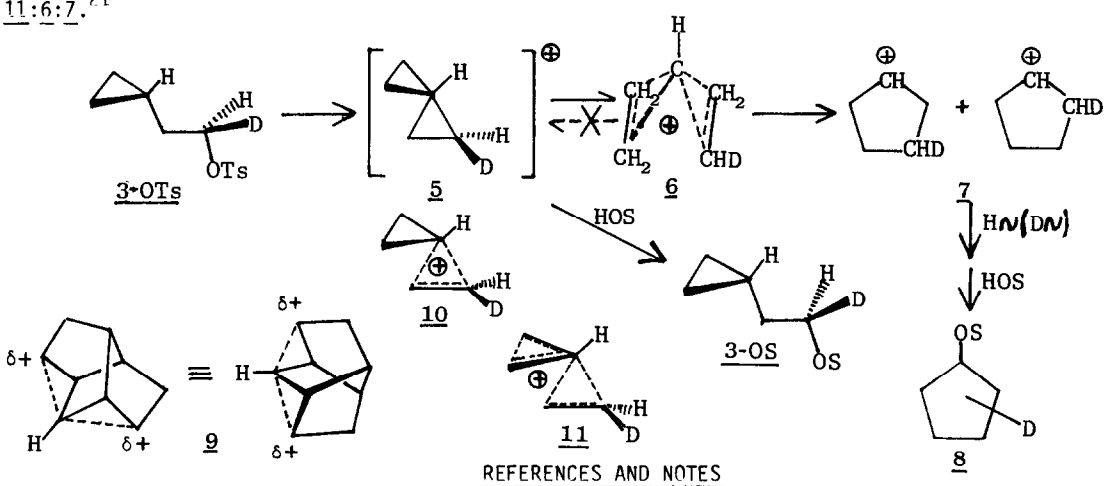
treated similarly. Acetolysis gave only 2-cyclopropylethyl acetate as reported previously.[2] Formolysis led to the formate esters of 2-cyclopropylethanol (69.5 ± 2.0%), cyclopentanol (20.3 ± 1.6%), 4-penten-2-ol (4.1 ± 0.3%), and 3-penten-1-ol (6.1 ± 0.8%).[2,4,5] 2-Cyclopropylethanol obtained from each solvolysis was esterified with (-)-camphanoyl chloride and analyzed by nmr as described above. It should be noted that, of the above reactions, a possible stereochemical change in the 2-cyclopropylethyl skeleton may occur only during solvolysis.

Table 2. Competing Mechanisms in Solvolysis of 1-OTs

Medium	% k_s	% $k_\Delta^{c\text{-}C_3H_5}$ (Cyclopropylethyl)[18]	% $k_\Delta^{c\text{-}C_3H_5}$ (Cyclopentyl)[18]	% k_Δ^{h}
acetic acid	83.	17.	0.	0.
formic acid	57.	13.	20.	10.
TFE[5,19]	41.		25.	34.

The relative % retention and inversion of configuration in the 2-cyclopropylethyl product were calculated from the integrated H_S and H_R nmr areas listed in Table 1, after the necessary corrections using the corresponding areas of the starting material.[16] The apparent differences in the % retention and inversion between the two "enantiomeric mixtures" are certainly

due to experimental uncertainty. Noting that retention of configuration is associated with the $k_{\Delta}^{c\text{-}C_3H_5}$ mechanism and inversion with k_s, these data can now be incorporated into the product composition, presented above, to obtain complete separation of the various processes (Table 2).[17] The present results indicate an increase in $k_{\Delta}^{c\text{-}C_3H_5}$ compared to previous reports.[1-3] Thus, even in the highly nucleophilic acetic acid there is 17% $k_{\Delta}^{c\text{-}C_3H_5}$, whereas in formic acid this value is increased to 33%. It is noteworthy that in the solvolyses of the deuterated tosylates, 2, 3, and 4, the deuterium label is randomly distributed over all carbon atoms of the cyclopentyl product, whereas in the unrearranged 2-cyclopropylethyl acetate and formate products, the deuterium is found solely at the 1-position. The retention of stereochemistry observed for 3- and 4-OTs requires a bridged intermediate ion which maintains the deuterium at the 1-position for both acetolysis and formolysis. A competing or subsequent intermediate is required to account for the deuterium scrambled cyclopentyl product. A rectangular pyramid,[2] 6, would distribute deuterium to the 2- and 3-positions (4- and 5- as well) of the cyclopentyl product. Hydride migration[22] is required to equilibrate the deuterium into the 1-position in the resulting cyclopentyl cation, or, alternatively, hydride migration may equilibrate all of the deuterium and hydrogen.[23] Solvent trapping of a symmetrical rectangular pyramid, 6, would give unrearranged 3-and 4-OAc with deuterium at all four methylene carbons, which is not observed. Thus, at least two intermediate ions are required to explain the observed results; subsequently formed ions if the products 3-OS (retained) and 8 arise along a common mechanistic pathway, or, competing ion forming pathways for cyclopropane participation. The initially formed (or in parallel to 6) intermediate 5 may be a trigonal bipyramidal-like structure, such as that found for 9,[24] which may then rotate to a more stable rectangular pyramid, 6; or 5 may have the structure of a cyclopropyl cation "solvated" by an ethylene molecule in a bisected form, 10, or a "half-opened" cyclopropyl cation as in 11. Calculations indicate an increasing order of cation stability 11:6:7.[21]



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8. We are indebted to Professor Gerlach for the donation of a sample of (-)-camphanoyl chloride, and for furnishing details of the esterification procedure.

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10. Eu (thd)$_3$ is tris(2,2,6,6-tetramethyl-3,5-heptadionato)europium (III).

11. Nmr spectra of (-)-camphanoate esters were obtained at 100 and 220 MHz in CS_2. Typical conditions at 100 MHz: [ester] = 0.42M, [Eu(thd)$_3$] = 0.23M: $\delta H_S - \delta H_R = 0.56$ ppm.

12. The initial alcohol 2-OH was contaminated with 4.8% 1-OH.

13. Typical conditions: [ROTs] = 0.078M, [NaOAc] = 0.063M: reflux for 56h (~99% reaction).

14. Typical conditions: [ROTs] = 0.076M, [NaO_2CH] = 0.12M: thermostated in a sealed glass vessel at 75°C for 28h (~75% reaction).

15. Deuterium analyses of 2-cyclopropylethanol isolated from the acetolyses and formolyses are in good agreement with those found for the corresponding starting material, indicating no loss of deuterium during these reactions.

16. For example, for acetolysis of 1-OTs+3-OTs:
(R)-enantiomer (or retention) = (41.3 ± 0.6)-(38.0 ± 0.7) = 3.3 ± 0.9
(S)-enantiomer (or inversion) = (58.7 ± 0.6)-(38.0 ± 0.7) = 20.7 ± 0.9

$$\% \text{ retention} = \frac{3.3 \pm 0.9}{(3.3 \pm 0.9)+(20.7 \pm 0.9)} \times 100 = 13.8 \pm 3.8$$

17. The average values of 16.6% retention, 83.4% inversion for acetolysis (entries 2 and 5 in Table 1), and 17.8% retention, 82.2% inversion for formolysis (entries 3 and 6 in Table 1) were employed for the calculation.

18. $k_{\Delta}^{C-C_3H_5}$ (2-cyclopropylethyl) and $k_{\Delta}^{C-C_3H_5}$ (cyclopentyl) represent participation by cyclopropane leading to 2-cyclopropylethyl and cyclopentyl products respectively.

19. Our efforts to dissect 1-OTFE into k_s and $k_{\Delta}^{C-C_3H_5}$ have been thwarted by our inability to cleave the ether with sodium naphthalide radical anion.[20]

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23. Note, however, that solvolysis of specifically deuterium labelled cyclopentyl brosylates does not lead to deuterium scrambling in the cyclopentyl products. R.C. Seib, V.J. Shiner, Jr., V. Sendijarević and K. Humski, J. Am. Chem. Soc., 1978, 100, 8133.

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(Received in USA 22 August 1983)