

1-(3-hydroxypropyl)uracil (**9**), are hydroxymethylated at the 5 position of the heterocycle. Moreover, careful monitoring of the progress of the reaction (Figure 1) has demonstrated that the relative rates of hydroxymethylation parallel those of the base-catalyzed 5-H exchange, supporting the existence of cyclonucleoside intermediates.

The data presented herein offers a reasonable chemical rationalization of the catalytic role of thymidylate synthetase.¹² It is suggested that this reaction may involve activation of the 5 position of 2'-deoxyuridine 5'-monophosphate toward electrophilic attack by addition of a nucleophilic group of the enzyme to the 6 position which can be eliminated in a subsequent step. Further investigations of possible mechanistic features of this enzyme are in progress.

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(12) Our data do not support a previous proposal² which involves covalent bond formation between the 5 position of dUMP and the enzyme or the cofactor, 5,10-methylenetetrahydrofolic acid.

(13) National Science Foundation Predoctoral Trainee, 1966-present.

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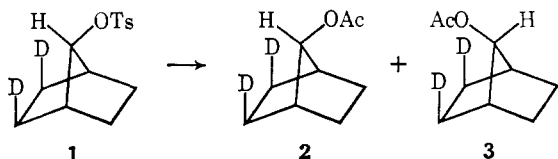
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The 7-Norbornyl Cation. Nonclassical or Nonplanar?

Sir:

The acetolysis of *exo,exo*-2,3-dideuterio-*anti*-7-tosyloxybicyclo[2.2.1]heptane (**1**) was recently reported to yield a mixture of **2** and **3** with 90% retention of stereo-



chemistry.^{1,2} Among the possible mechanistic explanations suggested for this unusual case of retention of stereochemistry were formation of a delocalized carbonium ion¹ and competitive frontside and backside displacement by solvent on the initially formed ion pair.² A definitive choice could not be made between these alternate mechanisms due to the limited experimental data. We report here the details of an extensive study of this intriguing system which indicate that competitive frontside and backside displacement on an initially formed ion pair is an inadequate explanation of the observed phenomenon.

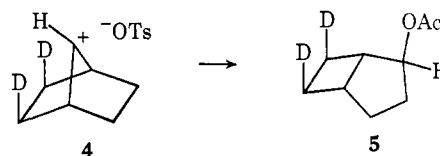
As demonstrated by Winstein and coworkers, the acetolysis of 7-tosyloxybicyclo[2.2.1]heptane yields small amounts (3–5%) of *exo*-2-acetoxycyclo[3.2.0]heptane in addition to 7-acetoxycyclo[2.2.1]heptane.³ If a single intermediate, such as ion pair **4**, was involved in this reaction, only the alkyl chain *trans*-antiparallel to the leaving tosylate function should migrate since

(1) P. G. Gassman and J. M. Hornback, *J. Am. Chem. Soc.*, **89**, 2487 (1967).

(2) F. B. Miles, *ibid.*, **89**, 2488 (1967); **90**, 1265 (1968).

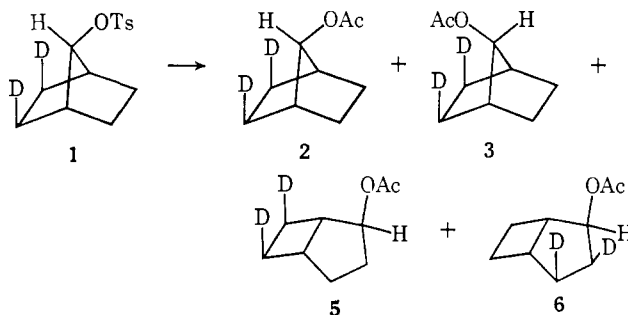
(3) S. Winstein, F. Gadiant, E. T. Stafford, and P. E. Klinedinst, Jr., *ibid.*, **80**, 5895 (1958).

the orbital arrangement is unsuitable for migration of the "cis" alkyl chain. By utilizing the deuterium labels



on **1** we should be able to test whether **4** is the sole intermediate involved in the formation of **2** and **3**, since if **4** were the only intermediate, **5** should be the only rearranged acetate.

When **1** was solvolyzed in acetic acid buffered with sodium acetate, a mixture of 7-acetoxycyclo[2.2.1]heptane (97% of the product) and *exo*-2-acetoxycyclo[3.2.0]heptane (3% of the product) was obtained. The mixture of **2** and **3** was separated from the 2-acetoxycyclo[3.2.0]heptane by preparative vpc.



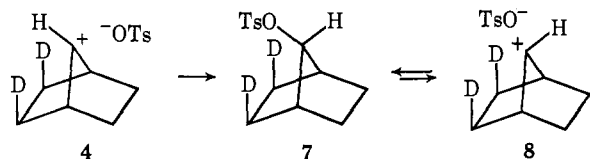
Analysis of these samples by quantitative infrared spectroscopy showed that the ratio **2**:**3** was $(90 \pm 3):(10 \pm 3)$, as previously reported.^{1,2} However, the 2-acetoxycyclo[3.2.0]heptane did not consist of a single deuterium-labeled isomer as would be predicted if **4** were the only precursor. Instead, quantitative infrared analysis vs. authentic samples of **5** and **6**⁴ showed that this sample consisted of a mixture of $95 \pm 3\%$ **5** and $5 \pm 3\%$ **6**. The presence of **6** in the reaction media precludes the intermediacy of a single ion pair such as **4**.⁵ The formation of **6** from an ion-pair precursor would require the internal return of **4** to **7**⁶ and ionization of **7** to **8**. Since it has been shown² that internal return of **8** to **7** should be two to three times faster than collapse with solvent, the intermediacy of **8** should be reflected

(4) The details of the synthesis of **5** and **6** will be presented in a full paper on this topic. The analyses were carried out by preparing authentic mixtures of **2** and **3** and of **5** and **6** starting with pure samples of **2**, **3**, **5**, and **6**. The methods of preparation of **2**, **3**, **5**, and **6** were all different, and the synthetic routes used precluded the possibility of any contamination of any of these samples by small amounts of any of the other materials being analyzed. Since **2** and **1**, and **3** and **7**, had common precursors, respectively, it follows that **1** and **7** were also epimerically pure.

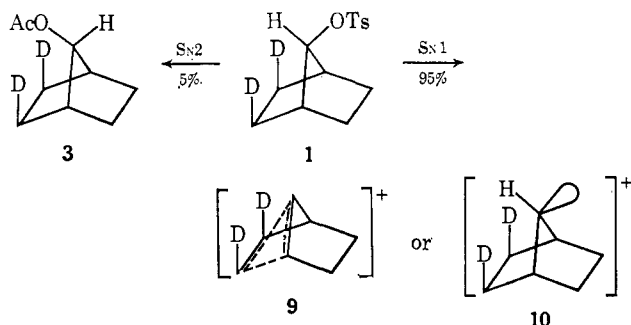
The authentic mixtures used for the quantitative infrared analysis were made up in 5% increments. Two different peaks in the authentic mixtures were compared with the same peaks from the solvolysis mixture. Both visual comparison of the spectra and plots of concentration vs. peak intensity ratios were used in the determinations. Since the change in the peak intensity ratios was relatively large, the experimental error was minimized. We feel that the actual error in the determinations was considerably less than the stated $\pm 3\%$.

(5) In order to ensure that an unexpected deuterium isotope effect was not playing a part in determining the product composition, the epimeric tosylate **7** was solvolyzed under the same conditions as **1**. It gave **2** and **3** in the ratio $(10 \pm 3):(90 \pm 3)$, respectively, and **5** and **6** in the ratio $(5 \pm 3):(95 \pm 3)$, respectively. Since identical results were obtained from the two epimerically pure tosylates, the solvolysis of **7** served as a check both of the method of analysis and of the experimental results.

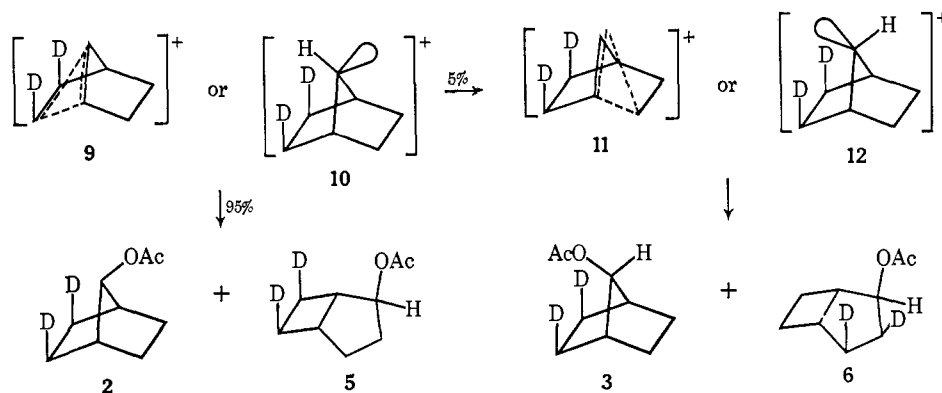
(6) For a recent example of tosylate inversion see A. Streitwieser, Jr., and T. D. Walsh, *J. Am. Chem. Soc.*, **87**, 3686 (1965).



in the presence of 7 in the partially reacted solvolysis mixture. Isolation of unreacted tosylate from the acetolysis of **1** after 50% reaction showed no detectable amount of 7. In addition the product ratio after one half-life was the same as after ten half-lives, indicating that conversion of **4** to **8** was not occurring.^{4,7}

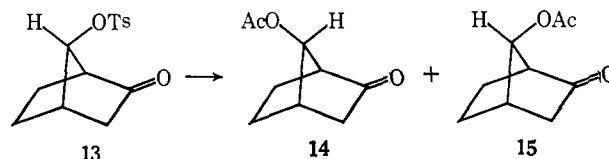


In view of the failure of frontside and backside displacement to explain the observed results, we wish to put forth a mechanistic explanation consistent with all of the available data. We propose that **1** undergoes solvolysis by a composite of SN1 and SN2 mechanisms. We further propose that the SN2 portion of the reaction occurs (as expected) with complete inversion. Our experimental data conform to these proposals in the



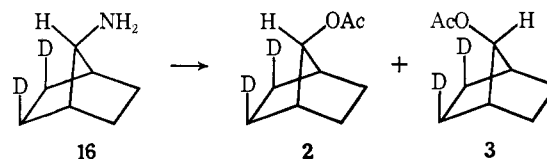
following manner: **1** reacts by an SN2 mechanism to the extent of 5% to yield **3**. The remaining 95% **1** ionizes to yield either the delocalized ion **9** or the nonplanar carbonium ion **10**. Of the 95% **1** converted to **9** or **10**, 95% reacts with solvent directly to yield a 97:3 mixture of **2** and **5**, respectively. The remaining 5% is inverted to either **11** or **12** which then collapses with solvent to a 97:3 mixture of **3** and **6**, respectively.

In support of the mechanistic sequence outlined above several factors merit presentation. The direct displacement of tosylate by acetic acid to the extent of >90% occurs in the solvolysis of *syn*-7-tosyloxybicyclo[2.2.1]heptan-2-one (**13**), which yields a 95:5 mixture of **14** and **15**, respectively. Clearly, SN2 displacement is the predominant reaction path in this case. Since the acetolysis of **13** occurs only ten times slower at 200° [$k = (5.45 \pm 0.19) \times 10^{-6} \text{ sec}^{-1}$] than



does **1** ($k = 5.49 \times 10^{-5} \text{ sec}^{-1}$), the direct SN2 displacement of tosylate from **1** to the extent of 5% is very reasonable. In line with this argument Miles has found that the ratio **2**:**3** was solvent dependent.² Whereas the amount of inversion (SN2 displacement) did not follow the order of increased ionizing power of the solvent,² it did correlate with the order of increasing solvent nucleophilicity.

In order to evaluate the nature of the 7-norbornyl cation under conditions where solvent nucleophilicity would be less important, we studied the deamination of **16** in acetic acid. Upon nitrous acid deamination, **16** gave **2** and **3** in the ratio 95:5, respectively. This is



the same ratio as that required for the SN1 portion of the mechanism outlined above for the acetolysis of **1**. This strongly supports the contention that 5% of **1** reacted via an SN2 mechanism.

The last point to be considered is whether **9** or **10** was the intermediate⁸ formed in the SN1 portion of the reaction. The experimental data require the presence

of either **9** or **10**. Leakage of **9** to the epimeric nonclassical ion **11** would produce the same net result as inversion of the nonplanar carbonium ion **10** to **12**. Unfortunately, we cannot distinguish between these two possibilities on the basis of presently available data.

Acknowledgment. This investigation was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society.

(8) The formation of **10** would be reasonable if the energy required to spread the 96° C₁-C₇-C₄ bond angle and to bring the hydrogen into coplanarity was greater than the energy gained in the rehybridization from sp³ to sp².

(9) Alfred P. Sloan Research Fellow, 1967-1969.

(10) National Science Foundation Trainee, 1965-1968.

(11) National Science Foundation Cooperative Predoctoral Fellow, 1962-1963, 1964-1966.

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(7) This experiment also demonstrates the stability of the reaction products to the reaction conditions.