Figure 1. High-field portion of the 60-Mc. n.m.r. spectrum of the equilibrium mixture of 5a and 6a in methanol. The band at 2.68 p.p.m. (downfield relative to the tetramethylsilane resonance) is due to an impurity in the methanol; the band at 2.24 p.p.m. is the high-field C-13 satellite of the methanol resonance.

benzenesulfonates are related linearly to the relative rates of reaction with thiosulfate of the corresponding unlabeled aziridinium iodides.[4] As the irreversible reactions with thiosulfate follow second-order kinetics, the observed linear relationship indicates that the slow step in the iodide ion catalyzed equilibrations is an S_N2 reaction. Also, halide ion catalyzed equilibration of aziridinium ions occurs considerably more rapidly in methanol than in more polar water,[5,6] which further indicates that the slow step involves attack of halide ion on the positively charged aziridinium ring.

5

6
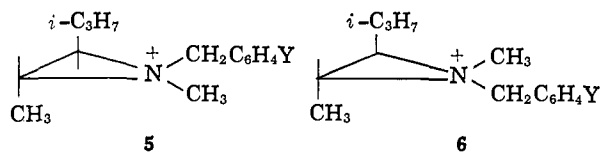
a, Y=H; b, Y=p-CH$_3$; c, Y=m-Cl; d, Y=p-NO$_2$

We have also examined the equilibria of several pairs of diastereomeric aziridinium ions (5a–d and 6a–d) prepared from 1 and benzyl bromides.[7] Because of the different steric requirements of the methyl and benzyl groups, the equilibrium constants of these diastereomers differ from unity. Examination of the n.m.r. spectrum of the equilibrium mixture of 5a and 6a (as the bromide salt) in methanol, the upfield portion of which is shown in Figure 1, confirms what had been anticipated, namely, that the more stable diastereomer is the one in which the C-2 methyl group is cis to the N-benzyl group, i.e., 6a, and reveals that the equilibrium constant 6/5 is 1.70.[8] Most significantly,

(4) cis-3-Methyl-, cis-3-ethyl-, trans-3-isopropyl-, and trans-3-t-butyl-1,1,2-trimethylaziridinium iodide. The unlabeled salts were characterized by means of n.m.r. spectroscopy, near quantitative (>96%) reaction with thiosulfate, and elemental analysis. The theoretical and experimental C and H analyses agreed in all cases to within 0.3%.
(5) See J. S. Gleave, E. D. Hughes, and C. K. Ingold, J. Chem. Soc., 236 (1935).
(6) For example, 5a and 6a are equilibrated by bromide ion about 200 times more rapidly in methanol than in water.
(7) A nonequilibrium mixture of 5a and 6a obtained from 1 and benzyl bromide in benzene gave a satisfactory elemental analysis. Anal. Calcd. for C$_{14}$H$_{22}$NBr: C, 59.16; H, 7.80. Found: C, 59.32; H, 7.82. The other diastereomeric aziridinium salts were not isolated but were characterized by means of n.m.r. spectroscopy. The upfield portions of their n.m.r. spectra are strikingly similar to that of the mixture of 5a and 6a.
(8) The proximity of the aromatic ring and the C-2 methyl group of 6a can be expected to result in an upfield shift of the C-2 methyl resonance relative to the resonance of the C-2 methyl group of 5a.[9] Consequently, the doublet centered at 1.94 p.p.m. is assigned to the C-2 methyl group of 6a, and the less intense doublet centered at 1.67 p.p.m. is assigned to the C-2 methyl group of 5a. Similarly, the less intense pair of doublets centered at 1.48 and 1.38 p.p.m. is assigned to the methyls of the isopropyl group of 5a, and the pair of doublets centered

the equilibrium constants (6/5) of the four pairs of diastereomeric aziridinium ions were the same to within experimental error (1.69 ± 0.03). This finding was particularly gratifying in that it appears to confirm the suppositions that the dipole moments of the diastereomeric aziridinium ions are nearly identical and that the difference in free energy can be ascribed solely to the difference in nonbonded interactions present in the diastereomers.

Because of the well-defined geometry of diastereomeric aziridinium ions such as 5 and 6 together with the absence of any significant contribution of electronic factors to the difference in their free energies, study of the thermodynamics of equilibria of diastereomeric trans-1,1,2,3-tetrasubstituted aziridinium ions appears to be ideally suited for assessing quantitatively the role of nonbonded interactions.

at 1.33 and 1.02 p.p.m. is assigned to the methyls of the isopropyl group of 6a.
(9) J. S. Waugh and R. W. Fessenden, J. Am. Chem. Soc., 79, 846 (1957).

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On the Stereochemistry of Quaternization of Amines[1]

Sir:

Knowledge of the confirmational equilibrium of trans-1,2-dimethyl-3-isopropylaziridine (1)[2] coupled with the fact that 1 can be quaternized to give reasonably tractable aziridinium salts[3] has made it possible to obtain an accurate answer to the question: knowing the stereochemistry of an ammonium salt formed by quaternization of a given tertiary amine, what inference can be made concerning the conformational equilibrium of the free base?[4] We report here the stereochemistry of quaternization of 1 under conditions that give rate-controlled products.

In order to examine the stereochemistry of quaternization of aziridines under conditions wherein equilibration of the products did not occur at a rate competitive with the quaternization reaction (see ref. 1b), we chose to study directly quaternization of aziridines with alkyl benzenesulfonates. Our choice was based on the fact that the benzenesulfonate anion is a much poorer nucleophile than iodide or bromide,[5] and thus would be far less likely to catalyze equilibration of the resulting aziridinium ions through the intermediacy of a 2-aminoalkylbenzenesulfonate.

We studied first the stereochemistry of quaternization of 1 with deuteriomethyl benzenesulfonate[6] in meth-

(1) (a) Structure–Activity Relationships of Ethylenimines. VII. Supported by Grant No. CA-05528 from the National Cancer Institute of the Public Health Service. (b) Part VI: A. T. Bottini, B. F. Dowden, and L. Sousa, J. Am. Chem. Soc., 87, 3249 (1965).
(2) A. T. Bottini, R. L. VanEtten, and A. J. Davidson, ibid., 87, 755 (1965).
(3) (a) A. T. Bottini and R. L. VanEtten, J. Org. Chem., 30, 575 (1965); (b) G. K. Helmkamp,R. D. Clark, and J. R. Koskinen, ibid., 30, 666 (1965).
(4) Leading references to the problem are: G. Closs, J. Am. Chem. Soc., 81, 5456 (1959); J. McKenna, J. White, and A. Tully, Tetrahedron Letters, No. 24, 1097 (1962). See also W. L. Meyers and N. Sapianchiay, J. Am. Chem. Soc., 86, 3343 (1964); J. McKenna, et al., J. Chem. Soc., 1711, 1726, 1729, 1733 (1965).
(5) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 7.

anol-d_3 and in benzene. In methanol at 25°, **1** exists as a 1:3.85 mixture of the conformers **1a** and **1b**; in benzene at 25°, the conformational equilibrium constant **1b**/**1a** is taken to be the same as in the neat liquid, 4.08.[2] Note that during quaternization of **1b** to give **2b**, the deuteriomethyl group approaches the side *cis* to the isopropyl group, whereas during quaternization of the less stable conformer **1a**, the deuteriomethyl group approaches the side *cis* to the C-2 methyl group. Consequently, more nonbonded interactions are introduced during quaternization of **1b** than during quaternization of **1a**. We therefore felt that the rate constant k_{2a} for quaternization of the less stable conformer (but not necessarily its rate) should be more than that of the more stable conformer (see ref. 3a).
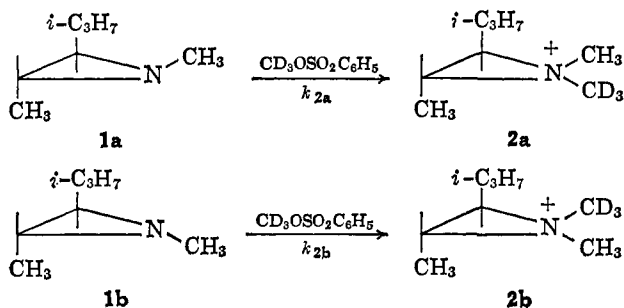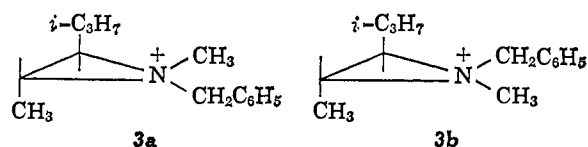

Deuteriomethyl benzenesulfonate (0.25 mmole) was dissolved in 500 μl. of benzene or methanol-d_3. To this was added 0.25 mmole of **1**. The reaction was allowed to go to completion, and the reaction mixture was diluted with 500 μl. of the appropriate solvent to give a solution that was 50% benzene–methanol-d_3 by volume. This precaution was taken to ensure that no difficulties in interpretation of the observed n.m.r. spectra would occur because of solvent-dependent chemical shifts. Product ratios were determined by comparison of the intensities of the N-methyl bands in the n.m.r. spectra taken at 60 Mc., and each product ratio is the average of at least eight measurements.

In benzene, the diastereomeric aziridinium ions **2** were formed in the ratio 2.54:1; in methanol-d_3, the ratio was 2.93:1. (The N-methyl band at higher field was the more intense.) The manner in which the product composition depended on solvent indicated to us that the principal product from both reactions was **2b**. Our reasoning is this. As benzene is the poorer solvating medium for ions, carbon–nitrogen bond making will have progressed to a greater extent at the transition state in benzene. Therefore, the steric requirements of the incoming deuteriomethyl group will be greater in benzene than in methanol-d_3 *relative* to those of the fully bonded N-methyl group. Because more nonbonded interactions are introduced during quaternization of **1b**, an increase in the steric requirements of the incoming deuteriomethyl group will result in a relatively greater increase in the free energy of the transition state leading to **2b**. This will cause k_{2a}/k_{2b} to be greater and the **2b**:**2a** product ratio to be less in benzene. Using the conformational equilibrium constants of **1** and the observed product compositions, we calculate that k_{2a}/k_{2b} is 1.32 in methanol-d_3 and 1.61 in benzene.

We tested our reasoning concerning the effect of

(6) Prepared from methanol-d_3 (Merck of Canada) and benzene-sulfonyl chloride.

solvent on the observed **2a**:**2b** ratios by examining the stereochemistry of quaternization of **1** with benzyl benzenesulfonate.[7] An important reason for this choice was that the bands in the n.m.r. spectra of the resulting diastereomeric *trans*-1-benzyl-1,2-dimethyl-3-isopropylaziridinium ions (**3a** and **3b**) can be assigned unequivocally.[1b] In both methanol-d_3 and benzene, the major product was that formed from the more stable conformer of **1**, but the **3b**:**3a** ratio of 1.26 obtained in benzene was significantly less than the 1.43 obtained in methanol-d_3.[8] Thus, as the solvating power of the medium was lessened, the less stable conformer of **1** accounts for a significantly larger amount of quaternization product.

The results reported here are particularly pertinent to the elucidation of the stereochemistry of amines. Quaternization of **1** with deuteriomethyl benzenesulfonate in methanol gives a mixture of diastereomeric aziridinium ions (**2a** and **2b**) in a ratio that is a fairly good estimate of the conformational equilibrium of **1**. Consider now quaternization with deuteriomethyl benzenesulfonate in methanol of a non-aziridine N-methyldialkylamine capable of existing as energetically different conformers. Because an ordinary N-methyl-dialkylamine is less electronegative than an N-methyl-aziridine, it can be argued that, at the transition state for quaternization of the ordinary amine, carbon-nitrogen bond formation will not have progressed as far as at the transition state for quaternization of the aziridine. If this argument is accepted, it can be further stated that the steric requirements of the incoming deuteriomethyl group will be less *relative* to those of the fully bonded N-methyl group at the transition state for quaternization of the ordinary amine than at the transition state for quaternization of the aziridine. As a consequence, quaternization of an ordinary N-methyldialkylamine with deuteriomethyl benzenesulfonate in methanol can be expected to give a mixture of quaternary products that is an even more accurate measure of the conformational equilibrium of the amine than was obtained by quaternization of **1** under identical conditions.

(7) J. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, 75, 3443 (1953).
(8) No significant equilibration of **3a** and **3b** (as the benzenesulfo-nates) occurs in benzene in 24 hr.
(9) Public Health Service Predoctoral Fellow, 1963–1964.

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The Structure of Anemonin

Sir:

Ranunculin (I), the crystalline glucoside of proto-anemonin (II), is found in buttercup and other *ranun-culaeceae*. Protoanemonin (II), the anhydroaglucone, may be obtained either by alkaline hydrolysis or by crushing the plant tissue, in which case it is released by an enzymatic process.[1] Protoanemonin (II) is an

(1) R. Hill and R. Van Heyningen, *Biochem. J.*, 49, 332 (1951).