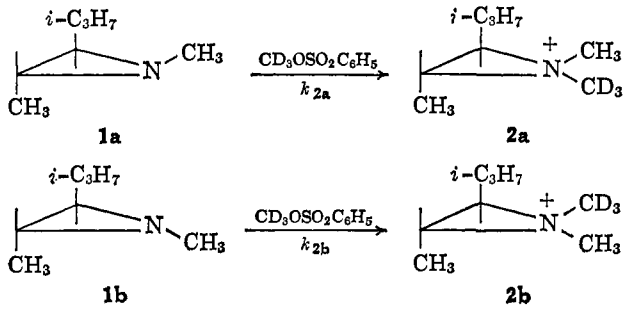
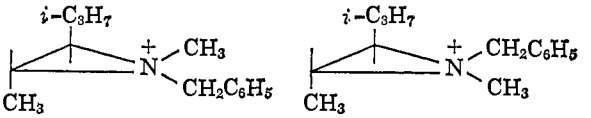
anol-d_3 and in benzene. In methanol at 25°, **1** exists as a 1:3.85 mixture of the conformers **1a** and **1b**; in benzene at 25°, the conformational equilibrium constant **1b**/**1a** is taken to be the same as in the neat liquid, 4.08.[2] Note that during quaternization of **1b** to give **2b**, 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 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-methyldialkylamine is less electronegative than an N-methylaziridine, 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.

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

(7) J. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, 75, 3443 (1953).

(8) No significant equilibration of **3a** and **3b** (as the benzenesulfonates) occurs in benzene in 24 hr.

(9) Public Health Service Predoctoral Fellow, 1963–1964.

Albert T. Bottini, Barry F. Dowden, Robert L. VanEtten[9]
Chemistry Department, University of California
Davis, California 95616
Received April 26, 1965

The Structure of Anemonin

Sir:

Ranunculin (I), the crystalline glucoside of protoanemonin (II), is found in buttercup and other *ranunculaeceae*. 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).

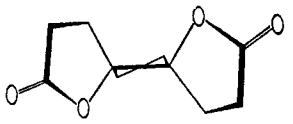
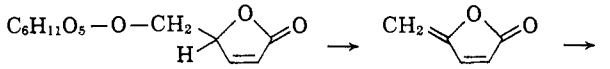
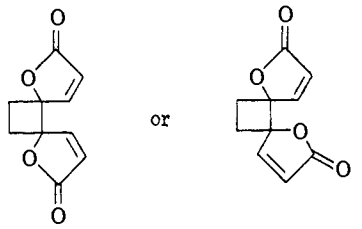


Figure 1.

extremely disagreeable liquid blistering agent which dimerizes spontaneously in aqueous solution to yield crystalline anemonin (III or IV). The latter possesses no vesicant properties. Anemonin was first isolated in 1792 by Heyer.[2] Asahina[3,4] established that protoanemonin (II) is the lactone of γ-hydroxyvinylacrylic acid. This was based upon synthesis of II and demonstration that the synthetic material underwent dimerization to yield anemonin. Of the numerous conceivable cyclodimerization products, Asahina proposed that anemonin possessed the 1,2-dihydroxy-1,2-cyclobutanediacrylic acid dilactone structure.



I II



III IV

Anemonin has never been related by chemical methods to a cyclobutane derivative of known structure. The stereochemistry of the dilactone rings has been assumed to be *cis* (III); this conclusion has also been deduced from chemical evidence.[5] While the "head-to-head" dimeric structure appeared fairly certain, the evidence for the stereochemical relationship of the dilactone rings was rather unconvincing.[5]

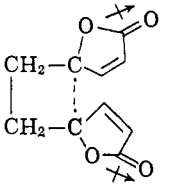
The fact that only one cyclodimer is formed from protoanemonin (II) is remarkable in that at least 12 cyclobutane structures are possible for various combinations of the monomer. This large degree of stereoselectivity provoked our interest in the structure of anemonin, particularly in that the structure has especial pertinence in the more general problem of thermal cyclodimerization reactions of olefins.[6] Therefore a crystal of anemonin[7] was investigated by X-ray diffraction in order to determine the structure of the molecule, in particular the stereoconfiguration of the lactone rings.

Anemonin crystallizes in the orthorhombic system, space group Pbca, with cell dimensions $a = 11.65 \pm 0.02$ Å., $b = 13.86 \pm 0.03$ Å., and $c = 11.07 \pm 0.02$ Å., and 8 molecules in the unit cell. The computed and observed densities are 1.418 and 1.428 g./cm.^{3}, respectively. Three-dimensional intensity data were collected using the equi-inclination Weissenberg technique with Ni-filtered Cu radiation. The crystal structure was solved by obtaining phases directly from the structure factor magnitudes by the use of the symbolic addition procedure.[8] All the hydrogen atoms were located from a difference map. A least-squares refinement of the coordinates and anisotropic thermal factors using 1436 data resulted in an R factor of 13.0%.

The crystal structure determination shows that the molecule is in the *trans* configuration (IV, Figure 1). It also shows that the cyclobutane ring is not planar but assumes a bent configuration

with a dihedral angle of 152°. The C–C bond lengths in the cyclobutane ring range from 1.530 to 1.545 Å., a normal range for single bonds.

Selective formation of the 1,2-disubstituted adduct probably results from the stability of diradical V. This head-to-head attachment allows for the maximum delocalization of the two unpaired electrons with the adjacent unsaturated groups. The *trans* relationship of the two lactone rings may be rationalized on the basis of lowered destabilizing dipolar interactions in



V

the transition state for its formation.

In the transition state for ring closure to yield the *cis* dilactone, the two polar lactone groups are adjacent to each other and also are pointed in the same direction. One would expect this arrangement to be less stable relative to the *trans* conformation because of the electronic instability associated with the promixity of the polar groups. In the *trans* case the lactone dipoles are opposed and the destabilizing dipolar interaction is minimized.

(2) M. Heyer, *Chemisch Journ. V. Crell*, **2**, 102 (1792); A. D. Wurtz, "Dictionnaire de Chemie," Vol. I, Librarie Hackette et C, Paris, 1870, p. 299.

(3) Y. Asahina and A. Fujita, *J. Pharm. Soc. Japan*, **455**, 1 (1920); *Chem. Abstr.*, **14**, 1384 (1920).

(4) For a discussion of the chemical transformations of anemonin see R. A. Raphael in Chemistry of Carbon Compounds, Vol. IIa, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1953, pp. 67–70.

(5) J. E. Harris, *Dissertation Abstr.*, **20**, 887 (1959).

(6) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 2 (1962).

(7) E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946).

(8) I. L. Karle and J. Karle, *Acta Cryst.*, **16**, 969 (1963).

Robert M. Moriarty, C. R. Romain
Catholic University of America
Washington, D. C.
I. L. Karle, J. Karle
U. S. Naval Research Laboratory
Washington, D. C.
Received May 17, 1965

The Estimation of the Angle of Twist for a Cyclobutane Derivative by Nuclear Magnetic Resonance

Sir:

In a preceding communication[1] the 1,1,2,2,-substituted cyclobutane ring of anemonin is reported to be puckered. The angle of twist, α, about the twofold axis C_2 (Figure 1) is calculated from the X-ray data to be $9.9 \pm 0.3°$. In this communication we wish to report that the angle of twist, α, can also be estimated

(1) R. M. Moriarty, C. R. Romain, I. L. Karle, and J. Karle, *J. Am. Chem. Soc.*, 87, 3251 (1965).