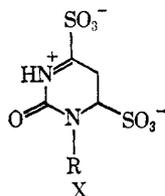


tonated species VII. It is possible that the negative charge of the unprotonated cytosine-bisulfite adduct greatly hinders attack by anionic species, slowing its deamination.

(3) The deamination step is catalyzed by basic substances, such as sulfite, bisulfite, and acetate anions. This is most clearly demonstrated in studies with the model compound, 1-methyl-5,6-dihydrocytosine. In moderately concentrated bisulfite solutions, at pH >4, the principal catalytic species is sulfite ion. Our data do not allow us to determine whether the catalytic effect is due to general base catalysis, or nucleophilic catalysis.<sup>17</sup> The latter possibility would involve the formation of X as a transient intermediate in the deamination of cytosine derivatives by bisulfite.



We have no direct evidence for the formation of such an intermediate. However, the possibility of attack at C-4 of a cytosine-bisulfite adduct by nucleophiles other than water has been demonstrated.<sup>18</sup> On the other hand, general base catalysis has been reported for other amidine hydrolyses.<sup>19</sup>

(17) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 137 (1967).

(18) (a) R. Shapiro and J. M. Weisgras, *Biochem. Biophys. Res. Commun.*, **40**, 839 (1970); (b) E. I. Budowsky, E. D. Sverdlov, and G. S. Monastyrskaya, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **25**, 201 (1972).

(19) (a) D. R. Robinson, *J. Amer. Chem. Soc.*, **92**, 3138 (1970); (b) D. R. Robinson and W. P. Jencks, *ibid.*, **89**, 7088 (1967).

(4) Acids influence the deamination reaction by converting the cytosine adduct, IV, to its reactive protonated form, II (specific acid catalysis). At constant pH and ionic strength, there is no rate effect produced by added acidic substances such as ammonium ion.

The optimal pH for the synthetic or mutagenic use of the deamination reaction is 5. The concentration of bisulfite used should be as high as possible. At pH values below 5, the deamination declines sharply (Figure 8) due to the protonation of the most effective catalytic species, sulfite. The rate also declines sharply at pH values above 5. There is an additional increase in the sulfite concentration above pH 5, but this effect is offset by a decline in the extent of adduct formation, and by the conversion of the protonated adduct II, to its unreactive nonprotonated form IV.

The rate of deamination of deoxycytidine measured at physiological pH is about 1% of that observed at the optimum pH. The possibility that ingested bisulfite and inhaled sulfur dioxide may be environmental mutagens remains open. To evaluate this possibility more fully, the following unknowns must be explored: the extent to which bisulfite reaches genetic DNA, the amount of this DNA which exists in single-stranded form (double-stranded DNA is unreactive to bisulfite<sup>20</sup>), and the ability of other cellular nucleophiles to catalyze the vital second step (II → V) of the deamination sequence.

**Acknowledgment.** This research was supported by Grant GM-18583 from the National Institutes of Health, U. S. Public Health Service.

(20) R. Shapiro, B. Braverman, J. B. Louis, and R. E. Servis, *J. Biol. Chem.*, **248**, 4060 (1973).

## Communications to the Editor

### Electrochemical Reduction of 1,4-Dibromobicyclo[2.2.2]octane. Formation of the [2.2.2]Propellane<sup>1</sup>

Sir:

The small ring "propellanes" have proven to be unusually interesting compounds.<sup>2</sup> The [2.2.2]propellane (I) is of particular interest in view of the results of theoretical treatments of its thermal rearrangement to 1,4-dimethylenecyclohexane,<sup>3,4</sup> and in connection with the origin of the low reactivity of cyclobutanes toward electrophiles.<sup>5</sup>

Eaton and Temme<sup>6</sup> have recently reported the syn-

(1) This investigation was supported by a grant from the National Science Foundation.

(2) For a review, see D. Ginsburg, *Accounts Chem. Res.*, **2**, 121 (1969).

(3) W. D. Stohrer and R. Hoffmann, *J. Amer. Chem. Soc.*, **94**, 779 (1972).

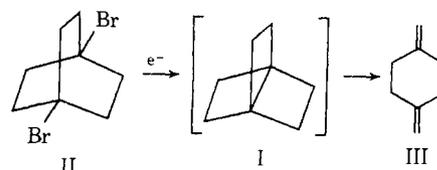
(4) M. D. Newton and J. M. Schulman, *J. Amer. Chem. Soc.*, **94**, 4391 (1972).

(5) K. B. Wiberg, K. C. Bishop III, and R. B. Davidson, *Tetrahedron Lett.*, 3169 (1973).

(6) P. E. Eaton and G. H. Temme III, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Tex., Apr 1973, No. ORGN-58.

thesis of a derivative of I, but their route does not appear to be a viable source of the hydrocarbon itself. An attempt to obtain I by a dissolving metal reduction of 1,4-dibromobicyclo[2.2.2]octane led to 1,4-dimethylenecyclohexane along with a small amount of bicyclo[2.2.2]octane.<sup>7</sup> The formation of the dimethylenecyclohexane was thought to result from a Grob-type fragmentation.

The observation of Eaton and Temme that their derivative of I underwent rearrangement to a 1,4-dimethylenecyclohexane revived the suggestion that the above reduction may have actually proceeded *via* the propellane as an intermediate and that the latter underwent ring opening under the reaction conditions to give the observed product.



(7) K. B. Wiberg and G. J. Burgmaier, *J. Amer. Chem. Soc.*, **94**, 7396 (1972).

Our observation that 1,4-dibromides may be efficiently converted to cyclobutanes by electrochemical reduction at a relatively negative potential<sup>8,9</sup> provides an attractive alternative to dissolving metal reduction. A potentiostatic electrochemical reduction may be performed at low temperature, and thus increase the lifetime of the unstable propellane.

The reduction of 1,4-dibromobicyclo[2.2.2]octane (II) in *N,N*-dimethylformamide was carried out under a constant stream of nitrogen at a temperature of  $-15$  to  $-25^\circ$ , using tetraethylammonium bromide as the supporting electrolyte. A three-electrode configuration was used, with a platinum mesh working electrode, a platinum counter electrode (separated from the cathodic cell by a sintered glass partition), and a mercury pool reference electrode. The current density was 0.12 A. Electrolysis was continued at  $-2.35$  V for 5 hr. Since the propellane, if formed, would be present in dilute solution from which it would be isolated with difficulty at this low temperature, chlorine was added to the reaction solution. By analogy to the known electrophilic additions to the central bond of the [3.2.1] propellane,<sup>7</sup> the chlorine should add across the central bond of this propellane to give 1,4-dichlorobicyclo[2.2.2]octane. This compound could only be formed from propellane I.

The electrolyte solution containing the dissolved chlorine was stored at  $-15^\circ$  for 14 hr, allowed to warm to room temperature, and then diluted with cold, saturated aqueous sodium chloride. The suspension was extracted with ether-pentane, the organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated to give a semicrystalline residue. Vapor-phase chromatography of the residue at  $150^\circ$  on a 19 in. by  $\frac{1}{4}$  in. column of 30% SE-30 on Anakrom showed there were two main products. The major product was easily identified as the chlorine addition product of 1,4-dimethylenecyclohexane (III). The other product (isolated by column chromatography or preparative gas chromatography) had a uniquely simple nmr spectrum consisting of a singlet at  $\delta$  2.2. It was identified as the desired 1,4-dichlorobicyclo[2.2.2]octane. The structure was confirmed by independent synthesis, using a modified Kochi reaction<sup>10</sup> on bicyclo[2.2.2]octane-1,4-dicarboxylic acid to give a compound<sup>11</sup> identical with that isolated from the electrolysis.

Thus, the presence of the 1,4-dichlorobicyclo[2.2.2]octane provides clear evidence for the formation of the [2.2.2]propellane in the electrochemical reduction of 1,4-dibromobicyclo[2.2.2]octane.<sup>12</sup> Although the yield was low (*ca.* 12%), it has not been determined whether this results from the Grob-type fragmentation of a reaction intermediate or rather from the thermal ring opening of the propellane while it is still adjacent to the electrode surface. However, an attempt to improve the yield by

running at a lower temperature led instead to a lowered yield of the desired product.

The successful formation of the [2.2.2]propellane illustrates the potential power of low-temperature potentiostatic electrolysis. It may provide a route to the still more interesting [2.2.1]propellane (IV). This would be expected to have a strain energy only slightly greater than that of I and should be formed more readily than I by electrolysis since the carbons bearing the halogens will be closer. If the theoretical treatments<sup>3,4</sup> of the thermal ring opening of I are correct, IV should have a markedly higher thermal stability since the orbitals forming the central bond cannot be moved far enough apart to make the antibonding arrangement of energy comparable to the bonding arrangement. Further efforts are being made to improve the electrochemical synthesis and to use it for the synthesis of IV and related compounds.

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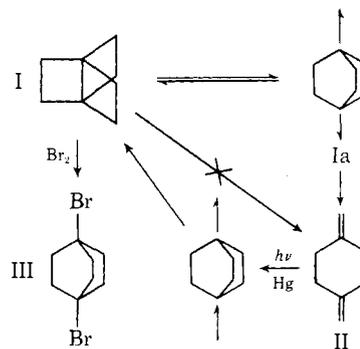
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Received September 22, 1973

### Preparation and Trapping of [2.2.2]Propellane

Sir:

There has been considerable recent interest in the synthesis and properties of [2.2.2.0<sup>1,4</sup>]tricyclooctane, commonly known as [2.2.2]propellane<sup>1</sup> (I). Hoffmann and Stohrer<sup>2</sup> suggested that the ground-state potential surface of I should have two minima, I and Ia. Although the orbital symmetry rules forbid a direct decomposition of I to 1,4-dimethylenecyclohexane (II),



they offer no impediment to the decomposition Ia to II.<sup>2</sup> Since the barrier between I and Ia is predicted to be only 29 kcal/mol,<sup>3</sup> a facile route from I to II might exist. The problem of synthesizing I, therefore, is complicated by the necessity of entering the energy surface of the product on the correct side of the barrier between I and Ia and preventing the product from decomposing long enough to prove its existence. We have previously reported that INDO calculations predict that the triplet-state energy surface for [2.2.2]propellane had only one minimum which corresponds to a ground-state geometry that is close to, but on the

(1) D. Ginsburg, *Accounts Chem. Res.*, **2**, 1216 (1969); **5**, 249 (1972).

(2) R. Hoffmann and W. D. Stohrer, XXIII International Congress of Pure and Applied Chemistry, Special Lectures, Vol. 1, Butterworths, London, 1971, 157; W. D. Stohrer and R. Hoffmann, *J. Amer. Chem. Soc.*, **94**, 779 (1972).

(3) M. D. Newton and J. M. Schulman, *J. Amer. Chem. Soc.*, **94**, 4391 (1972).

(8) K. B. Wiberg and G. A. Epling, to be submitted for publication.

(9) The electrochemical conversion of 1,4-dibromobutane to cyclobutane also has been noted by M. R. Rifi, *J. Amer. Chem. Soc.*, **89**, 4442 (1967).

(10) H. K. Hall, C. D. Smith, E. P. Blanchard, S. C. Cherkofsky, and J. B. Sieja, *J. Amer. Chem. Soc.*, **93**, 121 (1971).

(11) Elemental analysis gave Calcd for C<sub>8</sub>H<sub>12</sub>Cl<sub>2</sub>: C, 53.7; H, 6.8; Cl, 39.6. Found: C, 53.6; H, 6.8; Cl, 39.7.

(12) The supporting electrolyte, tetraethylammonium bromide, was carefully purified and was chlorine free. 1,4-Dibromobicyclo[2.2.2]octane does not react with chlorine in dimethylformamide to give 1,4-dichlorobicyclo[2.2.2]octane. Similarly, 1,4-dimethylenecyclohexane gives only the tetrachloride and no 1,4-dichlorobicyclo[2.2.2]octane on treatment with chlorine in dimethylformamide.