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Thermal Decomposition of *cis*-Tetrahydropyridazine-*3,4-d*$_2$. Relative Rates of Rotation, Cleavage, and Closure for Tetramethylene

Sir:

The only 1,4 biradical described by theorists[1] to date is tetramethylene. Despite the fact that substantial experimental work now exists on 1,4-biradical behavior,[3-8] the relative rates of rotation, cleavage, and closure of the parent system are unknown. Substituted tetrahydropyridazines have been shown to be excellent sources for the thermal generation of stereospecifically labeled 1,4 biradicals.[5] Application of this method to the tetramethylene problem provides an opportunity for the *direct* comparison of experiment and theory.

We report the stereospecific synthesis and thermal decomposition in the gas phase (439 °C) of *cis*-tetrahydropyridazine-*3,4-d*$_2$ (**2**). In addition, we describe the stereospecific syntheses of *cis*- and *trans*-cyclobutane-*1,2-d*$_2$ (**3** and **4**). Analyses of the cis/trans stereochemistry in the products from the decomposition of **2** allow an experimental determination of the relative rates of rotation, cleavage, and closure for tetramethylene. Moreover, a stereospecific cleavage reaction to ethylene and nitrogen in competition with a 1,4-biradical pathway from the thermal decomposition of tetrahydropyridazine becomes evident.

Synthesis of *cis*-tetrahydropyridazine-*3,4-d*$_2$ (**2**) was accomplished as shown in Scheme I.[9] For pyrolyses, a solution of **2** in benzene-d_6 was injected into an evacuated Pyrex chamber (439 °C) and the products were collected in a trap at −196 °C.

The ratio of the two ethylenes to cyclobutane was 83:17 from analytical VPC analysis.[10] These products were separated by preparative VPC for infrared analyses of their respective cis/trans-d_2 ratios.[11] The observed *cis/trans*-ethylene-*1,2-d*$_2$ ratio from the pyrolysis of **2**, obtained by comparison with authentic mixtures,[12] is 80:20.[13]

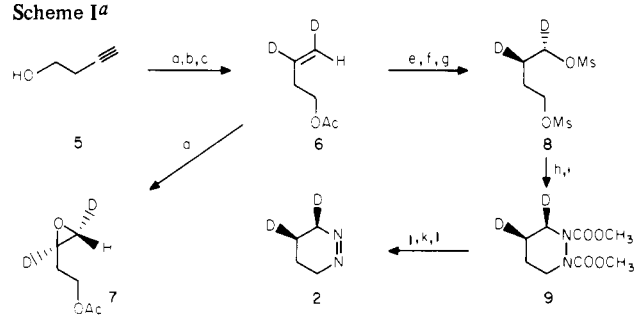
The syntheses of *cis*- and *trans*-cyclobutane-*1,2-d*$_2$ are shown in Scheme II.[14,15] The ratio of *cis/trans*-cyclobutane-*1,2-d*$_2$ products from the pyrolysis of **2** was determined by measuring the relative ratio of the 1307 (cis-1,2-d_2) and 1294 cm^{-1} (trans-1,2-d_2) bands in the infrared and comparing these with those of authentic mixtures. The *cis*-tetrahydropyridazine-*3,4-d*$_2$ (**2**) contains 93% d_2 and 7% d_1. Since cyclobutane-d_1 has a band at 1307, calibration mixtures contained 93% cis,trans-1,2-d_2 and 7% cyclobutane-d_1. The observed *cis/trans*-cyclobutane-*1,2-d*$_2$ ratio from the pyrolysis of **2** obtained by comparison with authentic mixtures is 56:44.

A summary of the stereochemical results from the thermal decomposition of *cis*-tetrahydropyridazine-*3,4-d*$_2$ (**2**) is shown in Scheme III.[18] By analogy to previously described decomposition pathways for *cis*- and *trans*-3,4-dimethyltetrahydropyridazines,[5d,e] consider Scheme IV.[19,20]

The ratio of k(cleavage)/k(closure) can be obtained directly. From **2**, the ratio of *crossover* products, *trans*-ethylene-*1,2-d*$_2$:*trans*-cyclobutane-*1,2-d*$_2$ is equal to the ratio of the rates for cleavage and closure in the unimolecular decomposition of biradical T. From Scheme III, k_2(closure)/k_3(cleavage) = 7.5:16.6 = 0.45. This k(closure)/k(cleavage) ratio (R_1) and the ratio of *cis-/trans*-cyclobutane-*1,2-d*$_2$ (R_2) allow a determination of the k(closure)/k(rotation) ratio, k_2/k_1, from a simple steady-state analysis of the proposed diradical scheme, i.e., $k_2/k_1 = (R_2R_1 - R_1)/(R_1 + 1)$. From the data, R_1 = 0.45 and R_2 = 1.27, we calculate k_2/k_1 = 0.083. The experimental ratio of *cis*-ethylene-*1,2-d*$_2$/*cis*-cyclobutane-*1,2-d*$_2$ is 66.4:9.52. From k_3/k_2, the amount of *cis*-ethylene-*1,2-d*$_2$ expected from C should be 2.22 times the *cis*-cyclobutane-*1,2-d*$_2$ observed (9.52 × 2.22 = 21.1%). Therefore the *extra stereospecific component* of *cis*-ethylene-*1,2-d*$_2$ is 66.4 − 21.1 = 45.3%.

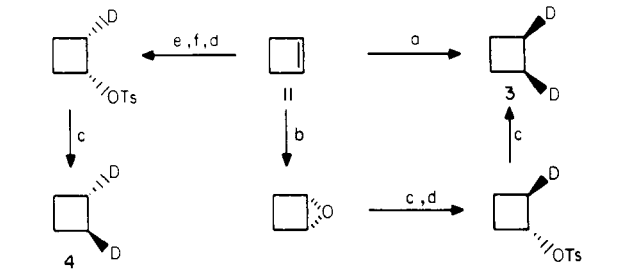
In summary, we find that, in the thermal decomposition of unsubstituted six-membered cyclic 1,2-diazenes at 439 °C in the gas phase, 55% proceeds via tetramethylene, and 45%

Scheme I[a]



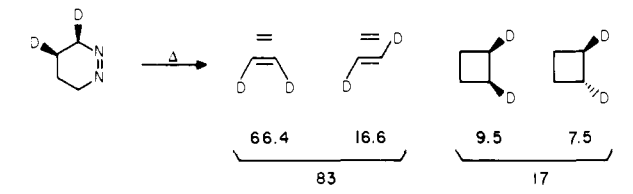
[a] (a) CH_3COCl, (b) $(C_6H_{10}D)_2BD$, (c) CH_3COOD, (d) mCPBA, (e) BH_3, (f) H_2O_2, (g) MsCl, (h) $(HNCOOCH_3)_2$/NaH, (i) NaH, (j) KOH/H_2O/N_2, (k) HCl/N_2, (l) O_2/C_6D_6.

Scheme II[a]

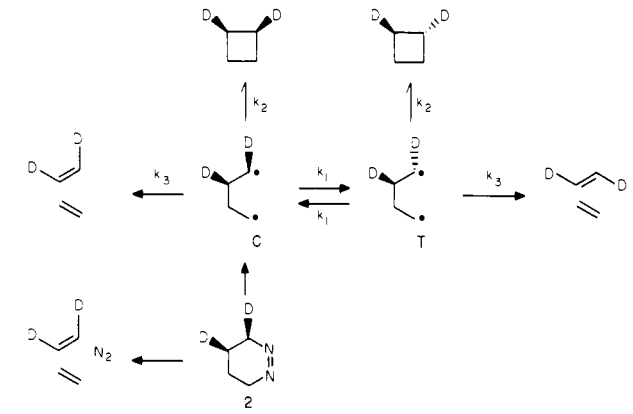


[a] (a) N_2D_2, (b) mCPBA, (c) $LiB(C_2H_5)_3D$, (d) TsCl, (e) BD_3, (f) H_2O_2/OH^-.

Scheme III



Scheme IV



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proceeds via a stereospecific olefin-forming pathway.[21] Tetramethylene-d_2 generated from a 1,2-diazene decomposition[23] has the properties k(cleavage)/k(closure) = 2.2 and k(rotation)/k(closure) = 12.[25]

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Supplementary Material Available: Reactions of compounds **2–11** (2 pages). Ordering information is given on any current masthead page.

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(9) Epoxide **7** allowed NMR analysis of the deuterium content of each olefinic position and confirmed the cis-3,4-d_2 assignment in **6**.

(10) 10 ft × 0.125 in., 30% SE-30 on 100/120 Chromosorb P; flame ionization detector; electronic integration. Assignment of the products were made by coinjection techniques using authentic samples. The ethylene/cyclobutane ratio was corrected for detector response.

(11) Perkin-Elmer Model 180 infrared spectrophotometer. We thank Dr. George R. Rossman, Division of Geological and Planetary Sciences, California Institute of Technology, for allowing us to use this instrument.

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(13) Ethylene products were analyzed[11] using the 842-cm^{-1} (and 724-cm^{-1}) bands for *cis*- (and *trans*-) ethylene-*1,2-d*$_2$. Ethylene-d_1 and ethylene-d_0 (half the ethylene from **2** is d_0) have bands at 809 and 945 cm^{-1}, respectively. These peaks did not interfere with the analyses.

(14) *cis*-Cyclobutane-*1,2-d*$_2$ (**3**): IR (gas) 2990 (C–H), 2200 (C–D), 1450 (CH_2), 1307 (CHD), 569, 562, (1294 < 2% *trans*-**4**-d_2); mass spectrum (9.0 eV), d_2/d_1 = 95.5:4.5 ± 1.[16] *trans*-Cyclobutane-*1,2-d*$_2$ (**4**): IR (gas) 2950 (C–H), 2190 (C–D), 1450 (CH_2), 1294 (CHD), 579, 543 (562 < 2% *cis*-**3**-d_2); mass spectrum, d_2/d_1 = 95.5:4.5 ± 1.[16]

(15) For an alternative synthesis and thermolysis of *cis*- and *trans*-cyclobutane-*1,2-d*$_2$, see recent work of Chickos, J. S. *J. Org. Chem.* **1979,** *49*, 780.

(16) The percent deuterium incorporation in the cyclobutane-*1,2-d*$_2$ was obtained by comparison with cyclobutane-d_0 sample using ion cyclotron resonance spectroscopy.[17]

(17) We thank Peter Armentrout and Professor J. L. Beauchamp for their generous assistance. See Beauchamp, J. L. *Ann. Rev. Phys. Chem.* **1971,** *22*, 527.

(18) Controls: (a) The hydrazone and the hydrazine **10** corresponding to *cis*-**2**-*3,4-d*$_2$ afforded hydrocarbon products in <1% yield under identical pyrolysis conditions as used for **2**. (b) *trans*-ethylene-*1,2-d*$_2$ was shown not to isomerize under the pyrolysis conditions. (c) Cyclobutane was stable under the reaction conditions. (d) Surface and pressure effects were checked. None were found.

(19) Recently, evidence[5d,e] was provided that *cis*- and *trans*-3,4-dimethyltetrahydropyridazines, six-membered cyclic 1,2-diazenes, undergo a stereospecific fragmentation reaction to olefin competitive with the generation of 3-methyl-1,4-pentanediyl, a 1,4-biradical intermediate which was *identical in behavior* with the intermediate(s) from the pyrolyses of 1,2-dimethylcyclobutanes.[3b]

(20) Neglecting deuterium isotope effects.

(21) In the case of 3,4-dimethyltetrahydropyridazines, a 36% stereospecific olefin-forming reaction in competition with a 64% 1,4-diradical pathway was found. Whether these stereospecific fragmentation reactions are [2 + 2 + 2] cycloreversions[22] or the decomposition of diazenyl biradicals that do not lose their stereochemical integrity cannot be distinguished from this data.

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(23) Characterization of tetramethylene from a stereochemical analysis of cyclobutane-d_4 is underway.[24]

(24) Private communication: Professor M. J. Goldstein, Cornell University.

(25) Benson[2a] estimates that A(cleavage) = $10^{13.07}$ and A(closure) = $10^{12.30}$ from parent tetramethylene. From the k(cleavage)/k(closure) ratio reported here (2.2), one calculates that E_a(cleavage) > E_a(closure) by 1.4 kcal mol^{-1} at 712 K.

(26) A. P. Sloan Research Fellow, 1977–1979. Camille and Henry Dreyfus Teacher-Scholar, 1978–.

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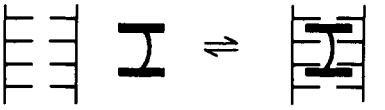
Molecular Recognition of Nucleic Acid by Small Molecules. Binding Affinity and Structural Specificity of Bis(methidium)spermine

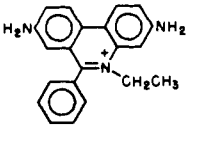
Sir:

Nucleic acids are biologically important receptors sufficiently characterized to encourage the syntheses of site specific probes. Molecules capable of binding to nucleic acid templates and interfering with processes in which nucleic acids participate are important in both antibiotic and cancer chemotherapy.[1] Some drugs bind to nucleic acids by intercalation, the insertion of a flat molecule between the base pairs of a double helix.[2] In the absence of unfavorable entropic or steric con-

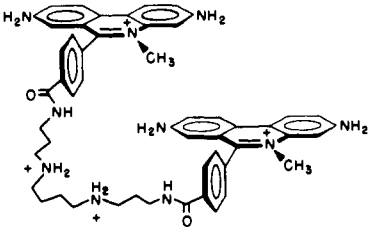


straints, an increase in binding affinity and sequence specificity would be expected for polyintercalators[3] which are capable of inserting two or more intercalating units into the nucleic acid double helix.

We report the *quantitative* determination of the nucleic acid binding affinity and specificity which result when two intercalating monomers of ethidium bromide (EB),[4] connected by a spermine[5] link, are incorporated into the same molecule, bis(methidium)spermine (BMSp).[3f] The results presented in this paper clearly demonstrate that dimers constructed from



EB



BMSp

two intercalating monomers can bind nucleic acids with a free energy approaching the sum of the free energies of the monomeric constituents resulting in substantial increases in both binding affinity and specificity.

BMSp (a) has a binding site size which is always twice that of EB,[3f,6] (b) increases the length of double helical DNA 1.6

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