(m), and 1030 (m); NMR δ 3.96-3.82 (m, 2 H), 2.84 (dd, J = 7.50, 13.6 Hz, 1 H), 2.79-2.70 (m, 1 H), 2.70 (dd, J = 6.7, 13.0 Hz, 1 H), 2.34 (dd, J = 3.6, 13.7 Hz, 1 H), 2.20 (dt, J = 3.8, 7.6 Hz, 1 H), 2.07-1.96 (m, 3 H), 1.90-1.75 (m, 2 H), 1.4-1.1 (m, 3 H), and 1.07 (s, 3 H); mass spectrum CI, m/z 177.1257 [$(M - 1)^-$, calcd for $C_{12}H_{17}O$, 177.1279].

Although minor ester **33** could not be obtained pure, NMR spectra could be measured on enriched mixtures of **33** and **32**: ^{13}C NMR δ 173.84, 56.29, 51.39, 45.28, 32.50, 41.47, 36.73, 37.32, 37.44, 33.51, 33.36, 35.79, and 24.13; NMR δ 3.650 (s, OCH_3), 3.477 (dd J_{cb} = 4.5, J_{cd} = 7.8 Hz, H_c), 2.99 (dd, J_{ef} = 13.6, J_{ed} = 7.2 Hz, H_e), 2.68 (dd, J_{gh} = 13.0, J_{gi} = 7.1 Hz, H_g), 2.6-2.4 (m, H_b, H_d), 2.34 (ddd, J_{fe} = 13.5, J_{fd} = 3.3, J_{fh} = 0.9 Hz, H_f), 2.1-1.1 (m, 6 H), 1.110 (s, 3 H).

(1α,3β,6α,7α,8β,10*S)-*N*-(4-Bromophenyl)-1-methyltetracyclo[4.3.1.0^{3,10}.0^{8,10}]decane-7-carboxamide (37).** A 25% solution of trimethylaluminum (0.1 mL) was added to a CH_2Cl_2 (3 mL) solution of *p*-bromoaniline (41 mg) under N_2 atmosphere. This resulting mixture was stirred for 10 min at room temperature followed by adding ester **32** (5 mg) in CH_2Cl_2 (1 mL). Stirring was continued for 3 h, and the reaction was quenched by adding 5% aqueous HCl (5 mL). Extractive workup with ether yielded crude anilide, which was purified by flash chromatography by using 33% ether in hexane to obtain colorless crystalline anilide **37** (6 mg, 72%, mp 173-174 °C): mass spectrum CI, m/z 344.0656 [$(M - 1)^-$, calcd for $C_{18}H_{19}{}^{79}BrNO$, 344.0650]. Slow crystallization from acetonitrile in a cold room (~4 °C) over 2 weeks gave crystals, which were suitable for X-ray crystallography.

Crystal Data and Data Collection. $p\text{-}BrC_6H_4N(H)COC_{11}H_{15}$, M_r 346.27, triclinic, $P\bar{1}$, a = 7.619 (2) Å, b = 10.047 (2) Å, c = 21.691 (5) Å, α = 76.89 (2)°, β = 81.02 (2)°, γ = 89.64 (2)°. The unit cell volume is 1596.6 (6) Å^3, Z = 4, $F(000)$ = 712, and the calculated density is ρ_{calcd} = 1.440 mg mm^{-3}. The cell chosen is the reduced basis.[36] A clear 0.35 mm × 0.075 mm × 0.03 mm crystal, bound by faces 010, 010, 001, 001, 101, 101, 101, and 101, was used for data collection. Data was collected on a Nicolet R3m automated diffractometer with an incident beam monochromator, λ = 1.541 78 Å (Cu Kα), at T = 295 K. Lattice parameters were determined from 22 centered reflections with $15 \leq 2\theta \leq 55$. The data collection range was $-8 \leq h \leq 8$, $0 \leq k \leq 10$, and $-23 \leq l \leq 23$ with $\sin \theta/\lambda_{max}$ = 0.55 Å^{-1}. Three standards were monitored every 60 reflections and exhibited a linear 8% decrease over the data collection; a correction was made on this basis. A total of 4908 reflections was measured in the $\theta/2\theta$ mode with a scan width of 2°; scan rate was a function of count rate (3°/min minimum, 30°/min maximum). There were 4367 unique reflections, R_{int} = 0.011 from merging equivalent reflections, 3248 observed with $F_o > 3\sigma(F_o)$. Lorentz and polarization corrections were applied and a numerical absorption correction was made, μ = 3.50 mm^{-1}, with maximum and minimum transmissions of 0.918 and 0.754, respectively.

Structure Solution and Refinement. The structure was solved by direct methods[37] with use of partial structure recycling.[38] The least-squares refinement program used program SHELXTL.[39] In the block-cascade least squares, the function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/(\sigma^2(|F_o|) + g(F_o)^2)$ where $g(F_o)^2$ is included to account for random instrumental error (g is estimated to be 0.0004). There were 499 parameters refined, including the atom coordinates and the anisotropic temperature factors for all non-H atoms. The isotropic temperature factors for the hydrogens were fixed at 1.2 times the equivalent isotropic thermal parameters of the atom to which they were bonded. The final residuals were R = 0.057 and R_w = 0.055, with an error in an observation of unit weight of 1.33. The largest shift to error parameter in the final cycle was 0.07. The final difference Fourier excursions were −0.44 and 0.44 e Å$^{\circ -3}$ for the largest peaks which were located near the bromine atoms. Atomic scattering factors are from the International Tables for Crystallography.[40] The final values for the fractional coordinates of the hydrogen atoms, anisotropic temperature factors, and structure factor amplitudes are available as supplementary data.

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are indebted to Phyllis Wilson for technical assistance, Francis Picart for 300-MHz spectra, and S. T. Bella for microanalyses. The 300-MHz NMR spectrometer was purchased with assistance from the National Science Foundation and the Camille and Henry Dreyfus Foundation.

Supplementary Material Available: Fractional coordinates of hydrogen atoms, anisotropic temperature factors, and structure factor amplitudes for compounds (24 pages). Ordering information is given on any masthead page.

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Bicyclic, Boatlike Cope Rearrangements. Probe for Conformational Preference by the Nodal Carbon Atoms

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Contribution from the Department of Chemistry, Harvard University,
Cambridge, Massachusetts 02138-2902. *Received January 28, 1985*

Abstract: 1,4-Bis(dideuriomethylene)cyclohexane (**1d$_0$**) and -cycloheptane (**2d$_0$**) were rearranged thermally to 1,4-dimethylene-2,2,3,3-tetradeuteriocyclohexane (**1d$_4$**) and -cycloheptane (**2d$_4$**), respectively. The Arrhenius parameters for these intramolecular boatlike Cope rearrangements were determined for **1d$_0$**, $\log k_1 = (12.7 \pm 0.7) - (45\,600 \pm 1800)/\theta$, and for **2d$_0$**, $\log k_1 = (12.0 \pm 0.4) - (41\,900 \pm 1200)/\theta$. The activation enthalpy was expected to be as much as 9 kcal/mol higher than that of the boatlike Cope rearrangement of 1,5-hexadiene if the transition state of the boatlike Cope required planarity of the nodal (C_2 and C_5) carbon atoms of the allylic systems. The theoretical prediction of Dewar that the nodal carbon atoms should prefer a pyramidal conformation is confirmed. That the enthalpy of the transition state of the Cope rearrangement of **1d$_0$** and **2d$_0$** can be approximated by that of the conjugate noninteractive radicals, bicyclo[2.2.2]octa-1,4-diyl and bicyclo[3.2.2]nona-1,4-diyl, is supported by analysis of heats of formation. The relation of the Cope enthalpy surface of **1** to that of [2.2.2]propellane is explored.

As extensive as studies of the Cope rearrangement have been,[1] no attention to possible geometric demands of the "nodal" atoms appears prior to the contribution of Brown, Dewar, and Schoeller.[2] Their MINDO/2 studies reveal a diradical as transition state for both the boat- and chairlike Cope rearrangement in which, unexpectedly, the "nodal" atoms are partially tetrahedralized (pyramidalized) and their substituents are inclined inward toward

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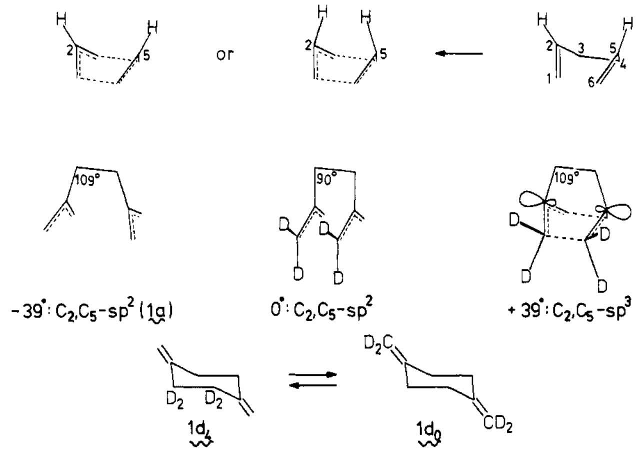
(1) Review: Gajewski, J. J. "Hydrocarbon Thermal Isomerization"; Academic Press: New York, 1981; pp 163–176.

(2) Brown, A.; Dewar, M. J. S.; Schoeller, W. *J. Am. Chem. Soc.* **1970**, *92*, 5516–5517.

0002-7863/85/1507-5739$01.50/0

Scheme I



each other as indicated in Scheme I.

This prediction has been confirmed for the chairlike Cope by subsequent MINDO/3 calculations (Dewar et al.[3] and Komornicki and McIver[4]) and by a multiconfigurational, self-consistent field calculation (Osamura et al.[5]).

The present effort seeks as its first goal an experimental resolution to the question whether the "nodal" carbon atoms, C2 and C5, prefer to remain planar and trigonal throughout the Cope rearrangement or whether they prefer a pyramidal conformation and as its second goal the placing on an enthalpy diagram of the two obligatorily boatlike Cope rearrangements.

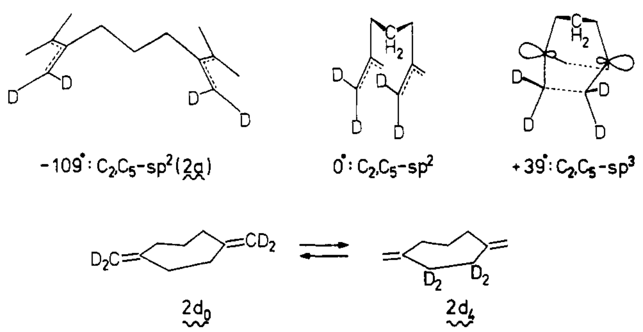
Hypothetical transition states and intermediates for the intramolecular Cope rearrangement incorporate its fundamental constitutional feature, breaking the 3,4-bond and making the 1,6-bond, and consist of various perturbations on the interaction between two allyl radicals. Each of these is represented by three molecular orbitals, of which the second (ψ_2) possesses a node at the central atom.

Among many orientations that can be assumed by a pair of planar allylic radicals, may be mentioned those at dihedral angles of $-180°$ (cf. bifurcated benzene) as in the chairlike Cope rearrangement, at $-120°$ as in concerted, boatlike Cope rearrangements of the bullvalene type, at 0° as in the bicyclic Cope rearrangements of this paper, and at 180° which, when twisted to 90° along the long axis, is the likely candidate for the transition state in the degenerate rearrangement of 1,2-dimethylenecyclobutane.[6]

The basis of the present experiments lies in the incorporation of two allylic radicals into a system of the bicyclo[2.2.2]octyl type. Were they planar and oriented at 0° as in Scheme I ($0°{:}C_2,C_5\text{-sp}^2$), the cost could be that associated with two contractions of tetrahedral angles to 90°. Alleviation of the resultant strain could be achieved at a high cost in bonding overlap by a large increase in distance between atoms 1 and 6, and 3 and 4 ($-39°{:}C_2,C_5\text{-sp}^2$), or at an unknown cost of increasing the separation between the nodal atoms, C_2 and C_5, through rehydridization to tetrahedral or pyramidal ($+39°{:}C_2,C_5\text{-sp}^3$).

If this cost is negligible, as theoretical calculations indicate,[3] 1,4-bis(dideuteriomethylene)cyclohexane (**1d$_0$**) is expected to participate in Cope rearrangement as readily as labeled hexa-1,5-diene participates in the boatlike Cope rearrangement.[7] If the cost is not negligible and the nodal atoms have an energetically significant preference to remain trigonal sp^2, **1d$_0$** is expected to rearrange to **1d$_4$** with a higher enthalpy of activation. The increment is conservatively estimated to be ~9 kcal/mol (one-half of the estimated angular contribution to the strain energy of cyclobutane (26.5 kcal/mol) less 8.0 kcal/mol, an estimate of the contribution of eight nearly eclipsed pairs of hydrogen atoms).

Scheme II



A bridge of three instead of two sp^3 carbon atoms in a system of the bicyclo[3.2.2]nonyl type (see Scheme II) confers a conformational flexibility so remarkable that Dreiding models should be consulted for a full appreciation. A range of dihedral angles from slightly positive through 0° (shown because the hydrogen atoms are near their van der Waals separation at this angle) to $-109°$ can be accommodated without strain, as can conformation, $+39°{:}C_2,C_5\text{-sp}^3$. In particular, the $0°{:}C_2,C_5\text{-sp}^2$ is also accommodated without angular strain.

In summary, if the obligatorily boatlike Cope rearrangement were to prefer an sp^2, planar conformation of the nodal atoms, C_2 and C_5, a two-carbon bridge might interfere significantly, whereas a three-carbon bridge should have little or no effect. If a pyramidal conformation were preferable or energetically accessible, neither bridge should occasion substantial departure from the behavior of the boatlike Cope rearrangement of the monocyclic paradigm, hexa-1,5-diene (Scheme I).

Quite independently, Gajewski, Hoffman, and Shih[8] studied compound **1** as an example of an indubitably boatlike Cope rearrangement and as an adjunct to studies of the four-membered[6] and five-membered[9] analogues. Their results were reported after the start of this work. Our studies being already well under way concern about possible conflict with Prof. M.J.S. Dewar having been graciously relieved by him, and our intention having been to include an investigation of the less strictly constrained, still obligatorily boatlike higher homologue, 1,4-bis(dideuteriomethylene)cycloheptane (**2d$_0$**), we continued with our work.

The preparation of **1d$_0$** was accomplished by a straightforward sequence in which *trans*-cyclohexane-1,4-dicarboxylic acid was converted seriatim into the bis(acid chloride),[10] the bis(*N*,*N*-dimethylamide),[11] 1,4-bis[(dimethylamino)dideuteriomethyl]cyclohexane,[11,12] and the corresponding bis(amine oxide),[13] pyrolysis of which at 165° afforded **1d$_0$**. Mass spectrographic analysis (70 eV) indicated a composition of 90% d_4 and 10% d_3. Further experimental details are available in the Ph.D. dissertation of C. A. Troise.[14]

For the preparation of **2d$_0$**,[14] cycloheptane-1,4-dione, obtained from cyclohexane-1,4-diol by published procedures,[15,16] was treated with dideuteriomethylene iodide (96% d_2, 4% d_1)[17] following a

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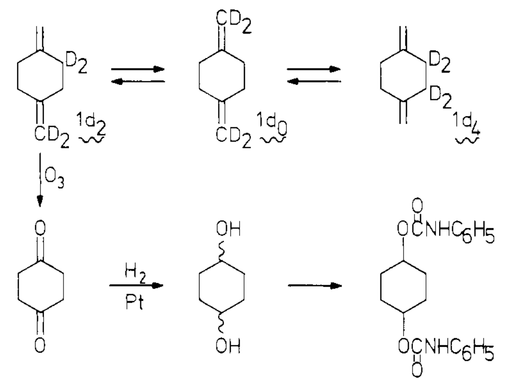
Scheme III



procedure developed by Wiberg and Burgmaier.[18] The resultant $\mathbf{2d}_0$ consisted of d_4 (89%) and d_3 (11%) as determined by mass spectroscopy.

Thermal rearrangements were effected in sealed, lead-potash (Corning 0120) ampules suspended in a bath of the vapors of boiling liquids. Benzophenone (bp 306 °C), hexachlorobenzene (bp 319 °C), and phenanthrene (bp 337 °C) served for the rearrangement of $\mathbf{1d}_0$ whereas biphenyl (bp 256 °C), bibenzyl (bp 281 °C), and benzophenone served for $\mathbf{2d}_0$. In addition, kinetic studies of $\mathbf{2d}_0$ (528–580 K) and of $\mathbf{1d}_0$ (579–610 and 688–729 K) were performed in a Techne FB-07 fluidized alumina bath.

Analysis of the olefinic products was effected by ozonolysis followed by either oxidative cleavage (tetracyanoethylene) or reductive cleavage (H_2, PtO_2, 500 psi). The resulting diketones and diols were unsatisfactory for mass spectrometric analysis. Many derivatives of the diketones (oximes, mono-, and diphenylhydrazones, semicarbazones, 4-nitro- and 2,4-dinitrophenylhydrazones) and the diols (trimethylsilyl ethers,[8] acetates and benzoates) were examined before finding that the bis(phenylurethanes) of the diols provided mass spectra having intense molecular ions free of extraneous peaks and otherwise satisfying the criteria for satisfactory analysis.[19] Each sample of urethane was introduced into the spectrometer 3 separate times and scanned 15 times each. Both cyclohexane-1,4-diol dicarbanilate and cycloheptane-1,4-diol dicarbanilate (Scheme III) gave five-peak molecular ion clusters at m/e 354–358 and m/e 368–372, respectively. Peak heights were used to calculate the relative amounts of the d_0–d_4 species.

Correction for M + 1 and M + 2 peaks arising from natural abundance of isotopes could be made by calculation[20] or by correction factors generated empirically from the mass spectra of unlabelled samples obtained by repeated measurements on bis(phenylurethanes) prepared from unrearranged, deuterium-labeled olefins by the full procedure of ozonolysis, hydrogenation, and reaction with phenyl isocyanate. Although a detailed discussion[14] is not given here, the empirical correction factors were preferred.

In the kinetic experiments with $\mathbf{1d}_0$ in the range 306.0–336.6 °C, and with $\mathbf{2d}_0$ in the range 255.4–306.5 °C, there was no systematic increase in the corrected d_1 and d_2 peaks with longer time of reaction. Thus, both pairs of labeled methylene groups rearrange into the ring to give a d_4 product unaccompanied by a d_2 product of nonconcerted rearrangement. Accordingly, the rearrangements are of the concerted Cope-type and do not involve to any appreciable extent a dissociative, randomly recombinative process of the type expected of the bisallylic intermediates depicted on the left sides of Scheme I and II.

By the nature of the analytical method, normalized values for d_0 as indicated for **1** and **2** in Table I include, as unreacted starting materials, the contribution from d_3. Small variations from the average temperature encountered in any particular run are corrected to the average temperature by an apposite adjustment in time, t, by application of the expression

Table I. Kinetic Parameters for the Thermal Rearrangement of **1** and **2**

T, K	t, s[a]	$d_0/(d_0 + d_3 + d_4)$	$10^5 k_s$, s^{-1} [b]	A_e [c]
	1,4-Bis(dideuteriomethylene)cyclohexane (**1**)			
579.12	7 041	0.810		
	21 152	0.565		
	36 245	0.460		
	134 430	0.314	4.54 ± 0.21 (4.7)[d]	0.313
591.76	3 481	0.794		
	6 980	0.658		
	14 952	0.472		
	29 500	0.351	10.07 ± 0.20 (2.0)	0.315
599.45	574	0.937		
	2 169	0.787		
	5 876	0.564		
	12 371	0.388	17.12 ± 0.34 (2.0)	0.305
609.75	1 788	0.683		
	3 569	0.549		
	7 321	0.380		
	21 508	0.314	32.11 ± 1.93 (6.0)	0.313
	1,4-Bis(dideuteriomethylene)cycloheptane (**2**)			
528.53	17 534	0.916		
	53 515	0.791		
	110 050	0.667		
	439 870	0.477	0.94 ± 0.033 (3.6)	0.468
554.34	7 430	0.814		
	14 578	0.700		
	28 565	0.560		
	83 159	0.472	5.86 ± 0.182 (3.1)	0.468
570.50	1 801	0.877[e]	15.73 ± 0.96 (6.1)	0.469
	3 602	0.760		
	7 504	0.625		
	14 344	0.528	17.38 ± 0.03 (0.2)[e]	0.485[e]
579.61	1 828	0.772	36.46 ± 3.04 (8.4)	0.499
	3 522	0.639		
	7 245	0.526		
	14 355	0.502[e]	31.88 ± 0.86 (2.7)[e]	0.473[e]

[a] Corrected; see text. [b] $k_s = k_1 + k_{-1}$. [c] A_e = equilibrium concentration. [d] Error in %. [e] Rate constants recalculated omitting the point indicated in the third column.

$$\log t' = \log t^0 - [E_a/R \ln 10][(T' - T^0)/T'T^0]$$

In this expression, E_a is given the approximate values 46 016 and 45 111 cal/mol in the first and second iteration of corrections to the data for **1** and 42 869 and 41 724 cal/mol for **2**. T' is the average temperature to which the data are being corrected. T^0 and t^0 are the actual temperature and time, respectively, and t' is the corrected time (shown in Table I) after two iteractions.

The data are then handled on the assumption of reversible, first-order reactions of the type

$$A(d_0) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B(d_4)$$

and the equation $1/k_s = t' \ln (1 - A_e)/(A - A_e)$, in which $k_s = k_1 + k_{-1}$ (s^{-1}), t' is the corrected time (s), A_e is the concentration of $A(d_0)$ at equilibrium, and A is the concentration at time, t. The value, A_e, reported at each temperature is that, obtained by trial and error, which leads to the maximum in the coefficient of correlation, r^2, obtained by conventional linear regression.

From the rate constants in Table I (in the case of **2** omitting the two points noted), Arrhenius parameters are calculated for k_s by linear regression ($\theta = RT \ln 10$):

1 $\log k_s = (12.64 \pm 0.26) - (45010 \pm 720)/\theta$; $r^2 = 0.9995$

2 $\log k_s = (12.32 \pm 0.12) - (41970 \pm 300)\theta$; $r^2 = 0.9995$

If all the data for **2** are used, the expression results:

2 $\log k_s = (12.56 \pm 0.79) - (42600 \pm 2000)/\theta$; $r^2 = 0.9956$

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Professor W. R. Roth of the Ruhr-Universität, Bochum, has kindly applied his uniquely appropriate program to the reduction of the original uncorrected data for **2** [Tables A1–A4].[14] Designed to handle the data from the shock tube experiments where each datum is associated with a different temperature and to assign idiopathic uncertainties to each rate constant in multivariable kinetic systems, this program employs a Simplex optimization procedure to calculate directly from the time, temperature, and concentration data best values for the preexponential and exponential factors of the Arrhenius equation and then calculate standard errors for each rate constant (reported as 2σ).

Based on all data points for **1** [Tables A5 – A8),[14] $\log k_1 = 12.7 - 45\,600/RT \ln 10$ results; if egregiously errorful points 5, 6, and 14 are omitted, $\log k_1 = (12.7 \pm 0.7) - (45\,600 \pm 1800)/RT \ln 10$ is the result. Similarly, based on the data in Tables A1–A4[14] for **2** excluding experiments 9 and 16, the expression $\log k_1 = (12.0 \pm 0.4) - (41\,900 \pm 1200)/RT \ln 10$ results.

Symmetry numbers for the rearrangements of **1** and **2** being 2 and and 1, respectively, rate constants for a single rearrangement, k_c, are also given (based on Roth's calculations). In the sequel, the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ relating to k_c are used for purposes of comparison.

1 $$k_c(321.29\ ^\circ\mathrm{C}) = 4.31 \times 10^{-5}\ \mathrm{s}^{-1};\ K_{eq} = 2.19$$

$$k_c(300.0\ ^\circ\mathrm{C}) = 1.03 \times 10^{-5}\ \mathrm{s}^{-1}$$

$$\Delta H^{\ddagger} = 44.4 \pm 1.8\ \mathrm{kcal/mol};\ \Delta S^{\ddagger} = -3.7 \pm 3.2\ \mathrm{eu}$$

2 $$k_c(280.92\ ^\circ\mathrm{C}) = 2.98 \times 10^{-5}\ \mathrm{s}^{-1};\ K_{eq} = 1.12$$

$$k_c(300.0\ ^\circ\mathrm{C}) = 1.06 \times 10^{-4}\ \mathrm{s}^{-1}$$

$$\Delta H^{\ddagger} = 40.8 \pm 1.2\ \mathrm{kcal/mol};\ \Delta S^{\ddagger} = -6.9 \pm 1.8\ \mathrm{eu}$$

Gajewski, Hoffman, and Shih[8] published the following details of their investigation of **1**: "Examination of the kinetics over a temperature range of 42 °C (to ± 0.3 °C) gave $\Delta S^{\ddagger} = -13.8 \pm 2$ eu and $\Delta H^{\ddagger} = 39.0 \pm 1.0$ kcal/mol for the conversion of I-d_4^{xo} to I-d_4^{R} ($K_{eq} = 2.1$ at 300 °C).

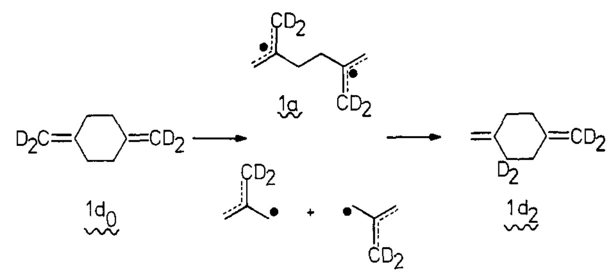
In a recent private communication, Prof. Gajewski has provided slightly modified rate constants and Arrhenius parameters: k(280.0 °C), k(299.8 °C), and k(322.0 °C) have the values 2.17 ± 0.0004, 8.43 ± 0.02, and 28.0 ± 0.8 × 10^{-6} s^{-1}, respectively, whence $\log k = (10.0 \pm 0.74) - (39\,800 \pm 2{,}000)/\theta$ [and $\Delta H^{\ddagger} = 38.7 \pm 2.0$ kcal/mol and $\Delta S^{\ddagger} = -16.1 \pm 3.4$ eu at 301 °C; $k(300\ ^\circ\mathrm{C}) = 0.67 \times 10^{-5}$ s^{-1}].

Although we cannot explain the disparity between their results and ours, we agree that the identity of their value for $\Delta S^{\ddagger}$ with that of the acyclic Cope rearrangement[21] is surprising. The value of −3.7 ± 3.2 eu emerging from the present work seems more in keeping with the greater rigidity of the monocyclic **1**.

In the derivation of $\Delta S^{\ddagger}$ and of equilibrium deuterium isotope effects per deuterium atom, correction is made for the symmetry number of 2 involved in **1**. Within experimental error, $K_{eq} = 1.11$ for **2** and $K_{eq} = 2.19$ for **1** translate into nearly identical isotope effects of 1.029 and 1.023 per deuterium atom, respectively. These values are not far from that found by Humski et al. for 1,1,6,6-tetradeuteriohexa-1,5-diene (1.05).[22]

Heating **1d**$_0$ above the range 305–335 °C, convenient for the Cope rearrangement, offers a chance of encountering two higher activation processes: opening to a bis allylic radical or cleavage to two trimethylenemethane radicals (Scheme IV). Either process would result, after ozonization, in the appearance of a d_2 species. Between 415–455 °C, this species does indeed appear but is accompanied by enough other reation products not to lend itself to quantitatively satisfactory kinetic study. At the higher temperatures, recovery of **1** is low, much p-xylene and unidentified colored impurities are produced, and attempts to extract activation parameters from results obtained in the presence of cumene are disappointing. Even with the omission of obviously bad runs [1, 9, 10, 14 of Tables A9–A12],[14] the Arrhenius expression, calculated by Roth's method, for the approach of the appearance of d_2 equilibrium is too inaccurate to be of value:

Scheme IV



$$\log k_s = (12.3 \pm 1.4) - (54\,300 \pm 4500)/\theta$$

Let it suffice to note the approximate rate constants ($k_1 + k_{-1}$) in s^{-1}: 0.24 × 10^{-4} (415.2 °C), 0.55 × 10^{-4} (429.9 °C), 1.0 × 10^{-4} (441.2 °C), and 2.1 × 10^{-4} (455.5 °C).

Conclusions

With a high degree of assurance, the thermal rearrangements of **1** and **2** are first order and intramolecular and involve the interchange of dideuteriomethylene groups in pairs. This latter feature is consistent with a rearrangement constitutionally of the Cope type. The intervention of the bisallylic diradicals, **1a** and **2a**, of Schemes I and II, respectively, can be considered, *provided* there are no internal rotations of a sort that would result in the introduction of a single dideuteriomethylene group into the ring. What distinguishes the concerted from the diradical pathways is a large, substantial discrepancy between observed enthalpies of activation of the Cope rearrangement and the minimal values predicted for the diradicals on the basis of estimated heats of formation.

The $\Delta H_f°$ of diradicals **1a** and **2a** are estimated from the $\Delta H_f°$ of 2,5-dimethylhexa-1,5-diene and 2,6-dimethylhepta-1,6-diene by reference to $\Delta H_f°(\mathrm{CH_3CH_2})$ and allylic resonance. An estimated $\Delta H_f°$ of 2,5-dimethylhexa-1,5-diene by the group-equivalent method[23] using Benson values[24] is obtained by subtraction of two methyl groups (−10.20) and addition of two methylene groups (−4.76) to the $\Delta H_f°$ of two molecules of isobutylene (−4.26): the resulting $\Delta H_f° = +2.36$ kcal/mol. Alternatively, $\Delta H_f°$ for the change $\mathrm{CH_2} \rightarrow \mathrm{C{=}CH_2}$ (+21.25 ± 0.6) obtained from four acyclic examples,[25] when applied to n-hexane (−39.92), gives $\Delta H_f° = +2.58$ kcal/mol. In a similar fashion, values of $\Delta H_f°$ for 2,6-dimethylhepta-1,6-diene are −2.56 and −2.35 kcal/mol, respectively.

When the heat of formation of the ethyl radical[26] is used ($\mathrm{C_2H_6} \rightarrow \mathrm{C_2H_5\cdot}$ +48.5 kcal/mol), then the appropriate allylic delocalization energy is ~13.5 kcal/mol[21,27,28] and the estimated heats of formation of the diradicals **1a** and **2a** are +72.5 and +67.5 kcal/mol, respectively.

The heat of formation of **1** may be estimated in three ways. Benson's group-equivalent values[24] give $\Delta H_f° = +14.16$ kcal/mol. Calculation by Allinger's molecular mechanics program (MM2)[29]

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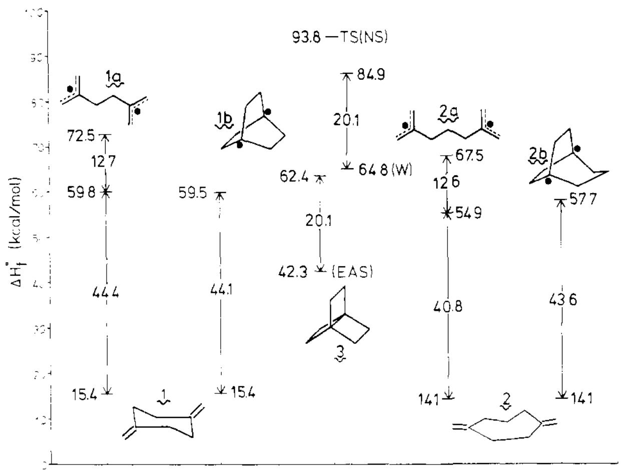


Figure 1. Enthalpy diagram for the Cope rearrangement of **1** and **2** including heats of formation and enthalpies of activation (kcal/mol), estimated heats of formation of the propellane **3**, and apposite transition states for thermal rearrangement of **1**.

gives +16.45 kcal/mol. Addition of twice the value of $\Delta\Delta H_f°(CH_2 \rightarrow C{=}CH_2$: +21.25 kcal/mol vide supra) to $\Delta H_f°$ (cyclohexane) gives a value of +13.00 kcal/mol. A similarly bothersome lack of agreement is found for methylenecyclohexane: Benson, −7.71 kcal/mol; MM2, −8.14; methylene replacement, −8.25; experimental, −6.07.[30] Recently, Roth and Lennartz have determined the heat of hydrogenation of I in *n*-octane by their published method[31] to be −58.95 kcal/mol. From the product being a mixture of *trans*-1,4-dimethylcyclohexane [71.5%; $\Delta H_f°$ = −44.10[25] kcal/mol] and *cis*-1,4-dimethylcyclohexane [28.5%; $\Delta H_f°$ = −42.20[25] kcal/mol], the heat of formation of **1** is +15.39 kcal/mol.[32]

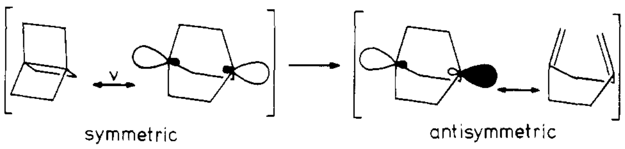
For the likewise unknown heat of formation of **2**, the Benson value (unstrained) is +9.23 kcal/mol, the Allinger MM2 value is 13.99 kcal/mol, and methylene replacement in cycloheptane gives +14.29 kcal/mol. We chose +14.14 kcal/mol.

Examination of an energy diagram (Figure 1) leaves little doubt that diradicals **1a** and **2a** lie too high (~12.5 kcal/mol) above the actual transition states to be considered as potential intermediates. Some confirmation in the case of **1** is found in the appearance of d_2 products only at much higher temperatures ($\Delta H^{\ddagger}$ = 56.1 ± 4.5 kcal/mol); whence the $\Delta H_f°$ of the transition state is 68.5 ± 4.5 kcal/mol.

Conclusions about the possible requirement of planarity at the nodal carbon may be based on diradicals bicyclo[2.2.2]octa-1,4-diyl (**1b**) and bicyclo[3.2.2]nona-1,5-diyl (**2b**) as models for the transition state of the rearrangements of **1d**$_0$ and **2d**$_0$, respectively. Their heats of formation can be estimated from those of the corresponding saturated bicyclic hydrocarbons. From the experimental value for bicyclo[2.2.2]octane, −23.66 kcal/mol[25] (MM2 value, −22.77), and the "1981" $\Delta H_f°$ of the *tert*-butyl radical,[26] $\Delta H_f°$ of **1b** is estimated to be +61.7 kcal/mol. A heat of formation of bicyclo[3.2.2]heptane is calculated by the MM2 method to be −24.5 kcal/mol and by Schleyer and Allinger to be −25.40 and −24.82 kcal/mol, respectively.[33] An estimated $\Delta H_f°$ of **2b** is thus +60.9 kcal/mol.

Whether the considerable strain energies in these saturated hydrocarbons, +9.7 and +13.4 kcal/mol, respectively, would remain unaffected by removal of the bridgehead hydrogen atoms is uncertain. The strain energy of interaction of a bridgehead hydrogen and its neighbors emerges from the MM2 calculations as 1.05 and 1.60 kcal/mol, respectively. Twice these values might be subtracted; whence the resulting estimated $\Delta H_f°$ of **1b** and **2b** would become +59.5 and +57.7 kcal/mol, respectively.

Scheme V



Any requirement by the nodal carbon atoms for planarity should be much more demanding of enthalpy in the reaction of **1** than in that of **2**. The estimated differences between the $\Delta H_f°$ of **1** and **2** and the $\Delta H_f°$ of their apposite diradicals **1b** and **2b** (Figure 1) are +46.3 and +43.6 kcal/mol, respectively. The comparable experimental values of $\Delta H^{\ddagger}$ are +44.4 and +40.8 kcal/mol, respectively. In both instances, agreement is close enough to admit the diradicals as enthalpic models for the transition states even though symmetry precludes their actually being transition states for the Cope.

The 2–3 kcal/mol discrepancies may indicate a small concert, but caution is advisable, given the several experimental uncertainties which remain unrefined.

In neither case, but more impressively in the case of **1**, is there any suggestion that the transition state of the boatlike Cope rearangement is *inhibited* by an inability to attain trigonal coplanarity at the nodal carbon atom. Thus, the theoretical predictions[2,4] for this structural feature of the diradical intermediate in the boatlike Cope rearrangement are well confirmed by these experimental results.

The absence of a requirement of coplanarity at the nodal carbon atom does not provide a basis for distinguishing between formulation of the transition state of the boatlike Cope rearrangement as a concerted transition state (both relevant bonds equivalent and long) or as a saddle point on the way to a biradical intermediate (both relevant bonds equivalent and short). Suffice it to give notice of a recent paper by Osamura et al.[5] on the chairlike Cope rearrangement in which, contrary to the results of Dewar with a MINDO/3 calculation,[3] an ab initio calculation (MCSCF optimized structure and 3-21G basis set) confirms a preference for pyramidalized nodal carbon atoms but points to a concerted transition state.

The finding of Eaton and Temme[34,35] that [2.2.2]propellane *N,N*-dimethylcarboxamide undergoes facile ring opening to a mixture of dimethylenecyclohexanes with an enthalpy of activation of $\Delta H^{\ddagger}$ = 20.1 kcal/mol[36] invites comparison with the transition state of the bicyclic boat Cope rearrangement of **1**.

In order to place this datum on the enthalpy diagram, the heat of formation of [2.2.2]propellane is needed. Unknown, and unlikely easily to be fixed experimentally, two theoretical calculations give severely conflicting results. A molecular mechanical calculation by Engler, Andose, and Schleyer[33] gives +42.3 kcal/mol, whereas an ab initio calculation by Wiberg[37,38] using the 6-31G* basis set and optimized geometry gives +64.8 kal/mol. Both resulting heats of formation are shown in Figure 1: T.S. (EAS) at +62.4 and T.S. (W) at +84.9 kcal/mol. Clearly any conclusions must be considered highly tentative until the conflict is resolved experimentally. However, Wiberg, in a private communication with permission to include here (see footnote 5 of ref 37), makes a strong argument against the lower value.

The reasoning is based primarily on a heat of formation of [3.2.1]propellane of +39 ± 3 kcal/mol deduced from an experimental heat of formation of 8-oxatricyclo[3.2.1.0^{1,5}]octane and

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(36) Calculation afresh from the specific rate constants recorded on p 43 of ref 35 gives the Arrhenius expression, log k = (11.9 ± 0.6) − (20700 ± 830)/θ ($\Delta H^{\ddagger}$ = 20.1 kcal/mol; $\Delta S^{\ddagger}$ = −6.3 eu; k[(35.0 − 6.9)/2 °C] = 2.9 × 10^{-4} s^{-1}).

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a known heat of acetolysis of tricyclo[3.2.1.$0^{1,5}$]octane ([3.2.1]-propellane). Given that the strain energies of bicyclo[2.1.0]-pentane[25] and bicyclo[2.2.0]hexane[31] are about equal, the heat of formation of tricyclo[2.2.2.$0^{1,4}$]octane ([2.2.2]propellane) must be at least 20 kcal/mol greater than that of [3.2.1]propellane owing to the exchange of a cyclopropane and cyclopentane ring for two cyclobutane rings, that is, $\geq$ 59 kcal/mol.

Independent theoretical analyses by Stohrer and Hoffmann[39] and Newton and Shulman[40] confirm that [2.2.2]propellane, like the paradigmatic cyclobutane, is forbidden to cleave by way of the symmetric diradical but is allowed to cleave by way of the antisymmetric diradical. The situation is diagramed in Wiberg and Matturro[41] and in Scheme V. Newton and Shulman[40] attempt a quantitative calculation and find a transition state joining [2.2.2]propellane and the antisymmetric diradical some 29 kcal/mol higher in energy at a C_1–C_4 bond distance of ~1.95 Å. Considering what kind of chemical accuracy might be expected, agreement with the experimental value of Eaton and Temme is excellent. Perhaps the relaxation of D_{3h} symmetry permitted by a calculation of the type made for the chair Cope rearrangement[5] would give even better results.

We presume that this transition state is not so much a "symmetric diradical" as represented by Stohrer and Hoffmann[39] and Wiberg and Matturro[41] as an excited vibrational level of [2.2.2]propellane in which distinction between symmetric and antisymmetric vanishes. The "symmetric diradical" is any one of a number of vibrational levels in which the 1,4-bond is longer at the extension. We prefer "vibrational" diradical.

The antisymmetric diradical, as clearly pointed out by Stohrer and Hoffmann,[39] may not be an intermediate either but rather is the transition state for cleavage to dimethylenecyclohexane. It may lie above the slightly "concerted" transition state implied by the enthalpy diagram in its current form (Figure 1) or it may be identified with the diradical **1b**, if through-bond interaction is neglible. In that event, the noninteractive construction of **1b** is an energetically acceptable model. We caution, however, that the tertiary CH bond in isobutane may be a poor model for the tertiary CH bond in bicyclo[2.2.2]octane and that the lack of an experimental heat of formation of [2.2.2]propellane is stultifying.

The general problem in orbital symmetrically "forbidden" reactions involves identifying a geometry that permits the molecule to circumvent the restriction. The problem is faced explicitly by Newton and Shulman[40] for [2.2.2]propellane, where the rigidity of the system leaves only stretching of the C_1–C_4 bond and twisting as the means of reducing transannular bonding to zero.

In less rigid bicyclo[2.2.0] systems, zero-bonding between C_1 and C_4 can easily be achieved by stretching into the twist-boat conformation of the continuous diradical as the transition state for inversion, coupled, perhaps, with enough additional twisting to achieve orthogonality between the two planes of the radical carbon atoms (no role need be considered for a strict boat conformation in light of the already twisted conformation of bicyclo[2.2.0]hexane). At this point, cleavage becomes independent of orbital symmetry and follows the stereochemistry associated with the twist boat or chair.[42] Interfere with the achievement of this zero-bonded conformation, as Wiberg and Matturro have so elegantly done with the aid of bridges, and the activation energies rise from 36 to as high as 46 kcal/mol.[41]

Cyclobutane encounters minimal difficultly in achieving a zero-bonding conformation in its *gauche*-1,4-tetramethylene vibrational diradical: slight internal rotations about C_1–c_2 and C_3–C_4 easily reach an orthogonal zero-bonding conformation. It follows that the enthalpies of activation of cleavage in cyclobutanes and unrestricted bicyclo[2.2.0]hexanes can be reliably estimated by estimating the heats of formation of the apposite noninteractive diradicals, but such a procedure fails miserably with [2.2.2]propellane and only a full quantum mechanical calculation can locate the conformation that allows symmetric–antisymmetric indistinguishability.

Although we are not hopeful of an early refinement of the [2.2.2] portion of the energy diagram, the [3.2.2] part seems much more readily accessible experimentally—at the possible expense, however, of sacrificing much of the rigidity of the [2.2.2] system.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer; chemical shifts are in ppm downfield from tetramethylsilane (δ). Infrared spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer. Mass spectrometric analyses were recorded on a AEI Model MS-9 double-focusing mass spectrometer. Gas chromatography employed Aerograph A 90-P, A 90-P3, and A-700 gas chromatographs for preparative separations and a Perkin-Elmer 990 gas chromatograph for quantitative analyses. Ozonolyses were conducted on a Supelco, Inc., Micro-Ozonizer. Hydrogenations were carried out on a Parr 310-mL stainless steel bomb with gage block assembly. High-temperature thermostat measurements were made in a Techne FB-07 fluidized alumina bath. Melting points (Hershberg apparatus) and boiling points were uncorrected. Detailed experimental procedures are to be found in Troise's dissertation,[14] which include otherwise unpublished NMR and IR spectra.

1,4-Bis(dideuteriomethylene)cyclohexane. 1,4-Bis(dimethylcarbamido)cyclohexane (5.00 g, 22.2 mmol) in 200 mL of dry benzene was added slowly to a vigorously stirred slurry of lithium aluminum deuteride (2.14 g, 56.5 mmol, 98.1% d_4) in 25 mL of anhydrous ethyl ether. After completion of the addition and boiling under reflux for 24 h, the reaction mixture was quenched following the procedure of Micovic and Mihailovic.[12] The free amine was extracted into ether, dried ($MgSO_4$), filtered, and concentrated to give 1,4-bis[(dimethylamino)dideuteriomethylene]-cyclohexane as a clear oil which solidified on standing: 3.56 g (81%); MS (70 eV); *m/e* 202 (d_4 91%), 201 (d_3 9%).

Conversion to the bis(amine oxide) followed the procedure of Murphy.[13] Pyrolysis of the amine oxide was effected at 1 mm and 165 °C in a flask fitted with a 12-cm Vigreux column leading to a first trap cooled by dry ice in acetone and a second trap cooled by liquid nitrogen. The contents of the traps were extracted with pentane, dried (Na_2SO_4), filtered, and concentrated to give 2.61 g (86%) of crude **1d$_0$**. Purification by GLC (5 ft, 20% SE-30 [NaOH] on Chromosorb W, 110 °C, 60 mL of He/min) gave 1.16 g (38% th. yield) of colorless liquid: NMR (CCl_4) δ 2.20 (s); IR (CCl_4) 2940 (s), 2900 (m), 2840 (m), 2760 (w), 2300 (w), 2200 (w), 2025 (w), 1620 (m), 1440 (s), 1330 (m), 1260 (w), 1235 (w), 1195 (w), 1155 (w), 1040 (w), 990 (w), 975 (w), 900 (w), 835 (w), 800–725 (br s), 660 cm^{-1} (s); MS (70 eV), *m/e* 112 (d_4 90%), 111 (d_3 10%).

1,4-Bis(dideuteriomethylene)cycloheptane (2d$_0$). The preparation begins with the conversion of cyclohexane-1,4-diol to 4-(benzoyloxy)-cyclohexanol,[15] proceeds to 4-(benzoyloxy)cyclohexanone and 4-hydroxycyclohexanone,[15] and thence by treatment with *N*-methyl-*N*-nitrosourethane to 4-hydroxycycloheptanone.[16]

Oxidation with pyridinium chlorochromate (31 g, 0.14 mol), suspended in 200 mL of methylene chloride, of this ketol (11.0 g, 0.086 mol) in 20 mL of methylene chloride produced a black solution, which was stirred for 3 h at room temperature. Decantation left a black gum that was dissolved in water and extracted with ether. Filtering of the ether extract through a short column of Florisil and concentrating afforded 10.7 g (99% of theoretical yield) of a colorless oil having an NMR spectrum identical with a sample prepared according to the procedure of Doering and Sayigh:[16] bp 107 °C/5 mm; NMR (CCl_4) δ 1.90 (m, 2 H), 2.57 (s, 4 H), 2.67 (m, 4 H); IR (neat) 2950 (s), 1700 (s), 1430 (s), 1350 (m), 1330 (s), 1275 (m), 1190 (s), 1170 (s), 1140 (s), 1060 (w), 1000 (w), 960 (w), 910 (m), 890 (m), 845 (w), 810 (w), 760 (m), 470 cm^{-1} (br s).

Following the procedure of Wiberg and Burgmeier,[18] a magnesium amalgam was prepared by adding 2.44 g of magnesium turnings to 453 g of mercury. After addition of 50 mL of ether, freshly distilled from lithium aluminum hydride, a solution of 4.84 g (17.9 mmol) of dideuteriomethylene iodide (96% d_2, 4% d_1; prepared according to Winstein et al.[17]) and 1.00 g (7.90 mmol) of 1,4-cycloheptanedione in 30 mL of anhydrous ethyl ether was added slowly and dropwise to the rapidly stirred magnesium amalgam. After subsidence of the initially vigorous reaction, the contents were gently refluxed for 3 h before quenching with saturated aqueous ammonium chloride and extracting with ether. Drying (Na_2SO_4), filtering, and distilling left a liquid, which was purified by GLC (2 m, 20% CW 20 M on Anakrom ABS, 70 °C, 30 mL/min) to yield 200 mg (20% of theoretical yield) of **2d$_0$**: NMR (CCl_4) δ 1.63 (m,

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J. Am. Chem. Soc. 1985, 107, 5745-5754

2 H), 1.93–2.43 (m, 4 H), 2.27 (s, 4 H); IR (neat) 2950 (s), 2875 (s), 2310 (m), 2225 (w), 1620 (m), 1450 (m), 1350 (m), 1190 (m), 925 (w), 785 (m), 755 (m), 720 (s), 710 (m), 625 (s), 470 cm^{-1} (br s); MS (70 eV), *m/e* 126 (d_4 89%), 125 (d_3 11%).

Cyclohexane-1,4-dione-d_8 and Cycloheptane-1,4-dione-d_8. A solution of diketone (2.00 g, 0.02 mol) in 10 mL of D_2O containing 10 μL of 40% NaOD in D_2O was stirred at room temperature. Chloroform extracts of the reaction mixture were dried (Na_2SO_4) and concentrated. Deuterium incorporation was determined by NMR (using methylene chloride as the internal standard) and mass spectrometry.

After two such treatments of 1- and 2-h duration, cyclohexane-1,4-dione, in 20% overall yield, appeared to be 99% exchanged by NMR, whereas mass spectrometry revealed the distribution of label to be 86% d_8, 9% d_7, 2% d_6, and 3% d_5 (97% exchanged).

Cycloheptane-1,4-dione required three exchanges (1, 2, and 6 h) to produce 95% deuterium incorporation. The NMR spectrum was unaltered after a fourth exchange of 6 h. The isotopic composition of the dione, recovered in 50% overall yield, was shown by mass spectrometry to be 85% d_8, 10% d_7, 3% d_6, and 2% d_5 (97% exchanged).

Thermal Rearrangements. All thermal rearrangements were performed in 1.5 × 10 cm o.d. Corning 0120 lead potash ampules, which had been soaked in concentrated NH_4OH overnight, rinsed with distilled water until the washings were neutral, rinsed with acetone, and oven-dried.

The olefins (10-μL samples) were introduced with a microsyringe and degassed (two freeze–thaw cycles). Cumene (2 μL) was added to 1,4-bis(dideuteriomethylene)cyclohexane for thermolyses at temperatures > 400 °C. The ampules were sealed under vacuum (10^{-4} mm) and either suspended in the vapors of a boiling solvent bath by a copper wire fastened to a hook at the base of the ampule or loaded into a probe carrier and lowered into the Techne fluidized alumina bath.

The vapor bath consisted of a 5 × 50 cm Pyrex tube fused to either a 500-mL or 100-mL round-bottom flask. The apparatus was insulated with several layers of asbestos tape, glass wool, and an outer wrapping of Fiberglas. The uninsulated upper 10 cm was cooled on all sides with a rapid stream of air.

The temperature of the vapor was measured with an iron-constantan thermocouple and a Leeds and Northrup No. 8686 millivolt potentiometer. For high-temperature work, the thermocouple was calibrated against boiling sulfur (448 °C).

After being heated for a specified time, the ampules were removed from the bath and cooled. Quantitative recovery of the rearranged olefin was revealed by GLPC analysis (*n*-decane was the internal standard). The contents of the ampule were then transferred to an NMR tube for recording of the spectrum. The progress of the rearrangement was monitored by observing the appearance of vinylic signals at 4.70 ppm.

Ozonolyses of Dienes. The NMR sample in CCl_4 was transferred with methylene chloride to a 15-mL, three-necked, round-bottom flask fitted with a dry ice condenser and gas inlet. Ozone was bubbled through the solution until a blue color persisted. Excess ozone was blown off with a stream of nitrogen.

Hydrogenations of Ozonides. The solution of ozonide and 20 mg of PtO_2 was added to a 25-mL Erlenmeyer flask containing a magnetic stirring bar. The flask was secured with glass wool inside the stainless steel Parr bomb lined with a 150-mL glass beaker. After being purged with nitrogen, the bomb was pressurized with 250 psi hydrogen and vented. After a second cycle of pressurizing and venting, a final adjustment of hydrogen pressure was made and stirring was started.

1,4-Dimethylenecyclohexane diozonide was converted to 1,4-cyclhexanediol in 1 h at room temperature under 250 psi hydrogen. The 1,4-dimethylenecycloheptane diozonide was similarly treated; however, an additional 2 h of stirring at 65 °C and 500 psi hydrogen was required for complete conversion to 1,4-cycloheptanediol.

The bomb was cooled and vented. The catalyst was removed by filtration, and the filtrate was checked by TLC for completeness of reaction. After removal of solvent, the diol was stirred with 50 mg of phenyl isocyanate in a well-stoppered flask at room temperature overnight, for conversion to the diphenylurethane. Unreacted phenyl isocyanate was removed under reduced pressure. The solid residue was suitable for mass spectrometric analysis without further purification.

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Registry No. **1**d_0, 81389-52-8; **2**d_0, 97135-84-7; 1,4-bis(dimethylcarbamido)cyclohexane, 97135-81-4; 1,4-bis[(dimethylamino)dideuteriomethylene]cyclohexane, 97135-82-5; 1,4-bis[(dimethylamino)-dideuteriomethylene]cyclohexane bis(oxide), 97135-83-6; 4-hydroxycycloheptanone, 67963-12-6; dideuteriomethylene iodide, 865-43-0; cycloheptane-1,4-dione-d_8, 97135-85-8; cyclohexane-1,4-dione-d_7, 97135-86-9; cyclohexane-1,4-dione-d_6, 97149-90-1; cyclohexane-1,4-dione-d_5, 97135-87-0; cycloheptane-1,4-dione-d_7, 97135-88-1; cycloheptane-1,4-dione-d_6, 97149-91-2; cycloheptane-1,4-dione-d_5, 97135-89-2; bicyclo-[2.2.2]octa-1,4-diyl, 97135-90-5; bicyclo[3.2.2]nona-1,4-diyl, 97135-91-6; 1,4-cycloheptanedione, 14950-46-0; cycloheptane-1,4-dione-d_8, 1680-86-0; 1,4-cyclohexanedione, 637-88-7.

Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Azadienes: Formal Total Synthesis of Streptonigrin

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Abstract: A formal, total synthesis of streptonigrin is detailed and is based on the sequential implementation of two inverse electron demand Diels–Alder reactions: cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with *S*-methyl 6-methoxy-5-nitro-2-quinolinethioimidate for construction of the streptonigrin ABC ring system followed by [4 + 2] cycloaddition of the resulting dimethyl 5-(6-methoxy-5-nitro-2-quinolyl)-1,2,4-triazine-3,6-dicarboxylate with enamine derivatives of 2-(benzyloxy)-3,4-dimethoxypropiophenone for preparation of the streptonigrin CD biaryl ring system and completion of the assemblage of the streptonigrin carbon skeleton. A study of the factors effecting the regioselectivity of the [4 + 2] cycloaddition of 1,2,4-triazines with electron-rich olefins is detailed. Factors influencing the Diels–Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with nucleophilic dienophiles containing a C=N double bond are examined and detailed.

Streptonigrin[2] (**1**), an antitumor antibiotic isolated from *Streptomyces flocculus*, was identified and characterized in 1959,[3] its structure correctly determined in 1963[4] by a combination of chemical degradative and spectroscopic studies and confirmed in

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