

Organic and Biological Chemistry

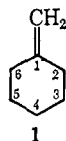
Proton Magnetic Resonance Studies of the Conformation of Methylenecyclohexane

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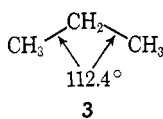
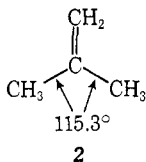
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Abstract: 4,4-Dideuterio- and 3,3,5,5-tetradeuteriomethylenecyclohexane have been synthesized and examined by proton magnetic resonance spectroscopy as a function of sample temperature. Chemical shifts and coupling constants obtained from low-temperature spectra establish that a chair form is the predominant ground-state conformation of methylenecyclohexane. The activation parameters ΔG^\ddagger , ΔH^\ddagger , and ΔS^\ddagger for the ring inversion process in the molecule were found to be 8.4 kcal/mol, 8.6 kcal/mol, and 1.4 eu, respectively. These results are discussed in terms of a conformational interconversion process that is similar to the one which occurs in cyclohexane.

Methylenecyclohexane (1), a six-membered carbocycle which contains one sp^2 -hybridized carbon atom in the ring, has recently been shown to have a proton magnetic resonance spectrum that is temperature dependent, suggesting that this olefin is conformationally similar to cyclohexane.^{2,3} The angle be-



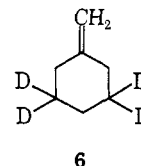
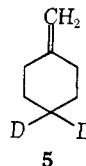
tween the methyl groups in isobutylene (2) is 115.3° ,⁴ not much larger than the analogous angle in propane⁵ (3) or cyclohexane⁶ (4), and the comparable carbon-



carbon bond lengths in all three compounds are also quite similar. It is thus possible to envision a nearly strain-free chair conformation for 1 that is similar to the known ground-state conformation of cyclohexane. Potential energy calculations by Allinger and coworkers are in accord with these expectations; these authors suggest that the chair form of methylenecyclohexane should be favored by at least 4 kcal/mol over the next most stable form, a twist-boat conformation.⁷ No

direct experimental support for these conclusions has been reported, however.

The pmr spectrum of the ring protons of 1 appears as a complex, partially resolved set of resonances at -139° ; the spectrum is too ill defined for meaningful analysis in terms of accurate exchange rate data. Introduction of deuterium atoms at specific ring positions has proven to be a useful procedure for simplifying the pmr spectrum of cyclohexane^{8a,8} and this technique was used in the present study by the preparation of the derivatives 5 and 6. By employing these compounds we hoped to obtain information about the ground state



of methylenecyclohexane and more reliable values for the energetics of the conformational equilibration which takes place in this substance.

Results

4,4-Dideuteriomethylenecyclohexane (5). At ambient temperature the pmr spectrum of 5 in $CBrClF_2$ - CBr_2F_2 solvent consisted of a pentuplet ($J = 0.9$ Hz, relative area 2) centered at 4.50 ppm downfield from internal tetramethylsilane, assigned to the vinyl protons, and the broadened pattern of signals shown in Figure 1. Upon irradiation of the sample at the vinyl proton frequency, the low-field part of this multiplet sharpened while irradiation at the deuterium frequency acuminated the high-field portion. The higher field part of the spectrum can therefore be assigned to the four protons on (equivalent) carbon atoms 3 and 5 and the low-field signals must be due to the four protons at carbon atoms 2 and 6. Simultaneous irradiation of

(1) U. S. Public Health Predoctoral Fellow, 1966-present. This work will form a portion of the Ph.D. Thesis of R. A. R.

(2) (a) J. T. Gerig, *J. Amer. Chem. Soc.*, **90**, 1065 (1968); (b) F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968).

(3) (a) F. A. L. Anet and A. J. R. Bourn, *ibid.*, **89**, 760 (1967); (b) P. T. Inglefield, E. Krakower, L. W. Reeves, and R. Stewart, *Mol. Phys.*, **15**, 65 (1968); (c) for a review of most of the cyclohexane literature, see G. Binsch in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, New York, N. Y., 1968, p 97.

(4) L. H. Scharpen and V. W. Laurie, *J. Chem. Phys.*, **39**, 1732 (1963).

(5) D. R. Lide, Jr., *ibid.*, **33**, 1514 (1960).

(6) M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963).

(7) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **90**, 5773 (1968).

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Table I. Proton Magnetic Resonance Parameters for 4,4-Dideuterio- and 3,3,5,5-Tetradeuteriomethylenecyclohexane

| | A. Chemical Shifts ^a | | | | | | |
|---------------------------------------|------------------------------------|---------------|---------------|---------------|---------------|---------------|-------------|
| | δ_{2a} | δ_{2e} | δ_{3a} | δ_{3e} | δ_{4a} | δ_{4e} | |
| 5, at 33° ^d | | 2.109 | | 1.543 | | | |
| 5, at -130° ^e | 1.975 | 2.252 | 1.318 | 1.836 | | | |
| 5, at 33° (computed ^b) | | 2.114 | | 1.577 | | | |
| 6, at 33° ^f | | 2.07 | | | | 1.50 | |
| 6, at -125° ^f | 1.90 | 2.22 | | | 1.28 | | 1.73 |
| | B. Coupling Constants ^c | | | | | | |
| | J_{2gem} | J_{3gem} | J_{4gem} | $J_{2a,3a}$ | $J_{2e,3e}$ | $J_{2a,3e}$ | $J_{2e,3a}$ |
| 5, at 33° ^h | <i>g</i> | <i>g</i> | | 8.06 | | | 4.40 |
| 5, at -130° ⁱ | -13.3 | -13.1 | | 13.5 | 2.59 | 4.72 | 3.90 |
| 5, at 33° (computed ^b) | -13.3 | -13.1 | | 8.05 | | | 4.31 |
| 6, at -125° ^j | ±13.3 | | ±13.2 | | | | |

^a In parts per million determined at 100 MHz relative to tetramethylsilane as the reference-lock signal. ^b Calculated by averaging the parameters found at low temperature. ^c In hertz. ^d Estimated error ±0.001 ppm. ^e Estimated error ±0.002 ppm. ^f Estimated error ±0.01 ppm. ^g This parameter was not well determined by the spectrum. ^h Estimated error ±0.1 Hz. ⁱ Estimated error ±0.2 Hz. ^j Estimated error ±0.3 Hz.

both the vinyl and deuterium nuclei of **5** produced the AA'BB' spectrum shown in trace D of Figure 1. This spectrum was analyzed with the aid of the Ferguson-Marquardt computer program.⁹ The chemical shifts

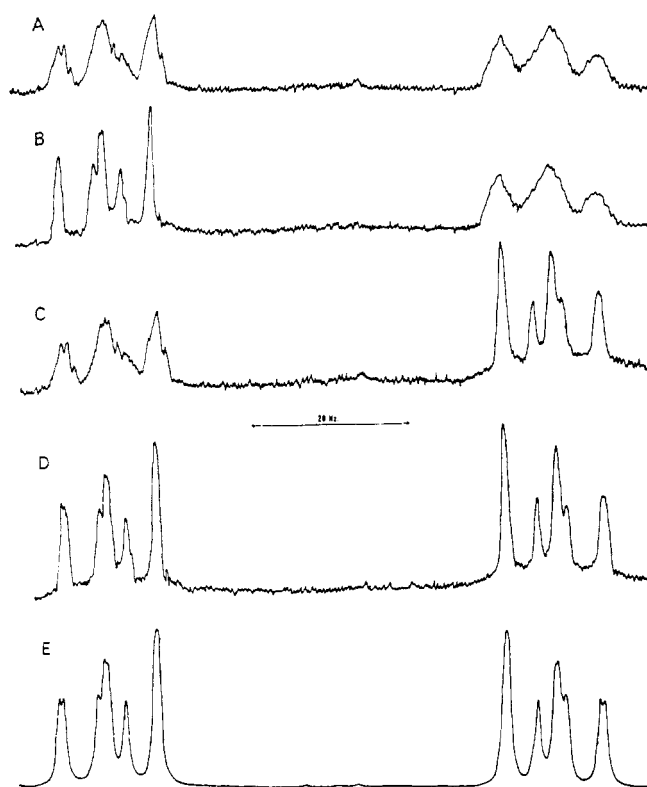


Figure 1. The alkyl portion of the pmr spectrum of **5** at ambient temperature. The solvent was an 80%-20% mixture of CBrClF₂ and CBr₂F₂, respectively. Trace A is the undecoupled spectrum, trace B shows the effects of irradiation at 451 Hz from the TMS lock signal, and trace C illustrates the effect of irradiation at 15.4 MHz, the deuterium resonance frequency. Trace D results from a triple resonance experiment in which the vinyl and the deuterium atoms are simultaneously decoupled. Trace E is the theoretical spectrum computed using the parameters in Table I.

(9) R. C. Ferguson and D. W. Marquardt, *J. Chem. Phys.*, **41**, 2087 (1964).

and coupling constants reported in Table I gave a good accounting of the experimental spectrum, as the computed theoretical spectrum (trace E) based on these parameters indicates.

As the temperature of this sample of **5** was progressively lowered, the alkyl portion of the spectrum broadened and then evolved into the ABCD spectrum reproduced in Figure 2. At approximately -130°, the

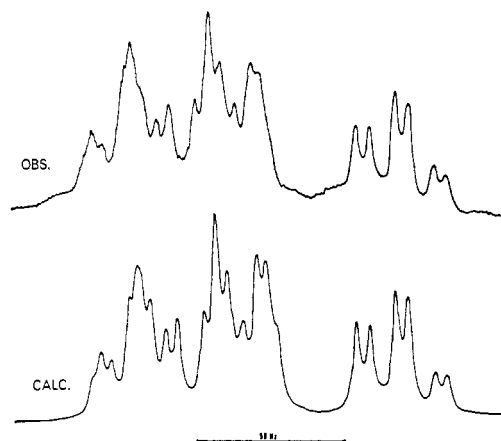


Figure 2. The alkyl portion of the pmr spectrum of **5** at about -130°: (A), obtained with vinyl and deuterium decoupling; the computed spectrum (B) was prepared using the chemical shifts and coupling constants in Table I.

vinyl signal was still reasonably sharp, with a width at half-height about 2 Hz greater than that observed at room temperature. Analysis of the ABCD spectrum afforded the coupling constant and chemical shift data listed in Table I. The effects of cross-ring spin coupling were neglected in this analysis since the magnitude of these couplings is expected to be small and, primarily, will have the effect of broadening the lines of the experimental spectrum. Chemical shifts and coupling constants for the low-temperature spectrum of **5** average to give values in good agreement with those obtained from the room temperature spectrum.

3,3,5,5-Tetradeuteriomethylenecyclohexane (6). The pmr spectrum of the alkyl portion of **6** consists of two

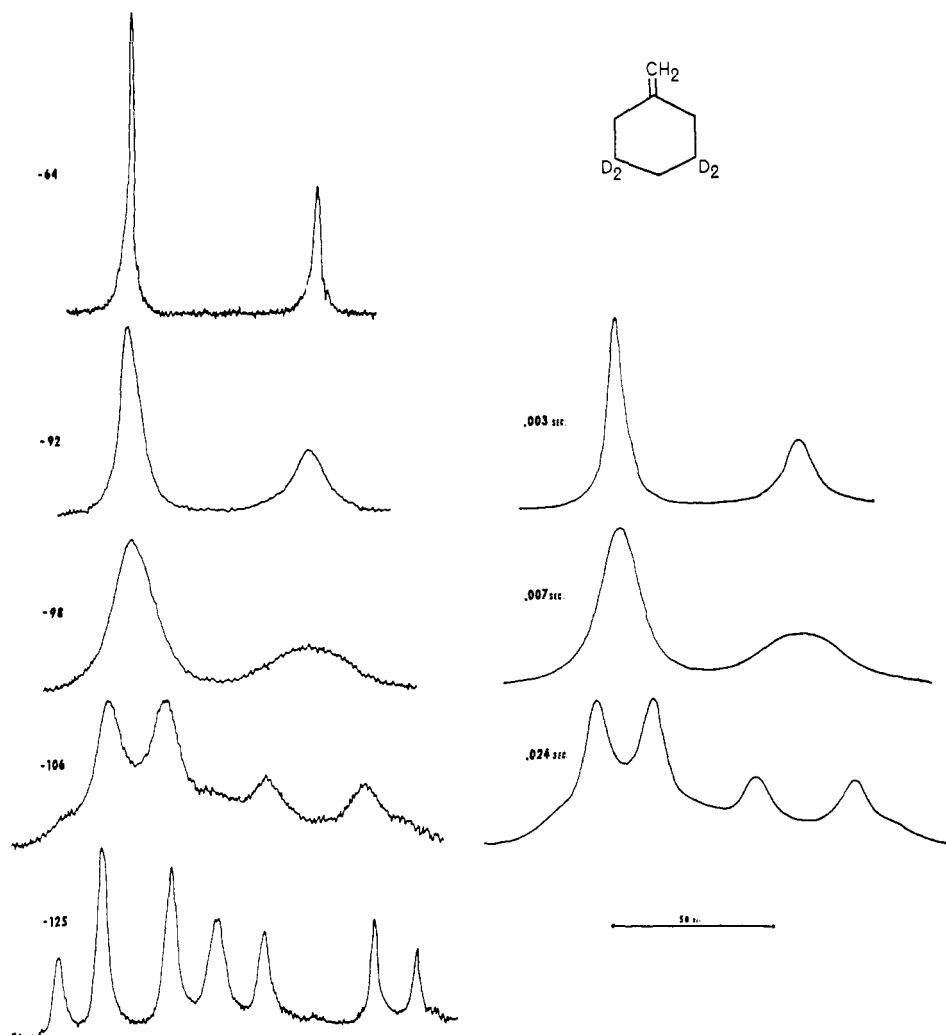


Figure 3. The alkyl portion of the pmr spectrum of 6 as a function of sample temperature. The solvent was Freon-11 (CFCl_3). Spectra were obtained with simultaneous vinyl and deuterium decoupling. An empirical abundance ratio of 2.0:1.2 was used in preparing the composite theoretical spectra.

broad peaks which, upon simultaneous vinyl and deuterium decoupling, sharpen to two singlets with an intensity ratio of 2:1. With continuous vinyl and deuterium decoupling, each peak broadened and then evolved into an AB quartet as the temperature of the sample was lowered. These changes are illustrated in Figure 3 and the chemical shifts and coupling constants obtained by analyses of these quartets are listed in Table I. The average preinversion lifetime, τ , at each of the temperatures studied was estimated by adjusting the input rate parameter of a computer program which produces theoretical spectra as a function of this variable until a good match between experimental and computed spectra was obtained.^{3c,10,11} The program allows one to prepare spectra that are composites of more than one AB quartet¹² and two appropriate quartets were combined in the proper abundance ratio to generate the calculated spectra shown in Figure 3. Good agreement between computed and experimental spectra of 6 could be obtained by using the same τ value for each

component of these composite spectra. It was thus demonstrated that it is the *same* conformational rate process which averages the chemical shifts at the 2, 6, and 4 positions of molecule 6.

The available temperature- τ data are collected in Table II. Assuming that the rate constant for inter-

Table II. Preinversion Lifetimes of 6 at Various Temperatures

| Temp, °C | τ , sec |
|----------|--------------|
| -76.3 | 0.00045 |
| -82.6 | 0.00085 |
| -91.6 | 0.0031 |
| -91.7 | 0.0033 |
| -97.7 | 0.0070 |
| -98.1 | 0.0072 |
| -102.1 | 0.0125 |
| -102.8 | 0.0135 |
| -103.0 | 0.0165 |
| -103.6 | 0.0160 |
| -105.4 | 0.0245 |
| -105.9 | 0.0230 |
| -107.8 | 0.0340 |
| -112.5 | 0.08 |

(10) J. L. Beauchamp, B.S. Thesis, California Institute of Technology, 1964.

(11) S. Alexander, *J. Chem. Phys.*, **37**, 967 (1962).

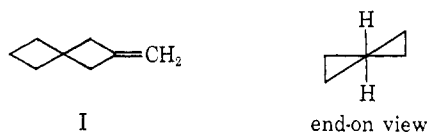
(12) R. Cramer, J. B. Kline, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 2519 (1969).

conversion, k , is the reciprocal of the preinversion lifetime, the rate data for compound 6 are fit by the equa-

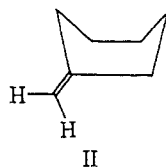
tion $k = 1.97 \pm 0.87 \times 10^{13} \exp(8.95 \pm 0.13/RT)$ from which the Eyring parameters ΔG^\ddagger , ΔH^\ddagger , ΔS^\ddagger were computed to be 8.4 kcal/mol, 8.6 kcal/mol, and 1.4 eu, respectively.

Discussion

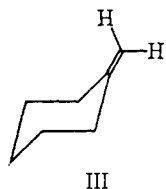
Ground-State Conformation. The relative simplicity of the pmr spectra of 4,4-dideuteriomethylenecyclohexane (5) and 3,3,5,5-tetradeuteriomethylenecyclohexane (6) at low temperatures indicates that the most stable conformation of methylenecyclohexane (1) has a mirror plane or a twofold (C_2) symmetry axis passing through the 1 and 4 carbon atoms of the ring. If this were not the case, one would expect to find at least two distinct ABCD patterns in the spectrum of 5 and three AB quartets in the low-temperature spectrum of 6. Similarly, the fact that distinct chemical shifts are observed for the two protons at position 4 of derivative 6 rules out a twist boat with C_2 symmetry (structure I) as the ground-state conformation of this molecule. The chemical-shift equivalence of the vinyl protons apparently persists even when the conformational rate process



is slow, so that boat conformations such as II, in which these nuclei are in nonequivalent environments, can also be tentatively excluded.¹³ The most likely ground-state conformation of methylenecyclohexane is, therefore, a



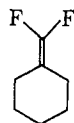
chair form, III, since this conformation is compatible



with the symmetry and chemical shift considerations discussed above.

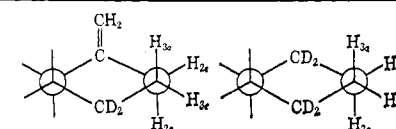
The coupling constant data reported in Table I support the notion that the chair is the dominant conformational form of methylenecyclohexane. For comparison, the analogous coupling constants in cyclohexane are reproduced in Table III. Cyclohexane clearly

(13) This is not a very strong argument since the chemical-shift difference in question could be small. To shed some light on this question the fluorinated derivative shown below was prepared and the fluorine-19



spectrum at 94.1 MHz was determined. At -102° , the fluorine signal is a sharp singlet (proton decoupling); a fluorine chemical-shift difference would likely be detectable under these conditions if appreciable amounts of the conformation analogous to II were present (J. T. Gerig and C. E. Ortiz, unpublished results).

Table III. Comparison of the Proton Magnetic Resonance Parameters of 4,4-Dideuteriomethylenecyclohexane and 1,1,4,4,5,5,6,6-Octadeuteriocyclohexane^{a, b}



| | | |
|------------------------|-------|--------|
| $\delta_{2a,2e}$, ppm | 0.277 | 0.479 |
| $\delta_{3a,3e}$, ppm | 0.518 | 0.479 |
| $\delta_{4a,4e}$, ppm | 0.45 | 0.479 |
| $J_{2a,3a}$, Hz | 13.5 | 13.12 |
| $J_{2a,3e}$, Hz | 4.72 | 3.65 |
| $J_{2e,3a}$, Hz | 3.90 | 3.65 |
| $J_{2e,3e}$, Hz | 2.59 | 2.96 |
| J_2^{gem} , Hz | -13.3 | -13.05 |
| J_3^{gem} , Hz | -13.1 | -13.05 |

^a The numbering of the positions in the cyclohexane derivative is arbitrarily done in this fashion so that the same numbers can be used for both compounds. ^b Data from Table I and ref 8. The solvent for the cyclohexane determination was carbon disulfide. The different solvents used in the present work should be noted.

has a chair ground state¹⁴ and the rather close similarity of the spin-coupling parameters of 4 and 1 strongly suggests that the latter also has the chair conformation. The similarity of the axial-equatorial proton chemical-shift differences at the 3, 4, and 5 carbon atoms of methylenecyclohexane to corresponding chemical-shift differences in cyclohexane also supports this assignment. Finally, we should note that a recent microwave study of cyclohexanone, another six-membered carbocycle with one sp^2 -hybridized carbon atom in the ring, establishes that this latter molecule has a chair conformational ground state.¹⁵

The small changes in the $2e,3a$ and $2e,3e$ coupling constants in methylenecyclohexane relative to cyclohexane are consistent with a small rotation about the intervening carbon-carbon bond such as would obtain if a slight flattening of the chair conformation were to occur. (If the empirical function describing the coupling constants in cyclohexane is used,^{8,16} the extent of rotation is estimated to be $\sim 1.5^\circ$.) However, the difference in the $2a,3e$ coupling constant (~ 1.1 Hz) seems to be too large to be explained strictly on the basis of simple variation in dihedral angles and one must look to other factors to rationalize this observation.

Although the dependence of vicinal coupling constants on stereochemical features of molecules other than the dihedral angle relationship is not well established experimentally, it is reasonable to expect that changes in (a) the geminal H-C-H angles,^{17a} (b) the H-C-C angles,^{17a,b} (c) the carbon-carbon and carbon-hydrogen bond lengths,^{17a,18} (d) the electronegativity of adjacent groups,¹⁹ (e) the presence of nearby unsaturated groups, and (f) the solvent^{20,21} can affect the

(14) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, pp 3-36.

(15) Y. Ohnishi and K. Kozima, *Bull. Chem. Soc. Jap.*, **41**, 1323 (1968).

(16) A. A. Bothner-By, *Advan. Magnetic Resonance*, **1**, 201 (1965).

(17) (a) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); (b) H. S. Gutowsky and A. L. Porte, *J. Chem. Phys.*, **35**, 839 (1961).

(18) J. C. Schug, P. E. McMahon, and H. S. Gutowsky, *ibid.*, **33**, 843 (1960).

(19) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1964).

(20) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron Suppl.*, **7**, 355 (1966).

(21) S. L. Smith and R. H. Cox, *J. Chem. Phys.*, **45**, 2848 (1966).

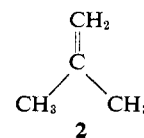
magnitude of this spin-coupling interaction. Factors *c*, *d*, and *f* can be safely neglected for the present discussion,^{20, 22} although their combined effects could be as large as the minor differences in $J_{2e,3a}$ and $J_{2e,3e}$. The geminal couplings at positions 3, 4, and 5 are very similar to each other and to the value found in cyclohexane. Geminal coupling constants are dependent upon H-C-H bond angle²³ and we, therefore, conclude that these bond angles are not extraordinary in each of these cases. The geminal coupling constants at carbons 2 and 6 of **1** are slightly larger than those observed in cyclohexane but this difference is to be expected in light of the known effects of adjacent unsaturation on this interaction.²⁴ It seems likely that some subtle changes in the H-C-C angles within the -CH₂CH₂- fragment of **5** are responsible for the abnormally large $2a,3e$ coupling constant observed. Minor geometrical reorganization in methylenecyclohexane, relative to cyclohexane, would be expected since nonbonded interactions with the double-bonded function at carbon 1 will be different in number and type when compared to the methylene (CH₂) group at the same position in cyclohexane. The nature of this reorganization and how it would be represented by the vicinal coupling constants are not clear at the present.

Lambert has suggested a technique for qualitative determination of ring geometry in six-membered rings under conditions of rapid ring inversion.²⁵ A ratio of coupling constants, *R*, was defined as J_{trans}/J_{cis} where $J_{trans} = 0.5(J_{aa} + J_{ee})$ and $J_{cis} = 0.5(J_{ae} + J_{ea})$ for a -CH₂CH₂- fragment of the ring system. (Under conditions of rapid inversion only the time-averaged values, J_{trans} and J_{cis} , can be extracted from the pmr spectrum.) Changes in the ratio, *R*, were presumed to reflect changes in dihedral angles brought about by rotation around the central carbon-carbon bond of this moiety and thereby report changes in the ring conformation. The value of *R* for methylenecyclohexane computed from the fast-exchange, room-temperature spectrum (1.83) agrees well with that calculated from the low-temperature, slow-exchange data (1.87) when experimental errors are considered and, by Lambert's proposal, we would conclude that methylenecyclohexane exists as a distorted chair.^{25, 26} However, this low value for *R* is due largely to an increase in *one* coupling constant and not the result of a synchronized change in all four of the coupling constants used to define *R*. While it seems quite reasonable that methylenecyclohexane exists in a somewhat flattened chair conformation this observation suggests that Lambert's criterion should be applied cautiously in the diagnosis of molecular conformations.

Kinetics of Conformational Interconversion. The use of computer-generated theoretical spectra to obtain the rate constants for ring inversion in methylenecyclohexane followed conventional procedures.^{3c, 27} Below the

coalescence temperature the computed and experimental spectra were matched with particular reference to peak separation, peak shapes, and the relative intensities of signals. Somewhat less reliance was placed on matching peak widths since the part of these widths due to cross-ring coupling effects will be expected to change slightly with the exchange rate.

The entropy of activation, ΔS^\ddagger , for the ring inversion in methylenecyclohexane is, within experimental reliability, very close to zero and also close to the value of ΔS^\ddagger for chair-to-chair interconversion in cyclohexane.³ The difference in rate observed between cyclohexane and **1** is, thus, entirely enthalpic in origin. It is instructive to note that the energy barrier to methyl group rotation in propane (**3**) is 3.3–3.6 kcal/mol,²⁸ while the corresponding barrier in isobutylene (**2**) is about 2.2 kcal/mol.²⁹ In light of these data and the conclusion that



methylenecyclohexane and cyclohexane have very similar ring structures in their ground state, the fact that the barrier to inversion in methylenecyclohexane is lower than the barrier in cyclohexane carries the implication that torsion about the 1–2 and 1–6 bonds in the former molecule is appreciably involved in reaching the transition state for interconversion. That is, the “flip” of the olefinic part of **1** is involved in the rate-determining step of the transformation. This suggestion is further supported by the observation that the difference in the energy barriers for methylenecyclohexane and cyclohexane (~2.0 kcal/mol) is about twice the difference in the barriers to methyl rotation in **2** and **3** (2×1.1 kcal/mol). The reasons for the diminution of the rotational barriers in the olefins are not clear,³⁰ but may be related to the reduction in hydrogen-hydrogen nonbonded interactions that occur when a methylene (CH₂) group is replaced by a double bond system ($>C=CH_2$).

Experimental Section

Proton magnetic resonance spectra of synthetic intermediates were recorded on Varian A-60 and Jeolco C-60H spectrometers. Variable temperature studies of deuterated methylenecyclohexanes (10% by volume in solvent with 5% tetramethylsilane present to supply an internal lock signal) were performed on a Varian HA-100 spectrometer operated at 100 MHz with a 250-sec sweep rate at 100- and 250-Hz sweep widths. It was equipped with a Nuclear Magnetic Resonance Specialties HD-60 spin decoupler for deuterium decoupling at 15.4 MHz. Sample temperatures were controlled by passing a stream of precooled nitrogen through the sample cavity. Cavity temperatures were monitored during runs with a copper-Constantan thermocouple that was placed just below the sample tube. Sample temperatures were estimated from cavity temperatures by calibrating the latter *vs.* temperatures in a sample tube containing CBr₂F₂ and another thermocouple. This calibration is probably reproducible to within 1°. Thermocouples were

(22) W. Moffitt, R. B. Woodward, A. Moscovitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(23) J. R. Dyer, “Applications of Absorption Spectroscopy of Organic Compounds,” Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 116.

(24) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1901 (1963).

(25) J. B. Lambert, *ibid.*, **89**, 1836 (1967).

(26) J. B. Lambert, R. E. Carhart, and P. W. R. Corfield, *ibid.*, **91**, 3567 (1969).

(27) S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *ibid.*, **89**, 88 (1967).

(28) (a) Reference 14, p 9; (b) L. H. Scharpen and V. W. Laurie, Abstracts, Symposium on Molecular Structure and Spectroscopy, The Ohio State University, Columbus, Ohio, June 14–18, 1965, S9.

(29) V. W. Laurie, *J. Chem. Phys.*, **34**, 1516 (1961).

(30) It may also be noted here that the barrier to ring inversion in methylenecyclobutane (0.46 kcal/mol³¹) is lower than the barrier in cyclobutane (1.28 kcal/mol³²).

(31) L. H. Scharpen and V. W. Laurie, *J. Chem. Phys.*, **49**, 3041 (1968).

(32) T. Ueda and T. Shimanouchi, *ibid.*, **49**, 470 (1968).

connected to a United Systems Model 564 Digitec digital thermometer and calibrated at the temperatures of ice-water, Dry Ice-acetone, and liquid nitrogen.

Cavity temperatures generally varied by only 0.1° during recording of a spectrum, and the maximum variation was 0.4°. Sample temperatures were estimated by the calibration procedure to vary by no more than the variation in cavity temperature during a recording and are considered accurate to better than 2°. Theoretical spectra were generated with IBM 360-50, -65, and -75 computers. Average preinversion lifetimes (τ) are probably accurate to at least 10% except at both extremes of the temperature range studied, where an error as large as a factor of 2 may be present.

Mass spectra were taken by Mr. T. L. Stanfield on an Associated Electrical Industries MS 902 spectrometer. Melting and boiling points are uncorrected.

Methylenecyclohexane (Aldrich, bp 102–103°) was used without further purification. Glpc analysis showed that only a minor amount of a second component was present.

The method of synthesis of derivatives **5** and **6** was essentially that used by Lambert for the preparation of 4,4-dideuteriocyclohexanone.²⁵

Malonic-*d*₂ Acid. Malonic acid (Matheson Coleman and Bell, mp 134–136°, 0.800 mol) was twice treated with 200 g (10.0 mol) of deuterium oxide (Stohler Isotope Chemicals, 99.8 atom % D) at 35° for 1 hr. After each treatment, the solvent was removed at 40° under vacuum until constant weight of solid residue was reached. This gave a 99.4% yield of white crystals, mp 127–129° (lit.³³ mp 127–128°). The product was shown to have 96–97% D incorporated at the methylene group by pmr spectroscopy.

1,3-Propanediol-2,2-*d*₂ was prepared by the combined methods of Lambert²⁵ and Steinhardt.³⁴ Lithium aluminum hydride (1.5 mol, Metal Hydrides, >95% purity) in 0.5 l. of anhydrous ether under a nitrogen atmosphere was mechanically stirred for 10 min. Malonic-*d*₂ acid (0.75 mol) in 1.5 l. of anhydrous ether was added dropwise over 2.5 hr, and the mixture was heated to reflux without stirring for 39 hr and then stirred without heating for 0.5 to break up the precipitate. Water was added dropwise with stirring over 1 hr, then 57 ml of 15% aqueous sodium hydroxide solution was added over 1 hr, and 171 ml of water was added over 2 hr. The mixture was filtered under reduced pressure, and the granular yellow precipitate was washed twice with 500 ml of ether. The solids were then washed 4 times with 600-ml portions of boiling tetrahydrofuran. The ether and THF solutions were combined. Removal of the organic solvent from this mixture afforded a 50% yield of the desired product as an orange oil. The 2 position contained 92–94% deuterium as adjudged by pmr spectroscopy.

1,3-Dibromopropane-2,2-*d*₂ was prepared in 72% yield from the diol by a method used by Lambert for preparation of 1,5-dibromopentane-2,2,4,4-*d*₄.³⁵

Glutaronitrile-3,3-*d*₂ and glutaric-3,3-*d*₂ acid were prepared in 93 and 87% yields, respectively, from the dibromopropane by known procedures.^{25, 36}

Glutaric-2,2,4,4-*d*₄ acid was synthesized in 75% yield by the method of Atkinson, *et al.*³⁷ This material contained 98% D in the 2 and 4 positions according to pmr spectroscopy.

1,5-Pentanediol-3,3-*d*₂ and -2,2,4,4-*d*₄ were prepared by adaptations of methods of Bloomfield and Lee,³⁸ Lambert,²⁵ and Steinhardt.³⁴ Lithium aluminum hydride (0.12 mol, 33% excess) in 100 ml of tetrahydrofuran under a nitrogen atmosphere was mechanically stirred for 10 min. Glutaric-2,2,4,4-*d*₄ acid (0.060 mol) in 50 ml of tetrahydrofuran was added dropwise over 1 hr and the mixture was stirred at reflux for 1 hr. Reflux was continued without stirring for 68 hr. Water (4.6 ml, 1 ml per g of hydride used) was added dropwise with stirring over 0.5 hr, then 4.6 ml of 15% aqueous sodium hydroxide solution was added over 0.5 hr, and 9.2 ml of water was added over 0.5 hr. After standing for 2 hr, the mixture was filtered under reduced pressure. The white precipitate was washed well with tetrahydrofuran and extracted three times with 50-ml portions of boiling tetrahydrofuran. Removal of solvent from the combined filtrates gave a 65% yield of pale yellow oil.

1,5-Dibromopentane-3,3-*d*₂ and -2,2,4,4-*d*₄ were prepared in 88 and 75% yields, respectively, from the diols by a published procedure.³⁵

Cyclohexanone-4,4-*d*₂ and -3,3,5,5-*d*₄ were prepared from the pentane dibromides in 29 and 27% yields, respectively, by the method of Lambert and Keske.³⁵

Methyltriphenylphosphonium iodide, mp 181–185°, was prepared in 99% yield by a procedure reported for preparation of the tri-deuteriomethyl derivative.³⁹

Methylenecyclohexane-4,4-*d*₂ and -3,3,5,5-*d*₄ were synthesized by minor modifications of a previously reported method.³⁹ Pure samples of the methylenecyclohexanes were isolated by glpc at 77° on a 0.25 in. × 15 ft column of 15% Apiezon M on 60–80 Chromosorb W. The two deuterated derivatives were characterized by their pmr spectra.

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