Molecular Geometry. VIII. Proton Magnetic Resonance Studies of Cycloheptane Conformations[1,2]

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Abstract: The seven possible dimethylcycloheptanes and partially deuterated derivatives were stereospecifically synthesized and their proton magnetic resonance spectra examined at 220 MHz. The results are interpreted as consistent with conformational prediction, the molecules pseudorotating rapidly among twist-chair forms and conformations with the methyl groups in equatorial or isoclinal environments being most stable. Bond anisotropy calculations afford predicted chemical shifts for ring protons which correlate well with observation. Similarly, coupling constants predicted from the model by the Karplus relationship are consistent with those observed. The few anomalies observed occur in the vicinal (1,2) isomers and are attributed to methyl–methyl interactions. Except for the cis-1,2 isomer none of the spectra exhibited much temperature dependence, as expected from the low barriers in pseudorotation. The temperature dependence of the cis-1,2 isomer is consistent with the presence of substantial amounts of conformations of higher energy at ambient temperatures.

Having developed a general outline of the conformational behavior of cycloheptane derivatives from calculations of molecular mechanics,[4] we were led to test this by proton magnetic resonance (pmr) studies at 100 and 220 MHz. As the calculations had been performed for hydrocarbons only, we chose for study the seven possible dimethylcycloheptanes, hoping that the pmr spectra would give significant information. These compounds and partially deuterated derivatives were synthesized by rigorously stereospecific routes which precluded the presence of other isomers in a sample of any one.[5]

Conformational Environments in Cycloheptane. Quite apart from calculated predictions, certain features of cycloheptane and its dimethyl derivatives are implicit in their structures. Cycloheptane has only four possible symmetrical forms: two with C_s symmetry, the chair (C) and boat (B) forms; and two with C_2 symmetry, the twist-chair (TC) and twist-boat (TB) forms. Because of the relatively low symmetry of these forms, the number of conformational environments (and hence of proton chemical shifts) is greater than in the familiar case of chair cyclohexane. For the C_s forms there are eight distinguishable environments, four axial and four equatorial. For the C_2 forms, the two substituents on the axis carbon are equivalent and their conformation is called isoclinal;[1b] hence there are seven distinguishable environments—three axial, three equatorial, and one isoclinal. The stability of the symmetrical forms of cycloheptane is calculated to be TC (most stable) > C > TB > B.[1b] The conformational environments for the two enantiomers of the TC form are indicated in Figure 1. The isoclinal environments are labeled 1 and 1′, respectively. The axial and equatorial environments in each enantiomer are then numbered in clockwise sequence around the ring, 2a, 2e, 3a, 3e, . . ., 7a, 7a, and 2′a, 2′e, . . ., 7′a, 7′e, respectively, for the two enantiomers.[6]

Because of the many conformational environments, each structural isomer of dimethylcycloheptane consists in principle of many conformational isomers. Without some theory to predict relative energies and hence relative populations of the conformational environments, the interpretation of the pmr spectra would be a hopeless task. In the following we shall assume that the previously calculated relative energies[1] are substantially correct, and attempt to interpret the pmr spectra accordingly.

Predictions for the Dimethylcycloheptanes. According to the previous calculations for the symmetrical forms of cycloheptane, if the relative energy ΔE_0 of the TC form is taken as zero, then $\Delta E_0 = 1.4$ kcal for C, 2.4 kcal for TB, and 2.7 kcal for B.[1a]

Two modes of interconversion are described for these symmetrical forms: *symmetrical modes* interconvert C and B, or TC and TB, without loss of C_s or C_2 symmetry (respectively) in the transition; *pseudorotation modes* equilibrate C with TC and B with TB, passing through a regular continuum of asymmetrical conformers.[1c] This occurs by a smooth, concerted set of single bond rotations that causes a rotation of the symmetry element (plane or axis) around the ring and an alternation of symmetry type (C_s and C_2), as depicted in Figure 2. This pseudorotation thus has the effect of allowing any substituent to pass through all possible conformational environments of the C and TC forms. According to the calculations for cycloheptane,[1c] the TC conformations are energy minima, the C conformations are energy maxima, and the activation energy for TC $\rightleftharpoons$ C pseudorotation is 1.4 kcal. A similar pseudorotation itinerary traverses all possible conformational environments of the B and TB forms. According to the calculations, the activation energy for this pseudorotation is 0.3 kcal, the B conformations being energy

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[1] Previous papers: (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7036 (1967); (b) *ibid.*, **89**, 7043 (1967); (c) *ibid.*, **89**, 7047 (1967).

[2] Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also wish to acknowledge the assistance of Dr. William D. Phillips (Dupont Central Research Laboratory, Wilmington, Del.) in providing the initial 220-MHz nmr spectra.

[3] National Institutes of Health Predoctoral Fellow, 1969–1970.

[4] Reference 1 and previous papers cited therein.

[5] J. B. Hendrickson and R. K. Boeckman, Jr., *J. Org. Chem.*, **36**, 2315 (1971).

[6] The convention adopted for numbering the conformational environments in Figure 1 differs from that used in ref 1b and c for cycloheptane and methylcycloheptane but is more convenient for discussing pseudorotation of the dimethylcycloheptanes. The relationship to the previous notation is as follows: 5 = 4, 6 = 3, 7 = 2.

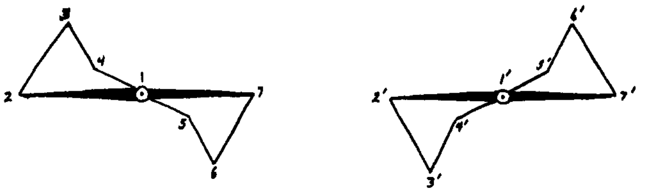

Figure 1. Conformational environments for the two enantiomers of twist-chair cycloheptane.

maxima and the TB forms energy minima. These itineraries are interconnected by symmetrical mode transitions, C $\rightleftharpoons$ B or TC $\rightleftharpoons$ TB. The latter is calculated to be the more facile, with an activation energy of 8.1 kcal. The full map of these linked cyclic itineraries is illustrated in Figure 6, ref 1c. Two substituents may be conveniently followed through pseudorotation together when it is appreciated that if pseudorotation causes one to move clockwise on the (C $\rightleftharpoons$ TC) itinerary, the other will also move clockwise if it is cis, but counterclockwise if it is trans.

Before discussing the predicted effects of methyl substituents we wish to introduce a useful simplifying assumption. To interpret the pmr spectra we use the energy calculations[1b] to predict (i) the most stable conformations, and (ii) the speeds of interconversion. Since the contribution of any conformer to the pmr spectrum is proportional to its concentration, conformations of relatively high energy may be neglected. We shall (somewhat arbitrarily) neglect any conformation whose energy is more than 2.0 kcal/mol above that of the most stable conformer. This approximation enables us to neglect the B and TB conformers. Regarding the speeds of interconversion, the calculations predict that TC $\rightleftharpoons$ C pseudorotation is the path of lowest activation energy and encompasses all C and TC conformational environments. *In considering energy barriers to interconversion we therefore need to consider TC* $\rightleftharpoons$ *C pseudorotation only.*

The introduction of a methyl group into C or TC cycloheptane has been calculated to introduce additional strain energy (E_{Me}) ranging from 0.3–4.4 kcal/mol, depending on the conformational environment. Details are given in Table I of ref 1b. In the TC conformation, methyl substituents are essentially strain free in equatorial environments ($E_{\mathrm{Me}} \approx$ 0.3–0.4 kcal/mol) and crowded in axial environments (E_{Me} = 1.8–3.3 kcal/mol). The important and unexpected prediction was also made that the isoclinal positions are strain free, *i.e.*, energetically equivalent to equatorial, for methyl substituents. The relative energy of the most stable TB conformation for methylcycloheptane (relative to that of the most stable TC conformation) is 2.4 kcal/mol, the same as without the methyl substituent. In TC $\rightleftharpoons$ C pseudorotation the C conformations are energy maxima, and the activation energies are lower than those for the change from TC to TB.

In predicting the preferred conformations for the dimethylcycloheptanes, we assume that the strain energies of the two methyl groups are approximately additive. In eq 1, ΔE_0 denotes the relative energy of

$$\Delta E = \Delta E_0 + E_{\mathrm{Me1}} + E_{\mathrm{Me2}} \qquad (1)$$

the given form (TC, C, TB, B) of cycloheptane, and the strain-energy terms E_{Me1} and E_{Me2} are equated to E_{Me} in methylcycloheptane. On this basis we predict that (i) the most stable ring conformation is TC; (ii) all seven dimethylcycloheptanes can take up unstrained TC conformations, with the two methyl groups equatorial and/or isoclinal; (iii) TC $\rightleftharpoons$ C pseudorotation continues to be the path of lowest activation energy for interconverting the TC and C conformations.

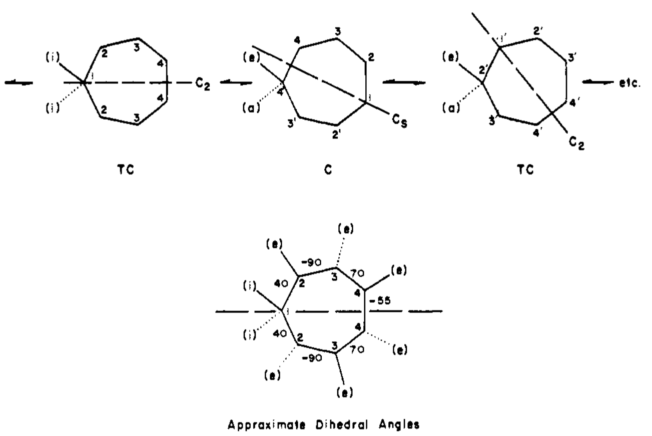

Figure 2. Pseudorotation of cycloheptane chair forms and predicted geometry of the twist-chair conformation.

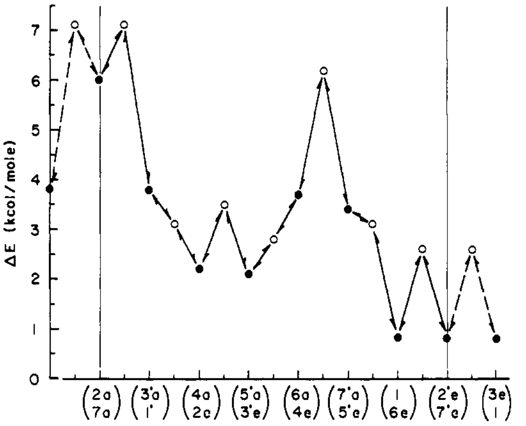

Figure 3. Predicted energy levels and pseudorotation itinerary for one enantiomer of *trans*-1,3-dimethylcycloheptane. (Abscissa shows conformational environments of the two methyl substituents: solid circles = TC; open circles = C).

Using eq 1 it is possible to plot an energy profile for the complete TC $\rightleftharpoons$ C pseudorotation itinerary of each dimethyl isomer. An example (for one enantiomer of *trans*-1,3-dimethylcycloheptane) is shown in Figure 3. In this case there are three low-energy TC conformations in which both methyl groups are equatorial and/or isoclinal. Next (in order of increasing ΔE) are four TC conformations in which one of the methyl groups is axial ($\delta\Delta E \approx$ 1.3 kcal/mol) and four C conformations in which the methyl groups are relatively strain free ($\delta\Delta E \approx$ 1.9 kcal/mol). All other conformations are more than 2.0 kcal/mol above the level of the lowest-energy conformations and their populations will be regarded as negligible. The most stable TB conformations lie 2.3 kcal/mol above the most stable TC forms. The predicted activation energy for complete TC $\rightleftharpoons$ C pseudorotation is equal to the difference between the highest and the lowest energy levels in Figure 3, or 6.3 kcal/mol. The molecular geometries envisaged in this pseudorotation are depicted in Figure 4.

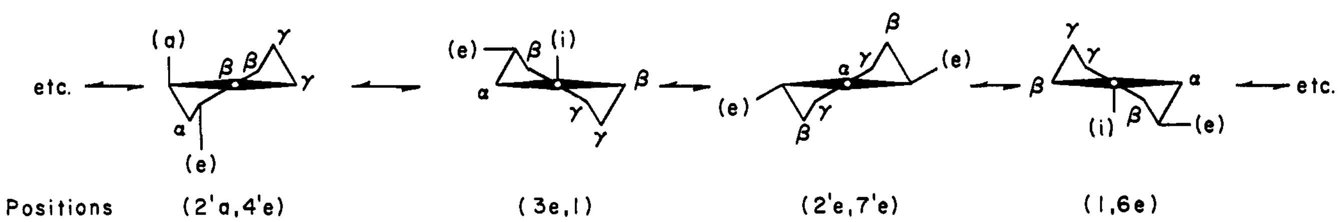

Figure 4. Partial pseudorotation of *trans*-1,3-dimethylcycloheptane.

Table I. Conformational Predictions for Dimethylcycloheptanes

Structural isomer	Conformational environment of CH_3 groups: Lowest energy TC	Next-higher energy[a]	$\delta\Delta E$, kcal/mol	E_{act},[b] kcal/mol
1,1	(1,1)	(4a,4e)(5a,5e)	1.2	5.3
Cis-1,2	(1,2e)(7e,1)	(3e,4a)(4e,5a) (4a,5e)(5a,6e)	1.2	5.6
Trans-1,2	(1,2e)(2e,3e) (3e,4e)(4e,5e) (5e,6e)(6e,7e)(7e,1)	Lowest C conformations	1.4	6.4
Cis-1,3	(1,3e)(2e,4e) (3e,5e)(4e,6e) (5e7e)(6e,1)	Lowest C conformations	1.5	6.7
Trans-1,3	(1,3e)(6e,1) (7e,2e)	(2e,4a)(3e,5a) (4a,6e)(5a,7e)	1.3	6.3
Cis-1,4	(1,4e)(5e,1) (7e,3e)(6e,2e)	(2e,5a)(4a,7e) (1,4a)(5a,1)	1.4	9.5 (5.6)[c]
Trans-1,4	(1,4e)(2e,5e) (3e,6e)(4e,7e)(5e,1)	(1,4a)(5a,1) and lowest C conformations	1.6	6.2

[a] TC unless stated otherwise. [b] For the complete cycle of pseudorotation. [c] For interconversion of all TC conformations without surmounting the highest barrier.

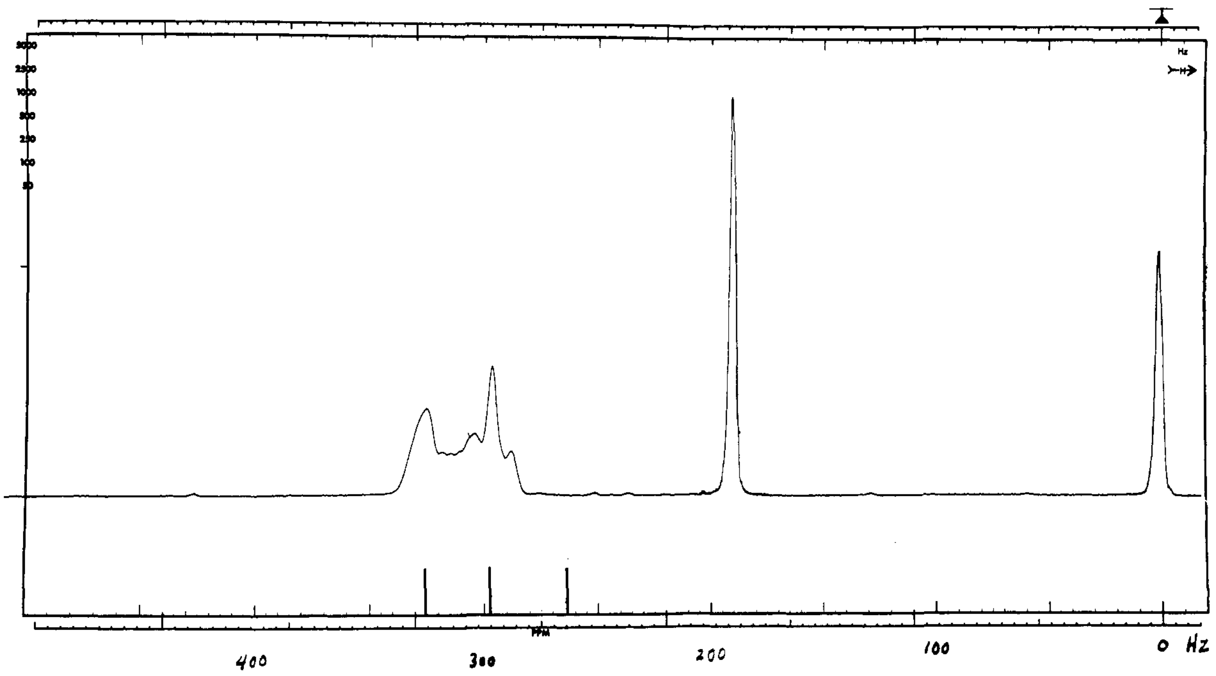

Figure 5. Nmr spectrum of 1,1-dimethylcycloheptane at 220 MHz, 23°

The relevant predictions made on the basis of eq 1 are summarized in Table I. Conformational environments are shown there explicitly only for the TC forms; the environments are those depicted in Figure 1 but no attempt is made to differentiate between mirror-image forms. Since we are studying optically inactive materials, the two TC forms represented by primed and unprimed numbers in Figure 1 are in each case present at equal concentrations. The various conformations labeled "lowest energy TC" are predicted to have nearly equal energies, which differ by not more than 0.3 kcal/mol. Similarly, the various conformations labeled "next higher energy" are predicted to have nearly equal energies (within 0.2 kcal/mol) for each structural isomer. $\delta\Delta E$ is the predicted difference in ΔE between the lowest and next-higher energy conformations.

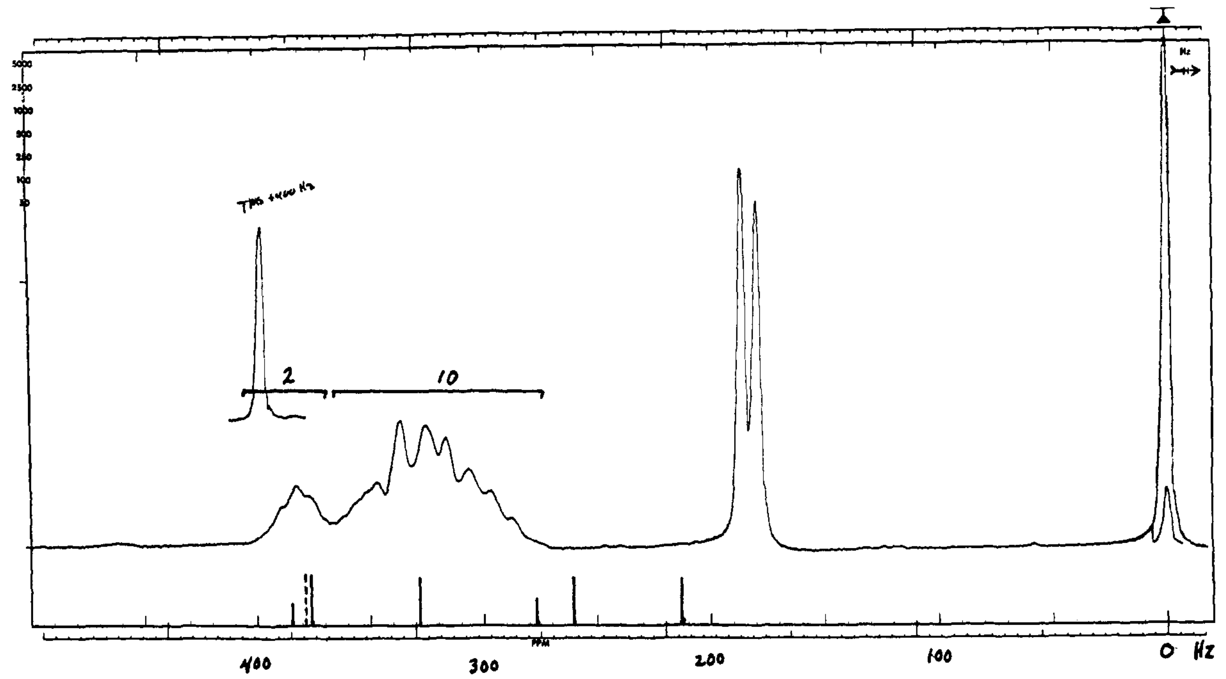

Figure 6. Nmr spectrum of *cis*-1,2-dimethylcycloheptane at 220 MHz, 23°.

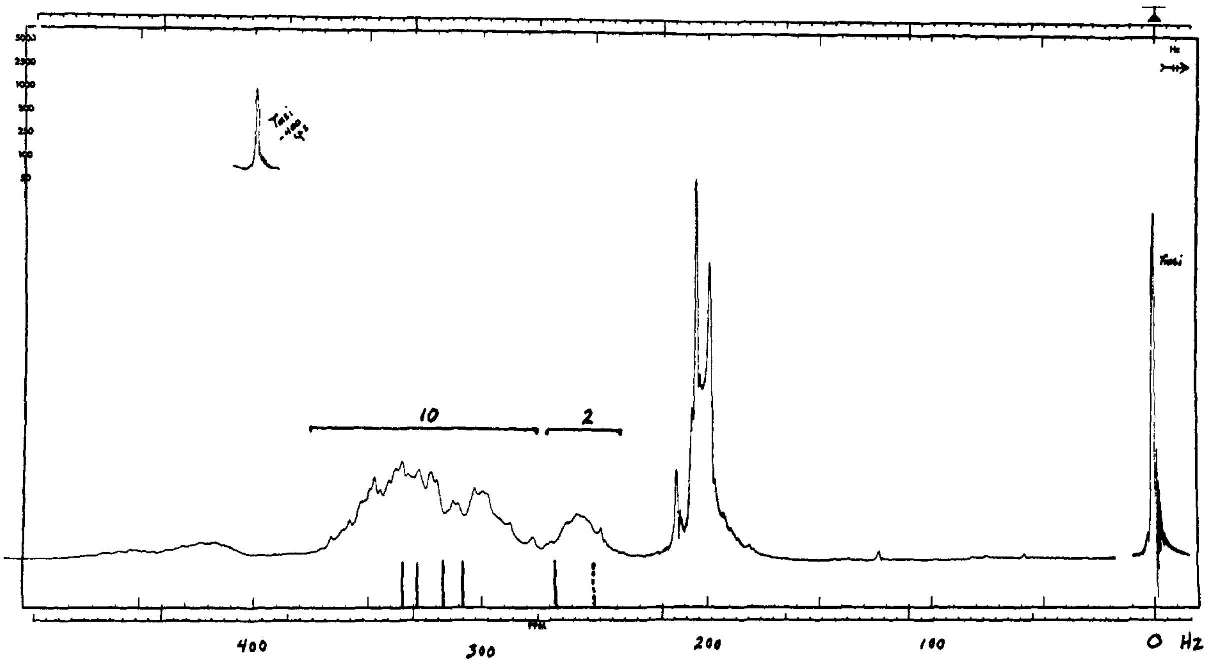

Figure 7. Nmr spectrum of *trans*-1,2-dimethylcycloheptane at 220 MHz, 23°.

A number of predictions about the pmr spectra are possible on the basis of Table I. (a) For each structural isomer, the pmr spectrum will be that of an equilibrium mixture of conformational isomers. (b) For each structural isomer, the activation energy for interconversion of significantly populated conformations will be quite low ($\leq$6.7 kcal/mol). Thus, at the experimental temperatures of 23 and $-47°$ (42 to $-103°$ for cis 1,2), we expect in each case to find a single exchange-averaged nmr spectrum rather than a superposition of separate nmr spectra for discrete conformational isomers. (c) Chemical shifts for the ring protons and spin–spin interactions in the exchange-averaged spectrum will be weighted averages, weighted according to mole fraction, for the given mixture of interconverting conformers. Since the mole-fractional composition of the conformers of a given structural isomer is expected to vary slowly with the temperature, we expect the nmr spectra to be only slightly temperature dependent. (d) The rapid conformational interconversion raises the *effective* symmetry for each structural isomer so that the chemical shifts of the two methyl groups should become identical. On comparing different structural isomers we expect the methyl chemical shifts to be quite similar since the methyl groups in the most stable conformations generally occupy equatorial or isoclinal

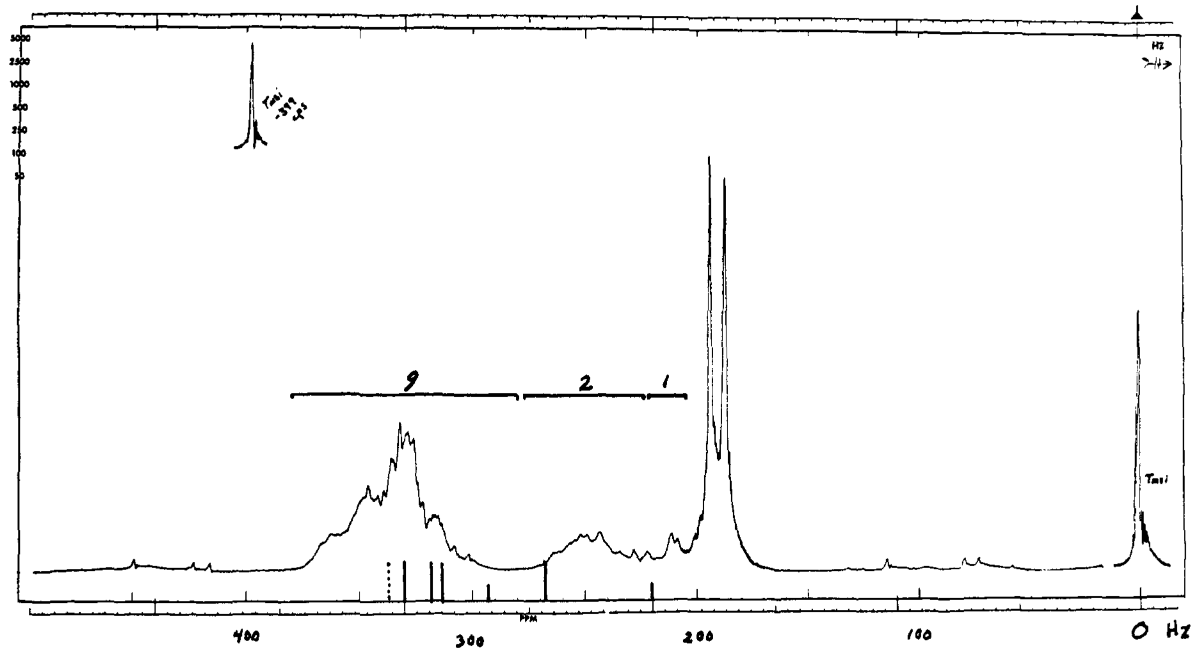

Figure 8. Nmr spectrum of *cis*-1,3-dimethylcycloheptane at 220 MHz, 23°.

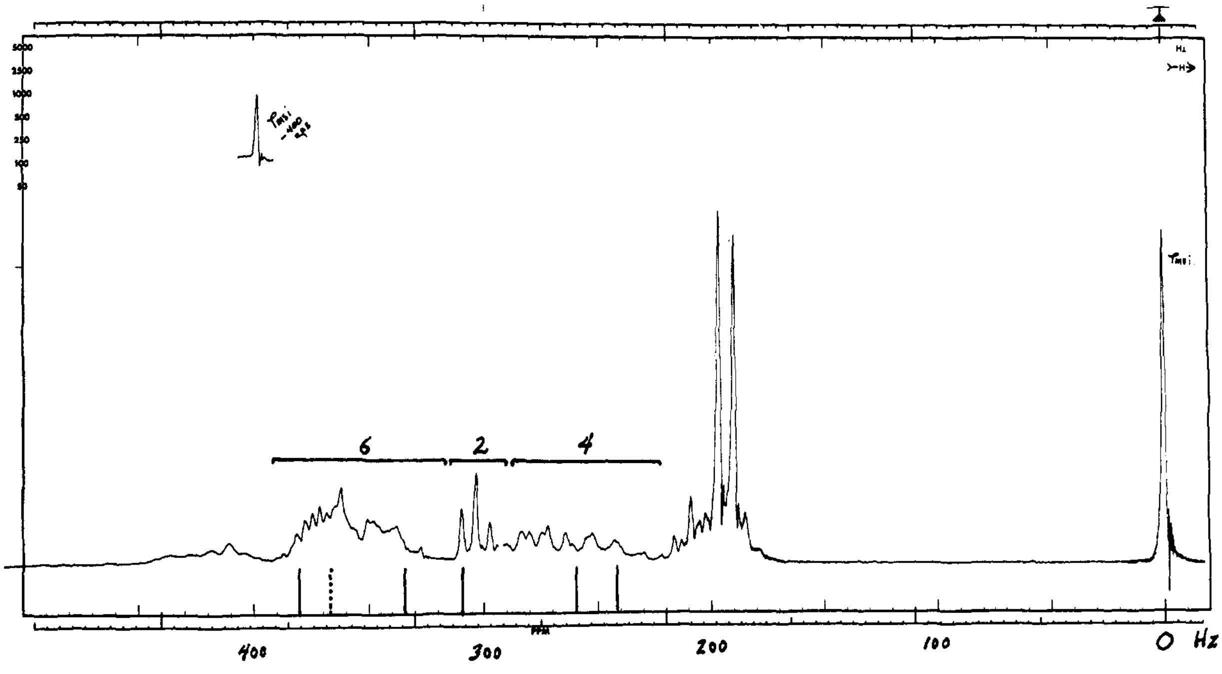

Figure 9. Nmr spectrum of *trans*-1,3-dimethylcycloheptane at 220 MHz, 23°.

positions of about equal strain, hence of similar nonbonded distances to other atoms. (e) For methylene protons, the chemical shifts in a given conformational isomer may be classified as axial, equatorial, and isoclinal. Although there are differences in conformational environment among the axial (2a, 3a, etc.) and equatorial (2e, 3e, etc.) sites, the axial proton resonances as a group should occur at higher magnetic field than the equatorial ones, as in cyclohexane.[17] In pseudorotation just among the lowest-energy TC forms in Table I, most protons retain their axial or equatorial integrity and so their spectra should reflect a spread of axial and equatorial chemical shifts. In the 1,1 isomer, however, pseudorotation between the two lowest-energy enantiomers [(1,1) ⇀ (1′,1′)] exchanges axial and equatorial protons at each position so that the spectrum should be much less spread in chemical shift, reflecting the average differences among methylene positions α, β, and γ.

Previous evidence on the conformations of cycloheptane derivatives is meager. Groth's X-ray studies of the dimeric peroxide of cycloheptane[7] verify the twist-chair ring with gem disubstitution as predicted at the axis carbon, and the details of geometry accord well with the calculated values.[1] Thermodynamic properties of dimethylcyclopheptanes were recorded by Mann,[8] who showed equal enthalpies for all isomers

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(7) P. Groth, *Acta Chem. Scand.*, **18**, 1801 (1964).

(8) G. Mann, M. Mühlstädt, R. Müller, E. Kesn, and W. Hadeball, *Tetrahedron*, **24**, 6491 (1968).

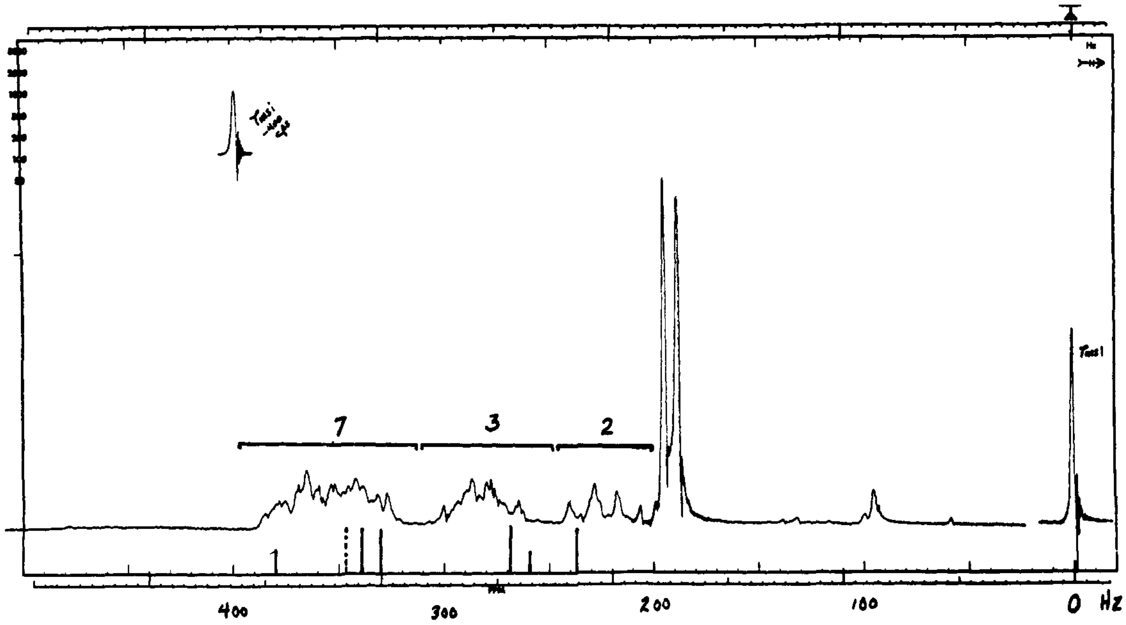

Figure 10. Nmr spectrum of *cis*-1,4-dimethylcycloheptane at 220 MHz, 23°.

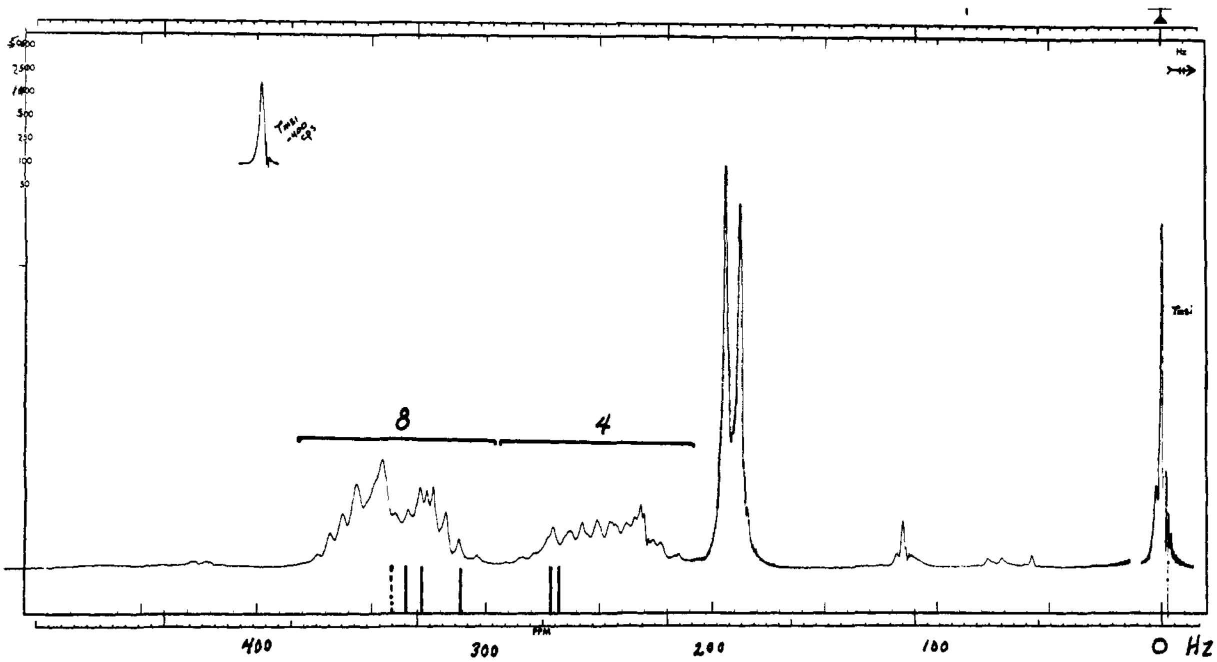

Figure 11. Nmr spectrum of *trans*-1,4-dimethylcycloheptane at 220 MHz, 23°.

except trans-1,2 and cis-1,2 which were 0.7 and 1.4 kcal higher, respectively. This implies vicinal methyl–methyl interactions for those two (not allowed for in eq 1), and a twist-chair 1,1 isomer with no axial methyls.[9] Roberts' studies on *gem*-difluorocycloheptane[10] also point to isoclinal occupancy of the two fluorine atoms and of the methyls in 1,1-dimethyl-4,4-difluorocycloheptane.

Method and Results

Spectra were recorded on a 220-MHz spectrometer equipped with variable-temperature accessory (Model H RSC-IX, Varian Assoc., Palo Alto, Calif.). The temperature was determined (to ± 1°) from the separation of the resonances of a methanol sample. Each substance was examined at 23 and −47°. Chemical shifts were measured relative to internal tetramethylsilane (TMS) by the side-band technique, using an electronic counter (Model 3734A, Hewlett-Packard Corp., Palo Alto, Calif.) which was also employed in spin decoupling experiments.

The pmr spectra of the seven dimethylcycloheptanes are shown as Figures 5–11. Several features of these

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(9) Mann's syntheses, especially of the 1,4 isomers, were not stereospecific, but relied on separations of the hydrocarbons. No evidence was offered that the samples were not cis–trans mixtures and in our experience the properties of the cis and trans isomers are very similar and the compounds exceedingly difficult to separate.[5]

(10) J. D. Roberts, C. Ganter, and R. Knorr, *Angew. Chem., Int. Ed. Engl.*, 6, 556 (1967).

Table II. Chemical Shifts of Methyl Resonances in the Dimethylcycloheptanes

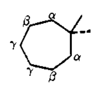
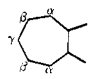
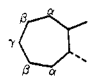
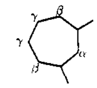
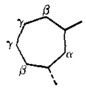
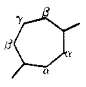
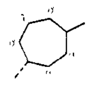
Isomer	Temperature, °C	
	23	−47
1,1	192.0	191.5
Cis-1,2	194.1	179.4
Trans-1,2	203.0	202.6
Cis-1,3	192.0	191.3
Trans-1,3	194.3	192.8
Cis-1,4	192.5	192.5
Trans-1,4	192.5	193.0

Splittings: 1,1 isomer, sharp singlet
all others, doublets
with J = 6.5 ± 0.25 Hz

Chemical shifts in Hz ±0.5, measured at 220 MHz

spectra deserve comment. In general they present in each case a sharp methyl resonance and a complex methylene and methine resonance. The sharpness of the methyl resonance indicates that the chemical shifts of the two methyl groups are equivalent owing to rapid interconversion of conformations, as expected. For the 1,1 isomer the methyl resonance is a singlet; for the other isomers it is a doublet with normal coupling to the methine protons (J = 6.50 ± 0.25 Hz at both 100 MHz and 220 MHz). The chemical shifts of the methyls at two temperatures are shown in Table II. They are much the same for most isomers and show virtually no temperature dependence (except for cis-1,2). This evidence implies very similar environments for the isoclinal and the several equatorial positions that the

Table III. Chemical Shifts of Ring Protons in Dimethylcycloheptanes

Isomer	Position	$\sigma \times 10^6$[a]	δ calcd[b]	δ obsd[b,c]
1,1 	β	0.1231	263	
	α	0.0237	298	
	γ	−0.0552	326	
cis-1,2 	α_{ax}	0.2696	212	289
	β_{ax}	0.1287	261	
	γ_{ax}	0.0794	278	
	α_{eq}	−0.0320	317	321
	β_{eq}	−0.1918	374	
	γ_{eq}	−0.2238	384	
	M[d]	−0.4362	460	376
	M[e]	−0.0732	332	
trans-1,2 	α_{ax}	0.1119	267	288
	β_{ax}	−0.0060	308	
	γ	−0.0321	318	
	β_{eq}	−0.0611	328	
	α_{eq}	−0.0704	331	333
	M[d]	−0.1968	375	
	M[e]	0.1599	250	250
cis-1,3 	α_{ax}	0.2436	221	206
	β_{ax}	0.1128	267	
	α_{eq}	0.0379	293	325
	γ_{eq}	−0.0161	312	
	γ_{ax}	−0.0320	318	
	β_{eq}	−0.0670	330	
	M[d]	−0.2778	404	337
	M[e]	0.0839	277	
trans-1,3 	β_{ax}	0.1866	241	
	γ_{ax}	0.1343	259	
	α	−0.0069	309	301
	β_{eq}	−0.0777	334	
	γ_{eq}	−0.2076	379	
	M[d]	−0.2351	389	366
	M[e]	0.1113	267	
cis-1,4 	β_{ax}	0.1932	238	223[f]
	γ_{ax}	0.1473	255	
	α_{ax}	0.1116	267	
	α_{eq}	−0.0624	328	
	β_{eq}	−0.0933	339	
	γ_{eq}	−0.1999	377	
	M[d]	−0.2318	388	
	M[e]	+0.1312	260	
Trans-1,4 	β_{ax}	0.1114	267	
	α_{ax}	0.0940	273	
	γ	−0.0058	308	
	β_{eq}	−0.0630	328	
	α_{eq}	−0.0820	335	
	M[d]	−0.2712	402	
	M[e]	+0.0879	275	

[a] Shielding constant averaged for all lowest-energy conformers equally weighted. [b] Chemical shift in Hz at 220 MHz. [c] From octadeuterated compounds. [d] Methine protons: calculation less valid, as discussed in text; value includes the term for the C–CH_3 bond anisotropy. [e] Same as d, but excluding the term for the C–CH_3 bond anisotropy. [f] High-field quartet in Figure 10.

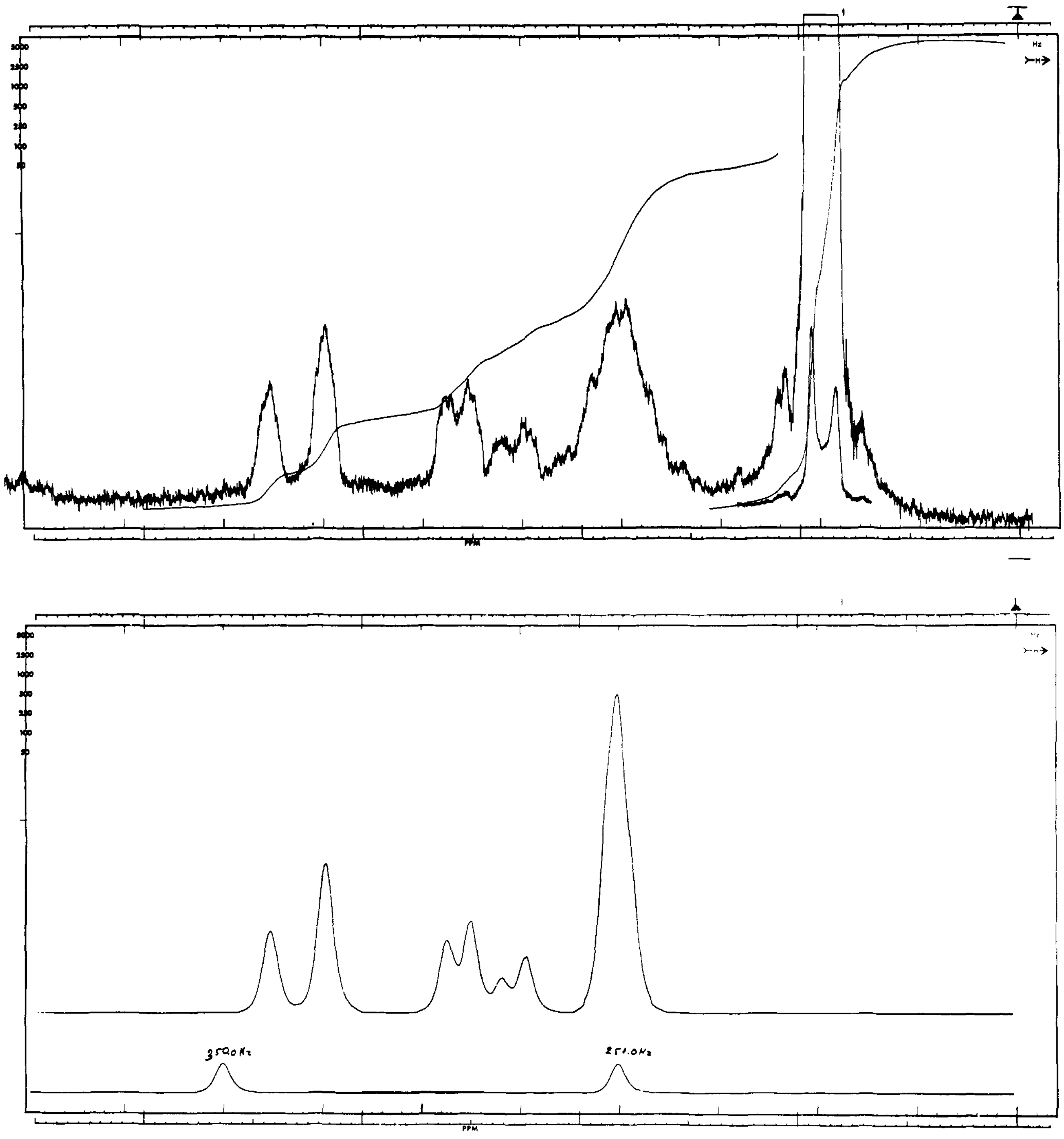


Figure 12. Experimental (upper) and simulated (lower) nmr spectrum of octadeuterio-*trans*-1,2-dimethylcycloheptane-4,4,5,5,6,6,7,7-d_8 at 220 MHz, 23°.

methyls are presumed to occupy in the most stable conformations.

The methylene and methine resonances are resolved in some cases into two or three bands of different intensities, but with no clear axial–equatorial distinction and few discernible splitting patterns. The 1,1 isomer shows a much more compressed spread of ring protons than the other isomers, as predicted above. The trans-1,3 isomer shows a triplet in the center of the spectrum. This may be assigned to the two protons at C-2 whose chemical shifts are equivalent (because the trans-1,3 methyl groups are equivalent owing to rapid conformational exchange) and which are coupled to two equivalent methine protons. The cis-1,4 isomer shows an approximate quartet just downfield from the methyl resonance, which may be assigned to the two equivalent axial protons at C-5 and C-7, as we shall show later.

As expected, there are some differences in the pmr spectra at 23 and −47°. However, for all but the cis-1,2 isomer the temperature dependence was small.[11]

Deuterated Compounds. Because of the complexity of the spectra in Figures 5–11, octadeuterio compounds

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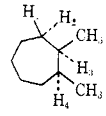
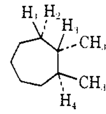
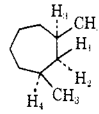
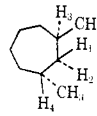
(11) The low-temperature spectra are not shown; methyl resonances are tabulated in Table II. The cis-1,2 isomer, which shows significant variation, is discussed below.

Table IV. Observed and Calculated Magnitudes of Coupling Constants for Octadeuteriodimethylcycloheptanes

Isomer	Coupling constant[a,b]	Obsd, Hz	Twist-chair Calcd, Hz a	Twist-chair Calcd, Hz b	Chair Calcd, Hz a	Chair Calcd, Hz b
Cis-1,2 	$J_{1,2}(\alpha_{ax} - \alpha_{eq})$	−14.4				
	$J_{1,3}(\alpha_{ax} - M)$	8.8	11.1	7.3	13.0	9.0
	$J_{2,3}(\alpha_{eq} - M)$	3.1	4.7	2.1	3.4	0.9
Trans-1,2 	$J_{1,2}(\alpha_{ax} - \alpha_{eq})$	−14.1				
	$J_{1,3}(\alpha_{ax} - M)$	6.2	10.6	7.0	11.4	7.6
	$J_{2,3}(\alpha_{eq} - M)$	0.8	4.0	1.6	4.2	1.6
Cis-1,3 	$J_{1,2}(\alpha_{ax} - \alpha_{eq})$	−13.8				
	$J_{2,3}(\alpha_{ax} - M)$	11.0	12.0	8.1	12.6	8.6
	$J_{2,3}(\alpha_{eq} - M)$	2.6	3.6	1.0	2.9	0.4
Trans-1,3 	$J_{1,2} = J_{2,4}(\alpha_{ax} - M)$	6.25	8.2	4.9	9.1	5.6
	$J_{2,3} = J_{1,4}(\alpha_{eq} - M)$	6.25	5.4	2.8	7.0	4.3

[a] Parameters for equation of the form $J = A + B \cos \phi + C \cos 2\phi^{23}$: (a) $A = 7.0$, $B = -1.0$, $C = 5.0$ (commonly used for cyclic compounds); (b) $A = 4.0$, $B = -0.5$, $C = 4.5$. [b] See Table III for identification of α protons. M = methine proton.

were synthesized by the same routes,[5] as described in the Experimental Section, for *cis*-1,2-, *trans*-1,2-, *cis*-1,3-, and *trans*-1,3-dimethylcycloheptane. In each case the eight deuterium atoms were introduced precisely at ring positions C-4, C-5, C-6, and C-7.

Before describing the 220-MHz nmr spectra of these compounds, it is helpful to introduce a simpler notation which allows for the averaging of chemical shifts owing to rapid conformational exchange. As shown in Table III, the methylene protons in each isomer are labeled α, β, or γ, depending on their ring position relative to that of the methyl groups. The methine protons are labeled M. When the two methylene protons on a given carbon atom are nonequivalent, we shall call them "axial" and "equatorial" (*e.g.*, β_{ax} or γ_{eq}), such that the chemical shift of the "axial" proton is upfield from that of its geminal "equatorial" proton. According to this notation, each of the octadeuterio molecules has two methine protons (M) and two geminal α protons.

The 220-MHz nmr spectra were simple enough to be analyzed by rigorous methods. The spectra were simulated using the LAOCOON program[12] on a Varian computer interfaced with the spectrometer.[13] The simulation was limited to the four ring protons with the methyls treated as deuterated owing to the incapability of the system to simulate all ten protons of the real octadeuterio isomers. With this exception, the final values produced simulated spectra which agreed well, both in intensity and line shape, with the experimental spectra. An example is illustrated in the observed and simulated spectra of the deuterated trans-1,2 isomer in Figure 12, and the chemical shift and coupling constant data so derived are collected in Tables III and IV, respectively. The assignments made in these tables are reasonably secure. For the trans-1,3 isomer the two equivalent α protons have the same chemical shift as that of the characteristic triplet in Figure 9. For the other isomers, the two nonequivalent α protons interact with typical geminal coupling constants of *ca.* −14 Hz.

Analysis of Chemical Shifts. We now wish to show that the observed chemical shifts are consistent with the predicted molecular geometry and conformational mixing. To do this, we shall apply the McConnell bond anisotropy treatment[14] to the predicted conformers to derive their expected chemical shifts. In this calculation, the shielding constant σ for a proton in a given conformational environment is obtained by eq 2 as the sum

$$\sigma = \Sigma(3 \cos^2 \theta_i - 1)(\chi_L - \chi_T)/3r_i^3 \qquad (2)$$

of contributions from all the C–C bonds in the molecule. In this equation, $(\chi_L - \chi_T)$ denotes the anisotropy of the C–C bond, r_i the distance from the proton to the midpoint of the ith C–C bond, and θ_i the acute angle that distance vector makes with that bond. Bothner-By's value[15] for $(\chi_L - \chi_T) = -5.5 \times 10^{-30}$ was used, with angles and distances developed from ring-angle values for twist-chair cycloheptane.[1b,16]

On applying this treatment to cyclohexane, Jackman was able to fit the axial–equatorial chemical shift

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(12) A modification of the program devised by A. A. Bothner-By.

(13) We wish to acknowledge use of the spectrometer facilities of Dr. Dan Urry, University of Alabama Medical Center, Birmingham, Ala.

(14) H. M. McConnell, *J. Chem. Phys.*, 27, 226 (1957).

(15) A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, 70, 833 (1958).

(16) C–H bond anisotropies were considered to make negligible contributions. The C–C bonds directly adjacent to the proton whose chemical shift is being calculated were also left out of the summation because they make an identical contribution to each ring-proton chemical shift and do not satisfy the "long range" assumption on which the treatment is based. On the other hand, our saturated hydrocarbons are good cases in that they are free of hybridization and electrostatic effects.

difference with good accuracy.[17] On applying it to various cyclopropyl hydrocarbons, Boikess and Brauman obtained semiquantitative agreement with experiment and thus were able to assign chemical shifts to specific protons.[18]

Calculated shielding constants (σ) for the protons of the parent cycloheptane are listed in Table V. This list shows the axial protons in an expected upfield group and the equatorial protons grouped below. The isoclinal protons approximate the equatorial protons with respect to magnetic environment, as they are calculated to do with respect to steric strain as well. Perhaps even more noteworthy is the marked dependence of both axial and equatorial shielding constants on conformational environment. It is largely because of this property that the measured chemical shifts can provide a significant test of our conformational model.

Table V. Calculated Shielding Constants for Cycloheptane Protons

Conformational environment	$\sigma \times 10^6$	Conformational environment	$\sigma \times 10^6$
1 (isoclinal)	−0.1057		
2e, 7e	−0.1062	2a, 7a	0.0544
3e, 6e	−0.1473	3a, 6a	0.3187
4e, 5e	−0.1785	4a, 5a	0.1025

The treatment was applied to each of the lowest-energy conformers (Table I) of each dimethylcycloheptane and the results were averaged to yield a list of predicted shielding constants for the protons of each isomer. In predicting the exchange-averaged shielding constants, these conformers were weighted equally in the averaging process as it was felt that the small differences ($\leq$0.2 kcal/mol) in their calculated energies would be irrelevant within the accuracy of the treatment. Because the temperature dependence of the nmr spectra was slight (except for the cis-1,2 isomer), it was felt also that conformers other than the lowest-energy conformers could be omitted from the average.

Results of the calculations are listed in Table III. The shielding constants show a high degree of specificity, both with respect to structural isomer and site of the proton. Part of this effect can be traced to our conformational model, according to which some protons retain their axial or equatorial integrity in the conformational mixing while others do not. For instance, all protons in the 1,1 isomer exchange axial and equatorial environments in pseudorotation, as do γ protons in the trans-1,2 and trans-1,4 isomers, and α protons in the trans-1,3 isomer. This may be confirmed for the trans-1,3 isomer by examination of Figure 4; considering only the three conformations of lowest energy, in the left-most conformer the two α protons (between the methyls) are in environments 2a and 2e. Pseudorotation carries them to equivalent isoclinal environments in the central conformer, and then on to reversal of axial and equatorial environments in the right-hand conformer, thus making them equivalent in the pseudorotational average.

In view of the high specificity of the calculated shielding constants for the methylene protons, their correlation with observed chemical shifts is quite satisfactory. A least-squares fit afforded the linear eq 3.[19] Values of δ calculated from eq 3 are included in

$$\delta\,(\text{Hz}) = 306 - 351(\sigma \times 10^6) \qquad (3)$$

Table III. The values not only fit the established chemical shifts, but also show a reasonable qualitative fit with the observed spectra for the undeuterated compounds, as shown by the vertical lines in Figures 5–11. Although the experimental spectra in these figures are complicated by spin–spin interaction, it is clear that the calculated chemical shifts reproduce the observed divisions of the spectra into more or less distinct bands, the relative intensities of the methylene resonances in the bands, and the frequency ranges.

On the other hand, for the methine protons the calculations do not reproduce the observations well. In the previously described calculations for the methylene protons, the two adjacent C–C bond contributions were omitted, as in previous treatments.[14,16–18] For the methine protons there is a third such adjacent (C–CH_3) bond. In our initial calculations (upper values for M in Table III) we included this C–CH_3 bond contribution and obtained chemical shifts at relatively low fields, as expected for the more substituted site. However, the experimental methine chemical shifts listed in Table III turned out to be surprisingly high, especially for the trans-1,2 isomer, for which in fact no clear rationale appears. Subsequent recalculations *excluding* the contribution from the C–CH_3 bond (lower values for M in Table III) gave results in somewhat better agreement with experiment, which now erred on the high-field side, rather than the low as before. In comparing observed spectra and calculated chemical shifts in Figures 5–11, the observed methine chemical shifts from the octadeuterated compound are shown as dotted lines while those for the (nondeuterated) 1,4 isomers are merely averages from the two modes of calculation.

Analysis of Spin-Coupling Constants. According to the theory of Karplus,[20] the spin–spin interaction of vicinal protons is given approximately by the relation, $J = A + B\cos\varphi + C\cos 2\varphi$, where φ is the inter-proton dihedral angle.[20–23] The various expected interproton dihedral angles (HCCH) for twist-chair (or chair) cycloheptanes may be computed from the calculated ring dihedral angles (CCCC) in ref 1a through the projection down the bond. The normal projection angle of 120° for a tetrahedral atom must be modified for these rings which have CCC bond angles (θ_{CCC}) of about 115 instead of 109.5°. The relevant geometry for dihedral angle relations is summarized in Figure 13.

The several spin-coupling constants of interest in each isomer (calculated *via* the Karplus equation) must

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[17] L. M. Jackman, "Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 117; see also 2nd ed, with S. Sternhell, 1969, especially p 239.

[18] C. D. Poulter, R. S. Boikess, J. I. Brauman, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2291 (1972).

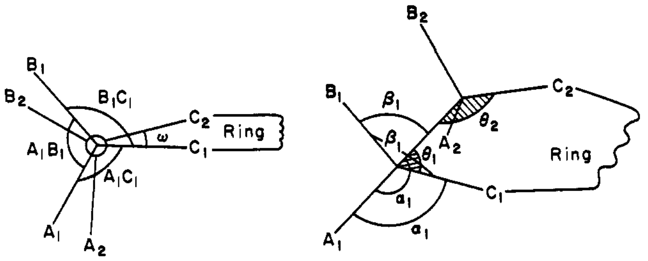
[19] The correlation coefficient is 0.89 and the standard error of fit is ±14 Hz. Only methylene protons were included in the correlation, and the cis-1,2 values were omitted because their relatively high temperature dependence indicated that conformations other than those of the lowest energy are important.

[20] M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

[21] N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 49–61.

[22] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

[23] A. A. Bothner-By, *Advan. Magn. Resonance*, 1, 195 (1965).



——Projection Angles——

$$\cos A_nC_n = \frac{\cos \alpha_n}{\sin \alpha_n}\left(\frac{1 - \cos \theta_n}{\sin \theta_n}\right)$$

$$\cos B_nC_n = \frac{\cos \beta_n}{\sin \beta_n}\left(\frac{1 - \cos \theta_n}{\sin \theta_n}\right)$$

——Bond Angles——

Ring bond angles = θ_n
Substituted bond angles
(to ring bonds) = α_n, β_n
for substituents A_n and B_n,
respectively

——Dihedral Angles (ϕ)——

cis ($A_1 - A_2$) = $\omega + A_1C_1 - A_2C_2$
trans ($A_1 - B_2$) = $\omega + A_1C_1 + B_2C_2$
trans ($B_1 - A_2$) = $\omega - B_1C_1 - A_2C_2$
cis ($B_1 - B_2$) = $\omega - B_1C_1 + B_2C_2$

Figure 13. Interrelation of ring and proton dihedral angles.

next be averaged among the several lowest-energy conformations (Table I) among which the isomer rapidly pseudorotates, in order to examine correlations with the observed coupling constants. The agreement with experiment should be at least semiquantitative.

In comparing observed and calculated coupling constants in Table IV, two commonly used sets of A, B, C parameters (one for cyclic and one for acyclic compounds)[23] were applied. In each case the overall coupling constants were calculated for a population of mixed lowest energy twist-chair forms and similarly for a population of the mixed low-energy chair forms with which the former alternate in pseudorotation, to estimate the sensitivity of predicted coupling constants to the conformational model. It turns out that the vicinal inter-proton dihedral angles in the chair conformers are not so different from those in the twist-chair forms with which they pseudorotate, so that large differences in coupling constants are not expected; see Table IV. (In contrast, shielding constants, according to eq 2, depend on the conformation of the entire ring rather than of a single dihedral angle). The calculated coupling constants show only approximate agreement with observation, although the correlation is probably as good as that of other correlations of this kind.[21-23]

As Figures 5-11 demonstrate, the ring protons of the undeuterated compounds show few clearly discernible first-order splitting patterns. One isomer which does, the trans-1,3 isomer, exhibits a spin triplet (Figure 9, *ca.* 300 Hz) owing to interaction of the two α protons with the two methine protons. In theory, the spin-splitting pattern should be more complex, the resonance being half of an AA′XX′ spectrum (as in $H_2C{=}CF_2$). However, the two AX coupling constants (α_{ax} − M and α_{eq} − M) happen to be nearly equal. Although our conformational model does not predict precise equality of these coupling constants, we note in Table IV that the calculated values for trans 1,3 are much closer than those for the other isomers.

Another isomer which shows a simple spin-splitting pattern is the cis-1,4 isomer (Figure 10) which exhibits an approximate quartet of $J \sim 12$ Hz at $\delta = 223$ Hz, assigned to the two β-axial protons (Table III). These protons retain axial positions through all four lowest-energy conformations and are coupled to vicinal axial protons on the methine side and the γ side as well as to the vicinal γ-equatorial proton and the geminal β-equatorial proton. The dihedral angle itinerary through the four conformers is determined and averaged and the expected coupling constants are calculated,[24] as follows.

$$\beta_{ax} - \text{M:}\quad 168° \rightarrow 173° \rightarrow 157° \rightarrow 153° \qquad \text{Av } J = 11.9 \text{ Hz}$$

$$\beta_{ax} - \gamma_{ax}:\quad 173° \rightarrow 168° \rightarrow 173° \rightarrow 157° \qquad \text{Av } J = 12.4 \text{ Hz}$$

$$\beta_{ax} - \gamma_{eq}:\quad 71° \rightarrow 54° \rightarrow 73° \rightarrow 87° \qquad \text{Av } J = 3.0 \text{ Hz}$$

Granting a value of 12–15 Hz for the geminal ($\beta_{ax} - \beta_{eq}$) coupling[25] and a probable value of the third coupling ($\beta_{ax} - \gamma_{eq}$) as nearer zero,[24] this reduces to the observed approximate quartet of $J = 12$ Hz in Figure 10.

***cis*-1,2-Dimethylcycloheptane.** The nmr spectrum of this substance is quite temperature sensitive and was studied in some detail. Chemical shifts and spin-coupling constants were evaluated for the octadeuterio compound at sixteen temperatures between −103 and 42°. The results are listed in Table VI. The effect of temperature is especially marked for the chemical shift δ_1 of the α-axial proton and much smaller for δ_2 of the α-equatorial proton. In the following, we shall analyze the temperature dependence of $\delta_2 - \delta_1$.

According to the energy calculations, *cis*-1,2-dimethylcycloheptane has two lowest energy conformations of equal energy in which one methyl group is isoclinal and the other equatorial, and four conformations of nearly equal energy at a level of 1.2 kcal/mol above the lowest in which one methyl group is equatorial and the other axial (Table I). Conformations of still higher energy begin at levels of 1.9 kcal/mol above the lowest. On this basis it seemed reasonable to interpret the chemical shifts in terms of an equilibrium (A ⇄ B) between these two low-energy groups of conformational subspecies.

Let A denote the population of the lowest energy conformations, let K = [B]/[A,] and let α = [B]/([A] + [B]) = $K/(1 + K)$. Then ($\delta_2 - \delta_1$) is given by eq 4 and K varies with temperature according to eq 5.

$$\delta_2 - \delta_1 = [K(\delta_{2B} - \delta_{1B}) + (\delta_{2A} - \delta_{1A})]/(1 + K) \qquad (4)$$

$$-RT \ln K = \Delta H° - T\Delta S° \qquad (5)$$

Equations 4 and 5 represent $\delta_2 - \delta_1$ in terms of four parameters: $\delta_{2B} - \delta_{1B}$, $\delta_{2A} - \delta_{1A}$, $\Delta H°$, and $\Delta S°$.

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(24) The following set of parameters was used in this calculation: $A = 7.0$, $B = -1.0$, $C = 5.0$.[23] Although these parameters are commonly used for cyclic compounds, it is clear (from the common experience that orthogonal protons show $J \approx 0$) that this equation must be inaccurate in the 90° region as it produces $J = 2.0$ at 90°. We expect, therefore, that the predicted value for $\beta_{ax} \approx \gamma_{eq}$ is somewhat too high and should be nearer the $J \approx 0$ value implied by the observed approximate quartet (Figure 10).

(25) J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1339 (1965).

Table VI. Nmr Results for *cis*-1,2-Dimethylcycloheptane as a Function of Temperature

Temp, °C	Chemical shift, ppm[a] (1) α_{ax}	(2) α_{eq}	(3) M	Spin coupling, Hz J_{12}	J_{13}	J_{23}	$\delta_2 - \delta_1$, ppm
−103	(1.193)	(1.457)	(1.746)	(−14.5)	(8.7)	(4.0)	0.264
−88.1	(1.228)	(1.452)	(1.726)	(−14.5)	(8.7)	(4.0)	0.224
−76.9	(1.233)	(1.449)	(1.723)	(−14.8)	(8.9)	(3.5)	0.216
−67.8	(1.242)	(1.449)	(1.724)	(−14.3)	(8.6)	(3.5)	0.207
−55.8	(1.259)	(1.452)	(1.727)	(−14.6)	(8.9)	(3.5)	0.193
−50	1.266	1.450	1.705	−14.3	8.7	3.1	0.184
−32	1.278	1.458	1.705	−14.3	8.8	3.1	0.180
−24	1.285	1.458	1.712	−14.4	8.8	3.1	0.173
−13	1.298	1.460	1.708	−14.4	8.8	3.1	0.162
−2	1.298	1.453	1.708	−14.6	8.8	3.1	0.155
7	1.307	1.460	1.712	−14.6	8.8	3.1	0.153
23	1.305	1.450	1.702	−14.4	8.5	3.3	0.145
32	1.322	1.459	1.719	−14.4	8.5	3.0	0.137
35.6	(1.330)	(1.475)	(1.753)	(−14.4)	(8.7)	(2.8)	0.145
40.2	(1.332)	(1.475)	(1.753)	(−14.4)	(8.7)	(2.8)	0.143
42	1.329	1.465	1.718	−14.4	8.7	2.8	0.136

[a] Downfield from tetramethylsilane. Values in parentheses measured at 100 MHz, others measured at 220 MHz.

However, the experimental data are not extensive enough to define more than three. In fitting the data, we therefore assumed that $\delta_{2A} - \delta_{1A}$ for the lowest energy conformations is given correctly by the "calculated" chemical shifts listed in Table III. On that basis, $\delta_{2A} - \delta_{1A} = 0.584$ ppm. A least-squares treatment then led to the following values for the other parameters: $\delta_{2B} - \delta_{1B} = 0.061$ ppm; $\Delta H° = 0.92$ kcal/mol, $\Delta S° = 6.4$ gibbs/mol. The standard error of fit is less than 0.004 ppm, as compared with an experimental error in $\delta_2 - \delta_1$ of about 0.005 ppm.

The values obtained for $\delta_{2B} - \delta_{1B}$ and $\Delta H°$ are of a plausible magnitude. For the four "next higher energy" cis-1,2 conformations in Table I, the average predicted chemical shift difference (on the basis of eq 2 and 3) is 0.035 ppm, and the predicted $\delta\Delta E$ is 1.2 kcal/mol. The relatively high value of $\Delta S°$ (which accounts for the relatively high population of the "next higher energy" conformations at room temperature) may be largely the result of an increased freedom of rotation of the vicinal methyl groups.[26] At 25°, $K = 5.3$. We conclude that the data are consistent with the presence of a substantial proportion of "next-higher energy" conformers.

Experimental Section

Exchange Experiments. All deuterium exchange experiments with both six- and seven-membered ring ketones were performed as follows. The ketone was mixed with an equal weight of deuterium oxide (99.5° isotopic purity) in which 0.25–0.50 g of clean sodium metal had been dissolved, and heated at reflux with stirring under a nitrogen atmosphere for 24 hr. The ketone was then isolated by ether extraction. This exchange process was repeated twice more by which time isotopic purities of d_4 or d_6 of $\geq 95\%$ had been achieved (assayed by nmr). The deuterated ketone was finally distilled under reduced pressure before use.

Ring Enlargement Experiments. The basic procedure used has been described in detail previously.[5] In order to assure that no deuterium loss would occur by exchange, ethanol-d_1 and deuterium oxide were used as solvents. The base, potassium hydroxide-d_1 was prepared by hydrolysis of a known amount of potassium *tert*-butoxide (MSA Corp) by deuterium oxide, and removal of the *tert*-butyl alcohol-d_1 under reduced pressure. Excess diazomethane was decomposed by addition of acetic acid-d_1 (from acetic anhydride and deuterium oxide). No attempt was made to hydrolyze the by-product ethyl *p*-toluenesulfonate, but rather the crude mixture was extracted with hexane, the hexane extracts were dried over anhydrous magnesium sulfate, and the residue after concentration on a rotary evaporator was carefully fractionated on a 24 Teflon annular spinning-band column to afford the desired ring enlarged ketone. This material was then subjected to further deuterium exchange as described above.

Reduction Experiments. In all cases, the Clemmensen reduction procedure which has been described previously[5] was used. The following precautions were instituted to prevent loss of deuterium by exchange; the amalgamated mossy zinc was prepared by washing with 0.1 *N* hydrochloric acid (twice) followed by shaking with 10% by weight of mercuric chloride (10% aqueous solution), washing successively with water (3×), acetone (3×), ether (3×), and drying under vacuum. Before use the zinc was washed with an additional 25-g portion of deuterium oxide. A solution of deuterium chloride in deuterium oxide–acetic acid-d_1 was prepared by the cautious hydrolysis of fresh acetyl chloride (weighed amount) with excess deuterium oxide. The work-up was identical with that described previously.[5]

The d_8 cycloheptanes were purified initially by short-path distillation and finally by preparative vpc (20% SE-30 at 135° with 20 psi of helium flow). The four isomers, 3,3,4,4,5,5,6,6-octadeuterio-*cis*-1,2-dimethylcycloheptane, 3,3,4,4,5,5,6,6-octadeuterio-*trans*-1,2-dimethylcycloheptane, 4,4,5,5,6,6,7,7-octadeuterio-*cis*-1,3-dimethylcycloheptane, and 4,4,5,5,6,6,7,7-octadeuterio-*trans*-1,3-dimethylcycloheptane obtained, had chemical purities of $\geq 99\%$ (3% SE-30 at 75°), d_8 isotopic purities of $\geq 95\%$ (nmr), and their physical constants (as well as those of the intermediates) agreed with those published previously for the undeuterated substances.[5] Furthermore all compounds exhibited the characteristic C–D stretching band(s) at 4.50 and 4.72 μ in the infrared spectrum.

Acknowledgment. The authors are indebted to Dr. W. D. Phillips for helpful discussion of the data and for measurement of some of these spectra on the HR-220 nmr spectrometer of the Dupont Co.

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(26) See, for example, K. S. Pitzer and D. W. Scott, *J. Amer. Chem. Soc.*, **65**, 803 (1943); W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 1.