

nearly equal energy all represent energy minima (unlike chair cycloheptane, above) on the complex interconversion profiles discussed in the third paper⁴¹ and so there is no surprise if substitution of fluorine atoms should tip the energy balance toward the S_4 form.⁴⁷

With cyclononane the several C_2 forms of ref 1 were reinvestigated only roughly and the best of them (TCB

(47) The S_4 form was not considered in the previous study¹ since the system devised there for identifying all the possible symmetrical rings was created to locate only planes and axes of symmetry passing through the ring of which the S_4 form (uniquely) has neither.

form in the third paper⁴¹) found to be still about 2.2 kcal/mole less stable than the favored D_3 form listed here; as this parallels the previous situation, there is nothing significant to add to the discussion there. The same is true of other cyclodecane forms: rough calculation of the other plane- and axial-symmetric C_{10} conformers showed none to be preferred over the favored BCB form listed here. The all-chair (CCC) conformation is less favored by 7.5 kcal/mole. A more detailed discussion of these rings is reserved for the last paper in this group.⁴¹

Molecular Geometry. VI. Methyl-Substituted Cycloalkanes¹

James B. Hendrickson²

Contribution from the Edison Chemical Laboratory, Brandeis University, Waltham, Massachusetts 02154. Received June 7, 1967

Abstract: The strain energies of the methylcycloalkanes of six- to ten-membered rings have been computed for all possible substituent positions on each symmetrical conformation. The results provide a basis for conformational analysis of substituted cycloalkanes.

For purposes of conformational analysis of the medium-ring cycloalkanes it is necessary to obtain the strain energies characteristic of substituents on the various possible positions of the several conformations of the cycloalkanes of six to ten members. In the familiar, highly symmetrical chair form of cyclohexane there are only two distinguishable positions for a substituent, *i.e.*, equatorial and axial, implying respectively one substituent lying more or less in the plane of the ring and the other perpendicular to that plane. With less symmetrical rings the situation is made more complex by the fact that since the steric environments at the various ring carbons are different, so will the energies of the pairs of substituent positions on these carbons also differ. Thus in a ring of N carbons and no symmetry elements there will be $2N$ possible substituent positions. Nevertheless, models reveal that at all these atoms the equatorial-axial distinction defined above remains clear enough for this convenient nomenclature to be carried over into rings larger and less symmetrical than the chair cyclohexane. The one exception to this procedure is the necessity of distinguishing the pair of substituents on a ring carbon lying on a twofold axis of symmetry (the axis carbon), which, by virtue of that symmetry, experience identical steric environments; such identical substituent positions, being neither axial nor equatorial, are labeled "isoclinal."³

The functions developed in the preceding paper¹ for saturated hydrocarbons have been used here to evaluate the energies of methyl substituents on each possible position of the symmetrical rings determined

(1) Paper V (preceding paper): J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7036 (1967). The author wishes gratefully to acknowledge financial support by a research grant from the National Institutes of Health as well as the opportunity to use the computation facilities of the Massachusetts Institute of Technology (IBM 7094) and Brandeis University (IBM 1620).

(2) Alfred P. Sloan Foundation Fellow, 1962-1966.

(3) J. B. Hendrickson, *J. Am. Chem. Soc.*, **86**, 4854 (1964).

previously.¹ The procedure taken is identical with that used in an earlier discussion of methylcyclohexanes and cycloheptanes⁴ with the exception that the newer functions were used and all nonbonded interactions (HH, HC, and CC) were included in the analysis. As before, both the CCC angle (ϕ_M) of methyl to ring carbons and the rotation (ω_M) of the methyl relative to a fully staggered orientation were allowed to vary independently in seeking the minimum.⁵ The optimum CCC angle (θ_{\min}) for use in the bond angle bending strain calculation for the methine carbon was taken as the mean of 112° for methylene¹ and 109.5° for $C(CH_3)_4$, or 110.7° , from which is derived the corresponding HCC optimum angle of 108.2° . The full equation for E_θ at the methine carbon was used (eq 1) and values for $K_{CC} = 0.0188$ and $K_{HC} = 0.0129$ kcal/(mole deg²) were derived by breakdown of the over-all $K_\theta = 0.0230$ derived previously for the methylene group¹ ($\psi_M =$ HCC angle at methine carbon).

$$E_{\theta-\text{methine}} = K_{CC}[(\theta - 110.7)^\circ]^2 + 2(\phi_M - 110.7)^\circ] + 3K_{HC}(\psi_M - 108.2)^\circ]^2 \quad (1)$$

This procedure has been applied to substituents on the major cycloalkane conformations with the results tabulated in Table I, the designation of substituents "down" or "up" at a given carbon when the ring is viewed from above being respectively α and β , as in the steroid convention. The relevant views and ring numbers are shown in Chart I.

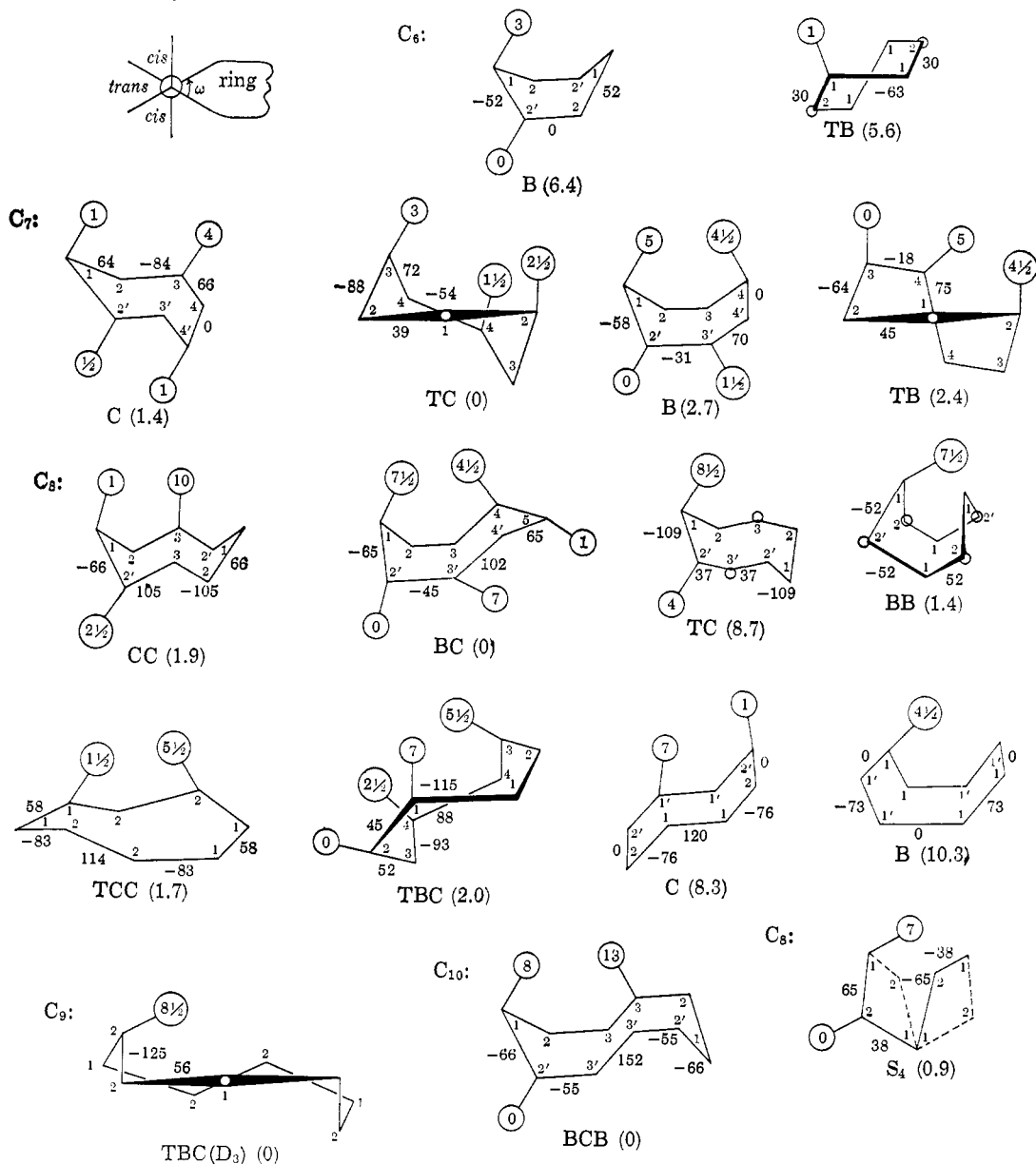
The value for methylcyclohexane in the chair form ($\Delta E = 0.7$) must be compared to an average of empirical values⁶ showing about 1.7 kcal/mole for the

(4) J. B. Hendrickson, *ibid.*, **84**, 3355 (1962).

(5) ϕ_M was varied by 1° increments, ω_M by 20° .

(6) A general discussion of these values is available in E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, John Wiley and Sons, Inc., New York, N. Y., 1965.

Chart I. Conformational Diagrams of Methylcycloalkanes



axial-equatorial methyl difference. In light of the excellent agreement obtained between calculation and experiment for the cycloalkanes with these functions in the preceding paper, this result is somewhat disappointing. Furthermore, it is at first sight surprising since the calculated energy difference between *trans*- and *gauche-n*-butane, which is a traditional model for the strain in axial *vs.* equatorial methylcyclohexane, is quite good at $\Delta E = 0.6$, which would imply a methylcyclohexane energy of twice that or 1.2 kcal/mole. The experimental values for this energy difference (*trans-gauche*) in *n*-butane and other alkanes range from about 0.5 to 0.9 kcal/mole.⁷

The two cases, *n*-butane and methylcyclohexane, are not, however, strictly comparable. In *gauche-n*-butane, some rotation of both dihedral angles ω_1 (terminal

methyl) and ω_2 (central bond) can serve to relieve nonbonded interactions between the two terminal methyl groups at some expense in torsional energy as they depart from 60° . In the optimum case these angles are 63 and 65° , respectively, in the present calculations;¹ the central bond is quoted at 61 – 68° by Bartell, Flory, and Kuchitsu.⁷ With an axial methyl group on cyclohexane rotation of the methyl (comparable to ω_1 for *n*-butane) cannot serve to relieve strain as the methyl is flanked on each side by *gauche* ring methylene hydrogens. However, flattening of the ring from tetrahedral to 112° bond angles reduces the ring dihedral angles to 54° so that the dihedral angle corresponding to ω_2 of *n*-butane is actually 70° (for $\phi_M = 111^\circ$) and the consequent nonbonded strain relief is achieved at no cost in torsional energy since the (ring) dihedral angle is the same in both the axial and equatorial methylcyclohexanes, whose energies are compared by subtraction. While it is therefore true that the axial methyl strain in cyclohexane need not be exactly twice the *gauche-n*-butane strain, it is not obvious on which side it will lie, experiment implying more strain

(7) R. A. Bonham and L. S. Bartell, *J. Am. Chem. Soc.*, **81**, 3491 (1959); L. S. Bartell and D. A. Kohl, *J. Chem. Phys.*, **39**, 3097 (1963); K. Kuchitsu, *J. Chem. Soc. Japan*, **32**, 748 (1959); R. A. Scott and H. A. Scheraga, *ibid.*, **42**, 2209 (1965); A. Abe, R. L. Jernigan, and P. J. Flory, *J. Am. Chem. Soc.*, **88**, 631 (1966). The last paper contains a thorough and recent discussion, as does ref 6.

Table I. Geometry and Energy^a of Methylcycloalkanes

Ring	Substituent position	ϕ_M^b	ω_M^c	E^a	Ring	Substituent position	ϕ_M^b	ω_M^c	E^a	
C ₆ -C	$\alpha(e)$...	0	0.0	C ₆ -BC	$1\alpha(e)$...	0	0.5	
	$\beta(a)$	113	0	0.7		$1\beta(a)$	118	0	8.0	
C ₆ -B	$1\alpha(e)$...	0	0.0		$2\alpha(a)$...	0	0.5	
	$1\beta(a)$	116	0	3.1		$2\beta(e)$...	0	0.5	
	$2\alpha(a)$	112	0	0.3		$3\alpha(a)$	118	80	7.6	
	$2\beta(e)$...	0	0.2		$3\beta(e)$...	0	0.5	
C ₆ -TB	$1\alpha(e)$...	0	0.1		$4\alpha(e)$...	0	0.5	
	$1\beta(a)$	114	0	1.1		$4\beta(a)$	117	100	5.1	
	$2(iso)$...	0	0.2		$5\alpha(a)$	113	0	1.4	
C ₇ -TC	$1(iso)$...	0	0.5	C ₈ -TBC	$5\beta(e)$...	0	0.6	
	$2\alpha(a)$	115	0	3.0		$1\alpha(e)$...	0	0.3	
	$2\beta(e)$...	0	0.4		$1\beta(a)$	118	80	7.2	
	$3\alpha(e)$...	0	0.3		$2\alpha(e)$...	0	0.4	
	$3\beta(a)$	116	0	3.3		$2\beta(a)$...	0	0.5	
	$4\alpha(a)$	114	0	1.8		$3\alpha(a)$	117	0	5.8	
C ₇ -C	$4\beta(e)$...	0	0.4		$3\beta(e)$...	0	0.5	
	$1\alpha(e)$...	0	0.4		$4\alpha(e)$...	0	0.6	
	$1\beta(a)$	113	0	1.6		$4\beta(a)$	115	0	3.0	
	$2\alpha(a)$	113	0	1.0	C ₈ -BB	$1\alpha(e)$...	0	0.6	
	$2\beta(e)$...	0	0.4		$1\beta(a)$	118	60	8.1	
	$3\alpha(e)$...	0	0.5		$2(iso)$...	0	0.6	
	$3\beta(a)$	117	0	4.4	C ₈ -S ₄	$1\alpha(e)$...	0	0.5	
	$4\alpha(a)$	112	0	1.3		$1\beta(a)$	118	80	7.4	
	$4\beta(e)$...	0	0.7		$2\alpha(e)$...	0	0.5	
C ₇ -TB	$1(iso)$...	0	0.4		$2\beta(a)$...	0	0.6	
	$2\alpha(a)$	117	80	5.1	C ₈ -B	$1\alpha(e)$...	0	0.8	
	$2\beta(e)$...	0	0.3		$1\beta(a)$	115	20	5.1	
	$3\alpha(e)$...	0	0.4	C ₈ -TC	$1\alpha(e)$...	0	0.3	
	$3\beta(a)$	112	0	0.5		$1\beta(a)$	120	0	8.8	
		$4\alpha(e)$...	0	0.4		$2\alpha(a)$	116	0	4.6
	$4\beta(a)$	117	80	5.3		$2\beta(e)$...	0	0.4	
C ₇ -B	$1\alpha(e)$...	0	0.3	C ₈ -C	$3(iso)$...	0	0.4	
	$1\beta(a)$	117	0	5.3		$1\alpha(e)$	118	20	7.4	
	$2\alpha(a)$...	0	0.4		$1\beta(a)$...	0	0.4	
	$2\beta(e)$...	0	0.4		$2\alpha(a)$	113	0	1.4	
		$3\alpha(a)$	114	0	2.0		$2\beta(e)$...	0	0.7
		$3\beta(e)$...	0	0.4	C ₉ -D ₃	$1(iso)$...	0	0.4
		$4\alpha(e)$...	0	0.5		$2\alpha(a)$	119	0	8.9
		$4\beta(a)$	116	80	5.1		$2\beta(e)$...	0	0.2
C ₈ -CC	$1\alpha(e)$...	0	0.4	C ₁₀ -BCB	$1\alpha(e)$...	0	0.6	
	$1\beta(a)$	113	0	1.5		$1\beta(a)$	118	0	8.6	
	$2\alpha(a)$	115	0	3.1			$2\alpha(a)$...	0	0.6
	$2\beta(e)$...	0	0.4			$2\beta(e)$...	0	0.5
	$3\alpha(e)$...	0	0.4			$3\alpha(a)$	121	100	13.4
	$3\beta(a)$	120	60	10.2			$3\beta(e)$...	0	0.2
C ₈ -TCC	$1\alpha(e)$...	0	0.4						
	$1\beta(a)$	118	0	6.0						
	$2\alpha(a)$	113	100	2.1						
	$2\beta(e)$...	0	0.5						

^a Energies shown are in excess of strain in the ring itself, given in kcal/mole. ^b CCC angle of methyl to ring only shown if different from normal (110.7°). ^c Angle of rotation of methyl relative to the staggered orientation.⁵

in methylcyclohexane than that in two *gauche-n*-butanes (1.7 vs. 1.4 ± 0.4).

In the present calculations, however, the axial methyl strain is smaller although that of *n*-butane is correct. In the previous calculations,⁴ using only HH interactions and assuming the optimum CCC angles to be tetrahedral, the axial methyl strain was computed at 1.0 kcal/mole. The effect here of changing to the use of all nonbonded interactions adds a net attraction owing to the added HC and CC interactions, most of which are negative, and the ring-flattening effect of assuming an optimum CCC angle of 112° lowers the methyl-methylene repulsion and also lowers the energy difference. These two effects are not fully compensated for by the use of the stiffer van der Waal's function¹ employed here so that the net effect is a lower value for ΔE (0.7 kcal/mole) in methylcyclohexane than previously. The largest part of the error arises from the

bond angle enlargement (and consequent ring flattening) since, in the present procedure, a tetrahedral cyclohexane with its methyl at $\phi_M = 112^\circ$ yields $\Delta E = 1.85$ and with $\phi_M = 114^\circ$, the preferred axial methyl orientation, $\Delta E = 1.25$.

Since the nonbonded distances involved in the axial methylcyclohexane strain are near that part of the van der Waal's curve with zero energy (the crossover from net attraction to net repulsion), only a very severe alteration of the interaction function used in the calculations can duplicate the experimental value of $\Delta E = 1.7$ for axial methyl strain in cyclohexane, and such a function cannot reproduce the angles and energy of our prime criterion, the cyclodecane ring.¹ Despite this impasse the present functions were used here to display the energies of methyl groups at various positions on the different rings since qualitative conclusions may yet be drawn from them with confidence. It is in

fact not likely that the values for rings other than cyclohexane will be as much in error.

Results and Discussion

The results of the calculations shown in Table I afford some useful observations. In the first place it is encouraging to find that the equatorial positions are virtually all less than 0.5 kcal/mole, thus upholding the traditional association of equatorial positions with freedom from strain. The isoclinal positions (labeled "iso" in Table I, as at C-1 in TC- and TB-cycloheptane) uniformly show themselves to be strain free also, energetically equivalent to equatorial sites, while axial positions are all clearly strained (several kcal/mole), with one exception. The axial positions on carbon atoms flanked by bonds of the same dihedral angle sign are also essentially strain free, as at the 2a positions of C₈-BC and C₁₀-BCB. Thus the criterion for a carbon with *both* substituent sites effectively strain free, in these cases as well as isoclinal positions, is one of being bounded by like dihedral angle signs. This situation, which does not occur in cyclohexane, is supported by the X-ray evidence cited in the preceding paper of the cycloalkane dimeric peroxides (compounds I and IV, ref 1) which show cycloheptane *gem*-disubstituted at the isoclinal positions (on the axis carbon) and cyclooctane *gem*-disubstituted at C-2, as predicted by these calculations. In general we may expect any *gem*-disubstituted cycloalkane to take up a conformation with the substituents located on a carbon bounded by bonds of the same dihedral angle sign (*i.e.*, C₇: TC, C-1; C₈: BC, C-2; C₉: TBC (D₃), C-1; C₁₀: BCB, C-2). In cyclohexane this does not occur since the axial methyl strain on the chair ring is only 1.7 kcal/mole, while conversion to a twist-boat ring with two strain-free isoclinal positions would cost 5.5 kcal/mole in ring strain.

Usually the methyl group is found to be in a staggered orientation ($\omega_M = 0$) with respect to the carbon to which it is bound. This is the expected situation as it is free of torsional strain, but in severely crowded positions, the optimum energy is reached by rotation of the methyl, accepting some torsional strain to avoid worse steric repulsion. This is most obvious in the very crowded axial positions of the BB-cyclooctane and occurs in several other axial situations.

The diagrams of Chart I summarize the information needed for conformational analysis. Each conformation is labeled with its name (see following paper) and

its energy relative to the lowest energy conformation of that cycloalkane (parent ring energies from ref 1, Table II). The dihedral angles (Table I, ref 1) are indicated at each bond except where symmetry duplication makes this unnecessary. Rings with only axes of symmetry are viewed down the axis and axis carbons are labeled with a circle. The balloons contain the (rough) energies of methyl groups placed at axial positions, taken as the difference of the axial values in Table I from the average of the equatorial position energies on that ring; equatorial and isoclinal substituents are not shown. The carbon atoms are also numbered to allow reference to the bond angles in ref 1 and discussion in all three papers, primed numbers designating mirror image positions.

The diagrams can be used to assess the most stable conformations of variously substituted rings by determining how many ways the substituents can be placed so as to be all equatorial (or in other strainless positions) on the most stable conformation. Where this is possible it may be expected that such forms, freely equilibrating, will compose the molecular population. If it is necessary to place one or more substituents in axial positions on the most stable ring, then one is obliged to consider the choice of reaching a lower energy conformation by reverting to a less stable ring conformation with, however, less strain energy for the substituent. In short, the lowest sum of ring energy and substituent energy should appoint the preferred conformation(s). The dihedral angles are useful in that they allow the dihedral angles of adjacent substituents to be readily obtained. In the upper left corner of Chart I is a Newman projection of a single ring bonded with a positive dihedral angle (ω); the dihedral angle between *cis* substituents is the same (ω) as that within the ring, while *trans* substituents are at roughly $\omega \pm 115^\circ$ (for a ring with bond angles $\theta = 115\text{--}117^\circ$), the exact angle depending on the bond angles at the substituents. These dihedral angles of the adjacent substituents are important both for assessment of the favorability of the stereoelectronic situation for certain reactions and for ascertaining the required dihedral angle within a second ring at the bond of fusion in saturated polycyclic molecules. These considerations have been applied previously in several complex examples which appear to bear out the general validity of the approach.^{3,4,8,9}

(8) J. B. Hendrickson, *Tetrahedron*, **19**, 1387 (1963).

(9) J. B. Jones, J. M. Zander, and P. Price, *J. Am. Chem. Soc.*, **89**, 94 (1967).