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GEOMETRY OF THE SUBSTITUTED CYCLOHEXANE RING

X-RAY STRUCTURE DETERMINATIONS AND EMPIRICAL VALENCE-FORCE CALCULATIONS

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Abstract—A quantitative description of the conformation of seven substituted cyclohexanes in terms of bond distances, bond angles and torsional angles is given. The geometrical details of the molecules from X-ray structure determinations are compared with those obtained by computer calculations (full relaxation molecular mechanics approach) of the same or of similar systems. Reasonable quantitative agreement is obtained. The effect of an equatorial substituent, Cl or CH_3, on the molecular geometry is relatively minor. The calculations show that the minimum energy conformation of the equatorial t-Bu group is twisted by ±17° away from the perfectly staggered form. The latter constitutes a low barrier (0·27 kcal/mol). An axial Me group causes a slight extra flattening of the ring structure (1°–2°), but exerts a strong influence on the torsional angles between α,β C—H bonds, ϕ_{ee} increasing from 58° to 64°, ϕ_{ea} decreasing from 59° to 50° (relative to cyclohexane).

INTRODUCTION

In 1963 Davis and Hassel[1] concluded from their important electron diffraction study of cyclohexane that the ring must be "slightly flatter" than that based on the classical tetrahedral angle but no torsional angle data were given in their paper. Following this lead, several investigators[2-4] (1964), independently and almost simultaneously, proposed the general concept of the flattened chair (mean bond angle > 109·5°, mean torsional angle < 60°) for cyclohexane and its derivatives,§ oxygen-substituted heterocyclics[2] and others. Altona[2] explored the geometrical consequences of Pauling's equation,[6,7] that relates bond angles to torsional angles in chair-shaped 6-membered rings, and compared the geometry of unsubstituted cyclohexane[1] to available diffraction data on heterocyclic ring systems (mostly substituted 1,4-dioxanes and -dithianes). It could be shown[2] that the much discussed outward tilt of the halogen atoms in axial halogenocyclohexanes[8] (6·3° for C-Cl) is rather a byproduct of the ring flattening and does not require special lines of explanation.

The chemistry of the "non-ideal" cyclohexane ring was first discussed by Wohl.[4] Early computer calculations of energy and geometry of flattened cyclohexanes and cyclohexenes were carried out by Bucourt and Hainaut.[3] These authors used a force-field that yielded perfect agreement between the calculated and the observed (electron-diffraction) torsion angle in cyclohexane (ϕ = 54·5°, correspondong C—C—C bond

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§ The "deformed or flattened" chair models proposed by Allinger and DaRooge[5] (1961) in connection with studies on certain cyclohexanones correspond with what now would be called half-chair and sofa forms.

angle 111·55°). Subsequent X-ray studies of substituted cyclohexanes, steroids and numerous other saturated 6-membered rings as well as chemical evidence and NMR spectroscopy[7b] amply supported the flattening effect which soon gained general recognition.* However, it was found that the A,B,C rings of a series of 5α-steroids showed a slightly greater puckering (55°–56°) than would be expected from the electron diffraction result on the parent compound, cyclohexane. In addition, recent X-ray structure determinations of simple cyclohexanes (1-, 1,1- and 1,4-substituted) also show less flattening than expected (observed range of mean torsional angle 53·2–57·1°).

These observations raised several questions:

(i) What, if any, is the effect of equatorial or axial substituents on the detailed geometry (bond distances, endo- and exocyclic valency and torsional angles) of the cyclohexane ring? Concomitant to this question is the problem of the direction of the C—H bonds. In principle, torsional angles ϕ_{HH} between C—H bonds can be obtained from NMR coupling constants. Recent progress in this field (μ^2/J method,[9, 10] R-value method[11]) has been considerable, but further advances will require a more reliable description of torsional angles between ee, ea and aa C—H valencies and their relationship to the ring torsion angles. Unfortunately, the location of H atoms, though quite feasible in modern X-ray analysis, is an order of magnitude less accurate than the location of carbon, oxygen and nitrogen.

(ii) Is it possible to simulate the experimental findings by means of computer calculations? Present-day valence-force minimization methods (molecular mechanics[12]), particularly programs that allow complete relaxation of all internal coordinates,[12–14] claim great success in being able to calculate geometries and energies of a variety of organic molecules, including those that contain heteroatoms.[13d] If calculated geometries match experimental ones, a better insight into the various strain factors that govern the exact shape of these simple ring compounds can be gained and one may place reasonable confidence in the geometries predicted for systems that have not been investigated by diffraction methods.

The purpose of this publication, then, is to compare the available cyclohexane geometries as found by accurate X-ray methods to those calculated for the same molecules (or for analogous ones). Our emphasis centers mainly on valency angles and torsional angles of the various ring systems.

METHODS

Geometries (observed values) were taken from recent X-ray analyses of high accuracy (standard deviation of bond angles $\leqslant 1°$). In most cases, the distances and angles were recalculated from the published atomic coordinates. The compounds to be discussed are shown in Table 1 and Fig. 1.

The calculations of model structures allowed complete relaxation with respect to all force-field parameters which include the usual separation of atomic interactions into: bond stretching, bond angle bending, 1,3-interactions, other non-bonded

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* It should be mentioned here that certain heterocyclic six-membered rings, notably dithianes, diselenanes and others are puckered chairs (mean endocyclic torsional angle >60°) by virtue of the small bond angles C-X-C in these systems. A comprehensive review of available data on simple heterocyclics is found in Ref. 7[b].

interactions, torsional strain and, where necessary, charge-charge interactions. The calculated structure is solely a function of the force-field employed and, for a given conformational energy minimum, does not depend on the input coordinates. Some details of the computational scheme are given in Appendix II.

At the present time, the calculation of geometries should probably best be regarded as a sophisticated extension of the "ball-and-spring" molecular model. However, there is reason for satisfaction to find that in many cases the internal coordinates so obtained agree well with X-ray structures. In the remainder of this paper, we will refer to a completely converged structure as "model".

We will briefly consider four possible sources of discrepancies between observed and model geometries (bond distances, bond angles, torsional angles), the relative importance of each remaining largely a matter of conjecture.

(1) Deficiencies in the force-field used. Particularly where systematic discrepancies occur (as in the presently calculated C—C bond distances, see Appendix II), the force-field equations and/or parameters are in need of correction.

(2) Experimental errors in the X-ray structure determination. An effort was made to

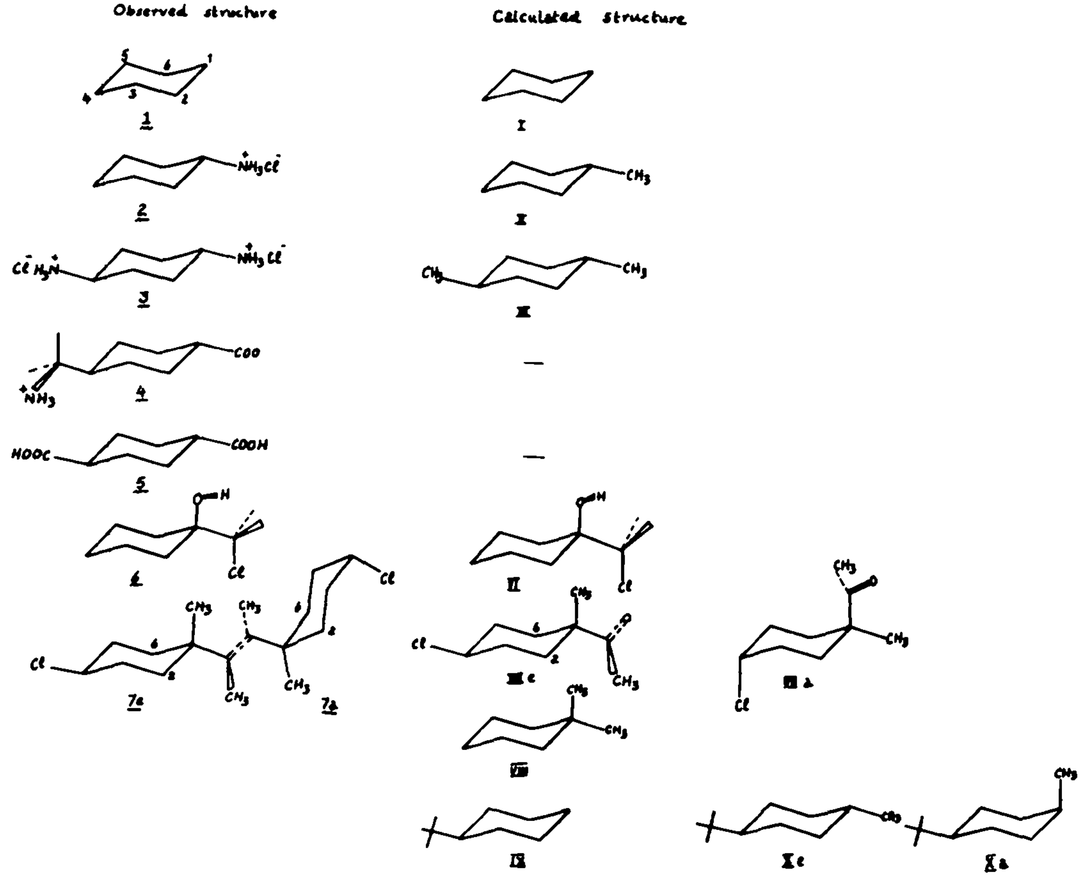

FIG. 1 Observed and calculated structures of cyclohexanes

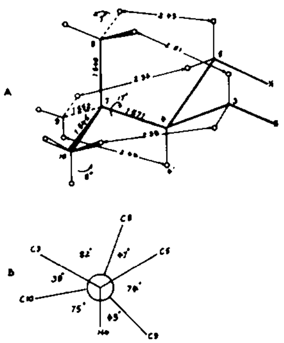

FIG. 2 Calculated structure of *t*-butylcyclohexane. A. Some carbon–carbon bond distances and shortest hydrogen–hydrogen non-bonded contacts. B. Newman projection along C_4–C_7

minimise this factor as far as was practically possible by accepting only those determinations that met a specified standard of accuracy (see above). The term "significantly different" has been used according to statistical criteria. A conservative viewpoint was taken; discrepancies between observed and calculated quantities are said to be significant if the difference exceeds three times the quoted standard deviation of the observation.*

(3) In some cases, the calculated structures contain other substituents than those actually employed for the X-ray determination. For example, the model of equatorial methylcyclohexane is compared to the observed structure of aminocyclohexane hydrochloride, because the various interactions of the $—CH_3$ group are known and tested whereas the calculation of an $—NH_3^+$ containing molecule would introduce many new parameters. It can be argued that the two groups should cause similar non-bonded repulsion effects.

(4) Crystal packing effects. The calculations were carried out for the free molecule

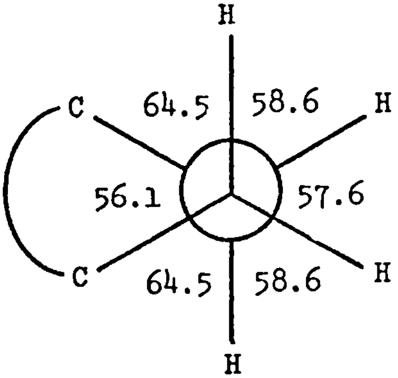

FIG. 3 Calculated projection along a C—C bond of cyclohexane

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* Of course, no limit of error can be quoted for the model structure. Only through detailed comparison of observed with calculated geometries and energies of many different compounds can the value of the method be established.

(gas phase), whereas the X-ray geometry will be affected by long-range non-bonded interactions and polar effects. Anticipating the results presented below, it can be said that crystal-packing forces seem to play a minor role as far as the geometry of the ring itself is concerned. In a few cases, particularly where bulky and/or strongly hydrogen-bonded groups protrude from the ring, the bond angles about the ring carbon to which the substituent is attached show interesting anomalies which might perhaps be ascribed to intermolecular forces.

DISCUSSION OF STRUCTURES

A. *Equatorial substituents*

The observed skeletal geometries of the equatorially substituted compounds **1–5** and the model structures I, IIe and III are summarized in Table 2. The observed *mean* C—C bond distances range from 1·526 to 1·529 Å, overall mean 1·527 Å. It should be noted that individual C—C bond distances in the compounds **1–7** show a fairly large spread from a low 1·500 Å to a high 1·556 Å. The spread in the calculated distances (excluding the t-Bu compounds IX and X) is much smaller (1·531–1·534 Å). The mean calculated C—C distance is 0·005–0·006 Å greater than the mean observed value (Appendix II).

More interesting is the distribution of 6 bond angles and 6 torsional angles as a function of size and nature of the substituent. The greatest variations in CCC bond angles occur at the substituted carbon atoms C_1 and C_4, where the range recorded is $\theta_0 = 109{\cdot}4 \pm 0{\cdot}2°$ (R = $CH_2NH_3^+$) to $\theta_0 = 113{\cdot}3 \pm 0{\cdot}5°$ (R = COOH). The difference between these two values is significant. The lower value, narrowing of the angle at the bulky (*gauche*) group $CH_2NH_3^+$, finds its parallel in the correspondingly small angle in the 4-t-Bu compound IX (108·9°, Table 4), and can be understood on the basis of non-bonded strain. No ready explanation presents itself for the observed widening in the case where R = COOH (but not COO^-). The bond angles about the methylene groups show much less spread (observed $\theta_0 = 110{\cdot}4$–$112{\cdot}2°$, calculated $\theta_c = 111{\cdot}0$–$111{\cdot}6°$). No systematic trend in the difference $\Delta\theta = \theta_0 - \theta_c$ can be detected.

The observed *mean* torsional angles in the five equatorially substituted cyclohexanes range from 53·2–57·1°. The greatest spread is found in the zwitterion **4** where strong inter- and intramolecular charge-charge interactions seem to dominate the picture. Evidently the model (1,4-dimethylcyclohexane) is, in this particular case, much too crude to give a satisfactory account of the observed trend in puckering (52·3–59·1°).

It is encouraging to note that the remaining models, except cyclohexane, agree quite well with the experimental results.

In summary, then, the effect of an equatorial substituent on ring geometry is seen to be relatively minor. The calculations show a slight extra flattening (compared to cyclohexane) on adding one methyl group, and a little more for two methyls in 1,4-position. Only the equatorial t-Bu substituent has some effect on the overall geometry of the ring (Table 4). The calculated geometry of the t-Bu group is of some interest and will be discussed separately.

B. *Axial substituents*

The observed geometrical data for compounds **6**, **7a** and **7e** are shown in Table 3 and compared with calculated values for VI, VIIa and VIIe. Compounds **6** and VI are identical. However, the butene moiety of **7a** and **7e**, connecting the two rings (**a**) and (**e**), was replaced by a keto group for purposes of calculation.*

In considering the observed geometries, one is struck by the fact that, although all three molecules carry one or two axial substituents (**6**: OH; **7a**; $C(CH_3) = C$, Cl; **7e**: CH_3), the mean torsional angles in these rings, thought to be a good measure of flattening effects, remain practically unaffected. The model calculated for VI agrees fairly closely with the observations (**6**), but VIIa and VIIe appear flatter than the observations indicate. The origin of the discrepancy is to be found in the bond angles about C_1. In both conformers **7a** and **7e**, the endocyclic angle 6-1-2 is amazingly small (~ 104°), a finding that is not reproduced in the models.†

A scrutiny of the remaining bond angles about the quaternary carbon C_1 reveals a considerable spread in value, much larger in fact than would have been predicted by the calculations:

6 obs. range 105·0–112·4°, VI calc. range 105·0–111·7°

7a obs. range 103·8–116·2°, VIIa calc. range 108·4–110·6°

7e obs. range 104·2–112·4°, VIIe calc. range 107·9–111·4°

Since the effects are noted in both **7a** and **7e**, it seems possible that in these cases (and to a different extent in **6** also) packing forces are, at least in part, responsible. The butene moiety binds the rings of **7a** and **7e** together, the —OH group of **6** is strongly hydrogen-bonded in the crystal lattice, so in each instance a long handle is "pulling" or "pushing" the substituents on C_1, resulting in deviations from the minimum-energy geometry about C_1 by several degrees. The resulting intramolecular energy increase is thought to be relatively small, and might easily be compensated for by relief of non-bonded interactions at close-packing distances.‡

Turning our attention to the bond angles and torsional angles of the methylene groups, we note that practically all calculated values agree satisfactorily with those observed. The deformations around C_2 and C_3, caused by an axial substituent on C_1, are particularly well reproduced. An axial C_1 methyl group increases the angle 1-2-3 by 1–2°; the distortion is enhanced to 3–4° when an equatorial C_1 methyl is added. We see here a weak manifestation of the "reflex effect",[22] caused by mutual repulsion of two *syn*-axial substituents (methyl and hydrogen, in our case). The endocyclic torsional angles (ϕ1-2-3-4) seem hardly affected.

A brief note on the geometry of the parent compound, cyclohexane, now seems to be in order. The mean observed torsional angle of the substituted cyclohexanes, **2**–**7**, centers at 55·4° (55·8° when the slightly anomalous results of the dicarboxylic acid, **5**, are left out of consideration.) This value is 1–1·5° greater than that reported for the

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* The oxygen/carbon and oxygen/hydrogen non-bonded interactions are slightly softer than the corresponding Csp^2/Csp^3 and Csp^2/H interactions. On the other hand, the C═O distance is shorter than the C═C distance and this is expected to partially compensate for the smaller interactions in the ketone as compared to the butene derivative.

† On account of the inverse relation between *mean* bond angle and *mean* torsional angle in chair-shaped six-membered rings,[2, 6–7] a *decrease* in even one bond angle results in an *increased* puckering.

‡ The validity of this hypothesis can be tested, at least in principle, by calculations based on the contents of one or more unit cells. So far, lack of sufficient memory capacity of the computer available to us has impeded progress in this direction.

parent ring (54·5°), although the calculations indicate that most substituents should cause some flattening. This leads us to suspect that the true torsional angle in cyclohexane might well turn out to be close to 56°.*

C. t-*Butylcyclohexanes*

The utility of the 4-t-Bu function as a holding group[23] in cyclohexane chemistry has been amply demonstrated over the years.[24] Comparison of chemical and physical data on systems biased by means of the t-Bu group with those obtained in other ways seems to support the usual assumptions made concerning the influence of the t-Bu moiety at long distance (*viz.*, the 4-t-Bu substituent does not exert a polar or steric effect at the 1- or 1,2-positions and produces a negligible distortion of the ring[24]).

Unfortunately, no experimental structural studies are yet available for this important class of compounds. Therefore, we have to be content to present the results of our calculations as predictions. The model structures are shown in Table 4 and Fig. 2.

The most surprising feature displayed by the minimum-energy conformation of t-butylcyclohexane (IX_{asym}) and the 1-methyl-4-t-butylcyclohexanes (Xe and Xa) is the large angle of twist of the t-butyl group (± 17°) concomitant with an asymmetrical distortion of the ring. It should be noted that all remaining models (including 1,1- and 1,4-dimethylcyclohexanes) converged from an asymmetrical to a symmetrical geometry within any desired degree of accuracy by virtue of the symmetry inherent in the force-field. However, in perfectly staggered t-butylcyclohexane† (IX_{sym}), unfavorable non-bonded interactions occur which are relieved by a twist of *ca.* 17° about the C_4—C_7 bond and by a twist of two of the three methyl groups by 7–8° (Fig. 2). In t-butylcyclohexane and 1-substituted 4-t-butylcyclohexanes,‡ there are, of course, two energetically equivalent positions (at + 17° and at − 17°), separated by the IX_{sym} form, which constitutes a *very low barrier* (0·2–0·3 kcal/mol). In fact, this barrier is so low that it can be ignored for most practical purposes of conformational analysis.§ For example, torsional angles to be used in evaluating proton spin coupling constants can safely be taken as the mean of the two forms, i.e., in IX_{asym} we have $\phi_{1-2-3-4} = 54{\cdot}3°$, $\phi_{1-6-5-4} = 57{\cdot}7°$, mean 56·0°. Similarly, the mean value of $\phi_{6-1-2-3}$ is 56·3°, much the same as in I. Hence, it can be concluded that the ground-state geometry in the C_1 region of the molecule remains virtually unchanged by the insertion of a 4-t-Bu group.‖ Thus the calculations lend support to

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* Recent calculated values for bond and torsional angles in cyclohexane show a similar trend:

Ref. 13: $\theta_c = 111{\cdot}3°, \phi_c = 55{\cdot}3°$
Ref. 14: $\theta_c = 111{\cdot}0°, \phi_c = 55{\cdot}9°$
this work: $\theta_c = 111{\cdot}0°, \phi_c = 56{\cdot}1°$

† Calculated by imposing the restriction that C_1, C_4, C_7, C_8 and the in-plane hydrogens attached to these C atoms lie in one plane. All parameters were allowed complete relaxation.

‡ In 2- and 3-substituted 4-t-butylcyclohexanes, the + and − rotamers are no longer equivalent; a similar non-equivalence is expected to occur in 1,4-di-t-butylcyclohexane (+,+ = −,− ≠ +,− = −,+).

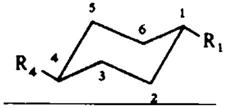
§ In a diffraction analysis of 4-t-butylcyclohexanes, the twisting phenomenon would be expected to reveal itself in anomalously high anisotropic "temperature factors" of the atoms constituting the t-butyl group (disorder) and, to a lesser extent, of the methylene carbons of the ring. A comparable case reported in the literature is, perhaps, the structure of hexamethylethane, for which Bartell *et al.*[12] calculated a twist angle of 12·6°, whereas the electron diffraction experiment[12] yielded a much smaller angle.

‖ This conclusion has been discussed by Allinger *et al.*[13b] from a different point of view.

TABLE 1. OBSERVED AND CALCULATED STRUCTURES OF CYCLOHEXANES

	Observed structure		Calculated structure	Orientation of substituents
1	Cyclohexane[1] (el. diff.)	I	cyclohexane	—
2	Aminocyclohexane hydrochloride[16]	IIe	methylcyclohexane	1e
3	*trans*-1,4-Diaminocyclohexane dihydrochloride[17]	III	1,4-dimethylcyclohexane	1e, 4e
4	*trans*-4-Aminomethylcyclohexan-1-carboxylic acid[18]		—	1e, 4e
5	*trans*-1,4-Cyclohexanedicarboxylic acid[19]		—	1e, 4e
6	*anti*-1-Chloromethylcyclohexan-1-ol[20]	VI	idem	1e, 1a
7a	2,3-Bis(*cis*-4-chloro-1-methyl-cyclohexyl)-*trans*-2-butene (ring 1)[21]	VIIa	(*cis*-4-chloro-1-methyl-cyclohexyl)methyl ketone	1a, 1e, 4a
7e	idem (ring 2)	VIIe	idem	1a, 1e, 4e

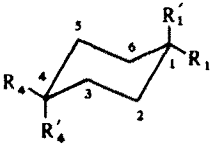
TABLE 2. OBSERVED AND CALCULATED BOND AND TORSIONAL ANGLES OF EQUATORIALLY SUBSTITUTED COMPOUNDS 1–5 (I–III) AND STANDARD DEVIATIONS (σ) OF THE OBSERVATIONS

		Observed[a]						Calculated			
	R_1 =	H	$NH_3^+Cl^-$	$NH_3^+Cl^-$	$CH_2NH_3^+$	COOH	Mean obs. compounds	H	CH_3	CH_3	Mean calc.
	R_4 =	H	H	$NH_3^+Cl^-$	COO^-	COOH	**1–3**	H	H	CH_3	I–III
Compound No.:		**1**	**2**	**3**	**4**	**5**		I	IIe	III (e,e)	
σ(C—C) × 10^3 Å		5	10	6	4	7					
Mean C—C (Å)		1·528	1·527	1·526	1·529	1·526	1·527	1·532	1·532	1·532	1·532
Bond angles (°)											
	σ	0·15	0·5	0·4	0·2	0·5					
6–1–2		111·6	111·3	111·1	109·4	113·3	111·3	111·0	110·8	110·8	110·9
1–2–3		111·6	110·5	110·4	110·6	111·4	110·8	111·0	111·6	111·6	111·4
1–6–5											
2–3–4		111·6	111·6	110·4	112·2	111·4	111·2	111·0	111·0	111·6	111·2
6–5–4											
3–4–5		111·6	112·4	111·1	110·4	113·3	111·7	111·0	110·8[b]	110·8	110·9
Mean		111·6	111·3	110·6	110·9	112·0	111·4	111·0[b]	111·1	111·3	111·1
Torsional angles (°)											
	σ	0·4	1·0	0·8	0·5	1·0					
6–1–2–3		54·5	56·7	57·2	59·1	53·6	56·1	56·1	55·7	55·0	55·6
2–1–6–5											
1–2–3–4		54·5	54·8	56·9	56·6	52·5	55·4	56·1	55·9	55·5	55·8
1–6–5–4											
2–3–4–5		54·5	53·4	57·5	52·6	53·6	55·2	56·1	56·3	55·0[b]	55·8
3–4–5–6											
Mean		54·5	55·2	57·1	56·1	53·2	55·6	56·1[b]	55·9	55·2	55·7

[a] In all cases the reported differences between mirror-equivalent distances and angles were not significant according to established criteria, therefore, only their mean value is given here.

[b] Calculated value differs from observed one by more than 3σ.

TABLE 3. OBSERVED AND CALCULATED BOND AND TORSIONAL ANGLES OF AXIALLY SUBSTITUTED COMPOUNDS 6–7 (IIa, VI–VIII) AND STANDARD DEVIATIONS OF THE OBSERVATIONS (σ)

		Observed				Calculated				
 R_1 = R_1' = R_4 = R_4' =	CH_2Cl OH H H	CH_3 $-C(CH_3)=$[b] H Cl	$-C(CH_3)=$ CH_3[c] Cl H	Mean obs	CH_2Cl OH H H	CH_3 $-C(CH_3)=O$ H H	$-C(CH_3)=O$ CH_3 Cl H	Mean calc	H CH_3 H H	CH_3 CH_3 H H
Compound No.:	**6**	**7a**	**7e**		VI	VIIa	VIIe		IIa	VIII
σ(C—C) × 10^3 Å	5	11	11							
Mean C—C (Å)	1·530	1·526	1·527	1·528	1·536	1·533	1·533	1·534	1·533	1·535
Bond angles θ (°)										
σ	0·3	0·6	0·6							
6–1–2	110·7	103·8	104·2		109·6[a]	108·4[a]	108·5[a]		110·5	109·0
1–2–3	112·4	113·0	115·0		111·7	114·1	114·8		112·8	114·6
1–6–5		112·8	115·6			113·2	115·6			
2–3–4	111·0	112·3	110·7		110·9	112·1	111·0		110·0	110·9
6–5–4		111·6	110·1			112·4	110·4			
3–4–5	110·0	112·1	112·3		110·8	110·1[a]	110·3[a]		111·2	110·9
Mean θ	111·3	110·9	111·3	111·2	110·9	111·7	111·8	111·3	111·6	111·8
Torsional angles ϕ (°)										
σ	0·6	1·2	1·2							
6–1–2–3	53·0	60·1	54·1		56·2[a]	53·5[a]	49·9[a]		52·8	51·1
2–1–6–5		60·1	54·8			54·0[a]	50·0[a]			
1–2–3–4	55·8	57·6	56·8		56·7	54·5	55·4		54·9	54·8
1–6–5–4		57·8	57·2			56·3	54·7			
2–3–4–5	57·2	50·2	54·5		56·0	52·5	56·8		55·9	55·8
3–4–5–6		50·0	54·5			53·7[a]	56·1			
Mean ϕ	55·3	56·0	55·3	55·5	56·3	54·1	53·8	54·7	54·5	53·9

[a] Calculated value differs from observed value by more than 3σ.

[b] Numbering as in original paper, double bond on side of C_2.

[c] Numbering as in original paper, double bond on side of C_6.

earlier findings that were based on coupling constants and dipole moments of 2-halocyclohexanones.[10]

Appreciable non-bonded strain seems to occur in the C_3—C_4—C_5 region as witnessed by several anomalous distances and angles:

(a) The C_4—C_7 bond is fairly long (calculated length, 1·570 Å; probable true length, 1·564 Å, see Appendix II).

(b) The axial hydrogen on C_4 is actually bent toward the center of the ring by about 5°; the C_3—C_4—H bond angle is reduced from a normal 109–110° to 105°. Similarly, the torsional angle $\phi_{6-5-4-H_4}$ is smaller by 6–7° compared to cyclohexane. Interestingly, the existence of this effect has been postulated in a more qualitative way by Pasto and Klein[25] to account for the observed isomer distribution in addition reactions of 4-t-butylcyclohexene.

TABLE 4. CALCULATED GEOMETRY FOR *t*-BUTYLCYCLOHEXANES IX–X

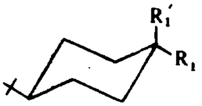
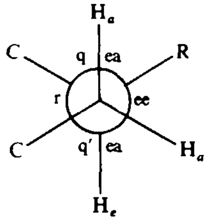
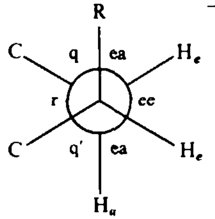
	Calculated			
	R_1 = H } mirror R_1' = H } sym.	H } minimum H } energy	CH_3 H	H CH_3
Compound No.:	IX (sym)	IX (asym)	Xe	Xa
Bond distances (Å)				
1–2	1·527	1·518	1·525	1·531
1–6		1·520	1·528	1·532
2–3	1·537	1·539	1·541	1·539
5–6		1·534	1·535	1·534
3–4	1·547	1·546	1·545	1·545
4–5		1·542	1·541	1·541
Mean	1·537	1·533	1·536	1·542
Bond angles (°)				
6–1–2	110·1	111·3	110·3	109·5
1–2–3	111·2	111·4	112·4	113·7
1–6–5		110·2	111·1	112·5
2–3–4	113·0	113·0	113·0	113·2
6–5–4		112·8	112·9	113·2
3–4–5	108·6	108·8	108·7	109·0
Mean	111·2	111·2	111·4	111·9
Torsional angles (°)				
6–1–2–3	56·7	55·6	54·5	52·8
2–1–6–5		57·0	55·8	54·1
1–2–3–4	56·5	54·3	54·3	53·5
1–6–5–4		57·7	57·7	56·7
2–3–4–5	53·3	52·7	52·7	51·6
3–4–5–6		54·8	54·8	53·5
Mean	55·5	55·4	55·0	53·7

TABLE 5. CALCULATED EXOCYCLIC TORSIONAL ANGLES IN CYCLOHEXANES SHOWING SUBSTITUENT EFFECTS

R equatorial	R_e	r	q	q′	ea(RH)	ee(HH)	ee(RH)	aa(HH)
	H[a]	55-57°	69–64°	—	—	56–59°	58–57°	170–175°
	Cl[b]	57	66	64°	57°	58	57	173
	Me	55	66	62	59	61	57	177
	t-Bu	53	67	58	65	63	53	181
R axial	**R_a**	**r**	**q**	**q′**	**ea(HR)**	**ea(HH)**	**ee(HH)**	**aa(RH)**
	Cl[c]	52	71	70	54	53	59	167
	Me	53	74	68	51	50	64	165

[a] The spread in angles of the CH_2-CH_2 fragment reflects the influence of neighboring substituents.

[b] Compound VIIe

[c] Compound VIIa

TABLE 6. SOME FORCE-FIELD PARAMETERS USED IN THE CALCULATIONS

Carbon–carbon stretching: $E = \frac{1}{2}k_s(l - l_0)^2 + k'(l - l_0)$. All C—C bonds k_s = 1·56 mdyn/Å, l_0 = 1·424 Å, k' (mdyn) for various combinations of primary, sec., tert., and quart. carbon: −0·077 (pp, ps, ss), −0·069 (pt, pq, st or Csp^2 on one end), −0·055 (tt), −0·049 (sq, tq, qq).

Bond bending. as in ref. 13c, k_b increased by 15%.

HCO k_b = 0·855 mdyn A/rad^2, θ_0 = 107·2°

CCCl k_b = 1·10 mdyn A/rad^2, θ_0 = 107·0°

Non-bonded parameters for use in the Hill equation:

as in ref. 13c, except:

H...Cl r* = 1·67 Å, ε = 0·153 kcal/mol (6/12 function)

H...O r* = 1·59 Å, ε = 0·053 kcal/mol

1,3-*Interactions*, parameters for use in the Hill (6/12) equation:

	r*	ε
H...H	1·00	0·015
H...C	1·215	0·09
H...Cl	1·27	0·12
H...O	1·18	0·05
C...C	1·39	0·22
C...Cl	1·50	0·16

Charges (electrons):

	—CH$_3$	H +0·025e, C −0·075e	
	—CH$_2$—	H +0·014e, C −0·028e	
	>CH—	H +0·005e, C −0·005e	
	Cl	−0·220e	neighbouring atom charges matched to produce neutral molecule
	=O	−0·470e	
ethers	—O—	−0·300e	
alcohols	—O—	−0·470e	

(c) The non-bonded repulsions between Me and $C_3(C_5)$ methylene groups are relieved in part by an increase of the C_3—C_4—C_7 bond angles (to 114°). Some strain still remains. The calculations show that the $C_3(C_5)$ *axial* hydrogen is less hindered than the equatorial one, in accord with the recent finding that a hydroxyl group *ortho* to t-Bu prefers to occupy the axial position.[26]

It might be mentioned in passing that the calculated conformational preference of the Me group (ΔH°_{Me}) in the 4-t-Bu compounds X (1·66 kcal/mol) is close to that in the methylcyclohexanes II (1·71 kcal/mol).

TABLE 7. CALCULATED STRAIN ENERGIES AND DIPOLE MOMENTS OF CYCLOHEXANES

Compound	I	IIe	IIa	III	VIII	VI	VIIa	VIIe
Total E (kcal/mol)	0·87	0·53	2·24	0·18	1·85	3·25	7·66	7·90
μ (Debye)	—	—	—	—	—	1·3	2·6	2·7
4-t-Butyl compound	IX$_{sym}$	IX$_{asym}$	Xe	Xa				
Total E (kcal/mol)	5·02	4·90	4·10	5·75				

APPENDIX I

Recently, a number of methods based on the Karplus equation[27] have been developed for the study of molecular geometry and conformational equilibria of systems in solutions. Both the μ^2/J method[10] (utilizing the combination of electric moments and vicinal coupling constants) and the R-value method[11] (applicable to inverting systems having two equivalent conformers) gave surprisingly good results. However, the present calculations tend to show that the assumption of trigonal projection symmetry when looking along a C—C bond in the CH_2-CH_2 (or CH_2-CHR) fragment does not hold well. Deviations up to 6° in torsional angles can readily occur, particularly between equatorial hydrogens (Fig. 3). This seemingly peculiar behavior of equatorial hydrogens is brought about by deviations of bond angles from the tetrahedral value, more in particular the H-C-H angles in methylene groups which are known to be much smaller than 109·5°, values of 106–107° being common (cf. propane,[28] butane,[29] compounds 4 and 6 of this paper and androsterone,[30] to name a few systems in which hydrogen atoms were located with reasonable accuracy). The calculated H-C-H angles of the compounds presently discussed range from 102·5° to 106·5° (105·9° in cyclohexane I). Some calculated Newman angles are shown in Table 5, from which several interesting conclusions can be drawn:

(i) In the CH_2-CH_2 moiety ϕ_{ea} (HH) $\sim$ ϕ_{ee} (HH) with values centering around 57–58°, the torsional angle between vicinal axial hydrogens ϕ_{aa} (HH) equals 174°, a neighboring axial methyl group causes a slight decrease to 170–171°.

(ii) An *equatorial* substituent in —CH_2—CHR— causes only minor changes in ϕ_{ee} (HH) and ϕ_{aa} (HH), except when R = t-butyl (Table 5).

(iii) The effect of an *axial* substituent strongly depends on its size; ϕ_{ea} (HH) tends to decrease, ϕ_{ee} (HH) tends to increase with increasing $\Delta G°$ value, in accord with the usual trend in vicinal coupling constants ($J_{ea} > J_{ee}$). However, we feel that a valid interpretation of J_{vic} in terms of bond angles, torsional angles and Karplus' parameters has to await further calculations.

APPENDIX II

The calculations of equilibrium geometries were carried out on a Univac 1108 computer utilizing a modified version of Boyd's elegant energy minimization scheme.[31] The total energy *Et* was minimized with respect to all internal coordinates. The following terms were involved (Eq. 1):

$$Et = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{non-bonded}} + E_{1,3} + E_{\text{coulomb}} \qquad (1)$$

The present program accepts up to 60 atoms and 1200 interactions simultaneously. Dipole interactions are treated as interactions between charges located on (non-bonded) atomic centers. The atomic coordinates can be located to within any desired degree of accuracy (usually $\ll$ 0·001 Å) of the minimum energy position, final strain energies are reproducible to within 0·001 kcal/mol.

The force-field chosen is based on that developed by Allinger and his coworkers (AFF).[13] Several modifications were found necessary. These mainly involve our treatment of the E_{stretch} and $E_{1,3}$ functions and will be discussed elsewhere.[32] Suffice it to say that a linear term was added to the usual harmonic stretching equation in order to reproduce the known variation in bond lengths with atomic surroundings[12] (which requires a smaller quadratic force constant than used in AFF), while the stretching energy is kept within reasonable limits.*

Our treatment of interactions between atoms bound to a common atom departs from previous usage. The prime motivation for including 1,3-interactions in the force-field lies, of course, in their power to reproduce reasonable bond distances in strained molecules such as norbornanes[33] (a 1,3 repulsion has a bond-stretching component, a 1,3-attraction gives rise to bond contraction; neither effect can be reproduced by a simple bond-bending function). We carried out some empirical manipulations of several possible 1,3-interaction potentials[12, 14] and finally settled on van der Waals (2-parameter 6/12 type) functions[13] using a 15–20% *smaller* radius than employed in normal non-bonded interactions. The exact values (in conjunction with and dependent on the remaining force-field parameters) were established by calculations of small molecules of known geometry (alkanes, chloroalkanes, alcohols, ketones and ethers). The force-field parameters employed, insofar as they differ from AFF,[13] are shown in Table 6. Although the calculated

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* Linear terms in angle deformation and Urey–Bradley field equations have been introduced for essentially the same purpose by several authors.[12–14] Our present scheme reproduces previously calculated strain energies of cyclohexanes[13] to within 0·3 kcal/mole, conformational energies to within 0·1 kcal/mol.

C—C bond distances match those observed by electron diffraction in simple alkanes[34] to within $\pm 0{\cdot}002$ Å, a detailed comparison of observed (X-ray) and calculated bond lengths in cyclohexanoid systems, including some steroids, has convinced us that the force-field in its present form yields values that are systematically too high by 0·005–0·006 Å. There are several ways to remedy this shortcoming, but, pending further work, we prefer to accept the deficiency for the time being.

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