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ALLINGER'S *GAUCHE* HYDROGEN HYPOTHESIS AS TESTED BY AN ALTERNATIVE FORCE FIELD MODEL

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Abstract—Allinger's hypothesis that *gauche* hydrogen, rather than *gauche* methyl interactions are mainly responsible for conformational equilibria was tested by molecular mechanics calculations using the Engler force field model. For the *gauche-anti* conformational energy of n-butane, effective cancellation among non-bonded interactions involving the methyl groups results in the *gauche* hydrogen interactions across the central C–C bond as the single largest contribution to the energy difference. However, the contribution of this interaction is only one third of the 0.9 kcal difference. For 2,3-dimethylbutane, strain analysis of the *gauche-anti* conformational energy contributions reveals that geminal and gauche CH_3/CH_3 interactions dominate over the *gauche* hydrogen interaction. Similar analyses for several monosubstituted cyclohexanes confirm that "across-the-ring" interactions between axial substituents and *syn*-axial hydrogen atoms are still largely responsible for the instability of the axial relative to the equatorial conformer. In disagreement with Allinger's proposal, the "equatorial hydrogen effect" is found to contribute only a minor amount to the conformational energy difference. Allinger's hypothesis is concluded to be force field dependent, and not to have general validity.

Recently, Wertz and Allinger[2] made a startling claim based on their interpretation of empirical force field (molecular mechanics) calculations that the interaction of *gauche* hydrogen atoms was the dominant factor involved in both the preference of *n*-butane for the *trans* conformation as well as the equatorial preference for cyclohexyl substituents. They emphasized that this interpretation was contrary to the prevailing belief[3] that methyl-methyl interactions gave rise to the *trans* orientation in *n*-butane while in substituted cyclohexanes 1,3-diaxial interactions destabilized the axial conformation. They further claimed, without supporting data, that "the general conclusions to be drawn... are not dependent on the exact values used for the force constants in the molecular mechanics calculations..."[2]

Recent advances in the field of molecular mechanics have made this technique a very useful method for obtaining quantitatively accurate structural information, heats of formation and internal potential energy of organic molecules.[4] It is necessary therefore to determine if Wertz and Allinger's claim is indeed independent of the particular parameterization or if it is merely an artifact of the empirical nature of the method.

Several attempts have been made to single out the contribution of distinctive interaction terms to the total steric energy of molecules—a logical extention of the application of the Westheimer principle wherein molecular steric energy is assumed to be the sum of stretching, bending, torsional, non-bonded and cross interaction terms. However, such assessment may be force field dependent. For example, the origin of strain in adamantane may be ascribed either to predominating non-bonded C/C[5] or H/H[6] repulsion depending on the force field used. Altona and Farber[4c] dispute such itemized energy arguments, based on the fact that no single component of the potential function in a molecule can be measured in the absence of the other potentials, and therefore the physical meaning of individual potential terms has never been established. In principle, we agree with these criticisms.

On the other hand, the significance of such an approach cannot be completely denied in view of the remarkable success[4] of molecular mechanics calculations based on the Westheimer principle. Heats of formation have been successfully calculated for a larger number of hydrocarbons of diverse structural types with an average accuracy of ±2 kcal/mole.[7-9] Furthermore, detailed evaluation of individual interaction potential terms is indispensable to upgrading form and parameterization of the various functions.

In this paper we test the Wertz–Allinger "gauche hydrogen" proposal by means of the alternative Engler force field.[7] It is difficult to prove or disprove the proposal, because of the reasons stated above. Of particular interest here is to determine if the proposal is dependent upon the specific parameterization of the force field in contrast to the unsupported claim by Wertz and Allinger[2] that it is not.

Comparison of force fields. The conclusions of molecular mechanics calculations resulting from different force field models usually agree well despite strikingly large differences in parameterization, program details, and energy minimization schemes.[4] However, in this particular case in which the H/H van der Waals interaction is the central problem, some reservations concerning the proposed generality of the Wertz–Allinger conclusion[2] is suggested by the strongly repulsive hydrogen potential used in the Allinger force field.

Figure 1 compares H/H and C/C non-bonded interaction potential curves of the Engler,[7,10] Allinger,[6] Allinger,[2] and Bartell[11] force field models.[12,13] The Bartell functions have the most shallow well at the minima, the smallest van der Waals radii and the smallest slopes in the repulsive region. The 1971 Allinger functions are just

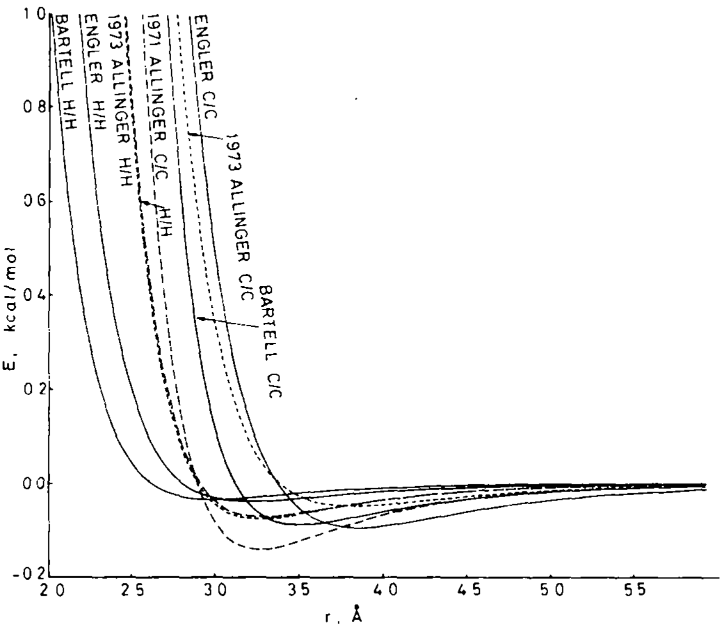
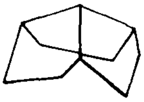


Fig. 1. Potential functions for non-bonded H/H and C/C interations employed in various force fields (for references see text).

the opposite as judged by these three criteria,[14] and this "hard" hydrogen can lead to overemphasis of non-bonded H/H interaction.[4] The latest example of this is the overestimation by 4.7 kcal/mole of the heat of formation of perhydrotriquinancene **1** by the 1971 Allinger force field.[16] **1** possesses a large number of severe H/H interactions in its calculated C_3 conformation **1**.[17,18] Allinger's *gauche* hydrogen proposal was made on the basis of his 1973 force field, in which, while the C/C non-bonded potential function became much more repulsive, the H/H function remains virtually the same as that in the 1971 force field (Fig. 1). It is thus probable that the conclusions based on the non-bonded H/H interactions resulting from the Allinger force field might be peculiar to the model employed.



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Despite some criticism of its strongly repulsive C/C non-bonded potential,[4a] the Engler force field correctly predicted[7] the heat of formation of **1**,[16] and provided better estimates of the heats of formation of several polymethylated diamantanes[8] that should be dominated by C/C interactions. The van der Waals radius of hydrogen in this force field is 1.6 Å, actually larger than Allinger's radius. However, as shown in Fig. 1, the potential at the minimum is shallow and the slope of the curve at shorter distances is much smaller compared to the Allinger H/H potential curve. Thus, it may be said that the hydrogen of this force field is intermediate between Allinger's much more repulsive and Bartell's less repulsive hydrogen.[13,19]

RESULTS AND DISCUSSION

n-Butane. The interpretation of the *gauche-anti* butane conformational enthalpy has been a cornerstone in conformational analysis and provides the simplest possible model for the evaluation of the Wertz–Allinger proposal. Results of steric energy analysis of completely relaxed *gauche* and *anti*-butane are summarized in Table 1 while the main geometrical features of the calculated structures are given in Table 2.

The calculated *gauche-anti* conformational enthalpy, 0.93 kcal/mole, is somewhat higher than the usually quoted value of 0.6–0.8 kcal/mole,[3,21,22] but in good agreement with the recent experimental value (0.966 kcal) obtained from Raman spectra[23] (and with the predicted value (0.925 kcal) based on a modified bond energy scheme.[24]) As shown in Table 1, the two main interaction types responsible for the steric energy differences between the two conformers are angle bending and non-bonded interactions. The angle bending contribution comes mainly from C–C–C angle deformation. In the *gauche* form, the C–C–C angle is calculated to be 114.0°, two degrees larger than the *anti* value of 112.0°,

Table 1. Strain analysis of *gauche*- and *anti*-butane (kcal/mol, 25°, gas)

	Gauche		*Anti*		Difference	
Stretch	0.19		0.14		0.05	
Bend[a]	0.60		0.24		0.36	
C–C–C		0.32		0.06		0.26
H–C–H (methylene)		0.08		0.04		0.04
Methyl		0.20		0.12		0.08
Twist	0.09		0.01		0.08	
Non-bonded[a]	2.40		1.97		0.43	
1,4-CH_3/CH_3		0.28		−0.23		0.51
1,3-CH_3/CH_2		0.08		0.54		−0.46
1,2-CH_3/CH_2		1.42		1.36		0.06
1,2-CH_2/CH_2		0.66		0.30		0.36
Total	3.29		2.36		0.93	

[a] The sum of individual types does not necessarily agree with the total angle or non-bonded strain due to processing of fractions, although the difference is insignificantly small.

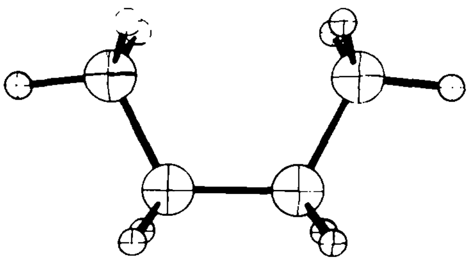
Table 2. Calculated geometry of *gauche*- and *anti*-butane (25°, gas)

Gauche	
$C_1\cdots C_4$	3.117 Å
$C_2—C_3$	1.536
$H_6\cdots H_{13}$	2.403
$H_9\cdots H_{10}$	2.420
$H_9\cdots H_{11}$	2.510
$\theta(C_1$-C_2-$C_3)$	114.0°
$\theta(H_6$-C_1-$C_2)$	111.3
$\theta(H_6$-C_1-$H_5)$	107.2
$\theta(H_8$-C_2-$H_9)$	106.8
$\phi(C_1$-C_2-C_3-$C_4)$	−66.5
$\phi(H_8$-C_2-C_3-$H_{10})$	−64.0
$\phi(H_9$-C_2-C_3-$H_{10})$	52.3
$\phi(H_6$-C_1-C_2-$C_3)$	65.7
Anti	
$H_8\cdots H_{11}$	2.510 Å
$\theta(C_1$-C_2-$C_3)$	112.0°
$\theta(H_6$-C_1-$C_2)$	110.8
$\theta(H_8$-C_2-$H_9)$	107.4
$\phi(C_1$-C_2-C_3-$C_4)$	180.0
$\phi(C_1$-C_2-C_3-$H_{11})$	−58.8
$\phi(H_8$-C_2-C_3-$H_{11})$	62.5

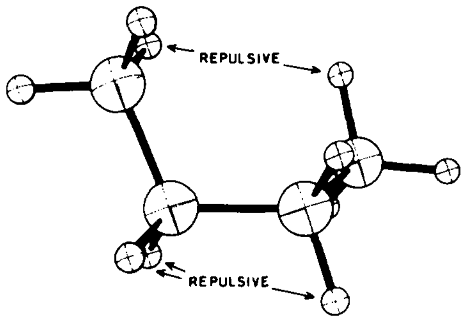
θ, Valence angle; ϕ, dihedral angle.

apparently as the result of repulsion between two *gauche* methyl groups.[25]

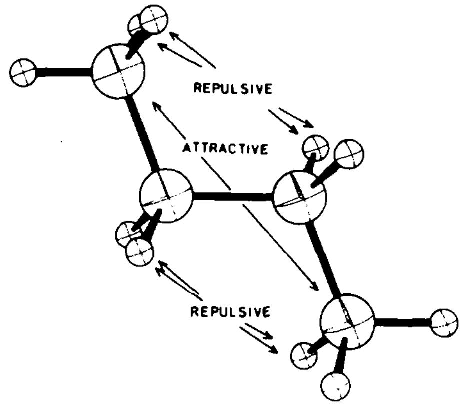
We have analyzed the contribution of non-bonded interactions to the conformational energy in terms of interactions between 1,2- and 1,3-CH_3/CH_2, 1,2-CH_2/CH_2 and 1,4-CH_3/CH_3 groups. This was felt to be a more reliable means of evaluation, rather than the alternative of analyzing individual H/H, C/H and C/C interactions because of the objections raised[4c] to interpretations of terms that do not correspond to experimental observables. The 1,4-CH_3/CH_3 term, generally thought as the decisive factor in the conformational energy,[3] is characterized by two kinds of atom/atom interaction pairs, namely strong 1,6-H/H repulsion (2.40 Å apart) in the *gauche* form and trans 1,4-C/C attraction in the *anti*-form. The disadvantage of *gauche* form from the 1,4-CH_3/CH_3 term is almost completely cancelled by destabilization of the *anti* form through 1,3-CH_3/CH_2 interactions. This interaction is strongly repulsive in the *anti* form because of four *eclipsed* 1,5-H/H pairs **4** while it is almost zero in the *gauche* form **3**. Since the 1,2-CH_3/CH_2 interactions remain almost the same in both conformers, the 1,2-CH_2/CH_2 interaction, which consists only of "*gauche* hydrogen interactions", is left by default to be responsible for the non-bonded contribution to the energy difference between the two conformers. It should be noted, however, that the contribution of this *gauche* hydrogen interaction is only one third of the total enthalpy difference, in contrast to the claim of Wertz and Allinger that the contribution is more than 75%. In our force field, the *gauche* H/H interaction is only as important as the C–C–C angle strain, while the remaining third comes from miscellaneous sources including stretch, twist and 1,2-CH_3/CH_2 non-bonded interactions.



2 *syn*



3 *gauche*



4 *anti*

Aside from the observation that the *gauche* hydrogen interaction is the principle *non-bonded* interaction responsible for the *gauche-anti* conformational energy of *n*-butane, the compensation between 1,4-CH_3/CH_3 and 1,3-CH_3/CH_2 interactions appears to be of some interest since this compensation can take place in any linear or branched alkane. In order to gain more insight into the balance between these terms and also other interaction terms in various possible conformations, calculations were extended to the internal rotation of *n*-butane around the central bond. Starting from the *syn* (eclipsed) conformer **2**, the dihedral angle C–C–C–C was changed in increments of five degrees while each remaining coordinate was completely relaxed.[26] Results of strain component analysis are illustrated in Fig. 2.[27] The highly repulsive 1,4-CH_3/CH_3 interaction in the *syn* conformer gradually decreases as rotation proceeds and finally turns into an attractive force beyond a dihedral angle of about 90°. A reverse trend is true with the 1,3-CH_3/CH_2 interaction. In the *syn* conformer, all the component H/H and C/H interactions in 1,3-CH_3/CH_2 pairs are attractive. As the central bond rotates, they gradually decrease and become repulsive beyond the *gauche* conformer. As the result, the sum of the 1,4-CH_3/CH_3 and 1,3-CH_3/CH_2 terms remains almost constant (0.3–0.7 kcal/mole) during internal rotation, and therefore the contribution of this sum to the conformational energy is always small. In this

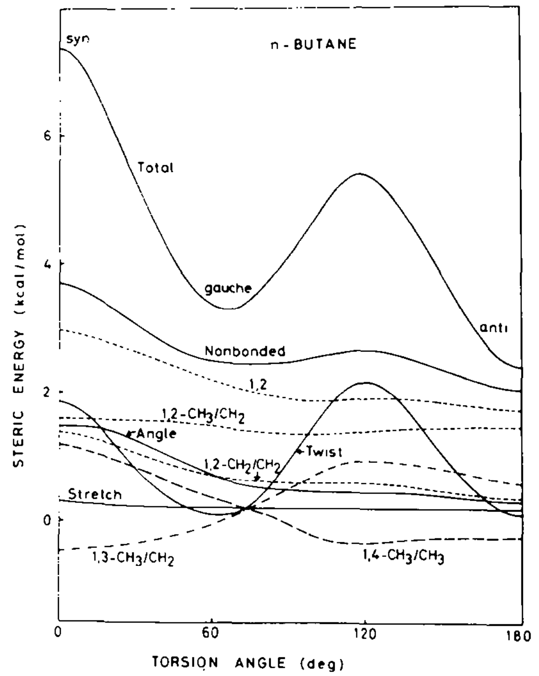
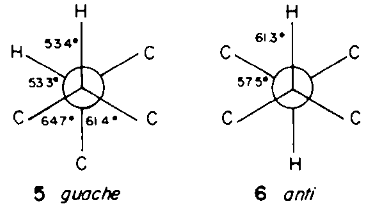


Fig. 2. Strain analysis of *n*-butane during internal rotation around the central C–C bond. Engler force field.

respect, the generally held concept[3] that the non-bonded 1,4-CH_3/CH_3 interaction destabilizes *gauche* relative to *anti* butane is further questioned, albeit within the limit of the present force field.[29]

2,3-*Dimethylbutane.* Wertz and Allinger[2] interpret the observed comparable enthalpies of *gauche* and *anti* 2,3-dimethylbutane (**5** and **6**) in terms of a decrease in vicinal H/H interaction across the central bond of the *gauche* form **5**. According to our analysis (Table 3), however, the contribution of the 1,2-CH/CH interaction to the *gauche-anti* enthalphy difference is almost the same (0.3 kcal/mole) as the 1,2-CH_2/CH_2 interaction in *n*-butane, as is the contribution of angle bending strain. Close comparison between Tables 1 and 3 reveals that the different behavior between *n*-butane and 2,3-dimethylbutane arises mainly from 1,3- and 1,4-CH_3/CH_3, and 1,3-CH_3/CH interactions. Namely, these repulsive forces are all larger in *anti* than in *gauche* conformer. Furthermore, in terms of the magnitude per CH_3/CH_3 pair, the interaction in the *anti* conformer is larger than that in the *gauche* conformer:

	gauche	*anti*
1,4-CH_3/CH_3	0.3–0.4 kcal/mole	0.9 kcal/mole
1,3-CH_3/CH_3	0.3	0.5



5 *gauche* **6** *anti*

2,3-Dimethylbutane

Table 3. Strain analysis of *gauche*- and *anti*-2,3-dimethylbutane (kcal/mol, 25°, gas)

	Gauche	*Anti*	Difference
Stretch	0.55	0.58	−0.03
Bend	1.65	1.23	0.42
Twist	0.16	0.27	−0.11
Non-bonded	3.93	4.23	−0.30
1,4-CH_3/CH_3	0.88	1.33	−0.45
1,3-CH_3/CH_3	0.57	0.96	−0.39
1,3-CH_3/CH	0.44	0.48	−0.04
1,2-CH_3/CH	1.75	1.52	0.23
1,2-CH/CH	0.29	−0.04	0.33
Total	6.29	6.32	−0.03

This arises since there is no way of relieving the CH_3/CH_3 interactions simultaneously in the *anti* conformer. If the geminal C–C–C angle is expanded in order to decrease the 1,3-CH_3/CH_3 repulsion, the *gauche* 1,4-CH_3/CH_3 interaction must increase, and *vice versa.* In contrast, both 1,3- and 1,4-CH_3/CH_3 interactions can be relieved by increasing the torsional angles in the *gauche* conformer. This point is especially interesting in view of Wertz and Allinger's interpretation of the same system. They claimed that the *gauche* form was stabilized because the vicinal hydrogens could avoid each other by a torsional displacement. As evidence of this, they point out that the H–C–C–H dihedral angle about the central bond widens to 72°. With the Engler force field, that angle is *reduced* to 53° to allow the methyl groups to avoid each other; precisely the opposite interpretation. A recent paper by Boyd[30] reaches a similar conclusion based on his own force field model.

The crowding around the "inner" methyl groups of the *gauche* form is further decreased by increasing C–C–C angles involving the central bond (114.9°). With regard to the 1,3-CH_3/CH terms, large repulsive interaction in the *gauche* form of 2,3-dimethylbutane contrasts with the almost zero interaction in *gauche*-butane. This arises mainly from the small dihedral angle of 53.3° between methine hydrogen and the methyl group **5**. In the *anti* conformer, the individual CH_3/CH repulsions are weak, but there are four such pairs compared to two in the *gauche* form.

As the consequence of this complex balance, the sum of 1,3- and 1,4-CH_3/CH_3 and 1,3-CH_3/CH interactions strongly destabilizes the *anti* relative to the *gauche* form and overwhelms the "*gauche* hydrogen effect" which destabilizes the *gauche* form. In other words, we maintain that the *anti* form is destabilized, rather than saying that the *gauche* form is stabilized. The overall result is the almost equal enthalpy of the two conformers, in agreement with experiments.[28,29] Here again, the dominant factor appears not to be the *gauche* H/H interactions but rather other terms, in this case CH_3/CH_3 interactions.

Substituted cyclohexanes. Wertz and Allinger[2] give three interpretations regarding the origin of the conformational enthalpy difference between axial and equatorial methylcyclohexane. They state first that the degree of the well known flattening in the cyclohexane ring[31] is practically unaffected by the presence of axial substituents including axial methyl group. Thus, "across-the-ring" interaction of the methyl group with the axial hydrogens, commonly accepted as the reason for the higher energy of the axial conformers,[3] is said not to be significantly responsible for the energy difference. Second, a ring hydrogen attached to the tertiary carbon atom bearing the methyl group is 0.9 kcal/mole more strained in the equatorial position (of the axial methyl conformer) than in the axial position (of the equatorial methyl conformer), because of the larger "*gauche* hydrogen interaction" of the equatorial hydrogen with vicinal methylene hydrogen atoms compared to those of the axial hydrogen. Combined with additional "*gauche* hydrogen interactions" with methyl hydrogens, the "isohydrogen" contributes 70–75% of the conformational energy in their analysis. Finally they conclude that the intrinsic increase (0.9 kcal/mole) in steric energy of the isohydrogen in going from the axial to the equatorial position remains constant for all monosubstituted cyclohexanes and should be called the "equatorial hydrogen effect".

Despite some degree of agreement of our *n*-butane calculations with those of Allinger, we do not agree with the above three arguments. The first argument as to the constancy of ring flattening in substituted cyclohexanes is not supported by experimental data. According to electron diffraction analysis, the ring of 1,1-dimethylcyclohexane is more flattened than cyclohexane itself. As shown in Fig. 3, its average endocyclic dihedral angle (51.7°)[32] is considerably smaller than that of cyclohexane (54.9°, 55.9°)[28,33] and of equatorial methylcyclohexane (55.3°).[32] The flattening of 1,1-dimethylcyclohexane is most prominent at the quaternary carbon atom as evidenced by the smallest endocyclic dihedral angle (50.4°) at this position. These observations are well reproduced by our calculations as shown in Fig. 3.[34] The good agreement of calculated geometry with experimental structure for 1,1-dimethylcyclohexane prompted us to examine several additional monoalkylcyclohexanes. Calculated structures, illustrated in Fig. 4, show that the ring geometry is *sensitive* to the axial substituent,[35] while the effect of equatorial substituents is small. The shortest internuclear "across-the-ring" distance of axial derivatives beyond ethyl derivative is always slightly smaller than the distances between "isohydrogen" and adjacent axial hydrogen. Clearly, the flattening of cyclohexane is not enough to accommodate the serious crowding over the ring produced by the axial substituent. This fact already suggests the importance of "across-the-ring" strain relative to the *gauche* hydrogen interaction of "isohydrogen".

Next, one can check directly the second point of the Wertz–Allinger argument pertaining to the difference in the conformational enthalpy of the "isohydrogen". The results of strain analysis in axial and equatorial methylcyclohexane are summarized in Table 4. The calculated conformational energy of 1.83 kcal/mole agrees well with the experimental A value.[36] It is clearly shown in the Table that the steric energy of methylcyclohexane is dominated by non-bonded interactions, according to our force field model. However, as far as the contribution to the conformational energy is concerned, angle bending terms contribute nearly as much as non-bonded terms, i.e. about one third. Excess angle strain in the axial conformer is localized around the tertiary carbon atom and its immediate vicinity (Fig. 4). Table 4 includes contributions of non-bonded interactions between some of the methyl, methylene, and methine groups. Although the listing is not exhaustive, these terms are mostly responsible for the contribution of non-bonded interactions to the conformational energy as indicated by their subtotal (0.91 kcal/mole) in comparison to the overall change in non-bonded terms (0.83 kcal/mole). The portion of the methylcyclohexane molecule contained in the list may be regarded as comprising two *gauche* butane units in the axial and two *anti* butane units in the equatorial conformer, and the observations made in the *n*-butane conformers (Table 1) appear to apply to the present analysis. 1,4-CH_3/CH_2 interactions of methylcyclohexane are, like 1,4-CH_3/CH_3 in *n*-butane, characterized by strong repulsion in the axial and strong attraction in the equatorial forms. 1,3-C/C interactions are characterized, again like 1,3-CH_3/CH_2 interactions in *n*-butane, by strong repulsion in the equatorial conformer.

In order to single out the contribution of the methyl group and the "isohydrogen", however, we must disregard the classification by the 1,2-, 1,3-, etc. types. Summation of the non-bonded difference terms for all the CH_3/CH_2 and CH/CH_2 interactions leads to 0.6 and 0.2 kcal/mole, respectively, which may be roughly regarded as the contribution of the CH_3 and CH groups to the conformational energy. We thus conclude, within the framework of the force field model used, that the conformational energy of axial and equatorial methylcyclohexane consists of about 30% of angle deformation around the tertiary carbon atom, about 30% of "across-the-ring" interactions between the axial methyl and axial hydrogen atoms, and the remainder from various sources including stretching and torsional strain and non-bonded interactions involving the CH group. Consequently, we continue to prefer the traditional interpretation of the origin of the conformational energy of methylcyclohexane: methyl group prefers to take the less crow-

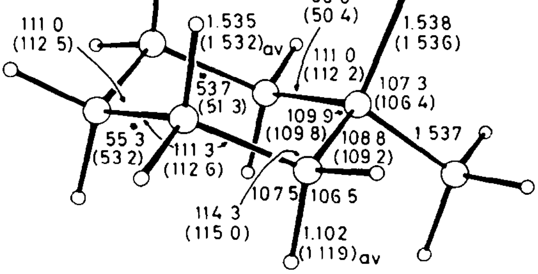
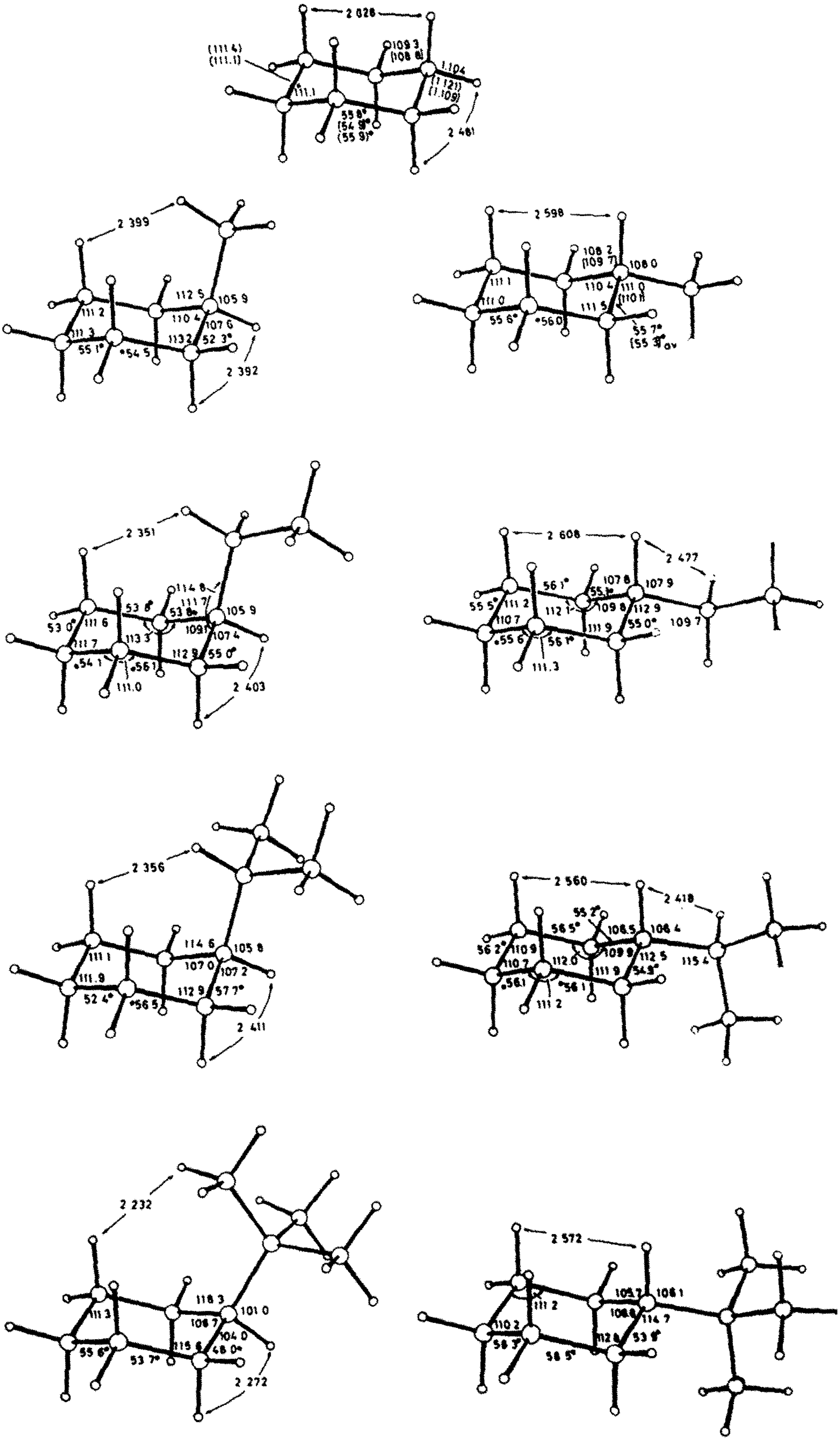


Fig. 3. Calculated and electron diffraction structures of gaseous 1,1-dimethylcyclohexane. Bond lengths in Ångströms, angles in degrees. Experimental values: ( ), Ref. 31.

Table 4. Strain analysis of axial and equatorial methylcyclohexane (kcal/mole, 25°, gas)

	Axial	Equatorial	Difference
Stretch	0.56	0.43	0.13
Bend	0.98	0.38	0.60
Twist	0.34	0.07	0.27
Non-bonded	5.99	5.16	0.83
1,2-CH_3/CH	0.47	0.38	0.09
1,3-CH_3/CH_2	0.24	0.60	−0.36
1,4-CH_3/CH_2	0.64	−0.38	1.02
1,5-CH_3/CH_2	−0.19	−0.12	−0.07
1,2-CH/CH_2	1.08	0.38	0.70
1,3-CH/CH_2	−0.14	0.28	−0.42
1,4-CH/CH_2	0.41	0.46	−0.05
Total	7.87	6.04	1.83


2 028
(111 4)
(111.1)
111.1
109 3
(108 8)
1.104
(1 121)
(1.109)
55 8°
(54 9°)
(55 9)°
2 481
2 399
111 2
111 3
55 1°
*54 5
112 5
110 4
113 2
105 9
107 6
52 3°
2 392
2 598
111 1
111 0
55 6°
*56 0
108 2
(109 7)
110 4
111 5
108 0
111 0
(110 1)
55 7°
(55 3)av
2 351
53 0°
111 6
111 7
*54 1
113 3
*56 1
111.0
53 8°
53 8°
114 8
111 7
109 1
105 9
107 4
112 8
55 0°
2 403
2 608
2 477
56 1°
55 5°
111 2
110 7
*55 6
56 1°
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55 1°
112 1
107 8
109 8
111 9
107 9
112 9
55 0°
109 7
2 356
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*56 5
114 6
107 0
112 9
105 8
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57 7°
2 411
2 560
2 418
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112 0
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109 8
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106 4
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2 232
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55 6°
53 7°
118 3
108 7
115 6
101 0
104 0
48 0°
2 272
2 572
111 2
110 2
58 3°
58 5°
105 7
108 8
112 8
108 1
114 7
53 9°

Fig. 4.

ded equatorial position. It may better be added that the "crowding" caused by the axial methyl group implies increased angle strain in addition to the non-bonded repulsion. A recent neutron diffraction study sheds further light on this point.[37] As evidence for their claim that equatorial hydrogens are more crowded than axial, Wertz and Allinger point out that the calculated C–H bond lengths of cyclohexane derivatives are longer for equatorial hydrogens than for axial hydrogens and attribute this to an attempt to relieve the greater crowding. The neutron diffraction results for *trans*-4-*t*-butylcyclohexyl toluene-*p*-sulphonate, surely a crowded system, show different behavior.[37] The average $\mathrm{C{-}H_{eq}}$ bond length (1.075 Å) is marginally shorter than the average $\mathrm{C{-}H_{ax}}$ bond length (1.080 Å) and, perhaps of equal significance, the results show methylene groups for which the axial C–H bond length is respectively longer, shorter or equal to the corresponding equatorial C–H bond length.

Concerning the third point of Allinger's argument, namely the transferability of the "equatorial hydrogen effect", we must first make it clear that the "equatorial hydrogen effect" is not directly related to the conformational energy *per se*. The "equatorial hydrogen effect" is defined as the increase in the strain energy of "isohydrogen" in the equatorial position relative to the axial position of monosubstituted cyclohexanes. Summation of all the strain terms that involve the "isohydrogen" amounts to 1.63 and 0.99 kcal/mole, respectively, for the equatorial and axial methylcyclohexane. The "equatorial hydrogen effect" is then 0.64 kcal/mole, close to the 0.9 kcal/mole as given by Allinger.[2] However, this figure includes contributions from other atoms involved in various strain terms and they must be subtracted in order to obtain the real contribution of the "isohydrogen" atom. Such correction is difficult if not impossible since not all the interactions are pairwise but some are three- and four-centered, such as angle and torsional strain, and there is no definitive way of correctly dividing interaction energies over the component atoms. As a crude measure, assuming that the "equatorial hydrogen effect" consists mainly of non-bonded interactions and that they may be equally distributed between the two atoms involved, one half of the "effect", about 0.3 kcal, may be regarded as the real contribution of "isohydrogen" to the conformational energy. This figure is quite close to the sum of the contributions of the CH group to the conformational energy (Table 4).

With this point in mind, we tested the proposed invariance of the "equatorial hydrogen effect" of several monoalkylcyclohexanes. Results of these calculations are summarized in Table 5. The Table includes calculated axial-equatorial conformational energies of monoalkylcyclohexanes, which are obtained from calculated heats of formation listed in Table 6. For some of the alkylcyclohexanes, rotational isomerism arises from the rotation of the $\mathrm{C_{ring}{-}C_{substituent}}$ pivot bond. In the axial conformers, the isomer with the bulk of the substituent over the ring is 3–8 kcal less stable than the other, whereas among equatorial conformers, the energy difference is small. Conformational energies given in Table 5 are based on the more stable isomer pairs. For equatorial isopropylcyclohexane, two rotamers have almost identical energy (Table 6), and therefore two corresponding conformational energies are given in Table 5. Calculated conformational energies are in good agreement with experimental A values despite the fact that A values pertain to free energies in solution while calculations refer to the gas phase.

Table 5. Equatorial hydrogen effects and axial-equatorial conformational energies of alkylcyclohexanes (kcal/mol, 25°, gas)[a]

Substituent	Equatorial hydrogen effect	Conformational energy	$\frac{\mathrm{EHE}}{2}\Big/\mathrm{CE}\cdot 100$ (%)
Methyl	0.64	1.83[b](1.8)[c]	17.5
Ethyl	0.60	1.91 (1.8)[c]	16.7
i-Propyl	−0.11[d]	1.91[d](2.1)[c]	—[d]
	0.47[e]	1.74[e]	13.5[e]
t-Butyl	2.22	5.42[b](>4.4)[c]	20.5
Neopentyl	0.62	1.77 (2.0)[c]	17.5
1-Adamantyl	2.27	5.38	21.1
2-Adamantyl	0.38	1.68	11.3

[a] Except for methyl, *t*-butyl, and 1-adamantyl derivatives, rotational isomers regarding the ring-substituent bond exist. The values listed in this Table refer to the most stable rotamer pairs. [b] Also described in Ref. 7. [c] Experimental A value taken from Ref. 36. [d] For *gauche* H–C–C–H rotamer at cyclohexy-isopropyl pivot bond (see text). [e] For *anti* H–C–C–H rotamer at cyclohexyl-isopropyl pivot bond (see text).

Upon inspection of the "equatorial hydrogen effects" in the first column of Table 5, we are disturbed to find a *negative* "effect" for isopropylcyclohexane (*anti* axial vs *gauche* equatorial). For this particular case, the tertiary ring hydrogen is more strained in the axial (1.46 kcal) than in the equatorial position (1.35 kcal)! Close analysis reveals that the extra strain in the axial hydrogen comes from strong *gauche* H/H interactions with the tertiary isopropyl hydrogen (Fig. 4).[38]

According to our analysis, the "equatorial hydrogen effect" is not constant, but varies widely. Presumably the "effects" for isopropyl- and 1-adamantylcyclohexane represent the lower and upper limits, respectively, and there can be continuous variation of the effect with the size and shape of substituent just as there is variation in A values.[36] More important, the contribution of the "equatorial hydrogen effect" to the axial-equatorial conformational energy hardly exceeds 20%, and thus cannot be the predominant part of the conformational energy. As in methylcyclohexane mentioned above, our analysis confirms the prevailing contribution of "across-the-ring" non-bonded interactions as well as angle bending terms of the axial conformation to the axial-equatorial conformational energy for the alkylcyclohexanes listed in Table 5.

CONCLUSION

Any calculation involving the position of the hydrogen atoms in organic molecules is difficult to prove, simply because very little experimental data are available. For example, although the geometry of the cyclohexane carbocyclic ring is accurately known,[31] there is no direct experimental measurement of the distance between *syn* diaxial hydrogens (Fig. 4); the value given (2.63 Å) is calculated. In this regard, the significance of the *gauche* hydrogen hypothesis is difficult to establish experimentally and computational methods will serve as the most readily available tool.

Detailed analysis of our force field calculations presented above clearly revealed the fact that conformational energies of small, unstrained hydrocarbon molecules depend on subtle balances between component interaction terms. Especially noteworthy is our result that

Table 6. Calculated heats of formation and strain energies of substituted cyclohexanes according to the Engler force field[a] (kcal/mol, 25°, gas)

Substituent	$H\text{–}C_{ring}\text{–}C_{subst}\text{–}H$ conformation	ΔH_f°	Strain
axial methyl[b]		−35.17	2.69
		(−35.38	2.71)[c]
equatorial methyl[b]		−37.00	0.86
		(−37.06	1.03)[c]
axial ethyl	*anti*[b]	−39.30	3.69
	gauche	−35.79	7.20
equatorial ethyl	*anti*[b]	−41.21	1.78
	gauche	−40.31	2.68
axial isopropyl	*anti*[b]	−44.56	5.51
	gauche	−41.50	8.57
equatorial isopropyl	*anti*	−46.30	3.77
	gauche[b]	−46.47	3.60
axial *tert*.-butyl[b]		−47.39	10.87
		(−48.05	10.29)[c]
equatorial *tert*.-butyl[b,d]		−52.81	5.45
		(−53.76	4.58)[c]
axial neopentyl	*anti*	−48.65	14.74
	gauche	−56.22	7.17
equatorial neopentyl	*anti*	−55.20	8.19
	gauche	−57.99	5.40
axial 1-adamantyl		−47.39	17.98
equatorial 1-adamantyl		−52.77	12.60
axial 2-adamantyl	*anti*	−49.76	14.50
	gauche	−41.68	22.58
equatorial 2-adamantyl	*anti*	−51.44	12.82
	gauche	−47.30	16.96

[a]Ref. 3. [b]Calculated structure illustrated in Fig. 4. [c]Allinger 1971 force field, Ref. 6. [d]From Table 20, Ref. 7.

the 1,4-H/H interaction of methine hydrogens in *gauche* 2,3-dimethylbutane is apparently intensified as the result of interactions among geminal and *gauche* methyl groups, which is in complete contradiction with Wertz and Allinger[2] who predict exactly the opposite. This contradiction could indicate an excessively repulsive potential for non-bonded C/C interaction in the Engler force field, again pointing out the danger of basing an interpretation on a single component of a force field.

In the molecular mechanics scheme of the Westheimer type, only the non-bonded potential functions are anharmonic. Thus, all the anharmonic components of other interaction terms are formally included in the non-bonded terms,[40] which consists of H/H, C/C and C/H potentials. The fact that all the existing force field models including the one used here reproduce structure and enthalpy of small molecules if they are not too severely strained, means that the combined non-bonded potentials somehow incorporate the anharmonicity of the intramolecular force field more or less correctly. However, since they can never be tested independently, there will always be some risk when they are interpreted separately. For this reason we have used the CH_3, CH_2 and CH groups in the analysis of non-bonded interactions rather than dividing them into atom/atom pairs. Even this approach is not without limitation, since 1,2- and 1,3-interactions do not involve C/C terms (which are included in the stretching and angle bending strain terms).

In conclusion, we maintain that, in *n*-butane and perhaps also other *n*-alkanes, the *gauche* hydrogen effect is of some importance in the non-bonded terms as the result of accidental cancellation between powerful interactions involving methyl groups. In 2,3-dimethylbutane, alkylcyclohexanes and perhaps also in other branched alkanes, methyl/methyl interactions prevail over the *gauche* hydrogen effect. We maintain that even in *n*-alkanes the overall contribution of the *gauche* hydrogen effect to the total *gauche-anti* conformational energy will not exceed one third.

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[8] Recent thermochemical data indicates that the predictions based on the force fields of Refs. 6 and 7 give rather large errors for complex diamondoid hydrocarbons: T. Clark, T. McO. Knox, H. Mackle, M. A. McKervey and J. J. Rooney, *J. Am. Chem. Soc.* **97**, 3835 (1975).

[9] It is claimed that reparameterization enabled reduction of the error range to one tenth of the original: B. van der Graaf and B. M. Wepster, *Tetrahedron Letters* 2943 (1975).

[10] The second term of van der Waals potential function printed in Table 3 of Ref. 7, $(r/r_m)^6$, should read $(r_m/r)^6$.

[11] E. L. Jacob, H. B. Thompson and L. S. Bartell, *J. Chem. Phys.* **47**, 3736 (1967).

[12] For thorough discussions of non-bonded potential functions used by other workers, see Refs. 4*a*, 4*c*, 7 and J. E. Williams, P. J. Stang and P. v. R. Schleyer, *Ann. Rev. Phys. Chem.* **19**, 531 (1968).

[13] After completion of this work, we learned that Prof. Bartell modified his potential functions, which now have a larger van der Waals radius for hydrogen than the previous one: S. Fitzwater and L. S. Bartell, *J. Am. Chem. Soc* **98**, 5107 (1976). The paper also criticizes Allinger's *gauche* hydrogen hypothesis.

[14] C. Altona and D. H. Faber[4c] claim that the calculated central bond length of 1,1′-biadamantane (experimental value[15]: 1.578 Å) provides a good test for the hardness of non-bonded potentials. While the Engler force field[7] gives a reasonable value of 1.583 Å, the Allinger 1971 force field[6] also correctly calculates a value of 1.575 Å.[7] Thus, in the Allinger 1971 force field, H/H and C/C potentials appear to be well balanced and this reasoning is in accord with many correct predictions of energy and structure based on this force field.[7]

[15] R. A. Alden, J. Kraut and T. G. Traylor, *J. Am. Chem Soc.* **90**, 74 (1968).

[16] T. Clark, T. McO. Knox, H. Mackle and M. A. McKervey, *J. Chem. Soc. Chem. Commun.* 666 (1975).

[17] Perhydrotriquinacene is believed to have a twisted conformation **1** in order to avoid *some* of severe non-bonded interactions present in the eclipsed C_{3v} conformer (which has nine *eclipsed*, twelve *gauche* and six 1,5-type H/H pairs). The twisting in **1** is, however, limited by increasing C–C–C angle strain and there remains considerable strain arising from severe near-eclipsed H/H interactions. Details of the calculations together with the calculated structures and energies of all 39 polyquinanes[18] will be published elsewhere.

[18] I. T. Jacobson, Ph.D. Dissertation, University of Lund (1973).

[19] The non-bonded potentials of the Engler force field can be regarded as a modification of Boyd's parameterization,[20] which proved to have a good balance between H/H and C/C non-bonded interaction according to a recent comparative survey.[4c]

[20] S. Chang, D. McNally, S. Shary-Tehrany, M. J. Hickey and R. H. Boyd, *J. Am. Chem. Soc.* **92**, 3109 (1970).

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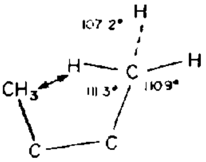
[25] Although energetically much less important than the C–C–C angle bending strain, angle deformations *within* the methyl group have never been discussed previously. Among six angles around the methyl carbon, three of them deviate about two degrees from normal ("preferred") angles (109.2° for H–C–H, and 109.5° for C–C–H).[7]



Close analysis revealed that the methyl group is tilted in a direction away from the opposing methyl group by 1.9°. An exactly analogous situation exists in *gauche*- and *anti*-2,3-dimethylbutane to produce again tilting of 1.9° in all four methyl groups.

[26] For computational technique, see K. B. Wiberg and R. H. Boyd, *J. Am. Chem. Soc.* **94**, 8426 (1972).

[27] Calculated *syn* barrier (5.01 kcal/mole) as well as the barrier between *gauche* and *anti* (2.92 kcal/mole) are considerably lower than the experimental values (6.9 and 3.8 kcal/mole, respectively) based on ultrasonic relaxation.[28] This tendency, apparently common to other force fields, has been noticed by Allinger[6] and may indicate that the molecule does not relax completely at the barriers. It should be also noted that the torsional strain may involve some of the non-bonded interactions such as 1,4-CH_3/CH_3 type.

[28] J. E. Piercy and M. C. S. Rao, *J. Chem. Phys.* **46**, 3951 (1967).

[29] This conclusion could be highly sensitive to the non-bonded potential function used.

[30] R. H. Boyd, *J. Am. Chem. Soc.* **97**, 5353 (1975).

[31] O. Bastiansen, L. Fernholt, H. M. Seip, H. Kambara and K. Kuchitsu, *J. Mol. Struct.* **18**, 163 (1973).

[32] H. J. Geise, F. C. Mijlhoff and C. Altona, *Ibid.* **13**, 211 (1972).

[33] H. J. Geise, H. R. Buys and F. C. Mijlhoff, *Ibid.* **9**, 447 (1971).

[34] Some of these values are given in Ref. 7.

[35] The manner in which the axial substituent perturbs the ring geometry appears to be rather complex. The straightforward way of avoiding crowding due to the axial substituent would be simply to increase the endocyclic C–C–C angle and decrease the exocyclic C–C–C angle at the position of substitution. However, according to the electron diffraction structure of 1,1-dimethylcyclohexane (Fig. 3), the endocyclic C–C–C angle at the quaternary carbon *decreases* compared to the cyclohexane value, apparently in response to the increase in the $C\text{–}C_{quat}\text{–}C_{methyl}$ angle. In order to keep the ring flat and the crowding over the ring at a minimum, the adjacent endocyclic C–C–C angle increases, which is mainly responsible for the decreased dihedral angle involving the quaternary carbon atom. The same trend appears in the calculated geometry of axial methylcyclohexane. The bending of the ring-substituent bond away from the ring increases to axial ethyl- and isopropylcyclohexane, apparently as the result of *gauche* CH_3/CH_2 repulsions. An accompanying decrease in the endocyclic $C\text{–}C_{tert}\text{–}C$ angle would have lead to increased folding of the ring unless compensated by an increase in the adjacent endocyclic C–C–C angle. In the cases of axial methylethyl, and isopropylcyclohexane, this compensation is not large enough, whereas in axial *tert*-butylcyclohexane a sufficiently large expansion of the adjacent endocyclic C–C–C angle is predicted (Fig. 4).

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[37] V. J. James and F. H. Moore, *Acta Cryst.* **B31**, 1053 (1975). We thank the authors for correcting some typographical errors in the publication: the y parameter (neutron) for H(15) should be −2910(3) and the three pairs of hydrogens H(9)–H(10), H(11)–H(12) and H(14)–H(15) in Fig. 1 should be reversed.

[38] Similar *gauche* H/H interactions also exist in *anti* equatorial ethylcyclohexane, but is not as strong as in the isopropyl case; this is shown by the somewhat longer distance (2.608 Å vs 2.560 Å) in Fig. 4. Why should the *gauche* H/H interactions in apparently similar environments differ from one another? According to our force field, in the isopropyl case two *gauche* C/C repulsive interactions between ring carbons and the methyl group located in the *anti* position with regard to the *axial* tertiary ring hydrogen push the *gauche* H/H pair closer than in ethylcyclohexane. Such a "downward" methyl group also exists in equatorial *tert*-butylcyclohexane, but there is no methine hydrogen atom in the *tert*-butyl group to interact with the axial methine ring hydrogen. In fact, the methine isopropyl hydrogen of *gauche* equatorial isopropylcyclohexane is more strained (1.62 kcal, engaged with five *gauche* H/H pairs) than the axial methine ring hydrogen (three *gauche* H/H pairs). With regard to *anti* equatorial isopropylcyclohexane, where the disposition between the axial methine ring hydrogen and the methine isopropyl hydrogen is *trans*, the equatorial hydrogen effect is estimated to be normal magnitude (0.47 kcal, Table 5).

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[40] While the angle bending function usually includes a cubic term, it becomes operative only at large angle deviations from the normal value, and in the molecules treated here the angle strain is entirely determined by the quadratic term.