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# Chair/Twist-Boat Energy Gap in Monocyclic, Conformationally Unconstrained Polyalkylcyclohexanes

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A conformational search procedure (HUNTER), in combination with the MM3(92) program, was used for the exploration of the conformational hypersurface of alkyl-substituted cyclohexanes and for the calculation of their chair/twist-boat (TB) energy gap. The systems studied were conformationally unconstrained polyalkylcyclohexanes (alkyl = methyl, ethyl, isopropyl, and *tert*-butyl) possessing either geminal and/or vicinal arrangements of the alkyl groups, but differing in the number of alkyl substituents and in their relative disposition (i.e., *cis* or *trans*). The calculations indicate that in 1,1,3,3,5,5-hexaisopropylcyclohexane the TB is the lowest energy form. Modification of the *cis,trans* relationship of vicinal alkyl groups changes the chair/TB energy gap, and in the minimum energy conformation of *cis,trans,trans*-1,2,3,4-tetraisopropylcyclohexane (**23c**) and *cis,syn,cis*-1,2,4,5-tetraisopropylcyclohexane (**31c**) the cyclohexyl ring adopts a TB conformation. The tetrasubstituted systems *cis,syn,cis*-1,2-diisopropyl-3,4-dimethylcyclohexane (**46**), *cis,syn,cis*-1,4-diisopropyl-2,5-dimethyl-cyclohexane (**47**), and *cis,trans,trans*-1,2-diisopropyl-3,4-dimethylcyclohexane (**41**) are the least crowded monocyclic unconstrained cyclohexanes found in which the TB conformation is of lower energy than the chair form. The present study indicates that two methyls and two isopropyl substituents are sufficient for stabilizing the TB form of a cyclohexyl ring relative to the chair form.

## Introduction

Cyclohexane adopts a chair (**1**) conformation, while the twist-boat form (TB, **2**) lies 5.5 kcal mol$^{-1}$ above it.[1,2] These conformational preferences may be altered by introducing structural constrains, e.g., by linking two or more atoms of the skeleton by an atom or a chain of atoms. These constrains may force the cyclohexyl ring to adopt an otherwise high energy conformation such as the TB[2] (as in twistane (**3**)), boat[3] (e.g., norbornane), and even a nearly planar arrangement.[4] Similarly, in some of the stereoisomers of systems containing multiple fused cyclohexane rings (e.g., perhydrophenanthrene) a ring may prefer a non-chair conformation.[1,5] At present, only few types of *unconstrained* monocyclic hydrocarbons are known where the TB form is energetically preferred over the chair conformation.[6] The first type comprises *tert*-butyl substituted cyclohexanes like *cis*-1,4-di-*tert*-butylcyclohexane in which the chair conformation is destabilized by the presence of an axial *tert*-butyl group.[7−10] The second type comprises per(cycloalkylated) cyclohexanes like the trispirane **4a**.[11,12] Not surprisingly, the accepted view is that "extreme substitution" is needed for the

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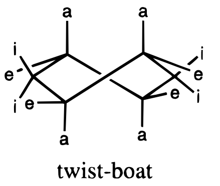
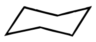
**Chart 1**



a=pseudoaxial positions ($\psi_a$)
e=pseudoequatorial positions ($\psi_e$)
i=isoclinal positions (Ic)

relative stabilization of the TB form.[1b] Although some computational studies have been performed on isolated systems, to the best of our knowledge no comprehensive study of the chair/TB energy gap has been carried out.[13] The goal of the present work was to study computationally by molecular mechanics (MM) calculations the influence of alkyl substituents on the chair/TB energy gap and to find the minimum steric requirements necessary for the relative stabilization of the TB form.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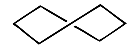
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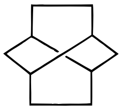
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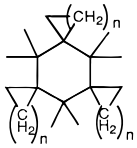
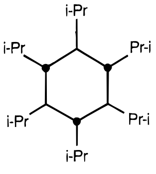


**4a** n = 1
**4b** n = 2
**4c** n = 3

## Results and Discussion

**General Considerations.** For the present study we decided to concentrate on monocyclic unconstrained cyclohexyl systems substituted by the simple alkyl substituents Me, Et, *i*-Pr, and *t*-Bu, which are ideally suitable to treatment by molecular mechanics. MM calculations have been shown to reproduce correctly the preferred conformation and structural parameters of the crowded *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane (**5**).[14] It is reasonable to assume that less crowded systems will be reproduced satisfactorily by the calculations.



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Polyalkylcyclohexanes may adopt a large number of conformations arising from those adopted by the cyclohexane ring (i.e., chair or TB), the location of the substituents (axial/equatorial in the chair form, pseudoaxial ($\Psi$a), pseudoequatorial ($\Psi$e) and isoclinal (Ic) in the TB form, Chart 1), and if the alkyl groups do not have conical symmetry (e.g., $R$ = Et, *i*-Pr) resulting also from the conformation adopted by the alkyl group (i.e., *ap*, ±*sc*).

For calculating the conformational hypersurface of each molecule we used the MM3(92) program[15] with a conformational search procedure (HUNTER)[16] involving a simulated annealing algorithm[17] and perturbation of the molecule by flapping the ring atoms[18] and rotating the bonds of the side chains. When discussing the relative energies of the different conformations we will refer to the forms having the lowest steric energy within the corresponding manifold of conformations. For each substitution pattern and disregarding the conformation of the alkyl groups, two chair forms related by a ring inversion process must be considered. These forms can be homomeric (as in the case of *cis*-1,4-di-*tert*-butylcyclohexane), enantiomeric (as for *cis*-1,2-di-*tert*-butylcyclohexane), or diastereomeric. In all cases where the ring inversion results in homomerization or enantiomerization, the chair form possesses necessarily an even number of substituents. Chair conformations having all or most of the alkyl substituents in equatorial or axial positions will be denoted chair(eq) and chair(ax), respectively.

**TB Conformations in Cycloalkylated Cyclohexanes.** Solution (NMR) and MW data suggests that the central ring of the cycloalkylated cyclohexane **4a** adopts a TB conformation.[11] The chair conformation of **4a** has been calculated as 0.2 kcal mol$^{-1}$ more stable (MM2′ force field)[19] and 10.65 kcal mol$^{-1}$ less stable (MM2[15] force field)[11b] than the TB form. Recalculation of the TB/chair energy gap by the MM3 program indicates that the TB form is more stable than the chair by 6.2 kcal mol$^{-1}$.[11c] According to the calculations, increasing the size of the external rings (i.e., **4a** → **4b** → **4c**) results in an increased stabilization of the chair form, the latter conformation being more stable than the TB by 4.8 (**4b**) and 9.0 (**4c**) kcal mol$^{-1}$.

The relative stabilization of the TB form of **4a** may be due to the geometrical constrains forced by the cyclopropyl groups. In **4a**, the cyclopropyl methylenes are located far from the "natural" positions (i.e., the axial and equatorial positions in the chair form) due to the geometrical requirements of the spirocyclopropyl groups (all endocyclic cyclopropyl angles should be near 60°), and this special geometry affects the relative stability of the chair and TB forms. Dodecamethylcyclohexane (**6**) (formally derived from **4a** by cleavage of three cyclopropyl C−C bonds), although sterically similar to **4a**, exists in a chair conformation,[20] which supports the view that the distortions in the positions of the axial and equatorial

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[13] (a) For an early review on MM calculations of the chair/TB energy gap see ref 2a. (b) For reviews on molecular mechanics calculations of cyclohexanes see: Osawa, E.; Varnali, T. in ref 1c, Chapter 4, p 137. (c) For a review on ab initio studies of cyclohexane rings see: Cremer, D.; Szabo, K. J. in ref 1c, Chapter 3, p 59. (d) For early molecular mechanics calculations of the chair/TB energy gap see: Hendrickson, J. B. *J. Am. Chem. Soc.* **1961**, *83*, 4537. Wiberg, K. B.; Boyd, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 8426.

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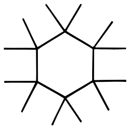
[20] Fitjer, L.; Scheuermann, H.-J. ; Wehle, D. *Tetrahedron Lett.* **1984**, *25*, 2329. Wehle, D.; Scheuermann, H.-J.; Fitjer, L. *Chem. Ber.* **1986**, *119*, 3127. For molecular mechanics calculations on the system see: Ermer, O.; Ivanov, P. M.; Osawa, E. *J. Comput. Chem.* **1985**, *6*, 401. According to the calculations the chair form of dodecamethylcyclohexane is more flattened and more flexible than the one of cyclohexane.

**Table 1. Calculated Relative Steric Energies and Heats of Formation (MM3, in kcal mol$^{-1}$) of *tert*-Butyl-Substituted Cyclohexanes**

| compd | chair(eq)[a] | | chair(ax)[b] | TB[c] | HFO[d] |
|---|---|---|---|---|---|
| *cis*-1,2-*t*-$Bu_2C_6H_{10}$ (**7a**)[e] | | 0.0 | | 4.8 (Ic,Ψe) | −57.69 |
| *trans*-1,2-*t*-$Bu_2C_6H_{10}$ (**7b**) | 6.2 | | 0.0 | 0.5 (Ic,Ψa) | −63.20 |
| *cis*-1,3-*t*-$Bu_2C_6H_{10}$ (**8a**) | 0.0 | | NF[f] | 6.4 (Ic,Ψe) | −76.87 |
| *trans*-1,3-*t*-$Bu_2C_6H_{10}$ (**8b**)[g] | | 0.9 | | *0.0* (Ψe,Ψe) | −71.53 |
| *cis*-1,4-*t*-$Bu_2C_6H_{10}$ (**9a**)[g] | | 0.6 | | *0.0* (Ψe,Ψe) | −71.51 |
| *trans*-1,4-*t*-$Bu_2C_6H_{10}$ (**9b**) | 0.0 | | 12.2 | 7.4 (Ic,Ic) | −76.91 |
| *all-cis*-1,3,5-*t*-$Bu_3C_6H_9$ (**10a**) | 0.0 | | NF[f] | NF[h] | −100.52 |
| *cis,trans*-1,3,5-*t*-$Bu_3C_6H_9$ (**10b**) | 0.3(aee) | | NF[f] | *0.0* (Ic,Ψe,Ψe) | −94.50 |

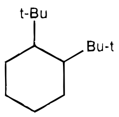
[a] Lowest energy conformation with all (or most) of the alkyl groups in equatorial positions. [b] Lowest energy conformation with all (or most) of the alkyl groups in axial positions. [c] Lowest calculated twist-boat conformation. [d] Heat of formation of the lowest energy conformation. [e] Two enantiomeric forms related by chair inversion. [f] No chair conformation was found. [g] Two homomeric forms related by chair inversion. [h] No twist-boat conformation was found

substituents are responsible for the TB/chair stability reversal in **4a**.

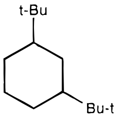


**6**

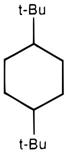
***tert*-Butylcyclohexanes.** The *tert*-butyl-substituted cyclohexanes represent one of the most thoroughly studied family of sterically hindered cyclohexanes. In general, chair conformations possessing a *tert*-butyl group located in an axial position are strongly destabilized by 1,3-diaxial interactions. NMR evidence suggests that *trans*-1,3-di-*tert*-butylcyclohexane (**8b**), *cis*-1,4-di-*tert*-butylcyclohexane (**9a**), and *cis,trans*-1,3,5-tri-*tert*-butylcyclohexane (**10b**) prefer nonchair (TB) over chair conformations, while *cis*-1,3-di-*tert*-butylcyclohexane (**8a**) and *trans*-1,4-di-*tert*-butylcyclohexane (**9b**) adopt chair conformations.[7−10] The results of the present calculations are collected in Table 1.



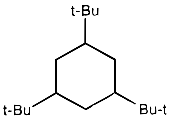
**7a** *(cis)*
**7b** *(trans)*



**8a** *(cis)*
**8b** *(trans)*



**9a** *(cis)*
**9b** *(trans)*



**10a** *(cis-cis)*
**10b** *(cis-trans)*

According to the MM3 calculations, the chair is favored by 4.8 kcal mol$^{-1}$ over the TB form in *cis*-1,2-di-*tert*-butylcyclohexane (**7a**) while for its *trans* stereoisomer (**7b**) the TB and chair(ax) forms have similar energies, the chair(ax) being favored by only 0.5 kcal mol$^{-1}$. Previous MM2 calculations have also indicated that both the chair(ax) and TB forms should be of similar energies, and the TB form was calculated as 0.4 kcal mol$^{-1}$ less stable than the chair(ax) form.[10d] X-ray diffraction of an analog of **7b** has shown that in the crystal the compound exists in a chair(ax) conformation.[21]

According to the MM3 calculations, the TB forms of **8b** and **9a** are preferred over the chair by 0.9 and 0.6 kcal mol$^{-1}$, respectively, in agreement with solution NMR data[8,9] and an electron diffraction study of **9a**, which has shown that both the chair and TB forms are populated.[9b] Previous calculations on **9a** have given either the chair or the TB forms as ground state forms.[10]

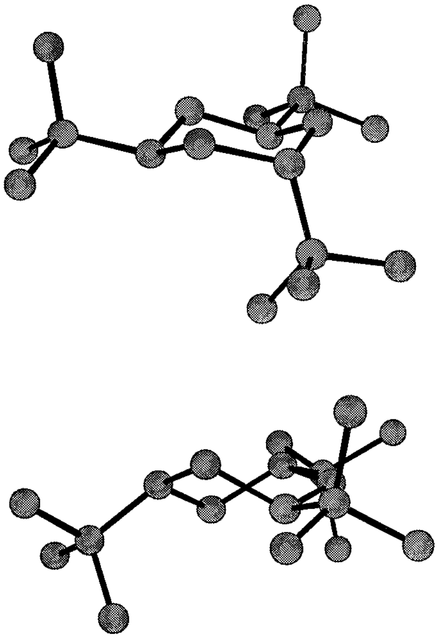


**Figure 1.** Calculated (MM3) structures of the chair (top) and twist-boat (bottom) forms of *cis,trans*-1,3,5-tri-*tert*-butylcyclohexane (**10b**).

In *all-cis*-1,3,5-tri-*tert*-butylcyclohexane (**10a**), the three alkyl groups can be accommodated in equatorial positions, and not surprisingly, the chair(eq) is the preferred form. However, for the *cis,trans* stereoisomer (**10b**) the TB is the global minimum with the chair(eq) form lying 0.3 kcal mol$^{-1}$ above it. These results are in agreement with spectroscopic data that suggest that both the TB and chair forms should be present in solution.[22] The calculated geometries of the chair(eq) and TB forms of **10b** are displayed in Figure 1. Examination of Table 1 indicates that in all the *t*-Bu-substituted cyclohexanes studied that exist in a ground state TB conformation, the TB/chair energy gap is not large, being at most 0.9 kcal mol$^{-1}$ for **8b**.

**Geminally Disubstituted Systems.** In order to overcome the intrinsic energy difference between the chair and TB forms, the formal introduction of substituents on the cyclohexane must result in a larger destabilization of the chair than of the twist form. We examined systems consisting of a cyclohexyl ring geminally substituted by two identical substituents (cf. **11**).

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(22) van Bekkum, H.; Buurmans, H. M. A.; van Minnen-Pathuis, G.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 779.

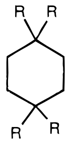
**Table 2. Calculated Relative Steric Energies and Heats of Formation (MM3, in kcal mol$^{-1}$) of Geminally Disubstituted Polyalkylcyclohexanes**

| compd | chair$^a$ | TB$^b$ | HFO$^c$ |
|---|---|---|---|
| 1,1-$Me_2C_6H_{10}$ | 0.0 | 5.7 (Ic,Ic) | −43.73 |
| 1,1-$Et_2C_6H_{10}$ | 0.0 | 5.1 (Ic,Ic) | −50.57 |
| 1,1-*i*-$Pr_2C_6H_{10}$ | 0.0 | 4.2 (Ic,Ic) | −53.57 |
| 1,1,2,2-$Me_4C_6H_8$ | 0.0 | 7.9 (Ic,Ic,Ψa,Ψe) | −52.68 |
| 1,1,2,2-$Et_4C_6H_8$ | 0.0 | 6.3 (Ic,Ic,Ψa,Ψe) | −57.88 |
| 1,1,2,2-*i*-$Pr_4C_6H_8$ | 0.0 | 8.5 (Ic,Ic,Ψa,Ψe) | −46.33 |
| 1,1,3,3-$Me_4C_6H_8$ | 0.0 | 5.0 (Ic,Ic,Ψa,Ψe) | −54.62 |
| 1,1,3,3-$Et_4C_6H_8$ | 0.0 | 4.2 (Ic,Ic,Ψa,Ψe) | −67.66 |
| 1,1,3,3-*i*-$Pr_4C_6H_8$ | 0.0 | 2.4 (Ψa,Ψe,Ψa,Ψe) | −71.19 |
| 1,1,4,4-$Me_4C_6H_8$ (**11a**) | 0.0 | 5.6 (Ic,Ic,Ic,Ic) | −57.59 |
| 1,1,4,4-$Et_4C_6H_8$ (**11b**) | 0.0 | 5.5 (Ic,Ic,Ic,Ic) | −71.35 |
| 1,1,4,4-*i*-$Pr_4C_6H_8$ (**11c**) | 0.0 | 2.7 (Ic,Ic,Ic,Ic) | −77.50 |
| 1,1,2,2,3,3-$Me_6C_6H_6$ (**12a**) | 0.0 | 5.6 (Ψa,Ψe,Ic,Ic,Ψa,Ψe) | −55.60 |
| 1,1,2,2,3,3-$Et_6C_6H_6$ (**12b**) | 0.0 | 4.0 (Ψa,Ψe,Ic,Ic,Ψa,Ψe) | −55.60 |
| 1,1,2,2,3,3-*i*-$Pr_6C_6H_6$ (**12c**) | 0.0 | 4.1 (Ψa,Ψe,Ic,Ic,Ψa,Ψe) | −12.52 |
| 1,1,3,3,5,5-$Me_6C_6H_6$ (**13a**) | 0.0 | 1.8 (Ic,Ic,Ψa,Ψe,Ψa,Ψe) | −62.76 |
| 1,1,3,3,5,5-$Et_6C_6H_6$ (**13b**) | 0.0 | 0.6 (Ic,Ic,Ψa,Ψe,Ψa,Ψe) | −81.61 |
| 1,1,3,3,5,5-*i*-$Pr_6C_6H_6$ (**13c**) | 0.9 | *0.0* (Ic,Ic,Ψa,Ψe,Ψa,Ψe) | −83.61 |

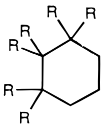
$^a$ Lowest energy chair conformation. $^b$ Lowest calculated twist-boat conformation. $^c$ Heat of formation of the lowest energy conformation.

Disregarding the possible different orientations of nonconical alkyl substituents, these systems should exist in a single chair conformation, in which repulsive alkyl/H diaxial 1,3-interactions should be present. The relative energies of the chair and the TB conformations together with the heat of formation of the lowest energy conformation of the systems are collected in Table 2.

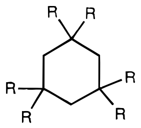
The calculations indicate that increasing the bulk of the substituent from Me to *i*-Pr in 1,1-dialkylcyclohexanes decreases the chair/TB energy gap from 5.7 to 4.2 kcal mol$^{-1}$. Although the formal introduction of additional geminal substituents at vicinal positions should result in repulsive 1,3-diaxial interactions between substituents in the chair form, according to the calculations the chair/TB energy gap is not reduced. For example, for the crowded **12c** the chair/TB energy gap is 4.1 kcal mol$^{-1}$. However, if the geminal disubstituted carbons are at 1,3- vicinal positions, the chair form is preferentialy destabilized by the *syn* 1,3-diaxial interactions between the alkyl groups. For example, whereas the chair/TB gap is 5.7 kcal mol$^{-1}$ for 1,1-dimethylcyclohexane, this gap is reduced to 5.0 and 1.8 kcal mol$^{-1}$ for 1,1,3,3-tetramethylcyclohexane and **13a**, respectively.[23] Although the energy gap between the two conformers of **13a** is smaller than for cyclohexane, the chair is still more stable than the TB form. The chair/TB energy gap is further reduced by the increased destabilization of the chair with the increase in bulk of the substituents and in the hexaisopropylcyclohexane derivative **13c** the TB form represents the lowest energy conformation.



**11**



**12**

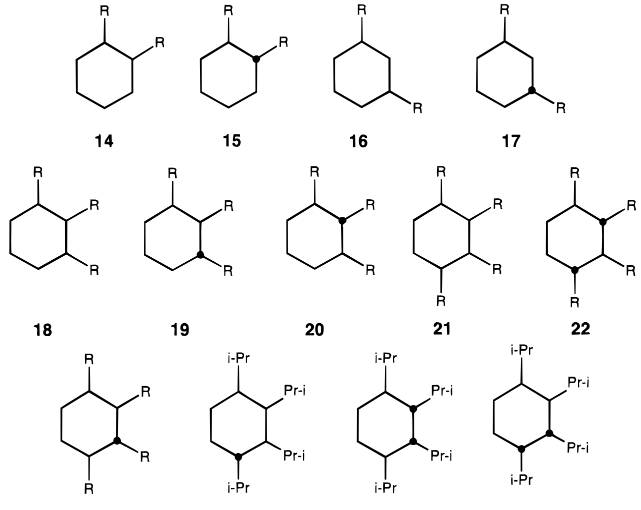


**13**

**a:** R = Me, **b:** R = Et, **c:** R = *i*-Pr

**Vicinal Substituted Systems.** In order to find out whether systems less substituted than **13c** may exist in a ground state twist conformation, we examined di-, tri-, and tetraalkyl systems vicinally substituted in different *cis-trans* stereochemistries (Chart 2).[13,24]

**Chart 2**



**a:** R = Me, **b:** R = Et, **c:** R = *i*-Pr

Increasing the number of vicinal *all-cis* alkyl groups does not reduce the chair/TB energy gap as shown by the calculations for the systems **14**, **18**, and **21** (Table 3).[25] For example, in *all-cis*-1,2,3,4-tetraisopropylcyclohexane (**21c**) the chair form is more stable than the TB form by 5.2 kcal mol$^{-1}$. The chair/TB energy gap decreases in the *all-trans* series **15c** → **20c** → **22c** with the increase in number of vicinal isopropyl groups, the lowest energy gap (0.6 kcal mol$^{-1}$) corresponding to **22c**. In order to reverse the chair/TB stability order, both the chair(eq) *and* the chair(ax) forms must be destabilized relative to the TB conformation. This is not fulfilled in the *all-trans* systems examined since the destabilization of the chair is not sufficient to render the TB the lowest energy form.

The relative destabilization of *both* the chair(eq) and chair(ax) may be achieved by a combination of *cis* and *trans* dispositions of the alkyl groups in the polyalkylcyclohexane. This guarantees that in each chair form both axial and equatorial substituents are present, which should result in the destabilization of both chair forms. We therefore examined different *cis*,*trans* arrangements of a 1,2,3-trialkyl system as well as of the system with the lowest chair/TB energy gap found, namely, 1,2,3,4-tetraisopropylcyclohexane. As shown in Table 3, in all 1,2,3-trialkyl derivatives examined the chair form is preferred. However, in the *cis*,*trans*,*trans* tetraisopropyl system (**23c**), the TB form represents the minimum energy conformation, being 2.2 kcal mol$^{-1}$ more stable than the chair(ax) form. Other *cis*−*trans* combinations resulted in systems that prefer chair conformations. Although **23c** is unknown, a sterically similar tetracyclohexyl analog (*cis*,*trans*,*trans*-1,2,3,4-tetracyclohexylcyclohexane (**27**)) has been prepared and shown to exist by X-ray crystallography in a TB conformation.[26] In the

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(23) Early MM calculations have also predicted a chair conformation for **13a**. Schmidt, H. G.; Jaeschke, A.; Friebolin, H.; Kabuss, S.; Mecke, R. *Org. Magn. Reson.* **1969**, *1*, 163. Friebolin, H.; Schmidt, H. G.; Kabuss, S.; Faisst, W. *Org. Magn. Reson.* **1969**, *1*, 147.

(24) Some of these systems were also calculated using the older MM2 program. We found consistently that the calculated relative stability of the TB form is larger using MM2 than using MM3.

(25) *all-cis*-1,2,3,4,5,6-Hexamethylcyclohexane has been shown to exist in a chair conformation. Werner, H.; Mann, G.; Mühlstädt, M.; Köhler, H.-J. *Tetrahedron Lett.* **1970**, 3563.

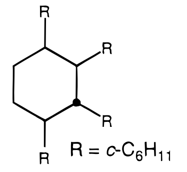
(26) (a) Columbus, I.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1994**, *116*, 10306. (b) Columbus, I.; Hoffmann, R. E.; Biali, S. E. *J. Am. Chem. Soc.* **1996**, *118*, 6890.

**Table 3. Calculated Relative Steric Energies and Heats of Formation (MM3, in kcal mol$^{-1}$) of Vicinally Substituted Polyalkylcyclohexanes**

| compd | chair(eq)[a] | chair(ax)[b] | TB[c] | HFO[d] |
|---|---|---|---|---|
| *cis*-1,2-Me$_2$C$_6$H$_{10}$ (**14a**)[e] | 0.0 | | 5.6 (Ic,Ψe) | −41.41 |
| *trans*-1,2-Me$_2$C$_6$H$_{10}$ (**15a**) | 0.0 | 2.6 | 6.2 (Ψe,Ψe) | −43.18 |
| *cis*-1,2-Et$_2$C$_6$H$_{10}$ (**14b**)[e] | 0.0 | | 5.6 (Ic,Ψe) | −50.42 |
| *trans*-1,2-Et$_2$C$_6$H$_{10}$ (**15b**) | 0.0 | 2.0 | 5.4 (Ψe,Ψe) | −51.50 |
| *cis*-1,2-*i*-Pr$_2$C$_6$H$_{10}$ (**14c**)[e] | 0.0 | | 3.0 (Ic,Ψe) | −56.10 |
| *trans*-1,2-*i*-Pr$_2$C$_6$H$_{10}$ (**15c**) | 0.0 | 2.1 | 6.0 (Ψe,Ψe) | −61.65 |
| *cis*-1,3-Me$_2$C$_6$H$_{10}$ (**16a**) | 0.0 | 5.7 | 6.9 (Ic,Ψe) | −44.49 |
| *trans*-1,3-Me$_2$C$_6$H$_{10}$ (**17a**)[e] | 0.0 | | 4.4 (Ψe,Ψe) | −42.86 |
| *cis*-1,3-Et$_2$C$_6$H$_{10}$ (**16b**) | 0.0 | 5.9 | 6.4 (Ic,Ψe) | −53.85 |
| *trans*-1,3-Et$_2$C$_6$H$_{10}$ (**17b**)[e] | 0.0 | | 3.8 (Ψe,Ψe) | −52.04 |
| *cis*-1,3-*i*-Pr$_2$C$_6$H$_{10}$ (**16c**) | 0.0 | 7.2 | 6.5 (Ic,Ψe) | −64.32 |
| *trans*-1,3-*i*-Pr$_2$C$_6$H$_{10}$ (**17c**)[e] | 0.0 | | 3.7 (Ψe,Ψe) | −62.60 |
| *all-cis*-1,2,3-Me$_3$C$_6$H$_9$ (**18a**) | 0.0 | 4.1 | 8.0 (Ic,Ψa,Ψe) | −47.17 |
| *all-cis*-1,2,3-Et$_3$C$_6$H$_9$ (**18b**) | 0.0 | 2.1 | 6.1 (Ic,Ψe,Ψa) | −58.45 |
| *all-cis*-1,2,3-*i*-Pr$_3$C$_6$H$_9$ (**18c**) | 0.0 | 5.0 | 7.0 (Ic,Ψa,Ψe) | −68.06 |
| *cis*,*trans*-1,2,3-Me$_3$C$_6$H$_9$ (**19a**) | 0.0 | 0.9 | 5.3 (Ψe,Ic,Ψe) | −47.32 |
| *cis*,*trans*-1,2,3-Et$_3$C$_6$H$_9$ (**19b**) | 0.0 | 0.2 | 4.7 (Ic,Ψa,Ψe) | −59.96 |
| *cis*,*trans*-1,2,3-*i*-Pr$_3$C$_6$H$_9$ (**19c**) | 3.1 | 0.0 | 2.1 (Ic,Ψa,Ψe) | −69.93 |
| *all-trans*-1,2,3-Me$_3$C$_6$H$_9$ (**20a**) | 0.0 | 5.3 | 6.3 (Ic,Ψe,Ψe) | −48.71 |
| *all-trans*-1,2,3-Et$_3$C$_6$H$_9$ (**20b**) | 0.0 | 4.3 | 6.0 (Ψe,Ic,Ψa) | −60.82 |
| *all-trans*-1,2,3-*i*-Pr$_3$C$_6$H$_9$ (**20c**) | 0.0 | 2.3 | 2.2 (Ψe,Ic,Ψa) | −71.47 |
| *all-cis*-1,2,3,4-Me$_4$C$_6$H$_8$ (**21a**)[e] | 0.0 | | 4.7 (Ψe,Ψa,Ic,Ψe) | −48.88 |
| *all-cis*-1,2,3,4-Et$_4$C$_6$H$_8$ (**21b**)[e] | 0.0 | | 7.1 (Ψe,Ψa,Ic,Ψe) | −65.35 |
| *all-cis*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**21c**)[e] | 0.0 | | 5.2 (Ic,Ψe,Ψa,Ic) | −72.95 |
| *all-trans*-1,2,3,4-Me$_4$C$_6$H$_8$ (**22a**) | 0.0 | 7.6 | 6.2 (Ic,Ψe,Ψe,Ic) | −54.12 |
| *all-trans*-1,2,3,4-Et$_4$C$_6$H$_8$ (**22b**) | 0.0 | 6.2 | 6.3 (Ψe,Ψe,Ic,Ψa) | −70.19 |
| *all-trans*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**22c**) | 0.0 | 1.6 | 0.6 (Ic,Ψa,Ψa,Ic) | −81.87 |
| *cis*,*trans*,*trans*-1,2,3,4-Me$_4$C$_6$H$_8$ (**23a**) | 0.0 | 3.6 | 5.3 (Ψe,Ic,Ψe,Ψe) | −52.90 |
| *cis*,*trans*,*trans*-1,2,3,4-Et$_4$C$_6$H$_8$ (**23b**) | 0.0 | 2.7 | 4.6 (Ψe,Ψa,Ic,Ψe) | −69.31 |
| *cis*,*trans*,*trans*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**23c**) | 4.4 | 2.2 | *0.0* (Ψe,Ψa,Ic,Ψe) | −81.29 |
| *cis*,*cis*,*trans*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**24**) | 0.0 | 1.7 | 3.9 (Ic,Ψe,Ψa,Ic) | −78.43 |
| *trans*,*cis*,*trans*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**25**)[e] | 0.0 | | 2.5 (Ic,Ψe,Ψa,Ic) | −80.73 |
| *cis*,*trans*,*cis*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**26**) | 0.0[f] | 11.0[g] | 10.8 (Ψe,Ψa,Ic,Ψa) | −81.24 |

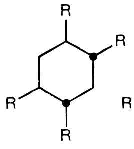
[a] Lowest energy conformation with all (or most) of the alkyl groups in equatorial positions. [b] Lowest energy conformation with all (or most) of the alkyl groups in axial positions. [c] Lowest calculated twist-boat conformation. [d] Heat of formation of the lowest energy conformation. [e] Two enantiomeric forms related by chair inversion. [f] Eq−ax−ax−eq conformer. [g] Ax−eq−eq−ax conformer.

TB form of **23c** the substituents are located at the Ψe, Ψa, Ic, and Ψe positions. The predicted locations of the substituents are identical to those found by X-ray crystallography in **27**.[26]

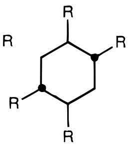


**27**

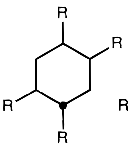
**1,2,4,5-Tetrasubstituted Systems.** Since a 1,2,3,4-disposition of four isopropyl groups may destabilize the chair form, we examined also whether two pairs or vicinal substituents (1,2,4,5 substitution) are capable of a similar effect.[27] As shown by the calculations, both the *trans-,syn,trans* and the *trans,anti,trans* isomers of a 1,2,4,5-tetraalkylcyclohexane (alkyl = Me, Et, *i*-Pr) prefer a chair conformation (Table 4). Although in the chair form of **29c** two substituents are axial, while in the TB form all alkyl groups are located at the relatively unencumbered Ψe positions, this is not sufficient to render the TB the lowest energy form. The preference for a chair conformation of **29c** has been confirmed experimentally by the synthesis and conformational study of its 1,2,4,5-tetracyclohexyl analog.[28]



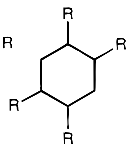
**28**



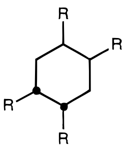
**29**



**30**



**31**



**32**

**a:** R = Me, **b:** R = Et, **c:** R = *i*-Pr

Among all the systems examined (**28**−**32**), cyclohexane **31** is unique because 1,3-diaxial alkyl/alkyl interactions must be present in its chair conformation.[29] The calculations indicate that, as observed for the vicinal substituted systems, increasing the bulk of the substituents results in the destabilization of the chair form. Notably, for the tetraisopropyl form **31c** the TB form is substantially more stable (6.8 kcal mol$^{-1}$) than the chair form (Table 4).

**Minimal Steric Crowding Necessary for the Stabilization of the TB Form.** Since for either **23c** and **31c** the TB is more stable than the chair form, we examined next whether less crowded systems than those found may also prefer the TB form. This was carried out as follows: firstly, the structure of either **23c** and **31c** was modified by replacing one of the isopropyl groups by a methyl. If in the resulting structure the TB was

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(27) The configuration of a 1,2,4,5-tetrasubstituted system will be described by the method commonly used for fused-ring cyclohexanes. The mutual disposition of two vicinal groups will be denoted as "*cis*" or "*trans*". If the two substituents at the 2 and 4 positions are in a mutual *cis* or *trans* relationship, this will be denoted by the "*syn*" and "*anti*" descriptors, respectively.

(28) Golan, O.; Biali, S. E. Unpublished results.

(29) The 1,3-diaxial repulsive interaction of two methyl groups has been estimated as 3.7 kcal mol$^{-1}$. See: Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765.

**Table 4. Calculated Relative Steric Energies and Heats of Formation (MM3, in kcal mol$^{-1}$) of 1,2,4,5-Tetrasubstituted Cyclohexanes**

<table>
<tr><th>compd</th><th>chair(eq)[a]</th><th>chair(ax)[b]</th><th>TB[c]</th><th>HFO[d]</th></tr>
<tr><td><i>trans,syn,trans</i>-1,2,4,5-$Me_4C_6H_8$ (<b>28a</b>)</td><td>0.0</td><td>9.8</td><td>9.8 (Ic,Ψa ,Ic,Ψe)</td><td>−56.53</td></tr>
<tr><td><i>trans,syn,trans</i>-1,2,4,5-$Et_4C_6H_8$ (<b>28b</b>)</td><td>0.0</td><td>8.4</td><td>7.8 (Ic,Ψa,Ic,Ψe)</td><td>−73.31</td></tr>
<tr><td><i>trans,syn,trans</i>-1,2,4,5-i-$Pr_4C_6H_8$ (<b>28c</b>)</td><td>0.0</td><td>14.0</td><td>10.2 (Ic,Ψa,Ic,Ψe)</td><td>−93.87</td></tr>
<tr><td><i>trans,anti,trans</i>-1,2,4,5-$Me_4C_6H_8$ (<b>29a</b>)</td><td colspan="2">0.0</td><td>4.1 (Ψe,Ψe,Ψe,Ψe)</td><td>−53.88</td></tr>
<tr><td><i>trans,anti,trans</i>-1,2,4,5-$Et_4C_6H_8$ (<b>29b</b>)</td><td colspan="2">0.0</td><td>3.2 (Ψe,Ψe,Ψe,Ψe)</td><td>−71.54</td></tr>
<tr><td><i>trans,anti,trans</i>-1,2,4,5-i-$Pr_4C_6H_8$ (<b>29c</b>)</td><td colspan="2">0.0</td><td>4.2 (Ψe,Ψe,Ψe,Ψe)</td><td>−91.90</td></tr>
<tr><td><i>cis,trans</i>-1,2,4,5-$Me_4C_6H_8$ (<b>30a</b>)</td><td>0.0</td><td>4.8</td><td>6.1 (Ψe,Ic,Ψe,Ic)</td><td>−54.71</td></tr>
<tr><td><i>cis,trans</i>-1,2,4,5-$Et_4C_6H_8$ (<b>30b</b>)</td><td>0.0</td><td>4.6</td><td>5.8 (Ψe,Ic,Ψe,Ic)</td><td>−72.32</td></tr>
<tr><td><i>cis,trans</i>-1,2,4,5-i-$Pr_4C_6H_8$ (<b>30c</b>)</td><td>0.0</td><td>7.3</td><td>3.9 (Ψe,Ic,Ψe,Ic)</td><td>−88.37</td></tr>
<tr><td><i>cis,syn,cis</i>-1,2,4,5-$Me_4C_6H_8$ (<b>31a</b>)</td><td colspan="2">0.0</td><td>3.3 (Ψe,Ic,Ψe,Ic)</td><td>−50.83</td></tr>
<tr><td><i>cis,syn,cis</i>-1,2,4,5-$Et_4C_6H_8$ (<b>31b</b>)</td><td colspan="2">0.0</td><td>1.8 (Ψe,Ic,Ψe,Ic)</td><td>−67.65</td></tr>
<tr><td><i>cis,syn,cis</i>-1,2,4,5-i-$Pr_4C_6H_8$ (<b>31c</b>)</td><td colspan="2">6.8</td><td><i>0.0</i> (Ψe,Ic,Ψe,Ic)</td><td>−82.52</td></tr>
<tr><td><i>cis,anti,cis</i>-1,2,4,5-$Me_4C_6H_8$ (<b>32a</b>)</td><td colspan="2">0.0</td><td>7.6 (Ψe,Ψa,Ψa,Ψe)</td><td>−52.75</td></tr>
<tr><td><i>cis,anti,cis</i>-1,2,4,5-$Et_4C_6H_8$ (<b>32b</b>)</td><td colspan="2">0.0</td><td>7.6 (Ψe,Ψa,Ψa,Ψe)</td><td>−70.81</td></tr>
<tr><td><i>cis,anti,cis</i>-1,2,4,5-i-$Pr_4C_6H_8$ (<b>32c</b>)</td><td colspan="2">0.0</td><td>3.0 (Ψe,Ψa,Ψa,Ψe)</td><td>−82.25</td></tr>
</table>

[a] Lowest energy conformation with all (or most) of the alkyl groups in equatorial positions. [b] Lowest energy conformation with all (or most) of the alkyl groups in axial positions. [c] Lowest calculated twist-boat conformation. [d] Heat of formation of the lowest energy conformation.

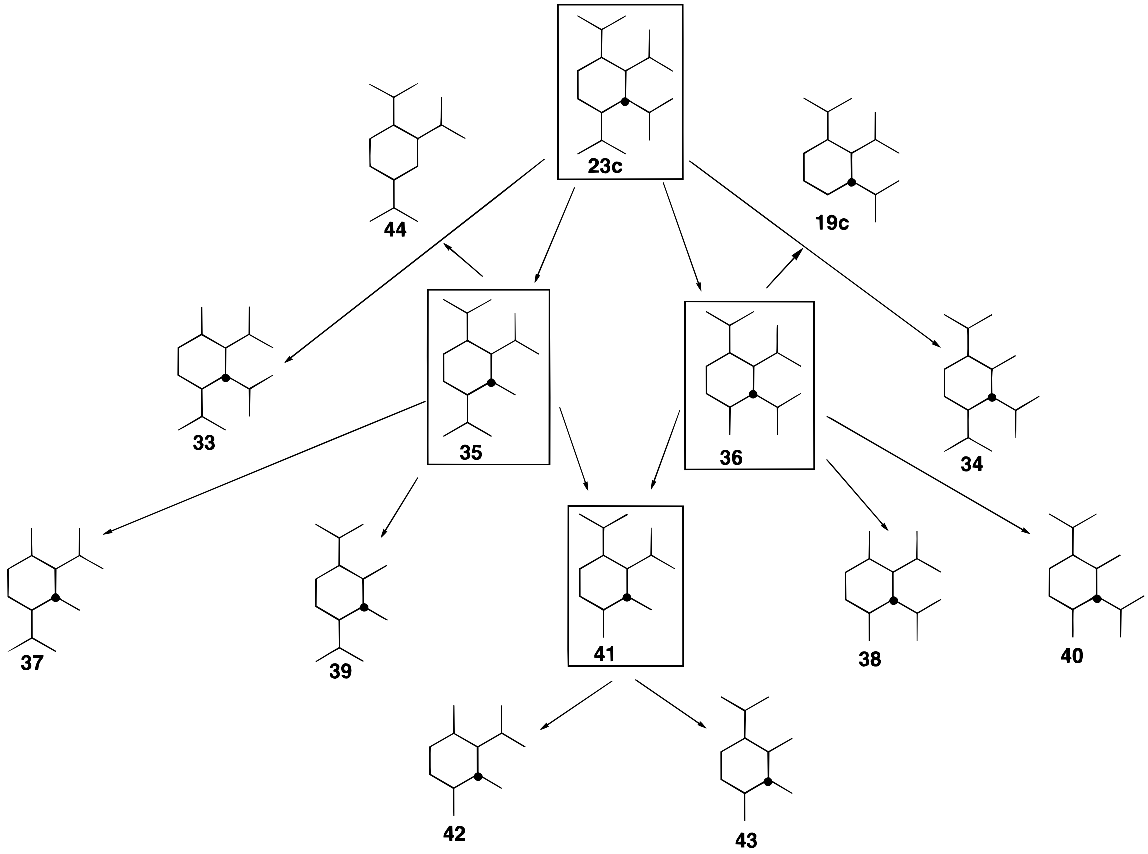


**Figure 2.** Reduction of the steric crowding of *cis,cis,trans*-1,2,3,4-tetraisopropylcyclohexane (**23c**). Structures in which the ring exists in a TB form in the lowest energy conformation are enclosed in boxes. The least crowded form prefering a TB conformation is **41**.

still calculated to be of lower energy than the chair form, two parallel substitutions were carried out: (i) The methyl group was replaced by a hydrogen. (ii) An additional isopropyl was replaced by a methyl. If in any of the resulting structures the TB was calculated as of lower energy than the chair form, the *i*-Pr → Me or Me → H replacement process was repeated starting from that structure until no more systems preferring the TB conformation were found. The structures derived from **23c** and **31c** are displayed in Figures 2 and 3. The results of the calculations (Tables 5 and 6) indicate that tetrasubstitution is needed but two isopropyl and two methyl groups are sufficient for the relative stabilization of the TB conformation. The less crowded systems found which prefer a TB ground state are *cis,trans,trans*-1,2-diisopropyl-3,4-dimethylcyclohexane (**41**), *cis,syn,cis*-1,2-diisopropyl-4,5-dimethylcyclohexane (**46**), and *cis,syn,cis*-1,4-diisopropyl-2,5-dimethylcyclohexane (**47**), for which the lowest energy chair form lies 0.8 kcal mol$^{-1}$ above the TB form. The calculated geometries for the chair(eq), chair(ax), and TB forms of **41** are shown in Figure 4. The calculated geometries of the TB conformation of **46** and **47** are displayed in Figure 5.

**Conformational Analysis of Twist-Boat Rings.** In the chair form of cyclohexane the HCCH torsional angles are ideally ±60° and 180°. In contrast, according to MM3

**Table 5. Calculated Relative Steric Energies and Heats of Formation (MM3, in kcal mol$^{-1}$) of Systems Derived from 23c**

| compd | chair(eq)[a] | chair(ax)[b] | TB[c] | HFO[d] |
|---|---|---|---|---|
| *cis,trans,trans*-1,2,3,4-*i*-Pr$_4$C$_6$H$_8$ (**23c**) | 4.4 | 2.2 | *0.0* (Ψe,Ψa, Ic,Ψe) | −81.29 |
| *cis,trans,trans*-1-Me-2,3,4-*i*-Pr$_3$C$_6$H$_8$ (**33**) | 0.0 (aeee) | 2.9 (eaaa) | 1.7 (Ψe,Ψa, Ic,Ψe) | −72.94 |
| *cis,trans,trans*-2-Me-1,3,4-*i*-Pr$_3$C$_6$H$_8$ (**34**) | 3.2 (aeee) | 0.0 (eaaa) | 0.55 (Ψe,Ψa, Ic,Ψe) | −76.68 |
| *cis,trans,trans*-3-Me-1,2,4-*i*-Pr$_3$C$_6$H$_8$ (**35**) | 0.8 (aeee) | 2.7 (eaaa) | *0.0* (Ψe,Ψa, Ic,Ψe) | −73.39 |
| *cis,trans,trans*-4-Me-1,2,3-*i*-Pr$_3$C$_6$H$_8$ (**36**) | 3.5 (aeee) | 1.7 (eaaa) | *0.0* (Ψe,Ψa, Ic,Ψe) | −72.13 |
| *cis,trans,trans*-1,3-Me$_2$-2,4-*i*-Pr$_2$C$_6$H$_8$ (**37**) | 0.0 (aeee) | 6.4 (eaaa) | 5.0 (Ψe,Ψa, Ic,Ψe) | −68.33 |
| *cis,trans,trans*-1,4-Me$_2$-2,3-*i*-Pr$_2$C$_6$H$_8$ (**38**) | 0.0 (aeee) | 2.5 (eaaa) | 2.6 (Ψe,Ψa, Ic,Ψe) | −64.63 |
| *cis,trans,trans*-2,3-Me$_2$-1,4-*i*-Pr$_2$C$_6$H$_8$ (**39**) | 0.2 (aeee) | 0.0 (eaaa) | 1.4 (Ψe,Ψa, Ic,Ψe) | −68.33 |
| *cis,trans,trans*-2,4-Me$_2$-1,3-*i*-Pr$_2$C$_6$H$_8$ (**40**) | 2.8 (aeee) | 0.0 (eaaa) | 0.4 (Ψe,Ψa, Ic,Ψe) | −67.44 |
| *cis,trans,trans*-3,4-Me$_2$-1,2-*i*-Pr$_2$C$_6$H$_8$ (**41**) | 0.8 (aeee) | 2.1 (eaaa) | *0.0* (Ψe,Ψa, Ic,Ψe) | −64.15 |
| *cis,trans,trans*-1,3,4-Me$_3$-2-*i*-Pr-C$_6$H$_8$ (**42**) | 0.0 (aeee) | 5.3 (eaaa) | 5.1 (Ψe,Ψa, Ic,Ψe) | −59.22 |
| *cis,trans,trans*-1-*i*-Pr-2,3,4-Me$_3$C$_6$H$_8$ (**43**) | 0.3 (aeee) | 0.0 (eaaa) | 1.5 (Ψe,Ψa, Ic,Ψe) | −59.13 |
| *cis,syn*-1,2,4-*i*-Pr$_3$C$_6$H$_9$ (**44**) | 0.0 | 8.6 | 2.9 (Ψe,Ic,Ψe) | −73.48 |

[a] Lowest energy conformation with one axial alkyl group and the rest equatorial. [b] Lowest energy conformation with one equatorial alkyl group and the rest axial. [c] Lowest calculated twist-boat conformation. [d] Heat of formation of the lowest energy conformation.

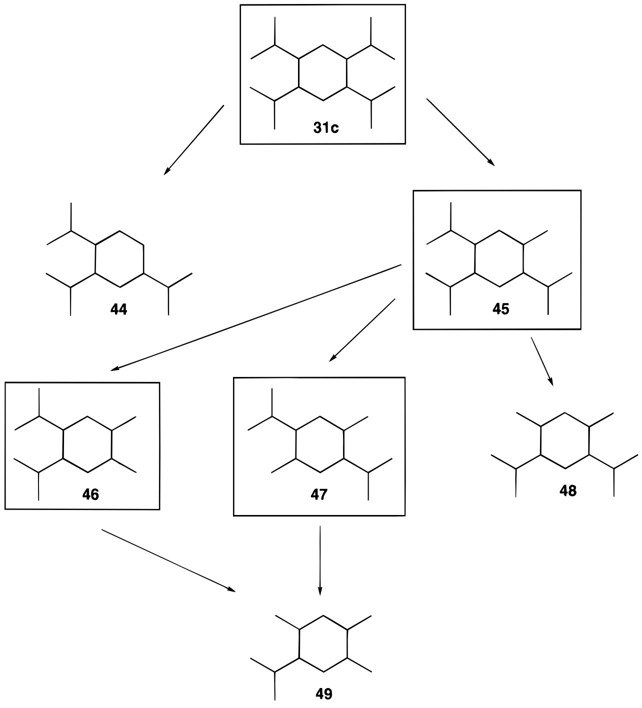
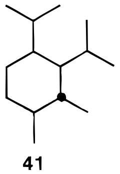
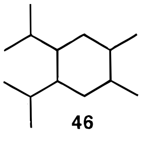
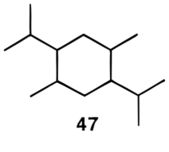


**Figure 3.** Reduction of the steric crowding of *cis,syn,cis*-1,2,3,4-tetraisopropylcyclohexane (**31c**) (see text). Structures in which the ring exists in a TB form in the lowest energy conformation are enclosed in boxes.


**41**


**46**


**47**

calculations in the TB form of cyclohexane the angle between two hydrogens at Ψe positions is 53°, while the angles between either a Ψe or Ψa hydrogen and the vicinal Ic hydrogens *cis* to them are 32°. Two vicinal *cis* substituents can adopt either (Ψe,Ψa), (Ψe,Ic), or (Ψa,Ic) arrangements while two vicinal *trans* substituents can adopt either (Ψe,Ψe), (Ψa,Ψa), (Ψe,Ic), or (Ψa,Ic) arrangements. Hendrickson's calculations indicate that, in analogy to the chair conformations, the Ψa positions are disfavored for alkyl substituents.[13d] Our calculations show that this rule holds for polymethyl systems, where, with no exceptions, in the TB form the substituents prefer Ψe or Ic over Ψa positions. In *cis*-dialkyl systems (R = Me, Et, *i*-Pr, *t*-Bu) the substituents adopt (Ic, Ψe) positions probably because this arrangement avoids locating substituents at the Ψa position.

The mutual interactions between the *t*-Bu groups play a central role in determining the preferred conformation of *trans*-1,2-di-*tert*-butylcyclohexane systems. It could be expected that the larger the dihedral angle between the groups the smaller the mutual steric repulsion. Although for the *trans* isomer the (Ψa,Ψa) arrangement allows the largest dihedral angle between the *tert*-butyls, the repulsive 1,4-interaction of the two groups with the Ψa hydrogens makes this arrangement energetically costly. The conformation adopted (Ψa,Ic) is the lowest in energy since, although a pseudoaxial group is present, the mutual dihedral angle between the substituents is large. The lowest energy TB forms of the rest of the *tert*-butyl substituted systems examined are all devoided of *tert*-butyls at Ψa positions. For the geminally disubstituted systems (Table 2) the calculations show that whenever possible the substituents will prefer the Ic positions, again avoiding the Ψa positions.

The axial/equatorial stability reversal observed in the chair conformation of polyalkyl cyclohexanes[14] (see below) is also observed for the TB form. One notable example is *all-trans*-**22** where for R = Me (**22a**) the substituents are located at (Ic,Ψe,Ψe,Ic) in the TB form while for R = *i*-Pr (**22c**) the substituents are located at the (Ic,Ψa,Ψa,Ic) positions. In all the *cis,trans,trans*-tetrasubstituted systems examined, the substituents are located at Ψe, Ψa, Ic, Ψe positions, which seem to be the positions of choice for locating four vicinal alkyl groups in a *cis,trans,trans*-stereochemistry.

**Axial/Equatorial Stability Reversal.** *all-trans*-Polyalkylcyclohexanes may prefer a conformation in which the groups are located at axial positions. For example, whereas in *all-trans*-1,2,3,4,5,6-hexaethylcyclohexane[30] and *all-trans*-1,2,3,4,5,6-hexa-*n*-propylcyclohexane[31] the alkyl groups are located in equatorial positions, both the computational and experimental evidence indicates that **5** exists in a chair conformation with all groups located at axial positions.[14] For the *all-trans* systems (**15**, **20**, and **22**) we found that the chair(eq) form was of lower energy than the chair(ax) and that the axial/equatorial energy gap (as evidenced by the energy difference between the chair(eq) and chair(ax) forms) decreases with the increase in bulk Me < Et < *i*-Pr. This is in agreement with previous MM2 calculations which suggested that at least four neighboring isopropyl groups

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**Table 6. Calculated Relative Steric Energies and Heats of Formation (MM3, in kcal $mol^{-1}$) of Polyalkylcyclohexanes Derived from 31c**

| compd | chair(eq)[a] | chair(ax)[b] | TB[c] | HFO[d] |
|---|---|---|---|---|
| *cis,syn,cis*-1,2,4,5-*i*-$Pr_4C_6H_8$ (**31c**) | 6.8 | | *0.0* (Ψe,Ic,Ψe,Ic) | −82.58 |
| *cis,syn,cis*-1-Me-2,4,5-*i*-$Pr_4C_6H_8$ (**45**) | 0.8[d] | 7.8 | *0.0* (Ψe,Ic,Ψe,Ic) | −74.48 |
| *cis,syn,cis*-1,2-$Me_2$-4,5-*i*-$Pr_2C_6H_8$ (**46**) | 0.8 | | *0.0* (Ψe,Ic,Ψe,Ic) | −64.92 |
| *cis,syn,cis*-1,4-$Me_2$-2,5-*i*-$Pr_2C_6H_8$ (**47**) | 0.8 | | *0.0* (Ψe,Ic,Ψe,Ic) | −66.53 |
| *cis,syn,cis*-1,5-$Me_2$-2,4-*i*-$Pr_2C_6H_8$ (**48**) | 0.0[d] | 11.3 | 5.2 (Ψe,Ic,Ψe,Ic) | −70.32 |
| *cis,syn,cis*-1,2,4,$Me_3$-5-*i*-$PrC_6H_8$ (**49**) | 0.0[e] | 4.6 | 3.6 (Ψe,Ic,Ψe,Ic) | −60.59 |

[a] Lowest energy conformation with all (or most) of the alkyl groups in equatorial positions. [b] Lowest energy conformation with all (or most) of the alkyl groups in axial positions. [c] Lowest calculated twist-boat conformation. [d] Heat of formation of the lowest energy conformation. [d] Methyl group(s) axial. [e] Isopropyl group equatorial.

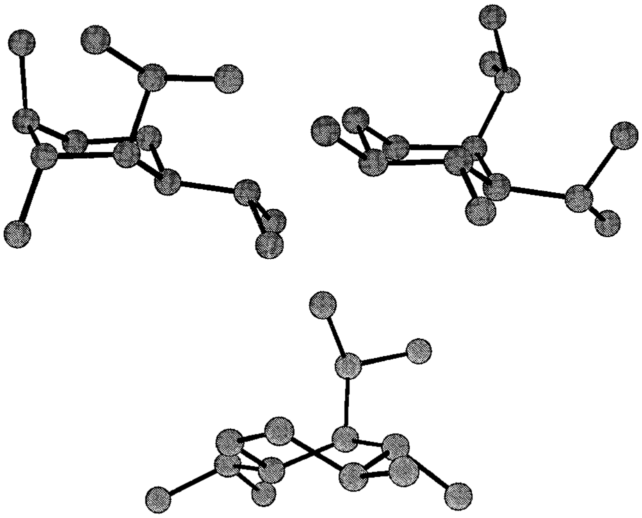


**Figure 4.** Calculated (MM3) structures of the chair(ax) (left), chair(eq) (right), and twist-boat (bottom) forms of **41**. The twist-boat form is the lowest energy conformation.

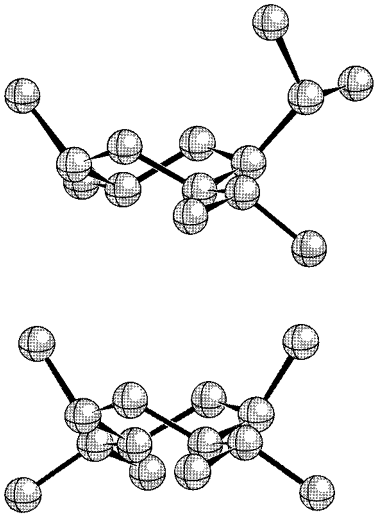
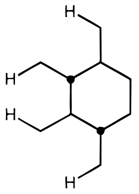


**Figure 5.** Calculated (MM3) TB conformation of **46** (top) and **47** (bottom).

are necessary for the relative stabilization of the chair(ax) form.[14] Notably, for other *cis,trans* dispositions of the substituents, three substituents seem to be sufficient to achieve stability reversal, as shown by 1,2,3-*cis,trans*-triisopropylcyclohexane (**19c**) where the chair(ax) is of lower energy than the chair(eq). A similar conformational behavior was observed for *cis,trans,trans* tetrasubstituted systems (e.g., **36**) but in some systems the chair(ax) is of higher energy than the TB form and therefore it does not represent the minimum energy form.

**Eclipsed Ground State Conformations.** According to MM2 calculations, in one of the low-energy conformations of *all-trans*-1-isopropyl-2,3,4,5,6-pentaethylcyclohexane, one ethyl group is eclipsed.[14] As generalized by Anderson, a primary alkyl group connected to an atom flanked by two bulky groups may adopt an eclipsed conformation in order to avoid the repulsive steric interactions existing in the staggered arrangements.[32,33] For example, an axial or equatorial ethyl group flanked by two bulky equatorial groups may exist in an eclipsed conformation. The present calculations provide additional examples for this effect. In both *all-cis*-1,2,3-triethylcyclohexane (**18b**) and *all-cis*-1,2,3,4-tetraethylcyclohexane (**21b**) the central axial ethyl group was found to be oriented in a nearly eclipsed arrangement (H−C−$CH_2$−Me angles of 22° and 18°, respectively).

In the lowest energy conformation of **22c** two pairs of isopropyl groups are gear meshed, with the methine protons of the groups at the 2 and 3 positions facing each other (cf., **50**). As shown previously,[26b] the gear meshed arrangement restricts the possible orientations of the groups and may force nearly eclipsed arrangements. Indeed, according to the calculations the dihedral angle between a central cyclohexyl methine and a neighboring methyl group is only 22.9°.



**50**

**Conclusions.** The twist-boat conformation may be more ubiquitous than previously realized since nonconstrained monocyclic polysubstituted cyclohexanes with moderate steric hindrance may display a ground state twist boat conformation. Two methyls and two isopropyl groups are sufficient for rendering the TB form the minimum energy conformation, as calculated for **41**, **46**, and **47**.

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