Axial/Equatorial Stability Reversal in *all-trans*-Polyalkylcyclohexanes

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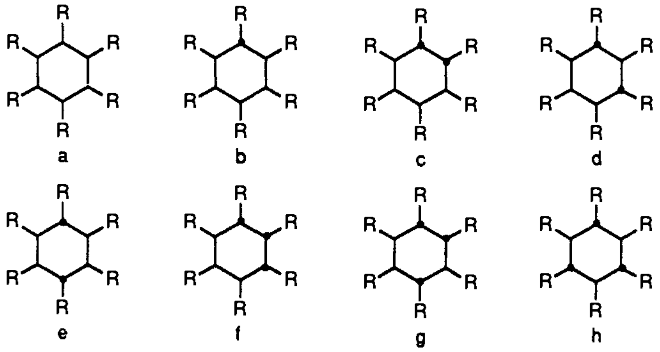
Abstract: The sterically crowded hexaalkylcyclohexane *all-trans*-hexaisopropylcyclohexane (**2**) was prepared by catalytic hydrogenation (Rh/alumina and Pd/C, 950 psi H_2, 130 °C) of an isomer (**3**) of dodecamethyl[6]radialene. Solution data, X-ray diffraction, and molecular mechanics calculations indicate that **2** prefers a conformation in which the isopropyl groups are located at *axial* rather than equatorial positions. Molecular mechanics calculations were carried out on a large number of *all-trans*-polyalkylcyclohexanes in order to find out what are the minimal steric requirements necessary for an appreciable (or exclusive) population of the all-axial conformer. Although some exceptions were indicated by the calculations, in general increasing the number and bulk of the alkyl substituent (Me → Et → *i*-Pr) results in the relative stabilization of the axial conformer. The calculations also predict that the preferred conformation of *all-trans*-polyethylcyclohexanes involves either antiperiplanar or eclipsed arrangements of one or more ethyl groups.

Introduction

Cyclohexane plays a key role in the development of stereochemistry in general and in conformational analysis in particular.[1] The paradigms of the last decades of conformational analysis are taught at the undergraduate level, usually in the form of a series of rules. After being taught that cyclohexane exists in a chair conformation, students learn that alkyl groups prefer equatorial positions over axial ones due to the repulsive interactions in the axial conformer between the alkyl group and the axial hydrogens of the 3- and 5-positions (the "1,3-diaxial interaction"). For systems containing a large number of alkyl groups, it is generally assumed that the preferred conformation will be such that as many groups as possible will adopt the equatorial positions. In the words of a popular undergraduate organic chemistry textbook "...In general the conformation with more substituents (other than hydrogen) in the equatorial position is more stable so long as the substituents are identical".[2] This rule is usually borne out experimentally. For example, X-ray diffraction showed that in the crowded *all-trans*-1,2,3,4,5,6-hexaethylcyclohexane (**1**) the six ethyl groups are located in equatorial positions.[3] Only in special cases such as alkylidene/alkylcyclohexane systems,[4] or systems displaying the anomeric effect[5] (e.g. a 2(*R*)-oxytetrahydropyran-type molecule), is there a clear tendency for the alkyl substituent to occupy the axial position. Recently, Anderson et al. reported a system in which an isopropyl group flanked by four vicinal methyl groups prefers the axial over the equatorial position.[6] The free energy difference between the axial and equatorial conformer of several monosubstituted cyclohexanes has been tabulated (the "A" value for the substituent) and in general it becomes larger with the increase in bulk of the substituent.[7] During our studies of sterically crowded gear-meshed compounds, we recently came across the first example of a molecule (*all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, **2**) that displays a novel conformational behavior, namely that *all* the alkyl groups occupy axial positions.[8] In this paper we describe the preparation and conformation of **2** and report extensive molecular mechanics calculations of *trans*-polyalkylcyclohexanes carried out in order to pinpoint the structural features responsible for the axial/equatorial stability reversal phenomenon.

Chart I



Results

Synthesis of 2. The rationale for selecting *all-trans*-hexaisopropylcyclohexane (**2**) as a synthetic target was based in our interest in gear-meshed compounds. Inspection of space filling models (CPK) indicate that in the all-equatorial conformer, the most likely conformation is such that all the groups are arranged in a gear-meshed, homodirectional fashion (i.e. all the isopropyl groups are pointing in the same direction) in a conformation which resembles the arrangement of groups in the related hexaisopropylbenzene.[9,10] Since few synthetic methods are known for the preparation of hexaalkylcyclohexanes,[11] we reasoned that it

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[1] For reviews on conformational analysis, see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965. Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: Lund, 1978.

[2] Wingrove, A. S.; Caret, R. L. *Organic Chemistry*, Harper and Row: New York, 1981; p 117.

[3] Immirzi, A.; Torti, E. *Atti Accad. Naz. Lincei, Cl. Sci. Fis. Mat. Nat. Rend.* **1968**, *44*, 98.

[4] For a review, see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375. See also: Lambert, J. B.; Clikeman, R. R.; Taba, K. M.; Marko, D. E.; Bosch, R. J.; Xue, L. *Acc. Chem. Res.* **1987**, *20*, 454.

[5] See for example: Aped, P.; Apeloig, Y.; Ellencweig, A.; Fuchs, B.; Goldberg, I.; Karni, M.; Tartakovsky, E. *J. Am. Chem. Soc.* **1987**, *109*, 1486, and references therein.

[6] Anderson, J. E.; Bettels, B. R.; Hoffman, H. M. R.; Pauluth, D.; Hellmann, S.; Beckhaus, H. D.; Ruchardt, C. *Tetrahedron* **1988**, *44*, 3701.

[7] Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267.

[8] For a preliminary communication, see: Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 893.

[9] (a) Arnett, E. M.; Bollinger, J. M. *J. Am. Chem. Soc.* **1964**, *86*, 4729. (b) Hopff, H. Gati, A. *Helv. Chim. Acta* **1965**, *48*, 509. (c) Siegel, J.; Gutiérrez, A.; Schweizer, W. B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* **1986**, *108*, 1569. (d) Mislow, K. *Chimia* **1986**, *40*, 395.

[10] For reviews on the static and dynamic stereochemistry of alkyl groups, see: Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* **1989**, *25*, 1. Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* **1985**, *18*, 80.

[11] (a) Farina, M.; Grassi, M.; Di Silvestro, G. *J. Am. Chem. Soc.* **1985**, *107*, 5100, and references therein. (b) Praefcke's group recently succeded in developing a multistep stereospecific synthesis of *all-trans*-hexahexylcyclohexane: Praefcke, K.; Psaras, P.; Kohne, B. Presented at the 6th Gentner Symposium on Chemistry, September 24-28, 1989, Rehovot/Eilat, Israel; Abstract p 17. (c) Several crowded cyclohexanes have been synthesized by Fitjer's group. See for example: Fitjer, L.; Giersig, M.; Wehle, D.; Dittmer, M.; Koltermann, G.-W.; Schormann, N.; Egert, E. *Tetrahedron* **1988**, *44*, 393, and references therein.

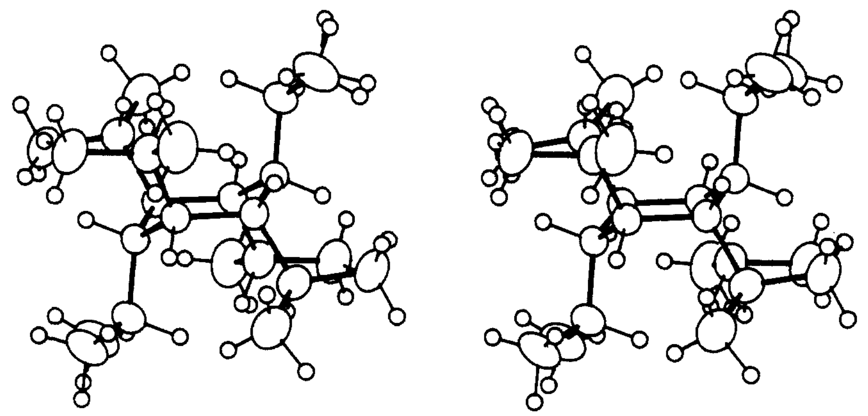
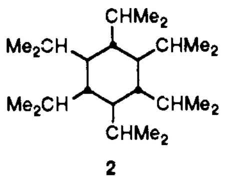


Figure 1. Stereoscopic view of the crystal structure of *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane (**2**).

would be desirable to build the C_{24} carbon skeleton in as few synthetic steps as possible followed by the modifications necessary to obtain the desired compound. Although in principle a possible route for the synthesis of **2** could be by Birch reduction of the known hexaisopropylbenzene[9] followed by catalytic hydrogenation of the resulting product, a disadvantage of this route is that the isopropyl groups effectively shield the π-cloud of the benzene ring and therefore should render extremely difficult its engagement in reactions.[12]



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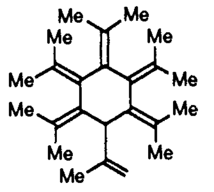

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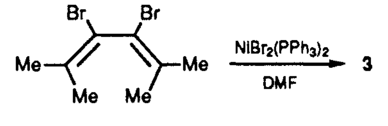
We decided to approach the synthesis of **2** from a different precursor. It was reported by Iyoda et al. that $NiBr_2(PPh_3)_2$-catalyzed trimerization of 3,4-dibromo-2,5-dimethylhexa-2,4-diene in DMF resulted in its high yield conversion into an isomer of dodecamethyl[6]radialene (**3**) (eq 1) and that the product could



(1)

be partially hydrogenated to the corresponding dihydro and tetrahydro compounds under relatively mild conditions (Pd/EtOH, cyclohexane, acetic acid).[13] We reasoned that under more drastic conditions, all the double bonds of **3** could be hydrogenated yielding the desired compound. It should be noted that if the reduction proceeds without any stereoselectivity, eight different diastereomeric products could be formed (a–h) (Chart I). However, we expected naively that the preferred product will be the all-trans product h since it is the only stereoisomer in which all the isopropyl groups can be located in equatorial positions. With all these considerations in mind we prepared **3** and attempted its exhaustive catalytic hydrogenation.

Several catalysts and conditions were tested for the **3** → **2** transformation. These included Pd(10%)/C (50 psi H_2), Rh/Al_2O_3 (48 psi H_2), and $RhCl_3$/aliquat 336/trioctylamine (1 atm H_2),[14] but in all cases the reduction proceeded only up to the tetrahydro stage, as shown by the NMR spectra. After several attempts, we found that a combination of the catalysts Rh/Al_2O_3 and Pd/C under drastic conditions (950 psi H_2, 130 °C) was successful in hydrogenating the radialene beyond the tetrahydro stage and yielded after one week of reaction a single product as evidenced by NMR.

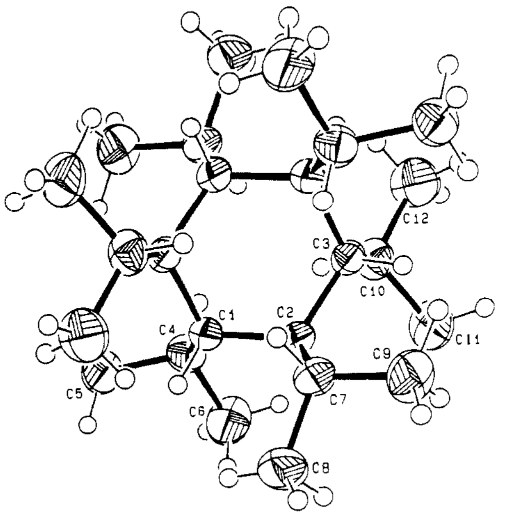


Figure 2. Top view of the crystal structure of **2** and numbering scheme.

The ^1H and proton-noise-decoupled ^{13}C NMR spectra of the isolated product (room temperature, $CDCl_3$, 200.133 and 50.33 MHz, respectively) are extremely simple. The ^{13}C NMR displays three signals at δ 23.47, 31.46, and 41.29, whereas the ^1H NMR spectrum displays signals at δ 0.97 (d, 36 H, J = 6 Hz, $CH(CH_3)_2$), 1.45 (d, 6 H, J = 10.1 Hz, C(ring)H), and 1.57 (m, 6 H, $CH(CH_3)_2$). Irradiation of the isopropyl methyl protons resulted in the conversion of the spectrum into an AB quartet (J = 10.1 Hz). The ^1H NMR spectrum remained unchanged by cooling the sample down to −70 °C in $CD_2Cl_2/CDCl_3$. The extreme simplicity of the spectra obtained was in contrast with our expectations. For the all-geared (homodirectional) equatorial conformation of **2** the two methyls of each of the six symmetry equivalent isopropyl groups are in diastereotopic environments and, therefore, are expected to display separate signals in the NMR. Although a rapid directionality reversal process could account for the observed isochrony of the methyls, this seemed to us an unlikely possibility, since the isopropyl rotational barrier of the related hexaisopropylbenzene was calculated as 35 kcal mol^{-1},[9c] and it was experimentally determined as 26.8 kcal mol^{-1} for one of its derivatives.[15]

In order to characterize structurally the obtained product and to try to understand the apparent incongruence of the NMR spectra of **2**, we decided to determine the crystal structure of the isolated product. A single crystal was grown by slow evaporation of a solution of **2** in MeOH/ether, and its structure was solved in the space group $P\bar{1}$ with one molecule per unit cell centered on a special position. To our astonishment, the X-ray structure

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[12] It has been reported (ref 9c) that in contrast to its less-crowded analogues hexaisopropylbenzene resists complexation.

[13] (a) Iyoda, M.; Tanaka, S.; Otani, H.; Nose, M.; Oda, M. *J. Am. Chem. soc.* **1988**, *110*, 8494. (b) Iyoda, M.; Tanaka, S.; Nose, M.; Oda, M. *J. Chem. Soc., Chem. Comm.* **1983**, 1058.

[14] Blum, J.; Amer, I.; Vollhardt, K. P.; Schwarz, H.; Hohne, G. *J. Org. Chem.* **1987**, *52*, 2804.

[15] Biali, S. E.; Mislow, K. *J. Org. Chem.* **1988**, *53*, 1318.

Table I. Positional Parameters and Estimated Standard Deviations for **2**[a]

atom	*x*	*y*	*z*
C(1)	0.0155 (4)	0.8277 (4)	−0.0152 (4)
C(2)	0.1796 (4)	0.8526 (4)	0.0393 (4)
C(3)	0.1476 (4)	1.0164 (3)	−0.0218 (4)
C(4)	−0.0268 (4)	0.7470 (4)	−0.2030 (4)
C(5)	−0.1523 (5)	0.6796 (5)	−0.2229 (5)
C(6)	0.1319 (5)	0.6029 (5)	−0.2540 (6)
C(7)	0.2841 (4)	0.8133 (4)	0.2336 (4)
C(8)	0.3564 (5)	0.6304 (5)	0.2666 (6)
C(9)	0.4379 (5)	0.8500 (5)	0.2978 (5)
C(10)	0.1652 (4)	0.9951 (4)	−0.2113 (4)
C(11)	0.3508 (5)	0.8720 (5)	−0.2166 (5)
C(12)	0.1184 (5)	1.1552 (5)	−0.2828 (5)

[a] Estimated standard deviations in the least significant digits are shown in parentheses.

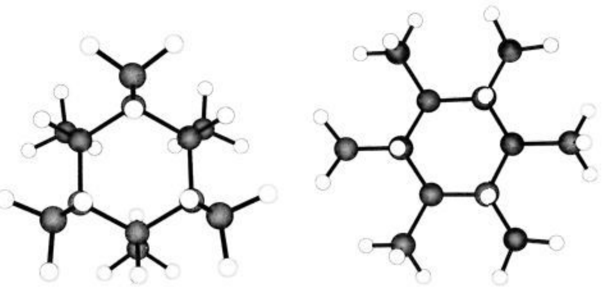
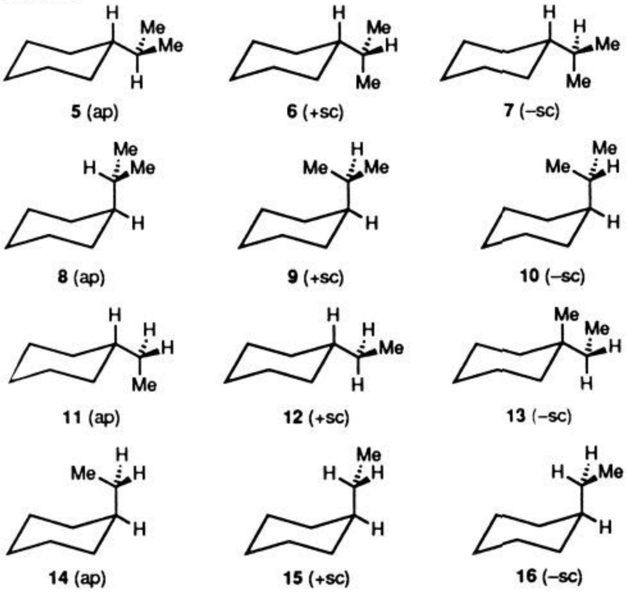


Figure 3. Top view of the calculated structure for the axial (left) and equatorial (right) conformers of *all-trans*-hexamethylcyclohexane (**4**).

Chart II



5 (ap) **6** (+sc) **7** (−sc) **8** (ap) **9** (+sc) **10** (−sc) **11** (ap) **12** (+sc) **13** (−sc) **14** (ap) **15** (+sc) **16** (−sc)

indicated that the reduction yielded the all-trans product as expected, but that all the isopropyl groups occupy *axial* rather than equatorial positions. A stereoview of the crystal structure is shown in Figure 1, a top view of the structure is shown in Figure 2, and positional parameters for the carbon atoms are collected in Table I.[16] As shown by the X-ray structure, all the isopropyl groups direct their methine hydrogens toward the center of the cyclohexane ring. Although the molecule has C_i symmetry in the crystal, the point group symmetry is approximately S_6. As shown in Figure 2, all the isopropyl groups are somewhat twisted in the same sense from their ideal bisected conformation and therefore the approximate point group symmetry is better described by the S_6 rather than the maximal D_{3d} symmetry. It seems highly likely that the conformation observed in the crystal is the same as the solution conformation. The isochrony of the methyl groups in both the ^{1}H and ^{13}C NMR is in agreement with a high symmetry (D_{3d}) species (a single minimum) or with a double minima of S_6 structures undergoing rapid mutual interconversion. The coupling constant observed between the methine protons of the isopropyl and ring atoms (10.1 Hz) corresponds to an antiperiplanar dihedral angle, according to the Karplus equation.[17] This arrangement fits an axial conformation in which the six axial *i*-Pr groups direct their methine protons toward the center of the cyclohexane ring. On the basis of the X-ray and solution data, it is therefore highly likely that the axial arrangement of the alkyl groups corresponds to the minimum energy conformation of **2**. In order to find out what are the reasons for this unexpected conformational behavior and the structural requirements for the relative stabilization of the axial form, we decided to resort to molecular mechanics calculations.

Molecular Mechanics Calculations. Molecular mechanics calculations on polydichloromethyl- and polyisopropylbenzenes have indicated that complete substitution of the phenyl ring plays an essential role in determining whether the gear-meshed conformation (homodirectional) will be the favored form.[18] When all the positions at the benzene ring are substituted by isopropyl or the sterically similar dichloromethyl groups, any arrangement other than the gear-meshed ones results in methyl or Cl contacts between neighboring *i*-Pr or dichloromethyl groups and leads to repulsive interactions. When not all the benzene positions are substituted, conformations other than the gear-meshed ones become allowed, provided that they do not involve contacts between neighboring methyl or Cl groups.[18] When studying the conformational preferences of polyalkylcyclohexanes it is therefore imperative to evaluate the conformational effects that are intrinsic of the nature of the substituent from the effects that are the result of mutual interactions between neighboring substituents. We therefore decided to carry out a systematic study of the configurational preferences of *all-trans*-polyalkylcyclohexanes by systematically changing the number and nature of the alkyl substituents. Since crystal structures are available for the crowded compounds **1**[3] and **2**, these two systems were first investigated as a test for the reliability of the molecular mechanics calculations for predicting the structure and preferred conformation of these crowded systems. For the calculations we used the MM2 implementation of the BIGSTRN-3 program.[19,20]

Generation of the Input Structures. In order to generate all the structures of this study in a consistent way, we decided to follow the following protocol. First, the structures of the equatorial and axial conformers of *all-trans*-hexamethylcyclohexane (**4**) were calculated. Both structures were minimized to conformers with D_{3d} symmetry, and it was found that the axial conformer lies 7.5 kcal mol^{-1} above the equatorial conformer. The calculated geometries for both conformations are shown in Figure 3. Input geometries for all the cyclohexanes were generated from the final calculated geometries of the axial and equatorial conformers of **4** by replacing selected methyl hydrogens with carbons, or if necessary (in the case of not fully substituted cyclohexanes) by replacing one or more methyl groups with hydrogen. While only one possible arrangement of the Me groups needed to be considered (staggered), the lower local symmetry of the ethyl and isopropyl groups resulted in a large number of possible conformations. These conformations were designated antiperiplanar (ap, e.g. **5**, **8**, **11**, and **14**), (+)-synclinal (+sc, **6**, **9**, **12**, **15**), and

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[16] The complete list of positional parameters, bond lengths and angles, and thermal parameters has been deposited as supplementary material of ref 8.

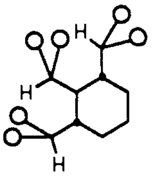
[17] Günther, H. *NMR Spectroscopy*; Wiley: Chichester, 1980; pp 106–107.

[18] Kahr, B.; Biali, S. E.; Schaefer, W.; Buda, A. B.; Mislow, K. *J. Org. Chem.* **1987**, *52*, 3713.

[19] Nachbar, R. B., Jr.; Mislow, K. BIGSTRN-3. *QCPE Bulletin* **1986**, *6*, 96, QCPE No. 514.

[20] A very thorough molecular mechanics study of the conformational preferences of dodecamethylcyclohexane has been published: Ermer, O.; Ivanov, P. M.; Osawa, E. *J. Comput. Chem.* **1985**, *6*, 401.

(−)-synclinal (−sc, **7**, **10**, **13**, **16**) (Chart II).[21] In order to limit the number of calculations, isopropyl groups in the axial conformation were always oriented in an ap fashion, whereas in the equatorial conformer they were oriented in a ±sc orientation. Other conformations were not considered, since it was assumed that for the axial form all arrangements in which a CH_3 group was directed toward the center of the ring should result in high energy conformations due to the steric repulsion with the axial hydrogens in the 3- and 5-positions, while ap arrangements in the equatorial conformation would result in unavoidable repulsive interactions between the methyl groups of neighboring isopropyl groups. These assumptions are supported by molecular mechanics calculations (see below). Ethyl groups were oriented in the axial form in a ±sc fashion whereas in the equatorial conformer they were oriented in both ap and ±sc fashions. For chiral conformations only one of the two enantiomeric arrangements was calculated. If not stated explicitly otherwise, all the structures calculated converged into minima. For each calculated conformation of a given molecule, a relative steric energy (RSE) was defined as the energy difference between the steric energy of the given conformation and the steric energy of the lowest energy (ground state) conformation of the molecule. For nomenclature purposes, systems possessing *n* ethyl or isopropyl groups and in which all the groups exist in the same arrangement (ap, +sc, or −sc) will be designated as $(ap)_n$, $(+sc)_n$, or $(-sc)_n$, respectively. Systems containing these groups in different arrangements will be specified by describing the conformation of each of the groups. For example one of the enantiomeric forms of the all-geared conformation of *all-trans*-1,2,3-triisopropylcyclohexane (**17**) will be described as (−sc, +sc, −sc). It should be noted that trans 1,2-dialkyl- and *all-trans*-1,2,3,4-tetraalkylcyclohexanes are chiral, irrespective of the nature or conformation of the alkyl groups. This introduces a source of ambiguity in the conformational descriptors, since for example for *trans*-1,2-diisopropylcyclohexane a $(+sc)_2$ descriptor corresponds either to a conformation in which the two isopropyl methine hydrogens are pointing toward each other, or for the enantiomeric form, to an arrangement in which the hydrogens are pointing away of each other. In order to remove the ambiguities of the conformational description, we arbitrarily chose in each case one of the enantiomers (depicted in **18** and **19**) as "skeleton" for the generation of all the diisopropyl and tetraisopropyl systems, and for the unequivocal description of the different conformations.



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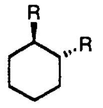

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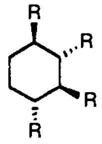

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***all-trans*-Hexaethylcyclohexane (1).** Eight axial and thirteen equatorial conformations were calculated for the molecule (Figures 4 and 5). According to the calculations all the axial conformations considered are of similar energies and are all within a steric energy range of 0.6 kcal mol^{-1}. The axial conformation with lower RSE corresponds to the chiral $(+sc)_6$ form of D_3 symmetry (Figure 6, left) and lies 8.0 kcal mol^{-1} above the ground state which corresponds to an $(ap)_6$ equatorial conformation of D_{3d} symmetry (Figure 6, right). The calculated geometry of the lower energy form is in complete agreement with the structural parameters determined by X-ray diffraction. For the other equatorial conformations an unexpected result was observed: in all cases, *energy minimization of the ±sc arrangements resulted in sp conformations of the ethyl groups, i.e. in eclipsed arrangements of the cyclohexyl methine hydrogen and the methyl of the ethyl group.*

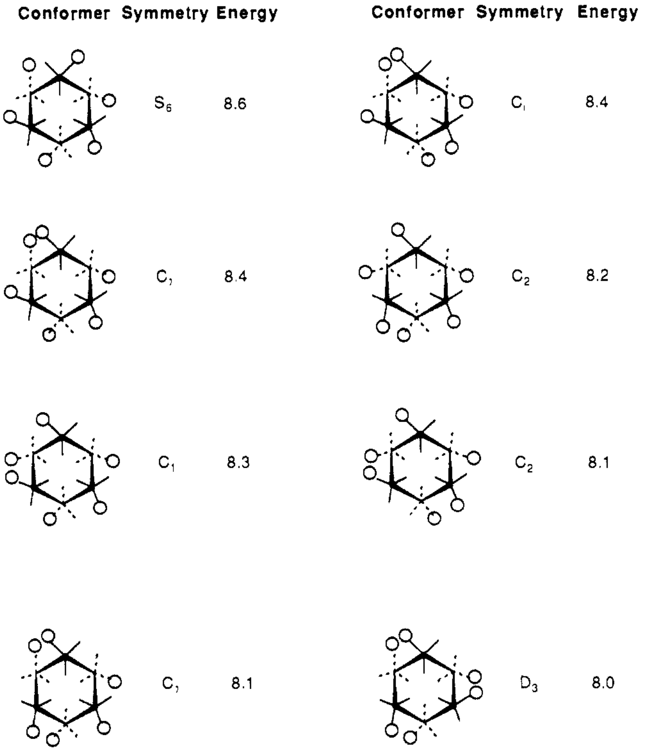

Figure 4. Calculated symmetries and relative steric energies of conformational isomers of the axial form of *all-trans*-hexaethylcyclohexane (**1**). Methyl groups are represented by circles.

As a result of this conformational preference, all the equatorial conformations calculated had either ap or sp ethyl groups.

In general, for each eclipsed ethyl group the RSE increased by 1.5–2 kcal mol^{-1} which indicates that its contribution to the steric energy is roughly additive. The equatorial conformation with the highest RSE (10.4 kcal mol^{-1}) corresponds to the $(sp)_6$ form with six eclipsed ethyl groups (D_{3d} symmetry). The conformation behavior calculated for hexaethylcyclohexane was obtained also for "mixed" hexaalkyl substituted systems containing ethyl and isopropyl groups (see below). In all cases the steric energy of the axial conformer was rather insensitive to the relative orientation (+sc or −sc) of the ethyl groups and the introduction of an ethyl substituent in a +sc orientation in to the equatorial form resulted in a minimized structure with an sp (i.e. eclipsed) ethyl group.

***all-trans*-Hexaisopropylcyclohexane (2).** The results of preliminary calculations on the conformational preferences of **1** have been published in our preliminary communication.[8] For the axial conformation we first considered a D_{3d} symmetry (i.e. the six isopropyl oriented in an ap fashion and bisected by mirror planes). Minimization of the structure using the full Newton–Raphson method resulted not in a minimum energy conformation but in a partial maximum (a hilltop, RSE = 4.8 kcal mol^{-1}) with two negative eigenvalues in the matrix of analytical second derivatives. Distortion of the transition structure along the negative and positive direction of the eigenvector associated with the negative eigenvalue resulted in two conformations of S_6 (RSE = 0.4 kcal mol^{-1}) and D_3 (ground state) symmetries. For the equatorial conformation, all possible combinations of ±sc arrangements of the isopropyl groups were considered. The results of the calculations are summarized in Figure 7. As in the case of **1**, excellent agreement was found between the calculated structural parameters of one of the lower energy conformations (S_6) and the crystal data,[8] as can be seen readily by comparison of Figures 2 and 8. In contrast with **1**, the calculated geometry of some equatorial conformations display severe distortions of the chair conformation. From all the calculated structures, the lower energy (RSE = 14.3 kcal mol^{-1}) "chair" equatorial form corresponds to the one with homodirectional isopropyl groups (i.e. the gear-meshed conformation suggested by the CPK models). The formal twisting of one of the

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[21] For the easy visualization of the different conformers, the isopropyl and cyclohexane methine protons were chosen as reference substituents for the description of the conformation of the isopropyl groups. In the case of the ethyl group, the reference substituents chosen were the ring methine proton and the methyl groups of the CH_2CH_3 moiety.

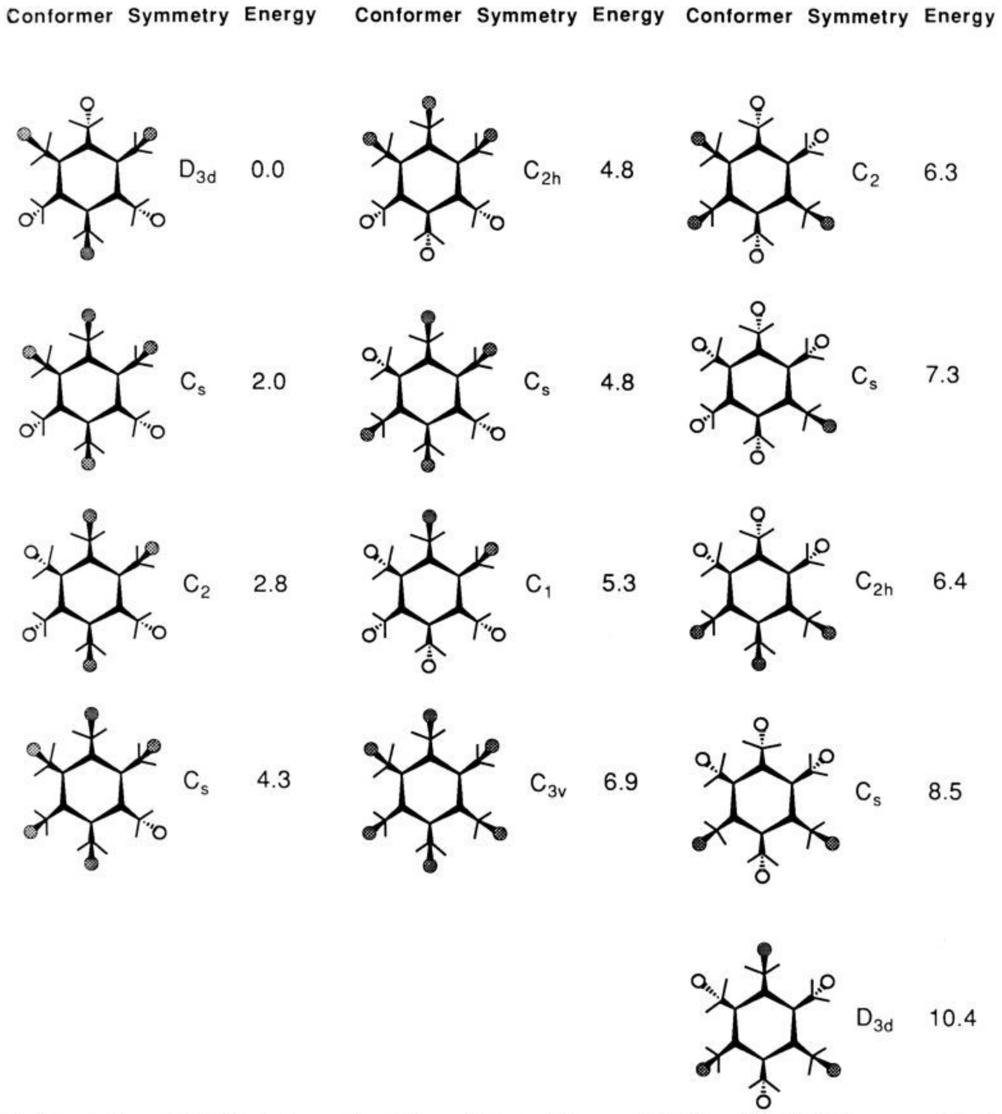


Figure 5. Calculated symmetries and relative steric energies of the conformers of the equatorial form of **1**. Methyl groups pointing toward the viewer are represented by a filled circle whereas groups pointing away are represented by open circles.

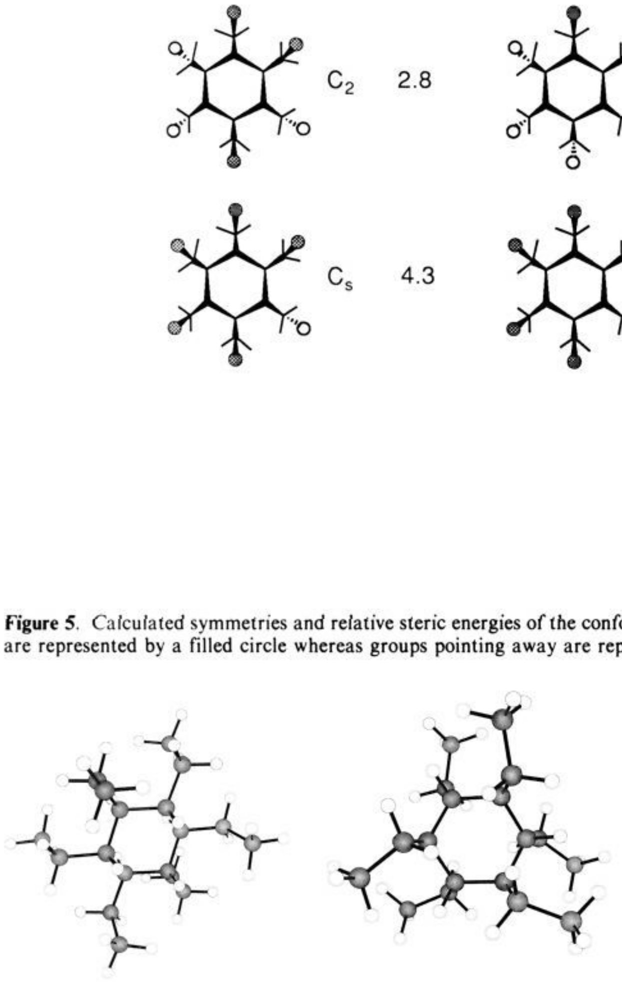
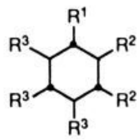


Figure 6. Calculated structure for the axial (left) and equatorial (right) conformers of **1**.

isopropyl groups results in a non-chair cyclohexane conformation (Figure 9) which has lower steric energy than the gear-meshed conformation and which lies 5.6 kcal mol^{-1} above the axial conformer. As shown in Figure 7 the axial conformation of **2** is significantly more stable than any of the equatorial conformations considered. From the calculations of **1** and **2** it can be concluded that whereas the "normal" conformational behavior is observed for **1**, and that the axial form is less stable than the equatorial ground-state conformation by 8.0 kcal mol^{-1}, the axial conformer of **2** is *more* stable than any of the equatorial forms by at least 5.6 kcal mol^{-1}.

In order to shed light on the structural factors responsible of the axial/equatorial stability reversal, we therefore decided to carry out a systematic computational study of the conformation of *all-trans*-polyalkylcyclohexanes by varying the number of groups on the cyclohexane ring and their relative bulk. The alkyl groups studied involved the series H, Me, Et, and *i*-Pr. The results of the calculations will be briefly described below for each of the systems.



1: $R^1 = R^2 = R^3$ = Et
2: $R^1 = R^2 = R^3$ = *i*-Pr
4: $R^1 = R^2 = R^3$ = Me
20: R^1 = *i*-Pr, $R^2 = R^3$ = H
21: R^2 = *i*-Pr, $R^1 = R^3$ = H
22: R^3 = *i*-Pr, $R^1 = R^2$ = H
23: $R^1 = R^3$ = *i*-Pr, R^2 = H
24: R^1 = *i*-Pr, $R^2 = R^3$ = Me
25: R^2 = *i*-Pr, $R^1 = R^3$ = Me
26: R^3 = *i*-Pr, $R^1 = R^2$ = Me
27: $R^1 = R^3$ = *i*-Pr, R^2 = Me
28: R^1 = *i*-Pr, $R^2 = R^3$ = Et
29: R^2 = *i*-Pr, $R^1 = R^3$ = Et
30: R^3 = *i*-Pr, $R^1 = R^2$ = Et

Isopropylcyclohexane (20). Two axial (ap and sc) and two equatorial conformations (ap and sc) were calculated. The four forms have calculated RSE's and point group symmetries of 1.7

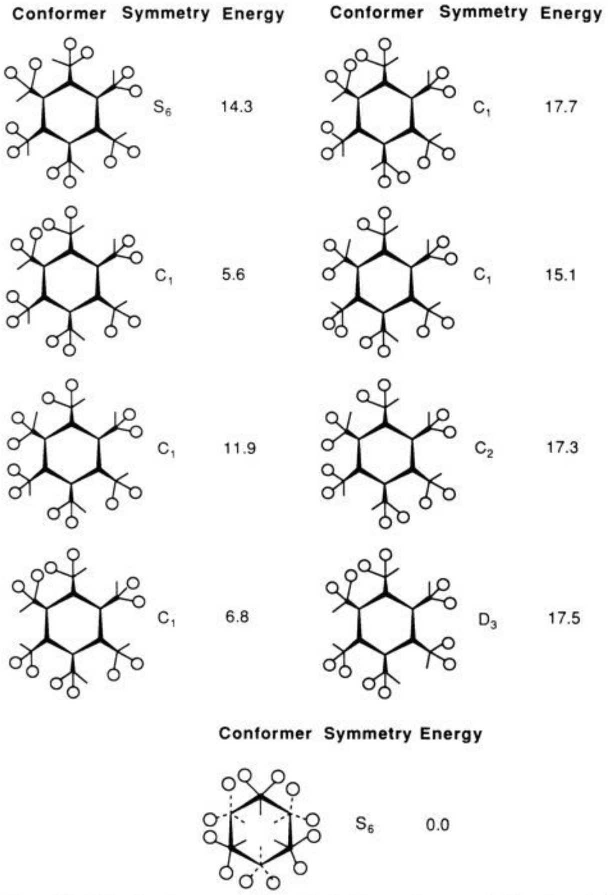


Figure 7. Calculated symmetries and relative steric energies for the axial (bottom) and equatorial (top) conformers of **2**.

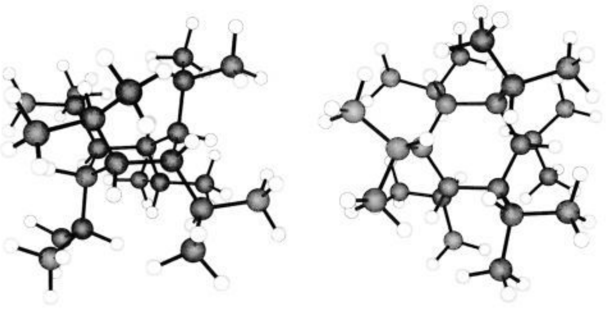


Figure 8. Top and side view of the calculated axial form of S_6 symmetry of **2**.

(C_s), 4.8 (C_1), 0 (C_s), 0 (C_1) kcal mol^{-1}, respectively. The calculated energy difference between the most stable axial and equatorial conformers (1.7 kcal mol^{-1}) is identical with the value calculated by Squillacote[22] and similar to the "A" value of the isopropyl substituent (2.1 kcal mol^{-1}).[7] The ap/sc energy difference in the axial conformation further supports our assumption that ±sc forms are higher in energy than ap arrangements and justify their exclusion in our calculations.

***trans*-1,2-Diisopropylcyclohexane (21).** Four conformers were calculated, one axial (RSE = 2.7 kcal mol^{-1}, C_2 symmetry), and three equatorial [one with homodirectional ((−sc,+sc), 2.0 kcal mol^{-1} (C_1)) and two with heterodirectional isopropyl groups ((−sc)$_2$, ground state, (C_2) and (+sc)$_2$, 7.1 kcal mol^{-1} (C_1))]. As shown by the calculations the lowest energy conformer corresponds to the equatorial conformation in which the isopropyl methine hydrogens are pointing toward each other ((−sc)$_2$), while the equatorial conformation in which the isopropyl methyls are facing each other is of relative high RSE. The calculated conformational preferences of **21** are therefore reminiscent of that of 1,2-diisopropylbenzene for which the conformation in which the two isopropyl methine hydrogens are pointing toward each other is 1.7 kcal mol^{-1} more stable than the homodirectional conformation.

***all*-*trans*-1,2,3-Triisopropylcyclohexane (22).** Five conformers were calculated, one axial (RSE = 2.5 kcal mol^{-1}, (C_1)), and four equatorial. All conformers have calculated C_1 symmetry. The ground-state conformation corresponds to the (−sc, −sc, +sc) equatorial form while the rest of the equatorial forms have RSE's of 1.8 (−sc,+sc,−sc), 5.9 (+sc,+sc,+sc), and 7.5 kcal mol^{-1} (+sc,+sc,−sc).

***all*-*trans*-1,2,3,4-Tetraisopropylcyclohexane (23).** One axial and 10 equatorial conformations were considered. The axial conformation minimized into a structure with C_2 symmetry and RSE of 1.3 kcal mol^{-1}. The ground-state conformation corresponds to an equatorial form with (−sc,+sc,+sc,−sc) arrangements of the isopropyl groups (C_2 symmetry) while the structures with (+sc,−sc,+sc,−sc) (i.e. gear-meshed) and (+sc,−sc,+sc,+sc) arrangements have RSE's of 3.5 and 1.0 kcal mol^{-1}, respectively.

***all*-*trans*-Isopropylpentamethylcyclohexane (24).** One axial conformation and two equatorial conformations (ap and +sc) were calculated. The ground-state conformation corresponds to the equatorial sc conformer of C_1 symmetry, while the ap conformer (C_s symmetry) and axial form (C_1 symmetry) have RSE's of 5.6 and 12.5 kcal mol^{-1}, respectively.

***all*-*trans*-1,2-Diisopropyltetramethylcyclohexane (25).** In addition to the axial conformation, three equatorial conformations ((+sc)$_2$, (−sc)$_2$, and homodirectional (+sc,−sc)) were calculated. The ground state corresponds to the (+sc,−sc) equatorial conformation (C_1 symmetry) while the (+sc)$_2$, (−sc)$_2$, and axial conformers have calculated C_2 symmetries and lie 3.4, 8.7, and 3.9 kcal mol^{-1} above the ground state.

***all*-*trans*-1,2,3-Triisopropyltrimethylcyclohexane (26).** As in the case of **22**, five conformers were calculated, one axial and four equatorial. All calculated conformations have C_1 symmetry. The ground state corresponds to the (−sc,−sc,+sc) conformation, and the axial is less stable than this form by 1.4 kcal mol^{-1}. The rest of the equatorial conformations have RSE's of 4.5 (−sc,+sc,−sc), 6.4 (+sc,+sc,−sc), and 11.0 kcal mol^{-1} (+sc,+sc,+sc).

***all*-*trans*-1,2,3,4-Tetraisopropyldimethylcyclohexane (27).** Eleven conformations were calculated, one axial (RSE = 1.8 kcal mol^{-1} (C_2 symmetry)) and 10 equatorial conformations. It is interesting to note that some conformations minimized into structures having either twist-boat or half-chair cyclohexane rings. The more stable "equatorial" conformation corresponds to a twist-boat (C_2 symmetry) formally derived from the equatorial conformation in which the *i*-Pr groups are oriented in a (+sc,−sc,−sc,+sc) fashion (i.e. a conformation with two sets of two vicinal homodirectional *i*-Pr groups which are directing their methyls toward each other). From all the conformations calculated in which the cyclohexane exists in a nondistorted chair conformation, the form with lowest RSE (3.5 kcal mol^{-1}) is the one with (+sc,−sc,+sc,−sc) arrangements of the isopropyl groups, i.e. with homodirectional isopropyl groups.

***all*-*trans*-Pentaethylisopropylcyclohexane (28).** Sixteen axial conformations were calculated differing in the ±sc orientation of the ethyl groups. As in the case of **1**, all the axial forms considered have similar steric energies (within a range of 0.5 kcal mol^{-1}). The lowest energy axial conformer has a (+sc)$_5$ arrangement of the ethyl groups and a RSE of 4.3 kcal mol^{-1}. Sixteen different arrangements of the ethyl groups were considered for the equatorial conformation. These arrangements differed in the torsional angle of the ethyl group (ap or sc) whereas the isopropyl group was always oriented in a sc conformation. According to the calculations, two conformations are the lowest in energy. In both of these, four vicinal ethyl groups exist in a (ap)$_4$ orientation, while the fifth ethyl group facing the isopropyl methine hydrogen exists either in an ap or a sp (eclipsed) arrangement (Figure 10).

***all*-*trans*-1,2,3,4-Tetraethyldiisopropylcyclohexane (29).** A total of 34 conformers were calculated (10 axial, 24 equatorial). In

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[22] Squillacote, M. E. *J. Chem. Soc., Chemm. Commun.* **1986**, 1406.

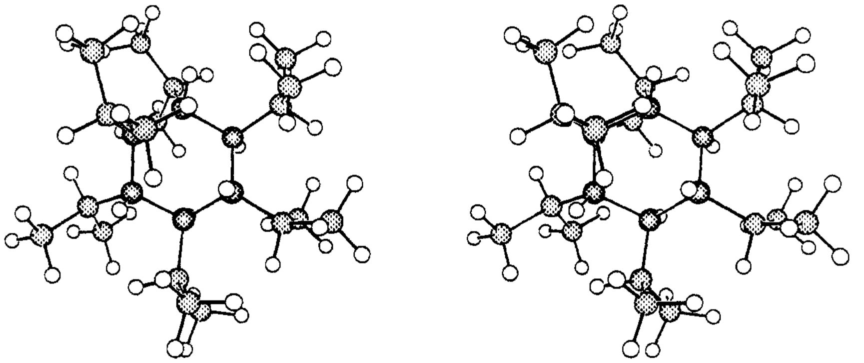

Figure 9. Stereoscopic view of the calculated lowest energy "equatorial" form of **2**.

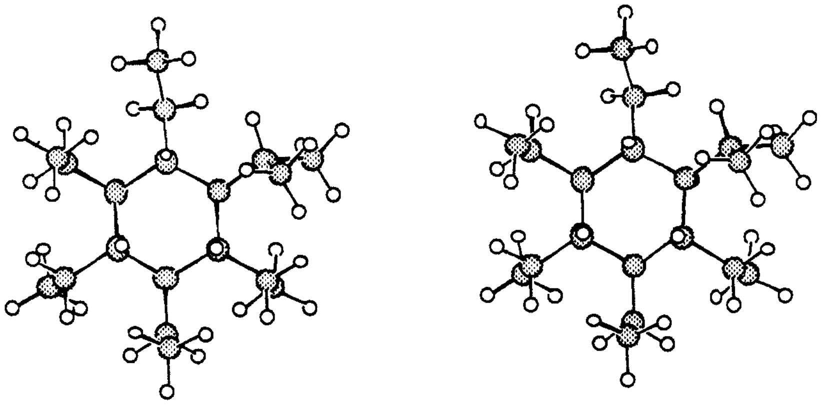

Figure 10. Stereoscopic view of the calculated low energy conformation of *all-trans*-pentaethylisopropylcyclohexane (**28**). The ethyl group facing the methine hydrogen exists in an eclipsed conformation.

all the axial forms the isopropyl group was oriented in an ap orientation, and the ethyl groups in either a +sc or −sc conformation. All axial conformations had RSE's within a 0.8 kcal mol^{-1} range, and the lowest energy axial conformation corresponds to the chiral $(+\mathrm{sc})_4$ conformer (C_2, 2.7 kcal mol^{-1}). From the 24 equatorial conformations calculated, 16 structures correspond to conformations with homodirectional, (+sc,−sc), arrangements of the isopropyl groups and eight structures to conformations with heterodirectional arrangements ($((-\mathrm{sc})_2)$). From the first set of equatorial conformations the lowest energy form (RSE = 1.3 kcal mol^{-1}, C_1 symmetry) corresponds to the conformation in which the ethyl groups are oriented in an (ap,ap,ap,sp) fashion, while the ethyl group facing the isopropyl methine hydrogen is oriented in an eclipsed arrangement. The lowest energy equatorial conformation corresponds to a form of C_2 symmetry with heterodirectional isopropyl groups, and in which the ethyl groups are all oriented in ap arrangements.

***all-trans*-1,2,3-Triethyltriisopropylcyclohexane (30).** Four axial and 24 equatorial conformations were considered. The four axial forms result from the four different possible arrangements of the Et groups in ±sc conformations. All axial forms have similar RSE's (i.e. within 0.2 kcal mol^{-1}). The axial conformations with the lowest steric energy (RSE = 0.2 kcal mol^{-1}) correspond to either a $(+\mathrm{sc})_3$ or a (+sc,−sc,−sc) arrangement of the ethyl groups. For the calculation of the equatorial conformers the isopropyl groups were oriented in four different ways (a)(+sc,−sc,+sc) (i.e. homodirectional fashion), (b)(+sc,+sc,−sc), (c) (+sc,−sc,−sc), and (d) (−sc,−sc,+sc). From all the conformers calculated, the ground state corresponds to a form of C_1 symmetry in which the isopropyl groups are oriented in a (+sc,−sc,−sc) fashion, and the ethyl groups oriented in $(\mathrm{ap})_3$ arrangements.

Discussion

Preferred Conformation in Polyethylcyclohexanes. A consistent pattern was observed for the axial conformers of *all-trans*-hexaethyl and ethyl/isopropyl-mixed systems. Although the steric energy of the axial form was rather insensitive to the orientation of the ethyl groups, in all cases the preferred conformation corresponds to a conformation in which all the ethyl groups are either in a +sc or −sc orientation. For the equatorial conformations, an unexpected result is that in addition to the preferred ap conformation, another favored form involves an eclipsed arrangement of the ethyl group with the methine of the cyclohexane ring. Of special interest is compound **28** which according to the calculations should exist preferably as an equilibrium of two equatorial conformations: one "normal" in which all the Et groups are oriented in an ap arrangement and the second "abnormal" in which one ethyl group is oriented in a sp arrangement, i.e. in an eclipsed conformation. It seems therefore likely that a polyalkylcyclohexane system could be found in which the ground-state conformation should include one or more eclipsed ethyl groups. This is of interest since the X-ray structure of a hydrated tricyclic orthoamide was recently reported showing the presence of a methyl group existing in an eclipsed conformation.[23] The conformational preference for the eclipsed arrangement was attributed to CH···OH interactions. Our computational results suggest that steric crowding could also induce the population of eclipsed conformations in systems such as the polyalkylcyclohexanes.

Conformation of 2 in Solution. Molecular mechanics calculations indicate that the axial crystallographic conformation (of approximate S_6 symmetry) of **2** is not the only low-energy conformation. The calculations predict that in addition, the axial conformation of D_3 symmetry should be populated. Both conformations should be interconvertible by twisting the isopropyl groups, and the process should possess a low barrier as indicated by the calculated hilltop of D_{3d} symmetry which lies 4.8 kcal mol^{-1} above the D_3 structure and interconnects the D_3 and the S_6 conformers. It seems likely that in solution both the D_3 and S_6 conformers are in rapid equilibrium on the NMR time scale, therefore resulting in the detection in the NMR of a single average D_{3d} structure.

Gear Meshing in Polyisopropylcyclohexanes. In general the same trends previously calculated for the polyisopropylbenzenes[18]

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(23) Seiler, P.; Weisman, G. R.; Glendening, E. D.; Weinhold, F.; Johnson, V. B.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1175. Seiler, P.; Dunitz, J. D. *Helv. Chim. Acta* **1989**, *72*, 1125.

Table II. Axial/Equatorial Steric Energy Differences (in kcal mol^{-1}) for *all-trans*-Polyalkylcyclohexanes

	1 *i*-Pr/5 R[a] ax − eq	2 *i*-Pr/4 R ax − eq	3 *i*-Pr/3 R ax − eq
R = H	1.7	2.7	2.4
R = Me	5.6	3.9	1.4
R = Et	4.3	2.7	0.2

[a] 1 *i*-Pr/5 R denotes an all-trans cyclohexane system substituted by one isopropyl group and five R groups.

are predicted by the calculations for the *all-trans*-polyisopropylcyclohexanes. In both systems, a clear preference for the homodirectional conformation is not observed unless a complete circuit of isopropyl groups is present. For example, for systems **21**, **22**, and **23**, the lower energy equatorial conformation is not the all-geared one. It seems that in both systems the conformational behavior is dictated by the need to avoid methyl contacts between neighboring isopropyl groups. However, the all-equatorial polyisopropylcyclohexane systems differ in three major aspects from the polyisopropylbenzenes. In addition to the smaller endocyclic ring angle and the noncoplanar arrangement of the isopropyl groups, the nonplanar cyclohexane skeleton can be easily distorted from the chair conformation in order to accommodate sterically interacting groups. As a result of these structural features it should be expected that the gear meshing of the isopropyl groups in the homodirectional conformation should be less efficient. It is of interest to note that for **2** the conformation which has one formal methyl contact is of lower energy than the homodirectional conformation, whereas for the hexaisopropylbenzene the conformation in which one isopropyl group is formally turned by 180° lies 12.3 kcal mol^{-1} above the homodirectional conformation.[9c] In the case of **2**, the contacts between the methyl groups are partially removed by distorting the cyclohexane ring from the chair conformation (cf. Figure 9) therefore allowing this otherwise high energy arrangement.

Axial/Equatorial Stability Reversal. The calculated axial/equatorial steric energy differences between the more stable axial and equatorial forms of **20–30** are collected in Table II. All values are smaller than the axial/equatorial energy gap calculated for *all-trans*-1,2,3,4,5,6-hexamethyl- and hexaethylcyclohexane (7.5 and 8.0 kcal mol^{-1}). As shown in Table II, for the mixed Me/*i*-Pr and Et/*i*-Pr systems, increasing the number of vicinal isopropyl groups *decreases* the axial/equatorial energy gap. According to the calculations, the axial and equatorial forms of *all-trans*-1,2,3,triethyl-4,5,6-triisopropylcyclohexane are of similar steric energies. It is therefore concluded that in order to have axial and equatorial forms of similar energies, an *all-trans*-polyalkylcyclohexane system must comprise at least three vicinal isopropyl groups and three ethyl groups. A special behavior is observed for the unsubstituted polyisopropylcyclohexanes. The formal introduction of a *trans*-isopropyl group in isopropylcyclohexane leads to an increase of the axial/equatorial energy gap (2.7 kcal mol^{-1}), but introduction of a third and fourth vicinal substituent leads to a reduction of this gap.

Although it is difficult to pinpoint the exact cause for the axial/equatorial stability reversal phenomenon in **2**, several qualitative considerations can be made. It seems likely that the stability reversal is not due to stabilization of the axial conformer (for example by attractive van der Waals interactions between the isopropyl methine hydrogens) but due to destabilization of the equatorial conformer. Assuming that the repulsive 1,3-interactions in the axial conformers are similar in **2** and **1**, one can estimate the destabilization of the equatorial form of **2** as >13.6 kcal mol^{-1}. We believe that this large destabilization is the result of two contributions: one steric and one torsional. Due to the special shape of the isopropyl group, the best way of arranging such groups on a chair cyclohexane is to orient them in a homodirectional fashion, i.e. in a conformation in which the isopropyl methine hydrogen points toward the empty space between the two methyls of a neighboring isopropyl group. However, although the homodirectional arrangement apparently minimizes the repulsive interactions between the methyl groups of vicinal isopropyls, it introduces torsional strain. For example, according to the calculations in the homodirectional conformation of **2** six methyl groups are nearly eclipsed (ϕ ca. 20°) with the methine protons of the cyclohexane ring. The unavoidable steric and/or torsional interactions result in the increased energy of the equatorial conformations and in the nearly exclusive population of the axial form in **2**.

Experimental Section

NMR spectra were recorded on a Bruker WP 200 SY pulsed FT spectrometer.

Preparation of 2. Hydrogenation of 40 mg (0.12 mmol) of **3**[13] in 5 mL cyclohexane was performed in an autoclave at 950 psi H_2/130 °C, with use of a mixture of 100 mg Rh/Al_2O_3 and 100 mg Pd/C as catalysts. After one week the catalysts were separated by filtration and the organic solvent evaporated to afford 25 mg (0.07 mmol, 60%) *all-trans*-hexaisopropylcyclohexane, mp 235 °C (sublimes). The compounds was purified by slow crystallization from a solution in ether/MeOH.

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