

# Stereochemistry and Conformational Anomalies of 1,2,3- and 1,2,3,4-Polycyclohexylcyclohexanes

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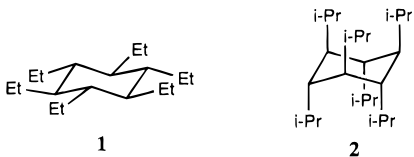
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**Abstract:** 1,2,3-Tricyclohexylcyclohexane (**3**) and 1,2,3,4-tetracyclohexylcyclohexane (**4**) were synthesized by catalytic hydrogenation of 1,2,3-triphenylbenzene and 1,2,3,4-tetraphenylbenzene, respectively. The systems provide examples of three conformational anomalies: axial/equatorial, twist-boat/chair, and eclipsed/staggered stability reversals. Two axial substituents are present in the lowest energy conformation of *cis,trans*-**3**. The substituents in *all-cis*-**3** are located in an equatorial–axial–equatorial disposition, with the axial substituent oriented in a nearly eclipsed arrangement with the central ring. In *all-trans*-**3** two substituents are gear meshed, which results in a nonstaggered arrangement. The central ring in *cis,trans,cis*-1,2,3,4-tetracyclohexylcyclohexane exists in a chair conformation while in the *cis,trans,trans* isomer this ring adopts a twist-boat conformation.

## Introduction

The conformational preferences of unconstrained saturated hydrocarbons can be summarized by a series of rules: (i) Monocyclic alkyl-substituted cyclohexanes prefer the chair over the twist-boat (TB) conformation. (ii) In the chair form an equatorial disposition of the substituent is favored over an axial one. (iii) Eclipsed arrangements represent a transition state between staggered forms.<sup>1–4</sup> In contrast to *all-trans*-1,2,3,4,5,6-hexaethylcyclohexane (**1**), in which all groups are disposed equatorially,<sup>5</sup> in *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane (**2**) all the alkyl groups are located at axial positions.<sup>6</sup>



The goal of the present work was to determine experimentally and computationally the structural boundaries of the second rule. We decided to study the conformational preferences of the polycyclohexyl systems 1,2,3-tricyclohexylcyclohexane (**3**) and 1,2,3,4-tetracyclohexylcyclohexane (**4**).<sup>7,8</sup>

<sup>®</sup> Abstract published in *Advance ACS Abstracts*, July 1, 1996.

(1) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(2) *Conformational Behavior of Six Membered Rings*, Juaristi, E., Ed.; VCH Publishers: New York, 1995. Kellie, G. M.; Riddell, F. G. *Top. Stereochem.* **1974**, *8*, 225.

(3) For a review on conformational flexible hydrocarbons, see: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.

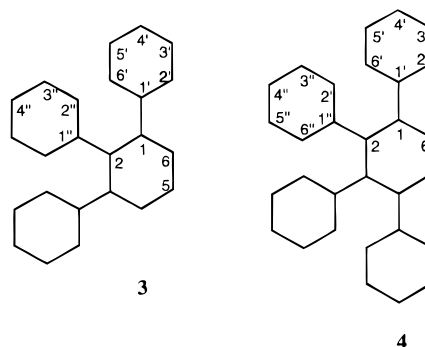
(4) Arbitrarily, we will denote dihedral angles in the range of  $\pm(60-40^\circ)$ ,  $\pm(40-20^\circ)$ , and  $\pm(20-0^\circ)$  as “staggered”, “nonstaggered”, and “eclipsed”, respectively. The terms *anti* and *gauche* will be used taking the methine protons of the central ring and the substituents as the reference groups.

(5) Immirzi, A.; Torti, E. *Atti. Accad. Naz. Lincei Cl. Sci. Fis., Mat. Nat. Rend.* **1968**, *44*, 98.

(6) Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300.

(7) For studies on polycyclohexyl systems, see: (a) Hoffman, R. W.; Sander, T.; Brumm, M. *Chem. Ber.* **1992**, *125*, 2319. (b) Columbus, I.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 7029.

(8) For a preliminary communication, see: Columbus, I.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1994**, *116*, 10306.



## Results and Discussion

**Structural Considerations in 1,2,3-Tricyclohexylcyclohexane.** 1,2,3-Tricyclohexylcyclohexane should exist in three stereoisomeric forms resulting from the different possible *cis/trans* arrangements of the substituents (*all-cis*, *cis,trans*, and *all-trans*). The *all-cis* and *all-trans* forms should possess effective dynamic  $C_3$  symmetry. Precluding accidental isochrony, both systems should display 14 signals in the <sup>13</sup>C NMR spectrum. The *cis,trans* form possesses  $C_1$  symmetry, and therefore should display 24 signals in the <sup>13</sup>C NMR spectrum.

**Synthesis of 1,2,3-Tricyclohexylcyclohexane.** Hydrogenation of 1,2,3-triphenylbenzene at 170 °C (Pd/C, 600 psi of H<sub>2</sub>/cyclohexane)<sup>9</sup> resulted in the *all-cis* isomer, whereas at 250 °C the *all-trans* and *cis,trans* isomers were obtained. The *all-cis* isomer corresponds to the kinetic product, which can be isomerized at higher temperature conditions to the *cis,trans* and *all-trans* isomers.<sup>10</sup>

**NMR Structural Characterization of the Isomeric 1,2,3-Tricyclohexylcyclohexanes.** The *cis/trans* configurational assignment of pairs of vicinal substituents was deduced by NMR spectroscopy from the magnitude of the coupling constants between vicinal methine protons on the central ring,<sup>11a</sup> and/or

(9) All pressures refer to the initial hydrogen pressures at room temperature.

(10) For a study on the mutual isomerization of polysubstituted cyclohexanes, see: Farina, M. Grassi, M.; Di Silvestro, G. *J. Am. Chem. Soc.* **1985**, *107*, 5100.

(11) Günther, H. *NMR Spectroscopy*; Wiley: Chichester, 1980; (a) p 106; (b) p 72.

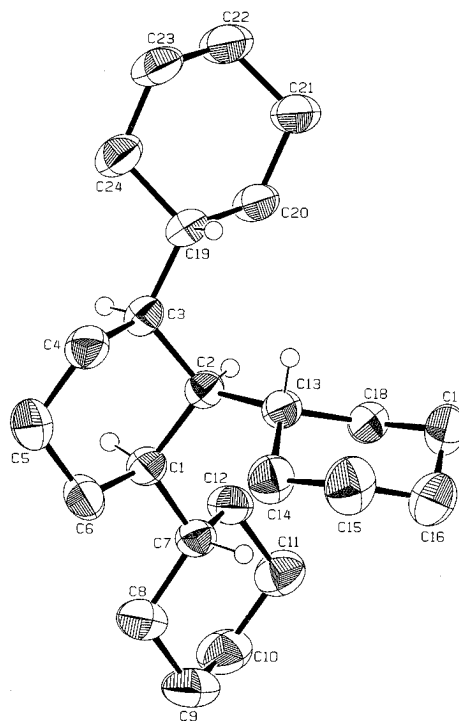
on the basis of chemical shifts.<sup>11b</sup> Similarly, both the mode of attachment (axial or equatorial) and the conformational arrangement (*gauche* or *anti*) of the cyclohexyl substituents were deduced from the coupling constants of the methine protons of the peripheral rings with their neighboring protons.

**(a) Kinetic (*all-cis*) Product.** The kinetic product displays 14 signals in the <sup>13</sup>C NMR spectrum, which is consistent with either an *all-cis* or an *all-trans* disposition of the substituents. A classification of the signals as corresponding to either methine or methylene carbons was achieved by a <sup>1</sup>H–<sup>13</sup>C inverse correlation spectrum.<sup>12</sup> Only the four low-field carbon signals display a single cross-peak with a proton signal, indicating that these signals correspond to methine groups.<sup>13</sup> Each pair of signals was assigned to the individual methine groups by a <sup>1</sup>H DQF COSY spectrum on the basis of the number of cross-peaks, which ideally should be identical to the number of nonequivalent vicinal neighbors. The *cis/trans* disposition of the substituents can be inferred from the relative location (axial or equatorial) of the methine protons of the central cyclohexyl ring.<sup>14</sup> From the coupling constant between H-1 and H-6a/H-6e (<sup>3</sup>J = 13.0 and 6.9 Hz) it can be concluded that this methine proton is located in an axial position. The relatively small coupling constant between H-1 and H-2 (<sup>3</sup>J = 7.3 Hz) corresponds to a *gauche* arrangement, and indicates that H-2 is located in an equatorial position. These assignments are further strengthened by chemical shift considerations, since the axial H-1 resonates at a higher field (0.95 ppm) than the equatorial H-2 (1.89 ppm).<sup>14</sup> It can be concluded therefore that the kinetic product is the *all-cis* isomer, with an eq–ax–eq (eq = equatorial, ax = axial) disposition of the substituents. The conformation of the cyclohexyl substituents was deduced from the coupling constants of their methine protons which indicated that all rings are attached by their equatorial positions and that the central axial ring adopts a *gauche* arrangement whereas the equatorial rings are oriented *anti*.

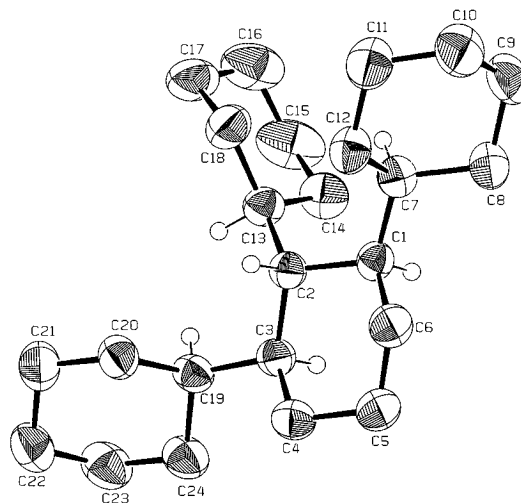
**(b) 1,2,3-*all-trans*-Tricyclohexylcyclohexane.** One of the products obtained by isomerization of the *all-cis* isomer displays 14 <sup>13</sup>C NMR signals, in agreement with a structure of C<sub>s</sub> symmetry. By exclusion, and since the *all-cis* compound has been characterized, this compound must be the *all-trans* isomer. Since both H-1 and H-2 resonate at a relatively high field (1.13 ppm), it can be safely concluded that all substituents are equatorial.

**(c) 1,2,3-*cis,trans*-Tricyclohexylcyclohexane.** The compound displays 24 <sup>13</sup>C NMR signals, and necessarily must correspond to the *cis,trans* isomer. For this configuration, two possible arrangements of substituents are possible: eq–eq–ax or ax–ax–eq. Unfortunately, we were unable to extract coupling constant information due to the complexity of the proton spectrum.

**Crystal Structures.** Single crystals of the *all-cis* and *all-trans* isomers were obtained from CHCl<sub>3</sub>/EtOH and submitted to X-ray crystallography (Figures 1 and 2). The crystal conformation in each system is identical to the one deduced from the analysis of the NMR data. In the *all-cis* isomer, all rings adopt a chair conformation and the cyclohexyl substituents are located at the eq–ax–eq positions of the central ring, while being attached by their equatorial positions (Figure 1). In both compounds the chair conformation of the central ring is only



**Figure 1.** Crystal structure and numbering scheme of *all-cis*-3. The torsional angle of the axial ring is only 22.3°.



**Figure 2.** Molecular structure of *all-trans*-3. The two external peripheral rings are staggered (the H–C(7)–C(1)–C(2) and H–C(19)–C(3)–C(2) torsional angles are 48.6° and 59.4°) while the central peripheral ring exists in a nonstaggered conformation (H–C(13)–C(2)–C(3) and H–C(2)–C(13)–C(18) dihedral angles of 32.1° and 36.0°).

slightly flattened, as indicated by the sum of the absolute values of the six internal C–C–C–C dihedral angles (326.7° (*all-cis*) and 335.9° (*all-trans*)).

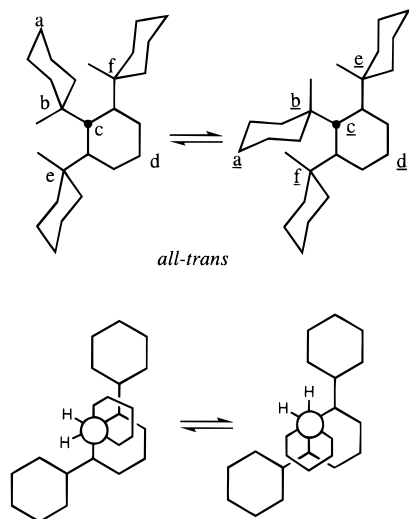
The arrangement of the substituents will be discussed in terms of several torsional angles: the HCCH angle between the methine protons of the substituent and the central ring ( $\phi_1$ ), the HCCC angle between the methine proton of the substituent and a carbon of the central ring ( $\phi_2$ ), and the HCCC angle between the methine proton of the central ring and a carbon of the substituent ( $\phi_3$ ).

In the *all-cis* form the equatorial rings are oriented *anti* ( $\phi_1$  angles of 164.3° and 164.0°) while the axial ring is oriented *gauche* ( $\phi_1$  is 91.4°). The HCCC dihedral angles of the axial substituent with the central ring markedly depart from the ideal staggered values,  $\phi_3$  and  $\phi_2$  being only 22.3° (HC(2)C(13)C(18)) and 23.0° (HC(13)C(2)C(3)).

(12) For a review on 2D NMR techniques, see: Kessler, H.; Gehrke, M.; Griesinger, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 490.

(13) Increased substitution of the aliphatic carbons results in downfield shifts. Breitmaier, E.; Volter, W. *<sup>13</sup>C NMR Spectroscopy*, 2nd ed.; Verlag Chemie: Weinheim, 1978; p 71.

(14) Obviously, the locations of the substituents are complementary to those of the methine protons; i.e., if a given methine proton is axial, the substituent attached to that methine group must be equatorial.

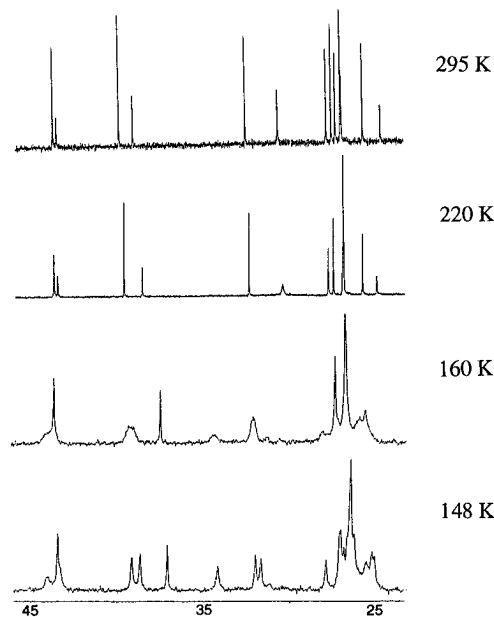


**Figure 3.** Top: Enantiomerization of *all-trans*-**3**. The four sites not affected by the dynamic process are marked by the letters a-d. Enantiotopic sites are denoted by the same letters underlined (i.e., a-d). The process mutually exchanges between the four pairs of enantiotopic groups while also exchanging between diastereotopic groups (e.g., e and f). Bottom: enantiomerization of *all-cis*-**3**.

In the *all-trans* isomer the substituents are attached to the equatorial positions of the central ring (Figure 2). The substituents adopt a *gauche* conformation (the  $\phi_1$  angles are for one enantiomer  $-57.9^\circ$ ,  $-80.1^\circ$ , and  $67.8^\circ$ , i.e., a -g, -g, +g arrangement of the substituents) with two neighboring rings oriented in a homodirectional fashion<sup>15</sup> in a gear-meshed arrangement.<sup>16</sup> The central substituent adopts a conformation with a  $\phi_2$  angle of  $32.1^\circ$ , whereas the neighboring ring which is oriented in a homodirectional fashion exists in an almost normal staggered arrangement ( $\phi_3 = 48.6^\circ$ ).

**Rotational Barrier of *all-trans*-**3**.** Although both the X-ray and NMR data indicate that both *all-cis*- and *all-trans*-**3** exist in chiral conformations of  $C_1$  symmetry, their  $^{13}\text{C}$  NMR spectra at room temperature are consistent with those of structures possessing mirror symmetry. A possible explanation for this discrepancy is that the central substituent ring is at room temperature rapidly rotating on the NMR time scale, resulting in an enantiomeric conformation (Figure 3).

We studied the low-temperature  $^{13}\text{C}$  NMR spectra of *all-trans* and *all-cis*-**3** in  $\text{CDCl}_2\text{F}$ <sup>17</sup> down to 150 K. The NMR of the *all-cis* sample remained unchanged throughout the entire temperature range. Assuming that the chemical shift difference under slow exchange conditions of a pair of mutually exchanging signals is 1 ppm, and that the coalescence temperature is 140 K or lower, a higher limit of  $\Delta G^\ddagger < 6.5 \text{ kcal mol}^{-1}$  can be set for the rotational barrier. In the *all-trans* isomer some (but not all) signals broadened and split (Figure 4). The four signals at 39.39, 27.00, 43.27, and 24.17 ppm (assigned to C-1'', C-4'', C-2, and C-5, respectively) remained sharp throughout the entire temperature range. The dynamic process followed can be assigned to an enantiomerization involving the rotation of the central substituent around the bond connecting it to the central ring. Freezing this process should result in splitting of most of the signals, with the exception of four (corresponding to the carbons which under fast exchange conditions are located on the average mirror plane) for which no decoalescence is



**Figure 4.**  $^{13}\text{C}$  NMR (100.62 MHz,  $\text{CDCl}_2\text{F}$ ) of *all-trans*-**3** at different temperatures. Four carbon signals remain sharp during the whole range of temperatures.

expected (Figure 3). From the chemical shift differences obtained under slow exchange conditions for C-2'', C-1' and C-2' ( $\Delta\delta = 8.71, 0.48, 0.31 \text{ ppm}$ ) and the coalescence temperatures (180 K for C-2'', 160 K for C-1' and C-2'), a barrier of  $7.7 \pm 0.1 \text{ kcal mol}^{-1}$  was calculated.<sup>18</sup>

A corroboration that the dynamic process followed is indeed an enantiomerization involving rotation of the central ring was obtained by molecular mechanics calculations (MM3 program).<sup>19</sup> The middle substituent of *all-trans*-**3** was rotated using the driver option of the program in a process which resulted in enantiomerization of the system (g, g, -g)  $\rightleftharpoons$  (g, -g, -g). Two diastereomeric pathways are possible, one via a structure with an *anti* arrangement of the central substituent ( $\phi_1 = 180^\circ$ ) and the second via a structure possessing an eclipsed arrangement of H-1'' and H-2. According to the calculations, these processes have barriers of 7.6 and 16.9  $\text{kcal mol}^{-1}$ , respectively, indicating that the first pathway is preferred. MM3 calculations indicate that the enantiomerization barrier of *all-cis*-**3** (via a rotation of the central substituent through a transition state with  $\phi_1 = 180^\circ$ ) is only 3.8  $\text{kcal mol}^{-1}$ . Since the middle ring substituent of *all-trans*-**3** is involved in gear meshing,<sup>16</sup> it seems likely that the higher barrier observed is partially due to the energetic requirements of releasing the ring from this arrangement.<sup>20</sup>

#### Isomerism in 1,2,3,4-Tetracyclohexylcyclohexane Systems.

On a time scale in which the rotation of the substituents and the ring inversion process are fast, system **4** should exist in six residual isomeric forms: *all-cis*; *cis,trans,trans* (*ctt*); *trans,-cis,trans* (*tct*); *cis,cis,trans* (*cct*); *cis,trans,cis* (*ctc*); and *all-trans*.

**Synthesis of 1,2,3,4-Tetracyclohexylcyclohexane.** Hydrogenation of 1,2,3,4-tetraphenylbenzene<sup>21</sup> (**5**) with Ru/C or Rh/C resulted in the formation of 2,3,6-tricyclohexylbiphenyl (**6**) which was characterized by X-ray crystallography.<sup>22</sup> Exhaustive hydrogenation of **5** was accomplished using Pd/C as catalyst

(18) The exchange rates at the coalescence temperatures were calculated according to Gutowski, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

(19) Allinger, N. L. *Molecular Mechanics. Operating Instructions for the MM3 Program. 1989 Force Field (updated 5/6/92)*; Technical Utilization Corp.

(20) Statically geared systems may possess high rotational barriers. See for example: Biali, S. E.; Mislow, K. *J. Org. Chem.* **1988**, *53*, 1318.

(21) MacKenzie, K. *J. Chem. Soc.* **1960**, 473.

(22) The crystallographic data of **6** are described in ref 8.

(15) Mislow, K. *Chimia* **1986**, *40*, 395. Biali, S. E.; Buda, A. B.; Mislow, K. *J. Org. Chem.* **1988**, *53*, 1289.

(16) See for example: Siegel, J.; Gutierrez, A.; Schweizer, W. B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* **1986**, *108*, 1569. Bomse, D. S.; Morton, T. H. *Tetrahedron Lett.* **1975**, 781.

(17) Siegel, J. S.; Anet, F. A. L. *J. Org. Chem.* **1988**, *53*, 2629.

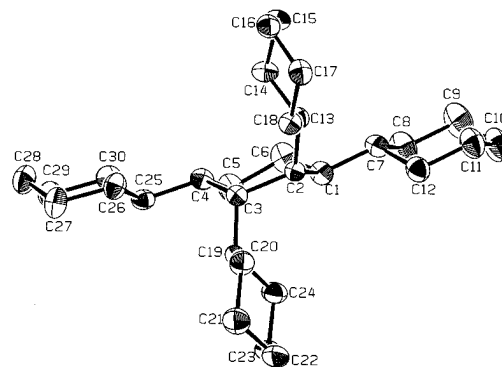
(cyclohexane, 170 °C, 600 psi of H<sub>2</sub>), and resulted in the formation of two products. The main product crystallized from CHCl<sub>3</sub>/EtOH in rectangular crystals (mp 145 °C) and was characterized as the *ctc* form (see below). The second isomer (mp 140°C) was separated manually from the first, taking advantage of the different morphology (rhombohedral) of the crystals, and was characterized as the *ctt* isomer. When the hydrogenation was conducted at 250 °C, the product consisted, as judged by <sup>13</sup>C NMR, of a mixture of the *ctt* form and an additional isomer. This isomer could be purified up to 90% by fractional crystallizations from CHCl<sub>3</sub>/EtOH and was characterized as the *all-trans* form.

**NMR Analysis of the Isomeric 1,2,3,4-Tetracyclohexylcyclohexanes. (a) *ctc* Form.** The compound displays 14 <sup>13</sup>C NMR signals (one signal of double intensity) in agreement with a system of either C<sub>2</sub> or C<sub>s</sub> symmetry. The methine proton H-1 is located axially since it displays a large *anti* coupling (<sup>3</sup>J = 14.0 Hz) with H-5a/H-6a. The small coupling constant between H-1 and H-2 (<sup>3</sup>J = 7 Hz) indicates that their mutual arrangement is *gauche*, i.e., H-2 is equatorial. Since the system also displays bilateral symmetry, its configuration can be *ctc* (i.e., an eq-ax-ax-eq disposition of the substituents) or *all-cis* if a ring inversion process which interconverts the two enantiomeric ax-eq-ax-eq conformations is fast on the NMR time scale. In the latter case the chemical shifts of the methine protons should be intermediate between those characteristic of axial and equatorial protons. However, since H-1 resonates at a relatively high field (1.29 ppm) while H-2 displays a chemical shift characteristic of equatorial protons (1.59 ppm), we conclude that the configuration of the compound is *ctc* with an eq-ax-ax-eq disposition of the groups.<sup>23</sup>

On the basis of the magnitude of the coupling constant <sup>3</sup>J<sub>H-1,H-1'</sub> and <sup>3</sup>J<sub>H-2,H-1'</sub> (11.0 and 7.0 Hz, respectively), it can be concluded that the equatorial groups are arranged in an *anti* orientation, while the axial groups are arranged *gauche*. The conformation of the system is therefore eq(*anti*)-ax(*gauche*)-ax(*gauche*)-eq(*anti*).

**(b) *cct* Form.** The isomer which crystallized in rhombohedral-shaped crystals displayed 30 signals in the <sup>13</sup>C NMR spectrum, in agreement with a system of C<sub>1</sub> symmetry (*ctt* or *cct*). Since the compound is thermodynamically more stable than the *ctc* product, and since molecular mechanics calculations of the model system 1,2,3,4-tetraisopropylcyclohexane indicate that the relative stability of the isomers increases with the increase in the number of *trans* arrangements,<sup>24</sup> it can be concluded that the product isolated is most likely the *ctt* form. Corroboration of this assignment was obtained by X-ray crystallography.

**(c) *all-trans* Form.** The compound displays 14 carbon signals (one of double intensity), in agreement with *ctc*, *all-trans*, *all-cis*, and *tet* configurations. The first arrangement can be safely excluded since the kinetic product has that stereochemistry. The protons at the 1 position (1.08 ppm) display a large *anti* coupling with H-5a and H-6a, indicating that these methine protons are located in axial positions. Unfortunately, the coupling constant between H-1 and H-2 could not be determined. However, the *all-cis* and *tet* forms can be excluded as possible configurations of the system on the grounds of the chemical shifts of the methine H-1 and H-2. In order to display



**Figure 5.** Crystal structure of one of the two independent molecules of *ctc*-4.

15 signals in the <sup>13</sup>C NMR spectrum, the ring inversion process must be fast on the NMR time scale. Since the process exchanges between the equatorial and axial protons of the central ring, these protons should resonate at a chemical shift which is intermediate between those of an equatorial proton and an axial proton. However, since the methine H-1 and H-2 resonate at chemical shifts (1.08 and 1.33 ppm) characteristic of axial protons, we conclude that the compound is *all-trans* with all substituents located in equatorial positions.

**Crystal Structure of the *ctc* and *ctt* Isomers.** Single crystals of the *ctc* and *ctt* isomers of **4** were grown from CHCl<sub>3</sub>/EtOH. The unit cell of the *ctc* form contained two independent structures of approximate C<sub>2</sub> symmetry of nearly identical conformations in which the central ring adopts a chair conformation (Figure 5). The crystal conformation is identical to the one deduced by solution NMR. The chair is only slightly flattened, as indicated by the sum of the absolute values of the six internal C-C-C dihedral angles (318.9° and 323.5°), and the two external cyclohexyl substituents are attached to the equatorial positions while the internal substituents are attached to the axial ones. The axial rings exist in a *gauche* conformation (the  $\phi_1$  angles are 78.2° and 68.6° for the first independent molecule and 80.7° and 68.7° for the second independent molecule), while the equatorial rings are oriented *anti* ( $\phi_1$  angles of 179.1° and 184.6° (first molecule) and 180.8° and 174.7° (second molecule)). The  $\phi_2$  and  $\phi_3$  angles of the axial rings are in the 32.6–46.5° region, the  $\phi_3$  angles being somewhat smaller. The nonstaggered arrangement of the rings is probably attained in order to avoid repulsive steric interactions between H-2'' and H-6'' and the axial hydrogens of the central ring H-4a and H-6a.

Notably, the central ring of the *ctt* form adopts a twist-boat conformation (Figure 6). The six C-C-C dihedral angles of the central ring of one enantiomer are -60.1°, 28.6°, 24.0°, -48.8°, 16.4°, and 37.2°.

**Molecular Mechanics Calculations of Polycyclohexylcyclohexanes.** In order to estimate the relative energies of the different conformers of the systems, we performed molecular mechanics calculations using the MM3(92) program.<sup>19</sup> In all cases only conformations in which the substituents are attached through their equatorial positions were considered.<sup>25</sup> Conformations in which the central ring exists in a chair conformation, and all or most substituents are located at its equatorial or axial positions will be denoted chair(eq) and chair(ax). The results of the calculations are summarized in Table 1. In all cases the agreement between the calculated structural parameters of the

(23) One of the "ortho" equatorial protons on the axial substituent (H-2''e or H-6''e) is shifted upfield (1.35 ppm). This signal is assigned to the proton located above the central cyclohexyl ring. A similar shielding effect is not observed in *all-cis*-3, since even at 150 K there is a fast enantiomerization process on the NMR time scale which renders the two edges of the axial ring equivalent (cf. Figure 3).

(24) Wieser, J.; Golan O.; Fijter, L.; Biali, S. E. unpublished results.

(25) The substituent in monoalkyl-substituted cyclohexanes always prefers an equatorial position. For an exception, see: Biali, S. E. *J. Org. Chem.* **1992**, *57*, 2979.

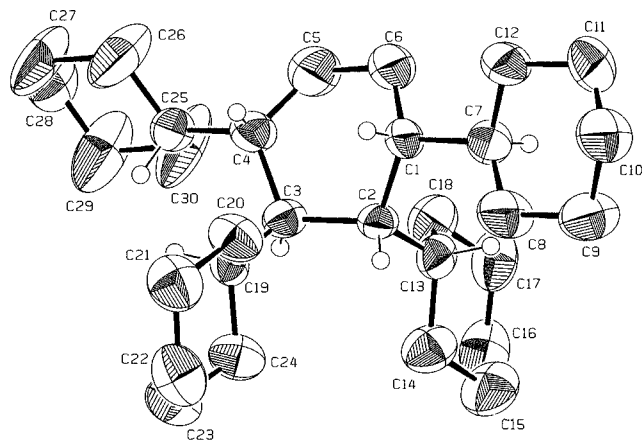
**Table 1.** Calculated (MM3) Geometries, Relative Steric Energies and Heats of Formation of the Conformers of Di-, Tri-, and Tetracyclohexylcyclohexane Systems<sup>a</sup>

system	chair(eq) <sup>b</sup>	chair(ax) <sup>c</sup>	TB	HF <sup>d</sup>	X-ray
<i>trans</i> -7	0.0 (61, 61)	2.5 (178, 178)	6.8 ( $\psi_e, \psi_e$ )	-71.2	
<i>cis</i> -7	0.0 (165, 179) <sup>e</sup>		3.3 ( $\psi_e, \psi_a$ )	-65.2	
<i>all-trans</i> -3	0.0 (55, 79, -65)	2.6 (167, 167, 173)	2.1 ( $\psi_a, I_c, \psi_e$ )	-85.7	chair (eq) (58, 80, -68)
<i>cis,trans</i> -3	2.4 (65, 49, 65)	0.0 (175, 161, 174)	2.5 ( $\psi_e, \psi_a, I_c$ )	-83.7	
<i>all-cis</i> -3	0.0 (171, 87, 172)	5.0 (-162, 179, -162)	6.6 ( $\psi_e, \psi_a, I_c$ )	-82.4	chair (eq) (164, 91, 164)
<i>all-trans</i> -4	0.0 (67, -93, -93, 67)	2.2 (166, 167, 167, 166)	1.0 ( $I_c, \psi_a, \psi_a, I_c$ )	-101.4	
<i>cis,trans,trans</i> -4	4.3 (65, 45, 81, -63)	2.3 (170, -154, 165, -167)	0.0 ( $\psi_e, \psi_a, I_c, \psi_e$ ) <sup>f</sup>	-100.5	TB (173, 75, 72, 74)
<i>cis,trans,cis</i> -4	0.0 (178, 74, 74, 178) <sup>g</sup>	10.2 (-157, 168, 168, -157) <sup>h</sup>	10.8 ( $\psi_a, I_c, \psi_a, \psi_e$ )	-100.5	chair (eq) (179, 81, 69, -175) <sup>i</sup> chair (eq) (179, 78, 69, -175) <sup>i</sup>
<i>trans,cis,trans</i> -4	0.0 (64, 48, 66, -171) <sup>e</sup>		2.2 ( $I_c, \psi_a, \psi_e, I_c$ )	-99.8	
<i>cis,cis,trans</i> -4	0.0 (172, 87, 46, 64)	1.1 (162, -178, 162, 178)	3.4 ( $I_c, \psi_e, \psi_a, I_c$ )	-97.0	
<i>all-cis</i> -4	0.0 (169, -131, 170, -179) <sup>e</sup>		5.0 ( $I_c, \psi_e, \psi_a, I_c$ )	-92.5	

<sup>a</sup> HCCH ( $\phi_i$ ) dihedral angles of the substituents in one enantiomer are given in parentheses. Energies are in kcal mol<sup>-1</sup>, angles in degrees.

<sup>b</sup> Chair conformation with all (or most) of the substituents in equatorial positions. <sup>c</sup> Chair conformation with all (or most) of the substituents in axial positions. <sup>d</sup> Heat of formation of the lowest energy conformation (global minimum). <sup>e</sup> Two enantiomeric conformations related by ring inversion.

<sup>f</sup> Calculated HCCH dihedral angles of the substituents: (176, 69, 68, 70). <sup>g</sup> eq-ax-ax-eq conformation. <sup>h</sup> ax-eq-eq-ax form. <sup>i</sup> Two independent molecules of similar conformation in the crystal.

**Figure 6.** Top view of the crystal structure of *ctt*-4.

minimum energy conformation and the X-ray structure was excellent.

**(a) Relative Stabilities.** The relative stabilities of the *cis/trans* isomers of **3** and **4** can be roughly estimated by comparing the heats of formation of the global minima of the different isomers. According to the calculations, the most stable isomer of **3** is the *all-trans* isomer, with the *cis,trans* and *all-cis* forms being 2.1 and 3.4 kcal mol<sup>-1</sup> above it. This is in full agreement with the stability order found in the high-temperature mutual isomerization experiment. According to the calculations, the relative energies of the isomers of **4** are (from more stable to less stable) *all-trans* > *ctt* = *ctc* > *tct* > *cct* > *all-cis*. These results are in agreement with the isomerization experiment which indicates that the isomer of lowest free energy (at 250°C) is the *all-trans* isomer followed by the *ctt* isomer. The three isolated forms of **4** represent the isomers which are most stable thermodynamically.

**(b) Gear Meshing and Nonstaggered Arrangements of Alkyl Groups.** During the last few years, several examples have been reported of unconstrained saturated systems displaying eclipsed primary alkyl groups in their lowest energy conformation.<sup>1,2,26-28</sup> 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.<sup>6</sup>

(26) Seiler, P.; Weisman, G. R.; Glendening, E. D.; Weinhold, F.; Johnson, J. D.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1175.

(27) Juaristi, E.; Martinez, R.; Mendez, R.; Toscano, R. A.; Soriano-Garcia, M.; Eliel, E. L.; Petson, A.; Glass, R. S. *J. Org. Chem.* **1987**, *52*, 3806. Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1343. Anderson, J. E.; Watson, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 1517.

(28) Forsyth, D. A.; Johnson, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 3364.

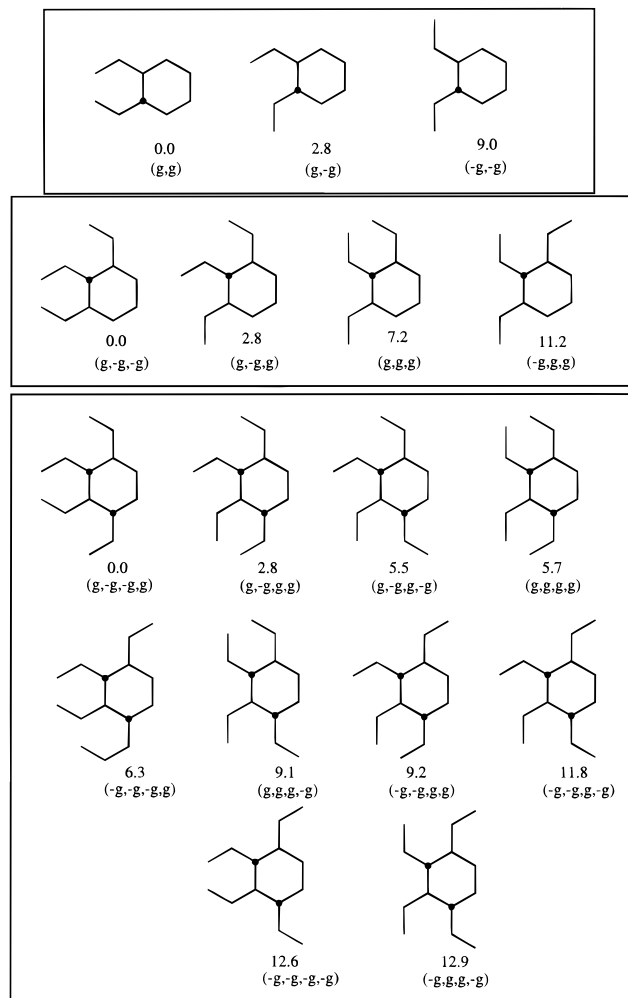
More generally, a primary alkyl group connected to an atom flanked by two bulky groups may adopt an eclipsed conformation in order to avoid the repulsive steric interactions existing in the staggered arrangements.<sup>27</sup>

Systems possessing secondary alkyl groups attached to a planar sp<sup>2</sup> frame may adopt a "tongue and groove" (gear-meshed) arrangement.<sup>16</sup> The mutual intermeshing of the groups results in an eclipsed arrangement of the methine CH groups with the planar central frame. Systems composed of vicinal cyclohexyl groups attached to a central polyatomic saturated frame (e.g., a cyclohexyl ring) may adopt an analogous gear-meshed conformation. In contrast to its unsaturated analog, this arrangement will not be perfectly eclipsed, since there is no intrinsic preference for the eclipsed arrangement,<sup>29</sup> nor are the bonds connecting the substituents to the central cyclohexyl ring coplanar. Yet, necessarily, gear meshing should induce non-staggered arrangements, and depending on the system, even eclipsed ones.<sup>30</sup>

Examination of space-filling models of the diequatorial conformer of *trans*-1,2-dicyclohexylcyclohexane (**7**) indicates that a gear-meshed arrangement of the groups can be achieved. MM3 calculations indicate that the lowest energy conformation of **7** is (g, g) with its methine protons facing each other, while the gear-meshed (g, -g), the "gear-clashing" (-g, -g), and the *anti,anti* conformations lay 2.7, 9.0, and 15.0 kcal mol<sup>-1</sup> above it (Figure 7). If three vicinal equatorial cyclohexyls are present, a gear-meshed arrangement of at least two groups must be adopted in order to avoid pairwise gear-clashing interactions. The calculations of the triequatorial form of *all-trans*-3 indicate that in the lowest energy conformation (g, -g, -g) two cyclohexyl rings exist in a gear-meshed arrangement. The (g, -g, -g) conformation is of lower energy than the homodirectional all-gear form (g, -g, g). Notably, the calculations predict that the  $\phi_2$  dihedral angle of the central substituent should be reduced from the ideal staggered angle of 60° to 34.1° (the experimental (X-ray) value is 32.1°, Table 2). The lowest energy conformation of *all-trans*-4 (g, -g, -g, g) is the one with two pairs of geared groups, while the homodirectional all-gear form (g, -g, g, -g) is 5.5 kcal mol<sup>-1</sup> above it. According to the calculations, the  $\phi_2$  and  $\phi_3$  angles of the internal substituents of the global minimum of **4** are only 22.6–21.5°.<sup>31</sup> The conformational behavior of the all-equatorial polycyclohexylcyclohexanes suggests that in these systems the cyclohexyl

(29) In the lowest energy conformation of propene one of the C-H bonds is eclipsed with the double bond.

(30) For studies on isopropyl groups attached to a saturated carbon, see: Anderson, J. E.; Koon, K. H.; Parkin, J. E. *Tetrahedron* **1985**, *41*, 561.



**Figure 7.** Calculated (MM3) relative steric energies ( $\text{kcal mol}^{-1}$ ) of the chair(eq) conformers of *all-trans-7*, *all-trans-3*, and *all-trans-4*, in which the methine protons of the substituents exist in  $\pm$ *gauche* orientations. All structures are chiral, and only one of the two enantiomeric forms is shown. For clarity, only the methine protons of the substituents are depicted.

substituents do not intrinsically prefer the gear-meshed arrangement, and that the conformation is adopted in order to avoid gear-clashing interactions.<sup>32</sup> The contributions of the gear-meshed and gear-clashed arrangements to the steric energy of the different conformers are roughly additive, being 2.8–3.0 and ca. 9.0  $\text{kcal mol}^{-1}$ , respectively.

The recognition that gear-meshed interactions may result in nonstaggered (and even eclipsed) arrangements led us to examine briefly the gear-meshed conformation obtained by geminally attaching cyclohexyl groups to a single tetrahedral central atom. The most impressive example of this effect is tricyclohexylmethane (**8**) which exists in a *gauche, gauche, anti* conformation with a pair of gear-meshed cyclohexyl groups.<sup>7b</sup> According to X-ray diffraction data, in the two crystal forms of **8**, the  $\phi_3$  and  $\phi_2$  angles are 15.3° and 14.5° in the racemic crystal form, and only 10.5° and 10.2° for the chiral one.<sup>7b</sup>

**(c) Axial/Equatorial Energy Gaps.** The calculations indicate that in the *trans* form of 1,2-dicyclohexylcyclohexane (**7**)

(31) Additional vicinal cyclohexyl rings do not further reduce  $\phi_2$ . According to the calculations, in the gear-meshed all-equatorial conformation of *all-trans*-1,2,3,4,5,6-hexacyclohexylcyclohexane this angle is 21.8°. However, this represents a high-energy conformer, the ground state conformation being the (non-gear-meshed) all-axial form.

(32) This behavior is analogous to that of the polyisopropylbenzenes. See: Kahr, B.; Biali, S. E.; Schaefer, W.; Buda, A. B.; Mislow, K. *J. Org. Chem.* **1987**, *52*, 3713.

**Table 2.** Calculated (X-ray) and Experimental (MM3) HCCC Torsional Angles of the Central Cyclohexyl Substituent(s) in the Lowest Energy Conformation of Selected Systems<sup>a</sup>

system	angle	X-ray	MM3
<i>all-cis-3</i>	HC(2)C(13)C(18)	22.3	27.7
	HC(13)C(2)C(3)	23.0	26.8
<i>all-trans-3</i>	HC(2)C(13)C(18)	32.1	34.1
	HC(13)C(2)C(3)	36.0	36.5
<i>cis,trans,cis-4</i>	HC(3)C(19)C(20) <sup>b</sup>	34.4	40.9
	HC(2)C(13)C(18) <sup>b</sup>	46.5	
	HC(19)C(3)C(4) <sup>b</sup>	32.6	39.3
	HC(13)C(2)C(1) <sup>b</sup>	45.2	
	HC(33)C(49)C(50) <sup>c</sup>	36.7	40.9
	HC(32)C(43)C(48) <sup>c</sup>	46.2	
	HC(49)C(33)C(34) <sup>c</sup>	35.0	39.3
<i>all-trans-4</i>	HC(43)C(32)C(31) <sup>c</sup>	45.4	
	HCCC( $\phi_2$ )		21.5
	HCCC( $\phi_3$ )		22.6

<sup>a</sup> Absolute values of the dihedral angles (deg). <sup>b</sup> First independent molecule in the crystal. <sup>c</sup> Second independent molecule in the crystal.

(Table 1) the chair(eq) is favored over the chair(ax) by 2.5  $\text{kcal mol}^{-1}$ . Whereas in the diequatorial conformation the groups are oriented *gauche*, in the diaxial form they exist in an *anti* arrangement. The calculations indicate that the global minima of *all-cis-3* and *all-trans-3* correspond to chair(eq) structures in which the substituents are oriented (a, g, a) and (g, g, -g), respectively. In the *all-trans* form, the triequatorial conformer is preferred over the triaxial form by 2.6  $\text{kcal mol}^{-1}$ . In contrast, in the *cis,trans* form the chair(ax) conformation is favored by 2.4  $\text{kcal mol}^{-1}$  over the chair(eq) form. This represents one of the simplest systems in which the chair(ax) form is energetically preferred over the chair(eq) form. According to the calculations, in the chair(ax) form the three substituents are oriented *anti*, which is the conformation preferred for an isolated cyclohexyl substituent. In the chair(eq) form, the two equatorial substituents adopt their preferred (g,g) conformation (cf. Figure 7) with the axial substituent also oriented *gauche*. The steric interactions between the central substituent and the axial ring result in the destabilization of the chair(eq) form.

The calculations indicate, in agreement with the experimental data, that *all-trans-3* and *all-trans-4* exist in chair(eq) conformations. This is in contrast to *all-trans-2* which exists in the chair(ax) conformation. Clearly, three or four neighboring cyclohexyl groups arranged in an *all-trans* fashion are not sufficient to render the chair(ax) form the global minimum. The destabilization of the chair(eq) form of **2** has been ascribed in part to the eclipsing interactions existing in that form.<sup>6</sup> Examination of the chair(ax)/chair(eq) energy gap of the isomers of **4** indicates that although in the *ctt* form the chair(ax) is favored by 2.0  $\text{kcal mol}^{-1}$  over the chair(eq) form, in no isomer does the chair(ax) represent the global minimum.

**(d) Chair/TB Energy Gap.** The TB/chair (TB = twist-boat) gap of *trans-7* is 6.8  $\text{kcal mol}^{-1}$  but is reduced to 3.3  $\text{kcal mol}^{-1}$  for the *cis* form (Table 1). Interestingly, for *all-trans-3* the TB form is of lower energy than the triaxial form. Examination of the calculations summarized in Table 1 shows that in the global minimum of *ctt-4* the central ring adopts a TB conformation. In *all-trans-4* the energy gap between the all-axial and all-equatorial forms is 2.2  $\text{kcal mol}^{-1}$ , with the TB form being more stable than the chair(ax) form by 1.2  $\text{kcal mol}^{-1}$ . The chair(eq)/TB energy gap of *ctc-4* is substantial (10.8  $\text{kcal mol}^{-1}$ ), indicating that the destabilization of the TB form by the substituents is larger than the destabilization of the chair forms.

**(e) Axial Nonstaggered Conformations.** Cyclohexyl substituents located at the axial positions of the central ring may ideally exist in either *anti* or *gauche* conformation. However,

whereas an isolated axial cyclohexyl substituent should prefer the *anti* arrangement, this conformation is destabilized by the presence of neighboring *cis* substituents, and the *gauche* form becomes the lowest energy arrangement.<sup>33</sup> Molecular models indicate that, in a perfectly staggered axial ring in a *gauche* conformation, severe steric interactions exist between the axial protons on the central ring and the "ortho" positions of the substituent. This repulsion can be reduced by twisting the axial ring toward an eclipsed conformation. This effect is observed in both the calculated and experimental HCCC torsional angles of the axial rings in several systems (Table 2). The MM3 calculations seem to underestimate the eclipsing degree of the substituent, since the calculated  $\phi_2$  and  $\phi_3$  angles are larger than the experimental values.

**Summary.** The lowest energy conformations of **3** and **4** provide examples of three conformational anomalies: (i) The central ring of *cis,trans,trans*-**4** exists in a twist-boat conformation. (ii) The *cis,trans* isomer of **3** adopts the chair(ax) conformation. (iii) In *all-cis*-**3** and *cis,trans,cis*-**4** the axial cyclohexyl substituent(s) is nearly eclipsed. Gear meshed interaction may force nonstaggered and even eclipsed arrangements.

## Experimental Section

**Crystallographic Data.** (a) *all-cis*-**1,2,3-Tricyclohexylcyclohexane**. C<sub>24</sub>H<sub>42</sub>, space group *P2<sub>1</sub>/n*, *a* = 18.230(3) Å, *b* = 13.632(2) Å, *c* = 8.458(1) Å,  $\beta$  = 98.62(2)°, *V* = 2078.2(6) Å<sup>3</sup>, *z* = 4,  $\rho_{\text{calc}}$  = 1.06 g cm<sup>-3</sup>,  $\mu(\text{Mo K}\alpha)$  = 0.54 cm<sup>-1</sup>, no. of unique reflections = 3041, no. of reflections with *I* ≥ 3 $\sigma_I$  is 2266, *R* = 0.045, *R<sub>w</sub>* = 0.066.

(b) *all-trans*-**1,2,3-Tricyclohexylcyclohexane**. C<sub>24</sub>H<sub>42</sub>, space group *Pc*, *a* = 9.863(2) Å, *b* = 13.096(1) Å, *c* = 9.072(1) Å,  $\beta$  = 115.68(1)°, *V* = 1056.1(3) Å<sup>3</sup>, *z* = 2,  $\rho_{\text{calc}}$  = 1.039 g cm<sup>-3</sup>,  $\mu(\text{Cu K}\alpha)$  = 3.88 cm<sup>-1</sup>, no. of unique reflections is 1656, no. of reflections with *I* ≥ 2 $\sigma_I$  is 1523, *R* = 0.041, *R<sub>w</sub>* = 0.061.

**1,2,3-Tricyclohexylcyclohexane.** (a) **Low Temperature Hydrogenation.** To a solution of 1.0 g of 1,2,3-triphenylbenzene in 70 mL of cyclohexane were added 1.0 g of Pd/C (10%) and a few drops of acetic acid. The mixture was hydrogenated for 24 h (170 °C, 600 psi).<sup>9</sup> After filtration of the catalyst, the solvent was evaporated and the residue was recrystallized from EtOH/CHCl<sub>3</sub>, yielding 550 mg (51%) of *all-cis*-1,2,3-tricyclohexylcyclohexane. Mp 123 °C. <sup>13</sup>C NMR

(100.62 MHz, CDCl<sub>3</sub>, rt):  $\delta$  24.69, 26.48, 26.73, 26.78, 26.82, 27.39, 28.36, 31.65, 31.99, 35.76, 39.02, 39.46, 39.61, 50.94 ppm. Anal. Calcd for C<sub>24</sub>H<sub>42</sub>: C, 87.19; H, 12.81. Found: C, 87.49; H, 12.98.

(b) **High Temperature Hydrogenation.** Hydrogenation of 1.0 g of 1,2,3-triphenylbenzene at 250 °C (600 psi of H<sub>2</sub>, Pd/C, 24 h)<sup>9</sup> gave a 3:7 mixture of the *cis,trans* and *all-trans* isomers of **3**. Recrystallization from EtOH/CHCl<sub>3</sub> or MeCN/CHCl<sub>3</sub> gave 300 mg (28%) of the *all-trans* isomer. Mp 77–78 °C. (*all-trans*) <sup>13</sup>C NMR (100.62 MHz, CDCl<sub>3</sub>, rt):  $\delta$  24.17, 25.47, 27.00, 27.04, 27.07, 27.54, 27.66, 27.82, 30.75, 32.58, 39.39, 39.91, 43.27, 43.31 ppm. (*cis-trans*) <sup>13</sup>C NMR (100.62 MHz, CDCl<sub>3</sub>, rt):  $\delta$  22.55, 23.78, 25.50, 26.56, 26.69, 26.71, 26.79, 26.84 (double intensity), 26.92, 26.93, 27.62, 31.13, 31.65, 31.76, 32.16, 32.82, 33.88, 37.94, 38.49, 39.31, 39.84, 40.08, 42.52 ppm.

**1,2,3,4-Tetracyclohexylcyclohexane.** To 1.0 g of 1,2,3,4-tetraphenylbenzene<sup>21</sup> dissolved in 70 mL of cyclohexane were added 1.0 g of 10% Pd/C and a few drops of acetic acid. The mixture was hydrogenated (170 °C, 600 psi of H<sub>2</sub>) for 24 h. Fractional crystallization from CHCl<sub>3</sub>/EtOH yielded 640 mg (60%) of *ctc*-**4**, mp 145 °C, followed by a mixture of the *ctc* and *ctt* isomers which were sorted manually by the external morphology of their crystals (rectangular for the *ctc*, rhombohedral for the *ctt*), yielding 100 mg (9%) of the *ctt*-**4**. Mp 140 °C. (*cis-trans-cis*) <sup>13</sup>C NMR (100.62 MHz, CDCl<sub>3</sub>, rt):  $\delta$  26.63 (double intensity), 26.66, 26.85, 26.98, 27.62, 27.72, 31.54, 31.89, 32.78, 34.50, 38.56, 39.23, 39.64, 44.32 ppm. Anal. Calcd for C<sub>30</sub>H<sub>52</sub>: C, 87.30; H, 12.70. Found C, 87.70; H, 12.32. (*cis,trans,trans*) <sup>13</sup>C NMR (100.62 MHz, CDCl<sub>3</sub>, rt):  $\delta$  21.00, 24.93, 26.55, 26.65, 26.76, 26.81, 27.03, 27.09, 27.25, 27.31, 27.38, 27.43, 27.44, 27.52, 27.62, 28.20, 31.63, 31.86, 32.46, 33.00, 33.15, 34.84, 38.52, 38.94, 40.26, 40.32, 40.44, 40.79, 41.51, 42.45 ppm. When the hydrogenation was carried out at 250 °C, the crude product consisted of a 6:4 mixture of the *all-trans* and *ctt* isomers. Fractional crystallizations from CHCl<sub>3</sub>/EtOH afforded the *all-trans* product in 90% purity. Mp, 60 °C. <sup>13</sup>C NMR (100.62 MHz, CDCl<sub>3</sub>, rt):  $\delta$  24.52, 26.93, 26.99 (double intensity), 27.43, 27.71, 27.83, 27.99, 30.17, 32.40, 33.45, 41.20, 42.55, 43.48, 43.86 ppm.

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**Supporting Information Available:** Tables listing the positional and thermal parameters for *all-cis*-**3** and *all-trans*-**3** (8 pages). See any current masthead page for ordering and Internet access instructions.

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(33) *trans* axial substituents can be arranged in *anti* arrangements as shown in **2** where the six isopropyl groups adopt *anti* arrangements.