10306 J. Am. Chem. Soc. 1994, 116, 10306-10307

Preparation and Molecular Structure Determination of a 1,2,3,4-Tetracyclohexylcyclohexane Existing in a Twist-Boat Conformation

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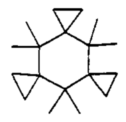
Received July 7, 1994

Polyalkylcyclohexanes usually prefer the chair over the twist-boat (TB) conformation of the cyclohexyl ring.[1-3] Exemptions to this rule are systems in which the cyclohexyl ring is constrained to exist in a TB form by chemical bonds (e.g., twistane), extremely crowded cyclohexanes (such as di-*tert*-butylcyclohexanes),[4] and systems with fused rings.[1] To the best of our knowledge, only a single unconstrained monocyclic system (**1**)[5] is known where the TB form is significantly energetically preferred over the chair conformation. The molecular structure of this system was determined using electron diffraction.[6] MM3 calculations indicate that "extreme substitution" is not a prerequisite for the relative stabilization of the TB form, and that in even the relatively noncrowded *cis-trans-trans* stereoisomer of 1,2,3,4-tetraisopropylcyclohexane (**2**) the TB is the lowest energy conformation.[7] The *cis-trans-trans* arrangement is unique in resulting in a lowest energy TB form, while the other configurations of **2** adopt the usual chair conformation. In this work we describe the experimental verification of these predictions.



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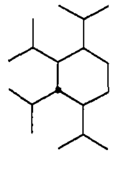

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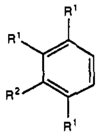
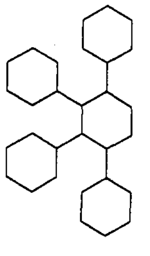


3 R^1 = R^2 = i-Pr
5 R^1 = R^2 = Ph
6 R^1 = c-C_6H_{11} R^2 = Ph



4a *cis-trans-cis*
4b *cis-trans-trans*
4c *all-trans*

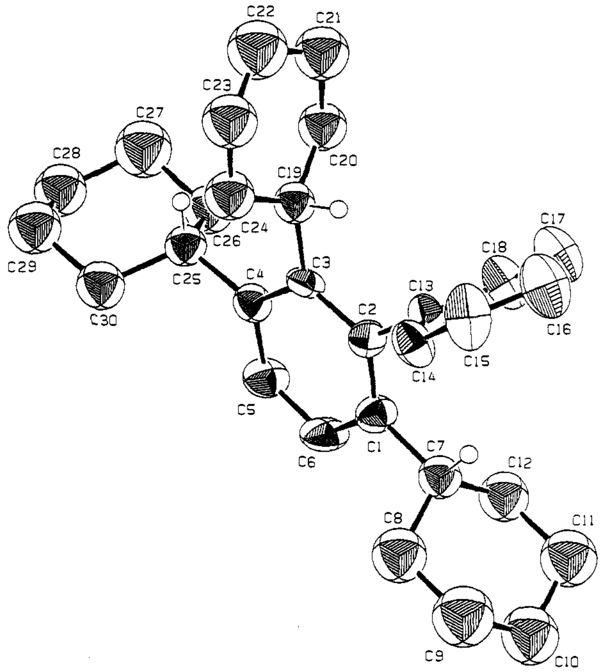


Figure 1. Crystal structure and numbering scheme of 2,3,6-tricyclohexylbiphenyl (**6**).

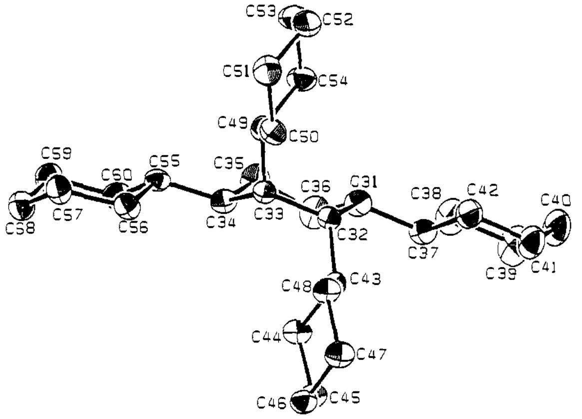


Figure 2. Crystal structure and numbering scheme of one of the two independent molecules of *cis,trans,cis*-1,2,3,4-tetracyclohexylcyclohexane (**4a**).

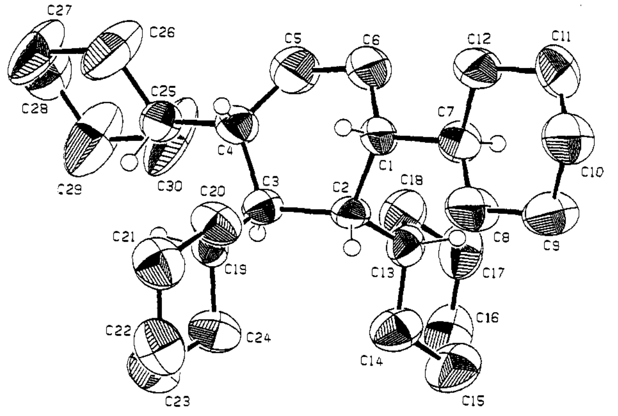


Figure 3. Top view of the crystal structure of *cis,trans,trans*-1,2,3,4-tetracyclohexylcyclohexane (**4b**).

The target compound **2** may be prepared in principle by hydrogenation of the unknown 1,2,3,4-tetraisopropylbenzene (**3**). However, since our attempts to prepare **3** proved unsuccessful, we decided to modify our target by replacing the isopropyl groups of **2** by cyclohexyls (i.e., *cis,trans,trans*-tetracyclohexylcyclohexane, **4b**).[8] The mutual steric interactions between the groups in **4b** should be similar to those present in **2** since the bulk of isopropyl and cyclohexyl groups are similar in the vicinity of their methine groups.[9] It could be expected therefore that **4b** also adopts a TB conformation. Cyclohexane **4b** could be obtained

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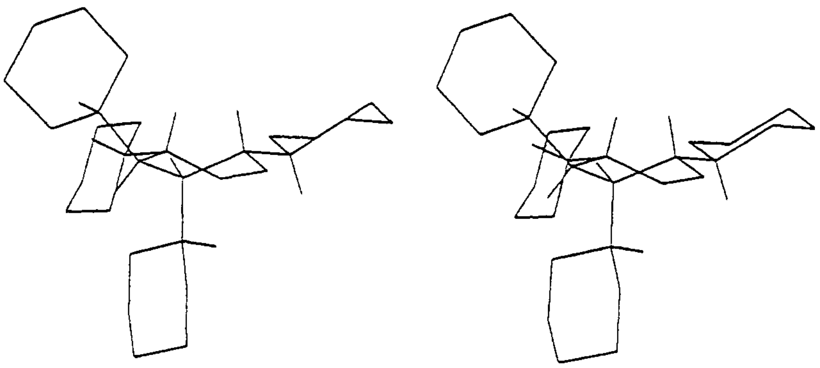

Figure 4. Stereoscopic side view of the crystal structure of **4b**.

in principle by catalytic hydrogenation of the readily available 1,2,3,4-tetraphenylbenzene (**5**).[10,11]

Hydrogenation of **5** with Ru/C or Rh/C (1:1 w/w, C_6H_{12}, 600 psi of H_2, 250 °C, 24 h) afforded a main product of mp 204–205 °C, which displayed in the ^{13}C NMR spectrum both aromatic and aliphatic signals, indicating only partial reduction of the aryl rings of **5**.[12] X-ray crystallography of a single crystal showed that this compound is 2,3,6-tricyclohexylbiphenyl (**6**, Figure 1).[13] The two vicinal cyclohexyl rings are statically geared,[9,14] and all cyclohexyl rings orient their methines toward the internal phenyl ring. The selectivity observed in the hydrogenation is probably due to steric hindrance. The central rings and the internal phenyl rings are probably more difficult to approach by the catalyst since they are "shielded" by the cyclohexyl groups.

Exhaustive hydrogenation of **5** was accomplished by using Pd/C as catalyst (1:1 w/w, C_6H_{12}, 600 psi of H_2, 170 °C, 24 h) yielding two stereoisomeric 1,2,3,4-tetracyclohexylcyclohexane products (**4a** and **4b**). Fractional crystallization of the mixture (EtOH/$CHCl_3$) yielded firstly rectangular crystals of **4a** (mp 145 °C) and then a mixture of **4a** with rhombus-shaped crystals of **4b** (mp 140 °C). The ^{13}C NMR spectrum ($CDCl_3$, room temperature, 100 MHz) of the main product (**4a**) displays 14 signals (one of apparently double intensity),[12] in agreement with a substitution pattern of bilateral symmetry, i.e., with either *all-cis*, *all-trans*, *cis-trans-cis*, or *trans-cis-trans* configurations. X-ray diffraction analysis of a single crystal of **4a** indicates that the compound is the *cis-trans-cis* isomer. Two independent molecules with very similar conformations and in which all the rings adopt chair conformations were observed in the unit cell. The central cyclohexyl ring in both molecules is only slightly flattened, as shown by the sum of the absolute values of the six internal C–C–C–C torsional angles of the rings (323.5° and 318.9°). The cyclohexyls at the 2- and 3-positions of the central ring are attached to the axial positions of the central ring and are oriented with the $HCC_{central}H$ torsional angles *gauche* whereas the rings at the 1- and 4-positions are attached equatorially and are oriented *anti* (Figure 2). The crystallographic conformations are very similar to the conformation predicted by the MM3 calculations as the global minimum of *cis,trans,cis*-tetraisopropylcyclohexane.

In contrast to **4a**, **4b** displays 30 signals in the ^{13}C NMR spectrum,[15] in agreement with a chiral structure of C_1 symmetry, which may correspond to either a *cis-trans-trans* or a *cis-cis-trans* configuration. Initial attempts of *cis–trans* isomerization of a sample of **4a** by heating in the presence of Pd/C in a pressure bomb resulted in substantial dehydrogenation. The catalytic isomerization of **4a** was finally accomplished using Pd/C and high temperatures (250 °C) under a hydrogen atmosphere (600 psi of H_2), yielding **4b** and, as the main product, an additional isomer (**4c**). The isomerization observed indicates that **4a** is the kinetic product of the hydrogenation while **4b** and **4c** are the thermodynamically preferred forms. Heat of formation calculations on **2** indicate that the relative stability order expected for the system is (from more stable to less stable) *cis-trans-trans* > *cis-trans-cis* > *cis-cis-trans*.[7] The configuration of **4b** is therefore more likely to be *cis-trans-trans*.[16] X-ray diffraction of **4b** corroborated that configuration.[13] The numbering scheme is shown in Figure 3, and a stereoscopic side view of the structure is shown in Figure 4. As shown by the X-ray data, in **4b** the central ring *exists in a twist-boat conformation*. This represents the first X-ray structure of an unconstrained polyalkylcyclohexane which exists in a TB conformation. The dihedral angles defined by the carbons of the central ring of one of the two enantiomeric forms present in the crystal are 37.2°, 16.4°, –48.8°, 24.0°, 28.6°, and –60.1°. The external cyclohexyl rings occupy the pseudoequatorial, pseudoaxial, isoclinal, and pseudoequatorial positions of the TB forms and have HCCH dihedral angles of –173.4°, –75.4°, –72.4°, and –73.8°, respectively.

In summary, we have experimentally shown that the presence of four neighboring isopropyl groups is sufficient for rendering the twist-boat the lowest energy conformation of a cyclohexyl ring.

Acknowledgment. We thank Dr. Roy E. Hoffmann for helpful discussions. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Supplementary Material Available: Tables of atomic coordinates for **6**, **4a**, and **4b** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(12) ^{13}C NMR data (100.62 MHz, $CDCl_3$): **6**, δ 26.17, 26.20, 26.31, 26.89, 27.35, 27.45, 31.69, 34.39, 35.03, 40.40, 41.17, 43.04, 123.28, 126.17, 127.00, 127.83, 128.84, 141.12, 141.42, 142.77, 143.18, 144.17 ppm; **4a**, δ 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.

(13) Crystal data for **5**: $C_{30}H_{40}$, space group $P2_12_12_1$; a = 21.632(4) Å, b = 11.360(2) Å, c = 10.419(2) Å, V = 2560.4(7) Å^3, z = 4, ρ_{calc} = 1.04 g cm^{-3}, μ(Mo Kα) = 0.54 cm^{-1}; no. of unique reflections, 2072; no. of reflections with $I \geqslant 2\sigma_I$, 1570; R = 0.086, R_w = 0.103. Crystal data for **4a**: $C_{30}H_{52}$, space group $P\bar{1}$; a = 16.482(1) Å, b = 12.658(1) Å, c = 10.374(1) Å, α = 90.61(1)°, β = 100.25(1)°, γ = 70.65(1)°, V = 2640.9(6) Å^3, z = 4, ρ_{calc} = 1.04 g cm^{-3}, μ(Cu Kα) = 3.88 cm^{-1}; no. of unique reflections, 6597; no. of reflections with $I \geqslant 2\sigma_I$, 5062; R = 0.046, R_w = 0.068. Crystal data for **4b**: $C_{30}H_{52}$, space group $P2_1/c$; a = 10.195(2) Å, b = 23.816(3) Å, c = 10.872(2) Å, β = 93.12(1)°, V = 2635.9(7) Å^3, z = 4, ρ_{calc} = 1.04 g cm^{-3}, μ(Cu Kα) = 3.88 cm^{-1}; no. of unique reflections, 3772, no. of reflections with $I \geqslant 2.5\sigma_I$, 1843; R = 0.093, R_w = 0.100.

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(15) ^{13}C NMR data (100.62 MHz, $CDCl_3$) of **4b**: δ 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.

(16) Isomer **4c**, which displays 15 signals in the ^{13}C NMR spectrum, is most likely the *all-trans* stereoisomer.