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cis-syn-cis-1,2,4,5-Tetracyclohexylcyclohexane. A Moderately Crowded Saturated Hydrocarbon Adopting a Twist-Boat Conformation

Oren Golan, Shmuel Cohen, and Silvio E. Biali*

Department of Organic Chemistry, The Hebrew University of Jerusalem Jerusalem 91904, Israel

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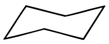
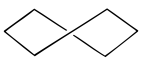
A cyclohexane ring usually prefers the chair (**1**) over the twist-boat (TB, **2**) conformation when present in unconstrained saturated hydrocarbons.[1,2] Bulky substituents (e.g., *tert*-butyl groups) can modify the chair/TB energy gap, and in some substitution patterns they may even render the TB the preferred conformation by preferentially destabilizing the chair form.[1−4] A computational study predicted that four isopropyls or just two isopropyls and two methyls attached to a cyclohexyl ring in a *cis,trans,trans*-1,2,3,4 or *cis,syn,cis*-1,2,4,5 pattern are sufficient for rendering the TB the preferred conformation.[4] This change in the normal conformational preferences is due to the selective destabilization of the chair conformation. A system with the first substitution pattern (*cis,trans,trans*-1,2,3,4-tetracyclohexylcyclohexane) was shown by X-ray crystallography to adopt a TB conformation.[5] In this note we demonstrate experimentally that a system with the *cis,syn,cis*-1,2,4,5 pattern prefers the TB conformation.



1



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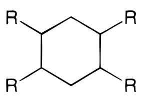
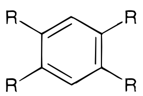


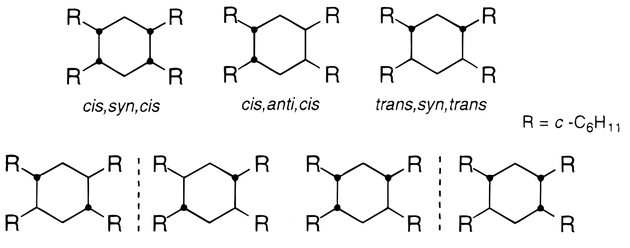
3
R = c-C_6H_{11}



4 R = Ph
5 R= c-C_6H_{11}

1,2,4,5-Tetracyclohexylcyclohexane (**3**) exists in seven stereoisomeric forms (three *meso* forms and two enantiomeric pairs, Scheme 1).[6] Calculations of the TB/chair gaps of 1,2,4,5-tetracyclohexylcyclohexanes were performed with the MM3(92) program[7] together with the HUNTER conformational search procedure (Table 1).[8] As indicated by the calculations, the *cis,syn,cis* form is predicted to adopt a TB conformation. The unusually large stability of the TB form relative to the chair form (7.1 kcal mol^{-1}) is most likely the result of unavoidable 1,3-diaxial interactions in the chair form. These interactions cannot be alleviated by ring inversion, because the process relocates the pair of equatorial substituents into axial positions (Scheme 2). The TB/chair energy gaps are similar to those previously calculated for the corresponding 1,2,4,5-tetraisopropylcyclohexanes.[4] This is reasonable because isopropyl and cyclohexyl groups are nearly isosteric near their attachment point.[9] In all of the configurational isomers of **3** calculated, in the lowest energy conformation the peripheral cyclohexyl rings were found to adopt a chair conformation and to be connected to the central rings through their equatorial positions.

Scheme 1



Catalytic hydrogenation of 1,2,4,5-tetraphenylbenzene[10] (**4**) at 250 °C (Pd/C, 660 psi H_2) afforded the *trans,syn,trans* and *trans,anti,trans* isomers of **3** (mp 221 and 240 °C), which were separated by fractional crystallization. According to the calculations (Table 1), these products correspond to the lowest energy isomers. X-ray crystallography indicated that in both compounds all rings adopt the chair conformation (Figures 1 and 2).[11] In the *trans,syn,trans* form the peripheral rings are all located at equatorial positions of the central ring, whereas in the *trans,anti,trans* form a pair of vicinal cyclohexyl substituents are located at axial and a pair at equatorial positions.

trans,anti,trans-**3** displays eight NMR signals in the ^{13}C NMR spectrum ($CDCl_3$, rt). Upon lowering of the temperature of a CD_2Cl_2 solution, the signals broadened and decoalesced. The barrier measured ($\Delta G_c^{\ddagger} = 9.7$ kcal mol^{-1} at 194 K) is ascribed to a ring inversion process of the central ring that exchanges the axial with the equatorial substituents (Scheme 3). This barrier is comparable to the barrier of cyclohexane ($\Delta G^{\ddagger} = 10.2{-}10.5$

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(1) (a) *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH Publishers: New York, 1995. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(2) For a review on nonchair conformations of cyclohexane see: Kellie, G. M.; Riddell, F. G. *Top. Stereochem.* **1974**, *8*, 225.

(3) A cyclohexane 1,4-*cis*-disubstituted by a quinone and a porphyrin moiety has been shown to adopt a twist-boat conformation, see: Dieks, H.; Senge, M. O.; Kirste, B.; Kurreck, H. *J. Org. Chem.* **1997**, *62*, 8660.

(4) Weiser, J.; Golan, O.; Fitjer, L.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8277.

(5) Columbus, I.; Hoffman, R. E.; Biali, S. E. *J. Am. Chem. Soc.* **1996**, *118*, 6890.

(6) For simplicity, the configurational isomers of **3** will be described by the method commonly used for fused-ring cyclohexanes. The mutual disposition of two vicinal groups will be denoted as “cis” or “trans”. If the two substituents at the 1 and 5 positions of the central ring are in a mutual *cis* or *trans* relationship, this will be denoted by the “syn” and “anti” descriptors, respectively.

(7) Allinger, N. L. *MM3(92)*: Technical Utilization Corporation.

(8) Weiser, J.; Holthausen, M. C.; Fitjer, L. *J. Comput. Chem.* **1997**, *18*, 1264.

(9) For a comparison of the rotational barriers of tetraisopropylethene and tetacyclohexylethene see: Columbus, I.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 3402.

(10) Harada, K.; Hart, H.; Du, C.-J. F. *J. Org. Chem.* **1985**, *50*, 5524.

(11) The authors have deposited atomic coordinates for the structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

10.1021/jo990453q CCC: $18.00

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

configuration	chair(eq)[a]	chair(ax)[b]	TB[c]	HFO[d]
trans,syn,trans	0.0	nf[e]	9.8 (Ic,Ψa,Ic,Ψe)	−113.04
trans,anti,trans	0.0		4.8 (Ψe,Ψe,Ψe,Ψe)	−110.95
cis,trans	0.0	nf	3.3 (Ψe,Ic,Ψe,Ic)	−107.25
cis,syn,cis	7.1		0.0 (Ψe,Ic,Ψe,Ic)	−101.84
cis,anti,cis	0.0		2.2 (Ψe,Ψa,Ψa,Ψe)	−101.15

[a] Lowest energy conformation with all (or most) of the alkyl groups in equatorial positions. [b] Lowest energy conformation with all (or most) of the alkyl groups in axial positions. [c] Lowest calculated twist-boat conformation. Ic, Ψa, and Ψe denote that the substituents are located at isoclinal, pseudoaxial, or pseudoequatorial positions of the central ring, respectively. [d] Heat of formation of the lowest energy conformation. [e] No chair(ax) conformation was found.

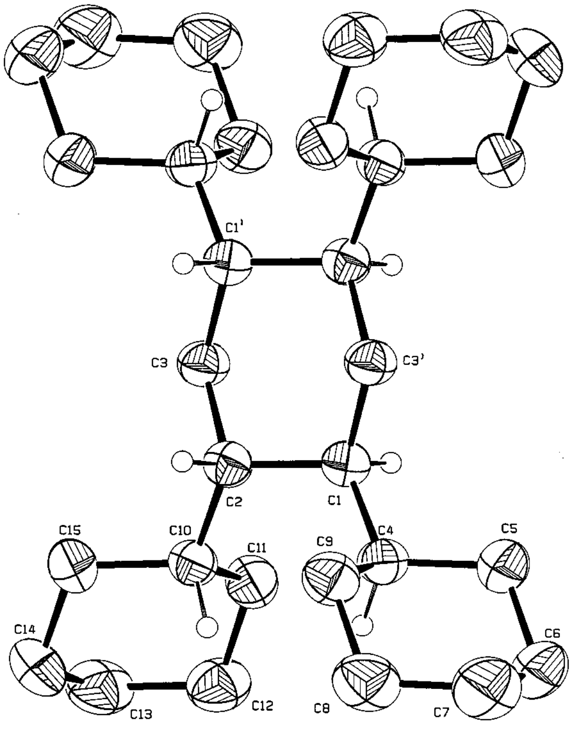


Figure 1. Crystal structure of *trans,syn,trans*-**3**.

kcal mol^{-1}),[1,12] indicating that the four cyclohexyl substituents in *trans,anti,trans*-**3** do not markedly affect the rigidity of the central ring.

According to heat of formation calculations, the *cis,syn,cis* isomer corresponds to a high energy form. To avoid epimerization of the product, the hydrogenation of **4** was carried out at a relatively low temperature of 85 °C (640 psi H_2). Fractional crystallization of the product afforded *cis,syn,cis*-**3** together with 1,2,4,5-tetracyclohexylbenzene (**5**). X-ray analysis of a single crystal of *cis,syn,cis*-**3**[11] corroborates the predictions of the calculations and indicates that the central ring adopts a twist boat conformation of approximately C_2 symmetry (Figure 3) with the peripheral "chair" cyclohexyls located at isoclinal and pseudoequatorial positions of the central ring. The ^3J coupling constants between the methylene and methine protons of the central ring of the chair and TB forms of *cis,syn,cis*-**3** were estimated using the MM3 geometry (for the chair form) and the crystal coordinates (for the TB form). The ^3J values were calculated by the Karplus equation (using Altona's parameters)[13] assuming that the chair form undergoes fast chair inversion while the TB form undergoes fast enantiomerization on the NMR time scale (Scheme 4). The calculated ^3J values were 9.6 and 1.4 Hz for the chair form and 12.4 and 4.7 Hz for the TB. Analysis of the NMR spectrum of *cis,syn,cis*-**3** ($CDCl_3$, rt, 600.132 MHz) indicated that these

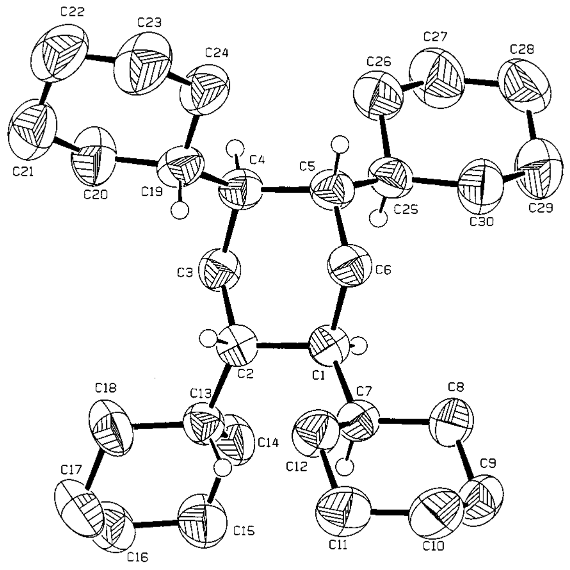


Figure 2. Molecular structure of *trans,anti,trans*-**3**.

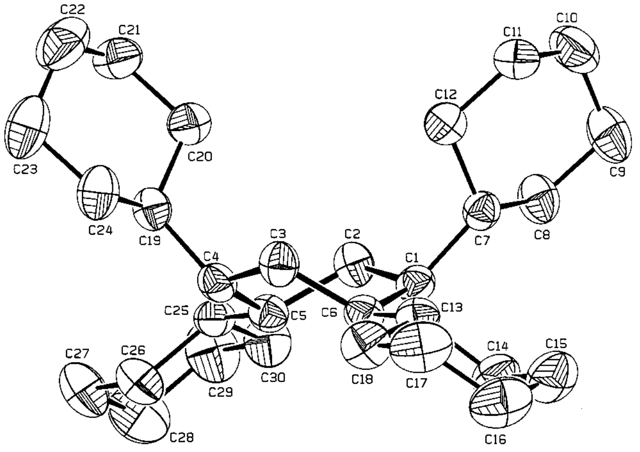
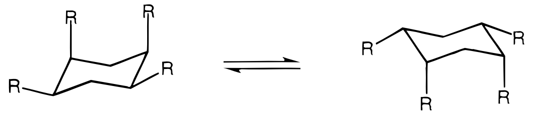
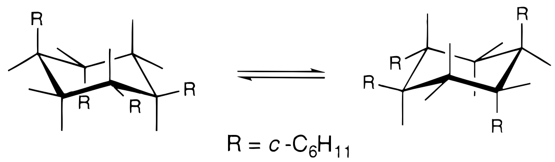


Figure 3. Numbering scheme of the crystal structure of *cis,syn,cis*-**3**. The central ring adopts a twist-boat conformation.

Scheme 2



Scheme 3



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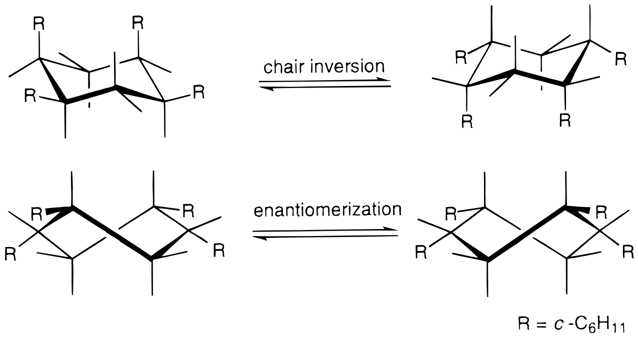
(12) For a recent determination of the inversion barrier of cyclohexane see: O'Leary, B. M.; Grotzfeld, R. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 11701.

(13) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

Scheme 4



coupling constants are 13.0 ± 0.4 and 4.3 ± 0.4 Hz, in agreement with the presence of a TB conformation in solution.

In conclusion, we have shown experimentally that four cyclohexyl groups in a *cis,syn,cis*-1,2,4,5 pattern render the TB the lowest energy conformation of the central ring.

Experimental Section

Pd/C (5% Pd) was purchased from Aldrich. Different batches of the catalyst showed different reactivity. Coupling constants were determined from the active couplings in the cross-peaks of the COSY DQF spectrum.[14]

***trans,syn,trans*- and *trans,anti,trans*-3.** Compound **4**[10] (0.2 g) dissolved in cyclohexane (40 mL) and acetic acid (0.5 mL) was hydrogenated using a Parr pressure reactor (0.21 g Pd/C, 650 psi H_2, 250 °C, 145 h). After work up, an additional hydrogenation was performed (0.20 g Pd/C, 640 psi H_2, 230 °C, 40 h), affording a mixture of *trans,syn,trans*-**3** and *trans,anti,trans*-**3** which were separated by fractional crystallization ($CHCl_3$/EtOH). The first fraction was *trans,syn,trans*-**3** (35%), and the second fraction afforded the *trans-anti-trans* isomer in 25% yield. *trans,syn,trans*-**3**: mp 240 °C; ^{13}C NMR ($CDCl_3$) δ 44.05 (C1), 37.72 (C1′), 32.03 (C6′), 27.50 (C5′), 27.12 (C3′), 27.06 (C4′), 26.87 (C2), 26.25 (C2′) ppm; MS *m*/*z* 412.4. Anal. Calcd for $C_{30}H_{52}$: C, 87.29; H, 12.71. Found: C, 87.00; H, 12.54. *trans,anti,trans*-**3**: mp 221 °C; ^{13}C NMR ($CDCl_3$) δ 38.93 (C1), 37.01 (C1′), 31.97 (C6′), 28.42 (C2′), 27.01 (C3′, C4′, or C5′), 26.94 (C3′, C4′, or C5′), 26.86 (C3′, C4′, or C5′), 22.92 (C2) ppm; MS *m*/*z* 412.4. Anal. Calcd for $C_{30}H_{52}$: C, 87.29; H, 12.71. Found: C, 87.13; H, 12.44.

***cis,syn,cis*-3.** Compound **4** (0.15 g) dissolved in cyclohexane (40 mL) was hydrogenated in a Parr pressure reactor (0.042 mg Pd/C, 640 psi H_2, 85 °C). The full hydrogenation of **4** required three hydrogenation cycles (22, 64, and 18 hs). After filtration of the catalyst and evaporation of the solvent, the residue was fractionally crystallized from $CHCl_3$/EtOH affording *cis,syn,cis*-**3** (27%) and 1,2,4,5-tetracyclohexylbenzene (23%). *cis,syn,cis*-**3**: mp 194 °C; ^1H NMR (600.13 MHz, $CDCl_3$, rt) δ 1.80 (m, 4H, H6′), 1.74 (m, 8H, H3′ + H4′ or H5), 1.67 (m, 4H, H4′ or H5′), 1.58 (m, 4H, H2′), 1.54 (m, 2H, H2), 1.48 (m, 4H, H1), 1.41 (m, 4H, H1′), 1.25 (m, 8H, H3′ + H4′ or H5′), 1.15 (m, 4H, H4′ or H5′), 1.07 (m, 2H, H2), 1.02 (m, 8H, H6′ + H2′); ^{13}C NMR (100.6 MHz, $CDCl_3$, rt) δ 39.87 (C1), 38.13 (C1′), 33.02 (C2′), 29.77 (C6′), 27.05 (C3′), 26.83 (C4′), 26.77 (C5′), 22.29 (C2) ppm; MS *m*/*z* 412.3. Anal. Calcd for $C_{30}H_{52}$: C, 87.29; H, 12.71. Found: C, 87.12; H, 12.71.

X-ray Crystallography. Data were measured on an ENRAF-Nonius CAD-4 or PW1100/20 Philips four-circle computer-controlled diffractometer. Cu Kα (λ = 1.541 78 Å) or Mo Kα (λ = 0.710 69 Å) radiation with a graphite crystal monochromator in the incident beam was used. *trans,syn,trans*-**3**: space group $P\bar{1}$, a = 10.098(1), b = 15.157(1), c = 9.672(3) Å, α = 91.38(2)°, β = 115.34(2)°, γ = 81.76(1)°, V = 1323.0(6) Å^3, z = 2, ρ_{calc} = 1.04 g cm^{-3}, μ(Cu Kα) = 3.87 cm^{-1}, no. of unique reflections = 4862, no. of reflections with $I \geq 3\sigma_I$ = 4206, R = 0.041, R_w = 0.071. *trans,anti,trans*-**3**: space group $P2/c$, a = 16.647(3), b = 10.172(2), c = 16.868(3) Å, β = 112.18(1)°, V = 3644.6(8) Å^3, z = 4, ρ_{calc} = 1.04 g cm^{-3}, μ(Cu Kα) = 3.87 cm^{-1}, no. of unique reflections = 5307, no. of reflections with $I \geq 3\sigma_I$ = 3248, R = 0.045, R_w = 0.065. *cis,syn,cis*-**3**: $C_{30}H_{52}$, space group $P2_1/n$, a = 16.336(3), b = 16.057(2), c = 10.388(1) Å, β = 102.69(2)°, V = 2658.3(7) Å^3, z = 4, ρ_{calc} = 1.03 g cm^{-3}, μ(Mo Kα) = 0.53 cm^{-1}, no. of unique reflections = 4882, no. of reflections with $I \geq 3\sigma_I$ = 2895, R = 0.042, R_w = 0.053.

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(14) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: Oxford, 1987; p 221.