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STERICALLY CROWDED CYCLOHEXANES - 9.[1] SYNTHESIS, CONFORMATION AND DYNAMICS OF HEXASPIRO[2.0.4.0.2.0.4.0.2.0.4.0]TETRACOSANE

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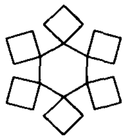
Abstract: The synthesis, conformation and dynamics of hexaspiro[2.0.4.0.2.0.4.0.2.0.4.0]tetracosane (**3**) are described. At room temperature in solution, **3** exists as 4:1 mixture of a rapidly interconverting twistboat conformation and a fixed chair conformation. The activation parameters for the chair-to-chair interconversion followed from a bandshape analysis of exchange broadened ^{13}C NMR spectra of [1,10,18-^{13}C]-**3** as $\Delta H^{\#} = 57.1$ kJ/mol, $\Delta S^{\#} = 35.4$ J/mol·K, and $\Delta G^{\#}_{298} = 67.6$ kJ/mol. **3** is only the second case where a per(cyclo)alkylated cyclohexane populates a chair and a twistboat, and the first case where the twistboat predominates. © 1997 Elsevier Science Ltd.

Introduction

Cyclohexanes normally adopt a chair conformation and the free energy of activation for the chair-to-chair-interconversion seldom exceeds 50 kJ/mol.[2] However, with fully substituted cyclohexanes most different anomalies have been observed.[3] Illustrative are the following: hexaspirane **1** ([6.4]rotane) adopts a chair conformation and exhibits the highest barrier of inversion ever detected ($\Delta G^{\#}_{487\ (C/C)} = 156.8$ kJ/mol),[4] hexaspirane **2** is the only example for a cyclohexane in a chair-to-twistboat equilibrium ($\Delta G^{\#}_{298\ (C/C)} = 92.0$ kJ/mol, $\Delta G^{\#}_{298\ (TB/TB)} = 35.9$ kJ/mol, $\Delta G^{\circ}_{336\ (C/TB)} = 5.3$ kJ/mol),[5] and trispirane **4** is one of the rare examples for a cyclohexane in a pure twistboat conformation ($\Delta G^{\#}_{298\ (TB/TB)} = 19.7$ kJ/mol).[6] Obviously, full substitution with substituents of identical opening angles as in **1** favours a chair conformation, full substitution with substituents with strongly alternating opening angles as in **4** favours a twistboat conformation, and full substitution with substituents of moderately alternating opening angles as in **2** falls in between. It was in this context, that we synthesized and investigated the conformation and dynamics of hexaspirane **3**.



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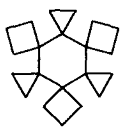

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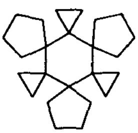

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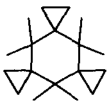

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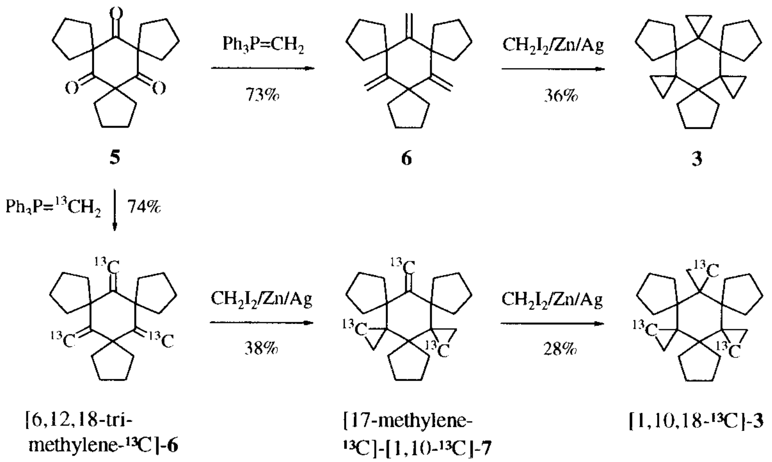
Syntheses

Starting with the readily available trione **5**,[7] the desired hexaspirane **3** was obtained by exhaustive methylenation followed by exhaustive cyclopropanation using a high temperature modification of the Wittig reaction[8] and a modified Simmons-Smith reaction,[9] respectively (**5** → **6** → **3**). The same sequence was used to prepare [1,10,18-^{13}C]-**3**. However, while the methylenation with [methylene-^{13}C]-triphenylphosphorane[10] yielded the expected [6,12,18-trimethylene-^{13}C]-**6**, the subsequent cyclopropanation proceeded incompletely and had to be repeated until hexaspirane [1,10,18-^{13}C]-**3** was obtained ([6,12,18-trimethylene-^{13}C]-**6** → [17-methylene-^{13}C]-[1,10-^{13}C]-**7** → [1,10,18-^{13}C]-**3**).



5 **6** **3**

[6,12,18-tri-methylene-^{13}C]-**6** [17-methylene-^{13}C]-[1,10-^{13}C]-**7** [1,10,18-^{13}C]-**3**

Conformation and Dynamics

At room temperature, the ^{1}H NMR spectrum (500 MHz, CD_2Cl_2, $CHDCl_2$ int) of **3** showed extremely broad resonances without any fine structure. However, at -80°C, two sets of well resolved signals appeared (Figure 1). The major component (80%) showed two singulets at δ = 0.33 (12H) and 1.31 (24H), and the minor component (20%) an AA′BB′ system at δ = 0.17 (12H), two triplets at δ = 0.66 (6H) and 2.14 (6H), and two quintets at δ = 1.23 (6H) and 1.44 (6H). At the same temperature, the ^{13}C NMR spectrum (125 MHz, CD_2Cl_2, CD_2Cl_2 int) showed five resonances (δ = 7.53, 25.25, 29.14, 35.04, 49.67) for the major component, but eight resonances (δ = 2.58, 6.68, 25.01, 26.64, 28.06, 28.62, 39.30, 51.97) for the minor component (Figure 1). It became thus clear, that **3** exists at -80°C as 4:1 mixture of a rapidly interconverting twist-boat conformation (effective symmetry D_{3h}) and a fixed chair conformation (symmetry C_{3v}). As the ^{13}C NMR spectrum of [1,10,18-^{13}C]-**3** (125 MHz, $(CD_3)_2O$, $(CD_3)_2O$ int) remained unchanged down to -154°C, the barrier of the twistboat-to-twistboat interconversion proved inaccessible but could be estimated to have an upper limit of $\Delta G_c^{\neq} \leq 24$ kJ/mol.[11]

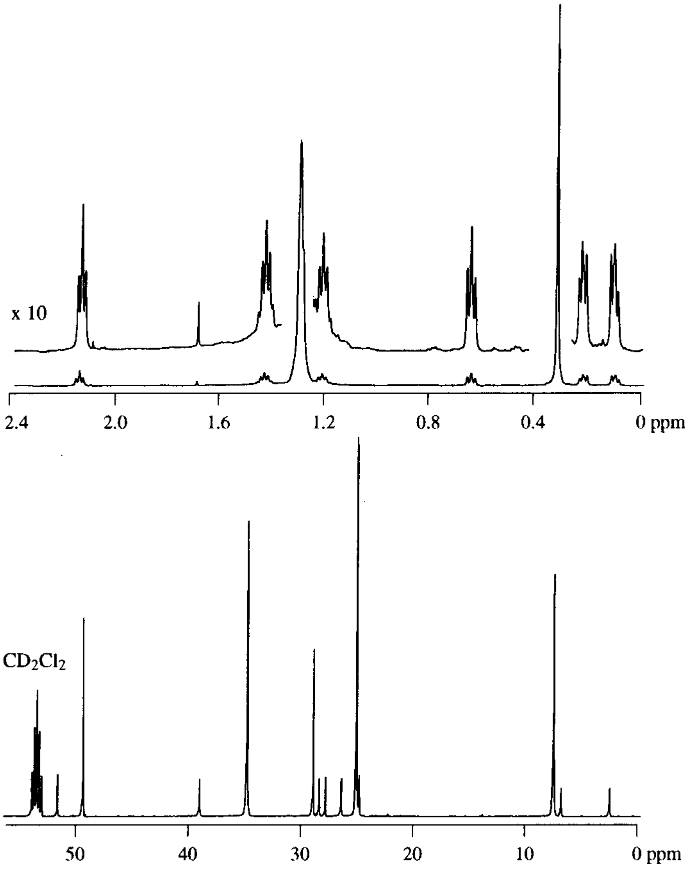


Figure 1. ^1H NMR (500 MHz, CD_2Cl_2, $CHDCl_2$ int) and ^{13}C NMR spectra (125 MHz, CD_2Cl_2, CD_2Cl_2 int) of **3** at -80° C.

For the determination of the barrier of the chair-to-chair interconversion, we performed a bandshape analysis of exchange-broadened ^{13}C NMR spectra of [1,10,18-^{13}C]-**3** (125 MHz, C_6D_5Cl, C_6D_5Cl int) using the computer program DNMR5.[12] The spectra were taken at 26.0°C and six further temperatures ranging from 35.0 to 125.0°C (Figure 2). The static parameters [δ = 3.49 (C_{ax} chair), 7.79 (C_{eq} chair), 9.14 (twistboat)] were taken from the low temperature spectrum, assumed to be independant from temperature, and used in the computational analysis of the high temperature spectra throughout. Experimental and computed bandshapes and the corresponding rate constants are shown in Figure 2. A weighted least squares adjustment of the rate data to the Eyring equation with the computer program ACTPAR,[13] shown graphically in Figure 3, then yielded the activation parameters and their standard deviations as $\Delta H^{\#} = (57.1 \pm 2.0)$ kJ/mol and $\Delta S^{\#} = (-35.4 \pm 5.7)$ J/mol·K. The free energy of activation was then calculated from the equation $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$ to give $\Delta G^{\#}_{298} = (67.6 \pm 3.8)$ kJ/mol.

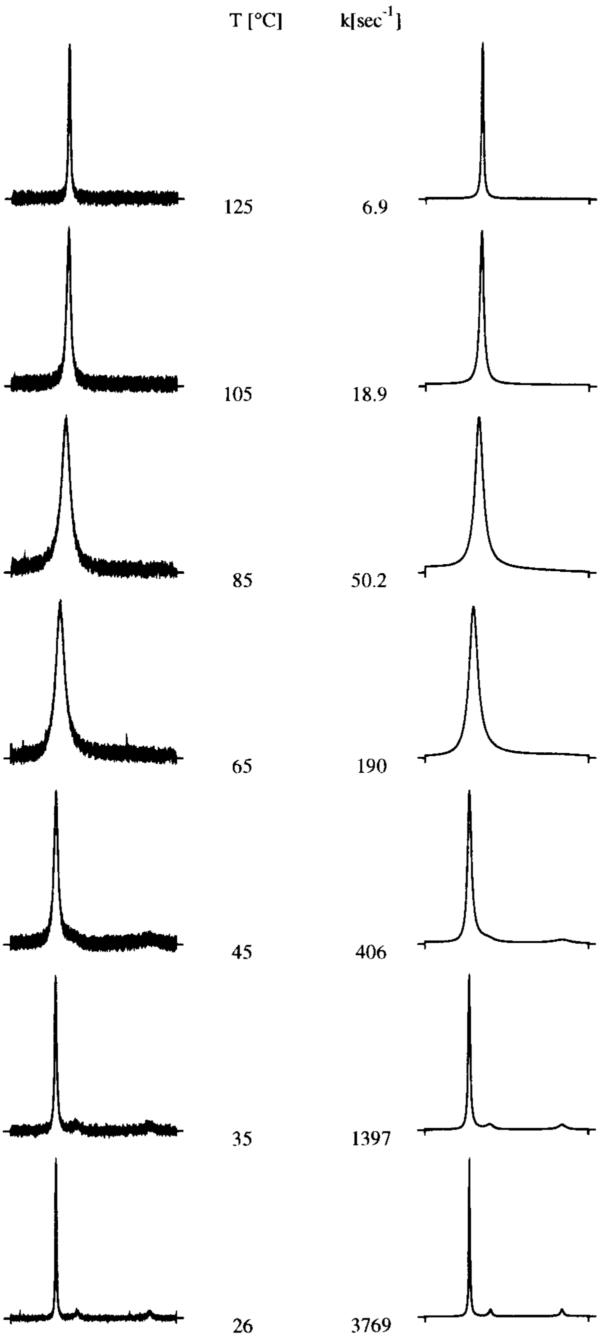


Figure 2. Experimental (left) and computed bandshapes (right) of the ^{13}C NMR spectra (125 MHz, C_6D_5Cl, C_6D_5Cl int) of [1,10,18-^{13}C]-**3** at different temperatures and corresponding rate constants derived therefrom.

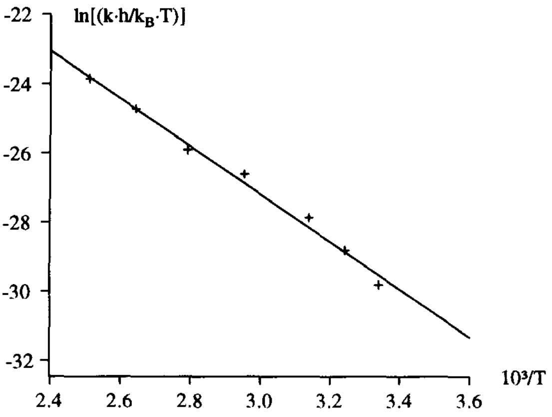


Figure 3. Eyring plot for the rate data of [1,10,18-^{13}C]-**3**.

Summary and Conclusion

Hexaspiro[2.0.4.0.2.0.4.0.2.0.4.0]tetracosane **3** exists at -80°C as 4:1 mixture of a rapidly interconverting twistboat conformation and a fixed chair conformation. The activation parameters of the chair-to-chair interconversion followed from a bandshape analysis of exchange broadened ^{13}C NMR spectra of [1,10,18-^{13}C]-**3** as $\Delta H^{\#} = (57.1 \pm 2.0)$ kJ/mol, $\Delta S^{\#} = (-35.4 \pm 5.7)$ J/mol·K, and $\Delta G^{\#}_{298} = (67.6 \pm 3.8)$ kJ/mol. **3** is only the second case of a per(cyclo)alkylated cyclohexane in a chair-to-twistboat equilibrium, and the first case where the twistboat predominates. Obviously, this unusual behaviour is caused by the fact, that of the six 1.3-diaxial interactions present, the three strong interactions of the cyclopentane rings and the three weak interactions of the cyclopropane rings operate at different sides of the ring. This special feature disfavours a chair and favours a twistboat. Based on this finding, other cases of favoured twistboat conformations should be detectable.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian FT 80A, VXR 200, VXR 500 or a Bruker AMX 300 spectrometer. For standards other than TMS the following chemical shifts were used: $\delta_H(CHCl_3) = 7.24$, $\delta_H(CHDCl_2) = 5.32$, $\delta_C(CDCl_3) = 77.00$, $\delta_C(CD_2Cl_2) = 53.80$, $\delta_C(C_6D_5Cl) = 132.80$ (C-4). Mass spectra were obtained with a Varian MAT 311 A or a Finnigan MAT 95 instrument operated at 70 eV. R_f values are quoted for Machrey & Nagel Polygram SIL G/UV$_{254}$ plates. Colourless substances were detected by oxidation with 3.5% alcoholic 12-molybdophosphoric acid (Merck) and subsequent warming. Impregnated TLC plates were prepared by dipping the plates into a solution of 10% (w/w) silver nitrate in methanol/water (2:1, v/v) and drying for 1 h at 110°C.[14] The silica gel impregnated with 10% (w/w) silver nitrate for column chromatography was prepared by adding the appropriate amount of silica gel to a solution of silver nitrate in acetonitrile, evaporating the solvent on a rotary evaporator, and drying the residue for 48 h at 80°C, 0.5 Torr, prior to use. Melting points are not corrected.

6,12,18-Trimethylenetrispiro[4.1.4.1.4.1]octadecane (6): To a stirred suspension of potassium-t-butoxide (2.51 g, 22.4 mmol) in dry benzene (150 ml) under nitrogen was added methyltriphenylphosphonium iodide (9.03 g, 22.3 mmol) and the mixture heated to reflux. After 1 h a solution of **5** (1.50 g, 5.20 mmol) in dry benzene (20 ml) was added and most of the benzene distilled off until the remaining slurry was heated for 64 h to 120°C. The mixture was homogenized with benzene, diluted with pentane (250 ml) and hydrolyzed with water (150 ml). The layers were separated, the aqueous layer was extracted with pentane (2 x 250 ml) and the combined organic layers were concentrated on a rotary evaporator (bath temperature 25°C/20 torr). The residue was extracted with pentane for 10 h in a Soxhlet apparatus. The solvent was distilled off and the residue chromatographed on silica gel (0.05-0.20 mm) in pentane (column 1.5 x 25 cm; R_f = 0.53) yielding 1.07 g (73%) of pure **6** as colourless liquid. IR (neat) C=C 1620 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, $CHCl_3$ int) 1.60-1.72 (m, 12H), 1.80-1.92 (m, 12H), 4.88 (s, 6H); ^{13}C NMR (20 MHz, $CDCl_3$, TMS int) 25.20, 41.95, 55.57, 104.51, 163.07: MS m/z 282 (35, M^{+}), 159 (100). Anal. Calcd for $C_{21}H_{30}$: C, 89.25; H, 10.71. Found: C, 89.13; H 10.71.

6,12,18-Trimethylene-^{13}C-trispiro[4.1.4.1.4.1.4.1]octadecane ([6,12,18-Trimethylene-^{13}C]-6): Analogously to the preparation of **6**, the methylenation of **5** (327 mg, 1.14 mmol) with methylene-^{13}C-triphenyl-phosphorane as generated from methyl-^{13}C-triphenylphosphonium iodide[10] (1.84 g, 4.54 mmol) with potassium-t-butoxide (509 mg, 4.54 mmol) in benzene resulted in the formation of 239 mg (74%) of pure [6,12,18-trimethylene-^{13}C]-**6** as colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int) 1.63-1.75 (m, 12H), 1.80-1.94 (m, 12H), 4.86 (d, J = 155 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$, $CDCl_3$ int) 104.44.

Hexaspiro[2.0.4.0.2.0.4.0.2.0.4.0]tetracosane (3): To freshly prepared zinc/silver couple (3.00 g), just covered with anhydrous ether, was added under nitrogen with stirring a mixture of **6** (200 mg, 0.71 mmol) and diiodomethane (3.00 g, 11.2 mmol) at such a rate as to induce and maintain gentle reflux. After the addition was complete, the mixture was heated for another 45 min to reflux. The mixture was hyrolyzed with a saturated solution of ammonium chloride (5 ml) and extracted with pentane (3 x 20 ml). The extracts were concentrated and the residue was chromatographed on silica gel (0.040-0.063 mm) impregnated with silver nitrate (10%, w/w) in pentane [column 1.6 x 55 cm, R_f = 0.69 (**3**), 0.41] yielding 83 mg (36%) of pure **3** as colourless solid (mp 65-81°C). ^{1}H NMR (500 MHz, CD_2Cl_2, $CHDCl_2$ int, -80°C) 0.17 (AA'BB', Δν = 60 Hz, 2H), 0.33 (s, 10H), 0.66 (t, J = 8 Hz, 1H), 1.23 (quin, J = 8 Hz, 1H), 1.31 (sbr, 20H), 1.44 (quin, J = 8 Hz, 1H), 2.14 (t, J = 8 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2, CD_2Cl_2 int, -80°C) 2.58, 6.78, 7.53, 25.01, 25.25, 26.64, 28.06, 28.62, 29.14, 35.04, 39.30, 49.67, 51.97; MS m/z 267 (100); HRMS m/z (M^{+}-C_2H_4) calcd 296.2504, obsd 296.2504.

[17-Methylene-^{13}C]-[1,10-^{13}C]-pentaspiro[4.0.2.0.4.0.2.0.4.1]doeicosane ([17-Methylene-^{13}C]-[1,10-^{13}C]-7): Under the conditions described for the preparation of **3**, the cyclopropanation of [6,12,18-trimethylene-^{13}C]-**6** (239 mg, 0.84 mmol) with freshly prepared zinc/silver couple (4.50 g) and diiodomethane (4.50 g, 16.8 mmol) in ether went not to completeness. Usual work up and chromatography on silica gel (0.040-0.063 mm) impregnated with silver nitrate (10%, w/w) in pentane [column 2 x 32 cm; R_f = 0.69, 0.41

([17-methylene-^{13}C]-[1,10-^{13}C]-**7**)] yielded 100 mg (38%) of [17-methylene-^{13}C]-[1,10-^{13}C]-**7** as colourless solid (mp 105-132°). ^{1}H NMR (300 MHz, $CDCl_3$, $CHCl_3$ int) 0.37 (dm, J = 168 Hz, 4H), 0.30-0.48 (m, 4H), 1.06-1.66 (m, 4H), 1.78-1.96 (m, 20H), 4.86 (d, J = 154 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, $CDCl_3$ int) 8.21, 108.56; MS m/z 195 (100).

[1,10,18-^{13}C]-Hexaspiro[2.0.4.0.2.0.4.0.2.0.4.0]tetracosane ([1,10,18-^{13}C]-3): Under the conditions described for the preparation of **3**, the cyclopropanation of [17-methylene-^{13}C]-[1,10-^{13}C]-**7** (65 mg, 0.21 mmol) with freshly prepared zinc/silver couple (3.00 g) and diiodomethane (3.00 g, 11.2 mmol) yielded 19 mg (28%) of [1,10,18-^{13}C]-**3** as highly viscous colourless oil. The material was isolated by chromatography on silica gel (0.040-0.063 mm) impregnated with silver nitrate (10%, w/w) in pentane (column 2 x 32 cm; R_f = 0.69). The ^{1}H NMR spectrum (300 MHz, C_6D_5Cl, TMS int, 25°C) showed broad resonances without fine structure. For the ^{13}C NMR spectrum see below. MS m/z 268 (100).

Kinetic measurements: The ^{13}C NMR spectra for the bandshape analysis of [1,10,18-^{13}C]-**3** were recorded on a Varian VXR 500 spectrometer equipped with a variable temperature probe. The temperature calibration was performed with a temperature sensor consisting of a 1.8 mm diameter high precision PT 100 resistor at the end of a glass rod which was introduced in a 5 mm o.d. dummy tube containing chlorobenzene such, that the active zone (15 mm length) was precisely positioned at the hight of the receiver coil. The temperatures were precise within ± 0.5°C. The experimental spectra for the bandshape analyses were obtained with a solution of 5 mg of [1,10,18-^{13}C]-**3** in 500 µl of C_6D_5Cl. The bandshape analyses were performed with the program DNMR5,[12] and the weighted least squares adjustments of the rate data to the Eyring equation was performed with the program ACTPAR.[13]

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11. Calculated from the equation $\Delta G_c^{\neq} = a \cdot T_c[9.972 + \log(T_c/\delta\nu)]$ with $a = 1.914 \cdot 10^{-2}$ and estimated upper and lower limits, respectively, for the coalescence temperature ($T_c \leq 113$ K) and the frequency difference of the resonances of the pseudoaxial and pseudoequatorial carbon atoms ($\delta\nu \geq 10$ Hz). For the methodology, see: Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; p 96.
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