



# Synthesis, conformation and dynamics of 4,4,5,5,6,6,7,7,8,8-decamethyl-1-oxa-spiro[2.5]octane and 1,2,3,3,4,4,5,5,6,6-decamethyl-cyclohexene

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## ABSTRACT

The fragmentation of a suitable methylated 1-oxa-spiro[2.5]octane yields permethyl-cyclohexene. The activation parameters for the chair to chair interconversion of the 1-oxa-spiro[2.5]octane and the half-chair to half-chair interconversion of permethyl-cyclohexene were determined via bandshape analyses of exchange-broadened  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, respectively.

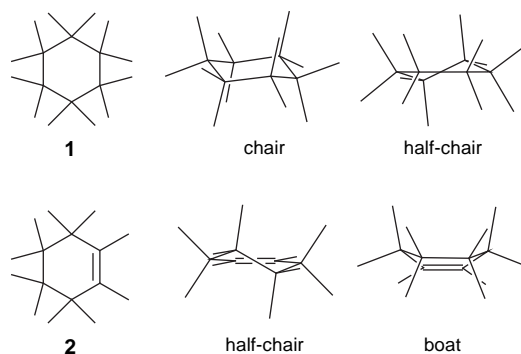
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## 1. Introduction

The stereodynamics of cyclohexanes<sup>1</sup> and cyclohexenes<sup>2</sup> are of fundamental interest in organic chemistry. Of the basic systems, cyclohexane adopts a chair conformation (symmetry  $D_{3d}$ ) in the ground state and inverts via a half-chair (symmetry  $C_2$ ) as transition state. In contrast, cyclohexene adopts a half-chair conformation (symmetry  $C_2$ ) in the ground state and inverts via a boat (symmetry  $C_s$ ) as transition state. According to dynamic NMR, the free energy of activation ( $\Delta G^\ddagger$ ) amounts to 43.1 kJ/mol for cyclohexane,<sup>3</sup> and to 22.2 kJ/mol for cyclohexene.<sup>4</sup>

Interestingly, the barriers of inversion of lower substituted cyclohexanes<sup>5</sup> and cyclohexenes<sup>4b,6</sup> differ from those of their parent system only slightly. This indicates that in most cases energy demanding eclipsed arrangements of substituents in the corresponding transition states may be avoided. However, in fully substituted systems such arrangements must occur. An example is 1,1,2,2,3,3,4,4,5,5,6,6-dodecamethyl-cyclohexane (**1**).<sup>7</sup> This compound passes a doubly eclipsed arrangement of two geminal dimethyl groups in the half-chair as transition state (Fig. 1) and exhibits a barrier of inversion ( $\Delta G^\ddagger_{298} = 72.3$  kJ/mol),<sup>7</sup> which exceeds that of cyclohexane by far.

The same could be true for the hitherto unknown 1,2,3,3,4,4,5,5,6,6-decamethyl-cyclohexene (**2**). In this case the transition state is a boat (Fig. 1), but, as in the half-chair as



**Figure 1.** Ground and transition state geometries of permethyl-cyclohexane and permethyl-cyclohexene.

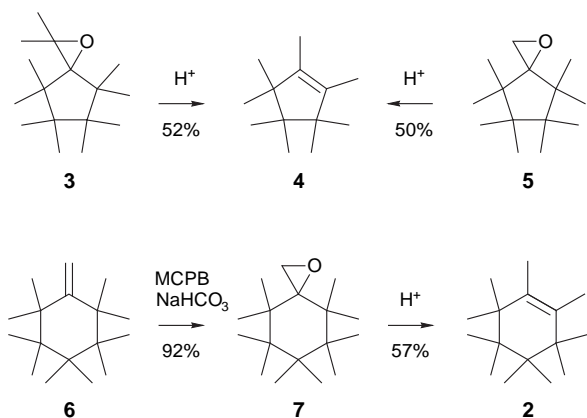
transition state of **1**, a doubly eclipsed arrangement of two geminal dimethyl groups is unavoidable. As the two flagpole methyl groups in the boat of **2** should cause additional strain,<sup>8</sup> it was tempting to speculate that the increase of the barrier of inversion in going from cyclohexene to **2** could even be larger than in going from cyclohexane to **1**. In the following, we report on the synthesis, conformation and dynamics of **2**, and its direct precursor, the 1-oxa-spiro[2.5]octane **7**.

## 2. Results

Previous work from this laboratory had shown that on treatment with acid the 1-oxa-spiro[2.4]heptanes **3**<sup>9</sup> and **5**<sup>10</sup> yield

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1,2,3,3,4,4,5,5-octamethyl-cyclopentene (**4**) as the main product (Scheme 1). For the synthesis of **2** we therefore envisaged an acid catalyzed fragmentation of the 1-oxa-spiro[2.5]octane **7**. For the synthesis of the latter, we treated the methylene-cyclohexane **6** under two-phase conditions<sup>11</sup> with *m*-chloroperbenzoic acid (MCPBA) and obtained the desired epoxide **7** as a colorless solid (mp 78 °C; yield 92%). According to <sup>1</sup>H NMR (200 MHz, CD<sub>2</sub>Cl<sub>2</sub>, CHDCl<sub>2</sub> int), this compound exists at –51.7 °C as 4:1 mixture of two chair conformations (symmetry C<sub>2v</sub>) as indicated by two singlets<sup>12</sup> for the protons of the methylene group [ $\delta$ =2.44 (major, CH<sub>2</sub>-a) and 2.92 (minor, CH<sub>2</sub>-e)]. In contrast to lower substituted 1-oxa-spiro[2.5]octanes,<sup>13</sup> the chemical shift difference for the protons of the equatorially and axially positioned methylene groups in **7** is large ( $\Delta\delta$ =0.48 ppm). Therefore, our assignment is based on the data of the structurally related tris-epoxide **8**. This compound adopts in the crystal state<sup>14</sup> and in solution<sup>15</sup> a chair conformation and exhibits for the protons of the equatorially ( $\delta$ =2.76 ppm, s, 2H) and axially bound methylene groups ( $\delta$ =2.26 ppm, AB-system, 4H)<sup>15</sup> a chemical shift difference ( $\Delta\delta$ =0.50 ppm) nearly identical with that of the two conformers of **7** (Fig. 2). However, a definite proof for the correctness of our assignment cannot be given.



Scheme 1.

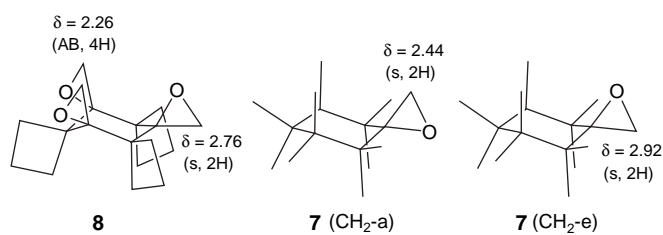


Figure 2.

For the synthesis of **2**, we treated the 1-oxa-spiro[2.5]octane **7** with an equivalent amount (w/w) of Nafion H<sup>®</sup><sup>16</sup> in benzene at 80 °C. After 0.5 h the reaction was completed. Work up and gas chromatography yielded **2** as colorless solid (mp 101 °C, yield 57%). Within the fast exchange limit (+60.1 °C), **2** showed in the <sup>1</sup>H NMR spectrum (200 MHz, C<sub>6</sub>D<sub>5</sub>CD<sub>3</sub>, C<sub>6</sub>D<sub>5</sub>CHD<sub>2</sub> int) three singlets [ $\delta$ =0.87 (6H), 0.98 (12H), 1.56 (12H)] for a rapidly inverting species (effective symmetry C<sub>2v</sub>). Within the slow exchange limit (–75.1 °C), five singlets [ $\delta$ =0.87 (6H), 0.93 (6H), 0.97 (6H), 1.13 (6H), 1.59 (6H)] for a fixed half-chair (symmetry C<sub>2</sub>) or boat conformation (symmetry C<sub>2v</sub>) appeared. Accordingly, the <sup>13</sup>C NMR spectrum (50.3 MHz, C<sub>6</sub>D<sub>5</sub>CD<sub>3</sub>, C<sub>6</sub>D<sub>5</sub>CHD<sub>2</sub> int) showed six resonances at +60.1 °C [ $\delta$ =15.68 (q), 23.46 (q), 26.92 (q), 41.80 (s), 42.36 (s), 131.02 (s)], but eight resonances at –49.2 °C [ $\delta$ =16.02 (q), 20.47 (q), 24.60 (q), 26.64 (q), 26.69 (q), 41.27 (s), 42.03

(s), 130.81 (s)]. Molecular mechanics calculations using the force field MM3<sup>17</sup> in connection with our conformational search program HUNTER<sup>18</sup> yielded a half-chair (H<sub>0</sub><sup>f</sup>=–43.05 kcal/mol) as the sole minimum conformation. This means that the bandshape analysis given below describes a half-chair to half-chair interconversion via a boat as transition state.

For the determination of the barriers of the chair to chair interconversion of the major and minor conformer of 1-oxa-4,4,5,5,6,6,7,7,8,8-decamethyl-spiro[2.5]octane (**7**) we performed a bandshape analysis of exchange-broadened <sup>1</sup>H NMR spectra. Towards this end, six <sup>1</sup>H NMR spectra (79.6 MHz, CDCl<sub>3</sub>, CHCl<sub>3</sub> int) within a temperature range from +42.4 °C to –47.5 °C were taken and the resonances of the methylene protons analyzed using the program DNMR5.<sup>19</sup> The static parameters [ $\delta$ (CH<sub>2a</sub>)=2.44,  $\delta$ (CH<sub>2e</sub>)=2.92;  $p$ (CH<sub>2a</sub>)=0.79,  $p$ (CH<sub>2e</sub>)=0.21] were taken from the spectrum at –47.5 °C, assumed to be independent of 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 3.

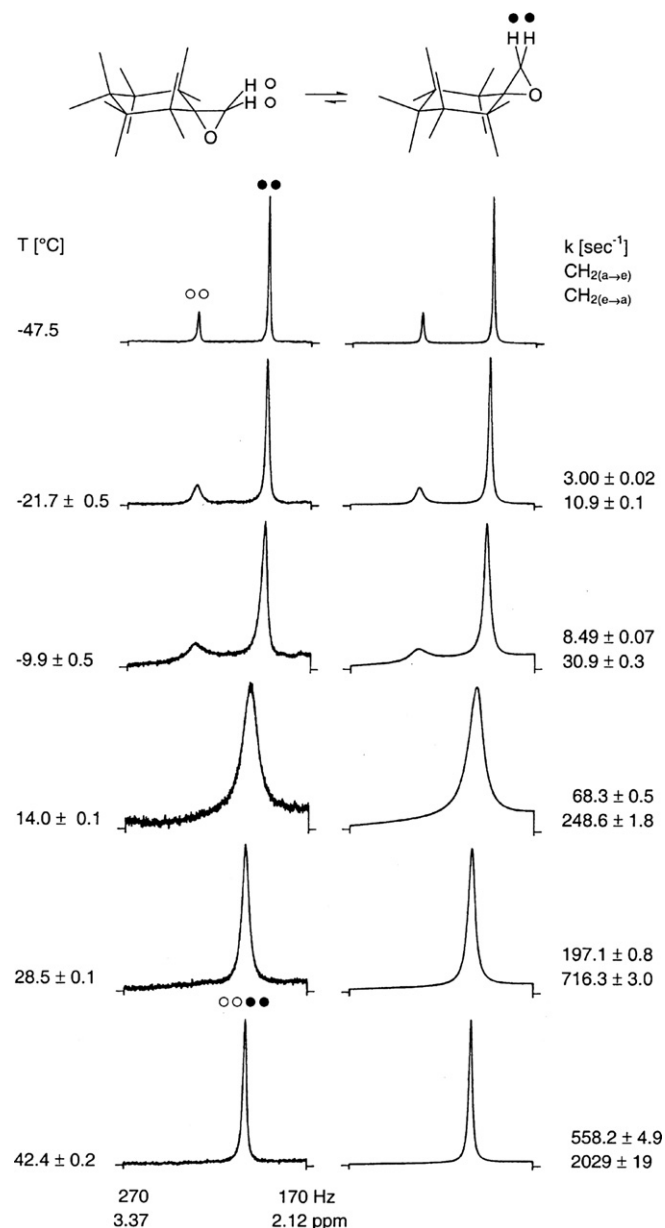


Figure 3. Chair-to-chair interconversion of **7**. Experimental (left) and computed bandshapes (right) at different temperatures and rate constants derived therefrom.

A weighted least-squares adjustment of the rate data to the Eyring equation using the program ACTPAR,<sup>20</sup> shown graphically in Figures 4 and 5, then yielded the activation parameters and their standard deviations as  $\Delta H^\ddagger = 52.0 \pm 1.1$  kJ/mol and  $\Delta S^\ddagger = -28.6 \pm 3.6$  J/mol K for the conversion of the major to the minor, and as  $\Delta H^\ddagger = 52.9 \pm 1.1$  kJ/mol and  $\Delta S^\ddagger = -17.9 \pm 3.6$  J/mol K for the conversion of minor to the major conformer. The free energies of activation were calculated from the equation  $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$  to give  $\Delta G^\ddagger_{298} = 57.8 \pm 0.1$  kJ/mol for the major and  $\Delta G^\ddagger_{298} = 57.3 \pm 0.1$  kJ/mol for the minor conformer.

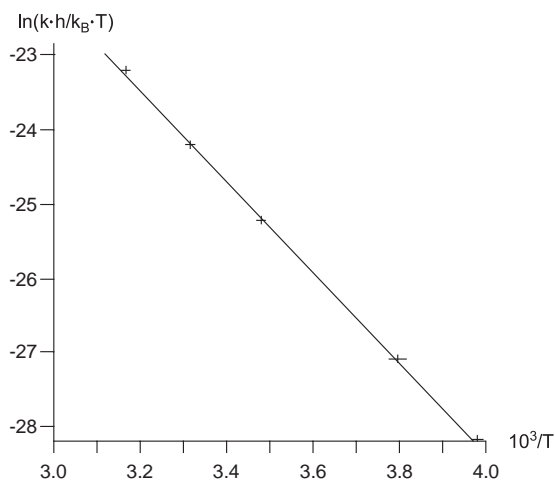


Figure 4. Eyring plot for the rate data of **7** [CH<sub>2</sub>(a→e)].

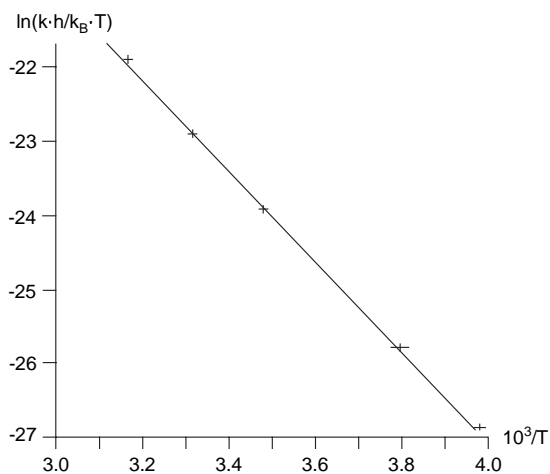


Figure 5. Eyring plot for the rate data of **7** [CH<sub>2</sub>(e→a)].

For the determination of the barrier of the half-chair to half-chair interconversion of 1,2,3,3,4,4,5,5,6,6-decamethyl-cyclohexene (**2**) we analyzed eight <sup>13</sup>C NMR spectra (20 MHz, CDCl<sub>3</sub>, CDCl<sub>3</sub> int) taken at +50.3 °C to -44.7 °C in CDCl<sub>3</sub>. In this solvent, within the slow exchange limit (-44.7 °C), a coincidence of the resonances of the equatorial methyl groups at C-4/C-5 and the pseudo-equatorial methyl groups at C-3/C-6 was observed. The static parameters [ $\delta = 20.08$  (C-4/C-5)<sub>a</sub>, 24.15 (C-3/C-6)<sub>pseudo-a</sub>, 26.21 (C-4/C-5)<sub>e</sub> and (C-3/C-6)<sub>pseudo-e</sub>] were taken from the spectrum at -44.7 °C, assumed to be independent from temperature, and used in the analysis of the high temperature spectra throughout. The experimental and computed bands and the corresponding rate constants are shown in Figure 6. A weighted least-squares adjustment of the rate constants to the Eyring equation with the computer program ACTPAR,<sup>20</sup> shown graphically in Figure 7, then yielded the

activation parameters and their standard deviations for the half-chair to half-chair interconversion of **2** as  $\Delta H^\ddagger = 53.8 \pm 0.7$  kJ/mol and  $\Delta S^\ddagger = -13.7 \pm 2.4$  J/mol K. From the equation  $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$  the free energy of activation followed as  $\Delta G^\ddagger_{298} = 57.8 \pm 0.1$  kJ/mol.

As may be seen from the free energies of activation for the inversion of the cyclohexanes and cyclohexenes given in Figure 8, the values for **7** fall in between those of cyclohexane and **1**. Obviously, in the transition state of **7** a doubly eclipsed arrangement of two geminal dimethyl groups, as in the transition state of **1**, can be avoided. An energetically less demanding singly eclipsed arrangement of the epoxide ring and a neighbouring geminal dimethyl group is passed through instead.

Interestingly, the difference between the free energies of activation of the half-chair to half-chair interconversions of **2** and cyclohexene ( $\Delta\Delta G^\ddagger = 35.6$  kJ/mol) exceeds that of the chair to chair interconversions of cyclohexane and **1** ( $\Delta\Delta G^\ddagger = 29.2$  kJ/mol)

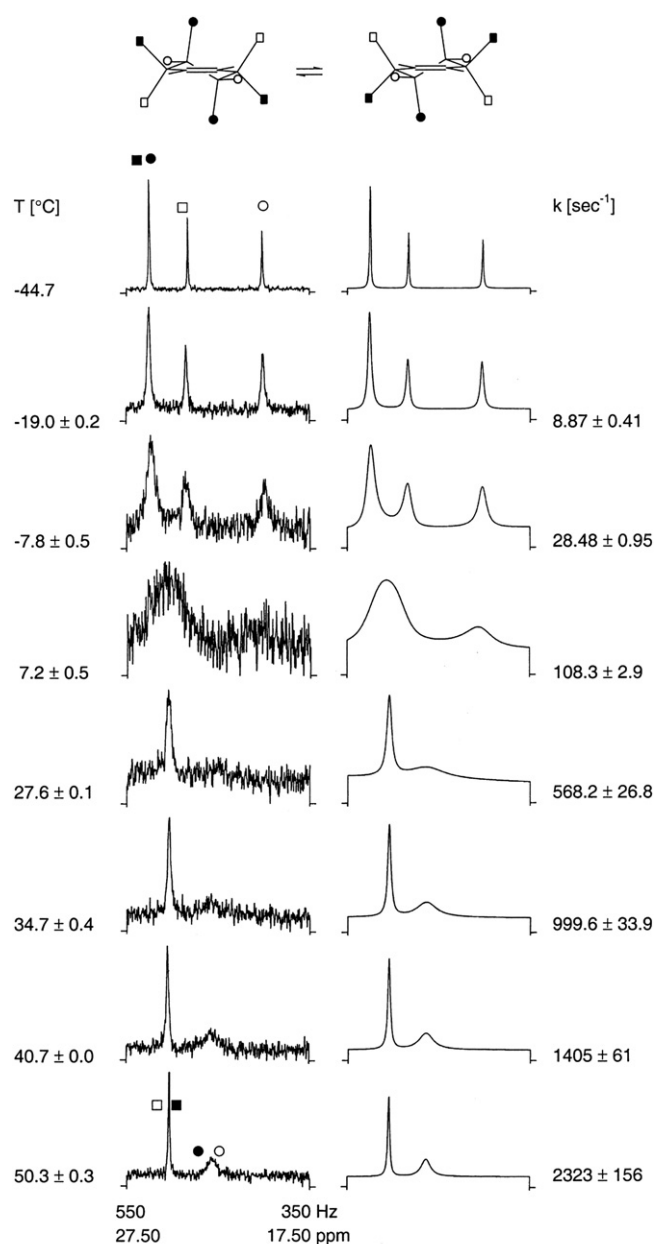


Figure 6. Half-chair to half-chair interconversion of **2**. Experimental (left) and computed bands (right) at different temperatures and rate constants derived therefrom.

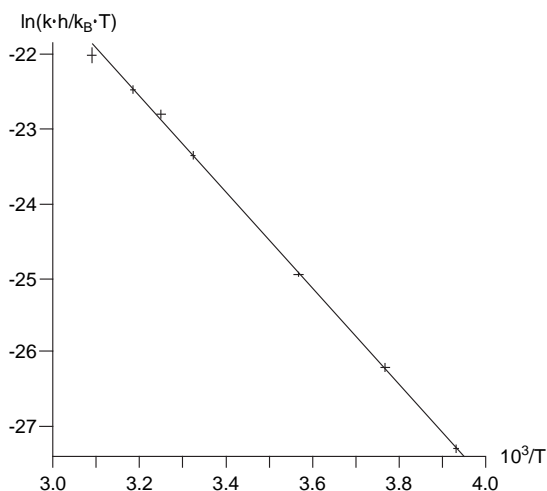


Figure 7. Eyring plot of the rate data of **2**.

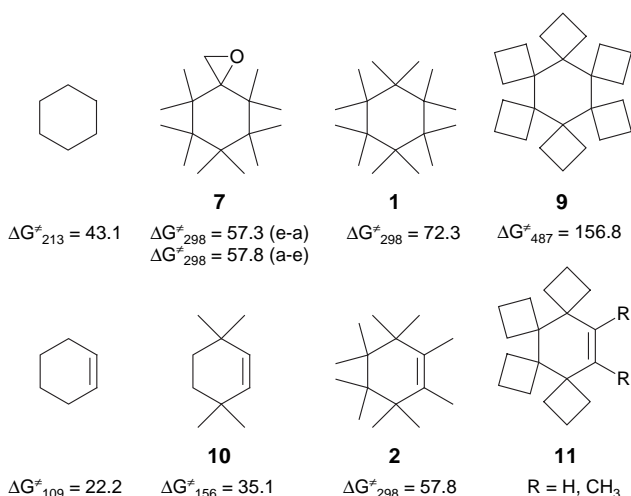


Figure 8. Free energies of activation (in kJ/mol) for the chair to chair interconversion of selected cyclohexanes, and the half-chair to half-chair interconversion of selected cyclohexenes.

distinctly. This indicates that in the transition state of **2** (a boat), in addition to a doubly eclipsed arrangement of two geminal dimethyl groups also present in the transition state of **1** (a half-chair), an energy demanding 1,4-interaction of two flagpole methyl groups exists. Support comes from the fact that the free energy of activation for the half-chair to half-chair interconversion of 3,3,6,6-tetramethyl-cyclohexene (**10**)<sup>8</sup> exceeds that of cyclohexene by far ( $\Delta\Delta G^\ddagger = 12.9$  kJ/mol), (Fig. 8).

An unsolved problem concerns the energy profile of the half-chair to half-chair interconversion of **2**. Recent ab initio calculations<sup>21</sup> have shown that the half-chair to half-chair interconversion of cyclohexene proceeds via a flat energy plateau representing a nearly free twist-boat to twist-boat interconversion via a boat. With **2** the situation may be different. In this case, a strongly negative entropy of activation ( $\Delta S^\ddagger = -13.7 \pm 2.4$  J/mol K) points to a well defined transition state, and hence to an energy profile without a plateau. However, as entropy data are notoriously difficult to obtain and values outside a range of  $\pm 10$  J/mol K have been questioned,<sup>3</sup> this assumption remains to be proved.

A concluding remark concerns the hitherto unknown tetra-spirane **11**. In view of the fact that in going from **1** to the hexaspirane **9**<sup>22</sup> the free energy of activation passes the border to

conformational isomerism at room temperature ( $\Delta G^\ddagger_{298} > 100$  kJ/mol), we believe that a similar phenomenon will be observed in going from **2** to **11**, regardless of whether the double bond is substituted or not.

In summary, we have synthesized the oxaspirooctane **7** and permethyl-cyclohexene **2** and have determined the activation parameters for the chair to chair interconversion of **7** and the half-chair to half-chair interconversion of **2** via analyses of exchange-broadened <sup>1</sup>H (**7**) and <sup>13</sup>C NMR spectra (**2**). Most interesting is the fact that the increase in the free energy of activation in going from cyclohexene to **2** exceeds that in going from cyclohexane to **1**. This means that in a boat as transition state of **2**, in addition to a doubly eclipsed arrangement of two geminal dimethyl groups, also present in a half-chair as transition state of **1**, an energy demanding interaction of two flagpole methyl groups is operative.

### 3. Experimental

#### 3.1. General

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian FT 80A or XL 200 spectrometer. For standards other than TMS the following chemical shifts were used:  $\delta_H$  (CHDCl<sub>2</sub>)=5.32,  $\delta_H$  (CHCl<sub>3</sub>)=7.24,  $\delta_H$  (C<sub>6</sub>H<sub>5</sub>CD<sub>2</sub>H)=2.09,  $\delta_C$  (CD<sub>2</sub>Cl<sub>2</sub>)=53.80,  $\delta_C$  (CDCl<sub>3</sub>)=77.00,  $\delta_C$  (C<sub>6</sub>H<sub>5</sub>CD<sub>3</sub>)=127.60. Mass spectra were obtained with a Varian MAT 311A spectrometer operated at 70 eV. Analytical and preparative GC was carried out on a Carlo Erba FTV 2450 instrument using a thermal conductivity detector and hydrogen as carrier gas. *R<sub>f</sub>* values are quoted for Machery and Nagel Polygram SIL G/UV 254 plates. Colorless substances were detected by oxidation with 3.5% alcoholic 12-molybdophosphoric acid and subsequent warming. Melting points were obtained on a Reichert microhotstage and are not corrected. Microanalytical determinations were done at the Microanalytical Laboratory of the Institute of Organic Chemistry, Göttingen.

**3.1.1. 4,4,5,5,6,6,7,7,8,8-Decamethyl-1-oxa-spiro[2.5]octane (7).** To a solution of **6**<sup>7</sup> (236 mg, 1.00 mmol) in dichloromethane (10 ml) was added a 0.5 M aqueous solution of sodium bicarbonate (4 ml). Under vigorous stirring, a solution of 3-chloroperbenzoic acid (263 mg, 80% w/w, 1.60 mmol) in dichloromethane (2.0 ml) was added drop wise. According to GC [1.2 m × 1/4" all-glass system, 15% OV 210 on Chromosorb W AW/DMCS 60/80 mesh, 190°; rel retention times (min): 1.00, 1.57 (**6**), 3.36 (**7**)], after 1.5 h **6** had been consumed. The mixture was diluted with dichloromethane (5 ml) and the organic phase was separated and washed with aqueous 2 N NaOH (5 ml), water (2 ml) and dried (molecular sieves 4 Å). The solvent was distilled off (bath temperature 50 °C/10 Torr), and the residue (250 mg) was chromatographed on silica gel (0.2–0.5 mm) coated with 5% (w/w) of sodium bicarbonate [pentane/ether 93:7, column 55 × 2 cm, control by TLC, *R<sub>f</sub>*=0.39 (**7**), 0.63 (**6**)] to yield 231 mg (92%) of pure **7** as colourless solid, mp 78 °C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>2</sub>, TMS int) (+21.6 °C): largely unresolved with broad resonances at  $\delta = 0.7$ –1.4 (30H) and 2.52 ppm (2H); (−51.7 °C): 4:1 mixture of two conformers; major conformer:  $\delta = 0.77$  (s, 6H), 0.95 (s, 6H), 1.00 (s, 3H), 1.05 (s, 6H), 1.26 (s, 9H), 2.43 (s, 2H, CH<sub>2</sub>-a); minor conformer:  $\delta = 0.75$  (s, 6H), 0.97 (s, 6H), 1.03 (s, 6H), 1.23 (s, 6H), 2.92 (s, 2H, CH<sub>2</sub>-e); the resonances of two methyl groups of the minor conformer were hidden; <sup>13</sup>C NMR (20.1 MHz, CDCl<sub>3</sub>, CDCl<sub>3</sub> int) [+20 °C]: partially unresolved with broad resonances at  $\delta = 22.8$ –26.7 (q) and 65.9 (t), and sharp resonances at  $\delta = 42.10$  (s), 43.19 (s) and 44.16 (s) and 81.75 (s). In view of the successful analysis of exchange-broadened <sup>1</sup>H NMR spectra (see Section 2), no temperature dependent <sup>13</sup>C NMR spectra were

recorded. MS (EI):  $m/z=222$  (1,  $M^+-CH_2O$ ), 57 (100). Anal. Calcd for  $C_{17}H_{32}O$ : C, 80.36; H, 12.78. Found: C, 80.87; H, 12.63.

3.1.2. 1,2,3,3,4,4,5,5,6,6-Decamethyl-cyclohexene (**2**). To a solution of **7** (202 mg, 0.80 mmol) in dry benzene (10 ml) was added under nitrogen with stirring Nafion H<sup>®</sup> (200 mg).<sup>16</sup> Afterwards the mixture was heated to 80 °C. According to GC [1.2 m×1/4" all-glass system, 15% OV 210 on Chromosorb W AW/DMCS 60/80 mesh, 130°; rel retention times (min): 1.00 (**2**), 3.00 (**7**)], after 30 min the fragmentation was complete. The mixture was filtered, and the filtrate was concentrated and purified by preparative GC to yield 101 mg (57%) of **2** as colourless solid, mp 101 °C. <sup>1</sup>H NMR (200 MHz,  $C_6D_5CD_3$ ,  $C_6D_5CHD_2$  int) (+60.1 °C):  $\delta=0.87$  (s, 12H), 0.98 (s, 12H), 1.58 (s, 6H); (−75.1 °C):  $\delta=0.87$  (s, 6H), 0.93 (s, 6H), 0.97 (s, 6H), 1.13 (s, 6H), 1.59 (s, 6H); <sup>13</sup>C NMR (50.3 MHz,  $C_6D_5CD_3$ ,  $C_6D_5CD_3$  int) (+60.1 °C):  $\delta=15.68$  (q), 23.46 (br, q), 26.92 (q), 41.80 (s), 42.36 (s), 131.02 (s); (−49.2 °C):  $\delta=16.02$  (q), 20.47 (q), 24.60 (q), 26.64 (q), 26.69 (q), 41.28 (s), 42.04 (s), 130.81 (s); MS (EI):  $m/z=222$  (14,  $M^+$ ), 207 (11), 151 (100). Anal. Calcd for  $C_{16}H_{30}$ : C, 86.40; H, 13.60. Found: C, 86.49; H, 13.45.

### 3.2. Variable temperature measurements

The <sup>1</sup>H NMR spectra of **7** and the <sup>13</sup>C NMR spectra of **2** used for the bandshape analyses were recorded on a Varian FT 80 spectrometer equipped with a variable temperature probe. Precision 5 mm o.d. NMR tubes (No. 507 PP, Wilmad Glass Co.) were filled with solutions of 12 mg of **7** and 40 mg of **2**, respectively, in 400  $\mu$ l of  $CDCl_3$ . A temperature sensor consisting of a 1.8 mm-diameter high precision PT 100 resistor (1/5 DIN; accuracy  $\pm 0.05$  °C from 0 °C to 200 °C) at the end of a glass rod was introduced such that the active zone (15 mm length) was positioned 10 mm above the height of the receiver coil but was still immersed in the solution. Immediately before and after taking a spectrum, the sensor was moved precisely to the height of the receiver coil, connected to a dual channel digital temperature-measuring instrument (Model S 1220, Systemtechnik, Sweden; resolution 0.01 °C) and the temperature measured against molten ice. Spectra for which the temperatures from these two measurements differed by more than 1.0 °C were discarded and rerun. The calculations of the static and dynamic spectra and the weighted least-squares adjustments of the rate data to the Eyring equation were performed on the Sperry Univac 1100 computer of the Gesellschaft für Wissenschaftliche Datenverarbeitung (GWDG) at Göttingen, employing the computer programs DNMR5<sup>19</sup> and ACTPAR,<sup>20</sup> respectively.

### Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.068.

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