Assignment of all Diastereomers of Perhydrofluorene in a Mixture Using ^{13}C NMR Spectroscopy

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Dedicated to Prof. Dr. Rolf Borsdorf on the Occasion of his 65th Birthday.

Abstract. By hydrogenation of fluorene **1** using different catalysts, mixtures containing variable amounts of the six possible diastereomers of perhydrofluorene **2** were obtained. The ^{13}C NMR spectra of all diastereomers have been determined in these mixtures whithout previous separation procedures. By molecular mechanics calculations the structures of the preferred conformations were simulated for all diastereomers. The substituent induced ^{13}C NMR chemical shifts in conformers were calculated by using increments for the *non-bonding 1,3-synaxial* interactions. Three stereo-chemical increments, combined with the shift values found earlier by Beierbeck and Saunders, were sufficient to calculate the chemical shift differences of conformers empirically. The assignment of relative configurations of the diastereomers was possible by comparison of the empirically calculated and experimental ^{13}C chemical shifts of the clearly distinguishable bridgehead carbons. The difference between calculated and experimentally determined shift values was only 1.3 ppm, averaged over all bridgehead carbons.

The so-called substituent induced chemical shift (SCS) depends mostly on the electronegativity and of the distance of a given substituent from the carbon atom in question. This distance is shown by greek letters (α-, β-, γ-, δ-effects) in a notation developed by Eliel et al. [1]. Substituent effects are well studied for the conformational and configurational analysis of alicyclic compounds [2]. Already in 1974 Dalling and Grant reported on the prediction of all ^{13}C resonance lines of the possible diastereomers of perhydroanthracene and perhydrophenanthrene, using a parameter set of chemical shift increments, derived from methyl decalins [3]. Beierbeck and Saunders derived the ^{13}C chemical shifts of saturated hydrocarbons of staggered conformation from three interactions in addition to a reference shift as follows [4]. The so-called hydrogen–carbon (HC) and carbon–carbon (CC) gauche interactions between an α-hydrogen or α-carbon and a β-carbon, deshields a carbon nucleus by ~4.7 ppm or ~1.7 ppm, respectively. Every non-bonded interaction between an α-hydrogen and a hydrogen on a γ-carbon (γC) leads to a shielding contribution of ~–4.5 ppm. With these shift increments, later enlarged by a *synaxial* δ-interaction term (δC), the calculation of ^{13}C resonances for different stereoids and terpens was possible [5]. These increments were also used for the calculation of chemical shifts of bicyclo alkanes [6]. However, the determination of ^{13}C NMR chemical shifts of tricyclotridecane by empirical calculations and spectroscopic measurements were not yet realized.

The aim of the present study was the prediction of ^{13}C chemical shifts of perhydrofluorene by application of these increments. Three stereochemical structural units were considered. They are pictured in a consistent form in Figure 1. Differently from the notation developed by Beierbeck and Saunders [4], we use the more consistent term '1,3-*synaxial* interaction'. It was shown earlier in the conformational analysis of acyclic ethers, that non-bonding 1,3-*synaxial* interactions are the major limiting factor in determining the position of the conformational equilibria [7]. Eliel and Ma-
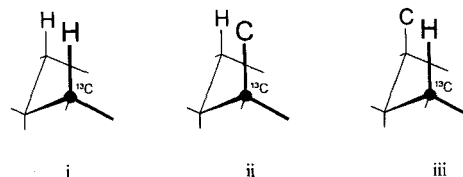
Fig. 1 Three stereochemical structural units illustrating the different non-bonding 1,3-*synaxial* interactions, used here for the calculation of ^{13}C chemical shifts of the bridgehead carbon atoms C-10, C-11, C-12 and C-13 in perhydrofluorene **2**. The values estimated by Beierbeck and Saunders [4] were used for describing shielding and deshielding effects quantitatively. i: 1,3-H,H = + 4.73 ppm, ii: 1,3-C,H = + 1.74 ppm, iii: 1,3-H,C = – 4.5 ppm.

noharan showed, that 1,3-*synaxial* interactions play an important role in the determination of predominant conformations of complex molecules with six-membered rings [8]. For the assignment of diastereomers only relative chemical shift values ($\Delta\delta$) describing differences of configurations were required. The variation of the ^{13}C chemical shifts of constitutionally equivalent carbon atoms in different diastereomers are caused only by the distinctions of the preferred conformations. So it was supposed that the non-bonding 1,3-*synaxial* interactions are the major limiting factor for the differences in ^{13}C chemical shifts of diastereomers. For subsequent empirical calculations we used the three values estimated by Beierbeck and Saunders for the shielding and deshielding effects of carbons [4]. 1,3-δ-*synaxial* interactions between carbons (δC) were not found here.

Experimental

Hydrogenation

Procedure **a**: 200 mg (1,2 mmol) Fluorene was hydrogenated in 10 ml *n*-hexane at 11.15 MPa hydrogen pressure using 1g Raney nickel as catalyst. The stainless steel autoclave was shaken for 30 minutes at 200 °C.

Procedure **b**: 1g (6 mmol) Fluorene was hydrogenated in 20 ml glacial acetic acid at 0.1 MPa hydrogen pressure using 1g platinum catalyst on charcoal. The autoclave was shaken for 200 hours at room temperature.

The products were filtrated, and the solution **b** was neutralized with KOH additionally. The residual aromatic compounds in the products of **a** and **b** were removed by column chromatography on silicagel with *n*-hexane as solvent.

GC: Capillary gas chromatography was carried out on an HP-5890/II instrument equipped with an HP 5 capillary, 25 m × 0.2 mm i.d. × 0.11 μm, fused silica. For separation of the enantiomers a CP-Cyclodextrin-B-2,3,6-M-19 capillary, 25 m × 0.25 mm i.d. × 0.25 μm, was used.

NMR: All spectra were recorded on a Varian Unity-400 spectrometer at room temperature with a 5 mm probe head. CDCl$_3$ was used as solvent and internal lock and TMS as an internal standard. Chromium acetylacetonate Cr(acac)$_3$ was added as paramagnetic relaxation reagent (0.15 M) to decrease the relaxation times, except for ^1H NMR measurements. Typical conditions were:

^1H: 399.95 MHz; 60° pulse; spectral width 1400 Hz; 12 K data points; 32 transients.
Quantitative ^{13}C: operating at 100.58 MHz; 45° pulse; 6.2 s repetition time; up to 2000 transients; 35 K data points; 14.7 kHz spectral width; IGATED proton decoupling; total aquisition time 3.4 h.
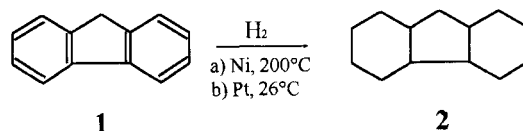HETCOR: 512 increments with 76 repetitions; total acquisition time 19.2 h.
INADEQUATE: 112 increments (two times) with 1024 repetitions; the 1/4 J delay was prepared for a coupling constant of $^1J_{CC}$ = 38 Hz; total acquisition time 132.5 h.

The commercial program packages HyperChem and ChemPlus (Hypercube, Inc.) were used for force field calculations.
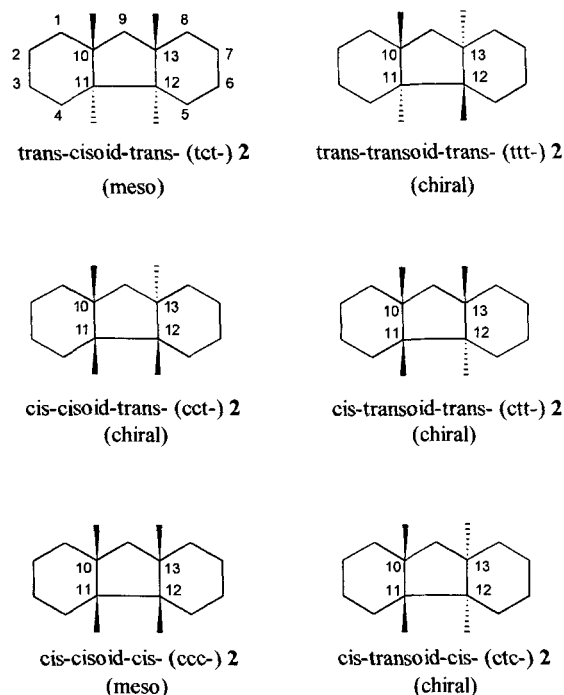
Results and Discussion

Perhydrofluorene **2** was obtained by hydrogenation of Fluorene **1** in two different ways (**a** and **b**, Scheme 1) [9]. Six different diastereomers of **2** are possible. They are portrayed in the Scheme 2. An unconventional numbering of the carbon atoms was used here for ease of comparison. The descriptors „cisoid" and „transoid" were used for the two adjacent ring junctures to the central ring involving the two peripheral rings [10]. So, these terms describe the *cis* or *trans* position of the methine protons H-11 and H-12.
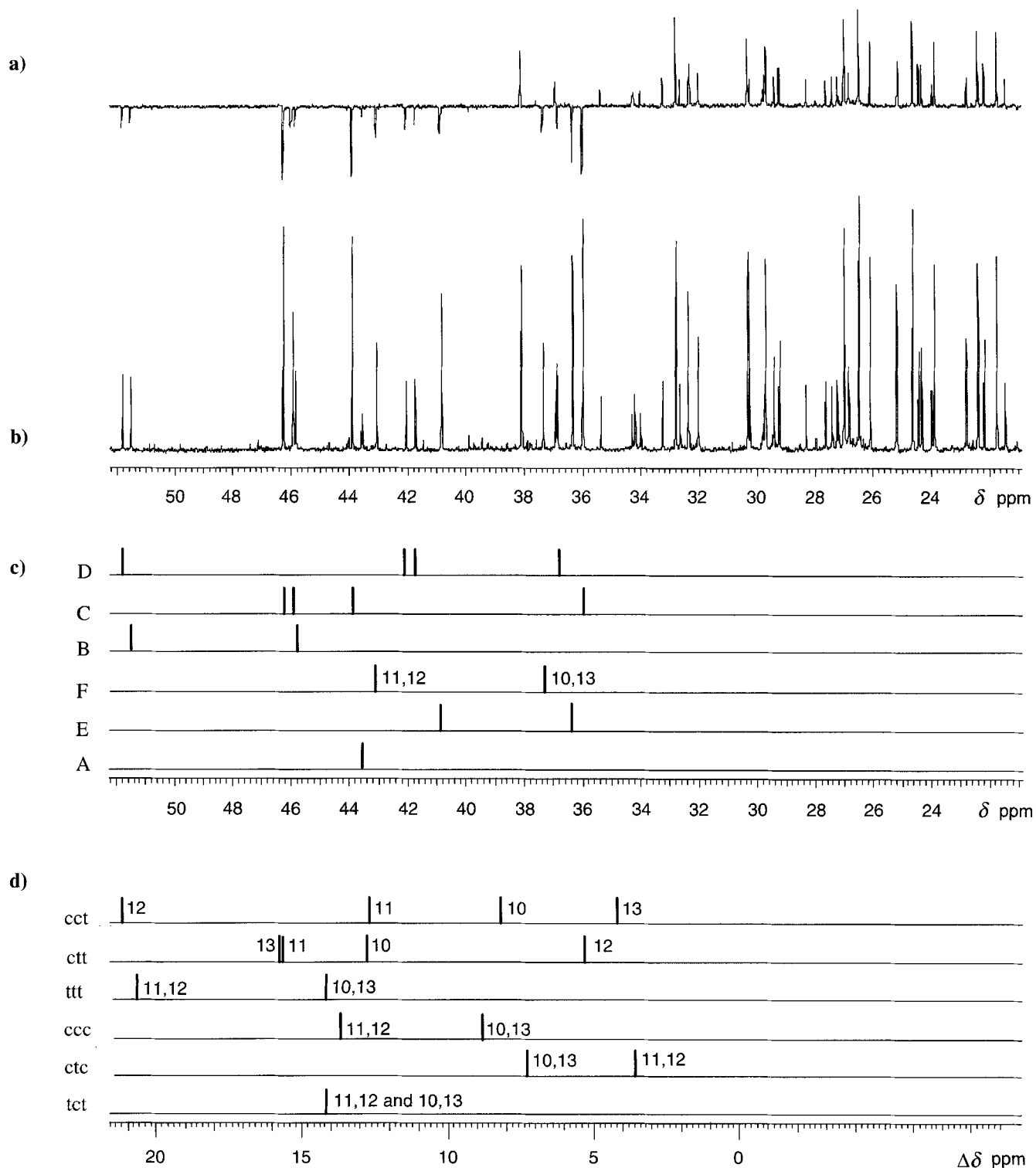
While the 400 MHz ^1H NMR spectra of the mixtures of all diastereomers of **2**, obtained by hydrogenation procedures **a** and **b** show only a broad hump in the range of 0.6 to 2.3 ppm, the ^{13}C NMR spectra consists of well-separated single lines in the range of 21 to 52 ppm. 15 CH-signals were clearly distinguished from methylene carbons by a simple Attached Proton Test (Figure 2a).

Scheme 1

trans-cisoid-trans- (tct-) **2**
(meso)

trans-transoid-trans- (ttt-) **2**
(chiral)

cis-cisoid-trans- (cct-) **2**
(chiral)

cis-transoid-trans- (ctt-) **2**
(chiral)

cis-cisoid-cis- (ccc-) **2**
(meso)

cis-transoid-cis- (ctc-) **2**
(chiral)

Scheme 2

a)

b)

```
   50    48    46    44    42    40    38    36    34    32    30    28    26    24   δ ppm
```

c)

```
D
C
B
F           |11,12        |10,13
E
A
   50    48    46    44    42    40    38    36    34    32    30    28    26    24   δ ppm
```

d)

```
cct  |12            |11       |10      |13
ctt        13|11   |10              |12
ttt  |11,12     |10,13
ccc        |11,12   |10,13
ctc                     |10,13   |11,12
tct        |11,12 and 10,13

   20          15          10           5            0            Δδ ppm
```

Fig. 2 Part of the quantitative ^{13}C NMR spectrum **b)** of the mixture of all diastereomers of **2** in $CDCl_3$ resulting from hydrogenation with nickel. In **a)** the signals from CH- (down) and CH_2-carbon atoms (up) are separated by an Attached Proton Test. The CH-signal pattern of the six diastereomers (**A** to **F**) is pictured in **c)**. An assignment of constitutional heterotopic CH-carbons was possible by an 2D-INADEQUATE experiment only for signals of diastereomer **F**. In **d)** the pattern of calculated CH-signals are shown for the six diastereomers. The scale of the relative chemical shift ($\Delta \delta$) is moved here in this way, that the most downfield shifted signals in c) and d) are superimposed.

These CH-signals are caused by the constitutional heterotopic and stereoheterotopic bridgehead carbon atoms C-10, C-11, C-12 and C-13. They are distributed over a range of nearly 16 ppm. All these CH-carbons are anisochronous only in the diastereomers cct-**2** and ctt-**2**, respectively. In all other cases the pairs of stereoheterotopic CH-groups are either homotopic (ttt-**2**), enantiotopic (tct-**2**) or undistinguishable for the NMR spectroscopy by rapid interconversion (ccc-**2**). So, for these diastereomers only two CH-signals were to be expected.

By both hydrogenation procedures six compounds were yielded in different amounts. They were named with the capitel letters **A** to **F**, according to their retention order. The intensities of all CH-signals were measured by quantitative ^{13}C NMR spectroscopy (Figure 2b). Signals with equal intensity and very similar differences between both mixtures were assigned to the same compound. The excellent agreement of the quantitative results allowed the transfer of the GC retention order nomenclature to the NMR spectra. In Table 1 the amounts of the diastereomers determined by capillary gas-chromatography and quantitative ^{13}C NMR spectroscopy are shown. The assignment of the ^{13}C NMR signals to diastereomers **A** to **F** are represented in Figure 2c. Only small amounts of the diastereomer **A** were

obtained in both hydrogenation procedures (Table 1). We assigned the small ^{13}C NMR signal at 43.5 ppm to this compound (Figure 2c). All results of the ^{13}C NMR measurements are collected in the Table 2.

For the assignment of all the constitutional heterotopic bridgehead and the CH_2-carbon atoms, respectively, a two-dimensional INADEQUATE spectrum was measured (Figure 3). The aim of this experiment was the analysis of the carbon skeletons of the diastereomers. Here, the neighbouring carbons are detected *via* their $^{1}J(^{13}C-^{13}C)$ coupling. Unfortunately, this method is very insensitive. The low natural abundance of carbon-13 leads to only 0.1‰ probability to find two neighbouring ^{13}C nuclei in the same molecule. However, in the product of the hydrogenation procedure b with the platinum catalyst, all $^{13}C-^{13}C$ connectivities within the main component **F** were observed. For the compound **E** the $^{13}C-^{13}C$ connectivities in the six-membered rings were assigned, too. The similarity in the chemical shifts of the C-9 carbon (36.9 ppm) and of one bridgehead CH-signal (36.4 ppm) aggravated the situation here. In Figure 3 the counter plot of the INADEQUATE spectrum and the results for compound **F** are shown.

By a HETCOR spectrum of the same mixture the differences in ^{1}H chemical shifts of some H-9 protons were observed (Table 2). In the compounds **C**, **D** and **F** diastereotopic H-9 protons were determined. For compound **E** undistinguishable H-9 protons were detected. This supports for **E** an axial-symmetrical structure (ttt-**2** or ctc-**2**).

Molecular mechanics calculations were applied to search for the low energy conformations of these flexible cyclanes. Eight torsion angles were randomly varied and the structures so generated were optimized using the MM$^+$-force field [11]. Conformers with a difference in heat of formation larger than 2 kcal/mol to the most stable form of the corresponding diastereomer were not considered. So, altogether 11 preferred conformers were obtained (**I** to **XI**). They are listed in Table 3 with their heat of formation and the calculated amounts in conformational equilibrium.

Table 1 Quantitative determination of the six diastereomers of **2** by GC and ^{13}C NMR spectroscopy in the two product mixtures

diastereomers [a]	product **a**(Ni)		product **b**(Pt)	
	GC %	NMR %	GC %	NMR %
A	4	2	1	<1
B	6	9	<1	<1
C	48	44	16	17
D	13	15	5	5
E	20	21	13	13
F	9	11	64	64

[a] in retention order on HP 5, 25m × 0.2 mm i.d. × 0.11 μm, fused silica

Table 2 ^{13}C NMR chemical shifts (δ, ppm) of the six Diastereomers (**A** to **F**) of **2** (in CDCl$_3$, TMS)

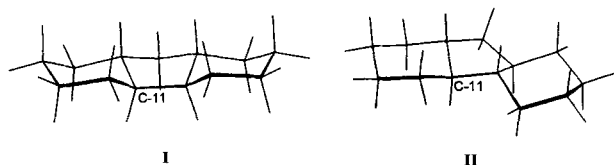|	C-1,8	C-2,7	C-3,6	C-4,5	C-9	C-10 [a]	C-11 [a]	C-12 [a]	C-13 [a]	Δ H-9 [b]
A [c]						43.5	43.5	43.5	43.5	
B						45.9	51.6	51.6	45.9	
C					38.1	44.0	46.0 [d]	36.1	46.3 [d]	1.25
D					34.2	41.8 [d]	42.1 [d]	51.9	36.1	0.32
E [e]	29.7	23.9	22.4	26.1	36.9	40.9	36.4	36.4	40.9	0
F [e]	29.3	22.2	24.3	24.4	35.4	37.4 [e]	43.1 [e]	43.1 [e]	37.4 [e]	0.41

[a] Assignment by using results of empirically calculations of relative chemical shifts, [b] Differences of the ^{1}H NMR chemical shifts of the H-9 protons, derived from HETCOR spectrum, [c] Only one small C–H signal was found at 43.5 ppm, [d] Interchangeable, [e] Assignment resulted from an INADEQUATE measurement
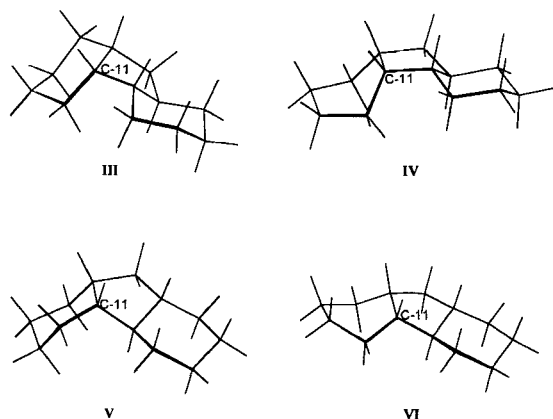
Scheme 3

The diastereomers tct-**2** and ttt-**2** are conformationally locked by trans ring junctions. Accordingly, only one preferred conformer was found, respectively. These conformers are pictured in the Scheme 3. The existence of elements of symmetry (symmetry plane in **I** and a C_2 symmetry axis in **II**) reduces the number of resonance lines in the NMR spectrum. While **I** (tct-**2** dias-

tereomer) shows a meso structure, conformer **II** (ttt-**2**) is chiral and gives a pair of enantiomers. In Table 3 the frequency of the three stereochemical structural units, describing the 1,3-*synaxial* interactions, were listed for all conformers. The high symmetry of the conformer **I** is also shown. All bridgehead carbon atoms C-10, C-11, C-12 and C-13 of **I** give rise to the same set of increments. For the constitutionally heterotopic carbon atoms equal relative values of the ^{13}C chemical shift were entailed in this special case.

For the chiral diastereomers cct-**2** and ctt-**2** always two preferred conformers resulted. These four conformers are pictured in Scheme 4. For the diastereomers cct-**2** and ctt-**2**, respectively, four different relative values of ^{13}C chemical shifts of bridgehead carbon atoms were
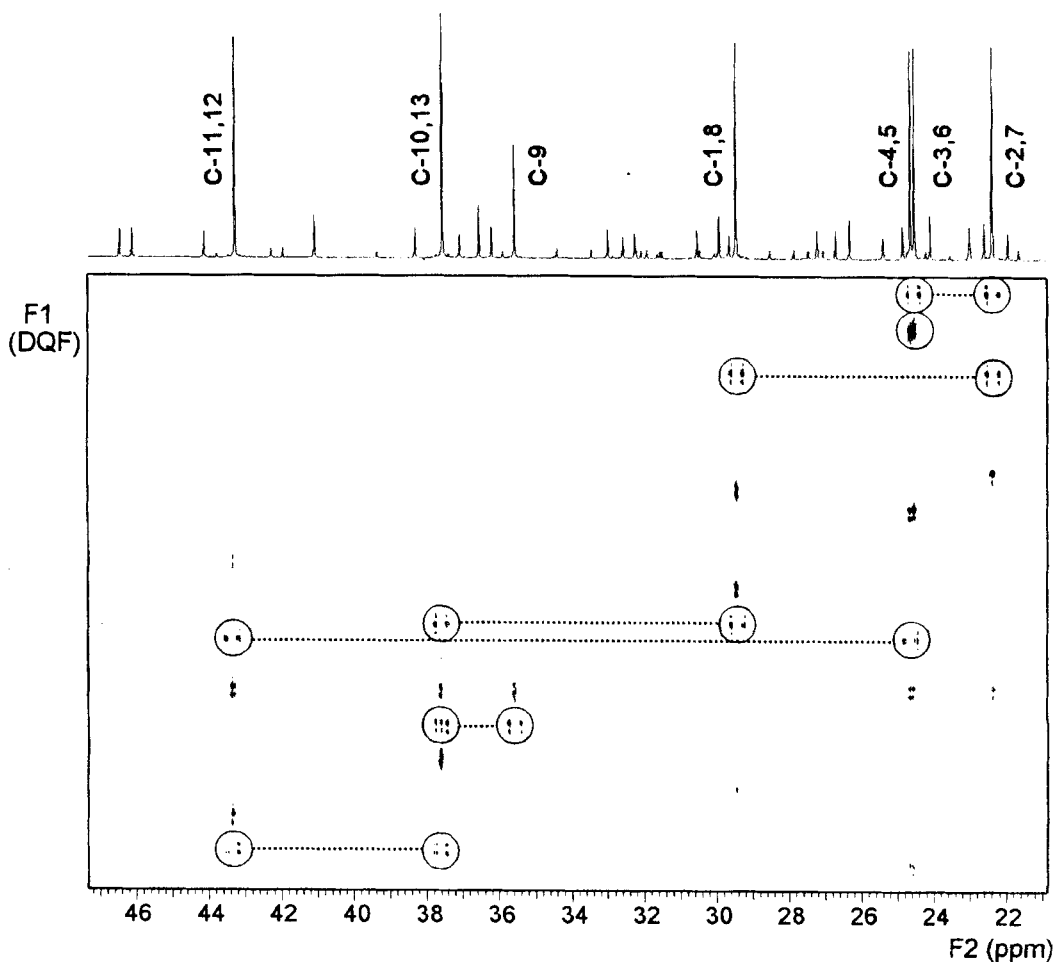

Fig. 3 Contour plot of a 2D-INADEQUATE spectrum of the hydrogenation product obtained by procedure b. The neighbouring carbon atoms in a molecule are separated along the F1 frequency axis on the basis of their different double quantum frequencies (DQF). Corresponding $^{13}C-^{13}C$-systems were observed only for the main product (diastereomer **F**). The signals caused by the $^{13}C-^{13}C$-couplings are circled. The resulting carbon skeleton of **F** is shown by auxiliary lines (·····). Other signals shown here, resulted from the remaining $^{13}C-^{12}C$-couplings. On top of the contour plot the corresponding part of the 1D ^{13}C NMR spectrum is pictured (F2-axis). ~300 mg (1.7 mmol) of product b was solved in 0.5 ml of a 0.15 M solution of $Cr(acac)_3$ in $CDCl_3$; measuring time was 132.5 h.
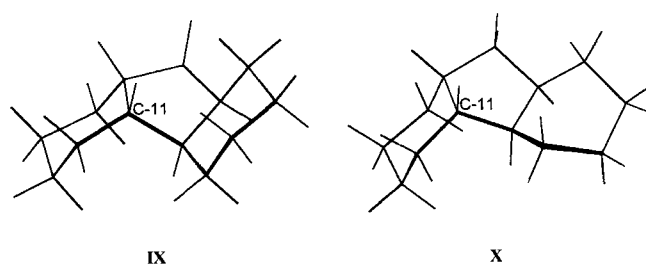
Scheme 4

calculated by using the increments for 1,3-*synaxial* interactions (Table 3). The most downfield shifted value was found for the carbon C-12 in cct-**2**. This is caused mainly by the four non-bonding 1,3-H,H-interactions in **III**, two inside the adjacent six-membered ring and two inside the central ring. On the other side, we found one of the most highfield shifted values for the same carbon atom C-12 in diastereomer ctt-**2**. This is caused by the shielding effect of the 1,3-H,C-interaction, observed twice in **V** and once in **VI**.
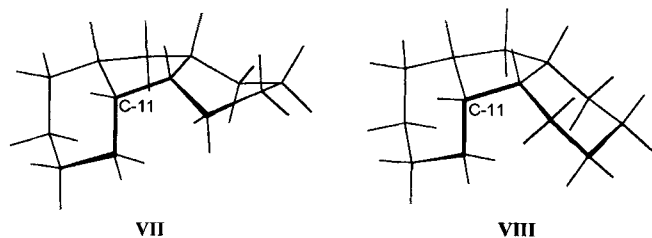
Scheme 5

Also two preferred conformers were found for the diastereomer ccc-**2** (**VII** and **VIII** in Scheme 5). The situation in diastereomer ccc-**2** is comparable to *cis*-1,2-dimethyl-cyclohexane [10]. In the planar representation (Scheme 2) it has a symmetry plane and appears to be a meso form. In contrast, the structure represented in Scheme 5 is chiral in either conformation. However, at normal temperatures the two conformers **VII** and **VIII** will be rapidly interconverting with their enantiomers of equal energy. The enantiomers or alternative conformers are not shown here. So, the NMR spectrum of ccc-**2** represents the averages of the two environments experienced by the pairs of carbon atoms.

The last compound ctc-**2** presents a puzzling aspect. From molecular mechanics calculations resulted an equilibrium of three conformers (**IX** 51%, **X** 25%, **XI** 24%). The most stable conformers **IX** and **X** are pic-

Scheme 6

tured in the Scheme 6. While the preferred chiral conformer **IX** shows a symmetry analogous to **II** (C_2 symmetry axis), no element of symmetry (except for C_1) exists in the conformer **X**. The situation here is analogous to **VII** and **VIII**. The conformer **X** is a racemate in which the enantiomers interconvert rapidly at room temperature. Finally, the conformer **XI** has a C_2 symmetry axis analogous to **IX**. So, we could find only two CH-signals in the NMR spectrum of this compound.

All 1,3-*synaxial* interactions of the bridgehead carbon atoms observed in the preferred conformations **I** to **XI** are listed together with the calculated and averaged relative chemical shift values in Table 3. The assignment of the relative configurations (Scheme 2) to the diastereomers **A** to **F** was done by minimization of the deviation between the calculated and the measured ^{13}C chemical shift values of all CH-signals. For it, the scale of relative chemical shift was moved so that the most downfield shifted experimental signal (one signal of the compound **D**) and the most downfield shifted calculated signal (C-12 in cct-**2**) are superimposed. The result is shown by the given order in the Figures 2c and 2d. In Figure 2d all empirically calculated relative ^{13}C chemical shifts ($\Delta\delta$) of the bridgehead carbon atoms are shown. By this order, also given in Table 3, the deviation between experimental and calculated chemical shifts was only 1.3 ppm, averaged over all fifteen CH-signals.

The assignment is in good agreement with the yields obtained in the different hydrogenation procedures. For the stereoselective catalyst platinum mainly the products with a *cis* configuration were to be expected. So, in the hydrogenation procedure b the ccc-**2** diastereomer was found as the main product (**F**, 64%) whereas the yield for the ttt-**2** and tct-**2** diastereomer, respectively, was low. Otherwise, through the use of the unselective nickel catalyst the products with the stereochemical more stable configuration were to be expected. With exception of the compound **B** and by consideration of similarity in heats of formation of compounds **D** and **E**, all yields found for the diastereomers in the hydrogenation procedure **a** (Table 1) followed the order of energy estimated by the force field calculations (Table 3).

Table 3 The preferred conformers of the six diastereomers of **2** and their heats of formation (E), estimated by molecular mechanics calculations. For the carbon atoms C-10, C-11, C-12 and C-13 the number of increments for the non-bonding 1,3-*synaxial* interactions (HH.CH.HC) are given and the relative ^{13}C NMR chemical shifts ($\Delta\delta$), calculated out of them.

	pref.. conf.	E	ΔE	%	C-10	Δδ [a]	C-11	Δδ [a]	C-12	Δδ [a]	C-13	Δδ [a]	Δδ$_{10,13}$ [b]	Δδ$_{11,12}$ [c]	comp.
		kcal/mol				ppm		ppm		ppm		ppm	ppm	ppm	
tct	I	29.1	–	100	3.0.0	14.2	3.0.0	14.2	3.0.0	14.2	3.0.0	14.2	14.2	14.2	A
ttt	II	24.9	–	100	3.0.0	14.2	4.1.0	20.7	4.1.0	20.7	3.0.0	14.2	14.2	20.7	B
cct	III	26.4	0.0	82	1.2.0		2.2.0		4.2.0		2.0.1				D
	IV	27.3	0.9	18	1.2.0	8.2	2.2.0	12.9	3.1.0	21.2	2.0.2	4.2	–	–	
ctt	V	25.3	0.0	66	2.1.0		2.3.0		2.1.2		3.0.0				C
	VI	25.7	0.4	34	3.2.0	12.8	3.2.0	15.7	3.1.1	5.3	4.0.0	15.8	–	–	
ccc	VII	27.9	0.0	65	1.2.0		3.1.0		2.1.0		2.0.0				F
	VIII	28.2	0.3	35	1.2.0	8.2	3.1.0	15.9	1.4.0	11.4	2.0.0	9.5	8.8	13.7	
ctc	IX	26.5	0.0	51	2.1.0		0.3.2		0.3.2		2.1.0				E
	X	26.9	0.4	25	2.2.0		2.3.0		1.0.2		1.1.1				
	XI	27.0	0.5	24	0.2.1	9.6	3.2.0	6.0	3.2.0	1.2	0.2.1	6.8	7.3	3.6	

[a] Relative values averaged over all preferred conformers per diastereomer, [b] Relative values averaged over C-10 and C-13
[c] Relative values averaged over C-11 and C-12

The results of capillary gas chromatography experiments also supported the assignment of configurations. As a rule, alicyclic compounds with *trans*-arrangements eluate faster than the *cis* products on polar and nonpolar stationary phases [12]. This was shown earlier for a series of bicylic systems [12] and for the perhydrophenanthrenes [3]. The retention order determined for the compounds **A** to **F** on a weak polar HP-5 capillary followed this rule (Table 1). The diastereomers emerged more slowly from the stationary phase the larger the number of *cis*-arrangements.

Another experiment to ascertain the assignment of the relative configurations by gas chromatography was done using β-cyclodextrin as an enantioselective stationary phase. This chiral stationary phase was used for the direct resolution of the enantiomers in the four chiral diastereomers (ttt, cct, ctt and ctc) of **2**. However, only for the compounds **C** and **E** the separation of the enantiomers was successful. The retention times of compounds **D** and **E** were very similar in all cases. So, the signals caused by the different enantiomers were overlapped considerably. For the compound **A** the detection was complicated by the small amount. Only one signal was obtained clearly for the diastereomer **F**. This points to one of the meso forms tct-**2** and ccc-**2**. In accordance with the large retention time, compound **F** should be the ccc-**2** diastereomer. The assignment of compound **E** to the ctc-**2** configuration was confirmed by isochronous H-9 protons together with the retention order. An uncertainty could not be eliminated in case of the compound **A** because of the small amounts obtained by both hydrogenation procedures. However, it has been shown that the ^{13}C NMR spectroscopy is a very powerful method for the differentiation and the assignment of relative configuration of diastereomers of alicyclic compounds.

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