

# Conformation and Internal Mobility of 5*H*-dibenzo[a,d]cycloheptene Derivatives in Solution. Conformational Analysis of Highly Flexible Structures, Part II [1]

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**Summary.** The conformational possibilities of 5-(3'-N,N-dimethylaminopropyl)-5*H*-dibenzo[a,d]-cycloheptene (**1**), 5-(3'-N,N-dimethylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (**2**), and 5-(3'-N,N-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (**3**) are analysed using empirical force field methods. Minimum energy conformations, interconversion pathways, interconversion graphs and interconversion energies are examined in view of the analysis of conformer equilibria of **1**, **2**, or **3** in solution. In addition, some basic requirements of the analysis of fast interconverting conformers using the lanthanide induced shift method are discussed.

**Keywords.** Conformational analysis; Empirical force field method; Tricyclic antidepressant drugs; Lanthanide induced shift method.

**Konformation und interne Beweglichkeit von 5*H*-Dibenzo[a,d]cyclohepten Derivaten in Lösung. Konformationsanalyse hochflexibler Strukturen, Teil 2 [1]**

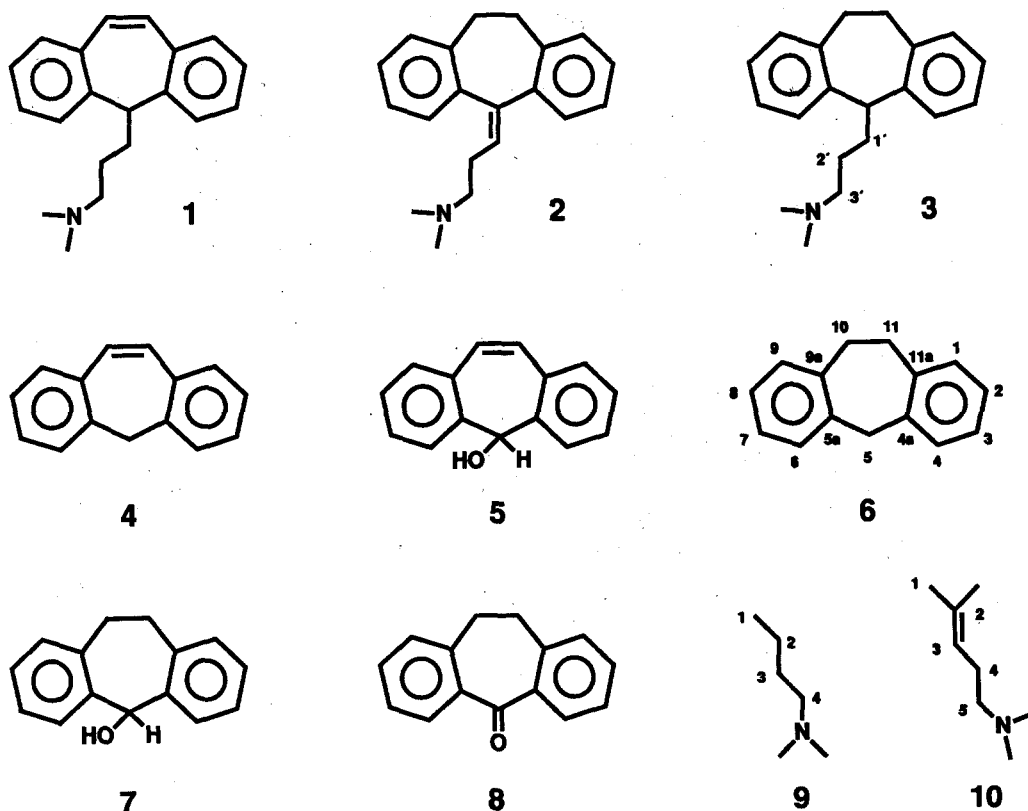
**Zusammenfassung.** Die konformativen Möglichkeiten von 5-(3'-N,N-dimethylaminopropyl)-5*H*-dibenzo[a,d]cyclohepten (**1**), 5-(3'-N,N-dimethylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten (**2**) und 5-(3'-N,N-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten (**3**) wurden mit Hilfe empirischer Kraftfeldmethoden analysiert. Jene Konformationen, die einem energetischen Minimum entsprechen, sowie Interkonversionswege, Interkonversionsgraphen und Interkonversionsenergien wurden in Hinblick auf die Analyse der Konformerengleichgewichte von **1**, **2** oder **3** in Lösung untersucht. Weiters werden noch einige grundlegende Voraussetzungen für die Analyse von sich schnell ineinander umwandelnden Konformeren mittels der Lanthaniden-induzierten Verschiebungsmethode besprochen.

## Introduction

Recently, we focused our attention on methods for analysing conformer mixtures of highly flexible – fast interconverting – molecules. We reported that with use of the lanthanide induced shift method, together with force field calculations and X-ray analysis, the conformations and interconversion modes of fast interconverting

conformers like those of 5-hydroxy-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (**7**) and 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-one (**8**) can be analysed [1].

In solution, the tricyclic parent compound 10,11-dihydrodibenzo[*a,d*]-cycloheptene (**6**) adopts chiral, biplanar conformations which interconvert by two different modes. One mode interconverts enantiomeric conformations, the other one homomers. The calculated interconversion barriers are 16.9 and 19.7 kJ/mol. Up to now, there are no experimental NMR data available on the interconversion barriers of **6** as well as **7** and **8**. Even at the lowest reachable temperatures the interconversions are fast on the NMR time scale, resulting in averaged parameters for chemical shifts and coupling constants [2–7]. However, in the case of **7** and **8**, the analysis of the room temperature lanthanide induced shift data gave detailed information about the conformer equilibrium in solution, including information about preferred geometries and population ratios.



The aim of this work is to extend our analysis to conformer equilibria with more than four interconverting conformers and to molecules with flexible side chains. In this and the following paper we report our results on the pharmacologically active compounds **1–3**, all aminopropyl or aminopropylidene derivatives of the tricyclic parent compounds **4** and **6**. We also examine critically the results of our analysis and discuss some limits of application of the LIS-method to equilibria of fast interconverting conformers.

## Results and Discussion

### *Method of Analysis*

Since the number of variables is usually significantly higher than the number of observables an iterative process must be used to analyse the data which is shown schematically in Fig. 1.

If  $n$  conformers interconvert fast on the NMR time scale, then a NMR experiment results in averaged observables. In case of the LIS experiment these averaged data are chemical shift differences [7]. (Of course any other method which results in averaged parameters related to the geometry of all conformers – like e. g. coupling constants or nuclear Overhauser enhancements – may be used instead, or if possible in addition to the LIS method). The iterative process is performed in the following way: In a first step the geometries of models of all  $n$  conformers are calculated and their interconversion modes are analysed. This is usually done by force field or semiempirical calculations. (Only in very favorable cases X-ray structures of all conformers are known). Starting from calculated proton positions of the individual conformers, geometrical factors are calculated. Then the geometrical factors of corresponding atoms are averaged. In a least squares procedure these averaged geometrical factors are scaled to the experimental LIS resulting in optimized var-

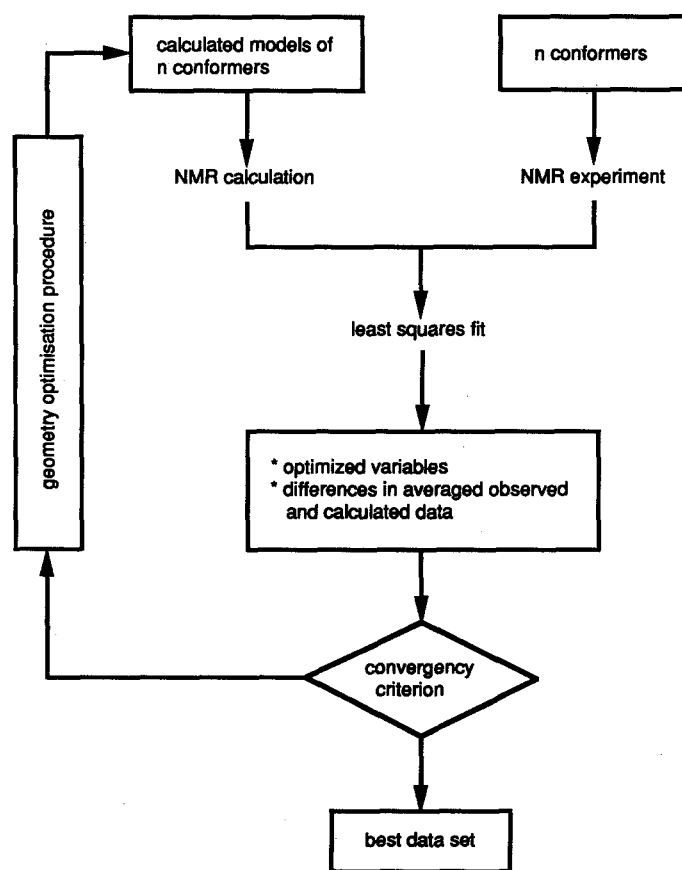


Fig. 1. Schematic representation of an iterative LIS calculation for  $n$  fast interconverting conformers

ables like, for example, the position of the lanthanide ion and population ratios. Finally, in a second optimisation procedure, the geometry of the individual conformers may be adjusted to give the best fit of averaged calculated and observed data. The quality of the fit is usually given by a *R*-factor, similarly defined as the crystallographic *R*-factor.

As pointed out, a first step in the analysis has to be the evaluation of possible conformers and interconversion modes. The relation of minimum energy conformations and interconversion paths is visualized best by interconversion graphs, where the vertices represent conformers and the edges interconversion modes [8].

5*H*-Dibenzo[*a,d*]cycloheptene (**4**), for example, adopts just one boat like  $C_s$  symmetrical minimum energy conformation which may interchange via a boat-boat interconversion into a conformation indistinguishable from that of the starting conformer. This homomerisation process is described by a single interconversion mode (mode a, Fig. 2). The 5-hydroxy derivative **5**, however, adopts two minimum energy conformations (**A** and **B**, Fig. 2) with the hydroxyl group either in a pseudo equatorial or a pseudo axial position. These diastereomeric conformers are again interconverted into each other by a boat-boat interconversion (skeletal flip).

10,11-Dihydrodibenzo[*a,d*]cycloheptene (**6**) adopts asymmetric, enantiomeric minimum energy conformations. The interconversion graph (Fig. 2) shows that

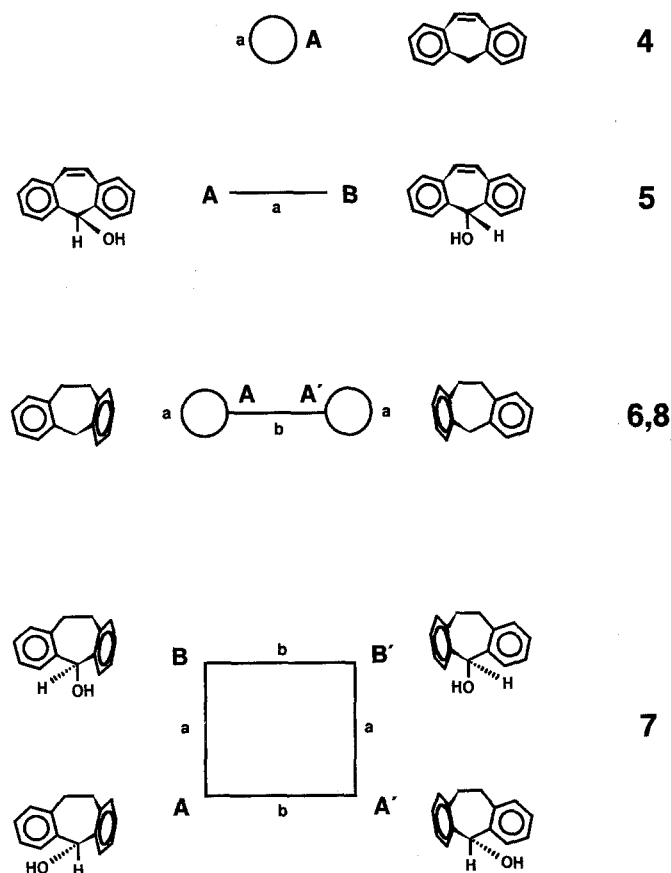


Fig. 2. Interconversion schemes of compounds 4–8

each enantiomer may either undergo a homomerisation process via a skeletal flip (mode a) or interconvert into its enantiomer via a torsional flip (a torsion about the single bond C10-C11, mode b, Fig. 2). Exactly the same interconversion graph applies to ketone **8**. Like for **6**, the asymmetric ground state conformer may undergo a homomerisation as well as an enantiomerisation process, described by two different modes, the skeletal and the torsional flip. Similar to **5**, substitution of **6** to the 5-hydroxy derivative **7** leads to diastereomeric minimum energy conformations. Since these diastereomeric conformers are asymmetric, their enantiomers are also expected to be present in a conformer equilibrium. Interconversion can take place via a skeletal or a torsional flip, as shown in Fig. 2.

To explore the conformational possibilities of **1–3** we resorted to empirical force field calculations which have already proved to be successful in modeling structures of **4–8** [9] and those of related compounds [10, 11]. Like **5**, **7** and **8**, compounds **1**, **2** and **3** are derivatives of the parent tricyclic systems **4** and **6**, substituted in position **5**, and hence, it is expected that their conformational possibilities and their interconversion graphs show some similarities. The number of possible minimum energy conformations of **1–3** is, of course, expected to be significantly higher as compared to **5–8**. To check the conformational possibilities of the aminopropyl and aminopropylidene side chains, we first analysed the model compounds *N,N*-dimethylaminopropane (**9**) and *N,N*-dimethylamino-4-methylpentene-3 (**10**).

#### *Side Chain Conformations*

If all possible combinations of staggered conformations of **9** are taken into account, a maximum of 27 (14 unique) conformers is expected (1  $C_s$  symmetrical, all anti-periplanar conformer, and 13 asymmetric pairs of enantiomeric conformers). With use of Allingers force field (programs BIGSTRN 3 [12] and MM2(87) [13]) 13 minimum energy conformations could be located. One, the all gauche arrangement  $g^+ g^- g^-$  (and its enantiomer) does not represent a minimum energy conformation. In such an arrangement one *N*-methyl group is in close contact to the butyl methyl group causing severe steric interaction. A similar situation applies to **10**. Conformers with carbon C5 above or below the plane defined by the double bond substituents (carbons C1, C2, and C4) as well as in plane conformers are feasible, again resulting into 27 (14 unique) conformers. (Synperiplanar in plane conformations are not taken into account, Fig. 4, conformations  $\delta$ ). All 18 (9 unique) out of plane conformers were found but just one in plane conformation—the all anti conformer—could be characterized. Table 1 lists the relative energies of all calculated conformers of **9** and **10**. Inspection of Table 1 shows that in both cases, **9** and **10**, under room temperature conditions several conformers must be expected to be present in an equilibrium in an individual ratio of more than 1%. According to the calculations for **9**, 8 unique conformers are expected to be present in an equilibrium in a ratio of more than 1%, and all 10 unique conformers for **10**. However, in each case 4 unique conformers account for more than 84%. All interconversion barriers lie in the range of 14–41  $\text{kJ mol}^{-1}$ . The interconversion graphs of **9** and **10** are both related to the general interconversion scheme for all 27 combinations of staggered conformations describing e. g. the interconversion possibilities of all 27 feasible conformers of *n*-hexane. (A detailed description of this general graph is given in Ref. [14]).

**Table 1.** Calculated relative steric energies (MM2(87)) and equilibrium ratios of all conformers of **9** and **10**

9 <sup>a</sup>	ΔE(kJ/mol)	% (298 K)	10 <sup>a</sup>	ΔE(kJ/mol)	% (298 K)
a g <sup>-</sup> g <sup>+</sup>	0.00	41.4	αg <sup>-</sup> g <sup>+</sup>	0.00	34.7
a g <sup>-</sup> g <sup>+</sup>	1.46	23.0	αa g <sup>-</sup>	0.08	33.6
g <sup>-</sup> a g <sup>+</sup>	3.10	12.0	αa g <sup>+</sup>	3.51	8.5
g <sup>-</sup> g <sup>-</sup> g <sup>+</sup>	4.18	7.7	αa a	3.51	8.5
g <sup>-</sup> a g <sup>-</sup>	4.56	6.5	αg <sup>-</sup> g <sup>-</sup>	4.27	6.2
a a a	3.56	5.0	αg <sup>+</sup> g <sup>-</sup>	6.28	2.8
g <sup>-</sup> a a	7.49	2.1	αg <sup>-</sup> a	6.69	2.4
g <sup>+</sup> g <sup>-</sup> g <sup>+</sup>	8.37	1.4	aa a	6.44	1.3
a g <sup>-</sup> g <sup>-</sup>	11.00	0.5	αg <sup>+</sup> g <sup>+</sup>	8.83	1.0
g <sup>-</sup> g <sup>-</sup> g <sup>-</sup>	15.10	< 10 <sup>-1</sup>	αg <sup>+</sup> a	8.83	1.0
g <sup>+</sup> g <sup>-</sup> a	15.56	< 10 <sup>-1</sup>			
a g <sup>-</sup> a	16.61	< 10 <sup>-1</sup>			
g <sup>-</sup> g <sup>-</sup> a	19.29	< 10 <sup>-2</sup>			
g <sup>+</sup> g <sup>-</sup> g <sup>-</sup>	-	-			

<sup>a</sup> Labels of the enantiomeric conformers have been omitted (e. g., ag<sup>+</sup>g<sup>-</sup> as enantiomer of ag<sup>-</sup>g<sup>+</sup>, a: antiperiplanar, g: gauche, +(-): positive (negative) sign of dihedral angles; α: positive sign of torsional angle C2-C3-C4-C5 (**10**), torsional angles are given in the order: C1-C2-C3-C4, C2-C3-C4-N, C3-C4-N-lone pair (**9**); and C2-C3-C4-C5 (α), C3-C4-C5-N, C4-C5-N-lone pair (**10**))

### Minimum Energy Conformations and Interconversion Paths of **1–3**

In **1** and **3** the N,N-dimethylaminopropyl side chain can be attached to the parent systems of **4** and **6** either in a pseudo axial or in a pseudo equatorial position. Furthermore, the side chain may adopt one of 3 possible staggered conformations when viewed along the single bond C5-C1' (Fig. 3). This leads to a maximum of 162 (82 unique) conformers of **1** and 324 (162 unique) for **3**, respectively. Attaching the N,N-dimethylaminopropylidene side chain to the parent system **4** results into a maximum of 108 (54 unique) conformers. In each case, **1–3**, it was tried to locate and to characterise all unique conformers.

Compounds **1–3** represent 3 different types of structures and therefore the result of the calculations will be discussed separately in the following paragraphs.

### Minimum Energy Conformations

**1:** In all calculated minimum energy structures the central seven membered ring of the dibenzo[a,d]cycloheptene substructure adopts a boat like conformation, very similar to that of the C<sub>s</sub>-symmetrical parent compound **4** or to that of the hydroxyl derivative **5**. As mentioned above the side chain can be attached to the parent system either pseudo-equatorially or pseudo-axially. Furthermore, in the ps-eq as well as in the ps-ax case the side chain is linked to the tricyclic system in one of 3 different conformations (Fig. 3, conformations α, β, γ). Conformers with side chain

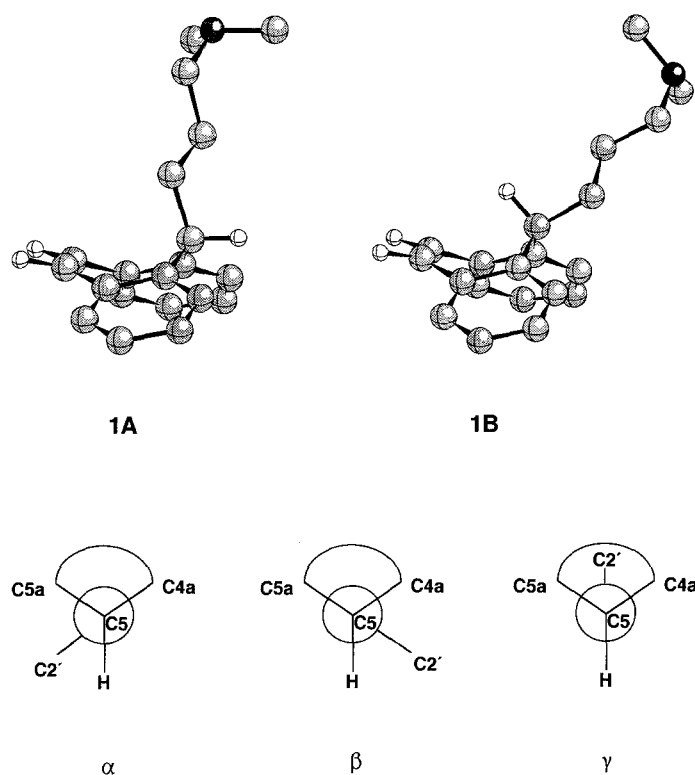


Fig. 3. Selected minimum energy conformations of **1** and possible side chain conformations viewed along bond C5–C1'

arrangements  $\alpha$  are enantiomeric to those of  $\beta$ , resulting into 27 unique (diastereomeric, symmetry independent) possible conformers for ps-ax/ $\alpha$  combinations as well as for ps-eq/ $\alpha$  combinations. 14 unique conformers are feasible for ps-eq/ $\gamma$  as well as for ps-ax/ $\gamma$  combinations. In both arrangements, ps-ax and ps-eq, 24 out of 27 conformers could be located. Like for **9**, the  $g^+g^-g^-$  and  $g^-g^+g^+$  arrangements of the side chain do not represent minimum energy conformations as well as the ps-ax/ $g^+g^-a$  and the ps-eq/ $g^-g^+a$  arrangements. The ps-eq conformers are higher in energy by at least 9 kJ/mol than the ps-ax once. The  $\gamma$  arrangements are higher in energy by at least 16 kJ/mol than that structure representing the global minimum. The conformer with the lowest energy shows a ps-ax/ $\alpha/ag^-g^+$  (or its enantiomeric) conformation. According to the calculations, in an equilibrium almost exclusively conformers with ps-ax side chains are expected to be present in significant amounts. Table 2 lists all conformers with relative energies up to 12.5 kJ/mol. The ratio of conformers is calculated to be **A**:**B** = 97 : 3.

**2:** The tricyclic system of all calculated conformers adopts  $C_1$  symmetrical, nearly biplanar conformations similar to that found for **8**. The planes are defined by one benzene ring (e. g. C11 a-C1-C2-C3-C4-C4 a) and two adjacent carbons (C5 and C11) and the second one by the other benzene ring plus 3 carbons of the central seven membered ring (C5-C10-C11).

The aminopropylidene side chain may again be attached in 2 different ways to the parent system, with – according to the double bond – carbons C5 a and C2 either

**Table 2.** Calculated relative steric energies (MM2(87)) and equilibrium ratios of conformers of **1** (conformers with ratios  $> 10^{-1}$  are listed)

<b>1A</b> <sup>a, c</sup>	$\Delta E(\text{kJ/mol})$	% (298 K)	<b>1B</b> <sup>b, c</sup>	$\Delta E(\text{kJ/mol})$	% (298 K)
a g <sup>-</sup> g <sup>+</sup>	0.00	22.0	a a g <sup>+</sup>	8.37	0.8
a a g <sup>-</sup>	1.05	14.4	a a g <sup>-</sup>	8.70	0.7
g <sup>+</sup> g <sup>+</sup> g <sup>-</sup>	1.30	13.1	a g <sup>+</sup> g <sup>-</sup>	8.79	0.6
a a g <sup>+</sup>	1.42	12.4	a g <sup>-</sup> g <sup>+</sup>	9.71	0.4
a g <sup>+</sup> g <sup>-</sup>	1.72	11.0	g <sup>+</sup> g <sup>+</sup> g <sup>-</sup>	11.55	0.2
g <sup>-</sup> a g <sup>+</sup>	2.97	6.7	g <sup>+</sup> a g <sup>-</sup>	11.59	0.2
g <sup>-</sup> g <sup>-</sup> g <sup>+</sup>	4.39	3.8	a a a	11.72	0.2
a a a	4.52	3.6			
g <sup>+</sup> a g <sup>-</sup>	4.90	3.1			
g <sup>-</sup> a g <sup>-</sup>	5.56	2.4			
g <sup>-</sup> a a	6.90	1.4			
g <sup>+</sup> a g <sup>+</sup>	7.20	1.2			
g <sup>-</sup> g <sup>+</sup> g <sup>-</sup>	9.46	0.5			
a g <sup>-</sup> g <sup>-</sup>	9.54	0.5			
g <sup>+</sup> a a	10.21	0.4			
g <sup>+</sup> g <sup>-</sup> g <sup>+</sup>	10.25	0.4			
a g <sup>+</sup> g <sup>+</sup>	12.26	0.2			

<sup>a</sup> Side chain axial

<sup>b</sup> Side chain equatorial

<sup>c</sup> Labels of the enantiomeric conformers have been omitted; torsional angles are given in the order: C5-C1'-C2'-C3', C1'-C2'-C3'-N, C2'-C3'-N-lone pair

in *cis* or in *trans* arrangements. Like for **10**, 18 out of plane (C3' above or below the plane of the double bond) and 9 in plane conformations are expected. (Like for **10**, synperiplanar in plane conformations – Fig. 4 conformations  $\delta$  – are not taken into account). This results into 54 unique conformers (27 with *cis* and 27 with *trans* arrangements). All 36 out of plane conformers were found and characterised. However, contrary to **10**, in plane conformations do not represent minimum energy structures, not even the all antiperiplanar arrangement. For better clarity, the 36 conformers are subdivided into 4 groups: combinations with the side chain – according to the double bond – either *cis* or *trans* and either above or below that plane. Fig. 4 shows one example of each group as well as possible side chain conformations viewed along the double bond carbons C1'–C2'. Table 3 lists the relative energies of all conformers as well as their relative ratios in an hypothetical conformer equilibrium. Since all 36 conformers are asymmetric their enantiomers are also expected to be present in an equilibrium. The calculated ratio of conformers belonging to groups A–D is A:B:C:D = 49 : 25 : 21 : 5.

**3:** Most conformers are characterised by an essentially biplanar tricyclic system. Like for **1** and **7**, the side chain may be attached to the parent system either pseudo-axially or pseudo-equatorially. Again in each case the side chain may adopt one of 3 different staggered positions along the bond C5–C1' ( $\alpha$ ,  $\beta$ ,  $\gamma$ , Fig. 3). Since the



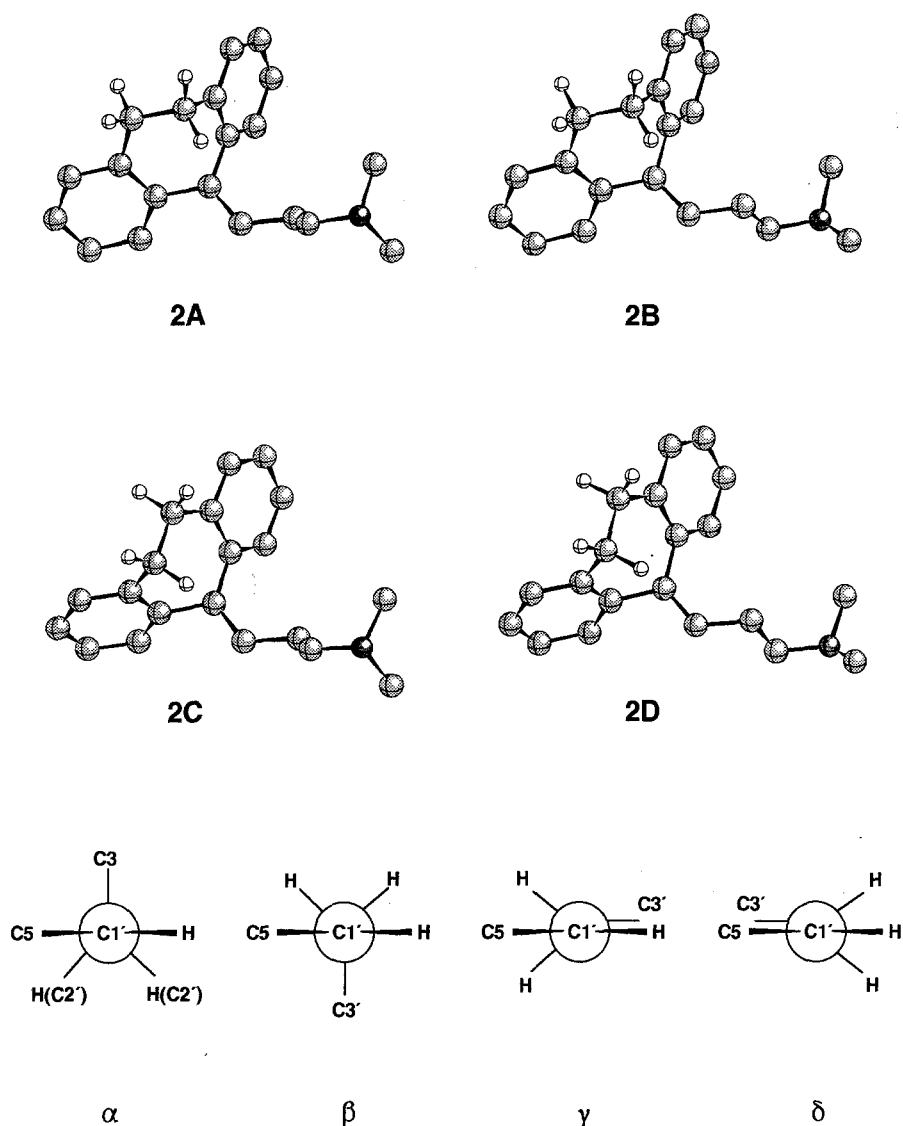


Fig. 4. Selected minimum energy conformations of **2** and possible side chain conformations viewed along bond C1'–C2'

parent system itself is asymmetric, 27 conformers are expected for each staggered position  $\alpha$ ,  $\beta$  or  $\gamma$ , resulting into 81 unique ps-ax and 81 ps-eq conformers. Out of the 27 conformers expected for ps-ax/ps-eq and  $\alpha/\beta$  combinations 23 could be located in each case. Like for **9** and **1**  $g^+g^-g^-$  ( $g^-g^+g^+$ ) conformations do not represent minimum energy structures. Furthermore the side chain conformations  $g^+g^-a$  and  $g^-g^+a$  could not be characterised as minima. Several conformations with a  $\gamma$ -side chain conformation were found, but are not considered further, since their energies are higher than that of the conformer with the lowest energy by at least 12.5 kJ/mol. Table 4 lists the relative energies and populations of 60 conformers; most of them are expected to be present in an equilibrium. Again for better clarity the conformers are divided into 4 groups, representing combinations of ps-

**Table 3.** Calculated relative steric energies (MM2(87)) and equilibrium ratios of all conformers of **2**<sup>a</sup>

	<b>2A</b> ( $\alpha$ ) $\Delta E$ (kJ/mol)	% (298 K)	<b>2C</b> ( $\alpha$ ) $\Delta E$ (kJ/mol)	% (298 K)	<b>2B</b> ( $\beta$ ) $\Delta E$ (kJ/mol)	% (298 K)	<b>2D</b> ( $\beta$ ) $\Delta E$ (kJ/mol)	% (298 K)
$g^-g^+$	0.00	30.3	1.59	16.0	4.56	4.9	8.41	1.0
$g^+g^-$	4.56	4.9	7.41	1.6	6.90	1.9	12.80	0.2
$a g^-$	4.52	4.9	8.45	1.0	3.85	6.5	7.24	1.7
$a g^+$	4.48	5.0	7.78	1.3	3.60	7.2	7.11	1.7
$a a$	7.66	1.4	11.84	0.3	6.32	2.4	9.75	0.6
$g^-g^-$	8.58	1.0	10.63	0.4	12.55	0.2	21.92	<10 <sup>-2</sup>
$g^+g^+$	10.75	0.4	15.61	<10 <sup>-1</sup>	8.16	1.1	13.01	0.2
$g^-a$	8.45	1.0	12.64	0.2	16.99	<10 <sup>-1</sup>	20.79	<10 <sup>-2</sup>
$g^+a$	14.60	<10 <sup>-1</sup>	20.50	<10 <sup>-2</sup>	10.08	0.5	21.92	<10 <sup>-2</sup>

<sup>a</sup>  $\alpha$  ( $\beta$ ): positive (negative) sign of torsional angle C5-C1'-C2'-C3'; order of torsional angles: C1'-C2'-C3'-N, C2'-C3'-N-lone pair

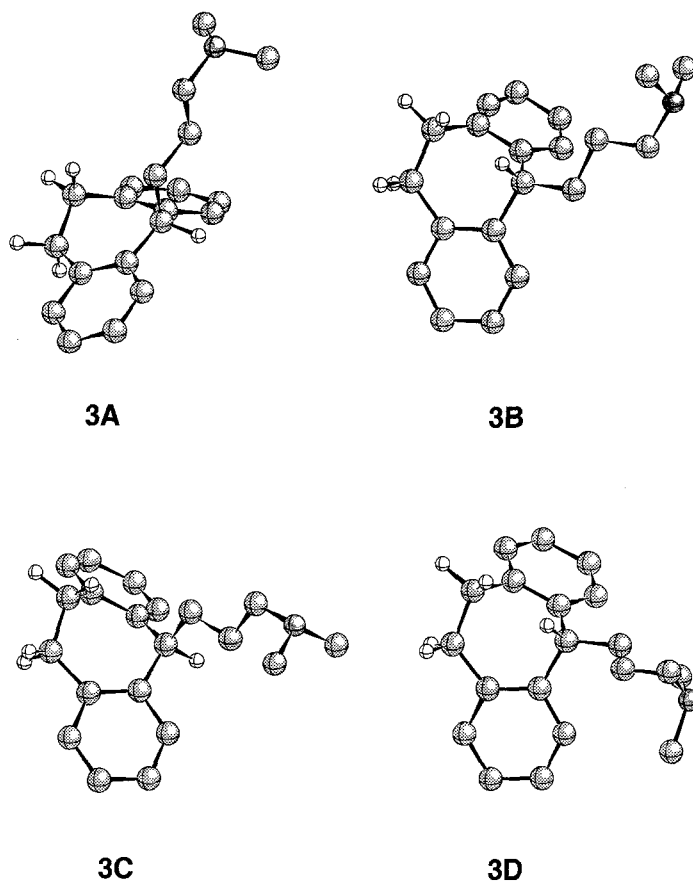


Fig. 5. Selected minimum energy conformations of **3**

*ax/ps-eq* and  $\alpha/\beta$  side chain arrangements. One example of each group (that with antiperiplanar side chains) is shown in Fig. 5.

For the corresponding equilibrium, the expected ratio of conformers belonging to groups **A–D** is calculated as **A:B:C:D** = 57 : 24 : 11 : 8.

### Interconversion Paths and Energies

As mentioned above, interconversion paths are visualised best by interconversion graphs, where the vertices represent minimum energy conformations and the edges interconversion modes. The interconversion graphs of **1–3** can be constructed from the interconversion graphs of the parent tricyclic systems (Fig. 2) and those of the side chains. Since the full interconversion graphs of **1–3** consist of a high number of conformers, a two dimensional representation is difficult to survey. However, the main interconversion features can also be seen on the simplified graphs for **1–3**, shown in Fig. 6. These graphs can be interpreted in 2 ways: (i) as full interconversion graphs of **1–3** with rigid side chains in—for example—antiperiplanar conformations, flexible only about the single bonds C5-C1' (**1**, **3**) or about C1'-C2' (**2**); such a restriction reduces the number of conformers to 4 (**1**) or 8 (**2**, **3**) (Figs. 3, 4 and 5 show the symmetry independent structures of these

**Table 4.** Calculated relative steric energies (MM2(87)) and equilibrium ratios of selected conformers of **3**

	<b>3A<sup>a</sup></b> ΔE(kJ/mol)	% (298 K)	<b>3B<sup>b</sup></b> ΔE(kJ/mol)	% (298 K)	<b>3C<sup>a</sup></b> ΔE(kJ/mol)	% (298 K)	<b>3D<sup>b</sup></b> ΔE(kJ/mol)	% (298 K)
a g <sup>-</sup> g <sup>+</sup>	0.00	12.1	3.81	2.6	5.61	1.3	5.69	1.2
a g <sup>+</sup> g <sup>-</sup>	1.97	5.5	2.72	4.1	4.48	2.0	5.98	1.1
a a g <sup>-</sup>	0.54	9.7	2.68	4.1	4.31	2.1	4.56	1.9
a a g <sup>+</sup>	0.63	9.4	2.34	4.7	4.14	2.3	4.98	1.6
a a a	3.72	2.7	5.73	1.2	7.45	0.6	8.28	0.4
g <sup>-</sup> g <sup>-</sup> g <sup>+</sup>	4.56	1.9	9.25	0.3	9.29	0.3	8.70	0.4
g <sup>+</sup> g <sup>+</sup> g <sup>-</sup>	2.72	4.1	4.69	1.8	8.62	0.4	14.64	<10 <sup>-1</sup>
g <sup>-</sup> a g <sup>+</sup>	2.43	4.6	9.12	0.3	9.00	0.3	8.66	0.4
g <sup>+</sup> a g <sup>-</sup>	4.31	2.1	4.73	1.8	7.28	0.7	13.22	<10 <sup>-1</sup>
g <sup>-</sup> a g <sup>-</sup>	4.48	2.0	10.84	0.2	10.04	0.2	10.33	0.2
g <sup>+</sup> a g <sup>+</sup>	6.32	1.0	7.36	0.6	9.62	0.3	13.77	<10 <sup>-1</sup>
g <sup>-</sup> a a	5.56	1.3	14.27	<10 <sup>-1</sup>	12.68	<10 <sup>-1</sup>	13.01	<10 <sup>-1</sup>
g <sup>+</sup> a a	8.08	0.5	9.25	0.3	11.21	0.1	17.70	<10 <sup>-2</sup>
g <sup>+</sup> g <sup>-</sup> g <sup>+</sup>	10.92	0.2	4.48	2.0	16.69	<10 <sup>-1</sup>	12.51	<10 <sup>-1</sup>
g <sup>-</sup> g <sup>+</sup> g <sup>-</sup>	10.00	0.2	11.38	0.1	19.54	<10 <sup>-2</sup>	10.04	0.2

<sup>a</sup> Side chain axial<sup>b</sup> Side chain equatorial; order of torsional angles: C5-C1'-C2'-C3', C1'-C2'-C3'-N, C2'-C3'-N-lone pair

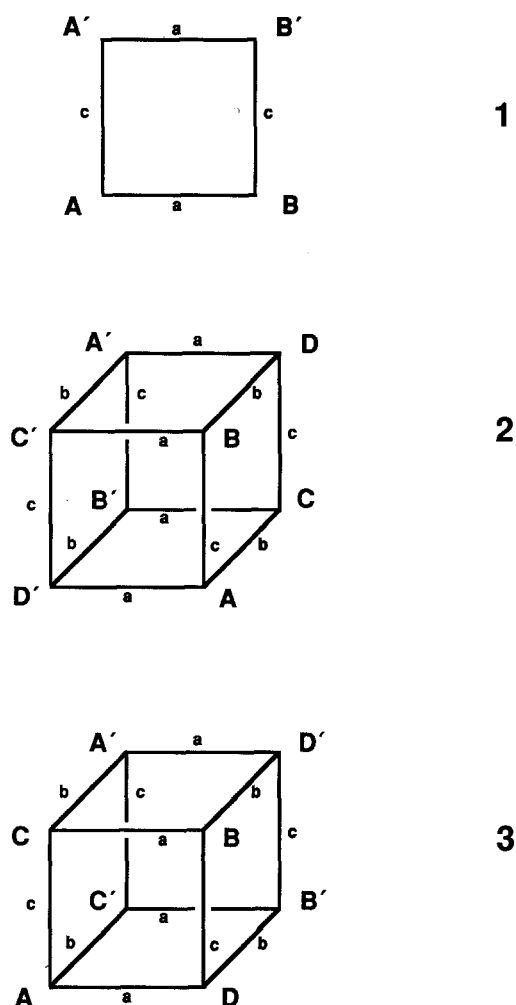


Fig. 6. Interconversion schemes of 1–3

conformers); (ii) as projection of the full interconversion graphs onto a square (**1**) or a cube (**2, 3**). In that case **A, B, C** and **D** no longer represent individual conformers but families of conformers differing only in side chain conformations. All conformational interconversions may be described by interconversion modes: modes *a* and *b* referring to interconversions of the tricyclic systems and several modes interconnected with side chain interconversions. Like for **4–8**, mode *a* describes a skeletal flip, mode *b* a torsional flip. Mode *c* describes in each case side chain torsions (interconversions of conformers  $\alpha$  into  $\beta$ ). All other modes describing further side chain interconversions have been omitted in the graphical representation in Fig. 6.

Table 5 lists interconversion barriers interconnected with modes *a*, *b*, and *c*. The given barriers were calculated assuming antiperiplanar side chain conformations (**1, 3**:  $\alpha\alpha\alpha$ , **2**:  $\alpha\alpha\alpha$  or  $\beta\alpha\alpha$ ). Test calculations for other side chain conformations gave barriers within the limits of  $\pm 7$  kJ/mol. Side chain interconversions not listed in Table 5 are within the range given for test compounds **9** and **10**. In the following

**Table 5.** Selected interconversion barriers interconnected with interconversion modes a, b, and c (kJ/mol). The given barriers refer to interconversions of conformers with antiperiplanar side chain conformations

Modes		a	b	c
1	75.7 <sup>a</sup>	(A–B)	–	15.6 (A–A')
2	69.3 <sup>b</sup>	(A–D')	28.9 (A–C)	7.7 (A–B)
			33.3 (B–D)	9.4 (C–D)
3	45.9 <sup>b</sup>	(A–D)	17.4 (A–C')	12.1 (A–C)
			12.9 (B–D')	26.7 (B–D)

<sup>a</sup> Experimental value Ref. [5]

<sup>b</sup> Upper limit

paragraphs the interconversion possibilities of **1–3** are discussed. In each case that conformer with the lowest energy belongs to the group of conformers labeled with **A**. Examples of conformers belonging to groups **A**, **B**, **C**, and **D** are given in Fig. 3, 4, and 5.

**1:** The interconversion graph of **1** (Fig. 6) shows that conformers **A**—with the side chain pseudo axial—change by action of mode a into the diastereomeric conformations **B**—with the side chain pseudo equatorial (the enantiomeric conformers **A'** change into **B'**). The skeletal flip (mode a) represents an inversion of the tricyclic system, mode c a torsion about the single bond C5–C1' by approximately 120° interchanging conformers with side chain arrangements  $\alpha$  and  $\beta$  ( $\alpha$ : C4 a and C2' in an antiperiplanar conformation when viewed along the single bond C5 a–C1'). In case of an all antiperiplanar side chain conformation action of mode c interchanges enantiomers (**A** into **A'** and **B** into **B'**). The energy of an interconversion of **A** into **B** (mode a) was determined previously as 75.6 kJ/mol, the energy associated with mode c has been calculated to be 15.6 kJ/mol (**A** into **A'**) and 26.7 kJ/mol (**B** into **B'**).

**2:** All conformers of **2** may interconvert via the skeletal flip. Conformers **A**, for example, are interconverted into **D'**. Conformers **D'** can also be thought as being the result of a *cis/trans* isomerisation of conformers **A**. Formally, for all conformers the skeletal flip has the same effect like a *cis/trans* isomerisation (C4 a–C2' *trans* into C4 a–C2' *cis*). Mode b is associated with a change of the sign of the torsional angle C11 a–C11–C10–C9 a (e. g. an **A/C** interconversion) and action of mode c results into a torsion of the side chain about bond C1'–C2' interchanging conformations  $\alpha$  (positive sign of the torsional angle C5–C1'–C2'–C3') into conformations  $\beta$  (negative sign of that angle, Fig. 4). The interconversion energies associated with modes a, b, and c are given in Table 5.

**3:** As for **1** and **7**, the skeletal flip changes the conformation of the tricyclic system in such a way that a pseudo equatorial side chain becomes pseudo axial and vice versa [e. g. **A** (axial) into **D** (equatorial)]. Like for **2** mode b is associated with a torsion of the ethylene bridge of the central seven membered ring, but like

for **1** mode c represents a side chain torsion about bond C5-C1' interchanging  $\alpha$  and  $\beta$  conformations (e. g., **A** into **C**, Fig. 6).

## Conclusions

As mentioned above, the calculation of relative steric energies is necessary to limit the number of possible conformers to those which are expected to be present in an equilibrium in significant amounts.

In addition to the steric energies, it is also necessary to analyse the interconversion energies associated with all interconversion modes, since on a given NMR time scale (or any other time scale of observation) some interconversions might be fast, some others slow, resulting into noninterconverting subsets of conformers (residual enantiomers or residual diastereomers [15]). For example, inspection of Table 5 shows that conformers of **1** (**A**, **A'**, **B**, **B'**; Fig. 6) interconvert by two different modes, a and c. If interconversion caused by mode a is slow but that by mode c fast on the time scale of observation, than the NMR spectrum will show **A** and **B** separately. But some NMR parameters will still be averaged by the interconversion of **A** into **A'** as well as **B** into **B'**. This situation is actually observed in the room temperature spectrum of **1** [5]. As a consequence, in a LIS calculation these interconversions (**A**–**A'** and **B**–**B'**) must be accounted for.

A similar situation applies to **2**. The conformers of **2** interconvert by several modes, but the interconversion energy related to mode a is much higher than those of all others (Table 5). Since the interconversion by mode a is expected to be slow on the NMR time scale, all conformers fall into two enantiomeric subsets **A**, **B**, **C**, **D** and **A'**, **B'**, **C'**, **D'** (residual enantiomers); each set interconverting fast. That one interconversion is slow on the NMR time scale can be confirmed experimentally. In a 250 MHz NMR spectrum (solvent CDCl<sub>3</sub>) the signals of protons attached to C10 and C11 are slightly broadened at room temperature sharpening on cooling to –30°C. Above room temperature these signal broaden further indicating an exchange process caused by action of mode a. Methyl or chloro substitution of the tricyclic system in positions 4 and 6 should raise the barrier to such a degree that it might become possible to actually resolve the residual enantiomers. A proposed LIS calculation must take into account interconversions caused by the action of mode b and all modes related to the side chain but not those caused by mode a.

Since all interconversion energies of **3** are relatively small, all conformers are expected to interconvert fast into each other and must be considered in the mixing procedure (Fig. 1). A detailed LIS-analysis of compounds **1**–**3** will be reported in the following paper.

### *Force Field Calculations*

The structures of **1**, **2**, **3**, **9**, and **10** were minimized with use of the original MM2(87) [13] program including  $\pi$  system calculations. In addition, for **3**, **9**, and **10** the program BIGSTRN3 [12] with the MM2 force field was used to better characterize minimum energy conformations. The results of both programs are almost identical for **3**, **9**, and **10**. All calculations were performed at the computer center of the University of Vienna using an IBM 3090.

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