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Conformational Analysis of 5-*H*-Dibenzo[a,d]cycloheptene Derivatives with Flexible Amino-Substituted Side-Chains by Means of Lanthanide Induced Shifts (*LIS*). Conformational Analysis of Highly Flexible Structures, Part III

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Summary. The *LIS* data of 5-(3-N,N-dimethylaminopropyl)-5*H*-dibenzo[a,d]cycloheptene (**1**), 5-(3-N,N-dimethyl- and 5-(3-N-methylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[a,d]-cycloheptene (**2**, **2a**) and 5-(3-N,N-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (**3**) were used to calculate populations of possible conformers in solution. The substrate geometries of the particular conformers were taken from force field calculations. A *LIS* simulation program was used which is able to handle up to four possible conformations. The limits and special features of the method for highly flexible structures – especially for the case that the coordinating group is within a flexible chain – are discussed.

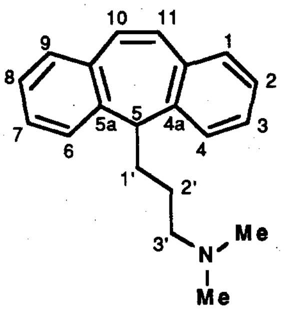
Keywords. Tricyclic antidepressants.

Konformationsanalyse von 5-*H*-Dibenzo[a,d]cyclohepten-Derivaten mit flexiblen aminosubstituierten Seitenketten mittels Lanthaniden-induzierter Verschiebungen.
Konformationsanalyse hochflexibler Strukturen, 3. Mitt.

Zusammenfassung. Die *LIS*-Werte von 5-(3-N,N-Dimethylaminopropyl)-5*H*-dibenzo[a,d]-cyclohepten (**1**), 5-(3-N,N-Dimethyl- bzw. 5-(3-N-Methylaminopropyliden)-10,11-dihydro-5*H*-dibenzo[a,d]-cyclohepten (**2** bzw. **2a**) und 5-(3-N,N-Dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten (**3**) wurden zur Berechnung von Populationen bevorzugter Konformerer herangezogen. Die Geometrien der einzelnen Konformeren wurden aus Force-Field-Rechnungen entnommen. Es wurde ein *LIS*-Programm verwendet, das bei der Simulation bis zu vier Konformationen berücksichtigen kann. Die Grenzen der Anwendbarkeit der Methode – insbesondere die speziellen Probleme die auftreten, wenn die Koordinationsstelle innerhalb einer flexiblen Kette liegt – werden diskutiert.

Introduction

In continuation of the conformational analysis of a set of pharmacologically active 5-aminopropyl(idene)-substituted 5*H*-dibenzo[a,d]cycloheptenes using force field



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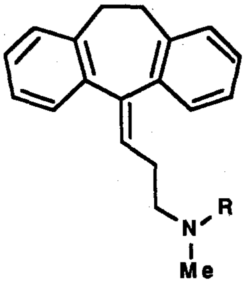
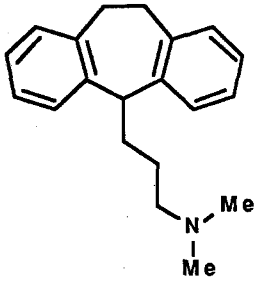


2 R= Me
2a R= H



3

calculations [1], we wish now to report results using the *LIS* technique. A quantitative evaluation of the lanthanide induced shifts should allow to check the force field results: in an optimal case for an independent confirmation, in a less favourable case it should be at least possible to check the compatibility (or non-compatibility) of the results of both methods.

The compounds chosen for this task were 5-(3-N,N-dimethylaminopropyl)-5*H*-dibenzo[a,d]cycloheptene (**1**), 5-(3-N,N-dimethyl- and 5-(3-N-methylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (**2**, **2a**), and 5-(3-N,N-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[a,d]cycloheptene (**3**). This series comprises a row of compounds with an identical carbon skeleton, but different degrees of flexibility of either the cyclic system or the aminopropyl(idene) side chain: rigid ring system and totally flexible side chain in **1**, flexible cycloheptene ring but partially rigid (aminopropylidene) side chain in **2**, both flexible dibenzocycloheptene unit and aminopropyl side chain moiety in **3**.

On the one hand, the *LIS* simulation should allow to collect information on the conformations of the substrates in solution, on the other hand a comparison of the complexing behaviour within the selected series of compounds with different degrees of flexibility should allow to gain insight in the limits of the method, especially for compounds where the coordination site is located within an open and therefore highly flexible chain.

Results and Discussion

General Considerations

Some aspects of the problems in the *LIS* simulation of conformer mixtures were already discussed in Ref. [2], where the complexing site was a hydroxyl or keto group attached directly at position 5 of closely related dibenzoheptene derivatives. For these cases mixing of two sets of coordinates was necessary in the *LIS* calculation. However, the treatment of the present molecules needs at least a set of 4 conformers to be mixed for the simulation of the experimentally obtained time averaged *LIS* values.

The *LIS* program designed for this special task follows still the ideas of the program *PDIGM* [3–5], e.g. the use of a Cartesian coordinate system for the substrate geometries with the coordinating atom in the origin, the polar coordinates for the lanthanide position search routine and the *R*-factor as a measure for the quality of the fit. However, some proper modifications allow to mix systematically the geometrical factors of up to four conformers in desired increments between 0 and 100% population. For all these substrate compositions the Eu(III) position may be optimized in the usual manner. One important assumption was made concerning the relative position of the lanthanide ion for the different conformers: we presumed that the bond parameters (bond distance, bond angle, torsional angle) of the Eu(III) coordination is equal for all populated conformers. A consequence of this assumption is that one relative Eu(III) position is valid for all conformers of a particular structure. In general, this is reasonable for molecules, where the coordination takes place at a part of the molecule which is of equal (or at least very similar) local geometry for all conformers. In our case the coordination site is located in an aliphatic side chain and changes in the somewhat distant part of the molecule should not change too much the coordination geometry in the vicinity of the amino nitrogen (therefore identical C2′ − C3′ − N ··· Eu arrangement).

The following computational sequence was applied: (i) calculation of geometrical factors for 1 − 4 conformers for a particular Eu(III) position (equal for all conformers), (ii) weighted mixture of the geometrical factors of corresponding atom positions of the conformers (conformer mixing), then, (iii) scaling the calculated (mixed) geometrical factors against the experimental data, and (iv) characterization of the quality of the fit by the *R*-factor. The lanthanide ion position and the weights for the geometrical factors corresponding to the population of conformers were systematically changed to find the best fit (minimal *R*-factor). For n conformers $4+(n-1)$ adjustable parameters have to be optimized in the calculation.

In the case of compound **2** with four diastereomeric conformers taking part in the conformational equilibrium this means seven parameters: three for the lanthanide ion position, one scaling factor of the geometrical factors (or magnetic field strengths) to the experimental *LIS*, and three population ratios for the four component mixture. Since we can rely on 14 different experimental *LIS* values for compounds **2** and **2a**, the conditions for a reliable *LIS* analysis are good.

Molecules with enantiomeric conformers in equilibrium (e.g. **1** and **3**) present a special problem, because a 1 : 1 enantiomeric mixture leads (on the NMR time scale) to an average overall mirror symmetrical species resulting in sets of magnetically equivalent protons. The most practical way to account for enantiomeric 1 : 1 conformer mixtures is the averaging of corresponding geometrical factors of symmetry equivalent proton positions before scaling to the experimental *LIS* data. Then the calculated *LIS* values are equal for both of the possible enantiomers and only one of the two possible enantiomeric geometries is needed in the input. *Note: care has to been taken to mix proper enantiomers interchanging with each other in solution.* In other words, only interchanging conformations can be mixed (e.g. conformers **A** and **B**, but not **A** with the enantiomer **B′**; this sounds trivial, however, careful checking of graphical presentations for all force field derived coordinate sets with three dimensional models is recommended).

Using the procedure outlined above, our program is able to handle a maximum of 4 enantiomeric pairs (corresponding to actually 8 different conformers; e.g. compound **3**).

In the *LIS* calculation of compound **3** nine different experimental *LIS* values can be used for the determination of seven adjustable parameters necessary for a maximum of four enantiomeric pairs. The presence of enantiomeric structures does of course not increase the number of adjustable parameters (due to the known 1 : 1 ratio of enantiomers), but it decreases the number of independent observables. However, 9 observables for 7 parameters is still reasonable.

The overall symmetrical compound **1** presents no problem at all, since 8 observables are available for a simple 4 parameter *LIS* calculation (no population ratios are needed in this case).

For all *LIS* calculations the geometries derived from the force field calculations [1] were used. Prior to the calculation of *LIS* values all molecules were reorientated in a way to put the coordinating N atom in the origin of a Cartesian coordinate system, the C3′ atom along the negative z-axis and C2′ in the x-z plane. Due to this coordinate transformations the calculated Eu(III) ion positions remain directly comparable for all molecules and the polar coordinates of the lanthanide ion position obtained in the calculation present then the distance, the bond angle, and the torsional angle of the Eu – N – C3′ – C2′ sequence. Inspection of Table 1 (footnotes e – g) shows that the calculated Eu(III) positions are indeed very similar for compounds **1** – **3**. This is rather reasonable for the almost identical topology in the close vicinity of the coordination sites of these molecules. The *LIS* data of the C3′-methylene protons were not used in the calculation, since these protons may be influenced by through-bond contact shifts in addition to the calculated paramag-

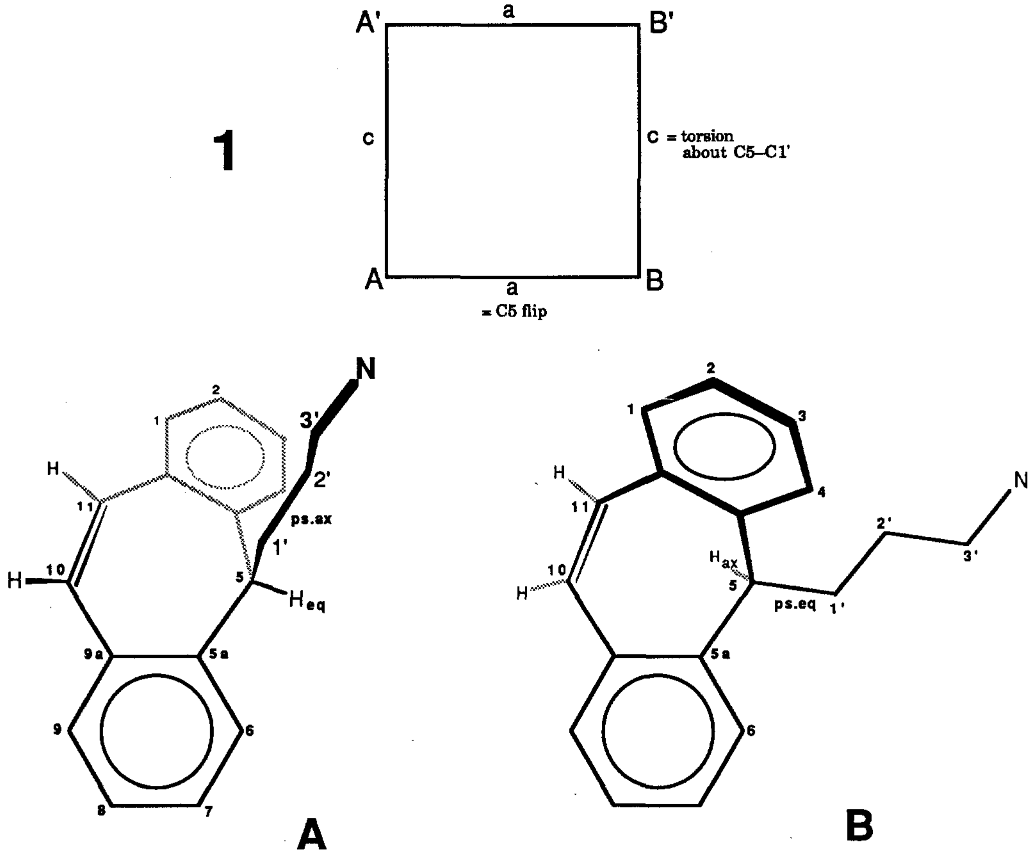


Fig. 1. Interconversion scheme for compound **1**

netic through-space pseudocontact shifts, which are proportional to the magnetic field strengths of a point dipole formulated in the MacConnell-Robertson equation.

Compound 1

Molecule **1** is characterized by a rigid boat-like conformation of the 5-*H*-dibenzo[a,d]cycloheptene system and a totally flexible 3-aminopropyl side chain. The conformers with either pseudo-axial (**A**) or pseudo-equatorial (**B**) side chain (Fig. 1) do not interconvert at room temperature, the energetically favoured isomer obtained in the synthesis is the axial one (**A**:**B** in synthesis 85:15%; **A**:**B** ratio obtained in force field calculation 97:3 [1]). The two possible enantiomeric conformations of the axial main isomer (**A**/**A**′) lead to an *averaged* molecular structure on the *NMR time scale*, (of apparent average C2 symmetry) with four different aromatic and one olefinic resonance in the dibenzoheptene system. These *LIS* values, together with the benzylic 5-H and amine side chain were used in the *LIS* simulation.

Since the rigid geometry of the dibenzocycloheptene moiety is known we can concentrate on the conformational possibilities of the flexible side chain bearing the coordination site. In fact, compound **1** represents an excellent model for the treatment of the side chain problem. The axially orientated side chain at C5 may be attached in three possible staggered conformations (by rotation about the C5-C1′ bond): either away from the ring systems (two enantiomeric structures causing the apparent C2 symmetry on the averaging NMR time scale, α and β in [1]) or direction of the side chain towards the ring system (which is energetically disfavoured by at least 16 kJ/mol, γ in [1]). The enantiomeric α and β families [1] can be easily simulated in one substrate geometry by proper averaging of geometrical factors in the *LIS* simulation (vide supra). The force field calculations indicate that a number of side chain conformations should be populated within the α (or the enantiomeric β) family: taking into account the whole α family, the torsion about C1′ – C2′ is still predominantly antiperiplanar (a), the following torsion C2′ – C3′ may be anti or gauche (g^- and g^+ [1]), the same is true for the torsion C3′ – N (however, this is already irrelevant for the *LIS* method, since the lone pair of nitrogen orients itself anyhow in an optimal torsion to coordinate the bulky shift reagent molecule).

Let us summarise the geometrical conditions for the *LIS* calculation of **1**: (i) "rigid" three ring system, (ii) only one pseudo-axial position for the attachment of C1′ (staggered and away from the ring system), (iii) a mixture of possible conformers with regard to torsion about C1′-C2′ and C2′-C3′: aa (27% anti-anti population in the force field calculation), ag^- (22% ff), g^+g^+ (13% ff), and ag^+ (11% ff) (the further minor conformers [1] need not to be considered in the *LIS* treatment).

A *LIS* calculation using the force-field distribution of 27:22:13:11 for the conformers aa : ag^- : g^+g^+ : ag^+ results in a terrible fit with an *R*-factor of 20.5% ($R < 5\%$ is good, 5 – 8% reasonable, $R > 10\%$ indicates wrong assumptions concerning the substrate or the complex simulation). However, checking the single conformers reveals an interesting result: for conformation aa in the side chain (torsion about C1′ – C2′ and C2′ – C3′) an *R*-factor of 1.98% was obtained, $R = 30\%$ for ag^-, $R = 33\%$ for g^+g^+, and $R = 36\%$ for ag^+. The only conclusion can be that in the complex only the all antiperiplanar structure is of importance.

This is not really surprising because the shift reagents are principally rather space demanding and a good complexation is only possible in a non-gauche arrangement in the close vicinity of the coordinating site. The conformation in an open chain may either be changed during complexation (the energy differences of the tested conformers are within 2 kJ/mol [1]) or the unfavourable conformations have simply a lower complex formation constant.

An important conclusion is that in similar cases – with the coordinating site attached to an open chain – a simple zig-zag geometry is a good approach for a successful *LIS* simulation (Ref. [7]). Another consequence is of course that no results concerning the conformation of the open chain part of the substrate itself can be expected. However, the topology of more distant parts of the molecule should not be affected and a conformational analysis is possible; this can be confirmed by characteristic coupling constants which do not change upon the addition of shift reagent.

The best fit for compound **1** was obtained for a population mixture $aa:ag^-:g^+g^+:ag^+ = 90:5:0:5\%$ ($R = 1.85\%$). It is interesting to note that g^+g^+

Table 1. Experimental and calculated lanthanide induced shifts of **1**–**3** [Eu(*fod*)$_3$, $\Delta\delta$/ppm, extrapolated to the 1 : 1 complex]

No.	**1** exp.	calc.	**2** exp.	calc.	**2 a** exp.	calc.	**3** exp.	calc.
1-H	1.35	1.41	1.63	1.58	1.75	1.78	1.26	1.35
2-H	1.11	1.20	1.55	1.44	1.75	1.70	1.08	1.18
3-H	1.56	1.51	1.94	1.81	2.35	2.08	1.26	1.54
4-H	2.40	2.58	4.00	3.86	4.62	4.34	2.70	2.88
5-H	3.96	4.08	–	–	–	–	4.00	3.80
6-H	2.40	2.58	1.90	2.15	2.00	2.29	2.70	2.88
7-H	1.56	1.51	0.77	0.87	0.70	0.85	1.26	1.54
8-H	1.11	1.20	0.60	0.61	0.60	0.58	1.08	1.18
9-H	1.35	1.41	0.70	0.74	0.70	0.72	1.26	1.35
10-H	1.74	1.86	1.25[a]	1.25	1.30[a]	1.31	2.00[c]	2.14
			1.25[b]	1.04	1.30[b]	1.00	1.55[d]	1.67
11-H	1.74	1.86	2.84[a]	3.22	3.20[a]	3.44	2.00[c]	2.14
			1.86[b]	1.62	1.95[b]	1.70	1.55[d]	1.67
1′-H	5.73	5.68	5.10	5.19	6.00	5.76	5.75	5.61
2′-H	12.3	12.22	12.2	12.14	14.0	14.16	12.6	12.55
3′-H	21.0	–	21.0	–	23.0	–	22.0	–
R	1.98%[e]		4.18%[f]		4.49 %[f]		3.15%[g]	

[a] axial

[b] equatorial

[c] closer to N 15 (and Eu)

[d] farther from N 15 (and Eu)

[e] Two enantiomeric conformers for the axial isomer (A/A′), Eu(III) position: $d = 2.8$ Å, $\rho = 130°$, $\varphi = 14°$ (bond distance, bond angle and torsional angle of the bond sequence Eu(III) – N – C3′ – C2′)

[f] 80 : 20% mixture of the two diastereomeric conformers **A** : **B**, Eu(III) position for both conformers: $d = 2.8$ Å, $\rho = 130°$ (**2**) and 125° (**2 a**), $\varphi = 27°$ (the *LIS* fit is not improved by adding **C** and **D** in the *LIS* simulation)

[g] 30 : 0 : 50 : 20% mixture of the enantiomeric pairs **A**/**A′** : **B**/**B′** : **C**/**C′** : **D**/**D′**, Eu(III) position: $d = 2.8$ Å, $\rho = 125°$, $\varphi = 30°$ for all conformers

does not take part in the fit at all and that ag$^-$ and ag$^+$ are equally populated with only 5% each, the combination ag$^-$/ag$^+$ giving again an "average" aa-conformation (g$^-$ counterbalanced by g$^+$). This "positional averaging" is frequently used in *LIS* simulations of the time averaged complex geometries (e.g. for the "average" position of the three protons of a methyl group at the center of the actual ones [5]). However, the participation of the ag$^-$/ag$^+$-conformers is not

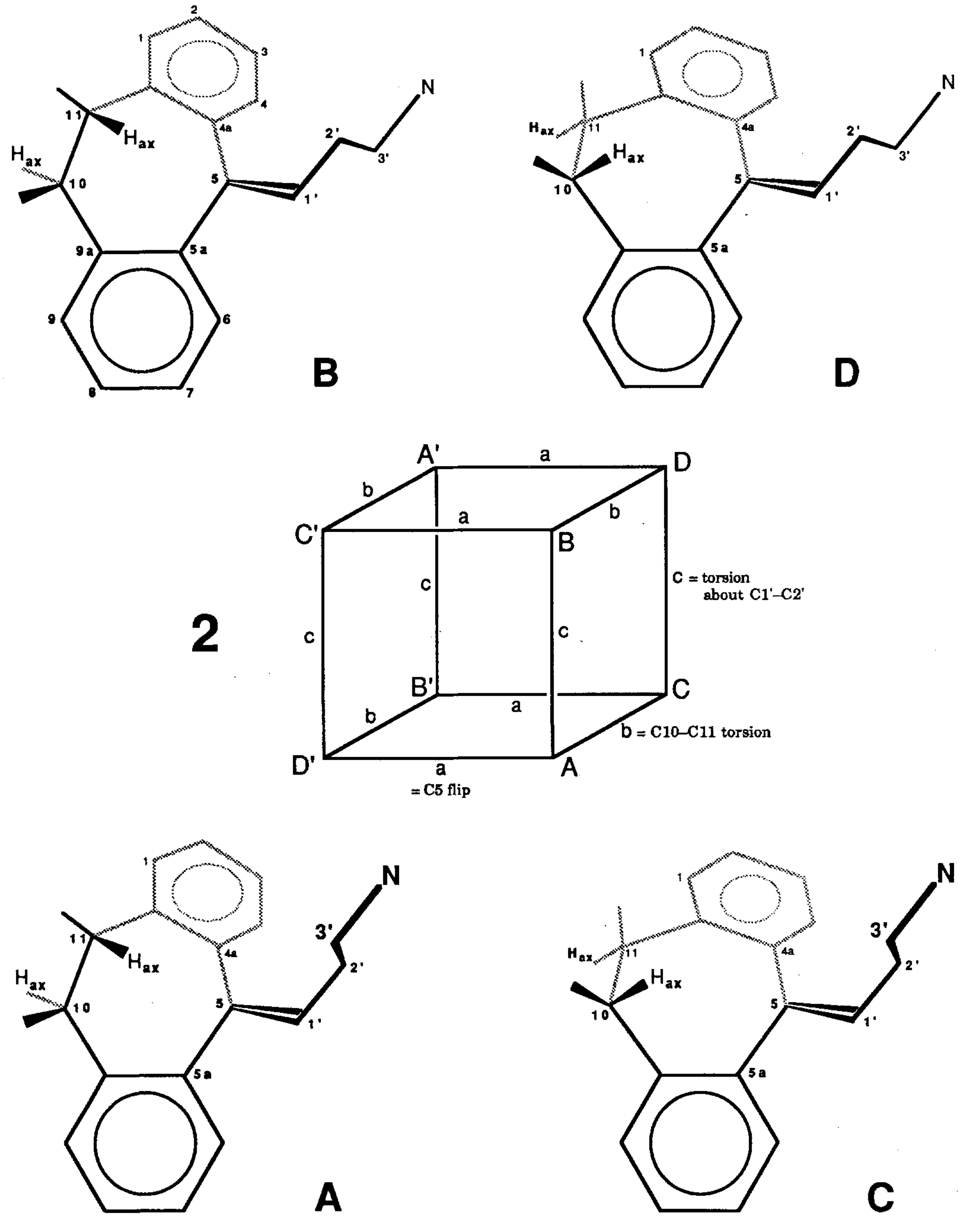


Fig. 2. Interconversion scheme for compound 2

essential for the outcome of the calculation, and the improvement from $R = 1.98\%$ to 1.85% with the introduction of two further conformers (and therefore two further variables) is neither significant nor necessary. For all similar cases a plain zig-zag all antiperiplanar conformation can be recommended.

Table 1 lists therefore the data for a simple aa-chain as shown in the schematical presentation of Fig. 1. Additionally it should be mentioned that the *LIS* assignments of the aromatic protons agree perfect with the coupling patterns of the resonances (two d and two t with respect to *ortho* couplings). The smallest lanthanide induced shift is exhibited by the protons at position 2 and 8. These protons are far from the Eu(III) ion, and the angle N-Eu ··· H is relatively large [3 – 5]. As important results derived from compound **1** we know now the approximate lanthanide ion position and the conformational behaviour of the saturated aminopropyl side chain for this type of dibenzocycloheptene complexes. This information will be essential for the more complicated interconversion system of compound **3**, but a comparison of relative lanthanide positions will be of interest for the closely related aminopropylidene side chain of compounds **2** as well.

Compounds **2** *and* **2 a**

For the exo-olefinic compounds **2** (dimethylated N) and **2 a** (monomethylated N) the energetic situation is more complex. In principle eight types of diastereomeric conformers may play an important role in solution (**A** – **D** and the enantiomers **A′** – **D′**, see Fig. 2). For the *LIS* calculation we can rely on eight different aromatic *LIS* values in addition to four different values for the dimethylene bridge and two further values for protons along the amine side chain (Table 1). This amounts to 14 usable values for the *LIS* calculation, which is rather good. On the other hand, unfortunately, no independent assignments of the aromatic resonances was possible. So this assignment must be done in the course of the *LIS* simulation which means testing of different combinations of proton positions and corresponding *LIS* data; however, the correct *LIS* assignments for **1** are promising for the reliability of the method. This confidence is further supported by the independent assignments of the C10-C11 dimethylene bridge protons. Decoupling experiments of the resonances of the dimethylene bridge allow to identify two clearly axial ($J_{ax/ax} = 13.5$ Hz) and two clearly equatorial protons ($J_{ax/eq} = 3.5$ Hz, $J_{eq/eq} = 6.5$ Hz) connected to C10 and C11 (straightforward assignment to either C10 or C11 was not possible). This independent information (assignment of *LIS* values to either axial or equatorial protons) is fully compatible with the final *LIS* results concerning the bridge protons. The *LIS* assignments additionally allow to identify the C11 ax/eq pair (in formula A of Fig. 2 closer to the coordinating function and therefore large *LIS* value for 11-H_{ax} and small value for the more distant 11-H_{eq} proton) and the C10 ax/eq pair (generally smaller *LIS* values for 10-H_{ax} and 10-H_{eq}; compare Table 1).

The essentially axial or equatorial character of the bridge protons is of great importance in the further reasoning, because it can only be explained by the fact that the dimethylene bridge has a clearly favoured conformation for *all conformers* taking part in possible interconversions in solution. A mixture of conformers due to bridge flipping (interconversion type b in Fig. 2) would necessarily lead to averaged vicinal coupling constants with values somewhere between ax – ax and ax – eq/eq – eq type coupling.

Model considerations concerning the topology of compounds **2** reveal a multitude of possible conformers interconverting either by "C5 flip" (transition a in Fig. 2), "C10/11 flip" (b) or torsion of single bonds within the aliphatic side chain (c). The conformers with reasonable energy (force field calculations Ref. [1]) are all characterized by an arrangement, where C3′ is non-planar with the olefinic moiety around C5 = C1′. C3′ might either be placed "above" (**A**, **C**) or "below" the olefinic plane (**B**, **D**). Together with two different torsional possibilities within the C10/C11 dimethylene bridge one obtains 4 families of conformers which differ only with respect to the torsion about the C2′ – C3′ and the C3′ – N bond: type **A** with 11-H_{ax} *endo* (relative to the double bond) and C3′ *endo* (relative to the dimethylene bridge; compare the schematic presentation in Fig. 2), type **B** with 11-H_{ax} *endo* and C3′ *exo*, type **C** with 11-H_{ax} *exo* (10-H_{ax} *endo*) and C3′ *endo*, and type **D** with 11-H_{ax} *exo* (10-H_{ax} *endo*) and C3′ *exo*. In the force field calculations the conformer with the lowest energy turned out to be of type **A** with g^-g^+ for the torsions about C2′ – C3′ (g^-) and C3′ – N (g^+). For the *LIS* simulation the torsion C3′ – N is not relevant (compare discussion for compound **1**). The **A**-conformer of **2** with a gauche$^-$ torsion for C1′-C2′-C3′-N (**2** **A** g^-) was checked in preliminary calculations and gave a terrible fit of $R = 47\%$. Using an antiperiplanar arrangement for C1′ – C2′ – C3′ – N (conformer **2** **A** a) lowered the *R*-factor to 6.58%. This indicates again that any gauche conformation close to the coordinating site is unrealistic for the complex, which is of course not necessarily true for the substrate itself (compare **1**). In the *LIS* calculations we used therefore the force field geometries for **A**, **B**, **C**,and **D** species with an antiperiplanar arrangement for C1′ – C2′ – C3′ – N (compare Fig. 2).

In the final *LIS* calculation the populations of all four possible diastereomeric conformers (**A** + **B** + **C** + **D**) were varied from 0 – 100%. In addition, the lanthanide ion position was allowed to move within reasonable limits (as a reasonable restriction the geometry of the C2′ – C3′ – N ··· Eu element was considered to be the same for all conformers; see the paragraph General Considerations). The best fit for both compounds **2** and **2 a** was obtained by mixing **A** : **B** : **C** : **D** in a population ratio of 80 : 20 : 0 : 0% ($R = 4.18$ for **2** and 4.39 for **2 a**). The absence of the conformers **C** and **D** is fully compatible with the measured coupling constants of the protons of the dimethylene bridge: participation of the dimethylene bridge flipped **C** and **D** conformers would result in averaged coupling constants and would disagree with the experimental (rather high) J_{ax-ax} value of 13.5 Hz. However, the force field calculations [1] suggest a population ratio of **A**:**B**:**C**:**D** = 50 : 25 : 20 : 5% indicating that at least some of the **C** type and traces of **D** type conformations might be present in the conformational equilibrium. From the coupling data and the *LIS* results a participation in the range of 20% for the **C**/**D** dimethylene bridge geometry seems rather high, however a population in the range of 10% cannot be excluded by the experimental methods used. Inspection of the *R*-factors in the vicinity of the absolute *R*-factor minimum suggests a possible deviation of ± 10% for the calculated populations and a small decrease in a purely ax – ax coupling would not be detectable either. The *R*-factors for the force field derived populations **A** : **B** : **C** : **D** = 50 : 25 : 20 : 5 are still reasonable (5.24% for **2** and 6.03% for **2 a**) but already significantly worse compared to a population of 80 : 20 : 0 : 0 giving the best *LIS* fit (Table 1).

As a result of the conformational analysis by the combination of force field, *LIS* and NMR spectroscopic evidence we can state that conformer **A** is the predominant one, that conformer **B** is still of importance and that components **C** and **D** might be present as minor components only.

Some further special features of the *LIS* calculation of compounds **2** should also be mentioned:

(i) In the discussion we have always used conformers **A/B/C/D**. Of course the enantiomeric conformers **A′/B′/C′/D′** are present at equal populations but there is no necessity for a special treatment in the *LIS* calculation.

(ii) If the assignment of the 10-H and 11-H *LIS* data is reversed, with 10-H_{ax} assigned to the larges shift value and 10-H_{eq} to the smallest one (comp. Table 1 for 11-H_{ax} and 11-H_{eq}) conformations **C/D** (population 80/20%) would be favoured over **A/B** (0/0%). However, since the *R*-factors are then significantly worse ($R=6.2$ for **2** and $R=6.8\%$ for **2a**) compared to the other solution and the result is not compatible at all with the force field calculations, this solution can be rejected.

(iii) A further *LIS* calculation using the planar zig-zag arrangement for all side chain atoms $C5=C1'-C2'-C3'-N$ (γ-conformer in [1]) reflects again the problems encountered with flexible side chains. In both actually present conformers **A** and **B** the $C3'-N$ is rotated out of the plane of the olefinic double bond, either up or down from a planar arrangement. If one substitutes this mixture of *two* out of plane conformations by *one* average planar (all antiperiplanar) conformation, one observes that the *LIS* fit becomes very good too. The *R*-factors for the simple all-antiperiplanar geometry are $R=3.95\%$ for **2** and $R=4.21\%$ for **2a**, even better than the *R*-factor of the (more realistic) mixture. This planar conformation corresponds to the already mentioned "positional averaging" of corresponding protons of two out of plane conformations; compare also the discussion for compound **1**. However, there is an essential difference between all-periplanar average geometries for a saturated chain (**1** and **3**) and a chain with a double bond (**2**, **2a**): in the former case an aaa arrangement represents a prominent energetically favourable minimum geometry, in the latter case the all-planar geometry is always energetically disfavoured [1, 7] and the good fit is the product of the artificial positional averaging of the side chain coordinates of conformers **A/B**. As a consequence of this behaviour one must accept that the *LIS* calculations alone may be misinterpreted with respect to the chain moiety (the correct geometry for the dibenzocycloheptene moiety remains unaffected), giving average structures instead of two (or more) conformers. The *LIS* results in combination with the force field geometries and energy values, together with the conclusions to be drawn from the undoped NMR spectra, however, give altogether a consistent and reliable picture of the conformer equilibria of componds **2** and **2a** in solution.

Compound 3

In compound **3** no double bond contributes to the rigidity of the system. From the undoped NMR spectrum one can derive that the flip of the $C10-C11$ dimethylene bridge (interconversion b in Fig. 3) and torsions about the single bonds (interconversion mode c) of the aliphatic side chain must have low barriers. These two interconversion modes lead – in a two step procedure – to the corresponding enantiomeric conformers (see Fig. 3). This is responsible for the time averaged symmetrical structure observed in the NMR spectrum: four different aromatic signals and two different resonances for the four dimethylene bridge protons. The latter ones occur as two somewhat broadened ddd for 2 H each at 3.24 and 2.90 ppm (pseudo q due to one geminal coupling of 16 Hz and two vicinal couplings of ca. 8 Hz). The two identical, averaged vicinal coupling constants originate from two vicinal protons in *cis* orientation *to each* other ($C10-H_{ax}+C11-H_{eq}$ or $C10-H_{eq}+C11-H_{ax}$), due to the allowed dimethylene bridge flipping and rotation about the $C5-C12$ bond. The proton pair with resonance at 3.3 ppm seems to be closer to the amino function of the C5 side chain (*LIS* value of 2.00, Tab. 1), the

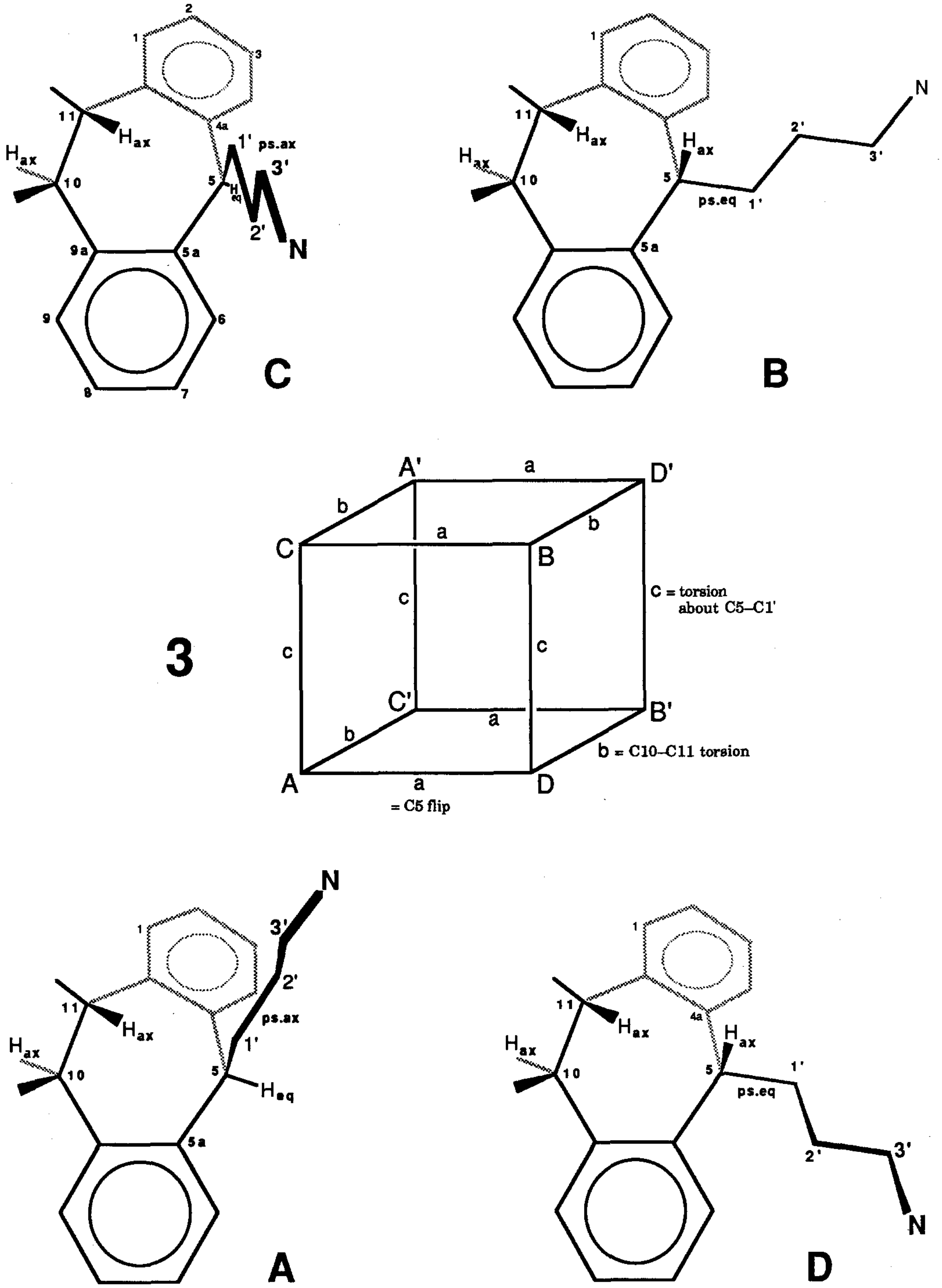


Fig. 3. Interconversion scheme for compound 3

other one at 3.0 ppm seems to be farther from the complexing nitrogen and the lanthanide ion in the chelate (*LIS* 1.55). However, the assignment to particular protons, either *cis* or *trans* relative *to the C5 side chain*, presents a problem. It depends on the orientation of the C5 side chain (either axial or equatorial or any mixture of both), which one of the two vicinal bridge proton pairs is closer or farther from the amino group (and the lanthanide ion): if the C5 side chain is pseudo-axial, the C10 and C11 protons *cis* relative to C1′ are closer, if the C5 side chain is equatorial, the other pair (*trans* relative to C1′) is closer. An important question in the conformational analysis of compound **3** is therefore presented by the C5 interconversion (mode a in Fig. 3). As a result of the force field calculation the interconversion barrier is low enough for a fast C5 flipping at room temperature (the path a between **A**/**C**/**A′**/**C′** and **B**/**D**/**B′**/**D′** is therefore open, see Fig. 3), on the other hand, due to the ground state energy, the conformer **A** with an axial C5 side chain should be favoured.

A – **D** describe again families of conformers. Within a family, the only difference is within the conformational possibilities of the flexible side chain, the torsions about C1′ – C2′, C2′ – C3′ (and C3′ – N which is not of importance for a *LIS* calculation). Force field calculations [1] show that all relevant conformers for **A** – **D** have an antiperiplanar arrangement for the C1′ – C2′ torsion, the C2′ – C3′ torsions of the low energy conformers are still dominantly of the antiperiplanar type although gauche$^-$ and gauche$^+$ are already of importance. However, in the *LIS* calculation only all-antiperiplanar side chains are reasonable (compare **1**). Especially in the case of molecule **3** this is a safe assumption, since the C1′ – C2′, C2′ – C3′ (a,a)-arrangements are anyhow the dominant ones and the remaining g$^-$/g$^+$ pairs (if at all present in the complex) will be subject to the already discussed "positional averaging". In the discussion of the lanthanide-induced shifts **A** – **D** denote therefore the all-antiperiplanar geometries of the **A** – **D** families: **A** with a pseudo-axial side chain and an all-antiperiplanar chain starting from C5 a (C5 a – C5 – C1′ – C2′ – C3′ – N), **B** with a pseudo-equatorial side chain starting from C5 a, **C** with a pseudo-axial side chain starting from C4 a (C4 a-C5-C1′-C2′-C3′-N all-antiperiplanar), and **D** with a pseudo-equatorial side chain starting from C4 a; compare the schematic presentation in Fig. 3).

In the *LIS* calculations all 8 possible conformers (4 enantiomeric pairs) were considered as potentially possible partners in an equilibrium in solution. The assignments of the four different aromatic *LIS* and the C5 and chain methylene proton *LIS* do not cause any problems. The crucial point is the assignment of the bridge methylene protons. There are two possibilities according to the considerations outlined above, leading to two possible optimal solutions of the *LIS* calculation:

(i) If the resonance at 3.3 ppm, giving the larger *LIS* value of 2.00, is assigned to the C10 – C11 proton pair *cis* to the C5-side chain, the corresponding solution favours the axial orientation of the C5 side chain. The substrate composition giving the absolute minimum with all possible adjustable parameters varied was **A** : **B** : **C** : **D** = 30 : 0 : 50 : 20% with an *R*-factor of 3.15%. Both important conformers **A** and **C** are characterized by an axial side chain at C5. This distribution of conformers agrees well with the force field calculation with respect to the preponderance of the axial configuration of the side chain (ax : eq *LIS* = 80 : 20, ax:eq FF = 68 : 32). The conformer ratio due to rotation about the C5 – C1′ bond, determining if the planar side chain starts from either C4 a or C5 a, is not well reproduced. Once again the conformational analysis of the open chain seems problematic, the outcome concerning the conformation at the ring system is much more reliable. However, the exact numerical values of the populations resulting from the

LIS calculations should be interpreted with caution for the present molecule **3**: deviations up to ± 10% give still reasonable *R*-factors in the *R* = 3.2% region (e.g. **A** : **B** : **C** : **D** = 35 : 20 : 35 : 10 with *R* = 3.29%). The force field derived population ratio of **A** : **B** : **C** : **D** = 57 : 24 : 11 : 8 [1] gives still a very good fit with *R* = 3.52%.

(ii) A second possible *LIS* solution may be obtained assigning the resonance at 3.0 ppm with the lower *LIS* value of 1.55 to the C10−C11 proton pair *cis* to the C5-side chain. This calculation favours conformer **B** with a pseudo-equatorial side chain at C5. The minimum mixture is **A** : **B** : **C** : **D** = 20 : 80 : 0 : 0 with an *R*-factor of 3.61%. This value is only slightly worse than the one obtained for (i) and without some other independent evidence no safe decision between (i) or (ii) would be possible. However, taking into account the force field results, this solution is most unlikely compared to the better *and* force field compatible fit (i). Additionally it should be mentioned that the force field distribution of **A** : **B** : **C** : **D** = 57 : 24 : 11 : 8 gives a significantly poorer fit with *R* = 4.62% for solution (ii) [compared with *R* = 3.52% for the approach (i)].

Conclusion

Compounds **1**, **2**/**2a**, and **3** exhibit an increasing flexibility of the ring and open chain moieties. Generally it turned out that a chain with flexible single bonds is best represented by an all-antiperiplanar geometry, especially if the complexing site is at the terminal atom. Hence conformational analysis of side chains bearing the coordination site is not possible. The *LIS* calculations encounter increasing difficulties within the series. For compounds **2** and especially for **3** (the most flexible molecule within the series) the *combination of* the theoretical force field method *and* the experimental proof by lanthanide induced shifts is essential to gain a reliable insight in the conformational possibilities of the molecules.

Experimental Part

NMR: Bruker AM 250 WB.

Compound **1** was purchased from Sigma. Compounds **2** and **3** were synthesized according to Refs. [8, 9].

Lanthanide-Induced Shifts. LIS values were determined by adding increasing amounts of Eu(*fod*)$_3$ (Merck) to a solution of ca. 10 mg of substrate in ca. 0.7 ml CDCl$_3$. The spectra were recorded at six different reagent concentrations up to a molar ratio of substrate : reagent = 1 : 0.75 allowing an accurate extrapolation to the ratio 1 : 1 (the so-called "1 : 1 complex"); these values are listed in Table 1.

For the *LIS* calculations a computer program CONF4 was written following the principles used in the program PDIGM [3, 4]. The options include input in either Cartesian or internal coordinates, proper rearrangement of the substrate coordinates within the Cartesian coordinate system, mixing of up to four conformations within variable limits and stepwise increments, and search for the optimal lanthanide ion position.

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