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^{1}H NMR Lanthanide-Induced Shift Investigations of Highly Flexible Molecules III: Applications to Alcohols, Aldehydes, Esters, and Amines[#]

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Summary. Two new methods (RANDOM-LIS and STEED-LIS) with random selection of up to ten dihedral angles were applied for the determination of preferred conformers of flexible molecules (alcohols, aldehydes, esters, and amines, respectively, with only one coordination site) by LIS studies. The results proved to be useful. The preferred complexation conformation was detected only in cases where conformational changes of the substrate took place to improve complexation to the LIS reagent. Force field calculations (RANDOM-PIMM) and Simple Hard Sphere Model calculations (RANDOM-SHSM and STEED-SHSM), using the same algorithm of randomly varying the dihedral angles, support the results obtained.

Keywords. Conformational analysis; LIS method; NMR spectroscopy.

^{1}H-NMR-LIS-Untersuchung leicht beweglicher organischer Verbindungen, 3. Mitt. Anwendung der Methode auf Alkohole, Aldehyde, Ester und Amine

Zusammenfassung. Zwei neue Methoden zur Bestimmung von Vorzugskonformeren leicht beweglicher Moleküle mit Hilfe lanthaniden-induzierter chemischer Verschiebungen (RANDOM-LIS und STEED-LIS mit Zufallsauswahl von bis zu 10 Diederwinkeln) werden auf unterschiedliche Substanzklassen mit nur einem potentiellen Koordinationszentrum (Alkohole, Aldehyde, Ester, Amine) angewandt. Die Ergebnisse der Konformationsanalyse stimmen mit der Literatur gut überein; Abweichungen werden unter Beachtung von Konformationsänderungen bei der Komplexierung der Substrate an das LIS-Reagens verständlich. Kraftfeldberechnungen (RANDOM-PIMM) und Berechnungen nach dem Simple Hard Sphere Model (RANDOM-SHSM und STEED-SHSM) unter ebensolcher Nutzung der Zufallsauswahl der Diederwinkel führen zu nahezu identischen Vorzugskonformeren.

Introduction

Lanthanide-induced Shift (LIS) calculations are difficult for highly flexible molecules containing more than one variable dihedral angle. To apply methods which

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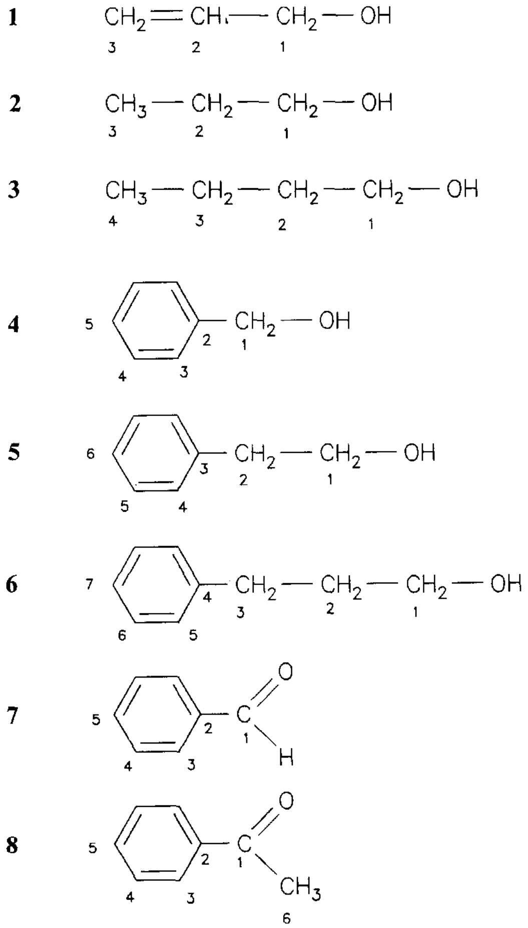
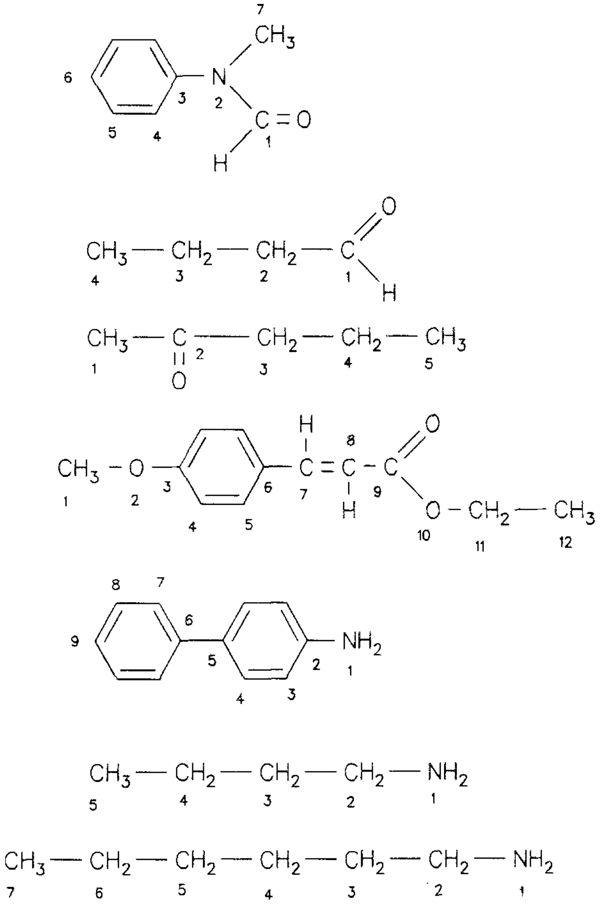
[#] For parts I and II, see Refs. [1] and [2] incrementally vary the dihedral angles is nearly impossible owing to the potentially increasing number of necessary calculations with increasing number of dihedral angles to change. Therefore, two recently developed new methods, RANDOM-LIS [1] and STEED-LIS [2], both using randomly generated structures for the LIS calculations using the PDIGM algorithm [3] were applied. Whereas RANDOM-LIS leads to a more statistical distribution of data points in comparison with an incremental change of dihedral angles (leaving the data density unchanged, however), STEED-LIS uses a random start structure but then searches for a better fit between experimental and calculated LIS values (with the *R* factor of coincidence between experimental and calculated results as the criterion [4]) by changing the given torsional angles of the start structure in small increments in order to find the 'steepest descent' on the '*R* factor hyper surface' to the local (or global) minimum. In addition, both force field calculations (RANDOM-PIMM [1, 5]) and Simple Hard Sphere Model (SHSM) calculations (RANDOM- and STEED-SHSM [6, 7]) were carried out employing the same algorithm of randomly varying the dihedral angles of the flexible molecules studied.

Results and Discussion

The compounds investigated in order to find the preferred conformer by the mentioned LIS calculations are summarized in Scheme 1. The compounds treated



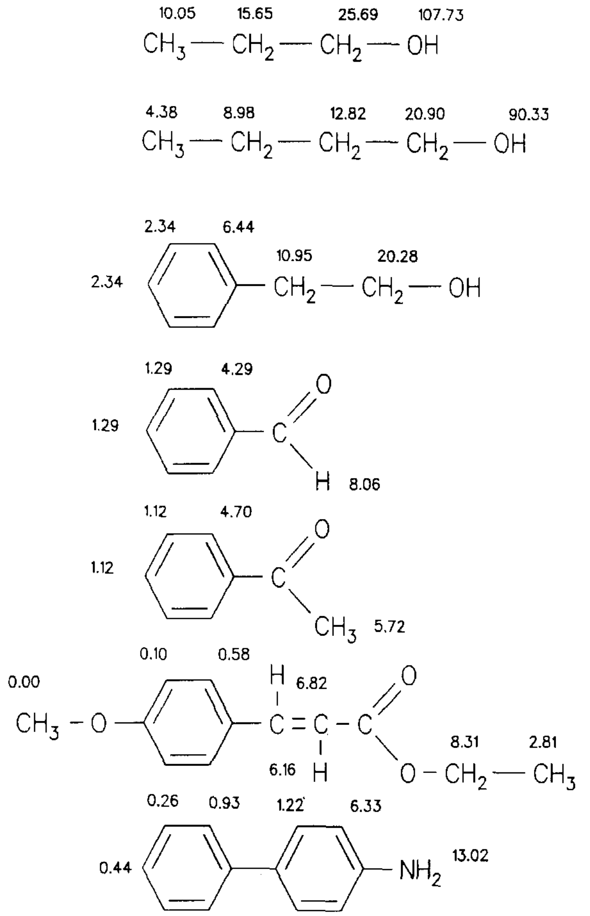


Scheme 1. Studied compounds (including numbering used for definition of dihedral angles in Table 1)

by the LIS method within this paper are given in Scheme 2 (the experimental ^{1}H NMR LIS values are also given); the ^{1}H LIS values of compounds **1**, **4**, **6**, **9**, **10**, **11**, **14**, and **15** used for the calculations were taken from Ref. [8].

The results obtained by the different methods of LIS calculation are in most cases very similar and ingenious except for those compounds where conformational changes due to the complexation with the LIS reagent Eu(*fod*)$_3$ have to be assumed. In Table 1, the dihedral angles calculated along with the different methods applied are summarized. The calculations result in a set of preferred conformers; only the one of lowest energy is given in Table 1. Because both the conformational equilibrium of the flexible molecules studied and the equilibrium *substrate* + *LIS reagent* ⇄ *substrate*∗*LIS reagent* are fast on the NMR time scale, only this preferred conformer, the so-called *preferred complexational conformer* of the compounds studied, will be further discussed; information about the exact position of present conformational equilibrium is, unfortunately, out of the scope of the methods applied.

For the alcohols **1** to **6**, good agreement between the preferred conformers using the different methods could be obtained. Figure 1 shows the resulting structures of the STEED-LIS calculations. In all cases where coupling constants could be determined (**2**, **3**, and **5**) no changes of $^3J_{\mathrm{H,H}}$ couplings were observable along with



Scheme 2. Experimentally obtained LIS values; ^1H NMR LIS values of the compounds **1**, **4**, **6**, **9**, **10**, **11**, **14**, and **15**, used for the calculations, were taken from Ref. [8]

Table 1. Preferred conformations of compounds **1**–**15** as obtained by random variation of dihedral angles (RANDOM-LIS, RANDOM-SHSM, and RANDOM-PIMM) and by Steepest Descent Methods (STEED-LIS and STEED-SHSM)

	Dihedral angle (*cf.* Scheme 1)	Dihedral angle (°) as obtained by method:				
		STEED LIS	RANDOM LIS	STEED SHSM	RANDOM SHSM	RANDOM PIMM
1	C3–C2–C1–O	80	104	66	65	169
	C2–C1–O–H	–	–	183	177	186
	value[a]	0.001	0.014	48.6	48.6	−118.6
2	C3–C2–C1–O	181	181	181	181	176
	value[a]	0.139	0.140	67.8	67.9	−247.5
3	C4–C3–C2–C1	182	182	182	180	179
	C3–C2–C1–O	180	179	180	180	178
	C2–C1–O–H	–	–	180	–	300
	value[a]	0.130	0.130	89.3	89.3	−268.5

Table 1. (*Continued*)

	Dihedral angle (*cf.* Scheme 1)	Dihedral angle (°) as obtained by method:				
		STEED LIS	RANDOM LIS	STEED SHSM	RANDOM SHSM	RANDOM PIMM
4	C3–C2–C1–O	273	273	267	265	287
	C2–C1–O–H	–	–	287	291	301
	value[a]	0.013	0.013	102.4	102.4	−237.8
5	C4–C3–C2–C1	271	276	275	273	260
	C3–C2–C1–O	180	178	304	292	180
	C2–C1–O–H	–	–	292	–	179
	value[a]	0.119	0.120	123.2	123.3	−116.6
6	C5–C4–C3–C2	248	271	261	255	–[b]
	C4–C3–C2–C1	220	209	62	74	–[b]
	C3–C2–C1–O	269	190	287	187	–[b]
	C2–C1–O–H	–	–	300	177	–[b]
7	C3–C2–C1=O	91	92	–[c]	–[c]	180
	value[a]	0.050	0.064	–	–	−143.8
8	C3–C2–C1=O	97	87	–[c]	–[c]	38
	value[a]	0.118	0.126	–[c]	–[c]	−101.1
9	C4–C3–N–C1	81	32	–[c]	–[c]	158
	C3–N–C1=O	154	173	–[c]	–[c]	182
	value[a]	0.215	0.261	–	–	−9.2
10	C4–C3–C2–C1	181	180	181	177	190
	C3–C2–C1–H	2	2	101	103	109
	value[a]	0.102	0.102	74.1	74.2	−203.9
11	C4–C3–C2=O	180	176	162	269	–[b]
	C5–C4–C3–C2	180	181	182	174	–[b]
	value[a]	0.125	0.126	96.3	96.4	–[b]
12	C4–C3–O2–C1	104	102	–[c]	–[c]	51
	C8–C7–C6–C5	328	257	–[c]	–[c]	35
	O10–C9–C8–C7	121	235	–[c]	–[c]	54
	C11–O10–C9–C8	189	219	–[c]	–[c]	174
	C12–C11–O10–C9	175	170	–[c]	–[c]	183
	value[a]	0.049	0.077	–	–	−422.9
13	C7–C6–C5–C4	3	1	–[c]	–[c]	37
	value[a]	0.090	0.090	–[c]	–[c]	−173.4
14	C5–C4–C3–C1	180	185	181	190	–[b]
	C4–C3–C2–N	180	182	180	70	–[b]
	C3–C2–N–H	–	–	296	–	–[b]
	value[a]	0.060	0.060	94.9	95.1	–[b]
15	C7–C6–C5–C4	182	200	185	197	–[b]
	C6–C5–C4–C3	183	204	184	301	–[b]
	C5–C4–C3–C2	182	177	189	192	–[b]
	C4–C3–C2–N	180	183	300	75	–[b]
	C3–C2–N–H	–	–	302	–	–[b]
	value[a]	0.037	0.042	137.2	137.8	–[b]

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[a] Value: *R*-factor (for STEED-LIS and RANDOM-LIS), relative free energy of the conformation (STEED-SHSM and RANDOM-SHSM), heat of formation in kJ/mol (for RANDOM-PIMM);
[b] RANDOM-PIMM calculations not performed due to missing useful starting geometries;
[c] SHSM calculations not performed due to presence of π-systems extending over more than one bond

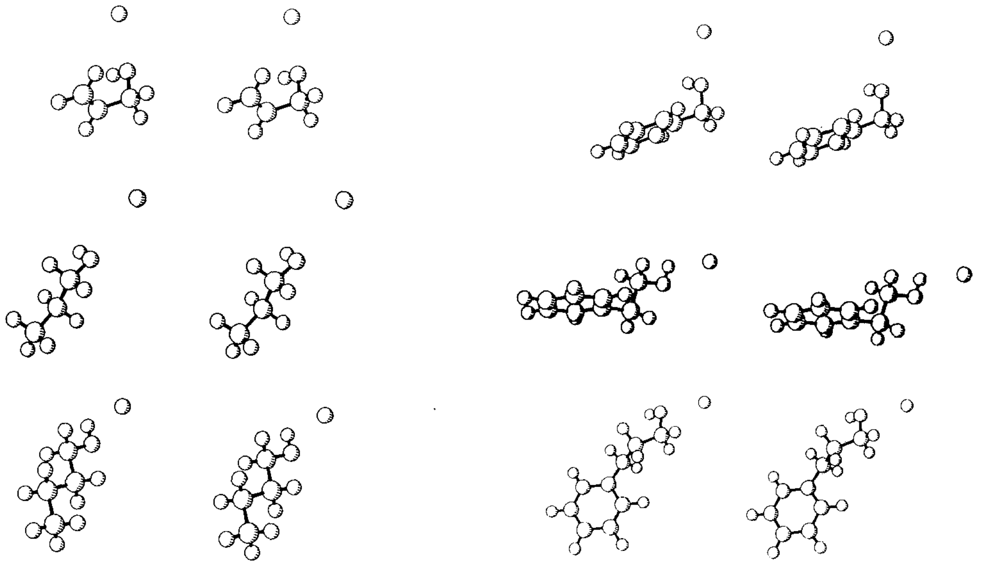

Fig. 1. Stereoplots of the preferred conformations of compounds **1**–**6** as obtained by STEED-LIS calculations (including the position of the europium atom)

the LIS study, *i.e.* for these compounds the calculated preferred conformers should be the same for both the non-complexed and the complexed flexible molecules. For allylalcohol **1**, the various calculations show that there is a small conformational change caused by the complexation to the LIS reagent (in the LIS complex, the OH group is nearly orthogonal to the CH_2=$CHCH_2$ plane; the SHSM and PIMM calculations result in *gauche* and *anti* conformations, respectively). For *n*-propanol (**2**) and *n*-butanol (**3**), the results expected were obtained by all applied methods; all C–C bonds therein are staggered and yield either antiperiplanar (*ca.* 180°) or (+)- or (−)-synclinal (*gauche*; *ca.* 60° or −60°) dihedral angle values. For benzylalcohol (**4**), the OH group is orthogonal to the benzene ring plane in the preferred conformer. In the case of 2-phenylethanol (**5**), the dihedral angle C4–C3–C2–C1 was determined to be 270° and the torsional angle C3–C2–C1–O to be 180° both by LIS and PIMM calculations. However, the SHSM calculations gave a value of 300° for the latter one; a possible reason could be the parameter set used for these calculations which probably cannot distinguish between this local and the global minimum for this compound. For 3-phenyl-*n*-propanol (**6**), the torsional angle C5–C4–C3–C2 was determined to be *ca.* 270°. The torsional angles C4–C3–C2–C1 and C3–C2–C1–O obtained from the LIS and the SHSM calculations are different. Whereas the SHSM calculation leads to the expected *gauche* and *anti* values of 60°, 180°, and 300°, respectively, the LIS values are different. Possible reasons could be too small differences of the minima values on the "LIS *R*-factor hypersurface" for the different conformations.

For compounds **7** to **12**, containing the C=O group as potential coordination site for the complexation with Eu(*fod*)$_3$, predominately similar results were obtained by the different methods. The results are summarized in Table 1. In Fig. 2 the minimum conformers of the STEED-LIS calculations are shown.

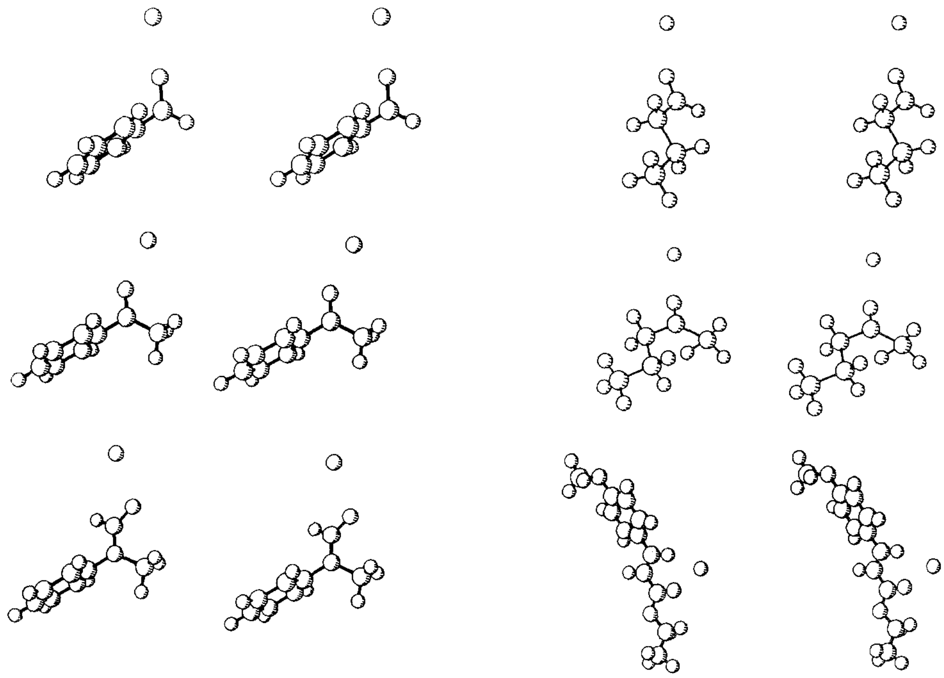

Fig. 2. Stereoplots of the preferred conformations of compounds **7**–**12** as obtained by STEED-LIS calculations (including the position of the europium atom)

For benzaldehyde (**7**) and acetophenone (**8**), the expected behaviour was observed: during complexation, the C=O group is twisted from the benzene plane to give the LIS reagent enough space for complexation. The RANDOM-PIMM calculations lead to the preferred conformer with the C=O group nearly *in-plane* with the benzene ring; in **8**, the $C(O)CH_3$ group is somewhat more twisted from the plane of the benzene ring because of the steric strain of the CH_3 group.

For N-methylformamide (**9**), the various results obtained are also different, obviously owing to probable conformational variations during complexation. In addition, this compound contains not only the C=O group but also a nitrogen atom which could also be involved in the complexational process. The calculations were carried out assuming only the oxygen of the carbonyl group as the coordination site for the LIS reagent.

In the case of butyraldehyde (**10**), all C–C bonds are staggered (*i.e.* the torsional angle C2–C3–C4–H is 60°, 180°, and 300°, respectively), and the dihedral angle C1–C2–C3–C4 is 180° as expected. The obtained values for the torsional angle H–C1–C2–C3 differ between *ca.* 0° obtained by LIS and *ca.* 100° obtained by molecular mechanics calculations. The possible reason for this result might be the space needed for a more effective complexation to Eu(*fod*)$_3$. In *n*-propyl-methyl-ketone (**11**), the dihedral angle C2–C3–C4–C5 calculated amounts to 180° (as expected), and the C–C bonds of the *n*-propyl chain are staggered and yield *gauche* conformations (60° and 300° were obtained). The torsional angle O=C2–C3–C4 was determined by LIS calculations to be *ca.* 180°, by SHSM calculations to be 270°. Again, the size of Eu(*fod*)$_3$ might be the reason for the difference. The minima obtained for ethyl *p*-methoxycinnamate (**12**) employing the LIS methods compared

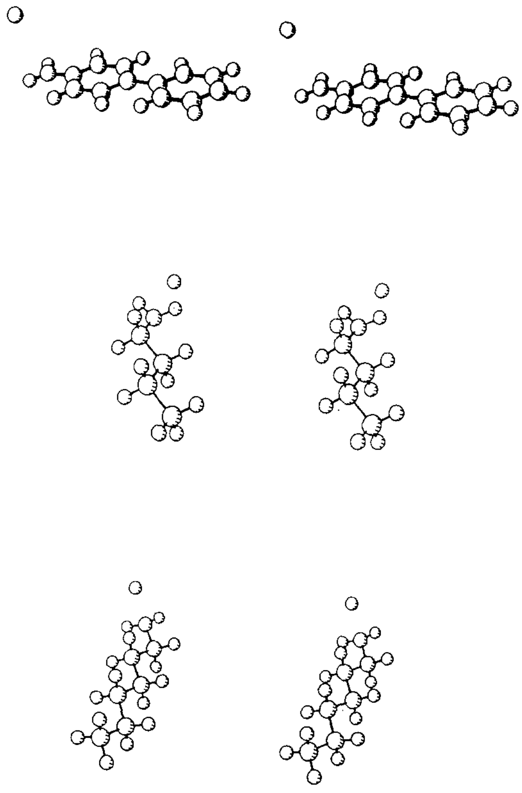

Fig. 3. Stereoplots of the preferred conformations of compounds **13**–**15** as obtained by STEED-LIS calculations (including the position of the europium atom)

to the minimum from RANDOM-PIMM are different; both torsional variations during complexation and the presence of three potential coordination sites for Eu(*fod*)$_3$ (only the carbonyl group was considered) are plausible reasons for this result.

The results of LIS and various other calculations for the amines **13** to **15** are also given in Table 1, and the preferred conformers obtained by STEED-LIS are shown in Fig. 3. For 4-aminobiphenyl (**13**), the expected structure was found in which the benzene rings are nearly coplanar. The results for *n*-butylamine (**14**) and *n*-hexylamine (**15**) are as follows: in both cases, the C–C bonds therein are staggered, and the torsional angles along the carbon skeleton are 180°, *i.e.* the alkyl chains prefer *all-trans* conformations.

Conclusions

The recently developed methods RANDOM-LIS and STEED-LIS proved to be useful tools especially in addition to molecular mechanics methods like PIMM and RANDOM-PIMM or geometrical estimation methods using the HILL function like RANDOM-SHSM and STEED-SHSM) to obtain information about the preferred conformers of highly flexible molecules containing more than one independently and freely rotating dihedral angle and only one potential coordination site (*e.g.* OH, C=O, or NH$_2$) for LIS investigations.

Experimental

Proton NMR Spectra were recorded on a BRUKER WP-200 NMR spectrometer operating at 200.13 MHz. The investigated compounds (*cf.* Scheme 2) were commercially available.

Lanthanide induced shifts

The LIS values were determined by adding increasing amounts of *tris*(1,1,1,2,2,3,3-hepta-fluoro-7,7-dimethyl-octane-4,6-dionato)europium(III) (Eu(*fod*)$_3$, Merck) to a solution of 5–10 mg of substrate in 0.5 ml of $CDCl_3$. The spectra were recorded at 6–14 different reagent concentrations up to a reagent:substrate molar ratio of 0.6; the LIS values for the 1:1 complexes were obtained by extrapolation. The LIS values of protons closer than three bonds to the coordination site of the substrate were not used for the LIS calculations in order to avoid the influence of possible through-bond contact shifts.

Computer programs

All programs are written in TURBO PASCAL 6.0 by Borland; the dialogue language of the programs is German. They require an IBM-compatible PC, the operating systems DR-DOS 5.0 (or higher) or MS-DOS 4.01 (or higher), a hard disk drive and $\geqslant 500$ kbyte free main memory. Additionally, the molecular mechanics calculations using RANDOM-PIMM require *ca.* 3 Mbyte of free storage capacity on the hard disk for saving temporary data files.

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