

Conformational Analysis of Thia Crown Ether Derivatives by NMR Spectroscopy and Molecular Mechanics Calculations[#]

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Summary. Addition of sulfur dichloride to tetrachlorocatechol-*bis*allylether (**1**) yields the 9- and 10-ring thia crown ether derivatives **2** and **3**, respectively, together with the dithia-18-crown-6-ether **4**. The 10-membered ring compound **3** represents the first thia macrocycle containing both *Markovnikov* and *anti-Markovnikov* constitution of the β -chloro-thio structural segments in the same molecule. By ¹H and ¹³C NMR spectroscopy, equal amounts of two preferred conformers of the only isolated diastereomer of **3** were observed at temperatures below -50°C . The signals were assigned to these conformers using COSY, HETCOR, and phase sensitive NOESY spectra at low temperatures. The preferred conformations and the relative configuration were determined using the different effects of γ_{gauche} - and γ_{anti} -positions in ¹³C NMR chemical shifts and analyzing vicinal $^3J_{\text{H,H}}$ coupling constants. These results were confirmed by molecular mechanics calculations.

Keywords. NMR; Thia crown ethers; Conformation; Molecular mechanics calculation.

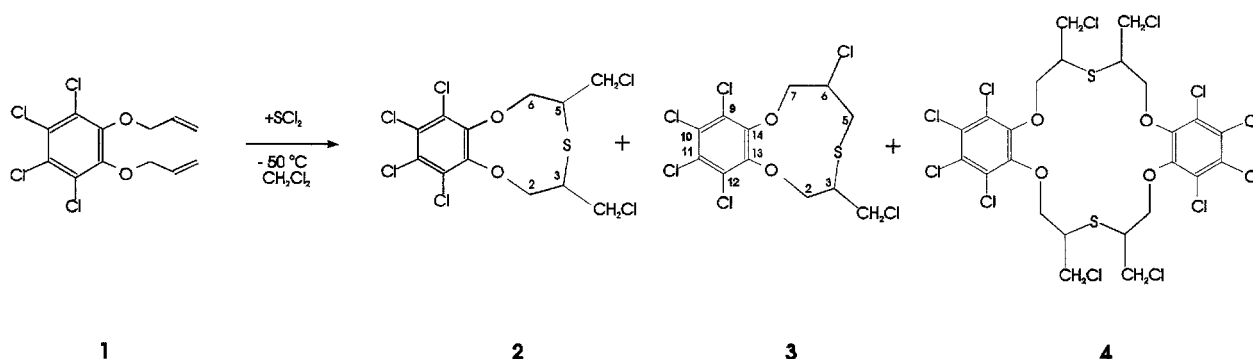
Konformationsanalyse von Thiakronenether-Derivaten mit Hilfe von NMR Spektroskopie und molekülmechanischen Berechnungen

Zusammenfassung. Aus Tetrachlorbrenzcatechin-*bis*allylether (**1**) und Schwefeldichlorid wurden neben der 1,10-Dithia-dibenzo-18-krone-6 **4** die 9- und 10-Ring-Derivate **2** und **3** erhalten. In der 10-Ring-Verbindung wurde erstmalig *Markovnikov*- und *anti-Markovnikov*-Konstitution der β -Chlorthio-Gruppierung in einem Thiamakrocyclus nebeneinander vorgefunden. Das isolierte Diastereomere von **3** zeigt bei Temperaturen unter -50°C zwei Konformere. Die Signalzuordnung war mit homo- und heteronuklearen COSY- sowie mit phasensensitiven NOESY-Spektren möglich. Mit Hilfe molekülmechanischer Rechnungen konnten aus den ¹³C-NMR-Verschiebungen und den vicinalen H,H-Kopplungskonstanten die Vorzugskonformeren und die relative Konfiguration bestimmt werden.

Introduction

Addition of sulfur dichloride to tetrachlorocatechol-*bis*allylether (**1**) afford the dithia crown ether **4** and the cyclic *bis*(β -chloroalkyl) thioethers **2** and **3** (Scheme 1) [1]. The chlorine atom can be bound either to the higher or to the lower branched carbon

[#] Dedicated to Prof. Dr. Rolf Borsdorf on the occasion of his 65th birthday



Scheme 1

atom. Therefore, two different types of regioisomeric β -chloro-thio units exist, exhibiting *Markovnikov* or *anti-Markovnikov* constitution. This kind of regioisomers has been discussed earlier by *Kleinpeter et al.* [2]. Whereas the symmetrical products **2** and **4** show 'pure' *anti-Markovnikov* constitution, **3** includes both of the different constitutional units in the same molecule. Only one of the two possible diastereomers was found and separated for compounds **2** and **3**, respectively (**2A**, **3A**). For **2A**, the (\pm)-form was determined by X-ray crystallography [1].

The conformational behaviour of crown ethers has been investigated in detail by NMR spectroscopy. *Kleinpeter* and co-workers have studied the stereochemistry and the complexation behaviour of a series of structurally related crown ethers in solution by means of both NMR spectroscopy and molecular mechanics calculations [3–8]. They found a good linear relation of the ^{13}C NMR chemical shift with the non-bonded in-plane interaction between the aromatic ring carbons and the $-\text{O}-\text{CH}_2-$ segments in γ -position [6]. *Buchanan et al.* compared the conformations of crown ethers in solution and in the solid state [9]. For the methylene carbons of cyclic 1,2-dialkoxybenzenes they observed relatively similar ^{13}C chemical shifts, both in solution and in the solid state [10]. *Nazhaoui* and co-workers recently reported the assignment of conformations of crown ethers prepared from *D*-mannitol using different NMR spectroscopic methods [11].

Numerous macrocycles containing sulfur atoms have already been synthesized [12]. In analogy to the crown ethers, they are of interest due to their ion selectivity. Recently, a cyclic thia crown ether utilized as ionophore with a silver ion optode was reported [13]. However, the structure and conformation of some thia crown ethers have been mainly determined by X-ray diffraction analysis [14]. The dithia crown ether derivatives studied here are flexible species. Therefore, the plane of the benzene ring will be used as a reference plane. The two methylene groups in the neighbourhood of the oxygen atoms may be arranged on the same (*syn*) or on different sides (*anti*) of the reference plane in **2** and **3**. Also, two possibilities exist for the alignment of the sulfur bridge ("up" and "down"). Conformations with a direction of the sulfur atoms inside in the ring must not be considered here with respect to previous observations [14]. Several different conformations are expected for the diastereomers of **2** and **3**. The aim of this work was the assignment of the relative configuration of diastereomer **3A**, the first that was found to contain *Markovnikov* and *anti-*

Markovnikov constitution of the β -chloro-thio structural segments in one macrocycle by NMR spectroscopy. This required the knowledge of the preferred conformations.

Results and Discussion

The results of the ^1H and ^{13}C NMR measurements are listed in Tables 1 and 2. The ^1H NMR spectra of the *anti-Markovnikov* product **2A** shows no significant temperature dependence in the range from $+45^\circ\text{C}$ to -55°C . The reason for this phenomenon might arise from chemically indistinguishable conformers or a low difference in their energy contents. The identical configurations (*R,R*) or (*S,S*) of carbon atoms C-3 and C-5 do not allow equivalent arrangements in both half sides of the molecule. These sides will be indistinguishable by a simple turn down movement of the sulfur bridge. The relatively large difference in the vicinal coupling constants between protons in positions 2 or 2' and 3 ($^3J_{2,3} = 3.2\text{ Hz}$, $^3J_{2',3} = 7.2\text{ Hz}$) indicates *gauche*- and *anti*-position, respectively, of coupled protons. This can be realized for both molecule segments only by a *syn*-arrangement of the $-\text{CH}_2-\text{CH}(\text{CH}_2\text{Cl})$ -segments with respect to the reference plane.

The *Markovnikov* structural segment, easily determined by the existence of an $-\text{S}-\text{CH}_2-$ group, was only found in the NMR spectra of **3A** (C-5 and H-5, H'-5). For this diastereomer with *Markovnikov* and *anti-Markovnikov* segments a strong temperature dependence was found: narrow ^1H NMR signals were obtained only at temperatures over $+40^\circ\text{C}$ and below -50°C . At -68°C in CD_2Cl_2 , the signals of two preferred conformers (**a** and **b**) were detected with equal intensities (Table 2). All signals were assigned to the spin systems by use of H,H-COSY, HETCOR, and

Table 1. ^{13}C chemical shifts of **2A** and **3A** in CDCl_3 at different temperatures (ppm relative to internal TMS)

	C-2	C-3	C-5	C-6	C-7	$-\text{CH}_2\text{Cl}$	9, 10, 11, 12 ¹	13, 14 ¹
2A $+26^\circ\text{C}$	76.8	44.6	44.6	76.8	–	44.4	128.8 127.9	148.7
2A -55°C	76.5 ²	44.2 ²	44.2 ²	76.5 ²	–	43.6	128.4 127.5	148.4
3A $+55^\circ\text{C}$	71.6	47.9	32.8	56.4	72.4	44.6	129.4 129.2 128.1 128.0	148.5 147.7
3Aa -56°C	69.9	49.4 ³	34.1	57.9	72.5	45.6	128.4 to	147.8
3Ab	70.5	44.3 ³	29.2	54.5	70.9	43.5	127.6	147 146.8
$\Delta_{\text{a-b}}$	-0.6	5.1 ³	4.9	3.4	1.6	1.9		

¹ Assignment not possible; ² line broadening observable; ³ interchangeable

Table 2. ^1H chemical shifts of **2A** and **3A** at different temperatures (ppm relative to internal *TMS*)

	H-2	H'-2	H-3	H-5	H'-5	H-6	H-7	H'-7	$-\text{CH}_2\text{Cl}$ H	H'
2A +45 °C ¹	4.52	4.6	3.57	equiv.	H-3	equiv.	–	–	3.81	3.75
2A –55 °C ¹	~4.5	~4.6	~3.6			H-2,2'	–	–	3.83	3.78
3A +55 °C ¹	4.42	4.3	3.4	3.45	3.26	4.28	4.4	4.7	3.8	3.68
3Aa –68 °C ²	4.45	4.06	3.43	~3.4	3.1	4.15	5.1	4.15	3.94	3.54
3Ab	4.3	4.3	3.43	3.28	3.28	4.55	4.1	4.45	3.68	3.7
$\Delta_{\text{a-b}}$	0.15	–0.24	0	~0.1	–0.18	–0.4	1.0	–0.3	0.26	–0.16

¹In CDCl_3 ; ²in CD_2Cl_2

phase sensitive NOESY measurements at high and low temperatures. The cross peaks in the last experiment were produced either by exchange processes or by Nuclear *Overhauser* Enhancements (NOEs); differentiation is possible by the sign of the cross peaks. No NOEs were observed between protons on different sides of the sulfur bridge. In Fig. 1, the ^1H NMR spectra of **3A** at selected temperatures (1a) and the H,H-COSY spectrum recorded at $-68\text{ }^\circ\text{C}$ (1b) are depicted. The assignment of signals is also presented as a result from all NMR measurements.

It has become popular to use different methods of computational chemistry as a tool for the refinement of molecular structures with respect to experimental data, especially from NMR measurements. A very comprehensive review of this computational methods has been presented by *van Gunsteren* and *Berendsen* in 1990 [15]. In this study, molecular mechanics and dynamics calculations were applied to search for low energy conformations of the compound **3**. Eight torsional angles were selected and randomly varied to generate new structures followed by a geometry optimization procedure. Using the MM^+ force field, four preferred conformers with nearly the same conformational energy were found for each diastereomer (two *syn* and two *anti* arrangements each). The conformers with both $-\text{O}-\text{CH}_2-$ carbons in a *syn*-position were found to be somewhat favoured. Comparable results on the most favoured arrangements were obtained employing the SYBYL force field, which is particularly directed to simulate a wide range of organic molecules [16]. However, the stability order found here was contrary to the one obtained by the MM^+ calculations: the conformers with an *anti* arrangement were the most preferred ones. Additionally, the heats of formation of the most stable conformers were supplied by semiempirical calculations with the AM1 program. These results confirm the stability order found by the molecular mechanics calculations with the SYBYL force field. Finally, two preferred conformations were estimated for each of the possible diastereomers of compound **3**: **I** and **II** for the (*R,S*)-form, and **III** and **IV** for the

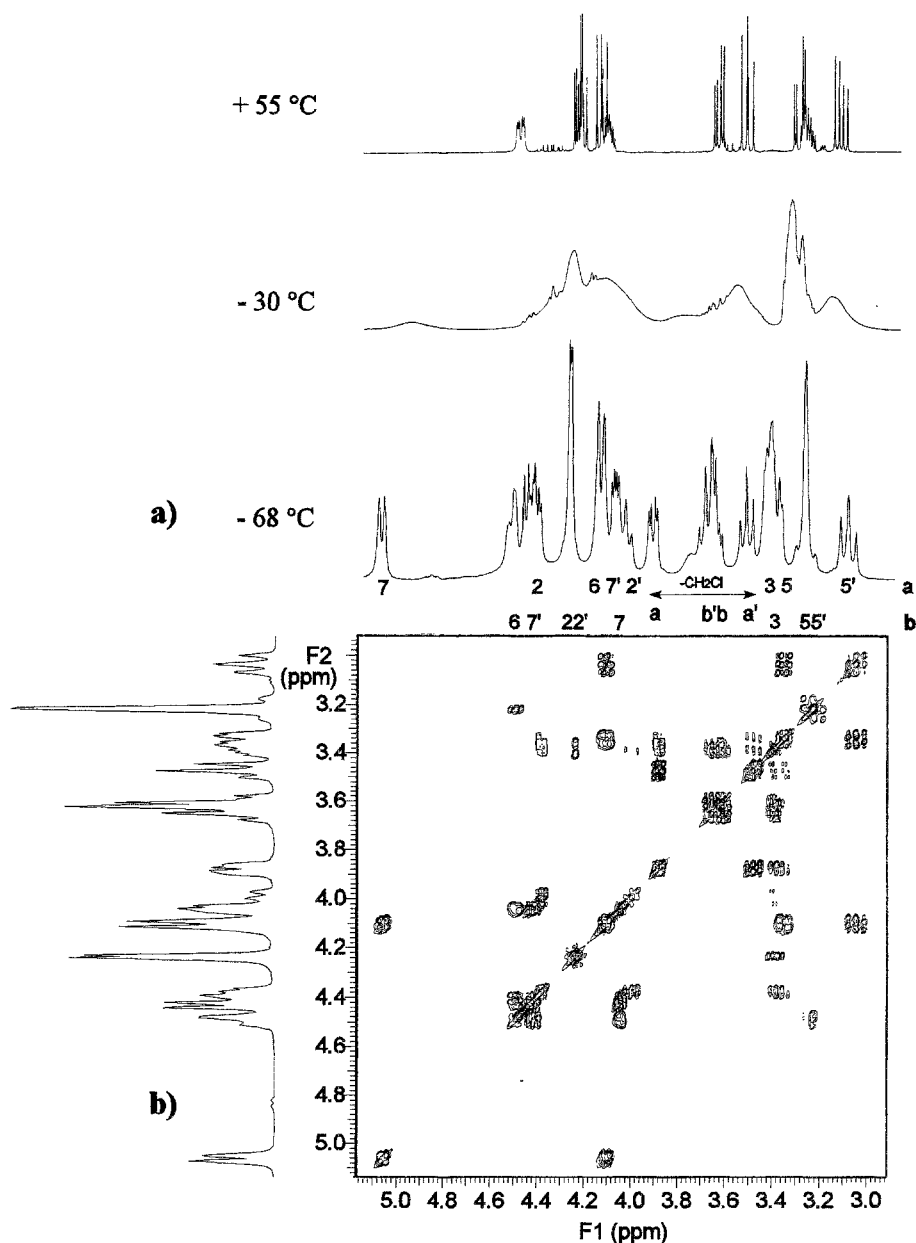


Fig. 1. a) Temperature dependent 400 MHz ^1H NMR spectra of **3A** recorded at +55 °C, -30 °C, and -68 °C; the assignment of conformers **a** and **b** is given at the bottom of spectrum; b) part of the H,H-COSY spectrum of **3A** in CH_2Cl_2 at -68 °C, plotted with same size as the one-dimensional spectra in 1a; on the left side, the F2-projection is shown

(*R,R*)- or (*S,S*)-form. These calculated conformations are shown in Fig. 2 together with the differences in the heat of formation. In all these conformations, the $-\text{CH}_2-\text{CH}(\text{CH}_2\text{Cl})-$ and $-\text{CH}_2-\text{CH}(\text{Cl})-\text{CH}_2-$ segments are arranged in an *anti*-position on different sides of the reference plane. The $-\text{O}-\text{C}-\text{C}-\text{S}$ -parts show always *gauche* arrangements. Differences in heat of formation larger than 2.5 kcal/mol with

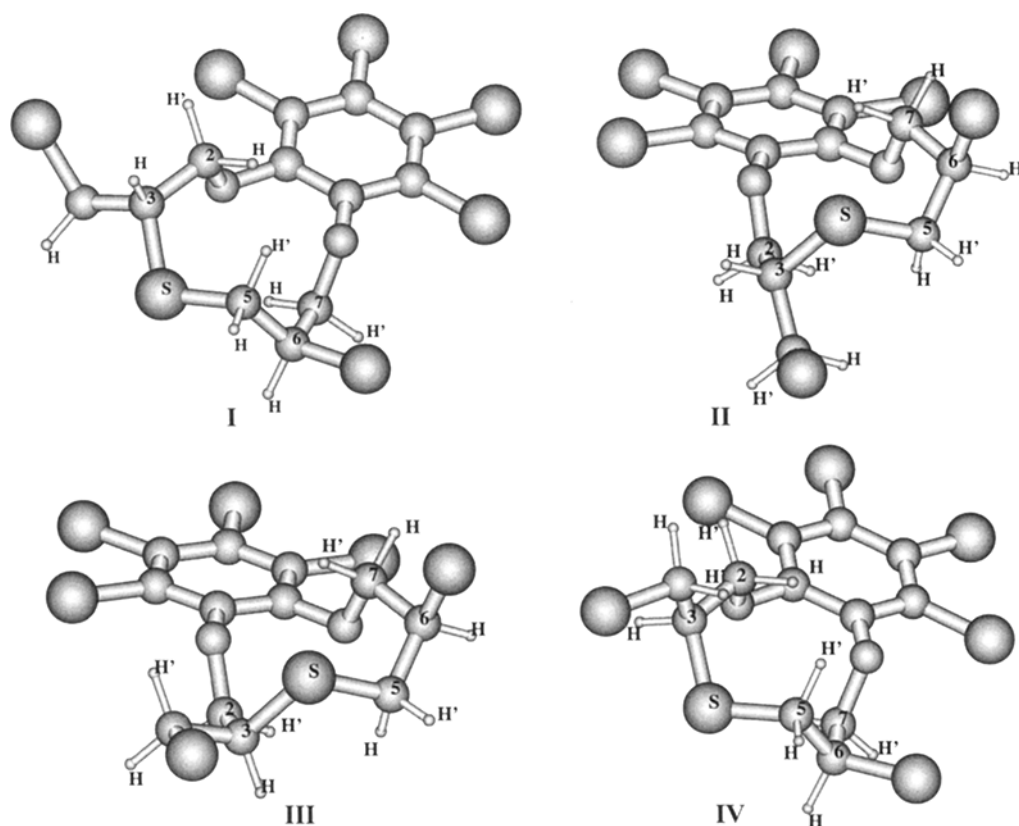


Fig. 2. Four preferred conformations of **3** as result of molecular mechanics calculations (SYBYL); the differences in heats of formation calculated by AM1 are given for the (*R,S*)/(*S,R*) diastereomer ($\Delta_{I-II} = 0.98$ kcal/mol) and for the (*R,R*)/(*S,S*)-diastereomer ($\Delta_{III-IV} = 0.91$ kcal/mol)

respect to the most stable form were found for conformations with a *syn* arrangement of the ring segments. In all calculated conformations the sulfur atoms were directed outwards from the center of the rings. This has been generally observed for thia macrocycles earlier [14, 17].

Another way for establishing the conformational space are molecular dynamics simulations. An efficient procedure consists of a combination of high temperature molecular dynamics and energy minimization. The results of these conformational analyses have often been used for comparison with structures derived from NMR measurements [18]. In our case, the available conformational space was sampled adequately by simulations at high temperature, followed by slow cooling. This procedure is called “simulated annealing” and was applied to different starting conformations. Simulated annealing has proved to be a very powerful approach to the global optimization of functions in many variables [19]. However, only one preferred conformation was obtained for each diastereomer of **3**: **II** for the (*R,S*) or (*S,R*)- and **IV** for the (*R,R*) or (*S,S*)-diastereomer.

The arrangements of the $-\text{CH}_2\text{Cl}$ group are the most important stereochemical differences between the diastereomers of **3**. Simultaneously, the ^{13}C chemical shift of

the carbon atom C-5 shows a strong dependence on the torsional angle in the C5–S–C3–CH₂Cl segment. For **3A**, we found a difference of nearly 5 ppm for C-5 in the conformers **a** and **b** at –56 °C (Table 1). The highfield shift observed in the conformer **b** results from a γ_{gauche} -effect caused by a *synclinal* (*gauche*) arrangement of the –CH₂Cl group to C-5 [20]. This arrangement exists only in calculated conformations **II** and **IV** (Fig. 2). On the other hand, a large vicinal coupling constant was observed for H'-5 and H-6 in conformer **a** ($^3J_{5,6} \sim 12$ Hz), caused by an *antiperiplanar* (*anti*) position of coupled protons. This arrangement can be found only in the calculated conformations **I** and **IV**. Finally, all conditions described here are realized only by the assignment of conformers **a** and **b** of **3A** to the calculated conformations **I** and **II**. Thus, for the diastereomer **3A** the (*R*, *S*)-configuration was determined. The *anti* position of the –O–CH₂– groups explains the absence of NOEs between these opposite methylene protons.

A further support of this assignment is the large ¹H chemical shift difference of proton H-7 between conformers **a** and **b** (1.0 ppm, Table 2). The deshielding observed for proton H-7 in conformer **a** is caused by *van der Waals* compressions of this proton by the *synaxial* sulfur S-4 and by oxygen O-1 (**I**, Fig. 2). Simultaneously, the highfield shift observed in conformer **b** corresponds to the position of H-7 outside of the ring in conformation **II**. For H'-7, the reverse case was found with the smaller value of $\Delta_{a-b} = -0.3$ ppm.

The (*R,S*)-configuration found for the diastereomer **3A** is in good agreement with results of isomerization experiments of **2A**. Heating (\pm)-**2A** in CH₃CN, the formation of **3A** as a single diastereomer was observed [1]. The result can be explained assuming a sulfur bridged intermediate (thiiranium ion) and an *anti* attack of the chloride ion in the ring opening (product determining) step at the C-atom originally bound to the sulfur atom. This means an inversion of configuration at carbon atoms C-3 and C-5, respectively, in **2A**.

Experimental

(*3RS,5RS*)-3,5-*bis*-chloromethyl-2,3,5,6-tetrahydro-1,7,4-tetrachlorobenzodioxathionin (**2A**) and (*3RS,6SR*)-6-chloro-3-chloromethyl-2,3,6,7-tetrahydro-5*H*-1,8,4-tetrachlorobenzodioxathiecin (**3A**) were separated by crystallization and column chromatography.

NMR spectra were obtained on a Varian UNITY-400 spectrometer equipped with a 5 mm probe head. CDCl₃ or CD₂Cl₂ were used as solvent and for internal lock, and *TMS* as an internal standard. Temperatures between +55 °C and –70 °C were obtained using the Varian variable temperature controller VTC-4. The sensitivity of the small amount of sample material was increased by use of a cylindrical micro-insert for 5 mm tubes (Wilmad). 2 mg of substance were dissolved in 150 μ l of solvent and the outer volume of the tube was filled with pure solvent. Typical measurement conditions: ¹H: 399.95 MHz, 45° pulse, 64 scans, 24 K data points, 3.3 kHz spectral width; ¹³C: 100.58 MHz, 45° pulse, 3.2 s repetition time, up to 4000 scans, 35 K data points, 14.7 kHz spectral width, WALTZ proton decoupling; H,H-COSY: 256 increments with 4 scans, total measurement: 65 min; 1024 \times 1024 word matrix, zero-filling to 2048 \times 2048 words prior to Fourier transformation; sinebell window in both dimensions; HETCOR: 128 increments with 64 repetitions, total time: 150 min; phase sensitive NOESY: 2 \times 128 increments, 16 scans, mixing time: 1s, measurement time: 120 min.

The following commercial program packages were used in calculations: Cerius² (Molecular Simulations, Inc.), HyperChem (Hypercube, Inc.), Spartan (Wavefunction, Inc.).

References

- [1] Heinicke J (1994) Untersuchungen zur Chemie und Stereochemie von Allylphenylether- SCl_2 -Additionsprodukten. Thesis, University of Leipzig
- [2] Kleinpeter E, Hollmann K, Mühlstädt M (1990) *Z Chem* **30**: 63
- [3] Stoss S, Schroth W, Kleinpeter E (1992) *Magn Reson Chem* **30**: 425
- [4] Stoss S, Kleinpeter E, Holdt HJ (1991) *Magn Reson Chem* **29**: 999
- [5] Kleinpeter E, Stoss S, Gäbler M, Schroth W (1989) *Magn Reson Chem* **27**: 676
- [6] Kleinpeter E, Gäbler M, Schroth W, Mattinen J, Pihlaja K (1988) *Magn Reson Chem* **26**: 387
- [7] Kleinpeter E, Gäbler M, Schroth W (1988) *Magn Reson Chem* **26**: 380
- [8] Kleinpeter E (1991) *J Prakt Chem* **333**: 817
- [9] Buchanan GW, Moghimi A, Bensimon C (1995) *Can J Chem* **73**: 100
- [10] Buchanan GW, Driega AB, Ratcliffe C (1993) *Magn Reson Chem* **31**: 1094
- [11] Nazhaoui M, Joly JPA, Jean-Claude BJ, Del Duca V, Aubry A, Boubouh M (1995) *J Chem Soc Perkin Trans 1*, **22**: 2919
- [12] Rossa L, Vögtle F (1983) *Topics in Current Chem* **113**: 1
- [13] Hisamoto H, Nakagawa E, Nagatsuka K, Abe Y, Sato S, Siswanta D, Suzuki K (1995) *Anal Chem* **67**: 1315
- [14] Dalley NK, Larson SB, Smith JS, Matheson KL, Izatt RM, Christensen JJ (1981) *J Heterocycl Chem* **18**: 463
- [15] Van Gunsteren WF, Berendsen HJC (1990) *Angew Chem* **102**: 1020
- [16] SYBYL: Molecular Modelling Software, Version 7.1 (1995) Tripos, Inc. St. Louis
- [17] Dietrich B, Viout P, Lehn JM (1993) *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*. VCH Verlagsgesellschaft, Weinheim, p 201
- [18] Salvino JM, Seoane PR, Dolle RE (1993) *J Comp Chem* **14**: 438
- [19] Otten RHJM, van Ginneken LPPP (1989) *The Annealing Algorithm*. Kluwer Academic Press, Boston
- [20] Pihlaja K, Kleinpeter E (1994) Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis. In: Marchand AP (ed) *Methods in Stereochemical Analysis*. VCH Verlagsgesellschaft, Weinheim New York Cambridge, p 58

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