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Synthesis of Cucurbit[5]uril-Spermine-[2]Rotaxanes

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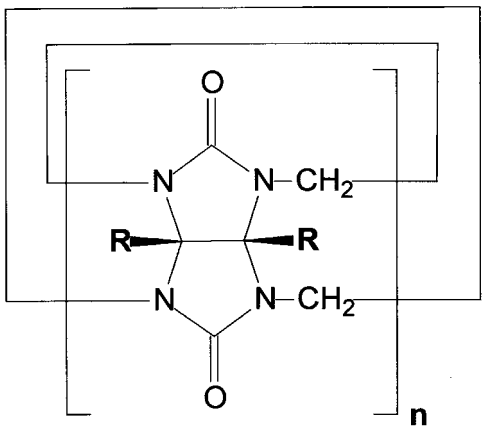
Abstract

Cucurbit[5]uril and decamethylcucurbit[5]uril are cyclic pentamers built from glycoluril or dimethylglycoluril respectively. Two different experimental methods have been used for the synthesis of the different [2]rotaxanes. The formed rotaxanes are characterized using ^{1}H-NMR spectroscopy, mass spectrometry and elemental analysis. In contrast to cucurbit[5]uril no [2]rotaxane could be obtained with decamethylcucurbit[5]uril.

Introduction

In 1905 Behrend *et al.* reported the synthesis of a molecule using urea, glyoxal and formaldehyde [1]. They described the behavior and the reactions of the synthesized substance with salts and a few organic compounds in detail. The macrocyclic structure of the reaction product was first reported by Freeman *et al.* [2] in 1981. Because the name in IUPAC nomenclature is very cumbersome, the trivial name "cucurbituril" was suggested for this macrocyclic ligand. Stoddart suggested a nomenclature for cucurbituril and its derivatives. The number of the glycoluril units are given in brackets. The substituents at the carbon atoms are given as a prefix [3]. Therefore cucurbituril is called cucurbit[6]uril (Cuc[6]) and its structure is given in Figure 1. Using the complexes of Cuc[6] with different amines and polyamines, rotaxanes, polyrotaxanes and molecular networks have been synthesized [4–7]. Polyrotaxanes incorporating Cuc[6] have also been synthesized by Steinke *et al.* [8]. Some polyamines, e.g., spermine and spermidine are important biologically active compounds. They are responsible for cell growth and cell death [9]. Up to now nothing is known about changes of the biological activity due to complex formation with Cuc[6].

Shih gave the first hint for the synthesis of another cucurbituril derivative [10]. He described the formation of a macrocyclic compound by the condensation of dimethylglycoluril. However, at that time no information was given about the number of monomers forming this macrocycle. Stoddart and coworkers synthesized and characterized this derivative as the cyclic pentamer decamethylcucurbit[5]uril (DMCuc[5]) from the X-ray crystal structure [3], see Figure 1. In the case of DMCuc[5] it has been shown that no inclusion complex is formed with 1,6-diamino hexane [11]. From a crystallographic study of the 1,6-diamino hexane complex with DMCuc[5] it is known that both amino groups



R = H	n = 6	Cucurbit[6]uril	**Cuc[6]**
R = CH_3	n = 5	Decamethylcucurbit[5]uril	**DMCuc[5]**
R = H	n = 5	Cucurbit[5]uril	**Cuc[5]**

Figure 1. Chemical structures of different cucurbituril derivatives.

interact with the carbonyl groups at the portals of two different molecules of DMCuc[5]. The methylene groups of the diamine are located outside of the cavity [11].

Just recently the syntheses of several cucurbituril derivatives with 5 to 8 glycoluril units have been reported [12, 13]. These derivatives are obtained from a reaction mixture, in which cucurbit[6]uril (Cuc[6]) is the main fraction with about ~60% [12]. In the meantime also the direct synthesis of cucurbit[5]uril (Cuc[5]) has been described [11]. The structure of Cuc[5] is also given in Figure 1. In contrast to the findings with DMCuc[5] some evidence for the formation of alkylamine complexes with Cuc[5] has been observed. For example, stability constants and complex

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formation enthalpies of some aliphatic and aromatic ammonium salts have been measured by calorimetric titrations. Also the ^{1}H-NMR spectrum show signals, which are typical for complexes, in which the amine is enclosed in the cavity of Cuc[5] [11].

These results inspired us to synthesize rotaxanes with both Cuc[5] and DMCuc[5] from the spermine complexes of these ligands.

Experimental

Elemental analyses were performed using a Carlo-Erba 1006 Analyser. The substances were purified by recrystallization from acidic solutions. They were dried in vacuum. However, not all water molecules could be removed under the experimental conditions. All ^{1}H-NMR-spectra were recorded using a WM 300 (Bruker, 300 MHz) or a Bruker avance DRX 500 (Bruker, 500 MHz) spectrometer. The solvents used were D_2O, 16% DCl/D_2O, CF_3COOD or a mixture of $CF_3COOD/CDCl3$ (1/0.37). In protic solvents 3-(trimethylsilyl) propionic-*2,2,3,3-d*$_4$ acid sodium salt (TMSPA) was used as internal standard. Using $CDCl_3$ TMS was the internal standard.

Mass spectra were recorded using Matrix Assisted Laser Desorption Ionization-Time of Flight-Mass Spectrometry (MALDI-TOF-Mass Spectrometry) (Voyager-DE RP Biospectrometry Workstation, PerSeptive Biosystems). The substances were dissolved in 5–20% CF_3COOH . After drying the mass spectra were measured. The accuracy of the experimental mass numbers varies between one and three units.

The existence of the DMCuc[5]-spermine complex was confirmed using Liquid-Secondary Ions Mass Spectrometry (Liquid-SIMS Mass Spectrometry) (AMD 604) from a glycerine matrix.

Synthesis of cucurbit[5]uril and decamethylcucurbit[5]uril

The synthesis and purification followed the procedure already described in the literature in detail [11].

Glycoluril (13.4 g, 94 mmol) or dimethylglycoluril (16.0 g, 94 mmol), 37% aqueous formaldehyde solution (32 mL), concentrated hydrochloric acid (64 mL) and water (20 mL) were heated under reflux for two hours. After this time 300 mL water were added to the clear dark solution and the resulting mixture heated for an additional hour. The solution was cooled to room temperature overnight. The precipitate was filtered off, washed three times with water, recrystallized several times from hydrochloric acid and dried in vacuum.

The elemental analysis and the NMR spectra of both compounds are in accordance with the values reported [11].

Yield Cuc[5]: 0.7 g (4.6%). $C_{30}H_{30}N_{20}O_{10}$. *Calc.* C, 43.38; H, 3.64; N, 33.72; O, 19.26; C/N ratio; **1.29**; *Exp*. C, 35.82; H, 4.60; N, 27.34; C/N, **1.31**. ^{1}H-NMR (300 MHz, DCl/D_2O): δ 4.49 (d, 10 H, J = 16 Hz), δ 5.53 (d, 10 H, J = 16 Hz), δ 5.72 (s, 10 H).

Yield DMCuc[5]: 1.9 g (10.4%). $C_{40}H_{50}N_{20}O_{10}$. *Calc.* C, 49.48; H, 5.19; N, 28.85; O, 16.84; C/N ratio **1.72**; *Exp*. C, 41.81; H, 5.73; N, 26.37; C/N ratio **1.59**. ^{1}H-NMR (500 MHz, $CF_3COOD/CDCl_3$ (1/0.37)): δ 1.92 (s, 30 H), δ 4.50 (d, 10 H, J = 16.5 Hz), δ 5.92 (d, 10 H, J = 16.5 Hz).

Synthesis of the cucurbit[5]uril- and decamethylcucurbit[5]uril-spermine complex

An equimolar solution of spermine and the macrocycles Cuc[5] (2 g, 2.4 mmol, in 100 mL H_2O) and DMCuc[5] (4 g, 4.12 mmol, in 200 mL H_2O) was prepared. The resulting suspensions were filled in an autoclave (V = 750 mL) in which they were heated at 200 °C for 3–4 hours. After this time no clear solution was obtained in the case of Cuc[5]. In contrast a clear solution resulted with DMCuc[5]. The solvent of the clear solution was removed in a rotary evaporator at a bath temperature of 120 °C. The resulting white powder has a solubility of approximate 175 g/L in water at room temperature.

Spermine: ^{1}H-NMR (500 MHz, D_2O): δ 1.44–1.53 (4 H), δ 1.57–1.65 (4 H), δ 2.54–2.61 (8H), δ 2.61–2.66 (4 H). ^{1}H-NMR (500 MHz, 16% DCl/D_2O): δ 1.78-1.91 (4 H), δ 2.12–2.25 (4 H), δ 3.10–3.28 (12 H). This spectrum is given in Figure 2.

DMCuc[5]-spermine complex: $C_{50}H_{76}N_{24}O_{10}$. *Calc.* C, 51.18; H, 6.53; N, 28.65; O, 13,64; C/N ratio **1.79**; *Exp.* C, 44.99; H, 6.40; N, 25.37; C/N ratio **1.77**.

^{1}H-NMR (500 MHz, D_2O): δ 1.53–1.64 (m, 4 H, spermine-CH_2), δ 1.76–1.88 (s, 30 H, DMCuc[5]-CH_3), δ 1.93–2.01 (m, 4 H, spermine-CH_2), δ 2.71–2.79 (m, 4 H, spermine-CH_2), δ 2.84–2.92 (m, 4 H, spermine-CH_2), δ 3.02–3.12 (m, 4 H, spermine-CH_2), δ 4.43–4.52 (d, 10 H, J = 16.0 Hz, DMCuc[5]-CH_2), δ 5.63–5.73 (d, 10 H, J = 16.4 Hz, DMCuc[5]-CH_2).

Synthesis of the cucurbit[5]uril- and decamethylcucurbit[5]uril-spermine complex

An equimolar mixture of the solid macrocycle (Cuc[5] or DMCuc[5]) (4 mmol) and solid spermine (4 mmol) was suspended in 150 mL aqueous hydrochloric acid (16%). The solvent was removed in a rotary evaporator at a bath temperature of 120 °C.

The solid light yellow Cuc[5]-spermine-complex has a solubility of approximate 3.5 g/L in water at room temperature. The ^{1}H-NMR spectrum indicated that Cuc[5] is threaded on spermine, see Figure 2. In contrast the ^{1}H-NMR spectrum of the DMCuc[5]-spermine complex gave evidence only for a mixture of DMCuc[5] and spermine, see Figure 2.

Cuc[5]-spermine complex: $C_{40}H_{56}N_{24}O_{10}$. *Calc.* C, 46.51; H, 5.46; N, 32.54; O, 15.49; C/N ratio **1.43**; *Exp.* C, 37.95; H, 5.72; N, 25.94; C/N ratio **1.46**. ^{1}H-NMR (500 MHz, D_2O): δ 0.57–0.61 (m, spermine-CH_2), δ 1.74–1.81 (m, spermine-CH_2), δ 2.06–2.14 (m, spermine-CH_2), δ 2.32–2.42 (m, spermine-CH_2), δ 3.06–3.21 (m, spermine-CH_2), δ 3.38–3.44 (m, spermine-CH_2), $(AX)_5$ (δ_A = 4.44 [10 H], δ_X = 5.74 [10 H], $|^2J_{AX}|$ = 15.6 Hz, Cuc[5]-CH_2), δ 5.70

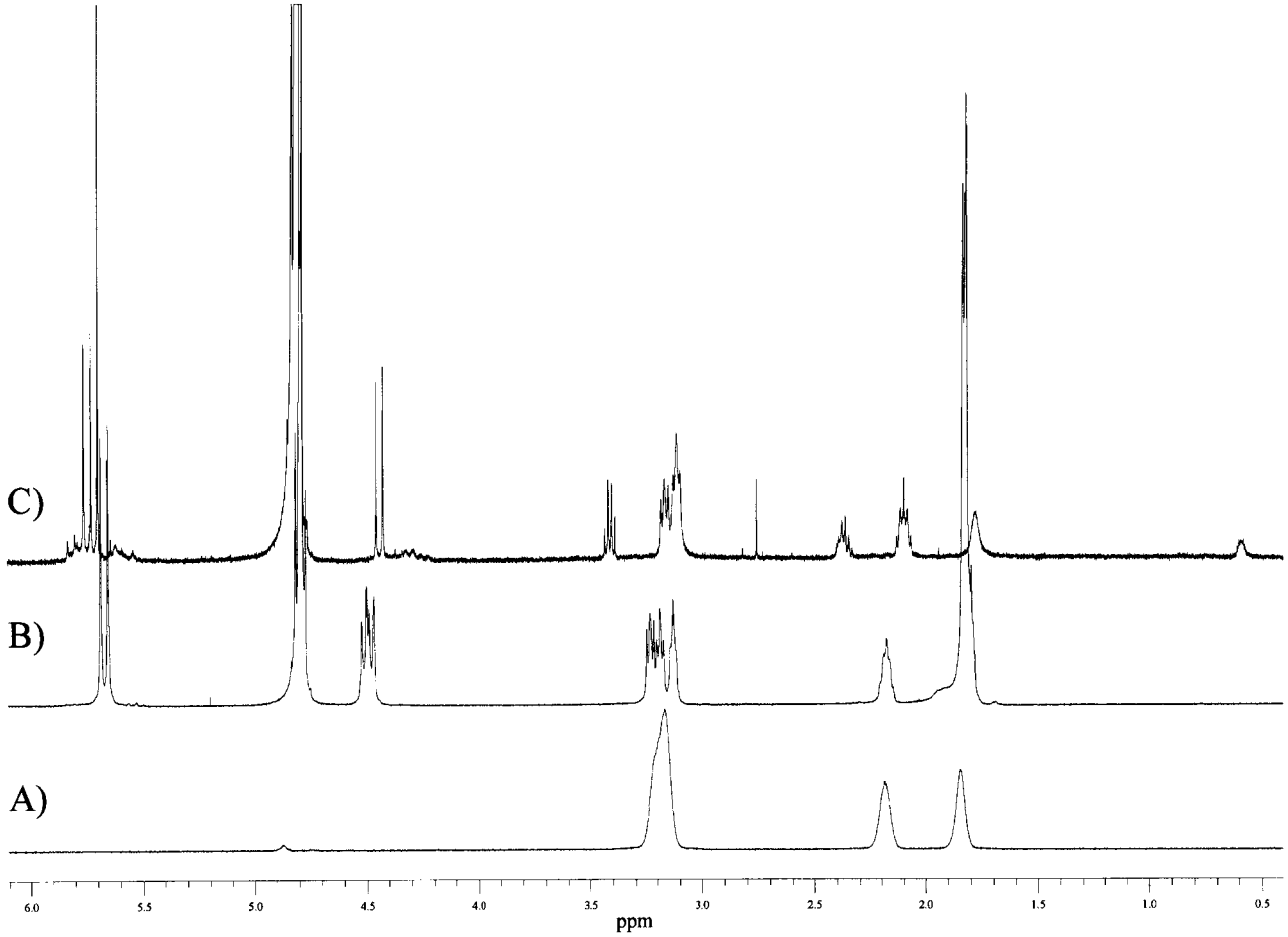

Figure 2. ^{1}H-NMR spectra of (A) spermine in 16% DCl/D_2O. (B) The DMCuc[5]-spermine complex in D_2O. (C) The Cuc[5]-spermine Complex in D_2O.

(s, 12 H, Cuc[5]-CH). This spectrum is also given in Figure 2. Mass spectrometry (L-SIMS): *Calc.* M^+ = 1033.03; *Exp.* M^+ = no result.

DMCuc[5]-spermine complex: $C_{50}H_{76}N_{24}O_{10}$. *Calc.* C, 51.18; H, 6.53; N, 28.65; O, 13,64; C/N ratio **1.79**; *Exp.* C, 37.92; H, 6.40; N, 22.48; C/N ratio **1.69**. The observed discrepancy is obviously caused by the presence of water and hydrochloride molecules (see elemental analysis of the DMCuc[5]-spermine complex formed in the absence of hydrochloric acid).

^{1}H-NMR (500 MHz, D_2O): δ 1.75–1.99 (m, spermine-CH_2, DMCuc[5]-CH_3), δ 2.13–2.24 (m, spermine-CH_2), δ 3.09–3.28 (m, spermine-CH_2), δ 4.43–4.55 (m, DMCuc[5]-CH_2), δ 5.64–5.70 (d, DMCuc[5]-CH_2). This spectrum is presented in Figure 2. Mass spectrometry (L-SIMS): *Calc.* M^+ = 1173.29; *Exp.* M^+ = 1173.5.

Synthesis of [2]-rotaxanes of cucurbit[5]uril and spermine

All rotaxanes reported in this paper were synthesized in two different ways. The first method (A) used the synthesized preformed Cuc[5]-spermine-complex. The second method (B) organized the complex of cucurbit[5]uril and spermine in a one step reaction. In both methods the primary amino groups of spermine react with different carboxylic acid chlorides. Because of this only the stopper groups vary. Therefore the synthesized rotaxanes are named by the macrocycle used and the acid chloride e.g., benzoyl-spermine-cuc[5]-[2]rotaxane. The chlorides of carboxylic acids (benzoyl chloride (Merck) and 2-furoyl chloride (Fluka)) were used without further purification.

Method A: Synthesis of Cucurbit[5]uril-[2]rotaxanes using the preformed solid complex. 500 mg (0.48 mmol) of the preformed Cuc[5]-spermine complex was dissolved in 150 mL water. To this solution benzoyl chloride (4.84 mmol, Fluka) and 3 mL of triethylamine were added. Upon intense stirring the acid chloride reacted with the primary amino group with the formation of a precipitate. This was filtered and washed with 15 mL 16% HCl followed by 15 mL water and finally 15 mL acetone.

Benzoyl-spermine-Cuc[5]-[2]rotaxane: Yield: 183 mg (24.5%). $C_{54}H_{64}N_{24}N_{24}O_{12}$. *Calc.* C, 52.25; H, 5.20; N, 27.08; O, 15.47; C/N ratio **1.93**; *Exp.* C, 38.28; H, 4.52; N, 21.31; C/N ratio **1.80**. Mass spectrometry (MALDI-TOF) *Calc.* M^+ = 1241.24; *Exp.* M^+ = 1306.32 (Rotaxane + 2 Na^+ + H_2O).

Method B: Synthesis of Cucurbit[5]uril-[2]rotaxane using Cuc[5] and spermine as starting materials.

An equimolar mixture of solid cucurbit[5]uril (0.6 mmol) and solid spermine (0.6 mmol) in 80 mL aqueous hydrochloric acid (16%) was stirred until a nearly clear solution

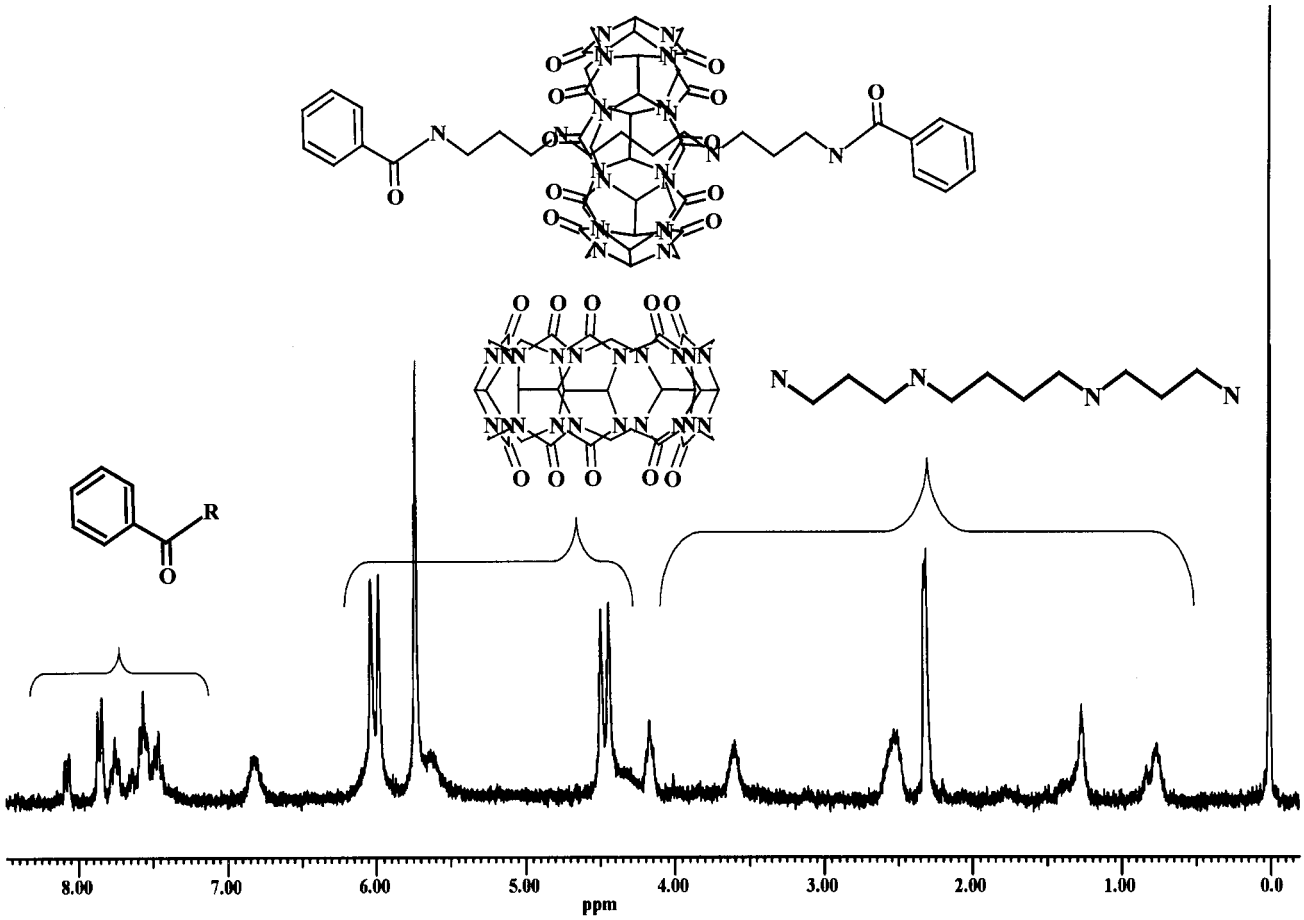

Figure 3. ^{1}H-NMR spectrum of the benzoyl-spermine Cuc[5]-[2]rotaxane.

was formed. Afterwards the pH-value of the solution was raised to 9–10 by the addition of solid LiOH. During this neutralization reaction the solution got hot. Afterwards the temperature of the solution was lowered to 25 °C by cooling. A clear light yellow solution was obtained. Now the carboxylic acid chlorides (benzoyl chloride or furoyl chloride, 3 mmol) dissolved in 20 mL diethylether were added. Upon stirring the reaction took place at the phase boundary with the formation of the precipitate. This was filtered off and washed with water and acetone or diethylether.

Benzoyl-spermine-Cuc[5]-[2]rotaxane: Yield: 103 mg (17.4%). $C_{54}H_{64}N_{24}O_{12}$. *Calc.* C, 52.25; H, 5.20; N, 27.08; O, 15.47; C/N ratio **1.93**; *Exp.* C, 43.17; H, 4.60; N, 22.04; C/N ratio **1.96**. ^{1}H-NMR (300 MHz, CF_3COOD): δ 0.69–0.91 (m, spermine-CH_2), δ 1.14–1.45 (m, spermine-CH_2), δ 2.18–2.39 (m, spermine-CH_2), δ 2.44–2.65 (m, spermine-CH_2), δ 3.50–3.69 (m, spermine-CH_2), $(AX)_5$ (δ_A = 4.47 [10 H], δ_X = 6.01 [10 H], $|^2J_{AX}|$ = 15.6 Hz, Cuc[5]-CH_2), δ 5.74 s (Cuc[5]-CH), δ 7.37–8.16 (m, aromatic-CH). This spectrum is given in Figure 3. Mass spectrometry (MALDI-TOF) *Calc.* M^+ = 1241.24; *Exp.* M^+ = 1306.15 (rotaxane + 2 Na^+ + H_2O) M^{2+} = 642.66 (rotaxane + 2 Na^+).

2-Furoyl-spermine-Cuc[5]-[2]rotaxane: Yield: 63 mg (8.6%). *Calc.* C, 49.18; H, 4.95; N, 27.53; O, 18.34; C/N ratio **1.79**; *Exp.* C, 34.35; H, 4.04; N, 24.07 C/N ratio **1.42**. The observed discrepancy is obviously again caused by the presence of water and hydrochloride molecules.

No suitable solvent was found for recording the ^{1}H-NMR spectrum of the [2]-rotaxane. Mass spectrometry (MALDI-TOF) *Calc.* M^+ = 1221.17; *Exp.* M^+ = 1217.17.

Results and discussion

Up to now all attempts to synthesize a DMCuc[5]-[2]rotaxane using the DMCuc[5]-spermine complex and different acid chlorides failed. Obviously DMCuc[5] does not form an inclusion complex with spermine. This hypothesis is confirmed by the crystal structure of a DMCuc[5]-1,6-diamino hexane complex, which has already been published [11]. In the crystal structure of the DMCuc[5]-1,6-diamino hexane complex, the primary amino groups of the amine are in the vicinity of the center of the portals built from five carbonyl groups of DMCuc[5]. All methylene groups of the diamine are located outside the cavity.

The ^{1}H-NMR spectrum of spermine was measured in a mixture of DCl/D_2O. In the ^{1}H-NMR spectrum of the DMCuc[5] and spermine mixture, the proton signals of spermine are in good agreement with the spectrum of spermine. One of the proton signals of spermine is overlapped by the proton signals of the CH_3-group of DMCuc[5]. Therefore the CH_3-group signal is broader and has small peaks, which are not present in the ^{1}H-NMR spectrum of the DMCuc[5]. The methylene group signals of DMCuc[5] in the

DMCuc[5]-spermine mixture splits from a doublet to two identical doublets. This may be caused by interactions of the methylene group protons of DMCuc[5] with spermine. The results of the ^{1}H-NMR spectrum of the DMCuc[5] and spermine mixture indicate that no inclusion complex is formed. Apparently, the portals of DMCuc[5] are too small and too rigid for the spermine to slip into the cavity of the macrocyclic ligand. Under the experimental conditions used spermine does not form an inclusion complex with DMCuc[5]. As a result no rotaxane formation can take place. On the other hand the solubility increases due to the interactions of the protonated secondary amino groups with solvent molecules.

In contrast Cuc[5] forms an inclusion complex with spermine indicating that spermine is threaded through Cuc[5]. For the formation of this complex the presence of protons at the amino groups and heating of the solution is essential. Due to the protonation of spermine the interactions of the amino groups and the carbonyl groups of the ligand increase. As a result complex formation is favored. The flexibility of the ligand increases with increasing temperature. Thus it becomes easier for the spermine to slip through the cavity of Cuc[5]. At least both factors enable the formation of [2]-rotaxanes with Cuc[5]. The ^{1}H-NMR spectrum indicates the formation of an inclusion complex between spermine and Cuc[5]. For example, the signal at about 0.5 ppm is typical for proton signals of methylene groups inside the cavity of cucurbit[6]uril. In addition to signals of threaded spermine also signals of unthreaded spermine were observed. Up to now, three [2]rotaxanes with Cuc[5] and spermine using two different methods have been synthesized. All [2]rotaxanes have been characterized positively by mass spectrometry.

The difference between the molecular structures of DMCuc[5] and Cuc[5] are the equatorial methyl groups. Obviously they are responsible for the increase of rigidity of DMCuc[5]. Thus, one may expect that under appropriate conditions even DMCuc[5] will form inclusion complexes suitable for the synthesis of rotaxanes. The existence of a nitrate complex with DMCuc[5] from crystallographic measurements has already been reported [2]. Up to now no reaction conditions for the formation of inclusion complexes with DMCuc[5] have been found. The synthesis of further rotaxanes with Cuc[5] is in progress.

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