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Steric factors influencing the complex formation with cucurbit[6]uril

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Abstract

The complex formation between cucurbit[6]uril and different diamides was studied using proton resonance spectroscopy and calorimetric titrations. The values of the stability constants and reaction enthalpies were determined using calorimetric titrations. In solution diamides obtained from the reaction of α,ω-alkyl diamines with aliphatic carbonic acids form inclusion complexes by threading. The stability of these complexes is independent of the number of methylene groups of the diamine compounds. With increasing chain length of the aliphatic carbonic acids the complex stability raises. The thermodynamic data for the reaction of cucurbit[6]uril with diamides containing branched alky-, cycloaliphatic- or aromatic carbonic acids give no evidence for the formation of inclusion complexes. However, ^{1}H-NMR-experiments give clear evidence of the complex formation between cucurbit[6]uril and branched alkyl diamides. Surprisingly cycloaliphatic and aromatic groups act as blocker groups although the cavity size of cucurbit[6]uril is larger than the diameter of the terminating groups. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cucurbit[6]uril; Calorimetry; Inclusion complex

1. Introduction

During the last years a great variety of mechanically bonded molecules has been synthesized. This subject has already been reviewed in detail by several authors [1–8]. Rotaxanes and polyrotaxanes containing cyclodextrins [9–11] and crown ethers [5,6] have been characterized.

Up to now only few examples of rotaxanes with cucurbit[*n*]uril type macrocyclic ligands (see Fig. 1) are known. The ligand cucurbit[6]uril was first synthesized in 1905 by Behrend et al. [12]. The structure of this ligand has been reported much later [13,14]. Cucurbit[6]uril forms very stable complexes with diammonium ions [15–17]. These complexes can be used as preorganized structures in further reaction steps. Thus, the reaction with different carboxylic acid chlorides results in the formation of rotaxanes or pseudorotaxanes [18,19]. Also the high stability constant of the complex formed between cucurbit[6]uril and spermine, an alkylamine containing four amino groups, provides this complex as a nearly perfect building block for the formation of rotaxanes and pseudorotaxanes [20,21].

Recently the formation of pseudorotaxanes with cucurbit[6]uril was reported [20,22]. Several rotaxanes [18,20,21] and polyrotaxanes [18,19] have been synthesized by reaction of preorganized cucurbit[6]uril

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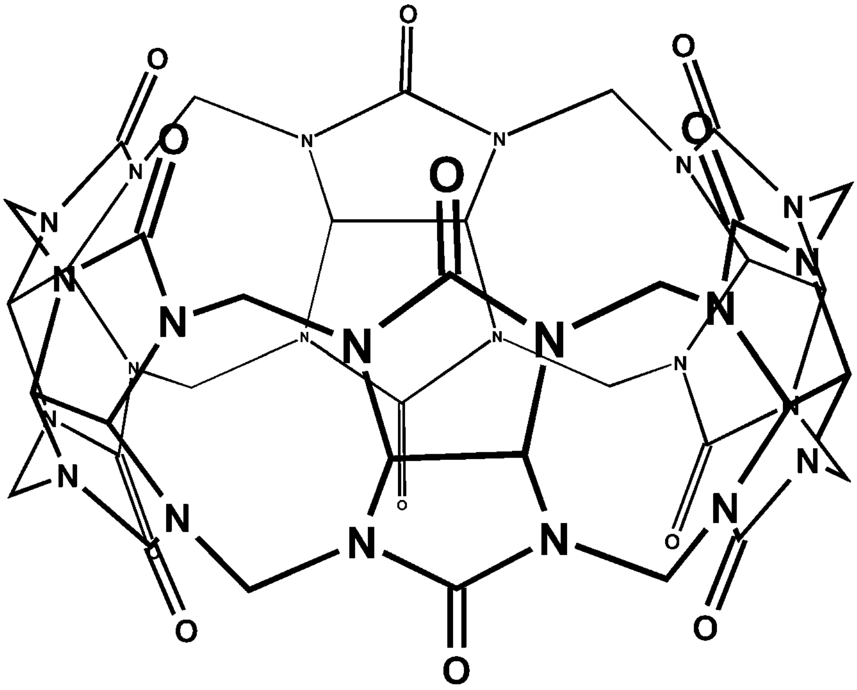


Fig. 1. Chemical structure of cucurbit[6]uril.

complexes. Steinke et al. present the synthesis of polyrotaxanes in a 1,3-dipolar cycloaddition catalysed by cucurbit[6]uril. Each reaction step extends the polymer backbone and results in threading of the macrocyclic ligand [23]. The coordination of pseudorotaxanes to metal ions leads to one- and two-dimensional coordination polymers [24–26].

By definition a rotaxane consists of a linear component encircled by a macrocyclic component, kept together without any chemical bond [27,28]. The cyclic compound is permanently confined between bulky blocker groups, as seen in Fig. 2. There are different lines of approach to the formation of rotaxanes.

- The *threading* method relies on the association of a macrocycle on a rod-shaped molecule. For threading the cavity of the cyclic species has to be larger

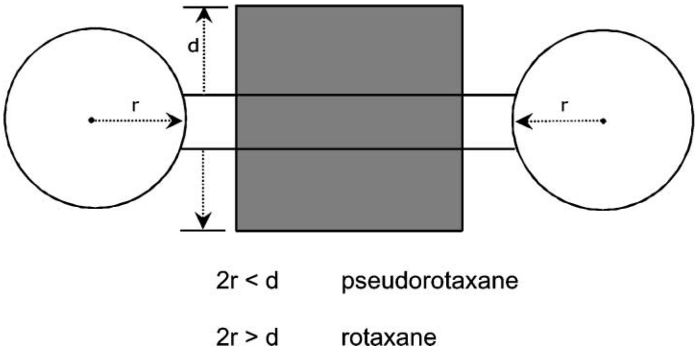


Fig. 2. Differentiation between rotaxane and pseudorotaxane.

than the cross-sectional area of the linear species. The assembly is prevented from dissociation by covalent bonding of bulky blocker groups at the ends of the thread. This process has been studied in detail for the threading of different benzo crown ethers on bipyridine containing dumbbell-shaped components [29–31].

- The *slipping* method is based on a cyclic compound sliding over blocker groups of a rod-shaped molecule, that nearly match the ligand's cavity size. The reversible reaction is favoured, if the desired product is more stable than the dissociated components. With decreasing size of the ligand's cavity and increasing size of the stopper groups, the activation energy of the threading or dethreading process increases. As a result, the yield of rotaxanes formed by slipping strongly depends on small sterical changes of the ligand's cavity or the stopper groups [32,33]. Slippage has been proven to be successful in some thermally promoted self-assembling systems. Vögtle and co-worker [34] report on this way of rotaxane preparation by brief melting of the components at 350 °C.

The present paper investigates the complex formation of several amide-type dumbbell components with the cucurbit[6]uril macrocycle by means of calorimetric titrations. Working at 25 °C, the activation energy of slipping is not acquired, which means this method is only suitable for the examination of threading processes.

2. Experimental

The diamides of 1,2-ethylenediamine, 1,3-propylenediamine, 1,4-butylenediamine, 1,5-pentylenediamine, 1,6-hexylenediamine and 1,7-heptylenediamine were prepared by the reaction with the corresponding carbonic acid chlorides (all Fluka) in dioxane. The resulting diamides were recrystallized from ethanol.

Due to the low solubility of cucurbit[6]uril in aqueous solution a 50% (v/v) mixture of formic acid (Fluka) and water was used as solvent [35]. All calorimetric titrations were performed using a Tronac calorimeter (Model 450).

The stability constants and reaction enthalpies were measured by means of calorimetric titrations. A solution of cucurbit[6]uril (0.03–0.04 mol/l) was added to a solution containing a diamide $(1.8-2.5 \times 10^{-3}$ mol/l). After corrections for all non-chemical heat effects like, e.g. dilution, stirring of the solution, the measured heat Q is related to the reaction enthalpy ΔH by the following equation:

$$Q = \Delta H\,\Delta n$$

with the number of moles Δn of the complex formed. Δn depends on the stability constant of the complex formed. The calculation of the stability constants and the reaction enthalpies from the experimental data has already been described in more detail [36–38]. The reliability of the results obtained from calorimetric titrations has been demonstrated by comparison with the results obtained using other experimental techniques [39].

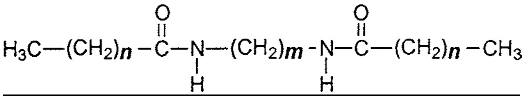
The ^{1}H-NMR spectra were recorded with a Bruker WM 300 using a mixture of DCl/D_2O (20 vol.%) as solvent. 2D-COESY spectra were recorded with a Bruker Avance DRX 500 using a mixture of DCl/D_2O (20 vol.%) as solvent. As internal standard the sodium salt of trimethylsilyl tetradeutero propionic acid was used.

3. Results and discussion

Cucurbit[6]uril is a macrocyclic ligand with a hydrophobic cavity. Aromatic and aliphatic organic compounds can be included inside the hydrophobic cavity of this host molecule. The stability of the formed complexes is influenced by as well the hydrophobic interactions as ion–dipol interactions between the host and the guest substance. Most stable complexes are formed between cucurbit[6]uril and hexamethylene diamine [17]. Here the aliphatic chain has the optimal length to fit into the cavity of the ligand. The two amino groups are located at the portals of cucurbit[6]uril formed by six carbonyl groups each. Thus, optimal ion–dipol interactions between the ammonium ions and the carbonyl groups take place.

In comparison to amin type guest substances the basicity of an amid type nitrogen atom is strongly reduced, due to the negative inductive effect of the carbonyl group. If guest components containing amid groups are included within the cavity of cucurbit[6]uril, the guest nitrogen atoms only weakly interact

Table 1
Stability constants log *K* (*K* in l/mol) and thermodynamic values (in kJ/mol) for the complex formation between cucurbit[6]uril and some diamides (***n*** is the number of methylene groups of the acids and ***m*** the number of methylene groups of the diamines) in aqueous formic acid (50% (v/v)) at 25 °C

 $H_3C-(CH_2)_n-\overset{O}{\overset{\Vert}{C}}-\underset{H}{N}-(CH_2)_m-\underset{H}{N}-\overset{O}{\overset{\Vert}{C}}-(CH_2)_n-CH_3$		log *K*	−Δ*H*	*T*Δ*S*
n	***m***			
0	2	2.77 ± 0.02	3.5 ± 0.5	12.2 ± 0.6
	3	2.63 ± 0.03	4.2 ± 0.6	10.7 ± 0.6
	4	2.57 ± 0.02	4.3 ± 0.3	10.3 ± 0.4
	5	2.61 ± 0.04	4.5 ± 1.2	10.3 ± 1.4
	6	2.70 ± 0.01	3.5 ± 0.5	11.8 ± 0.6
	7	2.80 ± 0.14	4.2 ± 0.9	11.7 ± 1.7
2	2	2.76 ± 0.01	7.2 ± 0.7	8.5 ± 0.8
	3	2.52 ± 0.14	9.9 ± 0.6	4.4 ± 1.4
	4	2.68 ± 0.01	7.9 ± 1.6	7.3 ± 1.7
	5	2.68 ± 0.01	3.7 ± 0.7	11.5 ± 0.8
	6	2.71 ± 0.04	4.5 ± 0.4	10.9 ± 0.6
	7	2.97 ± 0.24	4.0 ± 0.2	12.9 ± 1.6
3	2	3.56 ± 0.03	9.1 ± 0.3	11.2 ± 0.4
	3	3.21 ± 0.04	15.0 ± 2.2	3.2 ± 2.4
	4	3.53 ± 0.19	14.4 ± 2.3	5.8 ± 3.2
	5	3.59 ± 0.24	11.6 ± 0.3	8.8 ± 1.7
	6	3.86 ± 0.13	13.2 ± 0.6	8.7 ± 1.3
4	2	3.36 ± 0.17	19.1 ± 1.5	0.0 ± 2.5
	3	3.57 ± 0.08	13.3 ± 1.1	7.8 ± 0.7
	4	3.58 ± 0.03	14.4 ± 1.0	5.9 ± 1.2
	5	3.35 ± 0.07	13.4 ± 0.4	5.6 ± 0.8
	6	3.40 ± 0.21	13.1 ± 0.9	6.2 ± 2.1

with the carbonyl groups at the portals of the host molecule. For that reason the *N*,*N*′-di(alkanoyl)-1,6-diaminohexanes do not form as stable complexes with cucurbit[6]uril as hexamethylen diamin [15–17].

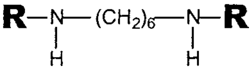
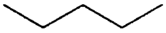
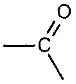
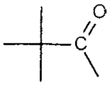
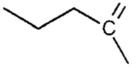
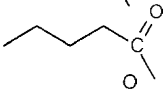
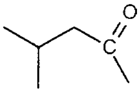
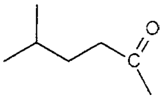
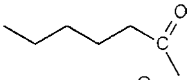
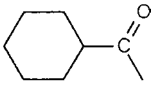
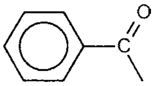
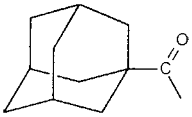
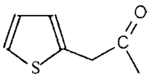
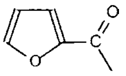
The stability constants and thermodynamic data for the complex formation between cucurbit[6]uril and several diamides are summarized in Table 1. The number of methylene groups ***m*** between the amide groups barely influences the complex stability and the complex formation enthalpy. In contrast the number of methylene groups ***n*** of the terminating carbonic acids has a stronger influence upon the stability constant and the reaction enthalpy of the complex formation. With increasing chain length ***n*** the stability constants and the formation enthalpies raise. Obviously, the inductive effect of the terminating alkyl groups changes the charge distribution at the amid groups.

Table 2 gives some stability constants and the thermodynamic data of the complex formation of cucurbit[6]uril with different *N*,*N*′-di(alkanoyl)-1,6-diaminohexanes. All guest compounds listed in Table 2 embody the hexamethylene diamine building-block. The terminating groups have different diameters. The complexe formation is only possible if the cavity size of the macrocyclic ligand is larger than the cross-sectional diameter of the guest molecule. This is schematically shown in Fig. 2. Bulky end groups prevent the threading procedure.

The thermodynamic values obtained by calorimetric titration experiments only show the inclusion complex formation with non-branched *N*,*N*′-di(alkanoyl)-1,6-diaminohexanes. Weak ion–dipol interactions as well as hydrophobic effects between host and guest components lead to poor exothermic reaction enthalpies.

Table 2

Stability constants log K (K in l/mol) and thermodynamic data (in kJ/mol) for the complex formation between cucurbit[6]uril and some diamides prepared from 1,6-diamino hexane in aqueous formic acid (50% (v/v)) at 25 °C

 $R{-}\underset{H}{N}{-}(CH_2)_6{-}\underset{H}{N}{-}R$	R	log K	$-\Delta H$	$T\Delta S$
	H	6.44[a]	29.6[b]	8.9[b]
		4.86 ± 0.10	25.0 ± 0.9	2.6 ± 1.5
Acetic		2.70 ± 0.01	3.5 ± 0.5	11.8 ± 0.6
Tert-butylacetic		–[c]	–	–
Butyric		2.71 ± 0.04	4.5 ± 0.4	10.9 ± 0.6
n-Valeric		3.86 ± 0.13	13.2 ± 0.6	8.7 ± 1.3
i-Valeric		–[c]	–	–
4-Methylvaleric		–[d]	−1.5 ± 0.1	–
Hexanoic		3.40 ± 0.21	13.1 ± 0.9	6.2 ± 2.1
Cyclohexane carboxylic		–[e]	–	–
Benzoic		–[c]	–	–
Adamantane carboxylic		–[e]	–	–
Thiophen-2-acetic		–[c]	–	–
2-Furoylic		–[c]	–	–

[a] Reference [33].

[b] Reference [23].

[c] No complex formation detectable.

[d] Not possible to calculate from the thermogram.

[e] Solubility of the diamide too low for calorimetric measurements.

Small positive values of the reaction entropies demonstrate only minor changes in the solvation of the reaction partners. The solvation of the macrocyclic ligand just as the solvation of the formed complexes are nearly constant. Only the solvation of the guest substance varies depending on the chemical structure. Forming the inclusion complex, some of these solvent molecules are released. As a result the reaction is mainly favoured by entropic contributions. For aromatic, cycloaliphatic and branched alkyl substituted diamides, mentioned in Table 2, calorimetric titration experiments give no indication of a complex formation.

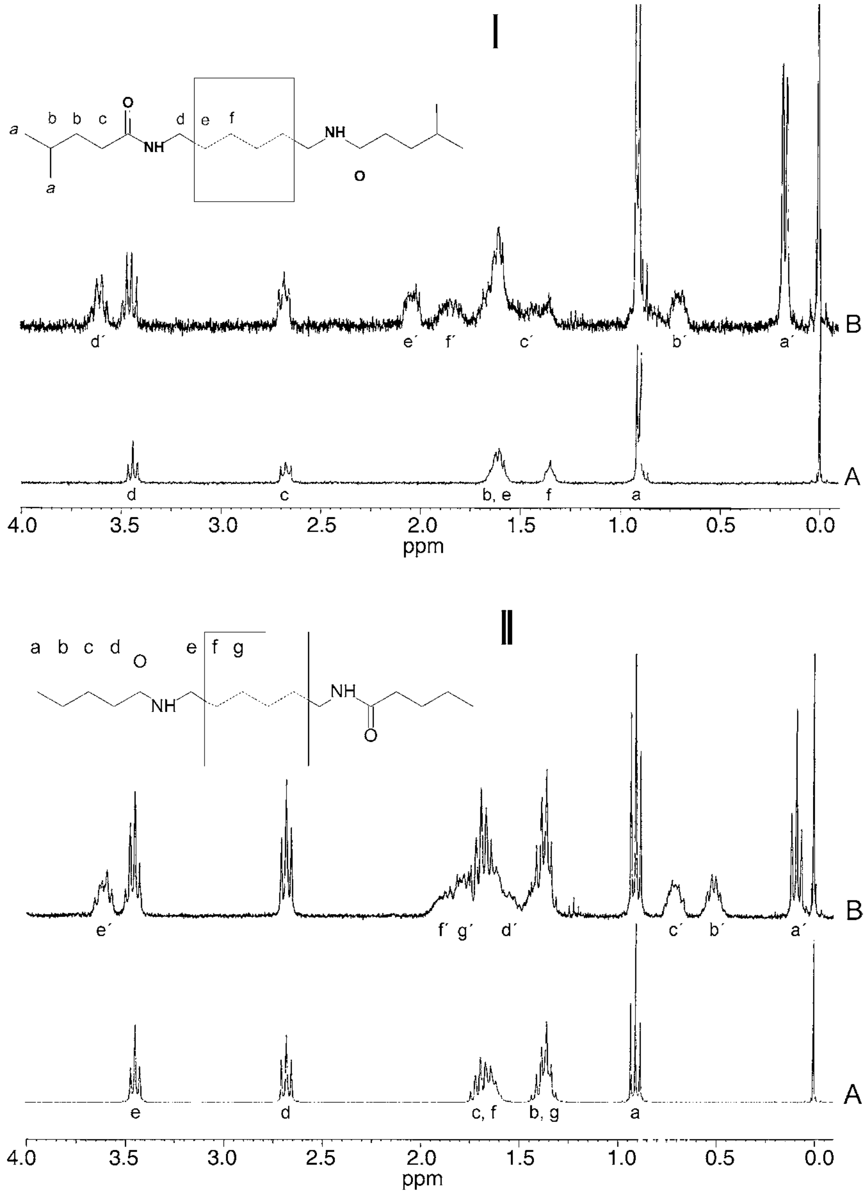


Fig. 3. 300 MHz ^{1}H-NMR spectra of *N*,*N*′-di(4-methylvaleroyl)-1,6-diaminohexane (I) and *N*,*N*′-di(valeroyl)-1,6-diaminohexane (II) in DCl/ D_2O (20 vol.%). (A) Shows the spectra of the pure diamide compounds, (B) in the presence of cucurbit[6]uril. An apostrophe marks the proton signals shifted due to complex formation with the macrocyclic ligand.

As known form literature the formation of inclusion complexes can be shown by proton resonance experiments. The hydrophobic cavity of cucurbit[6]uril is a magnetic shielding region. In contrast to the uncomplexed guest substance the signals of the groups of guest molecules included within the cavity of the macrocyclic ligand are shifted [40].

Fig. 3 shows the ^{1}H-NMR spectra of *N*,*N*′-di-(4-methylvaleroyl)-1,6-diaminohexane (I) and *N*,*N*′-di(valeroyl)-1,6-diaminohexane (II) in absence and presence of cucurbit[6]uril. The proton resonance spectra of the pure guest compounds are given as IA and IIA. The assignment of the proton signals investigated by 2D-COSY experiments is given by small letters underneath the base line of the spectra. In the presence of cucurbit[6]uril the aliphatic guest substances are complexed within the hydrophobic cavity of the macrocylic host molecule. The apolar environment of the cucurbit[6]uril interior results in shielding of the alkyl chain. Thus, the proton signals of the guest substances are shifted, as shown in IB and IIB. The small labels with an apostrophe assign the proton signals shifted due to the formation of the inclusion complexes.

The experimental results obtained by the calorimetric titration of *N*,*N*′-di(4-methylvaleroyl)-1,6-diaminohexane do not give any indication of an inclusion complex formation. On the other hand, the ^{1}H-NMR experiment clearly shows the inclusion of this diamide inside the cavity of cucurbit[6]uril.

The complex formation between cucurbit[6]uril and organic substances is a reversible process. Proton resonance spectra of the investigated guest molecules show both, the signals of the uncomplexed and the complexed material. Thus, the kinetic of the inclusion complex formation is slow on the NMR time scale. The new signals caused by the complex formation between cucurbit[6]uril and the aliphatic guests are widened compared with the uncomplexed compound. This proves the threading process to be dynamic. Therefore, the macrocyclic ligand is not fixed at a certain position on the rod-shaped guest molecule.

Proton resonance experiments with diamides containing terminating cycloaliphatic or aromatic groups do not show any proton signal shifts indicating the formation of inclusion complexes. However, cucurbit[6]uril forms stable inclusion complexes with various aromatic compounds like aniline or 4,4′-bipyridine derivatives [22]. Thus, the aromatic ring definitely fits into the cavity of cucurbit[6]uril. The neighbourhood of an aromatic ring and a carbonyl group obviously strongly influences the electron density at the amid group, strengthening the solvation of these dumbbell-shaped guest molecules. The presence of the bounded solvent molecules increases the steric and energetic requirements for the threading or dethreading process of cucurbit[6]uril. Even after heating the solutions of cucurbit[6]uril and these diamides no complex formation could be observed [41].

Acknowledgements

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