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Complex Formation of Crown Ethers with the Cucurbit[6]uril–Spermidine and Cucurbit[6]uril–Spermine Complex in Aqueous Solution

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Abstract

Alkyl amines are able to form complexes with either crown ethers or cyclodextrins or cucurbit[6]uril. The same is known for polyamines such as spermidine and spermine. However, the simultaneous formation of such polyamines with crown ethers and cucurbit[6]uril has not been studied. The ability of polyamines such as spermidine and spermine to form mixed complexes with different ligands, e.g. crown ethers and cucurbit[6]uril has been studied in aqueous solution using pH-metric and calorimetric titrations. The thermodynamic data of reaction between crown ethers with spermidine, spermine and their cucurbit[6]uril complexes have been determined. The presence of cucurbit[6]uril on the polyamines has no important influence upon the reaction of these amines with crown ethers. The reactions between polyamines, cucurbit[6]uril and crown ethers are simple examples for the self organization of molecules due to specific interactions.

Introduction

Cucurbit[6]uril is a very promising macrocyclic ligand. Though it was first synthesized in 1905 [1] it took a long time before this structure was established in 1981 [2]. Cucurbit[6]uril is formed during the reaction of urea and glyoxal followed by a reaction with formaldehyde in strong acidic solution. It was already noticed by Behrend *et al.* [1] that this compound is able to react with inorganic ions and organic molecules to form crystalline or insoluble products. Mock [3] studied the complex formation between cucurbit[6]uril and nitrogen containing organic molecules. He observed that parts of these molecules are included within the cavity of the ligand. The protonated amino groups interact with the six carbonyl groups located at each portal of the cavity. In the case of diamines, the most stable complexes are formed if both nitrogen atoms interact with the carbonyl groups at each portal. The stability of the complexes formed decreases if the number of methylene groups is too small or too high. In these cases only one amino group is able to interact with the six carbonyl groups located at one portal. Since the first results reported by Mock the number of published papers about cucurbit[6]uril increases rapidly from year to year. In the meantime, several derivatives of cucurbit[6]uril have been synthesized. The number of glycoluril units varies between 5 and 10 [4–7].

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The complex formation of cucurbit[6]uril with organic molecules [3, 8–10] and inorganic salts has been studied in detail [11–15]. The high complex stabilities of cucurbit[6]uril with some diamines and spermine favour the formation of rotaxanes and polyrotaxanes [16–19]. Even higher ordered structure can be obtained using these complexes with cucurbituril [20, 21]. With benzoyl or naphthoyl stopper groups the [2] rotaxanes with cucurbit[6]uril are able to form complexes with α-, β- and γ-cyclodextrin [22]. Due to the complex formation with cyclodextrins the solubility of the complexed rotaxanes increases.

The nitrogen atoms of spermine and spermidine not involved in the complex formation with cucurbituril should be able to form complexes with macrocyclic ligands, e.g. crown ethers. As a result, mixed complexes of spermine and spermidine with two different ligands should be present in solution. In this paper, we want to present the first experimental results for the formation of these complexes.

Experimental

Spermidine, spermine, pentylamine (all Fluka), $Ba(ClO_4)_2$, the crown ethers 12-crown-4 (12C4), 15-crown-5 (15C5) and 18-crown-6 (18C6) (all Merck) are used without further purification. The synthesis and purification of cucurbit[6]uril, see Figure 1, has already been described in detail [7]. As solvent bidistilled water

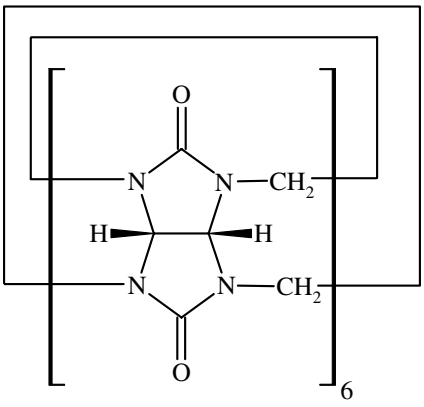

Figure 1. Structure of cucurbit[6]uril.

is used. The hydrochloride of pentylamine is prepared by passing dry hydrogenchloride through a solution of pentylamine in diethyl ether. The complexes of spermidine or spermine with cucurbit[6]uril are prepared in aqueous solution by addition of solid cucurbit[6]uril to the solutions of both amines.

Potentiometric titrations are performed using a GLpKa analyser (Sirius Analytical Instruments, Forest Row). The protonation constants and the stability constants are calculated directly from the experimental data using the software package Refinement Pro (Version V1.114, Sirius Analytical Instruments, Forest Row). From this titration curves stability constants for the formation of 1:1- and 2:1-complexes (ratio of crown ether to amino compound) can be calculated using more then 50 data points.

A titration calorimeter (Tronac Model 450, Orem Utah) is used for the calorimetric titrations. To measure the heat of complex formation between spermidine and spermine with cucurbit[6]uril, a solution of cucurbit[6]uril (0.04 mol/l) is added continuously for 1 min to a solution of the amine ($2–3 \times 10^{-3}$ mol/l). Due to the low solubility of cucurbit[6]uril, aqueous formic acid (50 vol.%) is used as solvent.

The solubility of the amine complexes with cucurbit[6]uril in aqueous solution is high enough for calorimetric titrations. For the measurements of the 1:1-complexes between crown ethers and pentylamine hydrochloride, the cucurbit[6]uril–spermidine or spermine complex a solution of a crown ether (1.8 ml, 0.06–0.08 mol/l) is added continuously to a solution of the amine or the corresponding complex with cucurbit[6]uril (40 ml, $2–5 \times 10^{-3}$ mol/l). Under these conditions the concentration of the crown ethers in the reaction vessel is smaller than the concentration of the spermine complex with cucurbit[6]uril. Thus, nearly exclusively the formation of 1:1-complexes takes place. The heat Q produced during titration is related to the reaction enthalpy ΔH_1 after correction for all non-chemical heat effects by the following equation:

$$Q = \Delta\, n_1 \Delta\, H_1, \tag{1}$$

with Δn_1 being the number of moles of the 1:1-complexes formed. The mathematical treatment of the experimental data has been described in detail in the literature [23–25]. The accuracy of the calorimeter is controlled using the reaction of 18-crown-6 with $Ba(ClO_4)_2$ in aqueous solution. The calculated values of the stability constant ($\log K = 3.58 \pm 0.02$) and of the reaction enthalpy ($\Delta H = -32.6 \pm 0.9$ kJ/mol) are in absolute accordance with the results from the literature [26]. All potentiometric and calorimetric titrations are repeated at least three times.

Results and discussion

The protonation reactions of spermidine and spermine show significant differences in the presence and absence of cucurbit[6]uril, see Table 1 and Figure 2. These differences are caused by the presence of cucurbit[6]uril. From the experimental results, it is obvious that a deprotonation of the amino groups interacting with cucurbit[6]uril is not possible under the experimental conditions. However, the values of the first protonation constant are nearly identical within experimental error with the exception of the cucurbit[6]uril complex with spermine. The values of the second protonation constant are lower in the presence of cucurbit[6]uril. Obviously, the basicity of this amino group is reduced.

Stability constants for the cucurbit[6]uril complexes with spermidine and spermine together with data from the literature are summarized in Table 2. The differences between the data measured in this work compared with the data taken from the literature are most reasonable explained by the different techniques used. In the literature, a competitive NMR technique has been performed. The accuracy of this method is sometimes lower compared with pH-metric titrations [27, 28]. The values of the stability constants of cucurbit[6]uril with spermidine and spermine are identical within the

Table 1. Protonation constants of spermidine and spermine and of the corresponding cucurbit[6]uril complexes in aqueous solution at 25 °C

	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$
$H_2N(CH_2)_3NH(CH_2)_4NH_2$	10.82 ± 0.07	9.89 ± 0.04	8.38 ± 0.02	–
$H_2N(CH_2)_3NH(CH_2)_4NH_2$*Cuc[6]	11.16 ± 0.19	9.11 ± 0.08	–	–
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$	11.04 ± 0.07	10.21 ± 0.05	8.97 ± 0.04	8.10 ± 0.02
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$*Cuc6	9.63 ± 0.26	8.95 ± 0.14	–	–

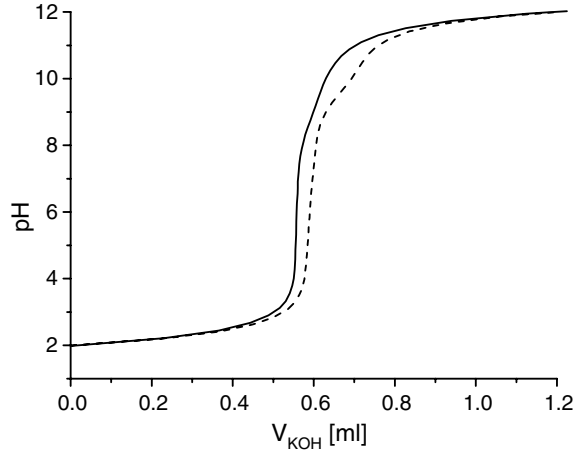

Figure 2. Potentiometric titration curves of spermine (–) and of the spermine cucurbit[6]uril complex (--) for the determination of the pK_a values.

Table 2. Stability constants log K (K in l/mol) and values of the reaction enthalpy ΔH (in kJ/mol) for the complex formation of cucurbit[6]uril with spermidine and spermine n aqueous solution at 25 °C

	log K	$-\Delta H^c$
$H_2N(CH_2)_3NH(CH_2)_4NH_2$	5.82 ± 0.13[a] 7.12[b]	19.4 ± 0.4
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$	5.61 ± 0.10[a] 6.13[b]	20.4 ± 1.0

[a] From pH-metric titrations.
[b] Ref. 3 (50 vol.% formic acid).
[c] From calorimetric titrations in aqueous formic acid (50 vol.%).

experimental error. This result is not surprising. In case of both amino compounds only the butylenediamine subunits are included within the cavity of the ligand. All other molecular groups of both amines are located outside the cavity. As a result, the values of the reaction enthalpies and of the reaction entropies for both amines are identical too.

After the cucurbit[6]uril complex has been formed one amino group of spermidine and two amino groups of spermine are not involved in this process. These primary amino groups are able to form additional complexes with crown ethers. A hypothetic schematic structure of the 2:1-complex of the crown ether 18C6 with a cucurbit[6]uril–spermine complex is shown in Figure 3. Up to now no crystals have been obtained suitable for crystallographic measurements.

In Table 3, the results for the complex formation of crown ethers with pentylamine hydrochloride, spermidine and spermine and their corresponding complexes with cucurbit[6]uril are given. Both pH-metric and calorimetric titrations give nearly identical values of the complex stabilities. In case of pentylamine hydrochloride, only the formation of a 1:1-complex with crown ethers is possible. These values are in accordance

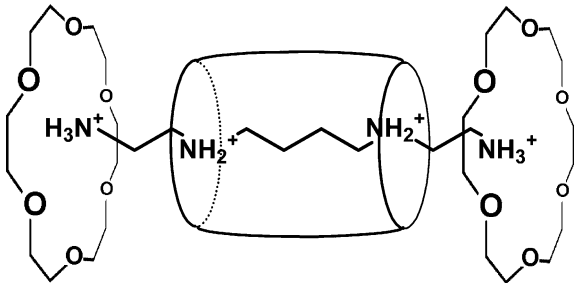

Figure 3. Schematic view of a 2:1 complex of 18C8 with the cucurbit[6]uril–spermine complex

with the results obtained for spermidine and spermine and their cucurbit[6]uril complexes.

Spermidine and spermine form 2:1-complexes (ratio of crown ether to amine) with the crown ethers used. The values of K_2 are always smaller then K_1 indicating a small influence of the first complexation upon the second reaction. The ring size of the crown ethers used is not sufficient to thread onto the chain and form complexes with the secondary amino groups. The crown ether 24-crown-8 and larger ones are able to thread and to form pseudorotaxanes [29]. The values of the stability constants and reaction enthalpies for the reaction of crown ethers with spermidine, spermine and their cucurbit[6]uril complexes are nearly identical with the values for the reaction of crown ethers with the ammonium or alkylammonium ions in aqueous solution [30].

In the case of spermidine, the presence of cucurbit[6]uril prevents the formation of 2:1-complexes with the crown ethers. Only one of the primary amino group is not involved in the complex formation with cucurbit[6]uril, and therefore only a 1:1-complex is formed with the crown ethers. However, spermine with its four amino groups is able to form a cucurbit[6]uril complex and afterwards to bind two crown ether molecules to both primary amino groups.

These measurements give the first clear evidence for the simultaneous formation of complexes with polyamines, cucurbit[6]uril and crown ethers. In case of spermidine, a 1:1:1-complex (amine:cucurbit[6]uril: crown ether) and in case of spermine even a 1:1:2-complex is formed. The reactions between these three different species in solution are simple examples for the self organization of molecules due to specific interactions. Even relative simple molecules can act as building blocks for the construction of nanoscalic structures.

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Table 3. Stability constants log K (K in l/mol) and thermodynamic values ΔH and $T\Delta S$ (in kJ/mol) for the complex formation of crown ethers with pentylamine hydrochloride, the cucurbit[6]uril-spermidine and cucurbit[6]uril-spermine complexes in aqueous solution at 25 °C

	Values	12C4	15C5	18C6
$H_2N(CH_2)_4CH_3$*HCl	log K^a	2.47 ± 0.26	2.25 ± 0.04	2.42 ± 0.05
	log K^b	2.53 ± 0.01	2.57 ± 0.01	2.58 ± 0.01
	$-\Delta H^b$	0.5 ± 0.1	1.0 ± 0.1	1.0 ± 0.2
	$T\Delta S^b$	14.9 ± 0.9	13.6 ± 0.2	13.7 ± 0.2
$H_2N(CH_2)_3NH(CH_2)_4NH_2$*3HCl	Log K_1^a	2.76 ± 0.02	2.72 ± 0.02	2.58 ± 0.12
	Log K_2^a	2.54 ± 0.08	2.15 ± 0.10	2.32 ± 0.50
	Log K_1^b	2.60 ± 0.10	2.56 ± 0.07	2.54 ± 0.03
	$-\Delta H_1^b$	2.0 ± 0.2	1.2 ± 0.1	1.2 ± 0.1
	$T\Delta S_1^b$	12.8 ± 0.7	13.4 ± 0.4	13.2 ± 0.3
$H_2N(CH_2)_3NH(CH_2)_4NH_2$*Cuc[6] *3HCl	log K_1^a	2.23 ± 0.03	2.19 ± 0.05	2.13 ± 0.15
	Log K_2^a	–	–	–
	log K_1^b	2.43 ± 0.08	2.48 ± 0.13	2.43 ± 0.08
	$-\Delta H_1^b$	0.3 ± 0.2	0.5 ± 0.1	1.0 ± 0.2
	$T\Delta S_1^b$	13.5 ± 0.7	13.6 ± 0.8	12.8 ± 0.7
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$*4HCl	Log K_1^a	2.63 ± 0.03	2.71 ± 0.06	2.98 ± 0.04
	log K_2^a	2.29 ± 0.07	2.35 ± 0.08	2.40 ± 0.12
	log K_1^b	2.45 ± 0.05	2.48 ± 0.08	2.51 ± 0.02
	$-\Delta H_1^b$	2.1 ± 0.2	1.6 ± 0.1	1.6 ± 0.1
	$T\Delta S_1^b$	11.8 ± 0.4	12.5 ± 0.6	12.7 ± 0.1
$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$*Cuc6*4HCl	Log K_1^a	2.85 ± 0.03	2.48 ± 0.05	2.80 ± 0.06
	Log K_2^a	2.48 ± 0.06	2.21 ± 0.07	2.15 ± 0.12
	log K_1^b	2.47 ± 0.06	2.50 ± 0.05	2.48 ± 0.03
	$-\Delta H_1^b$	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.1
	$T\Delta S_1^b$	13.5 ± 0.6	13.6 ± 0.5	13.5 ± 0.3

[a] From pH-metric titrations
[b] From calorimetric titrations

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