Short Communication

Cucurbit[6]uril as Ligand for the Complexation of Diamines, Diazacrown Ethers and Cryptands in Aqueous Formic Acid

H.-J. BUSCHMANN[1,*], L. MUTIHAC[2], K. JANSEN[1], and E. SCHOLLMEYER[1]
[1]*Deutsches Textilforschungszentrum Nord-West e.V., Adlerstrasse 1, D-47798, Krefeld, Germany;* [2]*Department of Analytical Chemistry, University of Bucharest, 4–12 Blvd. Regina, Elisabeta, Bucharest, 703461, Romania*

Abstract

The complex formation between cucurbit[6]uril and different diamines, diazacrown ethers, and cryptands has been studied in aqueous formic acid solution. The complex stabilities and the thermodynamic values for the complex formation of diamines are reduced if any further donor atom (e.g., sulfur, oxygen, or nitrogen) is present in the molecules. The inclusion of this polar group inside the cavity of cucurbit[6]uril has a negative effect upon the complex formation. Diazacrown ethers and cryptands do not form inclusive complexes. One nitrogen donor atom interacts with the carbonyl groups at one of the portals.

Introduction

The macrocyclic ligand, cucurbit[6]uril, obtained by the condensation of glycoluril with an excess of formaldehyde in acidic solution [1] exhibits binding abilities as receptor towards different substrates. Freeman *et al.* [2, 3] reported its structure 76 years after its synthesis in 1905. This structure is characterized by a hydrophobic cavity and two oxygen-crowned portals and makes today the cucurbit[6]uril an interesting host in molecular recognition chemistry. Based on its rigid structure and the ability to form stable complexes with salts and organic molecules, the host–guest chemistry of cucurbit[6]uril has led to new opportunities of applications. The factors involved in host–guest complexation of cucurbit[6]uril with different guest in aqueous solution were reported together with a detailed complexation mechanism in the presence of cations [4].

To simplify the current name of this substance, the trivial name 'cucurbituril' was suggested due to the structural resemblance with a pumpkin (latin Cucurbitaceae). Later on, Stoddart suggested to give substituents as prefixes and the ring size in brackets [5]. The area of applications of cucurbituril in molecular recognition was extended by the synthesis of cucurbituril homologues and derivatives having different cavities and good solubility in common solvents [6, 7].

Mock and Shih [8, 9] discovered the ability of cucurbit[6]uril to form strong complexes with amines and diamines. The most stable complexes are formed with diamines if the molecular size of the diamines and the heights of the receptor are nearly identical. Under these circumstances, both amino groups interact simultaneously with the carbonyl groups at each portal of the macrocyclic ligand. Starting from these complexes with cucurbit[6]uril, the rotaxanes have been synthesized [10, 11]. In the meantime even the rotaxanes with cucurbit[6]uril fixed on synthetic polymer surfaces [12] or attached on gold surfaces [13] have been reported. By using spectrophotometric and kinetic investigations, Hoffmann *et al.* [14] established the mechanism for the formation of association and inclusion complexes of cucurbituril with 4-methylbenzylammonium.

In the case of cucurbit[6]uril, the diamines are very interesting molecules for the complex formation and the subsequent synthesis of rotaxanes. Thus, we decided to extend the knowledge about the complex formation of cucurbit[6]uril with noncyclic, macrocyclic (diaza crown ethers), and macrobicyclic diamines (cryptands). These molecules themselves are able to form complexes with a large number of cations [15–18]. Due to the behavioural duality to act as both host and guest, these molecules may even form inclusion complexes with cucurbit[6]uril. The inclusion of one macrocyclic compound by another is already known from literature. Thus, the encapsulation of the macrocyclices cyclen and cyclam in the cavity of cucurbit[8]uril is already known [19]. Even the formation of an inclusion complex of cucurbit[5]uril with cucurbit[10]uril has been reported [20].

In this work, the complexation of some noncyclic diamines and different diazacrown ethers and cryptands with cucurbit[6]uril in aqueous formic acid (50 %v/v) by means of calorimetric titration has been studied. The stability constants and the reaction enthalpies and

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* Author for correspondence. E-mail: buschmann@dtnw.de

entropies of the complex formation have been determined.

Experimental

The synthesis and characterisation of cucurbit[6]uril has already been described in detail [21]. The structure of the ligand is shown in Figure 1. 1,8-Diamino-3,6-di-thia-octane (DATO) was synthesized according to published procedures [22]. The noncyclic diamines: 1,5-diamino pentane (DAP, Fluka), 1,5-diamino-3-thia-pentane (DATP, ICN), 1,5-diamino-3-oxa-pentane (DAOP, Acros), diethylenetriamine (DAAP, Aldrich), 1,8-diamino octane (DAO, Fluka), 1,8-diamino-3,6-diox-a-octane (DAOO, Merck) and triethylenetetramine (DAAO, Aldrich) were commercial samples. The macrocyclic and macrobicyclic diamines: 1,10-diaza-15-crown-5 (Kryptofix 21, Merck), 1,10-diaza-18-crown-6 (Kryptofix 22, Merck), 4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5] eicosan (Kryptofix 211, Merck) and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan (Kryptofix 222, Merck) were used without any further purification. All chemical structures of the amines are given in Figure 2. The aqueous formic acid (Fluka) (50% v/v) was used as solvent due to the low solubility of cucurbit[6]uril in pure water [21].

All calorimetric titrations were carried out using a calorimeter Tronac Model 450 (TRONAC, Orem Utah, USA). The solution of the ligand cucurbit[6]uril (0.04–0.06 mol/l) was added continuously to a solution of the amine (0.002–0.004 mol/l). The heat Q produced during the titration was related to the reaction enthalpy ΔH, after correction for all nonchemical heat effects, by the following equation:

$$Q = \Delta n \bullet \Delta H \qquad (1)$$

with Δn as the number of moles of the complex formed. The mathematical treatment of the experimental data has already been described in detail [23–25]. The accuracy of the calorimeter was checked using the reaction of 18-crown-6 with $Ba(ClO_4)_2$ in aqueous solution (log $K = 3.58 \pm 0.2$ and $\Delta H = -32.6 \pm 0.3$ kJ/mol). These values are in perfect accordance with the data reported in the literature [26].
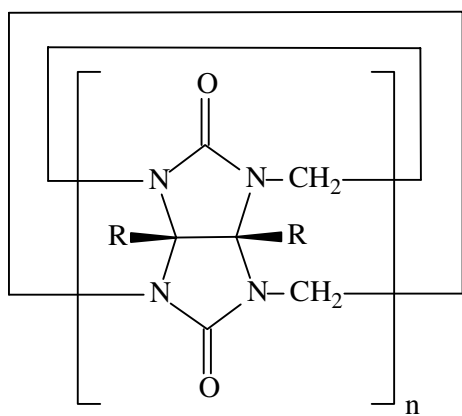
Results and discussion

The stability constants for the complexation of noncyclic diamines by cucurbit[6]uril in aqueous formic acid are summarized in Table 1 together with results taken from the literature. The differences between results originate from the experimental method used for the determination of the stability constants. The results reported by Mock and Shih [8] have been determined using competitive UV-spectroscopic measurements with 4-methylbenzylamine. No values of the reaction enthalpies and entropies have been reported.

The noncyclic diamino alkanes form the most stable complexes with cucurbit[6]uril. The presence of any
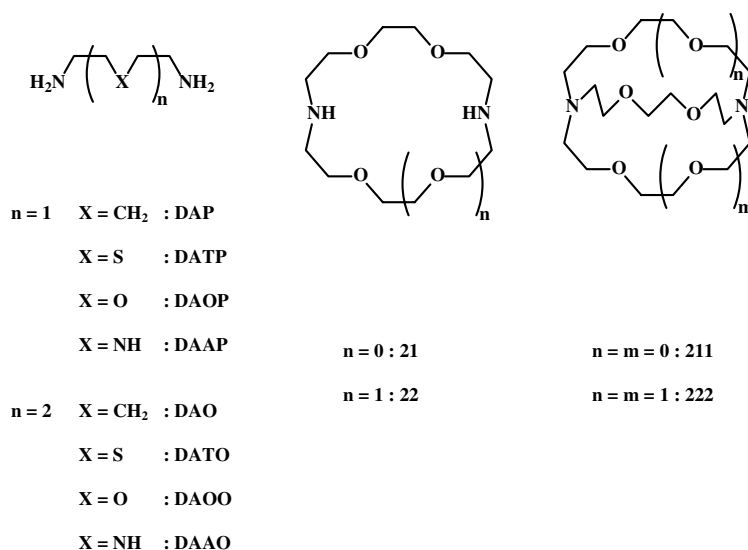

n = 6 ; R = H

Figure 1. Structure of cucurbit[6]uril.

n = 1   X = CH₂ : DAP

        X = S   : DATP

        X = O   : DAOP

        X = NH   : DAAP

n = 2   X = CH₂ : DAO

        X = S   : DATO

        X = O   : DAOO

        X = NH   : DAAO

n = 0 : 21

n = 1 : 22

n = m = 0 : 211

n = m = 1 : 222

Figure 2. Chemical structures of the diamines, diaza crown ethers and cryptands used.

Table 1. Stability constants K (l/mol) and thermodynamic values ΔH and $T\Delta S$ (kJ/mol) for the complexation of different noncyclic diamines with cucurbit[6]uril in aqueous formic acid (50% v/v) at 25 °C

	DAP	DATP	DAOP	DAAP	DAO	DATO	DAOO	DAAO
log K	>5	$-^b$	2.65 ± 0.04	$-^c$	3.63 ± 0.05	3.08 ± 0.02	2.54 ± 0.05	$-^c$
	6.39[a]	5.62[a]	3.72[a]		3.96[a]			
$-\Delta H$	20.3	16.4 ± 0.2	9.7 ± 0.5	7.9 ± 0.2	18.8 ± 0.1	11.6 ± 1.1	19.2 ± 0.2	7.7 ± 0.3
$T\Delta S$	16.0[d]	15.5[d]	5.4 ± 0.7		1.8 ± 0.4	5.9 ± 1.2	−4.8 ± 0.5	

[a] Ref. 8.
[b] No stability constant calculable from the titration curve.
[c] No 1:1-complex formation.
[d] Calculated using the stability constant given in Ref. 8.

heteroatome in the alkyl chain reduces the complex stabilities with the exception of DAOO. The values of the reaction enthalpies and entropies decrease in comparison with those of DAP and DAO. The values of the reaction enthalpies for the complex formation with DAAP and DAAO are identical. Thus, only interactions between one amino group and the carbonyl groups located at one portal of cucurbit[6]uril are observed. The presence of any additional nitrogen atom within the alkyl chain prevents the formation of an inclusion complex. All these observations can be explained by changes in the solvation of the different diamines.

For the inclusion into the cavity of cucurbit[6]uril all or nearly all solvent molecules in contact with the additional heteroatoms in the alkyl chain have to be removed. As a result, the values of the reaction enthalpy decrease. The inside of the cucurbituril cavity has a lipophilic character and, consequently, these diamines have to adopt inside the cavity a configuration with all nonpolar groups directed to the inner surface of the cavity. The diamine DAOO may adopt inside the cucurbit[6]uril a helical conformation with both oxygen atoms directed to the center of the cavity. Now water molecules are able to interact with both oxygen atoms simultaneously, see Figure 3. This assumption can explain the high value of the reaction enthalpy because no real desolvation of the diamine DAOO has to take place during complex formation. On the other hand, the sterical requirements for the formed complex are high resulting in a negative value of the reaction entropy. Unfortunately we have no crystal structure at the moment supporting this idea.

Due to the proposed structure of the cucurbit[6]uril complex with DAOO the sterical requirements during the complex formation are higher compared with DATO. The interaction between solvent molecules and the oxygen donor atoms in DAOO are stronger compared with the sulfur donor atoms of DATO. This effect is mainly responsible for the observed differences.

The stability constants and thermodynamic values for the reaction of cucurbit[6]uril and diazacrown ethers and cryptands in aqueous formic acid are given in Table 2. Surprisingly, the size and the number of oxygen donor atoms of the macrocyclic and macrobicyclic diamines do not influence the values of the stability constants and of the reaction enthalpies and entropies.
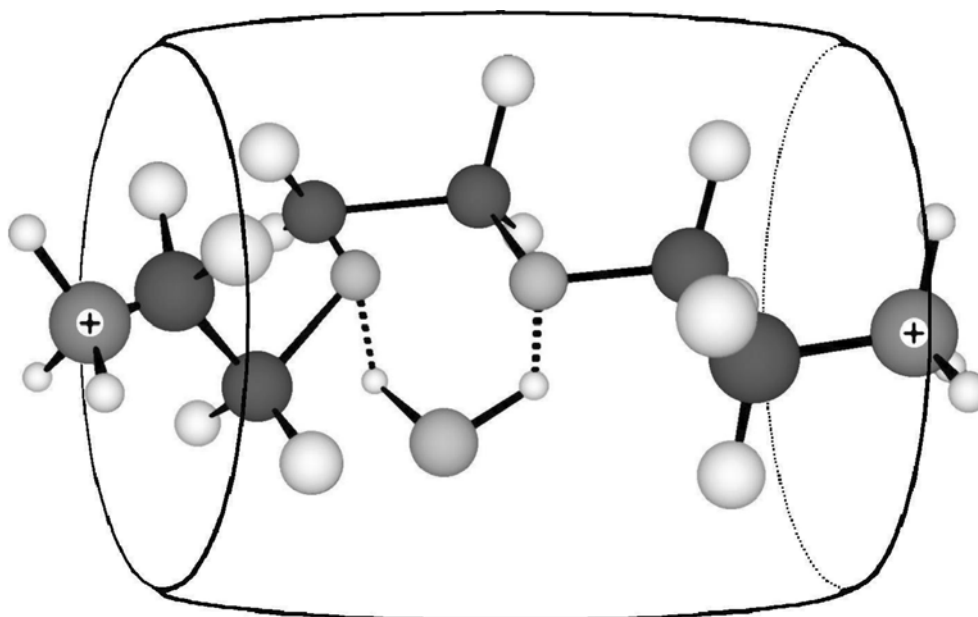

Figure 3. Schematical presentation of a complex formed between cucurbituril and DAOO still interacting with one water molecule.

Table 2. Stability constants K (l/mol) and thermodynamic values ΔH and $T\Delta S$ (kJ/mol) for the complexation of different diazacrown ethers (21) and (22) and cryptands (211) and (222) with cucurbit[6]uril in aqueous formic acid (50% v/v) at 25 °C

	(21)	(22)	(211)	(222)
log K	2.73 ± 0.03	2.79 ± 0.01	2.81 ± 0.03	2.76 ± 0.01
$-\Delta H$	4.9 ± 0.8	2.0 ± 0.1	2.6 ± 0.3	3.4 ± 0.2
$T\Delta S$	10.6 ± 1.0	13.9 ± 0.1	13.4 ± 0.4	12.3 ± 0.2

Obviously, during the complex formation only interactions between one nitrogen atom of the macrocyclic and macrobicyclic ligands and six carbonyl groups at one portal of cucurbit[6]uril take place.

Kinetic measurements of the complexation reaction between cucurbit[6]uril and cyclohexylmethyl amine [5] and 4-methylbenzyl amine [14] give clear evidence for a two step reaction mechanism:

$$L + A \leftrightarrow L \cap A \leftrightarrow L \subset A \qquad (2)$$

In a first reaction step between an amine A and the ligand cucurbit[6]uril L, an exclusive complex $L \cap A$ is formed. In this complex, the amino group is interacting with the carbonyl groups but the cyclohexyl or benzyl group is still outside the cavity. In a second reaction step, both compounds form a real inclusive complex $L \subset A$. Now the cyclohexyl or benzyl group is located within the cavity of cucurbit[6]uril. This two-step mechanism is well established for the formation of cryptand complexes with cations [27]. If the cations are too big to be accommodated within the cavity of the cryptands, exclusive complexes are formed only [28]. Obviously, cucurbit[6]uril and diazacrown ethers and cryptands are not able to form inclusive complexes. The reaction stops at the exclusive complex. The desolvation of the ether donor atoms of the macrocyclic and macrocyclic ligands and the subsequent inclusion inside the hydrophobic cavity of cucurbit[6]uril energetically disfavours the formation of an inclusive complex. The formation of an exclusive complex is also favoured by entropic contributions. During the formation of exclusive complexes solvent molecules are released from the amino groups from the guest molecules and from the carbonyl groups of the host. The number of released solvent molecules can be calculated using the entropy of fusion of water at 25 °C which is $T\Delta S = 6.6$ (kJ/mol) [29]. The values in Table 2 indicate that two molecules of water are released during the formation of exclusive complexes.

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