

Complex formation of cucurbit[6]uril with amines in the presence of different salts

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Abstract The complex formation of cucurbit[6]uril with cyclohexylmethylamine hydrochloride and hexylamine hydrochloride has been studied in aqueous solution using potentiometric titrations. The influence of salts like NaCl, KCl, RbCl, CsCl, BaCl₂ and tetramethylammonium chloride and tetraethylammonium perchlorate on the complex formation with amines has been studied at different concentrations of these salts. With increasing salt concentration the stability constants for the complex formation with cyclohexylamine hydrochloride and hexylamine hydrochloride decreases. However, no specific influence is observable. These results show that 2:1 complexes between these salts and cucurbituril are not formed or that their concentration in solution is rather low.

Keywords Cucurbit[6]uril · Amine complexes · Salt effects · Stability constants

Introduction

Cucurbit[6]uril is a synthetic macrocyclic ligand. Behrend et al. reported the synthesis in 1905 [1]. The structure of this ligand and its ability to form complexes has been reported by Mock and colleagues [2]. It is a highly symmetrical

molecule, see Fig. 1. It possesses a rigid cavity with two portals each formed by six carbonyl groups. These carbonyl groups are pointing in the middle of the portals. In the cavity of cucurbit[6]uril aliphatic or aromatic molecular groups are enclosed. Polar parts of the complexed molecules are located at the carbonyl groups or outside the cavity. Thus, the complex formation of alkylamines, diaminoalkanes and polyamines with cucurbit[6]uril has been studied intensively [3–13]. The amine complexes have also been used as starting materials for the synthesis of rotaxanes [14–16]. Just recently all information about cucurbit[*n*]urils has been reviewed [17].

Due to the dipole moment of the carbonyl groups located at the portals of cucurbit[6]uril mono and divalent cations can be complexed. Behrend was the first to observe the increase in solubility of the synthesized compound in the presence of salts. This can nowadays easily be understood by the complex formation of this ligand with protons and cations [8]. The first reported crystal structure is the complex of cucurbit[6]uril with Ca²⁺ [18]. Later the crystal structures of complexes with sodium [19], cesium [20] and rubidium [21] have been reported. All known crystal structures clearly show that one cucurbit[6]uril molecule complexes two cations.

However, in solution the situation may be quite different due to the influence of the solvation of the cations and the ligand. Up to now, only one experimental study dealing with the complex composition in aqueous solution has been reported [22]. From their measurements the authors conclude that only at very high salt concentrations 2:1 complexes with cucurbit[6]uril are formed. The electrostatic repulsion between both cations is responsible. Therefore the 1:1 complexes are mainly present in aqueous solution. Earlier attempts to separate the 1:1 and 2:1 complex stabilities measured in aqueous solution assuming similar

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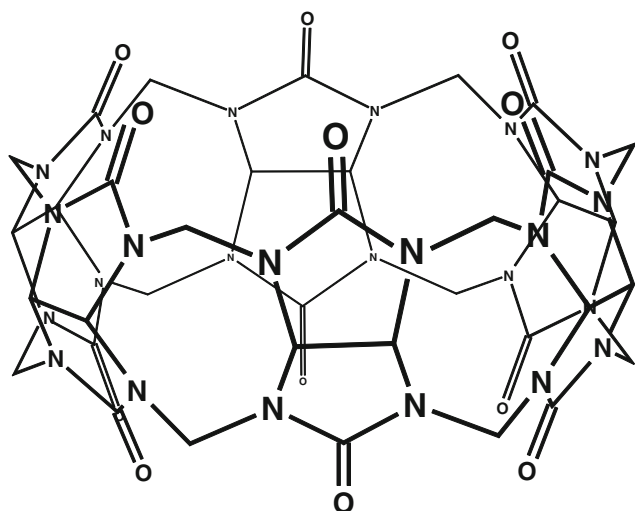


Fig. 1 Chemical structure of cucurbit[6]uril

complex stabilities for both complexes gives incorrect results [23]. This aspect will be discussed in detail in a separate paper [24]. At the moment some authors assume that the 2:1 complexes between cations and cucurbit[6]uril are the predominant species in solution [10, 11]. To clarify this situation we decided to study the formation of a cucurbit[6]uril complexes with cyclohexylmethylamine hydrochloride which has already reported in detail in the literature [13]. The complex formation is measured in the presence of different salts at varying concentrations to estimate their influence upon the complex formation.

Experimental

The macrocyclic ligand cucurbit[6]uril has been synthesized according to published procedures [8]. The ligand was purified by several recrystallizations from acidic aqueous solution.

Cucurbit[6]uril: $C_{36}H_{36}N_{24}O_{12} \cdot 6.5 H_2O$ Calcd. C, 38.82; H, 4.43; N, 30.18; O, 26.57.

Exp. C, 38.65; H, 4.11; N, 30.41; O, 26.83.

Cyclohexylmethylamine (CMA, Aldrich) and hexylamine (HA, Merck) tetramethylammonium chloride (TMAC, Fluka), tetraethylammonium perchlorate (TEAP, Fluka) and all salts (Merck) used were of the highest purity commercial available. As solvent bidistilled water was used. The hydrochlorides of cyclohexylamine and hexylamine were prepared by passing dry hydrogen chloride through a solution of the corresponding amines in diethyl ether. Potentiometric titrations were performed using a Sirius GIpKa (Sirius Analytical Instruments Ltd., Forest Row, UK). A solution of the amine (5×10^{-4} – 2×10^{-3} M) with an 10-fold excess of cucurbit[6]uril was adjusted

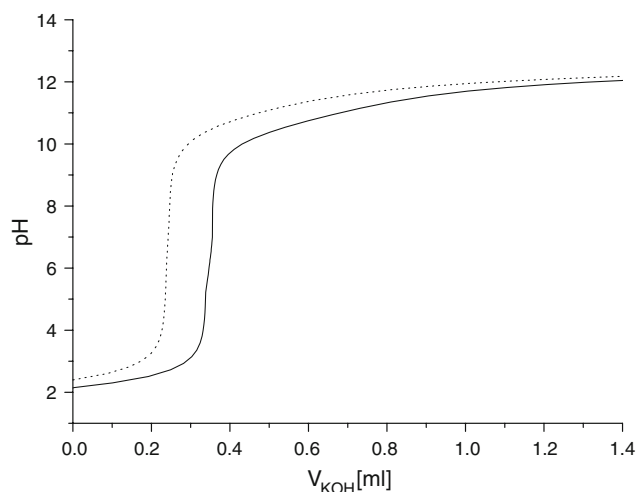


Fig. 2 Potentiometric titration curves of cyclohexylmethylamine hydrochloride solutions containing cucurbit[6]uril at different concentrations of KCl (..... 0.6 M; — 0.1 M)

to pH = 2 using hydrochloric acid (0.5 M). This solution (20 mL) was titrated with a standard solution of KOH (0.5 M) until a pH = 12 was achieved. The protonation constants and the stability constants were calculated directly from the experimental data using the software package Refinement Pro Version 1.114 (Sirius Analytical Instruments Ltd., Forest Row, UK). All titrations are performed at least three times. During the titrations the ionic strength was held constant using the corresponding salts. In Fig. 2 two representative titration curves are shown.

Results and discussion

The results for the complex formation between cucurbit[6]uril and CMA·HCl in aqueous solution in the presence of different salts are summarized in Table 1. The results published by Nau and colleagues [13] have been included in Table 1. Nau and coworkers used 1H NMR measurements in D_2O in the presence of different concentrations of sodium sulfate to measure the stability constants for the reaction between cucurbit[6]uril and CMA·HCl. Their results are in perfect accordance with our results. Obviously neither an isotope effect nor an anion effect is observable within the experimental error. Surprisingly also no influence of the cation present in solution is found. Even no effect upon the complexation reaction of cucurbit[6]uril with CMA·HCl is observed in the presence of mono and bivalent cations. To avoid any complex formation between a cation and cucurbit[6]uril TMAC was used as additional electrolyte. Also in this case the measured stability constants are identical within the experimental error when compared with the results obtained in the presence of other salts. For all of these cations

no specific effect upon the measured stability constants for the complexation of CMA·HCl is detectable.

To verify these results the reaction between cucurbit[6]uril and HA·HCl has been measured in the presence of different salts. These results are given in Table 2. Again the measured stability constants are not dependent on the nature of the cations present in solution. The general decrease of the experimental measured stability constants can be attributed to ionic strength effects. The complexation reaction with cucurbit[6]uril are obviously very sensitive against changes in the solvent medium.

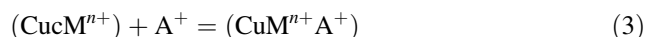
To get information about the presence of 2:1 and 1:1 complexes between cations and cucurbit[6]uril possible reactions between cucurbit[6]uril (Cuc), cations (M^{n+}) and amines (A) have to be taken into account. The formation of 1:1 and 2:1 complexes between cations and cucurbit[6]uril is described by Eqs. 1 and 2:

$$K_1 = \frac{[CucM^{n+}]}{[Cuc][M^{n+}]} \quad (1)$$

and

$$K_2 = \frac{[CucM_2^{2n+}]}{[CucM^{n+}][M^{n+}]} \quad (2)$$

If only 1:1 complexes between cucurbit[6]uril and cations are present in solution the complex formation with an amine (A^+) is given by Eq. 3:



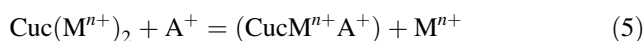
For this reaction the experimental stability constant is given by:

$$K(1:1)_{Amin} = \frac{[CucM^{n+}A^+]}{[CucM^{n+}][A^+]} \quad (4)$$

The presence of 2:1 complexes between cucurbit[6]uril and cations leads to Eq. 5 for the complex formation with an amine (A^+):

Table 2 Stability constants (log K; K in $L \text{ mol}^{-1}$) for the complex formation between cucurbit[6]uril and hexylamine hydrochloride (HA·HCl) in aqueous solution in the presence of different salts (c_M in mol L^{-1}) at 25 °C

HA·HCl	KCl	BaCl ₂	TMAC	TEAP
c_M				
0.1	3.11 ± 0.05	3.61 ± 0.08	3.37 ± 0.10	3.40 ± 0.10
0.2	3.11 ± 0.10	3.16 ± 0.10	3.19 ± 0.10	
0.3	3.10 ± 0.05	2.96 ± 0.05	2.99 ± 0.08	
0.4	2.91 ± 0.02	2.80 ± 0.10	2.83 ± 0.09	2.91 ± 0.08
0.5	2.83 ± 0.07	2.86 ± 0.06	2.83 ± 0.10	
0.6	2.79 ± 0.08	2.81 ± 0.10	2.77 ± 0.08	2.87 ± 0.10



The experimental stability constant for this reaction is:

$$K(2:1)_{Amin} = \frac{[CucM^{n+}A^+][M^{n+}]}{[Cuc(M^{n+})_2][A^+]} \quad (6)$$

Equation 6 can be transformed to Eq. 7 using Eq. 2:

$$K = (2:1)_{Amin} \frac{[CucM^{n+}A^+]}{[CucM^{n+}][A^+]} K_2 \quad (7)$$

The presence of 2:1 complexes with e.g. sodium or barium cations should have an pronounced effect upon the experimental obtained stability constant for the formation of the amine-cucurbit[6]uril complex. This is in contrast to the experimental results given in Tables 1 and 2. Thus, the value of K_2 should be very close to one for all cations. More realistic is that no 2:1 complexes are present or their concentration is low in solution. Therefore Eqs. 3 and 4 are sufficient to describe the complex formation with amines in the presence of mono and divalent cations.

Obviously 2:1 complexes between alkali and alkaline earth cations and cucurbit[6]uril are only formed in the crystalline state. In solution the 1:1 complexes are the dominant species.

Table 1 Stability constants (log K; K in $L \text{ mol}^{-1}$) for the complex formation between cucurbit[6]uril and cyclohexylmethylamine hydrochloride (CMA·HCl) in aqueous solution in the presence of different salts (c_M in mol L^{-1}) at 25 °C

CMA·HCl	Na ₂ SO ₄ (D ₂ O) ^a	NaCl	KCl	RbCl	CsCl	BaCl ₂	TMAC
c_M							
0	5.04	–	–	–	–	–	–
0.1	2.51	2.57 ± 0.09	2.44 ± 0.05	2.45 ± 0.08	2.38 ± 0.05	2.51 ± 0.04	2.45 ± 0.04
0.15			2.46 ± 0.05				
0.2	2.23	2.08 ± 0.05	2.17 ± 0.06	2.13 ± 0.06	2.30 ± 0.07	2.10 ± 0.07	2.37 ± 0.07
0.3	2.00	2.16 ± 0.07	1.95 ± 0.04	2.01 ± 0.06	2.09 ± 0.05	2.08 ± 0.08	2.25 ± 0.04
0.4	1.90	1.93 ± 0.04	1.84 ± 0.19	1.98 ± 0.05	1.92 ± 0.04	1.95 ± 0.10	2.13 ± 0.13
0.5	1.81	1.71 ± 0.15	1.75 ± 0.05	1.88 ± 0.05	1.84 ± 0.06	1.89 ± 0.10	1.83 ± 0.04
0.6	1.70	1.85 ± 0.10	1.68 ± 0.08	1.84 ± 0.07	1.77 ± 0.08	1.84 ± 0.15	1.73 ± 0.08

^a Ref. [13]

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