

# The formation of alkali and alkaline earth cation complexes with cucurbit[6]uril in aqueous solution: a critical survey of old and new results

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**Abstract** The solubility of cucurbit[6]uril in aqueous and in different solutions of alkali and alkaline earth salts has been measured. Due to the complex formation the solubility of the ligand increases. From this increase the stability constants of the cations are calculated. The solubility of cucurbit[6]uril in salt solutions after extrapolation to zero salt concentrations differs from salt to salt. These values of the solubility are different from the direct measured value of the solubility. The measured values of the stability constants with different salts are in accordance with most of the values reported. However, the presented method for the calculation of stability constants fails if the values of the stability constants exceed a certain value. This limiting value depends on the solubility of the ligand examined.

**Keywords** Cucurbit[6]uril · Complex formation · Salts · Solubility · Aqueous solution

## Introduction

In the first paper about a reaction product of glycoluril and formaldehyde Behrend describes a substance which

precipitates from aqueous solution but not from salt solutions [1]. The chemical structure of this compound was reported 76 years later and it was named cucurbituril [2]. With the synthesis of more derivatives of cucurbituril the name was modified to cucurbit[6]uril giving the number of monomer units in brackets [3] (see Fig. 1). Mock et al. observed the complex formation of different ammonium ions and reported the first quantitative values of the stability constants with these ions [4–6]. The formation of solid complexes with *p*-xylylenediammonium chloride and  $\text{Ca}^{2+}$  and their crystallographic structures were published by Freeman [7]. Later the structures of other complexes of cucurbituril with alkali ions have been reported [8–10]. From all of these studies the formation of alkali and alkaline earth cation complexes with cucurbituril is well known.

Due to the low solubility of the ligand in pure aqueous solution the determination of quantitative data for the complex formation with salts is not trivial. The first published results from the authors about the formation of salt complexes have been calculated from the increase in solubility of cucurbituril in the presence of different salts [11]. Due to the use of spectrophotometric measurements and the limited knowledge about the handling of these experimental data at that time these results may be potentially inaccurate. Knoche et al. used spectrophotometric competitive titrations of the 4-methylbenzylamine complex of cucurbituril with alkaline cations for the calculation of the stability constants of these cations [12]. Solubility data of cucurbit[6]uril in the presence of different alkali and alkaline earth cations have been published [8]. Unfortunately these measurements have not been used for the calculation of complex stabilities with cations.

Using the measurement of the total carbon content (TOC) of solutions as a sensitive detection method for the determination of the increase in solubility of cucurbit[6]uril

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in the presence of salts accurate values of the stability constants could be obtained [13]. The solubility of cucurbit[6]uril increases in aqueous formic acid, thus calorimetric titrations can be performed in this solvent to measure the complex formation between cucurbit[6]uril and cations [14]. However, these measurements are not comparable with those in pure water because the solvent composition has an influence upon the stability constants. This has been shown for the reaction of cucurbit[6]uril with amines in the presence of different salts [15, 16].

Unfortunately up to now no further authors published stability constants for the complexation of cations for comparison [17, 18]. All reactions known from the literature for the complex formation of cucurbit[6]uril with organic molecules have been performed in acidic or salt solutions. Thus, the knowledge of reliable data for the complexation of alkali and alkaline earth cation is important for the discussion of the results obtained for other complexation reactions with cucurbit[6]uril. Therefore, we decided to study the reaction of cucurbit[6]uril with cations in water again. The stability constants of the formed complexes have been calculated with an improved software for the evaluation of the experimental solubility data<sup>1</sup>. These new results will be compared with all published data.

## Experimental

### Materials

All salts used NaCl, KCl, RbCl, CsCl, CaCl<sub>2</sub>, SrCl<sub>2</sub>, BaCl<sub>2</sub> (all Merck, Suprapur) were of the highest purity commercially available. The macrocyclic ligand cucurbit[6]uril was synthesized according to published procedures [19]. The ligand was recrystallized several times from hydrochloric acid and finally dried in vacuo for several days. After this treatment neither HCl nor NH<sub>4</sub>Cl could be detected in the solid cucurbit[6]uril.

Cucurbit[6]uril: C<sub>36</sub>H<sub>36</sub>N<sub>24</sub>O<sub>12</sub> · 3.9 H<sub>2</sub>O. Calc. C, 40.52; H, 4.14; N, 31.50; Exp. C, 40.53; H, 4.02; N, 31.18.

The solid ligand was handled under nitrogen. As solvent bidistilled water was used.

To solutions of the salts ( $2 \times 10^{-3}$ – $2 \times 10^{-2}$  mol/L) solid cucurbit[6]uril was added. These solutions are stirred for two weeks at 25 °C. After this time solid cucurbit[6]uril was still present in solution. Thus, saturated solutions of the ligand have been formed. These solutions have been filtered using a membrane filter (polycarbonate, 0.4 μm) to remove undissolved cucurbit[6]uril. The amount of the total organic carbon content (TOC) of these solutions was analysed (TOC-5050, Shimadzu).

<sup>1</sup> The authors offer the computer program free of charge to all persons interested.

### Treatment of the experimental data

The experimentally measured value of the TOC of a saturated solution of the ligand in the absence of salts is directly related with the concentration of the ligand examined [L]<sub>0,sat</sub>:

$$\text{TOC}_{\text{sat}} = f_{\text{Cuc}}[\text{L}]_{0,\text{sat}} \quad (1)$$

The proportional factor  $f_{\text{Cuc}}$  gives the correlation between the carbon content of the solution and the molar ligand concentration. The factor is in case of cucurbit[6]uril:

$$f_{\text{Cuc}} = 12.011 * 10^3 * n_{\text{C}} \quad (2)$$

with the atomic mass of carbon and  $n_{\text{C}}$  the number of carbon atoms of the ligand examined. The cucurbit[6]uril molecule contains 36 carbon atoms (Fig. 1)

If cations are present in solution the ligand also forms complexes with these cations. Taking into account the low solubility of the ligand and the relative high salt concentrations in solution only 1:1 complexes between the ligand and the cations are formed:

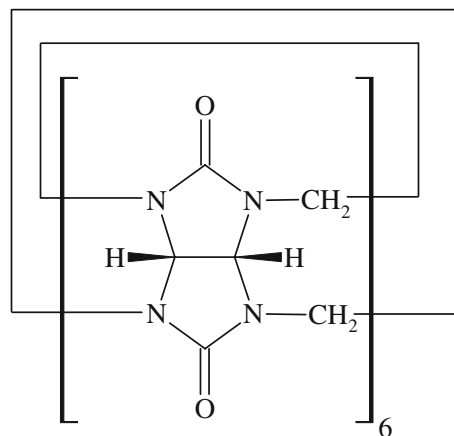


Due to the complex formation the amount of ligand present in the salt solution increases if the salt solution is always in contact with solid ligand. Now the experimental measured value of the TOC is related to the concentration of the ligand in solution by Eq. 4:

$$\text{TOC} = f_{\text{Cuc}}[\text{L}]_{\text{sat}} + f_{\text{Cuc}}[\text{LM}^{n+}] \quad (4)$$

The value of [L]<sub>sat</sub> is valid in the presence of salts. Using the mass balances for the total ligand  $c_{\text{L}}$  and total salt concentration  $c_{\text{S}}$  one obtains:

$$c_{\text{L}} = [\text{L}] + [\text{LM}^{n+}] \quad (5)$$



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

$$c_S = [M^{n+}] + [LM^{n+}] \tag{6}$$

Together with the equation for the stability constant for the formation of 1:1 complexes between the ligand and cations

$$K = \frac{[LM^{n+}]}{[L] * [M^{n+}]} \tag{7}$$

and Eqs. 4–6 one gets the following equation:

$$\begin{aligned} TOC &= f_{Cuc} [L]_{sat} + f_{Cuc} \frac{K * [L]_{sat}}{1 + K * [L]_{sat}} * c_S \\ &= a + b * c_S \end{aligned} \tag{8}$$

Equation 8 gives a correlation between the salt concentrations of solutions saturated with a ligand and the TOC value of these solutions experimentally measured. A straight line with the slope  $b$  and the intercept  $f_{Cuc} [L]_{sat}$  should be obtained by plotting TOC as a function of the total salt concentration  $c_S$ , see Fig. 2. Activities are used for the calculation of the stability constants. The activity coefficients are calculated using the extended Debye-Hückle expression which takes the finite size of ions into account [20].

After substitution of  $TOC_0 = f_{Cuc} [L]_{sat}$  Eq. 8 is transformed:

$$\frac{TOC}{TOC_0} - 1 = \frac{K}{1 + K * [L]_{sat}} * c_S = b * c_S \tag{9}$$

Using the slope  $b$  one can calculate the stability of the complex formed in solution:

$$K = \frac{b}{1 - b * [L]_{sat}} \tag{10}$$

If the solubility of the ligand is low then Eq. 11 is valid:

$$b * [L]_{sat} \ll 1 \tag{11}$$

If this condition is fulfilled the stability constant is identical with the slope  $b$ .

Unfortunately the values

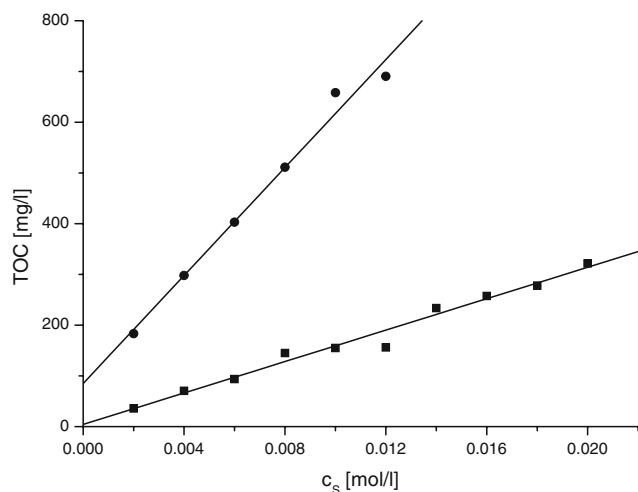
$$TOC_{sat} \neq TOC_0 \tag{12}$$

are not identical. Therefore the value of  $[L]_{sat}$  can not be calculated from the  $TOC_{sat}$  value (Eq. 1) obtained from a saturated solution of the ligand in pure water. The solubility of organic compounds in aqueous solution is influenced by the presence of salts [21, 22].

### Results and discussion

The amount of the total organic carbon content TOC of solutions can be measured very accurate. Therefore the solubility of cucurbit[6]uril in pure aqueous solution is measureable with high accuracy. Even small amounts of acid present in the solid cucurbit[6]uril have no influence upon the solubility in the presence of salts. The values of the TOC at zero salt concentration are calculated for the cations examined from a plot of the TOC values as a function of the salt concentration according to Eq. 8, see Fig. 2. Because of the extrapolation these values are less accurate compared with the TOC value measured in the case of pure saturated aqueous solution of cucurbit[6]uril. In the case of  $BaCl_2$  no intercept can be calculated. Due to the high value of the slope the extrapolated intercept has a huge error. The experimental results are summarized in Table 1.

The TOC values and the resultant concentrations of saturated solutions of cucurbit[6]uril calculated from the



**Fig. 2** TOC values of aqueous saturated solutions of cucurbit[6]uril as a function of the total salt concentration  $c_S$  ((filled square) KCl, (filled circle) CsCl)

**Table 1** Cucurbit[6]uril concentration  $[L]_{sat}$  of saturated solution calculated from the extrapolated  $TOC_0$  values using Eq. 8

Salt	$TOC_0$ (mg/L)	$[L]_{sat}$ (mol/L)
–	$10.5 \pm 0.6$	$(2.4 \pm 0.1) \times 10^{-5}$ <sup>a</sup> $(1.8 \pm 0.3) \times 10^{-5}$ <sup>b</sup> $2 \times 10^{-5}$ <sup>c</sup>
NaCl	$1.2 \pm 4.2$	$(2.8 \pm 9.6) \times 10^{-6}$
KCl	$6.9 \pm 5.6$	$(1.6 \pm 1.3) \times 10^{-5}$
RbCl	$43.8 \pm 14.3$	$(1.0 \pm 0.3) \times 10^{-4}$
CsCl	$61.8 \pm 14.3$	$(1.4 \pm 0.3) \times 10^{-4}$
CaCl <sub>2</sub>	$29.0 \pm 8.7$	$(6.7 \pm 2.0) \times 10^{-5}$
SrCl <sub>2</sub>	$130.9 \pm 36.9$	$(3.0 \pm 0.9) \times 10^{-4}$
BaCl <sub>2</sub>	–	–

<sup>a</sup> Directly obtained from saturated aqueous solution of the ligand ( $TOC_{sat}$ )

<sup>b</sup> Ref. [24]

<sup>c</sup> Ref. [15]

extrapolation to zero salt concentration are different compared with the values calculated directly from the measurement of saturated pure aqueous solution. The presence of salts influences the solvent properties. Thus, the intercept  $\text{TOC}_0$  from Eq. 8 can be interpreted as the solubility of the ligand in the presence of a salt at the ionic strength of zero. The results given in Table 1 give evidence that the charge and the size of the cations are responsible for this observation. The presence of the cations and anions in aqueous solution alter the properties of water as solvent. Since alkali and alkaline earth chlorides have been used only the cations are responsible for the observed changes in the solubility of cucurbit[6]uril. For a detailed discussion of the salt effect more salts have to be investigated.

In Table 2 the new measured stability constants for the complex formation of cucurbit[6]uril with alkali and alkaline earth cations are summarized together with all values reported in the literature.

Using Eq. 10 no stability constant can be calculated from the measurements in the case of  $\text{Ba}^{2+}$ . For this cation the condition given in Eq. 11 is obviously not fulfilled. Using for a rough estimation the value of the stability constant of  $\text{Ba}^{2+}$  [14] and the value of the solubility of the cucurbit[6]uril in aqueous solution, see Table 1, one obtains a value higher than 1. In this case the described procedure for the calculation of stability constants is no longer valid.

With few exceptions the stability constants are in accordance with values reported earlier. For a better understanding of possible errors and differences the experimental conditions for all reported stability constants will be discussed. The stability constants calculated from calorimetric titrations in 50% aqueous formic acid are not comparable with values obtained from aqueous solution. These values can be used only for comparison with that

measured in pure aqueous solution. The order of magnitude should be the same in both solvents. The first stability constants with salts have been measured using spectrophotometric methods [11]. The increase of the absorbance caused by dissolved cucurbit[6]uril in the presence of salts was used to calculate the stability constants. Unfortunately the maximum of absorbance is below 190 nm and therefore the measurements have been performed at wavelengths between 192 and 200 nm. For the calculation of the stability constants one has also to assume that the extinction coefficients of the ligand and the complex are nearly identical. This assumption has been proven in the case of dibenzo-crown ethers [23] but not for cucurbit[6]uril. Thus, small shifts in the maximum of the absorption band result in huge errors in the calculated stability constants. From a present point of view this method is not suitable to give reliable results for all cations. To avoid this problem, spectrophotometric competitive titrations have been performed by Knoche [12]. During these titrations salts are added to solutions of cucurbit[6]uril with 4-methylbenzylamine. The maximum of the absorption is at 271.5 nm and can be measured without any problem. The competitive reaction with 4-methylbenzylamine has also been used by Mock to study the complex formation of cucurbit[6]uril with a large number of amines [4–6].

Only two stability constants have been measured using high sensitive calorimetry for the reaction between cucurbit[6]uril and  $\text{Na}^+$  and  $\text{Ba}^{2+}$  in aqueous solution [14]. The value of the stability constant for  $\text{Na}^+$  is in perfect agreement with the value obtained from solubility measurements. The high stability constant of the  $\text{Ba}^{2+}$  complex is responsible for failure occurring by using Eq. 11 to calculate the stability of this complex from solubility measurements.

**Table 2** Stability constants (lg K; K in l/mol) for the complex formation between cucurbit[6]uril and cations in aqueous solution at 25 °C using different experimental methods

Method Cation	TOC	TOC <sup>a</sup>	Calorimetric titration <sup>c</sup>	UV-Vis Competition <sup>d</sup>	UV- Vis <sup>e</sup>	Calorimetric titration <sup>f</sup>
$\text{Na}^+$	3.45 ± 0.02	3.49	3.47	3.16	3.69	3.23
$\text{K}^+$	3.55 ± 0.02	2.85 3.20 ± 0.04 <sup>b</sup>		2.75	3.96	2.79
$\text{Rb}^+$	2.83 ± 0.02	2.98		2.61	4.41	2.68
$\text{Cs}^+$	2.82 ± 0.02	2.52			4.82	–
$\text{Ca}^{2+}$	3.60 ± 0.02	3.61			4.57	2.80
$\text{Sr}^{2+}$	2.56 ± 0.04	2.90				3.18
$\text{Ba}^{2+}$	>5	–	5.23			2.83

<sup>a</sup> Ref. [13]

<sup>b</sup> Recalculation of the experimental data

<sup>c</sup> Ref. [14] (aqueous solution)

<sup>d</sup> Ref. [12]

<sup>e</sup> Ref. [11]

<sup>f</sup> Ref. [14] (titration in aqueous formic acid 50% (v/v))

The previous reported stability constants from TOC measurements are with few exceptions in agreement with the new measurements. Differences in the stability constants are caused by variations of the extrapolated TOC values.

The improvement of the mathematical treatment of the solubility data results in accurate values of the stability constants for the reaction of cucurbit[6]uril with cations. These results can now be used to eliminate the influence of these salts present in solution upon the complex stabilities measured with organic guest molecules.

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