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Complexes of cucurbituril with alkyl mono- and diammonium ions in aqueous formic acid studied by calorimetric titrations

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Abstract

The thermodynamic data of the complexation reaction between the ligand cucurbituril and different alkylmonoamine and alkyldiamine hydrochlorides have been studied in aqueous formic acid. The stability constants, the reaction enthalpies and the reaction entropies are obtained from calorimetric titrations. At both rims of the cavity of cucurbituril the carbonyl groups interact with ions by ion–dipole interactions. If ammonium ions with longer alkyl chains enter the hydrophobic cavity of cucurbituril hydrophobic interactions participate in the complex formation. The hydrophobic contribution to the reaction enthalpy is calculated for the alkyl monoammonium ions. In 50% (v/v) formic acid the enthalpies of the hydrophobic interactions contribute more to the experimental reaction enthalpy than the ion–dipole interactions. © 1997 Elsevier Science B.V.

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1. Introduction

In 1905 the synthesis of a condensation product of urea with glyoxal and formaldehyde was reported [1]. The authors could not suggest any chemical structure of the reaction product. However, they described in detail some interesting reactions they observed with this molecule. It took more than 75 years before the chemical structure of this condensation product was determined [2]. It is a rigid molecule ($C_{36}H_{36}N_{24}O_{12}$) possessing a cavity and two identical portals formed by the carbonyl groups of the urea subunit. Mock suggested the name 'Cucurbituril' for this macrocyclic ligand (Fig. 1) [2].

The inclusion of organic guest molecules and the interactions of alkaline-earth cations with cucurbituril are confirmed by crystallographic studies [3]. Using NMR-techniques, Mock and co-workers investigated the complexation reactions between a large number of substituted ammonium ions and diammonium ions with cucurbituril [4,5]. Due to the low solubility of cucurbituril in aqueous and organic solvents, the complexation reactions were studied in aqueous formic acid solutions. They found that the stability of the complexes can change with the chemical structure of the substituted ammonium ions and with the distance between the interacting groups of the host and the guest molecules [4,5].

Strong complexes are also formed with protons and alkali and alkaline earth cations in aqueous solution [6,7]. The ligand, cucurbituril, was also used for the

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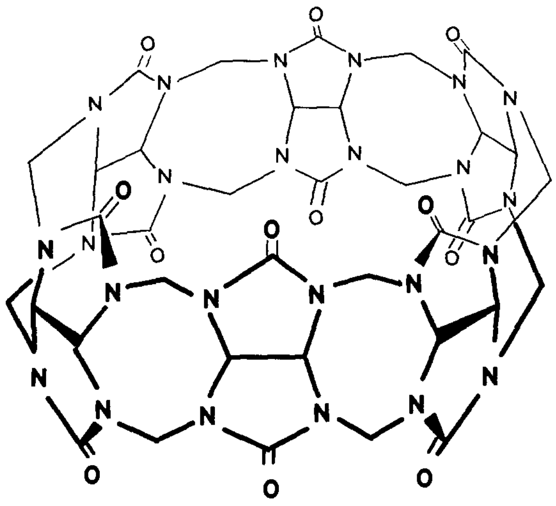

Fig. 1. Molecular structure of cucurbituril [5].

simulation of enzyme catalysed reactions [8,9]. The kinetics and the stability of the complex formation between the ligand cucurbituril and some ions have been studied [5,7].

Up to now no thermodynamic data for the complex formation with the macrocyclic ligand cucurbituril have been reported in the literature. The thermodynamic data are important for a better understanding of the factors influencing the complex formation. Mock and Shih [4,5] measured the stability constants for a lot of alkylammonium ions with cucurbituril using a NMR-technique. However, the NMR method may not be universally applicable [10]. Therefore calorimetric titrations were used in this study.

2. Experimental

Cucurbituril was prepared as reported in the literature and recrystallized from hydrochloric acid [1]. All amines (Fluka) and the ligand 18-crown-6 (18C6, Merck) were commercial samples of the highest purity available. The hydrochloride salts of the amines were prepared by passing hydrochloride gas through solutions of the amines in diethylether. The salts were filtered and washed with diethylether. The formic acid (Fluka) was also of the highest purity available and diluted with deionized water. Solutions were prepared in 30, 40 and 50% (v/v) formic acid–water media. All calorimetric titrations were performed using a Tronac calorimeter (Model 450). During the titration, a solution of the ligand (0.04–0.06 M) were added to a solution of an amine hydrochloride ($1\text{–}4 \cdot 10^{-3}$ M).

The solubility of cucurbituril (C) is influenced by the concentration of formic acid. The ligand cucurbituril forms strong complexes with protons [6] but the composition of the proton complexes with cucurbituril at high acid concentrations is unknown. The amine cations (A^+) and the protons compete with each other for the host molecule. The following reaction takes place during the titration:

$$[C(H^+)_x] + A^+[CA^+] + xH^+ \qquad (1)$$

The stability constant, K_{exp}, can not be splitted into separate terms for the individual reactions because of the unknown composition of the proton complexes Eq. (2).

$$K_{exp} = \frac{[CA^+][H^+]^x}{[C(H^+)_x][A^+]} = \frac{[CA^+]}{[C][A^+]} \cdot \frac{[H^+]^x[c]}{[C(H^+)_x]} \qquad (2)$$

Thus, for comparison all reactions have been measured at a acid concentration of 50% (v/v). The reaction enthalpy, ΔH, is calculated from the heat Q produced during the titration after the correction of non-chemical heat effects:

$$Q_t = \Delta n_t \cdot \Delta H \qquad (3)$$

The number of moles of the complex formed at any time during the titration is given by Δn_t. The mathematical treatment of the experimental data to calculate the stability constant and the reaction enthalpy has been described [11–13]. If the stability constant is higher than 10^5 M^{-1}, no value of the stability constant can be calculated from the thermal plot. The reliability of stability constants and thermodynamic values obtained from calorimetric titrations has been already demonstrated in detail [14].

3. Results and discussion

The acid concentration strongly influences the complexation reaction of cucurbituril with alkylamine salts. Table 1 shows the influence on the stability constants and the thermodynamic parameters for the complexation reaction of hexylamine hydrochloride

Table 1
Stability constants log K (K in M^{-1}) and thermodynamic parameters ΔH and $T\Delta S$ (kJ mol^{-1}) for the complexation of hexylamine hydrochloride with cucurbituril and crown ether 18C6 in different mixtures (v/v) of formic acid (%) with water at 25°C

Acid-mixture	Values	Cucurbituril	18C6
50	log K	3.83	2.53
	$-\Delta H$	22.1	4.9
	$T\Delta S$	–0.2	9.5
40	log K	3.15	
	log K [a]	3.36	
	$-\Delta H$	28.0	
	$T\Delta S$	–10.0	
30	log K	3.14	
	$-\Delta H$	35.5	
	$T\Delta S$	–17.6	
0	log K		2.54
	$-\Delta H$		2.8
	$T\Delta S$		11.7

[a] From [5].

Table 2
Dipole moments μ in debye (D) of compounds with ether groups and carbonyl groups [21]

Compounds	μ
Dimethyl ether	1.30
Diethyl ether	1.21
Acetone	2.88
Urea	4.56

Table 3
Stability constants log K (K in M^{-1}) and thermodynamic parameters ΔH and $T\Delta S$ (kJ mol^{-1}) for the complexation of alkylmonoamines salts $H(CH_2)_nNH_2{\cdot}HCl$ with cucurbituril in 50% (v/v) aqueous formic acid at 25°C

n	log K	$-\Delta H$	$T\Delta S$
0	2.70 1.92 [a] 2.23 [b]	3.7	11.7
1	2.73 1.92 [a]	3.8	11.8
2	2.73 2.00 [a]	4.6	11.0
3	3.54 4.09 [a]	14.2	7.0
4	4.05 5.00 [a]	26.8	–2.5
5	3.81 4.38 [a]	27.4	–4.6
6	3.83 3.36 [a]	22.1	0.9
7	2.67	9.6	5.6

[a] From [5], measured in 40% (v/v) aqueous formic acid.
[b] From [7], measured in 40% (v/v) aqueous formic acid.

with cucurbituril. For comparison the thermodynamic data of the complexation reaction of the hexylamine salt with the crown ether 18C6 are also given. The stability constants and the values of the reaction enthalpies of the crown ether complexes with hexylamine hydrochloride are nearly independent of the solvent composition. With protons, the ligand 18C6 only forms weak complexes in aqueous solution ($K = 0.40\ M^{-1}$ [15]; $19\ M^{-1}$ [16]; $29\ M^{-1}$ [17]). Cucurbituril builds indefinite associated complexes with the hydronium ions. The amine cations compete with the hydronium ions for the receptor binding sites. With increasing acid concentration, the values of the stability constants increase and the values of the reaction enthalpies and reaction entropies decrease. The stability constant for the complex formation of the hexylamine salt with cucurbituril is higher than with 18C6. With the hexyl ammonium ion, both ligands show ion–dipole interactions but the ligands differ in the strength of the dipole moments of the donor atoms. The carbonyl groups of cucurbituril have a higher dipole moment than the ether oxygen atoms of the crown ether (for comparison see Table 2). This also explains the lower stability constant of the complexation reaction with the ammonium ion (NH_4^+) and 18C6 ($\log K = 1.23\ M^{-1}$ [18]; $1.10\ M^{-1}$ [19]) compared to a complexation with cucurbituril ($\log K = 2.70\ M^{-1}$).

The stability constants and the thermodynamic data for the complexation reactions of different alkylmonoamine and alkyldiamine hydrochlorides with the ligand cucurbituril in 50% (v/v) aqueous formic acid are summarized in Tables 3 and 4. The complexation reactions of alkyl monoammonium ions $^+NH_3(CH_2)_nH$ show a maximum value of the reaction enthalpy at a chain length of 4–5 methylene groups. Stability constants also increase to a maximum in the case of butylamine hydrochloride. The stability constants measured by Mock using NMR gave similar results [20]. Cucurbituril has an interatomic distance between carbonyl oxygens axially spanning the cavity of 6×10^{-10} m which can be filled optimally by 4–5 methylene units [20]. At both rims of the cavity the negative ends of the dipoles of the six carbonyl groups are focused and they are able to undergo ion–dipole

Table 4
Stability constants log K (K in M^{-1}) and thermodynamic parameters ΔH and $T\Delta S$ (kJ mol^{-1}) for the complexation of alkyldiamines salts $NH_2(CH_2)_nNH_2 \cdot 2HCl$ with cucurbituril in 50% (v/v) aqueous formic acid at 25°C

n	log K	$-\Delta H$	$T\Delta S$
3	2.48 2.80 [a]	8.9	6.0
4	>5 5.19 [a]	16.1	14.9 [b]
5	>5 6.39 [a]	20.3	17.8 [b]
6	>5 6.44 [a]	29.6	8.9 [b]
7	4.78 4.64 [a]	23.9	4.7
8	3.25 3.96 [a]	23.2	−3.7
9	2.62 2.68 [a]	19.3	−4.3
10	2.49 2.02 [a]	15.9	−1.0
11	2.22	18.4	−5.1

[a] From [5], measured in 40% (v/v) aqueous formic acid.
[b] Calculated from the experimental data given in [5].

interactions with cations, for example, the alkyl ammonium ions. The cavity of cucurbituril is able to accommodate guest molecules with hydrophobic parts. The ion–dipole interactions of the alkyl ammonium ions stabilize the complexes and the hydrophobic contributions are responsible for the high values of the reaction enthalpies.

If the alkyl chains of the alkylmonoamine salts are longer than $n = 5$ methylene groups, the values of the reaction enthalpy decrease because the additional methylene groups pass the second rim of the cavity. Forcing parts of the hydrocarbon chain into the second cation-binding site destabilizes the complex. The measured reaction enthalpies for the complexation (ΔH_{exp}) of the alkyl monoammonium ions are the sum of different contributions: Ion–dipole interactions between the carbonyl groups and the positively charged nitrogen group ($\Delta H_{\mathrm{ion-dipole}}$), hydrophobic contribution ($\Delta\ H_{\mathrm{hydrophobic}}$) and the energy terms ($\Delta H_{\mathrm{solv}}$) for the solvation and desolvation processes. The measured reaction enthalpy is thus given by Eq. (4):

$$\Delta H_{\mathrm{exp}} = \Delta H_{\mathrm{ion-dipole}} + \Delta H_{\mathrm{hydrophobic}} + \Delta H_{\mathrm{solv}} \quad (4)$$

Enthalpic contributions from conformational changes are neglected because cucurbituril is a rigid molecule and only the alkyl chains possess a certain flexibility inside the cavity. If the value for the ion–dipole effect is subtracted from the experimental reaction enthalpies the values of the hydrophobic enthalpies are obtained together with solvation effects. The solvation effect is the sum of contributions from the desolvation of the ligand, the solvation of the complex and the solvation of the guest molecule outside the cavity.

$$\Delta H_{\mathrm{hydrophobic}} + \Delta H_{\mathrm{solv}} = \Delta H_{\mathrm{exp}} - \Delta H_{\mathrm{ion-dipole}} \quad (5)$$

At the moment it is not possible to separate these values into hydrophobic and solvation enthalpies. The values for the ion–dipole interactions can be taken from the complexation reaction of cucurbituril with the ammonium ion NH_4^+ (see Table 3). The sums of the calculated enthalpy values ($\Delta H_{\mathrm{hydrophobic}} + \Delta H_{\mathrm{solv}}$ for the complexation reaction of the alkyl monoammonium ions with cucurbituril are shown in Fig. 2. The hydrophobic contributions to the complexation of alkyl monoammonium ions with short alkyl chains as methyl and ethyl monoammonium ions are small. Above an alkyl chain length of three methylene groups the hydrophobic contribution is noticeable. The pentyl monoammonium ion shows the highest value because the maximal number of methylene groups fits into the hydrophobic cavity. The values of the hydrophobic

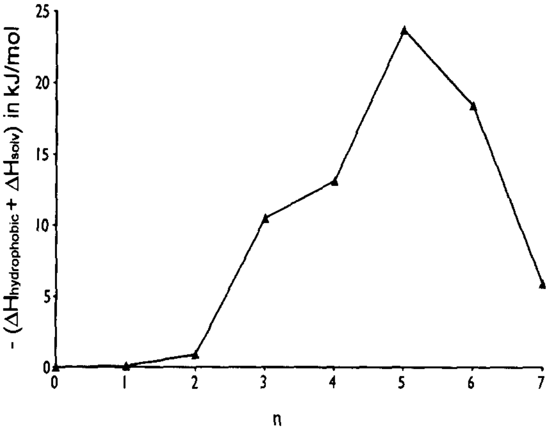

Fig. 2. Calculated hydrophobic enthalpy for the complexation of alkylmonoamine salts with cucurbituril in aqueous formic acid as a function of the number of carbon atoms n.

enthalpy decrease with longer alkyl chains because the methylene groups of the guest molecules are not accommodated inside the cavity and the solvations of the alkyl chains outside the cavity have to be considered. In the case of the pentyl momoammonium ion the hydrophobic interactions contribute more to the reaction enthalpy than the ion–dipole interactions in 50% aqueous formic acid.

The values of the reaction entropy for the complexation reactions with ammonium, methyl and ethyl monoammonium ion are nearly identical, see Table 3. The values of the reaction entropies decrease with increasing length of the alkyl chains.

The stability constants for the complexation reactions of the alkyl diammonium ions $^+NH_3(CH_2)_nNH_3^+$ with cucurbituril show a maximum between $n = 4-6$ methylene groups (Table 4). The values of the reaction enthalpies are nearly constant for the alkyldiamine hydrochlorides with more than nine methylene groups. The reaction entropy reaches its maximal value with the pentyl diammonium ion. If the alkyl chains of the alkyl diammonium ions are too short one positively charged amino group is located inside the hydrophobic cavity and only the second amino group interacts with six carbonyl groups at one rim of the ligand. Under these circumstances, a repulsion takes place between the two equally charged ammonium groups. This has already been observed for the formation of 2 : 1 complexes (ratio of cations to ligand) of cucurbituril of alkali and alkaline earth or ammonium cations [7]. The 2 : 1 complexes are only formed at very high concentrations of salt because of the repulsion between both cations.

The highest value of the reaction enthalpy for the complex formation between an alkyl diammonium ion and cucurbituril is observed for the hexyl diammonium ion. Obviously this di-cation fits optimally into the cavity of the ligand. Both positively charged amino groups are able to interact with the carbonyl groups at both rims of the ligand. Taking into account the different contributions to the measured value of the reaction enthalpy it is possible to calculate a theoretical value $\Delta H^{\mathrm{th}}_{\mathrm{diamine}}$ according to:

$$\Delta H^{\mathrm{th}}_{\mathrm{diamine}} = (\Delta H_{\mathrm{hydrophobic}} + \Delta H_{\mathrm{solv}}) + 2 \cdot \Delta H_{\mathrm{ion-dipole}}$$

The value of the hydrophobic enthalpy $((\Delta H_{\mathrm{hydrophobic}} + \Delta H_{\mathrm{solv}}) = 23.7\ \mathrm{kJ\ mol^{-1}})$ for the six methylene groups can be taken from the calculation of the hydrophobic enthalpy of the complexation reaction of the pentyl ammonium ion with cucurbituril. The hydrophobic chain of pentyl ammonium ion fits optimally into the cavity just as the six methylene groups of the hexyl diammonium ion. Using this assumptions Eq. (7) is obtain:

$$\Delta H^{\mathrm{th}}_{1,6\text{-diamine}} = -23.7 + 2 \cdot (-3.7) = -31.1\ \mathrm{kJ\ mol^{-1}}$$

Within the experimental error the calculated value is identical to the experimentally determined enthalpy:

$$\Delta H_{\mathrm{exp}} = -29.6\ \mathrm{kJ\ mol^{-1}} \qquad (8)$$

The complexes with cucurbituril and alkyldiamine salts with more than six methylene groups show a similar behaviour to the complexes with alkylmonoamine salts with more than six methylene groups. The second ammonium group is located outside the cavity so that the carbonyl groups of cucurbituril only interact with one ammonium group.

Ion–dipole interactions and the hydrophobic effect play an important role for the complexation of alkyl ammonium and alkyl diammonium ions. The present results clearly demonstrate that under the experimental conditions the main contributions to the measured reaction enthalpies come from hydrophobic interactions. Therefore, one can expect that a large number of organic molecules are able to form stable complexes with the ligand cucurbituril in solution.

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