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Thermodynamic Data for the Complex Formation of Alkylamines and Their Hydrochlorides with α-Cyclodextrin in Aqueous Solution

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Abstract

The formation of complexes between α-cyclodextrin and *n*-alkylamines and their hydrochlorides has been studied in aqueous solution using calorimetric titrations. All alkylamines form stronger complexes than the corresponding hydrochlorides. The values of the reaction enthalpies are smaller for the alkylamine hydrochlorides compared with the alkylamines. By increasing the number of methylene groups, these differences become smaller. In addition, the reaction enthalpies for protonation of the alkylamines and their complexes with α-cyclodextrin have been measured. The heat of protonation of these complexes is always smaller compared with the alkylamines. Due to the protonation and the formation of a strong solvation shell around the ammonium group the interactions with α-cyclodextrins are weakened. From a thermodynamic cycle using all measured reactions, it can be concluded that the aggregation of the alkylamines with long alkyl chains (heptyl-, octyl-, and nonylamine) has an influence on the values of the reaction enthalpies and entropies for the protonated form only.

Introduction

The cyclodextrins are cyclic molecules built from D-glucose units: six (α-cyclodextrin), seven (ß-cyclodextrin), and eight (γ-cyclodextrin). All hydroxyl groups of the D-glucose are directed outside the cavities of cyclodextrins. Thus, a large number of unpolar organic molecules can be included into the cavity of cyclodextrin. In the case of large organic guest molecules, only portions of the molecules are located within the cavity. As a consequence of their properties, the cyclodextrins are well known as ligands for the complexation of a great variety of organic compounds [1–9]. One of the most important aspects of cyclodextrin complexation with different compounds is given by the presence of water in the cyclodextrin cavity. Therefore, many studies in this field have been focused on establishing the structure and the nature of the interactions involved in inclusion complexes formed by cyclodextrins [10–13] in solution. The principal driving forces involved in complexation are weak interactions, such as hydrophobic effects and van der Waals interactions, determined by a combination of various factors. Hydrogen bonding is also involved in some complexes. The optimal fit between the guest molecules and the cavity of the cyclodextrins also has a pronounced influence upon the stability of the complex formed. Therefore, for a better comprehension of the mechanism and factors that are responsible for controlling the complex formation by weak interactions, the thermodynamic data have been intensively investigated for a variety of charged or uncharged compounds, including biologically-active substances and α-, ß-, and γ-cyclodextrins [14]. There are numerous studies dedicated to the experimental techniques used for investigation of inclusion complexes, such as NMR measurements, calorimetric or microcalorimetric titrations, potentiometric titrations, mass spectrometry, and ultrasonic measurements [5, 14–17].

Using thermodynamic and NMR studies, Rekharsky *et al.* [13] have investigated the equilibrium constants and standard molar enthalpies for the reactions of a series of acids, aliphatic amines, and cyclic alcohols with α- and ß-cyclodextrins concerning the structures of guests, such as the number of alkyl groups, the charge number, branching, and the presence of methyl and methoxy groups.

Recently [18] we have studied the thermodynamic data for the complexation of α-cyclodextrin with some amino acids and dipeptides in aqueous solutions. Due to the release of water molecules from the cavity of cyclodextrin, this complex formation was mainly favoured by the entropic contributions and with small values of reaction enthalpies.

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In this study we have investigated the complex formation between α-cyclodextrin and *n*-alkylamines and their hydrochlorides in aqueous solution by means of calorimetric titrations. Furthermore, the reaction enthalpies for protonation of the alkylamines and their complexes with α-cyclodextrin have been studied. By using the measured reactions, a thermodynamic cycle can be constructed.

Experimental

The *n*-alkylamines: ethylamine, propylamine, butylamine, pentylamine, hexylamine, heptylamine, octylamine and nonylamine (from Fluka) and the trifluoromethane sulfonic acid (Fluka) were used without further purification. The hydrochlorides were prepared from solutions of these amines in diethylether after passing gaseous hydrogen chloride. The hydrochlorides were dried in vacuum prior to use. α-Cyclodextrin (α-CD, Wacker, Figure 1) was of the highest purity available. As solvent bidistilled water was used.

Potentiometric titrations were performed using a Sirius GlpKa (Sirius Analytical Instruments Ltd., Forest Row, UK). A solution of the amine (1×10^{-3} – 6×10^{-3} mol l^{-1}) was titrated with hydrochloric acid (5×10^{-1} mol l^{-1}). The potentiometric titration curves were analysed using the software package Refinement Pro Version 1.114 (Sirius Analytical Instruments Ltd., Forest Row, UK). At least a tenfold excess of the ligand over the amine concentration was used for the titrations in the presence of α-cyclodextrin to ensure a complete complex formation.

The calorimetric titrations were performed using a Tronac calorimeter (Model 450). A solution of the ligands (3×10^{-2} – 8×10^{-2} mol l^{-1}) was added continously to a solution of the amines (1×10^{-3} – 5×10^{-3} mol l^{-1}). The following reaction between the ligand L and the amines A or ammonium ions A^+ takes place in solution:

$$L + A \rightleftharpoons LA \qquad (1)$$

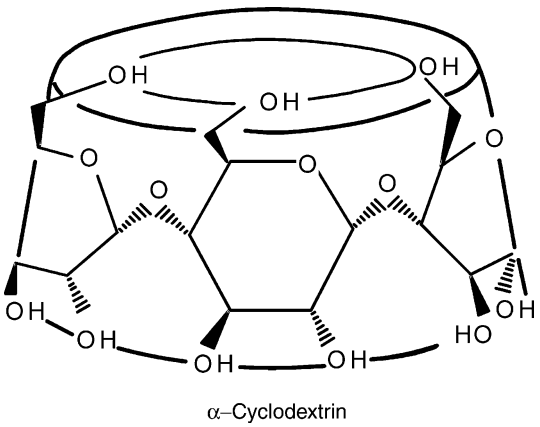


Figure 1. Chemical structure of α-cyclodextrin.

After correction of all non-chemical heat effects the heat Q produced during titration was related to the reaction enthalpy ΔH by the following equation

$$Q = \Delta n \cdot \Delta H \qquad (2)$$

with Δn as the number of moles of the complex formed. The mathematical treatment of the experimental data was described in detail in the literature [19–22].

To study the protonation reaction, a solution of acid (2×10^{-2} – 4×10^{-2} mol l^{-1}) was added to a solution of amine (1×10^{-3} – 2×10^{-3} mol l^{-1}):

$$H^+ + A \rightleftharpoons HA^+ \qquad (3)$$

Due to the high stability constants for the protonation ($\log K > 5$) the number of moles of acid added to the amine solution was identical with the number of moles of the protonated amine. Thus, only the reaction enthalpy could be calculated using equation (2).

The protonation reaction of the alkylamine complexes with α-CD was studied in an identical way. To ensure the complete complex formation between the alkylamines and α-CD, anywhere from three to eight times higher concentration of the ligand over the amine (1×10^{-3} – 2×10^{-3} mol l^{-1}) was used. The values of the experimentally obtained reaction enthalpies for the protonation of the alkylamine complexes were not influenced by the concentration of α-CD. To obtain comparable results for all reactions all measurements were performed in unbuffered solutions.

Results and discussion

The stability constants ($\log K$), enthalpies (ΔH) and entropies ($T\Delta S$) for the reaction between α-cyclodextrin and *n*-alkylamines and the corresponding hydrochlorides in aqueous solution at 25 °C are presented in Table 1. In most cases the agreement with experimental data from the literature is very good, see references given in Table 1. In the case of butylamine and its hydrochloride, significant differences for the stability constants and the reaction enthalpies are observed.

The strength of solvation of the amino group increases due to protonation. Some solvent molecules have been replaced from the protonated amino group during the complex formation. With increasing number of methylene groups on the amines, this difference decreases. In the case of nonylamine and the corresponding hydrochloride the values of the stability constants and reaction enthalpies are nearly identical within the experimental error. The strong solvation of the protonated amino group compared with the unprotonated has no influence on the complex formation. Due to the length of the alkyl chain, the solvation shell around the amino groups has only a minor influence on the inclusion of the alkyl chain into the cavity of α-cyclodextrin. These results clearly demonstrate the

Table 1. Thermodynamic data, log K (K in l·mol^{-1}), ΔH and $T\Delta S$ (kJ·mol^{-1}) for the reaction between α-cyclodextrin and *n*-alkylamines and their hydrochlorides in aqueous solution at 25 °C

Amines	log K	$-\Delta H$	$T\Delta S$
$CH_3(CH_2)_3NH_2$	2.50 ± 0.03[a]	6.8 ± 0.8[a]	7.4 ± 1.0[a]
	2.04[c]	15.1[c]	−3.5[c]
	1.83 ± 0.05[a]	0.7 ± 0.4[a]	9.7 ± 0.7[a]
$CH_3(CH_2)_3NH_2$•HCl	1.82 ± 0.04[b]		
	1.16[d]	9.1[d]	−2.5[d]
$CH_3(CH_2)_4NH_2$	2.48 ± 0.04[a]	19.3 ± 0.6[a]	−5.2 ± 0.8[a]
	2.67[c]	15.9[c]	−0.7[c]
	2.48 ± 0.02[a]	8.1 ± 0.5[a]	6.0 ± 0.6[a]
$CH_3(CH_2)_4NH_2$•HCl	2.14 ± 0.02[b]		
	1.97[e]	13.6[e]	−2.4[e]
$CH_3(CH_2)_5NH_2$	2.80 ± 0.02[a]	19.1 ± 0.5[a]	−3.1 ± 0.5[a]
	2.51 ± 0.04[a]	19.5 ± 0.6[a]	−5.2 ± 0.8[a]
$CH_3(CH_2)_5NH_2$•HCl	2.42 ± 0.02[b]		
	2.58[e]	17.6[e]	−2.9[e]
$CH_3(CH_2)_6NH_2$	3.26 ± 0.03[a]	21.7 ± 0.6[a]	−3.1 ± 0.7[a]
	2.90 ± 0.05[a]	19.7 ± 0.5[a]	−3.2 ± 0.8[a]
$CH_3(CH_2)_6NH_2$•HCl	2.73 ± 0.01[b]		
	3.03[e]	19.9[e]	−2.6[e]
$CH_3(CH_2)_7NH_2$	3.83 ± 0.04[a]	22.4 ± 0.7[a]	−0.5 ± 0.8[a]
$CH_3(CH_2)_7NH_2$•HCl	3.52 ± 0.04[a]	19.3 ± 0.7[a]	0.8 ± 0.8[a]
	3.37[e]	22.0[e]	−2.9[e]
$CH_3(CH_2)_8NH_2$	3.59 ± 0.06[a]	20.5 ± 0.1[a]	−0.1 ± 0.4[a]
$CH_3(CH_2)_8NH_2$•HCl	3.63 ± 0.06[a]	20.3 ± 0.5[a]	0.3 ± 0.9[a]

[a] from calorimetric titrations.
[b] from potentiometric titrations
[c] Ref. 23
[d] Ref. 13
[e] Ref. 24.

Table 2. Protonation constants log K (K in l mol^{-1}), heat of protonation ΔH (kJ mol^{-1}) and entropies of protonation $T\Delta S$ (kJ mol^{-1}) of *n*-alkylamines in aqueous solution in the absence and presence of α-cyclodextrin (α-CD) at 25 °C

Amines	In the absence of is α-CD			In the presence of α-CD		
	log K	$-\Delta H$	$T\Delta S$	log K	$-\Delta H$	$T\Delta S$
$H_2NCH_2CH_3$	10.72 ± 0.01	56.9[a]	4.0	10.53 ± 0.02	49.3 ± 0.5	10.5 ± 0.6
	10.68[b]					
$H_2N(CH_2)_2CH_3$	10.61 ± 0.17	57.4[a]	2.9	10.49 ± 0.02	52.0 ± 0.2	7.6 ± 0.3
	10.57[b]					
$H_2N(CH_2)_3CH_3$	10.67 ± 0.02	58.7[a]	1.9	10.44 ± 0.02	44.4 ± 0.6	14.9 ± 0.7
	10.64[b]					
$H_2N(CH_2)_4CH_3$	10.72 ± 0.27	59.5[a]	1.4	10.34 ± 0.01	45.2 ± 0.4	13.6 ± 0.4
	10.63[b]					
$H_2N(CH_2)_5CH_3$	10.78 ± 0.01	60.6 ± 0.3	0.7 ± 0.3	10.33 ± 0.02	47.5 ± 0.7	13.0 ± 1.0
	10.64[b]					
$H_2N(CH_2)_6CH_3$	10.75 ± 0.01	63.0 ± 0.1	−1.9 ± 0.1	10.32 ± 0.01	43.0 ± 0.5	15.6 ± 0.6
	10.66[b]					
$H_2N(CH_2)_7CH_3$	10.73 ± 0.03	65.6 ± 0.3	−4.6 ± 0.4	10.29 ± 0.05	43.7 ± 0.9	14.8 ± 1.2
$H_2N(CH_2)_8CH_3$	10.71 ± 0.03	67.6 ± 0.3	−6.8 ± 0.5	10.04 ± 0.02	39.1 ± 0.6	18.0 ± 0.7

[a] Ref. 25.
[b] Ref. 26.

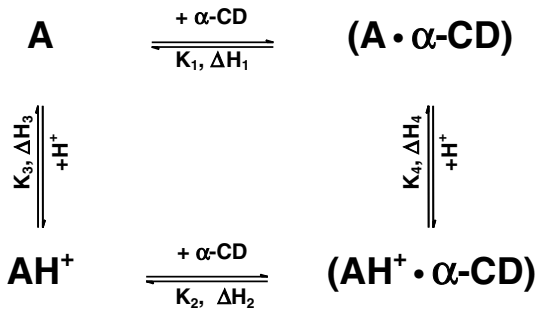
influence of the solvation of host molecules upon complex formation.

From this point of view, it is also of interest to study the protonation reaction of alkylamines in the absence and presence of α-cyclodextrin. These results are given in Table 2. In the presence of cyclodextrins, lower values of the protonation constants and reaction enthalpies are always observed, as compared to these without cyclodextrins. However, the differences between the protonation constants are rather small. In contrast, the values of the reaction enthalpies are more influenced by to the presence of α-CD. Due to the protonation of the amino groups, a strong solvation shell is formed. The presence of α-cyclodextrin weakens the interactions between the solvent molecules and the protonated amino group. The difference in the reaction enthalpies for the protonation of alkylamines in the absence or presence of α-cyclodextrin increases with increasing number of the methylene groups. Also, the values of the reaction entropies for the protonation reactions are strongly influenced in the presence of cyclodextrin. In the absence of α-CD, these values decrease with increasing number of methylene groups. However, all values of the reaction entropy for the protonation are small. In the presence of α-CD, the reaction entropies are nearly identical and positive. Obviously the disorder increases during the protonation. The sterical arrangements between all alkylamines examined and α-cyclodextrin are distorted by the protonation. The positively charged ammonium group is strongly solvated and the solvent molecules disturb the interactions between the alkylamine and the α-cyclodextrin. As a result, the values of the reaction enthalpies also decrease.

As can be seen from Scheme 1, a thermodynamic cycle can be constructed from the measured reactions. These cycles are widely used to calculate thermodynamic parameters for reactions that cannot be measured directly. In this study this circle can be used to describe accessory reactions that might take place in solution. On the other hand, the accuracy of the experimental results can also be proven.

From this thermodynamic cycle one expects the following stability constants without any further reaction:

$$\log K_1 + \log K_4 = \log K_3 + \log K_2 \qquad (4)$$



Scheme 1. Thermodynamic cycle for the protonation of alkylamines (A) and the complex formation with α-cyclodextrin (α-CD).

Table 3. Calculated differences of the thermodynamic data for the protonation and complexation of alkylamines with α-CD, according to Scheme 1, using the experimental data from Tables 1 and 2

Amines	Δ(log *K*)	Δ(Δ*H*)	Δ(*T*Δ*S*)
$H_2N(CH_2)_3CH_3$	0.44 ± 0.12	8.2	10.7
$H_2N(CH_2)_4CH_3$	−0.38 ± 0.32	3.2	1.0
$H_2N(CH_2)_5CH_3$	−0.16 ± 0.09	13.5 ± 2.1	14.4 ± 2.6
$H_2N(CH_2)_6CH_3$	−0.07 ± 0.10	18.0 ± 1.7	17.6 ± 2.2
$H_2N(CH_2)_7CH_3$	−0.13 ± 0.17	18.8 ± 2.5	18.8 ± 3.2
$H_2N(CH_2)_8CH_3$	−0.71 ± 0.17	28.3 ± 1.5	25.1 ± 2.5

and for the reaction enthalpies:

$$\Delta H_1 + \Delta H_4 = \Delta H_3 + \Delta H_2 \qquad (5)$$

An identical correlation is valid for the reaction entropies. Equations (4) and (5) can be rearranged:

$$\Delta \log K = \log K_1 + \log K_4 - \log K_3 - \log K_2 \qquad (6)$$

and

$$\Delta(\Delta H) = \Delta H_1 + \Delta H_4 - \Delta H_3 - \Delta H_2 \qquad (7)$$

The values of Δlog *K*, Δ(Δ*H*) and Δ(*T*Δ*S*) are summarized in Table 3. The differences of the stability constants are rather small. Only for the reaction enthalpies and entropies the calculated difference increases with increasing number of methylene groups of the alkylamines. These differences can be attributed to an additional reaction not mentioned in Scheme 1. From the obtained results no further information about this reaction is possible. However, the results reported in Table 2 for the entropies of protonation of alkylamines also show a distinct dependence on the number of methylene groups. The aggregation of alkylamines with long alkyl chains (heptyl-, octyl-, and nonyl-amine) may be responsible for this behaviour.

Conclusions

The combination of the results for the protonation reactions of alkylamines in the absence and presence of α-cyclodextrins and for the complex formation between unprotonated and protonated alkylamines with α-cyclodextrin gives deeper insight in the processes taking place in solution. In addition, the results clearly reflect the differences in solvation between unprotonated and protonated alkylamines.

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