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Complexation of Amino Acid Methylesters and Amino Alcohols by 18-Crown-6 and Benzo-18-crown-6 in Methanol

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Abstract

The complexation of protonated amino acid methylesters and amino alcohols by the ligands 18-crown-6 (18C6) and benzo-18-crown-6 (B18C6) has been studied in methanol using calorimetric titrations. No influence of the anions upon the stability constants and thermodynamic data for the reaction of protonated amino acid methylesters with both ligands has been noticed, which indicates the complete dissociation of the salts employed. A similar effect has been observed for the complexation of protonated and unprotonated amino alcohols with 18C6 and B18C6. The values obtained of the reaction enthalpies for the complexation of protonated amino acid methylesters with 18C6 are larger than those corresponding to the complexation with B18C6. The results demonstrate that the complex formation of unprotonated amino alcohols is favored by entropic contributions, while the complexation of protonated amino alcohols is favored by enthalpic contributions with both ligands. The influence of various substituents on the complexation behavior of amino acid and amino alcohol has also been investigated.

Introduction

Because of their major importance in most biological processes, the recognition of amino acids in their cationic [1], zwitterionic [2–4] or anionic forms [5, 6], including the recognition of their chirality by several groups of synthetic macrocyclic receptors, has been presented in many studies [7-16]. A variety of synthetic receptors has been designed and studied concerning the binding strength and selectivity toward various amino acids [8]. Amino acid binding by these receptors is based on the formation of hydrogen bonds combined with electrostatic attractions. The studies concerning the structural and thermodynamic aspects of interactions between macrocyclic receptors and biological compounds are useful for analysing biochemical systems. On the other hand, much attention has been directed towards the extraction and the transport through liquid membranes of amino acids using macrocyclic receptors as carriers [8, 11, 14]. Special emphasis has been placed on the study of amino acid derivatives. Using the ethyl ester of calix[6]arene as carrier through a chloroform membrane, Chang *et al.* [17] have reported a selective transport of amino acids in carboxylate form, a common form of amino acids and proteins in physiological fluids. The same type of mechanism has been used for the transport of ethylesters of amino acids [18]. Following the same topics, Okada *et al.* [19] have studied the extraction of some amino acid esters and Z-amino carboxylates by a calix[4]arene having a chiral pendant group.

Polyamine and polyamide macrocycles exhibit selective extraction and transport for various amino acid ester hydrochlorides [20]. It has been demonstrated that the transport is essentially controlled by the nature of the donor sites incorporated, the ring sizes of the macrocyclic systems, and the hydrophobicities of the co-transported anions. The diaza crown ethers have displayed high transport yields for various amino acid hydrochlorides [21].

In some previous studies [9–12] we have reported several aspects of the complexation, the solvent extraction and the transport through liquid membranes of amino acids by crown ethers, aza crown ethers, and cryptands. Experiments have suggested a good correlation between the structural properties of amino acids and their physicochemical characteristics. In order to obtain more information on the complexation of amine compounds with macrocyclic receptors we have proceeded to investigate the complexation of some amino acid derivatives and amino alcohols with crown ethers.

In this work the stability constants and thermodynamic data for the complexation reactions between protonated

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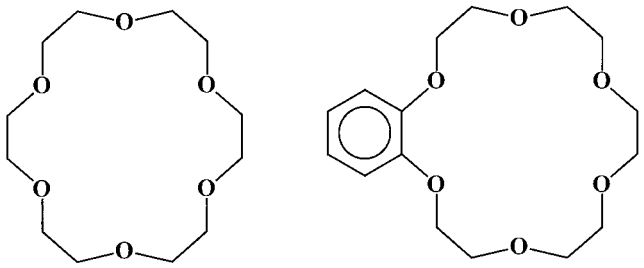

18C6 B18C6

Figure 1. Chemical structures of the crown ethers used in this study.

amino acid methylesters and protonated and unprotonated amino alcohols and 18-crown-6 and benzo-18-crown-6 in methanol have been determined.

Experimental

The amino acid methylesters L-alanine methylester hydrochloride (L-AlaOMe*HCl), L-valine methylester hydrochloride (L-ValOMe*HCl), L-leucine methylester hydrochloride (L- LeuOMe*HCl), L-phenylalanine methylester hydrochloride (L-PheOMe*HCl), L-serine methylester hydrochloride (L-SerOMe*HCl), L-isoleucine methylester hydrochlorides (L-IleOMe*HCl), L-cysteine methylester hydrochloride (L- CysOMe*HCl), the amino alcohols L-phenylalaninol, L-valinol (all Fluka), L-valinol hydrochloride (ICN) and iso-propylamine (Fluka) were commercially available.

The tetraphenylborates were prepared in the following way. An aqueous solution of sodium tetraphenylborate (Fluka) was slowly added to an aqueous solution of the amino acid methylester hydrochlorides or the acidified solution of the amine. A white precipitate was formed immediately. After stirring the mixture for some minutes the precipitate was filtered and washed with water several times. The tetraphenylborates were purified by recrystallization from water-methanol mixtures.

The ligands 18C6 (Merck) and B18C6 (Merck) were used without further purification. The chemical structures are given in Figure 1. Anhydrous methanol (H_2O content less than 0.005%, Merck) was used as solvent

The stability constants and reaction enthalpies were determined by means of calorimetric titrations (Tronac Calorimeter Model 450). To measure the stability constants and reaction enthalpies solutions of the ligands (0.06–0.08 mol/L) were added continously to a solution of the amino acid methylesters or amino alcohols (2–5 $\times$ 10^{-3} mol/L). The heat Q produced during titration is related to the reaction enthalpy ΔH after correction for all non-chemical heat effects by the following equation:

$$Q = \Delta n \Delta H,$$

with Δn being the number of moles of the complexes formed. Δn is a function of the stability constant. The mathematical treatment of the experimental data has been described in detail in the literature [22–24]. The accuracy of the results obtained from calorimetric titrations compared with other experimental techniques has already been proven [25].

Table 1. Stability constants (log K, K in M^{-1}) and thermodynamic parameters ΔH^0 and $T\Delta S^0$ (in kJ mol^{-1}) for the complexation of the ammonium ion and protonated amino acid methylesters by crown ethers in methanol at 25 °C

Amino acid methylester	Value	18C6	B18C6
NH_4^+	log K	4.32[a]	3.24[a]
	$-\delta H^0$	39.6[a]	30.0[a]
	$T\Delta S^0$	−15.1[a]	−11.6[a]
L-AlaOMe*HCl	log K	3.24 ± 0.02	2.50 ± 0.01
	$-\Delta H^0$	38.4 ± 0.3	29.7 ± 0.1
	$T\Delta S^0$	−19.9 ± 0.3	−15.5 ± 0.2
L-AlaOMe*$HBPh_4$	log K	3.38 ± 0.01	
	$-\Delta H^0$	38.2 ± 0.2	
	$T\Delta S^0$	−18.9 ± 0.2	
L-ValOMe*HCl	log K	3.00 ± 0.07	2.43 ± 0.03
	$-\Delta H^0$	34.4 ± 0.5	24.4 ± 0.7
	$T\Delta S^0$	−17.3 ± 0.8	−10.6 ± 0.9
L-ValOMe*$HBPh_4$	log K	2.85 ± 0.05	
	$-\Delta H^0$	39.6 ± 0.8	
	$T\Delta S^0$	−23.3 ± 0.9	
L-SerOMe*HCl	log K	3.31 ± 0.03	2.54 ± 0.01
	$-\Delta H^0$	43.2 ± 0.4	29.8 ± 1.0
	$T\Delta S^0$	−24.3 ± 0.5	−15.4 ± 1.1
L-SerOMe*$HBPh_4$	log K	3.23 ± 0.07	
	$-\Delta H^0$	43.8 ± 0.8	
	$T\Delta S^0$	−25.3 ± 1.0	
L-IleOMe*HCl	log K	3.13 ± 0.05	2.52 ± 0.06
	$-\Delta H^0$	33.6 ± 0.6	29.4 ± 0.9
	$T\Delta S^0$	15.8 ± 0.9	−15.1 ± 1.3
L-IleOMe*$HBPh_4$	log K	3.17 ± 0.04	
	$T\Delta S^0$	34.9 ± 0.5	
	$T\Delta S^0$	−16.8 ± 0.6	
L-PheOMe*HCl	log K	3.04 ± 0.06	2.50 ± 0.08
	$-\Delta H^0$	38.9 ± 0.9	26.5 ± 1.2
	$T\Delta S^0$	−21.5 ± 1.1	−12.2 ± 1.6
L-LeuOMe*HCl	log K	3.08 ± 0.09	2.45 ± 0.08
	37.4 ± 1.1	30.9 ± 2.5	
	$T\Delta S^0$	−19.8 ± 1.5	−17.0 ± 3.0
L-CysOMe*HCl	log K	3.16 ± 0.08	2.47 ± 0.05
	$-\Delta H^0$	37.7 ± 1.0	27.6 ± 0.9
	$T\Delta S^0$	−19.7 ± 1.4	−13.5 ± 1.1

[a] From Ref. 27.

Results and discussion

The measured stability constants and thermodynamic data for the reaction of protonated amino acid methylesters with the ligands 18C6 and B18C6 are summarized in Table 1. No data are available from the literature. The tetraphenylborates of the amino acid methylesters are used for comparison with the hydrochlorides to detect any effect resulting from incomplete dissociation. The tetraphenylborates are expected to be completely dissociated under the experimental conditions used. Although the hydrochlorides are not completely

Table 2. Stability constants (log K, K in M^{-1}) and thermodynamic parameters ΔH^0 and $T\Delta S^0$ (in kJ mol^{-1}) for the complexation of amino alcohols and protonated amino alcohols by crown ethers in methanol at 25 °C

Amino alcohols	Value	18C6	B18C6
L-phenylalaninol	log K	2.55 ± 0.04	2.54 ± 0.03
	$-\Delta H^0$	6.8 ± 0.7	3.4 ± 0.5
	$T\Delta S^0$	7.8 ± 0.8	11.1 ± 0.6
L-phenylalaninol*H^{+a}	log K	3.27 ± 0.02	2.57 ± 0.04
	ΔH_0	46.7 ± 0.5	43.0 ± 0.8
	$T\Delta S^0$	-28.1 ± 0.6	-28.3 ± 0.9
L-phenylalaninol*$HBPh_4$	log K	2.56 ± 0.08	
	$-\Delta H^0$	54.6 ± 1.0	
	$T\Delta S^0$	-40.0 ± 1.4	
L-valinol	log K	2.53 ± 0.07	2.52 ± 0.06
	$-\Delta H^0$	7.7 ± 0.4	2.8 ± 0.9
	$T\Delta S^0$	6.7 ± 0.8	11.6 ± 1.1
L-valinol*HCl	log K	2.51 ± 0.06	2.54 ± 0.01
	$-\Delta H^0$	47.7 ± 0.8	37.0 ± 2.0
	$T\Delta S^0$	-33.4 ± 1.0	-22.6 ± 2.0
L-valinol*$HBPh_4$	log K	2.54 ± 0.05	2.22 ± 0.05
	$-\Delta H^0$	46.9 ± 0.6	31.1 ± 1.1
	$T\Delta S^0$	-32.4 ± 0.8	-18.4 ± 1.3

[a] Acidified with trifluoromethane sulfonic acid.

dissociated, the existence of ion pairs should not influence the measured stability constants if the ion pair formation constant is lower than the complex stability [26]. The experimental results clearly do not show any effect of the anion upon the stability of the complex formed and upon the thermodynamic data.

Comparing the results for the complexation of the ammonium ion with the results for the complexation of the protonated amino acid methylesters one finds that the stability constant of the ammonium complexes are higher than those of the protonated amino acid methylesters. However, the values of the reaction enthalpies are nearly identical. The differences of the stability constants are mainly caused by the reaction entropies. The sterical requirements during complex formation depend on the substituents at the amino group.

Comparable results are observed for the complexation reactions of protonated amino acid methylesters with the ligand B18C6. The values of the reaction enthalpy are smaller compared with 18C6. With the exception of the protonated methylesters of L-isoleucine and of L-leucine the values of the reaction enthalpy are about 10 kJ mol^{-1} smaller with B18C6 than with 18C6. Also the values of the reaction entropy are smaller in the case of B18C6 compared with 18C6. The cavity sizes of both crown ethers are nearly identical. The benzene group reduces the basicity of the attached ether donor atoms and the flexibility of the ligand. Both effects should be responsible for the observed reduction of the values of the reaction enthalpy and entropy.

Stability constants and thermodynamic data for the reaction of protonated and unprotonated amino alcohols with 18C6 and B18C6 are given in Table 2. As already observed

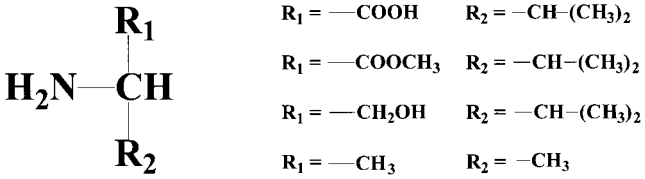

Figure 2. General structure of amines structurally related to valinol.

Table 3. Stability constants (log K, K in M^{-1}) and thermodynamic parameters ΔH^0 and $T\Delta S^0$ (in kJ mol^{-1}) for the complexation of amino compounds by crown ethers in methanol at 25 °C

Amino compounds	Value	18C6	B18C6
L-valine	log K	2.99[a]	2.98[a]
	$-\Delta H^0$	32.2[a]	18[a]
	$T\Delta S^0$	−15.2[a]	−1.1[a]
L-ValOMe*HCl	log K	3.00 ± 0.07	2.43 ± 0.03
	$-\Delta H^0$	34.4 ± 0.5	24.4 ± 0.7
	$T\Delta S^0$	-17.3 ± 0.8	-10.6 ± 0.9
L-valinol*HCl	log K	2.51 ± 0.06	2.54 ± 0.01
	$-\Delta H^0$	47.7 ± 0.8	37.0 ± 2.0
	$T\Delta S^0$	-33.4 ± 1.0	-22.6 ± 2.0
Iso-$C_3H_7NH_2$*$HBPh_4$	log K	3.56 ± 0.04 3.56[b]	2.75 ± 0.03
	$-\Delta H^0$	42.9 ± 0.6 −20.1[b]	34.1 ± 0.9
	$T\Delta S^0$	-22.5 ± 0.6	-18.4 ± 1.0
n-$C_4H_9NH_2$*HCl	log K	3.95[c]	
	$-\Delta H^0$	44.3[c]	
	$T\Delta X^0$	−21.9[c]	

[a] From Ref. 9.
[b] From Ref. 28.
[c] From Ref. 29.

for the complexation of the protonated amino acid methylesters no effect of the anion upon complex formation is also found for the reaction of protonated amino alcohols. The smallest values of the reaction enthalpy are measured during the complex formation of the unprotonated amino alcohols. Due to the absence of ion-dipole interactions only the formation of hydrogen bonds between the amino group and the ether donor atoms contribute to the reaction enthalpies. The complex formation is strongly favored by entropic contributions. The positive reaction entropies are only possible if the changes in solvation overcompensate the negative entropic contribution due to association of both reaction partners.

The situation is completely different after protonation of the amino group of the alcohols. Now the complex formation is only favored by enthalpic contributions and disfavored by entropic contributions. The values of the reaction enthalpy increase due to coulomb interactions between the protonated amino groups and the donor atoms of the ligands.

For a more detailed discussion about the influence of structural changes of the amine molecule upon the complexation behavior, it is necessary to restrict oneself to one molecular structure. In Figure 2 a general structure for valine and related molecules is given. The results for the complex formation of some of these molecules are summarized in Table 3. The ligand 18C6 forms more stable complexes with

the above mentioned compounds than B18C6. The values of the reaction enthalpies are larger for 18C6 compared with B18C6 in the order of 10 kJ mol^{-1} as already mentioned for the protonated amino acid methylesters. The carboxylic group or the ester group seems to reduce the basicity of the nitrogen atom. As a result the values of the reaction enthalpies are about 15 kJ mol^{-1} smaller in the case of the amino acids and the protonated amino acid methylesters compared with the protonated alcohol and the protonated alkylamines.

These results clearly demonstrate the influence of different substituents on the complexation behavior of amines. In addition, without the knowledge of the reaction enthalpies and entropies, no detailed insight into the factors responsible for molecular recognition is possible.

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