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CHARACTERISTIC EXTRACTION AND TRANSPORT PROPERTIES OF CROWN ETHERS AND CRYPTAND [2.2.2] FOR AMINO ACID METHYLESTERS

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ABSTRACT

The liquid–liquid extraction and the transport through liquid membrane of complexes of a series of amino acid methylesters and crown ethers such as 18-crown-6 (18C6), benzo 18-crown-6 (B18C6), cryptand [2.2.2] (222), and diaza crown ether [2.2] [22] were investigated. The experimental results strongly suggest that amino acid methylesters are extracted and transported by 18C6 and B18C6 more efficiently than the native amino acids. It was observed that crown ethers 18C6 and B18C6 exhibit different transport selectivities for the series of amino acid methylesters under study. The extraction constants ($\log K_{ex}$) of the amino acids involved were also determined. The extractability and the transport proved to be essentially controlled by factors such as

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the structure of the macrocycle, the nature of the amino acid, the nature of the anion, and the thermodynamic properties. The bottom line is the feasibility of optimal separation of amino acid derivatives.

Key Words: Amino acid methylesters; Macrocyclic ligands; Solvent extraction; Transport through liquid membrane

INTRODUCTION

The specificity of molecular interactions between biologically relevant molecules, i.e., amino acids, biogenic amines, peptides, proteins, and synthetic macrocyclic receptors, due to their importance in biological molecular recognition as well as in separation science was the topic of many studies.[1–7] The investigation of interactions involved in small molecule–peptide complexes is of particular relevance to the understanding of many biological peptide–protein interactions.[8]

The growing interest in the recognition and the transport of amino acids as the main structural components of proteins by various macrocyclic receptors is reflected by a large number of reports[9–14] published in recent years. The effect of the solvating properties of solvent on the complexation thermodynamics of some amino acids containing various functional groups with 18C6 in water was also investigated.[15] The importance of amino acid side-chain hydrophobicity in some protein folding was emphasized in many papers.[16]

It is well known that the crown ethers exhibit specific characteristics in the recognition and the transport of ammonium compounds.[17,18] An interesting study concerning the efficiency of the membrane transport of some amino acid esters by means of crown ether and lipophilic polyamine and polyamide macrocycles was also reported.[19,20] The oxaza macrocycles displayed transport properties for amino acid derivatives. The transport of ethyl esters of amino acids by calix[6]arene ester was reported[21] as well.

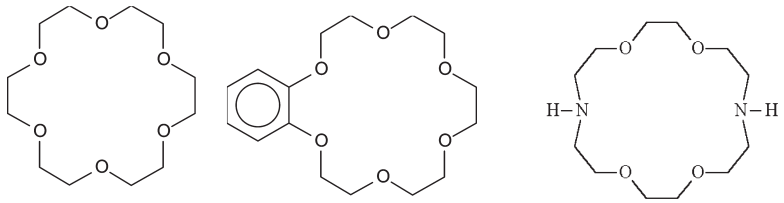
In some previous studies, we reported on the complexation, solvent extraction, and the transport through liquid membrane of miscellaneous native amino acids complexes with crown ethers, aza crown ethers, and cryptands.[3,9,13,18] As part of a continuing study of ammonium cation recognition, we recently investigated the possibility of various crown ethers to form complexes with some protonated amino acid methylesters and amino alcohols.[22] Additionally, we investigated through the present work, the liquid–liquid extraction and transport through liquid membrane of complexes of

protonated amino acid methylesters having biological significance and crown ethers and cryptand. Both the solvent extraction experiments and the transport through liquid membrane showed that the crown ethers (18C6, B18C6), diaza crown ether [2.2], and cryptand [2.2.2] display high extraction abilities and they also proved to act as good carriers through membrane for the amino acid methylester hydrochlorides under study. The influence of physicochemical transport parameters was evaluated by including the influence of the nature of the carrier, the pH of the aqueous phases, the nature of the solvent, the stirring velocity, and the structure of the substrate.

EXPERIMENTAL

Reagent grade 18C6, B18C6, Kryptofix [2.2], and Kryptofix [2.2.2] were obtained from Merck and used throughout the experiments without further purification (Fig. 1).

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-isoleucine methylester hydro-



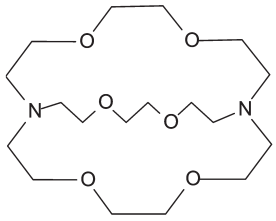


Figure 1. The chemical structures of macrocyclic ligands used in experiments: 18C6 (18-crown-6); B18C6 (benzo-18-crown-6); [2.2] (Kryptofix [2.2]) and [2.2.2] (Kryptofix [2.2.2]).

chloride (L-IleOMe*HCl), L-phenylalanine methylester hydrochloride (L-PheOMe*HCl), L-serine methylester hydrochloride (L-SerOMe*HCl), L-cysteine methylester hydrochloride (L-CysOMe*HCl) were used as commercially available from Fluka. Tropaeolin 00 ([4-(4′-anilinophenylazo)benzenesulfonic acid] as counterion was supplied by Fluka at the highest purity commercially available. Chloroform (dielectric constant $\varepsilon_r = 4.81$),[23] the organic solvent employed was distilled before use. Reagent grade picric acid (Fluka) was used. Distilled and deionized water was used throughout the experiments. The spectrometric measurements were recorded using a Jasco, V-530, UV–Visible Spectrometer. The pH was measured by a digital MV-870 Pracitronic pH-meter with glass electrode and saturated calomel electrode.

Equal volumes of $5 \times 10^{-4} - 2 \times 10^{-3}\,M$ of amino acid methylesters and $8.0 \times 10^{-5} - 1.0 \times 10^{-3}\,M$ of tropaeolin 00 or picric acid in aqueous phases with pH $\approx$ 2.01 were extracted with $2.5 \times 10^{-3} - 2 \times 10^{-2}\,M$ of ligands in chloroform phase (each phase presaturated with the solvent medium of the other). The phases were mixed and shaken for 25 min at 25 ± 1°C. The pH of the aqueous solutions was adjusted with HCl of 0.05 *N*. Each experiment was repeated five times. The hydrophobic ion pair $RNH_3L^+A^-$ was extracted into chloroform, where RNH_3^+ is the protonated amino acid, L the macrocyclic ligand, and A^- the counterion of picric acid or tropaeolin 00. The concentrations in the organic phases were determined by spectrometric measurements. The stoichiometry in chloroform indicated a concentration ratio of the components of 1:1:1 (ligand:amino acid:anion).

The transport experiments were carried out using a device reported earlier.[24] The phases were stirred at 200 rpm for 10 hr. Each experiment was repeated three times. Reproducibility was within ±10%. Similar transport experiments were performed for reference in the absence of the carrier.

RESULTS AND DISCUSSION

The values obtained for the extraction constants ($\log K_{ex}$) and the molar absorption coefficients of the complexes of some amino acids methylesters with 18C6 and B18C6 in chloroform in the presence of tropaeolin 00 are given in Table 1. The extraction experiments of amino acid complexes with respect to pH indicated that the optimal extraction occurs at pH $\approx$ 2.01, when the amino acid has positive charges.

The values of the extraction constants of amino acid methylesters with 18C6 in the presence of tropaeolin 00 were found to be in the range starting from 5.18 (L-CysOMe*HCl) to 6.31 (L-LeuOMe*HCl). Except for L-CysOMe*HCl, the values of the extraction constants of amino acids under study with 18C6 did not differ by more than 0.2. All values of the extraction constants for the

Table 1. Extraction Constants ($\log K_{ex}$), and Molar Absorption Coefficients of the Complexes of Some Amino Acids with 18-Crown-6 and B18C6 in Chloroform in the Presence of Tropaeolin 00

Ligand	Amino Acid	$\varepsilon_{\lambda=407\,nm}$ (L/mol cm)	Log K_{ex}
18C6			
	L-LeuOMe*HCl	12,850	6.31 ± 0.06
	L-ValOMe*HCl	11,970	6.24 ± 0.11
	L-IleOMe*HCl	18,130	6.21 ± 0.07
	L-PheOMe*HCl	19,990	6.14 ± 0.04
	L-CysOMe*HCl	10,340	5.18 ± 0.08
Benzo-18C6			
	L-PheOMe*HCl	23,500	5.44 ± 0.01
	L-IleOMe*HCl	17,050	5.44 ± 0.07
	L-LeuOMe*HCl	21,630	5.29 ± 0.04
	L-ValOMe*HCl	24,880	4.75 ± 0.09
	L-CysOMe*HCl	6,410	4.20 ± 0.08

[Amino acid methylester] $= 5 \times 10^{-4}$–$2 \times 10^{-3} M$; [tropaeolin 00] $= 8 \times 10^{-5} M$; [ligand] $= 2.5 \times 10^{-3}$–$2 \times 10^{-2} M$; pH $\approx$ 2.01; $T = 25 \pm 1$°C.

extraction of amino acid methylesters from aqueous phase into chloroform with B18C6 in the presence of tropaeolin 00 were less by one order of magnitude than those corresponding to the extraction of amino acid methylesters with 18C6. Thus, the values of extraction constants with B18C6 were between 4.20 (L-CysOMe*HCl) and 5.44 (L-PheOMe*HC $\approx$ L-IleOMe*HCl). One explanation is given by the structure of the crown ether used as an extractant. The flexibility and the basicity of B18C6 are reduced by the presence of the benzene group in the ring substitution of 18C6. Moreover, it is well known that the extraction constant is influenced by many structural contributions such as the nature and the size of the anion used as ion pair for substrate–receptor complexes,[25] the lipophilicity or hydrophobicity of the substrate and the ligand, the polarity of the solvent, the pH of aqueous phase and the thermodynamic properties, such as the stability constants of the complexes, and the enthalpies and entropies of the complexation. Therefore, in a previous study,[22] we showed that the values of the reaction enthalpies for the complexation of protonated amino acid methylesters with 18C6 in methanol are larger than those corresponding for the complexation with B18C6. According to the data presented in literature, the partition coefficients of different crown ethers were determined for various biphasic systems.[23]

The values of extraction constants of amino acids methylesters with 18C6 and B18C6 in the presence of picrate ion are shown in Table 2. As one may see from Table 2, the values of the extraction constants for amino acids under study with 18C6 and B18C6 in the presence of picrate ion are fairly high. The extraction for the complexes with 18C6 follows the descending sequence: L-LeuOMe*HCl > L-IleOMe*HCl > L-PheOMe*HCl > L-ValOMe*HCl > L-SerOMe*HCl > L-AlaOMe*HCl > L-CysOMe*HCl and for the complexes with B18C6 follows the sequence: L-ValOMe*HCl > L-IleOMe*HCl > L-LeuOMe*HCl > L-PheOMe*HCl > L-CysOMe*HCl > L-SerOMe*HCl > L-AlaOMe*HCl.

When the amino acid counterion is charged to picrate, the extractability is reduced in comparison to tropaeolin 00 in the case of complexes of amino acids methylesters under study with 18C6, as may be seen from the extraction data shown in Tables 1 and 2. On the other hand, in the presence of picrate ion, the extraction was possible of L-AlaOMe*HCl and L-SerOMe*HCl with good values

Table 2. Extraction Constants ($\log K_{ex}$), and Molar Absorption Coefficients of the Complexes of Some Amino Acids with 18-Crown-6 and B18C6 in Chloroform in the Presence of Picrate Ion

Ligand	Amino Acid	$\varepsilon_{\lambda=375\,nm}$ (L/mol cm)	Log K_{ex}
18C6			
	L-LeuOMe*HCl	16,078	6.14 ± 0.06
	L-IleOMe*HCl	18,993	5.79 ± 0.10
	L-PheOMe*HCl	20,703	5.76 ± 0.12
	L-ValOMe*HCl	15,518	5.35 ± 0.05
	L-SerOMe*HCl	7,655	5.14 ± 0.09
	L-AlaOMe*HCl	10,638	5.04 ± 0.11
	L-CysOMe*HCl	5,638	4.96 ± 0.08
B18C6			
	L-ValOMe*HCl	11,460	6.08 ± 0.11
	L-IleOMe*HCl	14,648	5.94 ± 0.09
	L-LeuOMe*HCl	14,308	5.61 ± 0.07
	L-PheOMe*HCl	20,597	5.31 ± 0.12
	L-CysOMe*HCl	16,397	4.93 ± 0.08
	L-SerOMe*HCl	11,370	4.40 ± 0.02
	L-AlaOMe*HCl	20,748	4.39 ± 0.12

[Amino acid methylester] = 5×10^{-4}–$2 \times 10^{-3}\,M$; [picric acid] = $8 \times 10^{-5}\,M$; [ligand] = 2.5×10^{-3}–$1 \times 10^{-2}\,M$; pH ≈ 2.01; $T = 25 \pm 1$°C.

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for extraction constants. L-Serine is more soluble in water than the other amino acids because of its hydroxyl group. Along the same line of reasoning, the sulfhydryl group on the side-chain of L-cysteine contributes to its solubility.

Concerning the values of the extraction constants for the extraction of amino acid methylesters with B18C6 into chloroform in the presence of picrate ion, they are larger than those obtained in the presence of tropaeolin 00, except for L-PheOMe*HCl.

The results strongly emphasized the influence of the nature of the anion used as ion pair for the substrate–receptor complexes. As noted previously, both the solvent extraction and the transport through liquid membrane are affected by the nature of the anion used as counterion by modifying the phase distribution of the substrate.[26] The solvent's dielectric constant is an important feature of the electrostatic interaction in forming the ion pairs. The ion pairing increases as the solvent dielectric decreases (dielectric constant of chloroform, $\varepsilon_r = 4.81$).[23]

Our results showed that, in the presence of picrate as counterion, the values of the extraction constants of amino acid methylesters with 18C6 were higher than those of the complexes with B18C6 except for L-ValOMe*HCl and L-IleOMe*HCl (Table 2). On the other hand, comparing the values of the extraction constants of amino acid methylesters with 18C6 and B18C6 in the presence of tropaeolin 00 and picrate in chloroform with those of the extraction constants of amino acids with the same ligands and the same anions,[13] the larger values were obtained for amino acid methylesters. For example, the extraction constant ($\log K_{ex}$) for L-leucine methylester was 6.31 in the presence of tropaeolin 00 and 6.14 in the presence of picrate, and for L-leucine, the extraction constant was 4.98 in the presence of tropaeolin 00 and 5.76 in the presence of picrate. The differences were larger when tropaeolin 00 was used as counterion. The effect of the anion on the extraction and transport processes was investigated elsewhere.[26,27]

The results presented in Table 3 show that cryptand [2.2.2] and diaza crown ether [2.2] exhibit a good extractability for the amino acid methylesters mentioned above.

The values of the extraction constants of amino acid methylesters using cryptand [2.2.2] as an extractant from aqueous phase into chloroform in the presence of tropaeolin 00 were lower than the extraction constants of the complexes of amino acid methylesters with 18C6. Except for L-CysOMe*HCl, the values of the extraction constants of amino acids under study with cryptand [2.2.2] were slightly lower than those of the complexes with B18C6. As from Tables 1 and 3, in the case of L-ValOMe*HCl the value of the extraction constant with B18C6 in the presence of tropaeolin 00 ($\log K_{ex} = 4.75$) was almost identical with the value of the extraction constant obtained with cryptand [2.2.2] in the presence of the same anion ($\log K_{ex} = 4.79$). In contrary, the values of the extraction constants of amino acid complexes with cryptand [2.2.2] and tropaeolin 00 as counterion were larger than those of the complexes of amino

Table 3. Extraction Constants ($\log K_{ex}$), and Molar Absorption Coefficients of the Complexes of Some Amino Acids with Cryptand [2.2.2] and Diaza Crown Ether [2.2] in Chloroform in the Presence of Tropaeolin 00 Ion

Ligand	Amino Acid	$\varepsilon_{\lambda=407\,nm}$ (L/mol cm)	$\log K_{ex}$
[2.2.2]			
	L-LeuOMe*HCl	17,480	5.27 ± 0.08
	L-IleOMe*HCl	16,310	5.17 ± 0.05
	L-CysOMe*HCl	15,200	5.02 ± 0.09
	L-PheOMe*HCl	16,680	4.96 ± 0.10
	L-ValOMe*HCl	18,550	4.79 ± 0.12
[2.2]			
	L-IleOMe*HCl	19,310	4.29 ± 0.20
	L-PheOMe*HCl	20,300	4.12 ± 0.09
	L-LeuOMe*HCl	19,600	3.98 ± 0.10
	L-ValOMe*HCl	21,500	3.76 ± 0.13
	L-CysOMe*HCl	19,180	3.55 ± 0.12

[Amino acid methylester] $= 5 \times 10^{-4}$–$2 \times 10^{-3}\,M$; [tropaeolin 00] $= 8 \times 10^{-5}\,M$; [ligand] $= 5 \times 10^{-3}$–$2 \times 10^{-2}\,M$; pH $\approx$ 2.01; $T = 25 \pm 1$°C.

acids with B18C6 in the presence of picrate ion (Table 2). Differences in the extraction of amino acid methylesters with crown ethers and the corresponding data for amino acid methylesters with cryptand [2.2.2] can be attributed to the different structural characteristic of these ligands, the substituents of the amino acids, and the nature of the anion. The extraction for the complexes of amino acid methylesters with cryptand [2.2.2] followed the sequence: L-LeuOMe*HCl > L-IleOMe*HCl > L-CysOMe*HCl > L-PheOMe*HCl > L-ValOMe*HCl.

Regarding the values of the extraction constants of amino acid methylesters with diaza crown ether [2.2] into chloroform in the presence of tropaeolin 00 given in Table 3, they were within 3.55 (L-CysOMe*HCl) and 4.29 (L-IleOMe*HCl). The sequence of extractability is the following: L-IleOMe*HCl > L-PheOMe*HCl > L-LeuOMe*HCl > L-ValOMe*HCl > L-CysOMe*HCl. Apart from 18C6 and B18C6, diaza crown ether [2.2] exhibited extractability for amino acids under study with lower values of the extraction constants than those obtained with cryptand [2.2.2] and crown ethers.

The selective ion transport was studied as a function of the experimental parameters. The transport experiments were carried out employing a device previously described.[24] At the source phase/membrane phase interface, an extraction process takes place. Thereafter, the amino acid is transported through

the membrane phase as an ion pair, and, finally, the amino acid and the anion used as an ion pair are both released at the membrane phase/receiving phase interface. The experimental data on the transport of amino acid methylesters through chloroform liquid membrane using 18C6 and B18C6 as carriers in the presence of tropaeolin 00 as counterion are shown in Fig. 2. The transport yields of amino acids methylesters under study through a chloroform membrane with 18C6 and B18C6 as carriers were found to be large for all amino acids.

The results shown in Fig. 2 point out that 18C6 and B18C6 exhibit different transport selectivities for a series of amino acid methylesters. The transport efficiencies were found to be the following: L-PheOMe*HCl > L-LeuOMe*HCl > L-IleOMe*HCl > L-ValOMe*HCl > L-CysOMe*HCl using B18C6 as carrier and the following L-IleOMe*HCl > L-LeuOMe*HCl > L-PheOMe*HCl > L-ValOMe*HCl > L-CysOMe*HCl using 18C6 as the carrier.

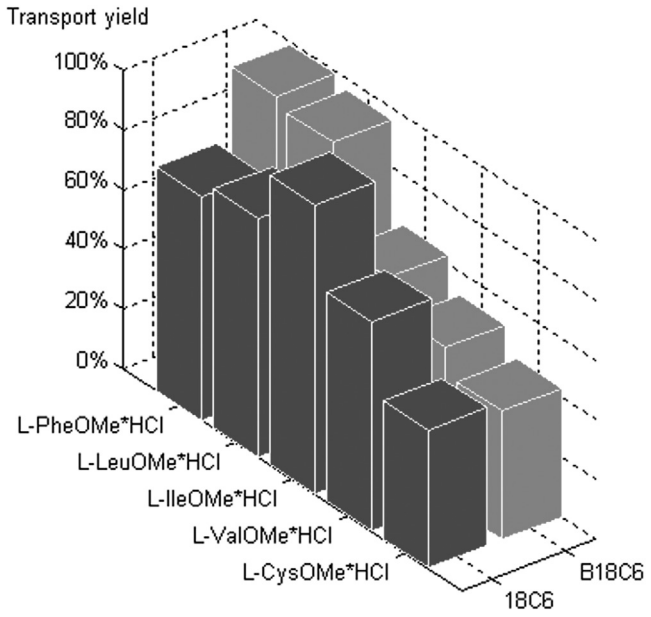

Figure 2. Experimental data of the transport of some amino acid methylester hydrochlorides through chloroform liquid membrane by crown ethers. *Source phase*: [Amino acid methylester hydrochloride]= 1.6 m*M*; [Tropaeolin 00]= 1.6 m*M*; HCl 0.05 *N* (pH ≈ 2.01); 5 mL. *Membrane*: Chloroform, [ligand] = 10 m*M*, 30 mL. *Receiving phase*: LiOH 0.01 *N* (pH ≈ 13.02), 5 mL. "*" Denotes Amino acid percentage found in the receiving phase after 6 hr of stirring.

When using B18C6, hydrophobic salts like L-phenylalanine and L-leucine methylesters were much more effectively transported than L-valine and L-cysteine methylesters. The transport yields of L-phenylalanine and L-leucine methylesters with B18C6 were remarkably high, namely 99 and 96%, respectively. It should be noted that L-phenylalanine methylester was significantly slowly transported by 18C6 than B18C6, namely 75%, while L-isoleucine methylester has a transport yield of 97% (Fig. 2). Although the hydrophobicity is an influent factor on the rate of transport through liquid membrane, other factors played a similarly important role. Addition of a carrier, B18C6 and 18C6, for improving the transport efficiency did not entail an increase in the values of the transport yields in the case of L-cysteine and L-valine methylesters (46 and 43% for L-cysteine methylester with 18C6 and B18C6, respectively, and 52% for L-valine methylester with B18C6).

The pH gradient of aqueous source phase and aqueous receiving phase played a certain role in the distribution ratio of the studied amino acids.

Experiments run with cryptand [2.2.2] in the membrane under our experimental conditions for the active transport of L-phenylalanine methylester showed that the amino acid methylester tends to accumulate itself in the chloroform phase and, consequently, lowers the transport yield. This aspect of highly hydrophobic species accumulating in the membrane phase rather than transporting them using cryptands as carrier was mentioned in literature in some transport experiments.[28] This behavior shows that the structure of the carrier is one of the most important parameter in transport experiments. According to the data presented in Tables 1–3, the values of $\log K_{ex}$ were sufficiently high to allow transport processes.

The experimental results obtained suggest that amino acid methylesters are extracted and transported by 18C6 and B18C6 more efficiently than the native amino acids. The results provide further means to optimal separation of amino acid derivatives and other biological species.

CONCLUSIONS

Our results on solvent extraction experiments demonstrated that the receptors involving crown ethers, diaza crown ether [2.2], and cryptand [2.2.2] have high extraction abilities for amino acid methylesters under study. We found relevant correlations between the values of $\log K_{ex}$ for complexes of various amino acid methylesters and crown ethers, and their transport yields through liquid membrane. The extractability was influenced by the structure of the amino acid, the nature of the receptor, and the nature of the anion used as ion pair for cation–receptor complexes. Similarly, 18C6 and B18C6 exhibited different transport selectivities for the amino acid methylesters used in our experiments.

Our results clearly revealed that the amino acid methylesters were extracted and transported by 18C6 and B18C6 more efficiently than the same native amino acids.

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