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Review Article

Complexation of Some Amine Compounds by Macrocyclic Receptors

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Abstract

Some aspects of complex formation, liquid–liquid extraction, and transport through liquid membrane of various amine compounds like ammonium ion, amines, amino acids and peptides, with macrocyclic receptors, such as crown ethers, cryptands, calixarenes, and cucurbituril are presented. Log K, ΔH, and $T\Delta S$ data are reported for reaction of some representative complexes of the amine compounds by macrocyclic receptors obtained from different techniques such as calorimetric and potentiometric titrations, or spectrophotometric methods in various solvents. Solvent extraction and transport of these complexes through bulk liquid membranes are also studied. Based on these studies, the effect of some factors that might influence the complex formation, the extraction, and the transport through liquid membranes are discussed.

Introduction

The amines are among the most important molecules in natural living systems. Many biologically active amines contain substituted ammonium compounds. In biological molecular recognition, the study of substituted ammonium compounds by receptor molecules is an essential issue for understanding the interactions between biological molecules and their applications in separation science.

Many studies were focused on the design and synthesis of a great variety of functionalized macrocycles like crown ethers, aza crown ethers, cryptands, calixarenes, and cucurbituril, which are able to recognize and/or exhibit catalytic activities on biologically interesting ammonium guests (amino acids, biogenic amines, and peptides) [1–3]. The attractive properties of synthetic macrocyclic receptors that are able to form complexes with various compounds by noncovalent interactions are used in understanding the phenomenon of biochemical specificity, especially in the area of molecular recognition.

Synthetic receptor molecules like crown ethers, first synthesized by Pedersen [4], cryptands [5, 6] and spherands [7], with multiple recognition sites and various geometries [8–11] are mostly important in biological studies such as enzyme models, in phase transfer catalysis, and in analytical chemistry [12–16]. Macrocyclic ligands are able to form stable and selective complexes with appropriate substrates by hydrogen bonds, ionic interaction, and/or hydrophobic interactions. The forces that contribute to the stabilization of the complexes formed between macrocyclic hosts and guests are of a noncovalent nature. They were extensively used to selectively separate alkali and alkaline earth cations, heavy metal ions, and ammonium compounds from their mixtures by solvent extraction [17–22] or by liquid membranes [23–26].

In supramolecular chemistry, liquid membranes are frequently used to evaluate complexation and transport properties of receptors. Liquid membranes in amino acids and peptides separations benefit from enhanced transport by using a selective carrier of anionic or cationic form dissolved in an organic solvent. The carriers used for this purpose include macrocyclic ligands. The approach in modeling biological transport systems made of enantiomeric amino acids may be figured out using liquid membranes containing chiral crown ethers. There was also reported the enantioselective binding capability of chiral macrocyclic receptors as chiral selectors [27–29]. Separation of optically active compounds by liquid membranes is of current interest [30–32]. The enantiomeric ammonium cation complexation by a chiral pyridine-containing macrocycle was studied by Bradshaw *et al.* [33].

The calixarene derivatives are well-known receptors, which are biomimetically important in host–guest chemistry since they are able to interact with organic guest molecules, i.e., ammonium and carboxylate ions via their aromatic cone cavity. They exhibit ion selectivity for several metal ions and they also recognize the chirality of amines and amino acids [34–37]. The calix[4]arenes have the ability to form complexes with quaternary ammonium cations, as well as choline and acetylcholine [38, 39].

Generally, the main importance of liquid–liquid extraction concerns ion separation. The factors that may influence the liquid-liquid interface in biphasic systems are usually the

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interfacial tension, potential, and the viscosity. For studying the structure of interfaces between two non miscible solvents, the spectroscopic methods and computer simulation were employed. One of the most important aspects of ligands (calixarenes, cryptands, crown ethers) as extractant molecules concerns their affinity for the interface and so they behave as surfactants [40].

Our experimental and theoretical work on these topics was mainly dedicated to (i) the complexation of some protonated and unprotonated amines (*n*-butylamine, *sec*-butylamine, *tert*-butylamine, aniline, 4-methylbenzylamine, *N*-methylbenzylamine, *N*, *N*-dimethylbenzylamine) with crown ethers (15-crown-5, (15C5), 18-crown-6, (18C6), dibenzo-18-crown-6, (DB18C6) in methanol) [41, 42], and interactions between protonated amines, azacrown ethers, and cryptands with dibenzocrown ethers by a new spectrophotometric technique in aqueous solution [43]; (ii) the solvent influence upon some complex formation between crown ethers and unprotonated amine and amino acids [44–47]; (iii) the complexation of some α-amino acids (L-leucine, L-isoleucine, L-phenylalanine, L-valine, L-methionine, glycine, L-cysteine, L-α-alanine, L-tryptophan) by several crown ethers, viz. 18C6, B18C6, monoaza-18-crown-6 (1 aza-18C6), diaza-18-crown-6, and cryptand [2.2.2] in methanol or aqueous solution [48–50]; (iv) solvent extraction and transport of these complexes through bulk liquid membranes [24–26, 51–53]. Based on these studies, the effect of some factors that might influence both the extraction and the transport through liquid membranes was found [22]. The molecular recognition aspects of complexation of dipeptide, glycyl-L-leucine, by various macrocyclic ligands (18C6, B18C6, and DB18C6) and cryptand [2.2.2] were investigated [54]. The ability of cucurbituril as a macrocyclic receptor to form complexes with amine compounds was also studied.

In the present review we survey some aspects of complexation, liquid–liquid extraction, and the transport through liquid membranes of some amine complexes by macrocyclic receptors. Due to a very large number of remarkable reports on these topics, we briefly refer to the most representative works and place the emphasis on our contributions in the field.

Structures and some properties of amine complexes

It is known that the most remarkable property of crown ethers and cryptands is their ability to bind various species (Figure 1).

Selective recognition of primary ammonium ions as guest molecules by synthetic receptors through the formation of hydrogen bonds has been studied in the last years. Electrostatic interactions between the nitrogen atom (positively charged) of the ammonium group and the oxygen donor atoms of the crown ethers also contribute to the stabilization of these complexes. As mentioned above, the noncovalent bonding presents a special interest in studying biological interactions.

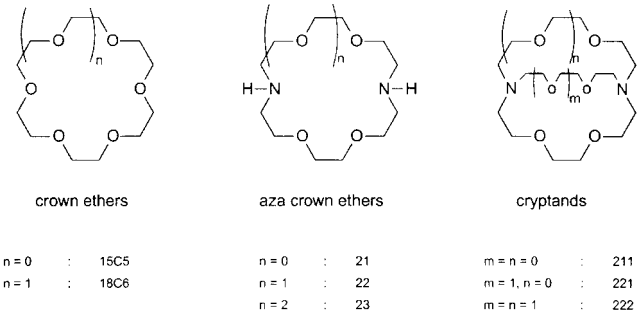

Figure 1. Crown ethers, aza crown ethers, and cryptands.

According to the data presented in the literature, the cryptands form stronger complexes with cations than crown ethers. This aspect is due to the greater encapsulation of the cation by the donor group chains [55].

There are many factors that favor the complexation strength, such as (i) low-polarity solvents, (ii) a good size correspondence between guest and host, (iii) lack of strain in the host, and (iv) the presence of donor groups in the host that are appropriate for the guest. Also, solvent dependence plays an important role in the complexation strength [55].

The thermodynamics of complexation between some dipeptides and 18C6 in water was also studied [56]. These studies demonstrated that the structure, the physicochemical properties of the complexes, and the selectivity in complexation depend on the macrocycle size, binding type, and the depth of peptide penetration into the ligand cavity.

The structure of ammonium cation complexes with crown ethers like 18C6 was observed in solution [57], in the solid state phase [58, 59], and in the gas phase [60]. The formation of macrocyclic ligand complexes with amine compounds can be studied by using many experimental techniques, such as calorimetric titration, NMR, conductometric titration, potentiometric titration, mass spectrometry, X-ray Langmuir or Langmuir–Blodgett techniques [61]. The solvent plays an important role in the complexation constant.

Complex formation of different amine compounds by macrocyclic receptors

Complex formation of different amines by crown ethers

The possibility of crown ethers to interact with the biologically interesting ammonium and substituted ammonium ions through hydrogen bond formation was extensively investigated [8, 18, 62–66]. Crystal structures of ammonium cation complexes suggest that the complementarity between NH_4^+ and 18C6 is perfect [6].

Concerning the complex formation between the macrocyclic ligand 18C6 and some protonated and unprotonated amines (*n*-, *sec*-, and *tert*-butylamine, *n*-dibutylamine, *n*-tributylamine, aniline, benzylamine, *4*-methylbenzylamine, *N*-methylbenzylamine and *N*, *N*-dimethylbenzylamine) the stability constants and the reaction enthalpies and entropies for these reactions by calorimetric titrations were performed in methanol [41, 42] (Table 1).

Table 1. Stability constants (log K, K in $dm^3\ mol^{-1}$) and thermodynamic parameters ΔH and $T\Delta S$ (in $kJ\ mol^{-1}$) for the complexation of different amines by crown ether, 18-crown-6 in methanol at 25 °C

Amines	Log K	$-\Delta H$	$T\Delta S$
n-$C_4H_9NH_2$	2.60 ± 0.05	31.5 ± 0.3	-16.7 ± 0.6
n-$C_4H_9NH_3^+$	3.95 ± 0.06	44.3 ± 0.1	-21.9 ± 0.5
sec-$C_4H_9NH_2$	2.40 ± 0.01	19.2 ± 0.2	-5.6 ± 0.3
sec-$C_4H_9NH_3^+$	3.38 ± 0.08	41.5 ± 0.2	-22.3 ± 0.7
tert-$C_4H_9NH_2$	2.46 ± 0.05	12.7 ± 1.3	1.3 ± 1.0
tert-$C_4H_9NH_3^+$	2.55 ± 0.03	44.4 ± 3.1	-29.9 ± 2.8
$(n\text{-}C_4H_9)_2NH$	2.51 ± 0.06	2.0 ± 0.3	12.3 ± 0.6
$(n\text{-}C_4H_9)_2NH_2^+$	2.37 ± 0.2	2.7 ± 0.2	10.8 ± 0.3
$(n\text{-}C_4H_9)_3N$	2.58 ± 0.04	2.3 ± 0.4	12.4 ± 0.7
$(n\text{-}C_4H_9)_3NH^+$	2.28 ± 0.03	5.5 ± 0.4	7.5 ± 0.6
$C_6H_5NH_2$	2.52 ± 0.02	1.6 ± 0.7	12.7 ± 0.6
$C_6H_5NH_3^+$	3.85 ± 0.21	41.6 ± 0.3	-19.7 ± 0.8
$C_6H_5CH_2NH_2$	2.46 ± 0.02	22.5 ± 0.3	-8.6 ± 0.3
$C_6H_5CH_2NH_3^+$	4.37 ± 0.17	47.7 ± 0.9	-22.9 ± 1.8
4-$CH_3C_6H_5CH_2NH_2$	2.54 ± 0.01	23.8 ± 0.4	-9.4 ± 0.4
4-$CH_3C_6H_5CH_2NH_3^+$	3.86 ± 0.01	49.4 ± 0.2	-27.5 ± 0.3
$C_6H_5CH_2NHCH_3$	2.47 ± 0.04	1.2 ± 0.3	12.8 ± 0.9
$C_6H_5CH_2NH_2(CH_3)^+$	2.43 ± 0.08	3.6 ± 0.7	11.0 ± 0.5
$C_6H_5CH_2N(CH_3)_2$	2.51 ± 0.01	2.1 ± 0.9	12.2 ± 0.9
$C_6H_5CH_2NH(CH_3)_2^+$	2.52 ± 0.01	3.3 ± 0.9	11.2 ± 1.0

As one may see from Table 1, the values of the stability constants obtained for the complex formation between 18C6 and some unprotonated amines in methanol have the same order of magnitude. In contrast, large differences in the reaction enthalpies and entropies are observed. Therefore, by comparing the results for *n*-butyl, *sec*-butyl and *tert*-butyl amines, obviously the values of the reaction enthalpies decrease and the reaction entropies increase. This aspect can be explained by the influence of alkyl and aryl substituents. In this study, the number of hydrogen bonds formed between the crown ether and the studied amines does not influence the complex formation in solution. In Table 1 there are also presented the values of stability constants and thermodynamic parameters for interaction between protonated amines and 18C6 in methanol using a calorimetric titration technique [42]. The ion-dipole interactions are responsible for these results and depend on the chemical structure of the substituent. The reaction enthalpies for complexes of secondary and tertiary substituted ammonium ions with 18C6 are identical but they differ for the other ammonium ions.

In order to obtain more information about the complexation of amino compounds by macrocyclic receptors, Buschmann *et al*. [52] studied the reaction between some amino alcohols with 18C6 (ethanolamine, *4*-amino-1-butanol, *6*-amino-1-hexanol) in methanol and nonprotein amino acids (β-alanine, *5*-amino-pentanoic acid, *8*-amino-octanoic acid) with 18C6 in methanol by means of calorimetric titrations. The number of methylene groups does not influence the complex formation. In the case of protonation of one amino alcohol, the value of the reaction enthalpy with 18C6 is doubled. By comparing with amino alcohols, the complexes of amino acids with 18C6 are more stable. The most important factor in this case is the protonation of the amino groups and the chemical structure of the amino acids. The self-protonation of the amino groups of the amino acids can explain the increase of the reaction enthalpy.

The effect of different crown ethers

It is well known that the ring size, the nature, and the position of the donor atoms of a crown ether have a strong influence on the complex formation with different compounds. The ligand structure-complexation relationship is the subject of many reports [22, 26, 67, 68]. The influence of different crown ethers (15C5, 18C6, B18C6) upon the complexation with some unprotonated amines (*n*-butylamine, *n*-dibutylamine, benzylamine, and *N*-methylbenzylamine) in methanol by means of calorimetric titrations was studied [44]. The values of the stability constants obtained are nearly identical. The complex formation between 15C5 and the above mentioned amines is favored by entropic contributions. In the case of 18C6, large values of the reaction enthalpies were obtained for primary amines and small ones for secondary amines. The complex formation of primary amines with 18C6 is therefore favored by enthalpic contributions and disfavored by entropic contributions. The opposite is true for the behavior of secondary amines. Using the crown ether B18C6, the values of the reaction enthalpy decrease as compared with 18C6. This aspect may be explained by the low basicity of the two oxygen donor atoms attached to the benzo group of the crown ether B18C6.

Extractions of some amine compounds (methylamine, diethylamine, dimethylamine and *n*-propylamine) by 18C6 and DB18C6 in 1,2-dichloroethane by coupling with the picrate anion as ion pair complexes were also studied [24]. The values of the extraction constants of the complexes of the above mentioned amines in protonated form decrease in the following sequence: 18C6 > DB18C6. The lowest values for the extraction constants were obtained using DB18C6, owing first to its aqueous insolubility, and secondly, to the influence of the number of benzo groups added to the ring of the ligand 18C6 (Table 2).

The transport yields for the amines under study, using 18C6, B18C6, and DB18C6 as carriers through 1,2-dichloroethane liquid membrane, were relatively low, between 25–40% (methylamine and *n*-propylamine, respectively, with 18C6 as a carrier), 18–31% (methylamine and *n*-propylamine, respectively, with B18C6 as a carrier), and 19–25% (diethylamine and *n*-propylamine, respectively, with DB18C6 as a carrier) [22, 24, 69]. The transport of the amine picrate was found to depend on the carrier, the cation, and the anion.

By using a new spectrophotometric technique [43, 49] the complexation of ammonium and alkylammonium ions and diprotonated diamine with nearly insoluble ligands, such as dibenzo crown ethers (Figure 2) in aqueous solution was investigated. In this case, the solubility of the dibenzo-crown ethers increases and only small amounts of ligands are necessary to determine the stability constants in homogen-

Table 2. Percentage of some protonated amines transported into the receiving phase by macrocyclic ligands through 1,2-dichloroethane liquid membranes and the values of log K_{ex} of their complexes[24]

Amines	18C6		DB18C6		Kryptofix [2.2]		Kryptofix [2.2.2]	
	*(%)	log K_{ex}	*%	log K_{ex}	*(%)	log K_{ex}	*%	log K_{ex}
$CH_3NH_3^+$	25	4.76 ± 0.08	20	2.45 ± 0.06	48	4.04 ± 0.01	65	4.47 ± 0.05
$(CH_3)_2NH_2^+$	38	4.20 ± 0.05	22	2.20 ± 0.05	44	3.91 ± 0.02	63	4.25 ± 0.03
$(C_2H_5)_2NH_2^+$	33	3.75 ± 0.02	19	2.05 ± 0.03	42	3.85 ± 0.03	58	4.02 ± 0.02
n-$C_3H_7NH_3^+$	40	5.12 ± 0.07	25	3.49 ± 0.06	52	4.34 ± 0.05	78	4.45 ± 0.03

*(%): Amine percentage found in the receiving phase after 6 hours of stirring.

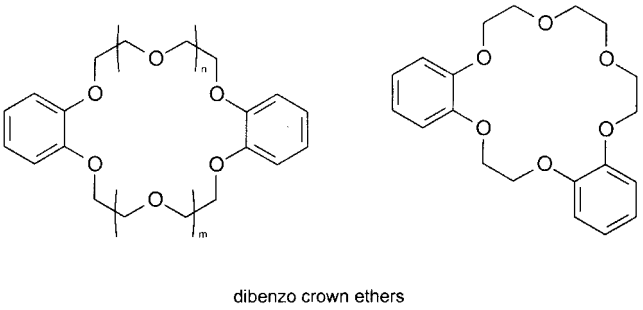

Figure 2. Chemical structures of some dibenzo crown ethers used throughout the experiments [49].

eous solution. The results suggest that the ligand DB18C6 forms the most stable complexes with the ammonium and alkylammonium ions examined (NH_4^+, $CH_3NH_3^+$, $C_2H_5NH_3^+$) (Table 3). The values of the stability constants are smaller than 10^2 dm^3 mol^{-1}. Studies on complex formation between protonated diamino compounds and DB18C6 and DB24C8 in aqueous solution, using a new spectrophotometric technique suggest that under the experimental conditions only 1 : 1 complexes with diamines are formed [43]. The complexes formed between DB18C6 and ammonium ions are more stable than in the case of DB24C8.

A very interesting aspect concerning the study of complexation between different crown ethers and aminobenzo crown ethers consists in the possibility of forming large aggregates of amino substituted crown ethers by self complexation of protonated aminobenzo crown ethers in solution. One protonated amino group of an aminobenzo crown ether is complexed by the crown ether part of another aminobenzo crown ether. In the case of aminobenzo-18-crown-6 the self-complexation is strong [71]. Studies on the topics are in progress.

Amino acids are important components of proteins, so that studies in the field (i.e., binding, solvent extraction, transport through liquid membranes) have a special significance for natural living systems. Their chemical and physical characteristic behavior, both of biological and pharmaceutical interest, should be well known in order to understand the reaction mechanism of the processes they participate in. The structures of complexes formed between some amino acids and macrocyclic ligands, as well as the increasing solubility of amino acids in organic solvents in the presence of macrocyclic ligands, together with thermodynamic data for the complex formation were reported [6, 8, 18, 62–68]. The values of the stability constants, the enthalpies, and the entropies of the complexes formed between some α-amino acids (L-α-alanine, L-cysteine, glycine, L-isoleucine, L-leucine, L-methionine, L-phenylalanine, L-serine, L-tryptophan and L-valine) with different macrocyclic receptors (18C6 and B18C6) in methanol have been reported [48]. Comparing the stability constants for the reaction of amino acids with the crown ether 18C6 with the stability constants for the reaction of the same amino acids with the crown ether B18C6 shows that these are nearly identical or only a bit smaller in the case of B18C6. The values of the reaction enthalpies are much smaller than with 18C6, and the reaction entropy compensates them. Generally, the amino acids exhibit zwitterionic character in neutral aqueous medium. The complexation reactions of the ligand 18C6 with the above mentioned α-amino acids in acidic, neutral and basic methanolic solutions were also studied. In methanolic solution, the amino acids exist in their zwitterionic form and the concentration of the zwitterionic form can be influenced under acidic, neutral or basic conditions. Some experimental aspects concerning both the solvent extraction and the transport of amino acids through liquid membranes using macrocyclic ligands (18C6, B18C6, and DB18C6) in 1,2-dichloroethane were studied [26]. The results suggested a good correlation between the structural properties of the amino acids and their physicochemical characteristics.

The distribution (log D) of some α-amino acid complexes with 18C6 and an accompanying ion in the water/1,2-dichloroethane biphasic system was correlated with the characteristics of the amino acids (e.g., hydrophobicity, the acidity constants pK_{a1}, pK_{a2}, and pI) using linear and multilinear regression analyses [72]. The correlation between the extraction constants in the biphasic system with the amino acid hydrophobicity log P (the hydrophobicity expressed as the logarithm of their partition coefficients between 1-octanol and water) is presented in Figure 3 [26].

As displayed by Figure 3, there is a good linearity between the values of the extraction constant of the amino acids and their hydrophobicity, when 18C6 and DB18C6 were used as extractants. Figure 4 presents the relationship between the transport value of some amino acids through liquid membranes [24] using carriers like 18C6, B18C6, and DB18C6, and the hydrophobicity log P. The sequence of the transport value as a function of their hydrophobicity is the following: L-Phe > L-Leu > L-Met > L-Val > L-Ala using 18C6 as a carrier. A good correlation can be observed

Table 3. Stability constants (log K, K in $dm^3\ mol^{-1}$) for the complex formation of dibenzocrown ethers with different ammonium ions in aqueous solutions at 25 °C

Cation	DB15C5	DB18C6	[2,4]DB18C6	DB24C8	DB30C10
NH_4^+	0.85 ± 0.09	1.54 ± 0.11 ≈ 0.30[a]	0.68 ± 0.05	0.61 ± 0.07	0.64 ± 0.13
$CH_3NH_3^+$	0.86 ± 0.14	1.31 ± 0.12	0.62 ± 0.04	0.44 ± 0.13	0.53 ± 0.21
$C_2H_5NH_3^+$	0.98 ± 0.05	1.35 ± 0.10	0.65 ± 0.03	0.58 ± 0.09	0.56 ± 0.10

[a]From ref. [70].

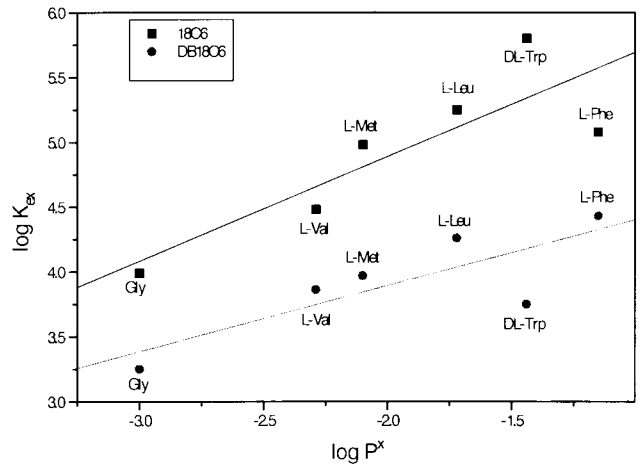

Figure 3. Correlation between log K_{ex} and the amino acid hydrophobicity, from Ref. [77].

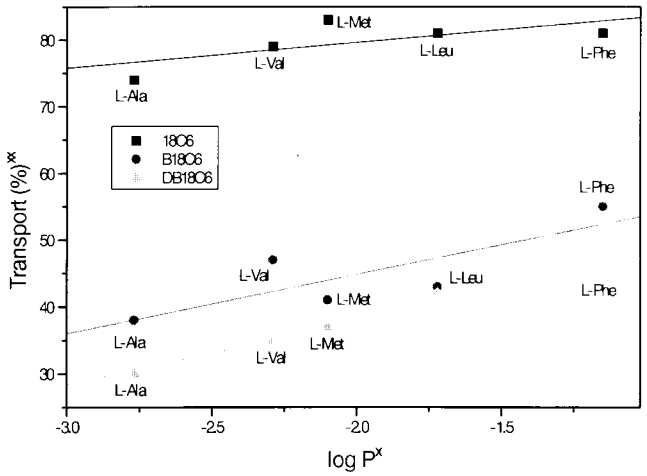

Figure 4. Relationship between the hydrophobicity and the transport through liquid membranes [26]; *from Ref. [77]; **(%) Amino acid percentage found in the receiving phase after 6 hours of stirring.

between the transport yields of the above amino acids and the hydrophobicity in the case of both B18C6 and DB18C6 as carriers through liquid membranes, yet lower values were obtained than corresponding to 18C6.

The development of synthetic receptors for peptides and amino acid derivatives [73, 74] is most important since the study of intermolecular interactions involved in small molecule-peptide complexes may lead to the understanding of many biological peptide-protein interactions. The thermodynamics of complexation of some small peptides with 18C6 in water was studied by Lipkowski *et al.* [56].

Table 4. Extraction constants (log K_{ex}) of glycyl-L-leucine in 1,2-dichloroethane by various macrocyclic ligands

Ligands	log K_{ex}	
	glycyl-L-leucine	L-leucine*
18C6	5.26 ± 0.02	5.76 ± 0.01
B18C6	5.05 ± 0.3	4.30 ± 0.05
DB18C6	4.89 ± 0.07	4.15 ± 0.05
[2.2.2]	5.10 ± 0.2	4.43 ± 0.04

*From Ref. 24.
$C_{ligand} = 2.5 \times 10^{-3} - 10^{-2}$ M; $C_{peptide} = 1.0 \times 10^{-3}$ M; [picric acid] = 8.0×10^{-5} M; $C_{aminoacid} = 6.0 \times 10^{-4}$ M; $pH \approx 2.02$. Temperature: 25 ± 1 °C.

Following the results obtained by X-ray diffractometry on zwitterionic peptides and 18C6 complexes, the complexes are formed by a set of hydrogen bonds. Some experimental aspects of the complexation (stability constants, reaction enthalpy, and reaction entropy) of glycyl-L-leucine in methanol, as well as the solvent extraction of this peptide in the form of ion pair complexes with 18C6, B18C6 and DB18C6, using picrate counterion in 1,2-dichloroethane were studied [54]. The ligand structure, stability constants, extraction constant and solvent nature were interpreted and compared with the corresponding values of the amino acids forming the peptide. Table 4 presents the extraction constants of Gly-L-Leu in 1,2-dichloroethane with 18C6, B18C6, DB18C6, and cryptand [2.2.2], respectively, using picrate anion under the same conditions.

Among the ligands tested, 18C6 was proved to be the most efficient extractant for Gly-L-leucine. In the case of dipeptide extraction, e.g., Gly-L-leucine, by macrocylic ligands, several parameters influenced the extraction process, such as: the nature of the cation, the complementary shape and size of the ligand with the bound ion, the anion size, and also the donor atom type.

The effect of solvents

It is well known that the thermodynamic stability of the complex depends on the nature of the solvent. The complex formation may be strongly affected by the solvation of the reactants. Generally, the interactions between complexes and solvents result from the summing up of hydrogen bond acidity or basicity values calculated with respect to the established acid (basic) scale of the solvents [75, 76]. In the case of transport processes involving liquid mem-

branes, the physico-chemical properties of the solvents play an important role in membrane stability.

Based on the results obtained from the study of interactions between uncharged primary and secondary amines with 18C6 in different solvents [44] by calorimetric titrations it was found that the solvent has a clear effect upon the complex formation. The values of the stability constants of complexes between some uncharged amines (*n*-butylamine, *n*-dibutylamine, benzylamine, and *N*-methylbenzylamine) with 18C6 in methanol, propylene carbonate, acetonitrile, toluene, cyclohexane, and carbon tetrachloride are nearly identical. However, there are differences between the values of the reaction enthalpies for the complexation of the above mentioned amines in different solvents, as compared with the methanol case. The results are explained by the solvation of the amines. In methanol, strong hydrogen bonds between primary amines and the solvent molecules are formed. In non-polar solvents, such as toluene, cyclohexane and carbon tetrachloride, complex formation with the amines is only favored by entropic contributions and the values of the reaction enthalpies are small and of the same order of magnitude.

The influence of some solvents (water, methanol, ethanol, dimethylsulphoxide, acetonitrile, propylene carbonate, acetone, and 2-butanone) upon the complexation of ammonium ion by 18C6, using calorimetric and potentiometric titrations, has been also studied [45]. The values of the stability constants obtained in the case of complexes of ammonium ion by 18C6 in water and dimethylsulphoxide had the lowest values as compared with all other solvents under scrutiny. The explanation of this behavior consists in the interactions of the ammonium ion with the solvent molecules. The values of the reaction enthalpies are small and the values of the reaction entropies are positive. In the case of acetonitrile it is known that the crown ether 18C6 interacts with this particular solvent. Hence, the explanation for the small value for the reaction enthalpy and the positive value of the reaction entropy which were obtained.

Regarding the experimental data of the transport of some protonated amines (methylamine and *n*-propylamine) through chloroform, 1,2-dichloroethane and methylene chloride membranes containing 18C6 as a carrier, the yields were in the range of 12–58%. The transport sequence follows the order: 1,2-dichloroethane > chloroform > methylene chloride of complexes of 18C6 with methylamine. The same results were obtained for complexes with *n*-propylamine. In the case of methylamine and *n*-propylamine, the transport sequence was proportional to the extraction efficiency [69].

The study concerning the possibility of correlating some characteristics of α-amino acids (L-leucine, L-tryptophane, L-phenylalanine, L-methionine, L-valine and L-isoleucine), such as pK_{a1}, pK_{a2}, and pI, partial hydrophobicity π [77], and total hydrophobicity log P [78] with those corresponding to chlorinated solvents (methylene chloride, chloroform and 1,2-dichloroethane), such as hydrogen bond acidity, $\sum \alpha_2^H$, or hydrogen bond basicity, $\sum \beta_2^H$, polarizability π_2^H, and molar refraction R_2^H, was performed by means of multilinear regression analysis. The results revealed a good correlation ($r > 0.8$) between some characteristics of the α-amino acids and of the different chlorinated solvents [46, 47] in the case of liquid-liquid transfer of the above mentioned α-amino acids from water to chlorinated solvents.

The stability constants of complexes between some amino acids (glycine, *4*-aminobutyric acid, *5*-amino-*n*-valeric acid, *6*-aminocaproic acid, β-alanine, L-serine and L-isoleucine) and the nearly insoluble ligand DB18C6 in aqueous solution were performed using a new spectrophotometric method [50]. The stability of the formed complexes depends mainly upon the number of CH_2 groups between the amino and carboxylic groups of the amino acid under study.

The thermodynamics of complexation of amino acids (L-isoleucine, L-histidine, DL-methionine, L-serine, L-threonine, L-asparagine, and L-glutamine) with 18C6 in water was studied [79] by the calorimetric method. The values of log K under study were moderate and lay in the range 0.6–1.5. The values of log K found for the aqueous solutions are considerable lower than those for the methanol solutions [48]. This difference is due to the stronger solvating ability of water.

Complex formation of different amines by aza crown ethers

The mixed-donor type crown ether (diazacrown ether) exhibited transport properties towards the ammonium cations of biologically important amine compounds. Tsukube [80, 81] reported the cation-binding and transporting properties of some polyamine and polyamide macrocycles for amino acid ester salts.

The transport yields of the methylamine, diethylamine, dimethylamine and *n*-propylamine complexes with the cryptand (2.2) (Table 2) are relatively high namely in the range of 42–52% (diethylamine and *n*-propylamine, respectively) [24]. The complex formation between some α-amino acids (L-alanine, L-cysteine, glycine, L-isoleucine, L-leucine, L-methionine, L-phenylalanine, L-serine, L-tryptophan, and L-valine) and the monoaza-18C6 and the diazacrown ether (2.2) in methanol was studied by calorimetric titration [48]. It is known that the substitution of one oxygen by one nitrogen donor atom in the crown ether molecule has no influence upon the measured stability constants. The values of the reaction enthalpies are smaller in comparison with the ligand 18C6. In this case, the complex formation is favored by entropic contributions. The substitution of two oxygen donor atoms by two nitrogen atoms determines a decrease of the stability constants caused only by entropic contributions. Comparing the values of the stability constants of complexation of the above mentioned amino acids by 18C6, monoaza-18C6 and cryptand [2.2.2] with the values of the stability constants of the same amino acids complexed with diaza-18C6 shows that the stability constants with diaza-18C6 are much smaller.

The stability constant of the complex between Gly-L-leucine and monoaza-18C6 in methanol was found to be

log K = 3.15. The reaction enthalpies of the peptide and the corresponding amino acids, such as glycine and leucine, respectively, with monoaza-18C6 were lower than in the case of 18C6. The stability constant of the above mentioned complexes is influenced by the structure of the ligand and the characteristics of the peptide [54].

Complex formation of different amines by cryptands

The cavity size of the ligand cryptand [2.2.2] (r = 1.4 Å) [82] corresponds best with the size of the $-NH_3^+$ group (r = 1.42 Å). In most cases, the macrobicyclic ligands, such as cryptand [2.2.2], form stronger complexes with organic species, as compared with macrocyclic ligands [45]. It is known that both the stability and selectivity of the complexes depend on the size of the macrocyclic ring. The formed cryptates depend on the macrobicyclic structure and can be extracted into organic solvents by coupling with an organic or inorganic anion.

The transport yields of the methylamine, diethylamine, dimethylamine and *n*-propylamine complexes with crypt- and [2.2.2] through 1,2-dichloroethane liquid membrane are relatively high, namely 65–78% (methylamine and *n*-propylamine, respectively) as presented in Table 2 [24].

The complex formation between some α-amino acids (L-alanine, L-cysteine, glycine, L-isoleucine, L-leucine, L-methionine, L-phenylalanine, L-serine, L-tryptophan, and L-valine) and the cryptand [2.2.2] in methanol was determined by calorimetric titration [48]. The complexation with the ligand [2.2.2] is favored by the reaction entropy and the values of the stability constants of the above mentioned amino acids complexes with the cryptand (2.2.2) and with the crown ether 18C6 are nearly identical. Yet the values of the reaction enthalpies are an exception, being much smaller than the ones corresponding to 18C6.

The reaction between some amino alcohols (ethanolamine, *4*-amino-1-butanol, and *6*-amino-1-hexanol) and non-proteic amino acids (β-alanine, *5*-amino-pentanoic acid, and *8*-amino-octanoic acid) with cryptand [2.2.2] was studied by calorimetric titration [52]. The values of the reaction enthalpies with amino acids were higher when compared with the amino alcohols. The self-protonation of the amino group is also responsible for the results. However, the number of methylene groups between the amino and the carboxylic groups has no influence on the stability constants and thermodynamic parameters with cryptand [2.2.2].

The value of the extraction constant, log K_{ex}, for Gly-L-Leu in 1,2-dichloroethane with cryptand [2.2.2] using the picrate anion was found to be 5.10 (Table 3). These results suggested that the extraction processes of peptides using cryptands are feasible and comparable with those obtained by using crown ethers [54].

The investigation of the solvent extraction of some α-amino acids in the protonated form (L-leucine, L-isoleucine, L-phenylalanine, L-methionine, L-valine, and L-α-alanine) in chloroform by cryptand [2.2.2] as ion pair complexes, using picrate anion as counterion, was also reported [83]. The values of the extraction constants obtained with cryptand [2.2.2] are good but lower than those given by 18C6 ligand; these values range between 4.55–4.15 for L-isoleucine and L-α-alanine, respectively. The stoichiometry in chloroform indicated a combination ratio of component species of 1 : 1 : 1 (ligand : amino acid : anion) [25]. The experimental results obtained suggest the influences of ligand size and the donor atom type on the extraction constants. The differences among the extraction constant values of the amino acid are not significant enough in order to permit their individual separation through extraction.

Table 5. Stability constants (log K, K in $dm^3\ mol^{-1}$) and thermodynamic parameters ΔH and $T\Delta S$ (kJ/mol) for the complexation of different amino alcohols and amino acids by the ligands 18C6 and [2.2.2] in methanol at 25 °C

Ligand	Amine	Log K	$-\Delta H$	$T\Delta S$
18C6	n-$NH_2C_4H_9$	2.60 ± 0.05[a]	31.5 ± 0.3[a]	-16.7 ± 0.6[a]
	$NH_2(CH_2)_2OH$	2.31 ± 0.10	29.7 ± 2.1	-16.6 ± 2.7
	$NH_2(CH_2)_4OH$	2.47 ± 0.41	35.9 ± 2.5	-21.9 ± 4.9
	$NH_2(CH_{2)})_6OH$	2.66 ± 0.12	33.8 ± 0.1	-18.7 ± 0.8
	l-ala$^-$			34.1 ± 2.0[b]
	$^+NH_3(CH_2)_6OH$	2.81 ± 0.22	60.4 ± 0.7	-44.4 ± 1.9
	l-ala	3.24 ± 0.01[b]	46.2 ± 2.6[b]	-27.8 ± 2.7[b]
	β-ala	4.19 ± 0.24	52.2 ± 1.1	-28.4 ± 2.5
	pent	3.56 ± 0.06	62.4 ± 0.5	-42.20 ± 0.9
	oct	3.53 ± 0.08	69.6 ± 0.6	-49.5 ± 1.0
[2.2.2]	$NH_2(CH_2)_2OH$	2.55 ± 0.09	17.4 ± 1.3	-2.9 ± 1.8
	$NH_2(CH_2)_4OH$	2.61 ± 0.10	20.8 ± 1.5	-5.9 ± 2.0
	$NH_2(CH_{2)})_6OH$	2.59 ± 0.08	17.5 ± 0.9	-2.8 ± 1.4
	l-ala	3.11 ± 0.09[b]	16.0 ± 0.8[b]	1.6 ± 1.2[b]
	β-ala	4.83 ± 0.05	39.7 ± 0.9	-12.2 ± 1.1
	pent	3.69 ± 0.07	40.7 ± 1.2	-19.7 ± 1.6
	oct	4.14 ± 0.04	38.1 ± 0.7	-14.6 ± 0.9

[a]From Ref. 11.
[b]From Ref. 15.

Complex formation of amine compounds with calixarenes

The calixarenes are prepared from phenols and aldehydes by an acid-catalyzed condensation. They can recognize cationic and anionic species, as well as neutral molecules. These receptors have the possibility of forming interesting complexes both with metal cations and biological compounds by exhibiting extractibility and selectivity. There are many studies dedicated to calixarene chemistry and especially in the molecular inclusion of biological substrates, such as amines and amino acids, by these receptors [34–36].

Chang *et al.* [84] used a calixarene derivative as a selective carrier for the separation of amino acids through a chloroform liquid membrane, and established a schematic mechanism concerning the interaction between ethyl esters of both phenylalanine and tryptophan by calix[6]arene. The results obtained suggest that the ethoxycarbonylmethyl derivative of *p*-tert-butylcalix[6]arene can be used as a carrier for selective recognition and separation of some important

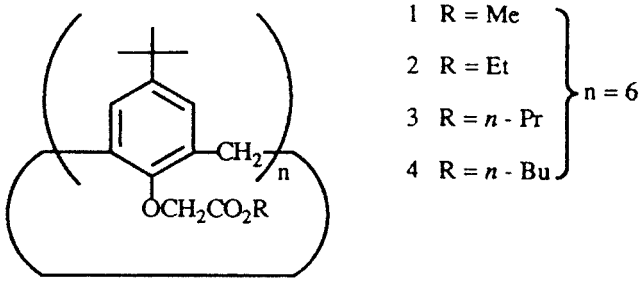

Figure 5. Chemical structure of ester derivatives of *p*-tert-butylcalix[6]arene [87].

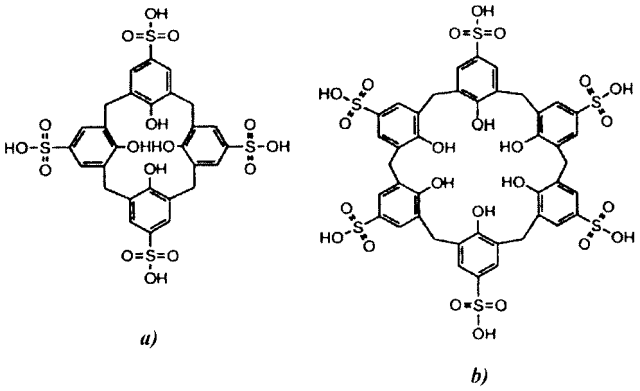

Figure 6. Chemical structures of (a) calix[4]arene *p*-sulfonic acid; (b) calix[6]arene *p*-sulfonic acid [96].

amino acids. Along the same line, Shinkai *et al.* [85] showed that the homocalix[3]arene exhibits enantiomeric recognition properties toward alanine ethyl ester and phenylalanine ethyl ester. Concerning the binding of NMe_4^+ to calixarenes, the same author [86] suggested that the cone of calix[6]arene could be a good cavity for a quaternary ammonium cation.

The selective recognition of butylamines by ester derivatives of *p*-tert-butylcalix[6]arene (Figure 5) compared with dibenzo-18-crown-6 was studied using a standard solvent extraction technique of butylammonium picrates into dichloromethane [87].

The hexaesters **1**–**4** interact with butylammonium guests in the following sequence: *n*-butyl > *iso*-butyl-*sec*-butyl > *tert*-butyl, which can be explained by reasoning from steric effects.

Recently, calixarenes, because of their recognition and discrimination ability, have attracted much attention as good extractants for amine compounds [88]. Okada *et al.* [89] prepared new calix[4]arene derivatives and used them for selective extraction and transport of some amino acid ethyl esters into CH_2Cl_2. The efficiency of extraction was explained by the hydrophobicity of the amino acids and the extractibility was determined by ultraviolet and NMR measurements. These receptors also recognized the chirality of the L-amino acids in transport experiments. Similarly reasoning, Lee *et al.* [90] studied the thermodynamics of solvent extraction of alkylammonium cations with alkyl calix[6]aryl esters.

Some reports are devoted to ionophoric macrocyclic compounds with electrochemically active functionalities like calix[4]arendiquinone compounds in the presence of various alkylammonium ions [91]. The capability of these redox-dependent receptors to form complexes with protonated amine-type compounds by multiple hydrogen bonds and the relationship between the properties of the guests and the electrochemical enhancement of the host were reported. The potential applications of quinone-modified macrocycles in the development of molecular electronics [92], potentiometric sensors [93], and a model study of electron transfer in biological systems [94] present a special interest in the field.

A theoretical study concerning molecular dynamics simulations on the NM_4^+ and NH_4^+ complexes of bridged calix[6]arene in chloroform with acetate as counterion was presented [95]. Their structure and the location of the guest inside the host were elucidated. The water-soluble tetrasulfonated calix[4]arene and hexasulfonated calix[6]arenes (Figure 6) bind very strongly the quaternary ammonium cations, and also acetylcholine [96]. X-ray crystallographic studies of the choline tetrasulfonated calix[4]arene complex established that the choline has its *N*-terminal inside the aromatic cavity of the receptor.

New selective receptors for amino acids were synthesized by Antipin *et al.* [97] utilising calix[4]arene-based α-aminophosphonates. These compounds exhibited remarkable selectivity as carriers of the zwitterionic form of aromatic amino acids through a supported liquid membrane composed of a porous polymeric support.

In an effort to develop improved optical receptors for biologically and/or chemically important cations and amines, Kubo *et al.* [98] synthesized chromogenic calixarenes. Also the calixarenes, which are cyclic phenol-derived macrocycles, are used for the construction of optical sensing systems [99] used in the visual detection, and enantiomeric distinction between amines and amino acids.

Complex formation of amine compounds with cucurbituril

The investigation of the structure and of the properties of the synthetic macrocyclic receptor, cucurbituril (Figure 7) and their applications was the subject of several papers [100–105] and reviews [106, 107]. Cucurbituril is a compound with a relatively rigid structure. Therefore, this molecule has a hydrophobic cavity for the inclusion of various molecules and is able to form stable complexes with amines, diamines [103, 104], alkali and alkaline earth cations [108, 109], dye molecules [110], aromatic compounds [111], alkyl mono- and diammonium ions [112], 4-methylbenzylammonium ion [113], and alkylammonium ions [114, 115].

Another challenging application is formation of mono-, oligo-, and polyamide rotaxanes with cucurbituril. The complex of cucurbituril with the 1,6-hexanediammonium ion is used as a preorganized structure to synthesize poly(amide rotaxane)s by interfacial condensation [116, 117]

As mentioned above, the macrocyclic ligand cucurbituril is able to form complexes with aliphatic amino acids, amino alcohols, and other amino compounds [118].

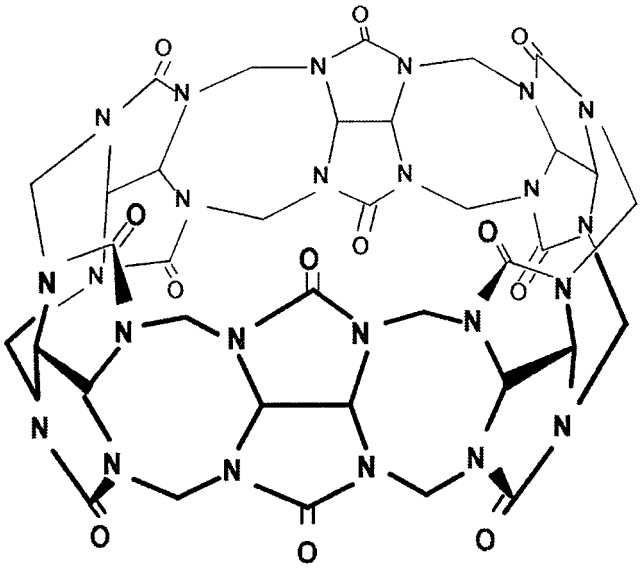

Figure 7. Chemical structure of cucurbituril.

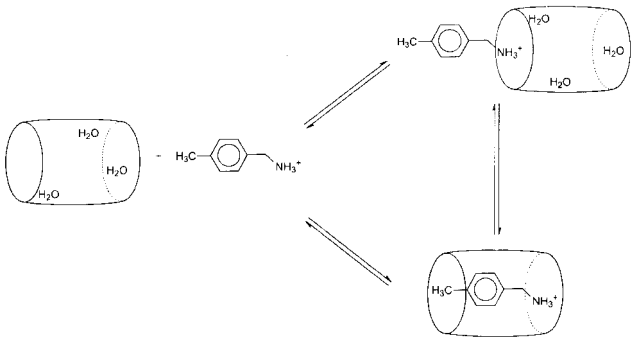

Figure 8. The association and the inclusion complex of cucurbituril and *4*-methylbenzylammonium ion [113].

Based on results obtained, one may see that the stability constants for the complexation of amino acids by cucurbituril in aqueous formic acid (50% v/v) are of the same order of magnitude, that is between 3.27 (*8*-amino octanoic acid) and 3.67 (*2*-amino ethanoic acid). One explanation could be that the complex formation of amino acids is less favored by enthalpic contribution, compared with *1,6*-diamino hexane. The number of methylene groups of the amino acids does not influence the values of stability constants, but in the case of amino alcohols the reaction enthalpies and entropies influence these. Increasing the number of methylene groups decreases the stability of the complexes formed.

Mock and Shih [114] studied by NMR techniques the interactions between cucurbituril and alkylammonium and alkyldiammonium ions. Their interest was focused upon the noncovalent binding properties of cucurbituril as a receptor for substituted ammonium ions. The results were explained in terms of ion-dipole attractions and shape complementarily between cucurbituril and alkylammonium ions. There are two kinds of noncovalent binding interactions: an ion-dipole interaction between the cationic ammonium moiety and the carbonyl group of cucurbituril, and a hydrophobic effect associated with the encapsulation of the hydrocarbon part of the guest. The same authors [115] also studied the rate of inclusion complex formation between cucurbituril and alkylammonium ion ligands and correlated their experimental results with the molecular diameter of ammonium compounds. The relationship between the thickness of the guest and its rate of complex formation with cucurbituril proved to play an important role in this case. The results were interpreted by using the shape complementarily between the host and guest.

Using spectrophotometric and kinetic investigations, Hoffmann *et al.* [113] reported the stability constants of cucurbituril with 4-methylbenzylammonium ion complex, as well as the influence of added alkali-metal or ammonium salts into solution upon the competitive binding of 4-methylbenzylammonium to cucurbituril. The results showed that the complex formation between cucurbituril and 4-methylbenzylammonium is reduced when alkali-metal cations are added. The authors established the mechanism for the formation of association and inclusion complexes of cucurbituril with 4-methylbenzylammonium (Figure 8).

In the complexation of alkyl monoammonium and alkyl diammonium ions with cucurbituril [112] in aqueous formic acid studied by calorimetric titrations, the ion-dipole interactions between the carbonyl groups of cucurbituril and the ammonium ions on one side and the hydrophobic effect on the other side are responsible for the complexation. The stability constants of cucurbituril with alkylamine salts increase with the increasing concentration of the acid, while the values of the reaction enthalpies and reaction entropies decrease.

Conclusions

The effect of some factors that might influence the complexation of some amines, amino acids, and peptides with different macrocyclic receptors, their extraction, and their transport through liquid membranes was investigated.

Stability constants and some thermodynamic data for the complexation of ammonium ion and some substituted ammonium ions with different macrocyclic receptors (crown ethers, aza crown ethers, cryptands, calixarenes, and cucurbituril) were discussed. Bulk liquid membranes are used to investigate the complexation and transport properties of the above mentioned synthetic macrocyclic receptors. Ion-pair extractibility of the crown compound complex with ammonium cations in various solvents in order to elucidate the extraction efficiency and selectivity of crown compounds was presented.

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