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Review Article

Complexation and Separation of Amines, Amino Acids, and Peptides by Functionalized Calix[*n*]arenes

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Abstract

The ability of calix[*n*]arenes to form complexes, to act as extractants in liquid–liquid extraction, and run as carriers in transport through liquid membranes of different biological amine compounds (e.g., ammonium ion, amines, amino acids, and peptides) has been the central topics of many reports. These features recommend the calix[*n*]arenes as competitive candidates for studying the interactions involved in host–guest recognition as well as useful receptors in separation processes. Some specific aspects of their applications in binding and separation of various amine compounds by extraction, and in transport through liquid membranes have therefore been considered. The effect of the factors that might influence the separation of above compounds by extraction, and the transport through liquid membranes using the calix [*n*]arenes has been presented.

Introduction

The recognition of biological substrates by synthetic receptors is a topic of current interest in supramolecular and analytical chemistry. The diversity in receptors design allows several applications in various fields. Along with the crown ethers, cryptands and cyclodextrins, the calix[*n*]arenes are one of the most important category of supramolecular hosts. They are prepared from phenols and aldehydes by a base catalyzed condensation. By comparing with cyclodextrins, the calix[*n*]arenes exhibit the big sterical flexibility which confer them a large area of applications [1–10]. These features recommend the calix[*n*]arenes as competitive candidates for studying the interactions involved in host–guest recognition as well as useful receptors in separation processes. These receptors have the possibility to form interesting complexes with both the metal cations and biological compounds by exhibiting extractability and selectivity. Moreover, it was reported that the calix[*n*]arenes are useful building blocks in molecular recognition [2].

By using calix[*n*]arene derivatives with functional groups such as ether, amide, ketonic, ester, and crown ether increases further their potential applications. There are many studies dedicated to calix[*n*]arenes chemistry especially in the molecular inclusion of biological substrates, such as amines and amino acids, by these receptors [11–13]. Among others applications like chromogenic and fluorogenic sensors and field effect transistors [14], ion selective electrodes [15], calixarene molecules for nonlinear optical devices[16], as liquid crystals [17] or as catalysts in synthetic reactions [18–21], the calix[*n*]arenes have an important role in chemical separations. Based on their unique three-dimensional surface and conformationally rigid structures, calix[*n*]arenes have been used for the design of various receptors and sophisticated molecular assemblies like cavitands, (hemi)carcerands, self-assembling capsules, and nanoscale multivalent entities, e.g., calix-peptides and calix-peptide-dendrimers [22–28].

Liquid membranes in amino acids and peptides separations are of current interest in biological systems and in industrial applications too. The carriers used for this purpose include calix[*n*]arenes. One of the most challenging areas of applications in separation for calix[*n*]arene involves chiral recognition of biologically active substrates using homooxacalix[3]arene [29] or calix[4]arene with chiral pendant groups as carrier through liquid membrane [30]. In an effort to explore, the abilities of chiral calix[*n*]arenes displaying enantiometric discrimination towards biologically compounds such as amines and/or amino acids the chromogenic calix[*n*]arenes were synthesized [31].

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The property of water-soluble calix[*n*]arenes to form inclusion complexes with several guest species in water opened a new direction of applications. In this area, the contributions of Shinkai and coworkers [13, 29], Ungaro and coworkers [32, 33], and Vicens and coworkers [8] have particular relevance since most of the biological processes take place in a such media.

It is well known that biogenic amines, amino acids, peptides, and proteins constitute one of the most fundamental substrates in biological and artificial processes. The family of calix[*n*]arenes are deeply involved in molecular recognition of these compounds especially in the understanding of specific biomolecular interactions which play a key role in modern supramolecular chemistry.

Our recent studies in this field were mainly dedicated to complex formation between some water-soluble calix[*n*]arenes with amino acids and peptides in water [34]. Also the extraction abilities and the transport through chloroform liquid membrane of *p*-tert-butylcalix[*n*]arenes ($n = 6$, 8) upon some native and derivative amino acids were performed. In this order the effect of some factors that might influence the separation of amine compounds by extraction, and the transport through liquid membranes using the calix[*n*]arenes as carriers were studied [35].

The present review focuses on recent studies about complexation, liquid–liquid extraction, and the transport through liquid membranes of some amine compounds such as amines, native and derivative amino acids and peptides by using calix[*n*]arenes as extractant or carrier. Due to a remarkable reports published in this field, we briefly present some of them with emphasis on our contribution.

Interactions involved in calix[*n*]arene complexes

The study of multiple interactions between host–guest complexes are of fundamental interest [36]. It is well known that noncovalent interactions play an important role in biological processes such as immune response, protein enzyme inhibitors, and signal transduction. Hydrophobic effects, van der Waals forces, hydrogen bonding, and in the last decade cation–π interaction are representative interactions for host–guest complexes and also involved in calix[*n*]arene complexes [37]. Recently, many papers have reported that noncovalent cation–π interaction play an important role in building up the structure of many biological important macromolecules and in promoting fundamental functions such as recognition, transport and chemical transformation of a substrate [38].

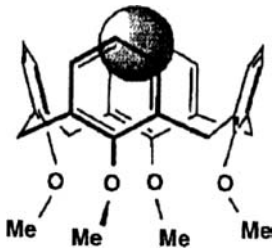
Particularly, the calix[*n*]arenes exhibit a special ability for cation–π interaction because their preorganized aromatic rings. It is well known that calix[*n*]arene derivatives act as receptors for ammonium cations through their aromatic cone cavity [2, 3, 6, 36, 39, 40]. A well documented review emphasized the cation–π interactions established between aromatic rings of different calix[*n*]arenes and ammonium, iminium and tropylium ions. It pointed out that the type, the shape, and the flexibility of both the host and the guest have the strongest influence on the stability complex [37]. Furthermore, noncovalent inclusion complexes of methyl, ethyl, and propyl ester derivatives of calix[6]arene with amino acids were observed in MALDI mass spectrometry suggesting that calix[6]arene derivatives show stronger binding of amino acids in the gas-phase than calix[4]arenes [27]. These complexes were significantly stronger than the corresponding inclusion complexes of cyclodextrin and crown ethers with amino acids. The ethyl and propyl amine as well as with guanidine and creatinine formed complexes with esters of calix[6]arene in gas-phase observed by Maldi mass spectrometry [27].

General aspects of calix[*n*]arene complexes

According to the thermodynamic data, the calix[*n*]arenes composed of several aromatic rings connected with methylene or oxyethylene chains show considerable conformational changes upon inclusion, probably due to the structural flexibility which is comparable to crown ethers [41, 42]. The binding properties of calix[*n*]arenes towards amino substrates have been studied in crystalline state [43], in gas-phase [25–28], and in solution [34, 44–46] by using investigation techniques like NMR spectroscopy, the X-ray crystallography, mass spectrometry, calorimetric or microcalorimetric and potentiometric titrations and for immobilized biomolecules at the solid/liquid interface: scanning probe microscopy and surface plasmon resonance. Many computational approaches have been especially used among the other techniques in studying the binding interactions involved in host-guest chemistry of calix[*n*]arenes [47–49].

It was established that the efficiency in metal ion binding by calix[*n*]arene ionophores depends on the ring size of the calix[*n*]arene, on the nature of the groups attached and on the conformation of the macrocycle such as cone, partial cone, 1,3-alternate, 1,2-alternate in the case of calix[4]arene derivatives [50]. Regarding the ability of calix[*n*]arenes to form inclusion complexes with amino substrates, the results have demonstrated that the ammonium cation could be included in the cone cavity of calix[4]arene owing to the cation–π interaction [13, 51–53] (Scheme 1). In the solid state it was observed that the calix[6]arene sulfonate may adopt a double partial cone conformation for the inclusion complex with quaternary ammonium cation [54]. Along the same line of reasoning, it was reported that choline, acetylcholine and others ammonium cations may form a stable complexes with calix[*n*]arenes [55, 56].

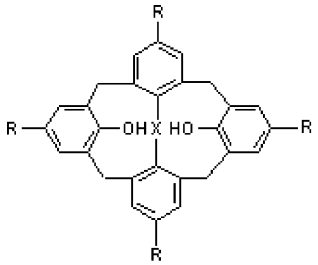
In some studies the recognition of primary amines by calix[6]arenes is presented such as the ammonium cation–crown ether complex [57] because these com-



Scheme 1. Inclusion of ammonium cation by calix[4]arene [13].

pounds have the structure and symmetry adequate to form tripodal hydrogen bonding with protonated ammonium group. In addition, it was reported two complexation geometries like *endo*-calix complex formed by inclusion of a guest cation into the cavity of calixarene, and *exo*-calix complex formed without inclusion of a guest molecule into the cavity [58, 59].

In spite of their relatively low volatility, the complexes of *p*-tert-butylcalix[4]arene with alkali metal cations, divalent cations and benzylammonium cation in gas-phase were studied using Fourier transform ion cyclotron resonance mass spectrometry [24]. Using ESI the complexes of calix[4]arenes with alkylammonium ions were obtained from solution [60].



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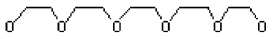

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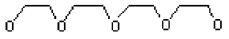

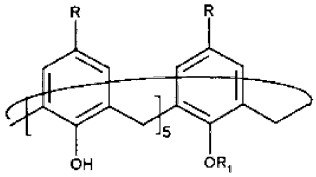

16: R = H $R_1 = CH_2COOH$
17: R = SO_3H $R_1 = CH_2COOH$

Chart 1. The structure of calix[*n*]arenes involve in experiments.

Calix[*n*]arene derivatives in the binding and separation of amines, amino acids, and peptides

Amines

Calix[*n*]arenes, because of their recognition and discrimination ability, have attracted much attention as good extractants for the amine compounds [61]. In this respect, the molecular selective recognition of butylammonium picrates by ester derivatives of *p*-tert-butylcalix[6]arene, **1**–**4** (Chart 1) compared with dibenzo-18-crown-6 was studied using a standard solvent extraction technique in dichloromethane as solvent [62].

The following sequence: *n*-butyl > *iso*-butyl-*sec*-butyl > *tert*-butyl was established by using the hexaesters **1**–**4** for extraction of butylammonium compounds. The binding selectivity of hexaethyl ester of calix[6]arene towards butylammonium picrates is greater than that of dibenzo-18-crown-6 which can be explained by invoking the steric effects. The alkylamines ranging from ammonia to butylamines and arylalkylamines were extracted into dichloromethane by calix[4]-crown-6 ether, **14** (Chart 1) and the binding strength decreased with the increasing size of the alkyl chain of the ammonium guests [63]. The calix[4]-crown-6 host exhibited a much larger discrimination than the dibenzo-18-crown-6 ligand, favoring linear over other isomeric amines. Except for the ammonium guest, the calix[4]-crown-5, **15** (Chart 1) exhibited poor extraction efficiency toward most alkylamines under studied [63].

The study of the system with multiple hydrogen bonds it is important in elucidating the role of the hydrogen bond in biological systems like in the interaction between enzyme and substrate and electron flow in biological membranes. It was reported that the calix[4]arenediquinones which are the ionophoric macrocyclic compounds with electrochemically active functionalities form the complexes with various alkylammonium ions characterized by multiple hydrogen bonds [64]. Based on obtained results it was established a relationship between the properties of the guests and the electrochemical enhancement of the host [64]. From this point of view, calix[*n*]arenes are important in the development of potentiometric sensors [65], molecular redox switching [66, 67], electrochemical detectors [68] and also as a model study of electro transfer in biological systems [67].

The elegant studies about anionic allosteric effect in the recognition of tetramethylammonium salts by flexible *cone* conformer of calix[4]arene was reported by Arduini *et al.* [69]. In this order, a heteroditopic receptor [70], which has the ability to bind simultaneously both the cation and the anion derived from a tetrapropoxycalix[4]arene functionalized at the upper rim with 4-hydroxybenzyl groups was synthesized. By using ^{1}H NMR measurements in $CDCl_3$ the binding ability of above-mentioned host was investigated toward a series of tetramethylammonium salts having different anions and compared to that of calix[4]arene-biscrown-3 [71] where the calixarene cavity was the only binding site. The results suggested the importance of the anion in the cation complexation coupled with the strongly increase

of binding efficiency of ion pairs which utilizes the allosteric effect of the anion.

Zolotov et al. [72] have synthesized *p*-1-adamantylcalix[8]arene ethyl ester (**5**, Chart 1) which was subsequently used in the extraction of octylamine (log $K_{ex} = 6.8 \pm 0.1$) and *tert*-butyl ester of phenylalanine (log $K_{ex} = 6.6 \pm 0.1$).

Molecular recognition of organic amines was presented in some reports [58, 73] by using of calix[6]arene derivatives in ion-selective electrodes. In this case the protonated amines can interact with the ester carbonyl groups of calix[6]arene by a tripodal hydrogen bonding [58]. By incorporation of calix[6]arene-hexaethylacetate (**6**, Chart 1) in mixture with tetrakis(*p*-chlorophenyl)borate as host molecule in the membrane of solid-state electrode, the sensitive potentiometric detection of some alkylamines, the biogenic amines putrescine (1,4-diaminobutane) and cadaverine (1,5-diaminopentane) and the neurotransmitter acetylcholine and choline was increased in cation-exchange, and in ion-interaction chromatography [74]. The results were most significant in the case of smaller amines which have the ability to form the stable complexes with the macrocycles.

Based on the remarkable property of some calix[*n*]arene derivatives to recognize compounds of biological interest in water, some studies were directed to this area of investigation. Specifically, the interactions of the water-soluble, tetra-*p*-sulphonated calix[4]arene with monoammonium ions, $H(CH_2)_n\ NH_3^+$, $n = (3–7)$ [75] and alkyl diammonium ions, $^+H_3N(CH_2)_n\ NH_3^+$, $n = (3–7)$, in aqueous solution at pH 7.1 by means of microcalorimetric titration were reported. The bottom line was that the observed interaction is more complex [76].

Moreover, the water-soluble calixarenes namely *p*-sulphonatocalix[4]arene (7, Chart 1) and *p*-sulfonatocalix[6]arene bind very strongly the quaternary ammonium cations, and also the neurotransmitter acetylcholine [55]. The both hosts form stable complexes with the cationic ammonium substrates studied showing large shielding effects in their ^1H NMR spectra that indicate that inclusion of substrates into aromatic cavities of the host probably takes place. The cation–π interactions between the positive charge of the ammonium cation and an electron rich aromatic ring is considered of special importance in biological recognition of the acetylcholine [77]. X-ray crystallographic studies of choline tetrasulfonated calix[4]arene complex established that the choline has its N-terminal inside the aromatic cavity of the receptor.

By synthesis of chromogenic calix[*n*]arenes, Kubo *et al.* [78] built optical receptors for recognized biologically and chemically important cations and amines. Calix[*n*]arenes, which are cyclic phenol-derived macrocyclic, were employed for visual detection and enantiomeric separation of amines and amino acids [79].

Some aspects of thermodynamics of solvent extraction of alkylammonium cations with alkyl calix[6]aryl esters were studied by Lee *et al.* [80].

The liquid membrane transport of some amines (*n*-butylamine, hexylamine) and aromatic amino acids methylesters (L-phenylalanine methylester, L-tryptophan methylester, and L-tyrosine methylester) in protonated form as ion pairs in the presence of picrate with *p*-tert-butylcalix[n]arenes, ($n = 6$, 8) (**9**, **10**, Chart 1) in chloroform as carriers has been investigated [81]. The transport driving force was the pH gradient between the source and the receiving phases. The complexation properties of the calixarenes under study towards amines and amino acids were evaluated. Several factors influencing the transport through liquid membrane were considered aiming to develop a mechanism model. The transport yields of amines and amino acids methylesters through a chloroform membrane with the above mentioned calixarenes as carriers were found to be large for all amino acids [81]. The obtained results demonstrated that the inclusion abilities of the investigated hosts were correlated with their conformational properties.

A mixture of six amines (methylamine, ethylamine, ethanolamine, morpholine, butylamine, and hexylamine) was separated in 7 min by use of *p*-sulphonato-calix[4]arene and *p*-sulphonato-calix[6]arene as selectivity modifiers in capillary electrophoresis separations [82].

Amino acids

One of the most important features of amino acids is to assemble a large variety of proteins and enzymes. Therefore, they may be considered the fundamental constituents of a wide variety of biological macromolecules. The calix[*n*]arenes as receptors are involved in recognition of amino acids, that is, solvent extraction and transport through liquid membrane in order to perform selective separation of amine compounds from mixtures. As previously mentioned, under Maldi conditions, the derivatized calix[6]arenes may be more effective receptors for amino acids in the gas-phase than the calix[4]arenes [27].

By employing a calix[6]arene derivative as selective carrier, Chang *et al.* [83] reported the transport of N-benzoyl amino acids through a chloroform liquid membrane. The transport rate depended on the hydrophobicity of guest anions and the size of alkaline metal cations, which coexisted in the source phase. The experimental results obtained by the same author [57] suggested that the ethoxycarbonylmethyl derivative of *p*-tert-butylcalix[6]arene can be used as a carrier for selective recognition and separation of some important amino acids. A schematic mechanism concerning the interaction between the phenylalanine and tryptophan ester on one side, and the calix[6]arene receptor on the other side was drawn in the same time. As extractant for

amino acid esters, Zolotov *et al.* [72] employed calix[8]-arene derivative **5** with good results.

The interesting studies concerning the ability of calix[6]arene carboxylic acid derivatives to be extractants and/or carriers for transporting amino acids through a liquid membrane of aromatic amino acids were reported by Oshima *et al.* [84, 85]. The extraction experiments of cationic species of L-tryptophan, L-phenyalanine and L-tyrosine and their esters from aqueous acidic phase (pH = 1.0–5.5) into organic phase were carried out with calix[6]arene hexacarboxylic acid (**11**, Chart 1) [84]. This host showed the highest extractability to the tryptophan ester forming a 1:1 complex between the calix[6]arene **11** and the amino acid. The stoichiometry of this complex was established by slope analysis and the Job method analysis. The driving force of the complexation was the interaction between the ammonium cation of the amino acid and the oxygen atoms of the calix[6]arene. The ^{1}H NMR spectra and CD spectra were used for the investigation of the structure of complex formation. Furthermore, the authors have established the extraction equilibrium equation for the complex formation between amino acid ester and calix[6]arene hexacarboxylic acid:

$$HA^+ + H_6R = (HA)H_5R + H^+$$

where H_6R and HA^+ denote the calix[6]arene hexacarboxylic acid and the protonated amino acid, respectively. In the case of using calix[n]arenes hexacarboxylic acid, $n = 4$, 8 (**12**, **13**, Chart 1) in liquid–liquid extraction experiments of amino acids the obtained results compared with those obtained by using calix[6]arene are much more definitely less. The results pointed out that the cavity size of calixarene is one of the most important factors for recognition of amino acids. The sequence of decreasing extraction behavior of amino acid methyl esters was TrpOMe > PheOMe > TyrOMe and for various tryptophan esters was TrpOBz > TrpOEt > TrpOMe > > Trp. It comes out that the extraction efficiency depends on the hydrophobicity of the amino acid and on the hydrophobicity of the ester groups as well [84]. Another important effect of the inclusion complexes of calix[6]arene is given by the asymmerization induced by the inclusion into the host molecule. In order to extend their experiments, Oshima *et al.* [84] investigated the calix[6]arene **11** which has a cyclic structure able to include an amino acid ester and bears six ionizable carboxylic acids to contribute electrostatic interaction, as a carrier through liquid membrane. This carrier has successfully transported the hydrophobic amino acid esters (L,D-tryptophan methyl ester hydrochloride, L-phenylalanine methyl ester hydrochloride, and L-tyrosine methyl ester hydrochloride) and L-tryptophan. Based on complexation characterized by a proton-exchange mechanism, the transport through membrane was controlled by changing the pH gradient between the source and the receiving aqueous phases. As in extraction experiments, the calix[6]arene **11** acid exhibited a high transport ability compared to the other calix[*n*]arene derivatives ($n = 4$, 8). By combining an enzyme reaction and a liquid membrane transport with the calix[6]arene **11**, an optical resolution system for a racemate of tryptophan methyl ester was developed [84]. Thus, it was realized a novel liquid membrane system for the chiral separation. Along the same line, Shinkai and Coworkers [29] showed spectroscopically that the pseudo-C_2-symmetrical homooxacalix[3]arene exibit enantiomeric recognition properties toward alanine ethyl ester and phenylalanine ethyl ester.

Okada *et al.* [30] prepared new calix[4]arene having chiral pendant groups and further used them for selective extraction and transport of some amino acid ethyl and methyl esters and Z-amino acid carboxylates 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. The extractability of receptors increased by replacing the methyl group with the ethyl group. The extractability for Z-amino acids was lower than that for the corresponding amino acid esters. The explanation could be that the large counter anion having Z-group is quite difficult to approach close to the hydrophobic cavity. These receptors also recognized the chirality of the L-amino acids in transport experiments. Hu *et al.* [86] have synthetized (R)-cysteine-containing calix[4]arenes which might serve as good chiral macrocyclic ligands in the studies of chiral recognition and chiral catalysis. Chiral recognition of amino acids by using the chiral calix[4]resorcinarenes in Langmuir films was also reported [87].

As we above mentioned [81] the transport of aromatic amino acids methylesters through a chloroform liquid membrane containing *p*-tert-butylcalix[6]arene (**9**), and *p*-tert-butylcalix[8]arene (**10**) as carriers in the presence of picrate was reported. The sequence of transport efficiency for the amino acid methylesters was found as: L-PheOMe > L-TrpOMe > L-TyrOMe when *p*-tert-butylcalix[8]arene was used as carrier.

Using a supported liquid membrane composed of a porous polymeric support, Antipin *et al.* [88] studied the separation of zwitterionic form of aromatic amino acids by calix[4]arene based α-aminophosphonates. The aminophosphonate groups contributed to the transport efficiency and the order of the transport rate.

The extraction abilities and the transport through chloroform liquid membrane of calixarenes **9** and **10** upon some amino acid methylesters (L-leucine, L-valine, L-cysteine, L-isoleucine, L-serine, and L-phenylalanine) were investigated [35, 89]. The experimental results suggested that amino acid methylesters are extracted into organic phase and transported by *p*-tert-butylcalix[*n*]arenes ($n = 6$, 8) in the presence of tropaeolin 00 ([*4*-(*4′*-anilinophenylazo)benzenesulphonic acid]) as counterion.

The extractability and the transport were proved to be essentially controlled by the structure of calixarene, and the nature of the amino acid. The effects of physicochemical parameters, such as the structure of calixarene, ionic strength, the pH, the nature of solvent, and the nature of the anion used as counterion were investigated. In addition, the influence of the composition and structure of the compounds under study upon the partition processes occurring in biphasic and triphasic systems was reported. The experimental data suggested that both calix[*n*]arenes are efficient extractants for the amino acid methylesters. Except of L-valine (35% extractability) and L-serine (37% extractability), the *p*-tert-butylcalix[6]arene provided better extractability than the *p*-tert-butylcalix[8]arene. The sequence of extractability using the *p*-tert-butylcalix[6]arene (Figure 1) as extractant was the following: L-PheOMe (*−1.45*) > L-CysOMe (*−2.55*) > L-IleOMe (*−1.80*) > L-LeuOMe (*−1.72*) > L-SerOMe (*−3.00*) > L-ValOMe (*−2.29*) [90], and by using the *p*-tert-butylcalix[8]arene it turns to: L-IleOMe > L-PheOMe > L-ValOMe ≅ L-SerOMe > L-LeuOMe > L-CysOMe [35].

The extraction experiments did not display any relationship between the extraction efficiency and the hydrophobicity of amino acid methylesters under study. It is known that the values of log *P* (listed in parentheses) is a quantitative indicator for the hydrophilic/lipophilic balance [90]. Contrarily, in the triphasic system, the *p*-tert-butylcalix[8]arene exhibited better transport ability than *p*-tert-butylcalix[6]arene for the amino acids methylesters through chloroform liquid membrane. The sequence of the transport yields of amino acids using *p*-tert-butylcalix[6]arene as carrier was the following: L-PheOMe > L-LeuOMe > L-IleOMe ≅ L-ValOMe and with the *p*-tert-butylcalix[8]arene as carrier the sequence of amino acid yields is the following: L-LeuOMe > L-PheOMe > L-ValOMe > L-IleOMe ≅ L-SerOMe. In Figure 2 is displayed the extractability of amino acid methylesters into chloroform phase in the presence of tropaeolin 00 at pH 5 together with their transport yields through chloroform liquid membrane with *p*-tert-butylcalix[8]arene [89].

From the correlation between the transport yields of amino acids and their hydrophobicity, it clearly pointed out that the hydrophobic species like as L-phenylalanine and L-leucine have better transport yields through liquid membrane than the other amino acids under study (Figure 3). Except L-isoleucine there was a good correlation between the transport yield of amino acid esters and their hydrophobicity [35].

The results suggest further possibilities for optimal separation of amino acids derivatives and other biological species. In chromatography, the silica-bonded calixarenes were used for retaining amino acid esters [91]. The elegant presentation of different factors that govern the affinity and the selectivity of calixarene derivatives was reported by Arnaud-Neu and Schwing-Weill [92].

It is well known that the thermodynamic parameters of complex formation are indispensable data concerning molecular recognition in supramolecular chemistry. The complexation properties of water-soluble calixarenes towards amino acids [32] in aqueous solution have been extensively investigated by ^{1}H NMR spectroscopy, calorimetric and microcalorimetric titration [75, 93]. Thus from ^{1}H NMR titration experiments in D_2O at pD 7.3 it was established that the complex formation between α-amino acids and *p*-sulphonatocalix[4]arene

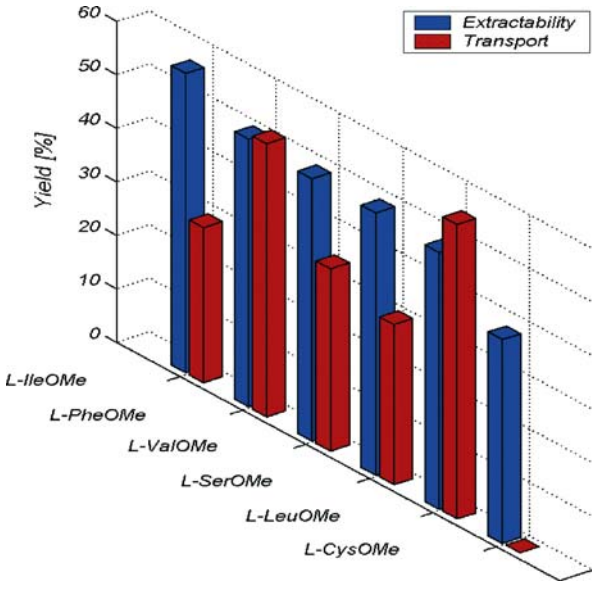

Figure 1. Experimental data of the extraction and the transport of amino acid methylesters through chloroform liquid membrane by *p*-tert-butylcalix[6]arene in the presence of tropaeolin 00 [89].

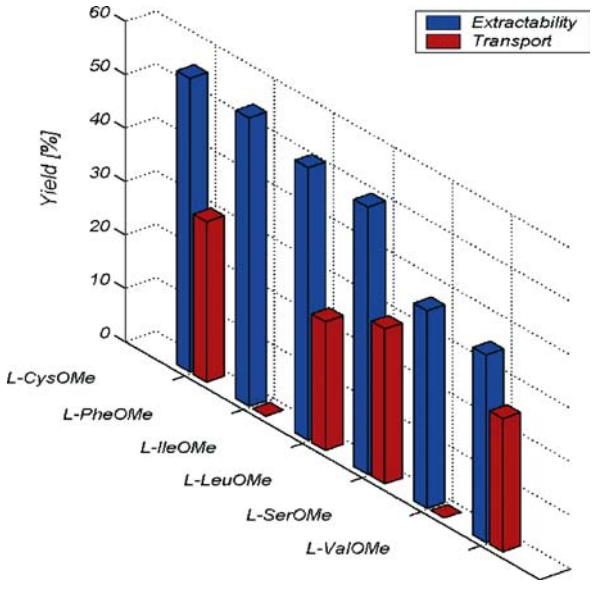

Figure 2. Experimental data of the extraction and the transport of amino acid methylesters through chloroform liquid membrane by *p*-tert-butylcalix[8]arene in the presence of tropaeolin 00 [89].

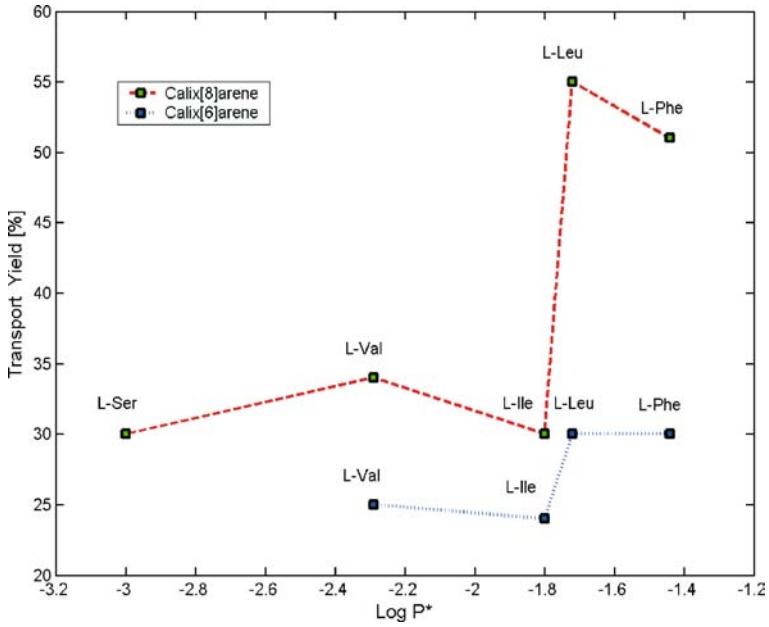

Figure 3. Correlation between the yields (%) of amino acid methylester hydrochlorides transport [35] through liquid membrane by *p*-tert-butylcalix[n]arenes ($n = 6, 8$) and their hydrophobicity (log *P*). *From Ref. [90].

(**7**) was feasible by inserting the aromatic or aliphatic group into the hydrophobic cavity of calixarene [32]. Similarly, by means of ^{1}H NMR spectroscopy [94] and microcalorimetry [95] it was shown that 1:1 complexes between basic amino acids arginine and lysine with *p*-sulphonatocalix[*n*]arenes ($n = 4, 6, 8$) were formed. An interesting comparative study of the inclusion complexes formed between *p*-sulphonatocalix[4]arene with some amino acids (glycine, alanine, lysine, arginine, aspartic acid, proline, histidine, phenylalanine, tryptophan, and tyrosine) as guests was performed by means of reversed-phase high-performance liquid chromatography (RP-HPLC) and ^{1}H NMR experiments [96]. The variations in the values obtained for the stability constants were explained in terms of the various interactions involved in these complexes of *p*-sulphonatocalix[4]arene and amino acids such as hydrophobic, ion-pairing, aromatic–aromatic, and electrostatic interactions [96]. Continuing their studies on the host–guest complexation of a series of amino acids with calixarenes by means of RP-HPLC, Coleman and Coworkers [46] have reported the stability constants of inclusion complexes of *p*-H-37-(2-carboxy-methyloxy)-calix[6]arene (**16**, Chart 1) and *p*-sulphonato-37-(2-carboxy-methyloxy)-calix[6]arene (**17**, Chart 1) with 15 amino acids in purely aqueous conditions. The formation of the inclusion complexes lead to the changes in the retention times and capacity factors of amino acids.

The nature of complex formation between *p*-sulphonatocalix[4]arene and hexasodium *p*-sulphonatocalix[6]arene (**8**, Chart 1) with some amino acids and peptides in aqueous solutions by means of calorimetric titration were studied [34]. In this respect the stability constants (log *K*), the reaction enthalpy (ΔH) and entropy ((ΔS) of the complexes formed between the amino acids and peptides with *p*-sulfonatocalix[4]arene and hexasodium *p*-sulfonatocalix[6]arene were determined.

As can be noticed in Table 1, the *p*-sulphonatocalix[4]arene formed relatively strong complexes with the amino acids under study (gly, L-alanine, L-valine, L-leucine, L-phenylalanine, L-tryptophan, L-threonine and L-lysine. By comparing the association constants obtained by calorimetric titration with those determined by RP-HPLC [96], ^{1}H NMR [32] and microcalorimetry [95], the results are quite different.

Obviously, direct comparison is difficult because of the differences in conditions such as pH, solvent polarities and experimental methodology (RP-HPLC, ^{1}H NMR, microcalorimetry, calorimetric titration). In the case of amino acids, the complexation with *p*-sulphonatocalix[4]arene in aqueous solution is favored by enthalpic contribution and disfavored by entropic contributions. No influence of the ring size of the water-soluble calix[*n*]arenes upon the complexation was observed [34].

A new water-soluble host molecule used for recognition of α-amino acids was tetrasulphonatomethylcalix[4]resorcinarene [97]. The binding properties of this ligand toward 12 α-amino acids were studied by means of ^{1}H NMR measurements (pD 7.2) and pH-metric titration in a broad range of pH values. They were based on H-bonding and electrostatic interactions with the carboxylic and amino groups typically for amino acids and specific interactions with the α-substituent. An important role was played by the variation of pH.

Coleman and Coworker [98] have synthesized a series of mono-substituted *p*-sulphonato-calix[*n*]arenes where

Table 1. Stability constants log K (K in M^{-1}) and thermodynamic values ΔH and $T\Delta S$ (in kJ mol^{-1}) for the complexation of some amino acids by p – sulfonatocalix[4]arene in aqueous solution at 25 °C together with the literature data [34]

Amino acids	log K	$-\Delta H$ (kJ/mol)	$T\Delta S$ (kJ/mol)
Gly	2.74 ± 0.02	38.3 ± 1.2	−22.7 ± 2.3
	2.26[96]		
L-Ala	3.22 ± 0.02	30.4 ± 0.09	−12.0 ± 1.3
	2.82[96]		
L-Val	3.20 ± 0.01	46.7 ± 1.7	−28.5 ± 1.8
	1.20[32]		
L-Leu	3.08 ± 0.02	51.7 ± 2.1	−34.2 ± 1.5
	1.70[32]		
L-Phe	3.14 ± 0.01		
		36.0 ± 1.62	−18.1 ± 1.6
	1.80[32]		
	2.77[96]		
L-Trp	3.13 ± 0.03	33.4 ± 1.8	−15.6 ± 2.2
	1.40[32]		
	3.18[96]		
L-Thr	3.19 ± 0.05	28.9 ± 1.5	−10.7 ± 2.0
L-Lys	3.83 ± 0.02	20.4 ± 1.3	1.8 ± 1.7
	2.87[95]	14.4	2.0

$n = 4$, 6, 8. The study concerned the host-guest complexation of them upon 11 amino acids by using ^{1}H NMR titration at pH 8, in the presence of NaOH. The association constants showed a 1:1 stoichiometry of complex formation. The results showed that the pendant functions (ethoxycarbonyl methoxy group, 2-carboxy methoxy group, 2-amido methoxy group or 2-amino ethoxy group) at the lower rim of calixarene modified the observed association constant as compared to the parent p-sulphonato-calix[n]arenes.

A group of seven amino acids (histidine, lysine, arginine, alanine, serine and threonine) was separated in less than 16 min [82] by means of capillary electrophoresis using a water soluble sulphonated calixarenes as mobile phase in combination with different sodium and potasium salts. This new system based on p-sulphonatocalix[n]arenes where $n = 4$, 6 as a buffer constituent was designed to facilitate the separation and quantification of compounds or groups of analytes which do not absorb in the UV region.

Peptides

The study of the nature of interactions involved in ligand–peptide complexes is of particular relevance in understanding many specific biomolecular interactions that play a key role in regulation of cellular processes [99–105]. The Still's group studied molecular recognition on polypeptides establishing the principles that govern peptide recognition by designed molecules [106, 107]. Schneider and Hossain [108] described the tripeptide binding by designed molecules. The protein surface recognition has been reported using a receptor with variant cyclic peptides attached to a calixarene core [109].

The difference in acid–base behavior of peptides given by its NH_2-terminal amino group, its COOH-terminal carboxyl group, and those other groups present in molecule allow the peptides of differing amino acid composition to be separated by various methods such as by chromatography, liquid membranes, capillary electrophoresis or solvent extraction.

Only a few studies that involve calix[n]arenes have so far been focused on the recognition of peptides [20, 46, 110, 111]. To extend our knowledge on the thermodynamics of water-soluble calix[n]arenes complexation we investigated the complex formation between water-soluble sulphonated calix[n]arenes **7** and **8** (Chart 1) and peptides (glycyl-glycine, glycyl-L-alanine, glycyl-L-leucine, glycyl-L-phenylalanine, L-leucyl-glycine, L-leucyl-L-alanine, glycyl-L-valine, L-leucyl-glycyl-glycine, and glycyl-glycyl-glycine) in aqueous solutions by means of calorimetric titration [34]. The stability constants, enthalpies and entropies of complexation were evaluated. There are no significant differences between the values of stability constants of peptide complexes formation with the calixarenes under study. As in the case of complexes of amino acids with water-soluble calixarenes, the complexation of peptides with the same ligands was favored by enthalpic contributions and disfavored by entropic contributions. However, no influence of the ring size of the calixarenes upon the complexation was observed.

An interesting thermodynamic characterization of the binding process of dipeptides and tripeptides bearing lysine or arginine by p-sulphonatocalix[n]arenes ($n = 4$, 6, 8) by means of NMR and microcalorimetric measurements have been reported by Douteau-Guevel *et al.* [110]. The binding process was controlled by the favorable enthalpy obtained by the inclusion of the

apolar part of the peptide into the hydrophobic cavity of the *p*-sulphonatocalix[*n*]arenes ($n = 4, 6, 8$) through van der Waals interactions. A similar important role was played by the entropy variation, which accompanied the desolvation of the charged groups upon ionic interaction [110]. It is worth to mention that due to multiple types of interactions like hydrophobic, π–π, ionic, cation–π, and hydrogen bonding, which are involved in complex formation, several aspects have to be critically considered and carefully evaluated.

The calixarene peptides and calixarene-peptide-dendrimers [21] are a new challenge of calixarene chemistry since they open the way to design of multifunctional receptors with interesting biochemical and biotechnological applications.

Conclusions

Some meaningful aspects of the applications of calix[*n*]arene derivatives in complexation, solvent extraction, and transport through liquid membrane of amines, amino acids and peptides were presented. The thermodynamic data for the complex formation of calix[*n*]arenes with above mentioned substituted ammonium ions were investigated by different techniques such as calorimetric and microcalorimetric titrations, ^{1}H NMR titration or by using liquid chromatography suggesting the ability of calix[*n*]arene to form interesting complexes by specific interactions. It was showed that calix[*n*]arene derivatives are good carriers in liquid membranes and they can be used in separation of amine compounds. The extractability properties of these receptors toward amine compounds were proved by liquid–liquid extraction.

The bottom line is that calix[*n*]arenes and their derivatives may constitute attractive hosts in molecular recognition of amine species and useful receptors in their separation processes.

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