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CRITICAL REVIEW

Recognition of amino acids by functionalized calixarenes

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The calixarenic receptors exhibit remarkable host–guest properties towards biologically relevant guests. Aspects of complex formation reactions between both native and derivatized amino acids, di-and tripeptides with calixarenic (chiral or not) receptors are summarized in this *critical review*. Thus, the discussions emphasize the parameters that affect the molecular binding selectivity and efficiency of functionalized calix[*n*]arenes towards these substrates. A brief survey on their application in separation of amino acids is also considered (123 references).

Introduction

Studies on molecular recognition of amino compounds, such as biogenic amines, amino acids, peptides, proteins, and carbohydrate like fundamental substrates in biological processes, by synthetic receptors is a topic of great interest from both a supramolecular chemistry and analytical application point of view.[1–6] In this respect, intensive research has been focused on the design and synthesis of macrocyclic receptors with specific properties and functions revealing their affinity and selectivity towards biologically relevant molecules.[7–13] The knowledge of molecular recognition properties of amino acids as fundamental constituents of a wide variety of biological macromolecules and peptides by macrocyclic receptors is useful for developing procedures of synthesis, purification, and their separation, as well as in elucidating the principle of their transport through biological membranes. Moreover, chiral recognition of amino acids and peptides has received considerable attention because of their importance in understanding many aspects of natural living processes with potential applications in catalysis, enzyme mimetics, and chemical asymmetric synthesis. The reactivity and biological activity of proteins in an aqueous phase depend on the hydration of their structural fragments and amino acid residues. Besides, the amino acid containing receptors constitute a class of hosts with a range of applications. In this respect, the development of anion receptors containing amino acids and peptides as building blocks, which lead to remarkably efficient systems that mimic the anion coordinating

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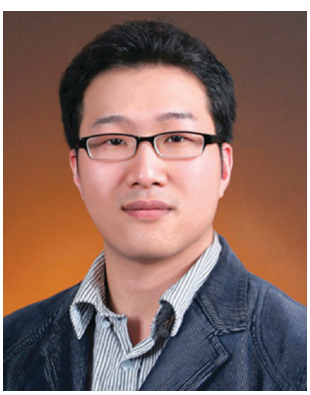
Lucia Mutihac

Lucia Mutihac studied Chemistry at the University of Bucharest and completed her PhD in 1990 at the Institute of Physical Chemistry of the Romanian Academy in Bucharest in the field of host–guest chemistry of amino acids and macrocyclic receptors. After several years as Senior Researcher within the same institute, she was appointed Lecturer at the University of Bucharest in the Department of Chemistry. In 1997, she was appointed Associate Professor and since 2000 she has been Professor. Her research interests concern molecular recognition of biological compounds, transport through membrane and biomembranes and supramolecular chemistry.



Jae Hong Lee

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properties of anion binding proteins, has been a subject of interest in recent years.[14]

It is well-known that the non-covalent interactions such as hydrophobic effects, π–π stacking, van der Waals forces, hydrogen bonding, metal coordination, and in the last decade, cation-π interactions, are responsible for the function of synthetic or natural supramolecular complexes.[15–19] These interaction types are of particular relevance for understanding several specific biomolecular interactions in biological processes, such as immune response, protein enzyme inhibitors, signal transduction or normal function of cellular/organelle structure.[20–24]

Calixarenes, with their unique three-dimensional surface and conformationally rigid structure, are one of the best known host molecules along with cyclodextrins, cucurbiturils, cryptands, and crown ethers. By their availability and easy functionalization at either the upper and/or lower rim of the molecular skeleton among potential building blocks, calixarenes have become important receptors in synthesis and applications as supramolecular receptors for molecular recognition, sensing and self-assembly, catalysis, nanoscience, drug delivery, and separation science. They have several conformational isomers and a large number of cavities of different sizes and shapes involved in molecular recognition. The recognition and formation of selective complexes with biological compounds is one of the most interesting applications of calixarenes and functionalized calixarenes. Likewise, the protein surface recognition has been studied by using various cyclic peptides attached to the calixarene core and establishing the importance of the functional group and geometric complementary in binding protein surfaces.[6,25,26] Obtaining water soluble *p*-sulfonato-calixarenes as receptors for biomolecules was specifically and carefully considered, since most biological processes occur in such media, as well as in view of their potential medical applications.[9–11,27] According to the data presented in the literature by renowned research groups, the binding properties of calixarenes and water soluble calixarenes towards amino substrates have been studied in solid state, gas phase, and in solution by different techniques. The calixarene complexes are significantly stronger than the corresponding inclusion complexes of cyclodextrins and crown ethers with amino acids. In spite of their small cavity, the preorganisation of the calix[4]arene scaffold, together with its appropriate functionalization, render this class of receptors as a template for the design and construction of special receptors for cations, anions and neutral species recognition. As such, the investigation of the interactions between functionalized calix[4]arenes and amino compounds is of fundamental interest by giving new insights into molecular recognition, self assembly processes, and a better understanding of the recognition processes running in biological systems.[28,29] Due to their ability to form reversible complexes with both neutral and charged compounds, the calixarenes are also involved in separation chemistry. Exhaustive molecular dynamic studies on liquid–liquid interfaces in assisted ion extraction involving calixarenes pointed out the importance of solvation effects and of small amounts of water on the selectivity.[30]

Apart from being efficient receptors and forming interesting complexes by specific interactions with a large variety of chemical and biological compounds (*e.g.*, ammonium ion, amines, amino acids, and peptides), a significant feature of functionalized calix[*n*]arenes is their ability to act as carriers through membranes or to be incorporated into channeling systems, with analytical and therapeutic applications.[31–33]

The aim of the present review is to summarize the recent studies about calix[*n*]arenes ($n = 4, 6, 8$) and their derivatives with respect to their complexation with amino compounds such as native amino acids and their derivatives, and di- and tripeptides (see Chart 1), as well as advancing some hints on future areas of scientific research related to the above topics.

Recognition of amino acids by calix[*n*]arenes derivatives

Following the above, amino acids as basic structural building blocks of proteins and other biomolecules are attractive targets in host–guest chemistry. A number of remarkable studies were addressed to this topic including their molecular recognition by calixarenes.[34–37]

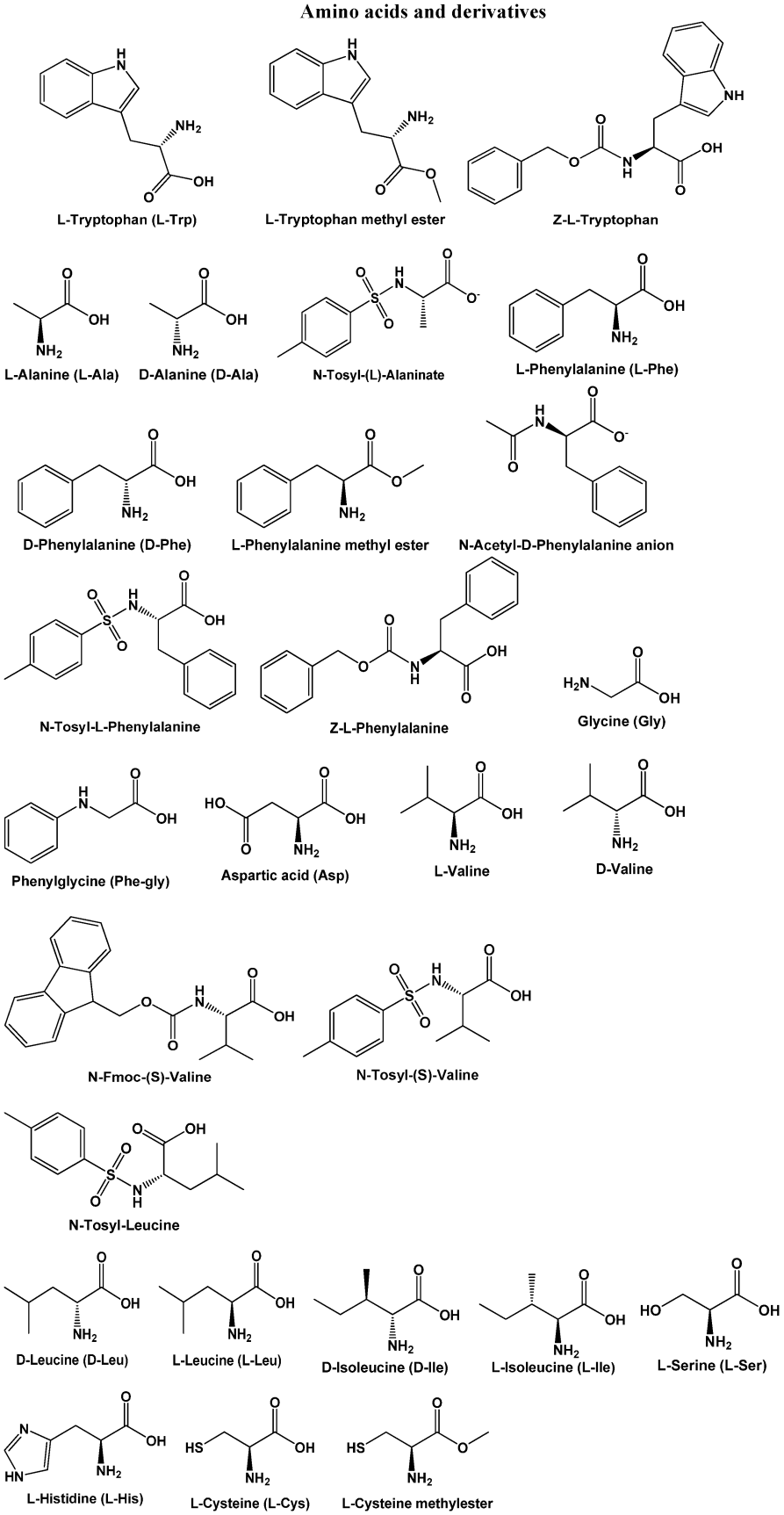
Jong Seung Kim

Jong Seung Kim received his PhD from the Department of Chemistry and Biochemistry at Texas Tech University. After one-year postdoctoral fellowship at University of Houston, he joined the faculty at Konyang University in 1994 and transferred to Dankook University. In 2007, he then moved to the Department of Chemistry at Korea University in Seoul as a Professor. To date, his research records 250 scientific publications and 25 domestic and international patents.

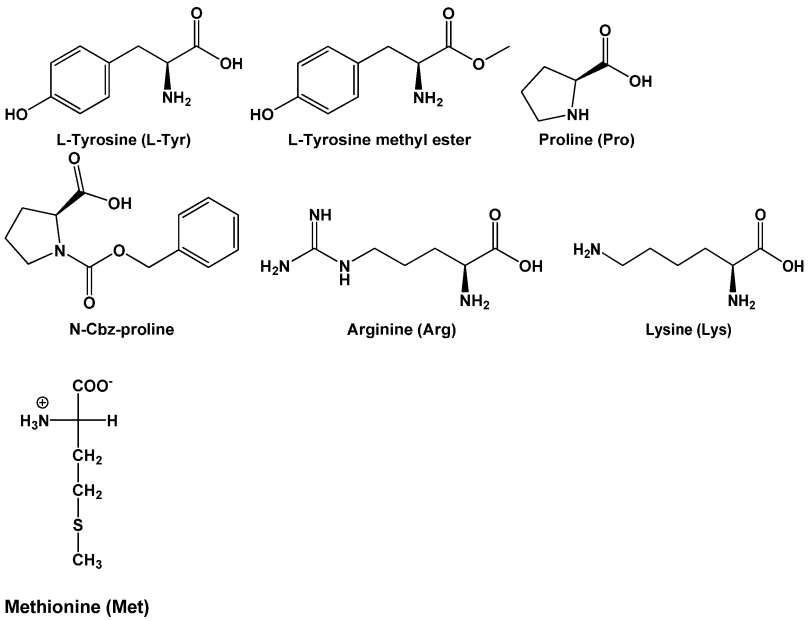
Jacques Vicens

Jacques Vicens completed his PhD in 1977 at the Université Louis Pasteur (ULP) de Strasbourg in France. Then, in 1978, he got a first post-doctoral position in Belgium at the Université Notre-Dame de Namur. In 1980, he was awarded a second post doctoral position at the Weizmann Institute at Rehovot in Israel. Then he entered the Centre National de la Recherche Scientifique in 1981 at the Université Claude Bernard de Lyon in France. In 1988, He joined back the Université de Strasbourg. Dr Vicens is author/co-author of 350 reviewed publications and 2 patents.

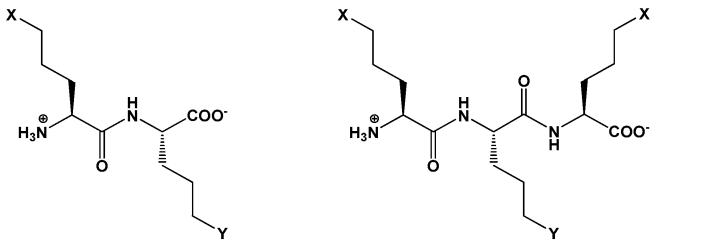
Amino acids and derivatives



contd Chart1



Di- and tri-peptides



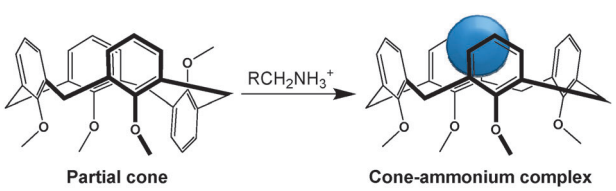
Lys-Lys: X = Y = $CH_2NH_3^+$
Arg-Arg: X = Y = $NHC(=NH_2^+)NH_2$
Lys-Arg: X = $CH_2NH_3^+$; Y = $NHC(=NH_2^+)NH_2$
Arg-Lys: X = $NHC(=NH_2^+)NH_2$; Y = $CH_2NH_3^+$

Lys-Lys-Lys: X= $CH_2NH_3^+$
Arg-Arg-Arg: X= $NHC(=NH_2^+)NH_2$

Chart 1 Native and derivatives of guest amino acids and peptides described in this review.

Due to the presence of an amino function in amino acids, the complexation of amines, ammonium cations, and amino acids have often been comparatively studied. In 1997, Ikeda and Shinkai advanced a preliminary representation of the complexation of a primary ammonium salt by tetramethylcalix[*4*]arene, showing that the ammonium cation directs the partial-cone conformation of the calix unit into the cone conformation by its inclusion in the hydrophobic part of the calix (Scheme 1).[8]

As such, complexation properties of calix[*n*]arenes functionalized with amino substrates like amines, amino acids and peptides, were studied in the crystalline state, in gas phase, and in solution by means of various techniques including:

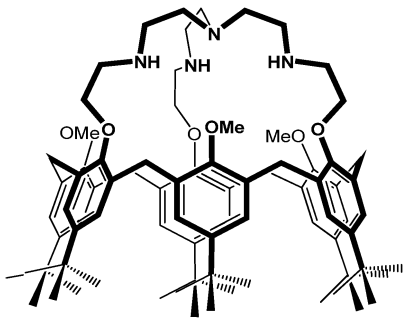


Scheme 1 Complexation of a primary ammonium by the tetramethylcalix[4]arene according to reference 8.

X-ray crystallography, NMR spectroscopy, high performance liquid chromatography, mass spectrometry, calorimetric or microcalorimetric and potentiometric titrations.[38–44] The MALDI mass spectrometry studies demonstrated that calix[6]arene derivatives form stronger complexes with amino acids in the gas-phase than calix[4]arenes.[40]

Starting from calix[6]arenes with a cavity size adapted for the selective inclusion of small organic guests compared to calix[4]arenes, Jabin and Reinaud[45–47] synthesized a series of molecular receptors based on calix[6]arenes and developed some valuable strategies to obtain them in a well-defined rigid cone conformation in order to display such host–guest properties. Thus, they reported an interesting class of calix[6]arenes bearing a tripodal aza-cap on the small rim called calix[6]-aza-cryptand (**1**). These compounds are excellent receptors towards neutral and charged substrates such as ammonium, metal ions, or neutral molecules. Moreover, in the case of a fully protonated tren unit, the tetra-cationic aza-cap offers a strong binding site for polar neutral substrates because of the hydrogen bonds and charge–dipole interactions. Additionally, the substrates are stabilized by CH–π interactions with

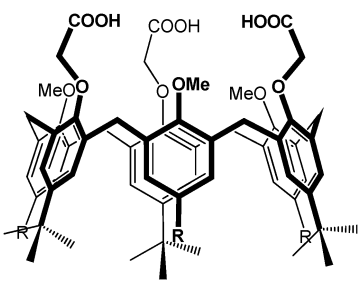
aromatic walls of the cavity. In spite of their remarkable binding properties, the first generation of these receptors was limited by the lack of methodologies for their selective functionalization. The binding properties of receptor **1** towards ammonium compounds were investigated by ^{1}H NMR spectroscopy in chloroform solutions. According to these measurements, *endo*-complexes with picrate salts of $PrNH_3^+$, $EtNH_3^+$, $nBuNH_3^+$, or $Me_2NH_3^+$, were obtained, whereas with $Me_4N^+Pic^-$, no inclusion could be detected.[43] The affinity decreases following the sequence $PrNH_3^+ > EtNH_3^+ > nBuNH_3^+$, as well as from primary to secondary ammonium salts. An important finding of this study consisted in developing an efficient strategy of receptor design for polar neutral molecules by polarization of a hydrophobic cavity with a polyammonium site.



1

Along the same line of reasoning, calix[6]azacryptands decorated with anion binding groups on the narrow rim lead to heteroditopic receptors able to bind either ammonium ions or organic ion pair salts with a positive cooperativity.[47] The host–guest properties toward picrate and chloride salts of propylammonium ions were studied by ^{1}H NMR spectroscopy in $CDCl_3$ solutions. Due to the binding of ammonium ions in the cavity and of the counter-ion at the level of the amido urea moieties through H bonding interactions, the calix[6]azacrypand was considered as a heteroditopic receptor. The interactions were also investigated by mass spectrometry and the results confirmed the inclusion of ammonium ion and the chloride complexation.

The binding affinities towards biological ammonium ions were demonstrated by calix[6]arene tris-carboxylic acid derivatives. The ability of calix[6]arene tris-carboxylic acid derivatives **2** and **3** to include ammonium guests ($EtNH_3^+$ and $PrNH_3^+$), even in polar and protic solvents, was investigated both in solution and solid state phase by NMR spectroscopic studies in $CDCl_3$ and crystallographic data, respectively.[48] The calix[6]arene structures were shaped in a cone conformation because of ion-paired cap formation between the carboxylate

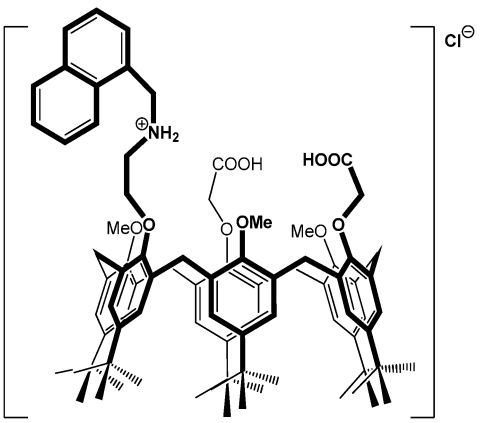


2 : R = *t*-Bu
3 : R = NO_2

groups of the calixarene and their ammonium counter-ions. In contrast to **2**, the open cavity of calix[6]tris-acid (**3**) was expected to allow the inclusion of large ammonium guests. The combination of hydrogen bonding, electrostatic and CH-π interactions together with a C_{3v} complementarity between the binding carboxylates of the host and the ammonium guest were found to be responsible for the recognition process. The feasibility of developing simple and efficient sensors for biological ammonium ions by using these receptors constituted a prior to the present study.

The calix[6]arene dissymmetrically substituted on the narrow rim by two carboxylic acid groups and one ammonium arm **4·HCl**, can encapsulate ammonium ions through a highly selective recognition process due to the presence of an internal ion-paired cap that pre-organizes the cavity, constituting an efficient binding site.[49] A bulky 1-naphthalenemethylamine residue on the narrow rim was introduced in order to prevent any competing self-inclusion of the ammonium part. The host–guest properties of the receptor **4·HCl** toward ethyl and propylammonium ions were investigated by ^{1}H NMR spectroscopy in $CDCl_3$ at 260 K. By addition of $PrNH_2$ (≥ 2 equiv.) to **4·HCl**, *in situ* formation of $PrNH_3^+$ through deprotonation of the COOH groups of the receptor was determined. A unique NMR pattern corresponding to the *endo*-complex **7-H**$^+$ $\supset$ $PrNH_3^+$ was also demonstrated. Moreover, high field signals corresponding to the inclusion of 1 equiv. of $PrNH_3^+$ ($\delta_{CH2CH3} = -0.85$ ppm, $\delta_{CH3} = -1.91$ ppm) were detected. The inclusion of $EtNH_3^+$ was also observed through the addition of $EtNH_2$ (≥ 2 equiv.) to a $CDCl_3$ solution of **4·HCl** (signals of the included $EtNH_3^+$ were the following: $\delta_{CH2} = 0.30$ ppm, $\delta_{CH3} = -1.51$ ppm). As such, experimental evidence was obtained proving the internal ion-paired cap can act as a binding site for a second ammonium ion encapsulated in the calixarene cavity. It comes out that the recognition of this cationic guest is performed through ionic and hydrogen bonding interactions, as supposed by the authors.

Although these receptors exhibit evident abilities towards ammonium ion recognition proved by NMR and X-ray investigations, only a few applications have been reported to date.



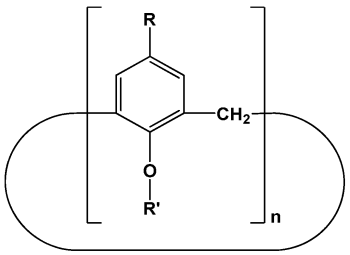
4•HCl

The binding properties of calix[6]arenes and some amines studied by NMR in $CDCl_3$ solution and by X-ray investigations reported by Lee *et al.*[50] emphasized that calix[6]arenes form a strong *endo*-complex with piperidine due to the strong basicity

and compact shape. The formation of the *endo*-complex was alternatively confirmed by the 2D-NOESY spectrum of the calix[6]arene-piperidine complex and the correlation peaks between piperidine (2.39 ppm and 0.92 ppm) and the aromatic protons of calix[6]arene were also demonstrated. In the case of triethylamine, no correlation peaks were observed between calix[6]arene and triethylamine in the NOESY spectrum.

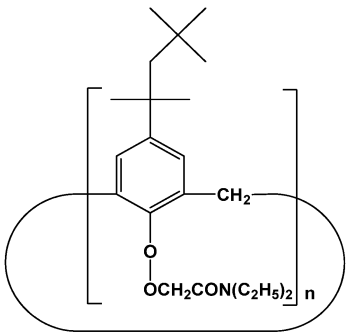
With respect to amino acids, relevant studies concerning the ability of calixarene carboxylic acid derivatives **5–7** for recognition of aromatic amino acid methyl esters (TrpOMe, PheOMe, and TyrOMe, Chart 1) were reported by Oshima *et al.*[51,52] The receptor **6** exhibits a strong affinity to a protonated amino group, $R–NH_3^+$, due to the appropriate cavity, the functional six carboxylic groups involved in electrostatic interaction, and the complementary C_{3v} symmetry. The decreasing extraction behavior of amino acid methyl esters followed the sequence 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. The structure of complexes was investigated by ^1H NMR spectroscopy in $CDCl_3$ solution and by circular dichroism spectroscopy. As a carrier, receptor **6** successfully transported the hydrophobic amino acid esters (L,D-TrpOMe, L-PheOMe, and L-TyrOMe) and L-Trp.[52] Based on the complexation that is characterized by a proton-exchange mechanism, the transport through the membrane was controlled by changing the pH gradient between the source and the receiving aqueous phases. As in extraction experiments, receptor **6** exhibited a high transport ability compared to **5** and **7**. By combining an enzyme reaction and liquid membrane transport with calix[6]arene, an optical resolution system for a racemate of tryptophan methyl ester was developed. A novel liquid membrane system for the chiral separation was developed in this way.

Based on slope analysis and Job's method of continuous variation, a 1 : 1 complex formation between calix[6]arene and aromatic amino acid derivative was confirmed. The same group also reported the molecular recognition of some amino acid derivatives by a series of *p*-*tert*-octylcalix[*n*]arene amide derivatives (n = 4, 6, 8) **8** as receptors with the following order of extractabilities: calix[6]arene > calix[8]arene > calix[4]arene. The calix[6]arene amide derivative was shown to act as a better extractant of aromatic amino acid derivatives (Chart 1). The slope analysis of the results as a function of perchlorate ion concentration and the extractant concentration indicated that the calix[6]arene amide derivative formed a 1 : 1 : 1 complex with the tryptophan methyl ester and the perchlorate ion.[53] The major interaction responsible for the complex formation might have been a cation–dipole interaction between the cationic group of the guest and the carbonyl groups of calix[6]arene amide derivative. Moreover, discrimination between the guanidinium group of arginine (arginine residue is present in valuable polypeptides such as enzymes and antibodies) and the primary amino group present in lysine, was not demonstrated by using the calix[6]arene amide derivative, even if the structures and the electric properties were different.



5 : R = *t*-Oct, R' = CH_2CO_2H, n = 4
6 : R = *t*-Oct, R' = CH_2CO_2H, n = 6
7 : R = *t*-Oct, R' = CH_2CO_2H, n = 8

9 : R = *t*-Bu, R' = H, n = 4
10 : R = *t*-Bu, R' = H, n = 6
11 : R = *t*-Bu, R' = H, n = 8



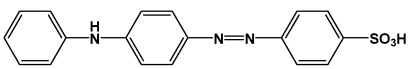
8 : n=4,6,8[53]

The calix[*n*]arene carboxylic acid derivatives, **5–7**, are convenient receptors for the solid–liquid extraction of aromatic amino acids from water and the results indicated a relationship between the size and feature of the calixarene.[54] The amino acid extraction from water (in neutral or acidic media), as a model of pharmaceutical pollutants studied by UV spectrometry, is followed by their photocatalytic degradation in the presence of TiO_2. It was shown that photodegradation follows first-order kinetics and the rate constant gradually increases with the amino acid concentration. From the recovery of amino acids, adsorption directly on calixarene carboxylic acid impregnated resins from an aqueous solution without organic solvents was reported.[55] The authors consider this method better than liquid–liquid extraction. Adsorption of amino acid derivatives on resins impregnated with a series of calix[*n*]arene carboxylic acid derivatives **5–7** highlighted that the adsorption capacity of the impregnated resin increases with the increasing cavity size of the impregnated calixarene. Thus, larger macrocycles calix[6]arene and calix[8]arene carboxylic acid derivatives exhibited better adsorption properties towards amino acid derivatives on the impregnated resin than the calix[4]arene derivative. The adsorption selectivity of amino

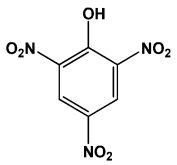
acid derivatives on the calix[6]arene impregnated resin was dependent on the hydrophobicity and the charge balance of the adsorbate. It is known that the L-tryptophan methyl ester hydrochloride forms a 1 : 1 complex with receptor **6**.[51] Comparatively, the molar quantity of L-tryptophan methyl ester adsorbed on the **6** impregnated resin was about twice the molar quantity of **6** impregnated in the resin, even if adsorption on the polymer support XAD-7 was taken into consideration. Moreover, the resin impregnated with receptor **7** adsorbed the L-tryptophan methyl ester to the extent of three times the number of molecules of **7**.

By immobilizing calix[4]arene derivatives on $Si/SiO_2/Si_3N_4$ transducers, sensors were obtained with the ability of using capacitance and flat band voltage as measurable quantities for determining amino acids that are neither electroactive nor having strong UV-vis absorption.[56] Different calixarene derivatives showed varying sensitivities to the amino acids which ranged from 8 to 137 mV decade^{-1}.

Amino acid methyl esters (L-TrpOMe, L-PheOMe, L-TyrOMe, L-LeuOMe, L-ValOMe, L-CysOMe, L-IleOMe, and L-SerOMe, Chart 1) were extracted from the aqueous phase (pH = 5.0) into the organic phase and transported through liquid membrane by *p-tert*-butylcalix[*n*]arene (*n* = 4, 6, 8), **9–11**, in the presence of counterions such as picrate[57] or tropaeolin 00 ([4-4′-(anilinophenylazo)benzenesulfonic acid]) as ion pairs.[58]



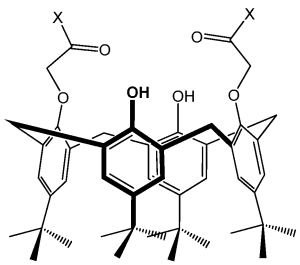
Tropaeolin 00



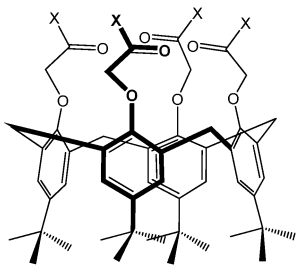
Picric acid

The results demonstrated that the extraction and transport depend on the structure of the calix[*n*]arenes, the structure of amino acids, the pH, and the nature of anion employed as the ion pair for cation–receptor complexes. The influence of the counterion on the stability of complexes between synthetic receptors and substrates, especially in apolar solvents like chloroform, is well-known. Thus, the interactions of a receptor with a substrate largely depend on the structure and electronic effects of the counterion present in the ion pair complex. With the exception of L-valine (35% extractability) and L-serine (37% extractability), the *p-tert*-butylcalix[6]arene, **10**, provided better extractability of amino acids as ion pairs in presence of trapaeolin 00 as the counterion at pH = 5.0, than both p-*tert*-butylcalix[4]arene, **9**, and p-*tert*-butylcalix[8]arene, **11**. The sequence of extractability using **6** as the extractant was the following: L-PheOMe > L-CysOMe > L-IleOMe > L-LeuOMe > L-SerOMe > L-ValOMe, and by using the **11** it turned to: L-IleOMe > L-PheOMe > L-ValOMe ≅ L-SerOMe > L-LeuOMe > L-CysOMe.[58]

In the membrane system, receptor **11** exhibited better transport ability than both *p-tert*-butylcalix[*n*]arenes (*n* = 4,6) for the amino acid methylesters through chloroform liquid membrane, except L-TrpOMe with **10**. The sequence of the transport yields of amino acids using **10** as carrier was the following: L-TrpOMe > L-PheOMe > L-LeuOMe > L-IleOMe ≅ L-ValOMe > L-TyrOMe and with the **11** as carrier the sequence of amino acid yields is the following: L-LeuOMe > L-TrpOMe > L-PheOMe > L-ValOMe > L-IleOMe ≅ L-SerOMe > L-TyrOMe. The L-CysOMe displayed no transport ability by receptors *p-tert*-butylcalix[*n*]arene (*n* = 4, 6, 8) even if it was extracted by these receptors. Its structure could be responsible for such behavior. The same situation subsists in the case of L-SerOMe and L-ValOMe. The correlation between the transport yields of amino acids and their hydrophobicity concluded that the hydrophobic species were more efficiently transported than other amino acids.[58]



12 : X = OH
13 : X = $NHCH(CH_2OH)_2$
14 : X = $NHC(CH_2OH)_3$



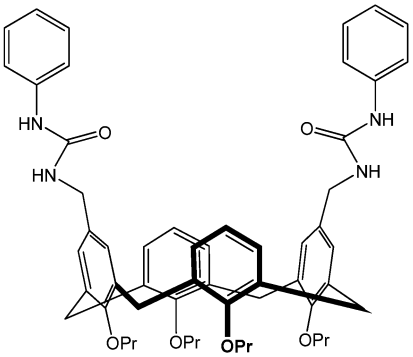
15 : X = OH
16 : X = $NH(CH_2)_2O(CH_2)_2OH$

Very large differences were noticed in the extractability of methyl esters and the native amino acid from the aqueous phase, pH = 5.5, into chloroform by using functionalized calix[4]arene (**12–16**) in the cone conformation varyingly substituted by acid or amido functions, glycolic chains and hydroxyl groups.[59] The hydrophobicity of the amino acid was an important factor in extraction behavior. The highest L-TrpOMe extractability (*E* = 65%) was detected for the tetraamido **16** and *E* = 61% for diamido **14** calix[4]arene derivatives as extractants and the values of extraction constants between log K_{ex} = 3.00 (receptor **14**) and log K_{ex} = 3.84 (receptor **13**) were obtained. In the case of L-PheOMe, the values of extraction constants (log K_{ex}) were ranging from 2.19 (with receptor **14**) to 2.90 (with receptor **16**) and for L-TyrOMe, log K_{ex} = 2.21 (with receptor **12**) and 2.24 (with receptor **14**). The extractability is essentially controlled by the structure of the calix[4]arene derivative and the nature of the amino acid. The functionalities, mainly the OH groups, glycolic chains, and amido functions known for their ability to form hydrogen bonds, oxygen-cation interactions and electrostatic interactions, can presumably play a role in binding of the amino acid ester through the interactions with the ammonium cation. The selective active transport through the liquid membrane assisted by the pH gradient of amino acid methyl esters by using receptors **12–16** as carriers, showed the following sequence of the decreasing transport yields of amino acids: L-TrpOMe > L-PheOMe > L-TyrOMe.[60] The receptors bearing diacid **12** and tetraamido **16** exhibited high transport yields towards L-tryptophan (98% with **12** and 87% with **16**) and L-phenylalanine (88% with **12** and 86% with **16**). The efficiency of receptors **12** and **16** for the transport of both amino acids is worth noting, whereas no selectivity was observed. All receptors **12–16** exhibited poor transport behavior towards L-TyrOMe. It was observed that the values of the transport yields were larger than those of the extraction yields. Obviously, the functional groups attached to calix[4]arene enhanced the recognition properties of calix[4]arene towards amino acids compared with those corresponding to parent

calix[4]arene. The nature of the amino acids was also responsible for the effective transport through the liquid membrane.

Preliminary evidence regarding the molecular recognition of *N*-protected α-amino acids by bis-1,3-*N*-substituted urea calix[4]arenes (**17**–**22**), fixed in the cone conformation as host receptors by means of ESI mass spectrometry investigations was reported by Bew *et al*.[61] Enhanced complexation between *N*-protected α-amino acids and bis-1,3-*N*-benzylureas calix[4]-arenes (**20**) was observed when methylene groups were present between the calix[4]arene and the urea motif. The bis-1,3-*N*-phenylurea calix[4]arene (**17**) was found to form a host–guest complex with *N*-Cbz-proline (intense mass peak at 1110.1 was recorded), and also with the aromatic amino acid, *N*-acetyl-(*S*)-phenylalanine, (a strong mass peak correlated to the anticipated complex formation was observed at 1067), considering that the aromatic group may aid the formation of the calix[4]arene complex *via* possible inclusion of phenyl ring of the amino acid within the calix cavity. One may observe that a strong complex between **17** and a few *N*-protected α-amino acids was formed especially when aromatic groups were present on the α-amino acid component. Furthermore the affinity of **17** toward N-Fmoc-(*S*)-valine (strong mass peak correlated with the expected mass for the complex formation at 1199 was observed), was put into evidence using ESI mass spectroscopy.

In order to investigate the effect that halogens like iodine could have on the ability of the host to form complexes with amino acids, the receptor bis-1,3-*N*-*para*-iodophenylurea calix[4]arene (**18**) was subject of experiments. Poor binding properties were



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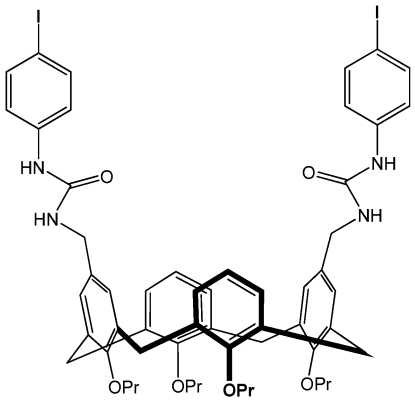

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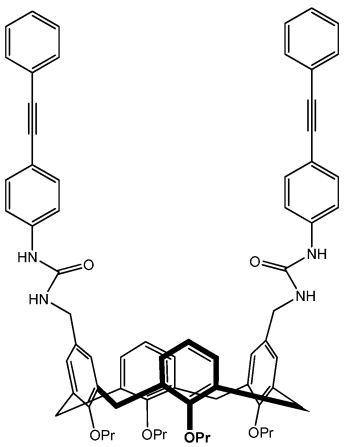

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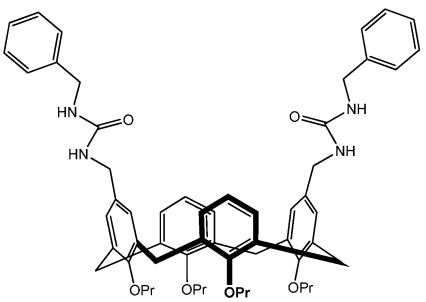

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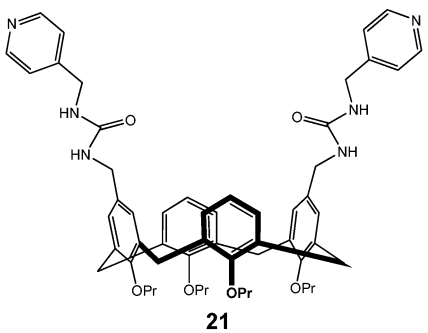

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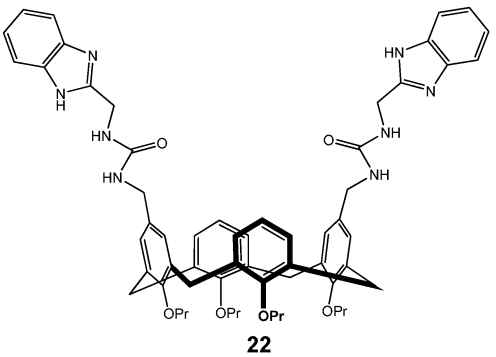

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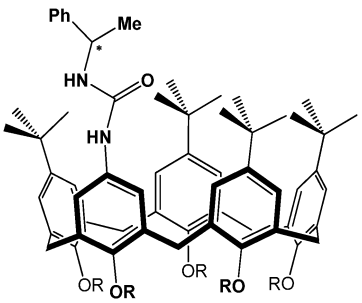
shown towards N-protected α-amino acids, so that the presence of the two sterical encumbered large iodine atoms inhibited host–guest formation. By using calix[4]arene (**19**) with "deep" and extended sides generating urea appended calix[4]arenes to enhance molecular recognition properties towards amino acids did not seem to offer any increased molecular recognition properties towards *N*-Cbz-proline, *N*-acetyl-(*S*)-phenylalanine, and *N*-Fmoc-(*S*)-valine. In addition, the authors demonstrated that subjecting mixtures of structurally diverse *N*-Fmoc-α-amino acids to a single bis-1,3-*N*-benzylurea derived calix[4]arene allows the calix[4]arene to selectively extract and complex a specific amino acid from the mixture presented. Nevertheless, the latter aspect requires more investigations.[61]

Another example of a receptor endowed with urea functionality at the upper rim, ureidocalix[5]arene (**23**), was reported by Parisi *et al.*[62] The receptor **23** behaved as a remarkably efficient abiotic receptor of ω-amino acids and biogenic amines, which were partly bound within the π-basic cavity and partly bound *via* secondary hydrogen bonding to urea motifs. By ^{1}H NMR studies in $CDCl_3$, the binding affinities of the amine-calix[5]arene complexes were established to have 1 : 1 stoichiometry between host and guest.



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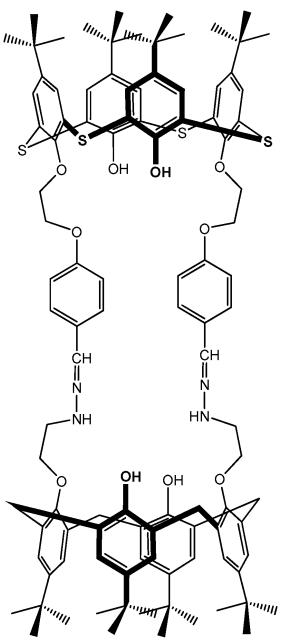
The biscalixarene **24**, composed of calix[4]arene and thiacalix[4]arene subunits showed extracting properties towards zwitterionic α-amino acids, *e.g.*, the extraction



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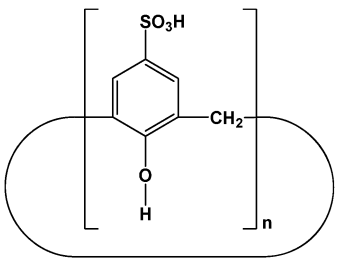
percentage of threonine was as high as 51.4%.[63] The complexation of amino acids may be attributed to the cooperative complexation of two calixarene subunits which could bind the ammonium ions and carboxylate by hydrogen bonds, respectively.

Recognition of amino acids by water soluble calix[*n*]arenes

The property of some functionalized calix[*n*]arenes, such as *p*-sulfonato-calix[*n*]arenes and phosphonato-calix[4]arene derivatives, to form inclusion complexes with several biological species in water was the subject of some extensive reviews recently reported by Coleman *et al.*[9,10] and Atwood *et al.*[64] The authors summarize the known association constants obtained by means of microcalorimetry,[65–72] NMR spectroscopy,[9,73–75] UV spectroscopy,[68] and RP HPLC measurements[76] for the complexation of some amino acids and di- and tripeptides with calixarenes and their derivatives. The results demonstrate that the inclusion properties of the investigated hosts are correlated with their structural properties. The solvent conditions, the pH values, and the buffers also influenced the results obtained. The electrostatically driven interactions characterize the complex formation between *p*-sulfonato-calix[*n*]arenes (**25–27**) and basic amino acids Arg and Lys (Chart 1).[66,67,73,76] The driving forces in complexation of the phosphonato calix[*4*]arene derivatives with amino acids and dipeptides mainly consist in electrostatic interactions.[68–70]

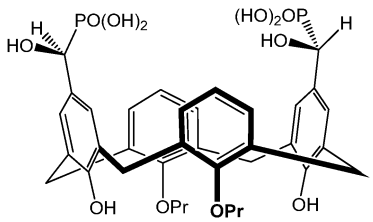


25 : n = 4
26 : n = 6
27 : n = 8

The thermodynamic characterization of the binding affinity of di- and tripeptides bearing lysine or arginine (lysyl-lysine, arginyl-arginine, lysil-arginine, arginyl-lysine, lysyl-lysyl-lysine, and arginyl-arginyl-arginine, see Chart 1) by receptors **25–27** employing NMR and microcalorimetric titrations[72] has proved that the complex formation was controlled by the favorable enthalpy obtained by the inclusion of the apolar part of the peptide into the hydrophobic cavity of the receptors **25–27** through van der Waals interactions. Likewise, an important role is played by the entropy which accompanied the desolvation of the charged groups upon ionic interaction.[72] Di- and tripeptides form stable 1 : 1 complexes with receptor **25** in aqueous buffer at pH 8.0. Both 1 : 1 and 1 : 2 complexes are observed with receptor **26**. Further on, the receptor **26** binds two lysyl-lysines which suggests that it adopts, in solution, a conformation of the 1,2,3-alternate type. By means of calorimetric titration, the stability constants, enthalpies, and entropies of complex formation between receptors **25** and **26** and a series of di- and tripeptides

(glycil-glycine, glycil-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) were evaluated and it was established that the complexation was favored by enthalpic contributions and disfavored by entropic contributions.[65] However, no selectivity was detected during these studies.

The particular interest in *p*-sulfonato-calix[*n*]arenes (**25–27**) is justified by their biological properties and activity ranging from enzyme inhibition, through anti-thrombotic activity, anti-viral activity, to anti-bacterial properties.[10,64] In addition, Atwood *et al.*[77] emphasized the activity of *p*-sulfonato-calix[*n*]-arene derivatives as chloride channel blockers. Since 1990, the research groups of Arena and Ungaro, and Coleman have studied the interactions of *p*-sulfonato-calixarenes and their derivatives with various amino acids and peptides. By micro-calorimetric and ^{1}H NMR titration (pD = 7.3; pH = 7.0) investigations supported by molecular modeling, Arena *et al.*[78] established that the complex formation between amino acid (L-alanine, L-valine, L-leucine, L-phenylalanine, L-tryptophan, L-tyrosine, and L-histidine) and calix[4]arene sulfonate in buffered aqueous solution occurs by inserting aromatic or aliphatic apolar groups into the hydrophobic cavity of the calixarene. The most efficient receptor was the calix[4]arene tetrasulfonate (**25**), which exists in solution at pH = 7 in a cone conformation; the inclusion was enthalpically favored and entropically unfavored, regardless of the nature of the side chain. In this respect, the driving force for the inclusion was the CH–π interaction of the alkyl chain for L-valine, and L-leucine, or a π–π interaction for L-phenylalanine and L-histidine.[78] Additionally, the authors revealed the major influence of the small changes of the substitution pattern at the lower rim on the binding properties of the apolar cavity of calix[4]arenes in water solution.[11] By ^{1}H and ^{13}C NMR and crystallographic studies of a *p*-sulfonatocalix[4]-arene–guest complex, Shinkai *et al.*[38] reported the formation a host–guest type complex with the phenyl moiety inserted into the cavity by hydrophobic and electrostatic forces.



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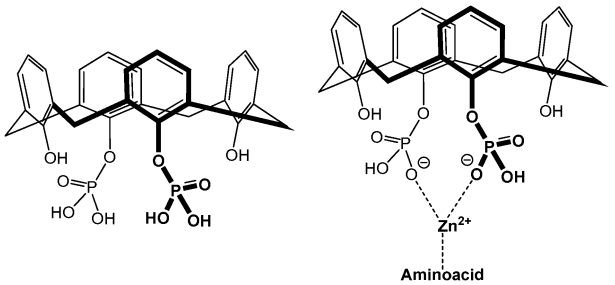
The 1 : 1 and 2 : 1 calixarene–amino acid complexes of calix[4]-arene *bis*-hydroxymethylphosphonic acid (**28**) and aliphatic amino acids, Gly, L-Ala, L-Val, L-Leu, L-Ile were found to be formed.[68,69] The full thermodynamic characterization of the complex formation by means of calorimetric titrations in methanol, NMR measurements in CD_3OD, and UV-Vis titrations in methanol suggested that the electrostatic interaction between negatively charged calixarene phosphoryl group and amino acid residue NH_3^+ group, and the hydrophobic interaction for the inclusion of the residue alkyl side-chain of amino acid into the calixarene cavity, controls the complex formation. Quantitative evaluation of amino acids affinity of **28** showed that K_{11}, the stability constant of the 1 : 1 complex between **28** and an amino acid is significantly higher than K_{21}, the stability constant of 2 : 1 complex formation. For instance, the stability constants log K_{11} and log K_{21} of the glycine complex of **28**, are 3.84 M^{-1} and 2.87 M^{-1} in methanol, respectively. Similarly, for Ala, log K_{11} = 3.89 and log K_{21} = 2.93 respectively, for Val, log K_{11} = 4.12 and log K_{21} = 3.00 respectively, for Leu, log K_{11} = 4.19 and log K_{21} = 3.15, respectively, and for Ile, log K_{11} = 4.23 and log K_{21} = 3.20, respectively. The two types of complexes differ from each other by the dominant interactions, one (1 : 1) is enthalpically favorable and the other one (2 : 1) is characterized mainly by the entropic effects. The results demonstrate that the major contribution to the complex originates in the electrostatic interactions driving the formation of the 1 : 1 complex, whereas the inclusion of the hydrophobic side-chain within the host cavity plays a minor role. Moreover, both ΔG values are strongly correlated with the hydrophobicity of the amino acid residue. For analogous compounds, in which the phosphonate group is bound directly to the aromatic ring, strong complexation was observed for the basic amino acids.

The complexation investigations of a series of amino acids (valine, isoleucine, lysine, arginine, histidine, proline, hydroxyproline, phenylalanine, tryptophan, cysteine, serine, threonine and methionine, see Chart 1) and dipeptides (alanyl-alanine, alanyl-leucine, alanyl-glutamic acid, glycyl-tyrosine, threonyl-leucine, see Chart 1) with phosporylated calix[4]arenes in pure *racemic* form and a 1 : 1 mixture of the *meso* and *racemic* forms in methanol solution by isothermal titration calorimetry showed an average variation in the changes of enthalpy, entropy and Gibbs free energy of complex formation.[70] The thermodynamic behaviour of both phosphorylated calix[4]arene derivatives towards amino acids were similar. The values of Gibbs free energy were not largely different and the pure *racemic* form was preferred in the complexation process. Thus, the values of stability constants (log K, K in M^{-1}) ranged between 3.46 (L-alanine) and 4.21 (L-methionine) for amino acids and between 4.43 (alanyl–alanine) and 4.64 (alanyl–leucine) for dipeptides. The enthalpy changes (ΔH^0) were in the range of −10 (glycine) and −2 kJ mol^{-1}(L-hydroxyproline) for amino acids and in the range of −10.5 (alanyl-alanine) to −5.9 kJ mol^{-1} (glycil-tyrosine) for dipeptides.[67] The complexation was driven by the electrostatic interactions between protonated N-terminal amino group of the guest and calix[4]arene phosphoryl groups. Moreover, the correlation between the complex stability and hydrophobicity of the amino acid residues highlighted the partition of the solvatophobic interactions.

By means of ESI mass spectrometry combined with ^{1}H NMR studies in buffered aqueous solutions, Perret *et al.*[80] figured out the ternary *exo* supramolecular complexes formation between 25,27-bis(dihydroxy-phosphoryloxy)calix[4]arene (**29**) and amino acids (Ala, Arg, Asp, His, Lys, Cys, Ser) and metal salts. It was demonstrated that the receptor **29** is endowed with both high affinity and strong selectivity under the complex form 25,27-diphosphoryloxy-calix[4]arene-Zn^{2+}-histidine (84%). The structure of the ternary complex suggested by the authors was **29-Zn^{2+}-His**. Hence, the

phosphonates groups of **29** acted as a clip binding His. In the presence of Zn^{2+}, there is no direct interaction between **29** and His, whatsoever.

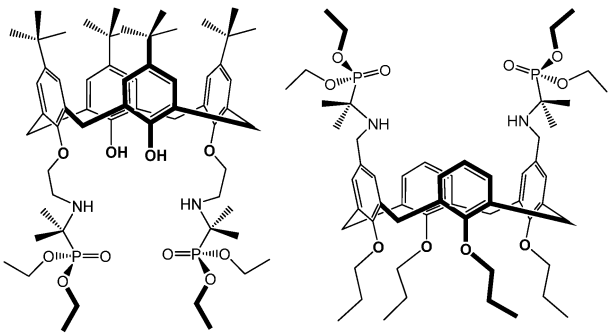


29 **29-Zn^{2+}-His**

The stability constants, binding ratio, reaction enthalpy and entropy of sulfonatocalixarene **25** complexation with L-tryptophan in aqueous solutions by means of spectrofluorimetric titration were evaluated by Li *et al.*[81] The fluorescence intensity of the L-Trp decreases upon the addition of **25**, accompanied by bathochromic/red shifts. The envisaged mechanism involved in this complex formation may be a combination of hydrophobic and electrostatic interactions and it was suggested that the benzene ring of amino acid penetrated into the hydrophobic cavity of calix[4]arene. Recently, Schrader *et al.*[75,82] have reported calixarenes tetraphosphonate, tetraammonium, and tetramine as specific receptors for basic amino acids, with preference for arginine entailing a color fingerprinting of proteins by calixarenes embedded in lipid/polydiacetylene vesicles.

The calix[4]arene phosphonic acids with various substituents at the lower rim **30–32** showed different complexation abilities towards some aliphatic and aromatic amino acid methyl esters.[83] The binding ability of these receptors was evaluated by means of ^{1}H NMR titration measurements (phosphate buffer solution at pD = 7.3). It was determined that the receptor **32** exhibited selectivity for basic amino acid methyl esters like LysOMe (1 : 1 stoichiometry in D_2O, K_a = 600 M^{-1}), ArgOMe (1 : 1 stoichiometry in D_2O, K_a = 600 M^{-1}), and HysOMe (1 : 1 stoichiometry in D_2O, K_a = 200 M^{-1}) compared to the rigid receptor **31** such as, LysOMe (1 : 1 stoichiometry in D_2O, K_a = 170 M^{-1}), ArgOMe (1 : 1 stoichiometry in D_2O, K_a = 120 M^{-1}), and HysOMe (1 : 1 stoichiometry in D_2O, K_a = 30 M^{-1}). In the case of **32** binding, the amino acids were bound inside the calix[4]arene cavity in a specific mode by inclusion of the functional group of the amino acid side chain. Mixtures of 1 : 2 and 2 : 1 (amino acid-calix[4]arene derivative) were formed with receptor **30** (flattened cone conformation) and amino acid methyl esters lysine, arginine, histidine, phenylalanine, leucine, and tryptophan, but the selectivity of this receptor was very low.

Calix[4]arene functionalized with α-aminophosphonates at the lower rim **33** or upper rim **34** exhibited high selectivity as carriers of the zwitterionic forms of aromatic amino acids transport through a supported liquid membranes in NitroPhenylOctylEther (NPOE).[84] It is worth noting that employing receptor **34**, the phenylalanine was transported 40 times faster than tryptophan. The molecular cavity of **34** is involved in the complexation and the three points interaction of amino acid like carboxylate, ammonium groups and side chain with the carrier ends up with higher transport efficiency and selectivity. The experiments did not infer any dependence between the flux of the transport through the membrane and the hydrophobicity of amino acids (log P). As for instance, the transport of tryptophan showed lower flux values, whereas higher fluxes of hydrophilic histidine were observed.

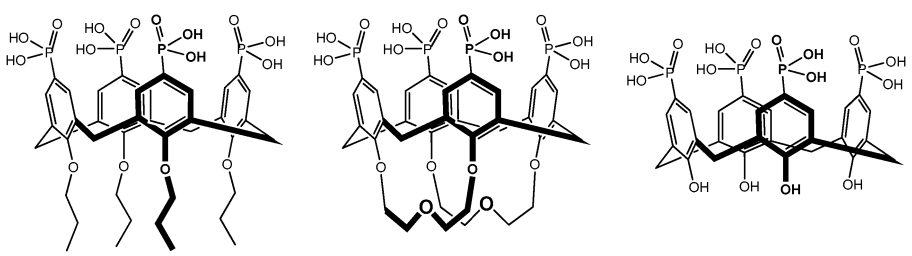


33 **34**

Chiral recognition of amino acids by chiral calix[*n*]arenes

Chiral recognition of α-amino acids has been investigated commencing with Shinkai *et al.*[85] who used a pseudo-C_2-symmetrical compound based on a C_3-symmetrical skeleton of homooxacalix[3]arene for chiral recognition of α-amino acids derivatives.

Aiming to develop a novel class of artificial enzymes with the chiral recognition ability, Shinkai *et al.*[86] investigated the introduction of chiral substituents onto calixarenes. As such, they reported back in 1987 the synthesis of chiral calixarene 5,11,17,23,29,35-hexasulfonato-37,38,39,40,41,42-hexakis[(*S*)-2-methylbutoxy]calix[6]arene and, later on, in 1991, the synthesis of chiral *p*-sulfonatocalix[*n*]arenes (*n* = 4, 6, 8)

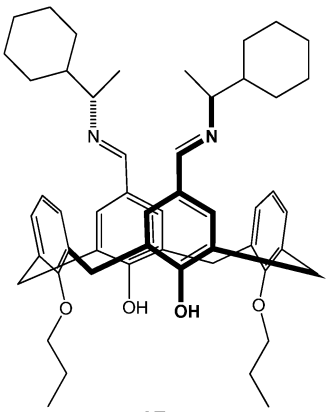


30 **31** **32**

bearing (*S*)-2-methylbutoxy groups.[87] Along the same line, Kubo *et al.*[88] synthesized chromogenic calix[*n*]arenes used in building of molecular sensors for chiral recognition of biological amines. Interesting studies concerning the chiral molecular recognition of some amino acid ethyl and methyl esters and *Z*-protected α-amino acids by calix[4]arene having four pendant chiral esters derived from (*S*)-1-phenylethanol were reported by Okada *et al.*[89]

The recognition properties towards selected amino acid methyl esters (L-PheOMe, D-PheOMe, L-AlaOMe, D-AlaOMe) and chiral α-phenylethylamine derivatives of *p-tert*-butylcalix[4]arene/calix[4]arene (**35** and **36**) were investigated by extraction experiments.[90] The receptor **35** showed higher abilities as the extractant than receptor **36** for both α-amino acid methyl esters and amines (**35**: (*R*)-(+)-1-phenylethylamine 95.3, (*S*)-(−)-1-phenylethylamine 96.1; **36**: (*R*)-(+)-1-phenylethylamine 53.5, (*S*)-(−)-1-phenylethylamine 55.7) yet no remarkable discrimination was seen. The extraction percentage of amino acids from aqueous phase in dichloromethane with receptor **35** are the following: L-PheOMe 95.2%, D-PheOMe 93.5, L-AlaOMe 96.1, D-AlaOMe 95.3 and with receptor **36**: L-PheOMe 27.4%, D-PheOMe 28.3, L-AlaOMe 26.7, D-AlaOMe 25.8. The formation of 1 : 1 complexes was demonstrated by slope analysis. A complex formation with the ammonium group located at the lower rim of the calix unit in the cone conformation is depicted (see Scheme 2). No assumption was made on the interactions maintaining the ammonium inside the chelation site.

Chiral calix[4]arene Schiff bases functionalized both on the upper and the lower rim have shown binding affinities for some chiral and achiral amines, and amino acid derivatives characterized by differential UV-Vis titration in chloroform.[91,92] Thus, compound **37** exhibited enantioselective recognition towards (*R*)- and (*S*)-phenylethylamine.[91] The results obtained with respect to molecular recognition and enantioselectivity towards guests were discussed from a thermodynamic point of view. The receptor formed 1 : 1 complexes with amines and amino acids (*L*-PheOMe, D-PheOMe, L-AlaOMe, D-AlaOMe) in chloroform. The enantiomeric discrimination, K_D/K_L = 4.36 for phenylalanine, and, K_D/K_L = 1.78 for alanine, obtained by using calix[4]arene Schiff bases, showed a good chiral recognition ability towards amino acids.[92] The D/L-enantioselectivies were highly sensitive to the Schiff base moiety attached to the upper rim of calix[4]arene and shape of the substituted group in amino acid derivatives. The cooperative binding of Schiff base moieties, structural rigidity or flexibility, steric effects, cation–π, and π–π stacking interactions were considered responsible for the enantiomeric recognition of amino acid derivatives.



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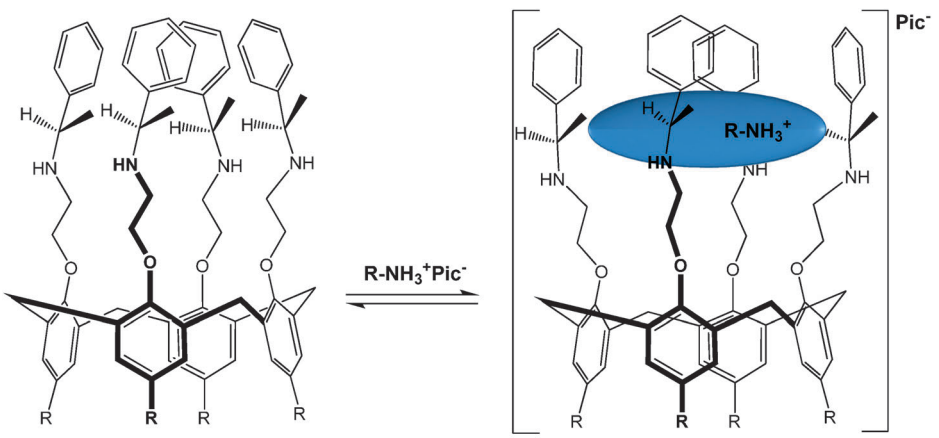
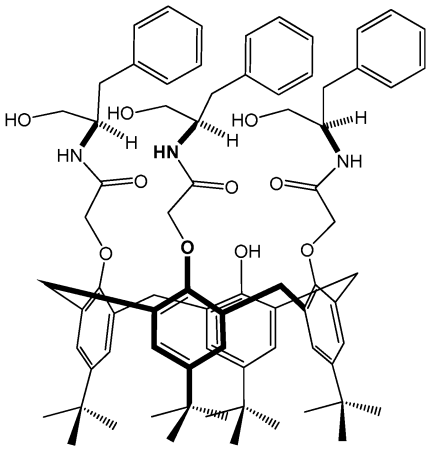
The chiral calix[4]arenes triamide derivatives obtained by synthesis of D/L-phenylalaninol substituted *p-tert*-butylcalix[4]arene triamide derivatives (**38** and **39**) for chiral recognition of some amino acids methyl esters highlighted affinity towards amino acids without any pronounced discrimination.[93] The extraction percentage of amino acid methyl esters as picrates in dichloromethane by receptor **38** was: D-AlaOMe 54.1%, L-AlaOMe 56.5%, D-PheOMe 71.3%, L-PheOMe 68.5%, D-TrpOMe 68.4%, L-TrpOMe 69.7% and by receptor **39** was: D-AlaOMe 59.5%, L-AlaOMe 57.4%, D-PheOMe 65.8%, L-PheOMe 67.5%, D-TrpOMe 62.6%, L-TrpOMe 68.3%. By slope analysis it was suggested that 2 : 1 complex **39** : amino acid was formed.



Scheme 2 Proposed 1 : 1 complexes of **35** and **36** with amino acids as depicted in reference 90.



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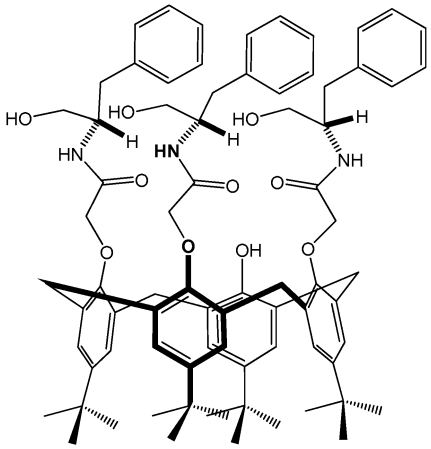

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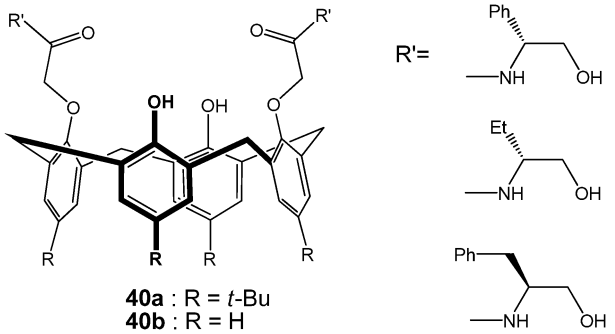
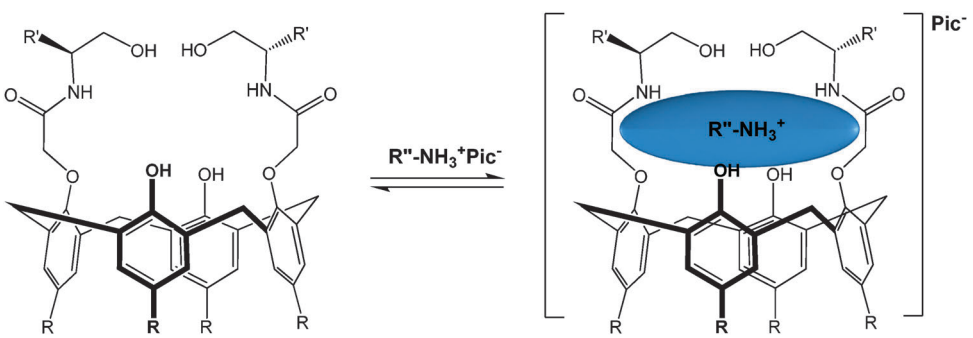
Kocabas *et al.*[94,95] reported the synthesis of chiral mono- and diamide derivatives of calix[4]arene in cone conformation for the enantiomeric recognition of amino acid derivatives. The binding properties of these receptors with various chiral amines were studied by UV-Vis spectrophotometric titrations in $CHCl_3$ and ^1H NMR spectroscopy in $CDCl_3$.[94] The binding constants of complex formation between all chiral receptors and enantiomers of phenylethylamine were higher than those of chiral receptors and enantiomers of cyclohexylethylamine due to π–π interactions and hydrogen bonding. These receptors formed 1 : 1 complexes with amines in chloroform.



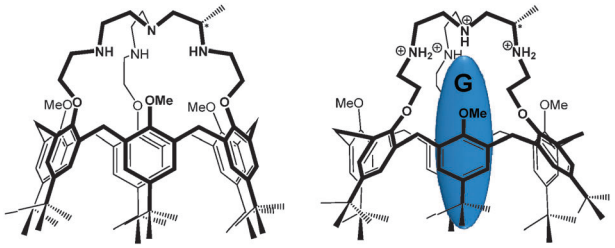
40a : R = *t*-Bu
40b : R = H

The affinity of chiral calix[4]arene diamide derivatives, **40a,b**, towards α-amino acid methyl esters (L-SerOMe, D-SerOMe, L-AlaOMe, D-AlaOMe, L-PheOMe, and D-PheOMe) as the picrate salts were studied by means of liquid–liquid extraction experiments in CH_2Cl_2.[95] Thus, the extraction percentage of amino acids with **40a** were the following: L-SerOMe 53.4%, D-SerOMe 54.5, L-AlaOMe 52.2, D-AlaOMe 53.1, L-PheOMe 48.3, D-PheOMe 49.6 and for **40b**: L-SerOMe 59.4%, D-SerOMe 66.8, L-AlaOMe 54.0, D-AlaOMe 62.4, L-PheOMe 54.9, D-PheOMe 56.7. By slope analysis, 1 : 1 complex formation between **40a** and amino acids was determined. The recognition ability of receptors was studied by UV-Vis measurements in dichloromethane. Although the receptors showed efficient extractability towards amino acid derivatives, they did not show any enantioselectivity. A proposal of the location of the amino acid was given by the authors without further details on the interactions (see Scheme 3).[92]

The first enantiopure calix[6]aza-cryptand (**41**) was synthesized by Jabin *et al.*[96] in five steps in cone conformation from 1,3,5-tris-*O*-methylated calix[6]arene. The ^1H NMR spectroscopic study demonstrated that this conformation could be ideal for host–guest applications. The tetra-protonated derivative displayed interesting properties towards polar neutral molecules as well as enantioselective recognition with chiral guests. Enantioselective molecular recognition processes inside the cavity of the obtained receptor **41**·**4H**$^+$ were performed with two structurally different racemic guests (chiral 1,2-diol and a chiral imidazolidin-2-one, see Scheme 4). These examples are not dealing with amino acids but they deserve to be cited due to chiral recognition of calixarene derivatives.

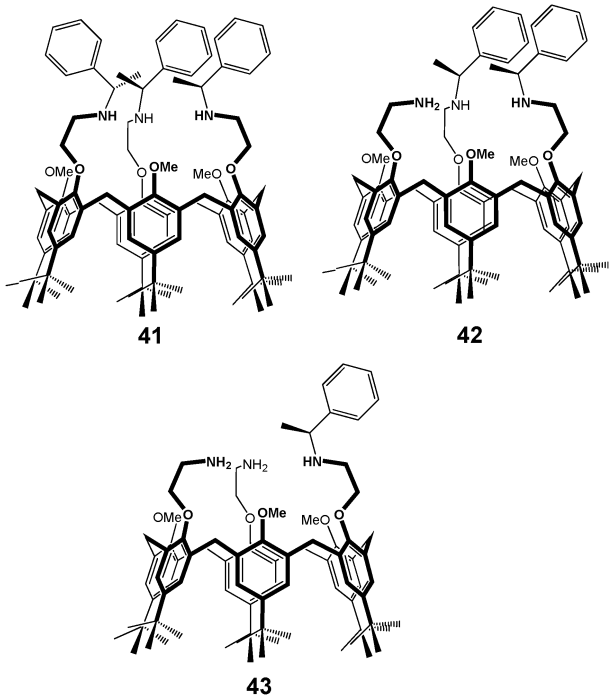


Scheme 3 Proposed complexes of chiral diamide derivatives of calix[4]arene (**40**) with amino acid methyl esters as depicted in reference 95.

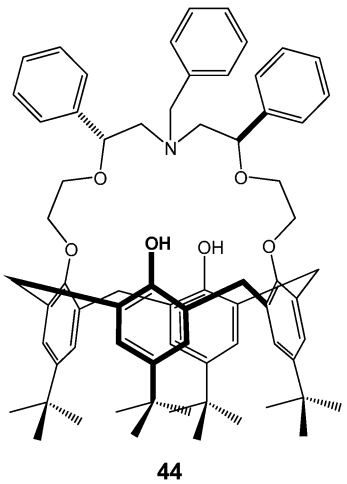


Scheme 4 Host–guest properties of the enantiomerically pure **41**·**4H**$^+$ according to reference 96.

Receptors **41–43** are optically pure calix[6]tris-ammoniums bearing, respectively, either one, two, or three chiral amino arms on the narrow rim, being useful for chiral discrimination between enantiomers of neutral compounds.[97] They were obtained with high yields and by an NMR conformational study, it was shown that all these chiral calix[6]tris-ammoniums possess a flattened cone conformation with the cavity occupied by the methoxy groups. Upon protonation, the chiral derivative **43**, bearing only one chiral arm, can switch to the opposite flattened cone conformation through self-assembly of its ammonium arms in an ion-paired cap which closes the cavity. Thus, the polarized host **43**·**3H**$^+$ behaves like an *endo*-receptor for small polar neutral compounds. Although these last examples are not concerning the complexation of amino acids, and we reported them because of a certain linking to amino acids through the complexation of related amino substrates.



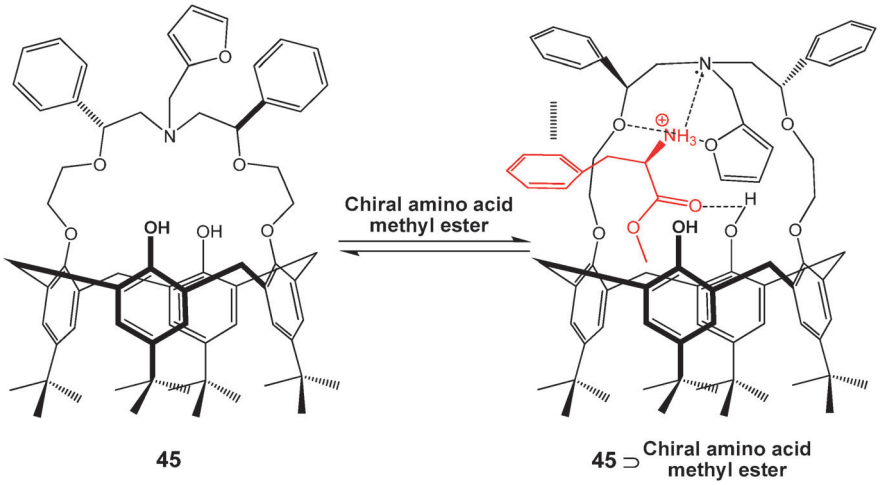
Demirtas *et al.*[98] reported the synthesis of chiral calix[4]-azacrown ethers by the reaction of dibromo or ditosyl derivatives of *p*-*tert*-butyl-calix[4]arene with a chiral diol for enantiomeric recognition of α-amino acid methylesters. By UV-Vis spectroscopic studies in chloroform, it was proved that chiral receptors **44** and **45** exhibited binding abilities and certain chiral recognition towards the enantiomers of PheOMe and AlaOMe. Both receptors formed stable 1 : 1 complexes with enantiomers of phenylalanine and alanine methyl esters in $CHCl_3$ verified by Job plot experiments.



The receptor **44** showed stronger binding and better recognition for aromatic amino acids than the aliphatic ones ($K_{D-PheOMe}$ = 583 M^{-1}, $K_{L-PheOMe}$ = 1049 M^{-1}, $K_{D-AlaOMe}$ = 315 M^{-1}, $K_{L-AlaOMe}$ = 356 M^{-1}). In this case, the receptor with an aromatic group attached to the nitrogen of the macrocyclic ring could have π–π interactions with that of PheOMe as an additional binding force. Hence, stronger binding was enforced. The enantiomeric discrimination of a pair of amino acids for receptor **44** were the following: K_L/K_D = 1.80 for the phenylalanine methyl ester, and K_L/K_D = 1.13 for the alanine methyl ester. The same behavior was observed in the case of receptor 45 (furfuryl-armed calix[4]-azacrown ether) concerning the binding properties toward aromatic and aliphatic amino acids. Thus, the values of the binding constants for PheOMe ($K_{D-PheOMe}$ = 809 M^{-1}, $K_{L-PheOMe}$ = 1684 M^{-1}) are significantly larger than for AlaOMe ($K_{D-AlaOMe}$ = 419 M^{-1}, $K_{L-AlaOMe}$ = 532 M^{-1}) which was attributed to the additional binding force of π–π interactions between the aromatic group attached to the nitrogen of the receptor and the aromatic group of the amino acid.

Furthermore, receptor **45** exhibited the best enantiomeric discrimination for the phenylalanine methyl ester (K_L/K_D = 2.08) and for the alanine methyl ester (K_L/K_D = 1.27) compared with receptor **44**. The enantiomeric recognition might be caused by multiple hydrogen bonding, steric hindrance, structural rigidity or flexibility, and π–π stacking interactions between the receptor and the aromatic side chain of the amino acid. The authors assumed that the oxygen atom of the furfuryl moiety possibly formed an additional chelation with the ammonium of the amino acid (see Scheme 5).

Chiral amide derivatives of octaester calixresorcarene were employed as chiral stationary phases for enantioselective discrimination of amino acid derivatives.[99] Thus, Amberlite XAD-16 impregnated with the chiral octamide containing a phenyl group was used as support material. In this respect, the enantiomers of phenylglycine and tryptophan were discriminated under the form of their sodium and potassium salts. Moreover, phenylalanine–tryptophan, phenylglycine–tryptophan mixtures were separated by column chromatography.



Scheme 5 Recognition mode of chiral calix[4]arene (**45**) towards a chiral amino acid methyl ester showing the implication of the furfuryl group according to reference 98.

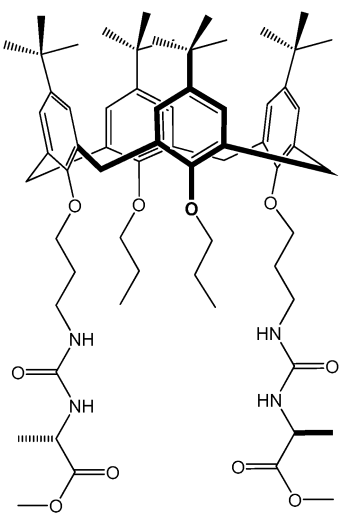
Chiral recognition of amino acids by peptido- and glycocalix[*n*]arenes

A particular area of interest within the calixarene field consists of conjugation of peptide or carbohydrate moieties to calixarenes to produce so called peptidocalixarene and glycocalixarene, respectively. The peptidocalixarenes obtained by linking amino acids or peptides to the calix[4]arene scaffold either through the terminal amino or carboxylic acid group, leading to *N*-linked **46** and **47** or *C*-linked peptidocalix[4]arenes (**48** and **49**), respectively, formed inclusion complexes with amino acids (See Scheme 6 for the mode of binding of *R*-amino acid by **49**).[100–106]

The N-linked peptidocalix[4]arenes exhibited binding ability towards ammonium and carboxylic acids but not to anionic guests.[11,104] By using *cone* peptidocalix[4]arenes with different conformation flexibility towards aliphatic and aromatic amino acids and their methylesters in D_2O (pD = 7.3, phosphate buffer 0.067 M), Sansone *et al.*[11] highlighted by ^{1}H NMR titration experiments, that the rigid receptor with two short di(ethylene glycol) units at the lower rim of the calix[4]arene skeleton, **50** showed better binding properties in complexation than the flexible analog one **47**. Amino acids were complexed by **50** through their apolar moiety driven by hydrophobic and π–π interactions, while the platform rigidity enforces the binding. Moreover, it was observed that the amino acid methyl esters were better complexed than amino acid zwitterion forms, due to a higher complementarity of substrates in a positive charge with tetra-anionic receptor **50**. The aromatic molecules bound more strongly than the aliphatic ones ($K_{\text{L-LeuOMe}}$ = 290 M^{-1}, $K_{\text{L-ValOMe}}$ = 220 M^{-1}, $K_{\text{L-AlaOMe}}$ = 110 M^{-1}, no inclusion for the native amino acids: L-Val, L-Ala, Gly, L-Leu <20 M^{-1}, and GlyOMe) with the highest association constants values for L-Trp and L-TrpOMe ($K_{\text{L-Trp}}$ = 110 M^{-1} and $K_{\text{L-TrpOMe}}$ = 620 M^{-1} respectively).[11] Bridged *N*-linked peptidocalix[4]arene with L-Ala,L-Ala through a 1,3,5-diethylenetriamine spacer showed binding affinity towards *N*-Ac-D-Ala-D-Ala, α-amino acids or carboxylic acids as well as and 1 : 1 complexes were formed.[101] The stabilities of the complexes increase in $CDCl_3$ from lauric acid (log *K* = 3.00) to *N*-lauroyl-D-Ala (log *K* = 4.10) or from *N*-lauroyl-L-Ala (log *K* = 4.05) to *N*-lauroyl-D-Ala-D-Ala (log *K* > 5). NMR diffusion studies carried out in $CDCl_3$ + 3%DMSO-d_6 showed that the *N*-Ac-L-Ala-L-Ala dipeptide was bound more strongly (log *K* = 3.4) than the amino acid derivative *N*-Ac-L-Ala (log *K* = 2.4).[107] Bridging of *N*-linked peptidocalix[4]arene with the L-Ala-L-Ala dipeptide chain instead of L-Ala entailed a significantly drop in activity, while protecting the central NH group with a Boc, or substituting it with a methylene group, completely inhibited the biological activity.[101] The active compounds had a behavior very close to that of vancomycin.

The chiral *C*-linked peptidocalix[4]arenes obtained from functionalized calix[4]arenes at upper rim of the cone with two or four L-alanine or L-phenylalanines were reported by the same group of Ungaro's.[108] Their properties were different from those of *N*-linked peptidocalix[4]arenes and they interacted preferentially with anionic species. Several aspects of the receptors involving the attachment of amino acids and peptides to calix[4]arene scaffold synthesized by Ungaro's group have recently been reviewed by Kubik.[14]

The bisurea calix[4]arene receptors having amino acid moieties at the lower rim such as receptor **51** having alanine



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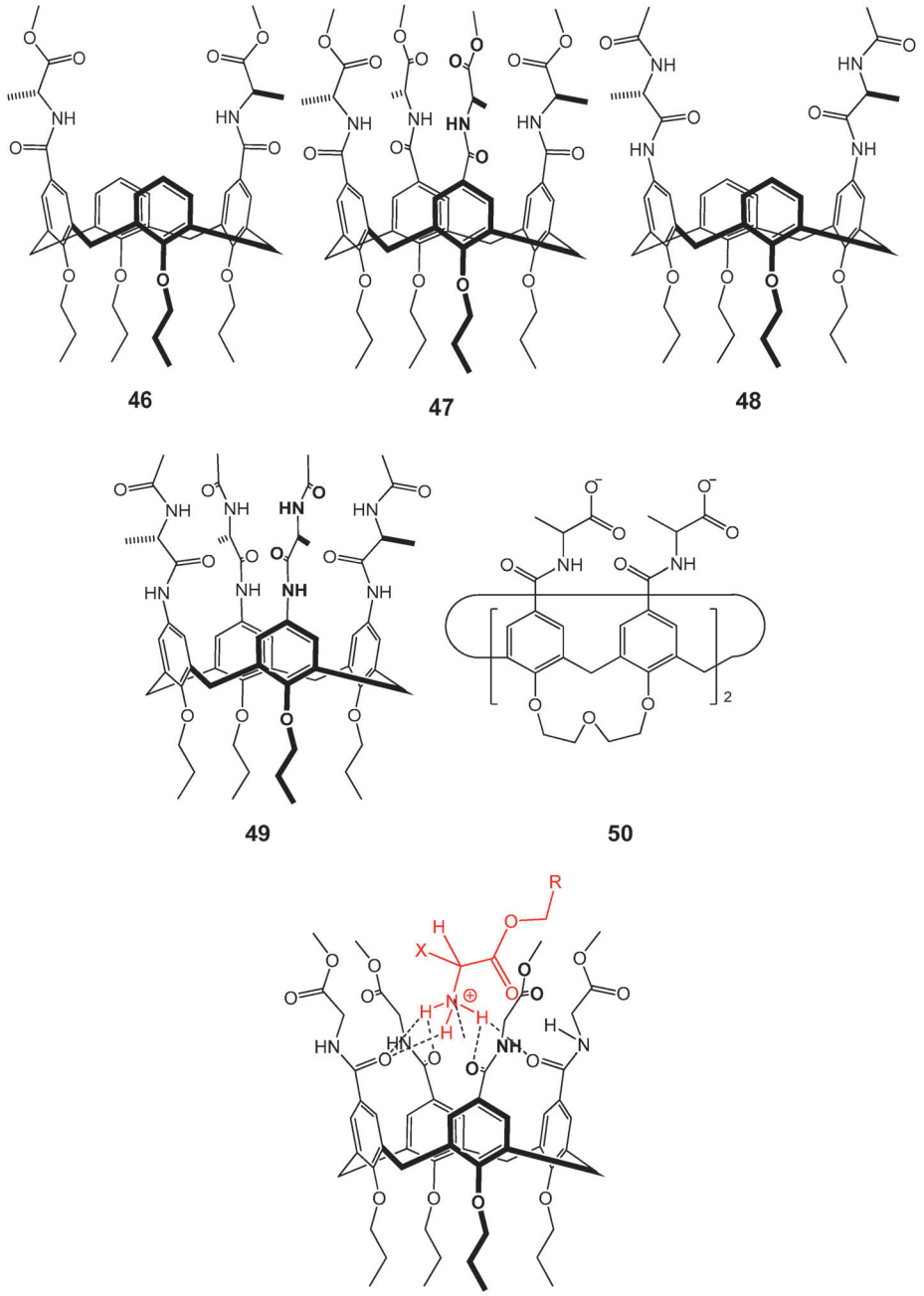


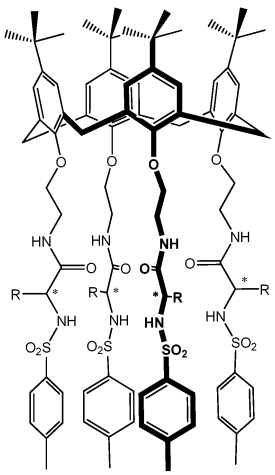
Scheme 6 Mode of binding the *R*-amino acid ester by tetraalanine methyl ester calix[4]arene (**49**) according to reference 100.

moieties close to urea binding groups are characterized by strong intramolecular hydrogen bonding between the urea and NH groups, as well as the vicinal phenolic oxygen atoms or the opposite urea C═O group.[109] The receptor **51** showed efficiently binding towards the *N*-acetyl-phenylalaninate anion. NMR studies in d_6-acetone solution highlighted its selectivity for the D- over the L-isomer of the guest (K (*N*-Ac-D-Phe-COO^-) = 1250 M^{-1}; K (*N*-Ac-L-Phe-COO^-) = 300 M^{-1}). A high value of the D/L selectivity (K_D/K_L = 4.14) was determined.

The chiral *p-tert*-butylcalix[4]arenes 1,3-difunctionalized at the lower rim with protected amino acid units (D/L-Ala, D/L- Ile, D/L-Leu, D/L-Phe, and D/L-Val) synthesized in the cone conformation are selective receptors for anions that are bound through hydrogen bonding with the NH groups.[110,111] The binding constants are dependent on the nature of the substituent at the lower rim. The 1,3-*N*-tosyl peptidocalix[4]-arenes investigated by ^{1}H and ^{13}C NMR spectroscopy showed that the compounds adopt a cone conformation and the binding constant of di-*N*-tosylpeptidocalix[4]arenes complexes depends on the length of the butylene spacer. A high binding constant was observed for *N*-tosyl-(L)-alaninate with receptor calixarene D-alaninate derivatives (K_{ass} = 6924 M^{-1}). The recognition properties were investigated by ^{1}H NMR experiments in $CDCl_3$. The stoichiometry 1 : 1 was confirmed by Job plots and the association constants were determined by the Benesi–Hildebrand method. Binding of guests by receptors entails a combination of hydrogen bonding interactions between the carboxylate anions and the amide NH groups,

π–π stacking interactions, and the influence of *N*-tosyl protecting group that had a cooperative role in the complex formation.[110]

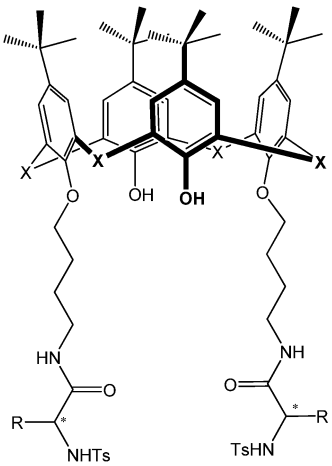
Structurally related with chiral receptors *p-tert*-butylcalix[4]arenes 1,3-difunctionalized are the chiral *p-tert*-butylcalix[4]arenes (**52a–e**) perfunctionalised at the lower rim with amino acid units.[112] The recognition properties of *N*-tosylated calix[4]arene derivative **52a** towards various anions, such as tetrabutylammonium chloride (K_{ass} = 4900 M^{-1}), bromide (K_{ass} = 3800 M^{-1}), dihydrogenphosphate (K_{ass} = 2300 M^{-1}), hydrogen sulfate (K_{ass} = 3700 M^{-1}) were investigated by ^{1}H NMR experiments in $CDCl_3$. This receptor forms 1 : 1 complexes in $CDCl_3$, confirmed by Job plots with all studied anions. Stronger complexation was observed for *N*-tosyl-(L)-alaninate and **52a**, characterized by a complex association constant K_{ass} = 6900 M^{-1} determined by the Benesi–Hildebrand method. It was also concluded that the tetra O-substituted calix[4]arene derivative is a more efficient receptor than the di-O-substituted calix[4]arene derivative. The enhancement of the association constants in the case of tetrasubstituted calix[4]arene derivatives was attributed by the authors to the free groups which could be available for the complexation because not all the hydrogen bond donors or acceptors were involved.



52a : R = Me (L-Ala)
52b : R = *i*-Pr (L-Val)
52c : R = CH_2Ph (L-Phe)
52d : R = *i*-Bu (L-Leu)
52e : R = $CH(CH_3)CH_2CH_3$ (L-Ile)

The chiral receptors peptido-calix[4]arenes **53** and thiacalix[4]arenes **54** grafted with amino acid units are able to discriminate the enantiomers of amino acid derivatives.[113] The introduction of amino acid moieties into the lower rim of calix and thiacalix[4]arenes, placed the chiral groups distant from the internal aromatic cavity of the calixarene core, which allowed secondary interactions with chiral guests. The rigid cone conformation of these receptors was investigated by ^{1}H NMR NOESY and ROESY experiments in order to elucidate the binding mode between the host and guest.

The NMR in $CDCl_3$ solutions at 300 K and mass spectrometry studies were carried out to disclose the supramolecular interactions involved in the enantioselective recognition of *N*-tosyl-amino acids (Val, Leu, and Phe). All receptors, **53a–b** and **54a–b**, formed stable 1 : 1 complexes with amino acids in $CDCl_3$ with moderate values of binding constants compared with those obtained for anionic guests,[110–112] which may be due to the rather weak hydrogen bonding interaction between the host and the guest. Receptors **53b**

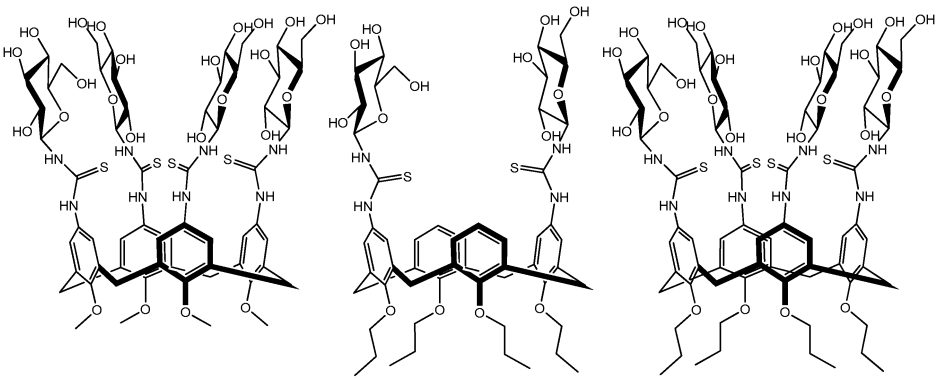


53a : X = CH_2, R = Me
53b : X = CH_2, R = *i*-Pr
54a : X = S, R = Me
54b : X = S, R = *i*-Pr

($K_{L-N-Ts-Phe}$ = 59 M^{-1}, $K_{D-N-Ts-Phe}$ = 47 M^{-1}, $K_{L-N-Ts-Leu}$ = 52 M^{-1}, $K_{D-N-Ts-Leu}$ = 56 M^{-1}, $K_{L-N-Ts-Val}$ = 59 M^{-1}, $K_{D-N-Ts-Leu}$ = 61 M^{-1}) and **54b** ($K_{L-N-Ts-Phe}$ = 50 M^{-1}, $K_{D-N-Ts-Phe}$ = 28 M^{-1}, $K_{L-N-Ts-Leu}$ = 42 M^{-1}, $K_{D-N-Ts-Leu}$ = 37 M^{-1}, $K_{L-N-Ts-Val}$ = 37 M^{-1}, $K_{D-N-Ts-Leu}$ = 42 M^{-1}), bearing valyl moieties, formed stronger complexes with all *N*-tosylated amino acids employed throughout the experiments. It is worth noting that the highest chiral discrimination was obtained with the receptor **54a** in the case of *N*-Ts-Leu ($K_{L-N-Ts-Leu}$ = 15 M^{-1}; $K_{D-N-Ts-Leu}$ = 31 M^{-1}, K_L/K_D = 0.48) and receptor **54b** in the case of *N*-Ts-Phe (K_L/K_D = 1.79). By replacing the methylene bridges with sulfur atoms into the calix[4]arene skeleton, the conformational behavior of thiacalixarenes changes.[114] Moreover, the thiacalixarenes exhibit higher flexibility in solution.[115] The shape of the receptor, the bulkiness of the guest, the ability to link through hydrogen bonding together with π–π stacking, influenced the value of the binding constant and the chiral recognition process. The chiral centre of the receptor was also involved in the recognition process.

The binding recognition of three glucosylthioureidocalix[4]arenes (**55–57**) towards α-amino acids (Phe, Trp, Tyr, Ser, Cys, Leu, and Asp) was studied by electrospray ionization mass spectrometry in negative mode.[116] The recognition studies were complemented by *ab initio* calculations. According to negative ion ESI-MS spectra, the diglucocalixarene **56** formed only singly charged $[M + Guest\text{-}H]^-$ complex ions with the amino acid while the tetraglycocalixarenes **55** and **57** formed double charged $[M + Guest\text{-}2H]^{2-}$ complex ions. In the case of Asp, the complexation was observed only with glucocalix[4]arenes (**55** and **56**).

The conformational and complexation properties of the receptors were dependent on the number of the glucose units at the upper rim and the length of the alkyl chains at the lower rim of the calixarene skeleton. All three glycocalixarenes exhibited preference towards aromatic amino acids, the complex formation being enhanced by the introduction of a polar H-bonding group to the side chain of the amino acid (Trp, Tyr, Phe ≫ Ser, Leu, and Asp). The affinities of **57** and **55** followed the order Trp > Tyr > Phe > Leu > Ser and Trp > Tyr > Phe > Ser > Leu, respectively. The side-chain H-bonding donor group containing Tyr was favoured over Phe. Tyr was also favoured over Ser in complexation, hence



55 56 57

the affinity of glycocalixarenes towards amino acids seemed to depend on the aromatic nature of the amino acid. Cysteine (thiol group in the side-chain) did not form any complexes with the receptors **55–57** which most likely results from the weak hydrogen donor nature of the SH group.[117] To conclude, the affinity of glycocalixarenes towards amino acids decreases with decreasing number of H-bonding groups, the strength of the H-bonding donor group and the aromatic nature of the amino acid. All glycocalixarenes favoured the L-enantiomer in complexation with Phe and Trp and D-enantiomer in complexation with Tyr. Enantiomeric selectivity (D/L ratio) was studied by competition measurements between D-amino acids Phe, Tyr, and Trp and their multiply deuterated L-amino acids (**55**: D/L-Phe = 0.66, D/L-Tyr = 1.34, D/L-Trp = 0.62; **56**: D/L-Phe = 0.78, D/L-Tyr = 2.58, D/L-Trp = 0.85; **57**: D/L-Phe = 0.61, D/L-Tyr = 1.17, D/L-Trp = 0.70). The type of residue and number of H-bonding groups on the guest are responsible for the inversion of the enantioselectivity observed for Tyr relative to Phe and Trp often reported in the literature.[118] Even though the enantioselectivity values obtained are moderate, they can be considered highly reliable.[119] The ESI-MS enantiomeric-labeling studies indicated that the enantiomeric selectivities span the range from 0.61 (D/L-Phe) with receptor **57** to 2.58 (D/L-Tyr) with receptor **56** which suggested that these types of glycocalixarenes could have a potential applications relevant to chiral recognition.

Concluding remarks

Although much work is currently devoted to the complexation of amino acids by calixarenes that provides the chemists with numerous data on the thermodynamics of complexation, very little is known on the specific interactions maintaining the complexes. A review has recently been published regarding the X-ray structure of such complexes in the crystal state.[79] However, most of the existing studies are focused on *p*-sulfonated-calixarenes.

Meaningful aspects of the functionalized calixarene binding towards amino acids and some di- and tripeptides investigated by different techniques have been presented in this review. It is worth mentioning that in most cases, the binding process is controlled by hydrogen bonding, van der Waals, cation-π, and π–π stacking interactions.

Particular attention has been paid to chiral recognition of amino acids by chiral calixarenes such as peptido- and glycocalixarenes. These compounds are characterized by the presence of hydrogen bonding moieties and apolar cavities, which allow them to form inclusion complexes with amino acids. The results obtained with respect to molecular recognition and enantioselectivity towards guests have been discussed from a thermodynamic point of view.

Special interest in *p*-sulfonated-calixarenes stems from their biological activities, as highlighted by Coleman[10] and Atwood.[77] These properties of *p*-sulfonato-calix[*n*]arenes may open up new future usage in medications after determining their toxicity, an issue which is currently in progress.[120]

Likewise, microchip-based calixarenes for the development of novel immunosensors with applications in clinical diagnostics have been studied.[121] Some related work has recently been published which presents potential applications of tetrakis-(dihydroxy-phosphorylmethyl) derivatives of calix[4]arene and thiacalix[4]arene displaying inhibition properties towards alkaline phosphatases from bovine intestine mucosa and shrimp and human placenta. The interaction modes of the calixarene derivatives with the adjacent amino acids of the shrimp alkaline phosphatise have also been analyzed.[122] Moreover, the involvement of calixarenes as synthetic ionophores in the challenging field of transmembrane ion transport has broadened their area of biochemical applications.[123]

Apart from their binding abilities to amino acids and peptides, the functionalized calixarenes are also able to act as extractants or transporters through membranes, performing separation of amino acids and peptides. Such a feature of calixarenes has also briefly been reviewed in the present contribution.

Acknowledgements

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