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REVIEW ARTICLE

Survey on thermodynamic properties for the complexation behaviour of some calixarene and cucurbituril receptors

Ana Delia Stancu · Hans-Jürgen Buschmann · Lucia Mutihac

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Abstract Some aspects of the complex formation reaction between amino acids, short peptides, and nucleobases with calixarenes and cucurbiturils in solution are presented. A brief survey of their stability constants, enthalpies, and entropies data obtained by different techniques in various solvents is reported, along with the ability of these receptors to be employed as carriers through liquid membrane in view of separating biological compounds.

Keywords Amino acids · Dipeptides · Nucleobases · Calixarenes · Cucurbiturils · Complexation

Introduction

Molecular recognition of relevant biomolecules with important role in biological systems by synthetic receptors is a challenging issue in host–guest and supramolecular chemistry [1–5]. Supramolecular chemists have designed and synthesized a wide variety of receptors with desired host–guest properties such as crown ethers, calixarenes, modified cyclodextrins, cucurbiturils, pillar[5]arenes, and so forth, which showed remarkable recognition by specific non-covalent interactions, sensing, transport, and separation properties towards specifically targeted guests [6–12]. Thus, the possibility to form complexes with biologically guest substrates like amino acids, peptides, proteins, and nucleobases constitute an important application in studying the interactions involved in host–guest complexation, as well as in analytical applications [13–17]. It is well-known that the study of binding constant of complex formation between receptor and substrate provides valuable information for investigation and characterization of molecular interactions [18, 19]. There are several techniques in usage performing thermodynamic data characterization of complexes, such as UV–Vis, NMR, mass spectrometry, potentiometry, fluorescence, conductometry, chromatography, electrophoresis, polarography, and calorimetry [20–24]. Due to their importance in chemical and biological systems, amino acids and small peptides as targets of interest in host–guest chemistry, have intensively been studied by means of several techniques. Particularly, their transport through liquid membranes highlighted the principle of their transport through biological membranes [25].

The present work is focused on recent studies on supramolecular properties of calixarenes and cucurbiturils pointing out their binding abilities towards some amino acids, nucleobases, and di- and tri-peptides. Moreover, their potential application as carriers in the transport through liquid membranes of some amino acids and peptides is shortly reviewed. Since numerous reports have been published on the topics, brief references only to some of them are following hereafter.

Complex formation of amino acids and short peptides with calix[*n*]arenes

Calix[*n*]arenes, obtained by phenol and formaldehyde condensation, along with cyclodextrins, crown ethers, and cucurbit[*n*]urils constitute attractive synthetic receptors

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involved in molecular recognition and transport through membrane, including channelling systems of various neutral and charged species like biological ones [26–29]. Various techniques have been employed to investigate the binding properties of calix[*n*]arenes with amino acids, biogenic amines, peptides, and nucleobases in solid state, gas phase, and solution, establishing the parameters which influence the complex formation. The overall conclusion was that the complexes of calix[*n*]arenes with amino acids were stronger that the corresponding inclusion complexes of cyclodextrin and crown ethers with amino acids and the ammonium cation inserted in the hydrophobic cavity of calix[4]arene [30]. Atwood et al. [31] have reported based on the studies in solid state that water soluble sulfonate calix[6]arene presented a double partial cone conformation in the case of complex formation with ammonium cation. In addition, other interesting biological compounds, such as choline and acethylcholine, also form stable complexes with calixarenes [32, 33].

The binding properties of calixarene carboxylic acid derivatives for recognition of aromatic amino acids (L-tryptophan methyl ester, L-phenyalanine methyl ester, and L-tyrosine methyl ester) studied by ^{1}H NMR spectroscopy in $CDCl_3$ solution, liquid–liquid extraction, and transport through chloroform liquid membrane reported by Oshima et al. [34, 35] suggested that calix[6]arene carboxylic acid formed a strong complex with protonated amino group, $R-NH_3^+$. An important finding of this study was that calixarene derivatives could be used as carriers through liquid membrane for amino acids separation. In related studies, Oshima et al. [36] reported better adsorption affinity by electrostatic interactions of calix[6]arene derivative impregnated resins towards amino acid derivatives as compared with calix[4]arene, and that the hydrophobicity on the amino acids was responsible for adsorption selectivity. It was noticed by the authors that, for the recovery of biomolecules, this method was more efficient than solvent extraction. By using aromatic amino acids as model of pharmaceutical pollutants, their preconcentration by means of solid–liquid extraction using calixarene carboxylic acid derivatives and their photocatalytic degradation in the presence of TiO_2 was carried out [37]. The influence of pH on the degradation showed a small decrease of amino acid concentration, while the rate of photocatalytic degradation was largely correlated with the initial concentration of the amino acid.

The special biological properties of water soluble calix[*n*]arenes render them prospective receptors for biomolecules with useful applications in biomedical area [38]. The binding abilities of *p*-sulfonatocalix[*n*]arenes, $n = 4, 6, 8$ to form inclusion complexes with amines, amino acids, and di- and tri-peptides investigated in water by different techniques, and in solid state by X-ray methods, have recently been reviewed [22], revealing the influence of host and guest structure, pH, solvent, and buffer solutions on the complex formation. In solid state, it was established that the hydrogen bonds together with C–H···O, C–H···π, and π–π interactions could be responsible for host–guest complex formation. As mentioned before, the complexation properties of water soluble calixarenes $n = 4, 6, 8$ towards some aromatic and aliphatic amino acids, as well as di- and tri-peptides in aqueous solution, have extensively been investigated by ^{1}H NMR spectroscopy, calorimetric, and microcalorimetric titrations, and molecular computer simulations by different research groups. In this respect, from ^{1}H NMR titration experiments in D_2O at $pD = 7.3$, Arena's group [39] has reported that the complex formation between α-amino acids and *p*-sulfonatocalix[4]arene was possible by including the aromatic or aliphatic group of amino acid into the hydrophobic cavity of calixarene [39]. Thus, the values of association constant was found to pertain to an interval ranging from $K_{ass} = 16\ M^{-1}$ (L-Val) to $K_{ass} = 63\ M^{-1}$(L-Phe).

The peptidocalixarenes obtained by Ungaro's research group, linking amino acids or peptides to the calixarene scaffold, either through the amino or carboxylic acid group, and obtaining N-linked **1** or C-linked **2** (Fig. 1), respectively, with the ability to form inclusion complexes with amino acids, enhanced the number of calixarene receptors with special recognition properties [40].

The stability constants (log *K*), the reaction enthalpy (ΔH) and entropy (ΔS) of the complexes formed between a series of amino acids and di-, and tri-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) with *p*-sulfonatocalix[4]arene and hexasodium *p*-sulfonatocalix[6]arene (Table 1) in aqueous solutions by means of calorimetric titrations have been studied by Buschmann et al. [41]. The conclusion drawn was that the complex formation was favored by enthalpic effects, whereas no selectivity was observed during these experiments. The complexation properties of calix[4]arene having two α-hydroxyphosphonic acid

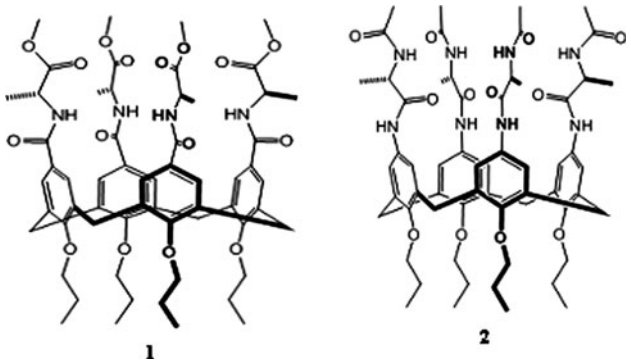

Fig. 1 The chemical structure of the peptidocalixarenes **1** and **2**

Table 1 Stability constants log K (K in M^{-1}) and thermodynamic values ΔH and $T\Delta S$ for the complexation of some peptides by hexasodium *p*-sulfonatocalix[*6*]arene in aqueous solution at 298.15 K [41]

Peptides	log K	$-\Delta H$ (kJ mol^{-1})	$T\Delta S$ (kJ mol^{-1})
Gly-Gly	3.30 (0.02)	43.6 (0.9)	−24.7 (1.8)
Gly-L-Ala	3.47 (0.04)	38.2 (1.2)	−18.4 (2.2)
Gly-L-Val	3.21 (0.01)	40.7 (1.7)	−22.4 (1.9)
Gly-L-Leu	3.19 (0.03)	60.6 (0.8)	−42.4 (2.4)
L-Leu-Gly	3.21 (0.02)	49.0 (1.3)	−30.7 (2.0)
L-Leu-L-Ala	3.16 (0.01)	52.7 (1.4)	−34.7 (1.6)
Gly-L-Phe	3.28 (0.02)	46.9 (1.1)	−28.1 (1.1)
Gly-Gly-Gly	3.25 (0.04)	47.9 (0.7)	−29.3 (1.7)
L-Leu-Gly-Gly	3.22 (0.03)	52.7 (1.5)	−34.3 (2.0)

Table 2 Thermodynamic parameters for the 1:1 and 2:1 guest–host complexation of amino acids with calixarene **3** in methanol at 298.15 K [42]

Host–guest ratio	log K (M^{-1})	ΔH^0 (kJ mol^{-1})	$T\Delta S^0$ (kJ mol^{-1})
Gly			
1:1	3.84	−10.55	11.39
2:1	2.87	2.24	18.69
Ala			
1:1	3.89	−8.54	14.02
2:1	2.93	2.13	19.00
Val			
1:1	4.12	−7.53	16.29
2:1	3.00	1.67	19.25
Leu			
1:1	4.19	−8.87	15.41
2:1	3.15	1.67	19.80
Ile			
1:1	4.23	−7.36	17.74
2:1	3.20	2.73	21.17

moieties at upper rim with some amino acids and di-peptides by means of calorimetric titrations, NMR titrations, and UV measurements in methanol solution, have been reported by Zielenkiewicz et al. [42, 43].

It was proved that the complexation of calix[4]arene *bis*-hydroxymethylphosphorous acid **3** (Fig. 2) with glycine, L-alanine, L-valine, L-leucine, and L-isoleucine was controlled by the direct electrostatic interaction formed between negatively charged calixarene phosphoryl group and the protonated amino group, NH_3^+ (Table 2). The stability of the inclusion complexes was found to be correlated with the size of the aliphatic amino acid side-chain. For analogous compounds, where the phosphonate group was bound directly to the aromatic ring, strong complexation was observed for the basic amino acids [43].

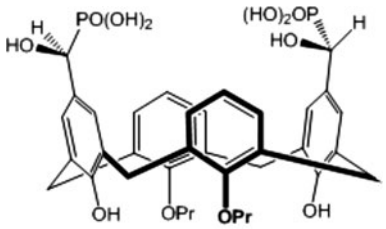

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Fig. 2 The structure of calixarene **3**

Spectrofluorimetric titrations were carried out to evaluate the stability constants, binding ratio, reaction enthalpy and entropy of sulfonatocalix[4]arene complexation with L-tryptophan in aqueous solutions [44]. The findings indicated that the fluorescence intensity of the L-Trp decreased during the addition of receptor, followed by bathochromic/red shifts. By means of ^1H NMR measurements, it was established that benzene ring of L-tryptophan was partially inserted into the calixarene cavity. The authors suggested a combination of hydrophobic and electrostatic interactions involved in forming this complex.

Taking into account the involvement of DNA molecules in anticancer drugs, Breitkreuz et al. [45] have studied the DNA recognition with large calixarene dimers, pointing out the possibility to evaluate the influence of amino acids and heterocycles on DNA affinity and selectivity. Along a similar line of reasoning, by using *p*-sulfonatocalix[4]arene as receptor for lysine and its methylated derivatives, Beshara et al. [46] have reported an increase in affinity for lysine derivatives with increasing of side chain methylation. Thus, it was found that the affinity of *p*-sulfonatocalix[4]arene for Lys(Me_3) was at least 30-fold higher than dimethylated arginine. Such studies are particularly relevant to biochemical applications.

Recently, an interesting review highlighting the biomolecular recognition of calixarenes such as small peptides and carbohydrates to ion transport through membranes, biomimetic catalysis, DNA condensation and cell transfection, protein binding, sensing and inhibition has been reported by Sansone et al. [17]. Thus, they disclosed the synthetic versatility of calixarenes, the possibility of controlling their conformational properties and their multivalent nature.

Calixarenes as carriers through liquid membrane

There are numerous studies dedicated to the usage of calixarenes and their derivatives as carriers through liquid membranes, starting with the first report on transport of amino acid derivatives due to Chang et al. [47], and continuing with their incorporation in synthetic ion channels studied by remarkable research groups [25–28, 48, 49] with several applications in separation science, drug

delivery, sensing, nanoscience, and clinical analysis [50–56]. Recently, aspects concerning the properties of functionalized calix[*n*]arenes to form complexes, to act as extractants in solvent extraction, and even as carriers of different biological amino compounds (e.g., ammonium ion, amines, amino acids, and peptides) through liquid membranes have been reported [5].

The selective active transport through liquid membrane assisted by pH gradient of amino acid methyl esters by means of functionalized calix[4]arene (**4–8**, Fig. 3) in the cone conformation varyingly substituted by acid or amido functions, glycolic chains and hydroxyl groups as carriers, indicated the following sequence of the decreasing transport yields of amino acids: L-TrpOMe > L-PheOMe > L-TyrOMe [57]. The receptors bearing diacid **4** and tetra-amido **8** exhibited high transport yields towards L-tryptophan (98% with **4** and 87% with **8**) and L-phenylalanine (88% with **4** and 86% with **8**). All receptors **4–8** exhibited poor transport behavior towards L-TyrOMe. It was clearly evidenced that the functional groups attached to calix[4]-arene enhanced the recognition properties of calix[4]arene towards amino acids as compared with those corresponding to parent calix[4]arene.

The calixcrowns receptors [58, 59] have been developed starting with the work of Ungaro and coworkers [60], which synthesized for the first time calixcrown carrying bridging polyethylenoxy moieties on the lower rim.

The solvent extraction and the transport through liquid membrane of some native and methyl esters amino acids with calix[4]azacrowns **9** (1,3-[ethylene-bis-aminocarbonylmethoxy)]-*p*-tert-butylcalix[4]arene, Fig. 4) and **10** (1,3-[propylene-bis-aminocarbonylmethoxy)]-*p*-tert-butylcalix[4]arene, Fig. 4) demonstrated that receptors **9** and **10** can be employed in the separation of amino acids [61]. The structure of calixarenes, the structure of amino acids, and the nature of anion used as counter ion significantly influenced the extraction and transport experiments. Thus, the calix[4]azacrown (**10**) with an additional methylene group in the bridging chain, exhibited higher ability as

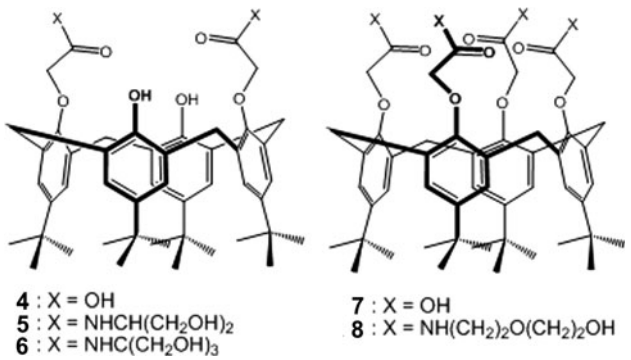

Fig. 3 The chemical structure of the calixarene derivatives **4–8**

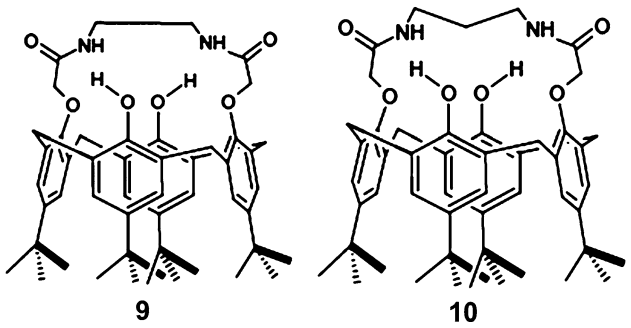

Fig. 4 Calixcrown receptors **9** and **10**

extractant compared with calix[4]azacrown (**9**) for the amino acids under study. Demirtas et al. [62] have studied the chiral recognition of amino acid methyl esters with chiral calix[4]azacrown derivatives highlighting that π–π stacking, multiple hydrogen bonding, steric hindrance, and the structural properties were involved in molecular recognition. Morever, the same authors reported the transport of some amino acid derivatives (phenylglycine, phenylalanine and tryptophan metyhyl ester hydrochlorides) and mandelic acid through a bulk liquid membrane by using chiral calix[4]arene bearing aminonaphthol moieties as carriers. The results indicated that the receptors with hydrogen bonding sites and aromatic groups proved better transport rates and enantioselectivity towards amino acids [63].

Recently, calixarenes have been employed in construction of new nanomaterials on the basis of their ability to participate in self-assembly processes [64–67]. Likewise, calixarenes proved to act as efficient surfactants, which were able to enhance the dispersion and self-assembly of metal nanoparticles [66]. Further developments of optical nanoparticles involved in biochemical applications based on the association of gold, silver, silica and quantum dots and calixarenes have been reported [68–71]. Moreover, calixarene-based fluorescent sensing systems for choline and acetylcholine and their application to enzymatic reactions have been reported by Guo et al. [72].

Complex formation of amino acids and peptides with cucurbiturils

Behrend et al. [73] have reported for the first time in 1905 the synthesis of cucurbit[6]uril by condensation reaction of glycoluril and formaldehyde during an acid-catalysed reaction. The structure and its properties have been determined by Mock et al. [74, 75]. The forces involved in binding of molecular guests by cucurbit[6]uril are a combination of electrostatic interactions with the carbonyl rims and hydrophobic interactions with the inner cavity. In recent years, the family of cucurbituril, **11** (Fig. 5) has been enhanced with several functionalized cucurbit[*n*]urils $n =$

5–8, 10, fluorescent cucurbiturils, nor-*sec*-cucurbit[10]uril, and hemicucurbit[*n*]urils $n = 6$, **12** (Fig. 5) [76–82].

Cucurbit[*n*]urils possess a relatively rigid structure and its hydrophobic cavity is accessible by two polar portals formed by carbonyl groups. The development of new water-soluble homologues and derivatives has generated many applications in the areas of supramolecular chemistry, which include sensors, molecular recognition, drug and gene carriers, catalysts, separation, nanomaterials, and others [83–85]. Recently, Scherman and coworkers [86] have reported a gold nanoparticle-polymer composite material in water using cucurbit[8]uril (CB[8]) to hold together viologen functionalized gold nanoparticles and a naphthalene-functionalized acrylamide copolymer. Briefly, they are new synthetic receptors with various cavities and portal sizes, having good solubility in common solvents (with the exception of cucurbit[6]uril) and specific molecular recognition properties [87–93].

The thermodynamics and kinetics of host–guest chemistry of cucurbit[*n*]urils have constituted the topics of many studies [87, 93, 94]. Moreover, the geometry, electronic properties, and NMR-shielding of cucurbit[5]uril, decamethylcucurbit[5]uril, cucurbit[6]uril, cucurbit[7]uril, and cucubit[8]uril have been investigated by density functional theory (DFT) calculations [95]. Buschmann et al. [96, 97] (Table 3) reported a thermodynamic study of complex formation of some amino acids (L-phenylalanine, L-alanine, L-valine, glycine, 4-amino butyric acid, 5-amino pentanoic acid, 6-amino hexanoic acid, 8-amino octanoic acid), dipeptides (glycyl-phenylalanine, glycyl-glycine, glycyl-leucine, and glycyl-valine), and cucurbit[6]uril in aqueous formic acid solutions (50% v/v). The ion-dipole interactions were involved in the complex formation and the complexation was favored by enthalpic and entropic contributions. For the native amino acids, these interactions are lowered due to the electrostatic repulsion between the carboxylic groups and the carbonyl groups of cucurbit[6]uril.

Continuing their studies on the host–guest complexation of biological compounds by cucurbit[*n*]urils, $n = 6$, 7, Buschmann et al. [98, 99] have reported a thermodynamic study on complex formation of cucurbit[6]uril with short polypeptides [98] and cucurbit[*n*]urils, $n = 6$, 7 with 11-aminoundecanoic acid [99]. A few studies only have been published so far concerning the molecular recognition of peptides by cucurbit[*n*]urils [100–102]. By means of calorimetric titrations in acidic aqueous solution due to the low solubility of cucurbit[6]uril in water, the stability constants and thermodynamic values of the complex formation between the following peptides: glycyl-L-alanine, L-leucyl-L-valine, glycyl-L-asparagine, L-leucyl-L-phenylalanine, L-leucyl-L-tryptophan, glycyl-L-histidine, L-glutathione reduced (γ-L-glutamyl-L-cysteinyl-glycine, GSH), and DL-leucyl-glycyl-DL-phenylalanine) with cucurbit[6]uril in aqueous formic acid (50%, v/v) have been reported (Table 4) [98]. The values of the stability constants did not show differences for the peptides under study and the reaction entropies were nearly constant for all peptides. The formation of exclusion complexes may explain the obtained results (Fig. 6).

Table 3 Stability constants log K (K in M^{-1}) and thermodynamic values ΔH and $T\Delta S$ for the complexation of some amino acids by cucurbit[6]uril in formic acid (50%, v/v) at 298.15 K

Amino acids	log K (M^{-1})	$-\Delta H$ (kJ mol^{-1})	$T\Delta S$ (kJ mol^{-1})
L-Phe [97]	3.16	6.7	11.3
L-Ala [97]	3.02	7.0	10.2
L-Val [97]	3.15	4.5	13.4
4-amino butyric acid [98]	3.40	8.6	10.7
5-amino pentanoic acid [98]	3.59	9.9	10.5
6-amino hexanoic acid [98]	3.57	12.0	8.4
8-amino octanoic acid [98]	3.27	12.2	6.4

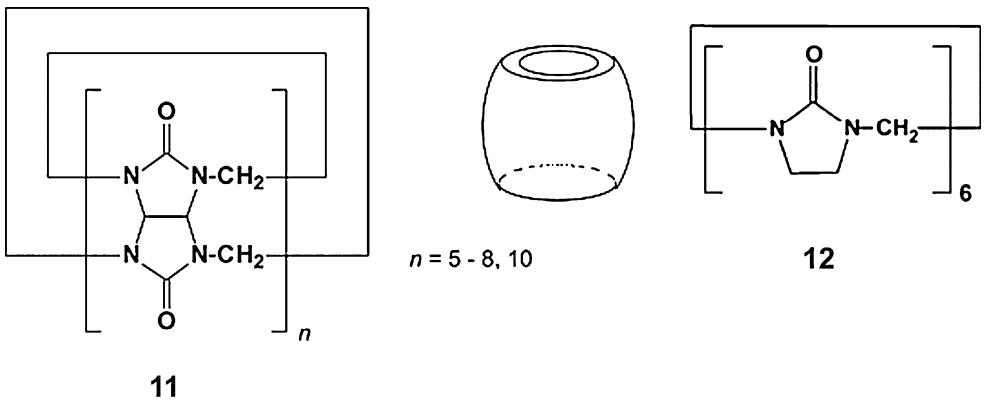

Fig. 5 Cucurbit[*n*]uril **11** and hemicucurbituril **12**

Table 4 Stability constants log K in and thermodynamic values ΔH and $T\Delta S$ for the complex formation of peptides with cucurbit[6]uril in aqueous formic acid (50% v/v) at 298.15 K [98]

Peptide	*log K* (M^{-1})	$-\Delta H$ (kJ mol^{-1})	$T\Delta S$ (kJ mol^{-1})
Gly-L-Ala	2.80 (0.03)	2.4 (0.1)	13.5 (0.2)
L-Leu-L-Val	2.79 (0.01)	2.1 (0.3)	13.7 (0.2)
Gly-L-Asn	2.82 (0.03)	3.2 (0.5)	12.9 (0.7)
L-Leu-L-Phe	2.78 (0.02)	3.2 (0.3)	12.7 (0.4)
L-Leu-L-Trp	2.92 (0.12)	3.6 (0.4)	13.1 (0.3)
Gly-L-His	2.79 (0.01)	4.8 (0.3)	11.2 (0.3)
L-Glutathione reduced (GSH)	2.74 (0.01)	2.4 (0.1)	13.3 (0.1)
DL-Leu-Gly-DL-Phe	2.80 (0.02)	4.9 (0.1)	11.1 (0.1)

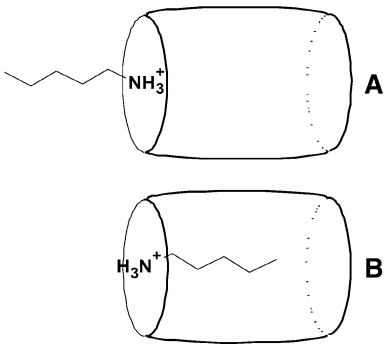

Fig. 6 Schematically presentation of the formation of an exclusion complex (**a**) and an inclusion complex (**b**) between cucurbit[*6*]uril and an protonated alkylamine [98]

The formation of 1:1 complexes of cucurbit[6]uril and cucurbit[7]uril, **13** (Fig. 7) with 11-aminoundecanoic acid has been carried out by means of calorimetric and potentiometric titrations (Table 5).

The values of the stability constants obtained by potentiometric titrations in aqueous solution and by calorimetric titrations in aqueous formic acid (50% v/v) were very close even though there were differences in the solvent composition and the complex formation was characterized by entropic effects. On the basis of these results, it was concluded that the number of solvent molecules released during the complex formation was quantitatively similar for both receptors. Further, some studies evidenced that cucurbit[6]uril exhibited strong interactions with water molecules [103, 104].

Isothermal titration calorimetric (ITC) studies in water on the complexation of cucurbit[7]uril with several zwitterionic di-peptides containing Phe, Tyr or Trp residue (Table 6), showed that the affinity of di-peptides with an aromatic moiety at the N-terminus was much higher than the affinity of di-peptides with an aromatic moiety at the C-terminus [100]. Selective complexation of CB[7] with

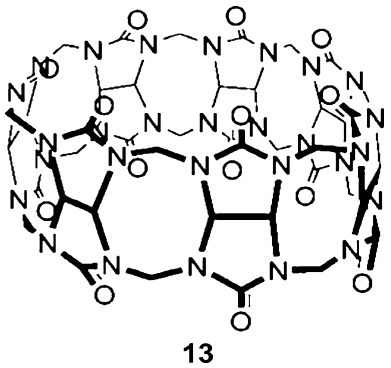

Fig. 7 The chemical structure of the cucurbit[*7*]uril **13**

Table 5 Stability constants log K and thermodynamic values ΔH and $T\Delta S$ for the complex formation of 11-aminoundecanoic acid with different receptors in aqueous solution at 298.15 K [99]

Ligand	log K (M^{-1})	$-\Delta H$ (kJ mol^{-1})	$T\Delta S$ (kJ mol^{-1})
CB[6]	2.65(0.04)[a]	2.3(0.1)[b]	12.9(0.2)[b]
	2.68(0.04)[b]		
CB[7]	2.47(0.12)[a]	6.1(0.9)[b]	9.2(0.4)[b]
	2.69(0.01)[b]		

[a] From pH-metric titrations in aqueous solution

[b] From calorimetric titrations in aqueous formic acid (50% v/v)

Table 6 Stability constants (K), standard enthalpies (ΔH^0) and entropy changes (ΔS^0) for the complexation of selected di-peptides with cucurbit[7]uril in water at 298.15 K [100]

Dipeptide	K (M^{-1})	$-\Delta H^0$ (kJ mol^{-1})	$-T\Delta S^0$ (kJ mol^{-1})
Phe-Gly	$(3.0 \pm 0.4) \times 10^7$	47.4 ± 0.5	4.7 ± 0.5
Gly-Phe	1300 ± 200	29.9 ± 0.3	12.2 ± 0.4
Tyr-Gly	$(3.6 \pm 0.2) \times 10^6$	44.1 ± 0.4	6.7 ± 0.4
Gly-Tyr	200 ± 20	23.1 ± 0.2	10.2 ± 0.3
Trp-Gly	$(5.6 \pm 0.2) \times 10^5$	44.6 ± 0.4	11.9 ± 0.4
Gly-Trp	280 ± 25	18.1 ± 0.2	4.3 ± 0.3

Aryl-Gly (Aryl = Phe or Tyr), which formed much stronger complexes by including the guest aromatic group in the cucurbituril cavity and by the electrostatic interactions between ammonium group and the carbonyl oxygens of the cucurbituril portal than Gly-Aryl guest was observed. These host–guest interactions were confirmed by ^{1}H NMR measurements. The complexes of di-peptides with an aromatic moiety at the N-terminus CB[6] were weak, instead strong interactions with the peptides bearing aliphatic residue such as Lys at the N-terminus were noticed [100].

Table 7 Thermodynamic binding data of complex formation between amino acids and both hosts cucurbit[8]uril·methyl viologen and cucurbit[8]uril [101]

Amino acid	CB[8]·methyl viologen + amino acids K_a (M^{-1})[a]	CB[8] + amino acids K_{ter} (M^{-2})[b]
Trp	4.3 (±0.3) × 10^4	6.9 (±1.3) × 10^7
Phe	5.3 (±0.7) × 10^3	1.1 (±0.2) × 10^8
Tyr	2.2 (±0.1) × 10^3	$<10^3$ M^{-1}
All 17 others	No binding obs.	No binding obs.

[a] Ref. [105]

[b] ITC experiments at 300.15 K

A remarkable study on binding amino acids by cucurbit[8]uril and cucurbit[8]uril methyl viologen at 1:1 ratio in purely aqueous solution by ^{1}H NMR spectroscopy and isothermal titration calorimetry has been reported by Urbach and coworkers [101, 105]. Both receptors manifested high selectivity for aromatic amino acids tryptophan, phenylalanine, and tyrosine. The receptor CB[8], together with methyl viologen, showed significant selectivity for recognition of N-terminal tryptophan in water [105]. In this case, ternary complexes were formed and electrostatic interactions of terminal peptide ammonium groups (Gly-Gly-Trp) or free amino acid with carbonyl groups of CB[8] were involved (Table 7).

Cong et al. [106] have studied the interactions of some aromatic amino acid hydrochlorides with cucurbit[*n*]urils, $n = 7$, 8 by means of ^{1}H NMR and UV–Vis titrations. They noticed that cucurbit[7]uril exhibited affinity towards aromatic moiety of the aromatic amino acids and the complex formation had a 1:1 (amino acid:cucurbit[7]uril) stoichiometry.

Nau and coworkers [107, 108] have introduced a supramolecular tandem enzyme assay method for the determination of amino acids enantiomeric excess like of up to 99.98% for D-lysine. Thus, they combined the generality of CB[7] encapsulation with the selectivity and enantiospecificity of enzymatic reactions. CB[7] was used to complex a dye by monitoring the fluorescence change accompanying the enzyme decarboxylation of the amino acid to determine D-lysine enantiomeric excesses. The stability constants and the thermodynamic values for the complex formation between CB[7] with amino acids and their decarboxylated products were determined by means of isothermal titration calorimetry and competitive fluorescence titrations employing Dapoxyl as an indicator fluorescent dye. The values of amino acids binding constants had 2–4 orders of magnitude lower affinity to CB[7] than their decarboxylation counterparts.

The inclusion interactions of cucurbit[7]uril with adenine, adenosine, and 2′,3′-*o*-isopropylideneadenosine studied by ^{1}H NMR spectroscopy, UV absorption spectroscopy, fluorescence spectroscopy and high performance liquid chromatography revealed the selective affinity of receptor towards adenine [109]. By investigation the pH effects, it was established that the optimal pH range was between 2 and 4, and the values of formation constants obtained with UV and fluorescence measurements, 1.90 and 1.34 × 10^5 L mol^{-1}, respectively, and 6.76 × 10^4 L mol^{-1} by high performance liquid chromatography for cucurbit[7]uril and adenine. The authors suggested the ability of cucurbit[7]uril to act as receptor for the delivery of biological species [109]. By using CB[7] and the fluorescent dye acridine orange, Ghale et al. [110] have developed an analytical method for the continuous monitoring of protease activity on unlabeled peptides in real time by fluorescence spectroscopy.

Conclusion

The molecular recognition of bioactive species such as amino acids and peptides by some synthetic receptors with special properties is a current topic in the field of supramolecular chemistry with several applications of interest in analytical chemistry. In this short overview, some aspects concerning the key factors that are likely to influence the complexation of some amino acids, adenine, and di- and tri-peptides with calixarenes and cucurbiturils were presented in the light of recent publications. As such, stability constants and thermodynamic data for the complexation of amino acids and peptides with calixarenes and cucurbiturils obtained by means of different techniques were discussed. The bottom line was that the structure, the physico–chemical properties of the complexes, and the selectivity in complexation depend on the macrocyclic receptor size, the nature and position of the donor atoms of a receptor, the binding type, and the solvent nature. The abilities of these receptors to be employed as carriers through liquid membrane aiming to amino acids and peptides separation were briefly presented in correlation with the separation and purification of biological compounds.

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