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Complexation of Native L-α-Aminoacids by Water Soluble Calix[4]arenes

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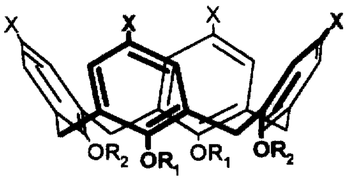
Abstract. The aromatic or aliphatic residue of native L-α-aminoacids is selectively included into the hydrophobic cavity of water soluble calix[4]arene receptors. The association constants values are determined by ^{1}H NMR titration experiments and the binding process is further elucidated by preliminary Molecular Mechanics calculations, which give results fully consistent with the NMR data.

Keywords: calixarenes, α-aminoacids, molecular recognition, molecular modeling.

The selective recognition of organic substrates of biological interest, such as sugars and amino acids, by synthetic receptors is a topic of current interest in supramolecular and bioorganic chemistry.[1] Of particular relevance are the studies performed in water, where most of the biological processes take place. Water soluble cyclophanes[2] and calixarenes[3-7] have been used, in the past, for the inclusion of charged and uncharged guest species, but very few synthetic receptors which complex amino acids in aqueous solution have been reported.[8] On the contrary, the inclusion of these guests in natural cyclodextrins has been extensively studied.[9]



1 $X = SO_3H$, $R_1 = R_2 = H$
2 $X = SO_3H$, $R_1 = R_2 = CH_2COOH$
3 $X = H$, $R_1 = R_2 = CH_2COOH$
4 $X = SO_3H$, $R_1 = H$, $R_2 = CH_2CH_2OCH_2CH_3$
5 $X = SO_3H$, $R_1 = R_2 = CH_2CH_2OCH_2CH_3$

The conformationally mobile tetrasulphonatocalix[4]arene **1** is able to form inclusion complexes with several charged and uncharged guest species both in the solid state[10,11] and in water.[4] In particular it has been shown[4] that **1** is able to complex trimethylanilinium ion (TMA) in an unselective fashion at pD = 7.3. A very high selectivity in the recognition of this charged guest species was obtained with hosts **2** and **3** both fixed in the *cone* conformation.[6] Compound **3**, which lacks the sulphonate groups at the upper rim was able to recognise selectively the trimethylammonium head group of TMA, whereas compound **2** complexed the aromatic moiety of this guest. A different behaviour between these two hosts

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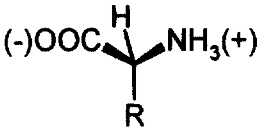
was also observed in the inclusion of ethanol in aqueous solution.[7] All these data allowed us to establish the crucial role played by the upper rim sulphonate groups in assisting the guest inclusion in the calixarene apolar cavity.



R (aliphatic):
L-Ala, L-Val, L-Leu.
R (aromatic):
L-Phe, L-Tyr, L-His, L-Trp

We have now extended these studies to L-α-aminoacids as guests, using compounds **1-5** as hosts. The synthesis of the conformationally mobile compound **1**[4] and compounds **2, 3, 5**,[12] blocked in the *cone* conformation, was previously reported. Compound **4**[13] will be reported elsewhere. The molecular inclusion properties of these hosts towards several amino acids was studied in D_2O by ^{1}H NMR at pD = 7.3. The complexation of the α-aminoacids occurs by inserting the aromatic or aliphatic apolar group (R) into the calixarene cavity. This seems to be determined by the need for the charged groups of the amino acids to stick out of the apolar calixarene cavity in order to be exposed to polar medium. As an example of inclusion, we report in Figure 1 the observed changes of chemical shifts of L-Phe induced by the complexation with host **2**. Upon inclusion both the H_{para} and the H_{meta} aromatic ring protons of the guest experience a remarkable upfield shift as compared with the free guest owing to the ring current effect of the aromatic nuclei of the host. The binding constants were obtained by ^{1}H NMR titration experiments run by keeping the guest concentration fixed (1 x 10^{-3} mol dm^{-3}) and allowing the host concentration to vary. The proton upfield shifts were treated by using a non-linear least-squares fitting procedure.[14] Association constants and binding free energies are reported in Table 1. To the best of our knowledge the present data are the first values ever reported for the complexation of native L-α-aminoacids by water soluble calixarenes. Interestingly L-Ala is not complexed by hosts **1-5**. One possible explanation is that, owing to the small size of the R methyl group, the inclusion of the L-Ala would involve also the encapsulation of the amino acid charged groups inside the hydrophobic cavity. No inclusion is observed for L-Tyr either, very likely owing to the polarity of the R group.

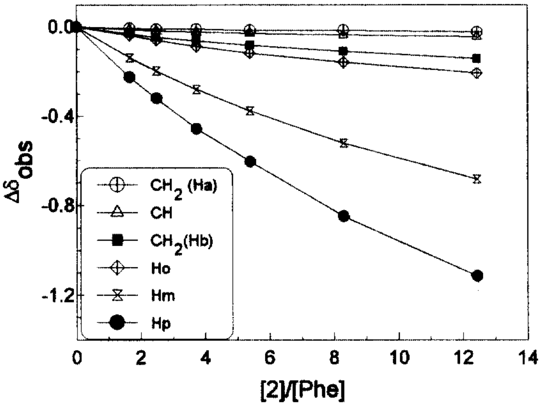


Figure 1.Plots of $\Delta\delta_{obs}$ (ppm) versus [2]/[L-Phe], in D_2O, 25 °C, [L-Phe] = 1 x 10-3 mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer).

The analysis of the data reported in Table 1 reveals some striking but interesting results. First of all, compound **3**, which lacks the sulphonate groups at the upper rim, does not complex any of the investigated amino acids. This result confirms the importance of charge assistance in the apolar binding of guests inside calixarene cavities.[5-7] However, host **5**, which has four sulphonate groups at the upper rim, shows no inclusion ability at all. L-His is complexed only by the conformationally mobile compound **1**, whereas compound **4** complexes neither L-Val nor L-His, therefore showing less efficiency towards the investigated amino acids. The most efficient receptors for all the amino acids are the sulphonatocalix[4]arenes **1** and **2**, which show comparable efficiency, although the *cone* compound **2** is slightly more efficient in the recognition of L-Leu.

Table 1.

Association constants K (M^{-1}) and binding free energies ($\Delta G°$, in kJ mol^{-1}) for complexes between L-α-aminoacids and hosts 1, 2 and 4 (pD = 7.3; 25°C). No complexation is observed for 3 and 5.

Complex	K	-ΔG°	Complex	K	-ΔG°	Complex	K	-ΔG°
1-L-Val	16(1)	6.8(5)	2-L-Val	10(1)	5.7(5)	4-L-Val	no inclusion	no inclusion
1-L-Leu	50(4)	9.7(5)	2-L-Leu	79(7)	10.8(5)	4-L-Leu	8(1)	5.1(5)
1-L-Phe	63(5)	10.3(5)	2-L-Phe	50(4)	9.7(5)	4-L-Phe	25(2)	8.0(5)
1-L-His	20(1)	7.4(5)	2-L-His	no inclusion	no inclusion	4-L-His	no inclusion	no inclusion
1-L-Trp	25(2)	8.0(5)	2-L-Trp	20(1)	7.4(5)	4-L-Trp	10(1)	5.7(5)

[a] σ in parentheses

The very striking difference between the complexing behaviour of hosts **1**, **2**, **4** and host **5**, can be explained on the basis of preliminary Molecular Modeling results obtained by MM+ optimisation. All free ligands have a C_{2v} elongated shape,[6,15-17] with two opposite benzene rings pointing inwards to maximise the π-π interaction and the other two benzene rings pointing outwards. The capability of these hosts to include the investigated amino acids decreases from **1** to **5** paralleling the C_{2v} elongation of the cavity. Host **1** has a more spherical cavity (Figure 2a) whereas in host **5** the lower rim substituents are diverging (Figure 2b) and this causes the cone to be very elongated and somehow less accessible; in fact none of the investigated amino acids is able to enter its cavity.

Since in all cases inclusion occurs via an aliphatic or aromatic apolar residue, very likely the

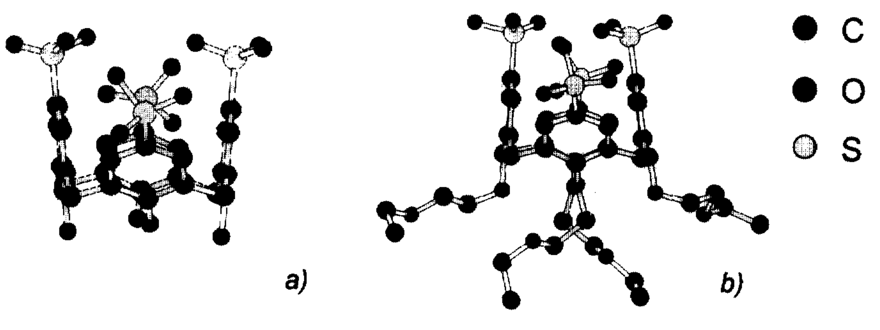


Figure 2. Optimised structures (Molecular Mechanics[20]) in water generated for *a)* host **1**; b) host **5**. Hydrogen atoms are omitted for clarity.

inclusion of the amino acids is due either to CH-π interactions[18] (L-Val and L-Leu) or to π-π interactions[19] (L-Phe, L-His, L-Trp).

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