

Recognition and Binding of Aliphatic Dicarboxylic Acids C4 – C10 by Diiminocalix[4]arene

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Host-Guest complexation of 5,17-bis-(N-tolyliminomethyl)-25,27-dipropoxycalix[4]arene with aliphatic dicarboxylic acids C4 – C10 has been studied in water-organic solution by the RP HPLC and molecular modeling methods. The stability constants ($\log K_A = 2.56 - 3.05$) of the supramolecular complexes are depended on structure, pK_a and $\log P$ values of the acids. The complexation is determined by the hydrogen bonds of the COOH group of the dicarboxylic acids with nitrogen atoms at the upper rim or oxygen atoms at the lower rim of the calixarene.

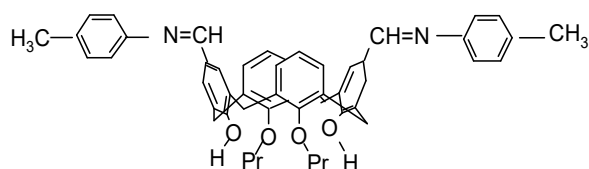
Introduction

Molecular recognition and binding of bio active compounds by artificial receptors constitute an important problem in chemistry and biology [1].

Calixarenes [2] bearing preorganized binding groups at the upper or the lower rim of macrocycle recognize different bio relevant molecules or ions and simulate substrate-receptor interactions in bio-chemical processes [3,4]. The receptor properties of the functionalized calixarenes toward the bio active molecules make them promising materials for sensor technologies [5-7] and for

drug delivery systems in pharmaceutical science [8,9].

Formerly it was shown that the functionalized calix[4]arenes are effective receptors for aromatic carboxylic acids [10]. The aim of this work is investigation of the Host-Guest complexation of the 5,17-bis-(N-tolyliminomethyl)-25,27-dipropoxycalix[4]-arene (CA) with the aliphatic dicarboxylic acids C4 – C10 **1-6 (Figure 1)**.



CA

- 1:** HOOC—(CH₂)₂—COOH
- 2:** HOOC—(CH₂)₃—COOH
- 3:** HOOC—(CH₂)₄—COOH
- 4:** HOOC—(CH₂)₆—COOH
- 5:** HOOC—(CH₂)₇—COOH
- 6:** HOOC—(CH₂)₈—COOH

Figure 1. Calix[4]arene CA and succinic **1**, glutaric **2**, adipic **3**, suberic **4**, azelaic **5**, sebacic **6** dicarboxylic acids.

Reversible-phase high-performance liquid chromatography method (RP HPLC) was used for determination of the stability constants of the Host-Guest supramolecular complexes formed.

Experimental part

Reagents

CA was synthesized by the method [11]. Methanol and acetic acid were obtained from the Acros Organics (Thermo Fisher Scientific, New Jersey, USA). Dicarboxylic acids were purchased from Sigma-Aldrich (Sigma-Aldrich Corporation, USA).

RP HPLC analysis

RP HPLC analysis was performed on the high pressure liquid chromatograph Hitachi (Hitachi, Ltd., Tokyo, Japan) in isocratic

conditions using the column Zorbax CN (Sigma-Aldrich) as a stationary phase. The calixarene based mobile phase was prepared by dissolving of the CA in the mixture H₂O/MeOH/CH₃COOH (94/5/1 v/v). The calixarene concentration in the mobile phase were 0.05 – 0.6 mM. A volume of the sample injected was 20 μL. All chromatograms were obtained at 26 °C. UV detector was operated at 210 nm and the flow rate was 0.8 ml/min.

Molecular modeling

The molecular modeling of the CA complexes with the acids was carried out by molecular mechanics MM+ method, force field PM3 (software package Hyper Chem, version 8) [12]. RMS gradient was 0.01 kcal/mol.

Results and Discussion

For the stability constants determination of the calixarene Host-Guest inclusion complexes with organic molecules NMR, UV-Vis, fluorescent, calorimetry methods are used. In some cases due to poor solubility of the calixarenes or the Guest molecules or the absence of a corresponding instrumental response on the complexation process the above mentioned methods are inefficient. To solve such problem the RP HPLC method for the determination of

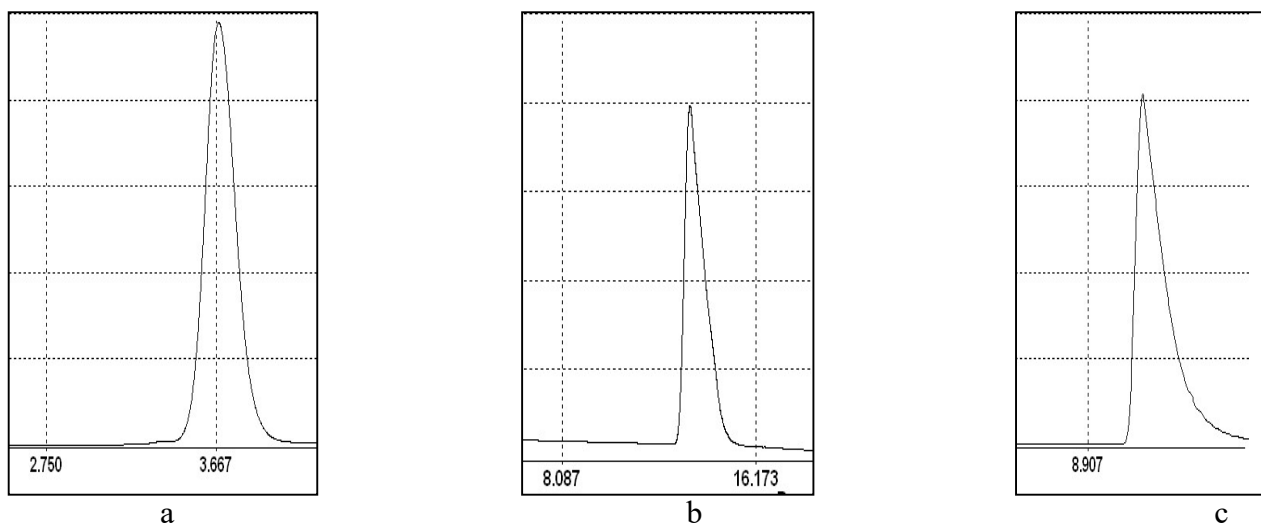


Figure 2. The chromatogram of CA (a) and the chromatograms of the adipic acid **3** before (b) and after (c) CA addition in the mobile phase.

stability constants of the calixarene complexes with organic compounds in water or water-organic solutions was developed [13,14]. The method is based on a determination of the capacity coefficient k' of the Guest molecule before and after calixarene addition to the mobile phase. The stability constant K_A of the calixarene complex with the Guest molecule (for 1:1 stoichiometry) can be calculated by equation (1):

$$1/k' = 1/k_0' + K_A \times [CA]/k_0', \quad (1)$$

where k_0' and k' are capacity coefficients of the Guest molecule determined in the absence and the presence of the calixarene in the mobile phase.

The HPLC investigation of complexation of calixarene CA with the dicarboxylic acids **1-6** was performed in solution H₂O/MeOH/CH₃COOH 94/5/1 v/v using Zorbax CN column. The conditions (the solvent and the stationary phase) provide a

good solubility of the Host and the Guest and their sharp peaks on the chromatograms (**Figure 2**). Linear adsorption isotherm of CA ($r=0.99$) is indicated on its reversible sorption on the support.

An addition of CA to the mobile phase decreases the capacity coefficient k' of the acids (**Figure 3**).

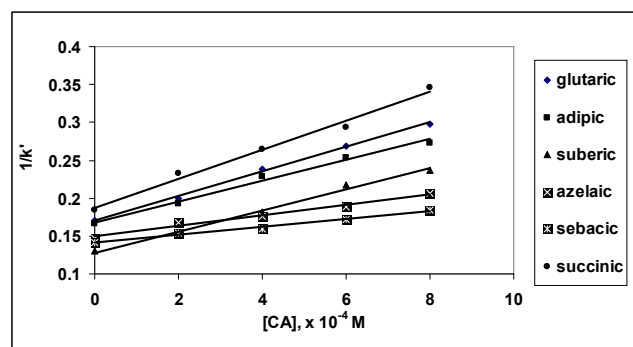


Figure 3. Plots of the $1/k'$ vs the CA concentration ($r=0.99$).

The linear character plots of k' vs the CA concentration (**Figure 3**) testifies the formation of the Host-Guest inclusion complexes with 1:1 stoichiometry and allows

the correct calculation K_A values by the equation (1).

The stability constants K_A and free Gibbs energy ΔG ($\Delta G = -RT \ln K_A$) for the CA–acid complexes are presented in **Table 1**.

Table 1. Stability constants $\log K_A$ (RSD = 3-6 %), free Gibbs energy ΔG (kJ/mol) of the complexes, $\log P$ and pK_a of the acids 1-6

Acid	$\log K_A$	ΔG	$\log P$	pK_a
Succinic 1	3.05	-17.39	-0.40	4.21
Glutaric 2	2.96	-16.88	-0.29	4.32
Adipic 3	2.94	-16.73	0.10	4.41
Suberic 4	2.93	-16.67	1.38	4.52
Azelaic 5	2.74	-15.61	1.57	4.53
Sebacic 6	2.59	-14.59	2.20	4.59

The stability constants are depended on number of carbon atoms in aliphatic chain of the acids and linearly increase from $\log K_A$ 2.56 (sebacic acid **6**) to $\log K_A$ 3.05 (succinic acid **1**). Decreasing of length of the acids chain increases the stability constants of the complexes (**Table 1** and **Figure 4**).

The calixarene Host-Guest complexes can be stabilized by hydrogen bonds formed between carboxyl groups of the acids and nitrogen or oxygen atoms at the upper or the lower rim of the calixarene, Van der Waals, and hydrophobic interactions. Role of the hydrophobic interactions in the complexation is confirmed by correlation of the stability constants K_A with the lipophilicity $\log P$ values of the dicarboxylic acids [15-18] (**Figure 5**).

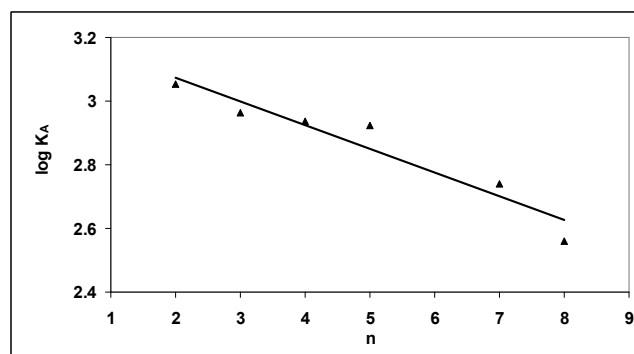


Figure 4. Plots of the $\log K_A$ vs the number of carbon atoms in aliphatic chain of acids 1-5 ($y = -0.0857x + 3.1856$; $r = 0.96$).

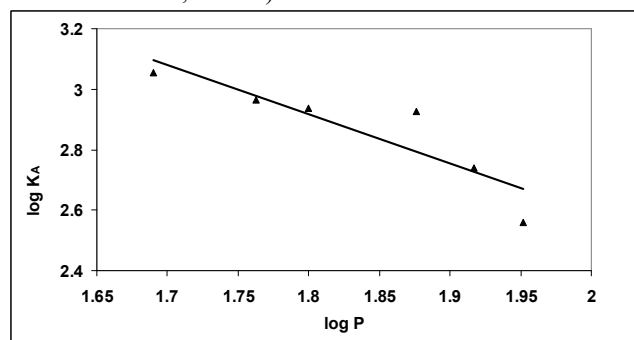


Figure 5. Plots $\log K_A$ vs $\log P$ of acids 1-6 ($y = -0.1454x + 2.974$; $r = 0.88$).

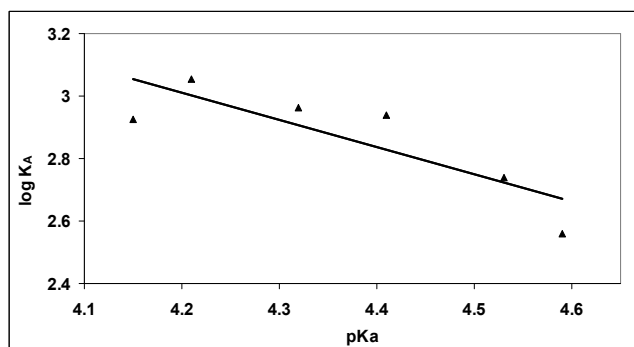


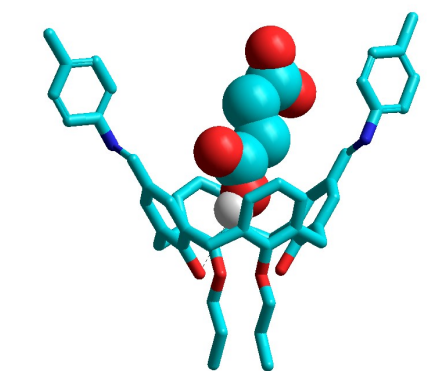
Figure 6. Plots of $\log K_A$ vs pKa of acids 1-6 ($y = -1.0464x + 7.498$; $r = 0.84$).

An increasing of the $\log P$ values of the acids decreases the $\log K_A$ values of their complexes (**Figure 5**).

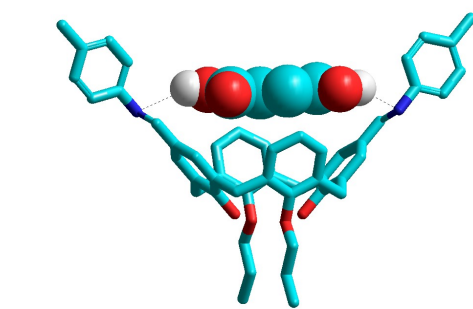
The stability constants ($\log K_A$) are dependent on the pKa values [19, 20] of the dicarboxylic acids (**Figure 6**).

Decreasing of the acid's pKa increases the K_A of the complexes (**Figure 6**).

To clarify the nature of the Host-Guest interaction the molecular modeling of the CA complexes with succinic acid **1** was performed (**Figure 7**).



A



B

Figure 7. Energy minimized structures of the oxygen-bonded complex **A** and the nitrogen-bonded complex **B** of CA with succinic acid **1**.

The complexes are stabilized by the hydrogen bonds of COOH groups of the acid with nitrogen or oxygen atoms of the CA molecule. Succinic acid **1** forms two types of the complexes. One of them **A** is stabilized by the hydrogen bond with the oxygen atom of OH group at the CA lower rim (O-H...O distance 3.02 Å). The second complex **B** is stabilized by two hydrogen bonds with distal nitrogen atoms at the upper rim (O-H...N distances 2.61 Å). Complex **B** is more stable compared with **A**. Differences between calculated energies $\Delta\Delta E$ of the complexes are 5.15-6.44 kJ/mol.

Table 2. $\Delta\Delta E$ values (kJ/mol) between **B** and **A** types of the **CA**-acid complexes

Acid	n*	$\Delta\Delta E$, kJ/mol
Succinic 1	2	6.44
Glutaric 2	3	6.57
Adipic 3	4	6.03
Suberic 4	5	6.36
Azelaic 5	7	5.36
Sebacic 6	8	5.15

*Number of carbon atoms in aliphatic chain of acids **1-6**

An increasing in the length of the dicarboxylic acid molecule destabilizes the nitrogen-bonded complexes of type **B**. This is confirmed by decreasing of the calculated values of $\Delta\Delta E$ for the nitrogen-bonded **B** and the oxygen-bonded **A** complexes vs the number of carbon atoms in aliphatic chain of acids **1-6** (**Table 2** and **Figure 8**). At the same time, the lengths of the hydrogen bonds O-H...N are increasing from 2.61 Å to 3.12 Å.

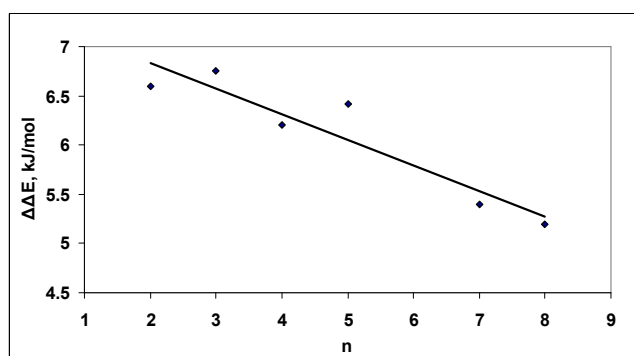


Figure 8. Plots of $\Delta\Delta E$ values of the complexes **B** and **A** vs number of carbon atoms (n) in aliphatic chain of acids **1-6** ($y = -0.2358x + 7.1229$; $r = 0.92$)

Conclusions

CA decorated with two proton acceptor imino groups at the upper rim of the macrocycle forms stable supramolecular Host-Guest complexes with aliphatic dicarboxylic acids in water solutions. The stability constants of the **CA** complexes determined by RP HPLC method are depended on the number of carbon atoms, $\log P$ and pK_a of the acids, and are in the region from $\log K_A$ 2.56 (sebacic acid **6**) to $\log K_A$ 3.05 (succinic acid **1**). Molecular modeling shows that the inclusion complexes are stabilized by the intermolecular hydrogen bonds of COOH groups with nitrogen atoms at the upper rim or with oxygen atom at the lower rim of the calixarene.

Acknowledgements

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