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Aminocalix[4]arene: the effect of pH on the dynamics of gate and portals on the hydrophobic cavity

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ABSTRACT

The pH of a solution shows a significant effect on the dynamics of the gate (formed by eight benzylic functions) and portal on the hydrophobic cavity of receptor. At pH 5.8 the gate closes and prohibits the entry of anionic guests. However, at pH 7.3 the gate opens and allows the entry of anionic guests into the hydrophobic cavity. It is the first time that anionic receptor efficiently recognizes anionic guests.

1. Introduction

Water plays a pivotal role in many aspects of living organisms,[1] such as for correct behavior of enzymes,[2,3] enzyme–substrate interactions,[4] membranes, and DNA structure.[5] In particular, enzymes are complex machines whose functions are strictly connected to their biological environment in which water molecules, as a solvent, have a major role.[6] The gates and portals on the cavity of the receptor can be opened or closed for the entry of substrate with specific stimulus.[7] Solvent effects also play a crucial role in controlling anion binding strength and selectivity.[8] Anions are ubiquitous throughout biological systems. They carry genetic information (DNA is a polyanion) and the majority of enzyme–substrates and co-factors is anionic.[9]

The design of selective receptors for anions requires that the geometry and basicity of the anion and the nature of the solvent medium be taken into account. Complementarity between the receptor and anion is clearly crucial in determining selectivities.[10] Water-soluble cyclophanes were the first examples with polar solubilizing groups.[10] Receptors based on clefts,[11] porphyrins,[12] and calixarenes/resocinarenes[13,14] have followed. Examples of good binding selectivity based on the pH effect for anions by the anionic receptor in water remain elusive.[15–17]

In this Letter, we describe the dynamics of water-soluble aminocalix[4]arene based receptor **1** at different pH. The gate of the receptor **1** closes at pH 5.8 and discriminates the anionic guests, such as sulfonic acid and carboxylic acid derivatives. Whereas, at pH 7.3 the gate of receptor **1** opens and allows the access of guests to the cavity and shows strong binding.

Receptor **1** can be obtained independently from **2** or **3** through a common intermediate **4**, as shown in Scheme 1. Precursors **2** and **3** were prepared according to the previously reported method.[18,19] As summarized in Scheme 1, precursor **2** was converted into the corresponding octa-substituted derivative of aminecalix[4]arene **4** by reacting with methyl 4-(bromomethyl)benzoate following route 1. In the other route, previously reported intermediate **3** was also reacted with the methyl 4-(bromomethyl)benzoate under similar conditions to obtain intermediate **4**. Interestingly, following either route to obtain **4** the yield is in the range of 86.3–88.5%. It is important to notice that being a single step reaction route one is the high yielding and convenient path to synthesize intermediate **4** or different derivatives.

Reaction of compound **4** with ethyl 2-bromoacetate allowed to isolate intermediate **5** in 89.8% yield. Saponification of **5** with KOH in ethanol and water mixture (2:1) resulted in receptor **1** as a dodecapotassium salt in 95.4% yield (for the detail synthesis of the compounds, please check the Supplementary data). The negatively charged carboxylate functions found on the wide and narrow rim of receptor **1** enabled its solubility in water at pH/p*D* = 5.8, 7.3

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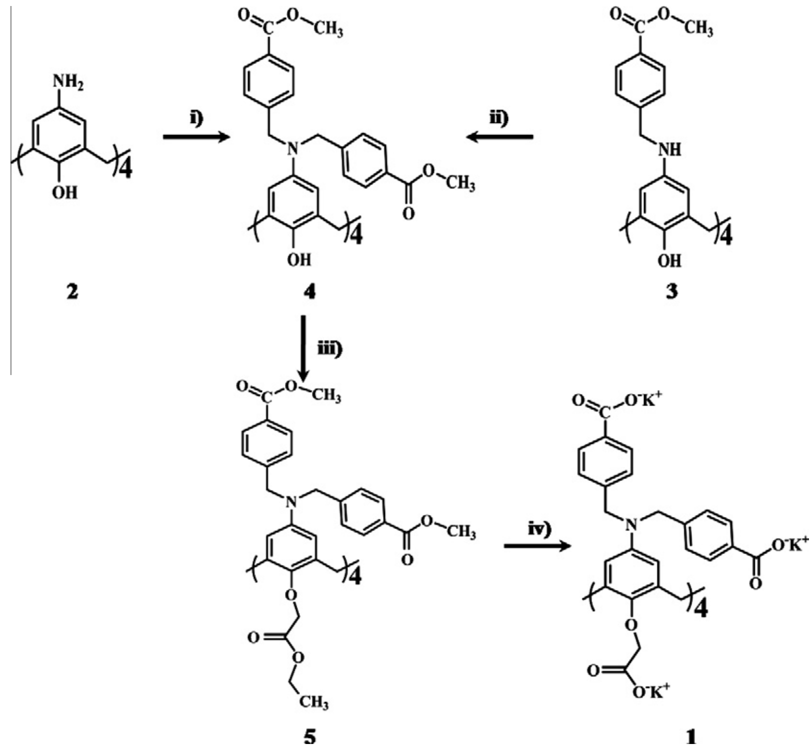

Scheme 1. Synthesis of receptor **1**. Reagents and conditions: (i) Br–C_6H_4–$COOCH_3$, C_6H_5N, CH_3CN; (ii) Br–C_6H_4–$COOCH_3$, C_6H_5N, CH_3CN; (iii) Br–$CH_2COOCH_2CH_3$, K_2CO_3, CH_3CN, Ar, reflux, 8 h; (iv) aq KOH, EtOH/water (2:1).

at levels up to 50–100 mM. Compound **1** loses its solubility below pH 5.4 in water.

A 1 mM sample of **1** in D_2O provides the NMR spectrum that has sharp signals and shows the characteristics and symmetry expected for a time-averaged C_{4v} conformation. The ^1H NMR spectrum of compound **1** showed a typical AB pattern for methylene bridge protons represented by two pairs of doublets at δ = 3.13 and 4.54 ppm for the axial and equatorial protons, respectively. This indicates that receptor **1** existed in a symmetrical cone conformation at both pH/p*D* = 5.8 and 7.3. As can be seen in Figure 1 the benzylic aromatic protons at δ = 7.19 and 7.82 ppm shift slightly upfield, while the calix[4]arene aromatic protons at δ = 6.42 shift downfield at p*D* = 5.8 as compared to that at p*D* = 7.3. The major change in *ortho* protons indicates that at p*D* = 5.8 benzoate groups (arms) come close to each other. In the upfield region, change is seen only for the benzylic –CH_2 protons, the peak at δ = 4.44 ppm shifts upfield at p*D* = 5.8 as compared to that of p*D* = 7.3 also confirms that the benzoate groups (arms) come close to each other, associating the phenomenon of flexing of arms.

The benzylic aromatic protons on the wide rim of compound **1** show correlations with the aceto-acetate proton on the lower rim at either pH, hence, the NOESY spectra of compound **1** did not show any clue for the flexing of the arms. To find a clue, we performed the NOESY experiment on compound **5** in $CDCl_3$. Compound **5** in its NOESY spectra shows the characteristic of opened arms. The –CH_3 in the benzoate function on the wide rim shows a correlation with the –CH_3 in the ethylacetate function on the narrow rim. This behavior of lipophilic compound **5** in organic solvent gives a clue for the open arm conformation of hydrophilic compound **1** in aqueous solution (See the Supplementary data). It was of particular interest then to investigate the effect of pH/p*D* on the flexing of arms. The phenomenon of flexing of arms was not clear from the NOESY experiments, thus probing the effect by the molecular recognition of anions by anionic receptor **1** was inevitable.

Small changes in NMR spectra with change in pH through the partial protonation dodeca acid functions may be related to the dynamics of the arms (eight benzylic functions) on the wide rim of aminecalix[4]arene nucleus to close or open the gate on the hydrophobic cavity. To investigate the dynamics of arms on the cavity, the molecular recognition experiments were conducted at p*D* = 5.8 and 7.3 using the anionic, cationic, and neutral guests as shown in Figure 2.

Receptor **1** at pH 5.8 recognizes guests **11**, **15–16**, whereas at pH 7.3 it recognizes guests **6**, **7**, **10–12**, and **15–18**. The 1:1 binding stoichiometry between receptor **1** and guest 6 is confirmed by Job's plot (see the Supplementary data). As shown in Figure 3**A**, the ^1H NMR titrations revealed that the protons of the methyl group *para* to the carboxylate moiety in guest **6** showed a maximum complexation-induced upfield shift (CIUS) of δ = 1.01 ppm upon complexation with receptor **1** at pH 7.3 and do not show any change at pH 5.8. Similarly, the protons on the *para* position to the functional groups in guests **7–18** showed maximum CIUS upon recognition by receptor **1** at pH 5.8 or 7.3. The binding of guests in this mode positions the guest's functional group (anionic, cationic, or neutral) in the proximity of the mouth of receptor **1**. It is noticeable that at pH 5.8 receptor **1** failed to recognize guest **6**, while shows strong recognition at pH 7.3. Receptor **1** at pH 5.8 showed similar patterns of recognitions toward anionic guests. These results indicate that at pH 5.8 the carboxylate functions on the benzylic groups form a gate on top of the hydrophobic cavity of receptor **1**, thus showing strong electrostatic repulsion toward anionic guests. Whereas, the strong recognition for anionic guests by receptor **1** at pH 7.3 indicates that the carboxylate functions on the benzylic groups on the top of the hydrophobic cavity of receptor **1** are far enough from each other making a room for the entry of anionic guests into the hydrophobic cavity. The recognition pattern of anionic guests by receptor **1** at pH 5.8 and 7.3 explains the flexing of arms on the hydrophobic cavity.