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Water-soluble aminocalix[4]arene receptors with hydrophobic and hydrophilic mouths

Satish Balasaheb Nimse [a], Van-Thuan Nguyen [a], Junghoon Kim [b], Hyung-Sup Kim [b], Keum-Soo Song [b], Woon-Young Eoum [b], Chan-Yong Jung [b], Van-Thao Ta [a], Sudhakara Reddy Seelam [a], Taisun Kim [a,*]

[a] Institute for Applied Chemistry and Department of Chemistry, Hallym University, Chuncheon 200-702, Republic of Korea
[b] Biometrix Technology, Inc. 202 BioVenture Plaza, Chuncheon 200-161, Republic of Korea

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ABSTRACT

We report the new water-soluble aminocalix[4]arene hosts **1** and **2** with deep hydrophobic cavity facilitating hydrophobic mouth and hydrophilic mouth, respectively. The ^{1}H NMR titrations revealed that host **1** shows high selectivity for neutral guests **9** and **10**, with log *K* of 4.2 and 4.6, respectively. The host **2** shows log *K* of 4.9 for binding with guest **15**. Moreover, the binding ability of the host **2** for guest **14** is stronger by a factor of 1000 than that of the host **1**.

1. Introduction

Mimicry of the molecular recognition features of naturally occurring proteins by synthetic receptors is one of the challenging research topics of supramolecular chemistry.[1] Biological receptors consist of large linear molecules that form three dimensional structures by specific intramolecular interactions. The recognition site offers a precise stereochemistry and exhibits very efficient recognition processes by means of specific functional groups that constitute the entrance and inner surface of the cavity.[2] The presence of specific functional groups at the mouth of the cavity suggests their role for accessibility of substrates into the cavity.[3,4]

Once the substrate enters the gorge it is guided to the active site and there it is held almost exclusively by aromatic residues.[5] The quaternary ammonium functions of substrates do not permit the use of conventional hydrogen bonds or salt bridges; rather, typically presents a cation–π interaction.[6] It is of particular interest then how the aromatic amines and ammonium ions are recognized by receptors, considering their relative abundance in nature.[7] However, the electronic effects, steric effects, and conformational aspects of pyridine derivatives seem to be the most crucial for their recognition by receptors.[8]

A possible strategy for synthetic receptors comprises a combination of medium-sized organic building blocks to which functional groups for molecular recognition can be attached. Cyclophanes were the first examples with polar solubilizing groups.[9] Receptors based on clefts,[10] porphyrins,[11] calixarenes/resocinarenes[12,13] have followed, and yielded a collection of the thermodynamically stable host–guest complexes. Examples of good binding selectivity and kinetic stability in water remain elusive.[10–14] Among the various calixarene derivatives, water-soluble calixarenes have become increasingly important after their introduction by Ungaro[15] and Shinkai[16] in the field of supramolecular chemistry. Water-soluble calix[4]arene derivatives allowed the study of basic forces involved in the host–guest recognition processes, in a solvent where, all biological processes take place.[17]

These features of the substrates and enzymes have inspired the synthesis of deep hydrophobic pocket synthetic receptors. Recently we have reported the synthesis and molecular recognition properties of water-soluble iminecaix[4]arene derivative.[18] The imine bonds in iminecalix[4]arene were found to be fragile, limiting its use as a receptor. Here, we report new, highly stable, water-soluble aminocalix[4]arene hosts, the one with hydrophobic function and the other with hydrophilic function on the top of the deep hydrophobic cavity (Fig. 1).

We developed a new approach based on the calix[4]arenes. According to our concept, the calix[4]arene is applied not only for its cavity but also as a platform on which a molecular cleft can be constructed by selective functionalization. The iminecalix[4]arene derivatives **3** and **4** obtained by selective modification of the wide rim of aminocalix[4]arene, keeping narrow rim free

* Corresponding author. Tel.: +82 33 258 6098; fax: +82 33 256 3421.
E-mail address: tskim@hallym.ac.kr (T. Kim).

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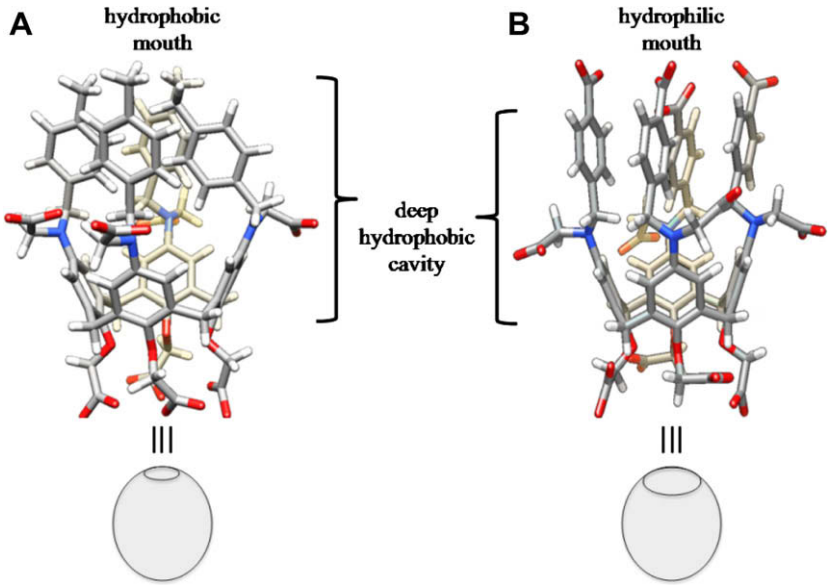


Figure 1. Hosts **1** and **2**, (A) host **1** (side view), (B) host **2** (side view).

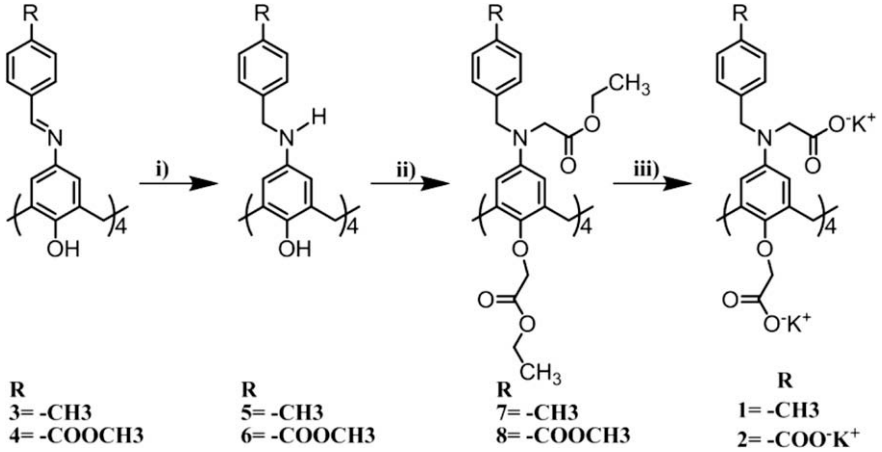
for further modifications, were used as precursors. The receptors **1** and **2** were prepared from the iminecalix[4]arene **3** and **4**, respectively, in three steps.

Reductions of **3**, **4** to the respective aminocalix[4]arene **5**, **6** with BH_3·THF complex, and the subsequent reaction of **5**, **6** with ethyl 2-bromoacetate in acetonitrile in the presence of K_2CO_3 at 80 °C afforded compounds **7**, **8** with 87.5–89.4% yields. The ester then hydrolyzed with KOH in ethanol and water mixture (2:1) to provide water-soluble aminocalix[4]arene derivatives **1** as the octapotassium salt, and **2** as dodecapotassium salt in 96.6% and 97.6% yields, respectively (Scheme 1, see the Supplementary data). The negatively charged carboxylate functions found on the upper rim, lower rim, and, or on the body of the receptors **1** and **2** enable their solubility in water at pH/pD 7.3 at levels up to 50 mM–100 mM.

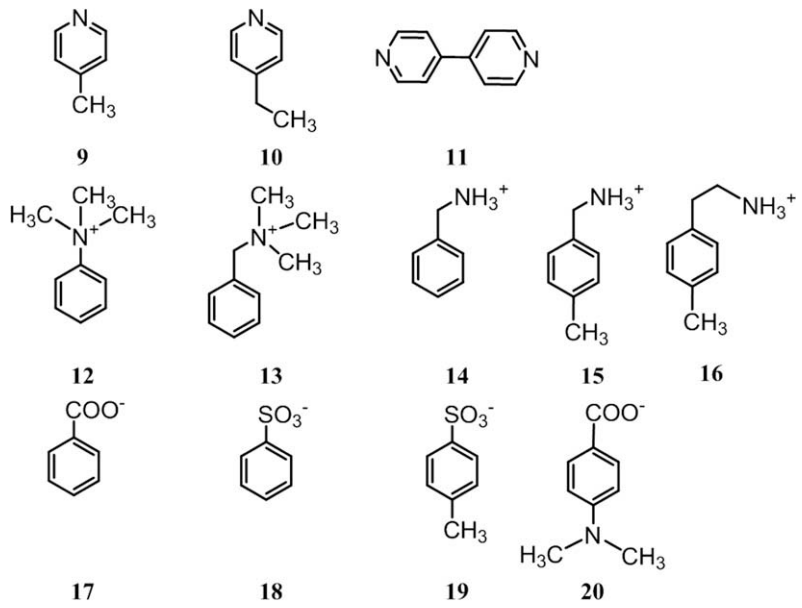
A 1 mM sample of **2** in D_2O provides a NMR spectrum that has sharp signals and shows the characteristics and symmetry expected for a time-averaged C_{4v} conformation. The ^{1}H NMR spectrum of compound **2** showed a typical AB pattern for methylene bridge protons represented by two pairs of doublets at δ = 3.13 ppm (J = 12.6 Hz) and δ = 4.38 ppm (J = 12.6 Hz) for the axial and equatorial protons, respectively, this indicates that compound **2** existed in a symmetrical cone conformation. It was further confirmed by the observation of a distinct signal at δ = 30.8 ppm for the methylene carbon in the ^{13}C NMR spectrum.[19] A similar pattern was found for the compound **1**.

The preformed cavities with the hydrophobic and hydrophilic mouths in hosts **1** and **2**, respectively, are stabilized by the four aminoacetate functions found on the body of the hosts. These functions point outward and interact with water, making the aromatic groups to form walls on the wide rim of calix[4]arene nucleus to generate an architecture with deep hydrophobic cavity. In water, the hydrophobic aromatic rings in host **1** come close to each other to reduce the hydrophobic surface, forming hydrophobic mouth on the top of the deep cavity. However, in the case of host **2**, the four carboxylate functions on the top of the cavity interact with water, forming hydrophilic mouth on the top of the deep cavity as illustrated in (Fig. 1).

When one equivalent of host **2** was added to a 1 mM solution of benzyltrimethylammonium bromide (**13**) (Scheme 2) in D_2O, a signal for the encapsulated trimethylammonium moiety appeared at δ = 1.19 ppm, which shifted δ = 1.93 ppm upfield of the free guest (Fig. 2d). The large anisotropy experienced by the bound guest shows that it is included deep within the pocket, surrounded by aromatic walls. NMR titrations in deuterated buffer solution



Scheme 1. Synthesis of hosts **1** and **2**. Reagents: (i) BH_3·THF, *p*-toluenesulfonic acid, THF; (ii) Br-$CH_2COOCH_2CH_3$, K_2CO_3, CH_3CN, Ar, reflux, 8 h; (iii) aq KOH, EtOH/water (2:1).



Scheme 2. Neutral pyridine (**9**–**11**), cationic (**12**–**16**) and anionic guests (**17**–**20**).

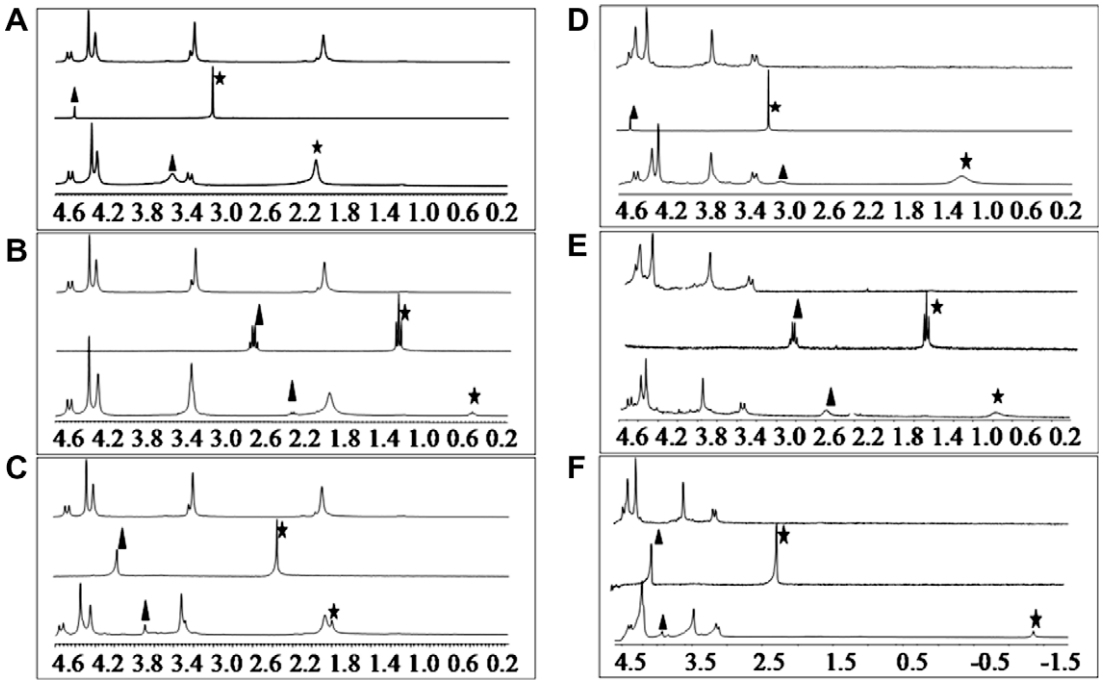


Figure 2. Partial ^{1}H NMR Spectra of complexes between host **1**, **2** and molecule of guests **10**, **13**, and **15**. (A) complex between host **1** and guest **13**; (B) complex between host **1** and guest **10**; (C) complex between host **1** and guest **15**; (D) complex between host **2** and guest **13**; (E) complex between host **2** and guest **10**; (F) complex between host **2** and guest **15**. (▲) and (★) indicate the changes in protons of guest upon addition of host. In each box, the partial ^{1}H NMR spectra is of free host (top), free guest (middle), and host–guest complex (bottom).

[pD 7.3] provide a log *K* of 3.7 and 4.7 for **13** with **1** and **2**, respectively (Table 1).

Similar 1:1 host–guest complexes were formed for **1** and **2** with **12**, with log *K* of 3.4 and 4.0, respectively. The NMR spectra of each host–guest complexes indicate that the trimethylammonium residue of each guest is bound deep within the aromatic pocket by the induced fit mechanism. It is clear that the cation–π interaction is a powerful force that aids the recognition between hosts with their guests.[20] The direct comparison between log *K* values obtained for binding of hosts **1** and **2** with cationic guests **12** and **13** reveals a preference for the binding by the host **2**. This interpretation is strongly supported by the ^{1}H NMR and NOESY (see the Supplementary data) results showing that in the **12**–**2** complex the guest is more deeply included into the cavity of the host **2** than into the cavity of the host **1**. It is accepted that the cation–π interactions play a major role in both cases, but maybe the difference is made by hydrophobic or hydrophilic mouth in hosts **1** and **2**.[17a] This phenomenon was not clear and hence, structurally flat neutral aromatic pyridine guests (**9**–**11**) were studied.

Table 1
Log *K* values of complex formation of guests **9**–**20** by hosts **1** and **2** in water (pD 7.3; 25 °C)[a]

Guests	9	10	11	12	13	14	15	16	17	18	19	20
Host **1**	4.2	4.6	ns[b]	3.3	3.7	1.0	3.4	2.4	ns	ns	ns	2.2
Host **2**	3.3	4.4	ns	4.1	4.7	3.8	4.9	4.4	ns	ns	ns	2.1

[a] All solutions were prepared in 200 mM sodium phosphate buffer (pD 7.3). The guest concentration was kept constant (1×10^{-3} M) while the host concentration was varied from 8×10^{-4} to 3×10^{-3} M, and the chemical shifts of the protons of guest were recorded at each concentration. The obtained ^{1}H NMR data was analyzed by the well-known method of nonlinear least square regression analysis, which allowed the calculation of association constant (log *K*).

[b] ns indicates no change in chemical shift of protons in guests upon addition of hosts.

Guests **9** and **10** enter in the deep hydrophobic cavities of hosts **1** and **2** with the hydrophobic open-chain substituent in pyridine guests, as 4-methyl and 4-ethyl moieties showed significant chemically induced upfield shift (CIUS) than aromatic protons (Fig. 2b and e). The guest **11** with hydrophilic ends on both sides did not show any change upon titration with hosts **1** and **2**, respectively. It is interesting to notice that host **1** showed higher association constants for guests **9** and **10** as compared to host **2** (Table 1). Structurally flat guest molecules like guests **9** and **10** enter into the deep cavity of host **1** through the hydrophobic mouth and get trapped in the cage formed by four aromatic rings, thus the optimized π-π stacking interactions result in the increased binding constant. The hydrophilic mouth of host **2** allows easy entry and exit of guests **9**, **10** into the deep hydrophobic cavity; therefore the reduced π–π stacking interactions result in the decreased binding constant.

It is noticeable that host **1** showed stronger binding with pyridine derivatives (**9**–**10**) as compared to aromatic quaternary ammonium ions (**12**, **13**). The hydrophobic mouth of host **1** is considered to play a major role in the recognition of structurally flat pyridine derivatives. Further, to put a light on the effect of the hydrophobic and hydrophilic mouths, more hydrophilic aromatic ammonium guests (**14**–**16**) were studied.

The ^{1}H NMR titrations revealed that the protons of the methyl group *para* to the benzylammoniomethyl moiety in guest **15** showed a maximum (CIUS) of δ = 0.61 ppm and δ = 2.76 ppm upon complexation with the hosts **1** and **2**, respectively (Fig. 2c and f). Similar pattern found for **14** and **16** indicates that aromatic nucleus enters deep into the hydrophobic cavity from position *para* to the benzylammonium or phenethylammonium functions in guests **14**, **15**, and **16**, respectively, projecting ammonium moiety outward from the host's cavity. The binding of guests **14**–**16** in this mode positions the guest's ammonium moiety in the proximity of the hydrophobic mouth and hydrophilic mouth of the host **1** and host **2**, respectively. Compared to guests **14** and **16**, guest **15** is better complexed by the hosts **1** and **2** (log *K* = 3.4 and 4.9, respectively). Interestingly, host **2** showed a preference over the host **1** for the binding of guests **14**–**16**. Moreover, the binding ability of the host **2** for benzylammonium ion (**14**) is stronger by a factor of 1000 than that of the host **1** (Table 1).

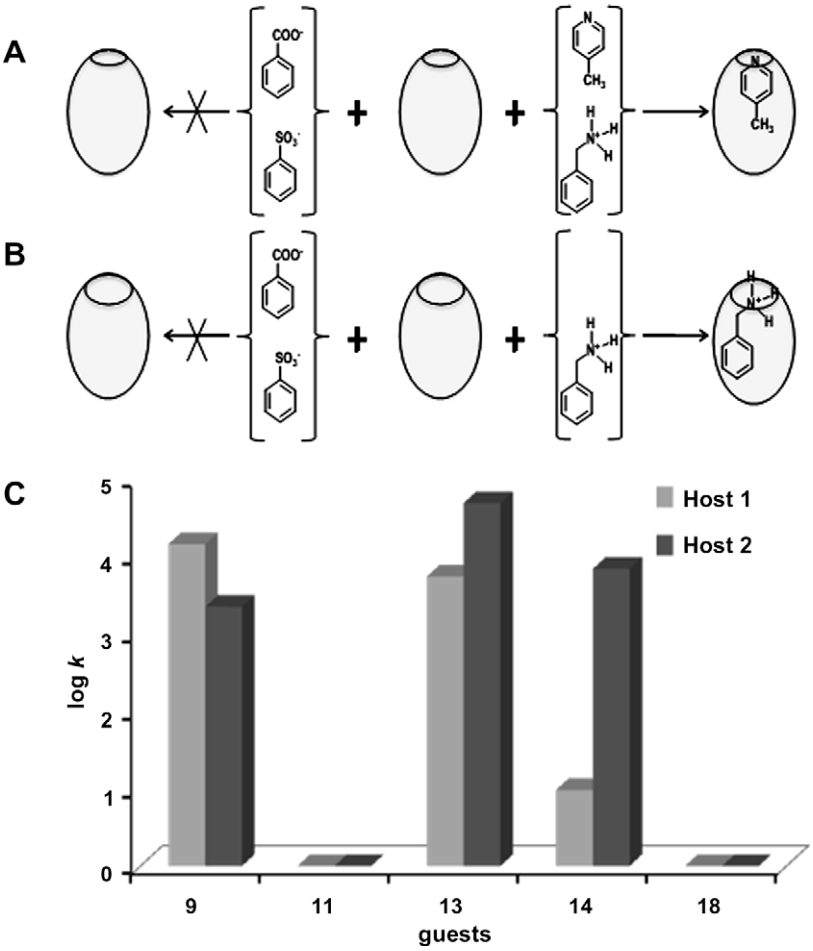


Figure 3. Functional group selectivity demonstrated by hosts **1** and **2**, (A) Host **1** with guests **10**, **15**, **17**, and **19**, (B) Host **2** with guests **10**, **15**, **17**, and **19**, (C) Comparison between log *K* values of hosts **1** and **2** for binding of guests **9**, **11**, **13**, **14**, **18**.

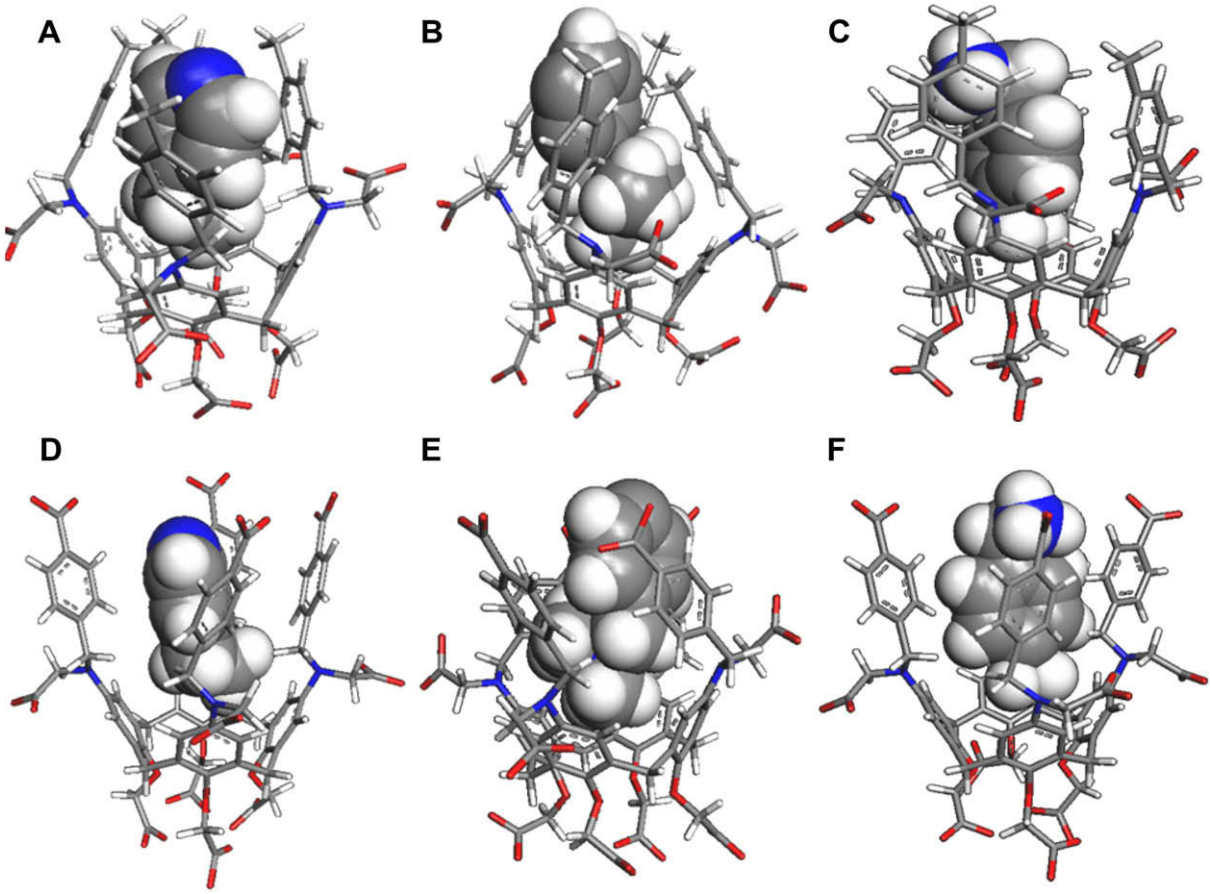


Figure 4. Energy-minimized structure of complexes between host **1**, **2**, and molecules of guests **10**, **13**, and **15** by Spartan® (MM⁺ Force Field) (A) complex between host **1** and guest **10** (side view); (B) complex between host **1** and guest **13** (side view); (C) complex between host **1** and guest **15** (side view); (D) complex between host **2** and guest **10** (side view); (E) complex between host **2** and guest **13** (side view); (F) complex between host **2** and guest **15** (side view).

The hydrophobic mouth of host **1** blocks the entrance of hydrophilic benzylammonium ions, hence the benzyl function cannot get deep into the cavity of host **1**. However, the hydrophilic mouth of host **2** allows the entry of guest **14** into its deep hydrophobic cavity and shows stronger binding. Substitution of methyl group at the *para* position of benzylammonium function increases the hydrophobic area of the guest **15**. This methyl function now can get deeper into the cavity of host **1**, which results in the increased binding constant as compared to the guest **14**.

Except the difference of a hydrophobic or hydrophilic mouth, the hydrophobic–hydrophobic interactions, –CH–π interactions, and π–π stacking interactions can be similar due to the structural similarities of the hosts **1** and **2** for the recognition of guests **14**–**16**. The ammonium functions of guests **14**–**16** show favorable electrostatic interactions at the hydrophilic mouth of host **2** in their respective complexes. In case of host **1**, the hydrophobic mouth blocks the entrance of guests **14**–**16** and avoids their access to the deep hydrophobic cavity. As shown in Table 1, it is interesting to notice that the affinity for guests **14**–**16** by the hosts **1** and **2** is in the order of **14** < **16** < **15**. This indicates that the substitution of methyl group at *para* position increases the strength of binding.

Upon complexation with host **1** the 4-methyl moiety in guest **16** showed less CIUS than the 4-methyl moiety in guest **15**, this indicates that the guest **16** cannot get deep inside the cavity through the hydrophobic mouth of host **1**. However, it enters into the cavity of host **2** through the hydrophilic mouth, but not to the depth achieved by guest **15**. The extended chain length by one carbon atom in 4-(methyl) phenethylammonium moiety in guest **16** puts ammonium function in the vicinity of the aromatic moiety thus reducing the overall hydrophobic surface to increase its solubility in water. Therefore, guest **16** showed a less association constant as compared to guest **15**. Hence, the advantage of the hydrophilic mouth over the hydrophobic mouth in the recognition of aromatic ammonium ions is clearly established.

Hosts **1** and **2** also demonstrate the functional group selectivity—except aromatic quaternary ammonium ions (guests **12**, **13**), aromatic ammonium ions (**14**–**16**), and neutral heterocycles (4-methylpyridine **9** and 4-ethylpyridine **10**), the aromatic anionic guests (**17**–**20**) do not form stable complexes with hosts **1** and **2** (Table 1, Fig. 3).

Irrespective of electrostatic interactions, host **1** shows low values of association constants with guests bearing small hydrophobic surfaces, as these guests cannot enter through the hydrophobic mouth. Whereas the hydrophilic mouth of host **2** allows the entry of guests into its cavity and shows different CH–π, π–π stacking, and hydrophobic interactions depending upon the depth the guest achieves.

The anions such as **17**, **18**, and **19** do not show evidence of complex formation with hosts **1** and **2**. While the guest **20** with extended arm of dimethylamino moiety was recognized by hosts **1** and **2** with log *K* of 2.2 and 2.1, respectively. The hydrophobic interactions along with –CH–π and π–π stacking interactions improve the binding of guest **20** in the hydrophobic cavities of hosts. The ^{1}H NMR titration indicates that the dimethylamino moiety show high value of CIUS as compared to aromatic protons in guest **20**, indicating that dimethylamino moiety is exclusively incorporated into the cavity of hosts **1** and **2**, respectively. The binding of 4-(dimethylamino)benzoate (**20**) in this mode positions the

guest's carboxylate group in proximity to the four carboxylate residues that decorate the opening of the pocket of the host **2**.

The negatively charged functions of guests **17**–**20** show unfavorable electrostatic interactions at the hydrophilic mouth of the host **2**. In the case of host **1** the hydrophobic mouth blocks the entrance of hydrophilic guests **17**–**19**. Hence, the hydrophobic and hydrophilic mouths of hosts **1** and **2**, respectively, play a vital role in the recognition of anionic guests too.

As shown in Figure 4, the plausible special orientation of complexes between hosts **1**, **2**, and molecules of guests **10**, **13**, and **15** is presented by the energy-minimized structures generated by Spartan® (MM + Force Field), respectively.

In summary, water-soluble aminocalix[4]arene derivatives with hydrophobic or hydrophilic mouth were synthesized in prominent yield. The binding behavior and geometrical properties of host complexes with aromatic cationic, aromatic anionic, and neutral pyridine molecules have been investigated in the aqueous medium where the entire natural processes occur. It was of particular interest to us to investigate how and to what extent the difference of a hydrophobic mouth and a hydrophilic mouth on the top of the deep hydrophobic cavity of the hosts affects the binding ability of hosts. The NMR investigations indicate that hosts **1** and **2** can form 1:1 host–guest inclusion complexes with aromatic cationic guests and pyridine derivatives with high binding constants. Both hosts refused to recognize the hydrophilic anionic guests. The host **1** with hydrophobic mouth showed high binding constant for 4-ethylpyridine amongst tested guests. However, the hydrophilic mouth of host **2** enhances the binding of 4-methylbenzylammonium ion, as the carboxylate functions of the mouth show strong electrostatic interactions with the ammonium function. It is clear from the data that the cavity of both hosts has a preference for structurally flat guests containing methyl groups (either a CH_3 in *para* position of an aromatic ring or a presence of trimethylammonium group) and very poor for smaller but more hydrophilic primary ammonium groups, which indeed do not enter the hydrophobic cavity.

These observations, along with the easy synthesis of water-soluble aminocalix[4]arenes indicate that with judicious design, highly ordered supramolecular arrays can be achieved conveniently in a controllable way, a situation which is useful for the understanding of natural recognition processes on a more global scale.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.073.

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