Articles

Molecular Recognition of Neutral Substrates by New Tetraaminocalix[4]arene Derivative

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The recognition of neutral aromatic substrates by different neutral calix[4]arene receptors **1**, **2**, and **3** was studied by NMR spectroscopy. The stoichiometry is 1:1 in all cases as was confirmed by jobs plot. Owing to the deep cavity, **1** affords stronger binding abilities for substrate **4** and **5**, while all receptors remained inert for substrates **6** and **7**. The binding constants determined by ^{1}H NMR titration show that the recognition of substrate **4** by **1** gives strongest complexation (K_a of 9.8×10^2 M^{-1}).

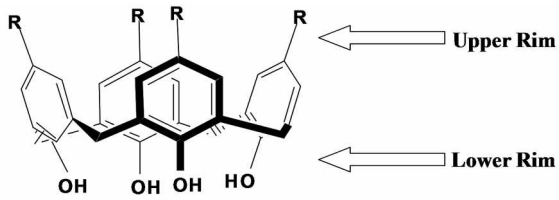
Key Words: Tetraaminocalixarene, Molecular recognition, Neutral substrates, Deep cavity

Introduction

Calixarenes are versatile bowl-shaped platform's which can be functionalized to provide a range of interesting molecular architectures with well defined special arrangement of the substituents.[1,2,3] The easily tunable shape of the molecules, together with almost unlimited possibilities of chemical transformations, make calixarenes a more sophisticated molecular system. Derivatives of the calix[4]arene and *tert*-butylcalix[4]arene shown in Scheme 1 have been widely used as molecular receptors[4,5] and as the scaffold for the design and synthesis of wide range of receptors with recognition ability towards both neutral and charged molecules.[6,7,8]

The development of upper and lower rim modified receptors has been tremendously exploited, which has resulted in to several derivatives such as ethers, aldehydes, imines, esters, amides.[9] These types of derivatives were targeted to recognize charged and neutral molecular species in aprotic solvents.[10,11] A large volume of research data is available on recognition of ionic substrates[12] but very few is available on recognition of neutral guests due to the limitations of forces involved in the molecular recognition process; as a consequence, the inclusion properties of neutral guests by neutral calixarene derivatives is considered to be stringent.[13,14] The neutral abiotic receptor for neutral substrates of biochemical, medical, and environmental importance is an area of intense research activity obligating the development of the neutral molecular receptor.[15]

It was hypothesized that the phenolic oligomers represented by calix[4]arenes could in principle provide excellent platforms for the construction of attractive recognition sites for host-guest interaction.[16,17] It is assumed that the new molecular receptors with deep cavities may enhance the recognition process of the aromatic guest in aprotic organic solvent. The tetraaminocalix[4]arene derivative **1** can be easily prepared by introducing tetraamino functional groups on the upper rim of calix[4]arene. In this paper, the recognition of aromatic guests by **1** was studied and the results were compared with those of **2** and **3**.



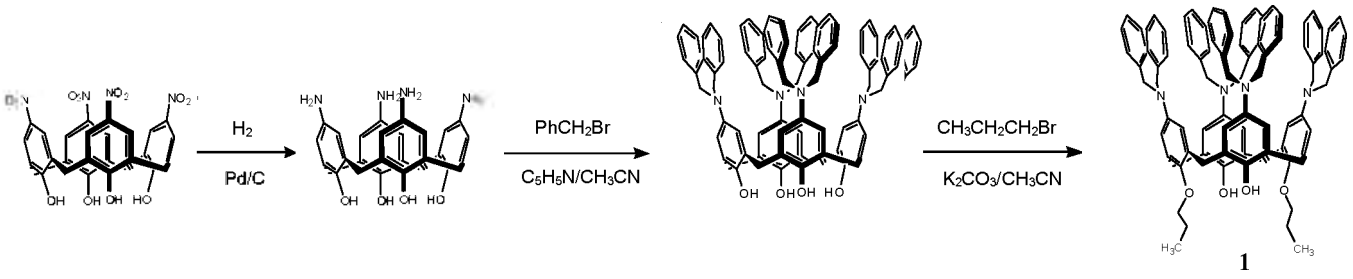
R= H, *tert*-Butyl

Scheme 1

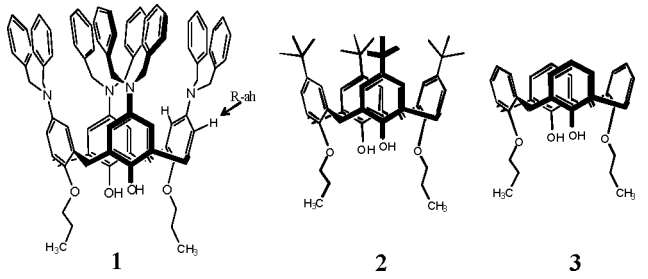
Result and Discussion

The required starting materials *tert*-butylcalix[4]arene and calix[4]arene were synthesized following literature procedures.[18] The dialkylation of these compounds was achieved by refluxing with 1-bromopropane in the presence of K_2CO_3 in anhydrous CH_3CN under nitrogen atmosphere to obtain receptor **2** and **3**.[19] As shown in Scheme 2, receptor **1** was obtained by slightly modified nitration[20] of calix[4]arene followed by well known reduction[21] to produce tetraaminecalix[4]arene. Tetraaminecalix[4]arene on selective *N*-alkylation[22] with benzyl bromide in the presence of a base resulted in tetradibenzylaminocalix[4]arene, which was dialkylated at the lower rim with a similar procedure as employed for receptor **2** and **3**. A detailed synthesis of receptor **1** will be reported elsewhere.

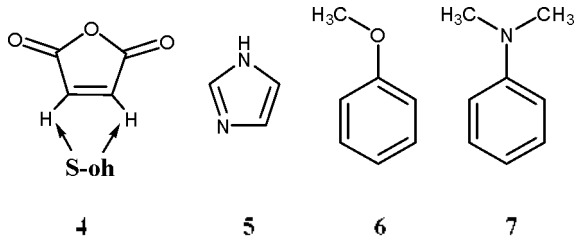
All of the receptors shown in Scheme 3 were characterized by analysis of their ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **1** showed a typical AB pattern represented by two pairs of doublets at δ 3.00 and δ



Scheme 2. Synthesis of receptor **1**



Scheme 3



Scheme 4

4.20 for the axial and equatorial protons, respectively, which indicated that **1** existed in a symmetrical cone conformation. This was further confirmed by the observation of a distinct signal at δ 32.82 for the methylene carbon in the ^{13}C NMR spectrum.[23]

The receptors **1**, **2**, and **3** were examined for their interaction with various substrates such as maleic anhydride **4**, immidazole **5**, anisole **6**, and *N,N*-dimethylaniline **7** as shown in Scheme 4.

The recognition characteristics of all receptors were investigated in detail by ^{1}H NMR experiments in deuterated chloroform, which revealed significant chemical induced upfield shifts (CIUS) for proton resonances in the selective substrates, while minimal or no changes were observed for the receptors themselves in the tested concentration range. The substrate protons were observed as averaged single resonances because of the fast exchange on the NMR timescale between the free and complexed substrate.

The ^{1}H NMR titration experiments conducted in $CDCl_3$ indicated that the CH=CH signal at δ 7.20 for substrate **4** and CH=CH signal at δ 7.13 for substrate **5** were markedly affected by the addition of receptors **1**, **2**, and **3**, while no effects on chemical shifts were observed for the aromatic as well as alkyl signals of substrates **6** and **7**. Figure 1 illustrates that the maximum upfield shift of 0.83 ppm was observed for the CH=CH protons of Substrate **4** upon the addition of 1.0 equivalent of receptor **1**, while marked upfield shifts of 0.44 ppm were also observed upon titration with receptors **2** and **3** respectively, as shown in Figure 2 and Figure 3.

The substrate concentration was kept constant (1×10^{-2} M) while the receptor concentration was varied from 0.125×10^{-2} to 1×10^{-2} M and the chemical shifts of the CH=CH protons were recorded at each concentration. The obtained ^{1}H NMR data was analyzed by the well known Rose-Drago method[24] which allowed the calculation of association constant (K_a). The values obtained are presented in Table 1. Receptor **1** showed maximum K_a of 9.8×10^2 M^{-1} with **4** and 6.1×10^2 M^{-1} with **5**, while receptor **2** shows K_a of 5.71×10^2 M^{-1} with **4** and

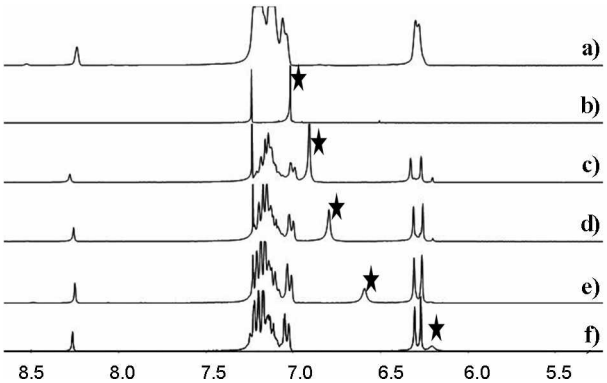


Figure 1. Partial ^{1}H NMR ($CDCl_3$ at 298 K) spectra of substrate **4** upon titration with receptor **1**. a) receptor **1**, b) substrate **4**, c) **4** + 0.125 equiv of **1**, d) **4** + 0.25 equiv of **1**, e) **4** + 0.5 equiv of **1**, f) **4** + 1.0 equiv of **1**.

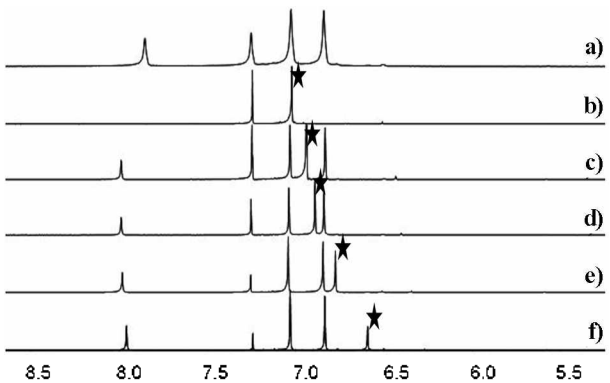


Figure 2. Partial ^{1}H NMR ($CDCl_3$ at 298 K) spectra of substrate **4** upon titration with receptor **2**. a) receptor **2**, b) substrate **4**, c) **4** + 0.125 equiv of **2**, d) **4** + 0.25 equiv of **2**, e) **4** + 0.5 equiv of **2**, f) **4** + 1.0 equiv of **2**.

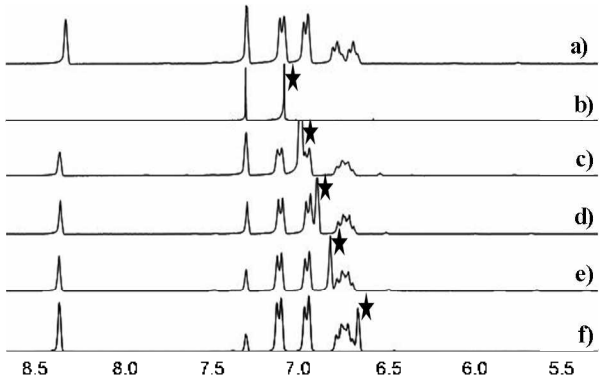


Figure 3. Partial ^{1}H NMR ($CDCl_3$ at 298 K) spectra of substrate **4** upon titration with receptor **3**. a) receptor **3**, b) substrate **4**, c) **4** + 0.125 equiv of **3**, d) **4** + 0.25 equiv of **3**, e) **4** + 0.5 equiv of **3**, f) **4**+ 1.0 equiv of **3**.

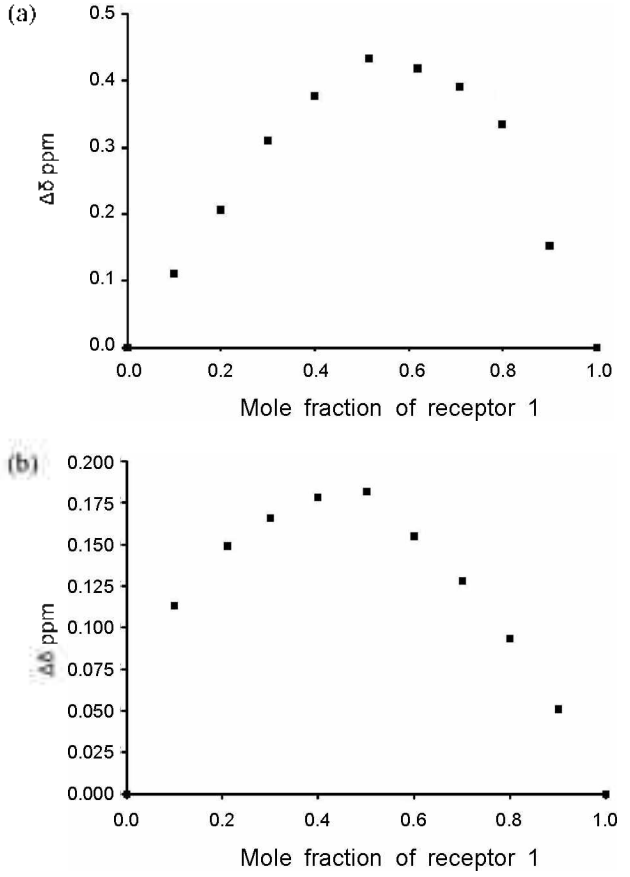


Figure 4. Job's Plot for the titration of receptor **1** with a) substrate **4**, b) substrate **5** in $CDCl_3$ at 298 K.

4.01 × 10^2 M^{-1} with **5**, receptor **3** shows K_a values of 5.49 × 10^2 M^{-1} and 3.81 × 10^2 M^{-1} with **4** and **5** respectively. While substrates **6** and **7** remained unbound. As shown in Figure 5, substrate **4** shows maximum CIUS of 0.83 ppm with receptor **1** compared to **2** and **3**.

Based on the NMR titration data, binding-stoichiometries of the above complexes were confirmed to be 1:1 by Job's plot method[25] with maximum complexation at 0.5 mol fraction of substrates **4** and **5** with receptor 1 as shown in Figure 4.

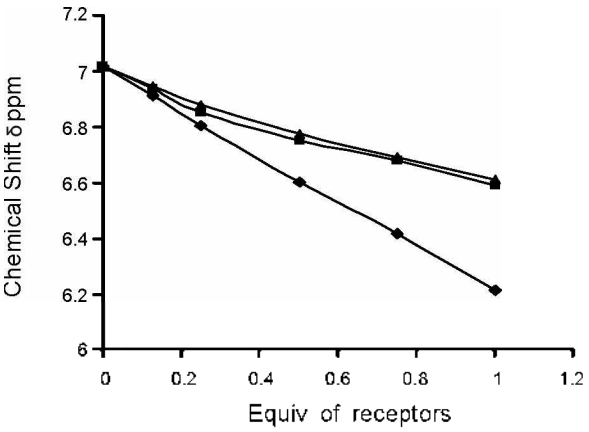


Figure 5. ^{1}H NMR titration curves of CH=CH proton of **4** upon titration with receptor ♦—1, ■—2 and ▲—3.

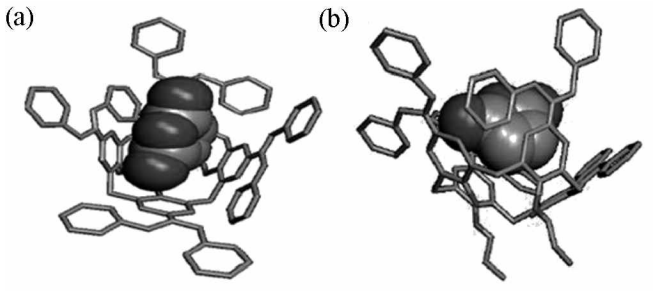


Figure 6. Energy minimized structure of complex between receptor **1** and substrate **4** by Spartan® (MM+ Force Field, the hydrogen's were removed for clarity). a) Top view, b) Side view.

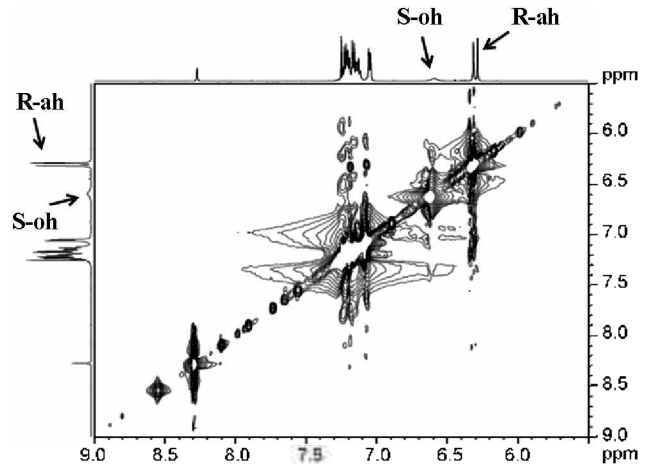


Figure 7. Partial 2D NOESY spectrum (Bruker 600 MHz NMR) of complex between receptor 1 and substrate **4**. The abbreviations R-ah and S-oh stands for aromatic protons of calix[4]arene and olefinic protons of substrate, respectively.

The results in Table 1 demonstrate that all of the receptors showed similar pattern of recognition towards substrates **4** and **5**, in fact substrate **4** is better accommodated in the cavity of receptor **1** than substrate **5**. From Figure 5, the increasing order of affinity of the receptors for substrate **4** can be presented as **3** < **2** < **1**. The similar order of affinity is also found

Table 1. Chemical shift values ($\Delta\delta$ ppm) and association constants (K_a M^{-1}) of substrates upon addition of receptors, in $CDCl_3$ (300 MHz and 298 K)

Receptor	Guest $\Delta\delta$ ppm (K_a M^{-1})			
	4	**5**	**6**	**7**
1	0.83 (9.78×10^2)	0.45 (6.11×10^2)	[a]ns	ns
2	0.44 (5.71×10^2)	0.36 (4.01×10^2)	ns	ns
3	0.44 (5.49×10^2)	0.33(3.81×10^2)	ns	ns

[a]ns indicates no change in chemical shift.

in case of substrate **5**. Substrate **4** as well as **5** show significant association constants with receptor **1** as compared with receptors **2** and **3**.

The energy minimized structure generated by Spartan® (MM+Force Field) for a complex between receptor **1** and substrate **4** was shown in Figure 6. As shown in Figure 7, the special arrangement of substrate **4** in receptor **1** was confirmed by NOESY measurements (600 MHz, $CDCl_3$, 298 K). The partial 2D NOESY spectrum of complex between receptor **1** and substrate **4** (the labeled protons shown in Scheme 3 and 4) shows that correlation exists between the broad peak of S-oh protons at δ 6.60 of substrate **4** and the peak of R-ah protons at δ 6.30 of receptor **1**. The high binding affinity of substrates **4** and **5** towards receptor **1** is attributed to its deep cavity generated by tetradibenzylamino groups on the upper rim of calix[4]arene.

Conclusion

These experiments demonstrate the utility of uncomplicated synthetic supramolecular model systems for probing experimentally the fundamental nature of weak noncovalent interactions in biological systems. Here, we have shown that calix-[4]arenes with deep cavities may exhibit high affinity for small and neutral substrates. Based on the results generated by our experiments, we are working on the development of water-soluble aminocalixarenes for the effective recognition of pathologically important biomolecules.

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23. **Receptor 1:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6H, *J* = 7.14 Hz, -CH3), 2.02 (q, 4H, *J* = 13.74 Hz, -CH_2-), 3.00 (d, 4H, *J* = 12.10 Hz, Ar-CH_2-Ar), 3.82 (q, 4H, *J* = 6.10 Hz, -OCH_2), 4.19 (d, 4H, *J* = 12.65 Hz, Ar-CH_2-Ar), 4.25 (s, 8H, -N-CH_2-Ar), 4.27

(s, 8H, -N-CH_2-Ar), 6.27 (s, 4H, Ar-H), 6.30 (s, 4H, Ar-H), 7.05-7.24 (m, 40H, Ar-H), 8.82 (s, 2H, Ar-OH). ^{13}C NMR ($CDCl_3$): δ 11.38, 23.72, 32.89, 54.76, 78.53, 113.59, 126.72, 126.89, 127.32, 128.56, 129.09, 134.50, 138.99, 139.60, 142.89, 144.19, 145.29, 146.79. MALDI-TOF MS *m*/*z* (M+): 1288.7

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25. (a) **Job's plot:** Solution of the receptor **1** (10 mM), substrate **4** (10 mM) and **5** (10 mM) in $CDCl_3$ were separately prepared. The ^{1}H NMR tubes were filled with 500 μL solution of the receptor and the substrate in the following volume ratios (all in μL): 50:450, 100:400, 150:350, 200:300, 250:250, 300:200, 350:150, 400:100, 450:50. (b) Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815.