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Tetrahedron 64 (2008) 741–748
Tetrahedron
www.elsevier.com/locate/tet

Calix[4]arene based neutral receptor for dihydrogen phosphate anion

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Received 21 June 2007; received in revised form 16 October 2007; accepted 1 November 2007
Available online 6 November 2007

Abstract

A series of novel calix[4]arene hydrazone and semicarbazone based neutral receptors have been synthesized and characterized by IR, UV–vis, and NMR spectroscopies. The preliminary UV–vis and ^{1}H NMR titration experiments revealed that 25,26,27,28-tetrapropoxycalix[4]arene tetra-semicarbazone can recognize $H_2PO_4^-$ through a 1:1 binding-stoichiometry in preference over other anions (Cl^-, Br^-, I^-, HSO_4^-, ClO_4^-, and CH_3COO^-).

Keywords: Calix[4]arene; Dihydrogen phosphate anion; Recognition; Neutral receptor; Semicarbazone

1. Introduction

The design and synthesis of neutral electron deficient abiotic receptors for anions of biochemical, medical, and environmental importance is an area of intense research activity.[1] As a consequence of their unique upper and lower rim topology, calixarenes are attractive molecular platforms for ion recognition.[2] Though generally examined for cation recognition,[3] the development of calixarene derivatives for recognition of anions is comparatively nascent, in part due to higher free energy of solvation of anions and their dependence on slight variations in pH.[4]

Some of the organic synthetic receptors examined for anions either have positively charged units (e.g., ammonium or guanidium units) or contain a metal center, which can directly coordinate to the anion of interest.[5] Anion binding in charged receptors is achieved by electrostatic interactions (as in the case of polyammonium receptors for binding ATP).[6] It was envisaged that in principle, anion receptors can also be possible by neutral molecular receptors that possess electron deficient or Lewis acid sites in their constitution to form hydrogen bond interactions.[7]

Crystal structures of sulfate[8a,b] and phosphate[8c] binding proteins provide useful insights into their binding characteristics. For instance, prokaryotic, periplasmic phosphate and sulfate binding proteins exhibit selectivities of more than 10^5 for binding phosphate over sulfate and of sulfate over phosphate, respectively.[8d] In both of these proteins the specific binding exclusively takes place through hydrogen bonding.

The availability of synthetic receptors for dihydrogen phosphate can lead to a better understanding of the processes involved in selective biological mimics. Recent reports on synthetic receptors containing urea, uranyl containing salenes, and sulphonamides derived from tris(aminoethyl)-amine (TREN) for $H_2PO_4^-$ support this view.[9] In this paper, we report our results on calixarene based molecular receptors for recognition of $H_2PO_4^-$ anions.

2. Result and discussion

2.1. Design and synthesis of calix[4]arene based receptors

The required starting materials, *p-tert*-butyl-calix[4]arene **1** and debutylated calix[4]arene, were obtained by following the procedures available in the literature.[10a,b] The 25,27-dimethoxy-calix[4]arene, 25,27-di(ethoxycarbonylmethoxy)-calix[4]-arene, and *p-tert*-butyl-25,27-di(ethoxycarbonylmethoxy)-calix[4]arene were obtained by refluxing calix[4]arene with respective alkyl halides with K_2CO_3 in CH_3CN for 48 h as

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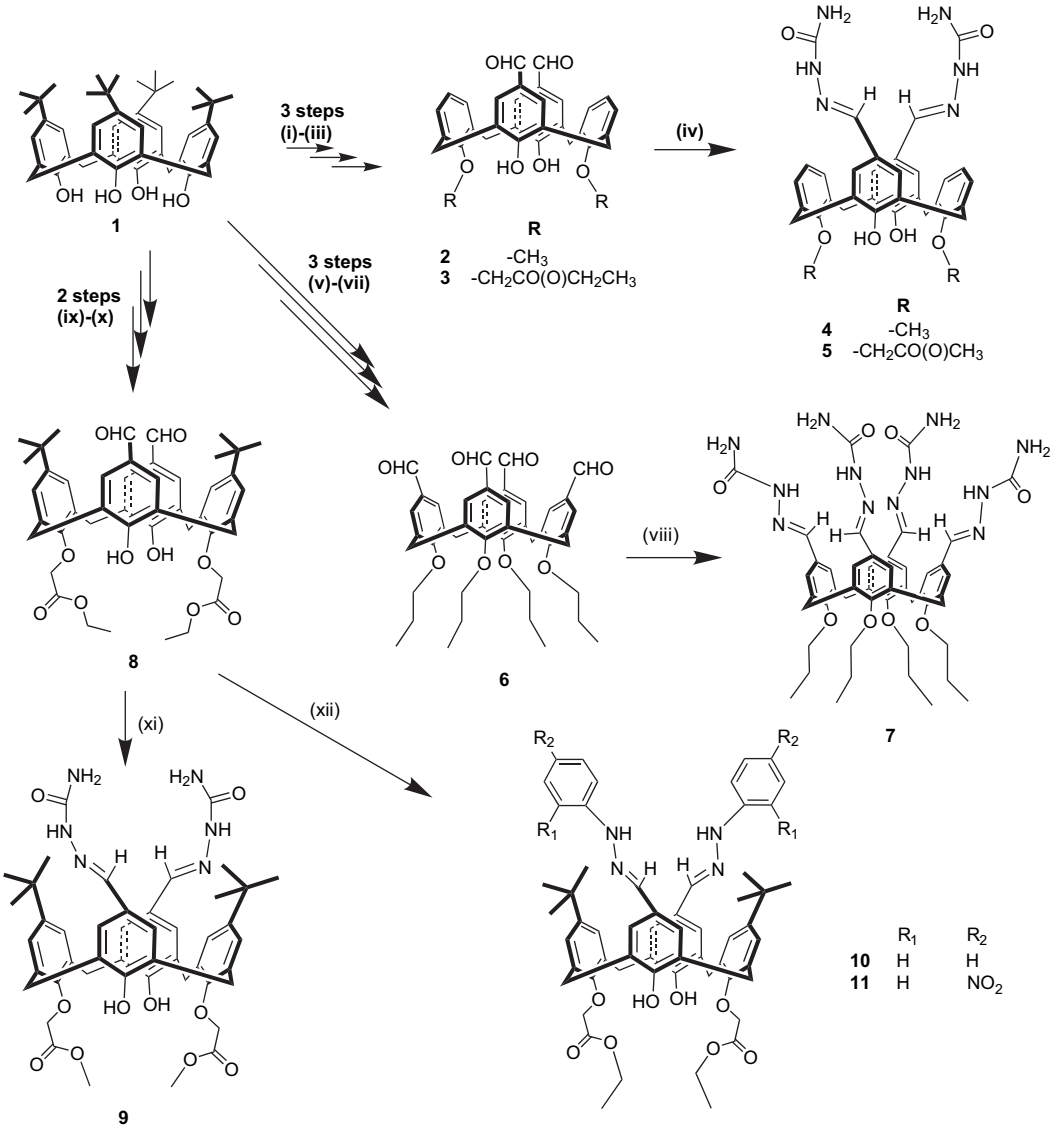
0040-4020/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tet.2007.11.010

described previously.[10c–f] 25,26,27,28-(Tetrapropoxy)-calix[4]arene was synthesized by alkylation with propyl bromide in the presence of NaH in DMF for 48 h.[10g,h] The synthesized calix[4]arene ethers and esters were formylated by using hexamethylenetetramine (HMTA)/trifluoroaceticacid (TFA) system to yield compounds **2**, **3**, **6**, and **8**,[11] which were further reacted with semicarbazide·hydrochloride, phenyl hydrazine, and its nitro derivatives to yield target compounds (**4**, **5**, **7**, and **9**–**11**) in good yields (>80%, Scheme 1).

2.2. Characterization of the synthesized compounds

The identification of the compounds (**4**, **5**, 7, and **9**–**11**) by IR, ^{1}H and ^{13}C NMR, FAB mass spectra, and elemental analysis revealed that the reaction exclusively takes place at the formyl groups. The synthesized iminamides showed characteristic absorptions for –(C=O)–N– (1670–1705 cm^{-1}) and –N–H (3310–3460 cm^{-1}) groups. Compounds **5** and **9**–**11** also showed characteristic absorptions for an ester functionality at ~1750 cm^{-1} (Table 1). The resonance signals for the methylene bridge carbon in the ^{13}C NMR spectra of **4**, **5**, **7**, and **9**–**11** suggested that they were present in their cone conformation.[12] The exact substitution pattern and conformation of these products were further confirmed by ^{1}H NMR spectroscopy. For instance, **7** exhibited signals at δ 9.93 (s), 7.57 (s), 7.23 (s), and 6.47 (s) for NH, CH, ArH, and NH_2, respectively, while methylene bridge and propyl protons could be observed at δ 4.37 (d), 3.30 (d) and 3.83 (br s), 1.95 (br q), 0.99 (br s) in the ^{1}H NMR spectrum indicating its tetrasubstituted symmetric cone conformation.



Scheme 1. Synthesis of **4** and **5**: (i) $AlCl_3$, phenol, toluene, rt, stirring, 1 h (yield=75%); (ii) $BrCH_2CO(O)CH_2CH_3$ or MeI, K_2CO_3, CH_3CN, reflux, 48 h (yields=62% and 60%, respectively); (iii) TFA, HMTA, reflux, 1 h (yields for **2**=64%, for **3**=85%); (iv) NH_2–NH_2–C(O)–NH_2·HCl, toluene/methanol, reflux, 24 h (yields for **4**=82%, for **5**=84%). Synthesis of **7**: (v) $AlCl_3$, phenol, toluene, rt, stirring, 1 h (yield=75%); (vi) $BrCH_2CH_2CH_3$, NaH, DMF, rt, stirring, 36 h (yield=57%); (vii) TFA, HMTA, reflux, 48 h (yield=65%); (viii) NH_2–NH_2–C(O)–NH_2·HCl, toluene/methanol, reflux, 24 h (yield for **7**=87%). Synthesis of **9**–**11**: (ix) $BrCH_2CO(O)CH_2CH_3$, K_2CO_3, CH_3CN, reflux, 48 h (yield=64%); (x) TFA, HMTA, reflux, 24 h (yield for **8**=82%); (xi) NH_2–NH_2–C(O)–NH_2·HCl, toluene/methanol, reflux, 24 h (yield for **9**=86%); (xii) NH_2–NH_2–Ph–R (R=H or NO_2), toluene/methanol, reflux, 24 h (yields for **10**=85%, for **11**=81%).

Table 1
Important IR and NMR signals of synthesized compounds

Compd. no.	IR ν_{max}/cm^{-1}	Characteristic ^1H NMR signals (δ, 25 °C, 300 MHz)						^{13}C NMR signals for $ArCH_2Ar$ (δ, 25 °C, 75 MHz)
		NH	OH	CH	$ArH_{calixarene\ core}$	NH_2	$ArCH_2Ar$	
4	3342, 1677	10.12 (s)	8.41 (s)	7.63 (s)	7.56 (s), 7.11 (d, J=7.5 Hz), 6.83 (t, J=7.5 Hz)	6.49 (br s)	4.19 (d, J=12.9 Hz), 3.53 (d, J=12.9 Hz)	29.9
5	3316, 3286, 1750, 1677, 1578	9.88 (s)	8.14 (s)	7.72 (s)	7.36 (s), 7.02 (d, J=7.2 Hz), 6.86 (t, J=7.2 Hz)	5.98 (br s)	4.43 (d, J=13.2 Hz), 3.48 (d, J=13.2 Hz)	—
7	3439, 2962, 2874, 1676	9.93 (s)	—	7.57 (s)	7.23 (s)	6.47 (s)	4.37 (d, J=11.4 Hz), 3.30 (d, J=11.4 Hz)	30.0
9	3437, 3284, 1751, 1705, 1578	9.94 (s)	8.20 (s)	7.61 (s)	7.44 (s), 7.15 (s)	6.37 (s)	4.34 (d, J=7.5 Hz), 3.48 (d, J=7.5 Hz)	30.5
10	3384, 3268, 1749, 1598, 1478	7.78 (br s)	7.95 (s)	7.78 (br s)	7.26 (br s), 7.02 (br s)	—	4.49 (br s), 3.42 (br s)	[a]
11	3424, 3278, 1750, 1597, 1477	7.84 (s)	8.19 (s)	7.61 (s)	7.31 (s), 7.04 (br s)	—	4.55 (d, J=13.5 Hz), 3.45 (d, J=13.5 Hz)	31.2

[a] ^{13}C NMR spectral data could not be collected due to instability in solution.

Likewise, **4** exhibited signals at δ 10.12 (s), 8.41 (s), 7.63 (s), 6.49 (br s), and 3.94 (s) for NH, hydroxyl, CH, NH_2, and methoxy protons, respectively, while aromatic and methylene bridge protons could be observed at δ 7.56 (s), 7.11 (d), 6.83 (t), 4.19 (d), and 3.53 (d) in its ^1H NMR spectrum indicating that **4** is a distally disubstituted compound present in its cone conformation with a symmetric configuration. A very similar ^1H NMR spectral pattern was observed for **5**. It was interesting to note that **5** had two methyl ester functions instead of ethyl ester functions present in the precursor compounds as indicated by a singlet for six protons at δ 3.88 in its ^1H NMR. The ^1H NMR spectral pattern of **9** also suggested it to have a methyl ester function instead of the expected ethyl ester units indicating that trans-esterification had occurred with the methanol solvent present in excess. In addition to singlets at δ 9.94 (s), 8.20 (s), 7.61 (s), 6.37 (s), 4.86 (s), 3.80 (s), and 1.09 (s) for NH, OH, CH, NH_2, $ArOCH_2$, OCH_3, and $C(CH_3)_3$ protons, the two signals each for aromatic and methylene bridge protons could be observed at δ 7.44 (s), 7.15 (s), 4.34 (d), and 3.48 (d). Similarly, compounds **10** and **11** could be characterized.

2.3. Interaction with anions

The anion co-ordination properties of the synthesized derivatives were investigated by UV–vis and ^1H NMR spectroscopic titrations in a DMSO solution. Various anions were taken as tetrabutylammonium (TBA) salts. The unstable nature of **10** in solution precluded the possibility of study of its utility for anion recognition. Consequently, calix[4]arene semicarbazones (**4**, **7**, and **9**) were examined for preliminary UV–vis studies. It was observed that the addition of TBA (Cl^-, Br^-, I^-, ClO_4^-, HSO_4^-, CH_3COO^-, and $H_2PO_4^-$) salts did not lead to any change in the case of **4** and **9** while a significant increase in absorption could be observed in the UV–vis spectrum of **7** when $TBA^+ \cdot H_2PO_4^-$ was added to its DMSO solution (Fig. 1).

To test the practical utility of **7** as a $H_2PO_4^-$ selective receptor, competitive experiments were carried out by addition of TBA salts in the presence of each other. These experiments revealed that there was an increase in the absorption and a shift in the λ_{max} of **7** upon addition of $TBA^+ \cdot H_2PO_4^-$ even in the presence of halides and other anions while other receptor molecules did not show such a differentiation.

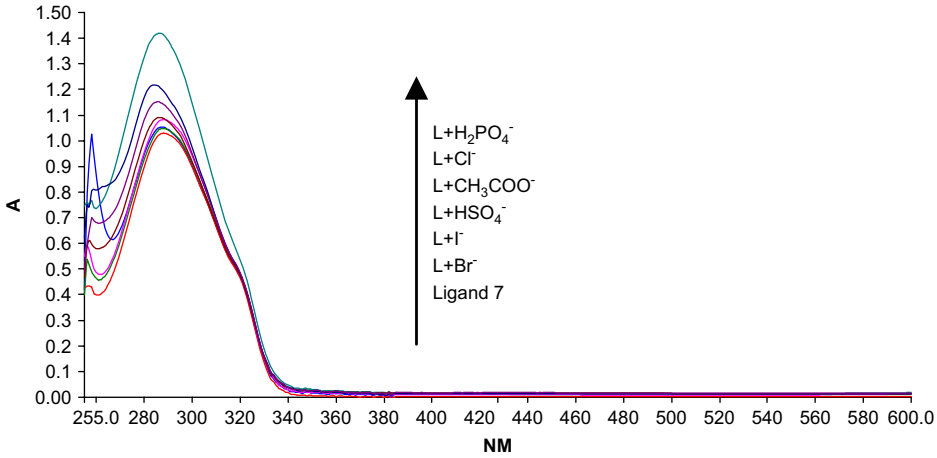


Figure 1. UV–vis spectra of host **7**(L) in DMSO-d_6 on addition of excess TBA salts.

Anion recognition properties of **7** were further examined to reveal that its ^{1}H NMR spectra continuously changed upon addition of variable amounts of tetrabutylammonium dihydrogen phosphate in DMSO-d_6 while no spectral changes were observed upon addition of other tetrabutylammonium salts (Cl^-, Br^-, I^-, ClO_4^-, and HSO_4^-) under the same experimental conditions (Fig. 2). In contrast, **4** and **9** were not found to exhibit any change in their ^{1}H NMR spectra even on addition of tetrabutylammonium dihydrogen phosphate. These results were found to be consistent with those observed in the UV–vis spectral titration indicating the specificity of interaction of **7** with $H_2PO_4^-$.

It was interesting to note that the NH signal at δ 9.88 was markedly affected by addition of tetrabutylammonium dihydrogen phosphate to **7** in DMSO-d_6 (Fig. 2). A significant downfield shift for NH proton and a marginal upfield shift for aromatic protons suggested the proximity of $H_2PO_4^-$ anion to amidic functions and that the $H_2PO_4^-$ anion is probably coordinated by hydrogen bonds. No change in the $CONH_2$ protons was observed, which indicated that these groups were not involved in the binding of $H_2PO_4^-$ anion. The stoichiometry of interaction of **7** and $H_2PO_4^-$ was determined by Job's continuous variation plot. The results obtained unambiguously indicated that a complex of unknown structure was formed between **7** and dihydrogen phosphate ion with a 1:1 stoichiometry (Fig. 3a). The association constant for **7** and $H_2PO_4^-$ was calculated as 1890 M^{-1} from changes in chemical shift for the NH protons of semicarbazone units by using WinEQNMR program.[14] ^{1}H NMR titration curve for observed change in chemical shift of NH proton of receptor **7** with tetrabutylammonium dihydrogen phosphate has been shown in Figure 3b.

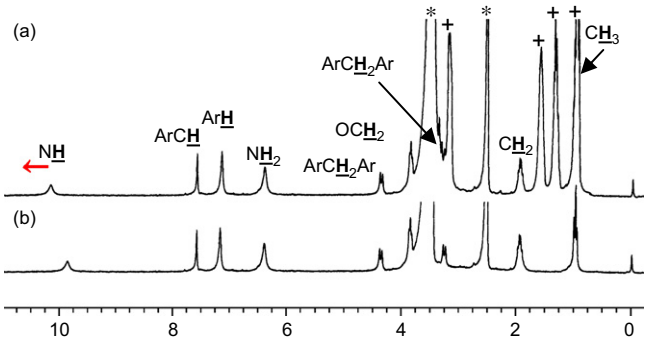


Figure 2. ^{1}H NMR (300 MHz) spectra of host **7** (10 mM) in DMSO-d_6 with (above) and without the addition of excess of $H_2PO_4^-$ (significant downfield shift in NH proton was observed, * indicate signal due to adventitious water and residual solvent, + indicate signals due to butyl protons of t-Bu_4N^+ salt).

The possibility of the presence of anion within the cavity of receptor **7** could be ruled out on the basis of its CPK model, which suggested that its cavity size was too small for $H_2PO_4^-$ anion. The experimental observations could be explained by assuming a four coordinate interaction of $H_2PO_4^-$ with NH protons at the upper rim of calix[4]arene through hydrogen bonds (Fig. 4a), which were further confirmed by NOESY and ROESY experiments.

The NOESY spectrum of a 1:1 solution of **7** and $TBA^+ \cdot H_2PO_4^-$ revealed strong correlations between the n-butyl chain of TBA^+ and propoxy chain of calix[4]arene to suggest the presence of TBA cation near the alkoxy group (Fig. 4a and b). The ROESY spectrum, which seemed similar to its NOESY spectrum further strengthened this view.

The similar experiments with the solution of **7** and $TBA^+ \cdot PF_6^-$ also revealed correlations between n-butyl chain of TBA^+ and propoxy chain of calix[4]arene. However, no shift in the CH, NH, NH_2, and ArH protons suggested that there was no effective binding of PF_6^-.

The above experiments revealed strong interaction between adventitious water and CH, NH and NH_2 protons and suggest that water prefers to stay near the polar groups through hydrogen bond donor–acceptor mechanism. These observations are in accordance with recent reports on the interaction of polar solvents with polar groups at the upper rim of calix[4]arene, which seems to play an important role in shaping the plausible expansion of aromatic cavity through hydrogen bond bridging.[13]

It should be noted that both **4** and **9** were not able to bind dihydrogen phosphate through only two semicarbazone units. The observed high selectivity with **7** suggested a special interaction for diphosphate anion through hydrogen bonding over other tetrahedral (ClO_4^- and HSO_4^-), spherical (e.g., Cl^-, Br^-, and I^-), and Y-shaped (e.g., acetate) anions, which calls for further studies on anion recognition through calix[4]arene based molecular receptors. Further work on this theme is in progress in our labs.

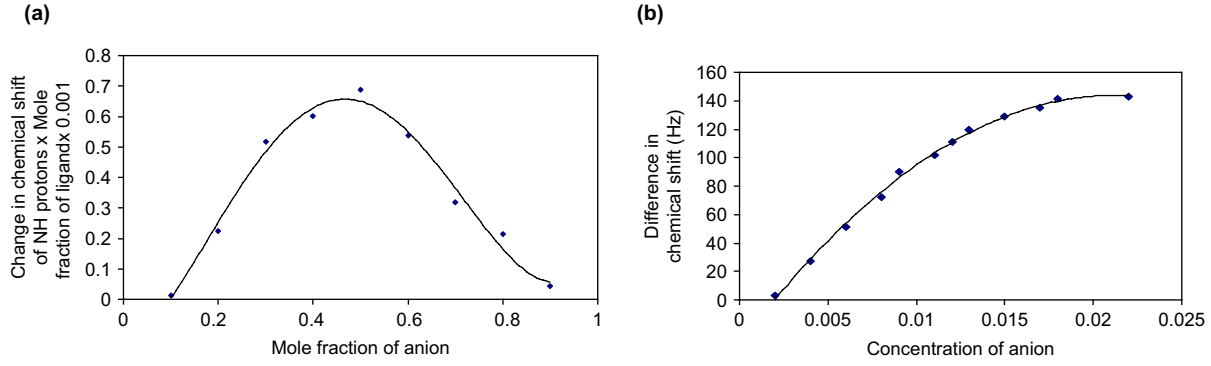


Figure 3. (a) Job's plot of the titration of 0.01 M $H_2PO_4^-$ with 0.01 M receptor **7** in DMSO-d_6 (anion used was in form of t-Bu_4N^+ salt). (b) ^{1}H NMR titration curve for NH proton of receptor **7** with $TBA \cdot H_2PO_4^-$ (DMSO-d_6, 300 MHz, 298 K).

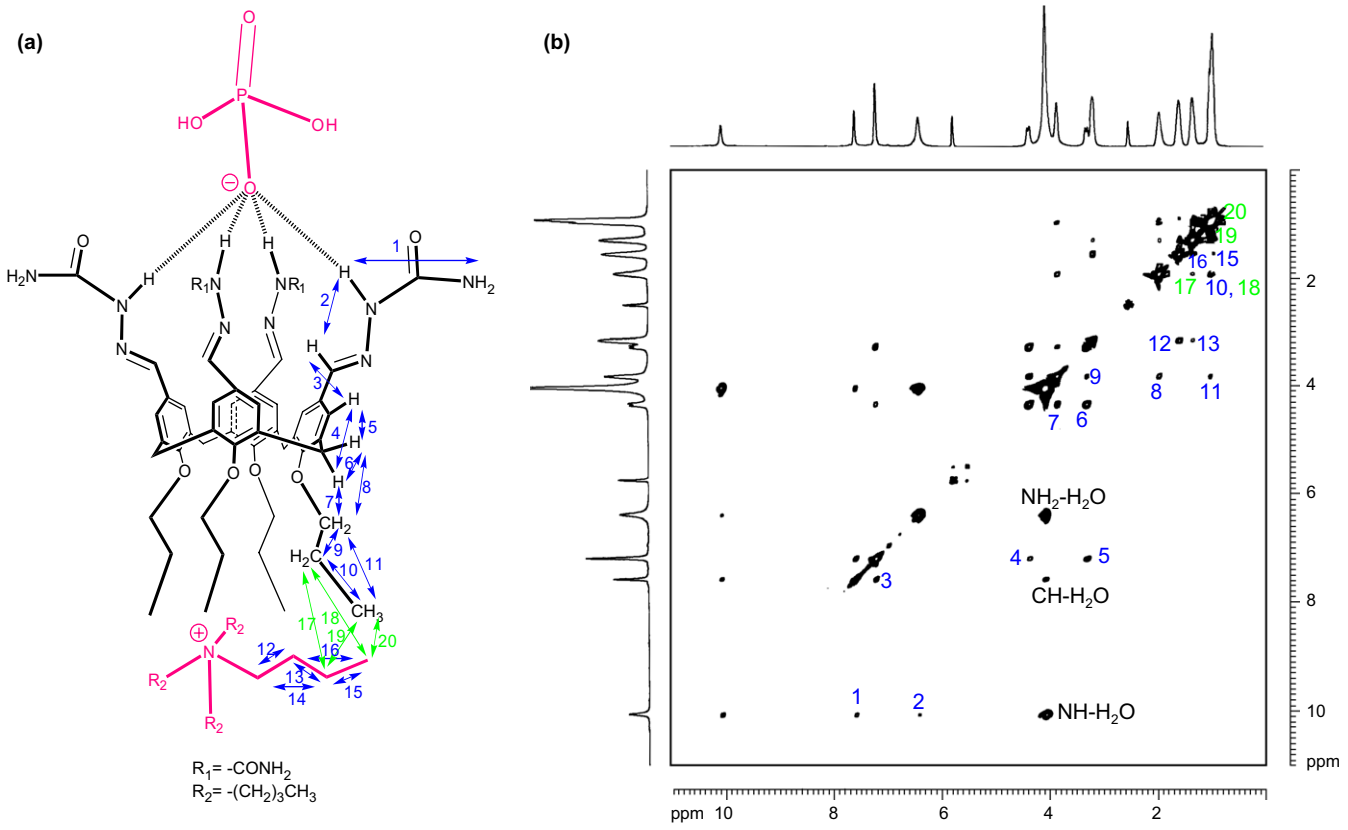


Figure 4. (a) Proposed structure of host **7**/$H_2PO_4^-$ complex and observed NOESY correlations in **7**/$TBA^+ \cdot H_2PO_4^-$ (1:1) mixture in DMSO-d_6 solution (intramolecular correlations have been shown in blue color while intermolecular correlations have been shown in green color, since molecule has 4-fold symmetry, correlation in only one fourth of the molecule have been shown). (b) NOESY spectrum of **7**/$TBA^+ \cdot H_2PO_4^-$ (1:1) mixture in DMSO-d_6 solution at 25 °C (300 MHz).

3. Conclusion

In summary, we have synthesized a series of new neutral molecular receptors based on calix[4]arene framework. Receptor **7** displays a high sensitivity and selectivity toward $H_2PO_4^-$ anion in preference to a wide range of tetrahedral, spherical, and Y-shaped anions.

4. Experimental section

4.1. General

All the reagents used in the study were purchased from Sigma–Aldrich or Merck and were chemically pure. The solvents used were distilled and dried except toluene and methanol. ^{1}H NMR, ^{13}C NMR, DEPT-135, NOESY, and ROESY spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) at 0.00 as an internal standard. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while the FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data System using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Melting points were determined on an electrothermal melting point apparatus obtained from M/S Toshniwal Brothers, Mumbai and were uncorrected.

4.2. Synthesis of starting material

p-tert-Butylcalix[*n*]arene, *n*=4 and its debutylated analog were synthesized by the method described by Gutsche et al.[10a,b] They were alkylated according to the literature precedent to yield desired 25,27-di(methoxy)-calix[4]arene, 25,27-di(ethoxycarbonylmethoxy)-calix[4]arene, 5,11,17,23-tetra(*p-tert*-butyl)-25,27-di(ethoxycarbonyl methoxy)-calix[4]-arene, and 25,26,27,28-tetra(propoxy)-calix[4]arene.[10c–h] These alkylated calixarene derivatives were further formylated by Duff reaction protocol (as given in the following section) to give the desired 5,11-bis(formyl)-25,27-di(methoxy)-26,28-di-(hydroxy)-calix[4]arene (**2**), 5,11-bis(formyl)-25,27-di(ethoxy-carbonylmethoxy)-26,28-di(hydroxy)-calix[4]arene (**3**), 5,11,17,23-tetra(formyl)-25,25,26,27,28-tetra(propoxy)-calix[4]arene (**6**), and 5,11-bis(formyl)-17,23-di(*p-tert*-butyl)-25,27-di(ethoxycarbonylmethoxy)-26,28-di(hydroxy)-calix[4]arene (**8**).[11]

4.3. General procedure for the synthesis of formylated calix[4]arene derivatives (*2*, *3*, *6*, and *8*)

Alkylated calix[4]arene (500 mg) and hexamethylenetetramine (40 equiv) were taken in trifluoroacetic acid (50 mL). The reaction mixture was refluxed until the starting materials had disappeared (TLC, reaction time has been mentioned in

Scheme 1). On completion, the mixture was quenched with ice cold water and extracted with dichloromethane. The organic layer was washed with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified as mentioned to yield the desired formylated calix[4]-arene products (**2**, **3**, **6**, and **8**). The spectral data of the synthesized formylated calix[4]arene derivatives were found to be similar to those reported earlier.[11]

4.4. General procedure for the synthesis of semicarbazone and hydrazone derivatives of calix[4]arene

To a solution of formylated calix[4]arene (200 mg) in 40 mL of toluene/methanol (1:1) was added a semicarbazide·hydrochloride or phenyl hydrazine derivative (1.1 equiv per one formyl group) and the mixture was refluxed for 12 h. The solvent was then evaporated under reduced pressure and the remaining solid was washed with methanol (for **7**) or water. The product was filtered and dried under vacuum to give target products.

*4.4.1. Compound **4***

Yellow colored solid, yield: 82%, mp>300 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3342, 2926, 1677. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 10.12 (s, 2H, N*H*), 8.41 (s, 2H, O*H*), 7.63 (s, 2H, C*H*), 7.56 (s, 4H, Ar*H*), 7.11 (d, J=7.5 Hz, 4H, ArH_{meta}), 6.83 (t, J=7.5 Hz 2H, ArH_{para}), 6.49 (br s, 4H, NH_2), 4.19 (d, J=12.9 Hz, 4H, ArCH_2Ar), 3.94 (s, 6H, CH_3), 3.53 (d, J=12.9 Hz, 4H, ArCH_2Ar). ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm): 139.1, 128.8, 126.8, 125.1 (aromatic *C*H and *C*H), 63.6 (O*C*H$_3$), 29.9 (Ar*C*H$_2$Ar). FABMS *m*/*z*: 623 (M^++1). Anal. Calcd for $C_{34}H_{34}N_6O_6$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.91; H, 5.48; N, 13.45.

*4.4.2. Compound **5***

White solid, yield: 84%. IR (KBr, ν_{max}/cm^{-1}): 3316, 3286, 2926, 1750, 1677, 1578. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 9.88 (s, 2H, N*H*), 8.14 (s, 2H, O*H*), 7.72 (s, 2H, C*H*), 7.36 (s, 4H, Ar*H*), 7.02 (d, J=7.2 Hz, 4H, ArH_{meta}), 6.86 (t, J=7.2 Hz, 2H, ArH_{para}), 5.98 (br s, 4H, NH_2), 4.75 (s, 4H, ArOCH_2), 4.43 (d, J=13.2 Hz, 4H, ArCH_2Ar), 3.88 (s, 6H, OCH_3), 3.48 (d, J=13.2 Hz, 4H, ArCH_2Ar). FABMS *m*/*z*: 739 (M^++1). Anal. Calcd for $C_{39}H_{40}N_6O_9$: C, 61.78; H, 5.18; N, 11.38. Found: C, 62.14; H, 5.16; N, 11.44.

*4.4.3. Compound **7***

White solid, yield: 87%, mp>330 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3439, 2962, 2874, 1676. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 9.93 (s, 4H, N*H*), 7.57 (s, 4H, C*H*), 7.23 (s, 8H, Ar*H*), 6.47 (s, 8H, NH_2), 4.37 (d, J=11.4 Hz, 4H, ArCH_2Ar), 3.83 (br s, 8H, ArOCH_2), 3.30 (d, J=11.4 Hz, 4H, ArCH_2Ar), 1.95 (br q, J=6.3 Hz, 8H, ArOCH$_2$CH_2), 0.99 (br s, 12H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm): 156.8, 139.8, 134.5, 128.9, 126.8 (*C*=O, aromatic *C*H and *C*), 76.6 (OCH_2), 30.0 (Ar*C*H$_2$Ar), 22.7 (O CH$_2$*C*H$_2$), 10.1 (*C*H$_3$). FABMS *m*/*z*: 933 (M^++1). Anal. Calcd for $C_{48}H_{60}N_{12}O_8$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.54; H, 6.51; N, 17.89.

*4.4.4. Compound **9***

White solid, yield: 86%, mp=205 °C. IR (KBr, ν_{max}/cm^{-1}): 3437, 3284, 2925, 1751, 1705, 1578, 1470. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 9.94 (s, 2H, N*H*), 8.20 (s, 2H, O*H*), 7.61 (s, 2H, C*H*), 7.44 (s, 4H, Ar*H*), 7.15 (s, 4H, Ar*H*), 6.37 (s, 4H, NH_2), 4.86 (s, 4H, ArOCH_2), 4.34 (d, J=7.5 Hz, 4H, ArCH_2Ar), 3.80 (s, 6H, OCH_3), 3.48 (d, J=7.5 Hz, 4H, ArCH_2Ar), 1.09 (s, 18H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm): 170.2, 157.6, 153.5, 150.9, 147.9, 140.9, 133.1, 129.4, 128.7, 127.4, 126.6 (*C*=O, *C*H, aromatic *C*H and *C*), 72.0 (ArO*C*H$_2$), 52.5 (O*C*H$_3$), 34.4 (−*C*(CH$_3$)$_3$), 31.4 (−C(*C*H$_3$)$_3$), 30.5 (Ar*C*H$_2$Ar). FABMS *m*/*z*: 851 (M^++1). Anal. Calcd for $C_{48}H_{60}N_{12}O_8$: C, 55.63; H, 3.33; N, 9.27. Found: C, 55.54; H, 3.35; N, 9.34.

*4.4.5. Compound **10***

White solid, yield: 85%. IR (KBr, ν_{max}/cm^{-1}): 3384, 3268, 2930, 1749, 1598, 1478. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 7.95 (s, 2H, O*H*), 7.78 (s, 4H, N*H* and C*H*), 7.26 (br s, 10H, Ar*H*), 7.02 (br s, 8H, Ar*H*), 4.83 (s, 4H, ArOCH_2), 4.49 (br s, 4H, ArCH_2Ar), 4.33 (br s, 4H, CO(O)CH_2), 3.42 (br s, 4H, ArCH_2Ar), 1.35 (br s, 6H, CH$_2$CH_3), 1.13 (s, 18H, C(CH_3)$_3$). FABMS *m*/*z*: 945 (M^++1). Anal. Calcd for $C_{58}H_{64}N_4O_8$: C, 73.70; H, 6.83; N, 5.93. Found: C, 73.46; H, 6.86; N, 6.02.

*4.4.6. Compound **11***

Red solid, yield: 81%, mp=218 °C. IR (KBr, ν_{max}/cm^{-1}): 3424, 3278, 2930, 1750, 1597, 1477. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.19 (s, 2H, O*H*), 8.15 (d, 4H, J=8.1 Hz, ArH_{phenyl}), 7.84 (s, 2H, N*H*), 7.61 (s, 2H, C*H*), 7.31 (s, 4H, ArH_{calix}), 7.04 (br s, 8H, ArH_{phenyl} and ArH_{calix}), 4.85 (s, 4H, ArOCH_2), 4.55 (d, J=13.5 Hz, 4H, ArCH_2Ar), 4.37 (q, J=6.9 Hz, 4H, CO(O)CH_2), 3.45 (d, J=13.5 Hz, 4H, ArCH_2Ar), 1.37 (t, 6H, J=6.9 Hz, CH$_2$CH_3), 1.15 (s, 18H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm): 168.9, 153.0, 150.4, 150.3, 147.3, 141.7, 137.9, 132.2, 128.8, 127.6, 126.3, 125.9, 125.5, 110.3 (*C*=O, aromatic *C*H and *C*), 71.4 (ArO*C*H$_2$), 60.7 (CO(O)*C*H$_2$), 33.6 (*C*(CH$_3$)$_3$), 31.2 (Ar*C*H$_2$Ar), 30.63 (C(*C*H$_3$)$_3$), 13.6 (OCH$_2$*C*H$_3$). FABMS *m*/*z*: 1035 (M^++1). Anal. Calcd for $C_{58}H_{62}N_6O_{12}$: C, 67.30; H, 6.04; N, 8.12. Found: C, 67.54; H, 6.01; N, 8.23.

4.5. General procedure for UV–vis experiments

All the UV–vis experiments were carried out in dimethyl sulfoxide. Any changes in the UV–vis spectra of the synthesized compound were recorded on addition of tetrabutylammonium salt (excess) while keeping the ligand concentration constant in all experiments. Tetrabutylammonium salt of anions (Cl^-, Br^-, I^-, ClO_4^-, HSO_4^-, CH_3COO^-, and $H_2PO_4^-$) was used for the UV–vis experiments.

4.6. General procedures for ^{1}H NMR titration

4.6.1. Interaction study

A solution of the hosts (**4**, **7**, and **9**) was prepared in DMSO-d_6. To 0.5 mL of this solution, approximately 10 equiv of tetrabutylammonium salts of anions (Cl^-, Br^-, I^-, ClO_4^-, HSO_4^-, CH_3COO^-, and $H_2PO_4^-$) were added in the ^{1}H NMR tube and the spectra were recorded again. The chemical shift of the NH protons was followed to observe significant change, if any.

4.6.2. Job plot

Solution of the host **7** (10 mM) and for the tetrabutylammonium dihydrogen phosphate (10 mM) in DMSO-d_6 were separately prepared. The ^{1}H NMR tubes were filled with 500 μL solution of host and the guest in the following volume ratios: 50:450, 100:400, 150:350, 200:300, 250:250, 200:300, 150:350, 100:400, 50:450. The ^{1}H NMR spectra of each tubes with above mentioned ratio were recorded to observe significant shifts in the position of NH protons in each experiment, which was plotted to give the Job plot in accordance with recent literature reports.[15]

4.6.3. Association constant

A solution (10 mM) of receptor **7** in DMSO-d_6 was titrated with aliquots from stock solution of tetrabutylammonium dihydrogen phosphate (40 mM) in the same solvent. The chemical shift change of the NH proton of semicarbazone units in receptor **7** was monitored. The association constants K_a was calculated using the WinEQNMR computer program.[14]

Acknowledgements

We thank the C.S.I.R. for a senior research fellowship (to SPS) and D.S.T; D.B.T., MOEF, MRD, and MFPI (Govt. of India) for financial assistance. We also thank Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow for the mass spectra reported in this paper.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.010.

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