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Pyrrolamidocalix[4]arenes: new receptors for anion recognition

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ABSTRACT

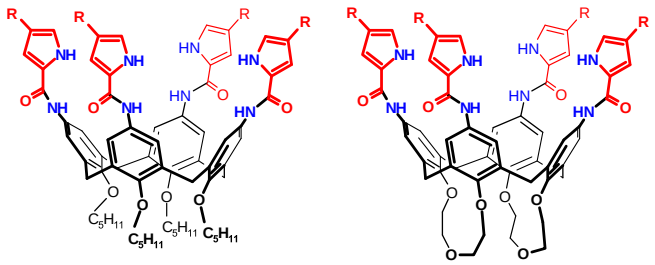
Pyrrolamidocalix[4]arenes **1**–**4**, members of a new class of anion receptors bearing pyrrolic units at the upper rim of calix[4]arene macrocycle, have been readily synthesized in good yields. Derivatives **1** and **3**, with unsubstituted pyrrole units, show a good selectivity for $H_2PO_4^-$ over F^- and AcO^-, while the presence of electron-withdrawing NO_2 substituents in **2** and **4** inverts the selectivity favoring more basic AcO^- and F^-. In addition, it is demonstrated that the flexibility of calix[4]arene skeleton, present in **1** but absent in **3**, is very important in the fitting process that leads the amidopyrrole moieties to wrap the tetrahedral $H_2PO_4^-$ guest.

Anions play a central role in areas as diverse as medicine, environment, and industry.[1] The recognition and sensing of anions by means of neutral receptors which recognize them through hydrogen bonding, have recently become highly successful.[2] Electroneutral anion receptors, such as amides,[3] ureas,[4] thioureas,[5] amidoureas,[6] and pyrroles[7] are particularly attractive for such scope. Thus, incorporation of such anion recognition moieties into larger macrocycles, such as calix[4]arene[8] skeleton, led to three-dimensional preorganized binding sites with interesting recognition properties toward anionic guests.[9]

Recently our group has reported *aramidocalixarene* derivatives, bearing aromatic amide (*aramid*) moieties at the upper rim, which display interesting selectivity toward trigonal planar anions such as nitrate.[10] Amidourea-based calix[4]arene sensors for anions have been reported, recently, by Matthews and Gunnlaugsson, which give rise to colorimetric responses visible to the naked eye.[6,11] Among the different anion recognition motifs, pyrrole units have attracted considerable attention in the recent years. In fact, it is well known that calix[4]pyrrole hosts[7] show an exceptional affinity for anionic guests.[12] In addition, the synthetic versatility of calix[4]pyrrole macrocycle allows the introduction of appropriate functional groups able to sense the presence of anionic guests by means of optical[13] or electrochemical[14] response.

These observations prompted us to investigate the incorporation of pyrrole units at the upper rim of calix[4]arene skeleton. In this Letter we wish to report the first[15] examples of *pyrrolamidocalix[4]arene* hosts **1**–**4** (Fig. 1) and their binding properties toward anionic guests.

The synthesis of derivatives **1**–**4** is outlined in Scheme 1. Derivative **1** was obtained, in 70% yield, by coupling tetrapentoxy-tetraminocalix[4]arene **5**[16] with 1-pyrrole-2-carbonyl chloride **6**[17] in the presence of NEt_3 in dry THF as the solvent.[18] The structure of C-linked pyrrolamidocalix[4]arene derivative **1** was readily confirmed by spectral analysis.[18] In particular, the presence of a pseudomolecular ion peak at m/z 1137 (MH^+) in the ESI(+) mass spectrum of **1** confirmed the molecular formula. The C_{4v} symmetrical structure of **1** was confirmed by pertinent signals in the ^1H and ^{13}C NMR spectra in DMSO-d_6. In fact, in the ^1H NMR spectrum of **1**, the –CONH– protons were observed as a singlet at 11.45 ppm (4H), while pyrrolic NH protons were present at 9.45 ppm (4H). The $ArCH_2Ar$ groups give rise to an AX system at 3.17/4.42 ppm



1 R = H
2 R = NO_2

3 R = H
4 R = NO_2

Figure 1. Structure of pyrrolamidocalix[4]arene hosts **1**–**4**.

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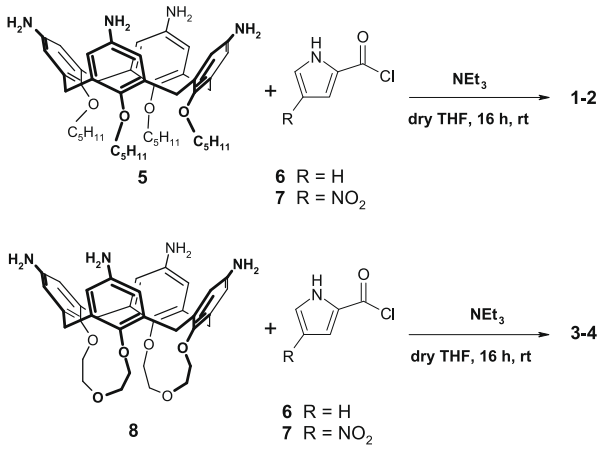

Scheme 1. Synthesis of Pyrrolamidocalix[4]arene derivatives **1**–**4**.

(J = 12.7 Hz), while the aromatic protons of calixarene skeleton give rise to a singlet at 7.15 ppm (8H), and the aromatic protons of pyrrole rings give rise to broad singlets at 6.06, 6.87, and 6.91 ppm. The ^{13}C NMR spectrum, in addition to calixarene resonances, displayed a characteristic signal at 158.8 ppm relative to the –CONH– carbonyl groups and the pertinent pyrrole peaks.[18]

Similarly, the coupling between tetrapentoxy-tetraminocalix[4]arene **5** and 4-nitropyrrole-2-carbonyl chloride **7**[19] gave nitropyrrolamidocalix[4]arene derivative **2** in 50% yield.[18] Analogously, receptors **3** and **4** were synthesized starting from the rigidified tetraminocalix[4]bis-crown-3 **8**[20] (Scheme 1). In particular, the coupling between **8** and acyl chlorides **6** and **7,** in the presence of NEt_3 in dry THF as the solvent, gave derivatives **3** and **4** in 65% and 45% yield, respectively.[18] Analogously to **1**, the structure of derivatives **2**–**4** was readily assigned by spectral analysis.[18]

The binding ability of pyrrolamidocalix[4]arene derivatives **1**–**4** toward selected anionic guests was studied by standard ^1H NMR titrations,[21] in which the host concentration was kept constant while the guest concentration was varied.[18] The addition of anions, in the form of tetrabutylammonium salts, to the solution of each receptor caused significant downfield shifts of the signals of both amide and pyrrolic NH protons in the ^1H NMR spectrum. This indicated that these groups were engaged in hydrogen bonding interactions with the anionic guest with a fast complexation equilibrium.

From the K_a values reported in Table 1,[18] it can be seen that **1** shows a high affinity toward $H_2PO_4^-$ over other anions. Interestingly, it can efficiently discriminate $H_2PO_4^-$ from F^- and AcO^-. In particular, the selectivity for dihydrogen phosphate anion is more than 38-fold higher than those for trigonal planar acetate and benzoate anions. Inspection of the energy-minimized[22] structures of $H_2PO_4^-$ complex of **1** (Fig. 2) suggests that host **1** adopts a flattened cone conformation, in which three amidopyrrole units form a planar trigonal arrangement of NHs that complement three H-bonding acceptor sites of tetrahedral $H_2PO_4^-$ anion. In fact, three coplanar oxygen atoms of $H_2PO_4^-$ guest are each one engaged in a bifurcated[23] hydrogen bonding with –CONH– and pyrrolic NH protons of host **1**. Naturally, bidentate Y-shaped carboxylato anions show less complementarity than tetrahedral guests for trigonal binding sites as reported in the literature.[2b]

Table 1
Complexation constants (K_a) of receptors **1**–**4** toward selected anions determined by ^1H NMR titrations in DMSO-d_6 (containing 0.5% of water) at 298 K

Anions[b]	K_a (M^{-1})[a]			
	1	**2**	**3**	**4**
$H_2PO_4^-$	2500	315	920	360
CH_3COO^-	65	1140	460	2530
$PhCOO^-$	40	530	200	1070
NO_3^-	[c]	[c]	[c]	[c]
F^-	650	220	670	1390
Cl^-, Br^-, I^-	[c]	[c]	[c]	[c]

[a] All errors are <±15%.
[b] As tetrabutylammonium salts.
[c] No changes in NMR spectra were observed.

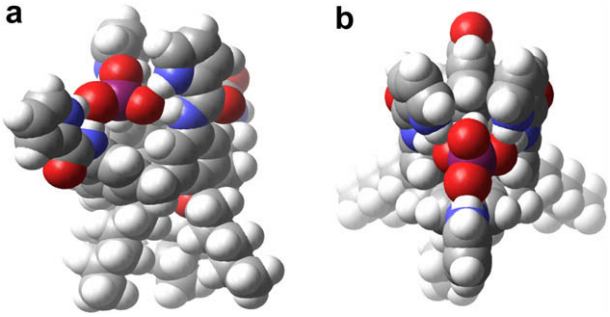

Figure 2. Lowest energy structure of $H_2PO_4^-$ complex of **1** found by Monte Carlo conformational search (10,000 steps, MacroModel V. 9.0, AMBER force field). (a) Side view. (b) Top view.

Differently by **1**, pyrrolamidocalix[4]arene **3** shows a selectivity for dihydrogen phosphate anion only twofold higher than that for trigonal planar guest such as acetate anion. In addition, the association constant of the $H_2PO_4^-$ complex of **3** is lower than the association constant of the $H_2PO_4^-$ complex of **1** (920 and 2500 M^{-1}, respectively). The lower affinity of **3** for $H_2PO_4^-$ anion could be related to the rigidification of the calixarene skeleton. In fact, host **3** is rigidified in a *cone* 'C_{4v}-symmetrical' conformation[24] by the two short crown ether bridges, which completely prevents the conformational change to a flattened cone conformation.[25] From the above results it can be concluded that, on the contrary, such a flexibility might be necessary for the fitting of amidopyrrolic moieties around at the $H_2PO_4^-$ guest.[26]

As reported by a recent review,[27] the introduction of electron-withdrawing substituents onto molecular skeleton of the host generally increases the polarization of the N–H bond and its H-bond donor tendency. Thus, we have studied the recognition properties of hosts **2** and **4** bearing 4-nitropyrrole rings at the upper rim of the calix[4]arene macrocycle. Comparison of the association constant values of pyrrolamidocalix[4]arene hosts **1** and **2** in Table 1, reveals that the selectivity order $H_2PO_4^- > AcO^-$ observed for **1**, is inverted for **2**. A similar selectivity inversion has been observed for hosts **3** and **4**. Analogously, for fluoride anion, the selectivity order $H_2PO_4^- > F^-$ observed for **1** is diminished for **2**, whereas it is inverted on going from **3** to **4** (Table 1). Thus, respect to receptors **1** and **3**, which show higher affinity for $H_2PO_4^-$ over AcO^-, $PhCOO^-$, and F^-, the introduction of electron-withdrawing NO_2 groups in **2** and **4** leads to a higher affinity versus more basic anions such as AcO^-, $PhCOO^-$, and F^-.

In conclusion, we have demonstrated that C-linked pyrrolamidocalix[4]arene derivatives are effective receptors for anion recognition. In particular, hosts **1** and **3** show a higher affinity for tetrahedral $H_2PO_4^-$ with respect to Y-shaped AcO^- and spherical F^- anions, while the introduction of electron-withdrawing NO_2 groups in **2** and **4** leads to an increased affinity for more basic anions such as AcO^- and F^- over $H_2PO_4^-$. We have also showed that the rigidity of the calixarene skeleton influences negatively the binding affinity of pyrrolamidocalix[4]arene hosts versus the tetrahedral $H_2PO_4^-$ guest.

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18. Synthesis of pyrrolamidocalix[4]arene derivative **1**–**4**. A cold solution of acid chloride (**6** or **7**, 2.2 mmol) in dry THF (20 mL) was added to a solution of tetraminocalix[4]arene derivative (**5** or **8**, 0.5 mmol) and NEt_3 (2.2 mmol) in dry THF (120 mL) at 0 °C. The reaction mixture was allowed to warm at room temperature and stirred overnight. For derivatives **1** and **3** the following work-up procedure was used: the solvent was removed under reduced pressure, the crude product was taken up in CH_2Cl_2, washed with saturated solution of $NaHCO_3$, (2 × 30 mL), with 1 M HCl (2 × 30 mL), and brine, dried on Na_2SO_4, and filtered. The solvent was removed by rotary evaporator to give a yellow solid that was dissolved in CH_2Cl_2 and precipitated by adding MeOH. Instead, for derivatives **2** and **4** the following work-up procedure was used: the solvent was removed under reduced pressure, the crude product was triturated with 1 M HCl, filtered and washed with water. The material precipitated was suspended in a mixture of MeOH and 1 M HCl, filtered again, washed with water and dried under vacuum. Compound **1**. White solid, 0.4 g; yield: 70%. Mp >275 °C dec; ESI(+) MS: m/z = 1137 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 0.95 (t, $OCH_2CH_2CH_2CH_2CH_3$, J = 6.5 Hz, 12 H), 1.41 (overlapped, $OCH_2CH_2CH_2CH_2CH_3$, 16H), 1.97 (m, $OCH_2CH_2CH_2CH_2CH_3$, 8H), 3.17 and 4.42 (AX, $ArCH_2Ar$, J = 12.7 Hz, 4H each), 3.89 (t, $OCH_2CH_2CH_2CH_2CH_3$, J = 7.5 Hz, 8H), 6.06 (br s, PyH, 4H), 6.87 (br s, PyH, 4H), 6.91 (br s, PyH, 4H), 7.16 (s, ArH, 8H), 9.45 (s, NH, 4H), 11.45 (s, NH, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 298 K): δ 14.0, 22.4, 27.9, 29.4, 31.0, 75.0, 108.8, 111.0, 121.0, 122.0, 126.2, 133.1, 134.1, 152.0, 158.8; Anal. Calcd for $C_{68}H_{80}N_8O_8$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.72; H, 7.16; N, 9.77. Compound **2**. Yellow solid, 0.33 g; yield: 50%. Mp >295 °C dec; ESI(+) MS: m/z = 1317 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 0.93 (br t, $OCH_2CH_2CH_2CH_2CH_3$, 12H), 1.39 (overlapped, $OCH_2CH_2CH_2CH_2CH_3$, 16H), 1.91 (m, $OCH_2CH_2CH_2CH_2CH_3$, 8H), 3.16 and 4.40 (AX, $ArCH_2Ar$, J = 12.4 Hz, 4H each), 3.87 (br t, $OCH_2CH_2CH_2CH_2CH_3$, 8H), 7.16 (br ss, ArH, 8H), 7.54 (br s, PyH, 4H), 7.83 (br s, PyH, 4H), 9.69 (s, NH, 4H), 12.61 (br s, NH, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 298 K): δ 14.1, 22.4, 28.0, 29.4, 31.0, 75.0, 105.9, 120.2, 122.9, 126.9, 132.7, 134.3, 136.3, 152.5, 157.3; Anal. Calcd for $C_{68}H_{76}N_{12}O_{16}$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.09; H, 5.73; N. 12.67. Compound **3**. White solid, 0.32 g; yield: 65%. Mp >310 °C dec; ESI(+) MS: m/z = 997 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 3.15 (d, $ArCH_2Ar$, J = 12.0 Hz, 2H), 3.22 (d, $ArCH_2Ar$, J = 12.0 Hz, 2H), 3.68 (t, $OCH_2CH_2CH_2CH_2CH_3$, J = 8.8 Hz, 8H), 4.15–4.30 (overlapped, OCH_2, 16H), 4.49 (d, $ArCH_2Ar$, J = 12.0 Hz, 2H), 5.03 (d, $ArCH_2Ar$, J = 12.0 Hz, 2H), 6.07 (br s, PyH, 4H), 6.87 and 6.90 (br s, PyH, 4H each), 7.29 (broad AB, ArH, 8H), 9.48 (s, NH, 4H), 11.53 (s, NH, 4H); ^{13}C NMR (62.90 MHz, DMSO-d_6, 298 K): δ 30.5, 31.2, 73.9, 76.5, 108.9, 111.0, 113.8, 121.6, 122.1, 122.2, 122.5, 126.2, 133.8, 135.0, 135.1, 151.8, 159.0; Anal. Calcd for $C_{56}H_{52}N_8O_{10}$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.38; H, 5.34; N, 11.32. Compound **4**. Dark yellow solid, 0.26 g; yield: 45%. Mp >330 °C dec; ESI(+) MS: m/z = 1177 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 3.18 and 4.29 (AX, $ArCH_2Ar$, J = 12.0 Hz, 4H each) 4.50 and 5.05 (AX, $ArCH_2Ar$, J = 12.1 Hz, 4H each), 4.20–4.31 (m, OCH_2CH_2O, 16H), 7.30 abd 7.32 (AB, ArH, J = 2.1 Hz, 8H), 7.59 (br s, PyH, 4H), 7.94 (br s, PyH, 4H), 9.85 (s, NH, 4H), 12.75 (s, NH, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 298 K): δ 30.5, 31.11, 74.4, 77.1, 106.6, 122.2, 123.0, 127.4, 133.7, 135.9, 137.0, 152.9, 158.2; Anal. Calcd for $C_{56}H_{48}N_{12}O_{18}$: C, 57.14; H, 4.11; N, 14.28. Found: C, 57.05; H, 4.20; N, 14.19.

    Binding studies. ^{1}H NMR titrations were performed at 298 K in DMSO-d_6 containing 0.5% of water. A 1:1 stoichiometry for each pyrrolamidocalix[4]arene/anion complex was determined by means of mole ratio or Job plots. The titration data were analyzed by nonlinear regression analysis. In all cases a good fit of the experimental data with the theoretical model confirmed the 1:1 stoichiometry of the complexes. Examples: [**1**] = 1.52 mM; [F^-] = 0.36–10.79 mM; [Cl^-] = 0.37–10.69 mM; [Br^-] = 0.35–10.99 mM; [I^-] = 0.32–10.59 mM; [$H_2PO_4^-$] = 0.38–11.26 mM; [$PhCOO^-$] = 0.38–12.10 mM; [AcO^-] = 0.31–10.00 mM. [**2**] = 1.59 mM; [F^-] = 0.40–12.60 mM; [Cl^-] = 0.35–10.59 mM; [Br^-] = 0.31–11.99 mM; [I^-] = 0.31–10.49 mM; [$H_2PO_4^-$] = 0.38–10.77 mM; [$PhCOO^-$] = 0.38–7.21 mM; [AcO^-] = 0.38–10.65 mM. [**3**] = 1.44 mM; [F^-] = 0.37–11.52 mM; [Cl^-] = 0.32–11.59 mM; [Br^-] = 0.31–11.89 mM; [I^-] = 0.20–10.49 mM; [$H_2PO_4^-$] = 0.37–8.01 mM; [$PhCOO^-$] = 0.36–10.21 mM; [AcO^-] = 0.38–10.55. [**4**] = 1.54 mM; [F^-] = 0.37–11.62 mM; [Cl^-] = 0.30–11.49 mM; [Br^-] = 0.32–11.09 mM; [I^-] = 0.24–10.79 mM; [$H_2PO_4^-$] = 0.36–11.41 mM; [$PhCOO^-$] = 0.38–12.21 mM; [AcO^-] = 0.38–12.25. For each system at least three titrations were carried out.
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