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A study of anion binding behaviour of 1,3-alternate thiacalix[4]arene–based receptors bearing urea moieties†

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Three novel thiacalix[4]arene receptors 4a~c, each with a 1,3-alternate conformation and possessing two urea moieties linking various phenyl groups substituted with either para electron-donating or withdrawing groups, have been synthesized. The binding properties of these receptors were investigated by means of 1H NMR spectroscopy and UV–vis absorption titration experiments using various anions. The structures and complexation energies were also studied by density functional theory (DFT) methods. The results suggested that receptor 4a, which possesses two p-(trifluoromethyl)phenyl ureido moieties, can complex most efficiently in the urea cavity and exhibits high selectivity towards F\(^-\) and AcO\(^-\) ions.

Introduction

Calix[n]arenes1 have three-dimensional tuneable shapes and are used as molecular building blocks with potentially many applications in supramolecular chemistry. Thiacalix[4]arenes2,3 are calix[n]arenes in which the phenolic groups are bridged by sulfur atoms instead of methylene groups, and have received much recent attention for potential applications in various fields across chemistry, biology and environmental science. Various anions such as F\(^-\) (e.g., in dental caries prevention, in inhalation anesthetics and in the treatment of osteoporosis) also play fundamental roles in biological, medicinal, catalysis, and environmental chemistry.4 The design and synthesis of anion-selective receptors5 is more difficult than that of cation-selective receptors. This is due to some unique features of anions such as their much larger sizes in comparison with those of cations, and also due to the large variety of geometries available,6 some anions are spherical (F\(^-\), Cl\(^-\), Br\(^-\), I\(^-\)) others are trigonal or Y-shaped (AcO\(^-\)) and others are tetrahedral (H\(_2\)PO\(_4\)\(^-\)), etc. Anion recognition using artificially-designed receptors7 based on calix[n]arenes is an important research topic in the area of supramolecular chemistry. Calix[n]arene urea derivatives are capable of effectively recognizing and sensing important anions via hydrogen-bonding interactions between the anions and the urea NH protons.7,8

Lhoták and co-workers9 have reported anion receptors based on either upper-rim substituted calix[4]arenes or thiacalix[4]arenes which contain two p-nitrophenyl or p-tolyl urea moieties.3a~c,h These anion receptors exhibited effective recognition abilities towards selected anions in common organic solvents. Recently, Kumar and co-workers reported an anion receptor based on a calix[4]arene in a 1,3-alternate conformation and bearing containing two p-nitrophenyl-ureido moieties.10 This compound exhibited strong binding and good selectivity towards Cl\(^-\) ion due to strong hydrogen bonding between the Cl\(^-\) ion and the N-H protons, both in THF or chloroform solutions. However, investigations concerning the influence on the acidity of the urea protons by either electron-donating or electron-withdrawing groups located on the p-position of phenyl groups of urea moieties in analogous thiacalix[4]arenes and the binding of various anions have received scant attention.11

In this article, we report the synthesis of three novel thiacalix[4]arenes receptors 4a~c with a 1,3-alternate conformation and possessing two urea moieties linking various...
phenyl groups bearing either para electron-donating or electron-withdrawing groups, together with two benzyl groups at the opposite sides of the thiacalix[4]arene cavity. In our studies, the complexation properties of $4_{a-c}$ towards F$, \text{Cl}^-$, Br$, $, $I^-$, AcO$^-$ and H$_2$PO$_4^-$ ions were investigated by $^1$H-NMR spectroscopy (with $4_{a-c}$) and UV-vis absorption (with $4_c$) titration experiments. Furthermore, the structures and complexation energies for all complexes of the receptors $4_{a-c}$ with various anions were also determined by theoretical studies using DFT methods.

**Results and discussions**

**Synthesis**

$O$-Alkylation of 1,3-$\text{alternate}$-$1$ was conducted using 2 equivalents of bromoacetamide in the presence of 2 equivalents of Cs$_2$CO$_3$ according to the reported procedure, and afforded the desired 1,3-$\text{alternate}$-$2$ in 60% yield. The amide reduction of 1,3-$\text{alternate}$-$2$ was carried out with a large excess of BH$_3$/THF solution, and afforded the desired 1,3-$\text{alternate}$-$3$ in 65% yield. The condensation of 1,3-$\text{alternate}$-$3$ with 2.2 equivalents of the appropriate isocyanate in CH$_2$Cl$_2$ furnished the receptors $4_{a-c}$ in good yields (Scheme 1).

The $^1$H NMR spectrum of receptors $4_{a-c}$ in CDCl$_3$ exhibits the characteristics of a 1,3-$\text{alternate}$ conformation such as two singlets (18H each) for the tert-butyl protons, two triplets (4H each) for the -OCH$_2$CH$_2$- protons, two singlets (4H each) for the aromatic protons and two singlets (2H each) for the four urea NH protons. Moreover, concentration dependence of the $^1$H NMR chemical shifts of the urea protons in receptor $4_c$ was not observed (Fig. S11). This (lack of) observation indicates that receptor $4_c$ has strong intramolecular hydrogen bonds between the two urea groups linking the $p$-(trifluoromethyl)phenyl moieties. The molecular structure of receptor $4_a$ was also verified by X-ray crystallographic analysis (Fig. 1, S12). Receptor $4_a$ was recrystallized from a mixture of CHCl$_3$–CH$_3$CN (3:2, v/v) by slow evaporation. These results indicate that receptor $4_a$ adopts the 1,3-$\text{alternate}$ conformation in the solid state. In case of receptor $4_a$, there are four thiacalixarenes, two CT ions, two tetrabutylammonium ions, one chloroform and two acetonitrile molecules in the asymmetric unit. Interestingly, it was found that the two urea groups approach each other and are oriented in parallel due to the existence of dual intramolecular hydrogen bonding (in the case of receptor $4_a$, for the molecule shown: N(3)–H(3)···O(5) 2.13(3); N(4)–H(4)···O(5) 2.17(3) Å; for the second molecule: N(1A)–H(1A)···O(6A) 2.15(3), N(2A)–H(2A)···O(6A) 2.20(3) Å; for the third molecule: N(3B)–H(3B)···O(5B) 2.30(3), N(4B)–H(4B)···O(5B) 2.17(2) Å; for the fourth molecule: N(1C)–H(1C)···O(6C) 2.31(3), N(2C)–H(2C)···O(6C) 2.27(3) Å) (Fig. 1, S12). Moreover, in the case of receptor $4_a$, pairs of calixarene molecules are linked via four H-bonds between two urea NH moieties on each calixarene and CT$^-$ ion.

![Scheme 1 Synthesis of receptors 1,3-$\text{alternate}$-$4_{a-c}$](image-url)
Binding studies

The binding properties of receptors 4a–c in the presence of various anions as their tetrabutylammonium (TBA) salts, in CDCl₃–CD₃CN (10:1) solution, were investigated by means of ¹H-NMR titration spectroscopic experiments. As shown in Fig. 2, for the complexation of F⁻ ion with receptor 4c, the signals for the NHₐ protons (red) progressively shifted downfield by 4.55 ppm (δ = 7.35 to 11.9 ppm) until five equivalents of F⁻ ion was added. On the other hand, the signals for the NHₐ protons (blue) progressively shifted downfield by 3.88 ppm (δ = 5.72 to 9.60 ppm) until five equivalents of F⁻ ion were added. These results are strongly suggestive of F⁻ ion recognition by receptor 4c via hydrogen–bonding interactions between the F⁻ ion and the N–H protons.

Table 1. Association constants of receptors 4a–c with anions.

<table>
<thead>
<tr>
<th>Host</th>
<th>R</th>
<th>F⁻</th>
<th>Cl⁻</th>
<th>Br⁻</th>
<th>I⁻</th>
<th>AcO⁻</th>
<th>H₂PO₄⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spherical</td>
<td>Spherical</td>
<td>Spherical</td>
<td>Spherical</td>
<td>Y-shape</td>
<td>Tetrahedral</td>
</tr>
<tr>
<td>4a</td>
<td>H</td>
<td>6,745±472</td>
<td>2,937±206</td>
<td>1,453±102</td>
<td>410±29</td>
<td>6,305±441</td>
<td>2,727±191</td>
</tr>
<tr>
<td>4b</td>
<td>Me</td>
<td>3,550±286</td>
<td>1,557±109</td>
<td>734±51</td>
<td>203±14</td>
<td>3,033±212</td>
<td>1,338±94</td>
</tr>
<tr>
<td>4c</td>
<td>CF₃</td>
<td>13,950±977</td>
<td>6,590±461</td>
<td>2,920±204</td>
<td>883±62</td>
<td>12,878±901</td>
<td>5,790±405</td>
</tr>
</tbody>
</table>

* Measured in CDCl₃–CD₃CN (10:1, v/v) at 298 K by the ¹H NMR titration method using the chemical-shift change of the NHₐ proton (Fig. S13–S49); host concentration was 4.0 × 10⁻³ M. Guests used: TBA salts.

Table 1. Association constants of receptors 4a–c with anions.

* Measured in CDCl₃–CD₃CN (10:1, v/v) at 298 K by the ¹H NMR titration method using the chemical-shift change of the NHₐ proton (Fig. S13–S49); host concentration was 4.0 × 10⁻³ M. Guests used: TBA salts.

Fig. 2 Binding mode of receptor 4c upon addition of F⁻ ion at 298 K as TBA salts and partial ¹H NMR spectra of 4c (4.0 × 10⁻³ M) in CDCl₃–CD₃CN (10:1, v/v) upon addition of F⁻ ion at 298 K.

Fig. 3 Titration curves of receptor 4c, with various anions as their TBA salts in CDCl₃–CD₃CN (10:1, v/v) at 298 K.
Fig. 4 UV–vis absorption spectra of receptor 4c (2.5 μM) upon the addition of F– (0–50 μM) at 298 K as a TBA salt in CH2Cl2.

Table 2. Association constantsa of receptors 4 with anions.b

<table>
<thead>
<tr>
<th>Anion</th>
<th>F–</th>
<th>Cl–</th>
<th>AcO–</th>
<th>H2PO4–</th>
</tr>
</thead>
<tbody>
<tr>
<td>(K_a [\text{M}^{-1}])</td>
<td>465,405±32,578</td>
<td>9,060±634</td>
<td>418,495±29,519</td>
<td>8,258±578</td>
</tr>
</tbody>
</table>

a Measured in CH2Cl2 at 298 K by UV–vis titration method (Fig. S50–S58); host concentration was 2.5 μM. b Guests used: TBA salts.

ureido moieties. The \(K_a\) values for 4c having the electron-withdrawing CF3 groups on the phenyl ureido moieties, were greater than those for the other two receptors. The \(K_a\) values for 4b which had the electron-donating CH3 groups on the ureido phenyl moieties were lower than those for 4a and 4c. Therefore, the introduction of electron–withdrawing groups at the \(p\)-position of the phenyl ureido groups appears to increase the acidity of the urea protons, and hence enhance the anion-binding ability through hydrogen-bonding interactions. Furthermore, receptor 4c had the highest \(K_a\) values of all three receptors with each of the anions tested and also had the most effective recognition ability toward F– and AcO– ions. Further complexation studies of 4c with F–, Cl–, AcO– and H2PO4– ions were carried out using UV–vis spectroscopic titration experiments. Receptor 4c (2.5 μM) exhibits a broad absorption band at 295 nm in its UV–vis absorption spectrum. Upon addition of F– ion (0–50 μM) to the solution of 4c, Fig. 4 reveals a gradual decrease in the absorption of the band at 288 nm with a simultaneous increase in the absorption at 320 nm and a clear isosbestic point at 295 nm. From the above, it is clear that receptor 4c bearing the CF3 groups has the most effective recognition ability toward F– ions. A Job’s plot for the binding between the receptor 4c and F– ion reveals a 1:1 stoichiometry (Fig. S52), and the \(K_a\) for the complexation13b of receptor 4c with F– ion was determined to be 465,405 ± 32,578 M\(^{-1}\) by the UV–vis titrations in CH2Cl2 solution (Fig. S51). These results strongly suggested that F– ion recognition by receptor 4c was via a hydrogen-bonding interaction between F– ion and NH protons, as shown in Fig. 4. The \(K_a\) values obtained by similar UV-vis titration experiments of 4c with the other anions are summarized in Table 2. To further investigate the binding properties of receptors 4a~c with the anions tested, a computational study was carried out. The individual structures for all studies in the gas-phase were fully geometry-optimized using Gaussian 0914 with the B3LYP level of DFT and the 3-21G basis set. Significant changes were observed for the distances between two urea NH moieties on each of the receptors 4a~c in their anion complexes. The conformation changes for 4c upon 1:1 complexation with F– ion can be seen in Fig. 5 (more precise details for the computation studies for receptors 4a~c with the different anions are shown in Fig. S59–S94). Fig. 5 shows the computed structure (right) of the 1:1 complex of 4c with F– ion. Because of the hydrogen-bonding between the F– ion and two urea NH protons, distances between two urea NH moieties (NH1···NH2 and NH3···NH4) on two p-(trifluoromethyl)phenyl ureido moieties decrease from 8.783 to 2.530 (Å) and from 8.379 to 3.251 (Å), respectively. This also strongly supports the experimental evidence obtained for the formation of a 1:1 (4c:F–) complex. The calculated complexation energies (\(\Delta E\) kJ mol\(^{-1}\)) for receptors 4a~c with the anion complexes are shown in Table 3. The trend for the complexation energies for 4a~c are in the order: F– > AcO– > H2PO4– > Cl– > Br– > I–, which is in agreement with the trend observed for the observed complexation data obtained by means of \(^1\)H NMR spectroscopy and UV-vis absorption titration experiments.

**Conclusion**

In summary, three novel receptors 4a~c bearing a thiacalix[4]arene in a 1,3-alternate conformation have been synthesized. These receptors possess two urea moieties linking various aryl groups bearing electron-donating or -withdrawing groups at their \(p\)-positions, which act as anion-binding sites and two benzyl groups at the opposite side of thiacalix[4]arene cavity. The binding of various anions at the two urea moieties was investigated by using \(^1\)H NMR, UV-vis absorption titration experiments. It was found that receptor 4c has a much higher

[Image 48x542 to 273x729]

Fig. 5 Geometry-optimized (ball-and-stick) structures of: Left: 4c; Right: 1:1 complex of 4c:F–. Colour code: F = magenta; nitrogen = blue; NH = light blue; NHb = light green; sulphur = yellow; CF3 (fluoride) = orange; and oxygen atom = red.
affinity towards all of the selected anions and especially for \( F^- \) and \( \text{AcO}^- \) ions.

**Experimental Section**

**General**

All melting points were determined with a Yanagimoto MP-S1 melting point apparatus. \(^1\)H-NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with TMS as an internal reference; J-values are given in Hz. UV-vis spectra were measured with a Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC. Elemental analyses were performed by Yanaco MT-5.

**Materials**

Unless otherwise stated, all other reagents used were purchased from commercial sources and were used without further purification. Compounds \(^1\)a,\(^{11d,12} \) \(^2\)^{12} and \(^3\)^{12} were prepared following the reported procedures.

**Preparations**

\(^4\)\(_2\): To a solution of compound 3 (150 mg, 0.166 mmol) in \( \text{CH}_2\text{Cl}_2 (10 \text{ mL}) \) was added phenyl isocyanate (44 mg, 0.37 mmol) and the mixture was stirred at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with \( \text{CH}_3\text{OH} \) to give receptor \(^4\) as a white solid. Recrystallization from \( \text{CHCl}_3-\text{CH}_2\text{OH} (2:1) \) gave receptor \(^4\) as a white solid. Recrystallization from \( \text{CHCl}_3-\text{CH}_2\text{OH} (2:1) \) gave receptor \(^4\) as a white solid.

\(^4\)\(_4\): To a solution of compound 3 (150 mg, 0.166 mmol) in \( \text{CH}_2\text{Cl}_2 (10 \text{ mL}) \) was added \( p-(\text{trifluoromethyl})\)phenyl isocyanate (68 mg, 0.366 mmol) and the mixture was stirred at room temperature for 24 h under argon. The resulting precipitate was collected by filtration, washed with \( \text{CH}_3\text{OH} \) to give receptor \(^4\) as a white solid. Recrystallization from \( \text{CHCl}_3-\text{CH}_2\text{OH} (3:2) \) gave receptor \(^4\) as a white solid. Recrystallization from \( \text{CHCl}_3-\text{CH}_2\text{OH} (3:2) \) gave receptor \(^4\) as a white solid.

**Determination of the association constants**

The association constants \((K_a)\) were determined by using \(^1\)H NMR spectroscopic titration experiments with a constant concentration of host receptor \( (4.0 \times 10^{-3} \text{ M}) \) and varying the guest concentrations \((0.80 \times 10^{-3} \text{ M})\). The \(^1\)H NMR chemical shifts of the urea protons \((NH)\) signal were used as a probe. The \( K_a \) values for the complexes of receptor \(^4\) were calculated by nonlinear curve-fitting analysis of the observed chemical shifts of the NH protons according to the literature procedure.\(^{13a}\)

\(^1\)H NMR titration experiments

A solution of \( \text{Bu}_4\text{NX} (X = \text{F}, \text{Cl}, \text{Br}, \text{I}, \text{AcO}, \text{H}_2\text{PO}_4) \) in \( \text{CD}_3\text{CN} (4.0 \times 10^{-3} \text{ M}) \) was added to a \( \text{CDCl}_3 \) solution of receptor \(^4\) in an NMR tube. \(^1\)H NMR spectra were recorded after addition of
the reactants and the temperature of the NMR probe was kept constant at 27 °C.

Crystallographic analyses of 4a
Diffraction data were collected on a Bruker APEX 2 CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation at 150(2)K. Data were corrected for Lorentz and polarisation effects and for absorption. The structures were solved by direct methods and refined by full-matrix least-squares methods, on F2. The asymmetric unit contains four calixarenes two chloride anions, two tetrabutylammonium cations, one chloroform and two acetonitrile molecules of crystallisation. Within each of the four calixarenes there are pairs of N–H···O hydrogen bonds between urea moieties to a single carbonyl O atom. Looking down on the S4 square-shaped planes of the four unique calixarenes, three are approximately geometrically aligned in parallel while one, containing S(1A), is slightly twisted.

Two tBu groups on calixarenes were modelled as disordered between both urea N–H moieties on each calixarene and a chloride ion. n-butyl ammonium cations reside close to the chloride anions, due to electrostatic attraction. So, each pair of calixarenes is able to capture one chloride ion. The overall packing type is in layers.

Crystal data for 4a: C144H160N8O12S8·C16H36N+·Cl−, M = 2829.91. Triclinic, space group P 1, a = 15.1315 (5), b = 28.8618 (11), c = 35.9491 (9) Å, V = 15113.8 (9) Å³, Z = 4, Dc = 1.244 g.cm–3, F(000) = 6044, T = 100 K, μ(Mo-Kα) = 0.226 cm–1, μ(Mo-Kβ) = 0.71073 Å, colourless crystal of size 0.16 × 0.13 × 0.04 mm³. The total number of reflections measured, to θmax = 25.3°, was 42128 of which 27707 were unique (Rint = 0.062); 8953 were 'observed' with I > 2σ(I). For the 'observed' data only, R1 = 0.068; wR2 = 0.185 for all 42128 reflections and 3705 parameters. Residual electron density within H+–0.86 eÅ–3.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1062186 for 4a. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Supporting information: 1H, 13C NMR & IR spectra of compounds 2, 3 and 4a–c.

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Notes and references

