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

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Three novel thiacalix[4]arene receptors 4a–e, each with a 1,3-\textit{alternate} conformation and possessing two urea moieties linking various phenyl groups substituted with either \textit{para} electron-donating or withdrawing groups, have been synthesized. The binding properties of these receptors were investigated by means of \textit{1}H 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 \textit{p}-(trifluoromethyl)phenyl ureo moieties, can complex most efficiently in the urea cavity and exhibits high selectivity towards \textit{F}– and \textit{AcO}– ions.

\textbf{Introduction}

\textit{Calix}[\textit{n}]	extit{arenes}1 have three-dimensional tuneable shapes and are used as molecular building blocks with potentially many applications in supramolecular chemistry. Thiacalix[4]arenes2,3 are \textit{calix}[\textit{n}]	extit{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 \textit{F}– (e.g., in dental caries prevention, in inhalation anaesthetics 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 (\textit{F}–, \textit{Cl}–, \textit{Br}–, \textit{I}–) others are trigonal or Y-shaped (\textit{AcO}–) and others are tetrahedral (\textit{H}_2\textit{PO}_4–), etc.. Anion recognition using artificially-designed receptors8 based on \textit{calix}[\textit{n}]	extit{arenes} is an important research topic in the area of supramolecular chemistry. Calix[\textit{n}]	extit{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 thiacalix[4]arenes or thiacalix[4]arenes which contain two \textit{p}-nitrophenyl or \textit{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-\textit{alternate} conformation and bearing containing two \textit{p}-nitrophenyl-ureido moieties.10 This compound exhibited strong binding and good selectivity towards \textit{Cl}– ion due to strong hydrogen bonding between the \textit{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 \textit{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–e with a 1,3-\textit{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 4a–c towards F–, Cl–, Br–, I–, AcO– and H₂PO₄– ions were investigated by ¹H-NMR spectroscopy (with 4a–c) and UV-vis absorption (with 4c) titration experiments. Furthermore, the structures and complexation energies for all complexes of the receptors 4a–c with various anions were also determined by theoretical studies using DFT methods.

Results and discussions

Synthesis

O-Alkylation of 1,3-alternate-1 was conducted using 2 equivalents of bromoacetamide in the presence of 2 equivalents of Cs₂CO₃ according to the reported procedure, and afforded the desired 1,3-alternate-2 in 60% yield. The amide reduction of 1,3-alternate-2 was carried out with a large excess of BH₃/THF solution, and afforded the desired 1,3-alternate-3 in 65% yield. The condensation of 1,3-alternate-3 with 2.2 equivalents of the appropriate isocyanate in CH₂Cl₂ furnished the receptors 4a–c in good yields (Scheme 1). The ¹H NMR spectrum of receptors 4a–c in CDCl₃ exhibits the characteristics of a 1,3-alternate conformation such as two singlets (18H each) for the tert-butyl protons, two triplets (4H each) for the -OCH₂CH₂- 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 ¹H NMR chemical shifts of the urea protons in receptor 4c was not observed (Fig. S11). This (lack of) observation indicates that receptor 4c has strong intramolecular hydrogen bonds between the two urea groups linking the p-(trifluoromethyl)phenyl moieties. The molecular structure of receptor 4a was also verified by X-ray crystallographic analysis (Fig. 1, S12). Receptor 4a was recrystallized from a mixture of CHCl₃–CH₃CN (3:2, v/v) by slow evaporation. These results indicate that receptor 4a adopts the 1,3-alternate conformation in the solid state. In case of receptor 4c, there are four thiacalixarenes, two CT ions, two tetraethylammonium 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 4a, 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 4c, pairs of calixarene molecules are linked via four H-bonds between two urea NH moieties on each calixarene and CT ion.
**Binding studies**

The binding properties of receptors 4a–c in the presence of various anions as their tetrabutylammonium (TBA) salts, in CDCl$_3$–CD$_3$CN (10:1) solution, were investigated by means of $^1$H-NMR titration spectroscopic experiments. As shown in Fig. 2, for the complexation of F$^-$ ion with receptor 4c, the signals for the NH$_a$ protons (red) progressively shifted downfield by 4.55 ppm ($\delta = 7.35$ to 11.9 ppm) until five equivalents of F$^-$ ion was added. On the other hand, the signals for the NH$_b$ protons (blue) progressively shifted downfield by 3.88 ppm ($\delta = 5.72$ 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. The titration curves shown in Fig. 2, 3 (for 4c) and Fig. S13–S49 show that further addition of various anions to the solution of each receptors 4a–c in CDCl$_3$ solution, resulted in clear downfield shifts of the 1H NMR signals of the NH$_a$ protons. All of the results obtained clearly suggest that anion recognition by the receptors is via hydrogen-bonding interactions between the anion and the N H protons. In particular, as shown in Fig. 2, receptor 4c exhibited the highest selectivity amongst all of the anions tested, toward F$^-$ and AcO$^-$ ions. $K_a$ values for receptors 4a–c and the anions tested were determined by $^1$H NMR spectroscopic titration experiments.$^{13a}$ (Table 1). These results suggest that the $K_a$ values are influenced by the electron-donating or electron-withdrawing groups located at the $p$-position of the phenyl group.

**Table 1.** Association constants$^a$ of receptors 4a–c with anions.$^b$

| Host | R | $F^-$ | | $Cl^-$ | | $Br^-$ | | $I^-$ | | $AcO^-$ | | $H_2PO_4^-$ |
|------|---|-------|---|-------|---|-------|---|-------|---|-------|---|
| $4_a$ | H | 6,745±472 | | 2,937 ±206 | | 1,453±102 | | 410±29 | | 6,305±441 | | 2,727±191 |
| $4_b$ | Me | 3,550 ±286 | | 1,557±109 | | 734±51 | | 203±14 | | 3,033±212 | | 1,338±94 |
| $4_c$ | CF$_3$ | 13,950 ±977 | | 6,590±461 | | 2,920±204 | | 883±62 | | 12,878±901 | | 5,790±405 |

$^a$ Measured in CDCl$_3$–CD$_3$CN (10:1, v/v) at 298 K by the $^1$H NMR titration method using the chemical-shift change of the NH$_a$ proton (Fig. S13–S49); host concentration was 4.0 × 10$^{-3}$ M. $^b$ Guests used: TBA salts.

**Fig. 2** Binding mode of receptor 4c upon addition of F$^-$ ion at 298 K as TBA salts and partial $^1$H NMR spectra of 4c (4.0 × 10$^{-3}$ M) in CDCl$_3$–CD$_3$CN (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 CDCl$_3$–CD$_3$CN (10:1, v/v) at 298 K.
effective recognition ability toward F– and AcO– ions. Further binding between the receptor

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>Kα [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 Kα values for 4c having the electron-withdrawing CF3 groups on the phenyl ureido moieties, were greater than those for the other two receptors. The Kα 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 Kα 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 Kα 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 Kα 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 (ΔE [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 1H 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 1H NMR, UV-vis absorption titration experiments. It was found that receptor 4c has a much higher
affinity towards all of the selected anions and especially for F⁻ and AcO⁻ ions.

**Experimental Section**

### General

All melting points were determined with a Yanagimoto MP-S1 melting point apparatus. ¹H-NMR spectra were determined at 300 MHz with a Nippon Densi 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 Densi 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, 2² and 3 were prepared following the reported procedures.

### Preparations

**4a**: To a solution of compound 3 (150 mg, 0.166 mmol) in CH₂Cl₂ (10 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 CH₂OH to give receptor 4a as a white solid. Recrystallization from CHCl₃–CH₂OH (2:1) gave receptor 4a (146 mg, 72 %) as a white solid. M.p. 200–202 °C. IR: \( \nu_{\text{max}} \) (KBr)/cm⁻¹: 3279, 2929, 1605, 1572, 1538, 1225, 1170, 1068, 905 and 794. ¹H NMR (300 MHz, CDCl₃): \( \delta = 0.82 \) (18H, s, \( t\text{Bu} \times 2 \)), 1.22 (18H, s, \( t\text{Bu} \times 2 \)), 3.05 (4H, br, \( CH₂NH \times 2 \)), 4.01 (4H, br, \( OCH₂CH₂ \times 2 \)), 5.08 (4H, s, \( OCH₂ \times 2 \)), 5.56 (2H, s, \( NH \times 2 \)), 6.96–7.18 (2H, s, \( NCH \times 2 \)), 7.13 (2H, s, \( NF \times 2 \)) and 7.41 (4H, s, \( Ar\text{–}H \times 4 \)) ppm. ¹³C NMR (100 MHz, CDCl₃): \( \delta = 20.0 \) (CH₃), 31.3 (CH₃), 34.3 (C(CH₃)₃), 39.4 (CH₂), 70.1 (OCH₂), 71.3 (OCH₂), 119.8 (ArC), 121.9 (ArC), 125.1 (ArC), 125.2 (ArC), 125.4 (ArC), 125.9 (ArC), 126.2 (ArC), 126.5 (ArC), 127.1 (ArC), 127.5 (ArC), 127.8 (ArC), 128.0 (ArC), 128.3 (ArC), 128.5 (ArC), 128.6 (ArC), 128.8 (ArC), 129.0 (ArC), 129.1 (ArC), 129.3 (ArC), 130.0 (ArC), 135.1 (ArC), 136.2 (ArC), 147.8 (ArC), 148.0 (ArC), 149.5 (ArC), 151.9 (ArC), 154.0 (ArC) and 158.4 (CO) ppm. FABMS: \( m/z: [M+H]^+ \) Calcd for C₇₃H₆₅N₆O₆S₄ (1253.5352) ; Found 1253.4812.

**4b**: To a solution of compound 3 (150 mg, 0.166 mmol) in CH₂Cl₂ (10 mL) was added p–(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 CH₂OH to give receptor 4b as a white solid. Recrystallization from CHCl₃–CH₂OH (3:2) gave receptor 4b (147 mg, 65%) as a white solid. M.p. 210–211 °C. IR: \( \nu_{\text{max}} \) (KBr)/cm⁻¹: 3220, 2958, 1683, 1542, 1439, 1214, 1206, 1118, 1034, 978, 919, 896, 874, 796, 788, 776 and 749. ¹H NMR (300 MHz, CDCl₃): \( \delta = 0.81 \) (18H, s, \( t\text{Bu} \times 2 \)), 1.19 (18H, s, \( t\text{Bu} \times 2 \)), 3.12 (4H, br, \( CH₂NH \times 2 \)), 4.03 (4H, br, \( OCH₂CH₂ \times 2 \)), 5.05 (4H, s, \( OCH₂CH₂ \times 2 \)), 5.50 (2H, br, \( NH \times 2 \)), 6.86 (2H, s, \( NH \times 2 \)), 6.96–7.18 (18H, m, Phenyl–H \times 18 \), 7.10 (4H, s, \( Ar\text{–}H \times 4 \)) and 7.41 (4H, s, \( Ar\text{–}H \times 4 \)) ppm. ¹³C NMR (100 MHz, CDCl₃): \( \delta = 29.1 \) (CH₃), 30.0 (CH₃), 31.2 (CH₃), 34.3 (C(CH₃)₃), 39.4 (CH₂), 70.1 (OCH₂), 70.9 (OCH₂), 119.8 (ArC), 121.9 (ArC), 125.1 (ArC), 125.2 (ArC), 125.4 (ArC), 125.9 (ArC), 126.2 (ArC), 126.5 (ArC), 127.1 (ArC), 127.5 (ArC), 127.8 (ArC), 128.0 (ArC), 128.3 (ArC), 128.5 (ArC), 128.6 (ArC), 128.8 (ArC), 129.0 (ArC), 129.1 (ArC), 129.3 (ArC), 130.0 (ArC), 135.1 (ArC), 136.2 (ArC), 147.8 (ArC), 148.0 (ArC), 149.5 (ArC), 151.9 (ArC), 154.0 (ArC) and 158.4 (CO) ppm. FABMS: \( m/z: [M+H]^+ \) Calcd for C₇₂H₆₃F₃N₆O₆S₄ (1361.4787): calcld C 65.32, H 7.05, N 4.41. Found: C 65.32, H 7.05, N 4.41.

**4c**: A solution of Bu₄NX (X = F, Cl, Br, I, AcO, H₂PO₄) in CD₃CN (4.0 × 10⁻³ M) was added to a CDCl₃ solution of receptor 4a~c with guest concentrations (0 –8.0 × 10⁻³ M). The ¹H NMR chemical shifts of the urea protons (NH) signal were used as a probe. The association constants \( K_a \) were determined by using ¹H NMR spectroscopic titration experiments with a constant concentration of host receptor (4.0 × 10⁻³ M) and varying the guest concentrations (0–8.0 × 10⁻³ M). The ¹H NMR chemical shifts of the urea protons (NH) signal were used as a probe. The \( K_a \) values for the complexes of receptor 4a~c were calculated by nonlinear curve-fitting analysis of the observed chemical shifts of the NH protons according to the literature procedure. ¹³a
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 over two sets of positions for the Me groups. See tables for the occupation factors. Two pairs of calixarene molecules are linked via four H-bonds over two sets of positions for the Me groups. Two ions. There are two molecules of acetonitrile of crystallisation. Within each of the four calixarenes there are pairs of N–H···O hydrogen bonds between urea moieties on each calixarene and a chloride ion. The overall packing type is in layers.

Crystal data for 4a: C144H160N8O12S8·C16H36N+·Cl

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