JOC The Journal of Organic Chemistry

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# Bidentate Urea Derivatives of *p-tert*-Butyldihomooxacalix[4]arene: Neutral Receptors for Anion Complexation

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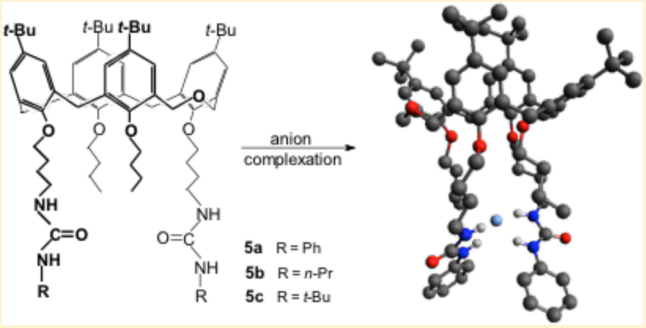
Supporting Information

**ABSTRACT:** Three new bidentate ureidodihomooxacalix[4]-arene derivatives (phenyl **5a**, *n*-propyl **5b**, and *tert*-butyl **5c**) were synthesized in four steps from the parent compound *p-tert*-butyldihomooxacalix[4]arene and obtained in the cone conformation, as shown by NMR studies. The binding ability of these neutral receptors toward spherical, linear, trigonal planar, and tetrahedrical anions was assessed by $^1$H NMR and UV−vis titrations. The structures and complexation energies of some complexes were also studied by DFT methods. The data showed that the association constants are strongly dependent on the nature of the substituent (aryl/alkyl) at the urea moiety. In general, for all the receptors, the association constants decrease with decrease of anion basicity. Ph-urea **5a** is the best anion receptor, showing the strongest complexation for $F^-$ (log $K_{assoc}$ = 3.10 in $CDCl_3$) and also high binding affinity for the carboxylates $AcO^-$ and $BzO^-$. Similar results were obtained by UV−vis studies and were also corroborated by DFT calculations.




## INTRODUCTION

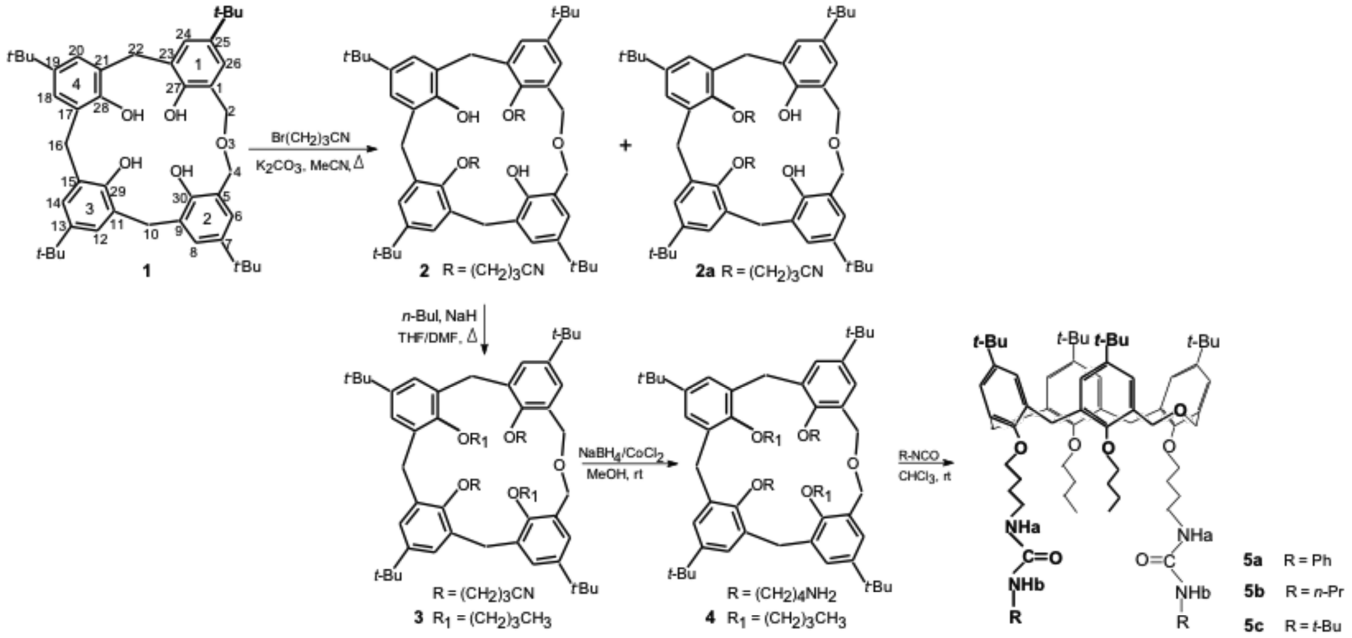
Calixarene-based molecules, in particular lower rim derivatives, have been widely used in the last three decades as metal cation binders.[1a−c] Conversely, the binding of anions by these macrocycles has received less attention in the past. Selective complexation of anions is more demanding than that of cations, mainly because of some unique properties of anions that need to be taken into account in the design of the receptors. Compared to cations, anions are larger and therefore have a lower charge to radius ratio. Consequently, they show less effective electrostatic interactions. They present a wide range of geometries and pH dependence, and they are more affected by solvation. However, more recently, the study of anion receptors based on calixarenes, as well as on other macrocycle compounds, has gained a growing interest due to the important role displayed by anions in biology, medicine, and environmental areas.[2−6]

To add hydrogen bond donor groups to organic hosts has been an important task for obtaining recognition for specific anions. Thus, urea and thiourea binding groups have been widely incorporated in the calixarene scaffold to produce anion receptors. These groups provide effective and directional hydrogen bonds. Over the last 15 years, calix[4]arene scaffolds, incorporating one or more urea and thiourea moieties at the lower[7−11] or upper rim,[12−14] have been the most studied for anion recognition. Ureidocalix[5]arene[15] and calix[6]arene[16,17] derivatives have also been tested as anion receptors.

Following our previous studies on the cation binding properties of dihomooxacalix[4]arenes (calix[4]arene analogues in which one $CH_2$ bridge is replaced by one $CH_2OCH_2$ group),[18] we have recently extended our research into the study of anion complexation. Dihomooxacalix[4]arenes have cavity sizes slightly larger than those of calix[4]arenes; they are therefore more flexible, but possess a cone conformation, being potential hosts for larger anions. This paper reports the synthesis, the NMR conformational analysis, and the complexation properties of three new bidentate urea derivatives of *p-tert*-butyldihomooxacalix[4]arene toward a large variety of anions (spherical, linear, trigonal planar, and tetrahedrical).

**Received:** November 27, 2013
**Published:** December 23, 2013

**Scheme 1. Synthetic Route for the Preparation of Bidentate Urea Derivatives 5a–c**




These properties have been assessed by proton NMR and UV absorption spectrophotometric studies. The structures and complexation energies for some urea-anion systems were also investigated by theoretical studies using DFT methods. The results are compared to those obtained with closely related calix[4]arene derivatives and discussed in terms of the nature of the substituent (aryl/alkyl) at the urea moiety.

## RESULTS AND DISCUSSION

**Synthesis and NMR Conformational Analysis.** Following our recent interest in anion binding by homooxacalixarenes modified with substituted urea groups at the lower rim, and to overcome the difficulties found to obtain the tetra-[(cyanopropyl)oxy] derivatives (precursors to urea-terminated compounds) in the cone conformation,[19] we decided to try the synthesis of bidentate urea derivatives. Thus, the parent compound *p-tert*-butyldihomooxacalix[4]arene (**1**) was treated with 2 equiv of 4-bromobutyronitrile and $K_2CO_3$ in refluxing acetonitrile for 6 days (Scheme 1). This reaction afforded a mixture composed of two disubstituted compounds. Separation by flash chromatography gave the 1,3-dicyanodihydroxy derivative **2** as the main product, along with a small amount of the 3,4-dicyanodihydroxy derivative **2a**.

The $^1$H NMR spectrum of **2** displays four singlets for the *tert*-butyl groups, five AB quartets for the $CH_2$ bridge protons, four pairs of doublets for the aromatic protons, two singlets for the OH groups, and several multiplets for the $-OCH_2CH_2CH_2CN$ methylene protons. The $^{13}$C NMR spectrum shows three $ArCH_2Ar$ resonances at 29.3, 30.0, and 32.7 ppm, indicating a cone conformation for this derivative.[20] Compound **2a** exhibits symmetric NMR spectra. The $^1$H NMR spectrum shows two singlets for the *tert*-butyl groups, three AB quartets in a 2:2:1 ratio for the $CH_2$ bridge protons, five multiplets for the $-OCH_2CH_2CH_2CN$ groups, two pairs of doublets for the aromatic protons, and one singlet for the OH groups. The $^{13}$C NMR spectrum displays two $ArCH_2Ar$ resonances at $\delta$ 30.7 (one carbon atom) and $\delta$ 31.6 (two carbon atoms), indicating a cone conformation. For both compounds, the cone conformation and the substitution patterns were further confirmed by proton–proton correlations observed in the NOESY spectra. As previously described by us for the formation of other disubstituted dihomooxacalix[4]-arenes,[21] the preferential formation of the 1,3-disubstituted derivative is expected. This type of substitution (Scheme 1) was confirmed for the asymmetric compound **2** (Figure 1) through

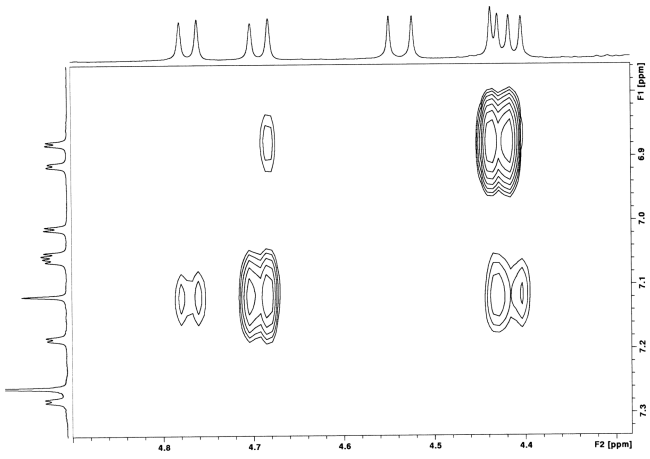


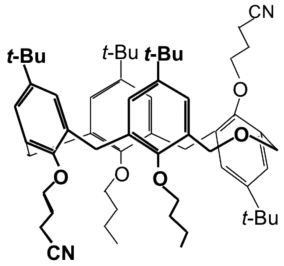

**Figure 1.** Section of the NOESY spectrum of 1,3-dicyanodihydroxy derivative **2**.

the simultaneous observation of two NOE effects between the OH proton at 7.12 ppm (position 30) and two axial methylene protons at 4.42 and 4.69 ppm (positions 10 and 4, respectively). In the case of the symmetric compound **2a** (Figure S1, Supporting Information), the 3,4-disubstituted pattern (Scheme 1) was confirmed by two simultaneous NOE effects observed between the OH proton (position 27) and two axial methylene protons at 4.20 and 4.67 ppm (positions 22 and 2, respectively), as well as between the (cyanopropyl)oxy protons (position 28) and the two axial methylene protons at 4.20 and 4.45 ppm (positions 22 and 16, respectively).


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742–751

Derivative **2** was further alkylated with *n*-butyl iodide and NaH in THF/DMF, yielding dicyanodibutoxy derivative **3** in the cone (major product) and partial cone A (Scheme 2)

**Scheme 2. Dicyanodibutoxy Derivative 3 in the Partial Cone A Conformation**




conformations. After separation of the two conformers, the $^{13}C$ NMR spectra displayed three $ArCH_2Ar$ resonances around 30 ppm for the cone conformer and three $ArCH_2Ar$ resonances, one around 39 ppm and the other two at 30 ppm, for the partial cone A conformer.[22] The $^1H$ NMR spectrum of the latter conformer displays an upfield multiplet ($\delta$ 0.73 ppm) corresponding to four methylene protons of an inverted group.[19] According to the COSY spectrum, these protons have no correlations with the methyl protons at 0.96 ppm, which indicates that they belong to a (cyanopropyl)oxy group and not to a (butyl)oxy group. Moreover, the identification of the inverted group was further corroborated by proton−proton correlations observed in a NOESY spectrum, mainly by the NOE enhancement observed between the aromatic proton at 7.03 ppm (position 20) and those methylene protons at 0.73 ppm (Figure S2, Supporting Information).

Reduction of the cyano groups of the cone derivative **3** with borohydride and cobalt chloride in methanol gave the diamine **4**, which reacted with aryl or alkyl isocyanate in chloroform to give the corresponding diaryl or dialkylurea derivatives (phenyl **5a**, *n*-propyl **5b**, and *tert*-butyl **5c**) in the cone conformation. These compounds have no symmetry. They are inherently chiral, as indicated by their NMR spectra. All the ureido derivatives show clear and sharp proton NMR spectra in $CDCl_3$ at room temperature and independent of the concentration, indicating absence of self-aggregation.[13,14] Parts a−c of Figure 2 show a section of those spectra with the two NHa and the two NHb protons of the ureido groups at the expected chemical shifts. When a more polar solvent like DMF was used, the NH signals remained sharp but shifted downfield, in agreement with the formation of intermolecular hydrogen bonds between the ureido groups and the solvent (see, for example, *n*-Pr-urea **5b**, Figure 2d).

**Anion-Binding Studies.** *$^1H$ NMR Studies.* The binding affinity of bidentate ureas **5a**, **5b**, and **5c** toward anions of spherical ($F^-$, $Cl^-$, $Br^-$, $I^-$), trigonal planar ($NO_3^-$, $AcO^-$, $BzO^-$), linear ($CN^-$, $SCN^-$), and tetrahedral ($HSO_4^-$, $H_2PO_4^-$, $ClO_4^-$) geometries was investigated in $CDCl_3$ by $^1H$ NMR titrations using tetrabutylammonium salts. The association constants, reported in Table 1, were determined following the urea NH chemical shift and using the WinEQNMR2 program.[23] In a few cases where those protons became broad or even completely disappeared, the binding constants were determined from the complexation induced shifts of the aromatic protons of the calixarene framework. The titration

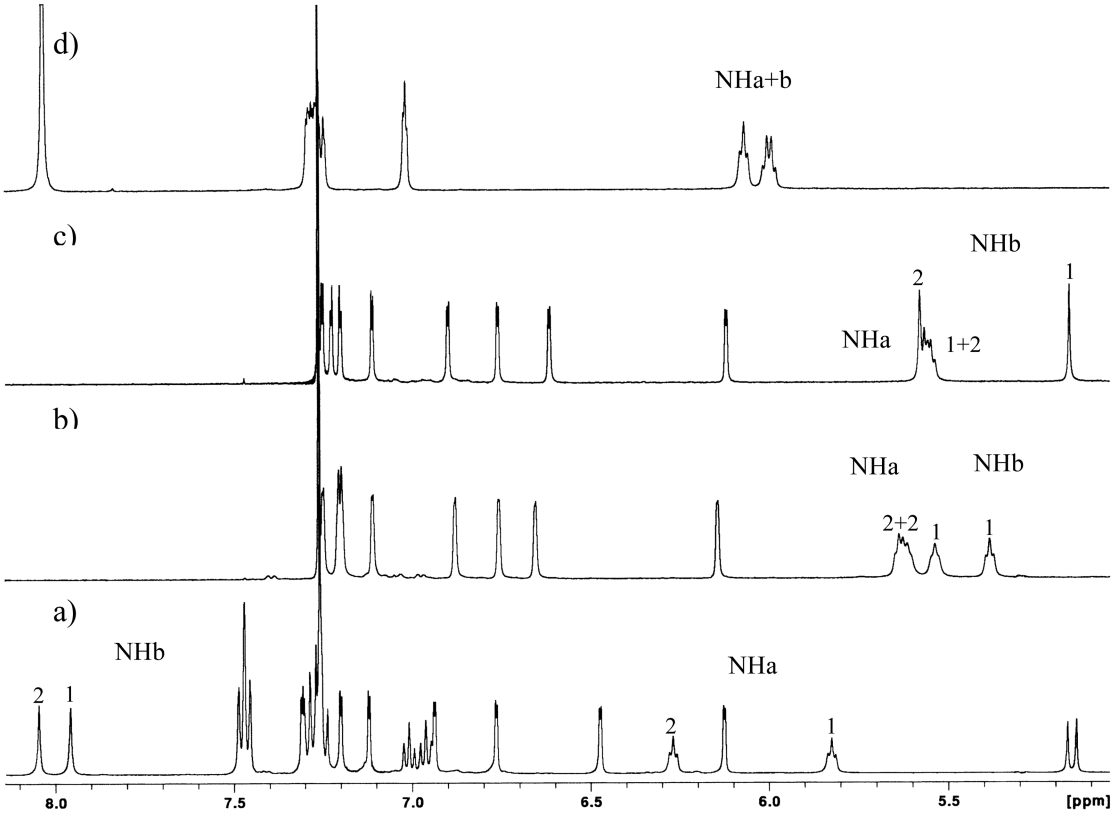



**Figure 2.** Partial $^1H$ NMR spectra (500 MHz, $CDCl_3$, 22 °C) of (a) Ph-urea-**5a**, (b) *n*-Pr-urea **5b**, (c) *t*-Bu-urea **5c**, (d) *n*-Pr-urea **5b** in DMF-$d_7$.


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742−751

**Table 1. Association Constants (log $K_{assoc}$)[a] of Dihomooxa Bidentate Ureas 5a–c in $CDCl_3$ at 25 °C Determined by $^1H$ NMR Experiments**

| | spherical | | | | linear | | trigonal planar | | | tetrahedral | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $F^-$ | $Cl^-$ | $Br^-$ | $I^-$ | $CN^-$ | $SCN^-$ | $NO_3^-$ | $AcO^-$ | $BzO^-$ | $HSO_4^-$ | $H_2PO_4^-$ | $ClO_4^-$ |
| i. radius[b] (Å) | 1.33 | 1.81 | 1.96 | 2.20 | 1.91 | 2.13 | 1.79 | 2.32 | | 1.90 | 2.00 | 2.40 |
| Ph-urea **5a** | 3.10 | 2.73 | 2.23 | 1.59 | 2.71 | 1.90 | 2.42 | 2.88 | 2.93 | 2.58 | 2.69 | 1.65 |
| *n*-Pr-urea **5b** | 1.65 | 1.57 | 1.35 | 1.34 | 1.61 | 1.46 | 1.54 | 1.59 | 1.65 | 1.40 | 1.21 | 1.56 |
| *t*-Bu-urea **5c** | 1.38 | 1.21 | 1.02 | 1.18 | 1.28 | 1.20 | 1.00 | 0.90 | 0.89 | 1.05 | 1.17 | 1.13 |

[a]Estimated error <10%. [b]Data quoted in Marcus, I. *Ion Properties*; Marcel Dekker: New York, 1997; pp 50–51.

profiles obtained in all cases (see for example Figure 3) clearly indicate the formation of 1:1 receptor–anion complexes, being this stoichiometry also confirmed by Job plots (see as an example the Job curve for **5a** + $Br^-$, Figure 4).

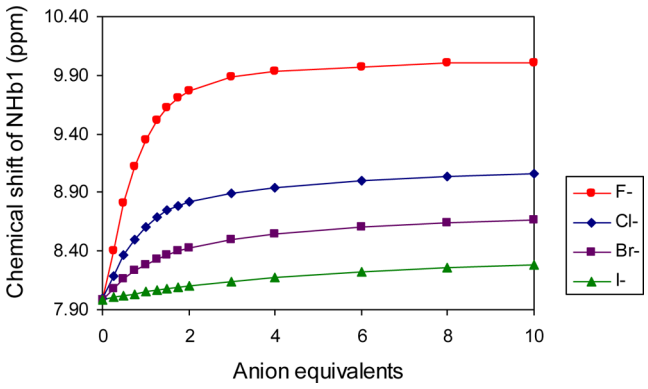



**Figure 3.** Titration curves of Ph-urea **5a** with TBA salts in $CDCl_3$.

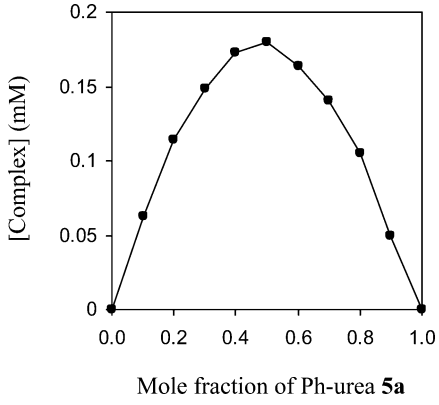



**Figure 4.** Job plot based on $^1H$ NMR data for Ph-urea **5a** + $Br^-$; total concentration $5 \times 10^{-3}$ M in $CDCl_3$.

The data show that the association constants for anion binding with the receptors **5a**, **5b**, and **5c** strongly depend on the nature of the substituted (aryl/alkyl) at the urea moiety. In general, arylureas are stronger anion receptors than alkylureas because of the higher acidity of their ureido NHs.[3] Ph-urea derivative **5a** is the best anion receptor, displaying moderate to reasonably high binding ability. *n*-Pr-urea **5b** and *t*-Bu-urea **5c** are weak receptors, with **5b** being slightly better than **5c**. The higher flexibility and the less bulky shape of the R group in the former receptor may lead to a conformational arrangement more favorable to the NH hydrogen bond donation. However, the three receptors show the same trend in the anion-binding affinities. The addition of anions to the receptors (**5a–c**) caused more or less significant downfield shifts of the NH protons, clearly indicating hydrogen-bonding interactions. In all cases, a fast exchange rate between the complexed and the free host was observed on the NMR time scale at room temperature. With very few exceptions, the association constants of **5a–c** with the anions decrease in the order of the anion basicity in $CHCl_3$ (Table 2). Although no p$K_a$ values

**Table 2. Anion Basicity in $CHCl_3$ and MeCN**

| geometry | anion basicity ($CHCl_3$/MeCN) |
|---|---|
| spherical | $F^- > Cl^- > Br^- > I^-$ |
| linear | $CN^- > SCN^-$ |
| trigonal planar | $AcO^- > BzO^- > NO_3^-$ |
| tetrahedral | $H_2PO_4^- > HSO_4^- > ClO_4^-$ |

were found in this solvent, it is known that p$K_a$ values follow the same trends in similar solvents.[24] Thus, it is completely justifiable to assume the same p$K_a$ order in $CHCl_3$ as was reported in 1,2-dichloroethane.

A systematic observation of the data in Table 1 and Figure 3 reveals that in the case of the halogen anions (spherical geometry) the addition of 2 equiv of TBA iodide to Ph-urea **5a** causes a small downfield shift for the urea $NHb_1$ proton (0.12 ppm), which increases for $Br^-$ (0.44 ppm) and even more for $Cl^-$ (0.83 ppm). In the case of $F^-$ a large downfield shift of 1.82 ppm can be observed, as well as another of 1.52 ppm for $NHa_1$ proton. Small downfield shifts for the *ortho* protons and small upfield shifts for the *meta* and *para* protons of the phenyl urea groups are also observed, as mentioned before for other analogue receptors,[7,10,25] and corroborate the expected effects for the formation of hydrogen-bonding complexes. These effects are the result of both the increase of electron density on the phenyl rings (through-bond) causing a shielding effect, and the polarization of the C–H bonds (through-space) causing a deshielding effect.[5] **5a** displays a log $K_{assoc}$ of 3.10 for $F^-$, the highest value obtained with these dihomooxa urea receptors. It shows some selectivity over $Cl^-$ and $Br^-$ ($S_{F^-}/_{X^-}$ = 2.3 and 7.4, respectively). The same trend is observed for urea derivatives **5b** and **5c** ($K_{assoc}$ decreases with decreasing of anion basicity), except for *t*-Bu-urea **5c** with $I^-$, which displays a slightly higher $K_{assoc}$ than that with $Br^-$.

Our results with $F^-$ showed no evidence for the formation of the $HF_2^-$ species, either generated in situ due to trace amounts of water[26] or by deprotonation of the receptor.[10,27,28] Thus, no sigmoidal shape can be observed in the titration curve shown in Figure 3, and the chemical shifts of the relevant protons followed the expected variations for the formation of an H-bond complex, namely the *ortho* protons of the urea phenyl rings, as mentioned before. These protons experienced small downfield shifts during all the titration ($\Delta\delta$ = 0.10 ppm with 10 equiv of $F^-$). On the other hand, the acidity of Ph-urea **5a** is lower when compared to receptors containing electron-


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742–751

withdrawing groups, such as $NO_2$.[28] In addition, solvent polarity plays an important role in stabilizing the H-bond complexes. The higher the polarity of the solvent (DMSO > MeCN > $CHCl_3$), the lower the stability of the H-bond complex. It was reported that in the poorly polar $CH_2Cl_2$, the 1,3-bis(4-nitrophenyl)urea gave only the H-bond complex with $F^-$.[28] In addition, deprotonation was never reported in $CHCl_3$.[25]

In the presence of the pseudohalides $CN^-$ and $SCN^-$ (linear geometry) a similar behavior was observed for all the receptors, which followed the same trend observed for the halogens. The more basic anion $CN^-$ was better complexed, mainly with Ph-urea **5a**, that exhibited a log $K_{assoc}$ of 2.71 and selectivity over $SCN^-$ of 6.5.

Concerning the trigonal planar oxoanions, Ph-urea **5a** showed a high binding affinity toward the carboxylates $BzO^-$ and $AcO^-$ (log $K_{assoc}$ of 2.93 and 2.88, respectively). In contrast to the previous situations, the trend observed with these oxoanions was slightly different. Receptors **5a** and **5b** displayed association constants that slightly increased from $AcO^-$ to $BzO^-$ and then decreased from $BzO^-$ to $NO_3^-$ (as expected). This slight inversion of the expected order for $AcO^-$ and $BzO^-$ according to their basicities is within the experimental error, and has no meaning if we compare the differences between the p$K_a$ of the corresponding acids in $CHCl_3$ [$\Delta pK_a$ (AcOH → BzOH) = 1.7 and $\Delta pK_a$ (BzOH → $HNO_3$) = 12.6].[29] This means that $AcO^-$ is a base only 50 times stronger than $BzO^-$, while $NO_3^-$ is a base almost $4 \times 10^{12}$ times weaker than $BzO^-$! However, as that inversion was not maintained in the UV studies (discussed below), a possible explanation may lie in a specific solvation mode of the urea–benzoate complexes in chloroform. *t*-Bu-urea **5c** is the weakest receptor, displaying a slightly higher log $K_{assoc}$ value for the smaller anion $NO_3^-$.This may be due to steric hindrance caused by the *t*-Bu groups.

Finally, concerning the tetrahedral oxoanions, Ph-urea **5a** followed the anion basicity order and exhibited much higher binding affinities toward $H_2PO_4^-$ and $HSO_4^-$ than to $ClO_4^-$. In the case of *n*-Pr-urea **5b** the basicity order is inverted. The less basic and largest anion $ClO_4^-$ is slightly better complexed than the others. This may be due to a suitable size complementarity of **5b** and the anion. Size-dependent binding has already been described, mainly for the spherical halides.[12] Furthermore, *n*-Pr-urea should have enough flexibility to allow a good binding environment in terms of size matching. *t*-Bu-urea **5c** showed again the lowest log $K_{assoc}$ values, but following the basicity order.

*UV–vis Studies.* The interactions between Ph-urea **5a** and some anions of different geometries ($F^-$, $Cl^-$, $SCN^-$, $NO_3^-$, $AcO^-$, $BzO^-$, $HSO_4^-$, and $H_2PO_4^-$) as TBA salts have also been studied by UV–vis absorption spectrophotometry in MeCN.

Significant spectral changes were observed for **5a** in the presence of $F^-$, $AcO^-$, $BzO^-$, and $H_2PO_4^-$, as shown in Figure 5 for $AcO^-$ as an example. Very small or no spectral changes occurred for all other systems, which could not be interpreted. As revealed by the association constant data (Table 3), Ph-urea **5a** displayed the strongest complexation for $F^-$ (log $K_{assoc}$ = 4.6), closely followed by $AcO^-$, $BzO^-$, and $H_2PO_4^-$ in agreement with the basicity order in MeCN. Compound **5a** forms 1:1 and also 2:1 complexes with all the anions and presents higher association constants than by NMR. It should be noted that in UV titration experiments the concentrations are much lower than those used in NMR, and this difference

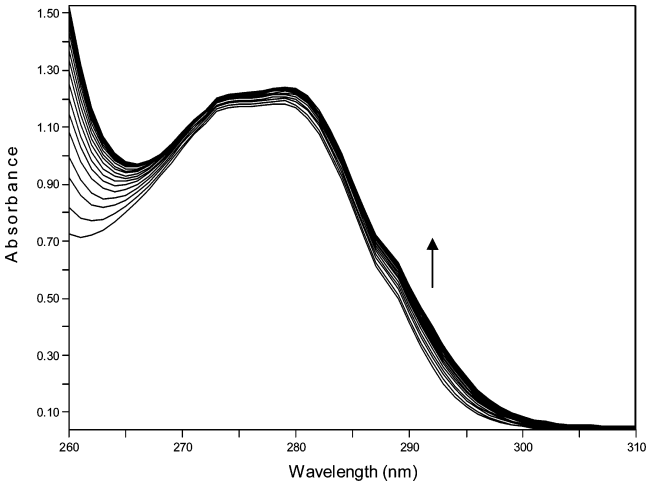



**Figure 5.** Changes in the UV spectra of **5a** upon addition of acetate ($C_L = 1.95 \times 10^{-4}$ M; $0 \le R = C_A/C_L \le 2$) in MeCN. The arrow indicates the increasing amounts of acetate.

**Table 3. Association Constants (log $K_{assoc}$)[a] of Ph-urea 5a in MeCN at 25 °C Determined by UV–vis Experiments**

| | X:L | $F^-$ | $AcO^-$ | $BzO^-$ | $H_2PO_4^-$ |
|---|---|---|---|---|---|
| Ph-urea **5a** | 1:1 | 4.6 | 4.5 | 4.2 | 4.2 |
| | 2:1 | 4.6 | 4.3 | 4.4 | 4.0 |

[a]Values are the average of at least two experiments; estimated error <10%.

can influence the stoichiometry of the species formed and also their association constants. The more diluted solutions used in UV studies favor the dissociation of the salts, providing a higher concentration of the anions available for complexation, and consequently the association constants become higher. Similar situations were reported before with other receptors.[14,15,25] However, these UV results follow the same trend observed in the NMR studies discussed above. No positive cooperative effect is observed, as the association constants are lower for the second complexation step than for the 1:1 complexes (except in the case of $BzO^-$).

*DFT Studies.* The binding affinity of Ph-urea **5a** was also studied by DFT methods to give more insight into the structures and electronic properties of the complexes.

All the structures (receptor and complexes) were fully optimized without symmetry constraints using the Becke three-parameter hybrid functional combined with the Lee, Yang, and Parr correlation functional (B3LYP).[30] Although the comparison between gas-phase and condensed-phase structures is not direct, all the structures were geometry optimized solvent free. They are therefore expected to correlate primarily with gas state complex geometries and not necessarily with NMR data, in which the solvent will influence the anion–receptor interactions and the relative complexation energies. However, they can give some insight into the key differences between the complexes under investigation.

The interactions of **5a** with some anions of each geometry group ($F^-$, $Cl^-$, $SCN^-$,$CN^-$, $AcO^-$, $BzO^-$, $HSO_4^-$, and $H_2PO_4^-$) were studied, and their minimum energy structures were initially determined with the B3LYP/3-21G basis set. After this minimization, single-point energy calculations were then carried out at the B3LYP/6-31G(d,p) level, to add polarization functions for hydrogen atoms and diffuse functions


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742–751

for both hydrogen and non-hydrogen atoms, to obtain a more accurate description of the hydrogen-bonding interactions involved in the complexation of the anions.[31]

The energies obtained for all the anion−receptor 1:1 complexes, either by optimization or single point, are presented in Table 4. All of the complexation energies calculated were negative, meaning that the complexes were thermodynamically favorable. The relative complexation energies were, however, very different. In general, it can be observed that independently of the basis set used (3-21G or 6-31G(d,p)), the stability of the complexes decrease with decreasing of anion basicity. The most stable complex was obtained with $F^-$ with a complexation energy double of the following one (**5a**-$AcO^-$). Moreover, the difference in energy between the two spherical anions $F^-$ and $Cl^-$ is much higher than the difference in energy between the two trigonal planar oxoanions $AcO^-$ and $BzO^-$ ($\Delta E_c$ = 73.93 and 13.53 kcal $mol^{-1}$, respectively). This is in complete agreement with the strength of these bases in $CHCl_3$ [$\Delta pK_a$ (HF → HCl) = 15.5 and $\Delta pK_a$ (AcOH → BzOH) = 1.7].[29]

**Table 4. Total Energies *E* (au) and Complexation Energies $\Delta E_c$ (kcal $mol^{-1}$)[a] for the Systems Studied. Optimization at B3LYP/3-21G and Single-Point at B3LYP/6-31G(d,p) Levels**

| | B3LYP/3-21G | | B3LYP/6-31G(d,p) | |
|---|---|---|---|---|
| | *E* | $\Delta E_c$[a] | *E* | $\Delta E_c$[a] |
| **5a** | −3645.10924 | | −3665.19423 | |
| **5a**·$F^-$ | −3744.53902 | −175.30 | −3765.14991 | −126.50 |
| **5a**·$Cl^-$ | −4103.25415 | −55.11 | −4125.53025 | −52.57 |
| **5a**·$AcO^-$ | −3872.46085 | −86.72 | −3893.79082 | −62.56 |
| **5a**·$BzO^-$ | −4063.14083 | −67.23 | −4085.53032 | −49.03 |
| **5a**·$HSO_4^-$ | −4341.12293 | −69.84 | −4364.91281 | −41.14 |
| **5a**·$H_2PO_4^-$ | −4285.30927 | −71.69 | −4308.83746 | −45.95 |
| **5a**·$CN^-$ | −3737.51271 | −69.88 | −3758.11448 | −60.07 |
| **5a**·$SCN^-$ | −4133.79539 | −40.39 | −4156.35055 | −35.75 |

[a] $\Delta E_c$ corresponds to the process **5a** + $X^-$ → [**5a**-$X^-$], where $X^-$ represents each one of the anions.

Figure 6 shows the optimized structures for Ph-urea **5a** and the eight complexes studied. It can be observed that the free receptor presents a distorted cone conformation, which becomes more symmetric upon the anion complexation, being this more noticeable in the case of $F^-$. It is also clear from Figure 6 (b and c) that for the spherical $F^-$ and $Cl^-$ a cage structure was formed with all four NH ureido groups directed into the center of the cavity, in which the anion is included. In the case of the linear $CN^-$ and $SCN^-$ anions (Figure 6, h and i), the four hydrogen bonds are directed into the more electronegative atom, while for the oxoanions they are directed to both oxygen atoms (or to the three oxygens in the case of $HSO_4^-$) of the anion molecule. This is confirmed in Table 5, where hydrogen-bond distances are listed. As expected, all the anions interact preferably with the four hydrogen atoms of the NH ureido groups. According to the distances NH···$X^-$ shown in Table 5, it is evident a strong concordance between these distances and the stability of the complexes, namely for $F^-$ and $AcO^-$ that show the shortest distances (in average 1.69 and 1.81 Å, respectively).

To better characterize and visualize the electrostatic equilibria in the complexes, electrostatic potential maps were calculated over an electronic isodensity surface of $\rho$ = 0.05 $Å^{-3}$ (Figure 7). Red regions are those of relatively lower or more negative electrostatic potential, while the blue ones correspond to higher or more positive electrostatic potential. Three structures are presented here: the receptor, the most stable complex (**5a**-$F^-$), and the least stable complex (**5a**-$SCN^-$). In all of the structures the oxomethylene bridge is a zone with negative electrostatic potential as well as the oxygen atom of the urea fragment. The presence of the anion pulls the lower limit of the electrostatic potential further down when compared to the free receptor. Also visible are the hydrogen bonds between the more electronegative atoms of the anions and the hydrogens of the NH ureido moiety. Overall, these structural representations give insights to the electrostatic rearrangement caused by the introduction of the anion molecules. Although the electrostatic potentials of the complexes are similar (Figure 7, b and c), the potential energy associated with each anion is very different, as represented by the color distribution observed.

## CONCLUSIONS

A new family of anion receptors based on dihomooxacalix[4]-arenes containing two urea moieties at the lower rim via a four carbon atom spacer, has been described. Three bidentate ureido derivatives (phenyl **5a**, *n*-propyl **5b**, and *tert*-butyl **5c**) were obtained in the cone conformation and complexed anions in a 1:1 stoichiometry through hydrogen bonding, as shown by $^1H$ NMR studies. The data revealed that the substituents (Ph, *n*-Pr, and *t*-Bu) on the urea moiety strongly influence the binding ability of the receptors. $^1H$ NMR, UV−vis, and DFT studies showed that, in general, the association constants decreased with decreasing of anion basicity. Ph-urea **5a** is the best anion receptor, showing the strongest affinity for $F^-$ (log $K_{assoc}$ = 3.10 and 4.6 in $CDCl_3$ and MeCN, respectively) and a complexation energy double of the next more stable complex. High complexation was also obtained for the oxoanions $AcO^-$ and $BzO^-$ with **5a**. *t*-Bu-urea **5c** was the weakest receptor, probably due to steric hindrance caused by the bulky *tert*-butyl groups. The binding results obtained followed the same trend by both techniques and were corroborated by DFT methods.

## EXPERIMENTAL SECTION

**Synthesis.** All chemicals were reagent grade and were used without further purification. Chromatographic separations were performed on silica gel 60 (particle size 40−63 μm, 230−400 mesh). Melting points were measured (not corrected) and FTIR spectra were recorded. $^1H$ and $^{13}C$ NMR spectra were recorded using a 500 MHz spectrometer, with TMS as internal reference. The conventional COSY 45 and the phase-sensitive NOESY experiments were collected as 256 × 2 K complex points. Elemental analysis was determined on a micro-analyser.

*7,13,19,25-Tetra-tert-butyl-27,29-bis[(cyanopropyl)oxy]-28,30-dihydroxy-2,3-dihomo-3-oxacalix[4]arene* (**2**). A mixture of *p-tert*-butyldihomooxacalix[4]arene (6.0 g, 8.85 mmol), $K_2CO_3$ (2.45 g, 17.7 mmol), and 4-bromobutyronitrile (1.81 mL, 17.7 mmol) in $CH_3CN$ (140 mL) was refluxed and stirred under $N_2$ for 6 days. After cooling, the solvent was evaporated under reduced pressure and the residue was dissolved in $CH_2Cl_2$ (250 mL) and washed with 1 M HCl (150 mL), $H_2O$ (2 × 100 mL), and brine (2 × 100 mL). The organic layer was dried over $Na_2SO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography on silica gel (eluent $CH_2Cl_2$/MeOH, 99.5:0.5) affording a white solid in 49% yield (3.5 g). An analytically pure sample was obtained from recrystallization from MeOH: mp 175−177 °C; IR (KBr) 2247 $cm^{-1}$ (CN); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 1.10, 1.23, 1.25, 1.27 [4s, 36H, $C(CH_3)$], 2.35−2.43 (m, 4H, $OCH_2CH_2CH_2CN$), 2.83−2.99 (m, 3H, $OCH_2CH_2CH_2CN$), 3.15−3.21 (m, 1H, $OCH_2CH_2CH_2CN$), 3.34, 4.42 (ABq, 2H, *J* = 13.1 Hz,


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742−751

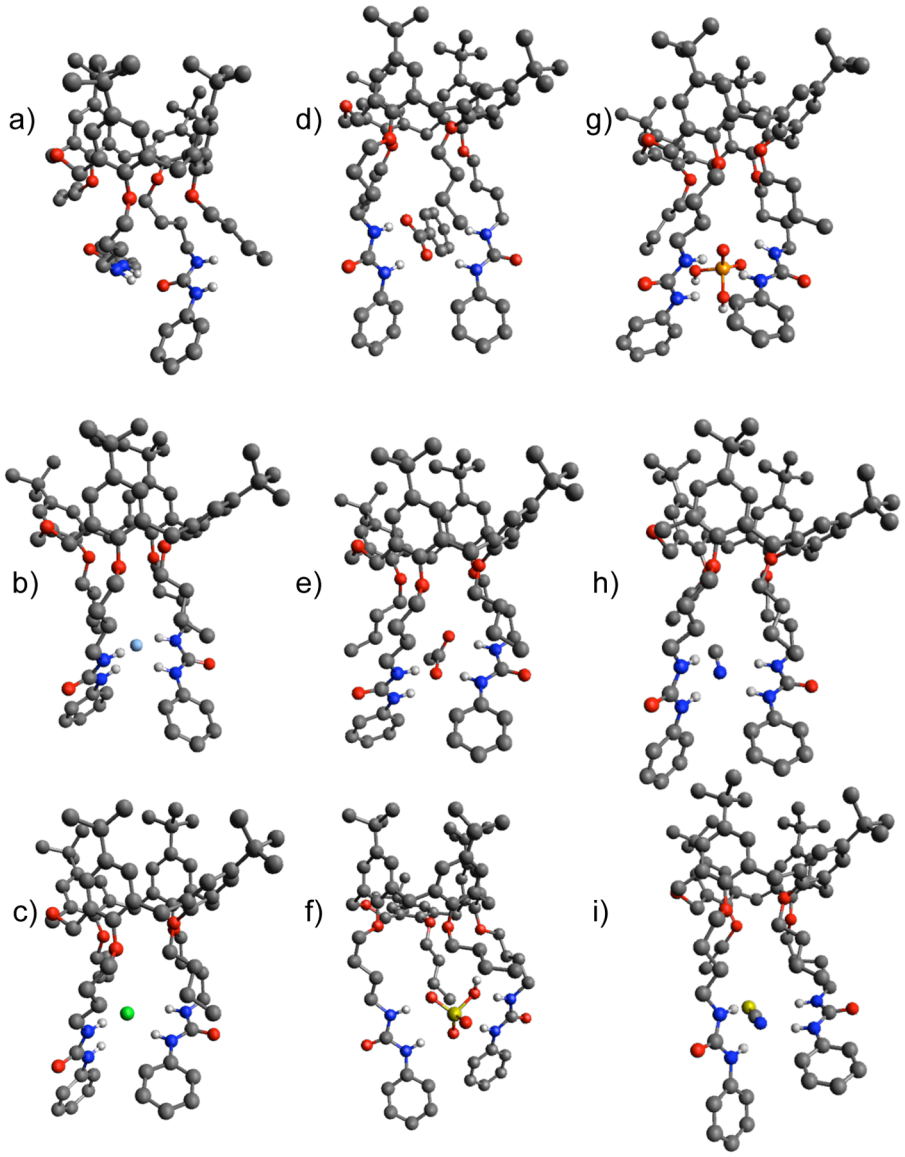



**Figure 6.** Optimized structures for Ph-urea **5a**-$X^-$ complexes: (a) **5a**, (b) **5a** + $F^-$ (c) **5a** + $Cl^-$, (d) **5a** + $BzO^-$, (e) **5a** + $AcO^-$, (f) **5a** + $HSO_4^-$, (g) **5a** + $H_2PO_4^-$, (h) **5a** + $CN^-$ and (i) **5a** + $SCN^-$. All of the hydrogen atoms were removed for clarity, except the urea NH hydrogens.

**Table 5. Selected Structural Data of 5a-$X^-$ Complexes (B3LYP/3-21G)**

| | NH···$X^-$ (Å) | | | |
|---|---|---|---|---|
| | $a_1$ | $b_1$ | $a_2$ | $b_2$ |
| **5a**·$F^-$ | 1.69 | 1.68 | 1.78 | 1.61 |
| **5a**·$Cl^-$ | 2.35 | 2.32 | 2.40 | 2.28 |
| **5a**·$AcO^-$ | 1.73 | 1.92 | 1.77 | 1.82 |
| **5a**·$BzO^-$ | 1.85 | 1.81 | 2.96 | 1.88 |
| **5a**·$HSO_4^-$ | 1.78 | 1.96 | 1.74 | 2.19 |
| **5a**·$H_2PO_4^-$ | 1.87 | 1.85 | 1.89 | 2.37 |
| **5a**·$CN^-$ | 1.89 | 2.38 | 1.89 | 2.37 |
| **5a**·$SCN^-$ | 1.92 | 2.25 | 1.97 | 2.62 |

1 and 2 refer to the two ureido groups of **5a**.

$ArCH_2Ar$), 3.35, 4.54 (ABq, 2H, $J$ = 12.8 Hz, $ArCH_2Ar$), 3.53, 4.10 (ABq, 2H, $J$ = 13.3 Hz, $ArCH_2Ar$), 4.02−4.23 (3m, 4H, $OCH_2CH_2CH_2CN$), 4.25, 4.77 (ABq, 2H, $J$ = 9.7 Hz, $CH_2OCH_2$), 4.43, 4.69 (ABq, 2H, $J$ = 10.0 Hz, $CH_2OCH_2$), 6.88, 6.91, 7.01, 7.05, 7.06, 7.18, 7.28, 7.51 (8d, 8H, ArH), 7.12, 7.78 (2s, 2H, OH); $^{13}C$ NMR ($CDCl_3$, 125.8 MHz) $\delta$ 14.4, 14.5 ($OCH_2CH_2CH_2CN$), 26.2, 26.7 ($OCH_2CH_2CH_2CN$), 29.3, 30.0, 32.7 ($ArCH_2Ar$), 31.1, 31.4, 31.5, 31.6 [$C(CH_3)$], 33.9 (2C), 34.2, 34.3 [$C(CH_3)$], 71.5, 72.4 ($CH_2OCH_2$), 72.8, 73.7 ($OCH_2CH_2CH_2CN$), 119.1, 120.1 (CN), 123.9, 125.1, 125.4, 125.6, 126.0, 126.2, 128.0, 129.6 (ArH), 122.3, 127.2, 127.4, 128.4, 129.1, 131.9, 132.2, 135.1, 141.9, 142.4, 147.2, 147.6, 149.3 (2C), 152.5, 153.3 (Ar). Anal. Calcd for $C_{53}H_{68}N_2O_5$·MeOH: C, 76.75; H, 8.59; N, 3.32. Found: C, 77.07; H, 8.51; N, 3.57.

*7,13,19,25-Tetra-tert-butyl-28,29-bis[(cyanopropyl)oxy]-27,30-dihydroxy-2,3-dihomo-3-oxacalix[4]arene* (***2a***). From the previous flash chromatography, another set of fractions were combined and chromatographed again (eluent $CH_2Cl_2$/MeOH, 99.8:0.2) yielding **2a** in low yield: mp 143−145 °C; IR (KBr) 2250 $cm^{-1}$ (CN); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 1.00, 1.26 [2s, 36H, $C(CH_3)$], 2.35 (m, 4H, $OCH_2CH_2CH_2CN$), 2.75, 2.87 (2m, 4H, $OCH_2CH_2CH_2CN$), 3.45, 4.20 (ABq, 4H, $J$ = 13.9 Hz, $ArCH_2Ar$), 3.46, 4.45 (ABq, 2H, $J$ = 13.5 Hz, $ArCH_2Ar$), 4.05, 4.23 (2m, 4H, $OCH_2CH_2CH_2CN$), 4.26, 4.67 (ABq, 4H, $J$ = 10.0 Hz, $CH_2OCH_2$), 6.81, 6.86, 6.93, 7.23 (4d, 8H, ArH), 7.53 (s, 2H, OH); $^{13}C$ NMR ($CDCl_3$, 125.8 MHz) $\delta$ 14.3 ($OCH_2CH_2CH_2CN$), 26.1 ($OCH_2CH_2CH_2CN$), 30.7, 31.6 ($ArCH_2Ar$), 31.0, 31.5 [$C(CH_3)$], 33.9, 34.0 [$C(CH_3)$], 71.6 ($CH_2OCH_2$), 72.8 ($OCH_2CH_2CH_2CN$), 119.7 (CN), 124.8, 125.1,


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742−751

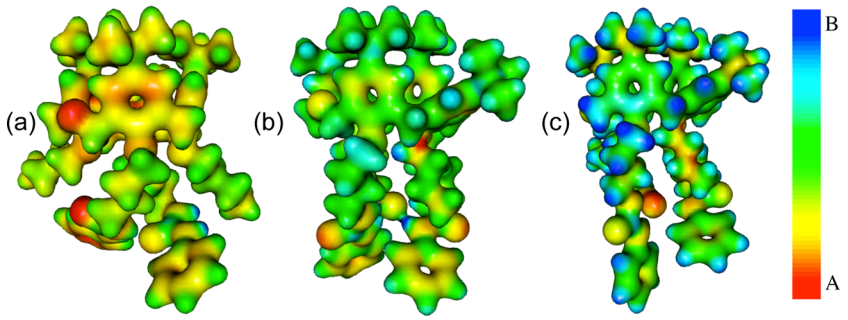



**Figure 7.** Electrostatic potential for Ph-urea **5a** and two anion complexes: (a) **5a**, (b) **5a** + $F^-$ and (c) **5a** + $SCN^-$. The electrostatic potential (in au) is represented over a constant electronic isodensity $\rho$ (in $Å^{-3}$) surfaces of volume $V_s$ (in $Å^{-3}$). All three figures correspond to $\rho$ = 0.05 $Å^{-3}$, and the potential varies: (a) from B = 0.33 (dark blue) to A = −0.17 (red) for the receptor; (b) from B = 0.13 (dark blue) to A = −0.31 (red) for the complex **5a**-$F^-$ and (c) from B = 0.07 (dark blue) to A = −0.37 (red) for the complex **5a**-$SCN^-$.

126.1, 128.0 (ArH), 123.3, 128.0, 132.8, 133.3, 142.2, 147.0, 151.0, 151.7 (ArH). Anal. Calcd for $C_{53}H_{68}N_2O_5$: C, 78.29; H, 8.43; N, 3.45. Found: C, 78.54; H, 8.74; N, 3.61.

*7,13,19,25-Tetra-tert-butyl-27,29-bis[(cyanopropyl)oxy]-28,30-dibutoxy-2,3-dihomo-3-oxacalix[4]arene (**3**).* A mixture of **2** (1.0 g, 1.23 mmol) and 0.30 g (7.4 mmol) of NaH (60% oil dispersion) in 40 mL of THF−DMF (7:1, v/v) was stirred under an atmosphere of $N_2$. After 1 h, 0.85 mL (7.4 mmol) of 1-iodobutane was added, and the mixture was refluxed and stirred for 14 h. After cooling, the solvent was evaporated, and the residue was dissolved in $CH_2Cl_2$ (75 mL) and washed with 1 M HCl (2 × 40 mL), $NH_4Cl$ saturated solution (3× 30 mL), and brine (40 mL). The organic layer was dried over $Na_2SO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography on silica gel (eluent gradient from *n*-heptane/ethyl acetate 95:5 to 90:10) to give **3** as a white solid in the cone (0.55 g, 54% yield) and partial cone A conformations (0.14 g, 14% yield).

*Cone*: mp 104−106 °C; IR (KBr) 2247 $cm^{-1}$ (CN); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.65, 1.04, 1.23, 1.34 [4s, 36H, $C(CH_3)$], 1.01, 1.03 (2t, 6H, $J$ = 7.4 Hz, $CH_3$), 1.47, 1.55 (2m, 4H, $OCH_2CH_2CH_2CH_3$), 1.84 (m, 4H, $OCH_2CH_2CH_2CH_3$), 2.16, 2.28, 2.37, (3m, 4H, $OCH_2CH_2CH_2CN$), 2.60, 2.66 (2m, 4H, $OCH_2CH_2CH_2CN$), 3.22, 4.30 (ABq, 2H, $J$ = 13.9 Hz, $ArCH_2Ar$), 3.23, 4.34 (ABq, 2H, $J$ = 12.9 Hz, $ArCH_2Ar$), 3.26, 4.32 (ABq, 2H, $J$ = 13.0 Hz, $ArCH_2Ar$), 3.59, 3.74, 3.85, 4.02 (4m, 8H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CN$), 4.33, 4.65 (ABq, 2H, $J$ = 13.2 Hz, $CH_2OCH_2$), 4.65, 4.77 (ABq, 2H, $J$ = 13.0 Hz, $CH_2OCH_2$), 6.28, 6.79, 6.85, 6.89, 7.10, 7.12, 7.20, 7.22 (8d, 8H, ArH); $^{13}C$ NMR ($CDCl_3$, 125.8 MHz) $\delta$ 14.0 (2C) $[O(CH_2)_3CH_3]$, 14.1, 14.4, 19.3, 19.5 ($OCH_2CH_2CH_2CN$ and $OCH_2CH_2CH_2CH_3$), 26.1, 26.3 ($OCH_2CH_2CH_2CN$), 29.7, 30.1, 30.5 ($ArCH_2Ar$), 31.2 (2C), 31.5, 31.6 $[C(CH_3)]$, 32.4, 32.5 ($OCH_2CH_2CH_2CH_3$), 33.8, 33.9, 34.2, 34.3 $[C(CH_3)]$, 67.7, 68.2 ($CH_2OCH_2$), 71.9 (2C), 74.8, 75.6 ($OCH_2CH_2CH_2CN$ and $OCH_2CH_2CH_2CH_3$), 119.7, 120.3 (CN), 123.2, 124.3, 124.6, 125.1, 125.4, 126.5, 126.6, 127.0 (ArH), 130.0, 131.9, 132.3, 132.4, 132.6, 133.7, 133.9, 135.2,144.8, 145.3, 145.8, 145.9, 151.3, 151.9, 152.0, 152.9 (Ar). Anal. Calcd for $C_{61}H_{84}N_2O_5$: C, 79.18; H, 9.15; N, 3.03. Found: C, 78.92; H, 9.12; N, 3.21.

*Partial cone A*: mp 108−110 °C; IR (KBr) 2243 $cm^{-1}$ (CN); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.73 (m, 4H, $OCH_2CH_2CH_2CN$ inverted), 0.96, 0.97 (2t, 6H, $J$ = 7.4 Hz, $CH_3$), 1.21, 1.25, 1.38, 1.39 [4s, 36H, $C(CH_3)$], 1.38 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.66, 1.75, 1.92, 2.37 (4m, 10H, $OCH_2CH_2CH_2CH_3$, $OCH_2CH_2CH_2CN$ and $OCH_2CH_2CH_2CN$ inverted), 3.30, 4.39 (ABq, 2H, $J$ = 13.1 Hz, $ArCH_2Ar$), 3.31, 4.28 (ABq, 2H, $J$ = 13.1 Hz, $ArCH_2Ar$), 3.49−3.77 (several m, 6H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CN$), 3.81, 3.88 (ABq, 2H, $J$ = 15.8 Hz, $ArCH_2Ar$), 4.10, 5.05 (ABq, 2H, $J$ = 11.9 Hz, $CH_2OCH_2$), 4.11 (s, 2H, $CH_2OCH_2$), 7.03, 7.05, 7.16, 7.22, 7.24, 7.32, 7.33 (7d, 8H, ArH); $^{13}C$ NMR ($CDCl_3$, 125.8 MHz) $\delta$ 12.2, 13.2 ($OCH_2CH_2CH_2CN$ inverted and $OCH_2CH_2CH_2CN$), 14.0 (2C) $[O(CH_2)_3CH_3]$, 19.2, 19.3 ($OCH_2CH_2CH_2CH_3$), 25.2, 26.1 ($OCH_2CH_2CH_2CN$ inverted and $OCH_2CH_2CH_2CN$), 29.1, 30.1, 39.2 ($ArCH_2Ar$), 31.4, 31.5, 31.6 (2C) $[C(CH_3)]$, 32.1, 32.2 ($OCH_2CH_2CH_2CH_3$), 34.1 (2C), 34.2, 34.3 $[C(CH_3)]$, 64.6, 68.5 ($CH_2OCH_2$), 70.3, 70.4, 73.9, 75.4 ($OCH_2CH_2CH_2CN$ and $OCH_2CH_2CH_2CH_3$), 119.7, 121.1 (CN), 125.3, 125.9, 126.2, 126.7, 126.8, 126.9, 127.0, 128.2 (ArH), 130.2, 130.6, 132.9, 133.2, 133.4, 133.44, 134.5, 143.53, 145.3, 145.4, 145.8, 146.6, 152.4, 152.9, 153.7, 154.3 (Ar). Anal. Calcd for $C_{61}H_{84}N_2O_5$: C, 79.18; H, 9.15; N, 3.03. Found: C, 78.79; H, 9.06; N, 3.21.

*7,13,19,25-Tetra-tert-butyl-27,29-bis[(aminobutyl)oxy]-28,30-dibutoxy-2,3-dihomo-3-oxacalix[4]arene (**4**).* To a suspension of 1.0 g (1.08 mmol) of **3** (cone conformation) and 1.54 g (6.48 mmol) of $CoCl_2·6H_2O$ in MeOH (35 mL) was slowly added 0.85 g (21.6 mmol) of $NaBH_4$. A black suspension was formed that was stirred at room temperature for 24 h. Then, another portion of $NaBH_4$ (0.85 g) was added, and the suspension was stirred for an additional 24 h. A 25% ammonia solution (110 mL) was added, and the mixture was stirred overnight. The solution was extracted with $CH_2Cl_2$ (3 × 50 mL) and dried over $Na_2SO_4$, and the solvent evaporated to dryness to afford diamine **4** as a beige solid (88% yield), which was pure enough to be immediately used in the next step: $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.90, 0.99, 1.16, 1.20 [4s, 36H, $C(CH_3)$], 1.00, 1.01 (2t, 6H, $J$ = 7.4 Hz, $CH_3$), 1.42−1.67, 1.77−2.05 (several m, 16H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2NH_2$), 2.79 (2t, 4H, $OCH_2CH_2CH_2CH_2NH_2$), 3.18, 4.38 (ABq, 2H, $J$ = 13.2 Hz, $ArCH_2Ar$), 3.18, 4.40 (ABq, 2H, $J$ = 13.2 Hz, $ArCH_2Ar$), 3.22, 4.39 (ABq, 2H, $J$ = 13.0 Hz, $ArCH_2Ar$), 3.61−3.90 (several m, 8H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2NH_2$), 4.59, 4.64 (ABq, 2H, $J$ = 13.1 Hz, $CH_2OCH_2$), 4.59, 4.68 (ABq, 2H, $J$ = 13.1 Hz, $CH_2OCH_2$), 6.62, 6.81, 6.93, 6.94, 6.97, 7.00, 7.03, 7.07 (8d, 8H, ArH).

**Procedure for the Synthesis of Ureas 5a, 5b, and 5c.** To a solution of **4** (0.90 g, 0.966 mmol) in $CHCl_3$ (30 mL) was added 1.93 mmol of the appropriate isocyanate. The mixture was stirred at room temperature under $N_2$ for 4 h. Evaporation of the solvent yielded the crude products which were purified as described below.

*7,13,19,25-Tetra-tert-butyl-27,29-bis[[(N′-phenylureido)butyl]-oxy]-28,30-dibutoxy-2,3-dihomo-3-oxacalix[4]arene (**5a**).* Flash chromatography ($SiO_2$, eluent $CH_2Cl_2$/MeOH, from 99:1 to 97:3) was followed by recrystallization from MeOH: 45% yield (0.56 g); mp 214−216 °C; IR (KBr) 3327 $cm^{-1}$ (NH), 1647 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.55, 1.08, 1.33, 1.37 [4s, 36H, $C(CH_3)$], 0.91, 0.94 (2t, 6H, $J$ = 7.4 Hz, $CH_3$), 1.44 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.50, 1.78, 1.92, 2.27 (4m, 12H, $OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 3.20, 4.31 (ABq, 2H, $J$ = 14.1 Hz, $ArCH_2Ar$), 3.21, 4.30 (ABq, 2H, $J$ = 12.7 Hz, $ArCH_2Ar$), 3.22, 4.38 (ABq, 2H, $J$ = 12.6 Hz, $ArCH_2Ar$), 3.21, 3.35, 3.55 (3m, 4H, $OCH_2CH_2CH_2CH_2NH_a$), 3.47, 3.58−3.81, 3.90, 3.99 (several m, 8H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_3$), 4.39, 4.91 (ABq, 2H, $J$ = 13.2 Hz, $CH_2OCH_2$), 4.40, 5.15 (ABq, 2H, $J$ = 12.6 Hz, $CH_2OCH_2$), 5.82, 6.27 (2t, 2H, $NH_a$), 6.13, 6.47, 6.76, 6.94, 7.12, 7.20, 7.30, 7.31 (8d, 8H, ArH), 6.96, 7.01 (2t, 2H, Ph-$H_p$), 7.25, 7.27 (2t, 4H, Ph-$H_m$), 7.46, 7.4 (2d, 4H, Ph-$H_o$), 7.96, 8.05 (2s, 2H, $NH_b$); $^{13}C$


dx.doi.org/10.1021/jo4026012 | J. Org. Chem. 2014, 79, 742−751

NMR ($CDCl_3$, 125.8 MHz) $\delta$ 13.9, 14.1 [$O(CH_2)_3CH_3$], 19.3, 19.4 ($OCH_2CH_2CH_2CH_3$), 25.4, 26.0, 26.2, 28.6 ($OCH_2CH_2CH_2CH_2NH_a$), 29.2, 30.9, 31.2 ($ArCH_2Ar$), 31.2, 31.3, 31.6, 31.7 [$C(CH_3)$], 32.2, 32.6 ($OCH_2CH_2CH_2CH_3$), 33.7, 33.9, 34.19, 34.21 [$C(CH_3)$], 39.6 (2C) ($OCH_2CH_2CH_2CH_2NH_a$), 70.8, 71.7 ($CH_2OCH_2$), 72.3, 74.7, 75.0, 75.5 ($OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 118.9, 119.2, 121.8, 122.7, 123.8, 124.8, 125.0, 125.2, 125.9, 126.2, 126.9, 128.5, 128.8, 129.2 (ArH), 129.1, 131.0, 132.0, 132.7, 132.9, 134.37, 134.43, 136.0, 139.6, 140.1, 144.3, 145.0 (2C), 145.5, 152.6, 153.0, 153.9, 154.5 (Ar), 156.2, 156.9 (CO). Anal. Calcd for $C_{75}H_{98}N_4O_7$: C, 77.15; H, 8.46; N, 4.80. Found: C, 77.15; H, 8.69; N, 4.79.

*7,13,19,25-Tetra-tert-butyl-27,29-bis[[(n-propylureido)butyl]oxy]-28,30-dibutoxy-2,3-dihomo-3-oxacalix[4]arene (**5b**).* Flash chromatography ($SiO_2$, eluent $CH_2Cl_2$/MeOH, from 99:1 to 96:4) was followed by recrystallization from $CH_2Cl_2$/*n*-hexane: 36% yield (0.42 g); mp 183−185 °C; IR (KBr) 3345 $cm^{-1}$ (NH), 1634 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.55, 1.06, 1.29, 1.36 [4s, 36H, $C(CH_3)$], 0.95, 0.96, 0.97, 0.99 [4t, 12H, $J$ = 7.3 Hz, $O(CH_2)_3CH_3$ and $NH_bCH_2CH_2CH_3$)], 1.43−1.61, 1.68 (several m, 10H, $OCH_2CH_2CH_2CH_3$, $NH_bCH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2NH_a$), 1.72−1.86, 1.91, 2.16 (3m, 10H, $OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 3.19, 4.31 (ABq, 2H, $J$ = 13.9 Hz, $ArCH_2Ar$), 3.20, 4.33 (ABq, 2H, $J$ = 12.9 Hz, $ArCH_2Ar$), 3.21, 4.36 (ABq, 2H, $J$ = 12.6 Hz, $ArCH_2Ar$), 3.14−3.35, 3.42 (several m, 8H, $NH_bCH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2NH_a$), 3.49, 3.59−3.70, 3.75, 3.84, 3.91 (several m, 8H, $OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 4.46, 4.59 (ABq, 2H, $J$ = 13.4 Hz, $CH_2OCH_2$), 4.50, 4.92 (ABq, 2H, $J$ = 12.9 Hz, $CH_2OCH_2$), 5.36, 5.59 (2t, 2H, $NH_b$) 5.51, 5.62 (2t, 2H, $NH_a$), 6.14, 6.65, 6.76, 6.88, 7.11, 7.20, 7.21, 7.25 (8d, 8H, ArH); $^{13}C$ NMR ($CDCl_3$, 125.8 MHz) $\delta$ 11.5 (2C) ($NH_bCH_2CH_2CH_3$), 14.0, 14.1 [$O(CH_2)_3CH_3$], 19.3, 19.4 ($OCH_2CH_2CH_2CH_3$), 23.7 (2C) ($NH_bCH_2CH_2CH_3$), 25.9, 26.4, 26.6, 28.4 ($OCH_2CH_2CH_2CH_2NH_a$), 29.4, 30.8, 30.9 ($ArCH_2Ar$), 31.2, 31.3, 31.6, 31.7 [$C(CH_3)$], 32.2, 32.6 ($OCH_2CH_2CH_2CH_3$), 33.7, 33.9, 34.1, 34.2 [$C(CH_3)$], 39.8, 40.0, 41.9, 42.2 ($OCH_2CH_2CH_2CH_2NH_a$ and $NH_bCH_2CH_2CH_3$), 69.5 (2C) ($CH_2OCH_2$), 72.6, 74.4, 74.9, 75.4 ($OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 123.6, 124.0, 124.5, 125.0, 125.6, 126.3, 126.9, 127.4 (ArH), 129.3, 131.6, 132.2, 132.66, 132.70, 134.2 (2C), 135.9, 144.3, 145.0, 145.1, 145.3, 152.5, 152.6, 153.3, 153.8 (Ar), 159.1, 159.2 (CO). Anal. Calcd for $C_{69}H_{102}N_4O_7$: C, 75.37; H, 9.35; N, 5.10. Found: C, 75.02; H, 9.29; N, 5.20.

*7,13,19,25-Tetra-tert-butyl-27,29-bis[[(tert-butylureido)butyl]oxy]-28,30-dibutoxy-2,3-dihomo-3-oxacalix[4]arene (**5c**).* Flash chromatography ($SiO_2$, eluent $CH_2Cl_2$/MeOH, from 99:1 to 95:5): 49% yield (0.59 g); mp 160−162 °C; IR (KBr) 3366 $cm^{-1}$ (NH), 1638 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 0.54, 1.07, 1.30, 1.36 [4s, 36H, $C(CH_3)$], 0.96, 0.98 [2t, 6H, $J$ = 7.5 Hz, $O(CH_2)_3CH_3$), 1.38, 1,43 [(2s, 18H, $NH_bC(CH_3)$], 1.41−1.52 (m, 6H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2NH_a$), 1.64−1.93, 2.19 (several m, 10H, $OCH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2NH_a$), 3.19, 4.36 (ABq, 2H, $J$ = 12.6 Hz, $ArCH_2Ar$), 3.20, 4.31 (ABq, 2H, $J$ = 12.6 Hz, $ArCH_2Ar$), 3.21, 4.29 (ABq, 2H, $J$ = 13.5 Hz, $ArCH_2Ar$), 3.18−3.27, 3.48 (several m, 4H, $OCH_2CH_2CH_2CH_2NH_a$), 3.36, 3.57−3.80, 3.87−3.98 (several m, 8H, $OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 4.46, 4.67 (ABq, 2H, $J$ = 13.3 Hz, $CH_2OCH_2$), 4.47, 4.95 (ABq, 2H, $J$ = 12.6 Hz, $CH_2OCH_2$), 5.16, 5.58 (2s, 2H, $NH_b$), 5.56, 5.57 (2t, 2H, $NH_a$), 6.12, 6.62, 6.76, 6.90, 7.11, 7.20, 7.22, 7.25 (8d, 8H, ArH); $^{13}C$ NMR ($CDCl_3$, 125.8 MHz) $\delta$ 14.0, 14.1 [$O(CH_2)_3CH_3$], 19.3, 19.4 ($OCH_2CH_2CH_2CH_3$), 25.5, 26.4, 26.5, 28.5 ($OCH_2CH_2CH_2CH_2NH_a$), 29.6, 30.8, 31.1 ($ArCH_2Ar$), 29.7, 29.8 [$NH_bC(CH_3)$], 31.2, 31.3, 31.6, 31.7 [$C(CH_3)$], 32.3, 32.7 ($OCH_2CH_2CH_2CH_3$), 33.7, 33.9, 34.1, 34.2 [$C(CH_3)$], 39.3, 39.5 ($OCH_2CH_2CH_2CH_2NH_a$), 49.9, 50.2 [$NH_bC(CH_3)$], 69.6, 69.9 ($CH_2OCH_2$), 72.4, 74.8, 74.9, 75.4 ($OCH_2CH_2CH_2CH_2NH_a$ and $OCH_2CH_2CH_2CH_3$), 123.6, 124.0, 124.5, 125.1, 125.6, 126.2, 126.9, 127.6 (ArH), 129.1, 131.5, 132.2, 132.7, 132.8, 134.1, 134.3, 136.0, 144.3, 144.9, 145.1, 145.4, 152.6, 152.7, 153.6, 153.9 (Ar), 158.4 (2C) (CO). Anal. Calcd for $C_{71}H_{106}N_4O_7$: C, 75.63; H, 9.47; N, 4.97. Found: C,75.60; H, 9.30; N, 5.03.

**$^1H$ NMR Titrations.** The association constants (as log $K_{assoc}$) were determined in $CDCl_3$ by $^1H$ NMR titration experiments. Several aliquots (up to 10 equiv) of the anion solutions (as tetrabutylammonium salts) were added to 0.5 mL solution of the receptors ($2.5 \times 10^{-3} - 5 \times 10^{-3}$ M) directly in the NMR tube. The spectra were recorded after each addition of the salts, and the temperature of the NMR probe was kept constant at 25 °C. For each anion−receptor system titrations were repeated at least two times. The association constants were evaluated using the WinEQNMR2 program[23] and following the urea NH chemical shifts. When possible, $K_{assoc}$ was calculated as a mean value of the four NH chemical shifts. The Job methods were performed keeping the total concentration in the same range as before.

**UV−vis Titrations.** The association constants were also determined in acetonitrile by absorption spectrophotometry at 25.0 ± 0.1 °C. The spectra were recorded between 260 and 310 nm, using quartz cells with an optical path length of 1 cm. The anions studied were provided as tetrabutylammonium salts, and were dried under vacuum for at least 24 h before use. Twenty additions of 10 $\mu$L of the anion solution were directly added into the cell containing 2 mL of the receptor solution ($C_L$ from $10^{-5}$ to $2 \times 10^{-4}$ M). The anion to receptor ratios were in the range 1−10. The spectral changes were interpreted using the SPECFIT program.[32]

**Theoretical Methods.** Computational density functional theory (DFT) methods were used to analyze the structure and electronic properties of all the conformers studied. All the structures were fully optimized without symmetry constraints using the Becke three-parameter hybrid functional combined with the Lee, Yang, and Parr correlation functional (B3LYP)[30] along with the split-valence double-$\zeta$ Pople basis set, which is well-known to produce accurate geometries. Following this optimization, a single-point energy calculation with the same functional and a bigger basis was made, using 6-31G(d,p) valence double-$\zeta$ polarized basis set.

The methods and basis sets used were those implemented in the Gaussian 03 software package.[33] The vibrational frequency calculations were performed at the same level of theory to check that all structures were at the global minima of the potential energy surface (denoted by an absence of negative vibrational frequencies) and to correct the computed energies for zero-point energies as well as translational, rotational and vibrational contributions to the enthalpy. All the figures and electrostatic potential surfaces were constructed using Molekel software.[34]

The electrostatic potential was drawn over a surface of constant electronic isodensity using Molekel software. All the data needed to generate these surfaces and electrostatic potentials were calculated with Gaussian 03 software.

For each anion several initial positions were tested, starting inside or outside the receptor cavity.The relative complexation energies ($\Delta E_c$ corresponding to the process **5a** + $X^-$ → [**5a** − $X^-$], where $X^-$ represents each one of the anions) were calculated as the energy difference at 298 K between the final energy of the complexes and the sum of the energies of **5a** and the anion in study, at the same theoretical level.[35]

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1H$ and $^{13}C$ NMR spectra of the new compounds **2**, **2a**, **3** (cone), **3** (cone partial), **5a**, **5b**, and **5c**, and 2D NOESY spectra of compounds **2a** and **3** (partial cone). Table of atom coordinates and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the Fundação para a Ciência e a Tecnologia, Project ref PTDC/QUI/69858/2006.

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