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Selective Binding of Spherical and Linear Anions by Tetraphenyl(thio)urea-Based Dihomooxacalix[4]arene Receptors

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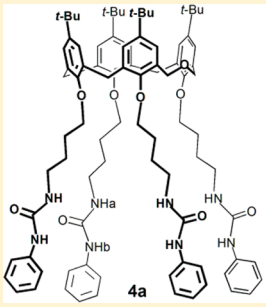
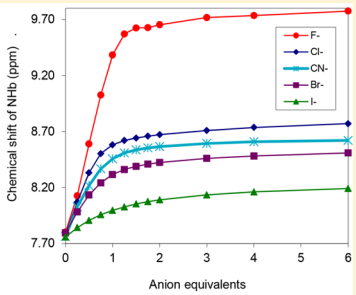
Supporting Information

ABSTRACT: Three novel tetra(thio)ureido dihomooxacalix[4]arene anion receptors (phenylurea **4a**, phenylthiourea **4b**, and *tert*-butylurea **4c**) were synthesized and obtained in the cone conformation in solution, as shown by NMR studies. The X-ray crystal structure of **4c** is reported. The host−guest properties of these receptors toward several anions were investigated by ^{1}H NMR titrations. Phenylurea **4a** displayed a very efficient binding toward the spherical F^- and Cl^- anions, and the linear CN^- (log K_{ass} = 3.46, 3.50, and 4.02, respectively). In comparison to related bidentate phenylurea dihomooxacalix[4]arenes, tetraphenylurea **4a** is more preorganized and the higher number of hydrogen bond donor sites provides a remarkable enhancement of its binding efficiency.





1. INTRODUCTION

Over the last two decades, a growing attention has been devoted to the study of anion recognition by calixarenes.[1,2] These compounds represent a very versatile class of macrocycles in host−guest and supramolecular chemistry,[3,4] and on the other hand, anions display an important role in biology, medicine, and environmental areas. The spherical fluoride, for example, is one of the most important anions affecting both biological and environmental areas. High concentration of fluoride in drinking water (>1.5−2 mg/L) can cause dental caries and fluorosis,[5] as well as water pollution when discarded into the rivers and seas.

Anion recognition by hydrogen-bonding receptors has been largely exploited, and has led to the incorporation of urea and thiourea moieties in the calixarene scaffolds. These groups originate strong and directional hydrogen bonds, giving rise to neutral, highly preorganized and selective receptors. Examples of calix[4]arene-based anion receptors containing (thio)urea groups on the upper or the lower rim are the most found in the literature,[6−10] but ureidocalix[5]arene,[11] calix[6]arene,[12,13] and thiacalix[4]arenes[14] have also been reported.

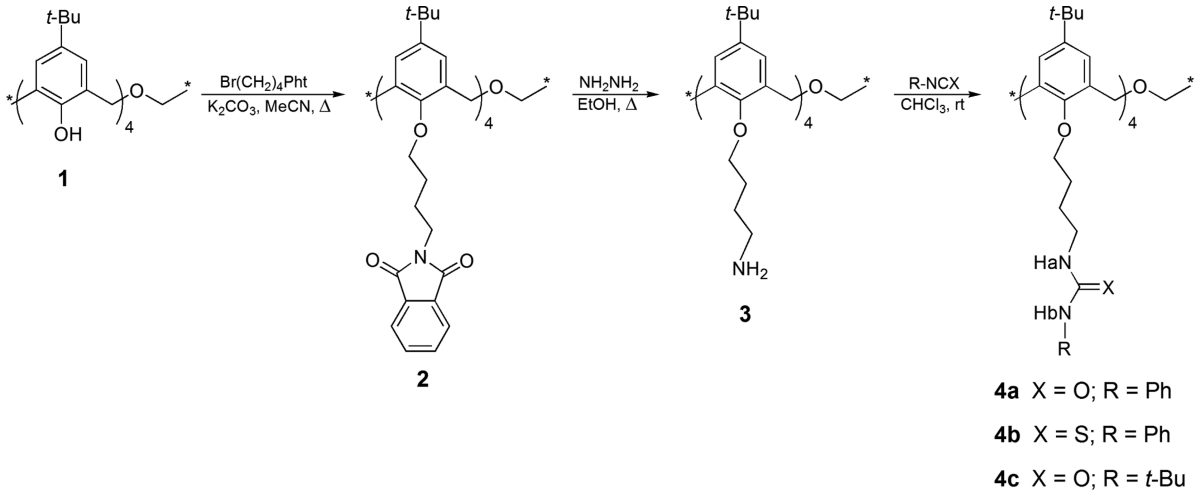
As part of our interest in the synthesis and study of homooxacalixarene-based receptors (calixarene analogues in which the CH_2 bridges are partly or completely replaced by CH_2OCH_2 groups)[15] for anionic species, we wanted to evaluate how the number of hydrogen bond donor sites on the receptors will influence their binding ability. In this context, we previously synthesized bidentate (thio)urea derivatives of *p-tert*-butyldihomooxacalix[4]arene.[16,17] It was shown that all the receptors form complexes with 1:1 stoichiometry, the substituents (alkyl/aryl) on the urea moiety strongly affect their binding ability, and the phenylurea derivatives are the best receptors, exhibiting strong affinity for F^- and also for the oxoanions AcO^- and BzO^-.

Herein we report the synthesis of three new dihomooxacalix[4]arene receptors, all in the cone conformation and bearing four (thio)urea groups at the lower rim via a four carbon atom spacer, as well as their NMR and X-ray structural analysis. The complexation properties toward several anions (spherical, linear, trigonal planar, and tetrahedral) were investigated by proton NMR titration experiments. The results are compared to those obtained with related dihomooxacalix[4]arene and calix[4]arene derivatives.

2. RESULTS AND DISCUSSION

2.1. Synthesis, NMR, and X-ray Conformational Analysis. Earlier, we reported the synthesis of some dihomooxacalix[4]arene derivatives bearing two alkyl or aryl(thio)urea substituents on the lower rim, together with two *n*-butyl[16] or benzyl[17] groups at the opposite positions of the dihomooxa cavity. Following these previous studies, we synthesized two

Scheme 1. Synthetic Route for the Preparation of Tetra(thio)urea Derivatives 4a−c



tetra ureido and one tetra thioureido dihomooxa derivatives, in a three step synthesis from the parent compound *p-tert*-butyldihomooxacalix[4]arene (**1**) (Scheme 1). Thus, reaction of **1** with *N*-(4-bromobutyl)phthalimide and K_2CO_3 in refluxing acetonitrile gave the phthalimide derivative **2**, after chromatographic separation. Subsequently, the phthalimido groups were removed with hydrazine in ethanol to give the tetraamine **3**, which by addition of phenyl(thio)isocyanate or *tert*-butylisocyanate in chloroform afforded the corresponding tetra(thio)urea derivatives (phenylurea **4a**, phenylthiourea **4b** and *tert*-butylurea **4c**). NMR conformational analysis in $CDCl_3$ indicated the cone conformation for all the compounds (including the intermediates), exhibiting the following characteristic ^{1}H and ^{13}C signals: two singlets for the *tert*-butyl protons, three AB quartets (in a 2:2:1 ratio) for the CH_2 bridge protons and two pairs of doublets for the aromatic protons of the calix framework,[18] as well as two Ar**C**H$_2$Ar resonances around 30 ppm.[19] The proton assignments of the new compounds were confirmed through COSY and NOESY NMR spectra.

Concerning ureido derivatives **4a** and **4c**, all peaks of their ^{1}H NMR spectra in $CDCl_3$ are clear and sharp at room temperature. In addition, the chemical shifts of the urea protons are independent of the concentration in the $5 \times 10^{-4} - 5 \times 10^{-3}$ M range (Figure 1), indicating the existence of intramolecular hydrogen bonding in these compounds.[14,20] Moreover, variable temperature studies were also performed with Phurea **4a** and showed no peak broadening from 5 to 50 °C, suggesting that **4a** exists as a stable conformation in that solvent. In contrast, Phthiourea **4b** exhibits a slightly broadened ^{1}H NMR spectrum, mainly for the NH resonances. However, concentration-dependence was also not observed with **4b** (Figure 2a and b). When the spectrum was recorded in better H-bond accepting solvents, such as $CDCl_3$/DMSO-d_6 (4:1) or DMSO-d_6, the NH signals remained broad, but shifted downfield in agreement with the formation of intermolecular hydrogen bonds between the thioureido groups and the DMSO molecules (NH···O). Variable temperature studies in $CDCl_3$ showed distinct and well-resolved peaks at 50 °C for both NHa and b protons (Figure 2c). Sulfur forms weaker hydrogen bonds than oxygen,[21] thus disfavoring the intramolecular interactions in the case of Phthiourea **4b**. The broadening of its NH signals at room temperature is likely due to some

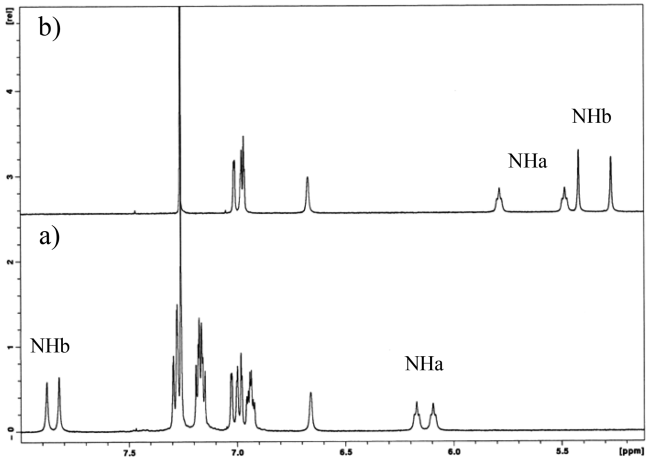


Figure 1. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of (a) Ph-urea **4a**, (b) *t*-Bu-urea **4c**.

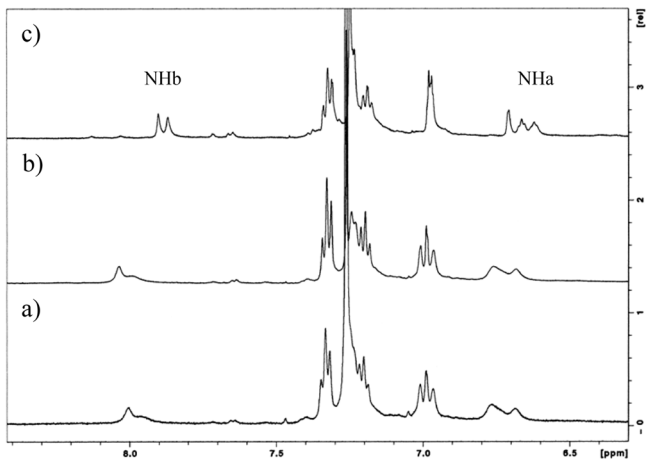


Figure 2. Partial ^{1}H NMR spectra of Ph-thiourea **4b** (500 MHz, $CDCl_3$) at various concentrations and temperatures: (a) 5×10^{-4} M, 25 °C, (b) 5×10^{-3} M, 25 °C, (c) 5×10^{-3} M, 50 °C.

interactions of these groups with H-bond acceptor groups, as for example residual water from the solvent.

Small single crystals of compound **4c** with *tert*-butylureido groups, suitable for X-ray investigation by synchrotron

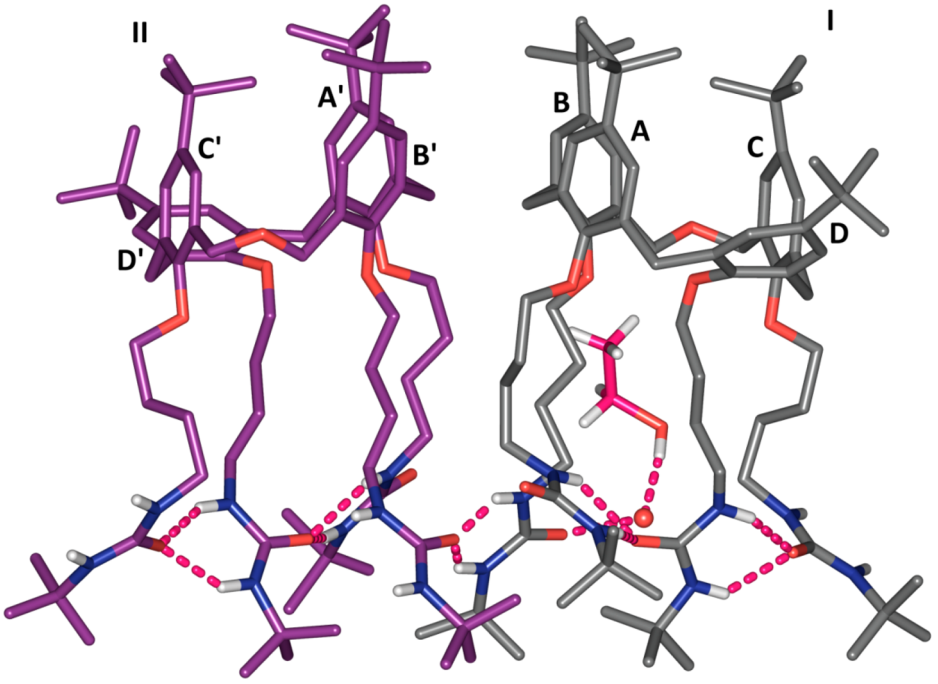


Figure 3. Solid state structure of compound **4c**. In the asymmetric unit two crystallographically independent molecules of oxacalixarene were identified: molecules **I** and **II** are depicted in gray and purple, respectively. A disordered water molecule and an ethanol molecule with partial occupancy were also found in the asymmetric unit. The labeling scheme used for aryl rings defining the oxacalixarene cavity is also shown for both molecules. The *tert*-butylureido fragments at the lower rim are involved in a dense network of double intra- and intermolecular N−H···O hydrogen bond. Hydrogen bonds are represented by dashed lines in magenta.

radiation, were obtained by slow evaporation of a $CHCl_3$/EtOH solution containing the calixarene. The structure determination reveals that the asymmetric unit of the monoclinic cell contains two molecules of dihomooxacalix[4]-arene **4c** (defined **I** and **II** in Figure 3), a disordered water molecule and an ethanol molecule with partial occupancy. The two crystallographically independent macrocycles show similar cone conformations for the cavities: in **I** the dihedral angles described between the B and D aryl rings and the oxacalixarene mean plane, defined by CH_2 and CH_2OCH_2 bridging groups, were 118.2(2) and 134.8(2)°, respectively, indicating that the two rings lean outward with respect to the cavity. On the contrary, the C ring tilts inward (dihedral angle 74.1(2)°), while the opposite A ring is only slightly tilted outward (dihedral angle 99.2(1)°). The conformation of the cavity in **II** is very similar, as observed by the values of the dihedral angles reported in Table S1 (Supporting Information).

As observed in Figure 3, the *tert*-butylureido groups at the lower rim of the two dihomooxacalix[4]arene molecules are involved in a dense network of intra- and intermolecular N−H···O double hydrogen bonds (details of distances listed in Table S2), a typical motif observed for ureido synthons.[17] In particular, both crystallographically independent dihomooxacalixarene molecules show three of the four ureido groups involved in an intramolecular N−H···O double hydrogen bonds (Figure 3). The ureido terminals (the H_2N_2C H-bond donor group, and the C═O H-bond acceptor group) of these intramolecular H-bond chains form intermolecular N−H···O double hydrogen bonds with two symmetrically equivalent dihomooxacalixarene molecules, with the cavity oriented in an up−down fashion (Figure S1a). These two crystallographically independent strands of dihomooxacalixarenes generated by the *n* glade planes are interconnected by intermolecular N−H···O double hydrogen bonds involving the fourth ureido groups not occupied in the intramolecular H-bonds and located in the B aryl rings involved in the oxa bridge (Figure 3). The two crystallographically independent dihomooxacalixarenes coupled by the intermolecular H-bond are almost iso-oriented with respect to the cavity with the oxa bridges in trans position (Figure 3). The H_2N_2C and C═O terminals of the *tert*-butylureido fragments involved in these intermolecular H-bonds complete their hydrogen bond network with an ethanol solvent molecule and a water molecule, respectively. Further H-bonds connecting the cocrystallized water and ethanol solvent molecules, replicated by the glide planes, generate a 1D H-bond network $[\cdots EtOH\cdots H_2N_2{-}C{=}O\cdots H_2N_2{-}C{=}O\cdots H_2O\cdots]_n$ along the ac diagonal direction. This H-bond chain is sandwiched between the two antiparallel H-bond chains connecting the crystallographically independent strands with the up−down alternate orientation of dihomooxacalixarenes (Figure S1b).

Attempts to cocrystallize **4c** in the presence of TBA salts resulted in crystals in which did not incorporate a guest, but the structure was that of **4c** only. Furthermore, attempts to obtain suitable crystals for structural determination of **4a** and **4b** were unsuccessful. A detailed description of these attempts can be found in Supporting Information.

2.2. Anion Binding Studies. The binding ability of tetraureas **4a** and **4c** and of tetrathiourea **4b** toward various anions of spherical (F^-, Cl^-, Br^-, I^-), linear (CN^-, SCN^-), trigonal planar (NO_3^-, AcO^-, BzO^-), and tetrahedral (HSO_4^-, $H_2PO_4^-$, ClO_4^-) geometries was investigated in $CDCl_3$ through ^1H NMR titrations using tetrabutylammonium salts. It was observed that residual water of $CDCl_3$ solvent does not interact through H-bonding with these receptors.[22] Some complexation experiments with thiourea **4b** were also done in $CDCl_3$/

Table 1. Association Constants (log K_{ass})[a] of Dihomooxa(thio)ureas 4a–c, 5, and 6 in $CDCl_3$ at 25 °C

	spherical				linear		trigonal planar			tetrahedral		
	F^-	Cl^-	Br^-	I^-	CN^-	SCN^-	NO_3^-	AcO^-	BzO^-	HSO_4^-	$H_2PO_4^-$	ClO_4^-
I. radius/Å[b]	1.33	1.81	1.96	2.20	1.91	2.13	1.79	2.32		1.90	2.00	2.40
Ph-urea **4a**	3.46	3.50	3.18	2.80	4.02	2.76	2.84	2.89	2.93	2.82	2.64	2.40
Ph-thiourea **4b**	2.78	2.79	2.63	2.03	2.99	2.04	2.58	2.68	2.68	2.53	2.55	2.02
t-Bu-urea **4c**	2.54	2.34	2.02	1.73	2.22	1.67	2.05	2.33	2.34	1.97	1.89	1.81
diPhurea-diBu **5**[c]	3.10	2.73	2.23	1.59	2.71	1.90	2.42	2.88	2.93	2.58	2.69	1.65
diPhurea-diBn **6**[d]	2.70	2.43	2.09	1.54	2.24	1.70	2.18	2.65	2.75	2.27	2.57	1.54

[a]Estimated error <10%. [b]Data quoted in Marcus, I. *Ion Properties*; Marcel Dekker: New York, 1997; pp. 50–51. [c]Data taken from ref 16. [d]Data taken from ref 17.

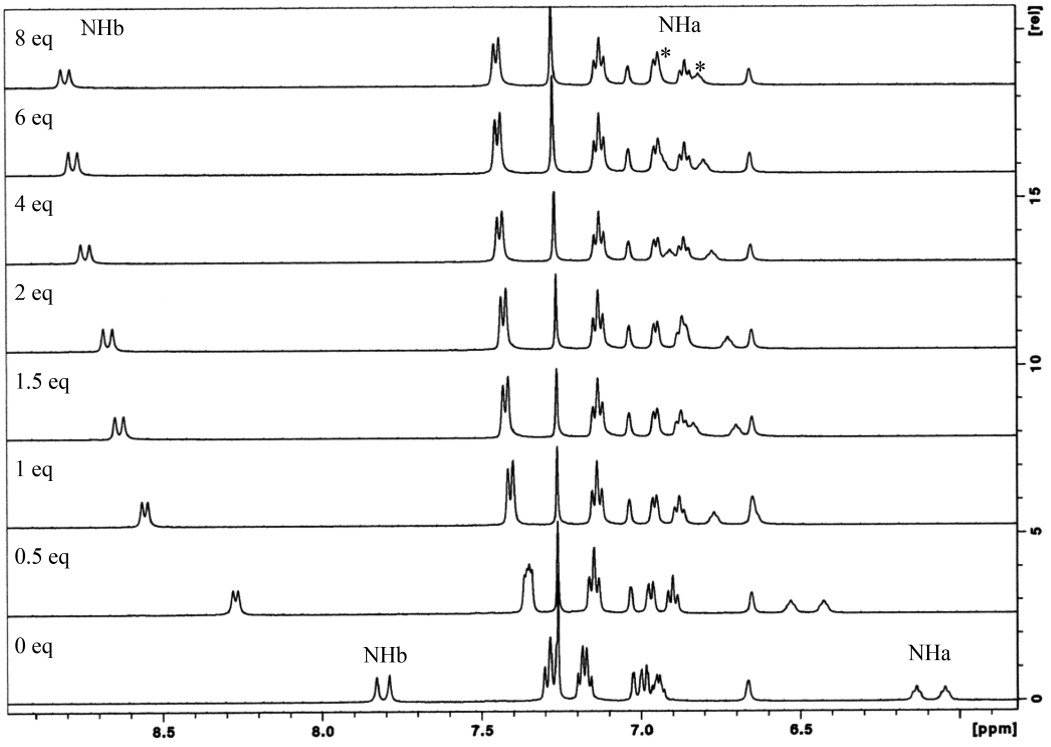


Figure 4. Partial ^1H NMR spectra of Ph-urea **4a** (500 MHz, $CDCl_3$, 25 °C) with several equiv of TBA Cl.

DMSO-d_6 (4:1). The association constants, reported in Table 1, were determined following the urea NH chemical shifts and using the WinEQNMR2 program.[23] When those protons became broad or even disappeared (in a few cases), the constants were determined from the complexation induced shifts of the aromatic *orto* protons of the phenyl group (**4a** or **4b**) or of the $ArCH_2Ar$ axial protons of the calixarene framework.

Hydrogen bonding interactions between the urea or thiourea groups of **4a–c** and the anions were clearly shown by the downfield shifts of the NH protons in the ^1H NMR spectra (see Figure 4 for **4a** + Cl^-). In all cases, fast host–guest exchange was observed on the NMR time scale. The titration profiles obtained (see Figure 5) indicate the formation of 1:1 receptor-anion complexes. This stoichiometry was also confirmed by Job plots (Figure S2). The data in Table 1 show that Phurea **4a** is the best anion receptor, displaying high association constants. For the halide anions (spherical geometry), **4a** displays a very efficient binding toward F^- and Cl^- (log K_{ass} = 3.46 and 3.50, respectively). These values are higher than those obtained by the calix[4]arene analogue

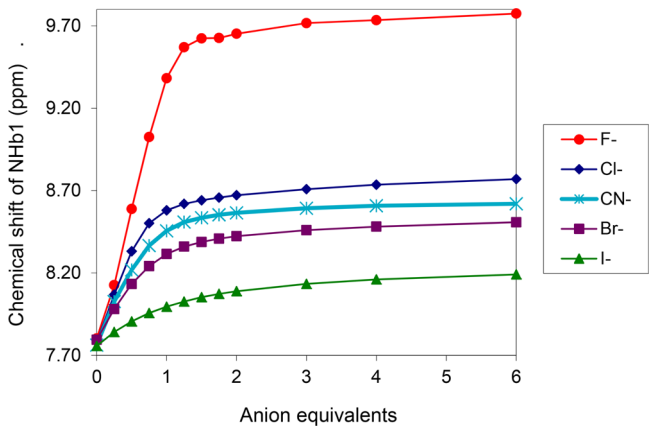
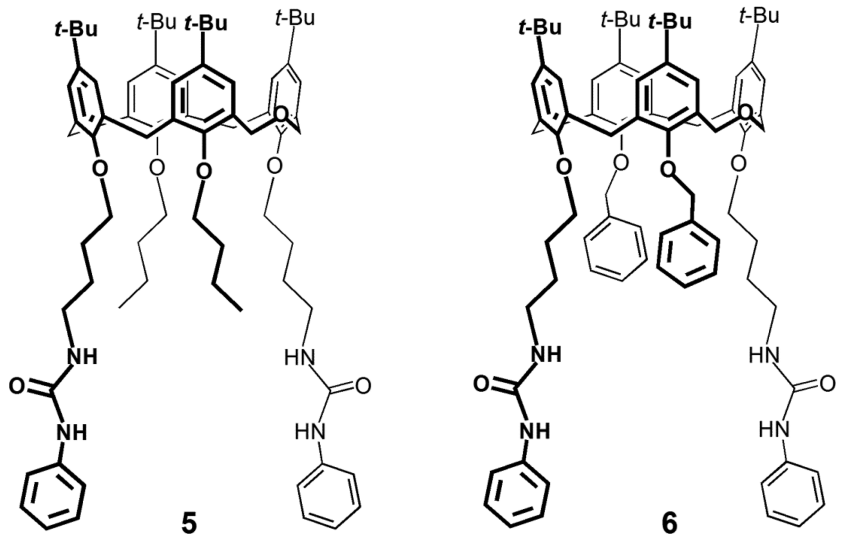


Figure 5. Titration curves of Ph-urea **4a** with TBA salts in $CDCl_3$.

derivative.[6] There is a slight inversion of these association constants according to the anion basicity order. In previous studies with the phenylurea bidentate derivatives **5** and **6** (Scheme 2), we observed some F^- over Cl^- selectivity. In

Scheme 2. Phenylurea Bidentate Derivatives 5 and 6



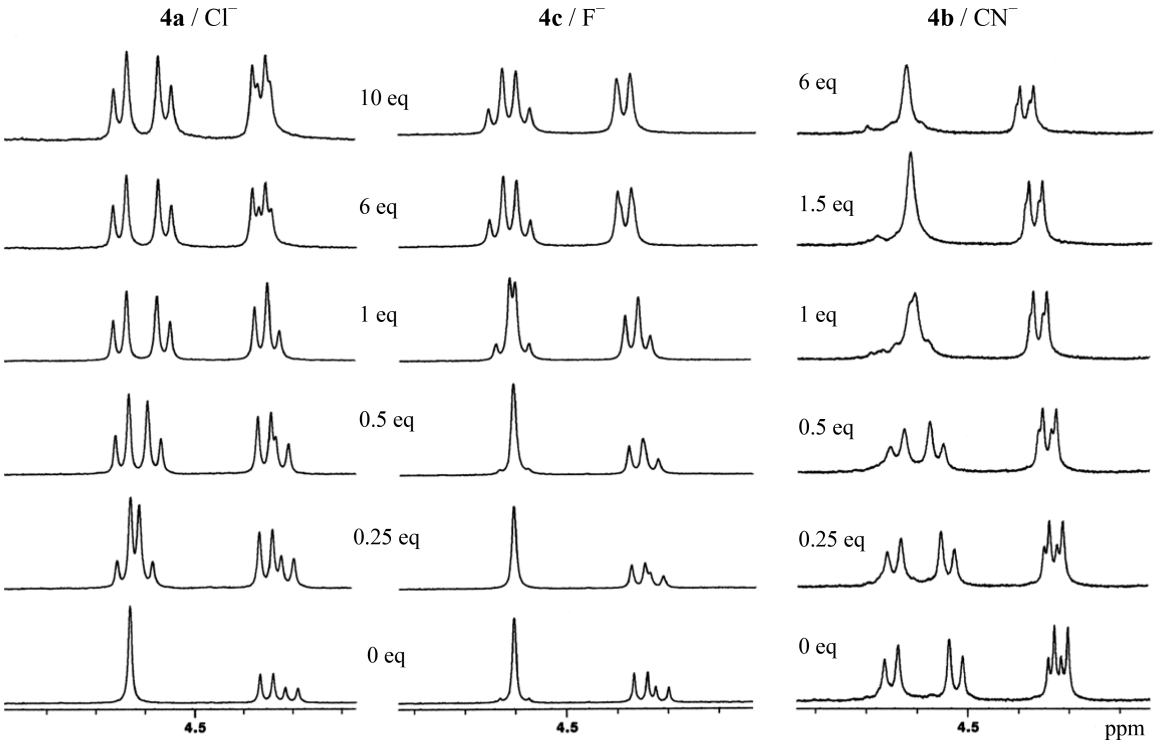


Figure 6. Partial methylene region of the ^{1}H NMR spectra of Ph-urea **4a**, *t*-Bu-urea **4c**, and Ph-thiourea **4b** with several equiv of TBA salts.

comparison with these bidentate derivatives, tetraphenyl urea is more preorganized and has four more potential hydrogen bond sites, exhibiting an enhancement of the binding efficiency that reaches one log unity in the case of Cl^- ($\Delta F^-_{4a-5/6}$ = 0.36, 0.76 and $\Delta Cl^-_{4a-5/6}$ = 0.77, 1.05, respectively). As a consequence of the lower flexibility, the selectivity is governed not only by the anion basicity, but also by its size. F^- seems to be too small to a perfect fit into the cavity, Cl^- having a more appropriate size for that. As shown in Figure 5, large downfield shifts are observed for the NHb_1 proton after the addition of 2 equiv of TBA fluoride and chloride (1.85 and 0.89 ppm, respectively). In the presence of the pseudohalide anion CN^- (linear geometry) a large downfield shift of 0.80 ppm can also be observed (Figure 5). Phurea **4a** displays a log K_{ass} of 4.02 for CN^-, the highest ever found with a dihomooxa urea receptor. This anion, besides a strong basicity, has an ionic radius of 1.91 Å, approximately the same as Cl^- (1.81 Å). In this case, the enhancement of the complex stability compared to those of the bidentate derivatives **5** and **6** is even higher ($\Delta CN^-_{4a-5/6}$ = 1.31, 1.78, respectively).

With regard to the trigonal planar oxoanions, Phurea **4a** showed a high binding ability toward the carboxylates BzO^- and AcO^- (log K_{ass} = 2.93, 2.89, respectively). As observed previously with the bidentate ureas, there is a slight inversion of the basicity order that may be related with a specific solvation mode of the urea-benzoate complex in chloroform. These log K_{ass} values are the same obtained with bidentate urea **5** and only slightly higher than those obtained with **6** ($\Delta AcO^-/BzO^-$ = 0.24, 0.18, respectively). These results indicate that for the

larger anions the cooperative action of the four ureido moieties in the tetrasubstituted ligand **4a** is no longer favorable. In the case of the tetrahedral anions, the results with **4a** show the highest association constant for HSO_4^- (ionic radius of 1.90 Å). Again, the size effect seems to prevail over the basicity one.

The binding efficiency of Phthiourea **4b** was also determined in $CDCl_3$. Despite the increased acidity of its NH groups compared to those of Phurea, **4b** revealed to be a weaker anion receptor, showing however the same trend as **4a**. Similar results were found for the bidentate dihomooxa Phthiourea derivative,[17] and also for thioureido-calix[4] and [6]arene derivative analogues.[6,12] As presented in Table 1, **4b** exhibits the highest association constant for the linear anion CN^- (log K_{ass} = 2.99), followed by the spherical F^- and Cl^- (log K_{ass} = 2.78, 2.79, respectively). The association constants were, in average, half log unity lower than those obtained with Phurea (even one log unity lower for CN^- anion), except for $H_2PO_4^-$ for which **4b** displayed the same log K_{ass} value. A similar result was reported with bis-Ph(thio)urea compounds.[24] This may be due to the larger sulfur atom distorting the cis−cis geometry required for anion binding. Phenyl thioureas are less preorganized than the urea ones, the former being energetically less favorable, thus decreasing their binding ability.[25] The complexation ability of **4b** toward the spherical anions was also performed in $CDCl_3$/DMSO-d_6 (4:1), a more competing solvent. A substantial decrease of the association constants was obtained for F^- and Cl^- (log K_{ass} = 2.08 and 2.12, respectively), and no complexation was observed in the case of I^-.

The influence of the substituent (aryl/alkyl) at the urea moiety on the association constants is clearly evidenced by comparison with *t*-Bu urea **4c**. This derivative is a weaker receptor than Phurea **4a**, showing association constants that are around 1 order of magnitude lower and that decrease with decreasing of anion basicity. **4c** shows the highest log K_{ass} value for F^- (2.54), followed by the oxoanions AcO^- and BzO^-.

Upon complexation, the calixarene skeletons of these receptors undergo slight conformational changes, since the *tert*-butyl and the aromatic protons experience small downfield or upfield variations of their chemical shifts: maximum variations of 0.03 and 0.06 ppm were observed for one of the two *t*-Bu groups and for two of the four ArH protons, respectively, while the other *t*-Bu and ArH protons remained almost unchanged upon the addition of 6 equiv of the salts. These modest structural changes are likely due to the preorganization and some rigidity that these tetra-substituted receptors assume before complexation, which will induce small variations only in the upper cavity of the macrocycles upon complexation. However, the oxygen bridge conformation changes significantly upon complexation. For both ureas **4a** and **4c** the equatorial and axial protons of the CH_2OCH_2 group are almost equivalent, showing a pseudosinglet at 4.63/4.60 ppm, respectively, but it splits into an AB quartet upon complexation (Figure 6). The fastest variations on the proton lineshapes were observed during the titrations of Phurea **4a** with Cl^- and CN^- anions, and in the case of *t*-Bu urea **4c** during the titration with F^-, according to the higher affinity of these ureas for these anions. An opposite situation was observed for Phthiourea **4b**, as shown in Figure 6 for the complexation with CN^-.

3. CONCLUSIONS

Three *p-tert*-butyldihomooxacalix[4]arene derivatives tetra-substituted with (thio)urea groups (phenylurea **4a**, phenylthiourea **4b**, and *tert*-butylurea **4c**) at the lower rim via a butyl spacer were synthesized and obtained in the cone conformation in solution. The X-ray structure of **4c** was reported. Its crystal packing shows that the *tert*-butylureido fragments at the lower rim are involved in a dense network of double intra- and intermolecular N−H···O hydrogen bonds involving all four ureido groups. These compounds form complexes with anions of spherical, trigonal planar, linear, and tetrahedral geometries in a 1:1 stoichiometry through hydrogen bonding, as indicated by ^{1}H NMR titrations. Phurea **4a** is the strongest anion receptor, displaying a very efficient binding toward the spherical F^- and Cl^- anions, and the linear CN^- (log K_{ass} = 3.46, 3.50, and 4.02, respectively). Comparing to bidentate phenylurea derivatives **5** and **6**, tetraPhurea **4a** is more preorganized and the higher number of hydrogen bond donor sites provides a remarkable enhancement on its binding ability. Furthermore, its selectivity is controlled not only by the anion basicity, but also by its size. Phthiourea **4b** is a weaker anion receptor, despite the increased acidity of its NH groups compared to those of Phurea **4a**, showing however the same trend. The larger sulfur atom may distort the cis−cis geometry required for anion binding.

These results open new perspectives for using phenylurea **4a** as a heteroditopic receptor for a variety of organic ion pairs, namely alkylammonium salts. Alkylammonium moieties are a constant presence in compounds of biological interest, as biogenic amines, trace amines, and amino acids.

4. EXPERIMENTAL SECTION

4.1. Synthesis. All chemicals were reagent grade and were used without further purification. Chromatographic separations were performed on Merck silica gel 60 (particle size 40−63 μm, 230−400 mesh). Melting points were measured (not corrected) and FTIR spectra were recorded. ^{1}H 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 microanalyser.

*7,13,19,25-Tetra-tert-butyl-27,28,29,30-tetra[(4-phthalimido-butyl)oxy]-2,3-dihomo-3-oxacalix[4]arene (**2**).* A mixture of *p-tert*-butyldihomooxacalix[4]arene[26] (2.5 g, 3.69 mmol), *N*-(4-bromobutyl)phthalimide (6.36 g, 22.1 mmol), K_2CO_3 (3.05 g, 22.1 mmol), and KI (1.83 g, 11.0 mmol) in CH_3CN (100 mL) was refluxed and stirred under N_2 for 5 days. After cooling, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (175 mL) and washed with 1 M HCl (2 × 100 mL), NH_4Cl saturated solution (2 × 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was subjected to flash chromatography on silica gel (eluent gradient from *n*-hexane/ethyl acetate 80:20 to 60:40) to afford a white solid in 36% yield (1.95 g): mp 103−105 °C; IR (KBr) 1709 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92, 1.18 [2s, 36H, $C(CH_3)_3$], 1.77 (m, 4H, $OCH_2CH_2CH_2CH_2N$), 1.88 (m, 8H, $OCH_2CH_2CH_2CH_2N$), 1.98 (m, 4H, $OCH_2CH_2CH_2CH_2N$), 3.14, 4.36 (ABq, 4H, J = 13.5 Hz, $ArCH_2Ar$), 3.21, 4.38 (ABq, 2H, J = 12.9 Hz, $ArCH_2Ar$), 3.64 (m, 4H, $OCH_2CH_2CH_2CH_2N$), 3.72−3.83 (several m, 10H, $OCH_2CH_2CH_2CH_2N$), 3.88 (m, 2H, $OCH_2CH_2CH_2CH_2N$), 4.57, 4.67 (ABq, 4H, J = 13.5 Hz, CH_2OCH_2), 6.64, 6.95, 6.98, 7.03 (4d, 8H, ArH), 7.63(m, 8H, ArH-Pht), 7.76 (m, 8H, ArH-Pht); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 25.3, 25.6, 27.5, 27.9 ($OCH_2CH_2CH_2CH_2NH_a$), 29.9, 30.7 ($ArCH_2Ar$), 31.4, 31.5 [$C(CH_3)_3$], 34.0 (2C) [$C(CH_3)_3$], 37.9, 38.1 ($OCH_2CH_2CH_2CH_2NH_a$), 68.4 (CH_2OCH_2), 73.5, 74.2 ($OCH_2CH_2CH_2CH_2NH_a$), 123.1 (2C), 133.6 (2C) (ArH-Pht), 123.5, 125.61, 125.63, 125.8 (ArH), 131.3, 132.2, 132.3, 133.27, 133.31, 134.1, 144.7, 145.0, 151.8, 152.7 (Ar), 168.2, 168.3 (CO). Anal. Calcd for $C_{93}H_{102}O_{13}N_4$: C, 75.28; H, 6.93; N, 3.78. Found: C, 75.68; H, 7.35; N, 3.45.

*7,13,19,25-Tetra-tert-butyl-27,28,29,30-tetra[(4-aminobutyl)-oxy]-2,3-dihomo-3-oxacalix[4]arene (**3**).* To a suspension of 1.50 g of **2** (1.01 mmol) in EtOH (60 mL) was added 9.70 mL (200 mmol) of hydrazine monohydrate. The mixture was refluxed and stirred under N_2 for 14 h. After cooling, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (80 mL) and washed with H_2O (80 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated to give tetra-amino **3** as a beige solid (0.79 g, 82% yield), which was pure enough to be immediately used in the next step; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94, 1.19 [2s, 36H, $C(CH_3)_3$], 1.58, 1.65 (2m, 8H, $OCH_2CH_2CH_2CH_2NH_2$), 1.85, 1.97 (2m, 8H, $OCH_2CH_2CH_2CH_2NH_2$), 2.80 (m, 8H, $OCH_2CH_2CH_2CH_2NH_2$), 3.18, 4.38 (ABq, 4H, J = 13.2 Hz, $ArCH_2Ar$), 3.23, 4.38 (ABq, 2H, J = 12.9 Hz, $ArCH_2Ar$), 3.60−3.72, 3.75−3.86 (4m, 8H, $OCH_2CH_2CH_2CH_2NH_2$), 4.59, 4.66 (ABq, 4H, J = 13.4 Hz, CH_2OCH_2), 6.68, 6.97, 6.99, 7.04 (4d, 8H, ArH).

*Procedure for the Synthesis of Ureas **4a** and **4c**, and Thiourea **4b**.* To a solution of **3** (0.75 g, 0.78 mmol) in $CHCl_3$ (40 mL) was added 3.12 mmol of the appropriate isocyanate (or phenylisothiocyanate in the case of **4b**). 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-27,28,29,30-tetra[[(N′-phenylureido)-butyl]oxy]-2,3-dihomo-3-oxacalix[4]arene (**4a**).* Flash chromatography (SiO_2, eluent CH_2Cl_2/MeOH 99:1) followed by recrystallization from CH_2Cl_2/*n*-hexane; it was obtained in 34% yield (0.38 g); mp 216−218 °C; IR (KBr) 3350 cm^{-1} (NH), 1647 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93, 1.20 [2s, 36H, $C(CH_3)_3$], 1.60−1.71 (m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 1.75−1.89, 1.94 (2m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 3.17, 4.35 (ABq, 4H, J = 13.3 Hz, $ArCH_2Ar$), 3.20, 4.30 (ABq, 2H, J = 12.9 Hz, $ArCH_2Ar$), 3.24, 3.32, 3.38 (3m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 3.57, 3.67, 3.78 (3m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 4.63 (m, 4H, CH_2OCH_2), 6.04, 6.13 (2t, 4H, NH_a), 6.66, 6.98, 6.99, 7.02 (4d, 8H, ArH), 6.94 (m, 4H, Ph-H_p), 7.17 (m, 8H, Ph-H_m), 7.28 (m, 8H, Ph-H_o), 7.78, 7.82 (2s, 4H, NH_b); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 27.16, 27.19, 27.7, 28.2 ($OCH_2CH_2CH_2CH_2NH_a$), 29.9, 30.7 ($ArCH_2Ar$), 31.5 (2C) [C-$(CH_3)_3$], 34.0 (2C) [$C(CH_3)_3$], 40.3, 40.4 ($OCH_2CH_2CH_2CH_2NH_a$), 68.5 (CH_2OCH_2), 74.0, 74.4 ($OCH_2CH_2CH_2CH_2NH_a$), 119.66, 119.69, 122.8 (2C), 123.7, 125.6, 125.7, 126.0, 129.0 (2C) (ArH), 130.8, 133.2, 133.4, 134.1, 139.1, 139.2, 145.0, 145.2, 152.2, 152.8 (Ar), 157.0 (2C) (CO). Anal. Calcd for $C_{89}H_{114}O_9N_8$: C, 74.24; H, 7.98; N, 7.78. Found: C, 73.86; H, 8.03; N, 7.83.

*7,13,19,25-Tetra-tert-butyl-27,28,29,30-tetra[[(N′-phenylthioureido)butyl]oxy]-2,3-dihomo-3-oxacalix[4]arene (**4b**).* Flash chromatography (SiO_2, eluent gradient from CH_2Cl_2/MeOH 99:1) followed by recrystallization from diisopropyl ether; it was obtained in 65% yield (0.78 g); mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93, 1.20 [2s, 36H, $C(CH_3)_3$], 1.75, 1.84, 1.96 (3 m, 16H, $OCH_2CH_2CH_2CH_2NH_a$), 3.16, 4.31 (ABq, 4H, J = 13.7 Hz, $ArCH_2Ar$), 3.23, 4.33 (ABq, 2H, J = 13.0 Hz, $ArCH_2Ar$), 3.60−3.86 (several m, 16 H, $OCH_2CH_2CH_2CH_2NH_a$), 4.52, 4.65 (ABq, 4H, J = 13.2 Hz, CH_2OCH_2), 6.68, 6.99, 7.23, 7.24 (4d, 8H, ArH), 6.76 (broad s, 4H, NH_a), 6.99 (t, 4H, Ph-H_p), 7.20 (t, 8H, Ph-H_m), 7.33 (m, 8H, Ph-H_o), 8.01, 8.04 (2s, 4H, NH_b); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 25.9, 26.1, 27.6, 28.1 ($OCH_2CH_2CH_2CH_2NH_a$), 29.7, 30.8 ($ArCH_2Ar$), 31.4 (2C) [$C(CH_3)_3$], 33.99, 34.04 [$C(CH_3)_3$], 45.4 (2C) ($OCH_2CH_2CH_2CH_2NH_a$), 69.3 (CH_2OCH_2), 73.9, 74.3 ($OCH_2CH_2CH_2CH_2NH_a$), 124.0, 125.0 (2C), 125.6, 125.8, 126.4, 126.7 (2C), 129.7 (2C) (ArH), 128.8, 130.8, 133.1, 133.4, 134.1, 136.9. 145.1, 145.3, 152.3, 152.7 (Ar), 180.6 (2C) (CS). Anal. Calcd for $C_{89}H_{114}O_5N_8S_4$: C, 71.07; H, 7.64; N, 7.45; S, 8.53. Found: C, 71.45; H, 7.39; N, 7.09; S, 8.46.

*7,13,19,25-Tetra-tert-butyl-27,28,29,30-tetra[[(N′-tert-butyl-ureido)butyl]oxy]-2,3-dihomo-3-oxacalix[4]arene (**4c**).* Recrystallization from 1-propanol/ethyl ether; it was obtained in 48% yield (0.49 g); mp 225−227 °C; IR (KBr) 3362 cm^{-1} (NH), 1630 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93, 1.19 [2s, 36H, $C(CH_3)_3$], 1.340, 1.344 [(2s, 36H, $NH_bC(CH_3)_3$], 1.64 (m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 1.78, 1.87, 1.95 (3m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 3.17, 4.35 (ABq, 4H, J = 13.4 Hz, $ArCH_2Ar$), 3.19, 4.31 (ABq, 2H, J = 12.8 Hz, $ArCH_2Ar$), 3.19−3.31 (m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 3.60, 3.69, 3.80 (3m, 8H, $OCH_2CH_2CH_2CH_2NH_a$), 4.60 (m, 4H, CH_2OCH_2), 5.27, 5.42 (2s, 4H, NH_b), 5.48, 5.79 (2t, 4H, NH_a), 6.67, 6.97, 6.98, 7.01 (4d, 8H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 27.4 (2C), 27.8, 28.3 ($OCH_2CH_2CH_2CH_2NH_a$), 29.68, 29.72 [$NH_bC(CH_3)_3$], 30.0, 30.7 ($ArCH_2Ar$), 31.4 (2C) [$C(CH_3)_3$], 34.0 (2C) [$C(CH_3)_3$], 40.1, 40.2 ($OCH_2CH_2CH_2CH_2NH_a$), 49.98, 50.03 [$NH_bC(CH_3)$], 68.3 (CH_2OCH_2), 74.4, 74.5 ($OCH_2CH_2CH_2CH_2NH_a$), 123.5, 125.5, 125.7, 125.9 (ArH), 130.8, 133.2, 133.4, 134.1, 144.8, 145.1, 152.4, 153.0 (Ar), 158.7, 158.9 (CO). Anal. Calcd for $C_{81}H_{130}O_9N_8$: C, 71.54; H, 9.64; N, 8.24. Found: C, 71.12; H, 9.99; N, 8.06.

4.2. Determination of the Crystallographic Structure. Small single crystals suitable for X-ray investigation were obtained by slow evaporation of the solvent from a solution of **4c** in a $CHCl_3$/EtOH mixture. Data collection was carried out at the macromolecular crystallography XRD1 beamline of the Elettra synchrotron (Trieste, Italy), by employing the rotating-crystal method and the cryo-cooling technique. Routinely a crystal dipped in Paratone, as cryoprotectant, is mounted on a loop and immediately flash-frozen under a nitrogen stream at a 100 K. Diffraction data of compound **4c** were indexed and integrated using the XDS package.[27] Scaling was carried out with XSCALE.[28]

The measured crystal was small and synchrotron radiation and cryo-cooling techniques were mandatory in order to collect data set with sufficient quality and resolution to solve and refine the structure. The structure was solved by direct methods using SIR2011.[29] In the asymmetric unit two crystallographically independent molecules of oxacalixarene were found. The two molecules showed disorder for the substituents both at the upper and lower rims. In molecule **I** (C1A−C4A) one *tert*-butyl group at the upper rim was disordered over two orientations, refined at 0.6/0.4 partial occupancy. At the bottom rim three substituents showed two orientations for the aliphatic chains between the oxygen and the ureido fragment: C2H−>C2M 0.6/0.4, C1H−>C1M 0.75/0.25, C4H−>C4M 0.55/0.45. In molecule **II**, (C5A--C8A) one *tert*-butyl group at the upper rim was disordered over two orientations, refined at 0.55/0.45 partial occupancy. At the lower rim one *tert*-butyl group linked to the ureido fragment was disordered over two orientations, refined at 0.6/0.4 partial occupancy. In the asymmetric unit an ethanol molecule with partial occupancy (0.5) was also located. In addition, a water molecule disordered over two positions (0.8/0.2) was also detected. With the exception of solvent molecules, non-hydrogen atoms at full occupancy, or with population equal to or higher than 0.5 were refined anisotropically by full-matrix least-squares methods on F^2 using SHELXL-13.[30] Hydrogen atoms were added in the calculated positions only on the non-H atoms with occupancy higher than or equal to 0.5. Restraints (DFIX, DANG, SIMU) on bond angles and distances and thermal parameters were applied on the atoms involved in the disordered fragments. Crystallographic data and refinement details are reported in Table S3.

4.3. ^{1}H NMR Titrations. The association constants (as log K_{ass}) were determined in $CDCl_3$ by ^{1}H 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_{ass} 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.

■ ASSOCIATED CONTENT

● Supporting Information

X-ray crystallographic data of compound **4c** (CIF)

Job's plot based on ^{1}H NMR data for **4a** + Cl^{-}, ^{1}H and ^{13}C NMR spectra of the new compounds **2**, **4a**, **4b**, and **4c** (PDF)

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Notes

The authors declare no competing financial interest.

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