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ORIGINAL ARTICLE

Structures of urea/thiourea 1,3-disubstituted thia[4]calixarenes and corresponding monofunctional receptors and their anion recognition properties

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Abstract Two thiacalix[4]arenes in 1,3-alternate conformation functionalized by two $(CH_2)_2NH(C{=}X)NHC_6H_4$-$NO_2$-*p* groups (X = S,O) as well as two related monofunctional receptors $MeO(CH_2)_2NH(C{=}X)NHC_6H_4$-$NO_2$-*p* were prepared and characterized by X-ray crystal structures. The thioureido and ureido derivatives have *E*,*Z* and *E*,*E* conformations respectively both in monofunctional receptors and thiacalixarenes. The thiacalixarene attached thiourea groups are well separated from each other, but respective urea groups are much closer to each other and have mutual parallel orientation making the bisurea derivative a better preorganized receptor as compared to bisthiourea. Binding of Cl^-, F^-, $H_2PO_4^-$ and AcO^- anions in chloroform and DMSO was studied by spectrophotometric and NMR titrations. In chloroform both bisurea and bisthiourea thiacalix[4]arenes bind anions 3–5 times stronger than corresponding monofunctional compounds in spite of better preorganization of the urea derivative. In DMSO simultaneous deprotonation of ureido NH groups of receptors and hydrogen bonding reactions are observed. Deprotonation by $H_2PO_4^-$ is accompanied by a strong association between liberated H_3PO_4 and $H_2PO_4^-$ (log $K = 3.9$). For hydrogen bonding associations the binding constants of $H_2PO_4^-$ and AcO^- with bisurea thiacalixarene are up to two orders of magnitude larger than those with corresponding monofunctional receptor, but with bisthiourea thiacalixarene the effect is less than two-fold. Thus in this solvent in contrast to chloroform the preorganization is an important factor.

Keywords Thiacalixarene · Urea · Thiourea · Structure · Anion recognition

Introduction

Anion recognition by hydrogen bonding receptors is an area of intensive current research [1–6]. Urea and thiourea functionalities are often used for design of neutral anion receptors due to their ability to form stable bidentate complexes with anions even in relatively polar solvents like DMSO and significant increase in affinity can be achieved by attaching two or more urea or thiourea groups to acyclic [7–11] or macrocyclic scaffolds [12–19].

Typically thiourea derivatives bind anions tighter than the respective urea derivatives due to higher acidity of the former. However, in several instances similar or even better binding by ureas was reported and attributed to unfavorable *E,Z* conformation of some substituted thioureas, which compensates the advantage of higher acidity [20]. It seems interesting therefore to see how this conformational difference can be manifested in binding properties of a bifunctional receptor in comparison with its monofunctional counterpart. To explore this aspect we have prepared 1,3-disubstituted urea and thiourea derivatives of thia[4]calixarenes **1**, as well as corresponding monofunctional receptors **2** (Scheme 1) all of which were

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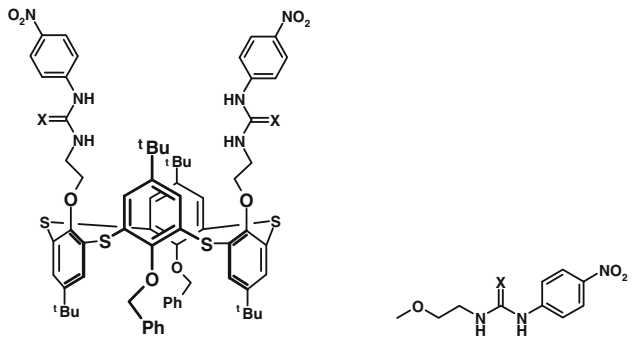


Scheme 1 Chemical structures of receptors employed

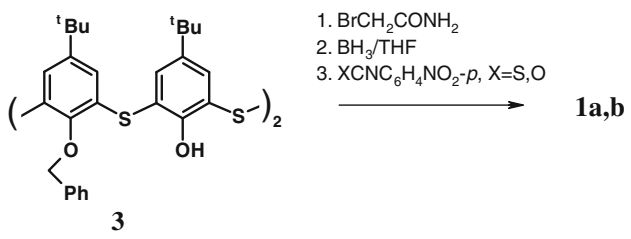
characterized by X-ray crystal structures. We chose for this study the thiacalixarene scaffold because ureido-substituted thiacalixarenes as well as thiacalixarenes in general attracted recently considerable interest due to their possible improved receptor properties as compared to traditional calixarenes [21–28]. In addition, the presence of heavy sulfur atoms facilitates the analysis of X-ray diffraction data for large macrocyclic molecules.

Since both affinity and selectivity of anion binding by urea receptors are solvent dependent [7, 29], we studied interactions of receptors **1a**, **1b** and **2a**, **2b** with anions in two solvents of strongly different polarities: DMSO and chloroform. As is shown below the expected advantage of a bifunctional receptor over a monofunctional one appears to be solvent dependent.

Results and discussion

Synthesis and structural characterization

The tetrathiacalix[4]arene **3** in cone conformation was prepared according to a published procedure [30, 31] and then transformed into **1** as shown in Scheme 2. The change of the conformation of thiacalixarene from cone to 1,3-alternate occurs at the first step during reaction with bromoacetamide



Scheme 2 Synthesis of functionalized thiacalix[4]arenes

in the presence of Cs_2CO_3. The monofunctional receptors **2a** and **2b** were prepared by condensation of 2-methoxyethylamine with the corresponding aryl-isothiocyanate or aryl-isocyanate. An additional thioureido-thiacalixarene derivative **1c** lacking the nitro group in the *para* position of phenyl ring was prepared, but was not used in anion binding studies because of too low affinity.

The molecular structures of thiacalixarenes **1** and the monofunctional receptors **2** were determined by X-ray diffraction analysis, Table 1.

Crystal structures of **2a**, **2b** are shown in Fig. 1. The thiourea receptor **2a** has *E,Z* (*syn,anti*) conformation, in which the N–H bond adjacent to aromatic ring is *syn*-oriented with respect to C=S bond. This is typical for many other N-aryl-N′-alkylthiourea derivatives [32]. Such a configuration is unfavorable for bidentate anion complexation and as a result thioureas in spite of their higher acidity are often poorer receptors for anions than ureas [12, 20, 32], which typically are pre-organized for double hydrogen bonding in their *Z,Z* conformation observed also for **2b**.

Both thiacalixarene derivatives have the expected 1,3-alternate conformation. The thiourea derivatives **1a** and **1c** have highly symmetric structures with the thiourea groups in *E,Z* conformations, Fig. 2 and Fig. S1 (Supplementary Material). The molecular structure of **1a** has crystallographic C_2-symmetry, in which the thiourea groups are far separated from each other, as it can be seen from the distance between the carbon atoms of the thiocarbonyl groups (10.96 Å). Opposite aromatic rings of the thiocalixarene have approximately parallel orientations, the interplanar angles being 3.7° for the rings carrying the thiourea group and 7.4° for the rings bearing benzyl groups. The ^{t}Bu substituents fill the space between the thiourea groups, thus inhibiting close approach of the thiourea groups, which is necessary for chelate anion binding. All these features show that this receptor is poorly preorganized for a potential chelation of anions by two thioureido groups.

Because of poor crystal quality, for thiacalixarene **1b** only data of low resolution could be measured (see Experimental Section). However, these were of sufficiently good quality to observe clearly the atom connectivity and conformation of the macrocycle. In contrast to **1a** the molecular structure of **1b** (Fig. 3) is asymmetric, since the benzyl groups have different orientations with respect to the macrocyclic ring. The urea groups have *Z,Z* configuration, which is also observed for the respective monofunctional receptor **2b** (Fig. 1). Importantly, the urea groups are now much closer to each other and have mutual parallel orientation with a distance of 5.07 Å between the carbons of the carbonyl groups. At the same time the interplanar angles between the aromatic rings are increased

Table 1 Crystallographic data for compounds **1a–1c** and **2a–2b**

Crystal data[a]	**1a**	**1b**	**1c**	**2a**	**2b**
Formula	$C_{72}H_{78}N_6O_8S_6$	$C_{72}H_{78}N_6O_{10}S_4$, MeCN	$C_{72}H_{80}N_4O_4S_6$	$C_{10}H_{13}N_3O_3S$	$C_{10}H_{13}N_3O_4$
MW (g mol^{-1})	1347.76	1356.70	1257.76	255.29	239.23
Space group	*C2/c*	$P2_1/c$	*C2/c*	*P*-1	$P2_1/c$
Temp. (K)	100	100	100	293	293
a (Å)	28.766(2)	15.409(2)	29.2418(19)	4.3166(15)	4.6208(7)
b (Å)	13.8975(10)	14.953(2)	12.5827(8)	9.494(3)	28.605(4)
c (Å)	19.3330(14)	30.206(5)	19.8058(13)	14.693(5)	8.9845(13)
α (°)	90	90	90	96.871(6)	90
β (°)	117.390(1)	93.596(3)	115.009(1)	95.003(6)	103.546(3)
γ (°)	90	90	90	101.148(6)	90
V (Å^3)	6862.4(8)	6945.9(18)	6604.1(7)	582.8(3)	1154.5(3)
Z	4	4	4	2	4
μ (mm^{-1})	0.259	0.201	0.259	0.278	0.108
ρ_{calcd} (g cm^{-3})	1.305	1.297	1.265	1.455	1.376
$R^{b,c}$	0.1003	0.1527	0.1146	0.0780	0.0548
$R_w^{d,e}$	0.2139	0.3784	0.2452	0.1911	0.1259

[a] $\lambda_{MoK}\alpha = 0.71073$ Å

[b] $I > 2\sigma(I)$

[c] $R = \Sigma(F_o^2 - F_c^2)/\Sigma F_o^2$

[d] All data

[e] $R_w = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$

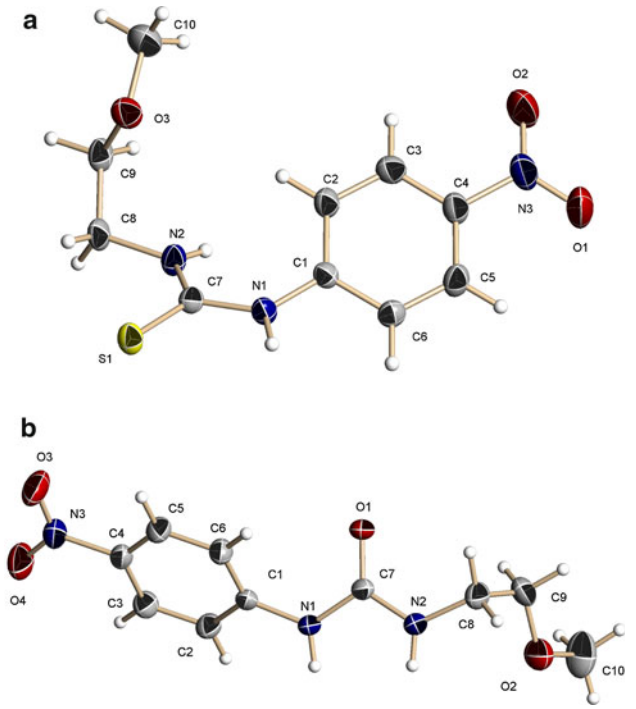


Fig. 1 Perspective view of the molecular structures of compounds **2a** and **2b**. Ellipsoids are shown at the 30% probability level

to 44.7° for those bearing benzyl substituents and 42.1° for those bearing urea groups. This conformational change mutually separates the ^{t}Bu groups, thus creating a void between the urea groups. Regarding the receptor properties of **1b**, a possible drawback in the structure might be the observation that there is an intramolecular hydrogen bonding interaction between the urea groups (C=O···H–N = 2.22 Å), but obviously **1b** is a much better preorganized receptor than **1a**.

The structural differences between thiacalixarenes **1a** and **1b**, which chemically differ just by the nature of one atom, S instead of O in the ureido group, are unexpectedly large. In part this can be attributed to different conformations of N,N′-disubstituted ureas (*Z,Z*) and thioureas (*E,Z*), which distort the macrocycle in a different manner, thus giving different spatial orientations of these groups. Another important factor is the hydrogen bonding between ureido groups in **1b**, which is absent in **1a** probably because of lower hydrogen bond accepting ability of thiourea sulfur atoms as compared to urea oxygen atoms. Recently similar structural differences between urea and thiourea derivatives of calix[6]arenes were inferred from analysis of their NMR spectra [33].

Interactions with anions in chloroform

Binding of anions to receptors **1a**, **1b** and **2a**, **2b** in chloroform was studied by spectrophotometric titrations. In all cases additions of anions induced a red shift and an increase in intensity of the receptor absorption band around

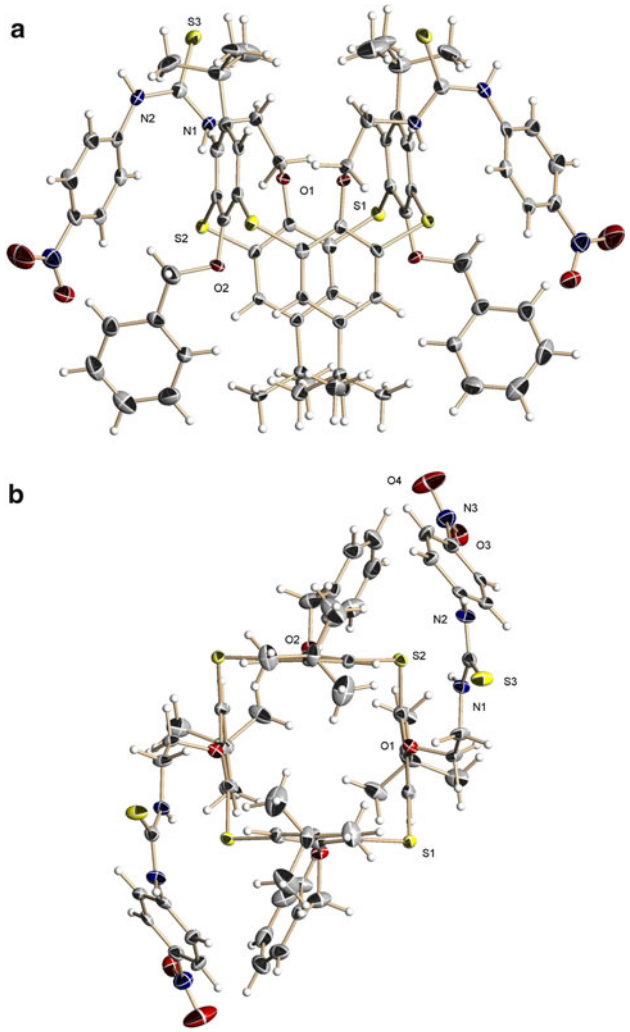


Fig. 2 Perspective view (**a** lateral and **b** top view) of the molecular structure of **1a**. Ellipsoids are shown at the 30% probability level

330 nm characteristic of the formation of hydrogen bonded complexes [34].

A typical course of the spectrophotometric titration is illustrated in Fig. 4a with **2a** and acetate as a guest. The absorption maximum of the free receptor at 335 nm is shifted to 368 nm with two isosbestic points at 258 and 345 nm. A similar shift was observed with dihydrogen phosphate and fluoride anions, but with less basic chloride anion the shift was smaller, only to 355 nm. Typical titration curves are shown in Fig. 4a (inset) and b. Binding constants obtained by fitting of these results are given in Table 2.

Spectrophotometric titrations of the thiacalixarene receptor **1a** showed a similar pattern as illustrated in Fig. 5a with acetate as a guest. All anions induced red shifts of the band at 339 nm to the same extent as for **2a**. Titration plots for Cl^-, F^- and AcO^- (Fig. 5b) were biphasic with rapid increase in absorbance at low anion concentrations followed by slow nearly linear increase at higher concentrations. Such profiles indicate the strong binding of the first anion apparently by chelation with two thioureido groups followed by weaker binding of the second anion affording a complex with two anions bound to each thioureido group separately. Fitting curves to such a model are shown by solid lines in Fig. 5b and the respective formation constants are given in Table 2. For Cl^- only an estimate of the upper limit of K_2 was possible due to very weak binding of the second anion. The interaction with $H_2PO_4^-$ (Fig. 5b) involves binding of only one anion.

Interactions of anions with urea derivatives **2b** and **1b** induced similar spectral changes, but shifted to shorter wavelengths (Fig. S2a and b, Supplementary Material). The fitting curves are shown in Fig. S3a and b (Supplementary Material) and the respective binding constants are given in Table 2. The 1:1 stoichiometry of binding with both receptors was confirmed by Job plots (not shown).

Examining K_1 values, which refer to the 1:1 association, shows that generally thiourea and urea derivatives bind anions with similar strength. Ureido thiacalixarene receptor **1b** binds anions stronger than the respective monofunctional receptor **2b** with log K increased on average by 0.6 units and with the same low selectivity. The thioureido thiacalixarene **1a** shows however a pronounced peak selectivity to acetate absent for the respective monofunctional receptor **2a**, which results from unexpectedly weak binding of $H_2PO_4^-$. Interestingly, the effect of stronger binding with other anions for the "unorganized" receptor **1a** is similar or even larger than that for preorganized receptor **1b**. A possible reason for this is that the hydrogen bonding between ureido groups in **1b** hampers the anion binding, thus eliminating the advantage of better preorganization of this receptor.

Interactions with anions in DMSO

In more polar DMSO solvent interactions of both thiourea receptors with all anions except chloride involve more or less pronounced deprotonation of the receptor. Both **2a** and **1a** form with Cl^- weak hydrogen bonded complexes manifested in red shifts of absorption bands and down-field shifts of ^1H NMR signals of ureido NH protons (Fig. S4a and b, Supplementary Material) with equilibrium constants given in Table 3. Both **2a** and **1a** undergo complete monodeprotonation probably of the NH group adjacent to the aromatic ring by fluoride anions manifested in appearance of an intense absorption band in the visible range (Fig. S5, Supplementary Material) [35–38]. Interaction of **2a** with acetate in DMSO has been studied previously [34]. It involves simultaneous hydrogen bonding and deprotonation, Eq. 1, with equilibrium constant K_3 defined by Eq. 2.

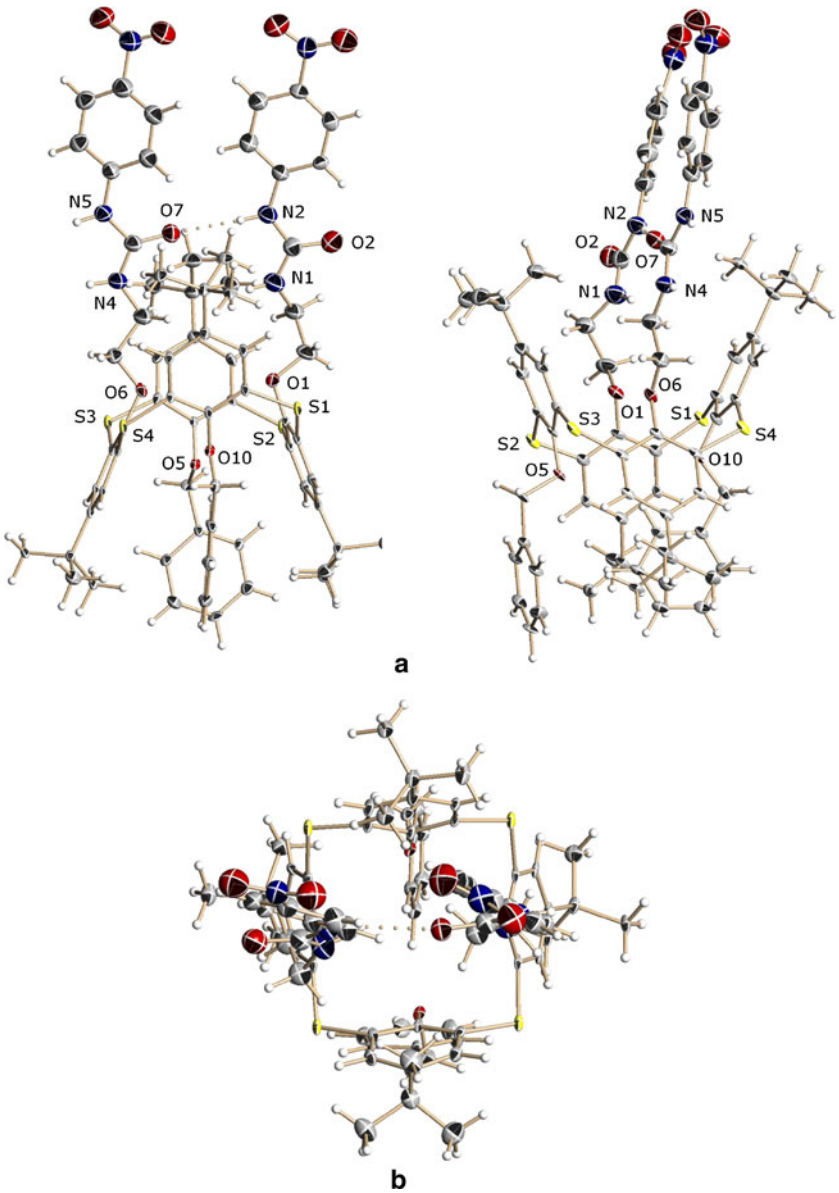


Fig. 3 Perspective view of the molecular structure of compound **1b**. **a** Lateral views and **b** top view. Ellipsoids are shown at the 30% probability level

$$RH + A^- \rightleftarrows R^- + HA \quad (1)$$

$$K_3 = [R^-][HA]/[RH][A^-] \quad (2)$$

The interaction of thiacalixarene **1a** with acetate qualitatively proceeds in the same way. Fig. 6a illustrates the course of spectrophotometric titration of **1a** by Bu_4NOAc indicating formation of a colored deprotonated form with λ_{max} 483 nm. The yield of the deprotonated form under "saturation" is less than 50% and therefore more than the half of the receptor should be transformed simultaneously into a hydrogen bonded complex.

The NMR titration of **1a** with acetate (Fig. S6, Supplementary Material) shows a behavior typical for hydrogen bonding [35–38]: broadening and strong downfield shifts by 3 ppm of the signals of N–H protons of the thioureido group, smaller downfield shift by 0.3 ppm of the signal of aromatic protons in *ortho* positions to thioureido group due to a through-space interaction with hydrogen bound acetate anion and even smaller upfield shift by 0.06 ppm of the signal or aromatic protons in *ortho* positions to nitro group due to an inductive shielding effect of the bound anion. The shape of titration plots for NH protons (Fig. 7) indicates the binding of two acetate anions to one receptor molecule and the fitting agrees with independent binding of each acetate anion to one thioureido group of **1a** with $K_1 = 3000 \pm 600\ M^{-1}$. The reason of why the hydrogen bonding is the predominant process in the NMR experiment is that in this case the concentration of receptor is 100 times higher than in UV–Vis experiment and a large amount of acetic acid liberated during deprotonation shifts the equilibrium (1) to the left.

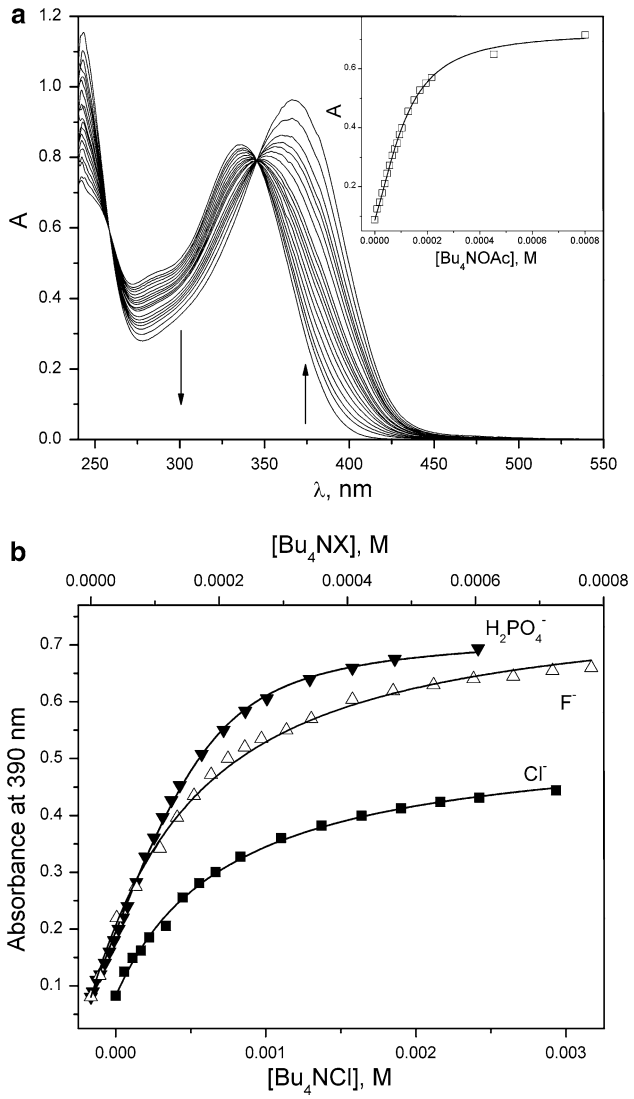


Fig. 4 **a** Spectrophotometric titration of 4.8×10^{-5} M **2a** by Bu_4NOAc in $CHCl_3$. In this and following figures arrows show the directions of spectral changes at increasing guest concentrations; inset—titration curve at 390 nm. **b** Titration curves for 4.8×10^{-5} M **2a** with Bu_4NCl (*lower scale*), Bu_4NF and $Bu_4NH_2PO_4$ (*upper scale*) in $CHCl_3$. *Solid lines* fitting curves to the 1:1 binding isotherm

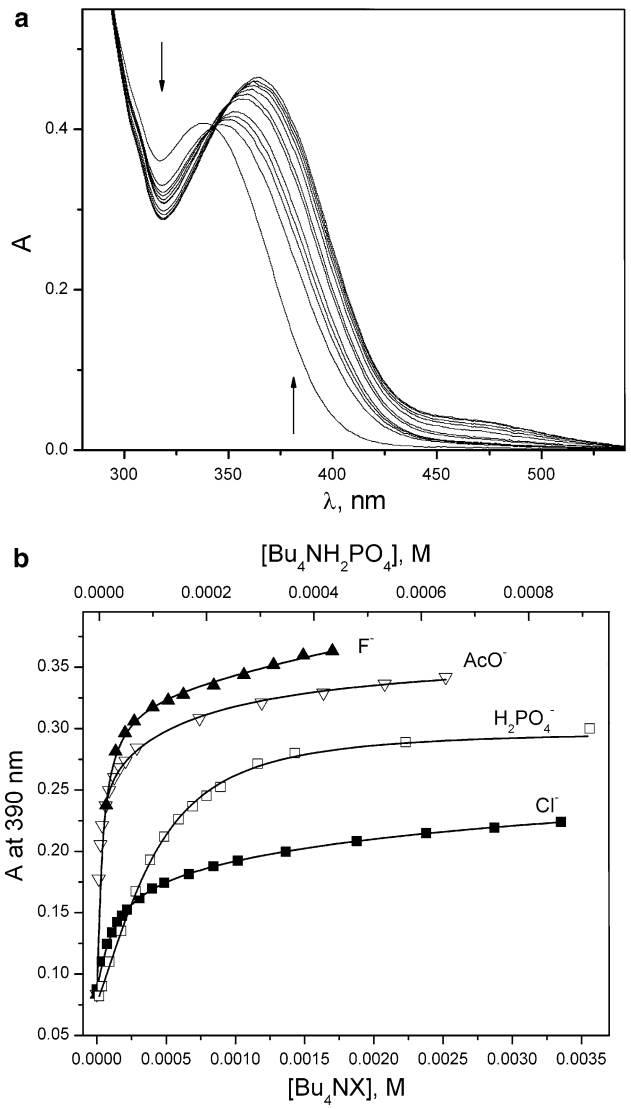


Fig. 5 **a** Spectrophotometric titration of 1.5×10^{-5} M **1a** by Bu_4NOAc in $CHCl_3$. **b** Titration curves for 1.5×10^{-5} M **1a** (absorbance at 390 nm) with Bu_4NCl, Bu_4NOAc, Bu_4NF (*lower scale*) and $Bu_4NH_2PO_4$ (*upper scale*) in $CHCl_3$

Table 2 Binding constants (log K) for association of anions with receptors **1a**, **1b** and **2a**, **2b** in chloroform. Relative error in K values ±10% (±0.04 in log K)

Anion	**1a**		**2a**	**1b**	**2b**
	log K_1	log K_2	log K_1	log K_1	log K_1
Cl^-	3.87	<1.7	3.17	4.26	3.52
F^-	4.57	2.00	3.86	4.42	3.90
AcO^-	5.30	3.32	4.46	4.65	4.01
$H_2PO_4^-$	4.00		4.58	4.30	3.88

The deprotonation of **1a** under conditions of UV–Vis titration can be confirmed by additions of small amounts of acetic acid, which suppress the deprotonation without affecting the hydrogen bonding equilibrium [34]. Indeed, the spectral course of titrations in the presence of 2–3 mM AcOH was typical for hydrogen bonding complexation (Fig. S7, Supplementary Material) and from these results the value of K_1 given in Table 3 was obtained. The inset in Fig. 6b shows the profiles of absorbance at 483 nm vs. acetate concentration in the presence of increased amounts of acetic acid. Fitting of these profiles by Hyperquad to a set of equations involving hydrogen bonding and deprotonation equilibria allowed us to estimate the value of

Table 3 Binding (log K_1) and deprotonation (K_3) constants for interactions of anions with receptors **1a**,**b** and **2a**,**b** in DMSO

Anion	**1a**		**2a**		**1b**	**2b**
	log K_1	K_3	log K_1	K_3	log K_1	log K_1
Cl^-	1.57 ± 0.03		1.12 ± 0.01		1.38 ± 0.02	1.20 ± 0.03
AcO^-	3.48 ± 0.05	0.32 ± 0.05	3.06[a]	0.05[a]	4.33 ± 0.05	3.04[a]
$H_2PO_4^-$	3.30 ± 0.05	(2.0 ± 0.1)×10^{-3}	3.08 ± 0.05	(3.2 ± 0.1)×10^{-4}	4.74 ± 0.05	2.86 ± 0.05

[a] Ref. [34]

$K_3 = 0.32 \pm 0.05$, which was six times larger than previously determined K_3 for **2a** (see Table 3). Since log K_3 = pK_a(AcOH) − pK_a(RH) and pK_a(AcOH) = 12.3, [39] one obtains pK_a(**1a**) = 12.8. Thus the thiourea group of the thiacalixarene receptor is somewhat more acid than the thiourea group of the corresponding receptor **2a** (pK_a = 13.6) [34].

The spectral course of the titration of **2a** by $H_2PO_4^-$ (Fig. S8, Supplementary Material) resembles that observed with acetate. Titrations in the presence of added AcOH were performed (a typical titration is shown in Fig. 8, solid squares) in order to separate H-bonding and deprotonation equilibria, which allowed us to determine the K_1 value given in Table 3. Since the conjugated acid for $H_2PO_4^-$ is H_3PO_4 rather than AcOH we repeated titrations of **2a** with $H_2PO_4^-$ but in the presence of H_3PO_4 instead of AcOH. The deprotonation was suppressed but the titration curves in the range 360–400 nm, where the absorbance changes are due to formation of the hydrogen bonded complex, displayed clear inflection points at the ratio $[H_2PO_4^-]/[H_3PO_4] = 1$, Fig. 8. This means that H_3PO_4 suppresses also the hydrogen bonding until an excess of the anion is applied and the only possible reason for this effect is the complexation of $H_2PO_4^-$ with H_3PO_4, Eq. 3.

$$AH + A^- \rightleftarrows A_2H^- \quad (3)$$

$$K_{A2H} = [A_2H^-]/[AH][A^-] \quad (4)$$

The quantitative analysis of titration curves obtained in the presence of phosphoric acid allowed us to estimate K_3 given in Table 3 and the homoconjugation constant log $K_{A2H} = 3.9 \pm 0.1$ (Eq. 4) for the formation of complex $[H_2PO_4^- \cdot H_3PO_4]$. Lower K_3 value for $H_2PO_4^-$ as compared with that for AcO^- reflects lower basicity of the former. Assuming pK_a = 13.6 for **2a** one obtains from this K_3 value the pK_a = 10.1 for H_3PO_4 in DMSO. The stability of complex $[H_2PO_4^- \cdot H_3PO_4]$ is much higher than that of analogous acetic acid—acetate complex (log K_{A2H} = 2.1 in DMSO) [34] apparently due to possibility of formation of two instead of one hydrogen bonds between the anion and acid. No detectable interaction was observed between $H_2PO_4^-$ and acetic acid. It is worth mentioning that weak association between H_3PO_4 and $H_2PO_4^-$ was detected even in water [40], and the respective homoconjugation complex was found, for example, in the crystal structure of $[(\eta^5\text{-}C_5Me_5)_2Co][H_3PO_4][H_2PO_4]$ [41]. At the same time to the best of our knowledge the homoconjugation of dihydrogenphosphate in DMSO has never been described. The

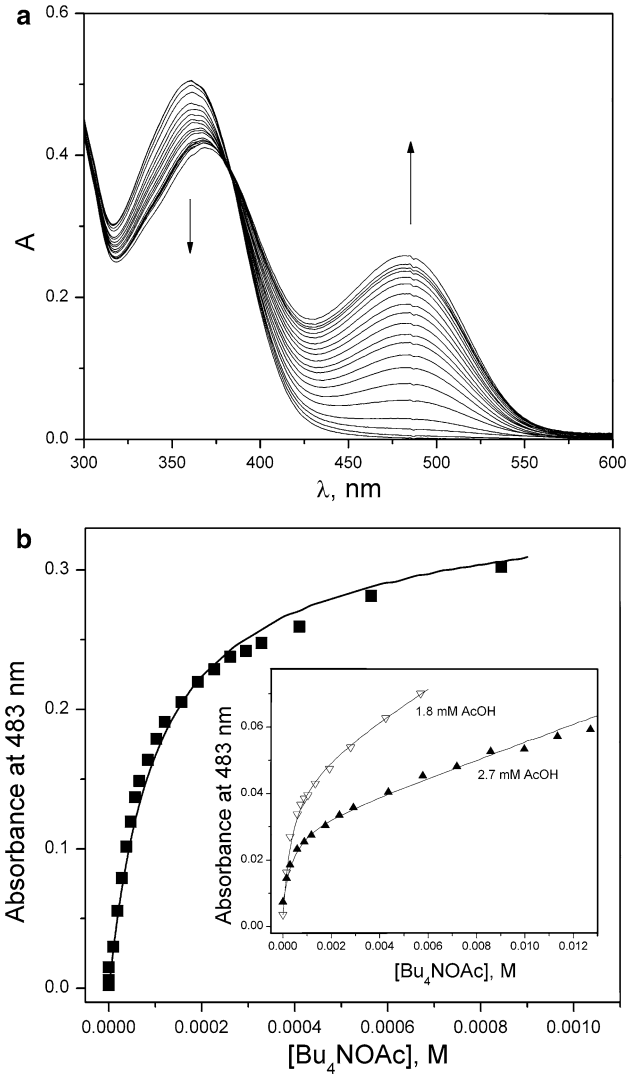


Fig. 6 **a** Spectrophotometric titration of 1.9×10^{-5} M **1a** by Bu_4NOAc in DMSO. **b** The titration curve at 483 nm; *solid line* is the fitting curve to a scheme involving simultaneous hydrogen bonding and deprotonation of **1a**; inset: titrations with added AcOH

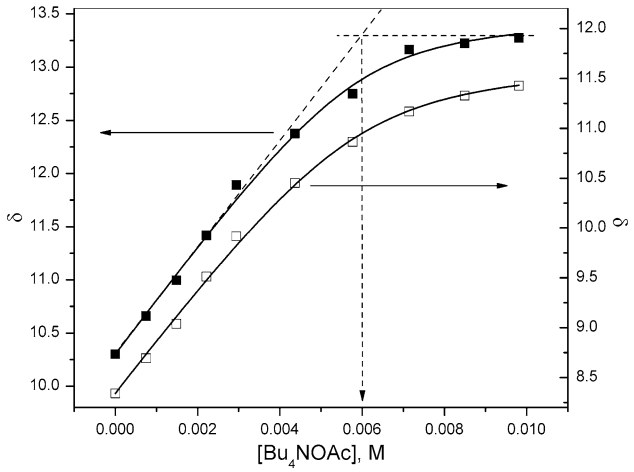


Fig. 7 Chemical shifts of NH protons (*left axis* NH group adjacent to the aromatic ring, *right axis* NH group adjacent to the methylene group) in the NMR titration of 3 mM **1a** by Bu_4NOAc in DMSO

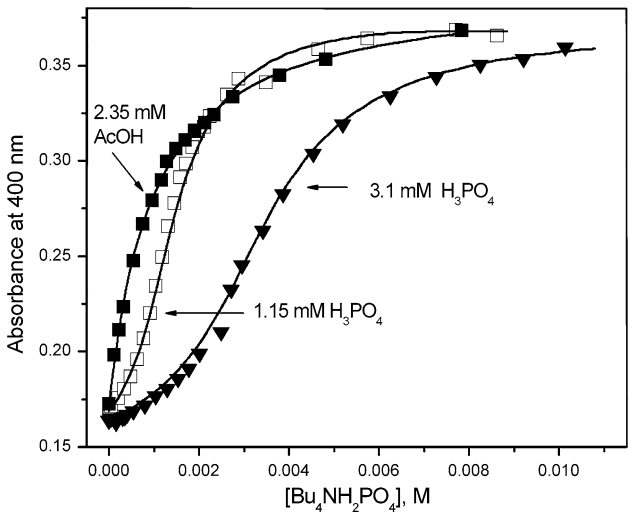


Fig. 8 Titration curves of 4.8×10^{-5} M **2a** at 400 nm by $Bu_4NH_2PO_4$ in DMSO in the presence of added acids: *solid squares* AcOH, *open squares* and *solid triangles* H_3PO_4

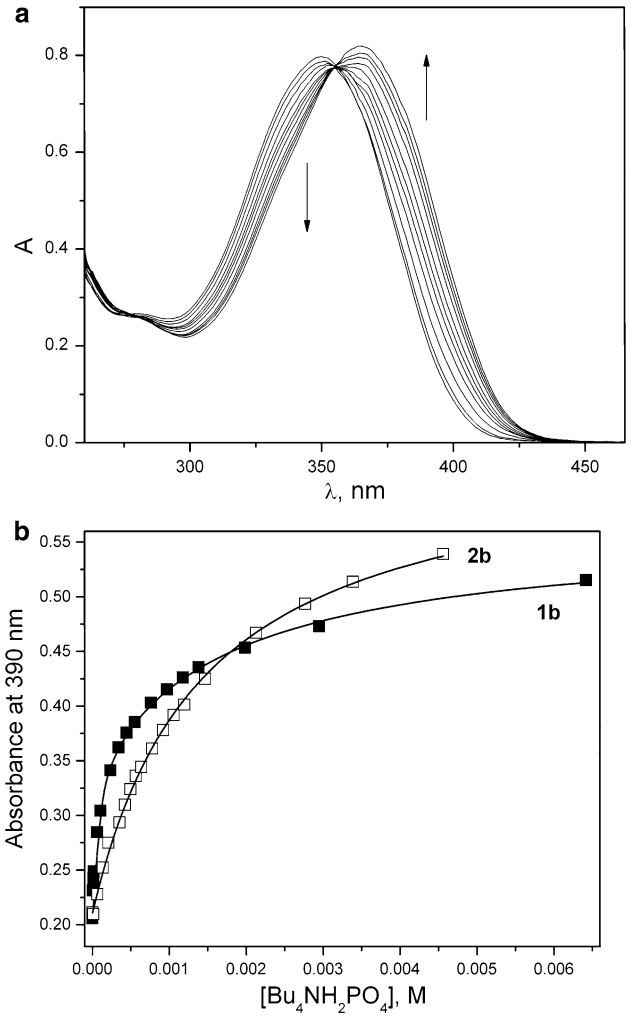


Fig. 9 **a** Spectrophotometric titration of 5.25×10^{-5} **2b** by $H_2PO_4^-$ in DMSO; **b** Titration curves for **2b** (*open squares*) and 2.2×10^{-5} **1b** (*solid squares*)

stronger homoconjugation of $H_2PO_4^-$ as compared to that of AcO^- explains why this less basic anion induces the deprotonation of **2a** to approximately the same extent as acetate. This can be attributed to the participation of two anions in the deprotonation process in accordance with the known mechanism when the equilibrium of deprotonation (1) is shifted to the right by complexation of the acid liberated at this step with the second anion [35–38].

Interaction of $H_2PO_4^-$ with **1a** also involved both deprotonation and hydrogen bonding. The similar analysis involving titration in the presence of added AcOH was employed to determine the true binding constant K_1 for the hydrogen bonding association and deprotonation constant K_3 given in Table 3. The value of K_3 agrees very well with that calculated as $\log K_3 = pK_a(H_3PO_4) - pK_a(\mathbf{1a}) = -2.7$.

Interactions of urea derivatives **1b** and **2b** with chloride anions involved simple hydrogen bonding with K_1 values similar to those for **1a** and **2a**, Table 3. Fluoride anions induced deprotonation of both **1b** and **2b**, but the spectral course of titration indicated a complicated reaction mechanism, which we were unable to fit to any scheme: the formation of the colored deprotonated form occurred very sharply in a narrow concentration range of fluoride about 1 mM. Similar behavior was reported recently for the interaction of fluoride anions with another N-nitrophenyl urea derivative in DMSO [42].

Interactions of **1b** and **2b** with AcO^- and $H_2PO_4^-$ involve mainly the hydrogen bonding with a very small, less then 5% formation of the deprotonated form in the case of thiacalixarene receptor **1b** (Fig. S9, Supplementary Material). Results for **2b** and AcO^- were reported previously

[34]. Spectrophotometric titrations of **1b** and **2b** by $H_2PO_4^-$ were of similar type. Figure 9a illustrates the titration experiment for **2b** and Fig. 9b shows the titration profiles for both receptors. Results for both receptor fit well to a simple 1:1 association model with K_1 given in Table 3.

The results collected in Table 3 allow us to compare the behavior of thiacalixarene urea and thiourea receptors and corresponding monofunctional compounds in two types of equilibria: hydrogen bonding (K_1) and deprotonation (K_3). The values of K_3 increase nearly by one order of magnitude on going from **2a** to **1a**. A possible reason for this is a strong electron accepting effect of the thiacalixarene macrocycle, which is transmitted even through the chain of two methylenes. A structural evidence in favor of this explanation is some elongation of the C=S bond from 1.652(5) Å in **2a** to 1.689(5) Å in **1a**. Also in line with this, signals of NH protons in **1a** are shifted by 0.07 ppm downfield as compared to their positions in **2a**. The hydrogen bonding of anions with **1a** is somewhat stronger, by a factor of 2 or less, than with **2a**. The effect is similar for all anions and most probably reflects increased acidity of the thiourea groups in **1a**, rather than a chelate complexation. For the urea receptors **1b** and **2b** deprotonation is observed only with the most basic fluoride anion and, unfortunately, cannot be characterized quantitatively due to the complexity of the system. In the hydrogen bonding association the advantage of bisurea receptor is clearly seen in greatly enhanced affinity of **1b** as compared to **2b** towards $H_2PO_4^-$. A smaller, but still significant effect is observed with AcO^-, but with Cl^- the effect is small. This selectivity of the chelate effect can be attributed to the different geometry of anions, which must fit the cleft between two ureido groups. Interestingly, in DMSO the chelate effect for ureido receptor **1b** is much larger than in chloroform (cf. Table 2). A possible reason for this is that DMSO disrupts intramolecular hydrogen bonds between urea groups in **1b** interfering with anion complexation in chloroform. Thus better preorganization of bis-ureido thiacalixarene receptor as compared to bis-thioureido derivative leads to a more efficient binding only in more polar solvent.

Conclusions

Crystal structures of disubstituted thiacalix[4]arenes indicate that the bisthiourea derivatives are especially poorly preorganized for anion complexation, firstly, due to *syn,anti* conformation of the thioureido group and, secondly, due to the divergent arrangement of these groups. In contrast, the bisurea derivative has a well preorganized structure. One observes however that the effect of preorganization is solvent dependent because in a low polar medium the intramolecular hydrogen bonding between urea groups offsets the advantage of cooperative anion complexation by correctly positioned functional groups. A previously unnoticed aspect is a strong complexation of phosphoric acid by $H_2PO_4^-$ in DMSO, which explains why this anion deprotonates thiourea receptors in spite of its low basicity.

Experimental section

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol, 5,11,17,23-tetra-*tert*-butyl-25,27-di[(benzyl)methoxy]-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene (**3**),[10] N-methoxyethyl-N′-(4-NO_2-phenyl)thiourea (**2a**) and N-methoxyethyl-N′-(4-NO_2-phenyl)urea (**2b**) were prepared according to the reported procedure [34].

5,11,17,23-Tetra-*tert*-butyl,25,27-di[(benzyl)methoxy]-26,28-bis(carbamoylmethoxy)-2,8,14,20-tetrathiacalix[4]arene (**4**)

To a solution of **3** (1 g, 1.11 mmol) in dry acetone (50 mL), Cs_2CO_3 (1.8 g, 5.55 mmol) and 2-bromoacetamide (76 mg, 5.55 mmol) were added and the mixture was refluxed for 24 h under argon, cooled at room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with 1 N HCl. The organic layer was separated, washed with brine (2 × 15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue triturated with MeOH to give **4** (676 mg, 64%) as a white solid. Recrystallization from $CHCl_3$–MeOH afforded **6** as white solid. M.p. 175–178 °C. ^{1}H NMR δ ($CDCl_3$) 0.81 (s, 18H), 1.26 (s, 18H), 4.48 (s, 4H), 5.07 (s, 4H), 6.87 (t, J = 4.98 Hz 5H), 7.01 (t, J = 4.98 Hz 5H), 7.09 (s, 4H), 7.40 (s, 4H). ^{13}C NMR δ 30.91, 31.43, 34.22, 34.58,67.48, 71.28, 127.17, 127.24, 128.12, 128.35, 128.89, 129.05, 129.52, 137.34, 147.80, 147.89, 154.94, 170.73. MS *m/z*: 1015.40 (M^+). Anal. Calcd. for $C_{58}H_{66}N_2O_6S_4$: C, 68.60; H, 6.55; N 2.76. Found: C, 68.33; H, 6.49; N, 2.75%.

5,11,17,23-Tetra-*tert*-butyl,25,27-di[(benzyl)methoxy]-26,28-bis(2-aminoethyloxy)-2,8,14,20-tetrathiacalix[4]arene (**5**)

To a 15 mL of BH_3/THF solution was added **4** (676 mg, 0.66 mmol) and the reaction mixture was stirred for 1 h at ambient temperature, then reflux for 5 h under argon. The mixture was allowed to cool to ambient temperature, and an additional aliquot (10 mL) of the borane solution added. The mixture was refluxed for an additional 15 h. The

solvent was removed under reduced pressure and the residue treated with 20 mL of 1 N HCl and reflux for 1 h. After cooling down to room temperature, 10% KOH was added until the solution became basic and extracted with CH_2Cl_2 (2 × 15 mL). The solvent was removed under reduced pressure to give **5** (423 mg, 65%) as a white solid. Recrystallization from $CHCl_3$–MeOH afforded **5** as white solid. M.P. 194–197 °C. ^{1}H NMR δ ($CDCl_3$) 0.82 (s, 18H), 1.29 (s, 18H), 2.46 (t, $J = 5.33$ Hz 4H,), 3.94 (t, $J = 5.35$ Hz 4H), 5.04 (s, 4H), 6.86 (t, $J = 4.99$ Hz 5H), 7.07 (s, 4H), 7.12 (t, $J = 4.99$ Hz 5H), 7.38 (s, 4H). MS *m/z*: 987.40 (M^+). ^{13}C NMR δ 29.92, 30.96, 31.56, 31.74, 41.98, 70.61, 71.31, 127.48, 128.14, 128.88, 129.40, 131.19, 143.90. Anal. Calc. For $C_{58}H_{70}N_2O_4S_4$: C, 70.55; H, 7.15; N, 2.84. Found: C, 70.76; H, 7.17; N, 2.85%.

5,11,17,23-Tetra-*tert*-butyl,25,27-di[(benzyl)methoxy]-26,28-bis[(4-nitrophenylthioureido)ethoxy]-2,8,14,20-tetrathiacalix[4]arene (**1a**)

To **5** (423 mg, 0.43 mmol) in 15 mL of CH_2Cl_2, was added 4-nitrophenyl isothiocyanate (232 mg, 1.29 mmol) and the mixture was stirred for overnight under nitrogen. The solvent was removed under reduced pressure and the residue triturated with MeOH and washed with hexane to give **1a** (409 mg, 65%) as a pale yellow powder. Recrystallization from $CHCl_3$–CH_3CN afforded **1a** as pale yellow crystals. M.p. >200 °C. ^{1}H NMR δ ($CDCl_3$) 0.83 (s, 18H), 1.21 (s, 18H), 3.81 (br t, 4H), 4.30 (br t, 4H), 4.93 (s, 4H), 7.13 (t, $J = 5.10$ Hz 5H), 7.16 (s, 4H), 7.22 (t, $J = 5.12$ Hz 5H), 7.38 (s, 4H), 7.43 (d, $J = 7.45$ Hz 4H), 7.86 (br s, 2H), 7.97 (br s, 2H), 8.17 (d, $J = 7.45$ Hz). ^{13}C NMR δ ($CDCl_3$) 30.96, 31.55, 34.12, 34.48, 70.86, 73.64, 122.72, 125.59, 127.34, 127.50, 127,86, 128.08, 128,59, 131.82, 132.43, 137.28, 143.61, 144.60, 146.43, 146.86, 157.31, 158.53, 180.84. MS (FAB, *m/z*) 1347 (M^+).Anal. Calcd. for $C_{72}H_{78}N_6O_8S_6$ (1347.82): C, 64.16; H, 5.83; N 6.24. Found: C, 64.09; H, 5.79; N, 6.20%.

5,11,17,23-Tetra-*tert*-butyl,25,27-di[(benzyl)methoxy]-26,28-bis[(4-nitrophenylureido)ethoxy]-2,8,14,20-tetrathiacalix[4]arene (**1b**)

Similar procedure as that for **1a** was applied with the yield 63%. Mp. >200 °C. ^{1}H NMR δ ($CDCl_3$) 0.83 (s, 18H), 1.15 (s, 18H), 3.17 (br t, 4H), 4.04 (br t, 4H), 5.05 (s, 4H), 5.90 (br s, 2H), 6.95 (t, $J = 5.10$ Hz 5H), 7.09 (t, $J = 5.12$ Hz 5H), 7.13 (s, 4H), 7.42 (d, $J = 7.45$ Hz 4H), 7.55 (br s, 2H), 8.07 (d, $J = 7.45$ Hz,4H). ^{13}C NMR δ ($CDCl_3$) 30.94, 31.29, 34.13, 34.45, 40.70, 70.38, 71.44, 117.96, 125.47, 127.42, 127.56, 127.91, 128.21, 128.32, 129.95, 137.20, 142.43, 145.54, 146.88, 155.45, 157.40. MS (FAB, *m/z*) 1315 (M^+).Anal. Calcd. for $C_{72}H_{78}N_6O_{10}S_4$ C, 65.73; H, 5.98; N 6.39. Found: C, 65.09; H, 5.89; N, 6.41%.

X-ray crystallography

X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector ($\lambda_{MoK\alpha} = 0.71073$ Å, monochromator: graphite). Frames were collected at $T = 100$ K (compounds **1a**,**1b**) and $T = 293$ K (compounds **2a**,**2b**) via ω/ϕ-rotation at 10 s per frame (SMART) [43]. The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT) [44]. Corrections were made for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL-NT program package [45, 46]. Non hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in geometrically calculated positions using a riding model.

For **1a** the asymmetric unit contains one molecule halve. Solvent molecules were present in the crystal lattice of compound **1b** (CH_3CN). Although relatively large crystals could be grown and the data collections were performed at $T = 100$ K, for compound **1b** the R value is somewhat elevated. Besides the large molecular structures, for compound **1b** this can be attributed to the weak diffraction of the crystals at theta angles >20°. However, the data were of sufficient quality to determine properly the molecular and crystal structures. It should, however, be noticed that the low resolution of the data affects the reliability of the bond lengths and angles, intermolecular distances and the refinement of the anisotropic thermal parameters. In the case of compound **1b** SIMU, DELU and ISOR instructions have been used during the refinement.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-706665-706669. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk).

Spectrophotometric and 1H NMR Titrations

The absorption spectra were recorded after additions of aliquots of stock solutions of tetrabutylammonium salts in respective solvents to a 10^{-5}–10^{-4} M receptor solution in DMSO or chloroform in a quartz cuvette placed in a compartment of a diode array spectrophotometer thermostated at 25 ± 0.1 °C with a recirculating water bath. NMR titrations were performed on a 300 MHz spectrometer with

more concentrated stock solutions in the respective deuterated solvents adding aliquots of them to 5–20 mM receptor solutions in DMSO-d_6 or $CHCl_3$-d directly to NMR tubes. In order to test possible autoassociation of receptors their NMR spectra were recorded in a range of concentrations from 3 to 25 mM in both solvents and signals of all protons were found unchangeable. The fitting procedure for the calculation of equilibrium constants from titration data was described previously [34].

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