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Design, Synthesis and Recognition Properties of Urea-Type Anion Receptors in Low Polar Media

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The binding efficiency of simple receptors bearing two NH hydrogen-bond donor groups, of general formula $PhCH_2NH$–Y–NHPh (Y = C=N–Ts, SO_2, CS, CO), towards selected anion guests has been evaluated in chloroform solution in order to assess the effect of the nature of different binding sites incorporated into the receptor scaffold. Experimental results together with molecular mechanics and quantum chemical calculations have revealed that the nature of the spacer Y induces important electronic effects and conformational changes that lead to different degrees of preorganisation of the NH binding groups. In addition, the synthesis and binding properties of new lipophilic urea-based receptors, having electron-withdrawing alkylsulfonyl substituents ($SO_2C_8H_{17}$) and characterised by enhanced NH hydrogen-bond donor ability, is reported.

Introduction

Over the past decade, compounds of general formula RNH–Y–NHR, where R is an alkyl or aryl group, have attracted considerable attention as neutral receptors for the recognition of anions.[1] These compounds are characterized by the presence of two NH groups able to donate two convergent hydrogen bonds to an acceptor species. This structural motif is found in several compounds characterized by a different spacer Y, such as isophthaldiamide, pyridine-2,6-dicarboxamide, squaramide and (thio)urea derivatives. In particular amide-based hosts[2] and (thio)urea derivatives[3] have been extensively employed either as simple monotopic acyclic receptors or arranged in more complex polytopic hosts for multipoint recognition.[4]

In principle, the binding efficiency of these receptors can be improved by enhancing the hydrogen-bond donor ability of their NH groups. Starting from the seminal work of Wilcox et al.[3b] who reported the anion-binding properties of a series of substituted *N*-aryl-*N*′-alkyl(thio)ureas, most of the work has usually been directed towards evaluating the electronic effects of substituents present on the R groups, when R = aryl, in a series of structurally related compounds.[5] In contrast, the effect of the spacer Y on the binding efficiency has been less investigated. The few studies reported in the literature on this topic mainly focused on the different binding efficiency of thiourea versus urea derivatives. These studies were usually carried out for solubility reasons in very polar and competing solvents such as acetonitrile or DMSO[3a,3c,4b] in which the better complexing properties experienced by the thiourea-based receptors were generally ascribed to the higher acidity of their NH.[6]

Compounds characterised by the same structural motif have also been extensively used as non-covalent catalysts in reactions operating under general acid catalysis conditions.[7] Indeed, these metal-free catalytic systems are particularly interesting because they mediate the activation of electrophilic substrates through hydrogen bonding and usually entail chemoselectivity, higher tolerance to functional groups and fewer environmental problems than traditional metal catalysts.

The design of new compounds able to operate with improved properties in both contexts should be based on the comprehension of the several factors that affect hydrogen bonding in these systems. It could thus be important to systematically study the effects induced by the nature of the spacer Y in a series of strictly related hosts that are soluble in low polar and less competing solvents.

Herein we report on the recognition properties towards anions in chloroform solution of a series of acyclic receptors characterised by a different spacer Y and having tosylguanidine (**1**, Y = C=N–Ts), sulfamide (**2**, Y = SO_2), thiourea (**3**, Y = C=S) and urea (**4**, Y = C=O) binding units,

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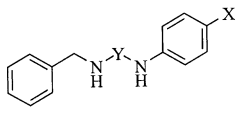
respectively. The synthesis and binding properties of new and lipophilic urea-based receptors bearing electron-withdrawing SO_2R (R = C_8H_{17}) substituents are also reported.



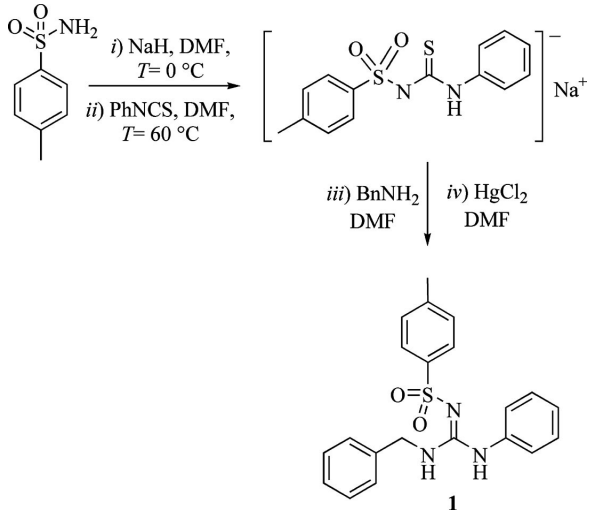
1 Y = C=N–Ts; X = H
2 Y = SO_2; X = H
3 Y = C=S; X = H
4 Y = C=O; X = H
5 Y = C=O; X = NO_2

Results and Discussion

Design and Synthesis of Urea-Type Receptors

The design of the acyclic receptors **1**–**4** was based on the requirement that the substituents attached to the NH groups should confer an overall lipophilicity to the resulting compounds to allow the evaluation of their binding properties in low polar solvents. With this aim all the receptors used in the present study are characterised by a central ureido-type group bearing a phenyl unit on one side and a benzyl unit on the other. The higher conformational flexibility of the latter substituent appreciably enhances the solubility of these compounds with respect to *N*,*N*-diaryl derivatives.

The sulfonylguanidine-based receptor **1** was synthesised in 30% yield according to the procedure reported by Zhang and Shi[8] for the preparation of sulfonylguanidinium analogues (see Scheme 1), whereas compounds **2**–**4** were prepared according to published procedures (see Exp. Sect.). In the ^{1}H NMR spectrum of **1**, taken in $CDCl_3$, the two non-equivalent NH protons resonate as two broad signals at δ = 5.1 and 9.1 ppm, respectively (see Supporting Information). The large downfield shift of the signal assigned to the NH proton adjacent to the phenyl unit seems to indicate that this group is probably involved in intramolecular hydrogen bonding with one of the two oxygens of the SO_2 moiety.



Scheme 1. Synthesis of the (tolylsulfonyl)guanidine-based receptor **1**.

Binding Studies

To determine the effect of the spacer Y on the binding properties of **1**–**4** in chloroform solution, chloride (Cl^-) and acetate (Ac^-) were selected as representative spherical and planar anions, respectively. The tetrabutylammonium (TBA) cation was chosen as the counterion for solubility reasons. However, it is known that TBA salts are present in solutions of low polar solvents either as solvated ion pairs or as their aggregates.[9] Moreover, the hydrogen-bond donor and acceptor nature of the –NH–Y–NH– binding unit of **1**–**4** might favour extensive host self-association, as found for instance in derivatives in which both the NH groups are substituted with phenyl units.[10] Both phenomena could in principle affect the host's binding efficiency. Therefore the complexation of organic salts in solvents of low dielectric constant requires an initial careful examination of the binding stoichiometry.

The extent of the host's self-association was initially evaluated through ^{1}H NMR dilution experiments. Upon dilution of a 2×10^{-2} M solution of each host up to 6×10^{-4} M, only **4** showed a not-negligible variation in the chemical shift of its ureido NH protons ($\Delta\delta$ = +0.3 ppm). However, attempts to obtain a reliable self-association constant through the fitting of the NMR dilution data either with a dimerization isotherm[11] or with an isodesmic model[12] did not give satisfactory results.

The stoichiometry of binding was thus verified by ^{1}H NMR spectroscopy in $CDCl_3$ solution through the use of continuous variation methods (see Exp. Sect.).[13] The Job plot obtained during the complexation of **4** with TBACl is shown in Figure 1. From the plotted data it emerges that, in the concentration range used in the experiment, the maximum of the complex formation occurs at x = $[\mathbf{4}]_0/([\mathbf{4}]_0+[\mathrm{TBACl}]_0)$ = 0.5, which corresponds to a 1:1 stoichiometry of binding.

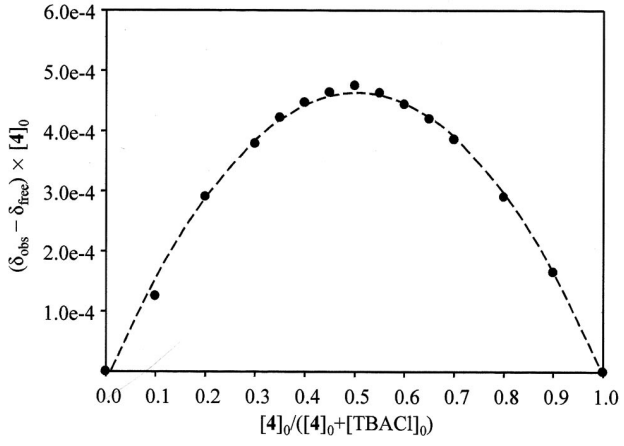


Figure 1. Job plot obtained by monitoring the chemical shift variation of the NH proton adjacent to the benzyl group of **4** during its binding with TBACl. During the experiment the relative concentration of the two interacting species was varied continuously, but their sum was kept constant (1.45×10^{-3} M).

To determine the binding efficiency of the hosts, ^{1}H NMR titration experiments were carried out in $CDCl_3$ solution using methods already published.[14] By adding increasing amounts of the guest solution ($1.0–1.3 \times 10^{-1}$ M) to a solution ($1.0–1.3 \times 10^{-2}$ M) of the host, all receptors but **1** showed an extensive downfield complexation-induced shift (CIS) of the two chemically different NH protons. As an example, in Figure 2 has been depicted a stack plot corresponding to the titration of receptor **4** with TBAAc. When the anion guest is present in solution in a large excess (Figure 2, a), the two NH protons are downfield shifted to 10.95 and 9.40 ppm, respectively. These findings suggest that anion recognition occurs mainly through the formation of hydrogen bonds with the NH protons of the hosts.

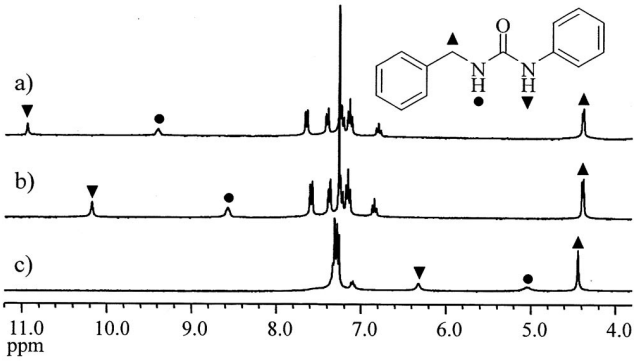


Figure 2. ^{1}H NMR stack plot (300 MHz, T = 300 K, expanded region) showing the chemical shift variation of the NH protons of **4** upon complexation with TBAAc in $CDCl_3$. Guest/host ratios: a) 4:1; b) 1:1 and c) free **4** ($c = 1.0 \times 10^{-2}$ M), respectively.

In all the titration experiments the NMR spectra showed time-averaged signals for the free and complexed species. The apparent binding constants (K) for host–guest complex formation were calculated by considering a 1:1 stoichiometry using methods previously described based on the nonlinear fitting of the chemical shift variation of the NH protons (see Exp. Sect.).[15] Best fits of the experimental data were obtained by using the chemical shift variation of the NH proton adjacent to the phenyl group. The ^{1}H NMR binding isotherms relative to the titrations of TBAAc with hosts **3** and **4** have been depicted in Figure 3.

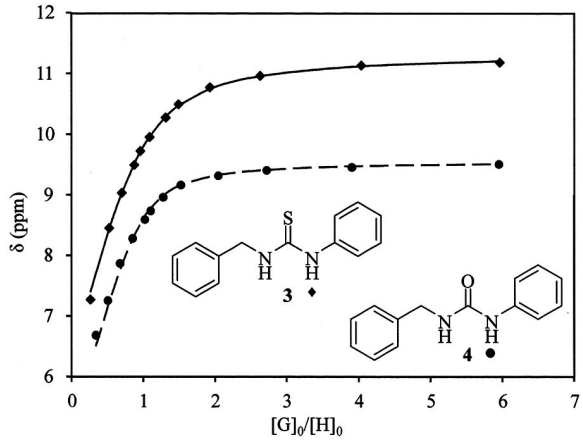


Figure 3. Binding isotherms obtained by monitoring the chemical shift variation of the PhNH–Y–N*H*CH$_2$Ph proton during the titration of **3** (♦, continuous line; $c = 1.2 \times 10^{-2}$ M) and **4** (●, dashed line, $c = 1.3 \times 10^{-2}$ M) with TBAAc in $CDCl_3$, respectively.

The binding data summarised in Table 1 show that the sulfonylguanidine derivative **1** experiences very weak complexation with all guests, as shown by the negligible downfield shift of its NHs. In contrast, hosts **2**–**4** show a relatively strong binding, especially with acetate. The general trend in the binding efficiency follows the order **4** > **3** ≈ **2** >> **1**.

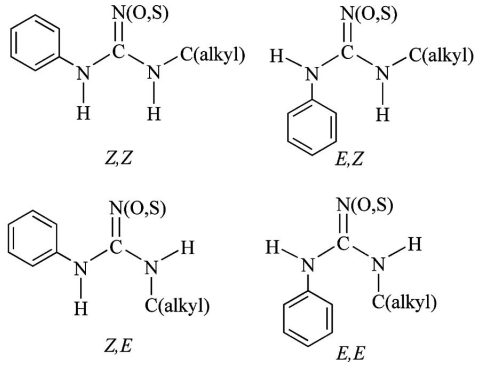
A better understanding of the complexing properties of **1**–**4** can be achieved by considering that, in principle, the nature of the spacer Y could affect both the hydrogen-bond donor ability and the preorganisation of the hosts. This latter aspect is particularly important because it is reasonable to assume that, due to restricted rotation around the two pseudoamide NH–Y bonds, these hosts have a different degree of preorganisation. The conformational behaviour of **1**–**4** was initially investigated through the analysis of several solid-state structures of compounds having the general formula PhNH–Y–NHR(alkyl) which were retrieved from the Cambridge Structural Database (see Exp. Sect.). The orientations of the N–H bonds with respect to the spacer Y were evaluated by considering the two dihedral angles H–N–C–O(S,N) along the two pseudoamide bonds.

Table 1. Apparent binding constants (K) for the complexation of hosts of general formula PhNH–Y–NHCH$_2$Ph (**1**–**4**) with tetrabutylammonium salts and DMSO in $CDCl_3$ solution.[a]

Host[b]	Y	TBAAc			TBACl			DMSO		
		K [M^{-1}]	δ_∞ [ppm]	$\Delta\delta_\infty$ [ppm]	K [M^{-1}]	δ_∞ [ppm]	$\Delta\delta_\infty$ [ppm]	K [M^{-1}]	δ_∞ [ppm]	$\Delta\delta_\infty$ [ppm]
1	C=N–Ts	$(1.5 \pm 0.5) \times 10^1$	9.4 ± 0.3	0.3	[c]	–	[d]	[c]	–	[d]
2	SO_2	[e]	–	–	$(2.2 \pm 0.2) \times 10^2$	9.5 ± 0.1	3.2	45 ± 8	7.0 ± 0.1	0.7
3	C=S	$(5.0 \pm 0.3) \times 10^2$	12.4 ± 0.1	4.7	$(1.0 \pm 0.1) \times 10^2$	11.0 ± 0.1	3.3	12 ± 5	8.6 ± 0.1	0.6
4	C=O	$(3.0 \pm 0.5) \times 10^3$	11.0 ± 0.1	4.7	$(1.5 \pm 0.5) \times 10^3$	9.7 ± 0.1	3.4	52 ± 10	7.1 ± 0.1	0.7

[a] Determined by ^{1}H NMR in $CDCl_3$ (T = 300 K) by monitoring NH ligand chemical shift variation upon complexation; standard deviations are given in parentheses. [b] C_6H_5NH–Y–$NHCH_2C_6H_5$: ^{1}H NMR signals for the free receptors (δ, ppm): **1** = 9.07, **2** = 6.30, **3** = 7.67, **4** = 6.40. [c] Negligible complexation. [d] No significant chemical shift variation. [e] Extensive broadening of the NH signals prevented binding constant calculation.

All the *N*-phenyl-*N*′-alkylurea derivatives investigated have their two pseudoamide bonds in the *Z*,*Z* form. The two N–H bonds are thus in an *anti* conformation with respect to the C=O bond. Interestingly, the most common geometry found for the corresponding thiourea derivatives is *E*,*Z*. In particular, the N–H bonds adjacent to the phenyl and alkyl units, respectively, are *syn* and *anti* with respect to the C=S bond. The *anti*,*anti* or *Z*,*Z* conformation becomes dominant in the solid state exclusively when both NHs are involved in intermolecular H-bonding. Unfortunately, no relevant crystal data were found in the CSD for compounds with Y = SO_2 or C=N–Ts. However, several structures corresponding to *N*,*N*-dialkylsulfamide derivatives show that these compounds usually adopt a geometry in which the two N–H bonds are oriented in opposite directions with respect to the plane containing the N–S–N atoms. In most cases this conformation is stabilised through the formation of intermolecular hydrogen bonding between the NHs and the oxygen of the SO_2 group belonging to different adjacent molecules.



Further insights into the conformational behaviour of **1**–**4** have been gained through computational studies. The conformational mobility of these compounds is greatly affected by the presence of the benzylic unit. Indeed, the rotational degree of freedom ranges from five for **2**–**4** to eight for **1**. A systematic search for all the possible rotamers was carried out by a Monte Carlo method by using the MMFF94 force field. Among the several local minima obtained, those derived from the different orientation of the phenyl and benzyl units with respect to the spacer Y were selected and further minimised either by molecular mechanics or by quantum chemical calculations using DFT methods (see Exp. Sect.). Such an approach yielded rotamers whose structures and relative energies have been summarised in Figure 4 and in Table 2, respectively.

Several local minima with very similar energies were found for **1**, although not one corresponds to the *Z*,*Z* geometry. A common motif of these rotamers is the presence of an intramolecular hydrogen bond between one of the NH groups and one of the oxygens of the tosyl moiety. In the less strained conformer, such an intramolecular interaction forces **1** to adopt an *E*,*Z* geometry (see Figure 4, a). In this arrangement only the less acidic NH adjacent to the benzyl unit is potentially able to donate a H-bond to a guest. This geometry could also explain the large downfield shift of the NH proton found in the ^{1}H NMR spectrum recorded in $CDCl_3$.

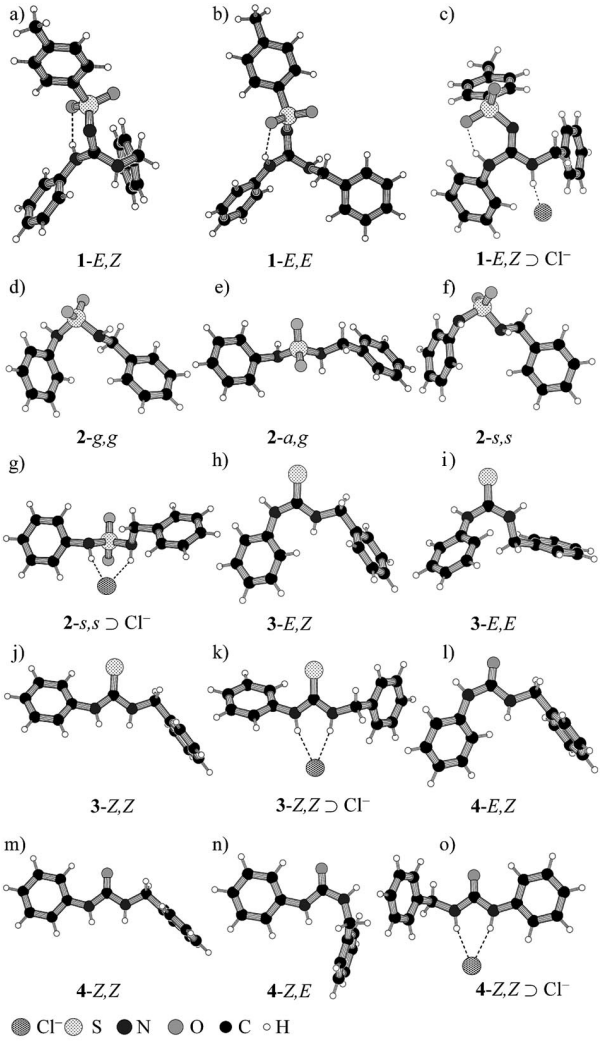


Figure 4. Selected conformations of compounds **1**–**4** generated through a Monte Carlo conformational search (see text for details).

The Monte Carlo search carried out on **2** yielded, as for **1**, several local minima. The three most stable minima found adopt the *gauche*,*gauche* (**2**-*g*,*g*), *anti*,*gauche* (**2**-*a*,*g*) and *syn*,*syn* (**2**-*s*,*s*) geometries. The second arrangement (see Figure 4, e) is similar to that usually found in the solid-state structures, whereas in the third both N–H bonds are almost parallel and oriented on the same side of the molecule (Figure 4, f). These minima all have very similar energies but, albeit in the gas phase, the **2**-*g*,*g* rotamer seems to be the least strained one (see Table 2).

The conformational search performed on compounds **3** and **4** was carried out by using an MMFF94 force field modified with new torsional parameters developed by Hay and co-workers for (thio)urea derivatives (MMFF94+).[16] This approach yielded the *E*,*Z* (Figure 4, h) and the *Z*,*Z* (Figure 4, m) conformers as the most stable rotamers in the gas phase for **3** and **4**, respectively (see Table 2).[17] The *Z*,*Z*,

Table 2. Computed relative energies for selected conformers of **1**–**4**.

Conformer	ΔE [kcal mol^{-1}] (MMFF94)[a,b]	Dihedral angle [°]	
		H–N_{Ph}–C–N	H–N_{Bn}–C–N
1-*E*,*Z*	0	58	151.3
1-*E*,*E*	0.3	–52.1	–17
1-*Z*,*E*	1.9	98	–4
1-*Z*,*Z*	[c]	–	–
		H–N_{Ph}–S–O	H–N_{Bn}–S–O
2-*g*,*g*	0	76.9	–46.5
2-*a*,*g*	1.4	–176.8	44.5
2-*s*,*s*	3.1	–33.7	27.7
		H–N_{Ph}–C–S	H–N_{Bn}–C–S
3-*E*,*Z*	0	3.8	172.2
3-*E*,*E*	5.7	9.1	4.7
3-*Z*,*E*	4.5	164.6	–1.1
3-*Z*,*Z*	3.1	–171.9	–177
		H–N_{Ph}–C–O	H–N_{Bn}–C–O
4-*E*,*Z*	2.8	–13	158.2
4-*E*,*E*	[c]	–	–
4-*Z*,*E*	3.3	166.8	–1.3
4-*Z*,*Z*	0	180	–180

[a] Local minima were obtained through a Monte Carlo conformational search by using the MMFF94 force field. [b] For **3** and **4** different torsional parameters were used (see ref.[16]). [c] Local minimum not found.

Z,*E* and *E*,*Z* conformers obtained from the previous molecular mechanics studies on **3** and **4** were further minimised by quantum chemical calculations using DFT methods at the B3LYP/6-31+G* level both in the gas phase and by applying the polarisable solvent continuum model (PCM)[18] to simulate the effect of the solvent molecules ($CHCl_3$). These preliminary and more accurate calculations did not substantially change the energy order found in the molecular mechanics studies, although the single-point calculation carried out using the PCM model revealed that for **4** the *E*,*Z* conformer is more stable than the *Z*,*Z* by around 1.4 kcal mol^{-1}.

The equilibrium structures of the complexes of **1**–**4** with the Cl^- anion were calculated in the gas phase by a molecular mechanics method using the MMFF94 force field. The outcome of these simulations showed that the complex between **1** and Cl^- is created only through the formation of one hydrogen bond with the host in the *E*,*Z* conformation (see Figure 4, c) whereas for **2**–**4** the complexation is generally assisted by the formation of two hydrogen bonds with the hosts in the *Z*,*Z* conformation (*syn*,*syn* for **2**).

Considering the relative stability of the free rotamers found for each host in the previous Monte Carlo search, it thus appears that, except for **4**, the binding of the anion needs, as a prerequisite, a significant conformational rearrangement of the hosts which implies rotation of the NH groups around the corresponding pseudoamide bonds. Such rotations are strongly dependent on the corresponding interconversion energies which were determined for **2**–**4** by using the MMFF94+ force field. For **2** variation of the (Ph)C–N–S–O dihedral afforded a very complicated energy pattern, characterised by several minima. However, by using the simpler $PhNHSO_2NHMe$ molecule as a model it was possible to estimate an interconversion energy of around 9 kcal mol^{-1}. For **3** and **4** both the (Ph)C–N–C–O(S) (see Supporting Information) and the (Bn)C–N–C–O(S) dihedrals were varied from –180 to 180°, affording rotational barriers that are generally higher for **3** (12.5–13.4 kcal mol^{-1}, depending on the path chosen) than for **4** (11–11.3 kcal mol^{-1}, depending on the path chosen). These results are consistent with those determined at a higher level of theory (MP2/aug-ccpVDZ) for *N*-phenyl-*N*′-alkylthiourea (9.8 kcal mol^{-1}) and *N*-phenyl-*N*′-alkylurea (9.1 kcal mol^{-1}) derivatives.[16] The higher interconversion energy for thiourea derivatives relative to the urea ones has mainly been ascribed to an increase in the partial double bond character of the corresponding C–N bond.[19]

The tendency of each host to interact with the anion species should also be correlated to the electronic effects exerted on the NH groups by substituents incorporated into the host scaffold. As previously mentioned, these effects have been extensively discussed in the literature (see Introduction) when the substituents are located on the aromatic unit directly linked to the hydrogen-bond donor group. By using a similar approach, the electronic effects of the spacer Y were initially extrapolated by considering either the Hammett substituent constants or the corresponding resonance and field parameters of substituents structurally related to Y such as $CONH_2$, $CSNH_2$ and SO_2NH_2. Unfortunately, no data were found in the literature corresponding to the electronic effects of substituents similar to Y = C=N–Ts. Regardless of the parameter chosen, it appears that the electron-withdrawing strength follows the order $SO_2NH_2 >> CONH_2 > CSNH_2$.[20] This trend was supported by the analysis of the molecular electrostatic potential (MEP) calculated at the B3LYP/6-31+G* level for the structures of **2**–**4** in the *Z*,*Z* conformation (*syn*,*syn* for **2**). MEPs can be considered as reliable descriptors of intermolecular interactions that have an important electrostatic component such as hydrogen bonding.[21] The MEP plotted either onto isodensity (0.002 e au^{-13}) or van der Waals surfaces (see Supporting Information) indeed showed evidence that the highest positive electrostatic potential calculated at the point at which an NH direction crosses the molecular surface is found for **2** (+39 kcal mol^{-1}), followed by **4** (+38 kcal mol^{-1}) and then **3** (+29 kcal mol^{-1}).

Considering the low polarity of the media used in the titration experiments, the findings of the molecular mechanics and quantum chemical calculations can be used with good reliability to rationalise the binding properties of the hosts. The poor complexing properties evidenced by **1** and **2** have mainly been ascribed to their large conformational flexibility. The entropic loss that these hosts must endure to adopt an appropriate geometrical arrangement to interact with the charged species is probably not fully compensated by the consequent enthalpic gain derived by the hydrogen-bonding interactions. This compensation is particularly disfavoured in the case of **1** since this host cannot cooperatively use its NH groups to bind charged guests. The impor-

tance of the role played by the host preorganisation is also evidenced by comparison of the results obtained for **2**–**4**. Indeed, the trend in the electron-withdrawing effect exerted by the spacer Y, as deduced both by the MEP analysis and resonance field parameters, can only partly account for the better recognition properties of **4** compared with **3**.

The experimental results obtained in $CDCl_3$ for thiourea **3** and urea **4** deserve further comment. These findings contrast with those reported in the studies carried out, for solubility reasons, in more polar solvents such as DMSO or CH_3CN in which the better properties of the thiourea derivatives have been explained on the basis of the higher acidity[22] of their NH groups (see Introduction). To verify our results, two series of experiments were designed. Initially, the affinity of **1**–**4** for DMSO was evaluated in $CDCl_3$ solution by means of ^1H NMR titrations. Analysis of the calculated binding constants (see Table 1) shows a trend in the host-binding efficiency similar to that found for the complexation of the anion species. The titration experiments with TBACl and TBAAc were then repeated in $[D_6]$DMSO solution. In this very polar solvent, **1** and **2** experienced negligible complexation, whereas **3** and **4** showed a similar binding efficiency (see Table 3). Considering that **4** is a better host than **3** for DMSO in $CDCl_3$, comparison of the binding constants calculated for urea **4** and thiourea **3** with acetate and chloride in $CDCl_3$ and $[D_6]$DMSO, respectively, indicates how the data obtained in the latter solvent are the result of competition between DMSO molecules, which through their S=O groups can behave as hydrogen-bond acceptor species, and the anions for the coordination site of the hosts.

Table 3. Binding constants (K) for the complexation of **3** and **4** with tetrabutylammonium acetate and chloride in DMSO solution.[a]

Host[b]	TBAAc			TBACl		
	K [M^{-1}]	δ_∞ [ppm]	$\Delta\delta_\infty$ [ppm]	K [M^{-1}]	δ_∞ [ppm]	$\Delta\delta_\infty$ [ppm]
3	570 ± 120	12.8 ± 0.1	3.2	24 ± 6	11.6 ± 0.1	2.0
4	360 ± 40	11.5 ± 0.1	3.0	26 ± 10	10.0 ± 0.1	1.5

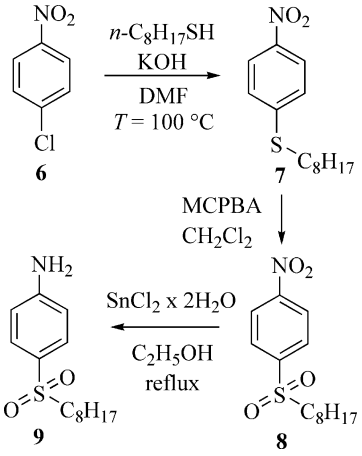
[a] Determined by ^1H NMR in $[D_6]$DMSO (T = 300 K) by monitoring NH ligand chemical shift variation upon complexation; standard deviations are given in parentheses. [b] C_6H_5NH–Y–$NHCH_2C_6H_5$ signal of the free receptors (δ, ppm): **3**: 9.60, **4**: 8.52.

Design and Synthesis of Lipophilic Urea-Based Receptors

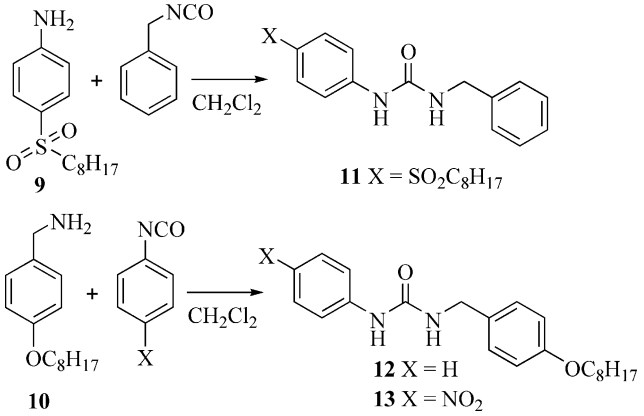
From the binding studies it emerges that the development of new and more efficient acyclic synthetic anion receptors able to operate in low polar solvents depends on two related requisites that need to be addressed in the design of the host: the host solubility and the hydrogen-bond donor ability of the binding unit. It can, however, be foreseen that an improvement of the latter property in **4**, through the incorporation of strong electron-withdrawing groups (EWG) onto the host aromatic scaffold, negatively affects the overall solubility of this compound in solvents of low dielectric constant. Indeed, the low solubility experienced in $CDCl_3$ solution by 1-benzyl-3-(4-nitrophenyl)urea (**5**), in which the *para* position of the phenyl unit of **4** is substituted with a nitro group, prevented the evaluation of its binding properties through NMR spectroscopic titrations.

A more promising alternative to the aforementioned approach is based on the use of EWGs that are themselves quite lipophilic; the alkylsulfonyl group (RSO_2-) possesses both features. In fact its electron-withdrawing strength is comparable to that of the nitro group[23] and the solubility of the corresponding host can be modulated by varying the nature of the R group.

The introduction of alkylsulfonyl groups onto the phenyl unit of **4** cannot, however, be carried out by direct synthetic methods. Therefore the new 4-(octylsulfonyl)aniline (**9**) was prepared in 32% overall yield following the synthetic pathway described in Scheme 2. The new lipophilic urea-based receptor **11** (X = $SO_2C_8H_{17}$) was synthesised in 38% yield by reaction of amine **9** with benzyl isocyanate in CH_2Cl_2. Compounds **12** (X = H) and **13** (X = NO_2) were hence synthesised in 40 and 70% yields, respectively, by reaction of the corresponding isocyanates with 4-(octyloxy)benzylamine (**10**) (see Scheme 3). These new hosts, which experience good solubility in chloroform solution due to the presence of an octyloxy chain on their benzyl units, were prepared for comparison with **11** in order to assess the effect of the electron-withdrawing nature of the SO_2R group on the binding properties.



Scheme 2. Synthesis of the lipophilic amino derivative **9**.



Scheme 3. Synthesis of the new urea derivatives **11**–**13**.

Binding Studies

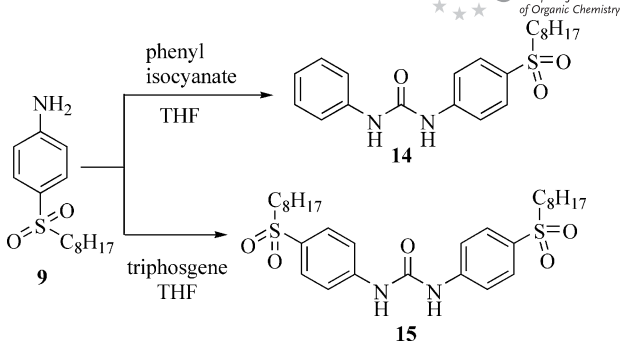
The first attempts to evaluate the binding properties of **11**–**13** towards TBAAc and TBACl in $CDCl_3$ solution by using ^1H NMR titrations were successful only for host **12** (see Table 4). In contrast, very steep isotherms were always obtained for binding when **11** and **13** were used as hosts regardless of the concentration of the interacting species used in the titrations. The non-linear fitting of the experimental data with a 1:1 binding isotherm was in fact very poor since the conditions of the Weber parameter p (see Exp. Sect.) were never entirely satisfied during the experiments[15] due to the high efficiency of binding experienced by these receptors.

The recognition behaviour of **11**–**13** was thus evaluated by UV/Vis spectroscopic titrations. A solution of the host ($2–5 \times 10^{-5}$ M) in $CHCl_3$ was titrated with a solution of the TBA salt ($2–5 \times 10^{-4}$ M) in $CHCl_3$. Upon complexation all hosts except for **12** showed a bathochromic shift of the main absorbing band with the formation of an isosbestic point. All the spectroscopic titration curves were fitted with the Specfit/32 software.[24] A non-linear least-squares treatment of the spectroscopic data applied to a 1:1 stoichiometry complexation model gave the binding constants reported in Table 4.

The marked effect of the substituent X on the binding efficiency is well evidenced by comparison of the binding constants calculated for **11** (X = $SO_2C_8H_{17}$) and **13** (X = NO_2) with that calculated for **12** (X = H). The introduction of electron-withdrawing substituents leads to stronger binding with both anions. Although this effect was expected for **13** on the basis of previously reported results,[25] the binding efficiency experienced by **11** confirms the hypothesis that the electron-withdrawing character of the $SO_2C_8H_{17}$ group can be successfully exploited for the preparation of more lipophilic urea-based receptors.

The good solubility properties of **11** prompted us to explore the possibility of employing the amine **9** in the preparation of new lipophilic diphenylurea derivatives. Compound **9** was converted by reaction with phenyl isocyanate and triphosgene into the unsymmetrical (**14**) and symmetrical (**15**) urea derivatives in 60 and 50% yields, respectively (see Scheme 4).

The binding properties of the new diphenylurea derivatives **14** and **15** towards acetate, chloride and fluoride, as TBA salts, were analysed in chloroform solution. UV/Vis



Scheme 4. Synthesis of the new lipophilic urea derivatives **14** and **15**.

titrations were carried out by using the same experimental conditions as employed for the binding studies of **11**–**13**. During the titrations a bathochromic shift of the receptors' main absorbing band was always observed upon addition of aliquots of solutions of the salts with the formation of an isosbestic point. It should, however, be pointed out that the addition of an excess of the guest solution usually induced a supplementary redshift of the maximum of the band corresponding to the complexed species. This effect was negligible for **14**, whereas it was very noticeable during the titration of **15**, especially with TBAAc and TBAF. In particular, the spectra reported in Figure 5 (a) shows that the addition of 1 equivalent of the acetate solution determines a redshift of the main absorbing band of **15** from λ = 282 to 298 nm with the formation of a definite isosbestic point (λ = 286 nm). The addition of an excess of the acetate solution causes a further drift of the maximum to λ = 302 nm.

In principle, this additional redshift observed during the titration of **15** could be ascribed to several phenomena such as dilution effects, variation of the solution ionic strength and the formation of adducts with different stoichiometries. Considering that this final effect could substantially affect the correct determination of binding constants, the stoichiometry of the binding was verified by the application of continuous variation methods. These experiments evidenced a change in the maxima of the Job plots as a function of the wavelength used for its determination. This behaviour could be ascribed either to a change in the binding stoichiometry during the titration or to self-association phenomena.[26] The self-association of both hosts was thus evalu-

Table 4. Absorption spectral parameters and binding constants ($\log K$) for the complexation of **11**–**13** with TBA acetate and chloride in $CHCl_3$.[a,b]

Host	λ_H(max.) [nm]	ε_H [$mol^{-1}\,L\,cm^{-1}$]	TBAAc			TBACl		
			λ_{HG}(max.) [nm]	ε_{HG} [$mol^{-1}\,L\,cm^{-1}$]	$\log K_{11}$[c]	λ_{HG}(max.) [nm]	ε_{HG} [$mol^{-1}\,L\,cm^{-1}$]	$\log K_{11}$[c]
11	259	2.4×10^5	280	2.3×10^5	4.73(4)	270	2.6×10^5	4.4(1)
12[d]	277	2.1×10^3	277	4.2×10^3	3.46(2)	277	4.8×10^3	2.91(5)
13	325	1.1×10^4	365	1.7×10^4	4.88(3)	353	1.4×10^4	4.22(2)

[a] Determined by UV/Vis spectroscopy in $CHCl_3$ (T = 297 K). [b] λ_H(max.) and λ_{HG}(max.) represent the wavelength of the main absorbing band of the free host and of the complex, respectively. [c] The uncertainty in the last figure is given in parentheses. [d] The binding constants for host **12** were also calculated by ^1H NMR spectroscopic measurements in $CDCl_3$ (T = 300 K), affording the following results: $\log K$(TBAAc) = 3.5(6) and $\log K$(TBACl) = 2.8(5).

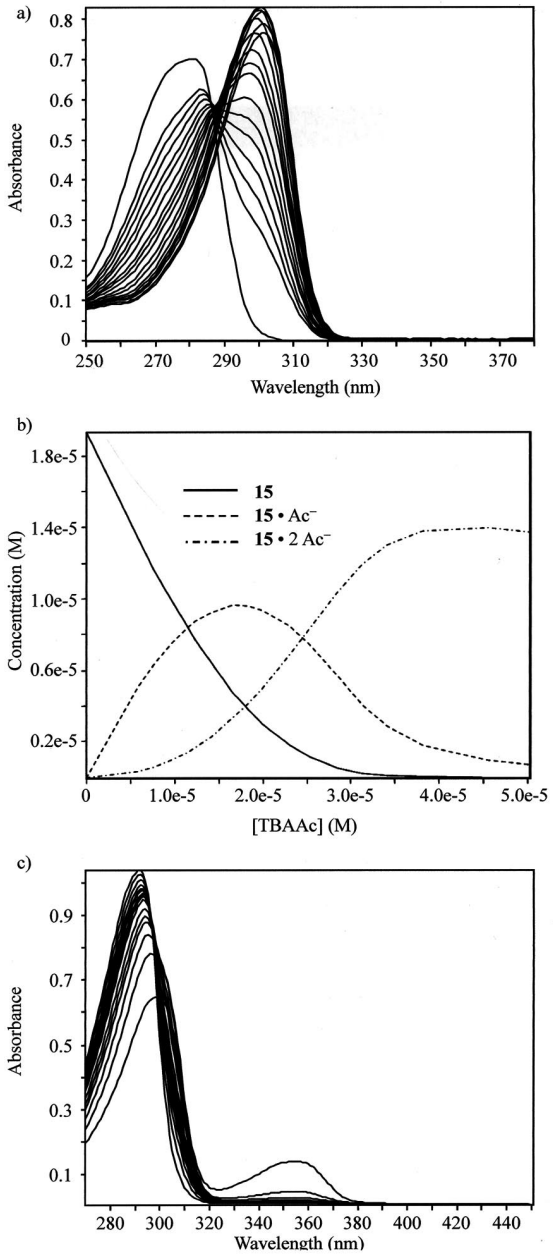


Figure 5. a) UV/Vis spectra for the titration of a solution of **15** [1.9×10^{-5} M] with a solution of TBAAc [2.0×10^{-4} M] in $CHCl_3$; b) distribution diagram for the chromophoric species present in solution during the titration of **15** with TBAAc; c) UV/Vis spectra for the titration of **15** (1.9×10^{-5} M) with TBAF (2.0×10^{-4} M) in DMSO.

ated by ^{1}H NMR dilution experiments. The chemical shift variation of the NH singlet was monitored in $CDCl_3$ upon dilution of the host solution from 5×10^{-2} to 9.8×10^{-4} M. In this concentration range the variation of the NH chemical shift of **15** was $\Delta\delta$ = 0.35 ppm. Application of the isodesmic model[12] gave reasonable results by considering the formation of dimers to have a self-association constant of 180 ± 30 M^{-1}. Although not negligible, the self-association of **15** cannot fully account for the deviation recorded in the UV titration experiments. In fact, any attempt to fit the spectroscopic data by considering the host dimerization process along with 1:1 complexation did not give satisfactory results. The spectroscopic data collected during the titration experiments of both receptors were thus analysed by using the evolving factor analysis (EFA)[27] tool implemented in Specfit/32.[24]

The factor analysis applied to the titrations of **14** always revealed the presence of only two chromophoric species in solution, that is, the free receptor and the corresponding 1:1 adduct. For this receptor the spectroscopic data were thus fitted by applying a pure 1:1 binding model. The calculated binding constants ($\log K_{11}$) were all characterised by satisfactory experimental errors (see Table 5). The EFA for **15** revealed a possible deviation from a pure 1:1 complexation model. With both TBACl and TBAAc more than two absorbing species might be simultaneously present in solution. The spectroscopic data were thus treated by using different binding models, as described by Equations (1), (2) and (3), where RH is the urea receptor and A^- the anion guest.

$$RH + A^- \rightleftharpoons [RH\cdots A]^- \quad (1)$$

$$[RH\cdots A]^- + RH \rightleftharpoons [RH\cdots A\cdots RH]^- \quad (2)$$

$$[RH\cdots A]^- + A^- \rightleftharpoons R^- + [HA_2]^- \quad (3)$$

With TBACl comparable results were obtained by fitting the data either with a simple 1:1 binding model ($\log K_{11} = 5.9 \pm 0.1$) or by considering two simultaneous equilibria, Equation (1) and Equation (2), with the formation of a 2:1 host–guest adduct along with the 1:1 adduct (see Table 5). The 2:1 adduct is probably present in solution at the beginning of the titration when **15** is present in large excess with respect to Cl^-. Such an adduct then dissociates to yield the 1:1 complex as the concentration of the salt increases in solution due to the large binding constant governing the first equilibrium (see Supporting Information for the distribution diagram).

In the case of TBAAc, application of the 1:1 binding model afforded a $\log K_{11} = 5.34 \pm 0.08$ with a satisfactory experimental error. However, bearing in mind the previous EFA results, good fittings of the spectroscopic data were also obtained that indicated the possible formation of, along with the 1:1 complex, an adduct with a 1:2 host–guest stoichiometry. This adduct started to appear in solution when more than 1 equivalent of TBAAc was added (see Figure 5, b). Application of this binding model afforded a $\log K_{11} = 6.7 \pm 0.1$ and a $\log K_{12} = 6.0 \pm 0.1$ and the maxima of the bands corresponding to the 1:1 and 1:2 adducts were found at λ = 298 (ε = 49200 $M^{-1}cm^{-1}$) and 302 nm (ε = 53700 $M^{-1}cm^{-1}$), respectively.

The nature of the possible 1:2 adduct formed between **15** and acetate in chloroform solution is, however, difficult to rationalise. Fabbrizzi and co-workers recently showed that in the more polar acetonitrile urea-based receptors, characterised by very acidic NH groups, can give rise either to oxoanions or fluoride complexes having a 1:2 host–guest stoichiometry.[3f–3i,28] The formation of these unusual ad-

Table 5. Absorption spectral parameters and binding constants for the complexation of receptors **14** and **15** with tetrabutylammonium acetate, chloride and fluoride, as calculated by UV/Vis titration experiments in $CHCl_3$ and DMSO (T = 297 K).

Guest	Solvent	**14**			**15**				
		λ_H(max.) [nm][a]	λ_{HG}(max.) [nm][a]	log K_{11}[b]	λ_H(max.) [nm][a]	λ_{HG}(max.) [nm][a]	log K_{11}[b]	log K_{12}[b]	log K_{21}[b]
TBAAc	$CHCl_3$	266	293	4.63(9)	282	298	6.7(1)[d]	6.0(1)	
	DMSO	282	292	3.77(3)	292	303	3.22(5)		
TBAF	$CHCl_3$	266	286	5.10(3)	283	297	6.4(4)		
	DMSO	283	295; 347[c]	2.9(1)	292	303; 356[c]	3.2(1)		
TBACl	$CHCl_3$	267	287	4.74(3)	284	296	6.02(8)[d]		4.6(1)

[a] λ_H(max.) and λ_{HG}(max.) indicate the wavelength of the main absorbing band of the free host and of the complex, respectively. [b] The uncertainty of the last figure is given in parentheses. [c] Wavelength of the new absorbing band that develops after the addition of more than 1 equivalent of the salt. [d] The binding constants (log K) calculated assuming only the formation of the 1:1 host–guest adduct were 5.9(1) and 5.34(8) for TBAAc and TBACl, respectively.

ducts was explained on the basis of the two-step equilibria described by Equation (1) and Equation (3). In the second step the hydrogen-bonded complex undergoes proton exchange with a second anion leaving a deprotonated species that is responsible for the development of a new band, usually at a longer wavelength, in the corresponding UV spectrum. The occurrence of the second equilibrium is related to several factors such as a) the acidity of the urea derivative, b) the basicity of the anion, c) the stabilisation of the charged host through delocalisation and d) the stability of the $[HA_2]^-$ species.[3h] It is also reasonable to foresee that the polarity of the media can sensibly affect the stability of the products of the second equilibria. Indeed, over the course of the titrations of **14** and **15** with both acetate and fluoride in chloroform solution there was no evidence of host deprotonation. In contrast, when the titration experiments were carried out in the more polar DMSO, in spite of a general decrease in the binding efficiency (see Table 5), weak absorption bands start to appear in the UV spectra after the addition of more than 1 equivalent of TBAF (see Figure 5, c). The occurrence of these new bands exclusively in the titration experiments with TBAF and not with TBAAc is consistent with the findings of Fabbrizzi and coworkers.[3h] The acetate anion can in fact form stable bifurcated 1:1 hydrogen-bonded complexes with **14** and **15** and the host deprotonation becomes less favoured than with fluoride.

These findings can also be useful in part to explain the redshift of the 1:1 complex's main absorbing band observed in chloroform when more than 1 equivalent of TBAAc was added to a solution of **15**. This shift can be ascribed to an incipient host–guest proton exchange induced by a neighbouring acetate anion that changes the overall polarity of the 1:1 adduct.

Conclusions

From the data reported in the present study it appears that the recognition of anions in solvents of low polarity by a series of structurally related urea-type acyclic hosts is governed both by conformational and electronic effects induced by the nature of the spacer Y bridging the hydrogen-bond donor NH groups. Among the compounds studied, the urea host **4** showed better recognition in chloroform solution towards the anion guests chosen as representative of spherical and planar anions. The complexing behaviour of hosts **1**–**4** has been explained also with the aid of molecular mechanics and DFT studies. These simulations showed that the urea **4** is the most preorganised among the hosts examined. The better complexing properties of thiourea **3** compared with urea **4** in more polar solvents such as DMSO and acetonitrile are mostly a result of the competing effect of the solvent molecules for the binding site inserted in **4**.

Moving on from these results, new urea-based receptors **14** and **15**, characterised by lipophilic electron-withdrawing groups on their phenyl units, have been synthesised. The interesting binding results obtained with these hosts indicate that alkylsulfonyl substituents are useful groups for enhancing the hydrogen-bond donor ability of these compounds without depressing their solubility properties in organic solvents, as found with nitro substituents. These findings lead to the possibility of employing such derivatives as non-covalent catalysts in reactions operating in low polar solvents under general acid catalysis conditions.

Experimental Section

All reactions were carried out under nitrogen. All solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use. Column chromatography was performed on silica gel 63–200 mesh. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Melting points are uncorrected. Compounds **2**,[29] **3**,[30] **4**,[31] **5**,[32] and **10**[33] were synthesised according to reported procedures. All other reagents were of reagent grade quality as obtained from commercial suppliers and were used without further purification.

***N*-(1-Benzylamino-1-phenylaminomethylidene)-4-methylbenzenesulfonamide (1):** NaH (0.35 g, 14.6 mmol) was added to a solution of 4-methylbenzenesulfonamide (2.5 g, 14.6 mmol) in dry DMF (100 mL), maintained at 0 °C through an external ice bath. After stirring for 15 min, phenyl isothiocyanate (2 g, 14.8 mmol) was added. The resulting solution was stirred for 30 min at 60 °C, cooled to room temperature and then benzylamine (1.6 g, 14.6 mmol) was slowly added. Upon addition of $HgCl_2$ (4 g, 14.6 mmol) a black solid precipitated from the solution which was filtered off through a plug of Celite. The collected filtrate was evaporated to dryness under vacuum and the residue taken up with ethyl acetate (100 mL) and with a saturated aqueous solution of Na_2CO_3

(100 mL). The separated organic layer was washed with water up to neutrality, dried with Na_2SO_4 and the solvents evaporated to dryness under reduced pressure. Purification of the solid residue by column chromatography (hexane/ethyl acetate = 2:1) afforded 1.7 g (30%) of **1** as a white solid (m.p. 147–149 °C). ^{1}H NMR (300 MHz): δ = 2.41 (s, 3 H), 4.48 (d, J = 5.7 Hz, 2 H), 5.14 (br. s, 1 H), 7.1–7.2 (m, 3 H), 7.2–7.3 (2 m, 6 H), 7.76 (d, J = 8.2 Hz, 2 H), 9.1 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 21.4, 45.2, 126.0, 127.4, 127.6, 128.6, 129.1, 130.1, 135.1, 140.7, 141.9, 153.9 ppm. MS [CI(+)]: m/z = 381 [MH + 1]$^+$. $C_{21}H_{21}N_3O_2S$ (379.48): calcd. C 66.47, H 5.58, N 11.07, S 8.45; found C 66.20, H 6.01, N 10.95, S 8.32.

1-Nitro-4-(octylsulfanyl)benzene (7): 1-Octanethiol (8.8 g, 60.2 mmol) and KOH (3.4 g, 60.5 mmol) were added to a solution of 1-chloro-4-nitrobenzene (**6**) (10 g, 63.5 mmol) in dry DMF (70 mL). The resulting reaction mixture was stirred at 100 °C for 6 h and then the solvent was evaporated to dryness under reduced pressure. The solid residue was taken up with a 10% aqueous solution of HCl (100 mL) and CH_2Cl_2 (100 mL). The organic layer was separated, washed with water up to neutrality, dried with Na_2SO_4 and the solvent completely evaporated under reduced pressure. The oily residue was taken up with cold methanol to afford 11.2 g (70%) of **7** as a yellowish solid which was collected by filtration (m.p. 31–32 °C; ref.[34] 29.5–31.0). ^{1}H NMR (300 MHz): δ = 0.88 (br. t, 3 H), 1.2–1.4, 1.4–1.5 and 1.6–1.8 (3 m, 12 H), 3.00 (t, J = 7.2 Hz, 2 H), 7.29 (d, J = 8.9 Hz, 2 H), 8.10 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.5, 28.4, 28.8, 29.0, 29.05, 31.7, 31.9, 123.8, 125.8, 144.7, 148.1 ppm. MS [EI(+)]: m/z (%) = 267 (100) [M]$^+$. $C_{14}H_{21}NO_2S$ (267.39): calcd. C 62.89, H 7.92, N 5.24, S 11.99; found C 63.08, H 7.92, N 5.40, S 11.62.

1-Nitro-4-(octylsulfonyl)benzene (8): A solution of 3-chloroperbenzoic acid (3.8 g, 22.4 mmol) in CH_2Cl_2 (150 mL) was added dropwise to a solution of **7** (5 g, 18.7 mmol) in CH_2Cl_2 (250 mL), maintained at 0 °C through an external ice bath. The resulting reaction mixture was stirred at room temperature for 4 h, then washed in turn with a 38–40% w/v aqueous solution of $NaHSO_3$ and with a saturated aqueous solution $NaHCO_3$. The separated organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the oily residue by column chromatography (hexane/ethyl acetate = 4:1), afforded 3.65 g (65%) of **8** as a pale yellow fluffy solid (m.p. 49.5–50 °C). ^{1}H NMR (300 MHz): δ = 0.88 (br. t, 3 H), 1.2–1.4, 1.4–1.5 and 1.6–1.8 (3 m, 12 H), 3.15 (br. t, 2 H), 8.14 (d, J = 8.8 Hz, 2 H), 8.44 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 13.9, 22.4, 28.1, 28.7, 28.8, 31.5, 56.1, 124.4, 129.5, 144.8, 151.2 ppm. MS [EI(+)]: m/z (%) = 299 (30) [M]$^+$. $C_{14}H_{21}NO_4S$ (299.39): calcd. C 56.17, H 7.07, N 4.68, S 10.71; found C 56.01, H 7.01, N 4.69, S 10.47.

4-(Octylsulfonyl)aniline (9): $SnCl_2{\cdot}2H_2O$ (7.5 g, 33.2 mmol) was added to a solution of **8** (2 g, 6.7 mmol) in ethanol (150 mL). The resulting heterogeneous solution was refluxed whilst stirring for 4 h and then the solvent was completely removed under reduced pressure. The residue was taken up with 1 N aqueous solution of NaOH (100 mL) and extracted with ethyl acetate. The separated organic phase was dried with Na_2SO_4 and the solvents evaporated to dryness under reduced pressure. Purification of the solid residue by column chromatography (hexane/ethyl acetate = 3:2) afforded 1.3 g (70%) of **9** as a white solid (m.p. 97.8–98.5 °C). ^{1}H NMR (300 MHz): δ = 0.88 (t, J = 7.2 Hz, 3 H), 1.2–1.4 and 1.6–1.7 (2 m, 12 H), 3.03 (br. t, 2 H), 4.2 (br. s, 2 H), 6.73 (d, J = 8.7 Hz, 2 H), 7.67 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.5, 22.8, 28.2, 28.8, 28.9, 31.6, 56.7, 114.0, 127.3, 130.1, 151.1 ppm. MS [EI(+)]: m/z (%) = 269 (20) [M]$^+$. $C_{14}H_{23}NO_2S$ (269.40): calcd. C 62.42, H 8.61, N 5.20, S 11.90; found C 62.70, H 8.57, N 5.11, S 11.91.

General Procedure for the Synthesis of Urea Derivatives 11–13: A solution of the appropriate isocyanate (15 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a solution of the amine **9** or **10** (15 mmol) in dry CH_2Cl_2 (30 mL), maintained at 0 °C through an external ice bath. The resulting mixture was stirred at room temperature for 48–72 h and then the solvent was evaporated to dryness under reduced pressure. The residue was taken up with a 10% aqueous solution of HCl (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with water up to neutrality, dried with Na_2SO_4 and the solvent evaporated to dryness under reduced pressure.

1-Benzyl-3-[4-(octylsulfonyl)phenyl]urea (11): Amine **9** and benzyl isocyanate were used as reagents. Purification of the residue by column chromatography (hexane/ethyl acetate = 7:3) afforded 2.3 g (38%) of **11** as a white solid (m.p. 76.0–76.8 °C). ^{1}H NMR (300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.2–1.4 and 1.5–1.7 (2 m, 12 H), 3.02 (br. t, 2 H), 4.36 (d, J = 5.7 Hz, 2 H), 6.11 (t, J = 5.7 Hz, 1 H), 7.1–7.3 (m, 5 H), 7.47 (d, J = 9.0 Hz, 2 H), 7.62 (d, J = 9.0 Hz, 2 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.4, 22.6, 28.1, 28.8, 28.9, 31.6, 44.0, 56.4, 118.1, 127.3, 128.6, 129.1, 138.5, 144.8, 154.9 ppm. MS [ESI(+)]: m/z (%) = 425 (100) [M + Na]$^+$. $C_{22}H_{30}N_2O_3S$ (402.55): calcd. C 65.64, H 7.51, N 6.96, S 7.97; found C 65.50, H 7.38, N 7.15, S 7.62.

1-[4-(Octyloxy)benzyl]-3-phenylurea (12): Amine **10** and phenyl isocyanate were used as reagents. Purification of the residue by recrystallisation from methanol gave 2.1 g (40%) of pure **12** (m.p. 101–102 °C). ^{1}H NMR (300 MHz): δ = 0.88 (br. t, 3 H), 1.3–1.5 (m, 10 H), 1.7–1.8 (m, 2 H), 3.92 (t, J = 6.6 Hz, 2 H), 4.79 (d, J = 5.4 Hz, 2 H), 6.2 (br. t, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 7.1–7.2 (m, J = 5 Hz), 7.39 (t, J = 7.5 Hz, 2 H), 7.69 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.6, 26.0, 29.2, 29.3, 31.8, 43.5, 68.0, 114.5, 120.6, 123.4, 125.2, 128.6, 129.0, 130.6, 138.6, 156.1, 158.3 ppm. MS [CI(+)]: m/z = 355 [MH]$^+$. $C_{22}H_{30}N_2O_2$ (354.49): calcd. C 74.54, H 8.53, N 7.90; found C 74.61, H 8.42, N 7.96.

1-(4-Nitrophenyl)-3-[4-(octyloxy)benzyl]urea (13): Amine **10** and 4-nitrophenyl isocyanate were used as reagents. Purification of the residue by recrystallisation from methanol gave 4.2 g (70%) of pure **13** (m.p. 162–163 °C). ^{1}H NMR (300 MHz, $CDCl_3$/[D$_6$]DMSO): δ = 0.63 (br. t, 3 H), 1.0–1.2 (m, 10 H), 1.4–1.6 (m, 2 H), 3.68 (t, J = 6.5 Hz, 2 H), 4.08 (d, J = 5.4 Hz, 2 H), 6.2 (br. t, 1 H), 6.61 (d, J = 8.4 Hz, 2 H), 6.98 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 9.0 Hz, 2 H), 7.85 (d, J = 9.0 Hz, 2 H), 8.6 (br. s, 1 H) ppm.^{13}C NMR: δ = (75 MHz, $CDCl_3$/[D$_6$]DMSO): δ = 13.9, 22.3, 25.7, 28.9, 29.0, 31.5, 43.0, 67.8, 114.3, 116.7, 124.8, 128.7, 130.7, 139.9, 146.7, 154.7, 158.2 ppm. MS [CI(+)]: m/z = 400 [MH]$^+$. $C_{22}H_{29}N_3O_4$ (399.48): calcd. C 66.14, H 7.32, N 10.52; found C 65.81, H 7.28, N 10.30.

1-[4-(Octylsulfonyl)phenyl]-3-phenylurea (14): Phenyl isocyanate (0.12 g, 1.0 mmol) was added to a solution of **9** (0.2 g, 0.7 mmol) in dry THF (50 mL). The resulting mixture was stirred at room temperature for 48 h and then the solvent was evaporated to dryness under reduced pressure. Purification of the solid residue by column chromatography (hexane/ethyl acetate = 3:2) followed by recrystallisation with methanol afforded 0.14 g (60%) of **14** as a white solid (m.p. 174–175 °C). ^{1}H NMR (300 MHz): δ = 0.88 (br. t, 3 H), 1.2–1.4 and 1.5–1.8 (2 m, 12 H), 3.11 (br. t, 2 H), 7.09 (t, J = 7.5 Hz, 1 H), 7.59 (t, J = 7.4 Hz, 2 H), 7.72 (t, J = 7.4 Hz, 1 H), 7.82 (d, J = 8.7 Hz, 2 H), 7.92 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H), 9.0 (br. s, 1 H), 11.3 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.5, 22.7, 28.2, 28.9, 29.0, 31.6, 56.5, 118.7, 120.6, 124.3, 129.2, 131.4, 144.4, 152.5 ppm. MS [ESI(+)]: m/z (%)

= 411 (100) $[M + Na]^+$. $C_{21}H_{28}N_2O_3S$ (388.52): calcd. C 64.92, H 7.26, N 7.21, S 8.25; found C 64.66, H 7.18, N 6.93, S 8.09.

1,3-Bis[4-(octylsulfonyl)phenyl]urea (15): Triphosgene (0.25 g, 0.8 mmol) was added to a solution of **9** (0.5 g, 1.9 mmol) in dry THF (50 mL). The resulting mixture was stirred at room temperature for 48 h and then the solvent was evaporated to dryness under reduced pressure. Purification of the solid residue by column chromatography (hexane/ethyl acetate = 1:1) followed by recrystallisation with methanol afforded 0.52 g (50%) of **15** as a white solid (m.p. 158.5–159.5 °C). ^{1}H NMR (300 MHz): δ = 0.85 (br. t, 6 H), 1.2–1.4 and 1.6–1.8 (2 m, 24 H), 3.14 (br. t, 4 H), 7.66 (d, J = 8.7 Hz, 4 H), 7.81 (d, J = 8.7 Hz, 4 H), 8.0 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.5, 22.7, 28.2, 28.8, 28.9, 31.5, 56.5, 118.7, 129.2, 131.5, 144.2, 151.4 ppm. MS [ESI(+)]: m/z (%) = 587 (100) $[M + Na]^+$. $C_{29}H_{44}N_2O_5S_2$ (564.80): calcd. C 61.67, H 7.85, N 4.96, S 11.35; found C 61.40, H 8.18, N 5.13, S 11.11.

Continuous Variation ^{1}H NMR Methods (Job Plot): Aliquots of stock solutions in $CDCl_3$ of **4** and of each of the TBA salts were added to several 5-mm NMR tubes in different ratios. The relative concentrations of the two interacting species were varied continuously in the tubes but their sum was kept constant (1.45×10^{-3} M). In this way, 14 samples were prepared in which the mole fraction (x) of **4** was varied from 0.1 to 1. A ^{1}H NMR spectrum was recorded for each sample. The corresponding Job plot was obtained by plotting a property proportional to the complex concentration, $(\delta_{obs} - \delta_{free})[\mathbf{4}]_0$, vs. the mole fraction of **4**. δ_{obs} and δ_{free} represent the chemical shifts of the host NH proton in the complex and in the free ligand, respectively, and $[\mathbf{4}]_0$ is the total concentration of **4** in each tube. The stoichiometry of binding was obtained from the value of the mole fraction in the abscissa corresponding to the maximum of the curve. For a host–guest ratio of 1:1, x = 0.5.

^{1}H NMR Titrations: Solutions (500 μL) of hosts **1**–**4** and **12** in $CDCl_3$ (usually $c = 1.2 \times 10^{-2}$ M) were prepared in a 5-mm NMR tube and small aliquots of solutions of tetrabutylammonium salts (usually $c = 1.2 \times 10^{-1}$ M) in $CDCl_3$ were added. A spectrum was recorded after each addition. The binding constants were calculated by using the Wilcox equation[15] implemented in the Sigmaplot package[35] by the non-linear fitting of the chemical shift variation of the host's NH protons. For each titration experiment the Weber parameter p = [concentration of complex]/[maximum possible concentration of complex] was determined according to the calculated binding constant. If necessary the concentrations of the two reactants were adjusted and the NMR titration experiment repeated to explore the proper p range (0.2–0.8).

Cambridge Structural Database: X-ray diffraction crystal structures of compounds having the general formula PhNH–Y–NHR(alkyl) were retrieved from the Cambridge Structural Database (CSD) and analysed with Mercury.[36] Searches yielded 12 structures for Y = O, eight structures for Y = S, one structure for Y = SO_2 although 39 structures were found for *N*,*N*-dialkylsulfamide derivatives.

Structure Calculations: The Monte Carlo search and determinations of the rotational barriers were performed by using the MMFF94 force field[37] implemented in the Spartan 4.0 molecular modelling software.[38] For **3** and **4**, a modified force field (MMFF94+) was implemented in the Spartan package, in accord with the torsional parameters reported in ref.[16]. The figures of the most representative conformers of **1**–**4** and the corresponding complexes with chloride were created with PLATON for Windows.[39] Further structure minimisation and molecular electrostatic potential (MEP) calculations on **2**–**4** were performed with PC GAMESS[40] by using ab initio and DFT methods. Illustrations of the MEP plotted on van der Waals molecular surfaces were obtained with Molekel.[41]

UV/Vis Titrations: Spectroscopic titrations with **11**–**15** were carried out in a quartz cuvette (path length = 1 cm) maintained at 293 K through an external thermostat by adding small aliquots of solutions of the guests (usually 2×10^{-4} M) in chloroform to a solution of the hosts in chloroform (usually 2×10^{-5} M). The spectroscopic data were collected in the 250–650 nm wavelength range. The binding constants were calculated by selecting different binding models with the Specfit/32[24] software. The fitting of the spectroscopic data was carried out by considering the optical variation for the 250–380 nm wavelength range. For each titration experiment the Weber parameter p = [concentration of complex]/[maximum possible concentration of complex] was determined from the calculated binding constant. If necessary the concentrations of the two reactants were adjusted and the UV/Vis titration experiment repeated to explore the proper p range (0.2–0.8).

Supporting Information (see also the footnote on the first page of this article): Spectral characterization (^{1}H and ^{13}C NMR) of new compounds **1** and **11**–**15**, calculated interconversion barriers for the rotation around the (Ph)C–N–C–O(S) dihedral from –180 to 180° in **3** and **4**, molecular electrostatic potential (MEP) plotted on the van der Waals surfaces of **2**–**4** and UV spectra with the species distribution diagram for the titration of **15** with TBACl (16 pages).

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