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ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · MAY 2011

Impact Factor: 5.73 · DOI: 10.1002/chem.201003411 · Source: PubMed

CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201003411

Urea-, Squaramide-, and Sulfonamide-Based Anion Receptors: A Thermodynamic Study

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Abstract: In this work, we compare the anion-binding capabilities of receptors **1**–**5**, characterized by similar structures, but possessing different hydrogen-bond-donor moieties (urea, squaramide, and sulfonamide). The presence of chromophoric substituents on the receptor's skeleton allowed the determination of association constants by performing UV/Vis titrations with the investigated anions on solutions of the receptors in pure acetonitrile. Additional quantitative studies of the anion-binding properties of receptors **1**–**5** were performed by isothermal titration calorimetry (ITC). The experimental results indicated that **1** and **2** formed 1:1 hydrogen-bonded complexes with most of the anions investigated. In the case of receptors **3**–**5**, the formation of the 1:1 adduct was observed only with anions of low basicity (i.e., chloride, bromide, iodide, and hydrogen sulfate). With more basic anions (i.e., acetate and dihydrogen phosphate), both spectrophotometric and ITC titrations accounted for the deprotonation of the sulfonamide group, involving the formation of the conjugated base of the receptor.

Keywords: anion receptors · calorimetry · hydrogen bonds · molecular recognition · supramolecular chemistry

Introduction

Over the past decade, many neutral receptors for anionic species have been developed. Most of them contain ureas, thioureas, squaramides, pyrroles, amides, and sulfonamides as the binding groups, for which the interaction with anions is mainly based on hydrogen bonding, involving polarized N–H fragments.[1] Except for pyrroles, the hydrogen-bond-donor ability and the polarization of N–H depend on the presence of a proximate electron-withdrawing group (i.e., C=O for ureas,[2a] amides, and squaramides;[3] C=S and O=S=O for thioureas and sulfonamides[4]). In the case of urea- and thiourea-based receptors, the Y shape of the donor group has been demonstrated to play an important role in anion recognition, in particular, by enhancing the receptor's affinity towards complementary Y-shaped anions, such as carboxylates.[2b] For plain amide and sulfonamide groups, the affinity towards anions can be increased and tuned by providing the receptor with several hydrogen-bond donor groups, placed at well-defined distances and geometries, according to the size and shape of the target anion. Higher selectivity can be achieved by placing the donor groups around the cavity of macrocycles[5] or cage-shaped receptors.[6] The hydrogen-bond donor ability of N–H groups can be further increased by introducing electron-withdrawing substituents on the receptor framework. Urea groups appended to electron-poor aromatic rings are known to display stronger affinity towards anions with respect to aliphatic ureas. Besides enhancing the hydrogen-bond donating tendencies, electron-withdrawing groups generally increase the acidity of N–H bonds, thus favoring proton-transfer processes.[7] In particular, it has been demonstrated that the presence of 4-nitrophenyl groups appended to urea deeply affects N–H acidity, thus favoring proton transfer to strongly basic anions, such as fluoride, in acetonitrile.[2b] The 4-nitrophenyl group also provides urea with a powerful chromophore, thus enabling the operator to distinguish the nature of the interaction with anions, that is, between proton transfer and hydrogen bonding, by UV/Vis spectroscopy. Recently, we compared the anion-binding abilities of the receptor *N*,*N*′-di(4-nitrophenyl)urea with those of a squaramide-based analogue.[8] This comparative study indicated, quite surprisingly, that, despite the significant geometric differences between urea and squaramide, the two receptors displayed very similar association constants towards oxo-anions. This result reinforced the hypothesis that, in oxo-anion recognition, anion basicity plays the major role. On the other hand, the enhanced affinity of the squaramide receptor towards halides seemed to depend on a more favorable orientation of the 4-nitrophenyl rings, with respect to the urea analogue.

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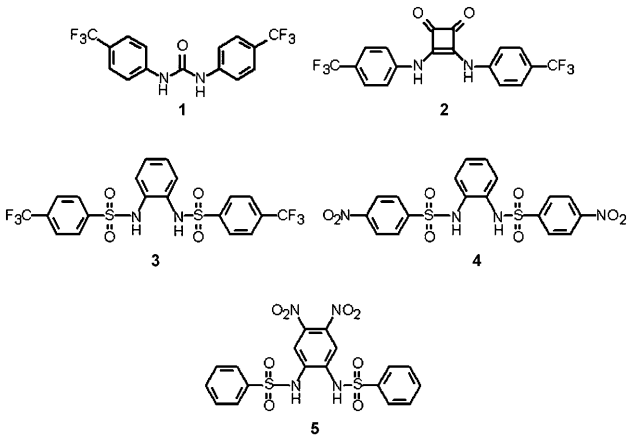
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003411.

In the case of squaramide, the two phenyl rings converge towards the anion, thus stabilizing the adduct through additional interactions between the polarized C–H fragments of the phenyl groups and the bound anion.[9] Herein, we extend our study to sulfonamide-based anion receptors. In particular, we compare the anion-binding capabilities of receptors **1**–**5**, characterized by similar structures, but possessing different hydrogen-bond donor moieties (urea, squaramide, and sulfonamide). The presence of chromophoric substituents on the receptor's skeleton allowed the determination of association constants by means of absorption spectroscopy; the results were confirmed by isothermal titration calorimetry (ITC) experiments. ITC also gave the opportunity to study, in depth, anion binding from the thermodynamic point of view and to better understand which thermodynamic contribution, whether enthalpic or entropic, played the major role in selectivity.[10]



Results and Discussion

Spectrophotometric studies: The synthesis of receptors **1**–**5** is reported in the Supporting Information. The affinity of receptors **1**–**5** towards anions was first investigated by UV/Vis spectroscopy. In particular, solutions of receptors **1**–**5** in acetonitrile were titrated with standard solutions of the tetrabutylammonium (TBA^+) salt of the envisaged anion. After each addition of sub-stoichiometric amounts of the anion, the UV/Vis spectrum of the solution was recorded.

Figures 1 and 2 (see below) show the UV/Vis spectra collected over the course of the titration of receptors **1**, **2**, and **5** with chloride and acetate. The titration profiles, plotted as absorbance at a fixed wavelength versus equivalents of anion (X^-), were fitted by means of a non-linear least-squares program,[11] thus the association constants shown in Tables 1 and 2 were obtained. The best titration conditions, for the safe determination of the binding constants, were determined by means of the *p* parameter.[12] The spectrophotometric titrations of receptors **1**, **2** and **5** with TBACl are reported in Figure 1.

Table 1. Association constants (as $\log K$ values) for the interaction of receptors **1**–**5** with anions (as TBA^+ salts) in pure acetonitrile at 25 °C, determined by UV/Vis spectroscopy. Numbers in parentheses are standard deviations to the last significant figure.

Anion	Receptor	$\log K_{11}$[a]	Anion	Receptor	$\log K_{11}$[a]
Cl^-	**1**	4.14(1)	I^-	**1**	<2
	2	5.81(1)		**2**	3.34(1)
	3	3.52(1)		**3**	<2
	4	3.81(1)		**4**	<2
	5	4.38(2)		**5**	<2
Br^-	**1**	3.37(1)	HSO_4^-	**1**	3.10(1)
	2	4.57(1)		**2**	3.93(1)
	3	2.40(3)		**3**	<2
	4	2.73(3)		**4**	<2
	5	3.15(1)		**5**	<2

[a] $\boldsymbol{R}H_2+X^- \rightleftarrows [\boldsymbol{R}H_2\cdots X]^-$.

Table 2. Association and deprotonation constants (in logarithmic units) for the interaction of receptors **1**–**5** with acetate and dihydrogen phosphate (as TBA^+ salts) in pure acetonitrile at 25 °C, determined by UV/Vis spectroscopy.

Anion	$\boldsymbol{n}H_2$	$\log K_{11}$[a]	$\log \beta_{21}$[a]	$\log K_d$[a]
CH_3COO^-	**1**	5.88(1)		
	2	>6		
	3–**5**			>6
$H_2PO_4^-$	**1**	3.37(1)		
	2	4.80(1)	9.05(9)	
	3–**5**			[b]

[a] $\boldsymbol{R}H_2+X^- \rightleftarrows [\boldsymbol{R}H_2\cdots X]^-$ ($\log K_{11}$); $2\boldsymbol{R}H_2+X^- \rightleftarrows [(\boldsymbol{R}H_2)_2\cdots X]^-$ ($\log \beta_{21}$); $\boldsymbol{R}H_2+X^- \rightleftarrows \boldsymbol{R}H^- + HX$ ($\log K_d$). [b] Fitting of the experimental data is not available due to the uncertain stoichiometry of the interaction.

As expected from the formation of hydrogen-bonded adducts, anion addition causes a redshift of the maximum of absorbance in the receptor's spectrum. For receptor **1** (3.8×10^{-4} M in acetonitrile), the band centered at 263 nm, belonging to a charge-transfer transition from the nitrogen atom of the urea unit to the proximate electron-deficient phenyl ring, undergoes a bathochromic shift of about 10 nm over the course of the titration with chloride (6.1×10^{-2} M). The association constant for Equilibrium (1), $\log K_{11}=4.14(1)$, was determined by fitting the titration profile. Figure 1d reports the corresponding distribution diagram, with the superimposed plot of molar absorbance versus the number of equivalents of TBACl.

$$\mathbf{1}H_2 + Cl^- \rightleftharpoons [\mathbf{1}H_2\cdots Cl]^- \quad (1)$$

Upon chloride addition to a solution of receptor **2** (2.0×10^{-5} M) in acetonitrile with TBACl (5.6×10^{-3} M) (see Figure 1b), the band centered at 330 nm, belonging to a charge-transfer transition from the nitrogen atom of the squaramide fragment to the proximate phenyl ring, is redshifted to 344 nm ($\Delta\lambda_{max}=14$ nm) and increases in intensity. Both hyper- and bathochromic effects depend on the increased dipole of the transition due to interactions with the anion. Two isosbestic points, at 268 and 335 nm, persist over the course of the titration. A single equilibrium [Equilibri-

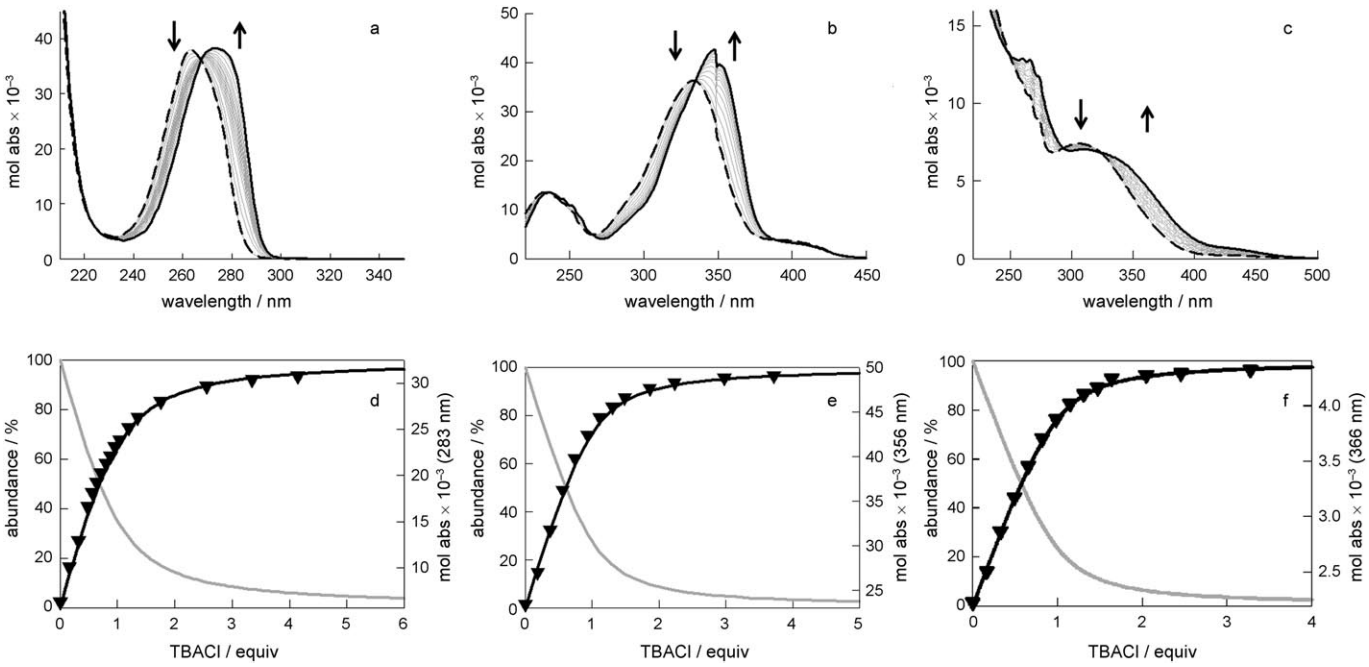


Figure 1. Absorption spectra taken over the course of a) the titration of a solution of **1** (3.8×10^{-4} M) in acetonitrile with a solution of the TBACl (6.1×10^{-2} M), $l=0.1$ cm; b) the titration of **2** (2.0×10^{-5} M) with TBACl (5.6×10^{-3} M), $l=1$ cm; c) the titration of **5** (9.8×10^{-4} M) with TBACl (7.3×10^{-2} M), $l=0.1$ cm. The distribution of species present at the equilibrium in titrations a), b), and c), are shown in d), e), and f), respectively. Gray line: free receptor; black line: bound receptor; black triangles: superimposed plots of molar absorbance (at a fixed wavelength) versus the number of equivalents of TBACl; $T=25$ °C.

um (2)], leading to a 1:1 adduct, is observed ($\log K_{11}=5.81(1)$). The corresponding distribution diagram is reported in Figure 1e.

$$\mathbf{2}H_2+Cl^- \rightleftharpoons [\mathbf{2}H_2\cdots Cl]^- \quad (2)$$

Sulfonamide receptors **3**–**5** were also titrated with TBACl. Bathochromic shifts of the UV/Vis bands and formation of 1:1 adducts were observed for all sulfonamide receptors; the association constants are reported in Table 1. Figure 1c displays the family of spectra collected over the course of the titration of receptor **5** (9.8×10^{-4} M) with TBACl (7.3×10^{-2} M); see Figures S2 and S3 in the Supporting Information for **3** and **4**, respectively. The absorption spectrum of the free receptor presents a benzene-like structured band around 270 nm, attributable to the phenyl groups, and a broad band centered at 306 nm, belonging to the nitro substituents. Also for receptor **5**, chloride induces the redshift of all bands; Equilibrium (3) is characterized by $\log K_{11}=4.38(2)$. The distribution diagram is reported in Figure 1f.

$$\mathbf{5}H_2+Cl^- \rightleftharpoons [\mathbf{5}H_2\cdots Cl]^- \quad (3)$$

Figure 2 shows the spectrophotometric titrations of receptors **1**, **2**, and **5** with $TBACH_3COO$. In particular, Figure 2a and b show the absorption spectra taken over the course of the titrations of receptor **1** and **2**, respectively, with the acetate anion. With respect to chloride, a larger bathochromic shift, accompanied by a hyperchromic effect, is observed ($\Delta\lambda_{max}=18$ nm for **1**; $\Delta\lambda_{max}=20$ nm for **2**). The stronger effect of acetate than chloride reflects the greater affinity of urea and squaramide towards basic anions (see Table 2).

A single equilibrium [Equilibrium (4)] is involved, leading to the formation of a 1:1 adduct. Due to the large association constants, the titrations were performed in dilute solutions. For receptor **2**, the titration profile is too steep to allow accurate determination of the binding constant, see Figure 2e.

$$\boldsymbol{R}H_2+CH_3COO^- \rightleftharpoons [\boldsymbol{R}H_2\cdots CH_3COO]^- \quad (4)$$

Titrations with $TBACH_3COO$ were also performed on **3**–**5**. For sulfonamide-based receptors, the development of new bands in the absorption spectrum, as well as the change in the color of the solution, indicate different interactions. The new bands in the UV/Vis spectra, peculiar to charge-transfer transitions, reach a plateau for 1:1 stoichiometry and can be attributed to the deprotonated form of the receptor. The titration spectra relative to the titration of **5** with the acetate anion are reported in Figure 2c (see Figures S4 and S5 in the Supporting Information for receptors **3** and **4**, respectively). A single equilibrium [Equilibrium (5)] was observed, attributable to a proton-transfer process from the receptor to acetate. The mono-deprotonated form $\mathbf{5}H^-$ is characterized by a charge-transfer transition band at 418 nm, reaching its maximum after the addition of 1 equivalent of anion (see Figure 2f). Due to the formation of a charge-transfer band in the visible region, acetate addition is accompanied by a change in the color of the solution from pale to bright yellow. Even when working at micromolar concentrations,

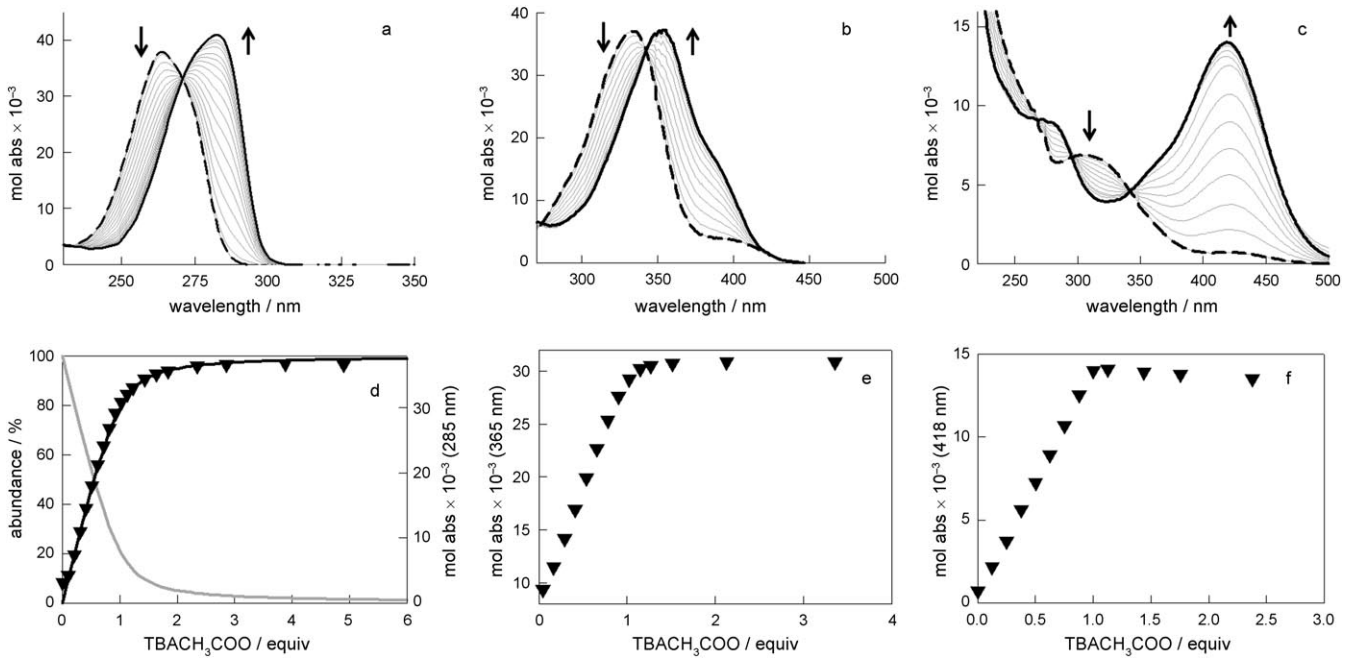


Figure 2. Absorption spectra taken over the course of a) the titration of a solution of **1** (2.0×10^{-5} M) in acetonitrile, with a solution of the $TBACH_3COO$ (2.4×10^{-3} M), $l=1$ cm; b) the titration of **2** (6.7×10^{-6} M) with $TBACH_3COO$ (2.4×10^{-3} M), $l=1$ cm; c) the titration of **5** (8.5×10^{-6} M) with $TBACH_3COO$ (2.4×10^{-3} M), $l=1$ cm. The distribution of the species present at equilibrium in titration a) are shown in d). Gray line: free receptor; black line: bound receptor; black triangles: superimposed plots of molar absorbance versus the number of equivalents of $TBACH_3COO$. Plots shown in e) and f) correspond to the titrations b) and c), respectively.

the experimental data plots of the titrations of **3**–**5** with acetate are characterized by very steep curves. For this reason, the corresponding constants could not be safely determined with non-linear least-squares methods (see Table 2).

$$\mathbf{5}H_2+CH_3COO^- \rightleftharpoons \mathbf{5}H^-+CH_3COOH \quad (5)$$

The receptors have two N–H groups that can interact with a single acceptor atom (as for halides) or with two adjacent oxygen atoms of an oxo-anion. Selectivity in anion binding may be interpreted in terms of anion basicity: the higher the basicity, the stronger the interaction and higher the stability of the hydrogen-bonded adduct.[13] Table 1 reports the binding constants obtained for the interaction of **1**–**5** with Cl^-, Br^-, I^-, and HSO_4^-; the experimental curves could be easily interpreted on the basis of a single equilibrium [Equilibrium (6)], leading to the formation of 1:1 hydrogen-bonded complexes.

$$\boldsymbol{R}H_2+X^- \rightleftharpoons [\boldsymbol{R}H_2\cdots X]^- \quad (6)$$

Among halides, the affinity varies along the series chloride > bromide > iodide, which reflects the decreasing negative-charge density of the anion. The results in Table 1 highlight the superiority of receptor **2** in interacting with halides. The peculiarity of the squaramide-containing aromatic molecules, as hydrogen-bond donors, has been already described by our group[8] and mainly depends on the contribution of the aromatic C–H_α bonds, in the interaction.[9] The cooperation of C–H groups, belonging to electron-deficient aromatic substituents on the receptor, is quite common in the formation of receptor–anion adducts.[14] With the anions reported in Table 1, sulfonamide-based receptors also form 1:1 adducts; anion affinity varies along the series **5** > **4** > **3**. These results indicate that nitro substituents, in particular, those directly conjugated to the N–H donor groups (as in receptor **5**), enhance the hydrogen-bond donor tendencies of the sulfonamide residue. Table 2 shows the equilibrium constants determined for titrations with basic anions: acetate and dihydrogen phosphate. On oxo-anion binding, the two N–H groups of the receptors can interact with two adjacent oxygen atoms of the anion. Receptor **1** forms 1:1 hydrogen-bonded adducts with both basic anions, whereas, for receptor **2**, a single equilibrium was observed only in the titration with acetate. With dihydrogen phosphate, analysis of the UV/Vis spectra indicates the formation of two different adducts characterized by 1:1 and 2:1 receptor/anion stoichiometry, respectively (see Figure S1 in the Supporting Information).

The experimental data could be fitted by taking into account the Equilibria (7) and (8):

$$\mathbf{2}H_2+H_2PO_4^- \rightleftharpoons [\mathbf{2}H_2\cdots H_2PO_4]^- \quad \log K_{11}=4.80 \quad (7)$$

$$\mathbf{2}H_2+[\mathbf{2}H_2\cdots H_2PO_4]^- \rightleftharpoons [(\mathbf{2}H_2)_2\cdots H_2PO_4]^- \quad \log K_{21}=4.25 \quad (8)$$

For receptors **3**–**5**, the acidic properties of the N–H fragments are thought to be responsible for the behavior of the sulfonamides towards basic anions (i.e., acetate and dihydrogen phosphate). In the titration with acetate, a single equilibrium [Equilibrium (9)] was observed, leading to the mono-deprotonated form of the receptor ($\log K_d > 6$, see Table 2).

$$\boldsymbol{R}H_2 + X^- \rightleftharpoons \boldsymbol{R}H^- + HX \quad (9)$$

Proton-transfer processes were also observed with dihydrogen phosphate, as indicated by the development of charge-transfer bands peculiar to the deprotonated species. With dihydrogen phosphate, the stoichiometry of the interaction was more uncertain, probably due to the tendency of the anion to form aggregates, thus the corresponding association constants could not be determined.

The Brønsted acidic behavior of receptors: To clarify the behavior of the receptors towards basic anions, we analyzed the acidic character of **1**–**5** in aqueous solution, by performing potentiometric and pH-spectrophotometric titrations in a mixture of acetonitrile/water (9/1, v/v). The pK_a values obtained are shown in Table 3.

Table 3. pK_a values of receptors **1**–**5** (5.0×10^{-4} M) measured by potentiometric titrations in acetonitrile/water (9/1 v/v; 0.1 M in $TBAPF_6$) at 25 °C. Numbers in parentheses are standard deviations to the last significant figure.

$\boldsymbol{R}H_2$	pK_{a1}[a]	pK_{a2}[a]
1	–	
2	10.9(1)	
3	8.3(1)	
4	8.3(1)	15.0(2)
5	4.3(1)	13.0(2)

[a] $\boldsymbol{R}H_2 + H_2O \leftrightarrows \boldsymbol{n}H^- + H_3O^+$ (pK_{a1}); $\boldsymbol{R}H^- + H_2O \leftrightarrows \boldsymbol{R}^{2-} + H_3O^+$ (pK_{a2}).

The least acidic compound is **1**, for which no deprotonation of the urea group was observed in aqueous solution, followed by **2** with a pK_a value of 10.9(1). The distribution diagrams are given in the Supporting Information (for the squaramide-based derivative, see Figure S6). Among the sulfonamides, receptor **3** undergoes a single deprotonation ($pK_a = 8.3(1)$; see Figure S7 in the Supporting Information); whereas **4** and **5** can dissociate two protons (**4**: $pK_{a1} = 8.3(1)$, $pK_{a2} = 15.0(2)$; **5**: $pK_{a1} = 4.3(1)$, $pK_{a2} = 13.0(2)$), as indicated by both potentiometric and pH-spectrophotometric titrations (see Figures S8 and S9 in the Supporting Information). The most acidic receptor is **5**, for which the two deprotonation steps are accompanied by a change in the color of the solution from bright yellow (first step) to dark red (second step).

The single- and double-deprotonated forms of **5** are characterized by different absorption bands: the mono-deprotonated species presents an intense charge-transfer band at 418 nm, very similar to that observed in the spectrophotometric titration with acetate in pure acetonitrile. The doubly deprotonated species presents two new bands at 370 and 475 nm: the latter is responsible for the red color in solution. The stronger acidic character of **5**, with respect to **3**–**4**, can be attributed to the stabilizing effect, exerted by the two nitro groups, on the negative charge(s) originated by deprotonation. With respect to **3**–**4**, in which the electron-withdrawing groups, either CF_3 or NO_2, are bound to the side arms of the sulfonamide, the two nitro groups in **5** are positioned on the central phenyl fragment and are directly conjugated to the acidic N–H bonds, thus favoring acidic dissociation.

The potentiometric results demonstrate that sulfonamide groups are more acidic than both urea and squaramide in a mixture of water/acetonitrile and reinforce the hypothesis that basic anions can easily induce proton transfer from sulfonamide-based receptors in pure acetonitrile. Further confirmation comes from the pH-spectrophotometric titrations: the final spectrum of the titration of receptors **3**–**5** with acetate in pure acetonitrile corresponds to the absorption bands of the mono-deprotonated species in a mixture of water/acetonitrile.

Calorimetric studies: Additional quantitative studies of the anion-binding properties of receptors **1**–**5** in pure acetonitrile were performed by ITC. In a typical experiment, a solution of the receptor in acetonitrile was added to a solution of the investigated anion, as the TBA^+ salt, in the same solvent.

Figure 3 reports the experimental curves corresponding to the ITC titrations of receptors **1**, **2**, and **5** with TBACl in acetonitrile (for receptors **3** and **4**, see Figures S12a and S13a in the Supporting Information, respectively). The ITC profiles indicate the presence of a single equilibrium in solution [Equilibrium (10)], corresponding to the formation of 1:1 hydrogen-bonded adducts. Similar results were obtained for most of the anions investigated, except for acetate and dihydrogen phosphate; the corresponding thermodynamic parameters and equilibrium constants are reported in Table 4.

$$\boldsymbol{R}H_2 + Cl^- \rightleftharpoons [\boldsymbol{R}H_2 \cdots Cl]^- \quad (10)$$

In Figure 4, the ITC profiles for the titrations of **1**, **2**, and **5** with $TBACH_3COO$ are shown. The experimental curves for **1** and **2** (see Figure 3a and b) indicate a single equilibrium in solution and confirm the formation of hydrogen-bonded 1:1 adducts. On the contrary, for the sulfonamide-based receptors **3**–**5**, the ITC titration profiles display multiple equilibria and the stoichiometry of the interaction is uncertain (see Figure 4c for receptor **5**; Figures S12c and S13c in the Supporting Information for receptors **3** and **4**, respectively).

To clarify the behavior of sulfonamide receptors with acetate, "reversed" titrations have been performed, by filling the cell of the calorimeter with the solution of receptor in

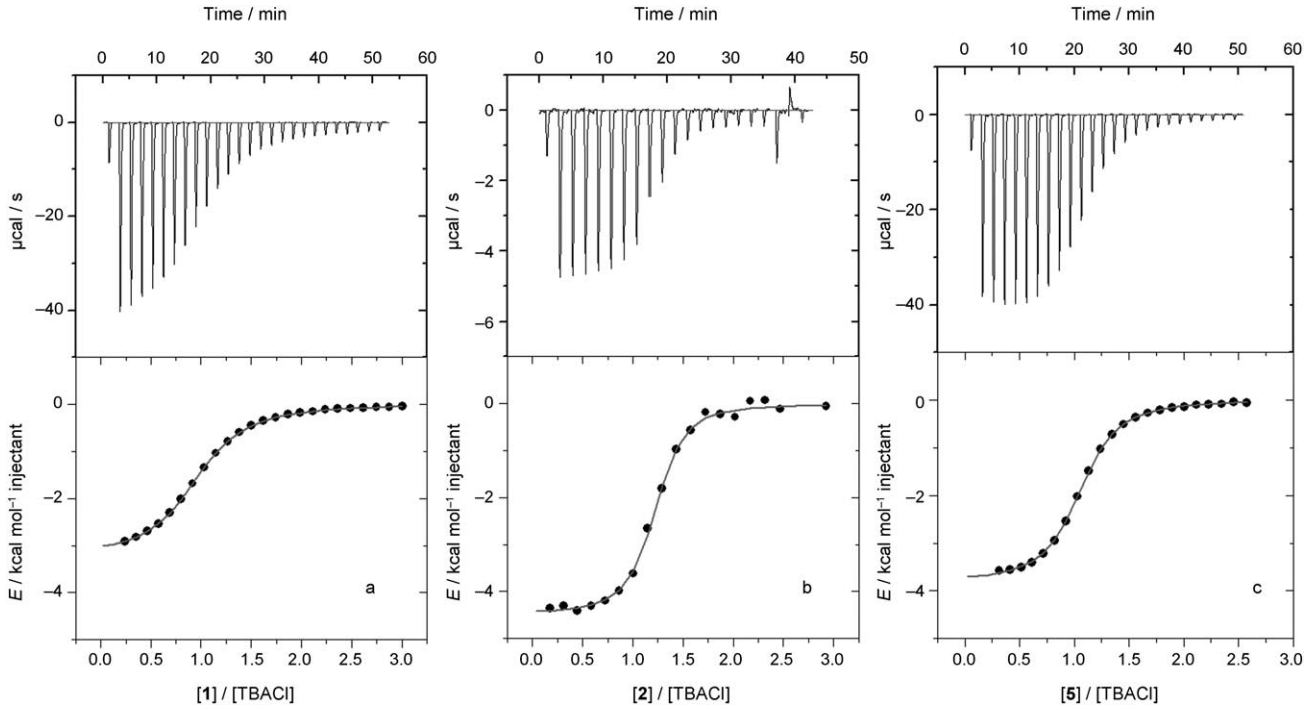


Figure 3. ITC profiles taken over the course of a) the titration of a solution of TBACl (1.59×10^{-3} M) in acetonitrile ($V_{cell}=1.345$ mL) with a solution of **1** (1.91×10^{-2} M); b) the titration of TBACl (1.0×10^{-4} M) with **2** (1.8×10^{-3} M); c) the titration of TBACl (1.59×10^{-3} M) with **5** (1.71×10^{-2} M). Circles: experimental data; line: fitting profile (one site model; ligand in the cell); $T=30$ °C.

acetonitrile and by adding the solution of $TBACH_3COO$ with a syringe. The ITC plots for **3–5** are reported in Figure 5 and the corresponding thermodynamic parameters are given in Table 5. The "reversed" ITC titration profiles clearly indicate two steps; the first step can be attributed to the proton-transfer process involving the sulfonamide receptor and the acetate anion, according to Equilibrium (11):

$$\boldsymbol{R}H_2+CH_3COO^- \rightleftharpoons \boldsymbol{R}H^-+CH_3COOH \quad (11)$$

Equilibrium (11), which is consistent with the spectrophotometric results, leads to the formation of acetic acid and the conjugated base of the receptor ($\boldsymbol{R}H^-$). The second step, which is not detected by the UV/Vis titration, can be attributed to the formation of the acetic acid/acetate self-complex, according to Equilibrium (12):

$$CH_3COOH+CH_3COO^- \rightleftharpoons [CH_3COO\cdots H\cdots CH_3COO]^- \quad (12)$$

This hypothesis was confirmed by comparing the thermodynamic parameters of the second step reported in Table 5, with those obtained by performing the ITC titration of a solution of CH_3COOH in acetonitrile with $TBACH_3COO$ (see Figure 6).

Tables 4 and 5 collect the thermodynamic parameters obtained under both the direct (Table 4) and reversed titration conditions (Table 5). ITC experiments on receptor **2** were limited by the low solubility of squaramide in acetonitrile, thus titrations were performed only with chloride, bromide, and acetate (see Table 4). The interaction with halides (chloride, bromide, and iodide) is exothermic and characterized by positive $T\Delta S_{11}$ values. This result is compatible with the formation of hydrogen-bonding receptor–anion interactions. The affinity reflects the decreasing negative-charge density of the anion, as

Table 4. Thermodynamic parameters at 30 °C ($\log K_{11}$, $-\Delta H_{11}$, $T\Delta S_{11}$) obtained from fitting of ITC titration curves ("direct" titrations) of receptors **1–5**. Numbers in parentheses are standard deviations to the last significant figure.

Anion	Receptor	$\log K_{11}$	$-\Delta H_{11}$ [kcal mol^{-1}]	$T\Delta S_{11}$ [kcal mol^{-1}]	Anion	Receptor	$\log K_{11}$	$-\Delta H_{11}$ [kcal mol^{-1}]	$T\Delta S_{11}$ [kcal mol^{-1}]
Cl^-	**1**	3.95(1)	3.24(1)	2.3	I^-	**1**	≅2	[a]	[a]
	2	5.76(5)	4.49(5)	3.5	HSO_4^-	**1**	2.87(3)	3.69(5)	0.3
	3	3.49(1)	3.74(1)	1.1	CH_3COO^-	**1**	5.80(2)	8.01(2)	0.1
	4	3.70(2)	3.23(5)	1.9		**2**	6.08(6)	5.70(7)	2.7
	5	4.38(1)	3.91(1)	2.2		**3–5**	[a]	[a]	[a]
Br^-	**1**	3.21(2)	2.63(2)	1.8	$H_2PO_4^-$	**1**	3.86(2)	6.14(5)	−0.8
	2	4.62(3)	4.04(5)	2.4		**2–5**	[a]	[a]	[a]
	3–4	≅2	§	§					
	5	2.97(3)	2.82(2)	1.3					

[a] No reliable fit could be made.

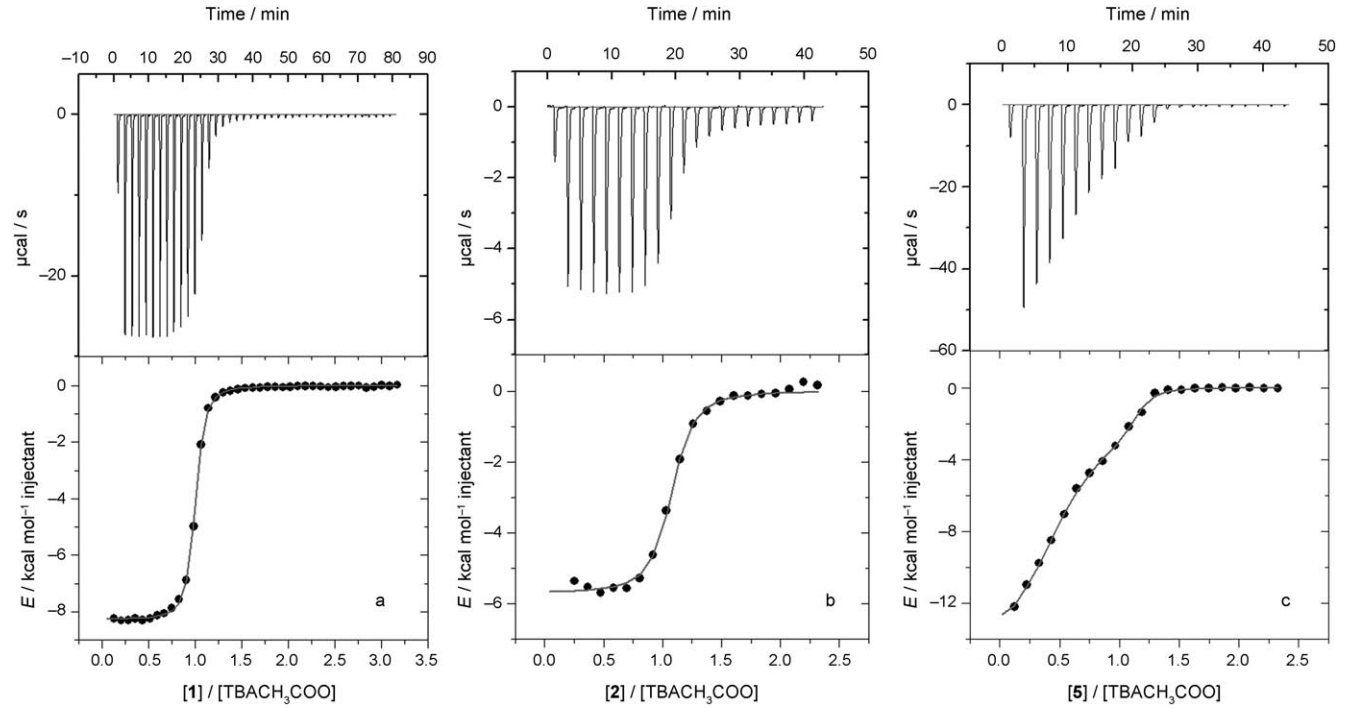


Figure 4. ITC profiles taken over the course of a) the titration of a solution of $TBACH_3COO$ (5.6×10^{-4} M) in acetonitrile ($V_{cell}=1.345$ mL) with a solution of receptor **1** (1.91×10^{-2} M); b) the titration of $TBACH_3COO$ (1.0×10^{-4} M) with **2** (1.8×10^{-3} M); c) the titration of $TBACH_3COO$ (5.1×10^{-4} M) with **5** (6.97×10^{-3} M). Circles: experimental data; line: fitting profile (one site model; ligand in the cell); $T=30$ °C.

hypothesized when discussing the results of spectrophotometric titrations. For the urea-based receptor, the interaction with oxo-anions is exothermic, but characterized by zero or negative entropic contributions. A remarkable dif-

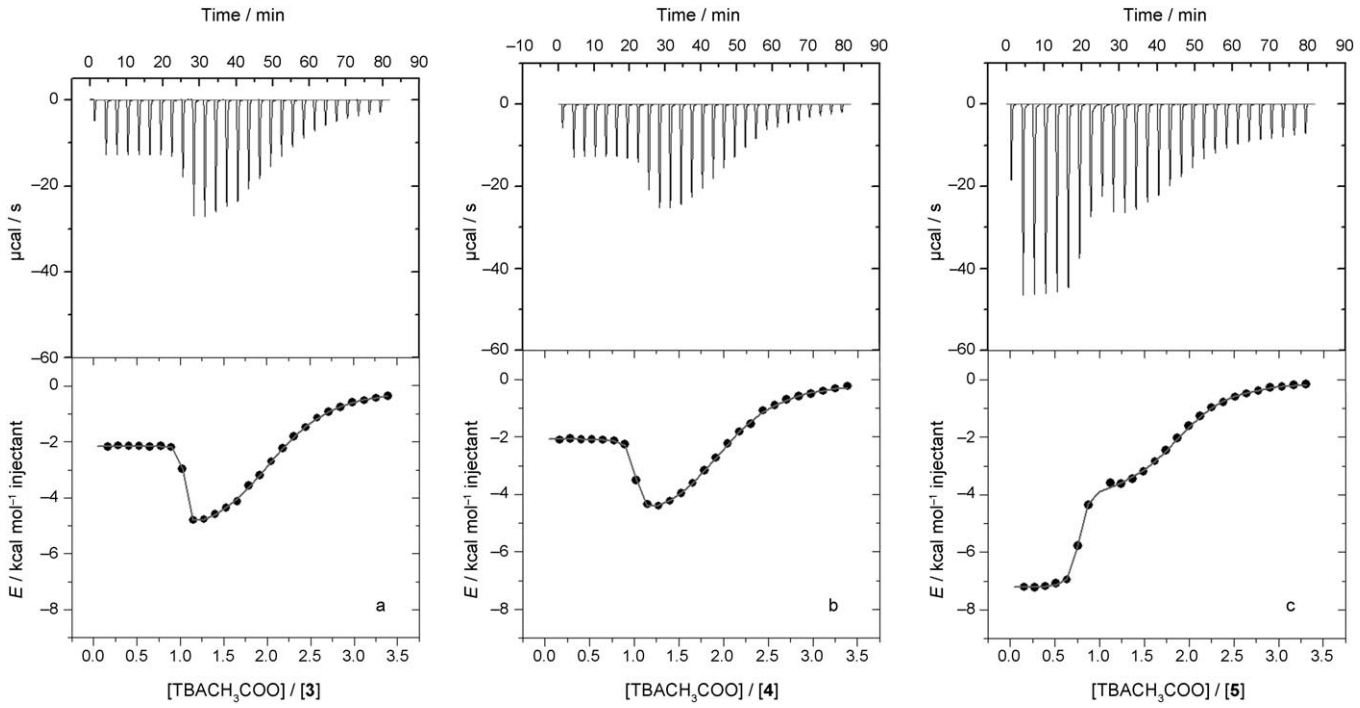


Figure 5. ITC plots corresponding to a) the titration of a solution of receptor **3** (8.2×10^{-4} M) in acetonitrile ($V_{cell}=1.345$ mL) with a solution of $TBACH_3COO$ (1.64×10^{-2} M); b) the titration of **4** (8.2×10^{-4} M) with $TBACH_3COO$ (1.64×10^{-2} M); c) the titration of **5** (8.4×10^{-4} M) with $TBACH_3COO$ (1.64×10^{-2} M). All experimental curves have been fitted for ligand in the cell; $T=30$ °C.

Table 5. Thermodynamic parameters at 30 °C obtained in the "reverse" ITC titration experiments of receptors **3**–**5** and acetic acid. Numbers in parentheses are standard deviations to the last significant figure.

Anion	Receptor	$\log K_1$	$-\Delta H_1$ [kcal mol^{-1}]	$T\Delta S_1$ [kcal mol^{-1}]	$\log K_2$	$-\Delta H_2$ [kcal mol^{-1}]	$T\Delta S_2$ [kcal mol^{-1}]
CH_3COO^-	**3**	7.52(1)	2.15(2)	8.3	4.00(2)	5.65(5)	−0.1
	4	6.97(1)	2.08(2)	7.6	4.03(2)	5.26(6)	0.3
	5	6.82(6)	7.23(3)	2.2	4.19(2)	4.17(6)	1.6
	CH_3COOH				4.09(1)	5.17(4)	0.5

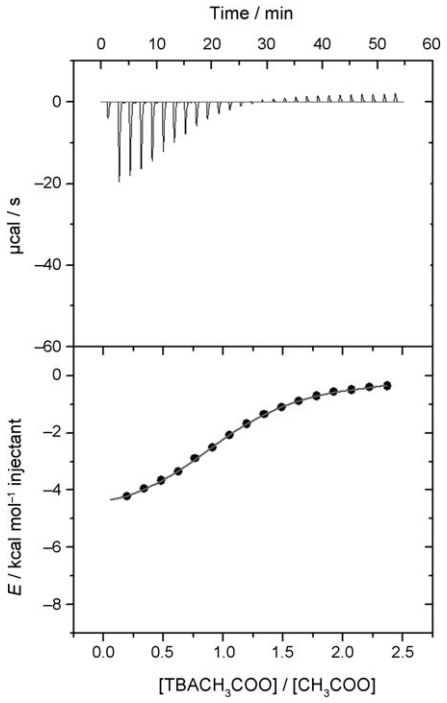


Figure 6. ITC plot of the interaction of CH_3COOH (4.5×10^{-4} M) with $TBACH_3COO$ (1.7×10^{-2} M) in acetonitrile; $T=30$ °C.

ference between **1** and **2** was observed with acetate. For receptors **1** and **2**, results obtained by ITC and absorption spectroscopy are in good agreement with each other and confirm the formation of 1:1 hydrogen-bonded adducts with all anions. The corresponding thermodynamic parameters ($\log K_{11}$, $-\Delta H_{11}$, $T\Delta S_{11}$) are shown in Table 4. For **1**, the interaction is mainly driven by the enthalpic contribution ($-\Delta H_{11}=8.01(2)$ kcal mol^{-1}; $T\Delta S_{11}=0.1$ kcal mol^{-1}). Whereas for **2**, the entropic effect seems to play a not negligible role ($\log K_{11}=6.08(6)$; $-\Delta H_{11}=5.70(7)$ kcal mol^{-1}; $T\Delta S_{11}=2.7$ kcal mol^{-1}). ITC experiments on sulfonamide-based receptors **3**–**5** do not always confirm the spectrophotometric results. In particular, the formation of genuine 1:1 hydrogen-bonded adducts is verified only for the investigated halides (see Table 4), whereas with more basic oxo-anions, such as acetate and dihydrogen phosphate, ITC binding curves display multiple equilibria. In the case of acetate, best-fitting results were obtained by performing reversed titrations (i.e., by filling the cell with the receptor solution and the syringe with the anion). The corresponding thermodynamic parameters are reported in Table 5.

The ITC plots of the reversed titrations indicated two consecutive equilibria, Equilibria (13) and (14):

$$\boldsymbol{R}H_2+CH_3COO^- \rightleftharpoons \boldsymbol{R}H^-+CH_3COOH \quad \log K_1 \tag{13}$$

$$CH_3COO^-+CH_3COOH \rightleftharpoons [CH_3COO\cdots H\cdots CH_3COO]^- \quad \log K_2 \tag{14}$$

For the first step, Equilibrium (13), the ΔH_1 parameter contains i) the endothermic contribution of the deprotonation of the receptor and ii) the enthalpic contribution of opposite sign (i.e., exothermic) relative to acetic acid formation. Table 5 indicates that for sulfonamide **5**, the deprotonation contribution of the receptor is less unfavorable than for **3** and **4**: the two nitro groups on the central phenyl ring probably favor deprotonation of **5**, thus stabilizing the corresponding conjugated base. Such an enthalpic advantage of receptor **5**, with respect to **3** and **4**, is mitigated by the entropic term, which is distinctly more positive for **3** and **4**.

The second step of the ITC plots was attributed to the formation of the acetic acid/acetate self-complex [Equilibrium (14)]. The nature of this second step was confirmed by the titration of acetic acid with TBA^+ acetate in acetonitrile (see Figure 6): the obtained thermodynamic parameters ($\log K=4.09(1)$; $-\Delta H=5.17(4)$ kcal mol^{-1}; $T\Delta S=0.5$ kcal mol^{-1}) are consistent with those obtained in the second step of the titration of sulfonamide-based receptors with acetate, in particular for **3** and **4** (the differences observed in the comparison with receptor **5** are attributable to the bad quality of this receptor's experimental data). Of the two steps observed by ITC, only the first directly involves the receptor and can be detected in the UV/Vis titration. The discrepancy between ITC and spectrophotometric results (which gave 1:1 equilibria for all receptors with acetate) marks the difference and, in this particular case, establishes the superiority of ITC with respect to the spectrophotometric technique. Actually, spectrophotometric titrations directly follow the effect of anion binding on the absorption properties of the receptor, whereas calorimetry determines the integral heat response of all processes happening simultaneously in solution upon anion binding.

Calorimetric titrations on sulfonamides **3**–**5** were also performed with dihydrogen phosphate (ITC curves are available in the Supporting Information). With respect to acetate, the prevalence of multiple equilibria and the lack of calorimetric events at distinct integral equivalents precluded accurate curve fitting.

^{1}H NMR spectroscopic titration experiments: To assess the equilibria in solution and to confirm the results obtained spectrophotometrically and by ITC, we performed ^{1}H NMR spectroscopic titrations on receptors **1**, **2**, and **3** in CD_3CN with two different anions: bromide and acetate. The NMR spectroscopy experiments with TBABr confirmed the results obtained by UV/Vis spectroscopy and calorimetry: the envisaged receptors formed stable 1:1 adducts with bromide and the affinity decreased along the series **2**>**1**>**3** (**1**: $\log K_{11}=3.27(2)$; **2**: $\log K_{11}=4.61(6)$; **3**: $\log K_{11}=2.37(1)$). Bromide induced the downfield shift of the N−H protons, involved in the receptor–anion interaction. Experimental conditions, titrations profiles, distribution diagrams, and the family of ^{1}H NMR spectra are available in the Supporting Information (see Figures S15, S17, and S19 for titrations of **1**, **2**, and **3**, respectively, with TBABr).

In the ^{1}H NMR spectroscopic titration with $TBACH_3COO$, the downfield shift of the N−H proton of **1** indicated the formation of the 1:1 adduct involving the urea moiety. Unfortunately, the ^{1}H NMR spectroscopic titration profile was too steep to allow the determination of the binding constant (Figure S16 in the Supporting Information). Also for the sulfonamide-based receptor (**3**), a 1:1 equilibrium was observed. In this case, the disappearance of the NH signal and the remarkable upfield shift of H_α on the central phenyl ring may be interpreted as anion-induced deprotonation of the sulfonamide group (Figure S20 in the Supporting Information). Deprotonation was confirmed by recording the UV/Vis spectrum of the final sample. Note that deprotonation was already observed for all sulfonamide receptors by UV/Vis spectroscopy and ITC titrations with acetate. The ^{1}H NMR titration of **2** with $TBACH_3COO$ indicated two equilibria, corresponding to the formation of 1:1 and 2:1 receptor/anion adducts (Figure S18 in the Supporting Information). Note that both ITC and spectrophotometric titrations evidenced only a single equilibrium in solution, corresponding to the formation of the 1:1 adduct. The formation of the 2:1 (receptor/anion) adduct could be followed only by ^{1}H NMR spectroscopy, probably because of the higher concentration used for both receptor and anion.

Conclusion

The affinities of receptors **1**–**5** towards anions were compared by performing spectrophotometric, ITC, and ^{1}H NMR spectroscopic titrations in acetonitrile. The results indicated that **1** and **2** formed 1:1 hydrogen-bonded complexes with most of the anions investigated. In the case of receptors **3**–**5**, hydrogen-bonding interactions were observed only towards anions of low basicity, for which single equilibria leading to 1:1 adducts were observed, whereas with the more basic anions, acetate and dihydrogen phosphate, the experimental data indicated proton-transfer processes from the receptor to the anion. Further equilibria, leading to the formation of self-complexes of the anions, could only be detected in calorimetric experiments. These processes, not directly involving the receptor, could not be detected by both ^{1}H NMR and UV/Vis spectroscopy. Notably, the basic structures of the receptors are vastly different (urea, squaramide, and sulfonamide), therefore, their basic solvation patterns will also differ. Solvation plays a fundamental role in the stabilization of both the initial and final state of complexation. For this reason, a discussion on binding selectivity should take into account the solvation effects and should not be done only in terms of weaker/better interactions of hydrogen bonding in the complexed state. Moreover, the calorimetric results show that the entropy component for most systems constitutes a major part (30–50% of the enthalpy; in some cases the entropic contribution is even the dominant component). Thus, it is not possible to focus the explanation on enthalpy only (in terms of geometric complementarity, distance, converging hydrogen bonds, etc.). In conclusion, even for the simple systems presented herein, there are still too many degrees of freedom to single out the individual contributions and to assign a defined cause for better binding.

Experimental Section

General: All reagents were purchased by Aldrich and Fluka. TBA^+ salts were all greater than 98% pure and dried in vacuo overnight before use. The solutions used for UV/Vis spectroscopy and ITC titrations were made from freshly opened, dry acetonitrile ($\leq$0.001% H_2O) packaged in crown-cap bottles over molecular sieves (Aldrich). Mass spectra were acquired on a Thermo-Finnigan ion-trap LCQ Advantage Max instrument equipped with an ESI source, NMR spectra were acquired on a Bruker AVANCE 400 spectrometer (operating at 9.37 T, 400 MHz). UV/Vis spectra were run on a Varian Cary 100 SCAN spectrophotometer. The potentiometric titrations were made with a Radiometer TitraLab 90 titration system.

Spectrophotometric titrations: All titrations were performed at 25°C. For the determination of binding constants in acetonitrile, the solution of receptor (**1**–**5**) was titrated with a 100-fold more concentrated solution of the anion as the TBA^+ salt. After each addition of a sub-stoichiometric amount of anion, the UV/Vis spectrum was recorded. The concentration of the receptor solution was chosen on the basis of the p parameter (p = [concentration of complex]/[maximum possible concentration of complex]), which ranged from 0.2 to 0.8.[12] Titration data were processed with the Hyperquad package[11] to determine the equilibrium constants.

Potentiometric titrations: All potentiometric titrations were performed at 25°C by using carbonate-free NaOH. Acidic dissociation constants of receptors **1**–**5** were determined in a mixture of acetonitrile/H_2O (9:1), with 0.05 M $TBAPF_6$ (see Table 3).Titrations were performed under a nitrogen atmosphere. In a typical experiment, a 5.0×10^{-4} M solution of the receptor (15 mL) was treated with an excess of a 1.0 M standard solution of HNO_3. Titrations were run by the addition of 10 μL portions of a standard 0.1 M solution of NaOH and collecting 80–100 points for each titration. Prior to each potentiometric titration, the standard electrochemical potential ($E°$) of the glass electrode was determined in a mixture of acetonitrile/H_2O (9:1, v/v), by a titration experiment according to the Gran method. Protonation and complexation titration data (emf vs. mL of NaOH) were processed with the Hyperquad package to determine the equilibrium constants.[11]

Isothermal titration calorimetry (ITC): ITC titrations were performed by using a MCS-ITC instrument (from MicroCal). All binding experiments were performed at 30°C. Stock solutions were prepared by directly weighing the substances into volumetric flasks. The results reported in Table 4 correspond to ITC experiments performed by adding the receptor solution to the TBA^+ salt solution, placed in the instrument cell,

whereas for the results in Table 5, the TBA^+ salt solution was added with a syringe to the receptor solution in the instrument cell. The association parameters (K, ΔH, and ΔS reported in Tables 4 and 5), as well as the interaction stoichiometry, were experimentally determined by the fitting procedure. Blank titrations in acetonitrile were performed and subtracted from the corresponding titrations to remove the effect of dilution.

^{1}H NMR spectroscopy titrations: All measurements were performed at 25 °C in CD_3CN. For the determination of binding constants, the receptor (**1**–**3**) was titrated with a 100-fold more concentrated solution of the anion as the TBA^+ salt. After each addition of sub-stoichiometric amount of anion, the ^{1}H NMR spectrum was recorded. Titration data were processed with the Hyperquad package[11] to determine the equilibrium constants.

Acknowledgements

This work was financially supported by the Italian Ministry of Research (MIUR), project Supramolecular Devices.

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Received: November 25, 2010
Published online: April 6, 2011

