What Anions Do to N−H-Containing Receptors

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ABSTRACT
Molecules containing polarized N−H fragments behave as H-bond donors toward anions and are widely used as receptors for recognition and sensing purposes in aprotic solvents ($CHCl_3$, MeCN, and DMSO). We present examples of receptors containing pyrrole and urea subunits, and we discuss the stability of their H-bond complexes with a variety of anions. It is demonstrated that the stability of the 1:1 complexes is strictly related to the acidic tendencies of the receptor and to the basic properties of the anion. It may happen also that more basic anions induce the deprotonation of the receptor, if equipped with electron-withdrawing substituents. This is typically observed on interaction with fluoride, due to the formation of the very stable $[HF_2]^-$ self-complex. For urea-based receptors armed with chromogenic substituents, the addition of a large excess of the anion (F^-, OH^-) may induce the consecutive deprotonation of both N−H fragments, processes signaled by the development of vivid colors.

Introduction

There exists an obvious correspondence between "transition metal coordination chemistry"[1] and its young sister "anion coordination chemistry".[2] Both disciplines belong to the broader area of supramolecular chemistry (the chemistry of noncovalent interactions)[3] and deal with chemical entities (complexes), which are characterized by a definite stoichiometry (the coordination number) and a distinct geometry. Significant analogies in geometrical features of both metal and anion complexes have been clearly discussed in a recent review.[4]

Ligands for transition metal ions can be neutral or negatively charged, and receptors for anions can be neutral or positively charged. The interactions exerted by electrically charged ligands or receptors have a similar nature (electrostatic, to a first approximation). Those established by neutral ligands and receptors have a different nature: Neutral ligands donate to the metal electron pairs (e.g., from amine nitrogen atoms), and neutral receptors donate to the anion hydrogen bonds (e.g., through the N−H fragment of amides, pyrroles, and ureas). This leads to a first substantial difference: The formation of metal−ligand complexes can be investigated in any solvent, provided that it ensures solubility of the ligand and of the metal salt; the study of anion complexes with neutral receptors is preferably carried out in aprotic media ($CHCl_3$, MeCN, and DMSO), to avoid the competition for the anion by the molecules of the H-bond-donating solvent (e.g., H_2O). Significant exceptions have been observed in the case of highly preorganized receptors capable of multipoint H-bond interactions with the anion (as shown, for instance, in the selective inclusion of the sulfate ion by a cyclic peptide in water).[5,6] Moreover, the donor tendencies of both ligand and receptors can be enhanced through electronic and substituent effects. In metal coordination chemistry, electron density and binding tendencies of the donor atom(s) can be increased by inserting onto the ligand's framework proper electron-donating substituents. In anion coordination chemistry, the N−H fragment of a receptor can be further polarized, and its H-bond donor tendencies increased, through the insertion onto the molecular framework of electron-withdrawing substituents (e.g., $-NO_2$, CF_3) or positively charged groups (e.g., alkylpyridinium). However, this procedure may be risky: In fact, extreme polarization may lead to the occurrence of a definitive proton transfer from the receptor to an especially basic anion, a feature that pushes the anion out of the supramolecular control of the receptor and extrudes the operator from the discipline of supramolecular chemistry.

In this account, we will consider the interaction of anions with H-bond-donating receptors, whose binding tendencies can be enhanced with the use of nearby electron-withdrawing substituents or positively charged groups, and how such features ultimately affect the selectivity of anion recognition processes.

Positively Charged H-Bond Donating Receptors: Carbolinium

We will first consider the 2-benzyl-9H-b-carbolin-2-ium system, $[\mathbf{1}]^+$, which contains a pyrrole N−H fragment.[10] H-bond-donating tendencies of pyrrole toward anions are clearly established.[11] Moreover, in $[\mathbf{1}]^+$, the C(1)−H fragment in the adjacent pyridinium ring, which is polarized

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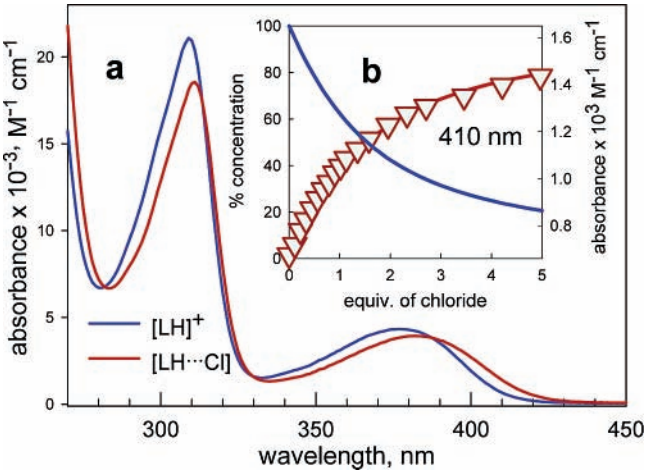
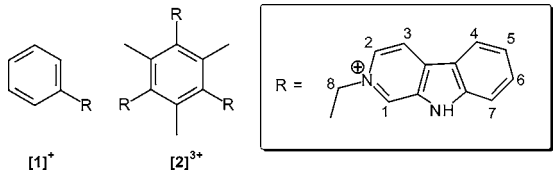


FIGURE 1. (a) Blue line, spectrum of an MeCN solution of [**1**]PF_6 (6.2×10^{-4} M); red line, spectrum of the same solution + 4 equiv of [Bu_3Bz]Cl. (b) Symbols: molar absorbance at 410 nm (right side vertical axis) vs equiv of Cl^-. Lines: % concentration (left side vertical axis); blue line, receptor $[\mathbf{1}]^+$; and red line, chloride complex, [**1**···Cl].

due to the close proximity of a positively charged group, can give an additional contribution to the interaction with the anion.



Binding tendencies of a given receptor for anions are typically studied through titration experiments: A solution of the receptor is titrated with a standard solution of the tetralkylammonium salt of the envisaged anion and modifications of ^{1}H NMR or UV−vis spectra are investigated. Spectral data are typically processed through a nonlinear least-squares method, to determine pertinent association constants. Additional pieces of information on the nature and on the structural aspects of the receptor−anion interaction can be provided by ^{1}H NMR titration experiments. The use of relatively concentrated solutions ($\geq 5 \times 10^{-3}$ M) sets a limit to the determination of binding constants higher than 10^4−10^5. On the other hand, in absorbance spectroscopy, rather intense charge transfer bands are recorded, which allows operation in more diluted solutions ($\geq 10^{-6}$) and determination of binding constants up to 10^7. Solvent plays an important role in the solution stability of anion complexes: The higher the polarity of the solvent (DMSO > MeCN > $CHCl_3$) is, the higher the anion desolvation energy term and the lower the stability of the H-bond complex are. Thus, stable anion complexes in a $CHCl_3$ solution may not form at all in DMSO.

Figure 1a shows the spectra of an MeCN solution of [**1**]PF_6 (6.2×10^{-4} m) (blue line) and of the same solution after the addition of a 5-fold excess of [Bu_3BzN]Cl (red line), obtained over the course of the titration (see the titration profile in Figure 1b, based on the absorbance at 410 nm).[10] The band centered at 380 nm undergoes a red

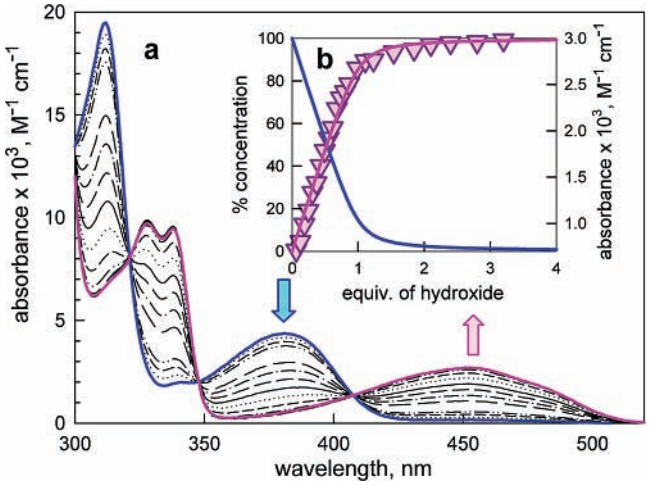


FIGURE 2. (a) Spectrophotometric titration of an MeCN solution of [**1**]PF_6 (5.2×10^{-4} M) with a standard MeCN solution of [Bu_4N]OH; blue spectrum, before OH^- addition; pink spectrum, after the addition of 4 equiv of OH^-. (b) Symbols: absorbance at 453 nm (right vertical axis) vs equiv of OH^-. Lines: blue line, % concentration (left vertical axis) of $[LH]^+$; pink line, % concentration of the zwitterion L.

shift, which reflects the stabilization of the charge transfer excited state, following the interaction of the receptor with the Cl^- ion. Spectral data were satisfactorily fitted on the basis of the following complex formation equilibrium: $[LH]^+ + Cl^- \leftrightarrows [LH\cdots Cl]$, to which a $\log K = 3.20 \pm 0.01$ corresponded (LH = **1**). A similar behavior (red shift of the band centered at 380 nm) was observed on titration with [Bu_4N]Br, and a $\log K = 2.48 \pm 0.01$ was determined. On titration with iodide, no spectral modifications were observed, which indicated a $\log K < 2$. To complete the list of halides, we should consider the titration experiment with fluoride. Before doing that, the interaction of $[\mathbf{1}]^+$ with OH^- was investigated. Such a study should allow us to define the tendency of $[\mathbf{1}]^+$ to behave as a Brønsted acid, rather than as an H-bond donor. In this connection, a solution of [**1**]PF_6 (5.2×10^{-4} M) was titrated with a standard MeCN solution of [Bu_4N]OH. Figure 2 shows the family of spectra recorded over the course of the titration.

On hydroxide addition, dramatic spectral changes are observed, while the colorless solution takes a bright yellow color. The titration profile in Figure 2b clearly indicates a 1:1 stoichiometry for the occurring process, which is described by the following acid−base neutralization equilibrium: $[LH]^+ + OH^- \leftrightarrows L + H_2O$ ($\log K = 6.42 \pm 0.02$, as calculated under more diluted conditions). In particular, the positively charged system $[LH]^+$ undergoes deprotonation at the pyrrole N−H group, to give the zwitterion L. The drastic red shift (of 70 nm) reflects the substantial increase of the dipole along which the optical transition takes place, induced by N−H deprotonation.

Fluoride displays a behavior similar to that of hydroxide, with drastic spectral changes and development of the band at 454 nm, which indicates the occurrence of N−H deprotonation (see the family of spectra recorded over the course of the titration in Figure 3). The difference with respect to OH^- is that the limiting value of the band at 454 nm is reached on addition of 2 equiv of fluoride. In

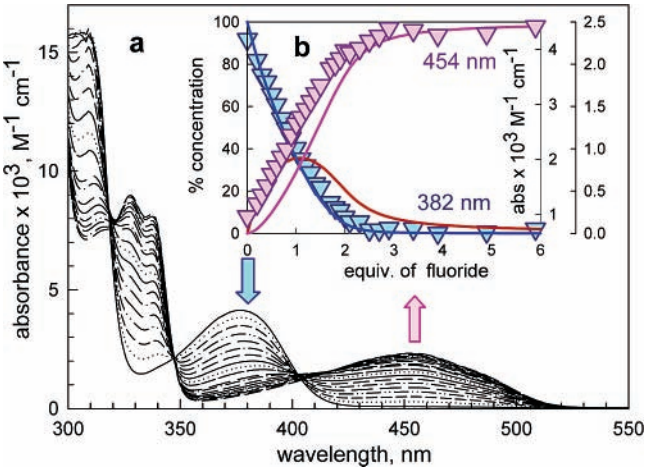


FIGURE 3. (a) Spectrophotometric titration of an MeCN solution of [**1**]PF_6 (1.1×10^{-4} M) with a standard MeCN solution of $[Bu_4N]F$. (b) Symbols: titration profiles of the titration of a 10^{-5} M solution of [**1**]PF_6 with fluoride; molar absorbance at 382 (blue symbols, right side vertical axis) and 454 nm (pink symbols, right offset vertical axis). Lines: % concentration (left side vertical axis) vs equiv of F^-; blue line, $[LH]^+$; red line, $[LH\cdots F]^-$; and pink line, L.

particular, best fitting of spectral data is obtained on assuming the occurrence of the two stepwise equilibria 1 and 2:

$$LH^+ + F^- \leftrightarrows [LH\cdots F] \quad (1)$$

$$[LH\cdots F] + F^- \leftrightarrows L + [HF_2]^- \quad (2)$$

First, F^- forms a genuine H-bond complex, $[LH\cdots F]^-$, and the high value of $\log K_1$ (6.19 ± 0.05) gives evidence of an enhanced stability, as compared to other halides. However, on further addition of F^-, the [LH···F] complex releases an HF molecule, to give the zwitterion L and the self-complex $[HF_2]^-$. Because of the closeness of K_1 and K_2 values, the L zwitterion begins to form in the early stages of the titration experiment, almost simultaneously with the H-bond complex [LH···F] (see the distribution diagram in Figure 3b, pink and blue lines, respectively), accounting for the premature appearance of the band at 454 nm, pertaining to the deprotonated receptor, and development of the bright yellow color.

To explain the peculiar behavior of fluoride, it is convenient to consider the overall neutralization equilibrium 3, in which X = F:

$$[LH]^+ + 2X^- \leftrightarrows [L] + [HX_2]^- \quad (3)$$

Equation 3 results from the sum of eqs 1 and 2, and its constant β_N is therefore given by the product of K_1 and K_2 ($10^{12.3}$, in the present case). More interestingly, eq 3 can also be considered as the sum of the two equilibria 4 and 5:

$$[LH]^+ \leftrightarrows [L] + H^+ \quad K_A(LH) \quad (4)$$

$$H^+ + 2X^- \leftrightarrows [HX_2]^- \quad \beta(HX_2^-) \quad (5)$$

from which results

$$\beta_N = K_A(LH) \times \beta(HX_2^-) \quad (6)$$

Table 1. Equilibrium Constants for the Interaction of Receptors $[1]^+$ and $[2]^+$ with Anions in an MeCN Solution at 25 °C[a]

anion	receptor $[1]^+$, log$K$	receptor $[2]^{3+}$, log$K$
Cl^-	3.20 (1)	>7
Br^-	2.48 (1)	6.65 (2)
I^-	<2	4.55 (2)
F^-	$\log K_1 = 6.19$ (5)	$\log K_1 = 5.04$ (2)
	$\log K_2 = 6.07$ (9)	$\log K_2 = 2.79$ (5)
		$\log K_3 = 4.02$ (6)
OH^-	6.42 (2)	$\log K_1 = 5.58$ (5)
		$\log K_2 = 3.92$ (9)
		$\log K_3 = 5.7$ (1)

[a] In parentheses is the uncertainty on the last figure.

Equation 6 indicates that the deprotonation of $[LH]^+$ in the presence of F^- in an MeCN solution mainly reflects the extreme stability of the $[HF_2]^-$ self-complex. However, one cannot exclude the occurrence of the deprotonation also in the presence of other anions, provided that the receptor is acidic enough.

At this stage, it seemed convenient to implant three carbolinium fragments on a 1,3,5-trimethylbenzene platform, to give the trifurcate receptor $[2]^{3+}$.[10] The 1,3,5-trialkylbenzene scaffold has been successfully employed to generate cavities suitable for the inclusion of trifunctional anions.[8,12,13] Hopefully, system $[2]^{3+}$ should be able to envelop spherical halide ions, giving rise to stable H-bond complexes. On the basis of spectrophotometric titration experiments, looking at the red shift of the charge transfer band at 380 nm, the formation of 1:1 complexes was ascertained for Cl^-, Br^-, and I^-. Pertinent association constants are reported in Table 1.

Figure 4 shows the geometrical arrangement of the $[LH_3\cdots Br]^{2+}$ complex ($[LH_3]^{3+} = [2]^{3+}$), as observed in the crystal structure. The bromide ion is located in the middle of the cavity and receives six H-bonds, three from the pyrrole N−H groups and three from the C−H(1) fragment

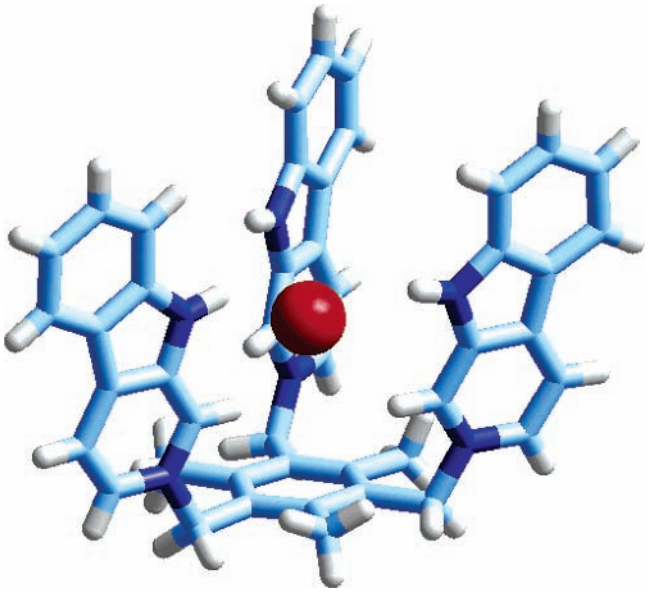


FIGURE 4. Structure of the $[LH_3\cdots Br]^{2+}$ complex ($[LH_3]^{3+} = [2]^{3+}$). The complex is a part of a dimeric capsule, which consists also of a doubly deprotonated subunit including a water molecule, $[LH\cdots H_2O]^+$.[10]

of each carbolinium arm. Such a full coordination accounts for the extremely large stability of the $[LH_3{\cdots}X]^{2+}$ complexes. In the case of chloride, even for a 10^{-6} M solution in the receptor, steep titration profiles were obtained, which prevented a safe determination of the association constant, to which a value $\log K > 7$ has to be assigned, i.e., more than 4 orders of magnitude larger than observed value with the corresponding complex for the "single-arm" donor $[\mathbf{1}]^+$. To our knowledge, this is the largest association constant observed for an H-bond complex of chloride with an artificial receptor, in whatever medium. Fluoride gave a more intricate behavior: In the first and in the second steps, two genuine H-bond complexes formed, $[LH_3{\cdots}F]^{2+}$ and $[LH_3{\cdots}2F]^+$. Then, addition of the third equivalent of F^- induced the release of three HF molecules and formation of the triply deprotonated receptor, according to eq 7:

$$[LH_3{\cdots}2F]^+ + F^- \leftrightarrows [L] + 3HF \qquad (7)$$

It should be noted that K_1 for F^- is more than 2 orders of magnitude lower than K of Cl^-, inverting the natural order of stability of halide complexes (observed, for instance, in the case of the monofurcated receptor $[\mathbf{1}]^+$). This may be ascribed to the fact that fluoride is too small to establish up to six H-bond interactions as other halide ions do and probably interacts with one single arm of $[\mathbf{2}]^{3+}$. However, the most noticeable behavior was observed with OH^-.

In fact, in the course of the titration with $[Bu_4N]OH$ of an MeCN solution of $[\mathbf{2}]^{3+}$, the band at 454 nm, suggestive of the occurrence of N−H deprotonation, formed and developed, but only after the addition of the first equivalent of OH^- (see spectra in Figure 5a and titration profiles in Figure 5b). This indicates that the first added hydroxide ion goes into the cavity and establishes somewhere H-bond interactions, without neutralizing any N−H group. Besides, the ^1H NMR titration experiment showed that the C−H(1) proton undergoes a downfield shift on addition of the first equivalent of OH^-, as typically observed when a hydrogen-bonding interaction is established. Then, on addition of the second and more equivalents of OH^-, the C−H(1) proton undergoes an upfield shift, a feature expected on deprotonation of the nearby N−H fragment. Thus, an unprecedented genuine $[LH_3{\cdots}OH]^{2+}$ H-bond complex forms and reaches its highest concentration (60%; see the distribution diagram in Figure 5b) on addition of 1 equiv of OH^-. The triply positively charged cavity must play a determining role in stabilizing the H-bond complex, whose formation is not observed with the single arm receptor $[\mathbf{1}]^+$, which undergoes immediate deprotonation. OH^- is an inorganic anion like many others and, after a long quest, has finally encountered its receptor.

Neutral H-Bond Donating Receptors: Urea

In the previous examples, we illustrated the interplay between the H-bond-donating features and the Brønsted acid behavior of pyrrole-containing receptors: Electron-withdrawing substituents polarize the N−H bond and

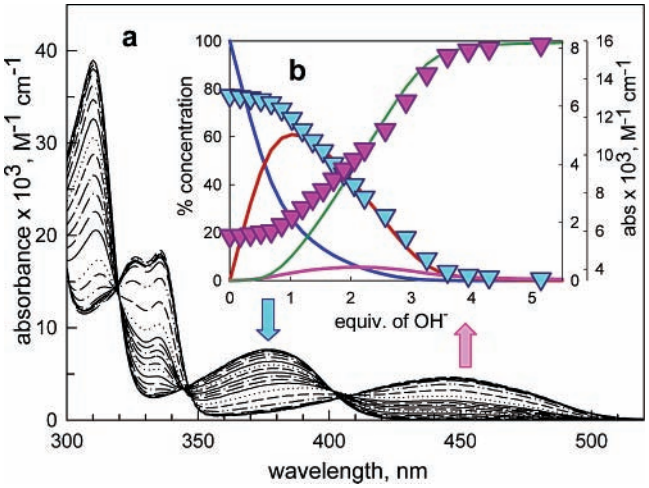
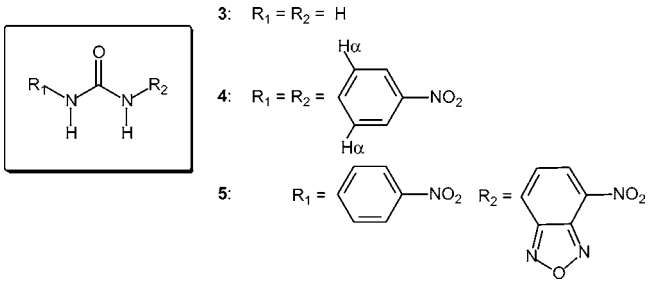


FIGURE 5. (a) Spectrophotometric titration of an MeCN solution of $[\mathbf{2}](PF_6)_3$ (1.0×10^{-4} M) with a standard MeCN solution of $[Bu_4N]OH$. (b) Symbols: molar absorbance at 310 (blue, right side vertical axis) and 450 nm (pink, right offset vertical axis). Lines: % concentration, left side vertical axis, vs equiv of OH^-; blue line, LH_3^{3+}; red line, $[LH_3{\cdots}OH]^{2+}$; pink line, LH^+; and green line, L.

favor H-bond formation, but in a limiting situation, they can promote N−H deprotonation, thus pushing the anion out of the receptor's control. One could argue that such an exaggerated effect has been just observed on carbolinium-based systems, due to the presence of the nearby positively charged group, and should not operate on neutral receptors. In this connection, it is convenient to consider the case of urea (**3**).



Friedrich Wöhler in 1828 synthesized this molecule, demolishing the generally accepted "vitalistic" belief that organic substances could be produced only by living organisms.[14] Wöhler's finding had a revolutionary effect on chemistry, comparable to those provoked by Galileo Galilei in physics and by Charles Darwin in biology. However, the social impact of this discovery was very moderate or nil, probably due to the scarce attention society and the Church paid to chemistry. Since then, urea and its derivatives have played important roles in science and life. Then, two decades ago, Wilcox[15] and Hamilton[16] independently observed that urea is a good receptor for anions and, in particular, can establish complementary hydrogen-bonding interactions with Y-shaped oxoanions such as carboxylates. Since then, urea has become a widely used fragment in the design of anion receptors and sensors.[17]

Figure 6 shows the geometrical arrangement of the acetate complex of a urea-based receptor, $[LH{\cdots}CH_3COO]^-$

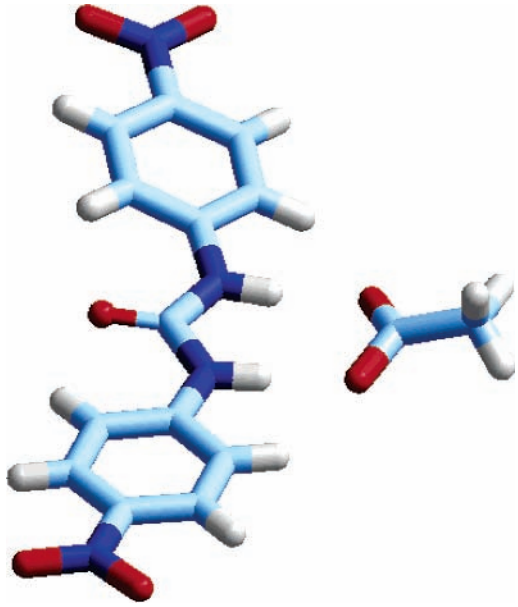


FIGURE 6. Structure of the $[LH\cdots CH_3COO]^-$ complex (LH = **4**).[18]

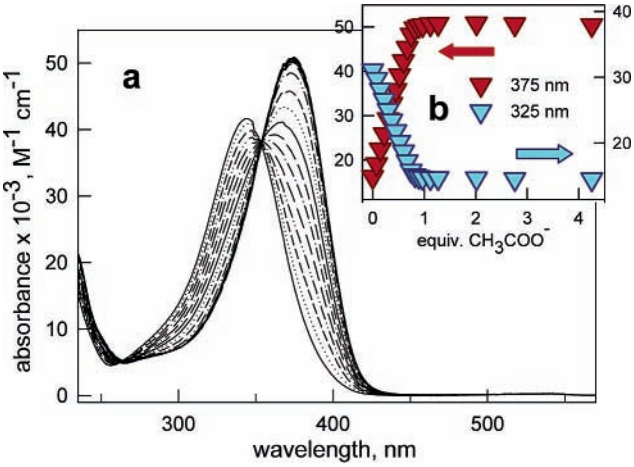


FIGURE 7. (a) Family of spectra taken over the course of the titration of an 2.6×10^{-5} M in **4** with a standard solution of $[Bu_4N]CH_3COO$ at 25 °C. (b) Corresponding titration profiles, which indicate the formation of a 1:1 adduct $[LH\cdots CH_3COO]$.

(LH = **4**), as observed in the crystal structure of its tetrabutylammonium salt.[18] Indeed, the urea subunit seems tailor-made for establishing complementary hydrogen-bonding interactions with carboxylates.

The stability of this $[LH\cdots CH_3COO]^-$ complex in an MeCN solution was investigated through spectrophotometric titration experiments, as shown in Figure 7.[18] The receptor itself presents a charge transfer band centered at 325 nm, which, on interaction with acetate, undergoes a distinct red shift. The titration profiles shown in Figure 7b refer to a solution 2.6×10^{-5} M in **4** and clearly indicate the 1:1 stoichiometry of the complex. Smoother profiles were obtained with a 1.0×10^{-6} M solution, from which a $\log K = 6.61 \pm 0.09$ was calculated. Notably, the complex formation can be visually perceived through a distinct color change, from pale to bright yellow, as shown by the photograph in Figure 8.

The formation of analogous 1:1 complexes was observed with a variety of oxoanions, and corresponding

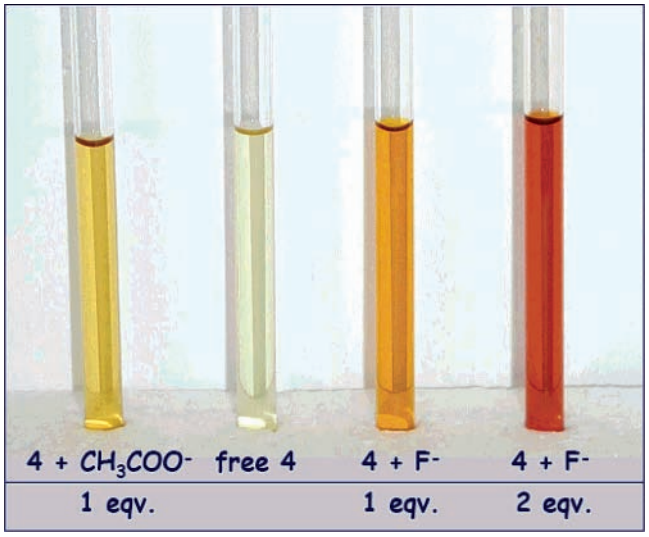


FIGURE 8. Color changes observed on addition of anions to an MeCN solution of **4**.

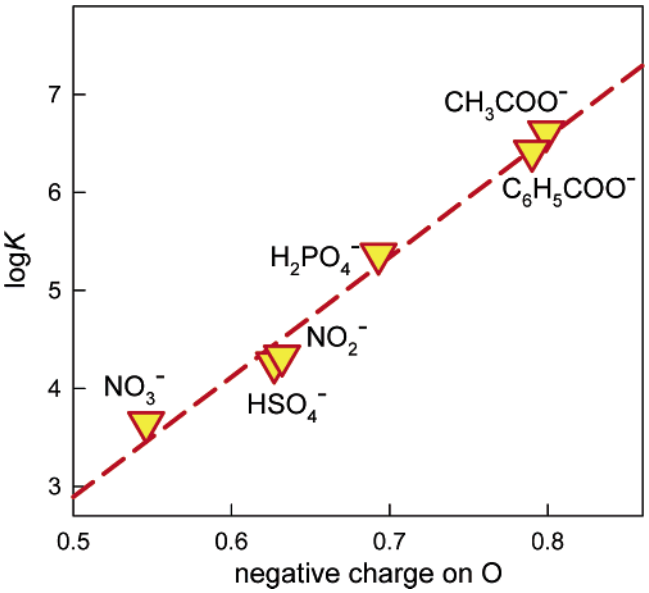


FIGURE 9. Linear relationship between the log$K$ value of the complexation equilibrium, $LH + X^- \rightleftarrows [LH\cdots X]^-$ in MeCN (LH = **4**), and the average negative charge on the oxygen atom of the oxoanion X^-. Partial charges were calculated through an ab initio method.[19]

association constants were determined through spectrophotometric titration experiments.

Quite interestingly, there exists a good linear dependence of log$K$ values upon the partial negative charge on the oxygen atoms of the oxoanions, as shown by the diagram in Figure 9. The higher the negative charge is, the higher the H-bond acceptor tendencies of the anion are. This linear relationship demonstrates that recognition selectivity is strictly related to the basicity of the anion.

Fluoride—not unexpectedly—displays its own behavior. Figure 10a shows the family of spectra obtained on titration of an MeCN solution of **4** with $[Bu_4N]F$.

On addition of the first equivalent of F^-, the receptor's charge transfer band undergoes a red shift from 325 to 375 nm, while the solution takes a yellow-orange color.

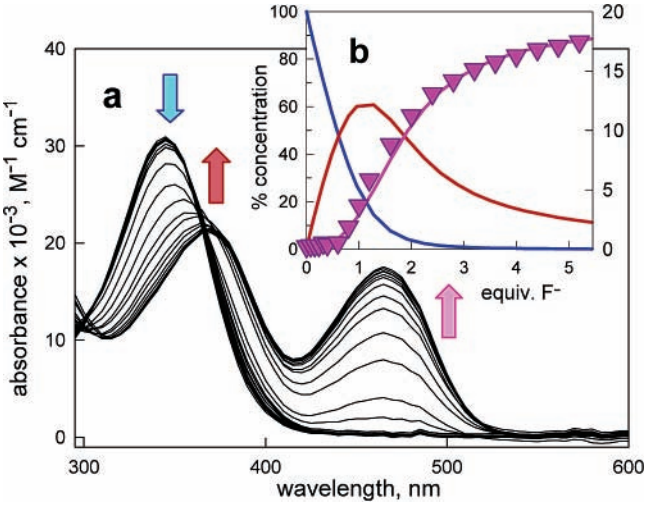


FIGURE 10. (a) Spectrophotometric titration of an MeCN solution of **4** (LH, 1.0×10^{-6} M) with a standard solution of $[Bu_4N]F$ at 25 °C. (b) Symbols: molar absorbance at 475 nm, right vertical axis, band pertinent to the deprotonated receptor L^-. Lines: % concentration, left side vertical axis, vs equiv of anion; blue line, LH; red line, $[LH\cdots F]^-$; and pink line, L^-.

Then, on addition of the second anion equivalent, a new band develops at 475 nm and the solution becomes red (see color changes in Figure 8). Best fitting of titration data was obtained on assuming the occurrence of two consecutive equilibria: 8, formation of a genuine H-bond complex, and 9, release of an HF molecule from the complex and, simultaneously, the receptor's deprotonation.

$$LH + X^- \leftrightarrows [LH\cdots X]^- \quad (8)$$

$$[LH\cdots X]^- + X^- \leftrightarrows L^- + [HX_2]^- \quad (9)$$

The following stepwise constants $\log K_1 = 7.4 \pm 0.1$ and $\log K_2 = 6.4 \pm 0.1$ were calculated. Because of the distinctly lower value of K_2 with respect to K_1, the formation of the $[LH\cdots F]^-$ complex and the deprotonation process do not overlap substantially (see the distribution of the species in Figure 10b). As a consequence, the band at 475 nm, pertinent to the deprotonated receptor L^- and responsible for the red color, forms only after the addition of the first equivalent of fluoride. The occurrence of equilibria 8 and 9 was corroborated by ^{1}H NMR titration experiments in a DMSO-d_6 solution (this solvent was chosen for solubility reasons): In particular, C−H_α protons were insensitive to the first equivalent addition of fluoride but underwent an upfield shift on addition of the second equivalent. Thus, it appears that the presence of the 4-nitrophenyl substituents increases the Brønsted acidity of the receptor and, according to eq 6, favors the deprotonation of one urea N−H fragment. The chromogenic 4-nitrophenyl group provides a further advantage, allowing one to monitor complex formation and deprotonation through definite color changes and spectral modifications.

Spectroscopic titration experiments are nice and convincing. However, the most compelling experimental evidence of the existence of the deprotonated receptor $[L]^-$ should come from its crystal and molecular structure.

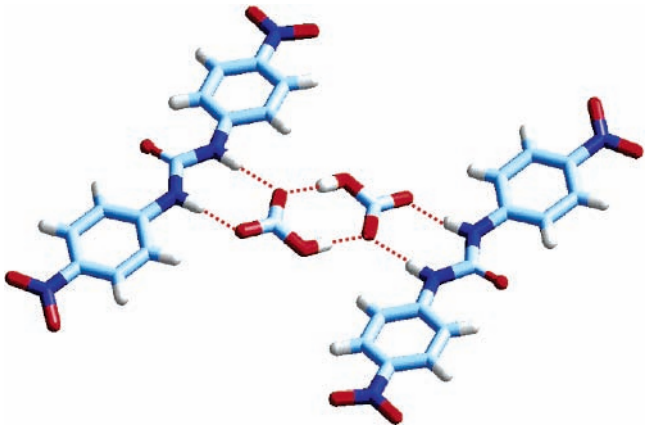


FIGURE 11. H-bond motif in the $\{[\mathbf{4}\cdots HCO_3]^-\}_2$ dimer, present in the $[Bu_4N][\mathbf{4}\cdots HCO_3]\cdot 2H_2O$ complex salt. H-bonds have been drawn as red dotted lines.[18]

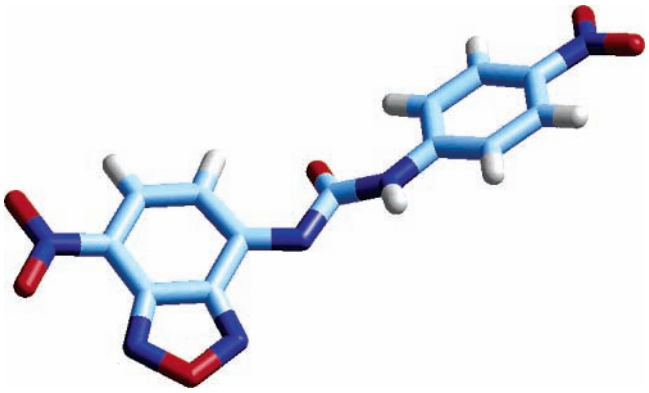


FIGURE 12. Structure of the L^- anion (LH = **5**). The tetrabutylammonium countercation has been omitted.[20]

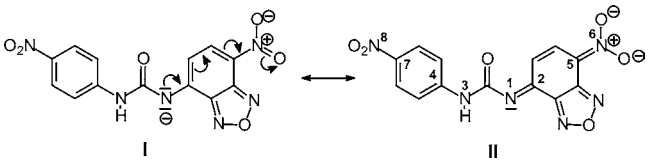
Indeed, yellow crystals were obtained from the slow evaporation in open air of a THF solution of **4**, in the presence of an excess of $[Bu_4N]F$. However, they corresponded to a compound of formula $[Bu_4N][LH\cdots HCO_3]\cdot 2H_2O$, containing a definite 1:1 H-bond complex between **4** and hydrogencarbonate. It is suggested that the $[LH\cdots HCO_3]^-$ complex formed on reaction of the deprotonated form of **4**, $[L]^-$, with carbon dioxide, in the presence of water, as described by eq 10:

$$L^- + H_2O + CO_2 \rightarrow [LH\cdots HCO_3]^- \quad (10)$$

The molecular structure, sketched in Figure 11, shows that the urea subunit of **4** gives a complementary hydrogen-bonding interaction with a HCO_3^- ion.[18] Moreover, each urea-bound HCO_3^- ion both donates and accepts a hydrogen bond to/from another urea-bound HCO_3^- ion, giving rise to a dimer.

Quite fortunately, the attempt of growing crystals of a deprotonated urea-based system was successful in the case of receptor **5**, in which two different electron-withdrawing substituents are appended to the urea subunit: 4-nitrophenyl and 5-nitrobenzofurazan.[20] In particular, on slow evaporation of an MeCN solution containing **5** and an excess of $[Bu_4N]F$, red crystals of a salt of formula $[Bu_4N]L$, suitable for X-ray diffraction studies, were ob-

Scheme 1. Resonance Representation of the Deprotonated Form of 5



I II

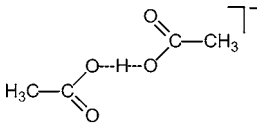
tained. The molecular structure of the L^- anion is shown in Figure 12.

It is observed that a proton has been abstracted from the N−H fragment close to the more electron-withdrawing substituent, i.e., the 5-nitrobenzofurazan moiety. Deprotonation induces significant structural modifications in the urea derivative. In particular, the plane containing the benzofurazan substituent and that containing the nitrophenyl subunit form a dihedral angle of 42.4°, whereas aromatic substituents in diarylurea derivatives are typically coplanar.[21] Thus, on deprotonation, the extended π-delocalization over the entire receptor's framework is strongly reduced, which represents a rather endothermic contribution to the deprotonation process (overwhelmed by the strong exothermic contribution associated to the formation of HF_2^-). Moreover, a detailed investigation of bond distances indicates that, on deprotonation, a substantial delocalization of negative charge on the 5-nitrobenzofurazan moiety takes place and that the $[L]^-$ anion is better described by the limiting formula II in the resonance representation reported in Scheme 1.

In particular, the N(1)−C(2) distance (1.32 Å) is significantly shorter than the N(3)−C(4) distance (1.39 Å) and the C(5)−N(6) distance (1.38 Å) is distinctly shorter than the C(7)−N(8) distance (1.46 Å), in agreement with the bonding description of formula II.

To verify and monitor the occurrence of the deprotonation process in the liquid phase, an MeCN solution of **5** was titrated with a $[Bu_4N]F$ solution. Best fitting of spectrophotometric titration data was obtained on the basis of the two consecutive equilibria 7 and 8, to which stepwise constants corresponded as follows: $\log K_1 > 6$ and $\log K_2 = 4.2 \pm 0.2$. The deprotonation of the receptor is clearly signaled by the development of a band at 382 nm, which begins to form after the addition of the first equivalent of F^- and reaches its limiting absorbance ($\epsilon = 40000\ M^{-1}\ cm^{-1}$) on addition of a 10-fold excess of anion (see Figure 13a). Quite surprisingly, a similar spectral pattern was obtained on titration of a solution of **5** with $[Bu_4N]CH_3COO$, as shown in Figure 13b. Also, in this case, the band at 382 nm, pertinent to the deprotonated receptor, develops after the addition of the first equivalent of acetate. Titration data were satisfactorily fitted on assuming the occurrence of the two stepwise equilibria 7 and 8, with $\log K_1 > 6$ and $\log K_2 = 3.8 \pm 0.1$. In particular, on addition of the second CH_3COO^- ion, a CH_3COOH molecule is released from the $[LH\cdots CH_3COO]^-$ complex, to give the deprotonated receptor $[L]^-$ and the $[CH_3COOH\cdots OOCCH_3]^-$ self-complex, whose structural arrangement is tentatively sketched below.

Receptor deprotonation, following the consecutive equilibria 7 and 8, was observed also in the case of $H_2PO_4^-$



6

($\log K_1 = 5.40 \pm 0.02$ and $\log K_2 = 3.83 \pm 0.05$), as signaled by the development of the band at 382 nm on addition of an anion excess. On the other hand, no deprotonation but simple formation of the $[LH\cdots X]^-$ H-bond complex were observed for other investigated anions, even on addition of a large excess of X^-: Cl^- ($\log K = 4.05 \pm 0.01$), NO_2^- ($\log K = 3.82 \pm 0.01$), and NO_3^- ($\log K = 1.99 \pm 0.03$). The tendency to deprotonation is expressed by β_n, i.e., the constant of the overall equilibrium of type 3. Equation 6 shows that β_n results from the combination of $K_A(LH)$ and $\beta(HX_2^-)$. In particular, eq 6 can be rewritten as follows: $\log\beta_n = \log\beta(HX_2^-) - pK_A(LH)$. On this basis, the different behavior of the two urea-based receptors **4** and **5** is pictorially explained in Figure 14.

In the diagram, the scales of $pK_A(LH)$ and that of $\log\beta([HX_2]^-)$ are tentatively juxtaposed. The diagram illustrates how (i) the intrinsic acidity of LH and (ii) the stability of $[HX_2]^-$ concur to determine a receptor's deprotonation: the receptor, either **4** or **5**, undergoes

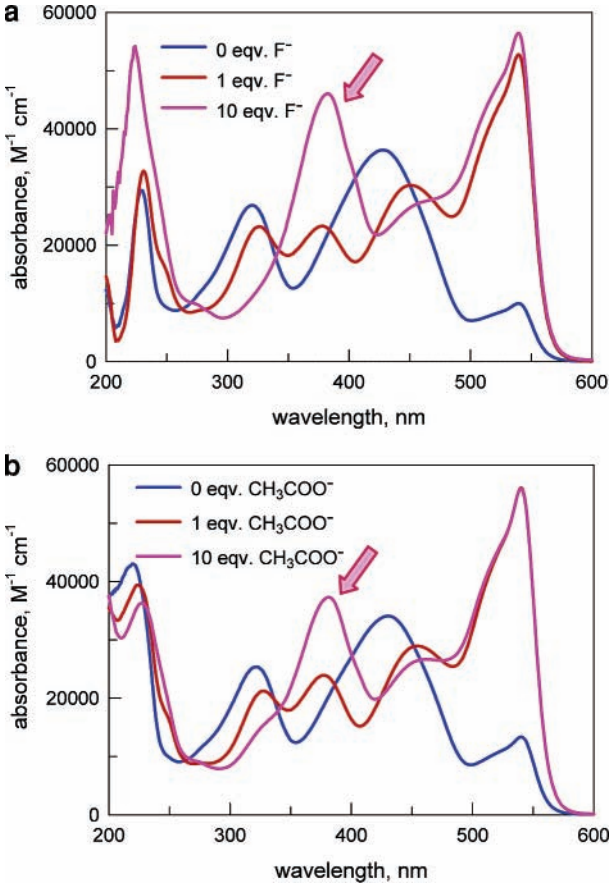


FIGURE 13. (a) Selected spectra recorded during the titration of an MeCN solution 4.11×10^{-5} M in **5** (LH) with $[Bu_4N]F$. (b) Selected spectra recorded during the titration of an MeCN solution 4.11×10^{-5} M in **5** (LH) with a $[Bu_4N]CH_3COO$. The band at 382 nm, indicated in both spectra by a pink arrow, pertains to the deprotonated form of the receptor, L^-.

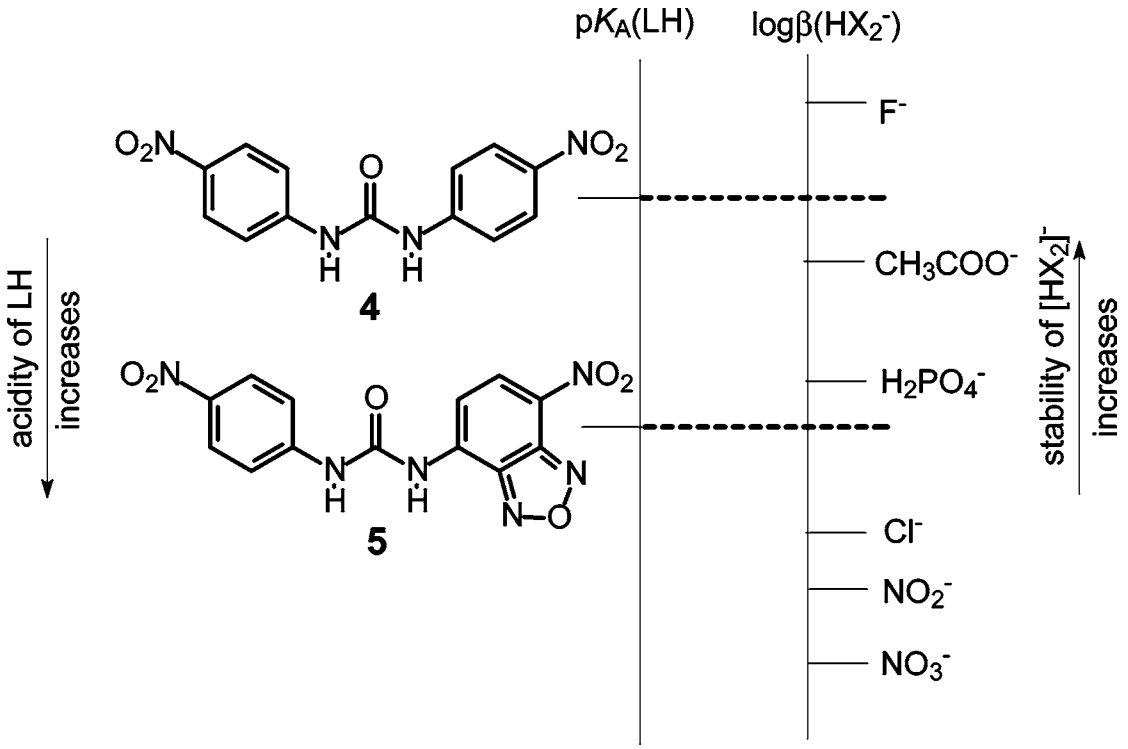


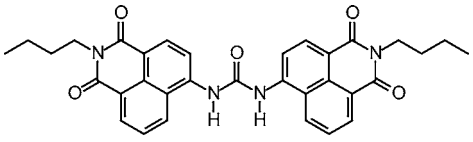
FIGURE 14. Tentative juxtaposition of the acidity scale of the receptor LH and of the stability scale of the self-complex $[HX_2]^-$. Each receptor LH deprotonates in the presence of an excess of anions whose $\log\beta([HX_2]^-)$ values lie above the pertinent dashed line: red for **4** and blue for **5**. Exact values of pK_A(LH) and $\log\beta(HX_2^-)$ are unknown and have been qualitatively assigned.

deprotonation in the presence of those anions whose $\log\beta([HX_2]^-)$ values are placed above the pertinent dashed line: red for **3** and blue for **4**. Receptor **5**, due to the presence of the more electron-withdrawing substituent 5-nitrobenzofurazan, is distinctly more acidic than **3** and undergoes deprotonation even in the presence of anions, like CH_3COO^- and $H_2PO_4^-$, less inclined to the formation of the self-complex $[HX_2]^-$.

It has to be noted that the anion-induced N−H deprotonation is even more favored for receptors containing a thiourea subunit,[22] due to the higher acidity of thiourea with respect to urea (pK_A values in DMSO are 21.1 and 26.9, respectively).[23] The fluoride-induced deprotonation of a thiourea-based receptor containing a naphthalimide substituent has been observed in a 1:1 water−ethanol mixture, while the concomitant formation of the $[HF_2]^-$ ion has been monitored through an ^{1}H NMR titration experiment in DMSO-d_6.[24]

Urea-Based Colorimetric Sensors for Anions: A Caveat

There exists a widespread and increasing interest in the design of colorimetric anion sensors, i.e., molecular systems that reveal through a color change the presence and the activity of a given anion in solution.[25,26] Typically, a colorimetric sensor is constituted by a chromogenic subunit covalently linked to a receptor. In this connection, the urea derivative **4** should be considered a (rather rudimentary) colorimetric sensor of fluoride, in the sense that it gives a vivid color change (from colorless to orange-red) on excess addition of F^- (up to 5 equiv), a change that is not observed in the presence of any other anion. We know now that such a sharp color change is associated with a receptor's deprotonation. Perhaps it is not accidental that most of the colorimetric sensors for anions reported during the last few years, and continuously appearing in the literature, contain one or more urea fragments, equipped with chromogenic (and electron-withdrawing) substituents, and display a unique selectivity for fluoride.[27−29] In general, beautiful colors develop on interaction of a given neutral sensor with F^-: yellow and red (expected and ascribed to the deprotonation of one N−H fragment) but also blue and green (less expected and to be explained). In this connection, we considered a further urea-based receptor (**6**), which had been symmetrically armed with a powerful chromogenic substituent, naphthalenimide, bringing a yellow color.[30]



6

We observed that, on addition of an excess of a few equivalents of $[Bu_4N]F$, the color of the DMSO solution of **6** turned from yellow to red. Then, on further addition of fluoride, up to tens of equivalents, a blue color developed (see the photograph in Figure 15).

The yellow-to-red color change is not surprising. Figure 16a reports the family of spectra obtained on titration of a DMSO solution of **6** with $[Bu_4]F$, which has been added up to 5 equiv.

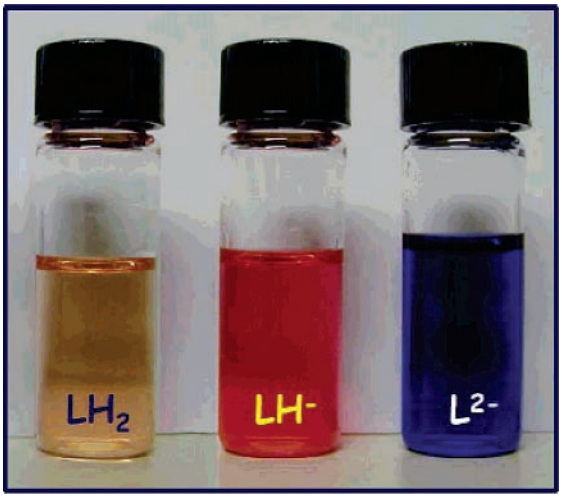


FIGURE 15. Color changes observed on addition of $[Bu_4N]F$ to a DMSO solution of receptor **6** (= LH_2). From the left-hand: no addition (species present, LH_2); plus 5 equiv of $[Bu_4N]F$ (dominant species, LH^-); and plus 40 equiv of $[Bu_4N]F$ (dominant species, L^{2-}).

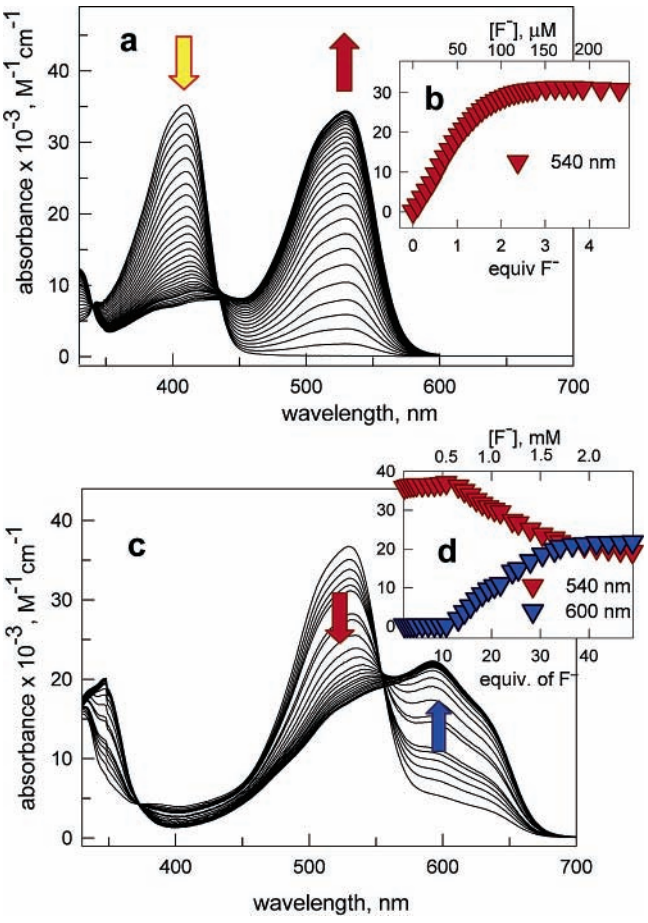


FIGURE 16. Family of spectra taken over the course of the titration of a DMSO solution 5.0×10^{-5} M in receptor **6** (LH_2) with a standard solution of $[Bu_4N]F$ at 25 °C. (a) From 0 to 5 equiv of $[Bu_4N]F$ (the band that develops at 540 nm pertains to the monodeprotonated receptor $[LH]^-$). (c) From 5 to 50 equiv of $[Bu_4N]F$ (the band that develops at 600 nm pertains to the doubly deprotonated receptor $[L]^{2-}$).

On fluoride addition, the charge transfer band of the naphthaleneimide chromophore undergoes a remarkable red shift (from 400 to 540 nm, of an extent similar to what observed for deprotonation of receptor **4**). Moreover, limiting absorbance is achieved on addition of 2 equiv of F^- (see the titration profile in Figure 16b). This suggests the occurrence of the overall equilibrium (LH_2 = **6**):

$$LH_2 + 2F^- \rightleftarrows [LH]^- + HF_2^- \qquad (11)$$

The preliminary step, in which the H-bond complex is formed, seems to be excluded in the present case, probably due to the stabilization of the $[LH]^-$ anion by the highly polar DMSO. Occurrence of the N−H deprotonation is confirmed by the upfield shift of all aromatic protons, as observed in a ^1H NMR titration experiment in DMSO-d_6. A similar behavior was observed on titration with $[Bu_4N]OH$, but in this case, the band at 540 nm reached its limiting absorbance on addition of 1 equiv of OH^-. On addition of a further excess of $[Bu_4N]F$ (10 equiv and more), the color of the solution turned from red to blue (see Figure 15), while, in the visible spectrum (Figure 16c), the band at 540 nm disappeared and a new band formed at 600 nm. Such a band reached its limiting intensity upon addition of ca. 30 equiv. It is suggested that the new band pertains to the doubly deprotonated receptor $[L]^{2-}$, which forms according to equilibrium 12:

$$[LH]^- + 2F^- \rightleftarrows [L]^{2-} + HF_2^- \qquad (12)$$

The process is fully reversible, as indicated by the fact that on progressive addition of water, the blue DMSO solution first turns red and then yellow. Double deprotonation of the urea subunit of **6** is observed also on titration with $[Bu_4N]OH$, but the limiting value of the band at 600 nm is achieved on addition of a smaller anion excess (5−6 equiv) than for fluoride. It has to be noted that the second deprotonation of **6** is induced by hydroxide and fluoride but not by other anions. Acetate induces deprotonation of one N−H fragments, according to a 1:1 stoichiometry (which defines the following acid−base equilibrium: $LH_2 + CH_3COO^- \rightleftarrows [LH]^- + CH_3COOH$, with a $\log K = 4.97 \pm 0.01$), but no appearance of the band at 600 nm and development of the blue color are observed, even after the addition of a huge excess of $[Bu_4N]CH_3COO$. The less basic anion $H_2PO_4^-$ is able to remove one proton from **6** but only after large excess addition. No deprotonation at all is observed with less basic oxoanions such NO_2^-, NO_3^-, HSO_4^-, and remaining halides, Cl^- and Br^-. Thus, not surprisingly, the interaction selectivity of **6** is solely related to the basicity of the anion and to the consequent capability of abstracting an H^+ from the receptor: OH^- (double deprotonation) > CH_3COO^- (single) > $H_2PO_4^-$ (single). Fluoride (double deprotonation) is a special case: F^- itself is a less strong base than acetate in DMSO ($pK_A = 15 \pm 2$ and 12.3, respectively).[23] However, two F^- ions behave as a strong base and exhibit a large affinity toward H^+, which is second only to OH^- (pK_A = 32 in DMSO)[23] and is due to the unique stability of the H-bond complex HF_2^-.

Thus, it appears that the development of vivid colors on the interaction of urea-containing receptors with fluoride does not necessarily indicate the formation of an

especially stable H-bond complex but may simply reflect the occurrence of the stepwise deprotonation of the two N−H fragments. The second deprotonation process requires the addition of a large excess of F^-. Perhaps such a circumstance is not realized by the reader in view of the tendency of many authors to indicate the concentration of the added anion rather than the number of equivalents or mole ratio (especially if the concentration of the receptor's solution is not specified). The above considerations should not prevent the colorimetric determination of the fluoride ion using N−H-containing receptors, which is indeed very efficient and suffers from the interference of only one analyte: hydroxide. Simply, one should keep in mind that the investigated recognition process does not take place within the sophisticated realm of supramolecular chemistry but technically belongs to the mature and congested class of Brønsted acid−base reactions.

Conclusion

Hydrogen bonding between an A−H donor and a B acceptor has been defined as a frozen proton transfer from A to B:[31] The more pronounced the proton transfer is, the higher the intensity of the H-bond interaction is, and in the world of anion recognition, the higher the stability of the [A−H···B] H-bond complex is. The examples previously discussed fit well the definition for two main reasons. First, there exists a correlation between the log$K$ value of the complexation equilibrium and the basic tendencies of the anion (which, for oxoanions, can be tentatively expressed by the partial negative charge on the oxygen atoms). Second, it has been shown that, in the presence of a strongly polarized A−H fragment, proton transfer takes place in a definitive way, to give distinct A^- and H−B species. Solvent polarity plays an important role, as it can stabilize and favor the formation of the deprotonated form A^-. For instance, in the poorly polar CH_2Cl_2, the urea-based receptor **4** gives only the H-bond complex $[LH_2\cdots F]^-$, even after addition of a large excess of fluoride. In MeCN, fluoride addition leads to the stepwise formation of the H-bond complex and of the singly deprotonated receptor $[LH]^-$. In the highly polar DMSO, progressive addition of F^- induces the consecutive deprotonation of both N−H fragments.

In conclusion, receptors containing a single H-bond donor fragment provide a selectivity, which is solely related to the basicity of the anion. A more valuable selective behavior can be achieved by strategically inserting the H-bond donor groups inside multidentate, cyclic, and polycyclic receptors, whose shape and size have been designed by taking into account the geometrical requirements of the envisaged anion. Whereas each N−H fragment will tend to impose its selectivity rules based on anion basicity, such a tendency can be contrasted and hopefully counterbalanced by properly designed steric constraints. In this connection, the structural criteria for the deliberate design of anion selective receptors containing two or more urea subunits have been recently and comprehensively discussed.[32]

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