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(Benzylideneamino)thioureas – Chromogenic Interactions with Anions and N–H Deprotonation

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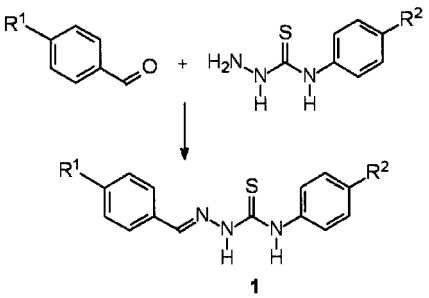
A family of neutral *N*-(R^1-substituted-benzylideneamino)-*N*′-(R^2-substituted-phenyl)thioureas (LH) were designed as anion receptors, and their interactions with anions in MeCN solution were investigated through spectrophotometric and ^{1}H NMR titration experiments. While oxo anions (e.g., CH_3COO^-, $H_2PO_4^-$) form genuine H-bond complexes based on complementary N–H···O interactions with LH receptors, the fluoride ion undergoes a two-step interaction, involving (i) formation of the $[LH\cdots F]^-$ complex, and (ii) release of an HF molecule to give $[HF_2]^-$ and the deprotonated form of the receptor (L^-). Deprotonation takes place at the N–H fragment closer to the R^2-substituted phenyl ring, as indicated by ^{1}H NMR spectroscopy. The log *K* values for the formation of the $[LH\cdots CH_3COO]^-$ H-bond complexes vary over the 3.1–3.8 range and are scarcely affected by the natures of the R^1 and R^2 substituents. The investigated systems may be of interest in the design of molecular devices in which the optical properties of different and distant substituents are modulated through the interaction of a chosen anion at the thiourea site.

Introduction

Ureas and thioureas participate in bifurcate H-bond interactions and are currently finding use as binding fragments in the design of neutral receptors for anions.[1] Hydrogen bonding has been defined as a more advanced or less advanced (and "frozen") proton transfer from the donor (the receptor) to the acceptor (the anion).[2] For this reason, the more acidic thiourea fragment (pK_A = 21.1 in DMSO)[3] typically produces stronger interactions with anions than urea (pK_A = 26.9).[3] In limiting situations, urea- and thiourea-based receptors, on interaction with strongly basic anions, may undergo deprotonation of one N–H fragment. In the presence of an excess of fluoride ion this is rather common behavior, due to the formation of the particularly stable HF_2^- hydrogen-bonding self complex.[4–7] In recent years, moreover, a variety of thiourea-based receptors have been modified with chromogenic and fluorogenic substituents to produce chemosensors: molecular systems capable of communicating the occurrence of the recognition event to the outside world through an optical signal (a color change, modulation of the fluorescent emission).[8] In the case of colorimetric chemosensors, the interaction with the anion typically stabilizes the excited state of the chromophore and induces a greater or lesser degree of redshift of the charge transfer absorption band, thus providing an efficient channel for qualitative and quantitative evaluation of anion activity in solution.[9,10]

Here we report a new class of thiourea-based receptors **1** that can be easily obtained through Schiff-base condensation of a benzaldehyde and a phenylthiosemicarbazide, all cheap and commercially available products. The receptor consists of a phenylthiourea subunit, suitable to interact with the anion, covalently linked to a benzylideneamino moiety, intended to act as a chromogenic signaling unit. We have investigated the interaction of anions with (benzylideneamino)thioureas **1a**–**f** in MeCN solution in detail, through spectroscopic titration experiments. In particular, we have tried to answer the following questions: (i) Does an N–H fragment of the receptor deprotonate in the presence of more basic anions, in particular fluoride? (ii) If yes, which one of the two N–H fragments deprotonates, that bound to the imino nitrogen atom or that bound to the phenyl carbon atom? (iii) To what extent do the R^1 and R^2 substituents influence these processes and modulate the spectral behavior and the color changes?



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1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = OCH_3$
1c $R^1 = NO_2$, $R^2 = H$
1d $R^1 = NO_2$, $R^2 = OCH_3$
1e $R^1 = CF_3$, $R^2 = H$
1f $R^1 = CF_3$, $R^2 = OCH_3$
1g $R^1 = F$, $R^2 = H$

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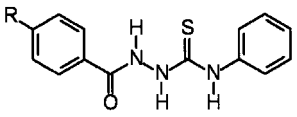
It should be noted that structurally related benzamidothioureas of type **2** have recently been shown to be versatile colorimetric chemosensors for anions, giving significant redshifts of the charge-transfer absorption band – distinctly more pronounced than in the case of simple thioureas – on interaction with F^-, CH_3COO^-, and $H_2PO_4^-$.[11]



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Results and Discussion

Structures of (Benzylideneamino)thioureas

The crystal structure of **1g** has been reported.[12] Figure 1 shows the molecular structure of the compound, as obtained from the Cambridge Data Base.

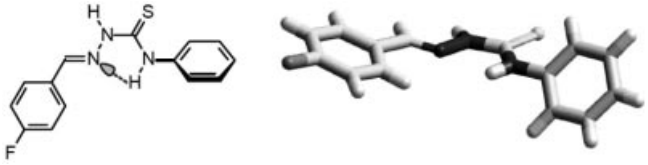


Figure 1. Molecular structure of **1g**, as obtained from X-ray diffraction studies on a single crystal.[12] The arrangement of the thiourea fragment may be stabilized by an H-bond interaction between one N–H group and the imino nitrogen atom.

Two structural features are noteworthy: (i) the urea fragment lies in the same plane as the benzylideneamino subunit, whereas the phenyl substituent lies on a plane rotated by ca. 40°, and (ii) the bulky substituents at the C=N double bonds are (*E*) to each other. The arrangement of the thiourea moiety favors the establishment of a hydrogen-bonding interaction between the N–H fragment linked to the phenyl substituent and the imino nitrogen atom. It is tentatively assumed that the analogous derivatives **1a**–**f** have similar structures, and that these are maintained in MeCN solution.

Reaction with OH^-

In order to establish the acid-base behavior of derivatives **1a**–**f**, we preliminarily carried out titration experiments with $[Bu_4N]OH$. On addition of hydroxide, the colors of MeCN solutions of the (benzylideneamino)thiourea receptors turned from yellow to varying shades of red. Figure 2 shows the family of spectra obtained over the course of the titration of a solution of **1c** ($5.00 \cdot 10^{-5}$ M) with $[Bu_4N]OH$ at 25 °C.

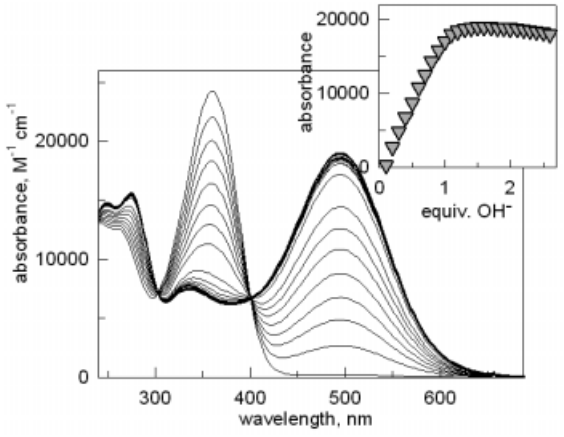


Figure 2. Family of spectra recorded over the course of the titration of an MeCN solution ($5.00 \cdot 10^{-5}$ M in **1c**) with a standard solution of $[Bu_4N]OH$ at 25 °C. Inset: titration profile of the band centered at 500 nm, corresponding to the deprotonated form of the (benzylideneamino)thiourea receptor.

It can be observed that, on hydroxide addition, the band centered at 350 nm, specific to the derivative **1c** and attributable to a charge-transfer transition from the imino nitrogen atom to the nitro group within the benzylideneamino moiety, progressively disappears, while a new band develops at 500 nm. This band reaches a limiting absorbance ($20000\ M^{-1}cm^{-1}$) on addition of 1 equiv. of OH^-, as indicated by the titration profile shown in the inset of Figure 2. The presence of sharp isosbestic points indicates that only two species are present at equilibrium over the course of the titration experiment, which suggests that an acid-base neutralization equilibrium takes place, involving the deprotonation of one N–H group of the thiourea subunit, as described in Equation (1).

$$LH + OH^- \leftrightarrows L^- + H_2O \quad (1)$$

The band centered at 500 nm should therefore represent the deprotonated form of receptor **1c** (= LH). In particular, the negative charge made available on proton release causes an increase in the intensity of the electrical dipole along which the optical transition takes place, which accounts for the substantial redshift of the band (150 nm). Note that the steepness of the titration profile, as well as the absence of any curvature at the equivalent point, prevent any reliable determination of the neutralization equilibrium constant according to Equation (1), the value of which can only be estimated ($K > 10^7$).

Semiempirical calculations (PM3 method) on LH and L^- molecular systems confirmed the charge-transfer nature of the optical transition. Figure 3 shows the HOMOs and LUMOs of the LH and L^- forms of **1c**.

It can be observed both for LH and for L^- that the electron density in the HOMO is essentially centered on the thiourea sulfur atom, whereas in the LUMO it is mainly located on the benzylidene ring. However, delocalization towards the $–NO_2$ group is distinctly more pronounced in the L^- form, which accounts for the marked redshift of the absorption band.

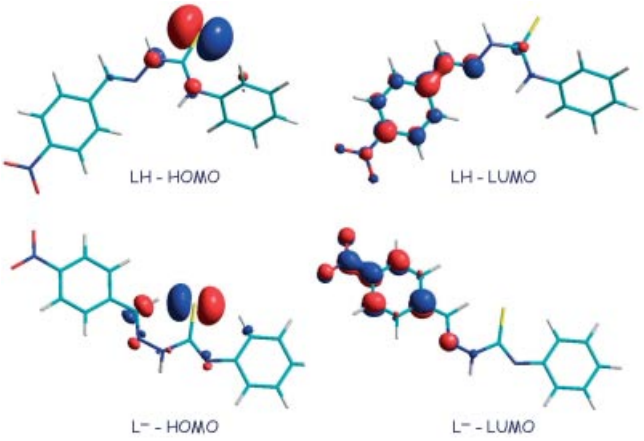


Figure 3. HOMOs and LUMOs of the LH and L^- forms of **1c**, calculated by the PM3 method.

Wholly similar behavior – (i) development of an intense absorption band in the visible region, (ii) achievement of the limiting absorbance on addition of 1 equiv. of OH^-, and (iii) steep titration profiles that prevented the determination of the equilibrium constants according to Equation (1) – was observed on spectrophotometric titration of all the other derivatives of type **1**. The positions of the bands of LH and L^- and the magnitudes of the redshifts varied depending upon the nature of the substituents R^1 and R^2, as shown in Table 1.

Table 1. Spectral parameters of the neutral (LH) and deprotonated (L^-) forms of receptors **1a**–**f**, determined at 25 °C in MeCN solution.

LH	R^1	R^2	LH, λ_{max} [nm]	L^-, λ_{max} [nm]	λ [nm]
1a	H	H	320	382	62
1b	H	OCH_3	314	386	72
1c	NO_2	H	360	500	140
1d	NO_2	OCH_3	360	508	148
1e	CF_3	H	320	410	90
1f	CF_3	OCH_3	324	410	86

Significant substituent effects on spectral properties are observed only for R^1 = $-NO_2$, which ensures absorption bands of relatively low energy for both LH and L^- forms and a pronounced redshift (up to 148 nm when R^2 = $-OCH_3$), which may be due to the particular capability of the nitro group to withdraw electrons through π-conjugation. Moderate redshifts are observed when R^1 = $-CF_3$ or –H.

At this stage it seemed important to characterize the structural details of the deprotonation process and, hopefully, to define and localize the acidic site. Useful insights in this sense were provided by ^{1}H NMR titration experiments: Figure 4 shows a family of ^{1}H NMR spectra taken over the course of a titration of a CD_3CN solution of **1c** with $[Bu_4N]OH$ and illustrates the spectral shifts of the C–H protons induced by base addition.

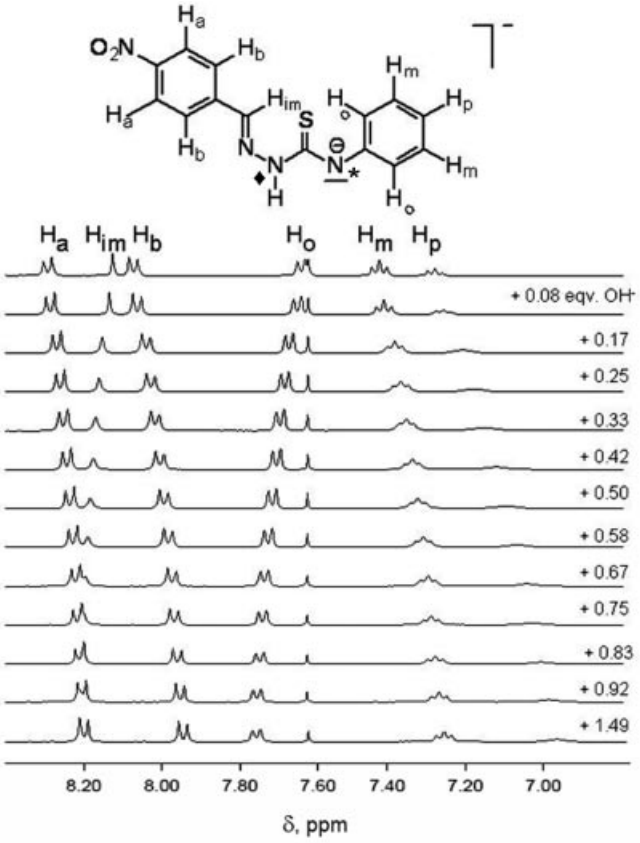


Figure 4. ^{1}H NMR titration of a $5.00 \cdot 10^{-3}$ M solution of **1c** in CD_3CN with $[Bu_4N]OH$.

It was anticipated that the ^{1}H NMR pattern would indicate that the deprotonation process would take place at the N–H fragment closer to the phenyl group (labeled with a star) and that, on deprotonation, the molecule would assume the structural arrangement sketched in the formula in Figure 4. Before examining the spectroscopic features in detail, one should consider that two effects would be expected to result from the deprotonation of one N–H fragment: (i) an increase in electron density in the phenyl rings, by through-bond propagation, according to a π-mechanism, which should cause a shielding effect and promote an *upfield* shift of the C–H signals, and (ii) a polarization of the C–H bonds, induced by a through-space effect, of an electrostatic nature; in particular, the partial positive charge shifted onto the proton should cause a deshielding effect and promote a *downfield* shift. This electrostatic effect should be stronger for protons close to the negatively charged thiourea nitrogen atom and should vanish with increasing CH···N^- distance. It can be observed in Figure 4 that C–H_{im} and C–H_o proton signals experience downfield shifts, whereas the signals of all the other aromatic protons undergo greater or lesser degrees of upfield shifts.

The variation in the different chemical shifts $\Delta\delta$ (ppm) over the course of the titration is shown in Figure 5.

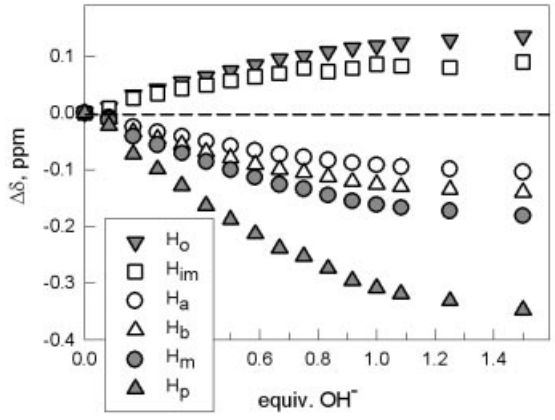


Figure 5. Chemical shift values obtained from the ^{1}H NMR titration in Figure 4.

A negative charge on the N* atom accounts for a dominating electrostatic effect on the nearby H_o atom, responsible for the downfield shift. Moreover, partial negative charge is delocalized onto the thiourea sulfur atom through a π-mechanism, which exerts a rather strong electrostatic effect on the H_{im} atom and induces an overwhelming downfield shift. In the cases of all the other C–H protons the through-space effect vanishes, due to the increased distances, and the through-bond effect dominates, which induces a general upfield shift. Such an effect is more pronounced for protons on the phenyl ring linked to the N* atom, in particular the H_p atom, onto which a larger amount of negative charge is transferred through a π-resonance mechanism. The through-bond effect and the consequent downfield shift are less marked for hydrogen atoms H_a and H_b on the other, more distant aromatic ring. It should be noted that extended π-delocalization implies that on N*–H deprotonation the phenyl ring becomes coplanar with the rest of the molecular framework. We suggest that it is solely the favorable energy term associated with the coplanarization of the phenyl ring that determines the deprotonation of the N*–H group. Such a contribution could not be observed on deprotonation of the N♦–H fragment, as the adjoining benzylideneamino system is already coplanar with the thiourea moiety.

On a purely spectroscopic basis, the deprotonation of the N♦–H fragment must be excluded because this circumstance (i) would not be compatible with the prominent downfield shift of the H_o signal, and (ii) would not account for the more pronounced upfield shift experienced by H_p and H_m signals relative to H_a and H_b signals.

Interaction with Fluoride

Similar spectrophotometric behavior was observed on titration with fluoride; Figure 5 shows the family of spectra obtained over the course of the titration of a solution of **1c** with [Bu$_4$]NF. The spectral pattern is the same as observed in Figure 2, the only difference being that the absorption band centered at 500 nm, representing the deprotonated form of the receptor, reaches its limiting value on addition of *2 equiv.* of anion [see the titration profile shown in inset (a) of Figure 6].

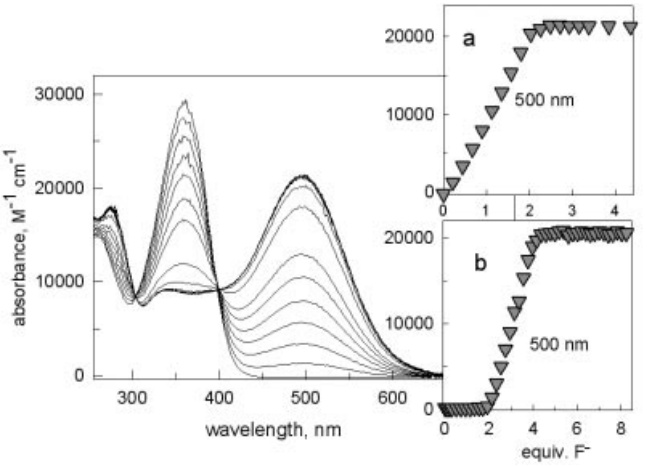


Figure 6. Family of spectra taken in the course of the titration of an MeCN solution ($5.00\cdot10^{-5}$ M in **1c**) with a standard solution of [Bu$_4$]NF at 25 °C. Inset (a): titration profile of the band centered at 500 nm. Inset (b): titration profile of the band centered at 500 nm for a titration experiment in which [Bu$_4$]NF was added to an MeCN solution ($5.00\cdot10^{-5}$ M both in **1c** and in CF_3SO_3H).

This indicates the occurrence of the following overall equilibrium (LH = **1c**) [Equation (2)], in which a proton is abstracted from one of the N–H fragments of the (benzylideneamino)thiourea receptor and bridges two F^- ions, to give the hydrogen difluoride H-bond self complex.

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

Significant details concerning the fluoride-induced deprotonation process were obtained through ^{1}H NMR titration; Figure 7 shows the spectra obtained over the course of the titration of a CD_3CN solution of **1c** with [Bu$_4$]NF. The spectroscopic pattern is very similar to that observed in the titration with OH^-. In particular, H_o and H_{im} signals are shifted downfield, whereas all the other signals of the aromatic protons undergo greater or lesser degrees of upfield shift.

It should be noted, however, that the shift of the C–H_{im} proton on addition of the first equivalent of fluoride is distinctly more pronounced than that observed on addition of OH^-. Moreover, the titration profile shown in Figure 8 indicates that a limiting value of $\Delta\delta(H_{im})$ is reached on addition of 1 equiv. of F^-.

This suggests that, in the first step, the fluoride ion establishes a hydrogen-bonding interaction with a thiourea subunit of the receptor, which, on complexation, should be arranged as illustrated in the formula in Scheme 1. In this situation, the H-bound anion may exert an effective electrostatic effect on the nearby H_{im} proton, inducing significant deshielding and a downfield shift. Then, on addition of the second F^- ion, an HF molecule is released from the H-bond complex, with formation of the $[HF_2]^-$ self complex and of the deprotonated receptor. The two stepwise equilibria are described by Equations (3) and (4).

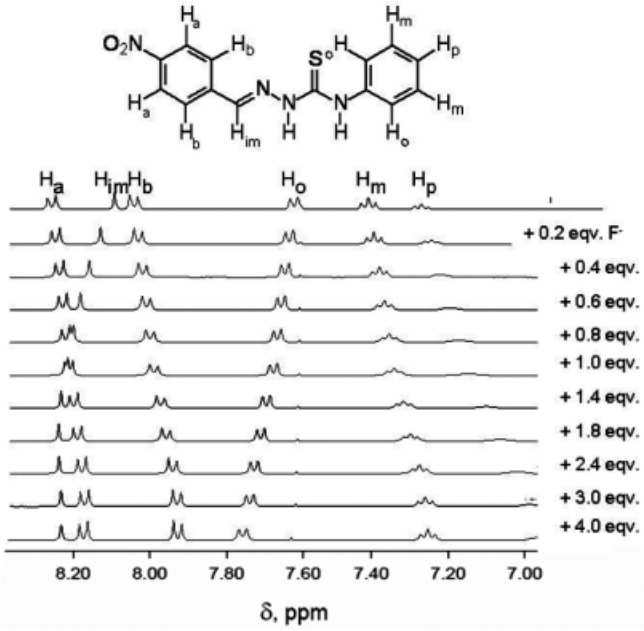


Figure 7. ^{1}H NMR titration of a CD_3CN solution of **1c** ($5.00 \cdot 10^{-3}$ M) with fluoride.

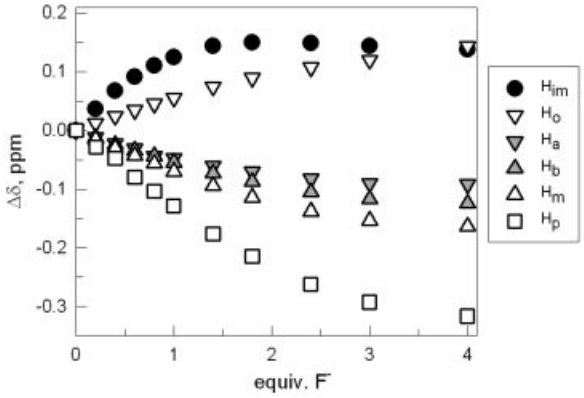
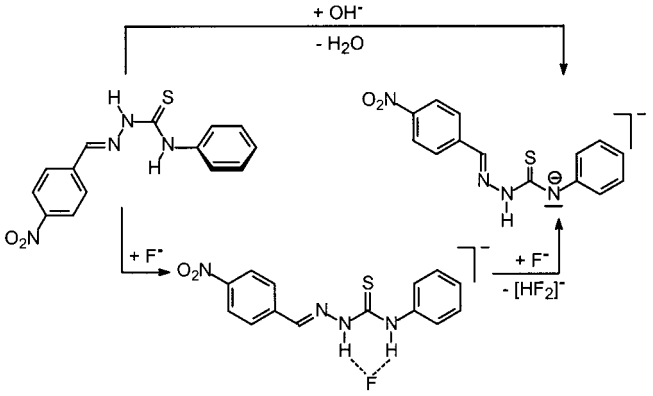


Figure 8. Chemical shift values obtained from the ^{1}H NMR titration in Figure 7.

$$LH + F^- \leftrightarrows [LH\cdots F]^- \quad (3)$$

$$[LH\cdots F]^- + F^- \leftrightarrows L^- + [HF_2]^- \quad (4)$$

The formation of the H-bond complex could not be detected by spectrophotometric titration experiments, as $[LH\cdots F]^-$ and L^- exhibit the same or very similar absorption spectra. In fact, the hydrogen-bonding interaction can be regarded as an either more pronounced or less pronounced proton transfer from the donor (the receptor) to the acceptor (the anion).[2] In the case of the basic fluoride ion, the proton transfer should be at a rather advanced state, which would account for a substantial increase in the negative charge on the thiourea nitrogen atom and a consequent modification of the dipole through which the optical transition takes place. The ^{1}H NMR experiment thus appears to be much more sensitive than the spectrophotometric investigation for the characterization of the receptor-fluoride H-bond complex. Moreover, it should be noted that the interaction of **1c** with hydroxide and fluoride involves conformational changes of the receptor, as inferred from spectroscopic studies and illustrated in Scheme 1.



Scheme 1. The interaction of receptor **1c** with OH^- (single step) and F^- (two steps).

In conclusion, it appears that the strong base OH^- directly takes up a proton from LH, whilst the F^- ion is not basic enough to abstract a proton and preliminarily forms an H-bond complex. On addition of a second F^-, however, the very stable $[HF_2]^-$ species can form and the receptor may undergo deprotonatation. Thus, although *one* F^- is not an especially strong base, *two* F^- ions are. Similar spectroscopic behavior was observed for all the other investigated (benzylideneamino)thiourea receptors.

We also carried out an additional experiment that confirmed the higher affinity of fluoride towards HF than towards urea-based receptors of type **1**. In particular, an MeCN solution ($5.00 \cdot 10^{-5}$ M both in **1c** and in triflic acid) was titrated with fluoride and UV/Vis spectra were recorded. No spectral changes were observed on addition of the first 2 equiv. of F^-, whilst after 2 equiv., the band at 500 nm formed and developed to reach its limiting absorbance value on addition of 4 equiv. of fluoride. The titration profile, based on the absorbance at 500 nm, is shown in Figure 5, inset (b). The profile clearly indicates that the first equiv. of F^- reacts with H^+ to give HF, and that the second equiv. of F^-, in the presence of the two neutral receptors HF and LH (= **1c**), then reacts with this to give the $[HF_2]^-$ complex. On further addition, fluoride goes on to interact with LH according to Equations (3) and (4), as described previously.

Interaction with Oxo Anions

Figure 9 shows the family of spectra obtained over the course of the titration of a $5.00 \cdot 10^{-5}$ M solution of **1c** in MeCN with $[Bu_4N]CH_3COO$.

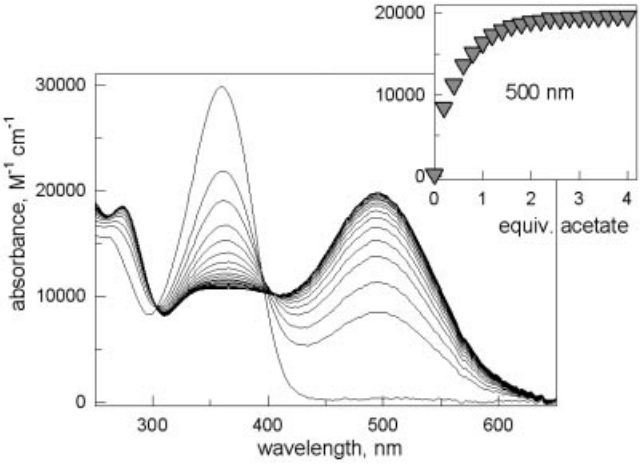


Figure 9. Family of spectra taken over the course of the titration of an MeCN solution of **1c** ($5\cdot10^{-5}$ M) with a standard solution of $[Bu_4N]CH_3COO$ at 25 °C. Inset: titration profile of the band centered at 500 nm.

The spectral features are the same as observed on titration with hydroxide and fluoride anions: a decrease in the band at 350 nm and the development of a band at 500 nm with a limiting absorbance of 20000 $M^{-1}cm^{-1}$. Best fitting of spectrophotometric data was achieved on assuming the occurrence of a 1:1 equilibrium, with a corresponding $\log K = 3.62 \pm 0.01$. Spectrophotometric investigation by itself, however, cannot tell us whether the equilibrium involves the formation of a genuine $[LH\cdots CH_3COO]^-$ complex or the deprotonation of LH, but such information has been provided by the ^1H NMR experiment. Figure 10

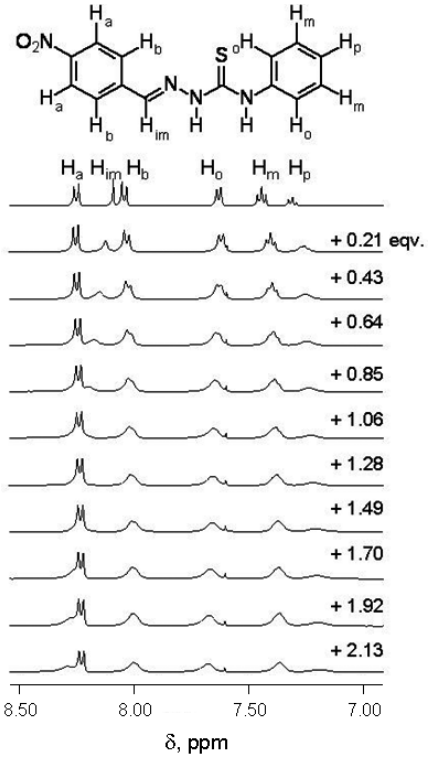
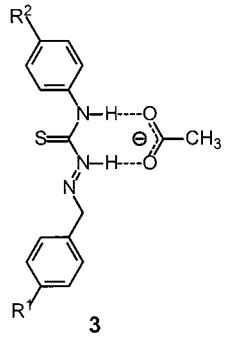


Figure 10. ^1H NMR titration of a solution of **1c** in CD_3CN ($5.00\cdot10^{-3}$ M) with $[Bu_4N]CH_3COO$.

displays the spectra obtained over the course of the titration of a CD_3CN solution of **1c** with $[Bu_4N]CH_3COO$.

Spectra observed on titration with OH^- and with F^- show similar features, such as downfield shifts of H_o and H_{im} signals and upfield shift of the signals of the other aromatic protons. However, two main differences are observed: (i) chemical shifts are less pronounced, and (ii) most signals undergo pronounced broadening. Such features may be indicative of the formation of a discrete H-bond complex, $[LH\cdots CH_3COO]^-$, the formula of which is indicated as **3**.



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In particular, complex formation slows down the rotation of the two aromatic rings, which causes line broadening. This effect is more pronounced for protons on the phenyl ring directly bound to the thioureido nitrogen atom, which is closer to the H-bound acetate. In any case, after the hydrogen-bonding interaction with CH_3COO^-, negative charge is transferred onto the receptor framework, which accounts for the distinct shifts of the C–H protons. Moreover, transfer of negative charge onto the receptor framework modifies the dipole along which the optical transition takes place to the same extent as observed in the case of LH deprotonation, which results in a completely similar change of spectral features. If the hydrogen-bonding interaction is considered an incipient proton transfer from the donor (e.g., –N–H) to the acceptor (e.g. $^-$O–), these results would suggest that the proton transfer is in a rather advanced state in the case of the strongly basic CH_3COO^- anion, and that the electronic properties of the receptor in the acetate complex are very similar to those of its deprotonated form.

Similar behavior was observed for all the other investigated receptors of type **1**. Table 2 reports the equilibrium constants for the formation of H-bond complexes of CH_3COO^- with systems **1a**–**f**, determined through spectrophotometric titration experiments.

The values given in Table 2 indicate that R^1 and R^2 substituents play only a minor role in determining the H-bond donor tendencies of the receptor. In fact, it can be seen that, taking **1a** ($R^1 = R^2 = H$) as a reference, the presence of an electron-withdrawing group ($-NO_2$, $-CF_3$) in the R^1 position induces an increase of ≤ 0.3 in $\log K$, while the presence of the electron-donating group $-OCH_3$ in R^2 causes a decrease of ≈ 0.3 in $\log K$.

On addition of the tetrabutylammonium salts of other common inorganic anions to MeCN solutions of **1c**, distinctive spectral changes were observed only in the case of

Table 2. Constants of the complexation equilibrium LH + $CH_3COO^- \leftrightarrows [LH\cdots CH_3COO]^-$ in an MeCN solution at 25 °C. In parentheses, standard deviations in the last figure.

LH	R^1	R^2	log *K*
1a	H	H	3.38(4)
1b	H	OCH_3	3.12(1)
1c	NO_2	H	3.62(1)
1d	NO_2	OCH_3	3.75(1)
1e	CF_3	H	3.77(1)
1f	CF_3	OCH_3	3.09(1)

$H_2PO_4^-$, which produced a family of spectra very similar to that obtained on titration with acetate. In addition, the ^1H NMR spectra were also very similar to those obtained in the titration with acetate, which suggested the formation of a genuine H-bond complex, the association constant of which, determined from a spectrophotometric titration, was 3.34 ± 0.05 log units. No other anion (HSO_4^-, NO_3^-, Cl^-, Br^-) induced any detectable spectral change in a $5.00 \cdot 10^{-5}$ M solution of **1c**, even if added in large excess. Such lack of interaction has to be attributed to the poor basicity of the anions and confirms that the selectivity of thiourea-based receptors (in the absence of designed steric constraints) is strictly related to the pK_A value of HA, the conjugated acid of the anion A^-.

Conclusions

We report a new family of (benzylideneamino)thiourea receptors, suitable for interaction with anions in aprotic media. The benzylidene derivative acts as an efficient chromophore, characterized by a charge-transfer transition, the energy of which is strongly influenced by the interaction with the anion: in the most favorable case ($R^1 = NO_2$; $R^2 = OCH_3$) a $\Delta\lambda$ value of 148 nm was observed. The natures of the receptor–anion interactions were unambiguously defined, whether (a) an acid-base neutralization process (with OH^-), (b) formation of an H-bond complex followed by receptor's deprotonation (with F^-), or (c) H-bond complex formation (with CH_3COO^- and $H_2PO_4^-$) occurred. The systems investigated here are structurally similar to the previously studied systems **2**,[11] in which the benzamido moiety is expected to increase the receptor's acidity, relative to the benzylideneamino subunit of **1**. Indeed, to point to a comparative example, the unsubstituted receptor **2** (R = H) forms an H-bond complex with acetate (log *K* = 5.47 in MeCN) distinctly more stable than its unsubstituted counterpart **1** (**1a**: log *K* = 3.38). However, in spite of the increased Brønsted acidity of the receptor **2**, the possibility of fluoride-induced N–H deprotonation was not considered by the authors.[11]

Systems of type **1** add to the broad family of neutral colorimetric sensors for anions, although, like all such receptors containing a single urea or thiourea subunit, they display a selectivity related solely to the anion basicity. Moreover, the fact that recognition studies unavoidably have to be carried out in aprotic solvents, in order to avoid successful competition from the medium (e.g., water), does not favor analytical applications. However, we believe that systems of type **1** may be of interest for the design of molecular devices possessing optical properties that can be controlled and modulated through a chemical input. In particular, systems such as **1** provide the potential for independent and inequivalent functionalization at the two distant sites R^1 and R^2 (e.g. with chromogenic and/or fluorogenic substituents), while the thiourea fragment may act as a control unit (to be activated through the interaction with a chosen anion). Preliminary investigations in this prospect are currently in progress in this laboratory.

Experimental Section

Materials: 4-[4-(Methoxy)phenyl]-3-thiosemicarbazide was purchased from Trans World Chemicals. MeCN, MeOH, 4-phenyl-3-thiosemicarbazide, all aldehydes, and tetraalkylammonium salts of anions (the counterion was Bu_4N^+ for all anions except for chloride, for which $BzEt_3N^+$ was used) were purchased from Sigma–Aldrich Chemical Co. Commercial reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX 400 (400 MHz) spectrometer; chemical shifts are reported in ppm downfield from TMS. Mass spectra were obtained with a Thermo Finnigan LCQ Advantage Max spectrometer fitted with an ESI source and an ion trap. UV/Vis spectra were taken with either a diode-array Hewlett–Packard 8452A or a scanning Varian Cary 100 Scan spectrophotometer.

General Procedures for Preparing 1-(4-Substituted-benzylidene)-4-(4-substituted-phenyl)thiosemicarbazides 1: Equal amounts (0.30 mmol) of the appropriate aldehyde and thiosemicarbazide were dissolved in MeOH (20 mL). A solution was obtained, which was stirred overnight. Compounds **1a**, **1b**, **1c**, and **1d** precipitated as microcrystalline solids, which were collected by suction filtration, washed with MeOH, and dried in vacuo. When precipitation did not spontaneously occur (**1e**, **1f**), the solution was concentrated by rotary evaporation until a substantial quantity of precipitate had formed, and this was collected by filtration, washed with cold MeOH, and dried under vacuum. In general, yields were not very high (mostly around 40%), presumably because of poor product recovery inherent in the workup methods presented; nonetheless, they were considered acceptable, in view of the high purity (verified through MS and NMR analyses) and ease of synthesis of the resulting compounds.

1-Benzylidene-4-phenylthiosemicarbazide (1a): ^1H NMR: δ = 11.84 (br. s, 1 H, NH), 10.13 (br. s, 1 H, NH), 8.16 (s, 1 H, CH=N), 7.919–7.985 (m, 2 H), 7.565 (d, *J* = 7.6 Hz, 2 H), 7.435–7.420 (m, 3 H), 7.373 (t, *J* = 7.6 Hz, 2 H), 7.210 (t, *J* = 8.5 Hz, 1 H) ppm. ESI-MS: *m*/*z* = 256.4 $[M+H]^+$.

1-Benzylidene-4-(4-methoxyphenyl)thiosemicarbazide (1b): ^1H NMR: δ = 11.76 (br. s, 1 H, NH), 10.22 (br. s, 1 H, NH), 8.14 (s, 1 H, CH=N), 7.90 (dd, J_1 = 6.6, J_2 = 2.6 Hz, 2 H), 7.43–7.38 (m, 5 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 3.77 (s, 3 H, OCH_3) ppm. ESI-MS: *m*/*z* (%) = 320.4 (100), 322.4 (33) $[M+Cl]^-$, 286.4 (70) $[M+H]^+$.

1-(4-Nitrobenzylidene)-4-phenylthiosemicarbazide (1c): ^1H NMR: δ = 12.11 (br. s, 1 H, NH), 10.34 (br. s, 1 H, NH), 8.25 (d, *J* = 9.0 Hz, 2 H), 8.23 (s, 1 H, CH=N), 8.20 (d, *J* = 9.0 Hz, 2 H), 7.54 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.9 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H) ppm. ESI-MS: *m*/*z* (%) = 335.1 (100), 337.1 (33) $[M+Cl]^-$, 301.1 (50) $[M+H]^+$.

1-(4-Nitrobenzylidene)-4-(4-methoxyphenyl)thiosemicarbazide (1d): ^{1}H NMR: δ = 12.03 (s, 1 H, NH), 10.24 (s, 1 H, NH), 8.24 (d, J = 8.8 Hz, 2 H), 8.22 (s, 1 H, CH=N), 8.19 (d, J = 9.1 Hz, 2 H), 7.38 (s, J = 8.8 Hz, 2 H), 6.95 (d, J = 9.1 Hz, 2 H), 3.77 (s, 3 H, OCH_3) ppm. ESI-MS: m/z = 331.0 $[M+H]^+$.

1-[4-(Trifluoromethyl)benzylidene]-4-phenylthiosemicarbazide (1e): ^{1}H NMR: δ = 12.07 (br. s, 1 H, NH), 10.33 (br. s, 1 H, NH), 8.21 (s, 1 H, CH=N), 8.14 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.4 Hz, 2 H), 7.54 (d, J = 8.0 Hz, 2 H), 7.39 (t, 2 H, 7.8 Hz), 7.23 (t, J = 7.4 Hz, 1 H) ppm. ESI-MS: m/z = 324.1 $[M+H]^+$.

1-[4-(Trifluoromethyl)benzylidene]-4-(4-methoxyphenyl)thiosemicarbazide (1f): ^{1}H NMR: δ = 11.93 (br. s, 1 H, NH), 10.18 (br. s, 1 H, NH), 8.20 (s, 1 H, CH=N), 8.14 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 3.78 (s, 3 H, OCH_3) ppm. ESI-MS: m/z = 354.2 $[M+H]^+$.

Methodologies: All titration experiments were performed in MeCN (polarographic grade) at $5.00\cdot10^{-5}$ M receptor concentration (**1a**–**f**). The quartz cuvette (1 cm path length) was kept in a cell holder thermostatted at 25 °C with circulating water. Typically, aliquots of a fresh alkylammonium salt standard solution of the anion of interest were added and the UV/Vis spectra of the samples were recorded. All spectrophotometric titration curves were fitted with the HYPERQUAD program.[13] The p parameter (p = [concentration of complex]/[maximum possible concentration of complex]), which should be < 0.8 for the safe determination of a reliable equilibrium constant,[14] was calculated for each titration. Such a requirement was fulfilled only in titration experiments with CH_3COO^- and $H_2PO_4^-$. ^{1}H NMR titrations were carried out on CD_3CN solutions, at a higher concentration of **1** ($5.00\cdot10^{-3}$ M).

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[1] P. A. Gale, "Amide- and urea-based anion receptors", in: *Encyclopedia of Supramolecular Chemistry*, Marcel Dekker, New York, **2004**, pp. 31–41.
[2] T. Steiner, *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76.
[3] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.
[4] M. Boiocchi, L. Del Boca, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, E. Monzani, *J. Am. Chem. Soc.* **2004**, *126*, 16507.
[5] M. Boiocchi, L. Del Boca, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, E. Monzani, *Chem. Eur. J.* **2005**, *11*, 3097.
[6] D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, *J. Org. Chem.* **2005**, *70*, 5717–5720.
[7] V. Amendola, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, *Acc. Chem. Res.* **2006**, *39*, 343–353.
[8] a) S. Nishizawa, P. Buhlmann, M. Iwao, Y. Umezawa, *Tetrahedron Lett.* **1995**, *36*, 6483; b) S. Nishizawa, R. Kato, T. Hayashita, N. Teramae, *Anal. Sci.* **1998**, *14*, 595; c) K. P. Xiao, P. Buhlmann, Y. Umezawa, *Anal. Chem.* **1999**, *71*, 1183; d) J. L. J. Blanco, J. M. Benito, C. O. Mellet, J. M. G. Fernández, *Org. Lett.* **1999**, *1*, 1217; e) T. Hayashita, T. Onodera, R. Kato, S. Nishizawa, N. Teramae, *Chem. Commun.* **2000**, 755; f) T. Tozawa, Y. Misawa, S. Tokita, Y. Kubo, *Tetrahedron Lett.* **2000**, *41*, 5219; g) R. Kato, S. Nishizawa, T. Hayashita, N. Teramae, *Tetrahedron Lett.* **2001**, *42*, 5053; h) T. Gunnlaugsson, A. P. Davis, M. Glynn, *Chem. Commun.* **2001**, 2556; i) S. Sasaki, D. Citterio, S. Ozawa, K. Suzuki, *J. Chem. Soc. Perkin Trans. 2* **2001**, 2309; j) D. H. Lee, H. Y. Lee, K. H. Lee, J. L. Hong, *Chem. Commun.* **2001**, 1188; k) G. Hennrich, H. Sonnenschein, U. Resch-Genger, *Tetrahedron Lett.* **2001**, *42*, 2805; l) M. H. Mei, S. K. Wu, *Acta Chim. Sin.* **2001**, *59*, 1112; m) D. Jiménez, R. Martínez-Máñez, F. Sancenón, J. Soto, *Tetrahedron Lett.* **2002**, *43*, 2823; n) D. H. Lee, H. Y. Lee, J.-I. Hong, *Tetrahedron Lett.* **2002**, *43*, 7273; o) S. Kondo, M. Nagamine, Y. Yano, *Tetrahedron Lett.* **2003**, *44*, 8801; p) T. Gunnlaugsson, P. E. Kruger, T. C. Lee, R. Parkesh, F. M. Pfeffer, G. M. Hussey, *Tetrahedron Lett.* **2003**, *44*, 6575; q) F. Sansone, E. Chierici, A. Casnati, R. Ungaro, *Org. Biomol. Chem.* **2003**, *1*, 1802; r) T. Gunnlaugsson, A. P. Davis, G. M. Hussey, J. Tierney, M. Glynn, *Org. Biomol. Chem.* **2004**, *2*, 1856–1863.
[9] R. Martínez-Máñez, F. Sancenón, *Chem. Rev.* **2003**, *103*, 4419.
[10] C. Suksai, T. Tuntulani, *Chem. Soc. Rev.* **2003**, *32*, 192.
[11] L. Nie, Z. Zhao Li, J. Han, X. Zhang, R. Yang, W.-X. Liu, F.-Y. Wu, J.-W. Xie, Y.-F. Zhao, Y.-B. Jiang, *J. Org. Chem.* **2004**, *69*, 6450–6454.
[12] M. B. Ferrari, S. Capacchi, G. Reffo, G. Pelosi, P. Tarasconi, R. Albertini, S. Pinelli, P. Lunghi, *J. Inorg. Biochem.* **2000**, *81*, 89–97.
[13] P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996**, *43*, 1739–1753.
[14] C. S. Wilcox, in: *Frontiers in Supramolecular Chemistry and Photochemistry*, VCH, Weinheim, **1991**, pp. 123–143.

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