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Synthesis and study of the use of heterocyclic thiosemicarbazones as signalling scaffolding for the recognition of anions

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ABSTRACT A family of heterocyclic thiosemicarbazone dyes (**1**-**9**) linked to different furan, thiazole, (bi)thiophene and arylthiophene π-conjugated bridges were synthesized in good yields and their response toward anions was studied. Acetonitrile solutions of **1**-**9** show bands in the 326-407 region that are modulated by the electron donor or acceptor strength of the heterocyclic systems appended to the phenyl-thiosemicarbazone moiety. Anions of different shape such as fluoride, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate, nitrate, acetate, cyanide and thiocyanate were employed for the recognition studies. From these anions, only fluoride, cyanide, acetate and dihydrogen phosphate displayed sensing features. Two different effects were observed, (i) a low bathochromic shift of the absorption band due to coordination of the anions with the thiourea protons and (ii) the growth of a new red shifted band with a concomitant change of the solution from yellow or pale yellow to orange-red due to deprotonation. The extent of each process is a balance between the acidity tendency of the thioureido-NH donors modulated by the donor or acceptor groups in the structure of the receptors and the basicity of the anions. Fluorescence studies were also in agreement with the different effects observed on the UV/Vis titrations. Stability constants for the two processes (complex formation + deprotonation) for selected receptors and the anions fluoride and acetate were determined spectrophotometrically using the program HYPERQUAD. Semiempirical calculations to evaluate the hydrogen-donating ability of the dyes and ^{1}H NMR titrations experiments with fluoride were carried out. A prospective electrochemical characterization of compound **3** in the presence of anions was also performed.

INTRODUCTION

The recognition and signalling of ionic and neutral species of varying complexity is one of the most intensively studied areas of contemporary supramolecular chemistry. In this field, the host molecules (commonly known as receptors) are usually designed in such a way that upon coordination with a guest a measurable signal such as changes in colour, fluorescence or redox potential is observed.[1] Host molecules are generally comprised by two subunits, i.e. the “binding site” (properly the host, responsible of coordination event) and the “signalling subunit” (in charge of the transduction event) that are usually attached forming a superstructure. This approach needs the design and covalently attach of the binding site and the signalling subunit in a pre-organized fashion that matches the size and shape of the target guest.[2] Apart of other reported paradigms,[3] the supramolecular signalling process in the “binding site”, “signalling unit” protocol comprises two steps: (i) selective coordination of a target guest by suitable coordinating groups, and (ii) a transduction of the coordination event through modulation of the optical or the electrochemical properties of the host.[4] Optical outputs are especially attractive with respect to the transduction of a modulated signal, because detection uses cheap, easy-to-handle and widely extended instrumentation. Besides fluorescence-based systems, colorimetric recognition has gained popularity in recent years because a shift of an absorption band is often intrinsically ratiometric, avoids the necessity for an internal reference and also offers the possibility of so-called “naked eye detection” for semiquantitative determinations.[5]

In addition to optically responsive hosts for metal ions, which have been investigated for more than 25 years, anionic guests have only recently shifted into focus.[6] This is basically due to the fact that the host–guest chemistry of inorganic anions is more challenging than for metal ions because of their more complex shapes, common pH dependence and the competition of water in hydrogen bonding interactions. The supramolecular approach often starts with the design of the recognition and transduction processes at the molecular scale. Most of the supramolecular chemistry of anions has been developed based on electrostatic and hydrogen bonding interactions between the receptor and the substrate. In particular, neutral receptors for anions generally contain NH fragments which act as hydrogen bond donors with the anion.[7] In contrast to merely electrostatic interactions, hydrogen bonds are directional, a feature which allows the design of receptors capable of differentiating between anions with different geometries and hydrogen-bonding requirements. As an example, ureas and thioureas have demonstrated to be excellent coordinating groups for Y-shaped anions such as carboxylates, through the formation of two directed hydrogen bonds. Of all the hydrogen-bonding donor groups, phenylthiourea derivatives have been a subject of intensive investigations for its performance in the construction of anion receptors via hydrogen-bonding interaction by thioureido-NH donors.[8] This interest has recently been enhanced because of the promising progress in the thiourea-based organocatalysts via hydrogen bonding.[9] Obviously the hydrogen bonding ability of the thiourea moiety is an important parameter, which in principle depends on the acidity of the thioureido NH protons and the number of binding sites. From a structural point of view, a direct means of tuning this acidity is to introduce substituents of varied electron-donating or withdrawing ability.[10] Additionally, experimental and theoretical studies have demonstrated that replacing the benzene ring of a chromophore bridge with easily delocalizable five-member heteroaromatic rings, such as thiophene, pyrrole and thiazole, results in an enhanced intramolecular electronic delocalisation. While the aromaticity of heteroaromatics affects the electron transfer between donor and acceptor groups, the electron-rich or electron-deficient nature of the heterocyclic ring systems may also play a major role in determining the overall electron-donating and accepting ability of the substituents: electron-rich heterocycles act as auxiliary donors and electron-deficient heterocycles act as auxiliary acceptors.[11]

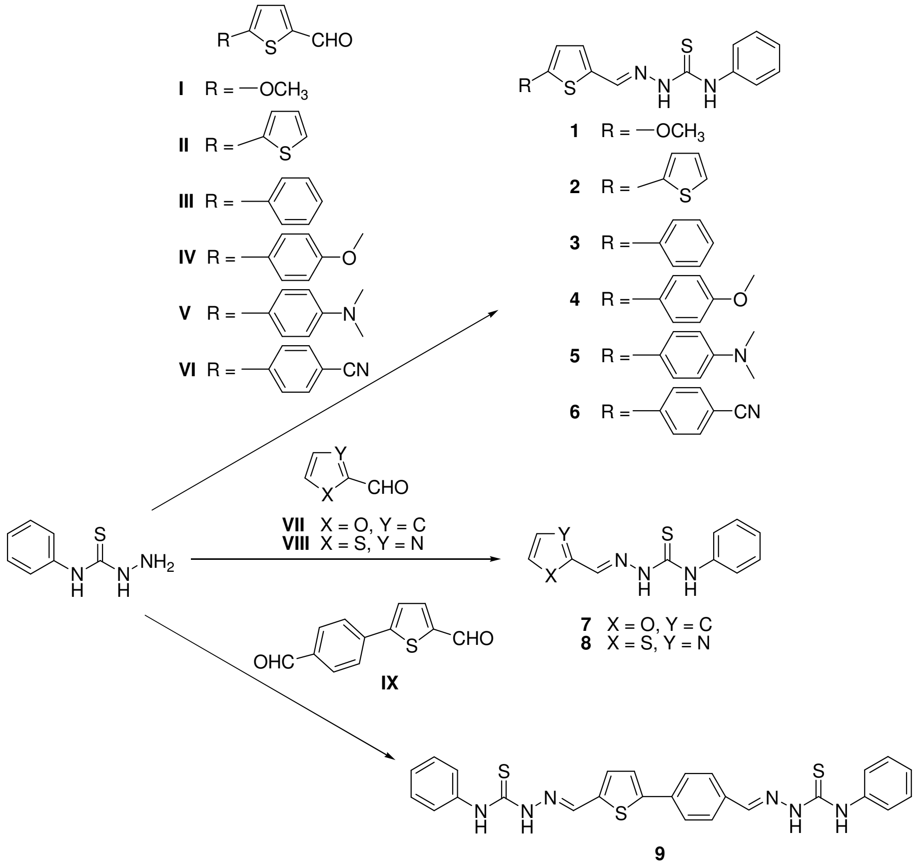
On the other hand, and inside the family of aromatic five-membered heterocyclic rings, thiophene is probably one of the less employed by now in the development of optical chemosensors for anions regardless of its interesting chemical properties.[12] Despite this lack of use in optical sensing, thiophenes are important heterocyclic compounds that are widely used as building blocks in many agrochemical and pharmaceutical applications. For instance thiophene derivatives are used in manufacturing dyes, aroma compounds and certain pharmaceutical derivatives. Moreover, polythiophenes have attracted increasing attention in certain applications such as electronic devices, nonlinear optics, energy storage, electrochromic devices, electrochemical sensors and modified electrodes.[13]

Recently some of us have reported the synthesis and the characterization of novel π-conjugated heterocyclic systems for several optical applications such as nonlinear optical materials,[11] OLEDs[14] and colorimetic and/or fluorimetric sensors.[15] Following this previous work on the synthesis and evaluation of heterocyclic derivatives for several optical applications and considering also our interest in chemosensing applications[15,16] we now report the synthesis and the characterization of new heterocyclic *N*-phenylthiosemicarbazones **1–9** containing thiourea binding sites. Our approach is original and different from other related reports,[8] due to the replacement of the usually used aryl moiety by the heteroaromatic π-conjugated systems. To our knowledge, we report herein one of the very few examples as probes using phenylthioureas functionalized with heterocyclic moieties.[17]

RESULTS AND DISCUSSION.

Synthesis and characterization: The formyl precursors **I–IX** functionalized with several groups such as alkoxy, *N,N*-dialkylamino and cyano, linked to different π conjugating bridges were used in order to evaluate the influence of the structure modification (*i.e* donating and accepting strength of these groups and nature and length of the π-conjugated bridge) on the optical properties of *N*-phenylthiosemicarbazones. The new compounds **1–9** with furan, thiazole, (bi)thiophene and arylthiophene π-conjugated bridges were synthesized in good yields (50-89%) through Schiff-base condensation of heterocyclic aldehydes **I-IX** with 4-phenyl-3-thiosemicarbazide in methanol at room temperature or in ethanol at 50 °C (see Scheme 1). Aldehydes **II-III** and **VII-VIII** are inexpensive and commercially available, and 5-formyl-2-methoxythiophene **I**[18] and formyl arylthiophenes **IV–VI** and **IX**[19] were easily synthesized in good yields respectively through metalation of 2-methoxythiophene followed by reaction with DMF or through a Suzuki cross-coupling reaction of hetero(aryl) boronic acids with hetero(aryl) bromides. All the compounds were completely characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, EA or HRMS and the data obtained were in full agreement with the proposed formulation (see experimental section).

The most characteristic signals in the ^{1}H NMR spectrum of this family of thiosemicarbazones were those corresponding to CH=N and N-H protons. ^{1}H-NMR studies using deuterated chloroform show CH=N protons in the 7.80-8.40 ppm range whereas thiourea-N-H protons are found in the 9.00-10.20 and 9.90-12.10 ppm interval for N-H adjacent to the monosubstituted phenyl ring and for the N-H adjacent to the CH=N moiety respectively. When the whole family of compounds is considered the highest variation in δ were found for the N-H protons located in the vicinity of the CH=N moiety adjacent to heterocyclic rings (thiophene, thiazole and furane) additional functionalized with electron withdrawing or electron donor moieties (Δδ = 2.20 ppm). Moreover, CH=N protons were the less affected by the substituents located in its vicinity (Δδ = 0.60 ppm), whereas the N-H protons adjacent to the monosubstituted phenyl ring show a wider interval with Δδ = 1.20 ppm.



Scheme 1. Synthesis of the thiosemicarbazone receptors **1**-**9**.

*Spectroscopic behaviour of **1**-**9***: Acetonitrile solutions (5.0 x 10^{-5} mol dm^{-3}) of thiosemicarbazone-functionalised receptors **1–9** show an intense absorption band (log ε ≈ 4.5) in the 326-407 nm region (see Table 1 for spectroscopic data). For example, receptor **8**, in which the thiosemicarbazone moiety is surrounded by phenyl and thiazolyl rings, shows an absorption band centred at 326 nm. Changing thiazolyl group by furanyl (receptor **7**) or thienyl (receptor **1**) rings induced moderate bathochromic shifts of the band to 341 and 354 nm respectively. However the more significant changes (bathochromic shifts) were obtained when another aromatic ring is attached into the structure of the receptors. These shifts were a direct consequence of the extension of the conjugation and the presence of auxiliary groups in the structure of the receptors. For instance, receptor **3** containing a phenyl ring attached directly to the thiophene heterocycle shows a band at 371 nm whereas receptor **6** containing a phenyl ring functionalised with a cyano electron withdrawing moiety absorbs at 382 nm. The presence of an electron donor *N*,*N*-dimethylamino moiety in receptor **5** induced the more pronounced red shift (λ_{max} = 407 nm) with respect to **8**.

Table 1. Spectroscopic data for compounds **1-9**.

[a] Measured upon addition of 100 equivalents of fluoride anion.

Receptor	$\lambda_{ab\ LH}$ (nm)	$\lambda_{ab\ L^-}$ (nm)[a]	Log ε (LH)	$\lambda_{em\ LH}$ (nm)	$\lambda_{em\ L^-}$ (nm)[a]	Φ	Δλ (nm)	Δυ (ab-em) (cm^{-1})
1	354	395	4.58	415	480	0.0027	61	4150
2	381	440	4.64	452	525	0.0068	71	4120
3	371	430	4.58	443	508	0.0090	72	4380
4	377	430	4.62	446	505	0.0129	69	4100
5	407	515	4.45	521	520	0.1840	114	5380
6	382	460	4.56	477	565	0.0274	95	5210
7	341	415	4.59	410	490	0.0015	69	4940
8	326	376	4.55	416	540	0.0014	90	6640
9	395	455	4.59	475	560	0.1310	80	4260

In order to further study the HOMO and LUMO difference in energy in this family of receptors we carried out quantum chemical calculations at the semiempirical level employing the PM3 model. Two clear different behaviours were observed. In the presence of electron withdrawing groups such as cyanide (for instance receptor **6**) and thiazolyl ring (for instance receptor **8**), and in agreement with previous works with other thiosemicarbazone derivatives,[20] the HOMO orbitals are mainly centred in the thiocarbonyl and phenyl groups and the LUMO orbitals are located at the thiophene ring. As a consequence the electronic transition between the HOMO and the LUMO has a strong charge-transfer character. In the opposite side receptor **5**, containing an electron donor *N*,*N*-dimethylamino moiety, both HOMO and LUMO are located over the entire molecule suggesting a more cyanine-like structure (see Figure 1).[21]

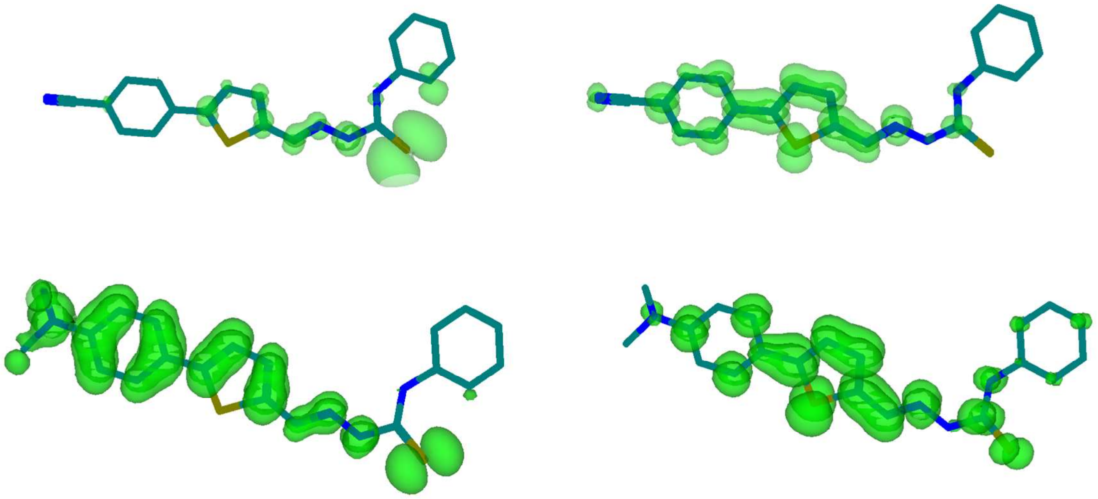


Figure 1. HOMO (left) and LUMO (right) orbitals of **6** (top) and **5** (down) obtained by PM3 semiempirical calculations.

UV-Vis studies involving anions: The UV-visible behaviour of receptors **1-9** in acetonitrile solutions (5.0 x 10^{-5} mol dm^{-3}) was studied at 25ºC in the presence of selected anions of different sizes and shapes such as fluoride, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate, nitrate, acetate, cyanide and thiocyanate. For all the receptors tested addition of increasing quantities (up to 100 equivalents) of chloride, bromide, iodide, hydrogen sulfate, nitrate and thiocyanate induced negligible changes in the UV-visible bands indicating no coordination. The more relevant results were obtained with anions that show a basic character in acetonitrile solutions such as fluoride, cyanide, acetate and dihydrogen phosphate. UV-visible titration experiments with receptors **1-9** and fluoride showed in most of the cases a similar behaviour, namely an intensity decrease and a small bathochromic shift of the absorption band together with a simultaneous growth of a new red-shifted band. The relative intensity of the absorption band of the receptor and the red-shifted band upon addition of fluoride, and the position of the new band depend on the receptor used. Thus for instance, the behaviour observed in the presence of F^- is exemplified in the titration profiles for receptors **3** and **5**. Acetonitrile solutions of **3** are pale-yellow due to the presence of a band centred at 371 nm. Upon addition of increasing quantities of fluoride anion this band progressively decreases and is red shifted to 377 nm, while a new absorption at 430 forms and develops (see Figure 2). The absorption ratio between bands centred at 371 and 430 nm observed upon addition of 10 equivalents of fluoride anion is 0.5. The formation of this new visible band induced a change in colour from yellow to orange-red. Receptor **5** showed a similar behaviour and upon addition of increasing quantities of fluoride the visible band centred at 407 nm suffers a small hypochromic effect together with a red shift to 418 nm. At the same time a new absorption band centred at 515 nm grows in intensity (see Figure 3). The ratio between the 407 and 515 nm bands upon addition of 10 equivalents of fluoride anion amounts to 4.1 for receptor **5**.

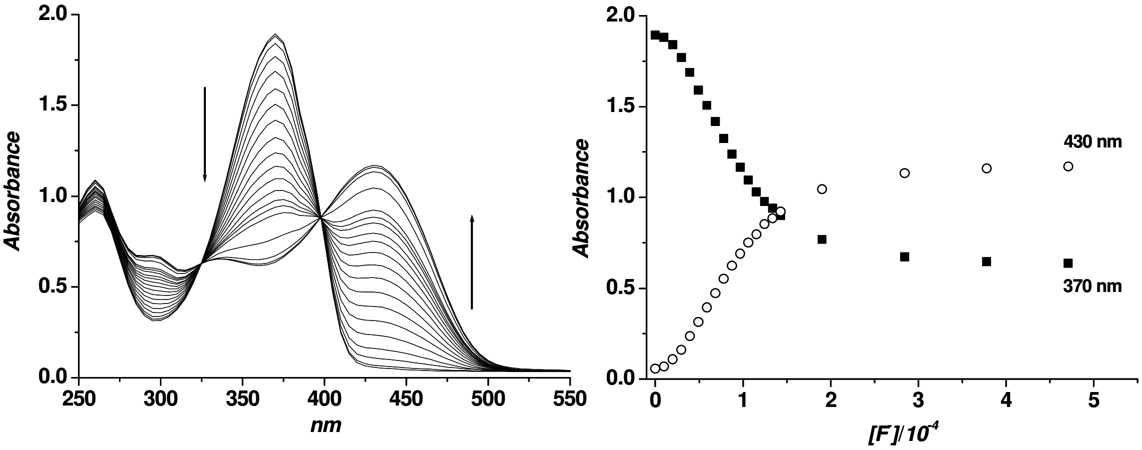


Figure 2. Left: UV-visible titration of receptor **3** (5.0×10^{-5} mol dm^{-3}) with fluoride anion (from 0 to 2.0×10^{-2} mol dm^{-3}) in acetonitrile. Right: Absorbance of acetonitrile solutions of receptor **3** at 370 and 430 nm versus concentration of fluoride anion (mol dm^{-3}).

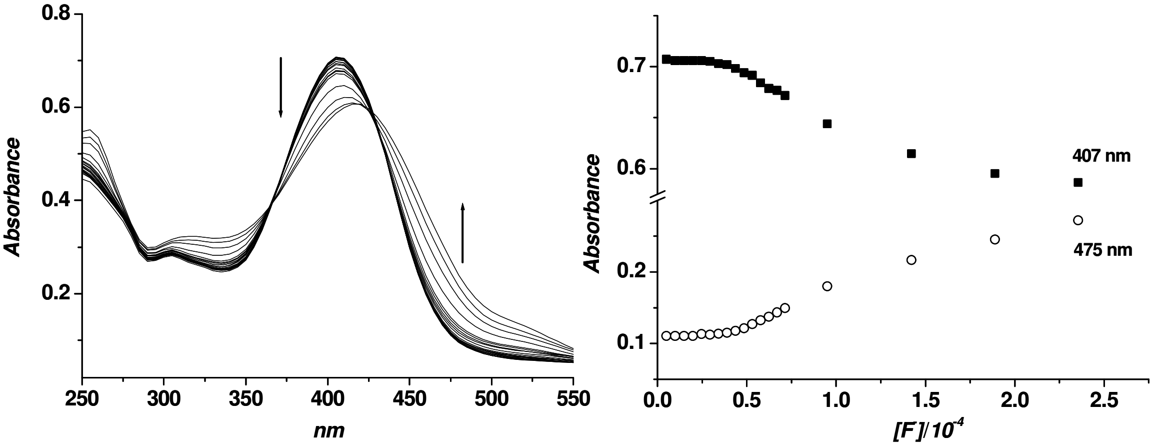


Figure 3. Left: UV-visible titration of receptor **5** (5.0×10^{-5} mol dm^{-3}) with fluoride anion (from 0 to 2.0×10^{-2} mol dm^{-3}) in acetonitrile. Right: Absorbance of acetonitrile solutions of receptor **3** at 407 and 475 nm versus concentration of fluoride anion (mol dm^{-3}).

In general, the results obtained reflect the expectation that the interaction between an electron-rich partner and a donor group in a push–pull system will produce a bathochromic shift. Such colour shifts, mainly in the presence of fluoride, have also been observed with other amide, urea, thiourea or pyrrole-containing hosts and have been attributed to the formation of strong hydrogen-bonding complexes between the receptors and the highly basic F^- anion that eventually is able to originate the deprotonation of the binding site of the host.[22] In fact we believe that it is this dual complex + deprotonation process what it occurs in our case for all the receptors in the presence of fluoride; i.e. a first step consisting in the formation of a hydrogen-bonding complex and a second step in which the receptor is deprotonated by the anion. The formation of the hydrogen-bonding complex between receptor and anion is reflected in a decrease in the intensity of the band centred at ca. 360 nm together with a very small bathochromic shift, whereas the deprotonation process induced the appearance of a new absorption band centred in the visible zone at ca. 400-450 nm. In particular, the negative charge generated upon proton release induced an increase in the intensity of the electrical dipole with the direct consequence of a substantial red shift of the band. The assignation of the band centred at 400-450 nm, formed upon addition of fluoride, to the deprotonated form of the corresponding receptor was confirmed via similar titration experiences carried out with tetrabutylammonium hydroxide that resulted also in the formation of the new red shifted band. The magnitude of both processes (complexation vs deprotonation) is thus a delicate balance between the basicity of the corresponding anion and the acidity of the N-H protons for a certain receptor.

In fact, a close view to the results suggests that the response toward basic anions of these receptors strongly depends on the chemical nature of the functional groups attached directly to the thiosemicarbazone moiety that modulated the acidity of the N-H protons. For instance, fluoride and cyanide anions were able to induce UV-Vis modulations for all the receptors tested whereas acetate is able to interact only with receptors **2**, **3**, **6-9** and hydrogen phosphate give negligible results with all the receptors tested with the exception of **6**. More in detail, for a certain anion (i.e. fluoride) at a given concentration, the development of the band due to deprotonation grows more or less in intensity depending on the receptors used. The presence of electron withdrawing moieties in the structure of receptors, such as a cyanide group in **6**, induced an increase in the acidity of N-H protons of the thiosemicarbazone favouring the interaction with fluoride anion and deprotonation whereas the presence of electron donor groups, such as methoxy and *N*,*N*-dimethylamino in **4** and **5** respectively, induced certain decrease in the acidity and the red-shifted band due to deprotonation develops in a lesser extent. Nearly the same trend was observed in the presence of cyanide anion, whereas as stated above acetate anion is able to induce the appearance of the red shifted band only with receptors **2**, **3**, **6-9** that contain the more acidic N-H moieties and dihydrogen phosphate only with **6** that contains a cyanide electron withdrawing group in its structure. Additionally for acetate with **6** and **8**, and dihydrogen phosphate with receptor **6**, the ratio between the absorption of the ligand and the absorption for the deprotonated from $[A(\lambda_L)/A(\lambda_{L^-})]$ is > 10 after addition of a large excess of anion indicating a poor presence of the deprotonated species even.

In this interaction of basic anions with the semithiocarbazones, the hydrogen bonding can thus be seen as a “frozen” intermediate between the pre-association state and the dissociation state after proton relocation (deprotonation) has taken place (see Equations 1 and 2). The formation of the final anion:ligand 2:1 (A_2H^-) species shown in equation 2 was confirmed from the corresponding Job’s plots.

$$LH + A^{-} \leftrightarrows LH\cdots A^{-} \quad (1)$$

$$LH\cdots A^{-} + A^{-} \leftrightarrows L^{-} + A_2H^{-} \quad (2)$$

The strength of both steps can be studied via the evaluation of the corresponding stability constants that were determined via UV-Vis spectroscopic titrations between the selected receptors **1**, **2**, **3**, **4**, **5**, **6** and **8** and the anions fluoride and acetate using the program HYPERQUAD. The set of data were adjusted to the two consecutive equilibria shown above (i) first the formation of the hydrogen-bonding complex and (ii) deprotonation. The stability constants are shown in Table 2.

Table 2. Logarithms of the stability constants measured for the interaction of receptors **1**-**8**~~**9**~~ with fluoride and acetate. Values in parenthesis are standard deviations of the last significant figure.

	F^-		**Ac^-**	
	$LH + A^{-} \leftrightarrows LH\cdots A^{-}$	$LH\cdots A^{-} + A^{-} \leftrightarrows L^{-} + A_2H^{-}$	$LH + A^{-} \leftrightarrows LH\cdots A^{-}$	$LH\cdots A^{-} + A^{-} \leftrightarrows L^{-} + A_2H^{-}$
1	4.32 (1)	4.57 (1)	-	-
2	4.56 (8)	3.86 (2)	4.10 (1)	0.40 (2)
3	5.3 (7)	5.50 (4)	4.83 (2)	1.26 (8)
4	3.7 (6)	3.52 (5)	-	-
5	4.3	3.5	-	-
6	5.52	7.76	4.16 (2)	1.43 (1)
7	4.13 (2)	3.32 (7)	- [a]	- [a]
8	4.2 (1)	4.45 (1)	4.12 (1)	1.65 (4)

[a] No reliable results were obtained.

As a general trend the logarithms of the stability constants measured for both equilibria with fluoride are higher than those obtained for acetate. The logarithms of the stability constants for the formation of

Y-shaped hydrogen-bonding complexes between receptors **2**, **3**, **6**, **8** and acetate anion range from 4.10 to 4.83, whereas the stability constants for the deprotonation process are about 3 orders of magnitude smaller. This is in agreement with the UV-Vis titration profiles observed for receptors **2**, **3**, **6**, **8** and acetate that show a moderate hypsochromic effect of the absorption band of the receptor and low intensity enhancement of the red-shifted band.

On changing from acetate to fluoride the stability constants for the deprotonation process are about 3 orders of magnitude higher reflecting the more basic character of fluoride anion, whereas the stability constants for the formation of the corresponding hydrogen-bonding complexes remain approximately the same for both anions.

It is noteworthy that the stability constants determined in this study for thiosemicarbazones are in general lower than that those reported for other urea/thiourea receptors functionalised with benzene rings containing electron withdrawing moieties. This is a clear consequence of the reduced acidity of receptors studied herein when compared with those other reported ligands. For instance, the compound 1,3-bis(4-nitrophenyl)urea has also been reported to display the two step process (coordination + deprotonation) upon addition of fluoride with logarithms of the stability constants for the formation of the complex and for deprotonation of 7.38 and 6.37 respectively.[23] Another urea based receptor (1-nitrobenzo[1,2,5]oxadiazol-4-yl)-3-(4-nitrophenyl)urea shows values logarithm values > 6 for the formation of the hydrogen-bonding complexes and 4.2 for the deprotonation step.[24] Finally the thiourea receptor 1-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-3-phenylthiourea also suffers a first coordination step and a second proton transfer process with basic anions being the logarithm of the stability constants 5.7 and 5.5 for fluoride and 6.02 and 3.23 for acetate.[25]

Fluorogenic studies involving anions: It is widely known that fluorescence, despite being in some cases a less extended technique, is much more sensitive to intermolecular interactions that colour changes. Therefore, fluorescence studies in acetonitrile solutions of the receptors upon addition of increasing amounts of the corresponding anion were carried out. Receptors were excited in the pseudo-isosbestic points observed in the course of UV-visible titrations and showed in all cases a broad, unstructured emission band. Quantum yields in acetonitrile ranged from quite low (receptor **8**, $\Phi = 0.0014$) to relatively high (compound **5**, $\Phi = 0.184$).

The emission behaviour of the selected receptors **1-6** was studied at 25ºC in the presence of selected anions. For all the receptors tested, addition of chloride, bromide, iodide, hydrogen sulfate, nitrate and thiocyanate induced negligible changes in the emission intensity profiles. In contrast, the fluorescence emission in presence of fluoride, acetate, cyanide and dihydrogen phosphate changed significantly.

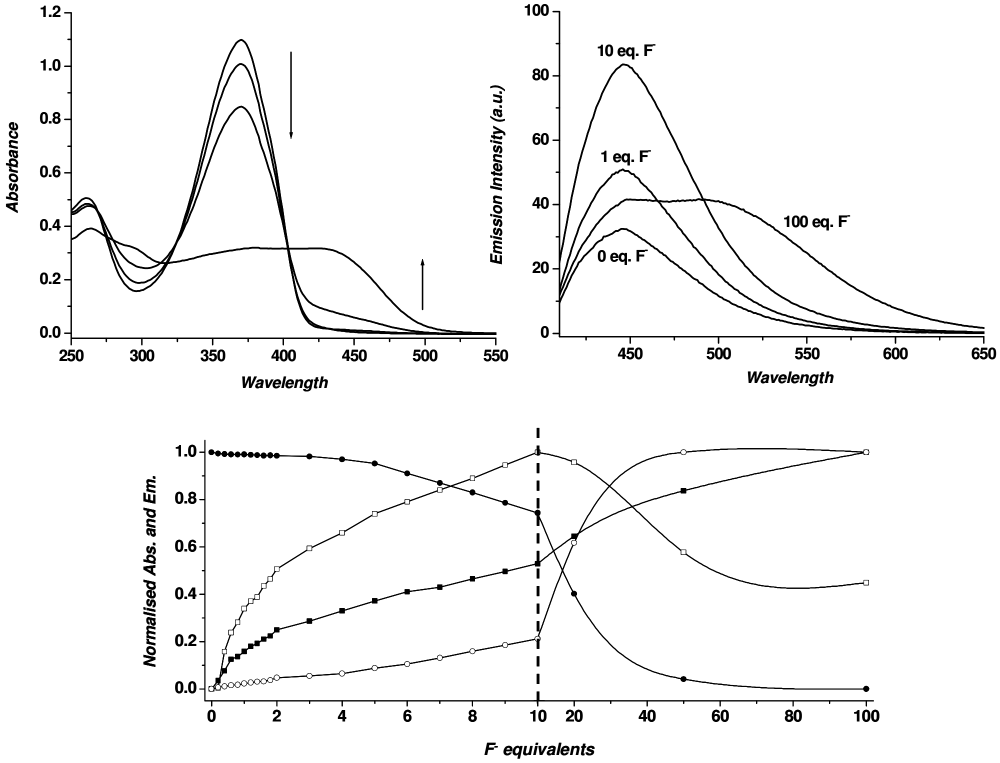
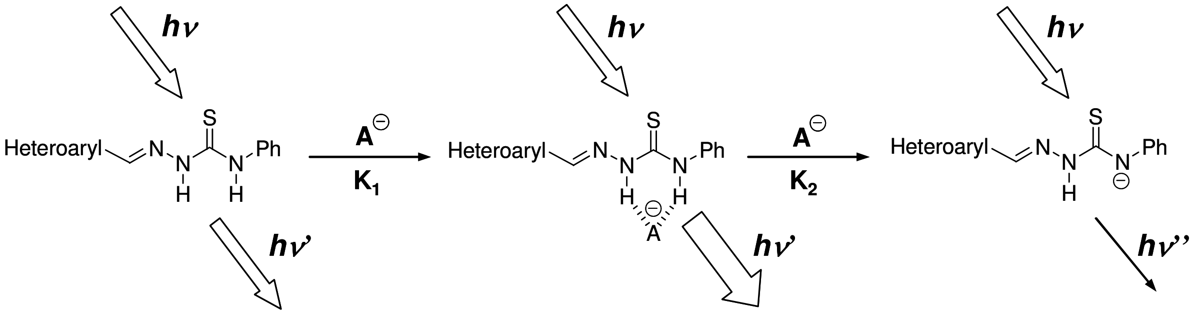


Figure 4. Interaction of receptor **3** (5.0 x 10^{-5} mol dm^{-3}) with fluoride anion. Up (Figure on the left): absorption spectra of receptor in the presence of 0, 1, 10 and 100 eq. of fluoride anion; (Figure on the right): emission spectra of receptor in the presence of 0, 1, 10 and 100 eq. of fluoride anion. Down: Normalised values (0-1) at different wavelengths for receptor **3** in the presence of fluoride, absorption at 365 nm (●), absorption at 420 nm (○), emission at 450 nm (□) and emission at 500 nm (■).

A different behaviour was observed depending on the anions and the receptor used in the studies. In the presence of fluoride, and as a general trend, the receptors tested (i.e. **1**, **2**, **3**, **4**, **5** and **6**) showed an enhancement of the fluorescence intensity upon the addition of moderate amounts of fluoride anion followed by a quenching of the emission band at higher anion concentrations and the growth of a new band at longer wavelengths (λ_{em} in the 410 - 560 nm range, see Table 1). Finally it was confirmed that a very similar behaviour was found with receptors **1-6** in the presence of cyanide anion.

In order to interpret this behaviour we have made a comparison between changes observed in the emission and absorption spectra. As a typical example we show below the behaviour found for ligand **3** in the presence of fluoride and acetate. As can be seen in Figure 4 for receptor **3** and small quantities of fluoride anion, while the intensity of the absorption band centred at 365 nm remains unaltered the fluorescence intensity at 450 nm progressively increases until 10 equivalents of fluoride were added. Upon addition of higher amounts of fluoride, the intensity of the band at 450 nm decreases due to the formation of a new compound that absorbs and emits at longer wavelengths (deconvolution studies reveals that the bands for the new product are centred at 450 and 500 nm for the absorption and emission spectra respectively). Finally, upon addition an excess of fluoride anion the emission band at 500 nm enhanced its intensity in a continuous fashion.

Thus, fluorescence measurements suggest that interaction of the receptors with fluoride takes place in two steps as it was observed in the UV-Vis studies. In the first step the anion coordinates with the acidic NH protons of the thiourea moiety through hydrogen bonding interactions leading to an increase in the donor capacity of the binding site. This hydrogen bonding interactions only induces a small shift in the UV-Vis bands but is able to induce a remarkable enhancement of the emission. Upon addition of more equivalents of the anion, a deprotonation process of the receptor occurs. This deprotonation process induced a strong electronic rearrangement of the receptor with the direct consequence of the appearance of a red-shifted visible and emission bands (see Scheme 2).



Scheme 2. Schematic representation of the dual coordination/deprotonation process for the interaction of thiosemicarbazone receptors with basic anions.

The overall shape and intensity of the emission band for a certain receptor-anion pair also depends of the LH/LH···A^-/L^- ratios. For instance, a close look to the titration experiments (not shown) with fluoride indicated that in order to induce the appearance of the red-shifted emission band higher amounts of fluoride are necessary for receptor **3** than for receptor **6** in agreement with the larger acidity of **6** versus **3**.

UV-Vis and fluorescence titrations with receptors **3** and acetate were also carried out (Figure 5). For this receptor a 4-fold enhancement in the emission intensity upon addition of increasing quantities of acetate anion was observed. This enhancement in the emission intensity was assigned to the formation of Y-shaped hydrogen-bonding complex between the NH thiourea protons of the receptor and acetate anion. This is reflected in the UV-Vis spectrum in the decrease in the absorption intensity and in a low bathochromic shift of the visible band, whereas in the fluorescence titration a continuous increase in the emission intensity at 500 nm occurs. As acetate is less basic than fluoride only a poorly developed red-shifted visible band due to deprotonation is observed whereas the red-shifted band in the emission spectra can not be observed and probably lies below the intense emission of the band at 450 nm.

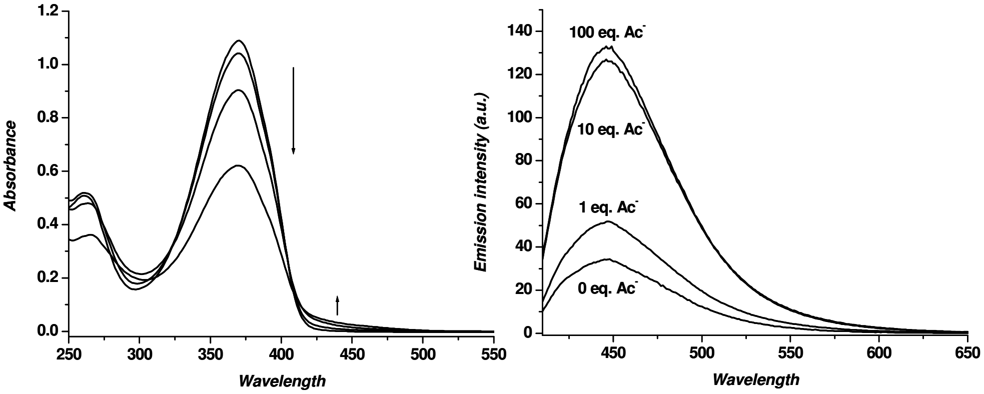
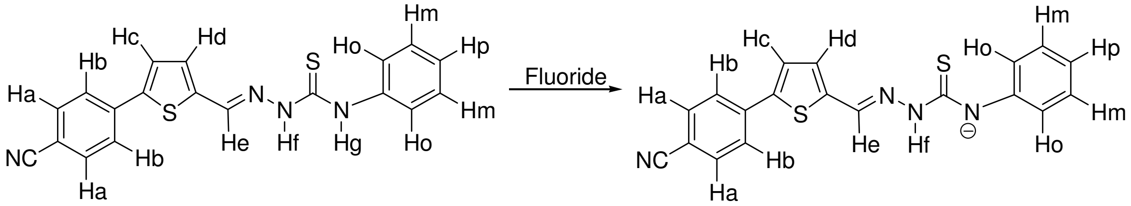


Figure 5. Interaction of receptor **3** (5.0 x 10^{-5} mol dm^{-3}) with acetate anion. Left: absorption spectra of receptor in the presence of 0, 1, 10 and 100 eq. of acetate anion; Right: emission spectra of receptor in the presence of 0, 1, 10 and 100 eq. of acetate anion.

^{1}H-NMR spectroscopic and quantum chemical studies in the presence of anions: UV-Vis and fluorescence measurements of thiosemicarbazone receptors **1-9** in the presence of anions showed a rich response that range from hydrogen bonding interactions between receptor and anion to deprotonation of the receptors. The extents of the colorimetric shifts in the series **1–9** upon addition of the target anions represent a delicate balance between the deprotonation tendencies of the different binding sites and the proton affinities of the anions. For instance, a comparison of **6** and **7** reveals how small variations in the signalling group and the corresponding anions can result in different modulations in their response; i.e. **6** displays response in the presence of dihydrogen phosphate whereas **7** does not.

In order to confirm when a coordination or deprotonation process takes place the interaction of receptor **6** and the anions fluoride, cyanide and acetate was investigated by means of ^{1}H-NMR titration experiments in DMSO. Receptor **6** was selected because this receptor shows spectroscopic changes upon anion addition and deuterated DMSO was selected as solvent due to the poor solubility of **6** in deuterated acetonitrile. ^{1}H-NMR spectra of receptor **6** showed the expected signals in the aromatic zone due to the presence of two aromatic benzene rings and one thiophene heterocycle (see Scheme 3 for proton assignation). The monosubstituted benzene ring shows resonances at 7.21 (1H, triplet), 7.38 (2H, triplet) and 7.61 (2H, broad doublet) ppm whereas protons of the *p*-disubstituted benzene ring display a broad singlet at 7.90 ppm. The protons of the 1,4-disubstituted thiophene ring (Hc and Hd) appeared at 7.61 (overlapped with two protons of the monosubstituted benzene ring) and at 7.77 ppm as narrow triplets because formed an ABX system with a long range coupling to the proton of imine moiety (He). Finally, the imine proton is a broad singlet at 8.33 ppm and the N-H protons of the thiosemicarbazone group also are broad singlets at 9.88 and 11.97 ppm.



Scheme 3. Proposed mode for the fluoride-induced deprotonation of receptor **6**.

In a first step we studied the shifts of the protons of receptor **6** upon addition of increasing quantities of fluoride anion. The most important fact is the disappearance of the H_f and H_g protons upon addition of 0.25 equivalents of fluoride. Additionally, the variation in the chemical shifts Δδ (ppm) over the course of the titration for the protons of receptor **6** with fluoride is shown in Figure 6. As could be seen protons H_a, H_b, H_c, H_d and H_e show negligible changes in their position in the NMR spectrum. In contrast, remarkable shifts were obtained for H_o, H_m and H_p suggesting that deprotonation takes place in the N-H group closer to the phenyl group. Upon deprotonation of the N-H group two effects would be active (i) an increase in the electron density in the phenyl ring, by through-bond propagation, according to a π-mechanism, which should cause a shielding effect (promote upfield shifts of the C-H signals), and (ii) a polarization of the C-H bonds, induced by a through-space mechanism, of an electrostatic nature, that causes a deshielding effect (the partial positive charge shifted onto the proton induced downfield shifts and this effect vanish by the increasing of the distance between the proton and the negative charge).

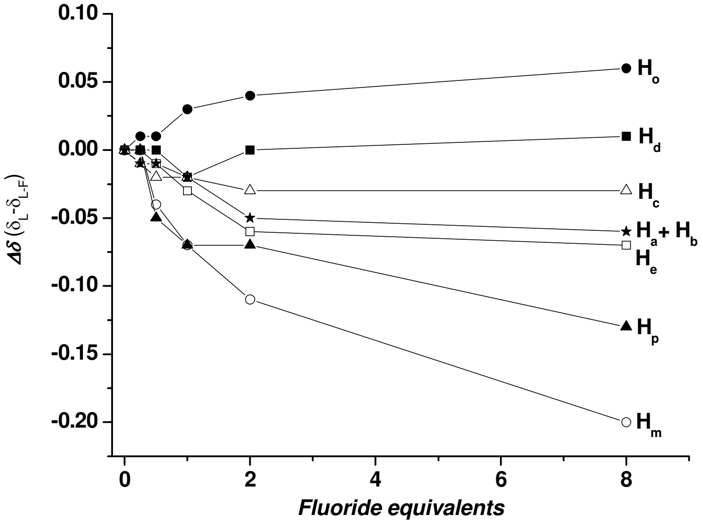


Figure 6. ^{1}H-NMR shifts for the protons of receptor **6** in the presence of increasing quantities of fluoride anion (DMSO-d$_6$).

Figure 6 shows that H$_o$ protons experience important downfield shifts indicating strong electrostatic effects due the proximity to the negatively charged thiourea nitrogen atom. Protons H$_m$ and H$_p$ experienced upfield shifts due to the fact that the through-space effects vanished with distance and the through-bond effect dominates inducing general upfield shifts. Such effect is more pronounced for the protons located in the phenyl ring linked to the deprotonated nitrogen atom. Fabbrizzi *et. al.* in a closely related (benzylideneamino)thioureas have observed a similar behaviour; i.e. deprotonation of the apparently less acidic protons attached to the phenyl ring.[20]

Nearly the same behaviour was observed upon addition of increasing quantities of cyanide anion to deuterated DMSO solutions of receptor **6** (data not shown). Moreover in the presence of acetate anion the behaviour is again quite similar than those presented by fluoride and cyanide but more equivalents of anion are necessary to induce the same shifts in the ^{1}H-NMR signals.

Table 3. Stabilisation energy of the deprotonation for receptors **1-6**. The more negative the value the stronger the hydrogen-bond donor character (i.e. more acidic is the receptor).

	$E_{(n)}^{-}$ - $E_{(n)H}$ (kcal mol^{-1})	
Receptor	R=N-NH-C(S)-*N*-Ph [a]	R=N-*N*-C(S)-NH-Ph [b]
1	2.34	-4.67
2	0.99	-6.26
3	1.76	-5.43
4	2.03	-5.17
5	27.0	-4.65
6	-1.26	-8.65

[a] Deprotonation at the H_g proton (see Scheme 3)

[b] Deprotonation at the H_f proton (see Scheme 3)

This observed behaviour in the ^{1}H NMR spectra with basic anions (i.e. deprotonation of the N-H group closer to the phenyl group) contrasts with the ^{1}H NMR chemical shifts observed for H_f and H_g protons of receptor **6** that appear to indicate that H_f is more acidic than H_g. In order to contrast this observation, quantum mechanical calculations were carried out. A convenient, simplified way of describing the hydrogen bond-donating or -accepting ability of a molecule at a particular site can be assessed through the gas-phase deprotonation energy determined by quantum chemical calculations. We thus determined the acidity of the receptors at a semiempirical level, employing the PM3 model by subtracting the energy of the receptor alone from that of the deprotonated form. For this calculations receptors **1-6** containing thiophene heterocycles were selected in order to obtain data that would be comparable. These thiosemicarbazone receptors contain two N-H groups and calculations suggest that the most acidic is the one attached to the imine carbon directly bonded to the thiophene heterocycle (H_f in Scheme 3). The results obtained for the theoretical calculations are shown in Table 3, but are not in agreement with the ^{1}H-NMR results that suggest that deprotonation occurs at the H_g proton. This discrepancy reflects that the question related with the interaction of basic anions with urea and thiourea derivatives (complexation versus deprotonation) is still far of being a resolved goal and suggest that more studies should be carried out.

Despite this impossibility of decide with certainty which is the proton involved in the deprotonation process, the predicted acidity of the different ligands **1**-**6** using quantum chemical calculations agrees with the observed chromo-fluorometric behaviour in the presence of anions. Thus, anion basicity in acetonitrile is expected to follow the order $F^- > CN^- > AcO^- > H_2PO_4^-$, Cl^-, HSO_4^-, SCN^-, NO_3^-, Br^-, I^- in agreement with the Hoffmeister series, whereas the acidity of the studied receptors follow the order **6** > **2** > **3** > **4** > **1** > **5** (see Table 3). Fluoride and cyanide, as the most basic anions, induced spectroscopic changes for all six **1**-**6** receptors, acetate as the next most basic anion, is only capable of coordinate with receptors showing larger hydrogen-bond donor properties (compounds **2**, **3** and **6** from the family containing thiophene heterocycles), whereas dihydrogen phosphate only coordinate to the more acidic receptor (**6**).

Electrochemical studies in the presence of anions: The receptors used are characterised by the presence of electroactive groups that have been reported to suffer oxidation or reduction processes. The electrochemical behaviour of product **3** as representative derivative was studied alone and in the presence of certain anions in acetonitrile with platinum as working electrode and $[Bu_4N][PF_6]$ as supporting electrolyte. The cyclic voltammogram of **3** shows a very complex behaviour with irreversible oxidation peaks at 0.80 and 1.26 V vs. SCE when sweeping to anodic potentials. These oxidations are most likely due to oxidation involving the phenyl-thiophene group.[26] However, the addition of anions such as fluoride to solutions of **3** resulted in poorly defined oxidation peaks hampering a detailed study of the possible redox potential shifts of the oxidation processes upon anion coordination.

Table 4. Electrochemical data of **3** in the presence of anions fluoride, cyanide and acetate in acetonitrile (0.1 M Bu_4NPF_6) at 298 K.

	$\Delta E(\mathbf{3})$ [a]
AcO^-	140
F^-	140
CN^-	40

[a] $\Delta E(L^n) = E\ (L^n + M^{n+}) - E\ (L^n)$ (ΔE in mV)

Additionally cyclic voltammograms carried out on acetonitrile solution of **3** at negative potentials showed several reduction peaks that must be associated with the thiosemicarbazone moiety. In fact the redox properties of thiosemicarbazone derivatives containing thiophenes have been previously studied and multiple reduction processes have been reported to occur depending on the nature of the appended groups. Thus for instance the compound 4-phenyl-1-[(thiophen-2-yl)methylene]thiosemicarbazide has been reported to suffer reduction processes at -0.70, -1.16 and -1.50 V versus SCE.[27] In our case two poorly defined peaks at -0.85 and -1.58 V and an intense irreversible reduction process at -2.04 V vs. SCE were observed. This later peak may be attributed to the reduction of the imine moiety of the thiosemicarbazone group,[28] although reduction of the C=S bond or cleavage of the N-N group have also been suggested as possible mechanism for the reduction processes in derivatives of thiosemicarbazones.[29] The electrochemical studies with **3** in the presence of certain anions show clear redox shifts especially for the more cathodic reduction process. Thus, the addition of increasing amounts of anions fluoride, acetate and cyanide to acetonitrile solutions of **3** (C = 0.125 mol dm^{-3}) resulted in a remarkable anodic shifts of 140, 140 and 40 mV of the wave at -2.04 V respectively (see Table 4). In contrast, addition of other anions resulted in no change of the redox behaviour of **3**. This is in agreement with the chromo-fluorogenic response observed for **3** (vide ante) for which colour of fluorescence modulation where only found for F^- Ac^- and CN^- anions. As an example of the electrochemical behaviour Figure 7 plots the changes in the redox process at -2.04 V upon addition of fluoride.

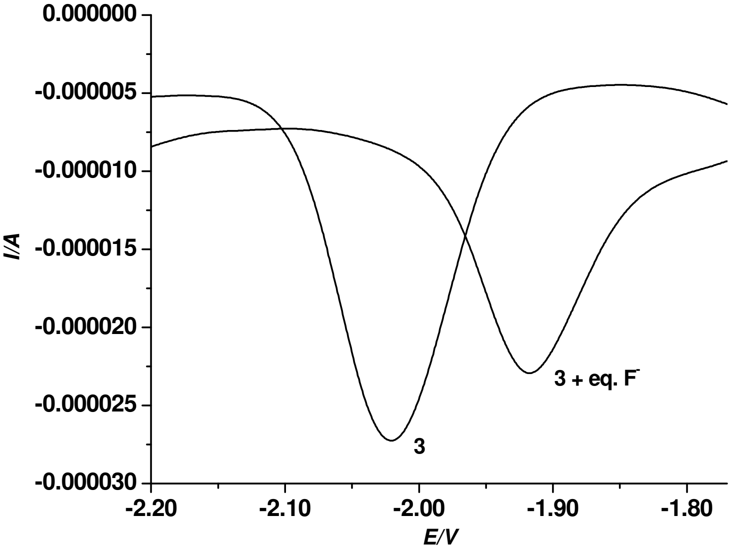


Figure 7. Differential pulse voltammetry of **3** and **3**+F$^-$ (5 equivalents) in acetonitrile (Pt working electrode, 0.1 mol dm^{-3} [Bu_4N][PF_6] at 298 K).

CONCLUSIONS

A family of heterocyclic thiosemicarbazone dyes have been prepared and their interactions with anions monitorized via UV-Vis, fluorescence and ^{1}H NMR titrations. Additionally quantum chemical calculations and electrochemical studies completed the studies carried out. The heterocyclic thiosemicarbazone dyes show a modulation of their hydrogen-bonding and electron-donating capabilities as a function of the electronic nature of the chemical groups attached and display two different chromo-fluorogenic responses towards anions in acetonitrile solutions. The more basic anions fluoride and cyanide are able to induce the dual coordination-deprotonation processes for all the receptors studied, whereas acetate only interacts with receptors **2**, **3**, **6**, **7**, **8**, **9** and dihydrogen phosphate displays sensing features only with the more acidic receptors **6**. Coordinative hydrogen bonding interactions is indicated by a small bathochromic shift, whilst deprotonation results in the appearance of a new band at ca. 400-450 nm corresponding to a colour change from colourless-yellow to yellow-red depending on the receptor. In the emission fluorescence, hydrogen bonding interaction is visible through the enhancement of the emission band, whereas deprotonation induced the growth of a new red-shifted emission. The chromo-fluorogenic behaviour could be explained on the basis of the deprotonation tendency of the binding sites and the proton affinity of the anions. PM3 and ^{1}H NMR calculations are in agreement with the existence of the dual complexation-deprotonation process, whereas both studies are in discrepancy in relation to which is the proton involved in the deprotonation. Electrochemical studies carried with receptor **3** showed a quite complex redox behaviour and anodic shifts of the reduction peaks in the presence of the basic anions fluoride, cyanide and acetate.

EXPERIMENTAL.

Materials and methods: Thin layer chromatography was carried out on 0.25 mm thick precoated silica plates. All melting points were measured on a melting point apparatus and are uncorrected. NMR spectra were obtained on a spectrometer at an operating frequency of 300 MHz for ^{1}H NMR and 75.4 MHz for ^{13}C NMR or a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR using the solvent peak as internal reference at 25 ºC. The solvents are indicated in parenthesis before the chemical shift values (δ relative to TMS and given in ppm). All the solvents were of spectrophotometric grade. Air-/water-sensitive reactions were performed in flame-dried glassware under argon. The aldehydes **II–III**, **VII–VIII** and 4-phenyl-3-thiosemicarbazide were purchased from Sigma-Aldrich reagents and used without further purification. The synthesis of 5-formyl-2-methoxythiophene **I**[18] and formyl arylthiophenes **IV–VI** and **IX**[19] was described elsewhere.

*General procedure for the synthesis of heterocyclic phenylthiosemicarbazones **1-9***: Equal amounts (0.4 mmol) of the appropriate aldehyde and thiosemicarbazide were dissolved in (30 mL) of MeOH at room temperature or in EtOH at 50 ^{o}C. A solution was obtained, which was stirred overnight. Compounds precipitated as microcrystalline solids, which were collected by suction filtration, washed with cold EtOH and dried in vacuum. Further recrystallization steps using ethanol-water mixtures were performed if necessary.

1-((5-Methoxythiophen-2-yl)methylene)-4-phenylthiosemicarbazone **1** was obtained as a yellow solid (74%). Mp > 168.0 ºC with decomposition. ^{1}H NMR (CDCl$_3$): $\delta = 3.95$ (s, 3H, OCH$_3$), 6.18 (d, $J = 3.9$

Hz, 1H, 4’-H), 7.00 (d, J = 3.9 Hz, 1H, 3’-H), 7.23-7.29 (m, 1H, 4-H), 7.42 (br t, J = 7.5 Hz, 2H, 3 and 5-H), 7.65 (br d, J = 7.5 Hz, 2H, 2 and 6-H), 7.95 (s, 1H, -CH=N), 9.02 (s, 1H, NH), 10.0 (s, 1H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 60.3, 104.8, 124.5, 125.2, 125.4, 128.1, 131.0, 130.0, 139.0, 168.6, 175.0 ppm. IR (Nujol) ν 3335, 3137, 1589, 1556, 1536, 1511, 1488, 1446, 1416, 1390, 1345, 1314, 1274, 1206, 1076, 1046, 980, 923, 764, 740, 700 cm^{-1}. MS (EI): *m/z* (%) = 291 (M$^+$, 13), 257 (3), 198 (58), 156 (14), 141 (77), 118 (53), 98 (69), 93 (100), 77(12). EI-HRMS: calcd. for $C_{13}H_{13}N_3OS_2$ 291.0500, found 291.0501.

1-((5-(Thiophen-2-yl)thiophen-2-yl)methylene)-4-phenyl-thiosemicarbazone **2** was obtained as a yellow solid (61%). Mp 188.5-189.0 ºC. ^{1}H NMR (CDCl$_3$): δ = 7.03-7.08 (m, 1H, 4’’-H), 7.14 (d, J = 3.9 Hz, 1H, 3’-H), 7.21 (d, J = 3.9 Hz, 1H, 4’-H), 7.25-7.32 (m, 3H, 4-H, 3’’ and 5’’-H), 7.44 (br t, J = 7.8 Hz, 2H, 3 and 5-H), 7.68 (br d, J = 7.8 Hz, 2H, 2 and 6-H), 8.06 (s, 1H, -CH=N), 9.10 (s, 1H, NH), 10.2 (s, 1H, NH) ppm. ^{13}C NMR (CDCl$_3$): δ = 124.0, 124.7, 124.9, 125.7, 126.3, 128.1, 128.8, 132.2, 136.2, 136.6, 137.2, 137.7, 140.7, 175.3. IR (Nujol) ν 3322, 1588, 1546, 1515, 1459, 1268, 1201, 1074, 1055, 925, 842, 792, 764, 742, 716, 702, 688, 612 cm^{-1}. $C_{16}H_{13}N_3S_3$ (347.49): calcd. C 55.95, H 3.81, N 12.23, S 28.01; found C: 55.99, H 3.87, N 12.33; S 27.66.

1-((5-Phenylthiophen-2-yl)methylene)-4-phenyl-thiosemicarbazone **3**[30] was obtained as a yellow solid (89%). Mp 178.0-179.0 ºC. ^{1}H NMR (CDCl$_3$): δ = 7.27-7.46 (m, 8H, 4, 3’, 4’, 2”, 3”, 4”, 5” and 6”-H), 7.63-7.71 (m, 4H, 2, 3, 5 and 6-H), 8.04 (s, 1H, -CH=N), 9.13 (s, 1H, NH), 9.79 (s, 1H, NH) ppm. ^{13}C NMR (CDCl$_3$): δ = 109.7, 123.6, 124.3, 125.9, 126.0, 128.4, 128.7, 129.0, 132.1, 133.4, 136.9, 137.1, 147.5, 175.4 ppm. IR (Nujol) ν 3435, 1623, 1589, 1457, 1509, 1493, 1444, 1268, 1210, 924, 796, 755, 730, 707, 688 cm^{-1}. MS (EI): *m/z* (%) = 337 (M$^+$, 2), 244 (22), 185 (100), 160 (18), 135 (8), 118 (13), 115 (87), 93 (60), 77 (18). EI-HRMS: calcd. for $C_{18}H_{15}N_3S_2$ 337.0707, found 337.0705.

1-((5-(4-Methoxyphenyl)thiophen-2-yl)methylene)-4-phenylthiosemicarbazone **4** was obtained as a yellow solid (65%). Mp 196.4-196.8 ºC. ^{1}H NMR (CDCl$_3$): δ = 3.86 (s, 3H, OCH$_3$), 6.94 (d, J = 8.7 Hz, 2H, 3’’and 5’’-H), 7.17 (d, J = 3.9 Hz, 1H, 3’-H), 7.25 (d, J = 3.9 Hz, 1H, 4’-H), 7.26-7.32 (m, 1H, 4-

H), 7.44 (br t, *J* = 7.8 Hz, 2H, 3 and 5-H), 7.57 (d, *J* = 8.7 Hz, 2H, 2’’ and 6’’-H), 7.69 (d, *J* = 7.8 Hz, 2H, 2 and 6-H), 8.08 (s, 1H, -CH=N), 9.13 (s, 1H, NH), 10.14 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ = 55.4, 114.5, 122.6, 124.6, 126.2, 126.3, 127.3, 128.8, 132.6, 135.7, 137.6, 137.8, 147.9, 160.0, 175.2 ppm. IR (Nujol) ν 3335, 3182, 1589, 1549, 1515, 1502, 1275, 1256, 1205, 1179, 1057, 1023, 833, 792, 747, 707, 692 cm^{-1}. $C_{19}H_{17}N_3OS_2$ (367.49): calcd. C 62.10, H 4.66, N, 11.43, S, 17.45; found C 61.91, H 4.68, N 11.35; S 17.48.

1-((5-(4-(Dimethylamino)phenyl)thiophen-2-yl)methylene)-4- phenylthiosemicarbazone **5** was obtained as a orange solid (57%). Mp 199.1-199.8 ºC. ^{1}H NMR ($CDCl_3$): δ = 3.05 (s, 6H, $N(CH_3)_2$), 7.16 (d, *J* = 3.9 Hz, 1H, 3’-H), 7.25 (d, *J* = 3.9 Hz, 1H, 4’-H), 7.26-7.30 (m, 3H, 3, 4 and 5-H), 7.43 (br t, *J* = 7.5 Hz, 2H, 2 and 6-H), 7.56 (d, *J* = 8.7 Hz, 2H, 3’’ and 5’’-H), 7.70 (d, *J* = 8.7 Hz, 2H, 2 and 6-H), 7.99 (s, 1H, -CH=N), 9.12 (s, 1H, NH), 9.44 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ = 44.1, 114.3, 122.2, 124.5, 126.2, 126.3, 127.2, 128.2, 132.0, 135.4 137.4, 137.6, 146.5, 150.0, 174.2 ppm. EI-HRMS: calcd. for $C_{22}H_{24}N_4S_2$ 408.1027, found 408.1018.

1-((5-(4-Cyanophenyl)thiophen-2-yl)methylene)-4-phenylthiosemicarbazone **6** was obtained as a orange solid (58%). Mp 201.8-202.5 ºC. ^{1}H NMR ($CDCl_3$): δ = 7.27-7.33 (m, 3H, 3, 4 and 5-H), 7.39-7.47 (m, 3H, 2, 6 and 4’-H), 7.67-7.75 (m, 5H, 3’, 2’’, 3’’, 5’’ and 6’’-H), 8.06 (s, 1H, -CH=N), 9.11 (s, 1H, NH), 9.91 (s, 1H, NH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 110.2, 118.7, 125.4, 125.5, 126.0, 126.9, 128.2, 132.3, 133.2, 137.4, 137.5, 138.9, 140.0, 143.2, 175.6 ppm. IR (Nujol) ν 3291, 3129, 2220, 1599, 1551, 1517, 1496, 1266, 1206, 1175, 926, 943, 799, 767, 746 cm^{-1}. MS (EI): *m/z* (%) = 362 (M^+, 20), 331 (22), 295 (10), 227 (100), 193 (15), 159 (15). EI-HRMS: calcd. for $C_{19}H_{14}N_4S_2$ 362.0660, found 362.0652.

1-((Furan-2-yl)methylene)-4-phenylthiosemicarbazone **7** was obtained as a yellow solid (50%). Mp 171.5-172.3 ºC. ^{1}H NMR ($CDCl_3$): δ = 6.49-6.51 (m, 1H, 4’-H) 6.73-6.74 (d, *J* = 3.9 Hz, 1H, 3’-H), 7.21-7.27 (m, 2H, 4 and 5´-H), 7.38 (br t, *J* = 7.8 Hz, 2H, 3 and 5-H), 7.62 (br d, *J* = 7.8 Hz, 2H, 2 and 6-H), 7.89 (s, 1H, -CH=N), 9.29 (s, 1H, NH), 10.7 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 112.2, 114.8, 123.8, 124.8, 126.3, 128.7, 132.5, 137.7, 144.9, 175.4 ppm. IR (Nujol) ν 3292, 1619, 1598, 1590, 1542, 1511, 1272, 1209, 1065, 1011, 923, 882, 769, 735, 670 cm^{-1}. MS (EI): *m/z* (%) = 245 (M$^+$, 100), 257 (18), 227 (15), 212 (10), 165 (8). EI-HRMS: calcd. for $C_{12}H_{11}N_3OS$ 245,0623, found 245,0617.

1-((Thiazol-2-yl)methylene)-4-phenyl-thiosemicarbazone **8** was obtained as a yellow solid (70%). Mp 165.0-166.0 ºC. ^{1}H NMR ([D$_6$]DMSO): δ = 7.21 (br t, *J* = 7.5 Hz, 1H, 4-H), 7.37 (br t, 7.5 Hz, 2H, 3 and 5-H), 7.53 (br d, *J* = 7.5 Hz, 2H, 2 and 6-H), 7.84 (dd, *J* = 3.3 and 1.0 Hz, 1H, 5'-H), 7.94 (d, *J* = 3.3 Hz, 1H, 4'-H), 8.38 (br s, 1H, -CH=N), 10.1 (s, 1H, NH), 12.1 (s, 1H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 122.3, 125.6, 125.9, 128.2, 137.3, 138.9, 144.0, 163.6, 176.3 ppm. IR (Nujol) ν 3322, 1596, 1542, 1498, 1476, 1443, 1312, 1257, 1190, 1152, 1091, 1055, 938, 916, 898, 876, 790, 751, 687 cm^{-1}. EI-HRMS: calcd. for $C_{11}H_{10}N_4S_2$ 262.0347, found 262.0370.

1,1-((5-Phenylthiophen-2-yl)methylene)-bis-4-phenylthiosemicarbazone **9** was obtained as a orange solid (77%). Mp > 234.5 ºC with decomposition. ^{1}H NMR ([D$_6$]DMSO): δ = 7.16-7.24 (m, 2H, Ar-H), 7.30-7.42 (m, 4H, Ar-H), 7.52-7.60 (m, 5H, ArH and 3'-H), 7.66 (d, *J* = 3.9Hz, 1H, 4'-H), 7.75 (d, *J* = 8.7 Hz, 2H, 2'' and 6''-H), 7.96 (d, *J* = 8.7 Hz, 2H, 3'' and 5''-H), 8.15 (s, 1H, -CH=N), 8.32 (s, 1H, -CH=N), 9.84 (s, 1H, NH), 10.2 (s, 1H, NH), 11.87 (s, 1H, NH), 11.90 (s, 1H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 125.3, 125.4, 125.5, 125.6, 126.0, 128.1, 128.1, 128.5, 132.5, 133.8, 134.5, 137.7, 138.2, 138.3, 139.0, 139.1, 142.1, 145.0, 175.5, 176.0 ppm. IR (Nujol) ν 3316, 3144, 1661, 1595, 1551, 1500, 1445, 1268, 1197, 1073, 1028, 1004, 939, 920, 898, 866, 825, 793, 746, 723, 703, 691, 661, 614 cm^{-1}. MS (microTOF): *m/z* (%) = 515 (M$^+$ + 1, 15), 483 (10), 420 (5), 334 (4) 269 (22), 208 (84). (microTOF-HRMS: calcd. for $C_{26}H_{23}N_6S_3$ 515.1168, found 515.1141.

Physical measurements: Stock solutions of the anions (F$^-$, Cl$^-$, Br$^-$, I$^-$, NO_3^-, $H_2PO_4^-$, HSO_4^-, AcO$^-$, BzO$^-$, CN$^-$, OH$^-$ as tetrabutylammonium [TBA] salts) were prepared at 10^{-3} mol dm^{-3} in acetonitrile. The concentrations of ligands used in these measurements were ca. 5.0 x 10^{-5} mol dm^{-3}. The NMR studies were carried out under similar conditions.

Theoretical studies: Quantum chemical calculations at semiempirical level (PM3, within restricted Hartree–Fock level) were carried out in vacuo with the aid of Hyperchem V6.03. The Polar–Ribiere algorithm was used for the optimization. The convergence limit and the RMS gradient were set to 0.01 kcal mol^{-1}.

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SUPPORTING INFORMATION AVAILABLE

Proton and carbon NMR spectra of reported compounds, atom coordinates and total energies of calculated structure. This material is available free of charge via the Internet at http://pubs.acs.org

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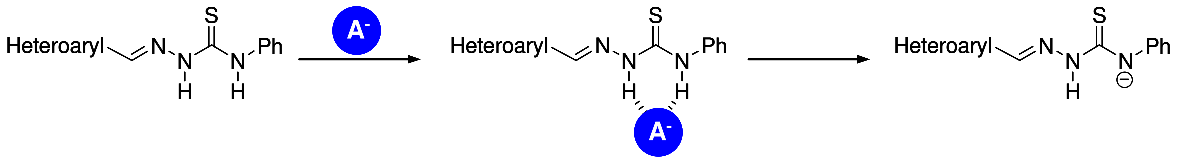

Heteroaryl = *thienyl*, *bithienyl*, *arylthienyl*, *furanyl*, *thiazolyl*