

## Metal-Enhanced H-Bond Donor Tendencies of Urea and Thiourea toward Anions: Ditopic Receptors for Silver(I) Salts

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The heteroditopic receptors **1** and **2** firmly include an Ag<sup>I</sup> ion into the NS<sub>2</sub>O<sub>2</sub> crown and establish selective H-bond interactions with anions at the covalently linked urea/thiourea (U/T) subunit. Studies in MeCN solution showed that the metal center induces a 10<sup>3</sup>–10<sup>6</sup>-fold enhancement of the anion association constant, due to a coordinative interaction with the O/S atom of the U/T moiety. In the presence of F<sup>-</sup>, the Ag–O interaction promotes the release of a proton from one of the urea N–H fragments. Ag<sup>I</sup> coordination to the S atom of the thiourea derivative **2** promotes the formation of unusually stable H-bond complexes with Cl<sup>-</sup> and Br<sup>-</sup>.

### Introduction

There exists an increasing interest on ion-pair recognition, i.e., the simultaneous selective complexation of a metal ion and an anion by a heteroditopic receptor.<sup>1</sup> These systems are typically neutral and consist of (i) a multidentate compartment suitable for the coordination of the metal ion and (ii) a binding site for the anion, containing H-bond donor groups (in general N–H fragments from amides or ureas). While useful suggestions for individual ion binding can be provided by the old discipline of metal coordination chemistry,<sup>2</sup> and by the rather new discipline of anion coordination chemistry,<sup>3</sup> the mutual location of the two compartments is a matter of design, as it may produce favorable effects, of an electrostatic and/or conformational nature. For instance, Smith has recently designed polycyclic receptors containing amide N–H fragments, capable of accommodating a cation (e.g. K<sup>+</sup>) and an anion (e.g. Cl<sup>-</sup>) in close contact: in the presence of K<sup>+</sup>, the receptor's affinity toward Cl<sup>-</sup>, in a DMSO solution, was 13-fold enhanced, due to a cooperative electrostatic effect.<sup>4</sup> On the other hand, Beer has shown that, in a ditopic receptor containing oxa-crown and amide binding

sites, the presence of K<sup>+</sup> inverts the selectivity toward Cl<sup>-</sup> and H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, due to the different inference of cooperative electrostatic and allosteric conformational effects.<sup>5</sup>

Inorganic anions, at least in principle, can be discriminated on the basis of geometrical parameters: size and shape (spherical, trigonal, tetrahedral, etc.).<sup>6</sup> Metal ions are much more numerous than inorganic anions and can be divided into four main classes, according to their electronic configuration: (i) those having an inert gaslike electronic configuration (alkali and alkaline earth); (ii) those with partly filled d levels; (iii) those with a d<sup>10</sup> configuration; (iv) block f elements. Each class presents its own binding features and requires a particular set of donor atoms. Most of the work on ion-pair recognition has been centered on alkali metal halides, providing accommodation either for separated or close-contact cations and anions;<sup>7–28</sup> moreover, receptors for recognition of nickel(II) and copper(II) sulfates have been

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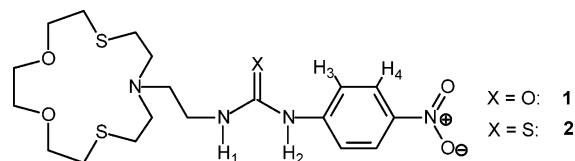
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reported.<sup>29,30</sup> No attention has been paid so far to ion pairs involving metal ions of classes iii and iv, despite the potential interest in separation science and technology (e.g. precious metal recovery, in the case of d<sup>10</sup> cations, and treatment of wastewater from nuclear plants, for 5f cations). We describe here the two new ditopic receptors **1** and **2**, suitable for the recognition of ion pairs involving the d<sup>10</sup> metal ion Ag<sup>I</sup>.



In particular, a 15-membered NO<sub>2</sub>S<sub>2</sub> crown was linked, though a –CH<sub>2</sub>CH<sub>2</sub>– spacer, to a nitrophenylurea/thiourea moiety. The crown ligand, due to the presence of the two thioetheral sulfur atoms, is expected to form stable complexes with d<sup>10</sup> metal centers (soft). The complex of Cd<sup>II</sup> with the NO<sub>2</sub>S<sub>2</sub> macrocycle has been crystallographically characterized and shows full coordination of all the five donor atoms to the metal.<sup>31</sup> Notably, an Hg<sup>II</sup> complex of the NS<sub>2</sub>O<sub>2</sub> crown, to which a chromogenic subunit had been covalently linked, was successfully employed as colorimetric reagent for anion sensing.<sup>32</sup> On the other hand, urea and thiourea subunits are favorably inclined to establish two directional H-bonds with two complementary oxygen atoms of an oxoanion (e.g. acetate, phosphate) or to chelate a spherical anion (e.g. halides).<sup>33,34</sup> The nitrophenyl chromogenic fragment has been appended to the urea/thiourea moiety to signal, through color change and spectral modifications, the occurrence of the receptor–anion interaction.

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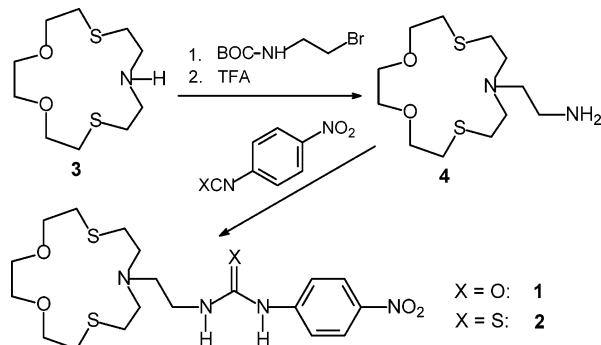
We have recently observed that the presence of electron-withdrawing substituents, like nitrophenyl, enhances the hydrogen-bonding donor properties of urea/thiourea-based receptors toward anions and that, in the presence of an excess of an especially basic anion X<sup>−</sup>, it may induce the deprotonation of one of the N–H fragments, with formation of the [HX<sub>2</sub>]<sup>−</sup> H-bond self-complex.<sup>35</sup> Thus, it seemed of particular interest to evaluate the effect of a nearby Ag<sup>I</sup> ion on the tendencies of the urea/thiourea site to form an H-bond complex with a given anion and/or to release an N–H proton, thus behaving as a Brønsted acid.

## Experimental Section

**General Procedures and Materials.** All reagents employed in the syntheses were purchased from Aldrich/Fluka and used without further purification. UV–vis spectra were recorded on a Varian CARY 100 spectrophotometer, with a quartz cuvette (path length: 0.1–1 cm). The cell holder was thermostated at 25.0 °C, through circulating water. <sup>1</sup>H NMR spectra were obtained on a Bruker AVANCE400 spectrometer (400 MHz), operating at 9.37 T. Spectrophotometric titrations were performed on 10<sup>−3</sup>–10<sup>−4</sup> M solutions of **1** and **2** in MeCN (polarographic grade). As for the titrations with Ag<sup>I</sup>, aliquotes of a fresh Ag(CF<sub>3</sub>SO<sub>3</sub>) standard solution were added and the UV–vis spectra of the samples were recorded. In the titrations with anions, UV–vis spectra of the samples were recorded after the addition of aliquotes of an alkylammonium salt solution of the envisaged anion ([Bu<sub>4</sub>N]<sup>+</sup> for CH<sub>3</sub>COO<sup>−</sup>, H<sub>2</sub>PO<sub>4</sub><sup>−</sup>, NO<sub>2</sub><sup>−</sup>, HSO<sub>4</sub><sup>−</sup>, NO<sub>3</sub><sup>−</sup>, F<sup>−</sup>, Br<sup>−</sup>; [BzBu<sub>3</sub>]<sup>+</sup> for Cl<sup>−</sup>). Fitting of all spectrophotometric titration curves was performed with the HYPERQUAD program.<sup>36</sup> Care was taken that, in each titration, the *p* parameter (*p* = [concentration of complex]/[maximum possible concentration of complex]) was lower than 0.8, a condition required for the safe determination of a reliable equilibrium constant.<sup>37</sup> <sup>1</sup>H NMR titrations were carried out in DMSO-*d*<sub>6</sub> at a higher concentration of the receptors (**1** and **2**) or their Ag(CF<sub>3</sub>SO<sub>3</sub>) 1:1 complexes (10<sup>−2</sup> M).

**2-(1,4-Dioxo-7,13-dithia-10-azacyclopentadec-10-yl)ethylamine (4).** In a round-bottomed flask, fitted with a magnetic stirrer and a reflux condenser, 0.40 g of macrocycle **3** (1.60 mmol),<sup>38</sup> 0.54 g of (2-bromoethyl)carbamic acid *tert*-butyl ester (2.40 mmol), and excess K<sub>2</sub>CO<sub>3</sub> were suspended in 100 mL of dry MeCN and heated to reflux for 12 h. The carbonate was filtered off, and MeCN was removed at reduced pressure. The sticky crude reaction product was purified by column chromatography on Al<sub>2</sub>O<sub>3</sub> with a hexane/ethyl acetate mixture. The protected functionalized macrocycle was isolated as a yellow oil (0.5 g, 80%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) [δ (ppm)]: 1.50 (s, 9H, BOC), 2.60 (t, 4H, CH<sub>2</sub>N), 2.75 (m, 8H, CH<sub>2</sub>S), 3.20 (t, 4H, CH<sub>2</sub>N), 3.40 (t, 4H, CH<sub>2</sub>N), 3.52 (t, 4H, CH<sub>2</sub>N), 3.65 (s, 4H, CH<sub>2</sub>O), 3.80 (t, 4H, CH<sub>2</sub>O). MS(ESI) (*m/z*): 395 (M<sup>+</sup>). To a CH<sub>2</sub>Cl<sub>2</sub> solution of the protected functionalized macrocycle (1.53 mmol in 5 mL) was added 5 mL of trifluoroacetic acid (TFA) dropwise under stirring. The reaction mixture was stirred at room temperature for 1 h, when TLC tests showed complete disappearance of the protected functionalized macrocycle. After removal of

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Scheme 1. Synthetic Route to **1** and **2**

$\text{CH}_2\text{Cl}_2$  and TFA at reduced pressure, the crude product was dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with aqueous 0.1 M NaOH. The organic extracts were collected, dried over anhydrous magnesium sulfate, filtered, and concentrated, to give the deprotected functionalized macrocycle **4** as a yellow oil (0.43 g, 95%). MS (ESI) ( $m/z$ ): 295 ( $\text{M}^+$ ).

**1-[2-(1,4-Dioxo-7,13-dithia-10-azacyclopentadec-10-yl)ethyl]-3-(4-nitrophenyl)urea (1)**. A 0.4 g (1.36 mmol) amount of **4** and 0.22 g (1.36 mmol) of 4-nitrophenyl isocyanate were dissolved in 10 mL of  $\text{CH}_2\text{Cl}_2$ , and the resulting solution was stirred at room temperature for 16 h (Scheme 1). After evaporation of the solvent, the crude reaction product was purified by column chromatography on  $\text{Al}_2\text{O}_3$ , using a hexane– $\text{CH}_2\text{Cl}_2$  mixture, as the eluent, to give 0.45 g (0.98 mmol, 72%) of **1**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) [ $\delta$  (ppm)]: 2.66 (t, 2H,  $J = 5.3$  Hz,  $\text{NCH}_2\text{CH}_2\text{NHCO}$ ), 2.75–2.88 (m, 12H,  $\text{SCH}_2\text{CH}_2\text{N}$ ,  $\text{OCH}_2\text{CH}_2\text{S}$ ), 3.38 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{NHCO}$ ), 3.71 (s, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 3.81 (t, 4H,  $J = 5.5$  Hz,  $\text{OCH}_2\text{CH}_2\text{S}$ ), 6.34 (s, 1H,  $\text{HNC}=\text{O}$ ), 7.61 (d, 2H,  $J = 9.2$  Hz, Ar), 8.15 (d, 2H,  $J = 9.2$  Hz, Ar), 8.21 (s, 1H,  $\text{HNC}=\text{O}$ ). MS (ESI) ( $m/z$ ): 459 ( $\text{M}^+$ ).

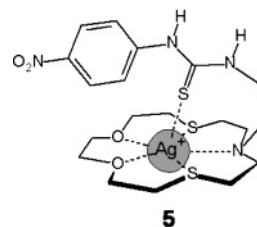
**1-[2-(1,4-Dioxo-7,13-dithia-10-azacyclopentadec-10-yl)ethyl]-3-(4-nitrophenyl)thiourea (2)**. A 0.4 g amount of **4** (1.36 mmol) and 0.25 g of 4-nitrophenyl isothiocyanate (1.36 mmol) were dissolved in 10 mL of  $\text{CH}_2\text{Cl}_2$ , and the solution was stirred at room temperature for 16 h. The solvent was evaporated, and the crude reaction product was purified by column chromatography on  $\text{Al}_2\text{O}_3$ , using a hexane– $\text{CH}_2\text{Cl}_2$  mixture, as the eluent, to give 0.51 g (1.09 mmol, 80%) of **2**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) [ $\delta$  (ppm)]: 2.73 (t, 4H,  $J = 5.3$  Hz,  $\text{OCH}_2\text{CH}_2\text{S}$ ), 2.79 (t, 2H,  $J = 5.0$  Hz,  $\text{NCH}_2\text{CH}_2\text{NHCS}$ ), 2.83 (s, 8H,  $\text{SCH}_2\text{CH}_2\text{N}$ ), 3.63 (s, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 3.73 (t, 4H,  $J = 5.3$  Hz,  $\text{OCH}_2\text{CH}_2\text{S}$ ), 3.76 (b, 2H,  $\text{NCH}_2\text{CH}_2\text{NHCS}$ ), 7.67 (d, 2H,  $J = 8.5$  Hz, Ar), 7.80 (s, 1H,  $\text{HNC}=\text{S}$ ), 8.25 (d, 2H,  $J = 8.5$  Hz, Ar), 8.55 (s, 1H,  $\text{HNC}=\text{S}$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) [ $\delta$  (ppm)]: 31.7 ( $\text{CH}_2\text{S}$ ), 32.3 ( $\text{CH}_2\text{S}$ ), 43.1 ( $\text{CH}_2\text{N}$ ), 53.7 ( $\text{CH}_2\text{N}$ ), 54.2 ( $\text{CH}_2\text{N}$ ), 72.4 ( $\text{CH}_2\text{O}$ ), 74.0 ( $\text{CH}_2\text{O}$ ), 122.5 (Ar), 125.4 (Ar), 144.2 (Ar), 147.0 (Ar), 180.1 ( $\text{C}=\text{S}$ ). MS (ESI) ( $m/z$ ): 475 ( $\text{M}^+$ ).

## Results and Discussion

**1. Formation of  $\text{Ag}^{\text{I}}$  Complexes with Receptors **1** and **2**.** The binding tendencies of **1** and **2** toward  $\text{Ag}^{\text{I}}$  were investigated spectrophotometrically. In particular, an MeCN solution of the receptor was titrated with a standard MeCN solution of silver(I) triflate. The family of UV–vis spectra recorded over during the titration are shown in Figure 1a (receptor **1**) and in Figure 1b (receptor **2**).

Addition of the silver(I) salt caused appreciable modifications of the spectral pattern. In particular, metal addition

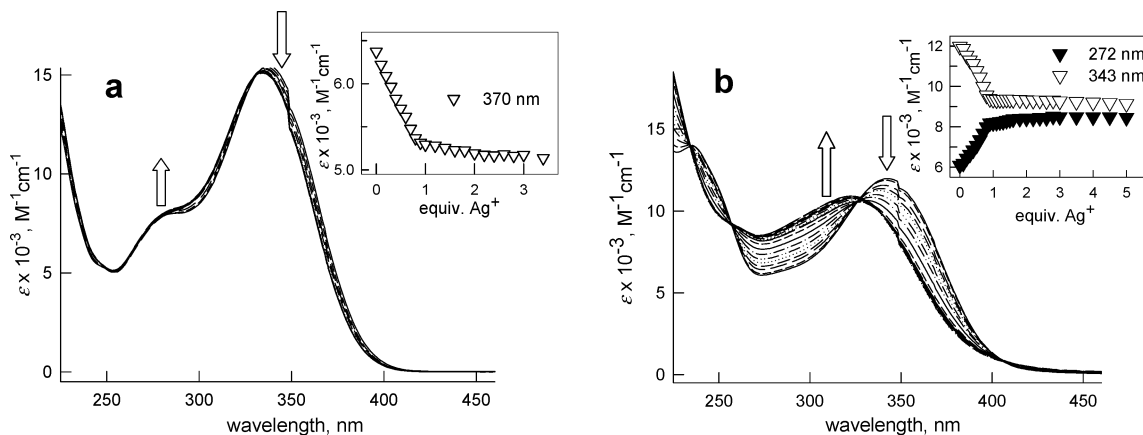
induced a blue shift of the charge-transfer bands centered at 330 nm (receptor **1**) and at 345 nm (receptor **2**). Titration profiles (absorbance vs equivalents of  $\text{Ag}^{\text{I}}$ ; see insets of Figure 1a,b) clearly indicated the formation of 1:1 complexes. However, the sharp bending of the titration profiles prevented us from a safe determination of the formation constants, whose values are in both cases  $> 10^6$ . Notice that spectral changes are very moderate for receptor **1** and quite large for receptor **2**. For both receptors, the investigated band results from a charge-transfer transition from the urea/thiourea to the  $-\text{NO}_2$  group of the appended nitrophenyl moiety. In the case of receptor **2**, the less electronegative sulfur atom provides most of the negative charge. Thus, the metal-induced blue-shift of the absorption band indicates that  $\text{Ag}^{\text{I}}$  binding significantly contrasts the transfer of negative charge from the thiourea sulfur atom to the  $-\text{NO}_2$  group. It is suggested that such a behavior results from the formation of a direct coordinative interaction between the S atom and the silver(I) center encircled by the macrocycle. A tentative sketch of the binding mode in the metal–receptor complex is shown as follows:



In particular, coordination to the metal reduces the electron density on the thiourea sulfur, thus reducing the intensity of the S-to- $\text{NO}_2$  dipole, which is reflected in the blue-shift of the charge-transfer band. Coordination of the thiourea sulfur atom to  $\text{Ag}^{\text{I}}$  has been confirmed by  $^1\text{H}$  NMR titration experiments.

Figure 2 shows the spectra taken during the titration of a DMSO- $d_6$  solution of **2** (0.014 M) with silver(I) triflate. DMSO was used, as it allows detecting and monitoring N–H signals, which were not defined in  $\text{CH}_3\text{CN}-d_3$ . On silver addition, a neat downfield shift of the two N–H protons of the thiourea was observed. It is suggested that  $\text{Ag}^{\text{I}}$  coordination to S withdraws electron density from the thiourea moiety. As a consequence, a partial positive charge is created onto the N–H protons, which causes a deshielding effect and promotes the downfield shift. In particular, this effect is more pronounced for N–H(1), as indicated by the larger downfield shift if compared to N–H(2). This can be explained by the higher basicity of the nitrogen atom of N–H(1) induced by the aliphatic chain. On the other hand, the lone pair on the N–H(2) nitrogen atom becomes less involved in the delocalization on the thiourea. This increases the mesomeric effect on the aromatic ring, as shown by the shielding of the ortho protons, C–H(3), which undergo a significant upfield shift.

As far as absorption spectra are concerned, addition of  $\text{Ag}(\text{CF}_3\text{SO}_3)$  to a solution of **1** induces a moderate blue-shift of the charge transfer band (see Figure 1a). In this connection,



**Figure 1.** Spectra taken during the titration of a  $10^{-4}$  M solution of **1** (a) and **2** (b) with a standard solution of  $\text{Ag}^+\text{CF}_3\text{SO}_3$ . Inset: titration profiles at selected wavelengths.

it should be considered that the strongly electronegative oxygen atom of the urea subunit poorly contributes to the charge-transfer transition. Moreover, even in the presence of an  $\text{Ag}^{\text{I}}$ –urea oxygen coordinative interaction, the energy of the charge-transfer transition of **1** should not be seriously modified on silver(I) addition. However, titration of a DMSO- $d_6$  solution of **1** with  $\text{Ag}(\text{CF}_3\text{SO}_3)$  did not induce any significant modification of the  $^1\text{H}$  NMR spectrum (see Figure 4, spectrum b), which rules out any hypothesis of oxygen coordination to  $\text{Ag}^{\text{I}}$ , according to the binding mode illustrated in structural formula **5**. Failure of **1** to interact with the metal by means of the urea pendant group may be ascribed to the nonavailability of empty  $d_{\pi}$  orbitals on the oxygen atom, a feature from which the sulfur atom of **2** takes profit for establishing an additional  $\text{Ag}^{\text{I}} \rightarrow \text{S} \pi$  bonding contribution.

## 2. Anion Interactions with **1** and $[\text{Ag}^{\text{I}}(\mathbf{1})]^+$ : Oxoanions.

To evaluate the effect of  $\text{Ag}^{\text{I}}$  on the anion binding properties of the urea fragment in receptor **1**, two series of experiments were carried out. In a first experiment, an MeCN solution of **1** was titrated with a standard solution of the chosen anion; in a second experiment, titration was carried out on a solution of **1** containing an equimolar amount of  $\text{AgNO}_3$  (the reason for which nitrate was preferred as a counterion to the much less basic triflate will be discussed later). Due to its large stability constant ( $>10^6$ ), it is assumed that the  $[\text{Ag}^{\text{I}}(\mathbf{1})]^+$  complex is present at 100% in the starting solution.

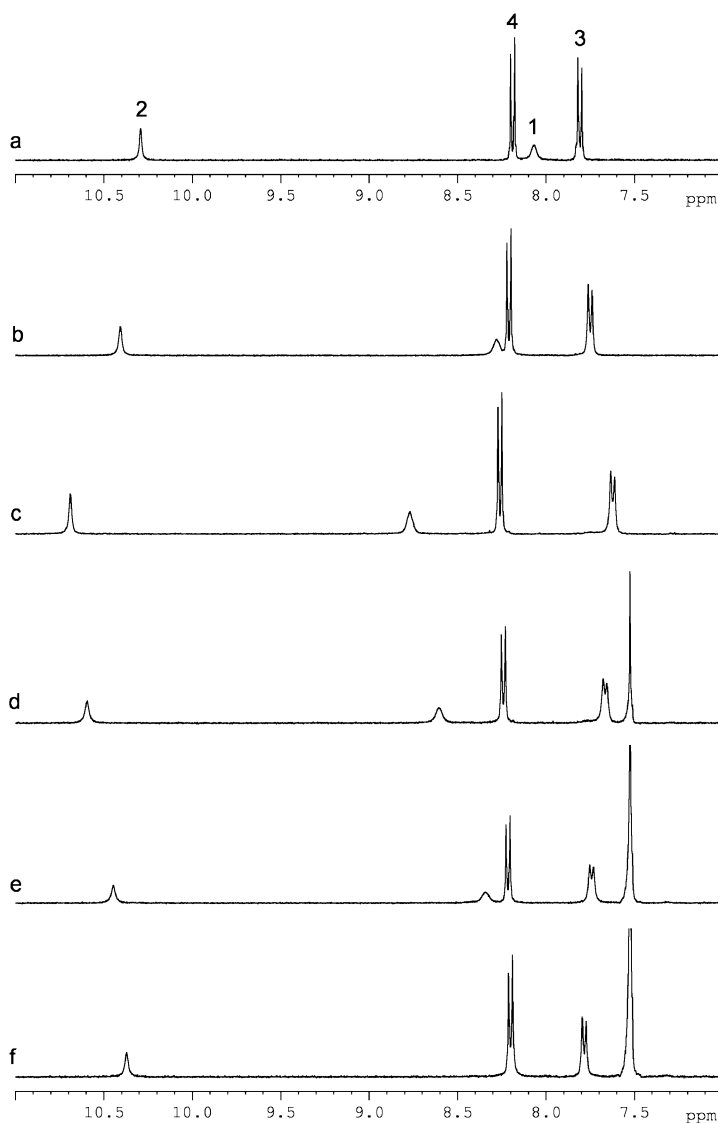
Figure 3a shows the spectra taken during the titration of **1** with  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$ . On anion addition, the band at 330 nm undergoes a distinct red-shift, from 332 to 363 nm. This shift is ascribed to the occurrence of an H-bond interaction involving the two N–H fragments of the urea subunit and the two oxygen atoms of the acetate ion: in particular, electron density is transferred on the urea moiety, which makes the intensity of the dipole increase and shifts the charge-transfer band to a longer wavelength. Nonlinear least-squares analysis of the titration curve (see a typical titration profile in the inset of Figure 3a) indicated the formation of a complex of 1:1 stoichiometry, with an association constant  $\log K = 4.49 \pm 0.01$ .

Figure 3b shows the spectra taken during the titration with  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$  of a solution containing both **1** and  $\text{AgNO}_3$ .

Also in this case, a well-defined red-shift of the charge-transfer band is observed, from 332 to 350 nm. However, the titration profile is much steeper than observed in the absence of  $\text{Ag}^{\text{I}}$ , which indicates an association constant  $>10^6$ . Thus, the metal center increases the anion affinity of the urea subunit by more than 30 times. Similar spectral patterns were observed on performing titration experiments with  $\text{H}_2\text{PO}_4^-$  and  $\text{HSO}_4^-$ . In both cases, an enhancement of anion affinity was observed, by a factor of 10 and 4, respectively (see  $\log K$  values in Table 1).

However, the approach we used is not intrinsically correct. In fact, in titration experiments on a metal-containing solution, the nitrate ion was present in equimolar amount with respect to **1**, as silver(I) had been added as  $\text{AgNO}_3$ , and nitrate itself can compete for coordination to the urea subunit. Indeed, on titration with  $[\text{Bu}_4\text{N}]\text{NO}_3$  of a solution containing both **1** and  $\text{Ag}(\text{CF}_3\text{SO}_3)$ , a distinct red-shift of the charge-transfer band was observed and the corresponding association constant ( $\log K = 2.91 \pm 0.01$ ) was calculated. It derives that the constants reported in Table 1 refer not to a genuine association equilibrium but rather to a process in which a nitrate ion is displaced from the receptor by the investigated anion. Thus, adding 2.9 to the  $\log K$  values of Table 1 should obtain absolute association constants. It results therefore that the presence of nitrate was essential to obtain smooth titration profiles and computable  $\log K$  values. In fact, on using  $\text{Ag}(\text{CF}_3\text{SO}_3)$  as silver(I) source, one would obtain steep profiles, without any curvature, on titration with any anion, and could assess only the lower limit of 6 for  $\log K$  values. Notice also that, in the absence of  $\text{Ag}^{\text{I}}$ , nitrate addition, even in large excess, did not induce any modification of the charge-transfer band, indicating poor or nil affinity toward the urea subunit.

Thus, from the absolute values of association constants, the following metal-induced enhancement (MIE) factors can be calculated:  $\text{CH}_3\text{COO}^-$ ,  $3 \times 10^4$ ;  $\text{H}_2\text{PO}_4^-$ ,  $8 \times 10^3$ ;  $\text{HSO}_4^-$ ,  $2 \times 10^3$ . Such an increase can be hardly associated to a through-space electrostatic effect, which could not account for enhancement factors of  $10^3$  and more. On binding of an oxoanion to the N–H fragments of the urea subunit, electron density is transferred onto the oxygen atom, which



**Figure 2.**  $^1\text{H}$  NMR experiment on a 0.014 M solution of **2** in  $\text{DMSO-}d_6$  in the absence of  $\text{Ag}^{\text{I}}$  (spectrum a) and after the addition of 0.4 equiv (spectrum b) and 1.0 equiv of silver(I) triflate (spectrum c). To the 1:1  $[\text{Ag}^{\text{I}}(\mathbf{2})]^+$  complex (spectrum c),  $[\text{BzBu}_3\text{N}]\text{Cl}$  is progressively added (spectrum d, 0.3 equiv of  $\text{Cl}^-$ ; spectrum e, 0.6 equiv; spectrum f, 2.0 equiv).

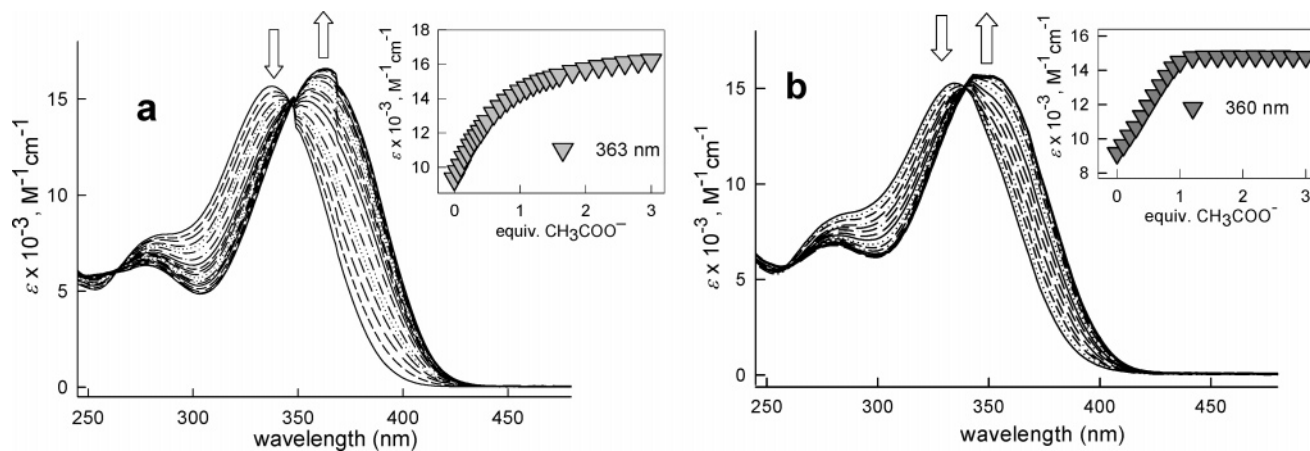
is now prone to establish a direct coordinative interaction with the  $\text{Ag}^{\text{I}}$  center. Noticeably, the establishment of complementary directional H-bond interactions between the two oxygen atoms of the acetate and the two N–H fragments of **1** has been confirmed by  $^1\text{H}$  NMR experiments.

Spectrum a in Figure 4 pertains to a solution 0.012 M of **1** in  $\text{DMSO-}d_6$ . On addition of 1 equiv of silver(I) triflate (spectrum b), no significant modifications of the spectral pattern are observed for both N–H and aromatic C–H protons, which rules out the C=O coordination to  $\text{Ag}^{\text{I}}$  (vide supra). Further spectra were recorded on titration with  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$ : on acetate addition, a progressive downfield shift of the N–H protons is observed, according to a saturation profile. A structural sketch of the  $[\text{Ag}^+(\mathbf{1})\cdots\text{CH}_3\text{COO}]$  complex (**6**) is shown in Scheme 2.

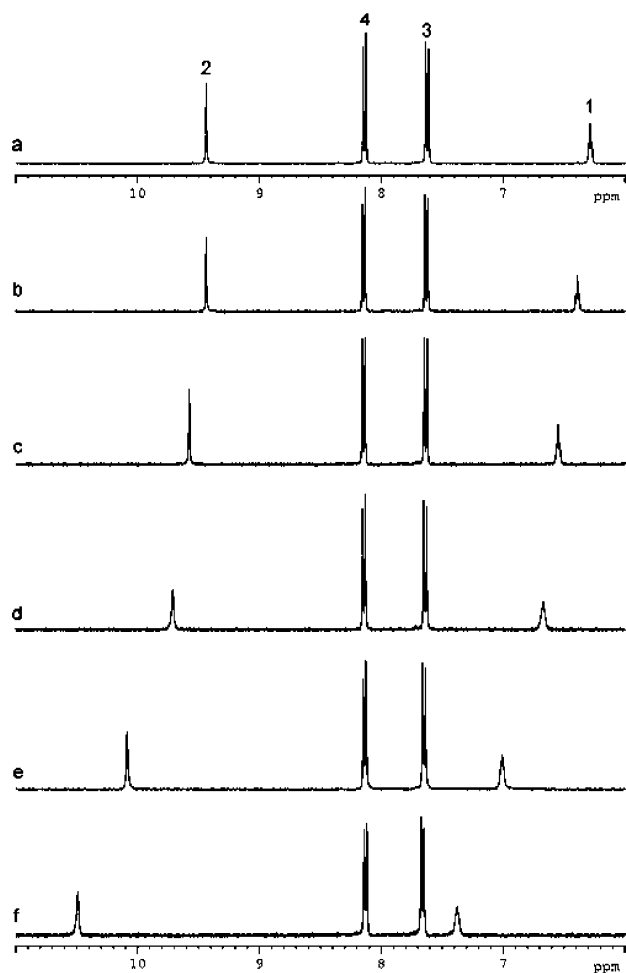
A similar geometrical arrangement is suggested for the complexes with other investigated oxoanions. In all cases,

coordination of the urea oxygen atom to the metal reduces the negative charge to be transferred from the urea subunit to the  $-\text{NO}_2$  group in the optical transition, thus accounting for the observed decrease of the magnitude of the red-shift (e.g. for  $\text{CH}_3\text{COO}^-$ : in absence of  $\text{Ag}^{\text{I}}$ , 31 nm; in the presence of  $\text{Ag}^{\text{I}}$ , 19 nm).

$\text{NO}_2^-$  showed an unexpected behavior. In absence of silver(I), an association constant  $\log K = 2.21 \pm 0.01$  was calculated from the typical modification of charge-transfer absorption band. Such a value fits well the generally observed affinity sequence of oxoanions for urea-based receptors, which ultimately reflects the amount of partial negative charge present on the anion oxygen atoms:  $\text{CH}_3\text{COO}^- > \text{H}_2\text{PO}_4^- > \text{HSO}_4^- > \text{NO}_2^- > \text{NO}_3^-$ .<sup>33</sup> However, in the presence of  $\text{AgNO}_3$ , the surprisingly high value of  $\log K = 5.12 \pm 0.01$  was observed, which made nitrite overcome sulfate and phosphate in the affinity sequence for **1**. We



**Figure 3.** Spectra taken during the titration: (a) an MeCN solution  $1.0 \times 10^{-4}$  M in **1** with a standard solution of  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$ ; (b) an MeCN solution  $1.0 \times 10^{-4}$  M in **1** and in  $\text{AgNO}_3$  with a standard solution of  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$ . Inset: titration profiles at selected wavelengths.



**Figure 4.**  $^1\text{H}$  NMR experiment on a 0.012 M solution of **1** in  $\text{DMSO-}d_6$  in the absence (spectrum a) and in the presence of  $\text{Ag}^+$  (spectrum b). Spectra c–f: progressive additions of  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$  to a solution equimolar in **1** and  $\text{Ag}^+$  (spectrum c, 0.1 equiv of  $\text{CH}_3\text{COO}^-$ ; spectrum d, 0.3 equiv; spectrum e, 0.7 equiv; spectrum f, 1.0 equiv).

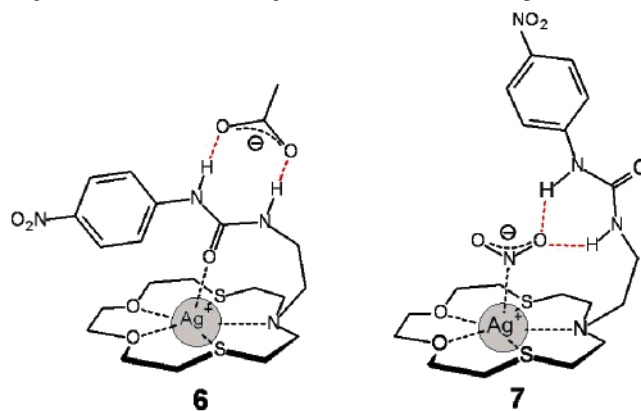
suggest that this is due to the unique capability of  $\text{NO}_2^-$  of coordinating a metal center through the nitrogen atom (according to the so-called *nitro*-binding mode) and to accept electron density from a filled  $d_\pi$  orbital of the  $d^{10}$  metal into its empty  $\pi^*$  molecular orbital (a binding mode impossible for all the other investigated oxoanions). A possible geo-

**Table 1.** Equilibrium Constants for the Interaction of **1** and **2**, in the Absence or in the Presence of  $\text{AgNO}_3$ , with Anions, in an MeCN Solution, at  $25^\circ\text{C}^a$

anion	$\log K_1$ for <b>1</b>	<b>1</b> + $\text{AgNO}_3$		<b>2</b>		$\log K_1$ for <b>2</b> + $\text{AgNO}_3$
		$\log K_1$	$\log K_2$	$\log K_1$	$\log K_2$	
$\text{CH}_3\text{COO}^-$	4.49(1)	>6		5.44(1)	3.24(2)	*
$\text{H}_2\text{PO}_4^-$	3.72(1)	4.71(1)		4.27(1)	1.53(3)	*
$\text{HSO}_4^-$	3.18(1)	3.58(1)		3.30(2)		3.88(1)
$\text{NO}_2^-$	2.21(1)	5.12(1)		2.50(2)		5.20(1)
$\text{F}^-$	4.05(1)	>6	>6	nd	>6	*
$\text{Cl}^-$	2.88(1)	*		2.82(1)		5.35(1)
$\text{Br}^-$	2.29(1)	*		2.26(1)		5.01(1)

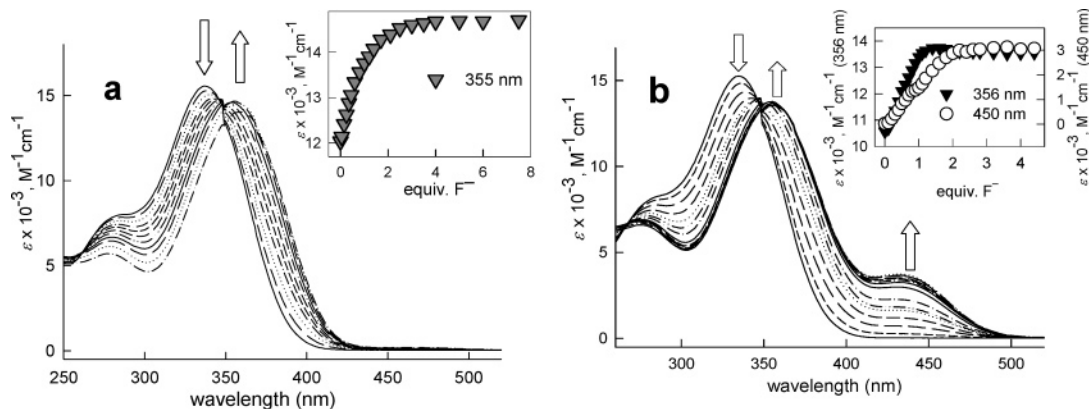
<sup>a</sup>  $\log K_1$  refers to the formation of a genuine H-bond complex  $\text{LH} + \text{X}^- \rightleftharpoons [\text{LH}\cdots\text{X}]^-$ ;  $\log K_2$  refers to the deprotonation equilibrium  $[\text{LH}\cdots\text{X}]^- + \text{X}^- \rightleftharpoons \text{L}^- + \text{HX}_2^-$  ( $\text{LH} = \mathbf{1}, \mathbf{2}$ ;  $\text{X}^- = \text{anion}$ ). The symbol \* indicates that a precipitate forms during the titration.

**Scheme 2.** Hypothesized Geometrical Arrangements of  $[\text{Ag}^+(\mathbf{1})\cdots\text{CH}_3\text{COO}]$  (**6**) and  $[\text{Ag}^+(\mathbf{1})\cdots\text{NO}_2]$  (**7**) H-Bond Complexes



metrical arrangement accounting for the simultaneous binding of  $\text{NO}_2^-$  to both  $\text{Ag}^+$  ion and the urea subunit is tentatively illustrated in the structural formula **7** in Scheme 2. In particular, it is suggested that the nitrite oxygen atom closer to the urea subunit gives a bifurcate interaction with the two N–H fragments. In any case, the establishment of a hydrogen-bonding interaction between one nitrite oxygen atom and one N–H fragment must be hypothesized, to account for the red-shift of the band at 332 nm.

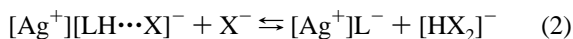
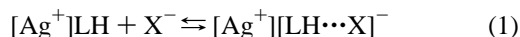
**2. Anion Interactions with **1** and  $[\text{Ag}^+(\mathbf{1})]^+$ : Halides.** The most remarkable effect exerted by the silver(I) center on the binding features of receptor **1** has been observed with



**Figure 5.** Spectra taken during the titration: (a) an MeCN solution  $1.0 \times 10^{-4}$  M in **1** with a standard solution of  $[\text{Bu}_4\text{N}]\text{F}$ ; (b) an MeCN solution  $1.0 \times 10^{-4}$  M in **1** and in  $\text{AgNO}_3$  with a standard solution of  $[\text{Bu}_4\text{N}]\text{F}$ . Inset: titration profiles at selected wavelengths.

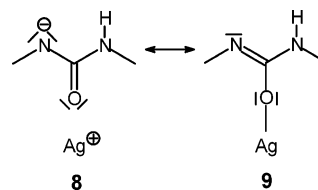
$\text{F}^-$ . Figure 5a shows the spectra taken during the titration of an MeCN solution of **1** ( $10^{-4}$  M) with  $[\text{Bu}_4\text{N}]\text{F}$ . The typical red-shift of the charge-transfer band was observed, and the titration profile (see the diagram in the inset) indicated the formation of a stable H-bond, with an association constant  $\log K = 4.01 \pm 0.01$ . Notice that  $\text{F}^-$  forms with **1** a less stable H-bond complex than  $\text{CH}_3\text{COO}^-$ , despite the higher electronegativity of fluorine with respect to oxygen. This behavior is generally observed for urea-based receptors and reflects the fact that  $\text{F}^-$  establishes a single, even if especially strong, H-bond interaction with one N–H fragment, whereas the Y-shaped  $\text{CH}_3\text{COO}^-$  ion forms two complementary H-bonds with the two N–H groups of the urea subunit.

However, on titration of the solution containing also  $\text{AgNO}_3$ , something more was observed (see Figure 5b). The typical red-shift of the band at 332 nm and the steep titration profile (filled triangles in the inset) clearly indicate the formation of a very stable H-bond complex of 1:1 stoichiometry, with  $\log K > 6$ . However, a new band formed at 440 nm, which reached a *plateau* after the addition of 2 equiv of fluoride (white circles in the inset). We have recently demonstrated that development of a further absorption band at a longer wavelength reveals the occurrence of the anion-induced deprotonation of one of the N–H fragments of the urea subunit, a feature which has been corroborated by  $^1\text{H}$  NMR titration experiments and direct crystallographic evidence.<sup>35</sup> Thus, the following two stepwise equilibria take place over the course of the titration with fluoride:



Here  $\text{LH} = \mathbf{1}$  and  $\text{X} = \text{F}$ . In particular, a second  $\text{F}^-$  ion removes an HF molecule from  $[\text{Ag}^+][\text{LH}\cdots\text{F}]^-$  to give the H-bond self-complex  $[\text{HF}_2]^-$ . Occurrence of reaction 2 has to be mainly ascribed to the extremely high stability of  $[\text{HF}_2]^-$ .<sup>39</sup> Notice also that, following N–H deprotonation, electron density is transferred, through a  $\pi$  conjugative mechanism, from the nitrogen atom to the oxygen atom, which changes to an  $\text{sp}^3$  hybridization and can establish an

especially strong interaction with the metal, as roughly represented by the resonance formulas **8** and **9**.



Chloride and bromide formed moderately stable H-bond 1:1 complexes with **1**, with  $\log K_1 = 2.88$  and  $2.29$ , respectively. Very disappointingly, in the presence of  $\text{AgNO}_3$ , precipitation of silver halides occurred at the early stages of the titration.

Thus, it appears that **1** is an excellent receptor for ion pairs involving  $\text{Ag}^+$  and oxoanions. A substantial cooperative effect is observed, which derives from the transfer of negative charge from the H-bond anion to the metal center through the coordination of the urea oxygen atom. In the case of fluoride, such a coordinative interaction is strong enough to promote the deprotonation of one of urea N–H fragments.

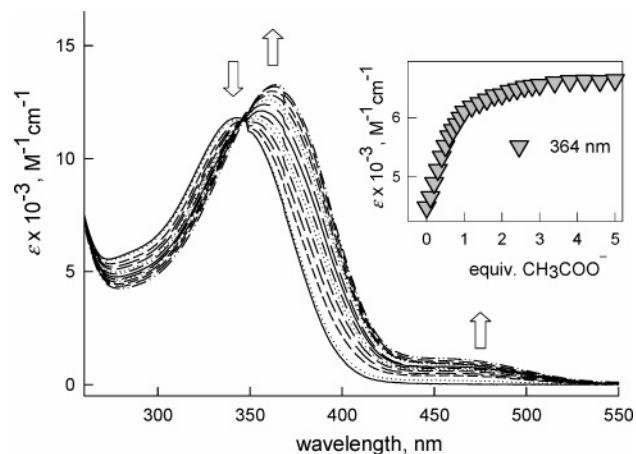
**3. Anion Interactions with **2** and  $[\text{Ag}^+(\mathbf{2})]^+$ : Oxoanions.** Thiourea is a much stronger protonic acid than urea ( $\text{p}K_{\text{A}} = 21.1$  and  $26.9$ , respectively, in DMSO),<sup>40</sup> a feature which is expected to increase both the H-bond donor properties and the tendency to N–H deprotonation.<sup>41</sup> Indeed, such a feature is observed in the interaction of the thiourea based receptor **2** with acetate.

Figure 6 shows the family of spectra recorded during the titration of an MeCN solution of **2** ( $10^{-4}$  M) with  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$ . Acetate addition causes the characteristic red-shift of the charge-transfer band, which indicates the formation of a 1:1 H-bond complex, with  $\log K_1 = 5.44 \pm 0.01$ , a value distinctly larger than that observed with the urea-based receptor **1**. However, on further addition of acetate, a new band begins to develop at 460 nm. The long wavelength of the band is indicative of the deprotonation of the N–H group of thiourea as described by eq 2. In particular, the second

(40) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

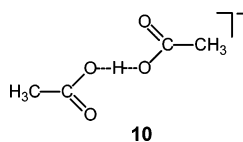
(41) Esteban-Gómez, D.; Fabbri, L.; Licchelli, M.; Monzani, E. *Org. Biomol. Chem.* **2005**, *3*, 1495.

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**Figure 6.** Spectra taken during the titration of a MeCN solution  $1.0 \times 10^{-4}$  M in **2** with a standard solution of  $[\text{Bu}_4\text{N}]\text{CH}_3\text{COO}$ .

acetate ion removes a  $\text{CH}_3\text{COOH}$  molecule from the  $[\text{LH}\cdots\text{CH}_3\text{COO}]^-$  complex, to give rise to the H-bond self-complex  $[\text{CH}_3\text{COO}-\text{H}\cdots\text{OOCCH}_3]^-$ , sketched in formula **10**. However, due to the relatively low value of  $K_2$ , a detectable amounts of  $\text{L}^-$  is observed only on addition of excess acetate.

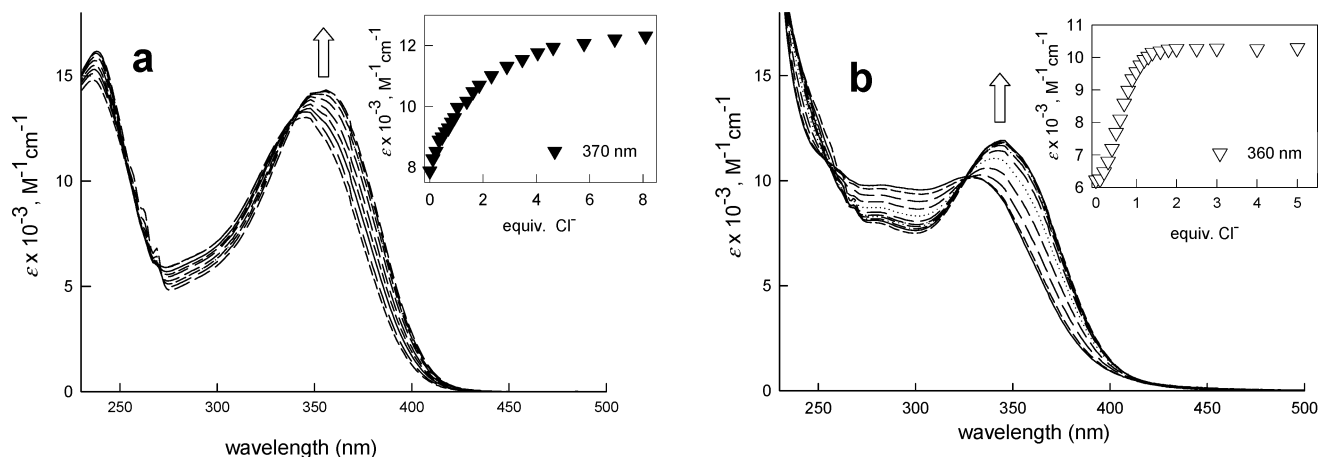


On titration with acetate of a solution containing equimolar amounts of both **2** and  $\text{AgNO}_3$ , formation of a precipitate occurred in the early stages of the experiment. It is possible that metal coordination promotes deprotonation of  $\text{N}-\text{H}$  even on addition of subequivalent amounts of acetate, with formation of the insoluble  $[\text{Ag}^+(\text{L}^-)]$  neutral complex. A similar behavior was observed with  $\text{H}_2\text{PO}_4^-$ : in the absence of metal, formation of the H-bond complex was followed by the deprotonation of the receptor (with  $K_1$  and  $K_2$  values lower than those observed for  $\text{CH}_3\text{COO}^-$ ; see Table 1). In presence of  $\text{AgNO}_3$ , a precipitate formed.

**4. Anion Interactions with **2** and  $[\text{Ag}^+(\text{2})]^+$ : Halides.** On titration of **2** with fluoride, no red-shift of the receptor's

charge transfer band was observed, but the band at 460 nm, pertinent to the deprotonated receptor, began to develop in the early stages of the titration. This indicates that  $K_2 \gg K_1$  and that the concentration of the  $\text{L}^-$  form predominates over that of the  $[\text{LH}\cdots\text{F}]^-$  H-bond complex, even during the addition of the first 1 equiv of fluoride. The effect of the  $\text{Ag}^+$  ion could not be investigated because, on fluoride addition to the MeCN solution containing both **2** and  $\text{AgNO}_3$ , a precipitate immediately formed, probably the already mentioned neutral silver(I) complex of  $\text{L}^-$ .

On addition of chloride or bromide to a solution of **2**, a red-shift of the charge transfer transition was observed (Figure 7a reports the family of spectra taken on titration with chloride), which indicates the formation of genuine H-bond complexes, with association constants  $2.82 \pm 0.01$  and  $2.26 \pm 0.01$ , respectively (see Table 1). These values are almost coincident with those determined for the urea derivative **1**. This behavior may be surprising in view of the higher protonic acidity of the thiourea subunit with respect to urea,<sup>39</sup> from which an enhanced tendency to donate H-bonds should derive. Indeed, **2** forms with oxoanions distinctly more stable H-bond complexes than **1** (compare pertinent  $\log K_1$  values in Table 1). This behavior may be ascribed to the fact that oxoanions establish two directional H-bond interactions with the two  $\text{N}-\text{H}$  fragments of the urea/thiourea receptor. Hydrogen bonding has been defined as an incipient and frozen proton transfer between the donor and the anion.<sup>42</sup> Thus, the receptor's affinity toward the anion reflects the state of advancement of the proton transfer along the  $\text{N}\cdots\text{H}\cdots\text{O}$  direction and more basic anions (e.g. acetate) should form more stable H-bond complexes than less basic anions (e.g. nitrate). On the other hand, the spherical chloride and bromide ions ( $\text{X}^-$ ) cannot establish collinear  $\text{N}\cdots\text{H}\cdots\text{X}$  hydrogen bonding interactions, do not promote any partial proton transfer, and therefore cannot feel the different acidity of the receptor, whether urea or thiourea: they simply establish electrostatic interactions with both  $\text{N}-\text{H}$  fragments (which are conventionally defined H-bonds but are qualitatively different from the collinear H-bonds established with oxoanions).



**Figure 7.** Spectra taken during the titration: (a) a MeCN solution  $8.6 \times 10^{-4}$  M in **2** with a standard solution of  $[\text{BzBu}_3\text{N}]\text{Cl}$ ; (b) a MeCN solution  $1.0 \times 10^{-4}$  M in **2** and in  $\text{AgNO}_3$  with a standard solution of  $[\text{BzBu}_3\text{N}]\text{Cl}$ . Inset: titration profiles at selected wavelengths.



Very interestingly, on titration with chloride or bromide of a solution containing both **2** and AgNO<sub>3</sub>, no silver halide precipitation occurred, but a distinct red-shift of the charge-transfer band was observed, due to the formation of stable [Ag<sup>I</sup>(**2**)⋯X] hydrogen-bonding complexes. Figure 7b shows the spectra taken during the titration with chloride of a solution containing both **2** and AgNO<sub>3</sub>. Notice that the titration profile is much steeper than that observed for the titration in absence of AgNO<sub>3</sub>, a feature that emphasizes the drastic enhancement of anion affinity exerted by Ag<sup>I</sup> (2.5 log units for Cl<sup>-</sup>, 2.7 for Br<sup>-</sup>).

Useful insights on the coordinating mode of Cl<sup>-</sup> to the metal-containing receptor can be obtained from <sup>1</sup>H NMR titration experiments (see Figure 2, spectra d–f). The progressive addition of chloride to the [Ag<sup>I</sup>(**2**)<sup>+</sup>] complex induces upfield shift of the N–H protons, inverting the effect observed on silver(I) addition to **2** (spectra a–c). This indicates that the interaction of the chloride ion with the thiourea subunit counterbalances the polarization induced by metal coordination to C=S: this makes deshielding decrease and induces upfield shift of the N–H signals.

It has to be noted that, also in the case of **2**, log *K*<sub>1</sub> values reported in Table 1 refer to equilibria in which an H-bound nitrate ion is displaced by the investigated anion. In particular, on titration with [Bu<sub>4</sub>N]NO<sub>3</sub> of a solution containing equimolar amounts of **2** and Ag(CF<sub>3</sub>SO<sub>3</sub>), a log *K*<sub>1</sub> = 3.28 ± 0.01 was determined. Thus, absolute log *K* values for the interaction of the [Ag(**2**)<sup>+</sup>] complex with anions should be calculated by adding 3.3 to the values reported in Table 1 and, in particular, the MIE factor should be corrected accordingly. Actually, corrected MIE

values are 7 × 10<sup>3</sup> for HSO<sub>4</sub><sup>-</sup>, 6 × 10<sup>5</sup> for Cl<sup>-</sup>, and 1 × 10<sup>6</sup> for Br<sup>-</sup>.

## Conclusion

This work has disclosed a novel way in which metal ions can enhance the affinity of neutral receptors for anions. In particular, it has been shown that the coordinative interaction of a metal ion, e.g. Ag<sup>I</sup>, with the C=X fragment (X = O, S) can drastically increase the H-bond donor tendencies of a urea/thiourea subunit. As a strict geometrical requirement, the urea/thiourea subunit must be a part of a pendant arm covalently linked to the macrocycle hosting the metal center. The pendant arm coordinates the metal ion according to a *scorpionate* mode,<sup>43</sup> and its interaction with the metal is either promoted (urea) or reinforced (thiourea), following anion binding to the N–H fragments. The Ag<sup>I</sup>-induced enhancement effect on anion affinity varies over the range 10<sup>3</sup>–10<sup>6</sup> and is much higher than that observed in the previously investigated systems containing alkali metal ions. In the presence of more basic anions, and in particular with the more acidic thiourea subunit, the C=X–Ag<sup>I</sup> interaction induces the deprotonation of one of the N–H fragments.

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