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Colorimetric macrocyclic anion probes bearing nitrophenylurea and nitrophenylthiourea binding groups



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1. Introduction

The study of new ligands, hosts, or receptors for cations and anions has been an area of considerable interest in the field of supramolecular chemistry.¹ Historically, cation complexation has received greater attention, but during recent years, the study of receptors for anions, such as halides and acid anions has become an area of vigorous research effort.²

The slower development of anion sensors, compared to cation sensors, is due in part to the fact that detecting small inorganic anions is often more difficult than detecting cations.³ Furthermore, while cations are often monatomic and spherical, polyatomic inorganic anions exhibit a range of geometries with charges that are delocalized over a number of atoms. The variety of anions makes each receptor less general and requires it to incorporate individual design elements.⁴

ABSTRACT

Two novel molecular probes bearing two urea (sensor 1) or thiourea (sensor 2) groups (as anion recognition site) coupled with a nitrophenyl group (chromogenic unit) were synthesized and evaluated according to the binding site-signaling subunit approach.

The behavior of these different compounds toward metal ions (Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , and Cd^{2+}) and anions (F^- , Cl^- , Br^- , I^- , ClO_4^- , NO_3^- , CN^- , OH^- , CH_3COO^- , and $H_2PO_4^-$) was investigated by UV–vis spectroscopy in DMSO.

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In recent years, considerable attention has been paid to the development of colorimetric and fluorescent chemosensors for sensing anionic species.^{5–7} Commonly, such sensors offer many advantages, such as high sensitivity and simplicity, especially for real-time and on-line analysis of analytes.⁸

The design and synthesis of colorimetric neutral chemosensors for anions^{9,10} usually involves the covalent linking of a chromogenic fragment to a neutral receptor capable of establishing selective interactions with the envisaged anion.^{11,12} Although various supramolecular interactions have proven to be significant, the most frequent binding motif is arguably hydrogen bonding.^{13,14}

It is well-known that urea/thiourea with a nitrophenyl group as a signaling unit showed an enhancement in both the hydrogenbond donor tendency and acidity.¹⁵

Selectivity of receptors containing one or more urea and thiourea subunits is related to the energy of the receptor—anion interaction; in this sense, strong H-bond interactions are established with anions containing the most electronegative atoms as fluoride¹⁶ or inorganic oxoanions.^{17,18} Solvent cannot be water or any other hydrogen bond-forming medium (e.g., alcohols) since they



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would compete successfully with the receptor for the anion. Thus, aprotic solvents of varying polarity are currently employed in anion recognition studies based on H-bonds (e.g., CHCl₃, MeCN, and DMSO) in order to preclude the competition of the solvent as a hydrogen-bond donor.¹⁹

In recent years, polyazamacrocycle-based receptors have been well-studied for anions,²⁰ and some of them have been proven as effective systems showing high selectivity and affinity for simple inorganic²¹ to biological anions.²² Compared to acyclic anion sensors, reports on cyclic anion sensors are quite limited, which often require complicated synthetic pathways.²³

With this idea in mind and continuing our efforts in producing new macrocyclic receptors²⁴ we set out to synthesize two novel colorimetric anion sensors that comprise two urea (sensor **1**) and thiourea (sensor **2**) groups (anion binding site) coupled with a nitrophenyl group (chromogenic unit) (Fig. 1). The behavior of these different compounds toward anions (F⁻, Cl⁻, Br⁻, I⁻, ClO₄⁻, NO₃⁻, CN⁻, OH⁻, CH₃COO⁻, and H₂PO₄⁻) and also toward metal ions (Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, and Cd²⁺) was investigated by UV–vis spectroscopy in DMSO.

(Scheme 1) with ethyl bromoacetate and subsequent reaction of the intermediate ester with hydrazine hydrate.²⁵ The infrared spectrum (KBr disc) of L^B shows bands at 769 and 3316 cm⁻¹ assigned to the out-of-plane bending and stretching vibrations of the hydrazone groups, respectively, together with a band at 1675 cm⁻¹ associated with the ν (C=O) vibration of the carbonyl groups. The ESI mass spectrum presents an intense peak at 528 amu corresponding to the molecular ion $[L^B+H]^+$. The ¹H NMR spectrum shows signals corresponding to the NH groups (8.9, 8.5 ppm). In the ¹³C NMR spectrum the signal at 170.3 ppm corresponds to a carbonyl group.

2.2. Synthesis and characterization of the colorimetric probes 1 and 2

Therefore, we propose the synthesis of two new potential anion receptors **1** and **2** containing nitrophenylurea and nitrophenylthiourea moieties, respectively, outlined in Scheme 1.

In the first step, a solution of 4-nitrophenylisocyanate or 4nitrophenylisothiocyanate in dry dichloromethane was added





Fig. 1. Schematic representation of chemosensors 1 and 2.

2. Results and discussion

2.1. Synthesis and characterization of L^B

Ligand L^B was isolated as an air-stable yellow oil in 72% yield by using a two-step procedure involving the alkylation of L^A dropwise to a refluxing solution of the precursor L^B in the same solvent. ^{24a,26} The resulting solutions were gently refluxed with magnetic stirring for ca. 24 h and then evaporated to dryness. The residues were extracted with water–chloroform. The organic layers were dried over anhydrous Na₂SO₄, and the final solutions were evaporated to dryness yielding solids, characterized as the



Scheme 1. Synthesis of chemosensors 1 and 2.

pure chemosensors **1** and **2**, in good yields (65 and 70%, respectively).

In the infrared spectra (KBr disc) of **1** and **2** the stretching vibrations of the pendant groups appear in their expected position. The ESI mass spectra of **1** and **2** present intense peaks at m/z 856 (100%) and m/z 887 (100%) corresponding to the molecular ions $[1+H]^+$ and $[2+H]^+$, further confirming the presence of **1** and **2** receptors. The ¹H and ¹³C NMR data have been recorded using DMSO- d_6 as a solvent, and they confirm the integrity of the ligands and its stability in solution.

2.3. UV-vis spectral responses of sensors 1 and 2

Probes **1** and **2** show very low solubility in water; and in water–DMSO solutions (50:50, v/v) those ligands precipitated. For

systems **1** and **2** and we explored their interaction with cations $(Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Cd^{2+})$ and anions $(OH^-, CN^-, H_2PO_4^-, CH_3COO^-, NO_3^-, CIO_4^-, F^-, CI^-, Br^-, I^-)$ by spectrophotometric and spectrofluorimetric titrations. To do so, a standard solution of the corresponding salts in DMSO was added to a solution of compounds **1** and **2** at room temperature in the same solvent.

Upon adding anions, such as OH^- or F^- to a solution of **1** and **2** in DMSO (Fig. 2), the absorption maxima at ca. 345 and 375 nm decreased gradually, and new absorption maxima at ca. 463 and 496 nm increased, respectively. These results suggested a perturbation in the ICT character of the sensor, due to the recognition of the anions at the amidourea and amidothiourea moieties. This enhances the push–pull character of the ICT state, and consequently a red-shift is observed, upon deprotonation of the receptor by the anion.²⁸



Fig. 2. Changes in UV–vis spectra for compound **1** with addition of $[(Bu)_4N]OH$ (a), compound **2** with addition of $[(Bu)_4N]OH$ (b), compound **1** with addition of $[(Bu)_4N]F$ (c), and compound **2** with addition of $[(Bu)_4N]F$ in DMSO. Absorptions read at 345 and 463 nm (compound **1**); and 376 and 496 nm (compound **2**), $[\mathbf{1}]=[\mathbf{2}]=1.00 \times 10^{-5}$ M.

the aforementioned reasons all the spectroscopic studies have been done in a non-protic solvent, DMSO.

In the absence of anions, the UV–vis absorption spectra of **1** and **2** showed an absorption maximum peak at ca. 345 and 371 nm, respectively, which could be attributed to π – π * transition in the ligand.²⁷ Both systems show very low fluorescence emission, showing bands centered at ca. 437 (probe **1**) and 462 nm (probe **2**) (data not shown).

Probes **1** and **2** were developed to give a highly ordered hydrogen donating cavity, which could give rise to colorimetric changes upon anion recognition.

With the aim to compare the influence of the oxygen and the sulfur atoms in the colorimetric properties, we synthesized these The presence of the other anions with weaker basicity (CN⁻, $H_2PO_4^-$, CH₃COO⁻) also resulted in negligible changes in UV–vis spectra of probes **1** and **2** (data not shown). No change occurred upon interaction with NO₃⁻, ClO₄⁻, Cl⁻, Br⁻, and I⁻ anions. This result suggests the absence of interaction between these anions and receptors **1** and **2**.

Both nitrophenylurea and nitrophenylthiourea-based receptors **1** and **2**, respectively, allow naked-eye detection of F^- , OH^- , CN^- , CH_3COO^- , and $H_2PO_4^-$ anions, showing more intense colors in the case of compound **2** (see Fig. 3).

Is very important to remark that probe **1** showed better chemosensor properties than **2**, because it gave different response and color changes in the presence of F^- , OH^- , CN^- , CH_3COO^- , and 1+CI

1+F

1+1

1+Br



Fig. 3. Colorimetric effect in systems 1 and 2 after interaction with 1 equiv of different ions in DMSO solution.

 $\rm H_2PO_4^-$ anions, as a result, 1 could discriminate between these different anions.

Moreover, in order to explore the sensorial ability of receptors 1 and 2 in DMSO solution, the effect of metal cations, such as Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , and Cd^{2+} on the absorption, was studied.

As an example, Fig. 4A and B depicts the absorption spectra of a solution of probes **1** and **2** in the presence of increasing amounts

of Ni(BF₄)₂ dissolved in DMSO. Upon addition of 1 equiv of this metal ion to a DMSO solution of probe **1**, the absorption maxima at ca. 345 decreased gradually, and new absorption band at ca. 463 increased. In the case of chemosensor **2**, the band centered at ca. 376 nm decreased with the addition of 1 equiv of this metal ion (see Fig. 4B). Similar results were obtained after the titration of molecular probes **1** and **2** with the other metal ions explored. In respect to



Fig. 4. Changes in UV-vis spectra for compound 1 (A) and 2 (B) (1.00×10⁻⁵ M) in DMSO with addition of NiBF₄. Absorptions read at 345 and 463 nm (compound 1); and 376 nm (compound 2).

the colorimetric detection, although addition of nickel(II) develop a new band at ca. 463 nm (yellow color), the naked-eye detection was not observed due to the previous colored **1** solution. However, addition of copper(II) produces a change from yellow to green.

The stability constants for the interaction of receptors **1** and **2** in the presence of the different ions were calculated using the spectrophotometric data and the HypSpec software.²⁹ For all cases very good mathematical fits were obtained.

The stability constants for the interaction of receptors **1** and **2** in the presence of the F⁻, OH⁻, CN⁻, CH₃COO⁻, and H₂PO₄⁻ anions and Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, and Cd²⁺ metal ions are summarized in Table 1.

Table 1

Stability constants for chemosensors 1 and 2 in the presence of some anions and the metal ions Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , and Cd^{2+} in DMSO for an interaction 1:1 (X:L), (X: metal ion or cation; L=receptor 1 or 2)

Compound	Interaction (A ⁻ :L)	$\Sigma \log \beta$ (abs) (emission)	
1	OH ⁻ (1:1)	$4.30 \pm 4.77 \times 10^{-3}$	
	F ⁻ (1:1)	$4.23 \pm 2.22 \times 10^{-3}$	
	CN ⁻ (1:1)	$4.46{\pm}2.04{\times}10^{-3}$	
	$H_2PO_4^{-}(1:1)$	$3.29 \pm 1.99 \times 10^{-3}$	
	CH ₃ COO ⁻ (1:1)	$4.72 \pm 1.95 \times 10^{-3}$	
2	OH ⁻ (1:1)	$10.45 \pm 3.31 \times 10^{-3}$	
	F ⁻ (1:1)	$9.96 \pm 3.79 \times 10^{-3}$	
	CN ⁻ (1:1)	$10.69 {\pm} 4.37 {\times} 10^{-3}$	
	$H_2PO_4^-(1:1)$	$8.89 {\pm} 5.41 {\times} 10^{-3}$	
	CH ₃ COO ⁻ (1:1)	$10.76 {\pm} 3.49 {\times} 10^{-3}$	
Compound	Interaction (M:L)	$\Sigma \log \beta$ (abs) (emission)	
Compound 1	Interaction (M : L) Co ²⁺ (1:1)	$\frac{\Sigma \log \beta \text{ (abs) (emission)}}{6.80 \pm 1.50 \times 10^{-3}}$	
Compound 1	Interaction (M:L) Co ²⁺ (1:1) Ni ²⁺ (1:1)	$\Sigma \log \beta$ (abs) (emission) 6.80±1.50×10 ⁻³ 5.76±1.51×10 ⁻³	
Compound 1	Interaction (M:L) Co^{2+} (1:1) Ni^{2+} (1:1) Cu^{2+} (1:1)	$\frac{\Sigma \log \beta \text{ (abs) (emission)}}{6.80 \pm 1.50 \times 10^{-3}}$ 5.76±1.51×10 ⁻³ 5.86±1.75×10 ⁻³	
Compound 1	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c } \hline Σ log β (abs) (emission) \\ \hline $6.80 \pm 1.50 \times 10^{-3}$ \\ $5.76 \pm 1.51 \times 10^{-3}$ \\ $5.86 \pm 1.75 \times 10^{-3}$ \\ $6.41 \pm 1.39 \times 10^{-3}$ \end{tabular}$	
Compound 1	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c }\hline Σ log β (abs) (emission) \\\hline $6.80 \pm 1.50 \times 10^{-3}$ \\\hline $5.76 \pm 1.51 \times 10^{-3}$ \\\hline $5.86 \pm 1.75 \times 10^{-3}$ \\\hline $6.41 \pm 1.39 \times 10^{-3}$ \\\hline $4.54 \pm 1.21 \times 10^{-3}$ \end{tabular}$	
Compound 1 2	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\label{eq:stars} \begin{array}{ c c c c c } \hline \Sigma \ \log \beta \ (abs) \ (emission) \\ \hline 6.80 \pm 1.50 \times 10^{-3} \\ \hline 5.76 \pm 1.51 \times 10^{-3} \\ \hline 5.86 \pm 1.75 \times 10^{-3} \\ \hline 6.41 \pm 1.39 \times 10^{-3} \\ \hline 4.54 \pm 1.21 \times 10^{-3} \\ \hline 5.93 \pm 2.30 \times 10^{-3} \end{array}$	
Compound 1 2	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\label{eq:stars} \begin{split} \underline{\Sigma} & \log \beta \ (\text{abs}) \ (\text{emission}) \\ \hline 6.80 \pm 1.50 \times 10^{-3} \\ 5.76 \pm 1.51 \times 10^{-3} \\ 5.86 \pm 1.75 \times 10^{-3} \\ 6.41 \pm 1.39 \times 10^{-3} \\ 4.54 \pm 1.21 \times 10^{-3} \\ 5.93 \pm 2.30 \times 10^{-3} \\ 5.20 \pm 1.45 \times 10^{-3} \end{split}$	
Compound 1 2	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\label{eq:stars} \begin{split} & \Sigma \log \beta \ (\text{abs}) \ (\text{emission}) \\ & 6.80 {\pm} 1.50 {\times} 10^{-3} \\ & 5.76 {\pm} 1.51 {\times} 10^{-3} \\ & 5.86 {\pm} 1.75 {\times} 10^{-3} \\ & 6.41 {\pm} 1.39 {\times} 10^{-3} \\ & 4.54 {\pm} 1.21 {\times} 10^{-3} \\ & 5.93 {\pm} 2.30 {\times} 10^{-3} \\ & 5.20 {\pm} 1.45 {\times} 10^{-3} \\ & 5.20 {\pm} 2.74 {\times} 10^{-3} \end{split}$	
Compound 1 2	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\label{eq:starting} \begin{split} & \Sigma \log \beta \ (\text{abs}) \ (\text{emission}) \\ & 6.80 \pm 1.50 \times 10^{-3} \\ & 5.76 \pm 1.51 \times 10^{-3} \\ & 5.86 \pm 1.75 \times 10^{-3} \\ & 6.41 \pm 1.39 \times 10^{-3} \\ & 4.54 \pm 1.21 \times 10^{-3} \\ & 5.93 \pm 2.30 \times 10^{-3} \\ & 5.20 \pm 1.45 \times 10^{-3} \\ & 5.20 \pm 2.74 \times 10^{-3} \\ & 5.30 \pm 2.30 \times 10^{-3} \end{split}$	

Although the naked-eye anion detection is better developed in compound **1**, taking into account the values reported in Table 1, the strongest interaction with anions was observed for chemosensor 2. This fact, it is probably due to the presence of sulfur atoms in the thiourea groups. In previously similar reported systems,^{16a} sulfur atoms form weaker intramolecular hydrogen bonds than oxygen, and hence the intermolecular interactions (host-guest) were more favorable allowing the alignment of the thiourea functionality for the interaction with fluoride ions, being much easier that it was compared with the urea receptor. It would be expected that probe 2 acts as better anion receptors at room temperature in comparison with probe 1. These results are in agreement with the more intense color changes observed in sensor **2** in the presence of the different anions. The sequence of the strongest interaction observed for probes 1 and 2 with the anions studied in decreasing order is:

$$CH_3COO^- > CN^- > OH^- > F^- > H_2PO_4^-$$

For the interaction of probes **1** and **2** with the metal ions, the sequence obtained was $Co^{2+} \approx Zn^{2+} > Cu^{2+} \approx Ni^{2+} > Cd^{2+}$. In that case, the results were similar for both probes. It could probably be explained as the cavity size of both macrocyclic ligands and the structure flexibility is the same in both guests, making the interaction of **1** and **2** with the metal ions very similar.

The limit of detection (LOD) and the limit of quantification (LOQ) for metal ions were performed having in mind their use for real anion detection and for analytical applications. For these measurements, ten different analyses for the selected receptor were

performed in order to obtain the LOQ. The LOD was obtained by the formula:

ydl = yblank + 3 std

where, ydl=signal detection limit and std=standard deviation.

Therefore, the study of the limit of detection (LOD) and the limit of quantification (LOQ) for the explored anions and metal ions was performed for probes **1** and **2** bearing in mind their use for real anion and metal-ion detection for analytical applications.

For these measurements, ten different analyses for each receptor were performed to obtain the LOQ, and a calibration fit was applied to determine the LOD. Table 2 includes the LOD and the LOQ in our experimental conditions, at room temperature, in DMSO.

Table 2

Limits of detection (LOD) and quantification (LOQ) (ppm) for, F^- , OH^- , CN^- , $CH_3COO^-, H_2PO_4^-$, $Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}$, and Cd^{2+} with compounds ${\bf 1}$ and ${\bf 2}$

Compound	Anions	LOD (ppm)	LOQ (ppm)
1	F ⁻	12.23±0.01	59.63±0.01
	OH-	$5.91 {\pm} 0.01$	$19.93 {\pm} 0.01$
	CN^{-}	$6.09 {\pm} 0.01$	$21.63 {\pm} 0.01$
	CH_3COO^-	$4.38 {\pm} 0.01$	$14.02 {\pm} 0.01$
	$H_2PO_4^-$	$6.86 {\pm} 0.01$	$18.56 {\pm} 0.01$
2	F	$3.59 {\pm} 0.01$	$5.68 {\pm} 0.01$
	OH-	2.73±0.01	$6.18 {\pm} 0.01$
	CN ⁻	4.01 ± 0.01	$6.19 {\pm} 0.01$
	CH ₃ COO ⁻	3.62 ± 0.01	$4.42{\pm}0.01$
	$H_2PO_4^-$	2.06 ± 0.01	$4.87{\pm}0.01$
Compound	Metal ion	LOD (ppm)	LOQ (ppm)
1	Co ²⁺	3.09±0.01	5.34±0.01
	Ni ²⁺	5.51 ± 0.01	$8.80{\pm}0.01$
	Cu ²⁺	$2.54{\pm}0.01$	$5.96 {\pm} 0.01$
	Zn^{2+}	$3.69 {\pm} 0.01$	$6.49 {\pm} 0.01$
	Cd^{2+}	$5.48 {\pm} 0.01$	$8.37{\pm}0.01$
2	Co ²⁺	$0.96 {\pm} 0.01$	$2.16 {\pm} 0.01$
	Ni ²⁺	$1.08 {\pm} 0.01$	$4.16{\pm}0.01$
	Cu ²⁺	$0.74{\pm}0.01$	$3.32{\pm}0.01$
	Zn ²⁺	$0.88 {\pm} 0.01$	$2.98{\pm}0.01$
	Cd^{2+}	$1.24{\pm}0.01$	5.16 ± 0.01

As previously stated, in comparison with the other anions and metal ions explored, the stability constants were higher for the interaction of probes **1** and **2** with CH₃COO⁻ and Co²⁺ \approx Zn²⁺>Cu²⁺ \approx Ni²⁺.

In order to explore these systems as potential ditopic receptors, addition of increasing amounts of CuF_2 and ZnF_2 to a DMSO solution of probes **1** and **2** (1.00×10^{-5} M), at 298 K, was carried out. Changes in the absorption spectra were only observed after the addition of CuF_2 to a DMSO solution of probe **1**. A moderate decrease in the absorption band centered at 345 nm, and an increase in the band centered at 373 nm was observed, suggesting a simultaneous interaction of this receptor with the anion F⁻ and the Cu²⁺ metal ion (see Fig. 5A and B).

2.4. NMR responses of sensors 1 and 2

¹H NMR titration of receptors **1** and **2** with tetrabutylammonium fluoride was performed in order to understand the effect of this compound on the NH protons of receptors **1** and **2**.³⁰

¹H NMR spectra were registered in DMSO- d_6 --0.5% water solution. The urea NH signals in compound **1** appear at 9.85, 9.55, and 8.43 ppm (Fig. 6). Addition of 0.5 equiv of tetrabutylammonium fluoride to the solution of receptor **1** in DMSO- d_6 is enough to initialize deprotonation processes.³¹ In that case, the deprotonation of the urea subunits in the receptor does not induce effects on the aromatic substituents. Similar results were obtained in the case of sensor **2** (data not shown).



Fig. 5. Changes in UV-vis spectra for compound 1 (1.00×10⁻⁵ M) in DMSO with addition of [CuF₂]. Absorptions read at 345 and 373 nm (compound 1).



Fig. 6. ¹H NMR spectra taken in the course of the titration of a DMSO- d_6 solution of **1** (4.00×10⁻² M) with a standard solution of [Bu₄N]F. Key: no [Bu₄N]F addition (bottom); addition of 1 equiv of [Bu₄N]F (top).

3. Conclusions

In summary, two novel nitrophenylurea and nitrophenylthioureabased receptors **1** and **2** were designed and synthesized. Both systems allow the naked-eye detection of F^- , OH^- , CN^- , CH_3COO^- , and $H_2PO_4^-$ anions. Strongest interaction with anions and more intense color changes were observed for chemosensor **2**. It would be explained by the fact that sulfur atoms form weaker intramolecular hydrogen bonds, and hence, chemosensors containing this atom should act as better anion receptors at room temperature.

Host–guest ability of receptors **1** and **2** in solution towards the metal ions Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , and Cd^{2+} in DMSO was very

similar. It could probably be explained because the cavity size of both macrocyclic ligands and the structure flexibility is similar in both cases.

4. Experimental

4.1. Synthesis of chemosensors 1 and 2

Chemicals and solvents of the highest commercial grade available were used as received. Oxaazamacrocycle **L**^A was synthesized as described in the literature.³² 4.1.1. Synthesis of macrocycle L^B. L^A (0.766 g, 2 mmol) was dissolved in acetonitrile (50 mL) and Na₂CO₃ (1.27 g; 12 mmol) was added. The mixture was refluxed and ethyl bromoacetate (2.1 g; 12 mmol) dissolved in acetonitrile (10 mL) was added dropwise to the refluxing solution. The mixture was refluxed for 24 h, filtered off and evaporated to drvness. The residue was then extracted with water-chloroform. The organic laver was dried over anhydrous Na₂SO₄ and evaporated to vield a vellow oil. This was dissolved in absolute ethanol (10 mL) and hydrazine hydrate (2.6 g; 80 mmol) was added. The solution was slowly stirred for one night and concentrated to dryness under reduced pressure. The crude solid was extracted with water-chloroform. The organic phases were dried (Na₂SO₄), filtered and concentrated to dryness under reduced pressure to give the desired pure product, characterized as the ligand L^B.

Yield: 72% (0.76 g). Anal. Calcd for C₂₇H₄₁N₇O₄·4H₂O: C, 54.1; H, 8.2; N, 16.4. Found: C, 54.1; H, 8.1.; N, 16.6%. IR (KBr, cm⁻¹): 3316 $[\nu(N-H)_{st}]$, 1675 $[\nu(C=O)]$, 1526 $[\delta(N-H)_{ip}]$, 1242 $[\nu(C-N)]$, 769 $[\delta(N-H)_{oop}]$. (ESI, m/z): 528 $[L^{B}+H]^{+}$. Color: yellow. ¹H NMR (400 MHz, DMSO-d₆): 8.9-8.5 (m, 6H, NH); 7.5-6.88 (m, 8H); 4.5 (s, 4H); 3.6 (s, 4H); 3.14 (s, 4H); 2.4 (t, 4H), 2.2 (t, 4H); 1.99 (s, 3H); 1.5 (t, 4H). ¹³C NMR (100 MHz, DMSO): 24.5, 43.7, 49.7, 54.1, 59.8, 63.3, 119.2-155.0, 170.3.

4.1.2. Synthesis of colorimetric probe 1. A solution of 4nitrophenylisocyanate (0.5 g, 3 mmol) in dry CH₂Cl₂ (25 mL) was added dropwise to a refluxing solution of the oxaazamacrocvcle L^{B} (0.599 g, 1 mmol) in the same solvent (25 mL). The resulting solution was refluxed with magnetic stirring for 24 h. and then evaporated to dryness under reduced pressure. The solid residue was dissolved in CHCl3 and extracted with deionized water. The organic phase was dried with Na₂SO₄, filtered, and concentrated to dryness in a rotary evaporator and dried under vacuum, to give the desired pure product, characterized as the ligand 1.

Yield: 65% (0.56 g). Anal. Calcd for C₄₁H₄₉N₁₁O₁₀·H₂O: C, 56.3; H, 5.9; N, 17.6. Found: C, 56.5; H, 5.7; N, 17.6; IR (KBr, cm⁻¹): 3300 $[\nu(N-H)_{st}]$, 1714 $[\nu(C=0)]$, 1559 $[\nu(NO_2)_{as}]$, 1303, 1329 $[\nu(NO_2)_{sim}]$, 1111 [ν (C–N)]. (ESI, m/z): 856 [**1**+H]⁺. Color: yellow. ¹H NMR (400 MHz, DMSO-*d*₆): 9.85 (s, 2H, NH); 9.55 (s, 2H, NH); 8.4 (s, 2H, NH); 8.15 (d, 4H); 7.66 (d, 4H); 7.37-6.88 (m, 8H); 4.36 (s, 4H); 3.71 (s, 4H); 3.14 (s, 4H); 2.27-2.12 (m, 8H); 1.99 (s, 3H); 1.62-1.45 (m, 4H). ¹³C NMR (400 MHz, DMSO): 25.0, 43.4, 48.7, 51.4, 54.7, 59.0, 67.8, 115.0-158.1, 168.5, 170.5.

4.1.3. Synthesis of colorimetric probe 2. A solution of 4-nitrophenylisothiocyanate (0.54 g, 3 mmol) in dry CH₂Cl₂ (25 mL) was added dropwise to a refluxing solution of the oxaazamacrocycle L^{B} (0.599 g, 1 mmol) in the same solvent (25 mL). The resulting solution was refluxed with magnetic stirring for 24 h. and then evaporated to dryness under reduced pressure. The solid residue was dissolved in CHCl₃ and extracted with deionized water. The organic phase was dried with Na₂SO₄, filtered, and concentrated to dryness in a rotary evaporator and dried under vacuum, to give the desired pure product, characterized as the ligand **2**.

Yield: 70% (0.62 g). Anal. Calcd for C₄₁H₄₉N₁₁O₈S₂·H₂O: C, 54.4; H, 5.7; N, 17.1; S, 7.1 Found. C, 54.1; H, 5.8; N, 17.2; S, 7.4. IR (KBr, cm⁻¹): 3292 [v(N–H)_{st}], 1590 [v(C=O)], 1559 [v(NO₂)_{as}], 1303, 1329 $[\nu(NO_2)_{sim}]$, 1330 $[\nu(CS)]$, 1111 $[\nu(C-N)]$. (ESI, m/z): 887 $[2+H]^+$. Color: orange. ¹H NMR (400 MHz, DMSO-*d*₆): 10.26 (s, 2H, NH); 9.15 (s, 2H, NH); 8.26 (d, 4H); 8.07 (s, 2H, NH); 7.36 (d, 2H); 7.25-7.11 (m, 6H); 7.05-6.79 (m, 4H); 5.29 (s, 4H); 4.34 (s, 4H); 4.09 (s, 4H); 3.49–3.20 (m, 8H); 2.88–2.55 (m, 3H); 1.31–1.06 (m, 4H). ¹³C NMR (400 MHz, DMSO): 24.7, 43.4, 50.1, 51.4, 55.0, 59.6, 67.3, 114.2-156.1, 169.6, 182.0.

Author contributions

R.B., A.M., C.N., C.L., L.V., and P.P.-L. conceived and design the experiments, analyzed the data, contributed to discussion, and cowrote the manuscript. A.A. and V.G. performed the synthesis and characterization of both probes. C.N. performed the UV-vis spectroscopy measurements. A.A. and C.N. performed and discuss the NMR studies, R.B., C.N., A.M., and C.L. coordinated the project. All authors have revised the manuscript.

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Supplementary data

Proton and carbon NMR spectra of reported compounds. This material is available free of charge via the internet at http://pubs.acs.org. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.04.016.

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