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A simple thiourea based colorimetric sensor for cyanide anion

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ABSTRACT

A simple and easily synthesized colorimetric anion sensor, based on a thiourea moiety as a binding subunit on a 1,2-cyclohexane backbone and a *p*-nitrophenyl group as a signaling unit, has been synthesized in a one step procedure. The selective sensing of anions, particularly cyanide, has been investigated in DMSO by UV–vis titration, ^{1}H NMR titration techniques and through 'naked eye' observation experiments.

1. Introduction

The recognition and sensing of anions have recently been an area of great interest and this is due to the importance of anions in biological, industrial, and environmental processes.[1] Most of the anion sensors developed so far tend to incorporate a binding subunit and a signal recognition subunit, and fluorescent chromophores have gained considerable attention due to their highly sensitive nature.[2–5] Metal complexes, such as rhenium tricarbonyls, have also been used as fluorescent signaling units for anion recognition, in which fluorescence enhancement or quenching serves as an indicator of binding and molecular interaction between the guest and host molecules.[6–9]

During the last few years, a large number of receptors utilizing groups, such as amide,[6,7,10] urea,[11] pyrrole,[12,13] and thiourea,[14,15] which involve hydrogen bonding to the anion, have been reported. Some of these receptors have a chromogenic moiety,[16,17] capable of signaling binding events through intramolecular charge transfer (ICT) processes, which lead to distinct color changes that are even visible to the 'naked eye'.

While a number of colorimetric anion sensors have been developed using urea and thiourea based binding units[18,19] on different scaffolds and containing different chromogenic moieties, such as naphthalimide[20] and *p*-nitrophenyl,[19] most of these receptors bind different anions, such as fluoride, nitrate, acetate, dihydrogenphosphate, pyrophosphate, and dicarboxylates. It is still a challenge, however, to find a suitable chromogenic sensor that is selective to cyanide, which is one of the most toxic inorganic anions known.[21]

Despite the acute toxicity of cyanide and hydrogen cyanide, they are still widely used in a large number of applications, for example, to make certain synthetic fibers and resins, in herbicides, and in gold mining.[22] Thus, due to its wide range of applications and serious toxicity, the development of new molecules for cyanide determination or sensing is certainly of great interest. The development of chromogenic receptors, which respond to the presence of cyanide ions with fast and visible color changes, would offer the opportunity to screen the samples relying exclusively on the naked eye. To this end, calix[4]arene thiourea recognition, which was selective and sensitive to cyanide has been reported.[22]

Recently a number of fluorogenic cyanide sensors that utilize the strong affinity of cyanide to transition metals, particularly to Cu^{2+}, have been reported.[23] In these systems, addition of Cu^{2+} to fluorescent compounds, such as fluorescein derivatives, cause significant fluorescence quenching, which is then reversed by the addition of cyanide, resulting in an 'off-on' type sensing system. Other researchers have also employed the use of boradiazaindacene (BODIPY)-derivatives, where the ability of Cu^{2+} ions to quench the fluorescence of a BODIPY-dipicolylamine derivative resulted in a 'turn-off-on' sensor, and detection of cyanide ions was reported as low as 20.0 μM.[24] Similarly, the Cu^{2+}displacement approach has been reported in a ratiometric fluorescent and colorimetric sensor, utilizing 4,5-disubstituted-1,8-naphthalamide as the receptor, where intramolecular charge transfer (ICT) and deprotonation mechanisms were demonstrated in sensing cyanide ions in 100% aqueous solution.[25] Another recently reported system has exploited the nucleophilic nature of cyanide, where nucleophilic addition of cyanide to a 2-hydroxy-1-naphthaldehyde hydrazone derivative resulted in both fluorescent and colorimetric changes, which are selective for cyanide ions.[26]

In this article, we report a simple to synthesize, yet sensitive and selective cyanide anion colorimetric sensor based on the *trans*-1,2-dithioureacyclohexane derivative and utilizing the *p*-nitrophenyl chromophore (**1**) as a signaling subunit. Consequently, we have found that the ICT transition in this system is as a result of the anion–receptor interaction. For comparison purposes, the *trans*-

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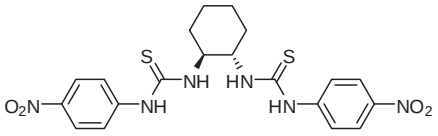
1,2-diureacyclohexane derivative (**2**) was similarly synthesized (in their racemic forms) and the anion recognition properties of this have also been studied.



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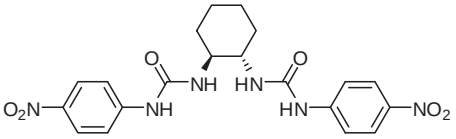

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2. Results and discussion

2.1. UV–vis spectroscopy

To determine the selectivity of these receptors to various anions, UV–vis absorption spectroscopic experiments were conducted using standard solutions of the receptors **1** and **2** in dry and degassed DMSO by adding up to 10 mol equiv of various anions as their tetrabutylammonium salts (TBA–X, where X=CN^-, F^-, AcO^-, BzO^- Cl^-, Br^- I^-, ClO_4^-, and $H_2PO_4^-$), and recording the absorbance changes. The various responses by different anions to receptor **1** are shown in Figure 1.

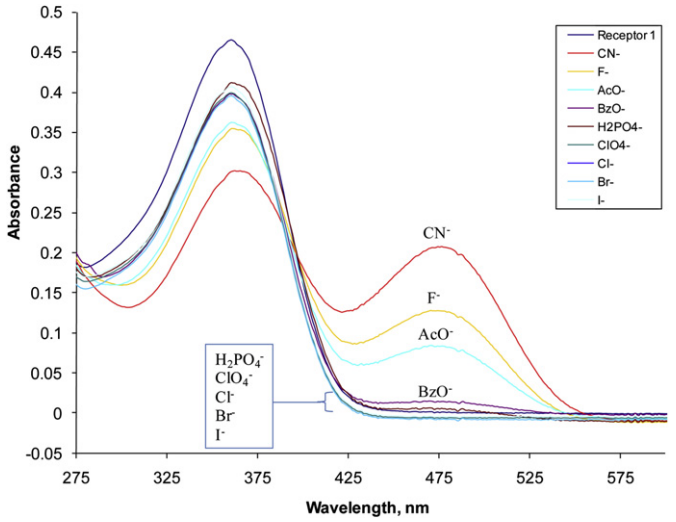


Figure 1. UV–vis absorption spectra of receptor **1** (1.0×10^{-5} M solution in DMSO) with various anions, showing the addition of 10 equiv of each tetrabutylammonium salt (TBA–X).

It was observed that compound **1**, as the free receptor molecule, showed a single absorption band at 360 nm in the near-visible to visible region. Upon addition of 10 equiv of the various anions to the receptor **1** solution in DMSO, there were significant changes observed with CN^-, F^-, AcO^-, and $BzO,^-$ with each of these anion additions causing an emergence of a new absorption band at 475 nm. For the other anions, $H_2PO_4^-$ was faintly responsive, while the remaining anions (Cl^-, Br^-, I^-, ClO_4^-) did not show any noticeable changes other than a decrease in absorbance at 360 nm, which was observed for all the anions. Receptor **1** was then found to be more sensitive and selective to the cyanide anion relative to all the other anions tested, forming a distinct color change from yellow to orange-red that could be clearly seen by the naked eye. It is worth noting at this point that similar procedures were carried out with receptor **2**, and there was no absorption band emerging at 475 nm on addition of any of the anions.

Similarly, the colorimetric properties of these receptors were explored to establish if the changes in absorbance could be observable through the 'naked eye' and the findings are illustrated in Figure 2. It was observed that receptor **1** showed selectivity toward the anions in the order of $CN^->F^->AcO^->BzO^->>H_2PO_4^-$ and was essentially not responsive to Cl^-, Br^-, I^-, and ClO_4^- anions. These color changes were observed by 'naked eye' experiments in which the solution changed from pale yellow to orange-red and then, in the case of cyanide, to wine red. It was noted that it required about 2.5 equiv of fluoride to produce the same color as the 1.0 equi of cyanide. Similar experiments were carried out for receptor **2**, and there were no observable color changes for any of the anions tested in solutions of this compound.

On addition of increasing amounts of tetrabutylammonium salts of cyanide, acetate, fluoride, and benzoate to the solution of receptor **1**, the absorption band at 360 nm decreased while a new peak emerged at 475 nm, with formation of a clear isosbestic point at 386 nm. These results are shown for the most selective anion, cyanide (see Fig. 3a). The observation of an isosbestic point in the UV–vis spectra indicates the formation of a stable complex or new species with unique spectroscopic properties as a result of interaction between the host and the guest. These data are also plotted in Figure 3b and it can be observed that after adding

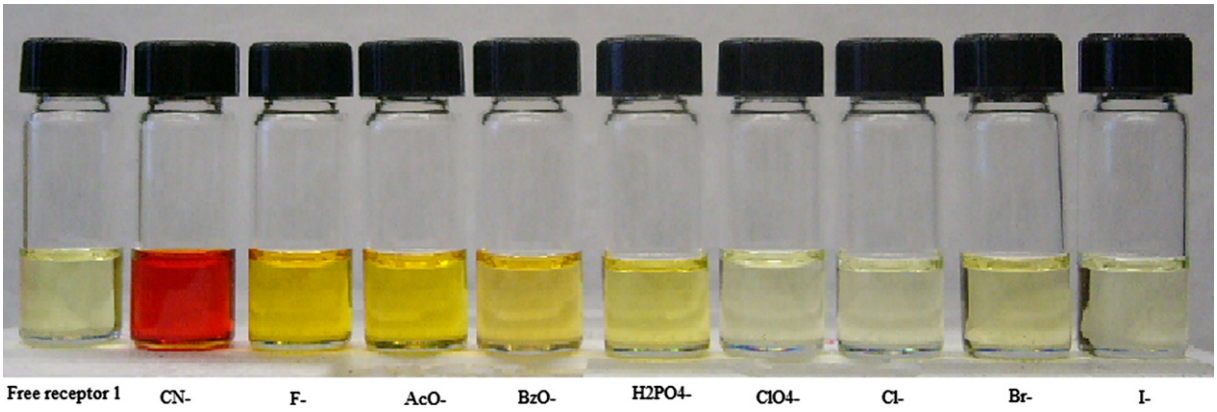
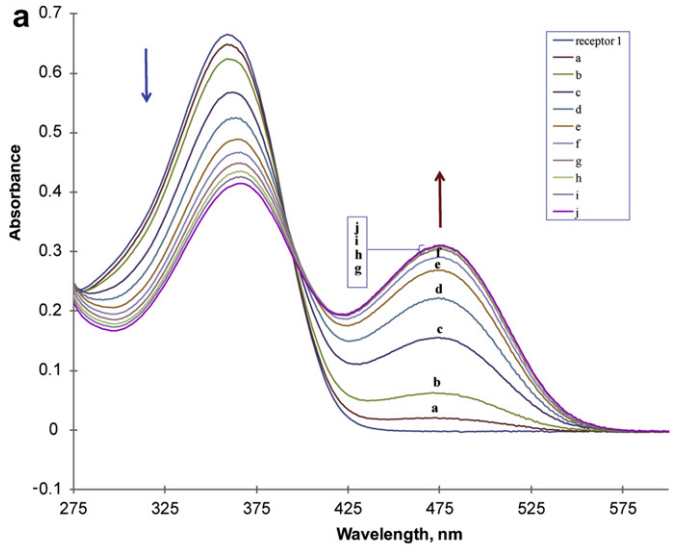


Figure 2. Color changes observed for receptor **1** (2.0×10^{-3} M) in DMSO upon the addition of 1.0 equiv of various anions as tetrabutylammonium salts (TBA–X) at room temperature.



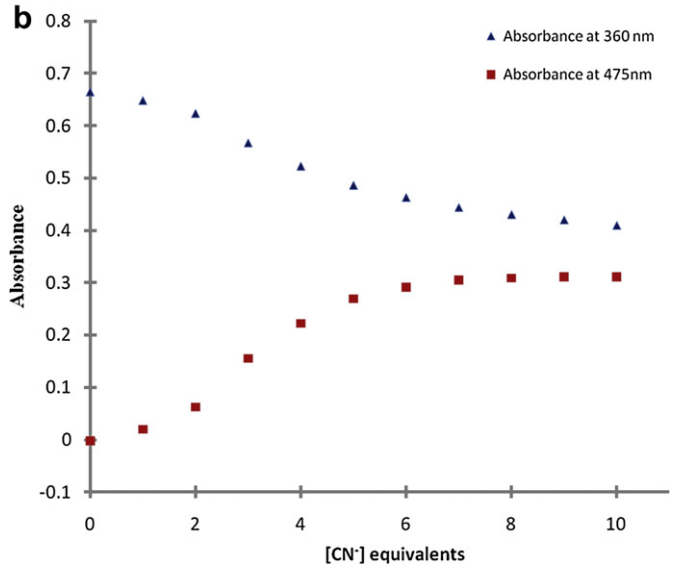
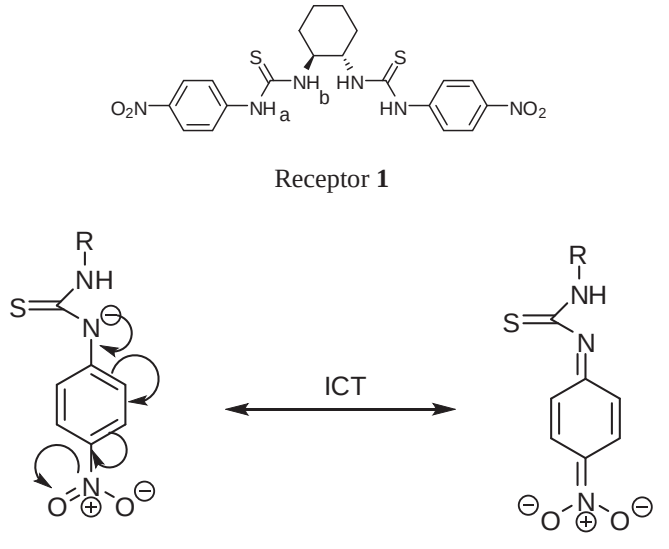


Figure 3. UV–vis absorption spectrophotometric titration of receptor **1** (2.0×10^{-5} M) with increasing concentrations of TBA–CN: (a)1.0 (b) 2.0, (c) 3.0, (d) 4.0, (e) 5.0, (f) 6.0, (g) 7.0, (h) 8.0, (i) 9.0, and (j) 10 equiv. (b) An isotherm for the titration data in Figure 3a, which shows the changes in the absorbances at 360 and 475 nm upon addition of cyanide ions.

10 equiv of CN^-, the absorbances associated with the new band at 475 nm and the original band at 360 nm both reached plateau values. These results show that compound **1** is able to detect cyanide in the range 10^{-5}–10^{-4} M, comparable to the recently published fluorescent sensors.[24,26] However, the current system is not only a very simple molecule to prepare, but it acts effectively as a colorimetric sensor.

The orange-red color of the solution observed upon addition of cyanide to receptor **1** is attributed to the intramolecular charge transfer (ICT) transition from the thioureido nitrogen atom (N–H_a) to the electron deficient *p*-nitrophenyl group. It is understood that, in the absence of cyanide (or any of the anions), the ICT transition does not occur as there is no interaction leading to deprotonation. However, in the presence of cyanide, the extent of ICT from the thioureido atom is enhanced, being facilitated by the deprotonation of the thiourea proton (H_a) by cyanide ions (see Scheme 1).

It was also noted that upon addition of traces of water or any protic solvents (such as methanol or ethanol) to the receptor **1**



Scheme 1.

and cyanide mixture, the orange-red color of the complex disappeared and reverted to the original pale yellow color. This observation also indicates that, on addition of water or other competitive protic solvents, the deprotonation of the NH group of the receptor by the cyanide can be reversed by protic solvents, which results in the disappearance of the new band at 475 nm.

The water-addition experiment was carried out to confirm the restoration of the original UV–vis spectrum, and after normalization, the original UV–vis spectrum was restored, suggesting the reversibility of this process via proton transfer of the NH. Figure 4 shows the increasing absorbance caused by addition of up to 13 equiv of CN^- to the mixture of receptor **1**, and then subsequent addition of up to 13 equiv of water to this mixture. It can be seen that the absorption band at 475 nm, which was formed upon the addition of CN^- ions, disappeared with increasing addition of water.

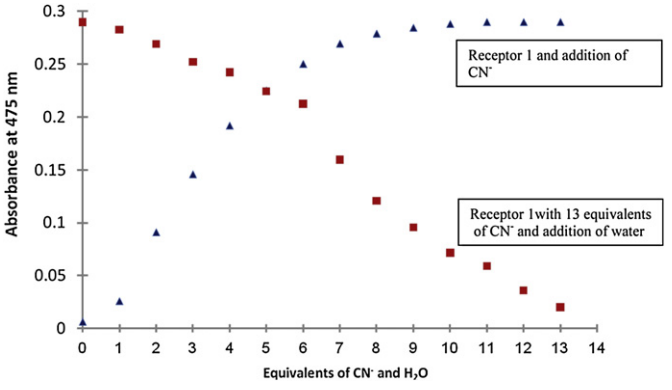


Figure 4. UV–vis absorption analysis at 475 nm of receptor **1**, upon addition of cyanide and subsequent addition of water.

Additionally, it was considered as to whether phenolphthalein would show similar results with TBA–CN, but there was, in fact no color change observed. This result indicates that cyanide ion is not basic enough to effect a color change with phenolphthalein.

It is proposed that the observed spectral changes are due to deprotonation of the thiourea proton (N–H_a), and this suggests that a negatively charged *p*-nitroanilide ion is formed as shown in

Scheme 1, which causes a significant increase in the charge density on the thioureido nitrogen atom. This enhances the charge-transfer interactions between the electron-rich and electron deficient moieties, resulting in the visible color change (Fig. 2). Similar results were obtained when the relatively strong base, Bu_4NOH, was specifically employed, providing further evidence that the proton transfer between the thioureido group ($N-H_a$) of the receptor and the cyanide ion is responsible for the pronounced color change. Even though hydroxide is a much stronger base than cyanide and is expected to show a very strong response, the cyanide ion still produced the greatest color change. At equivalent concentrations of 2.0×10^{-4} M, the absorption band at 475 nm for the addition of cyanide was approximately 1.3 times that observed when hydroxide was added. This result suggests that, although the interaction is mainly acid–base in type, it is not solely of this nature, and the cyanide ion is providing greater spectral recognition, perhaps due to its high nucleophilicity.

Competition studies were carried out in both non-responsive anions (iodide) and in competitive anions fluoride. The response of receptor **1** with 2.5×10^{-4} M cyanide remained unchanged in the presence of 2.5×10^{-4} M of iodide, indicating that the latter anion does not substantially interact with the receptor molecule. Contrastingly, the absorption spectrum of receptor **1** with 2.5×10^{-4} M cyanide and 2.5×10^{-4} M of fluoride together, resulted in an absorption maximum at 475 nm that was 1.4 times higher than the cyanide ion alone; this indicates that the ability of the receptor is affected in the presence of a strongly competing anion.

To make a comparison with the urea analogue, UV–vis titrations were conducted with receptor **2**, using TBA–CN, which had already been shown to interact strongly with receptor **1**, but interestingly there was no color change and no emergence of a longer wavelength peak around 475 nm, despite adding up to 60 equiv of the analyte CN^- anion (see Fig. 5). Unlike receptor **1**, that showed relative selectivity toward CN^-, F^- AcO^- BzO^-, and $H_2PO_4^-$, in this case there were no such observations. We attributed this behavior to the fact that thioureas are relatively more acidic than their urea counterparts, due to the different electronegativities of the sulfur and oxygen atoms. These results show that the simple system presented here is useful in a non-aqueous solvent but it does not show promise for an aqueous environment.

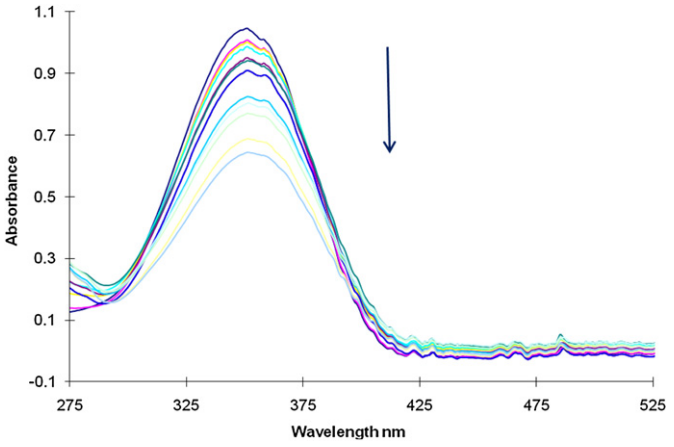
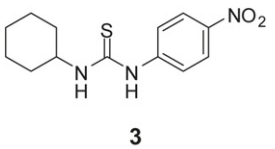


Figure 5. UV–vis titration of the receptor **2** with cyanide. Starting with 1.0×10^{-5} M solution of **2** in DMSO with subsequent addition of 10^{-3} M TBA–CN at increments of 1.0, 2.0, 3.0, 5.0, 7.0, 14, 19, 29, 39, 49, and 59 equiv.

It can be seen that receptor **1** has multiple NH sites, enabling it to act as a receptor for anions. To make a comparison, the simpler monomeric analogue, receptor **3**, was synthesized and the titration experiments were done with cyanide. Similar results were found for receptor **3**, with a new absorbance band centered at 485 nm appearing and a decrease in the main absorbance band at 360 nm, although the sensitivity is approximately half that of receptor **1**. Figure 6 shows a comparison of the titration results obtained by addition of cyanide ions up to 10 equiv to 20.0 μM solutions of receptors **1** and **3**. It can be observed that receptor **3** exhibits nearly half the response at the same concentration of cyanide, in comparison to receptor **1**.



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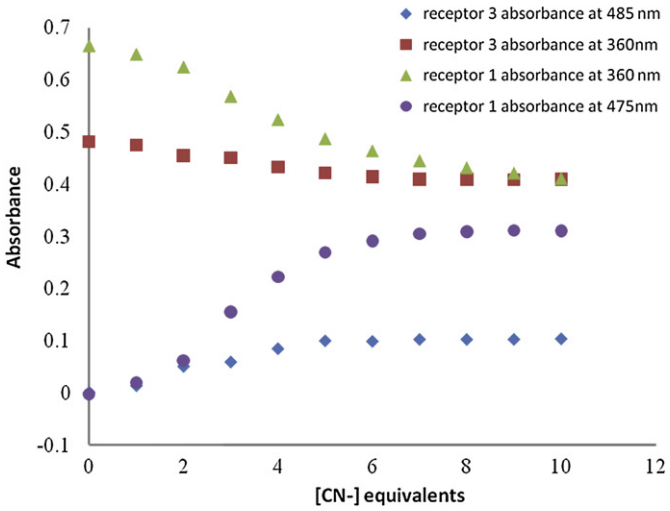

Figure 6. Isotherms for the titration of receptors **1** and **3**, which show the changes in the band absorbances upon addition of cyanide ions.

2.2. ^{1}H NMR spectroscopy

^{1}H NMR experiments were undertaken to gain further insight and monitor the anion binding interaction of receptors **1** and **2** with various anions in DMSO-d_6, using the anion candidates that had been shown to interact with the receptor **1** in the UV–vis experiments. The interaction of the anions with the receptor NH protons through hydrogen bond interactions is known to result in line broadening of the concerned ^{1}H NMR signals, and are usually accompanied by a downfield shift of the resonances of these protons with increasing concentrations of anion.[27,28] The disappearance of a peak is usually attributed to deprotonation and urea groups are known to show a downfield shift upon hydrogen bonding, with broadening and subsequent disappearance of the peak.[29]

A ^{1}H NMR titration of receptor **1** (0.02 M in DMSO-d_6) with TBA–CN was done (see Fig. 7), and after addition of 0.2 equiv of the cyanide, there was significant line broadening of both the NH peaks of the thiourea. This indicates interaction of the cyanide with both the NH protons (NH_a and NH_b). When more of the CN^- anion was added, all the N–H peaks disappeared completely with only 0.4 equiv of CN^- present. This evidence strongly supports the earlier notion that the cyanide anion participates in deprotonation of the NH. Addition of more CN^- to 0.6 and 0.8 equiv did not significantly change the ^{1}H NMR spectrum. An attempt to add D_2O to the complexed sample to find out if the NH peaks would reappear owing to proton exchange and

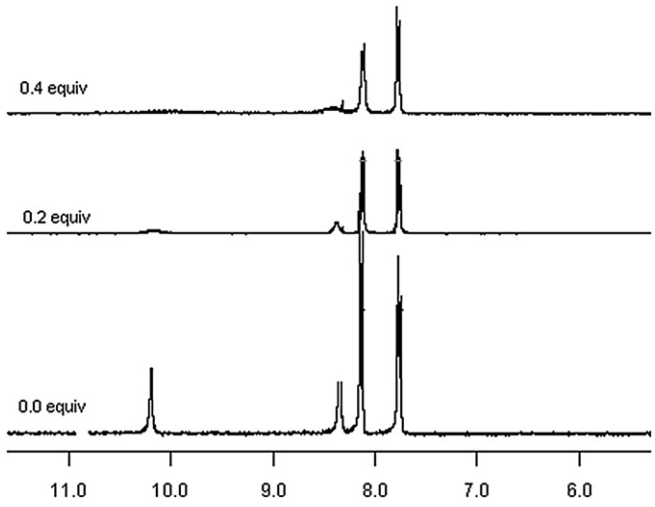

Figure 7. ^{1}H NMR titration of receptor **1** (0.02 M) in DMSO-d_6 with TBA–CN adding 0.2 and 0.4 equiv, respectively.

possible reprotonation was successful with evidence of the NH peaks re-emerging.

To compare the cyanide with a relatively less responsive anion, ^{1} H NMR titration of the receptor **1** was done with tetrabutylammonium acetate (TBA–OAc), which resulted in an expected downfield shift of the peak corresponding to the NH of the thiourea (see Fig. 8). This indicates that there is a hydrogen bonding interaction taking place and the observed broadening of these peaks is interpreted to be evidence of deprotonation by the anions. It is worth noting that unlike the case of cyanide, where addition of 0.4 equiv not only resulted in substantial broadening but almost complete disappearance of peak, the effect of acetate on the same receptor is relatively small (see Fig. 8). Addition of higher concentrations of up to 1.0 equiv of the acetate ion resulted in a complete flattening of the more downfield NH peak.

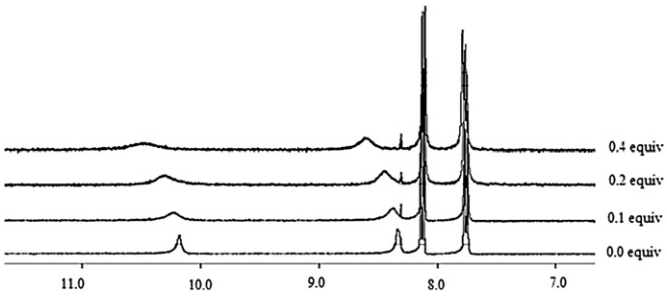

Figure 8. ^{1}H NMR of receptor **1** when titrated against TBA–OAc, up to 0.4 equiv.

Further ^{1}H NMR titrations were carried out with receptor **2** to establish the stoichiometry of interaction with cyanide anion (see Fig. 9a) and the results of the titration monitored by the changes in the resonance of NH protons with increasing concentrations of the CN^- anion (see Fig. 9b). This was indeed concomitant with what is anticipated for a 1:2 *receptor-to-anion* stoichiometry, showing a downfield shift up to 1.51 ppm and 1.33 ppm, respectively, for the NH protons of the urea, that are associated with the hydrogen bonding. The resonances of the ArN*H* and the CHN*H* showed significant downfield shifts, with the ArN*H* broadening to the point of being almost unrecognizable after 1.0 equiv of CN^- was added, while the CHN*H* did not broaden even after addition of 2.0 equiv of CN^-, although it substantially shifted downfield. While broadening and subsequent disappearance were observed for ArN*H*, the other protons CHN*H* tended to remain the same in relative area, an indication that there was no deprotonation of these protons by CN^-, unlike the case of receptor **1**.

3. Experimental

3.1. Materials

All the reagents for the synthesis were obtained commercially from Sigma–Aldrich, unless otherwise noted, and were used without further purification. The *trans*-cyclohexane-1,2-diamine was used as a racemic mixture of both (RR and SS) stereoisomers. In both the UV–vis and ^{1}H NMR titration experiments, all the anions were added in the form of tetrabutylammonium (TBA) salts, which were purchased from Sigma–Aldrich, and stored in desiccators and dried before use. DMSO was dried over CaH_2 and distilled under reduced pressure; typically, calcium hydride powder is stirred with DMSO in a flask vented through a phosphorus pentoxide tube. After 18 h, it is then distilled under reduced pressure. Since DMSO is highly hygroscopic, in some cases better drying was achieved using activated Linde-molecular sieves (4 Å×50 mesh), while in ^{1}H NMR titrations, DMSO-d_6 was used as solvent.

3.2. Instrumentation

^{1}H NMR spectra were obtained on a Brucker AM-360 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. UV–vis spectra were recorded on a Hewlett–Packard 8453 spectrophotometer with a quartz cuvette (1 cm path length) at 298 K. Mass spectrometry was performed on a Thermo-Scientific LCQ-Fleet 2100 spectrometer (San Jose, CA) in negative electrospray ionization (ESI) mode ($[M-H]^-$).

3.3. Synthesis

*3.3.1. Synthesis of 1, 1′-(cyclohexane-1, 2-diyl) bis (3-(4-nitrophenyl) thiourea) **1**.* 4-Nitrophenylisothiocyanate (0.300 g, 1.67 mmol) was added to a solution of cyclohexane-1,2-diamine (0.095 g, 0.830 mmol) in $CHCl_3$ (25 mL), in a 50.0 mL schlenk flask filled with argon. The mixture was refluxed under magnetic stirring for 4 h at 60 °C, and then was left stirring at room temperature for a further 12 h. During the reaction, the yellow 4-nitrophenylisothiocyanate slowly dissolved and a white precipitate formed. The product was collected by filtration, washed with water (3×4 mL), and dried in vacuo (0.352 g; yield: 89%). $C_{20}H_{22}N_6O_4S_2$. ^{1}H NMR (DMSO-d_6): δ 10.17 (s, 2H, N–H), 8.33 (s, 2H, N–H), 8.11 (d, J=9.4 Hz, 4H), 7.75 (d, J=9.4 Hz, 4H), 4.35 (m, 2H), 2.16 (m, 2H) 1.71 (m, 2H), and 1.28 (m, 4H). ^{13}C NMR (360 MHz, DMSO-d_6): δ 40.1, 47.0, 72.5, 136.4, 140.5, 157.8, 162.0, 195.6. HRMS (ESI) calcd for $C_{20}H_{22}N_6O_4S_2$ $[M-H]^-$ 473.1146, found 473.0460.

*3.3.2. Synthesis of 1, 1′-(cyclohexane-1, 2-diyl)bis(3-(4-nitrophenyl) urea) **2**.* Compound **2** was synthesized according to known procedure.[27]

4-Nitrophenylisocyanate (0.640 g, 3.90 mmol) was added to a solution of cyclohexane-1,2-diamine (0.022 g, 1.63 mmol) in $CHCl_3$ (50 mL), in a schlenk flask filled with argon. The mixture was refluxed under magnetic stirring for 4 h, and then it was left stirring at room temperature for further 12 h. During the reaction, the yellow 4-nitrophenylisocyanate slowly dissolved and a white precipitate formed. The product was collected by filtration, washed with water (3×7 mL), and dried in vacuo (0.56 g; yield: 80%). $C_{20}H_{22}N_6O_6$. ^{1}H NMR (DMSO-d_6, dH/ppm): δ 9.27 (s, 2H, N–H), 8.07 (d, J=9.4 Hz, 4H), 7.56 (d, J=9.4 Hz, 4H), 6.37 (d, J=8.1 Hz, 2H, N–H),

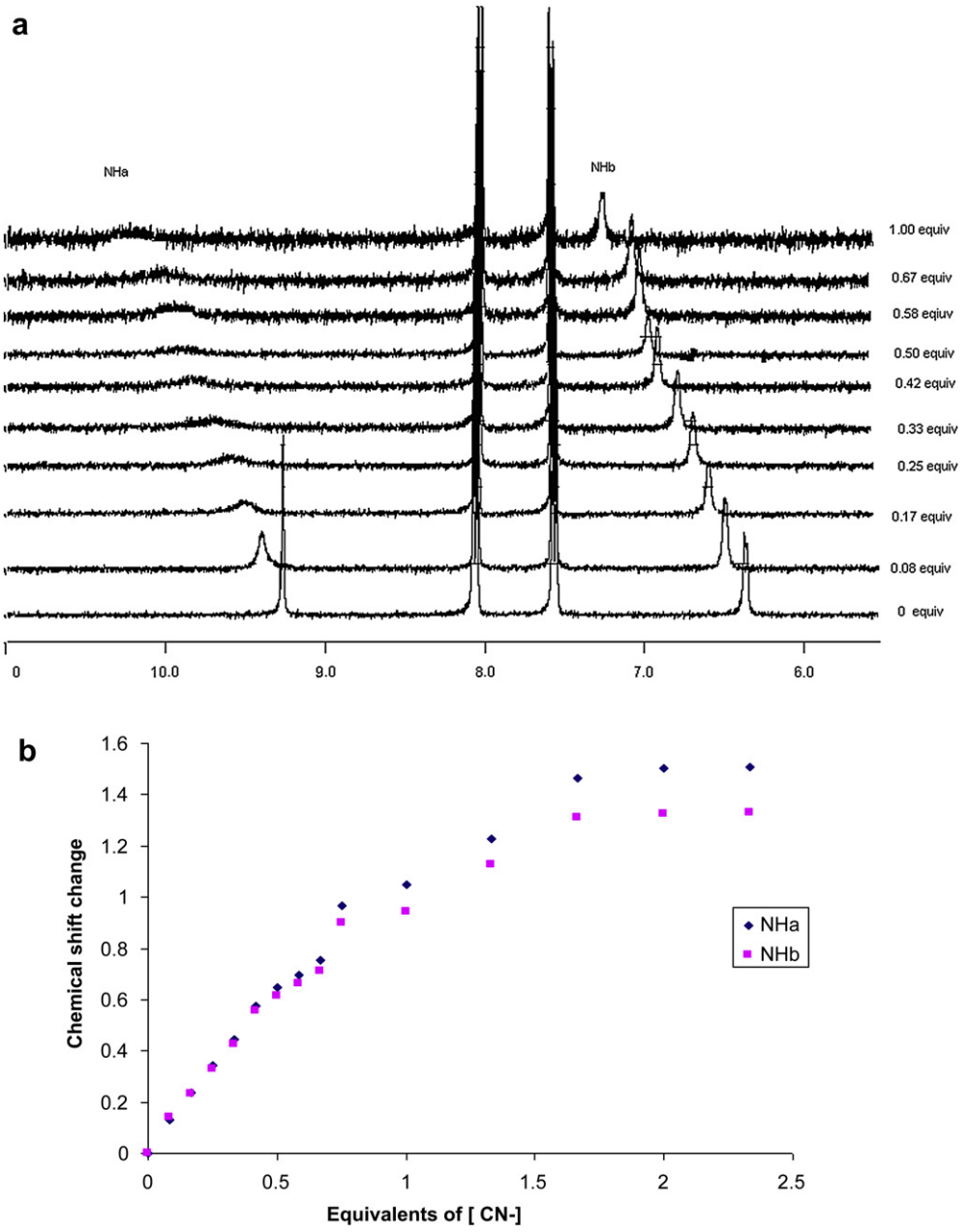

Figure 9. ^{1}H NMR titration of receptor **2** in DMSO at 298 K with the addition of TBA–CN. (b) ^{1}H NMR titration results for receptor **2** from Figure 8a. Downfield chemical shift changes ($\Delta\delta$) of the urea protons at δ=9.26 (ArN*H*) and δ=6.36 (CHN*H*) are plotted.

3.48 (s, 2H), 1.95 (m, 2H), 1.68 (m, 2H), and 1.28 (m, 4H). ^{13}C NMR (360 MHz, DMSO-d_6): δ 24.3, 32.5, 52.8, 116.7, 125.0, 140.3, 147.1, and 154.3. HRMS (ESI) calcd for $C_{20}H_{22}N_6O_6$ $[M-H]^-$ 441.1602, found 441.0696.

3.3.3. Synthesis of 1-cyclohexyl-3-(4-nitrophenyl)thiourea **3**. Compound **3** was synthesized by a similar procedure as for receptors **1** and **2**, where 4-nitrophenylisothiocyanate (0.908 g, 5.04 mmol) was added to a solution of cyclohexylamine (0.500 g, 5.04 mmol) in $CHCl_3$ (50.0 mL), in a 100 mL schlenk flask filled with argon. The mixture was refluxed under magnetic stirring for 4 h at 60 °C, and then was left stirring at room temperature for a further 12 h. the reaction yielded a bright yellow product, which was collected by filtration and dried in vacuo (1.13 g; yield: 80%). $C_{13}H_{17}N_3O_2S$. ^{1}H NMR (DMSO-d_6, *d*H/ppm): δ=9.09 (s, 1H, NH,), 7.32 (d, *J*=8.6 Hz, 2H,), 7.01 (d, *J*=8.6 Hz, 2H), 1.66 (m, 1H), 1.10 (m, 4H), 0.84 (m, 4H), 0.74 (m, 2H), 0.46 (m, 4H). ^{13}C NMR (360 MHz, DMSO-d_6): δ 24.4, 25.1, 31.5, 52.2, 120.1, 124.4, 141.6, 146.5, and 178.7. HRMS (ESI) calcd for $C_{13}H_{17}N_3O_2S$ $[M-H]^-$ 278.1043, found 278.1223.

4. Conclusions

A simple colorimetric anion sensor, which allows for 'naked-eye' detection as well as UV–vis detection of CN^- anion with high sensitivity and selectivity, has been synthesized. The sensor utilizes the molecule's intramolecular charge transfer (ICT) mechanism as a mode of detection. ^{1}H NMR titrations of receptor **1** with AcO^- confirmed the N–H hydrogen bonding interaction, which in the case of the addition of CN^- anions, leads to deprotonation. Hence, the compound 1,1′-(cyclohexane-1,2-diyl)bis(3-(4-nitrophenyl)

thiourea) may have potential importance in a real-life application for cyanide detection.

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