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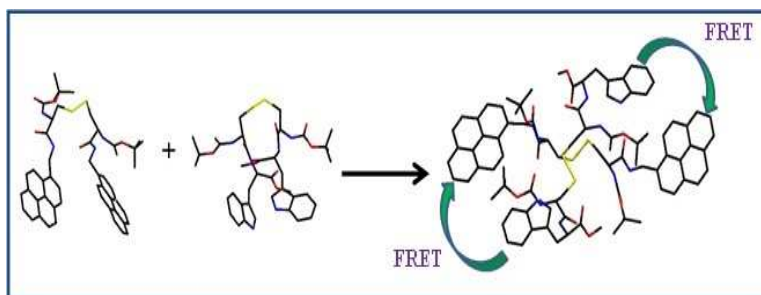
A supramolecular approach to metal ion sensing: Cystine-based designer systems for Cu^{2+} , Hg^{2+} , Cd^{2+} and Pb^{2+} sensing

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Emergent properties are generally novel and unexpected. Here, we demonstrate an emergent property from a mixture of two simple cystine containing molecules. The 1:1 mixture of pyrene-labelled **S1** and tryptophan appended **S2** form the heterodimeric system **S1:S2**, which shows metal binding ability very different from the constituent units.



ARTICLE

A supramolecular approach to metal ion sensing: Cystine-based designer systems for Cu^{2+} , Hg^{2+} , Cd^{2+} and Pb^{2+} sensing

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We have synthesized two cystine containing molecules **S1** (pyrene-labelled) and **S2** (tryptophan-labelled) and demonstrated that the former can detect Cu^{2+} , and the latter can detect Hg^{2+} in acetonitrile. The 1:1 mixture of **S1** and **S2** forms a heterodimeric system **S1:S2**, which was confirmed by mass spectrometric, UV-Visible and fluorescence spectroscopic studies. Additional proof for the formation of **S1:S2** came from ^1H NMR, CD, ITC, ultramicroscopic and computational studies. The supramolecularly assembled **S1:S2** detects Pb^{2+} in nanomolar level. A control compound **S3** containing tryptophan and pyrene units showed totally different binding properties compared to **S1**, **S2** and **S1:S2**. DFT studies on **S1:S2** establish that **S1** in **S1:S2** adopts an extended conformation, thereby keeping the pyrene units proximal to the indole moiety of **S2** for energy transfer. The binding of Pb^{2+} with **S1:S2** brings the two pyrene units to proximity resulting in a folded structure and the formation of the excimer. These results clearly demonstrate that a hitherto unknown and unexpected organization of two fluorescent molecules leading to a new supramolecular system capable of Pb^{2+} detection.

Introduction

Molecular structure is the key to functional properties and this notion spearheaded the design and synthesis of a wide variety of molecules with unusual architectures.¹ Chemical synthesis, therefore became a powerful discipline because it can create new molecular entities. The last few decades of developments in chemistry have shown that the association of molecules through non-covalent interactions lead to intricate molecular assemblies. Such supramolecular assemblies are capable of exhibiting new emergent properties.² The emergent property is a higher level property, which cannot be predicted from the properties of constituent entities.³ The emergent behaviour of a collection of molecules is more than the sum of the behaviors of its parts. Under this rubric, chemists have attempted to design and synthesize a variety of chemical systems that demonstrate emergent properties such as the self-replicating property,⁴ supramolecular chirality,⁵ and chirality transfer.⁶ The control and predictability of the non-covalent interactions are the challenges for the design of functional materials with emergent properties.⁷ Conjugating a well known hydrogen bonding motif such as melamine or diketopiperazine to a molecule of interest for achieving desired supramolecular assembly is an approach used by chemists.⁸ Herein, we report a

hitherto unknown and unexpected organization of two fluorescent molecules based on cystine. In the present study, we chose cystine as a basic structure for the design since, the S-S bond in cystine could serve as potential metal ion binding site.⁹ In addition to that, N and C- termini of cystine can be easily functionalizable with a variety of metal ion binding motifs or by fluorescent probes or both. The other reason being, orthogonality of S-S bond provides a kink and can induce a turn architecture, such a preorganization could further facilitate the metal ion binding.

Results and Discussion

The synthesized cystine-based molecules **S1-S3** are given in Fig. 1. Due to the orthogonality of disulfide linkage in **S1** and **S2**, the appended fluorophores could align closely (conformer 1, Fig. 1) or they could be far apart (conformer 2, Fig. 1). In **S1**, pyrene is chosen as a fluorescent probe owing to its distinctive monomer and excimer emissions coupled with high detection sensibility. In addition to these, the emission wavelength of pyrene is sensitive to the polarity of the local environment.¹⁰ In the case of **S2**, tryptophan is the fluorophore and the molecule can be described as a completely peptidic system. The choice of Trp was primarily due to its fluorescence and the metal ion

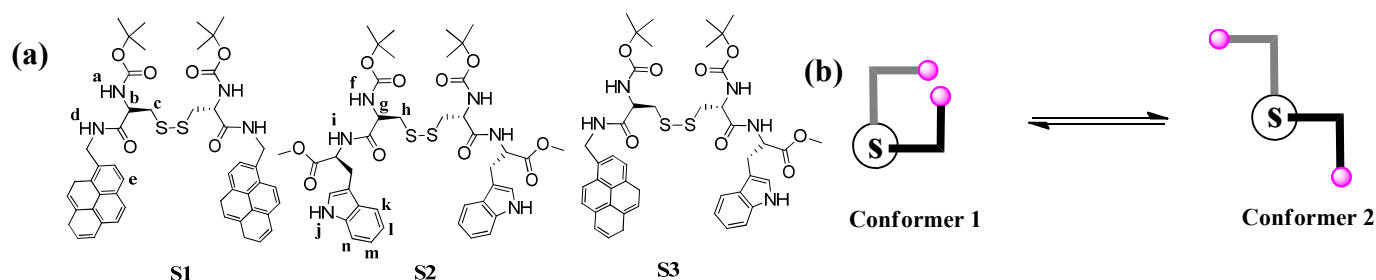


Fig. 1 (a) Structures of cystine-based sensors used in the study (b) Conformational equilibrium of **S1**.

binding capability of its indole ring. In fact, Trp plays a fundamental role in many important metal ion binding proteins. For example, EF-hand motif and in CusF protein, indole ring of Trp binds to Ca^{2+} and Cu^{2+} respectively through cation- π interaction.¹¹

For the synthesis of **S1**, the C-termini of Boc-cystine were functionalized with pyrene, by coupling pyrene methylamine to bis-Boc-Cystine using dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (NHS). Similarly, **S2** was synthesized from Boc-cystine and TrpOMe.

S1 on excitation at 340 nm shows two closely spaced emission bands at 380 nm and 390 nm with a broad band at 480 nm (Fig. 2a). The bands at 380 and 390 nm attribute to monomer emission and the 480 nm is due to the excimer emission. The I_{480}/I_{380} values measured over a range of concentrations indicate that the excimer was independent of concentration (Fig. S1a in ESI†).¹² The excitation spectra of **S1** recorded at 380 nm and 480 nm in acetonitrile was different suggesting the formation of a ground state intramolecular pyrene dimer (Fig. S2a in ESI†).¹³

The metal ion binding ability of **S1** in CH_3CN was studied by fluorescence spectroscopy. The order of metal ion binding was found to be $\text{Cu}^{2+} > \text{Hg}^{2+} > \text{Fe}^{3+} > \text{Ag}^+ > \text{Cs}^+ \sim \text{Mg}^{2+} \sim \text{Ba}^{2+} \sim \text{Pb}^{2+} \sim \text{Mn}^{2+} \sim \text{Co}^{2+} > \text{Zn}^{2+} > \text{Cd}^{2+} > \text{Na}^+ > \text{K}^+$ (Fig. S3a in ESI†). The fluorescence quenching was higher for Cu^{2+} and Hg^{2+} compared to other metal ions tested. The Stern-Volmer quenching constant (K_{sv}) of **S1** with Cu^{2+} was found to be $6 \times 10^5 \text{ M}^{-1}$ (Fig. S4a in ESI†) with a detection limit of 0.6 μM . The competitive binding experiments revealed that **S1** can detect Cu^{2+} even in the presence of higher concentrations of other metal ions (Fig. S5a in ESI†). The time-resolved fluorescence spectroscopic studies showed that the fluorescence lifetime of **S1** decreases upon adding Cu^{2+} . The ratio of fluorescence intensity of **S1** using a steady-state fluorescence studies was found to be equal to the ratio of decay time ($F_0/F = \tau_0/\tau$), (where τ_0 and F_0 are the fluorescence lifetime and intensity in the absence of Cu^{2+} , τ and F are the fluorescence lifetime and intensity in the presence of Cu^{2+}) indicating a dynamic quenching mechanism (Fig. S6, Table S2 in ESI†).¹⁴ The circular dichroism (CD) spectrum of **S1** revealed a maximum at 213 nm and minimum at 206 nm with a crossover at 211 nm (Fig. 2d) indicating a turn-like conformation.¹⁵ The addition

of Cu^{2+} to **S1** resulted in very small changes in the CD signal intensity (Fig. S7a in ESI†) implying no significant conformational changes upon binding. The stoichiometry of **S1**- Cu^{2+} complex was found to be 1:1 by Job's plot (Fig. S8a in ESI†).

The binding studies of **S2** with various metal ions showed that it exhibits a high binding affinity for Hg^{2+} followed by Cu^{2+} (Fig. S3b in ESI†). The selectivity of **S2** for metal ions is in the order $\text{Hg}^{2+} > \text{Cu}^{2+} > \text{Ag}^+ > \text{Ba}^{2+} > \text{Cs}^+ > \text{Fe}^{3+} \sim \text{Pb}^{2+} > \text{Na}^+ > \text{Co}^{2+} \sim \text{Zn}^{2+} > \text{Sn}^{2+} > \text{K}^+ \sim \text{Mg}^{2+} \sim \text{Cd}^{2+} \sim \text{Mn}^{2+}$ (Fig. S5 in ESI†). The fluorescence band at 330 nm was quenched by the addition of Hg^{2+} to a solution of **S2** in acetonitrile. The stoichiometry of the **S2**- Hg^{2+} complex was found to be 1:1 by Job's plot (Fig. S8b in ESI†). **S2** displayed a color change from colorless to orange brown upon binding to Cu^{2+} (Fig. S9a in ESI†), and this visible colorimetric response was not observed with other metal ions. The involvement of Trp side chain for binding Hg^{2+} was confirmed by the ^{13}C NMR spectrum.¹⁶ Considerable downfield shifts in the ^{13}C NMR for the $-\text{S}-\text{CH}_2$ -carbon atoms (0.91 ppm) and amide carbonyls (0.48 ppm) indicates that Hg^{2+} binds to $-\text{S}-\text{S}-$ atoms and amide carbonyls. The aromatic carbon atoms also showed a downfield shift of 0.2 ppm indicating the involvement of aromatic moieties in Hg^{2+} binding (Fig. S10, Table S1 in ESI†). The interference of the potentially competing metal ions on Hg^{2+} detection has also been investigated in the presence of other metal ions and the results demonstrate that **S2** is very selective to Hg^{2+} (Fig. S5b in ESI†). **S2** showed a binding constant of $3.3 \times 10^3 \text{ M}^{-1}$ (Fig. S4b in ESI†) and a detection limit of 1.5 μM .

The time-resolved fluorescence measurements showed that the quenching observed in the **S2** with Hg^{2+} is static type (Table S3, Fig. S11b in ESI†), since there is no change in the fluorescence decay time for **S2** even after the addition of 3 equiv of Hg^{2+} .¹⁴ The CD spectrum of **S2** revealed a minimum at 215 nm and a maximum at 225 nm with a cross over point at 221 nm supportive of a turn-like conformation (Fig. 2e).¹⁵ The CD spectrum remains the same after the addition of 10 equiv of Hg^{2+} indicating no conformational change in **S2** upon complexation with Hg^{2+} (Fig. S7b in ESI†).

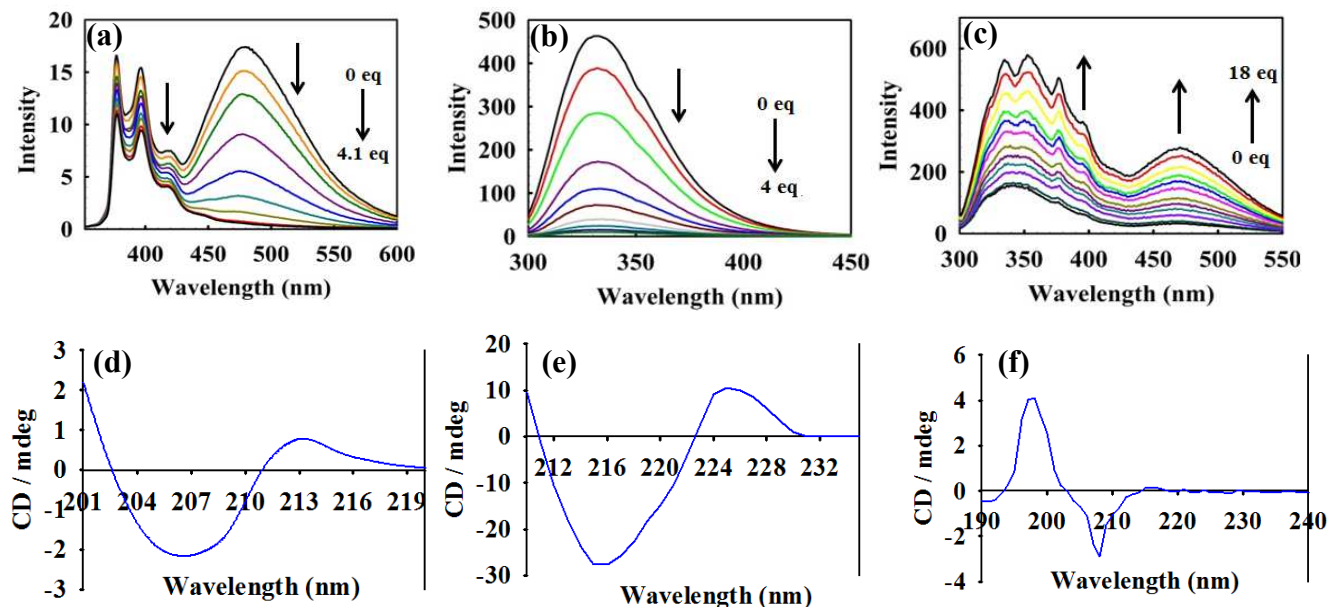


Fig. 2 (a) Fluorescence spectra of **S1** [10 μ M] in acetonitrile with and without addition of $\text{Cu}(\text{ClO}_4)_2$, $\lambda_{\text{ex}} = 340$ nm (b) Fluorescence spectra of **S2** [15 μ M] in acetonitrile with and without addition of $\text{Hg}(\text{ClO}_4)_2$, $\lambda_{\text{ex}} = 290$ nm (c) Fluorescence spectra of **S3** [12 μ M] in acetonitrile with and without addition of $\text{Cd}(\text{ClO}_4)_2$, $\lambda_{\text{ex}} = 290$ nm (d) CD spectrum of **S1** [500 μ M] in acetonitrile (e) CD spectrum of **S2** [500 μ M] in acetonitrile (f) CD spectrum of **S3** [500 μ M] in acetonitrile.

The two fluorophores (pyrene and Trp) can form fluorescence resonance energy transfer (FRET) pair, as the absorption spectrum of pyrene overlaps with the emission spectrum of tryptophan.¹⁷ We envisioned that an asymmetric system equipped with probes capable of forming FRET will widen the versatility of our system. With this in mind, we performed disulfide exchange reaction by reacting **S1** and **S2** under reducing condition and further oxidation produced disulfide shuffled product **S3** (Fig. 1). Excitation of **S3** at 290 nm gives an emission band at 335 nm that corresponds to the tryptophan emission band with low intensity excimer band of pyrene at 470 nm, this observation indicates FRET. When **S3** is titrated with Cd^{2+} ion, there is an increase in the intensity of emission bands at 335 and 470 nm (Fig. 2c); indicates that Cd^{2+} binding enhances FRET between Trp and pyrene. Time-resolved fluorescence measurements showed that the decay time (τ) of Trp in **S3** decreased in comparison to the decay time of **S2** (Tables S3 and S4 in ESI†), this indicating that the energy transfer mechanism is by FRET between donor Trp and acceptor pyrene. The fluorescence decay time of Trp further decreased upon the addition of Cd^{2+} ion indicating an enhanced FRET upon complexation. Excimer formation upon Cd^{2+} binding (Fig. S2c in ESI†) supported intermolecular dimerization and the Job's plot clearly revealed a 2:1 stoichiometry for **S3** and Cd^{2+} (Fig. S8e in ESI†). The binding constant was found to be $2.2 \times 10^6 \text{ M}^{-2}$ with a detection limit of 2 μM . Mass spectrometric data confirmed a Cd^{2+} bound intermolecular dimer at m/z 1821.5470 (**S3**+ Cd^{2+} + H^+) (Fig. S12a in ESI†). **S3** displayed a color change from colorless to yellow upon the addition of Cd^{2+} indicating that **S3** can act as a visual detector for Cd^{2+}

(Fig. S9b in ESI†). The CD spectrum revealed only intensity changes in the CD signal after the addition of Cd^{2+} , signifying no conformational change in **S3** as a result of Cd^{2+} complexation (Fig. S7c in ESI†).

Computational studies using density functional theory (DFT) supported a dimeric structure with Cd^{2+} in octahedral geometry (Fig. S13d in ESI†). Only one of the sulphur from each disulfide bond is coordinated to the metal. Average Cd-O distance is 2.28 Å. One of the pyrene units comes in the vicinity of the indole moiety (closest C(pyrene)-C(indole) ring distance is 4.08 Å, thus supporting the observed FRET.

Since pyrene and Trp can form a FRET pair, we envisioned that a supramolecular assembly of **S1** and **S2** may lead to an intermolecular FRET and possibility for an emergent property. In fact, a 1:1 mixture of **S1** and **S2** namely **S1:S2** in acetonitrile displayed a very different absorption spectrum compared to the summed absorption spectra of **S1** and **S2** indicative of intermolecular heterodimeric supramolecular interactions (Fig. S14a in ESI†). The UV spectrum of **S1:S2** is characterized by a drastic redshift of 15 nm compared to the UV spectra of **S1** and **S2** (Fig. S14b in ESI†). Similarly, the emission spectrum of **S1:S2** ($\lambda_{\text{ex}} = 290$ nm) showed an excimer at 470 nm, while the excimer in **S1** was found to be at 480 nm. ^1H -NMR spectrum of an equimolar mixture of **S1** and **S2** in CD_3CN displayed, a downfield shift of amide NHs (a, d, f, and i) (0.3 ppm) and indole NH (j) (0.2 ppm) supporting the formation of supramolecular complex **S1:S2** by non-covalent interactions (Fig. S15a in ESI†). The mass spectrometric analysis of **S1:S2** showed m/z 1706.6360,

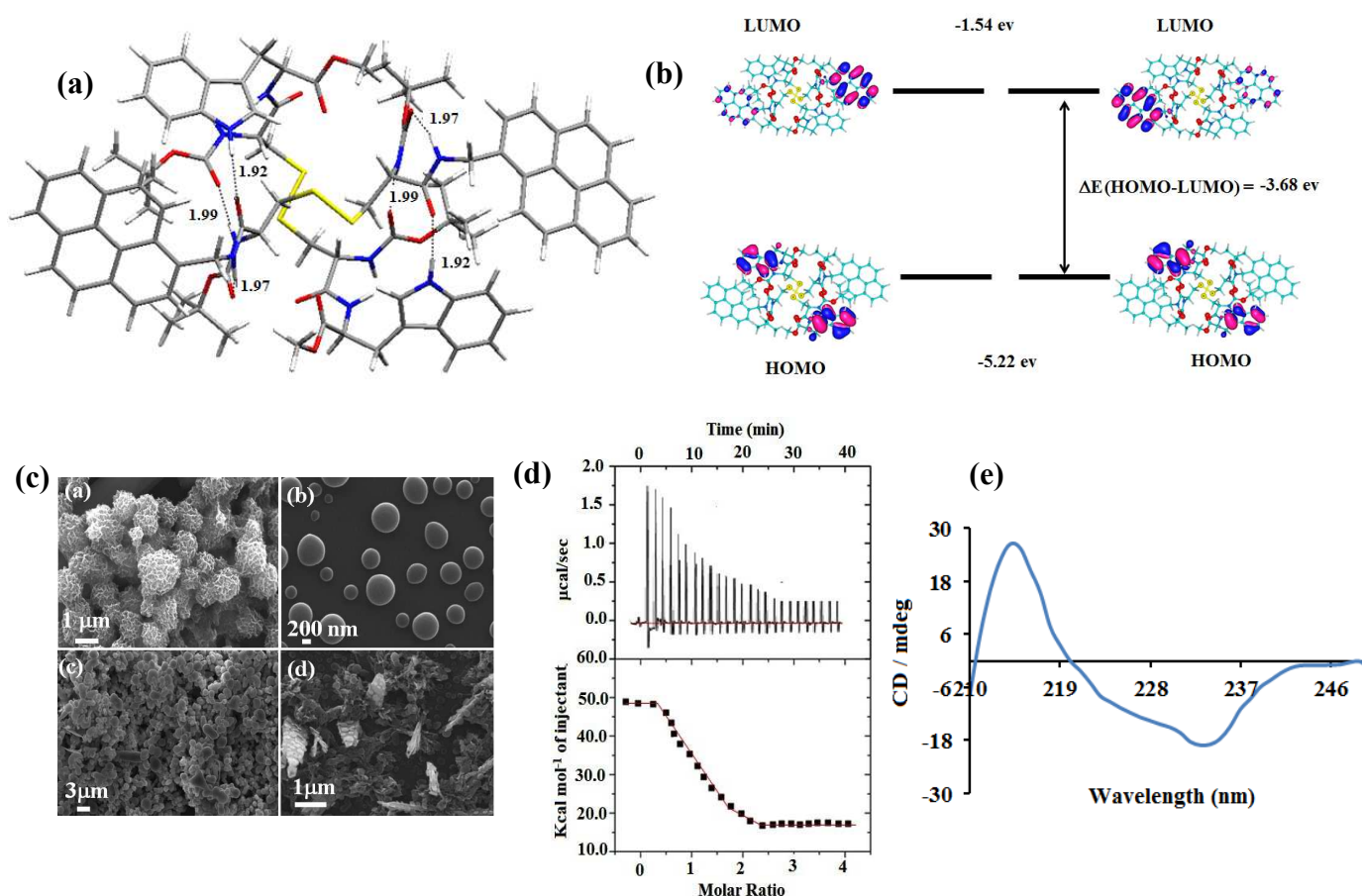


Fig. 3. Optimized structures of (a) the heterodimer **S1:S2** (b) HOMO-LUMO orbital diagram for **S1:S2** heterodimer using B3LYP/6-31G* DFT method. The HOMO orbitals are on the indole units, while LUMO orbitals are on pyrene units. An energy gap of -3.68 eV supports the observed FRET in **S1:S2** (c) SEM images of (a) **S1** (b) **S2** (c) **S3** (d) **S1:S2** in acetonitrile (d) ITC titration data of **S1** [200 μM] upon titrating against **S2** [50 μM]; ($n = 1.01$, $K_a = 3.2 \times 10^3 \text{ M}^{-1}$). Titrations were performed at 25 °C in acetonitrile and each titration was composed of 25 successive injections of 1 μL of **S2**. Upper graphs represent experimental data and lower panels represents the binding isotherm obtained by plotting the integrated heats from each injection against the molar ratio of the compounds (e) CD spectrum of **S1:S2** [500 μM] in acetonitrile.

which supports the formation of a heteromeric dimer (Fig. S12b in ESI†). The titration of **S1** and **S2** was monitored UV spectroscopically and the Job's plot showed a 1:1 complexation (Fig. S8c in ESI†).

The fluorescence spectrum of **S1:S2** ($\lambda_{\text{ex}} = 290 \text{ nm}$) showed a band at 470 nm indicating the energy transfer from Trp to pyrene. These results support the formation of a heterodimeric structure for **S1:S2** in which pyrene moiety of **S1** and indole unit of **S2** are in proximity for exhibiting FRET. In order to confirm the formation of a FRET pair, we performed lifetime measurements on individual compounds and the mixture. The fluorescence lifetime of donor (Trp) decreased from 1.01 ns (in **S2**) to 0.48 ns in **S1:S2** which clearly indicates resonance energy transfer (Table S5 in ESI†).¹⁴ The CD spectrum of the **S1:S2** in acetonitrile revealed a minimum at 234 nm and a maximum at 214 nm, with a crossover at 220 nm (Fig. 3e). The different CD spectrum of **S1:S2** compared to that of **S1** and

S2 indicates conformational changes and supports the formation of supramolecular structure (Fig. 3e).

Theoretical supports to the experimental findings have been obtained from DFT studies using B3LYP/6-31G* method on **S1**, **S2** and **S1:S2**. These studies showed that the conformation of **S1** changed from a folded (conformer 1) to an extended (conformer 2) upon the formation of the heterodimer **S1:S2** supporting the fluorescence spectroscopic results on **S1**, **S2** and **S1:S2** (Figs. 3a and S13 in ESI†). For instance, the pyrene excimer intensity of **S1** decreased significantly upon subsequent addition of **S2** suggesting that the pyrene units in **S1** are distant in **S1:S2** compared to **S1** alone. This fact is clearly captured in the computed structure of **S1:S2**. The nearly C2 symmetric heterodimer is stabilized by three pairs of hydrogen bonds between (indole NH and pyrene O=C (1.92 Å); Boc O=C of **S2** with Boc NH of **S1** (1.99 Å); Boc O=C of **S1** with amide

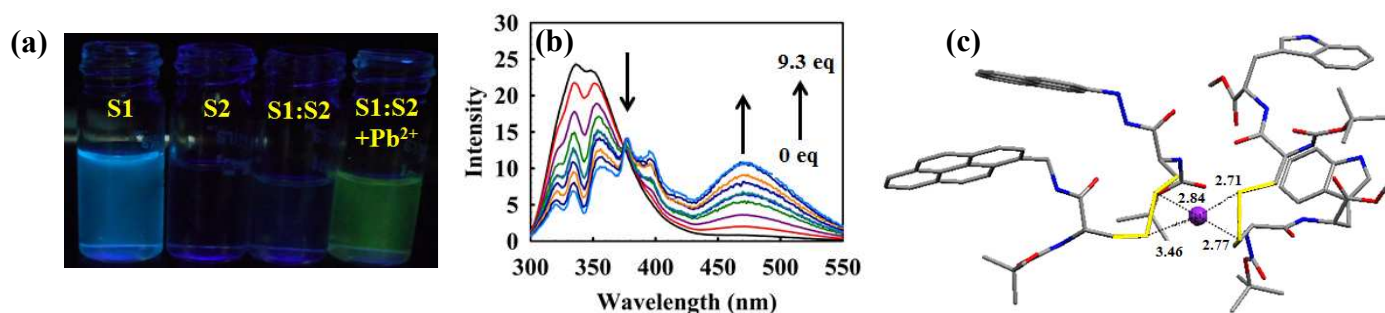


Fig. 4. (a) Observed color change under UV light upon binding of **S1:S2** [10 μ M] with Pb^{2+} (b) Fluorescence spectra of **S1:S2** (1.1×10^{-5} M) in acetonitrile with and without addition of $\text{Pb}(\text{ClO}_4)_2$, $\lambda_{\text{ex}} = 290$ nm (c) Optimized structure of the heterodimer with Pb^{2+} .

NH of **S1** (1.97 Å) and the overall stabilization is found to be 16.6 kcal/mol (Fig. 3a). The calculations showed that the donor indole and acceptor pyrene moieties are at an average distance of 10 Å, facilitating FRET pair (Fig. 3a). The HOMO orbitals are located on the indole units of **S2**, whereas LUMO is concentrated on pyrene moieties of **S1** with a HOMO-LUMO gap of 3.68 eV (Fig. 3b). Hence, FRET can be attributed mainly to the transfer of electron density from indole unit of Trp to pyrene moiety.

Clear evidence for the supramolecular nature of the binding interaction between **S1** and **S2** is obtained from isothermal calorimetric (ITC) titration studies. The ITC studies (Figs. 3d and S16a in ESI†) confirmed that the interaction between **S1** and **S2** is an entropy-driven endothermic process¹⁸ because the change in enthalpy (ΔH) of 48.9 calmol⁻¹ and a change in entropy ($T\Delta S$) of 4.83 kcalmol⁻¹ resulted in a favourable change in free energy (ΔG) -4.7 kcalmol⁻¹. The calculated binding constant was 3.2×10^3 M⁻¹ with a stoichiometry of 1:1. The observed 1:1 stoichiometry is supported by mass spectrometric analysis (Fig. S12b in ESI†). Further, direct evidence for the supramolecular interaction in **S1:S2** complex is obtained from their morphological studies using scanning electron microscopy (SEM). **S1** showed a cotton candy-like morphology, whereas **S2** showed vesicles with diameters in the range of 610-980 nm. The morphology of **S1:S2** showed no resemblance to the morphology of **S1** or **S2**. The morphological difference observed for **S1:S2** compared to **S1** and **S2** supports the supramolecular interactions between **S1** and **S2** (Fig. 3d).

The differential scanning calorimetry (DSC) revealed a sharp melting transition at 177.32 °C and 134.98 °C for **S1** and **S2**, respectively. The **S1:S2** showed an endothermic phase transition at 114.31 °C corresponding to the melting point. The different and distinct thermal transition value of **S1:S2** from either of the individual components signifies the formation of a new molecular entity (Fig. S17 in ESI†).

The DFT optimized geometry of **S1:S2**, revealed a heterodimeric structure. We envisioned that the heterodimer

S1:S2 with two disulfide linkages has the potential to bind compatible metal ions. The binding studies of **S1:S2** showed that it has a high binding affinity towards Pb^{2+} (Fig. S3d in ESI†). The competitive binding experiments further revealed that **S1:S2** can detect Pb^{2+} even in the presence of higher concentrations of other metal ions (Fig. S5d in ESI†). This is an emergent property due to assembly, because **S1** alone can sense only Cu^{2+} , while **S2** alone can sense only Hg^{2+} (Fig. S3 in ESI†). The **S1:S2** display a fluorescence “turn-on”, behavior upon binding to Pb^{2+} . It also offers a ‘naked-eye’ detection of Pb^{2+} as the color of **S1:S2** solution changed from colorless to green after the addition of Pb^{2+} under UV light (Fig. 4a). The Pb^{2+} binding facilitated excimer formation, as evident from the enhancement in intensity of band at 470 nm (Fig. 4b), supporting the close proximity of pyrene-Trp and pyrene-pyrene moieties. Job’s plot and mass spectrometric studies revealed a 1:1 stoichiometry (Figs. S8d and S12c in ESI†.) for the lead complex. Time-resolved fluorescence spectroscopic studies of Pb^{2+} complex of **S1:S2** showed a decrease in the lifetime of the donor with an enhancement in FRET efficiency (Table S6 in ESI†), suggesting that the distance between pyrene and tryptophan decreases as a result of the complexation.¹⁹ The detection limit of **S1:S2** for Pb^{2+} is found to be 2.4 nM with a binding constant of 6.2×10^4 M⁻¹ (Fig. S4 in ESI†.). The ¹H NMR titration (Fig. S15b in ESI†) of **S1:S2** with Pb^{2+} displayed upfield shift for indole NHs (j) and aromatic protons (e+k+l+m+n) presumably as a result of the steric crowding between the indole and the pyrene moieties. The absence of any downfield shift of indole protons strongly suggests that Trp is not taking part in the complexation. The DFT calculations showed that binding of Pb^{2+} to sulfur atoms results in more compact structure of the dimer (Fig. 4c). The CD studies revealed only changes in the signal intensity indicating no major conformational changes upon Pb^{2+} binding (Fig. S7d in ESI†).

Energy minimized structure of **S1:S2** with Pb^{2+} by using B3LYP/6-31G* indicated that the four sulfur atoms bind to metal ion with an average -S- Pb^{2+} - distance of 2.9 Å to form

a distorted square planar complex (Fig. 4c). The extended conformation (conformer 2) of **S1** changes to folded conformation (conformer 1) when Pb^{2+} binds to **S1:S2**. In **S1:S2**, the distance between the sulfur atoms of **S1** and **S2** is ~ 6.3 Å which got compressed to 4.2 Å as a result of binding with Pb^{2+} (Fig. 4c). The Pb^{2+} binding leads to significant reduction in the indole-pyrene and pyrene-pyrene distances facilitating FRET, and excimer formation.

Conclusion

In conclusion, we report three cystine-based systems **S1**, **S2** and **S3** for the selective detection of Cu^{2+} , Hg^{2+} and Cd^{2+} ions. We also demonstrated the supramolecular system **S1:S2** formed from **S1** and **S2** can selectively detect the Pb^{2+} by fluorescence 'turn on' behavior through a FRET mechanism. The formation of **S1:S2** was supported by UV, CD, ITC, SEM, DSC and by mass spectrometric methods. The experimental observations were rationalized by DFT studies. The emergent property of **S1:S2** to bind Pb^{2+} is a noteworthy finding. The demonstrated cystine-based systems open up strategies for the construction of novel supramolecular systems for various sensing applications.

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Notes and references

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[†] Electronic Supplementary Information (ESI) available: Experimental details for synthesis of **S1**, **S2** and **S3**, absorption and fluorescence spectra, HRMS, ^1H and ^{13}C NMR spectra. ITC and DFT calculations for **S1:S2**. See DOI: 10.1039/b000000x/

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