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Anthracene possessing amide functionality as a *turn-on* fluorescent probe for Cu^{2+} and Zn^{2+} ions

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ABSTRACT

An anthracene appended PET chemosensor, anthracene-9-carboxylic acid (3,4-dimethoxy-phenyl)-amide (**A**₁), has been synthesized through condensation of corresponding acyl chloride and 3,4-dimethoxyaniline containing C=O and NH as receptors. The sensor **A**₁ exhibited selective fluorescence *turn-on* behavior towards Cu²⁺ and Zn²⁺ ions in CH₃CN. Cu²⁺ ions displayed 18-fold enhancement ($\Phi = 0.006 \rightarrow 0.071$) in the fluorescence spectrum of **A**₁, which are otherwise well known for fluorescence quenching phenomenon. Moreover, **A**₁ could easily discriminate between Zn²⁺ and Cd²⁺ ions, the two metal ions of similar nature. The Job's plots analysis determined 2:1 (**A**₁:Cu²⁺/Zn²⁺) stoichiometry between the sensor **A**₁ and Cu²⁺/Zn²⁺ ions. The LOD values were calculated to be 1.75 and 3.08 μ M for Cu²⁺ and Zn²⁺, respectively.

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Chemosensor; turn on; amide sensor; PET



1. Introduction

Metal ion recognition is an important area of research in supramolecular chemistry on account of relevance in biological, environmental and clinical areas [1]. Of various metal ions, Zn^{2+} ion is of immense importance for processes occurring in the human body and is the second most abundant transition metal ion after iron [2]. It plays

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significant roles in various pathological and physiological processes such as apoptosis, catalytic co-factor in enzymatic reactions, regulation of gene expression and neurological signal transmission making it an essential trace element [3–6]. Abnormal levels of Zn^{2+} ions in a human body is associated with disruption of the ongoing metabolic processes responsible for various neurological disorders, Parkinson's disease and Alzheimer's disease, hypoxia ischemia, epilepsy, *etc.* [7–11]. Numerous fluorescence based chemosensors for Zn^{2+} ion have been reported. However, it is still a challenge for detecting Zn^{2+} ions without interference of similar transition metal ions such as Cd^{2+} [12, 13]. Similarly, Cu^{2+} is the third essential metal ion in the human body after Zn^{2+} ions, playing roles of cofactor in various enzymes, cytochrome c oxidase, superoxide dismutase, tyrosinase, galactose oxidase and many more [14, 15]. Abnormal amounts of Cu^{2+} disrupt the normal functioning of enzymes, affecting kidney, liver and neurological disorders [16].

Anthracene fluorophore has been extensively used as a signaling unit in the fluorescence based chemosensors mainly for detection of metal ions and anions because of its high emission properties. Absorbance and colorimetric based recognition in this case are less, which might be because of difficult perturbations of the ground state of the anthracene π -electron cloud [17–22].

In this work we have synthesized an amide (A_1) incorporating anthracene fluorophore with oxygen-rich dimethoxybenzyl moiety through semi-rigid amide functional groups acting as a conjugating spacer. The sensor displayed efficient sensing ability in detecting Cu²⁺ and Zn²⁺ ions. This is a rare example, where addition of paramagnetic Cu²⁺ ions result in fluorescence enhancement by 18-fold.

2. Experimental

2.1. Materials and instrumentation

All chemicals and solvents were procured from Aldrich and used without purification. Solvents were purchased from Avra synthesis and dry-distilled following the standard purification methods. Stock solutions of metal perchlorates (Na⁺, K⁺, Mg²⁺, Al³⁺, Mn²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺ and Hg²⁺) were prepared in double distilled water. For carrying out UV-vis. and fluorescence experiments, distilled CH₃CN was used as solvent. All experiments were carried out at room temperature (298 K). UV-vis spectra were recorded on a Shimadzu UV-240 spectrophotometer. Fluorescence spectra were scanned on a Hitachi F–7000 equipped with 220–240 V Xe-lamp with a quartz cuvette of 1.0 cm path length. FT-IR spectra were recorded on a Slico FT-IR spectrophotometer from 4000-500 cm⁻¹. ¹H NMR spectra were recorded on a Bruker Advance II spectrometer operating at 400 MHz in CDCl₃ using trimethylsilane as internal reference and 13C NMR were collected at 100 MHz.

2.2. General procedure for spectroscopic measurements

Stock solutions of A_1 (10⁻² M) and metal ions (10⁻¹ M) were prepared in DMSO and de-ionized water, respectively. All metals were added as their perchlorate salts for the UV-vis. and fluorescence experiments. The solutions were allowed to stand



Scheme 1. Synthetic protocol for preparation of sensor A1.

undisturbed for two hours before carrying out optical studies. In fluorescence, the excitation wavelength (λ_{ex}) was 370 nm along with 5.0 nm of excitation and emission slit widths. The association constants were calculated using the Benesi-Hildebrand equation and LOD values were calculated using formula $3\sigma/s$, where σ is standard deviation and s is slope of titration curve between absorption/fluorescence intensity and concentration of ion [23, 24].

2.3. Synthesis of anthracene-9-carboxylic acid (3,4-dimethoxy-phenyl)-amide (A₁)

The procedure for synthesis of A_1 is outlined in Scheme 1. Initially acyl chloride 1 was synthesized by taking 9-anthracene carboxylic acid (0.8 gm, 3.8 mmol) and one drop of N,N-dimethylformamide in 3 ml of thionyl chloride in a vacuum dried two neck round bottom flask. After the reaction was complete (4-5 h), the *in situ* generated HCl was removed with a gas trap apparatus containing KOH pallets and excess of N,N-dimethylformamide was removed by vacuum. This formed acyl chloride (1) was further used without purification.

To a stirring solution of **1** (0.5 g, 2.07 mmol) in dry distilled CH_3CN in a round bottom flask, 3,4-dimethoxyaniline (0.317 g, 2.07 mmol) and K_2CO_3 (0.343 g, 2.48 mmol) were added along with a catalytic amount of TBAHSO₄ (tetrabutylammonium hydrogensulphate). The reaction was monitored via thin layer chromatography and took approx. 6 h to complete. After completion of reaction, the contents of the flask were cooled and filtered. The filtrate was then concentrated and left undisturbed. Light brown crystals of pure **A**₁ were obtained on slow evaporation.

2.4. Characterization of chemosensor A₁

Light brown solid, yield 60%; m.p.: 214-216 °C; **FT-IR** (cm⁻¹) 1656.22 ($v_{C=O}$), 3301.25 (v_{N-H}); ¹**H NMR** (CDCl₃, 400 MHz) δ (ppm): 8.44 (s, 1H, Ar-H) (e), 8.09 (d, 2H, Ar-H, J=8.52 Hz) (c), 7.96 (d, 2H, Ar-H, J=7.64 Hz) (d), 7.6 (s, 1H, amide NH), 7.55 (s, 1H, Ar-H) (e)



Figure 1. Preliminary fluorescence spectral responses in sensor A_1 (20 μ M) in the presence of 100 equiv. of various metal ions in CH₃CN on excitation at 360 and 350 nm, respectively.

H) (f), 7.48-7.40 (m, 4H, Ar-H) (a,b), 7.01 (dd, 1H, Ar-H, $J_1 = 2.24$ Hz, $J_2 = 6.16$ Hz) (g), 6.79 (d, 1H, Ar-H, J = 8.61 Hz) (h), 3.87 (s, 3H, -OCH₃), 3.82 (s, 3H, -OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 167.50, 149.27, 146.21, 131.76, 131.64, 131.10, 128.68, 128.63, 128.09, 127.01, 125.64, 124.97, 111.61, 111.46, 104.64, 56.21, 56.07; **ESI-MS**: m/z (relative abundance (%), assignment) = 358.32 [100, (M + 1)⁺]. ¹H NMR, ¹³C NMR and ESI-MS spectra of **A**₁ are shown in Figures S1–S3.

3. Results and discussion

3.1. UV-vis spectral properties of sensor A₁

The UV-vis. preliminary studies of A_1 (20 µM) towards various metal ions such as Na⁺, K⁺, Mg²⁺, Al³⁺, Mn²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Cd²⁺ and Hg²⁺ were performed in CH₃CN. The absorption spectrum of A_1 exhibited three bands at 345 nm, 362 nm and 382 nm characteristics of anthracene moiety along with a shoulder band at 327 nm, which may be ascribed to n- π^* transitions in the molecule [25]. The addition of 100 equiv. of various metal ions and anions did not show any noticeable changes in the spectrum of A_1 , as shown in Figure S4. This behavior can be attributed to the negligible electronic changes in the ground state of sensor A_1 .

3.2. Fluorescence spectral properties of sensor A₁

The preliminary investigation of fluorescence properties of **A**₁ (20 μ M) towards metal ions were performed in CH₃CN on excitation at 360 nm. The sensor displayed a nonfluorescent behavior ($\Phi = 0.006$) in CH₃CN, probably due to effective PET between anthracene and phenyl ring [26–28]. On addition of 100 equiv. of various metal ions, only Cu²⁺ and Zn²⁺ ions exhibited significant enhancement of fluorescence intensity. All other metal ions resulted in negligible changes in fluorescence spectrum of **A**₁. In the presence of 100 equiv. of Cu²⁺ and Zn²⁺ ions, the fluorescence intensity underwent an increase of 18-fold ($\Phi = 0.071$) and 11-fold ($\Phi = 0.047$), respectively, with emergence of three peaks at 390, 410 and 430 nm corresponding to anthracene



Figure 2. Fluorescence spectra taken in the course of the titration of A_1 (20 μ M) in CH₃CN with (a) Cu²⁺ ions and (b) Zn²⁺ ions; Inset: plot of fluorescence intensity at 390, 410 and 430 nm vs. the concentration of Zn²⁺/Cu²⁺ ions ($\lambda_{ex} = 360$ nm).



Figure 3. Job's plot of A_1 at 410 nm with (a) Cu^{2+} and (b) Zn^{2+} (λ_{ex} 360 nm).

emission spectrum (Figure 1) [29]. Here, addition of Cd^{2+} ions did not display any changes in the spectrum, signifying the discriminating nature of **A**₁ between Zn^{2+} and Cd^{2+} ions, which otherwise share quite similar chemical properties and binding efficiencies [12, 13].

The emission properties of sensor A_1 were evaluated quantitatively by performing its titration with Cu²⁺ and Zn²⁺ ions in CH₃CN. With progressive addition of Cu²⁺ ions (0-5.8 equiv.) to 20 μ M solution of A_1 , the fluorescence intensity increased continuously until the concentration of Cu²⁺ ions reached saturation at ~5 equiv. (Figure 2a). Likewise, the progressive addition of Zn²⁺ ions from 0 to 9.1 equiv. to A_1 resulted in a similar kind of fluorescence *turn-on* response (Figure 2b). The saturation in the titration was attained at ~8 equiv. of Zn²⁺ ions.

The Job's plots revealed 2:1 stoichiometry between A_1 and Cu^{2+}/Zn^{2+} ions as depicted in Figure 3. Based on the Benesi-Hildebrand equation, the association constants were calculated to be 6.32×10^5 and 4.90×10^5 M⁻² for Cu^{2+} and Zn^{2+} ions, respectively (Figures S5a and S6a). The limit of detection values were calculated to be 1.71 and $3.08 \,\mu$ M for Cu^{2+} and Zn^{2+} ions, respectively (Figures S5b and S6b).

3.3. Interference studies of sensor A₁

To investigate the selective nature of sensor A_1 , the interference studies were performed. For this purpose, an array of 10 ml solutions of A_1 (20 μ M) were prepared containing 5/8 equiv. (or 100/160 μ M) of Cu²⁺/Zn²⁺ ions. To each solution, 50/80 equiv.



Figure 4. Interference profile of various metal ions on the fluorescence intensity of (a) $A_1 + Cu^{2+}$ and (b) $A_1 + Zn^{2+}$ (λ_{ex} 360 nm) in CH₃CN.



Figure 5. FT-IR spectra of A_1 and its complexes, A_1 +Cu²⁺ and A_1 +Zn²⁺.

(or 1000/1600 μ M) of each of the different metal ions were added to the solutions separately and kept undisturbed for 15 min before recording the fluorescence spectra. Selective recognition of Cu²⁺/Zn²⁺ by **A**₁ was affected only by the presence of Fe³⁺ ions, which caused ~29% decrease in the fluorescence intensity of solution of **A**₁+Cu²⁺ complex (Figure 4a). In the case of Zn²⁺ recognition, only Fe³⁺ and Cu²⁺ ions perturbed the fluorescence intensity of **A**₁+Zn²⁺ solution by causing 36.9% of decrease and 63% of increase in the fluorescence intensity, respectively, among the various added metal ions, as shown in Figure 4b. The fluorescence quenching caused by Fe³⁺ ions could be considered to result from paramagnetism of Fe³⁺ ions. Number of literature reports points to the deactivation of the excited state by paramagnetic metal ions via a non-radiative quenching process [30, 31].



Scheme 2. Plausible sensing mechanism of Cu^{2+}/Zn^{2+} ions by sensor A₁.

3.4. FT-IR studies

FT-IR spectra were recorded for A_1 and its Cu^{2+}/Zn^{2+} complexes as depicted in Figure 5. The C=O and N-H stretching peaks of A_1 initially present at 1656 and 3301 cm⁻¹ shifted to 1639 and 3038 cm⁻¹, respectively, in the presence of Cu²⁺ ions, while in the presence of Zn²⁺ ions the corresponding peaks shifted to 1638 and 3238 cm⁻¹. These shifts clearly indicated binding of both ions occurred through interaction with C=O group which also affected the strength of the N-H bond of A_1 . Similar interaction can be expected between sensor A_2 and Cu²⁺ owing to structural similarities with A_1 .

3.5. Plausible sensing mechanism

The binding mechanism was investigated via fluorescence titration studies and observing the changes in FT-IR spectrum of A_1 and its complexes with Cu^{2+} and Zn^{2+} ions (Scheme 2). The PET process occurring from 3,4-dimethoxybenzyl group to the excited state of anthracene core in the amide (A_1) was responsible for the fluorescence *turnoff* response. As confirmed from FT-IR data, the Cu^{2+} and Zn^{2+} ions bind through carbonyl O atoms of amide receptors A_1 which might hamper the ongoing PET process and thereby releasing the fluorescence, by which anthracene type fluorescence spectrum was observed in A_1 - Cu^{2+} and A_1 - Zn^{2+} complexes.

4. Conclusion

We have synthesized a new anthracene amide chemosensor A_1 with high binding affinities for Cu^{2+}/Zn^{2+} ions in CH_3CN . The amide sensor was non-fluorescent owing to PET from di-methoxybenzyl ring to anthracene acceptor. However, enhancement in fluorescence intensity was observed after metal ion binding due

to the inhibition of PET occurring in bare sensors. Here, 18-fold fluorescence enhancement was observed with paramagnetic Cu^{2+} ions, which are known for fluorescence quenching. Also, sensor **A**₁ could discriminate two chemically similar Zn^{2+} and Cd^{2+} metal ions.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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