



UNIVERSITÀ
DEGLI STUDI
DI UDINE

Università degli studi di Udine

Differential Metal Ion Sensing by an Antipyrine Derivative in Aqueous and β -Cyclodextrin Media: Selectivity Tuning by β -Cyclodextrin

Original

Availability:

This version is available <http://hdl.handle.net/11390/1192413> since 2020-11-04T10:21:50Z

Publisher:

Published

DOI:10.1021/acs.analchem.8b03810

Terms of use:

The institutional repository of the University of Udine (<http://air.uniud.it>) is provided by ARIC services. The aim is to enable open access to all the world.

Publisher copyright

(Article begins on next page)

Differential Metal Ion Sensing By An Antipyrine Derivative In Aqueous And β -Cyclodextrin Media: Selectivity–Tuning By β -Cyclodextrin†

G. Tamil Selvan,¹ P. Sumathi,² P. Mosase Selvakumar,¹ Israel V. M. V. Enoch,^{1*} Sara Gracia Lanas,³ Andrea Melchior^{3*}

Author addresses:

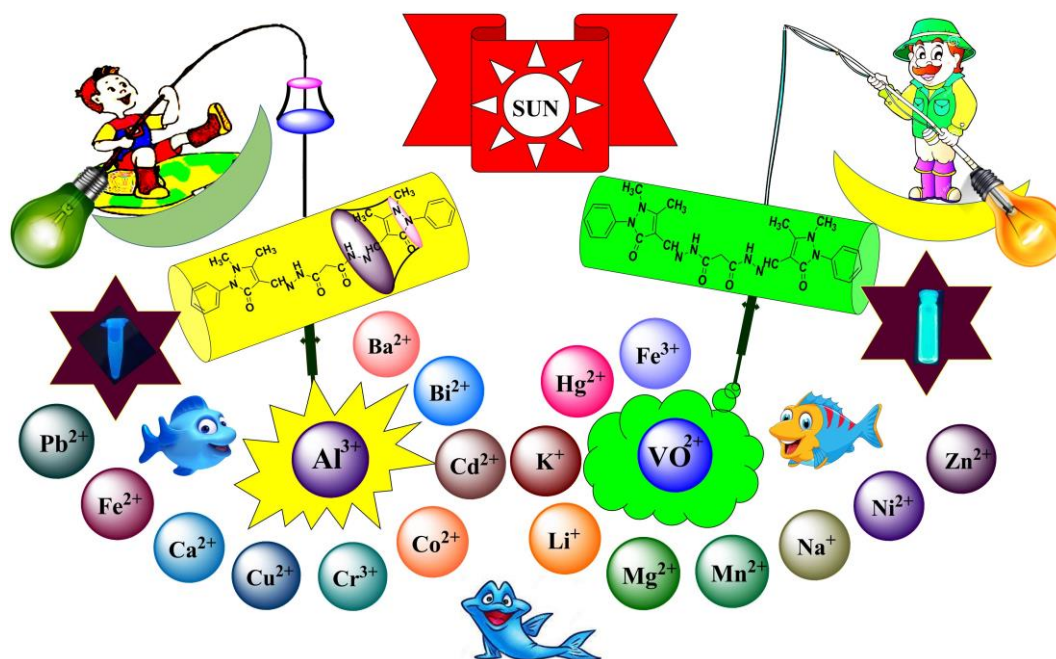
¹Chemistry Research Lab and Nanotoxicology Research Lab, Karunya Institute of Technology & Sciences, Coimbatore 641114, Tamil Nadu, India.

²Department of Chemistry, Muthayammal College of Arts and Science, Namakkal District, Tamil Nadu, India.

³University of Udine, Polytechnic Department of Engineering, Chemistry Laboratories via del Cotonificio 108, 33100 Udine, Italy.

*Corresponding authors, E-mail addresses: drisraelenoch@gmail.com (IVMVE); andrea.melchior@uniud.it.

Abstract



Introduction

Cyclodextrins (CD) are cyclic oligosaccharides shaped as a hollow truncated cone with a hydrophilic outer surface and lipophilic inner cavity. This structure allows CDs to interact with hydrophobic guests and ultimately to increase their solubility in water. This features make CDs useful in a variety of applications, in particular they have been used as drug delivery vectors.¹ Furthermore, cyclodextrins find application as supramolecular devices metal ion sensing has been explored.²⁻⁴ Enhancement of sensing and improvement of the metal ion detection limit have been reported.²⁻⁴ One of the most common cyclodextrins, β -cyclodextrin, is known to alter the fluorescence emission of complexed guest molecules. Fluorescence enhancement is the most observed property on such host–guest complex formation, whereas quenching of fluorescence also is scarcely reported.⁵⁻⁸

Knowing the exact structure of the host–guest complex is of paramount importance in understanding the alteration of the physicochemical properties and the spectroscopic behavior of the guest molecules. Also, since the binding constants and the thermodynamic parameters of the interaction of a guest with CDs are also of great importance for understanding the phenomena of molecular recognition. To this purpose isothermal titration calorimetry (ITC) has been previously demonstrated to be a powerful tool in the investigation of β -CD-guest interaction.⁹

Several Al(III) sensors have been reported in the literature.¹⁰⁻¹³ Contrary to this, reports on vanadyl sensors are very rare with the first one published in 2018.¹⁴ Aluminum has connection with Alzheimer's disease, possibly influencing the formation of amyloid fibrils.¹⁵ In agriculture, the release of aluminum ions from acidic soils is toxic to plant roots.¹⁶ Vanadyl compounds, after absorption via gastrointestinal track, enter into the blood stream and bind to transferrin forming binary complexes.

Antipyrines are popular fluorescent probes and have frequently been employed as fluorescent chemosensors.^{19–21} In this work, the binding of an antipyrine derivative (compound **1**, Scheme 1) to β -CD is studied by means of fluorescence titration, ITC, NMR spectroscopy and theoretical calculations. Then, the sensing of a series of metal ions by the supramolecular β -CD complex of the compound is reported.

Experimental

Chemicals

4-Aminoantipyrine carboxaldehyde was purchased from Aldrich, India. The solvents viz., chloroform, methanol, dimethylformamide were the products of Merck. Ethanol (99%) was used as received from Aldrich. The solvents were dried and distilled from drying agents under an inert atmosphere prior to use. All inorganic salts used were of analytical grade. Twice-distilled water was used throughout all experiments. Phosphate buffer solutions were prepared by mixing appropriate amounts of o-phosphoric acid and sodium hydroxide solution under adjustment by a pH meter.

Compound characterization

FT-IR spectra were recorded in the range of 4000–500 cm^{-1} at a resolution of 4 cm^{-1} using KBr pellets (1% w/w) on a Prestige 21 Shimadzu FT-IR spectrophotometer. Mass spectrometric analysis was performed using an electron spray ionization (ESI) technique on a waters Q ToF–micro mass spectrometer. ^1H NMR spectra were recorded in appropriate deuterated solvents on a Bruker Varian Inova 300 MHz FT-NMR spectrometer. Chemical shifts for proton resonances are reported in ppm (δ) relative to tetramethylsilane.

Synthesis of Compound 1

N'-1,N'3-bis((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl)methylene)malonohydr- azide (Compound **1**): A condensation reaction was carried out by adding a methanolic solution of malanohydrazide (0.13212 g, 0.001 mol) to 4-antipyrine carboxaldehyde (0.43248 g, 0.002 mol) and heating at 60 °C. The reaction mixture turned into dark yellow color and it was stirred for 4 hours. A yellow precipitate was obtained (Yield: 89%). Formula C₂₇H₂₈N₈O₄ (C-61.35, H-5.34, N-21.20, O-12.11) ¹H NMR:(δ , DMSO) 9.6 (s, CH=N, 2H), 7.49-7.81 (m, Ar-phenyl, 8H), 7.31–7.42 (m, Ar, 4H) 3.48–3.79 (s,CH₂, 2H), 3.20–3.39 (s, -N-Me, 6H), 2.44–2.59 (s, -C-Me, 6H) ¹³C-NMR: (δ , DMSO) 183.51 ppm (C=O), 163.39 ppm (N-C=O), 153.16 ppm (CH=N), 152.13 ppm (C-CH₃), 133.35 ppm (C-N),127.42–129.39 ppm (C=C, Ar, ring), 100.48 ppm (C-C), 46.9 ppm (C-C=O) 34.29 ppm (N-CH₃) 12.05 ppm (C-CH₃) IR: (KBr, cm⁻¹) 3511–3360 (m, N-H Stretch), 1660 (m-C=O stretch), 1575 (C=N), 1481 (C-C), 1342 (C-N), 752 (C-H) ESI-MS, m/z for C₂₇H₂₈N₈O₄ (M+H)⁺, 529. UV-Vis: (DMF, λ_{max} , 310 nm).

UV-vis and fluorescence spectroscopy

UV–visible and fluorescence spectra were recorded using a double–beam Jasco V630 spectrophotometer and a Jasco FP-8300 spectrofluorometer respectively. To record the spectra, cuvettes of path length 1 cm were used. The spectrofluorometer used a 120 W Xenon lamp as the excitation source and the excitation and emission bandwidths were fixed at 5 nm. pH was measured using an Elico LI 120 (India) pH meter. The absorption spectra were recorded against appropriate reference solutions which did not contain the compound.

The Compound **1** (0.0052 mg, 0.001 mmol) was diluted in solution of DMF. Test solutions of various concentrations were prepared (1×10^{-5} , 2×10^{-5} , 3×10^{-5} , 4×10^{-5} , and 5×10^{-5} mol

dm⁻³). After shaking the standard measuring flask for a few minutes, UV-vis and fluorescence spectra were recorded for these samples at room temperature.

Metal ion binding - Compound **1** (0.0052 mg, 0.001 mmol) was dissolved in DMF (dimethylformamide, 10 ml). 100 µl of the solution was diluted to 10 ml using water pH=7.0) to make the final concentration of 1×10^{-5} mol dm⁻³. The solutions of various cations (100 µl, 0.001 mmol) were transferred into the solution of the receptor (1×10^{-5}) prepared as mentioned above. UV-vis spectra and fluorescence were recorded at room temperature.

Solvatochromism- Compound **1** (0.0052 mg, 0.001 mmol) was prepared using various solvents (DMF, Water, Chloroform, Ethanol, and Methanol) and made up to 10 mL. After shaking the standard measuring flask for a few minutes, UV-Vis and fluorescence spectra were recorded at room temperature. Fluorescence images were recorded using a laser scanning confocal microscopy (Nikon Eclipse TS100).

2D-NMR

The 2D-ROESY spectrum (**1**-β-CD complex) was recorded on a Bruker AV III spectrometer. The operating frequency was 500 MHz, and the solvent used was deuterated water after sonication of the solution. The mixing-time ROESY spectrum was 200 ms under spin lock conditions.

Isothermal titration calorimetry

Isothermal titration calorimetry (ITC) experiments have been carried out at 298.15 K using a TAM III thermostat (TA Instruments) equipped with a nanocalorimeter (1 mL cell volume) and an automatic titration syringe. The sample (V = 0.7 mL) was stirred continuously at 90 rpm. Reagents were dissolved in milliQ water with 3% DMSO. In a typical experiment,

solutions of Compound **1** ($C_{\text{Compound 1}} = 3.0$ and 2.4 mM) were titrated with β -CD ($C_{\beta\text{-CD}} = 22.9$ mM). The reference cell was filled with 0.8 mL of the same solvent. Titrations were carried out in duplicate.

Dilution heat (q_{dil}) was also determined to correct the total heat measured (q_{meas}) by the instrument. Thereby $q_{\text{cum}} = q_{\text{meas}} - q_{\text{dil}}$, represents only the heat involved in the association reaction. Data analysis has been done within the MS-Excel using Solverstat and EST utilities.^{22,23}

Computational details

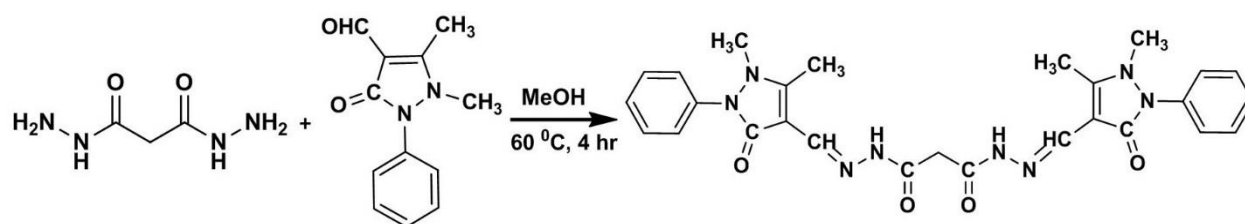
The Compound **1**- β -CD interaction has been characterized by means of quantum chemical calculations. Both the inclusion and the external-interaction complex have been studied. Geometries have been optimized at PM6 level²⁴ and then the interaction energy has been calculated at DFT level employing the B3LYP functional^{25,26} including the D3 version of the Grimme's empirical dispersion correction²⁷ along with a 6-31+G(d,p) Gaussian basis set. Interaction energies have been calculated in presence of PCM²⁸ water and for the basis set superposition error (BSSE). All calculations were performed with Gaussian16.²⁹

Preparation of VO²⁺ Complex

To a solution of Compound **1** (0.001 mol) 1 equivalent of vanadyl sulfate solution was added drop by drop at room temperature. The reaction mixture turned pale yellow to dark brown and stirred for 48 hr at room temperature.

Results and discussion

Compound **1** was synthesized by a condensation of 1 mole of malanohydrazide with 2 moles of 4-antipyrine carboxaldehyde in methanol at 60 °C (Scheme 1).



Scheme 1. Synthesis of Compound **1**

The complex formation of **1** with β -CD was followed by UV-visible absorption and fluorescence spectroscopic methods. A spectral titration of **1** (kept at a constant concentration) against incremental addition of β -CD solutions of progressively increasing concentration showed a hypochromic shift of the absorption spectral band at 310 nm. β -CD mobilizes the electrons of the bound molecule of **1**, and the excitable electrons are partially shielded, leading to the changes in the spectrum.³⁰ The shift of wavelength of the absorption band was not appreciable enough, giving indirect evidence that the **1**- β -CD complex was not a tight-fit one. Despite providing first evidence of the occurrence of associative interaction, the absorbance data could not be used for determination of the binding constant and the stoichiometry of the **1**- β -CD complex as their spectral changes were small.

The fluorescence spectral titration of **1**- β -CD interaction (Fig. 1A) provided an intriguing result i.e., the quenching of fluorescence of **1** by β -CD. Quenching phenomena arising due to the interaction of CDs with fluorophores have been previously reported.³¹ Specific interaction of the lone pair of electrons on atoms of the fluorophore and the electron density of β -CD has been considered as the reason for the quenched fluorescence.³² In the present case, we observed a fluorescence quenching along with the splitting of the fluorescence band centered at 375 nm on the interaction with β -CD. As the amount of β -CD increased, the spectral band furcated, along with a clear redshift of the longer wavelength band to 395 nm. This 20 nm

bathochromic shift should occur due to a charge transfer state arising due to the interaction of **1** with β -CD. Such an interaction could lead to deactivation of **1** from the excited state, resulting in a quenching of fluorescence.³¹ The energy gap between the ground and the excited state diminished, probably due to the stabilization of the excited state.³³ The redshift of the band may arise due to the formation of hydrogen bonds involving the hydrogen atoms of the host and the guest molecules.³⁴ The Stern-Volmer plot (Fig. 1B) of the quenching of fluorescence gave a K_{SV} value of $217 \pm (11) \text{ M}^{-1}$ ($\log K_{SV} = 2.34 \pm 0.02$).

The binding process has been studied also by ITC (Fig. 2). The best-fitting binding constant obtained for the equilibrium $\mathbf{1} + \beta\text{-CD} \rightleftharpoons \mathbf{1}\text{-}\beta\text{-CD}$ is $\log K = 2.09 \pm 0.04$ ($\Delta G = -11.9 \text{ kJ mole}^{-1}$) in good agreement with the $\log K_{SV}$ value. Moreover, the ΔH value of $-2.17(5) \text{ kJ mole}^{-1}$ confirms the formation of a weak complex. The $\mathbf{1} : \beta\text{-CD}$ (1 : 2) species was discarded by the fitting software. The obtained positive ΔS value of $+32.6 \text{ J mole}^{-1} \text{ K}^{-1}$, related to the desolvation of the reagents^{35–37} due to the complex formation and the negative ΔH are often found for cyclodextrin-drug interactions.³⁸

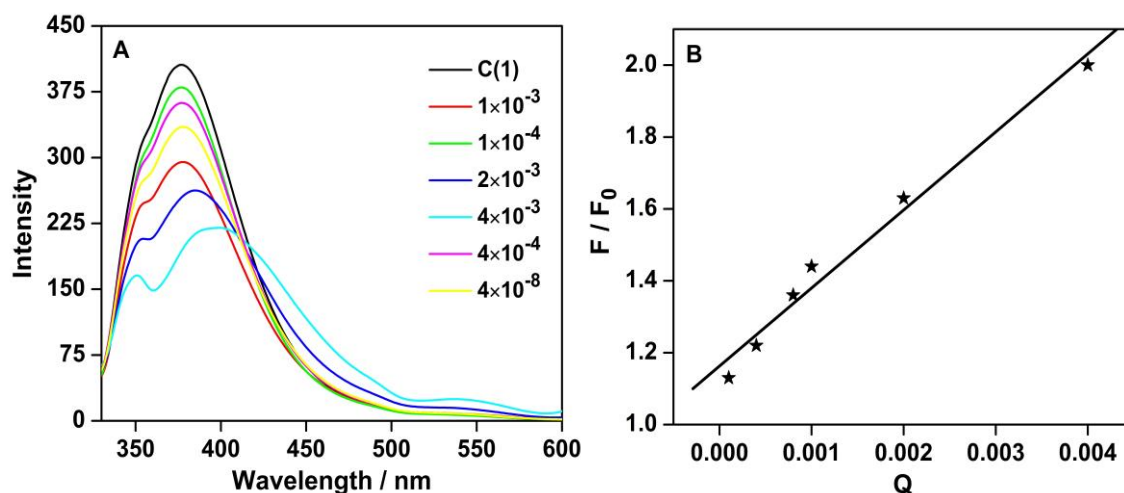


Fig. 1. (A) Fluorescence Spectra of **1** with various concentrations (mol dm^{-3}) of β -CD. (B) Stern-Volmer quenching plot of the interaction of **1** with β -CD (1: 1).

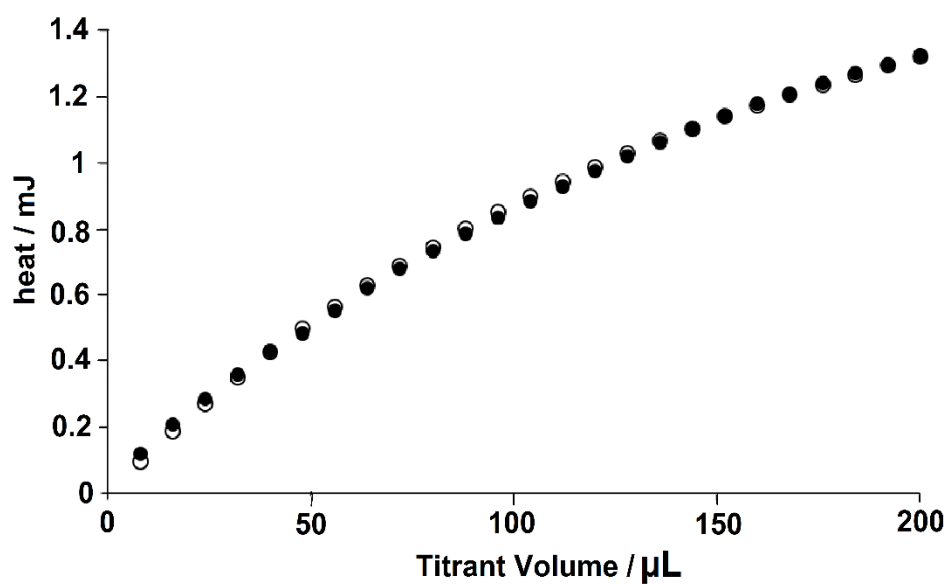


Fig. 2. Total observed (empty circles) and calculated (full circles) heat evolved during the titration of **1** ($C_1 = 2.4 \text{ mM}$) with β -CD ($C_{\beta\text{-CD}} = 22.9 \text{ mM}$). Here, the positive sign stands for an exothermic reaction.

To gain information on the mode of binding of **1** to β -CD, we recorded a 2D ROESY spectrum of the **1**- β -CD complex in D_2O (prepared as a solid by mixing equimolar amounts

of **1** and β -CD and evaporating water, re-dissolving the solid complex for making test solution of concentration 1×10^{-5} M). 2D NMR experiment aids deriving reliable information about the proximity of the protons of the binding molecule and those lining the rims of β -CD through displaying cross peaks. The ROESY spectrum displayed NOE cross-peaks between the H-5 protons of the glucopyranose rings of β -CD and the methyl protons (C-CH₃) of **1** (marked with circles in Fig. 3). This suggested the close proximity of the methyl protons of the guest molecule **1** and the H-5 protons which are lined at the cavity of β -CD. Hence, the **1**- β -CD complex was formed by the encapsulation of **1** by sliding of β -CD molecule about the axis of **1**. It was noteworthy that the aromatic region of the spectrum was completely free of any NOE correlations, meaning that the β -CD molecule did not interact with the phenyl rings of **1** through inclusion complexation. The stoichiometry of 1:1, inferred from the fluorescence spectra, and the cross-peaks obtained from ROESY suggested the structure of the **1**- β -CD complex as depicted in Scheme 2.

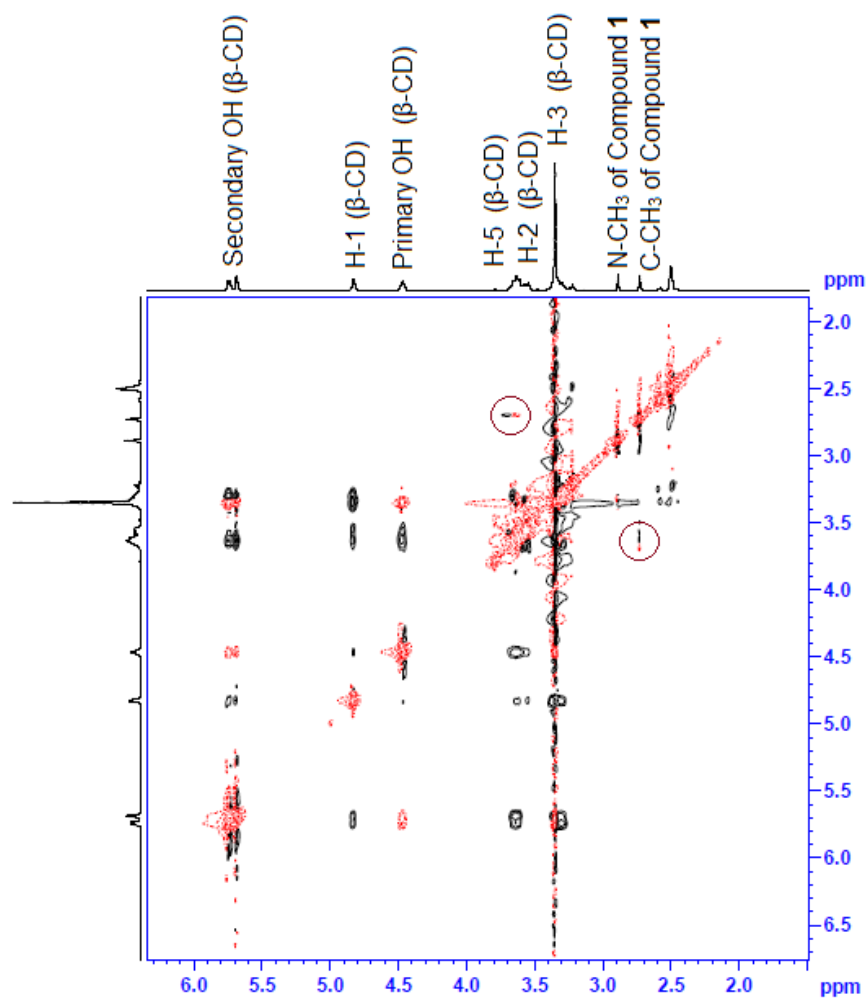
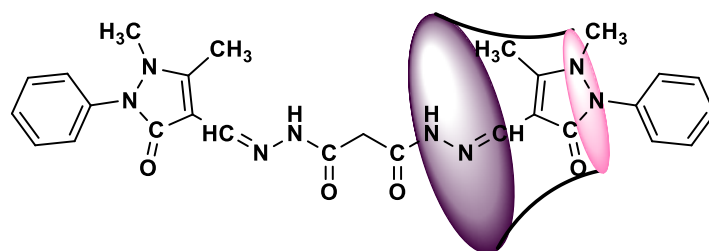


Fig. 3. Partial 2D ROESY spectrum showing the complex formation of Compound **1** with β -CD.



Scheme 2. Schematic representation of the complex formed between **1** and β -CD.

The minimum energy structures of the interaction energies of the **1**- β -CD complexes are reported in Fig. 4 and the interaction energies ($E_{\text{int}} = E(\mathbf{1}\text{-}\beta\text{-CD}) - E(\mathbf{1}) - E(\beta\text{-CD})$) are in Table 1. It is evident from the structures in Fig. 1 that the **1**- β -CD interaction is assisted by

inter-molecular hydrogen bonds between the central carbonyl oxygen atoms and the OH groups of the ring. Moreover, the interaction energies show that the inclusion complex is largely energetically favored.

Table 1. Interaction energies for the inclusion and external **1**- β -CD (kcal mol⁻¹).

	E _{int}	
	gas phase	water
Internal	-38.7	-24.7
External	-24.5	-11.8

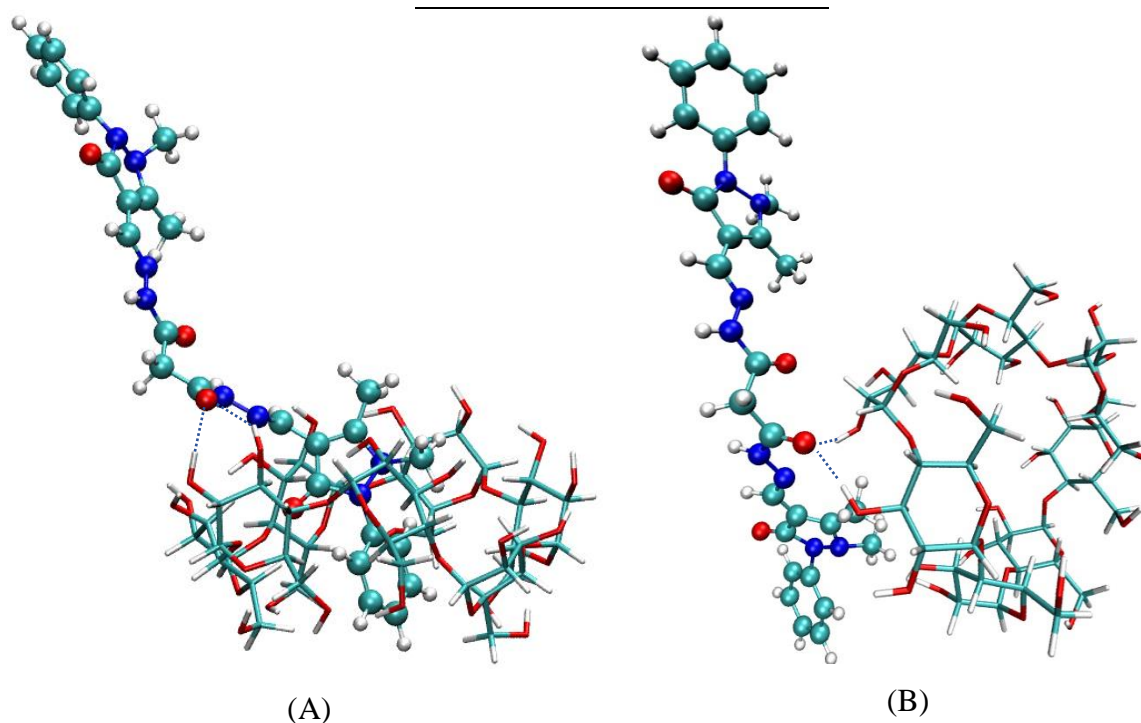


Fig. 4. Minimum energy structures of the (A) inclusion and (B) external **1**- β -CD complex. Intermolecular hydrogen bonds are shown as dotted lines.

Metal ion sensing by Compound 1 in aqueous medium

The UV-Visible spectral responses of **1** for various metals ions in the pool of Li^+ , Na^+ , K^+ , Ca^{2+} , Ba^{2+} , Mg^{2+} , Pb^{2+} , Cd^{2+} , Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Zr^{3+} , Hg^{2+} , VO^{2+} , and Al^{3+} were studied in water containing 1% methanol ($\text{pH} = 7.4$). The spectral changes could not allow any particular metal ion to stand out by influencing the absorption band dramatically of **1**, albeit different metal ion-added spectra were different in terms of absorbance and hence the molar extinction coefficients. For reasons which will become clear later, it needs to be stated here that the addition of either VO^{2+} or Al^{3+} does not affect the absorption band significantly (Fig. 5A).

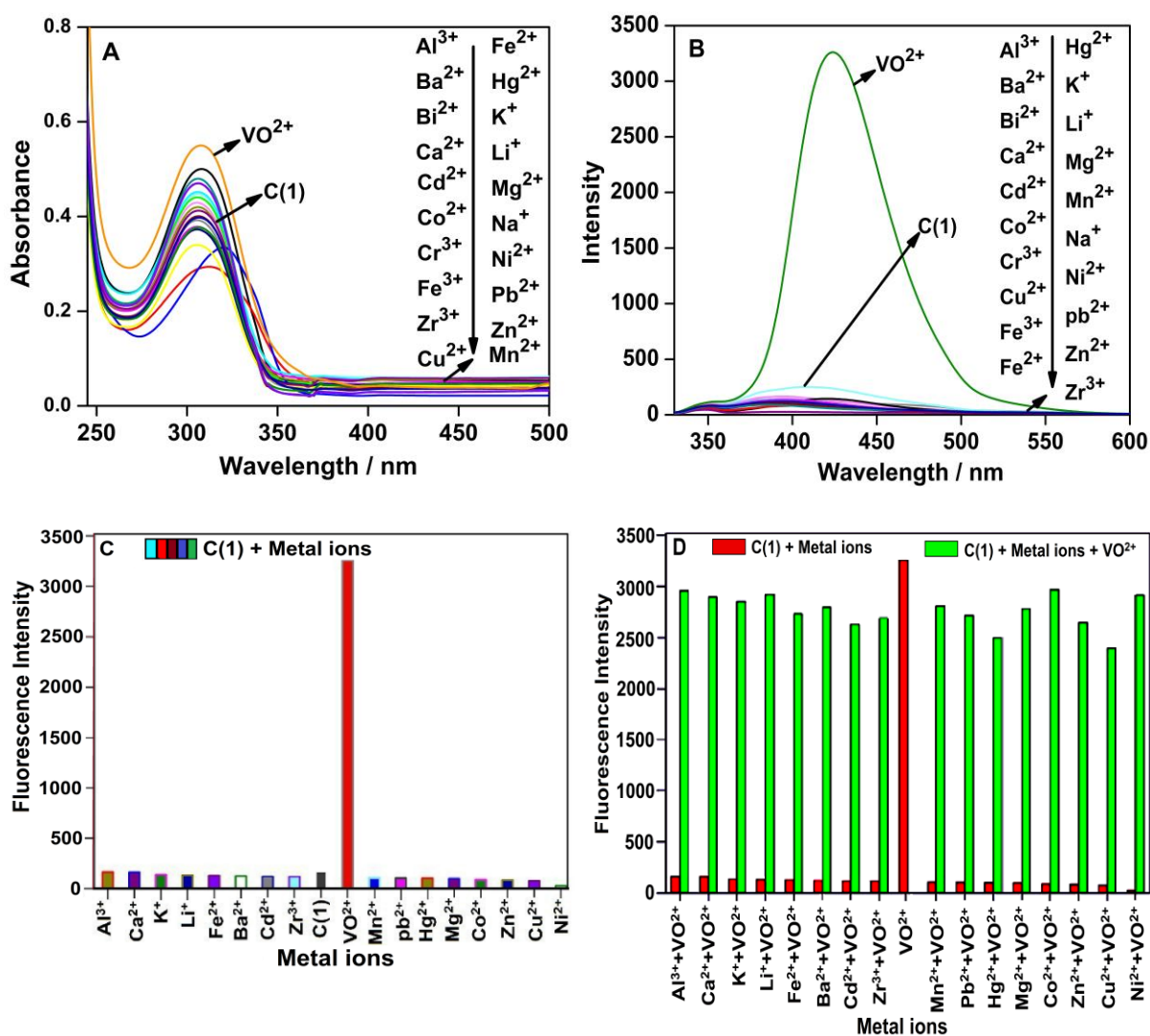


Fig. 5. (A) UV-vis spectra of **1** with various metal ions. (B) Fluorescence Spectra of **1** with various metal ions. The concentrations of the metal ions, **1**, and β -CD are 1×10^{-5} M. (C) Fluorescence response of Compound **1** with various metal ions. (D) Competitive binding of VO^{2+} to **1** in the presence of other metal ions.

The fluorescence spectrum of **1** shows two emission bands viz., 352 and 390 nm (Fig. 5B). The bands are weaker before the addition of any metal ion. Addition of VO^{2+} ions into **1** leads to nearly a 15 times enhancement of fluorescence of the longer wavelength (425 nm)

band. Contrary to the result, the other metal cations did not influence the fluorescence of **1**. The result revealed a high VO²⁺ reflectivity of **1**, facilitating the molecule to behave as a chemosensor for VO²⁺ ions in water (1% methanol). The 1:1 stoichiometry of the **1**–VO²⁺ complex was determined from the linear double reciprocal plot (see Supporting Information, SI 1A) following the Benesi–Hildebrand equation.³⁹ The association constant of the bound **1**–VO²⁺ structure is $4.96 \times 10^{-2} \text{ M}^{-1}$. Further, the stoichiometry of the binding of **1** to VO²⁺ was examined by the continuous variation method of mole fraction (Job's plot, see SI 1B),^{40,41} again normalizing the measured quantities to their maximum value. The Job's plot shows a maximum intensity at a mole fraction of 0.5, which corresponds to the 1:1 complex formed between **1** and VO²⁺ ion.

The fluorescence response of **1** ($1 \times 10^{-5} \text{ mol dm}^{-3}$) to the various metal ions ($\lambda_{\text{ex}} = 310 \text{ nm}$) are shown in the bar diagram in (Fig. 5C). The short bars show the drastic differences in the intensity of fluorescence of various metal ion–added **1** compared to the tall bar corresponding to the VO²⁺–bound **1**. A testing on the possible interference of the metal ions to the **1**–VO²⁺ binding was done by adding VO²⁺ ions to **1** having the each of the other metal ions. The bar chart in (Fig. 5D) shows the competitive binding of VO²⁺ to **1** in the presence of other metal ions. Addition of VO²⁺ enhanced the fluorescence of **1** showing that the former bound more efficiently and competitively to the latter. This result indicated that **1** could function as a chemosensor of VO²⁺ ions. The lower limit of detection (LOD) of the VO²⁺ ions by **1** was determined to be $5 \times 10^{-8} \text{ M}^{-2}$ (for the plot showing the linear range of detection and the calculation of LOD, see S4).

Metal ion sensing by compound **1** in β -CD

To determine the effect of the presence of β -CD on the metal ion selectivity by **1**, we carried out experiments on the metal ion binding in a fashion similar to those discussed in the previous section, but for **1** (1×10^{-5} mol dm⁻³) in the presence of the added β -CD (1×10^{-5} mol dm⁻³), since the encapsulation of **1** by β -CD partially shielded the guest molecule, it intrigued us to know further the possibility of metal ion interaction with the latter.

The UV-visible spectra of the **1**- β -CD complex in presence of the various metal ions are depicted in Fig. 6A. In this case, Al³⁺ ions were observed to markedly enhance the absorbance of **1**, leading it to stand out amidst the other metal ion in the spectral behavior. The VO²⁺ ions did not affect the absorption spectrum significantly.

The fluorescence response of **1**, on the other hand, was even more pronounced than that of absorption. (Fig. 6B) Addition of Al³⁺ to **1**- β -CD enhanced the fluorescence nearly 25 times in intensity than that of free **1**- β -CD. Of the other metal ions added to **1**- β -CD, viz., Li⁺, Na⁺, K⁺, Ca²⁺, Ba²⁺, Mg²⁺, Pb²⁺, Cd²⁺, Mn²⁺, Fe²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Zr²⁺, Hg²⁺, and VO²⁺, except Ba²⁺, the rest of the cations quenched the fluorescence. The slightly enhanced fluorescence of Ba²⁺-added **1**- β -CD was also not significantly different from the fluorescence response of pure **1**- β -CD in solution. Hence, quite unequivocally, the β -CD complex shows Al³⁺ ion selectivity as opposed to the VO²⁺ selectivity of the free ligand **1** in water. The stoichiometry of the **1**- β -CD-Al³⁺ complex was determined as 1:2 from the Job's plot, made using the mole fraction of Al³⁺ and the fluorescence response of **1**- β -CD-Al³⁺ as the inflection point was observed at the mole fraction of **1**. The association constant of the Al³⁺ complex of **1**- β -CD in the equilibrium $\text{Al}^{3+} + \text{1-}\beta\text{-CD} \rightarrow \text{Al}^{3+}\text{-1-}\beta\text{-CD}$ was determined as $5.3 \times 10^4 \pm 0.8 \text{ M}^{-2}$, from the Benesi-Hildebrand plot shown in (Fig. 6C). Hence, the β -CD molecule

redirects the metal-ion selectivity and the stoichiometric binding of metal ion to **1**. The lower limit of detection of Al^{3+} by **1**- β -CD was $5 \times 10^{-7} \text{ M}^{-2}$ (see S5)

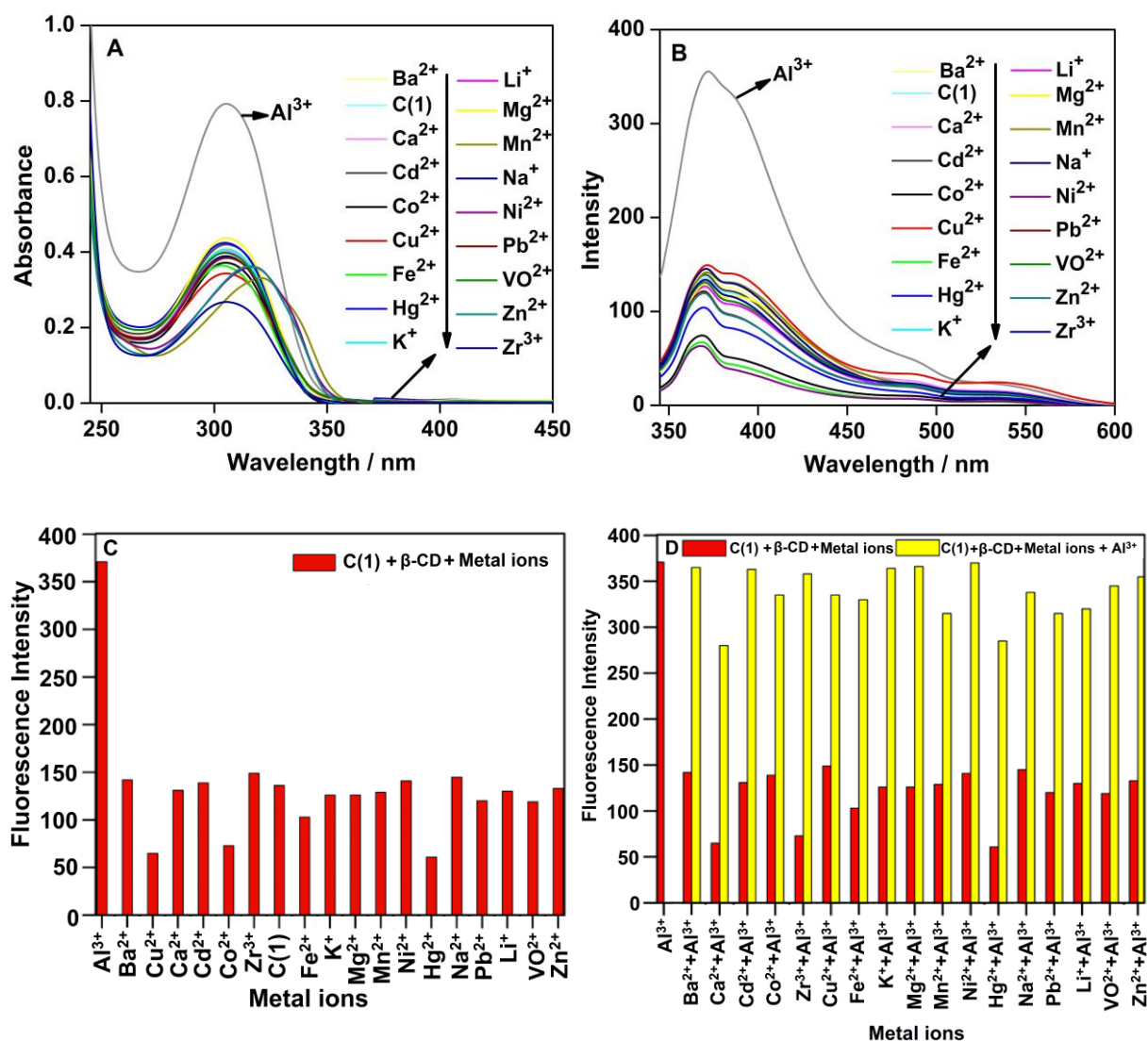


Fig. 6. (A) Absorption Spectra of **1** with various metal ions in β -CD Solution. (B) Fluorescence Spectra of **1** with various metal ions in β -CD Solution. (C) and (D) show respectively the bar diagrams revealing the intensity differences of fluorescence of various metal ion-added **1**- β -CD and the competitive binding of Al^{3+} to **1**- β -CD amidst other metal ions.

Mode of binding of metal ions

Compound **1** acts as a VO^{2+} ion sensor in water (1% methanol) and as an Al^{3+} ion sensor in aqueous β -CD. Molecular encapsulation might modulate the metal chelation center of the ligand. As discussed in the complex formation of **1** with β -CD, the β -CD molecule masked the $-\text{COCH}_2\text{CO}-$ moiety of **1**, and hence, the carbonyls could not participate in the chelation of metal ions. The IR spectra of the compound **1** and the **1**- VO^{2+} complex are shown in (Fig. 7A). The ligand shows C=O str. at 1660 cm^{-1} and the C=N str. at 1575 cm^{-1} . The bands appear red shifted on chelation of vanadyl ions by the ligand. The intensities are also enhanced. These results suggest an occurrence of the polarization of electron density from the carbonyl to the vanadyl ion. New bands appear in the fingerprint region and the 510 cm^{-1} band corresponds to the oxygen–vanadyl bond in the metal complex. Similarly, the IR spectra of the **1**- β -CD structure and the **1**- β -CD- Al^{3+} complex are shown in (Fig. 7B). The C=O and the C=N stretching modes are diminished in intensity, and the band position is slightly shifted to a longer frequency. There is also the appearance of O–Al bond in the metal ion complex of **1**- β -CD at 625 cm^{-1} . Hence, it can be inferred that the VO^{2+} ions interact with **1** when the latter is in free form and Al^{3+} when in its β -CD-bound form. The C=O and the C=N bonds are not strongly chelating Al^{3+} in the presence of β -CD, although the free compound forms a stronger complex with VO^{2+} ions. The β -CD molecule is found to interact with the C=O and the C=N bonds of **1**, as observed from the intensity changes of these bands of **1**- β -CD. This provides evidence that the differential binding of **1** with metal ions is due to the influence of β -CD at the chelation center.

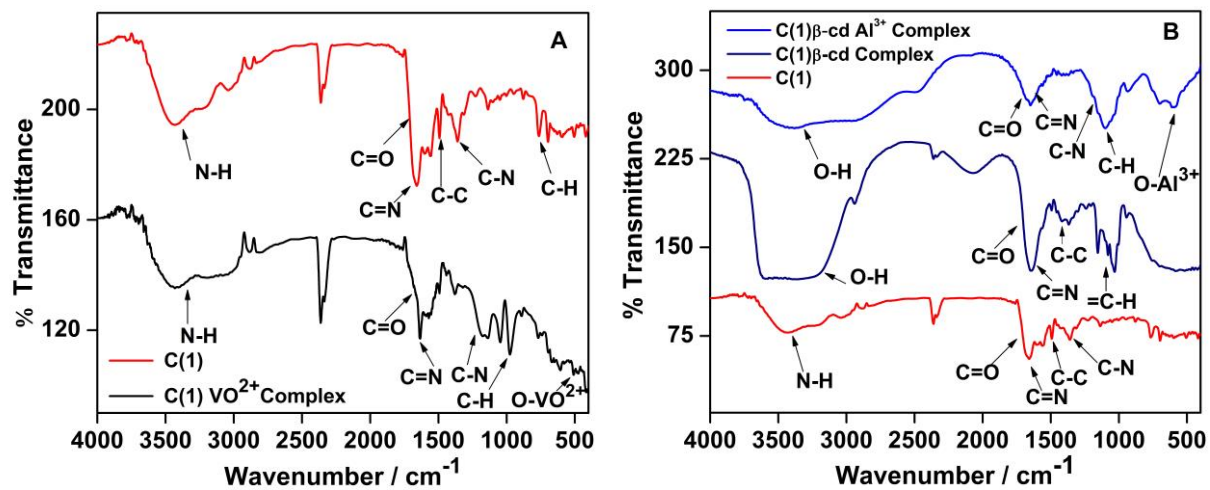
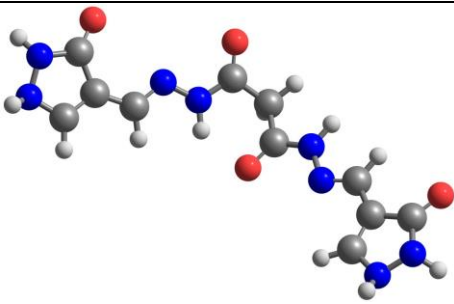
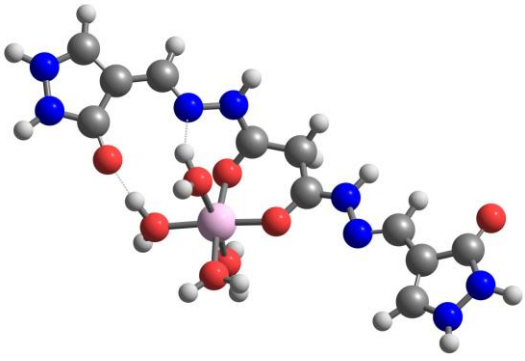


Fig. 7. (A) IR spectra of Compound **1** and **1**-VO²⁺ Complex, (B) IR spectra of Compound **1**, **1**- β -CD Complex and **1**- β -CD-Al³⁺ Complex.

Figure x. DFT optimized structures of **1** and the relative complexes with Al^{3+} and VO^{2+} .

C=O vibrations (cm^{-1})	C1
1804, 1786, 1778, 1747	
	$\text{Al}^{3+}\text{-C1}$
1819*,1725*,1706,1650,1624, 1.594,1.587	

*C=O of the heteroaromatic ring.

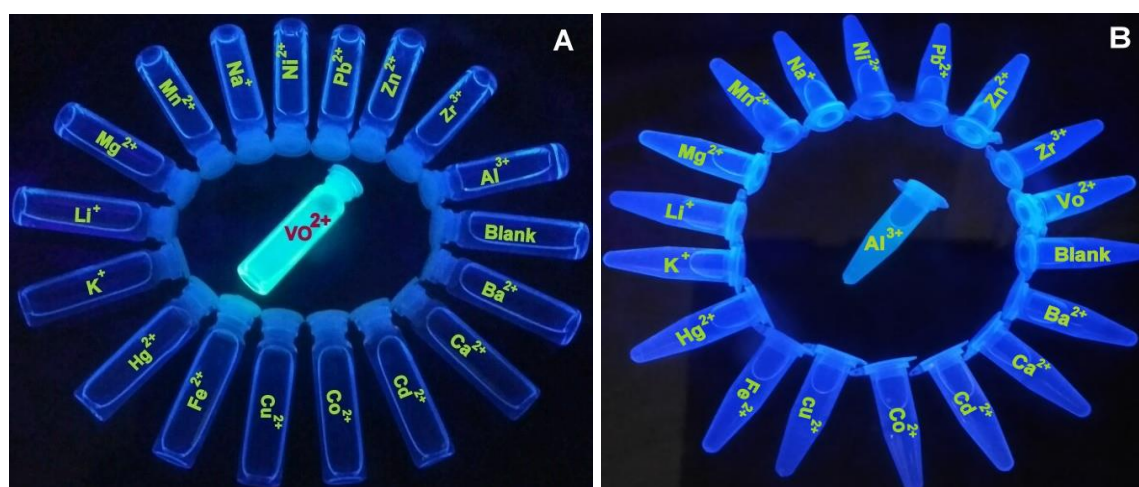


Fig. 8. (A) Color change of **1** on chelating VO²⁺ ions when irradiated by UV light (365 nm).
(B) Longer wavelength UV light irradiation of **1** with β -CD in various metal ions.

Conclusions

The synthesis and binding of a new antipyrine derivative (compound **1**, Scheme 1) to β -CD has been studied by a combination of experimental and theoretical tools. The compound **1** forms an encapsulation complex with β -CD with 1:1 stoichiometry and a $\log K = 2.09$ (2.34 by ITC). The encapsulation is proved by ROESY NMR spectrum and also in line with the positive ΔS value likely related to the desolvation of the β -CD cavity. Theoretical calculations confirm this since the encapsulated complex is largely more stable than that formed in an external interaction. Furthermore the formation of hydrogen bonds between the OH groups of the β -CD and compound **1** is evidenced.

The sensing of a series of metal ions by compound **1** and the supramolecular 1- β -CD complex provides an interesting result: while the free compound shows a strong fluorescence enhancement when binding VO²⁺ ion, in the supramolecular form Al³⁺ is selectively detected.

References

- (1) Zhang, J.; Ma, P. X. Cyclodextrin-Based Supramolecular Systems for Drug Delivery: Recent Progress and Future Perspective. *Adv. Drug Deliv. Rev.* **2013**, *65* (9), 1215–1233.
- (2) Paulpandi, R. Q.; Ramasamy, S.; Paulraj, M. S.; Díaz Baños, F. G.; Villora, G.; Cerón-Carrasco, J. P.; Pérez-Sánchez, H.; Muthu Vijayan Enoch, I. V.; Xu, Y.; Liu, X.; et al. Enhanced Zn²⁺ Ion-Sensing Behavior of a Benzothiazole Derivative on Encapsulation by β -Cyclodextrin. *RSC Adv.* **2016**, *6* (19), 15670–15677.
- (3) Xu, M.; Wu, S.; Zeng, F.; Yu, C. Cyclodextrin Supramolecular Complex as a Water-Soluble Ratiometric Sensor for Ferric Ion Sensing. *Langmuir* **2010**, *26* (6), 4529–4534.
- (4) Comuzzi, C.; Polese, P.; Melchior, A.; Portanova, R.; Tolazzi, M. SOLVERSTAT: A New Utility for Multipurpose Analysis. An Application to the Investigation of Dioxygenated Co(II) Complex Formation in Dimethylsulfoxide Solution. *Talanta* **2003**, *59* (1), 67–80.
- (5) Del Piero, S.; Melchior, A.; Polese, P.; Portanova, R.; Tolazzi, M. A Novel Multipurpose Excel Tool for Equilibrium Speciation Based on Newton-Raphson Method and on a Hybrid Genetic Algorithm. *Ann. Chim.* **2006**, *96* (1–2), 29–49.
- (6) Becke, A. D. A New Mixing of Hartree-Fock and Local Density-Functional Theories. *J. Chem. Phys.* **1993**, *98* (2), 1372–1377.
- (7) Lee, C. T.; Yang, W. T.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula Into A Functional of the Electron-Density. *Phys. Rev. B* **1988**, *37* (2), 785–789.
- (8) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Continuum Solvation Models. *Chem. Rev.* **2005**, *105* (8), 2999–3093.
- (9) Liu, Y.; Li, L.; Zhang, H.-Y.; Fan, Z.; Guan, X.-D. Selective Binding of Chiral Molecules of Cinchona Alkaloid by Beta- and Gamma-Cyclodextrins and Organoselenium-Bridged Bis(beta-Cyclodextrin)s. *Bioorg. Chem.* **2003**, *31* (1), 11–23.
- (10) Samanta, A.; Guchhait, N.; Bhattacharya, S. C. Preferential Molecular Encapsulation of an ICT Fluorescence Probe in the Supramolecular Cage of Cucurbit[7]uril and β -Cyclodextrin: An Experimental and Theoretical Approach. *J. Phys. Chem. B* **2014**, *118* (46), 13279–13289.
- (11) Bencini, A.; Bianchi, A.; Del Piero, S.; Giorgi, C.; Melchior, A.; Portanova, R.; Tolazzi, M.; Valtancoli, B. Coordination Features of a Polyaza-Bipyridine-Macrocyclic Ligand toward Co(II) and Cd(II) in Water and Dimethylsulfoxide. *J. Solution Chem.* **2008**, *37* (4), 503–517.
- (12) Melchior, A.; Peralta, E.; Valiente, M.; Tavagnacco, C.; Endrizzi, F.; Tolazzi, M. Interaction of d¹⁰ Metal Ions with Thioether Ligands: A Thermodynamic and Theoretical Study. *Dalt. Trans.* **2013**, *42* (17).
- (13) Melchior, A.; Peralta, E.; Valiente, M.; Tolazzi, M. Solvent Effect on Heavy Metal Coordination with Thioether Ligands: A Thermodynamic and Theoretical Study. *Polyhedron* **2014**, *75*, 88–94.
- (14) Mura, P. Analytical Techniques for Characterization of Cyclodextrin Complexes in Aqueous Solution: A Review. *J. Pharm. Biomed. Anal.* **2014**, *101*, 238–250.
- (15) Job, P. Formation and Stability of Inorganic Complexes in Solution. *Ann. Chim* **1928**, *9*, 113–203.
- (16) Renny, J. S.; Tomasevich, L. L.; Tallmadge, E. H.; Collum, D. B. Method of

Continuous Variations: Applications of Job Plots to the Study of Molecular Associations in Organometallic Chemistry. *Angew. Chemie Int. Ed.* **2013**, 52 (46), 11998–12013.