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Synthesis, crystal structure and complexation behaviour study of an efficient Cu²⁺ ratiometric fluorescent chemosensor based on thiacalix[4]arene

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Synthesis, crystal structure and complexation behaviour study of an efficient Cu$^{2+}$ ratiometric fluorescent chemosensor based on thiacalix[4]arene

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ABSTRACT

A new thiacalix[4]arene based fluorescent chemosensor L bearing two pyrenyl groups in a 1,3-alternate conformation has been synthesized, and its metal ion-binding and fluorescence-sensing properties were investigated in ethanol. The designed chemosensor L was capable of acting as an efficient ratiometric fluorescent chemosensor at low ion concentration or as a fluorescence quenching type chemosensor due to the PET and heavy atom effects operating in high ionic strength solution. Further studies revealed that chemosensor L acted as a reversible sensor in the presence of Cu$^{2+}$ and ethylenediamine.

1. Introduction

Copper is the third most abundant essential trace element in the human body and plays a critical role in various biological processes.$^1$ For example, copper is a catalytic cofactor for a variety of metalloenzymes, including superoxide dismutase, cytochrome oxidase and tyrosinase.$^{1,2}$ However, it can often be toxic to certain biological systems when the levels of Cu$^{2+}$ exceed cellular needs. Excess levels of the copper (II) ion in the human body can cause kidney damage, gastrointestinal problems and Wilson’s disease,$^3$ and are associated with brain diseases such as Parkinson’s, Huntington’s, Alzheimer’s and prion diseases, even when present in trace amounts.$^{1,4}$ Consequently, the U.S. Environmental Protection Agency (USEPA) has set the limit of copper in drinking water to be 1.3 ppm ($\sim$20 µM). Also, the average concentration of blood copper in the normal group is 100–150 µg/dL (15.7–23.6 µM).$^5$

In view of the importance of the copper ion, Cu$^{2+}$ selective fluorescent chemosensors appear to be particularly attractive over the other methods due to their specificity, high sensitivity, high selectivity, and real-time monitoring with fast response times.$^7$ However, Cu$^{2+}$ presents an inherent problem for fluorescent sensing because of the likely quenching of the fluorescence by mechanisms inherent to paramagnetic species.$^8$ Most of the classic and early-reported Cu$^{2+}$ sensors generally show low sensitivity, and moreover, low selectivity.$^9$ Additionally, most of the chemosensors are based on single emission intensity changes such as fluorescence quenching$^{10}$ or enhancement,$^{11}$ which tend to be affected by a variety of factors such as instrument efficiency, probe molecule concentration, and micro-environment.$^{12}$

To overcome these disadvantages, ratiometric fluorescent sensors have been well developed in recent years.$^{13}$ Ratiometric fluorescent measurements observe changes in the ratio of the intensities of the emission at two wavelengths. Thus, ratiometric fluorescent sensors have important features that can be used to evaluate the analytical concentration and provide a built-in correction for environmental effects.$^{12}$ Among the various fluorophores, pyrene exhibits monomer–excimer dual emission wavelength fluorescence,$^{14}$ and the
Fluorescence intensity ratio of the excimer to monomer emission ($I_{E}/I_{M}$) is sensitive to conformational changes of the pyrene-functionalized system. Additionally, pyrene possesses photophysical properties that make it appropriate for such purposes due to its high fluorescence quantum yield, chemical stability, and long fluorescence lifetime. Consequently, pyrene has been employed as a fluorophore in this paper.

Based on our previous research, a good chemosensor not only contains an efficient fluorophore, but also needs to take into account the geometry of the coordination sites for a specific cation (or anion).

In general, copper ions release soft heteroatoms, such as nitrogen and sulfur, as electron donors to coordinate with the metal cation.

Thiacalix[4]arenes are widely exploited as a molecular platform for many fluorescent chemosensors in the construction of selective binding sites given its structural rigidity, various conformations and given that it allows for the facile introduction of fluorophores. Recently, we have reported that a pyrenyl-linked triazole-modified thiacalix[4]arene chemosensor displayed high affinity for silver ion by changing the monomer and excimer emission of the pyrene moieties.

However, other heavy metal ions, especially Cu$^{2+}$ and Hg$^{2+}$ can be also strongly quench both the monomer and excimer emission of pyrene. We have also reported chemosensors with similar structures namely, pyrenyl-linked triazole-modified homooxacalix[3]arene. It was found that the chemosensor having acetate groups (–CH$_2$-COO–) linking the triazole groups to the homooxacalix[3]arene showed a higher selectivity than the other in which the triazole groups were linked directly to the lower rim oxygen atoms. Therefore, we hypothesized that by analogy, introducing similar acetate group-linkages between the triazoly(pyrenyl) groups and the thiacalix[4]arene should help to improve the selectivity. In the present work, therefore, the synthesis and properties of the fluorescent chemosensor L derived from thiacalix[4]arene with pyrene as a subunit is reported.

2. Results and discussion

2.1. Synthesis

The synthesis of the parent compound I was carried out according to the published literature procedure. Recently, we described the synthesis of hexahomotrioxacalix[3]arene triacetic acid with propargyl alcohol, obtained by the Steglich esterification reaction with 1,3-dicyclohexylcarbodiimide (DCC) as a coupling reagent and 4-(N,N-dimethylamino)pyridine (DMAP) as a catalyst. However, in accordance with the above-mentioned method, we found that the reaction of the thiacalix[4]arene derivative I, even with a large excess of propargyl alcohol, only leads to the expected molecule in a very low yield. Fortunately, an alternative, efficient route was found by using propargyl bromide (instead of propargyl alcohol) in the presence of K$_2$CO$_3$ as base, and we successfully obtained 2 in high yield (73%). Following this, the click reaction, i.e. Cu(1)-catalysed azide–alkyne cycloaddition, was used to synthesize the new chemosensor L. The synthetic route for this new chemosensor L is given in Scheme 1.

Compounds 2 and L were characterized by IR, $^1$H and $^{13}$C NMR spectroscopy and by mass spectrometry. The $^1$H NMR spectrum of 2 exhibits two singlets for the tert-butyl protons at higher field, viz. $\delta$ 0.84 and 1.26 ppm; two singlets for the aromatic protons at $\delta$ 7.15 ppm and 7.52 ppm, respectively, all of which is indicative of a C$_2$-symmetric structure for the 1,3-alternate conformation. One terminal triple bond hydrogen signal is found at $\delta$ 2.47 ppm, which reveals that the propargyl group has been successfully introduced. In compound L, the proton signal of the propargyl hydrogens has disappeared, whilst a new singlet appearing at about $\delta$ 7.40 ppm is attributed to the protons of the newly formed triazole skeleton (for details, see the Supporting Information, Figures S1-S8).

X-ray quality pale yellow crystals of L were obtained by recrystallization from a MeOH/CHCl$_3$ solution. ORTEP representations of the molecular structure of L are shown in Figure 1. It is clear that L adopts the 1,3-alternate conformation. There is a crystallographic twofold symmetry axis normal to the $S_4$ mean-plane, passing down the centre of the calixarene cage. Opposing phenyl rings, related by this symmetry, are essentially parallel with their normals only 0.14(9) and 1.16(12)$^\circ$ apart. These normals lie almost parallel to the $S_4$ plane, i.e. at angles of 89.93(7)$^\circ$ and 89.42(6)$^\circ$ to the normal of that plane. There are turns in the long substituent chain on O(1) [and O(1)'] so that the triazole ring lies nearly parallel to the $S_4$ mean-plane, and the pyrene group is folded back to form an outer sheath around the cage.
2.2. Binding studies

The fluorescence spectra of L reveal a strong excimer emission at 484 nm and weaker monomer emissions at 379 and 397 nm (excitation wavelength 344 nm), with an intensity ratio of monomer to excimer emission \( \frac{I_{379}}{I_{484}} \) = 0.54. Among the various metal ions (Li\(^+\), Na\(^+\), K\(^+\), Cs\(^+\), Cu\(^{2+}\), Ag\(^+\), Zn\(^{2+}\), Co\(^{2+}\), Hg\(^{2+}\), Pb\(^{2+}\), Ni\(^{2+}\), Cu\(^{2+}\), Fe\(^{3+}\) and Fe\(^{2+}\) as their perchlorate salts), chemosensor L displays highly selective ratiometric changes upon the addition of Cu\(^{2+}\) (Figure 2). As expected, the pyrene moiety serves successfully as a source of these ratiometric changes. The formation of an excimer band at 484 nm indicates a strong face-to-face \( \pi-\pi \) stacking between the two pyrene units. The relative intensity ratio of monomer to excimer emission \( \frac{I_{379}}{I_{484}} \) of the free sensor L is 0.54 and this was increased 228-fold to 123 upon the addition of 20 equiv. of Cu\(^{2+}\) (Figure 2b) and the formation of a L–Cu\(^{2+}\) complex. We postulate that the excimer quenching in sensor L is due to a conformational change that takes place during the binding of a Cu\(^{2+}\) ion between the nitrogen atoms of the triazole ring and the adjacent oxygen atoms. In this altered conformation, the coordination forces the pyrenyl groups to move away from one another thereby inhibiting the \( \pi-\pi \) stacking of the pyrene moieties which is necessary for the generation of the excimer emission.

In order to obtain more detailed complexation information for chemosensor L with the copper ion, fluorescence titration experiments were carried out. Interestingly, when we gradually increased the amounts of Cu\(^{2+}\) from 0 to 4 equiv., the fluorescence intensity of the excimer emission of L gradually decreased and was accompanied by an enhancement of the monomer emission in EtOH solution (Figure 3a). However, when the concentration of Cu\(^{2+}\) was increased beyond 4 equiv. (5 equiv. to 45 equiv.), the fluorescence intensity of monomer emission exhibited a dramatic decrease (Figure 3b). These unique phenomena can also be visualized in the colour changes of the solution under UV light (Figure 3b inset) and, to the best of our knowledge, is the first such case observed in thiacalixarene chemistry. A similar phenomenon was observed by Dabestani and coworkers in calix[4]arene. They suggested that the gradual quenching of the emission from L observed at high concentrations of Cu\(^{2+}\) (Figure 3c) may be attributable to a medium effect caused by changes in the ionic strength of the solution. Additionally, the fluorescence of monomer emission quenching by the heavy atom (Cu\(^{2+}\)) in the chemosensor L generally can be attributed to a reverse PET (Photoinduced Electron Transfer) from the pyrene unit to the nitrogen atoms of triazole ring or to a heavy atom effect. In other words, the chemosensor L acts as an efficient ratiometric fluorescent chemosensor at low ion concentration or as a fluorescence quenching type chemosensor due to the PET and heavy atom effect at high ionic strength of the solution.
Figure 3. (a) Fluorescence intensity changes of L (1.5 μM) upon addition of increasing concentrations of Cu²⁺ in EtOH solution (0–4 equiv.); (b) (4–45 equiv.) at 298 K with an excitation at 344 nm; (c) Changes in the emission spectra (379 nm) of L (1.5 μM) in EtOH upon addition of Cu²⁺ ion (EtOH solution).

On the basis of the fluorescence titration experiments, the association constant \( K_{	ext{ass}} \) for L·Cu²⁺ was determined to be 3.5 × 10⁵ M⁻¹ using a Benesi-Hildebrand plot (Figure S9, Supporting Information). The detection limit of the receptor was investigated, and a low detection limit of 1.44 × 10⁻⁷ M (Figure S10, Supporting Information) was observed. A Job plot for the complexation revealed a 1:1 stoichiometry (Figure S11, Supporting Information). All of these results are clear evidence that chemosensor L possesses high sensitivity and high selectivity for Cu²⁺.

To investigate further the practical applicability of the chemosensor L as a Cu²⁺ ion selective fluorescent sensor, competitive experiments were carried out in the presence of Cu²⁺ ion (30 μM) mixed with Li⁺, Na⁺, K⁺, Cs⁺, Ag⁺, Zn²⁺, Co²⁺, Hg²⁺, Pb²⁺, Ni²⁺, Fe³⁺, Fe²⁺ at 30 μM. As shown in Figure S12, no obvious interference to the selective response of chemosensor L·Cu²⁺ was observed, indicating that the chemosensor L can be used as a selective fluorescent sensor for the Cu²⁺ ion in the presence of most competitive metal ions.

Furthermore, in order to look further into the binding properties of chemosensor L with Cu²⁺, ¹H NMR titration experiments were carried out in CDCl₃ : CD₃CN = 10 : 1 solution. The chemical shift changes for chemosensor L·Cu²⁺ were evaluated by ¹H NMR titration experiments, which are illustrated in Figure 4.

The peaks of \( H_a, H_b, H_c, H_d, H_e \) and \( H_f \) completely disappeared as soon as 0.25 equiv. of Cu²⁺ were added, and the signals of the pyrene ring protons (\( H_g \)) and benzyl protons (\( H_h \)) were blurred; this was attributed to the paramagnetic effect of Cu²⁺. The chemical shift of protons \( H_h (-OCH₂Benzyl) \) were shifted to downfield with \( \Delta \delta = +0.31 \text{ppm} \) due to the protons \( H_g \) of free L is in the ring current shielding effect which is operating in the two thiacyclarene benzene rings (See the single-crystal structure of L, Figure 1a).

However, when L complexed with Cu²⁺, the conformation of L was changed which lead to the ring current shielding effect being decreased. This affected the protons \( H_h \) and the downfield shift close to the normal benzyl protons chemical shift (5.49 ppm). Peaks corresponding to the thiacyclarene benzene rings (\( H_g \) and \( H_h \)) underwent a slight chemical shift, which can be attributed to both the conformation changes and the paramagnetic effect of the Cu²⁺ (Figure 4). All of this evidence suggested that the 1,2,3-triazole and the adjacent oxygen were directly involved in coordinating with Cu²⁺. There was no appreciable change in the signal positions on addition of 1.0 to 2.0 equiv. of Cu²⁺ to L, confirming a 1:1 binding stoichiometry for L and Cu²⁺. Interestingly, it was observed that upon addition of ethylenediamine to a solution containing the L·Cu²⁺ complex, all of the disappeared peaks were immediately recovered (Figure 4f). This indicated that the complexation behaviour between L and Cu²⁺ ion was reversible.

IR spectroscopy was employed to give further evidence to support the possible complexation mode The IR spectra of the complex (L·Cu²⁺) vs. the free host (L) are shown in Figure S13. In the spectrum of free L, there are two relatively strong absorptions (bands at 1770 and 1740 cm⁻¹) which are correspond to –COO– group, which are dramatically changed to a weak absorption (band at 1743 cm⁻¹) after complexation with Cu²⁺. A similar phenomenon also has been observed for the triazole group bands at 1604 and 1588 cm⁻¹ which disappear after complexation with Cu²⁺. In other words, all of these evidences strongly indicate that Cu²⁺ is captured by these groups. The concept of Cu²⁺ complexation by the host chemosensor L is shown in Figure 5. Once the Cu²⁺ was captured by the nitrogen and oxygen atoms, the protons which are located in the adjacent area of the Cu²⁺ would be affected strongly by Cu²⁺ due to the inherent paramagnetism of Cu²⁺, which led to the adjacent protons disappearing.

To better understand the binding properties of chemosensor L with Cu²⁺, density functional theory (DFT) computational studies were carried out to determine the geometry-optimized energies of chemosensor L with Cu²⁺ ion. The starting structure was generated from the X-ray structure of L. The large distance between the nitrogen atoms of the triazole rings shown by the X-ray structure of the ligand L prevented effective binding, in the DFT-optimized structures between the Cu²⁺ and the two triazole units as evidenced by the ¹H NMR data (Fig. 4) was modified using

Figure 5. Plausible binding model of L·Cu²⁺ complex.
3. Conclusion

In summary, we have synthesized a new type of selective and sensitive fluorescent sensor having triazole rings as the binding sites on the lower rim of a thiacalix[4]arene scaffold in a 1,3-alternate conformation. The selective binding behaviour of chemosensor L has been evaluated by fluorescence spectra and $^1$H NMR spectroscopic analysis. It was observed that chemosensor L acted as an efficient ratiometric fluorescent chemosensor at low ion concentration or as a fluorescence quenching type chemosensor due to the PET and heavy atom effect at high ionic solution strength. All the results suggested that chemosensor L is highly sensitive and selective for Cu$^{2+}$.

4. Experimental section

4.1 General

Unless otherwise stated, all reagents used were purchased from commercial sources and were used without further purification. Compound 1$^{19}$ was prepared following the reported procedures. All solvents used were dried and distilled by the usual procedures prior to use. All melting points (Yanagimoto MP-S1) are uncorrected. $^1$H NMR and $^1$C NMR spectra were obtained on a Nippon Densi JEOL FT-300 NMR spectrometer and Varian-400MR-vnmrs400 with SiMe$_4$ as an internal reference; J-values are given in Hz. IR spectra were measured for samples as KBr pellets on a Nippon Densi JIR-AQ2OM spectrophotometer. Mass spectra were obtained with a Shimadzu UV-3150UV-vis-NIR spectrophotometer. Fluorescence spectroscopic studies of compounds in solution were performed in a semimicro fluorescence cell (Hellma®, 104F-QS, 10 × 4 mm, 1400 μL) with a Varian Cary Eclipse spectrophotometer.

4.2. Materials

4.2.1 Synthesis of compound 2. A suspension of 1 (203 mg, 0.2 mmol) and K$_2$CO$_3$ (400 mg, 2.9 mmol) was heated at reflux for 1 h in dry acetone (20 mL), and a solution of propargyl bromide (345 mg, 2.9 mmol) in dry acetone (10 mL) was added. The reaction mixture was refluxed for 24 h. The solvents were evaporated and the residue partitioned between 10% HCl and CH$_2$Cl$_2$. The organic layer was separated and dried (MgSO$_4$) and the solvents were evaporated. The residue was dried to afford the product 2 (180 mg, 72.7%) as a white solid. M.p.: 267–268 °C. IR (KBr) (cm$^{-1}$): 3292, 3065, 3033, 2961, 2906, 2890, 2131, 1778, 1746, 1576 and 1498. $^1$H NMR (400 MHz, CDCl$_3$) δ = 8.04 (18 H, s, tBu), 1.28 (18H, s, tBu), 2.47 (2H, s, HCC), 4.64 (4H, s, HCCCHO$_3$), 4.76 (4H, s, -OCH$_3$COO$^-$), 4.99 (4H, s, -OCH$_3$Benzy), 7.15 (4H, s, ArH), 7.19 (10H, s, PhH) and 7.52 (4H, s, ArH) ppm. $^1$C NMR (100 MHz) δ 29.8, 30.2, 32.8, 33.2, 51.0, 65.7, 72.0, 74.1, 126.1, 126.5, 127.0, 127.2, 127.5, 129.8, 131.8, 136.9, 145.1, 145.3, 150.0, 157.2 and 166.1 ppm. HRMS (ESI-TOF): calcd for C$_{48}$H$_{48}$O$_{12}$S$_4$ [M + H]$^+$ m/z = 1093.3875; found 1093.3961 [M + H]$^+$. 

4.2.2. Synthesis of receptor L. Copper iodide (20 mg) was added to a mixture of 2 (150 mg, 0.14 mmol) and 1-(azidomethyl)pyrene (108 mg, 0.42 mmol) in 25 mL THF/H$_2$O (4:1)
Tetrahedron

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Supplementary data

Electronic Supplementary Information (ESI) available: Details of the 1H, 13C NMR, MS and IR spectra of compounds 2 and L; fluorescent and computational studies of L with Cu2+. See DOI: 10.1039/b000000xs

References and notes


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