



A Novel Calix[4]Crown-Based 1,3,4-Oxadiazole as a Fluorescent Chemosensor for Copper(II) Ion Detection

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Specialty section:

This article was submitted to
Supramolecular Chemistry,
a section of the journal
Frontiers in Chemistry

Received: 29 August 2021

Accepted: 18 October 2021

Published: 12 November 2021

Citation:

Sun C, Du S, Zhang T and Han J (2021)
A Novel Calix[4]Crown-Based 1,3,4-
Oxadiazole as a Fluorescent
Chemosensor for Copper(II)
Ion Detection.
Front. Chem. 9:766442.
doi: 10.3389/fchem.2021.766442

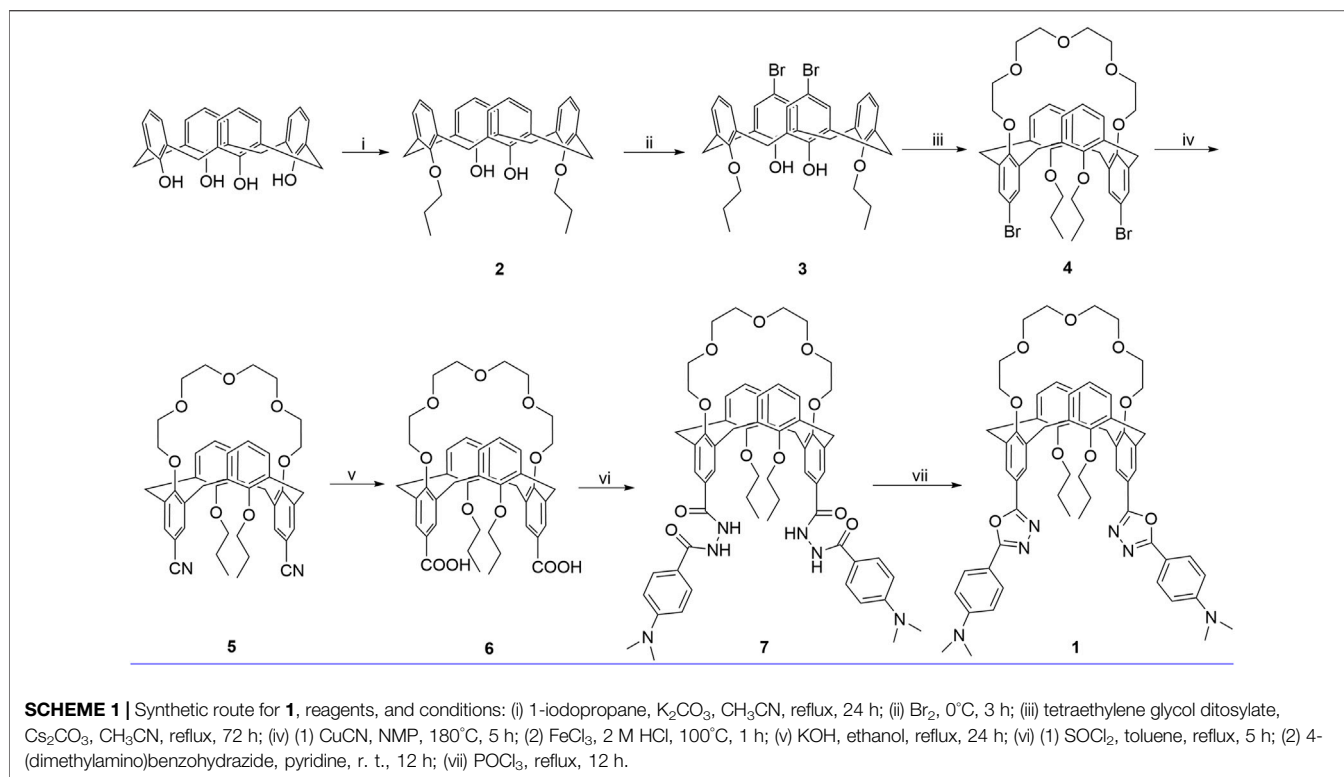
The synthesis and characterization of a novel fluorescent chemosensor **1** with two different types of cationic binding sites have been reported in this work, which is a calix[4]crown derivative in 1,3-alternate conformation bearing two 2-phenyl-5-(4-dimethylaminopyrenyl)-1,3,4-oxadiazole units. The recognition behaviors of **1** in dichloromethane/acetonitrile solution to alkali metal ions (Na^+ and K^+), alkaline earth metal ions (Mg^{2+} and Ca^{2+}), and transition metal ions (Co^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} , Cu^{2+} , Mn^{2+} , and Ag^+) have been investigated by UV-Vis and fluorescence spectra. The fluorescence of **1** might be quenched selectively by Cu^{2+} due to the photo-induced electron transfer mechanism, and the quenched emission from **1** could be partly revived by the addition of Ca^{2+} or Mg^{2+} ; thus, the receptor **1** might be worked as an on-off switchable fluorescent chemosensor triggered by metal ion exchange.

Keywords: calix[4]crown, 1,3-alternate conformation, 1,3,4-oxadiazole, copper (II) detection, fluorescent chemosensor

INTRODUCTION

As the third most abundant transition metal ion after zinc and iron in the human body, copper is required by many living organisms for normal physiological processes (Turski and Thiele, 2009; Cotruvo Jr et al., 2015). Maintaining optimal concentration of Cu^{2+} ion for living cells is an essential factor to keep the normal functioning of enzymes and intracellular metabolic balance. Thus, the development of new fluorescent chemosensors for Cu^{2+} ion has drawn continuous interest during the past decades. The main progress in this area has been well reviewed (Cao et al., 2019; Sivaraman et al., 2018; Udhayakumari et al., 2017; Liu et al., 2017), and many fluorescent chemosensors for Cu^{2+} ion based on various fluorophores such as coumarin (Zhang et al., 2019), Bodipy (Ömeroğlu et al., 2021), rhodamine (Fernandes and Raimundo, 2021), Schiff base (Singh et al., 2020), pyrene (Kowser et al., 2021), and 1,3,4-oxadiazole (Wang, et al., 2018) have been reported by different research groups. Among these fluorescent chemosensors, the 1,3,4-oxadiazoles have drawn special interest due to their electron-deficient nature, high photoluminescence quantum yield, and excellent chemical stability, and have found practical applications in the fields of organic light-emitting diodes (Meng et al., 2020) and liquid crystals (Han et al., 2013; Han et al., 2015; Han et al., 2018). In addition, the nitrogen and oxygen atoms of the 1,3,4-oxadiazole unit can provide potential coordination sites with metal ions, which makes it usable as a signaling component in fluorescent chemosensors.

Calixarenes, as one kind of the most important super-molecules, have been widely used in design of fluorescent chemosensors for ions and neutral molecules due to their outstanding



features such as preorganized binding sites, easy derivatization, and flexible three-dimensional structures (Kim et al., 2012; An et al., 2019; Miranda et al., 2019; Noruzi et al., 2019; Chen et al., 2020). Many calixarene-based fluorescent chemosensors for transition metal ions have been reported in recent years (Ma et al., 2015). However, the fluorescent switchable chemosensors triggered by different ions are quite few (Chung et al., 2007), which remains a challenge in the field of supramolecular chemistry. Herein, as part of our continuous research in the design and synthesis of new fluorescent chemosensors (Liu et al., 2021; Xie et al., 2016; Han et al., 2012), we utilize the 1,3-alternate calix[4]crown scaffold to construct an on-off switchable fluorescent chemosensor **1** in this work. The synthetic route for **1** is shown in **Scheme 1**. There are quite a number of chemosensors based on various macrocycles for copper detection reported in literatures (Lvova, et al., 2018; Doumani, et al., Kamei, et al., 2021), in which the macrocycles often only worked as receptors for Cu^{2+} ions. In contrast, the chemosensor **1** in this work is special in that it has two kinds of macrocycles: one is from the 1,3-alternate calixarene, which provides a three-dimensional scaffold with two appending 1,3,4-oxadiazole units as both signaling component and fluorophore; the other is from the calix[4]crown, which can bind the Mg^{2+} or Ca^{2+} ions and has an allosteric effect on the 1,3,4-oxadiazole units on opposite rings. The selective binding of 1,3,4-oxadiazole with Cu^{2+} ions results in the fluorescence quenching, while the binding of calix[4]crown with Mg^{2+} or Ca^{2+} ions can partly revive the fluorescence consequently. Thus, the compound **1** might work as a new type of switchable off-on fluorescent chemosensor.

MATERIALS AND METHODS

25,27-Dihydroxy-26,28-dipropoxycalix[4]arene **2** and 5,17-dibromo-25,27-dihydroxy-26,28-dipropoxycalix[4]arene **3** were synthesized according to the literature procedures (Hobzova, 2010). Dichloromethane and acetonitrile used for photophysical studies were of spectrometric grade. All the other chemicals and solvents were of analytical grade and used as received from commercial sources. The solutions of metal ions were all prepared from their perchlorate salts. Column chromatography was performed on silica gel (200–300 mesh).

Solution 1H NMR (Proton Nuclear Magnetic Resonance) and ^{13}C NMR (Carbon-13 Nuclear Magnetic Resonance) spectra were recorded on a Bruker AV400 spectrometer and the chemical shifts are quoted in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. ESI-HRMS (Electrospray Ionization-High Resolution Mass Spectrometry) data were obtained with a FTICR-MS mass spectrometer. Melting points were determined with an X-4 melting point apparatus, and the thermometer was uncorrected. Data for single x-ray structure were collected on a SMART1000 CCD-X diffractometer with graphite-monochromatized MoK α x-ray radiation ($\lambda = 0.71073 \text{ \AA}$) and Saturn CCD area detector. The x-ray crystal structure of **4** was solved by direct method and expanded using Fourier synthesis technique. No absorption correction was done. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using riding model. Structural refinement based on full-matrix least-squares refinement on $|F|^2$ was performed by using Crystal Structure or SHELXL97 suite program (Sheldrick, 1997).

Synthesis of 4

A mixture of **3** (9.23 g, 13.9 mmol) and Cs_2CO_3 (11.30 g, 34.7 mmol) in MeCN (700 ml) under nitrogen was stirred at reflux for 30 min and then a solution of the tetraethylene glycol ditosylate (7.85 g, 15.6 mmol) in MeCN (40 ml) was added during an hour. The mixture was refluxed for 72 h and allowed to cool to room temperature. After evaporation of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2 (30 ml \times 3) and the resultant solution was washed with 1 mol/L HCl (30 ml) and brine (30 ml \times 2). The organic layer was dried over MgSO_4 and evaporated *in vacuo*. Recrystallization of the residue from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ gave **4** a pale-yellow solid. Yield, 75%. Mp: 230–232 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.17 (s, 4H), 7.08 (d, $J = 8.0$ Hz, 4H), 6.87 (t, $J = 8.0$ Hz, 2H), 3.78 (d, $J = 4.0$ Hz, 8H), 3.54 (s, 8H), 3.45 (t, $J = 8.0$ Hz, 4H), 3.25–3.20 (m, 4H), 3.15 (m, 4H), 1.31 (m, 4H), 0.78 (t, $J = 7.5$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.97, 155.14, 136.29, 133.81, 132.17, 129.70, 122.77, 115.15, 72.59, 72.09, 70.50, 70.13, 69.03, 37.89, 22.53, 10.23. HRMS-MALDI calculated for $\text{C}_{42}\text{H}_{48}\text{Br}_2\text{O}_7$ $[\text{M} + \text{Na}]^+$ 847.1639, found 847.1652.

Synthesis of 5

Under nitrogen, a mixture of **4** (10.17 g, 12.3 mmol) and cuprous cyanide (7.68 g, 86.4 mmol) in 20 ml of 1-methyl-2-pyrrolidinone was stirred at 180°C for 4 h. Then, the reaction mixture was cooled slowly to 100°C, and a solution of 23.23 g (86.4 mmol) of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in 5 ml of concentrated hydrochloride and 25 ml of water was added to the reaction mixture. The reaction mixture was further stirred at 100°C for 1 h and cooled to room temperature. The solid was filtered off and recrystallized from chloroform/hexane yielding 5.5 g of compound **5** as yellow solid. Yield 62%. ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 4H), 7.10 (d, $J = 7.4$ Hz, 4H), 6.90 (s, 2H), 3.82 (d, $J = 5.5$ Hz, 8H), 3.55 (s, 8H), 3.46 (t, $J = 7.4$ Hz, 4H), 3.30 (t, $J = 6.1$ Hz, 4H), 3.17 (t, $J = 6.1$ Hz, 4H), 1.24 (m, 4H), 0.74 (t, $J = 7.5$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.98, 156.80, 135.72, 133.54, 133.05, 129.94, 123.05, 119.17, 106.08, 77.36, 72.52, 72.17, 70.56, 69.85, 69.13, 37.75, 22.81, 10.05; HRMS: calcd for $\text{C}_{44}\text{H}_{48}\text{N}_2\text{O}_7$ $[\text{M} + \text{NH}_4]^+$ 734.3800, found 734.3796.

Synthesis of 6

A solution of 5.18 g (9.2 mmol) of KOH in 100 ml of water was added to the suspension of 1.32 g (1.80 mmol) of **5** in 20 ml of ethanol. The reaction mixture was heated under reflux for 24 h. After cooling, the aqueous solution hydrogen chloride (10% w/w) was added dropwise until the solution became slightly acidic. The precipitate was filtered off, washed with water, and dried to yield a yellow solid product **6** (1.33 g, 96%). Mp: 296–298°C. ^1H NMR (400 MHz, CDCl_3) δ 12.52 (s, 2H), 7.81–7.77 (m, 8H), 6.98–6.94 (m, 2H), 3.93–3.80 (m, 12H), 3.62 (s, 16H), 1.42–1.31 (m, 4H), 0.69 (t, $J = 7.5$ Hz, 6H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 167.03, 158.48, 156.72, 135.62, 133.71, 132.13, 130.41, 125.24, 122.05, 71.17, 70.07, 69.72, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 35.98, 21.74, 9.52. HRMS: calcd for $\text{C}_{44}\text{H}_{50}\text{O}_{11}$ $[\text{M}-\text{H}]^+$ 753.3280, found 753.3285.

Synthesis of 1

To a round-bottomed flask was added **6** (80 mg, 0.1 mmol), 10 ml of toluene, and 1 ml of thionyl chloride, and the mixture was refluxed for 5 h. After cooling, the solvent and the excess of thionyl chloride were removed at reduced pressure to give the benzoyl chloride, which was added to a solution of 4-(dimethylamino)benzohydrazide (39 mg, 0.22 mmol) in 10 ml of dichloromethane and 0.1 ml of pyridine. The reaction mixture was stirred for 12 h at ambient temperature and filtered. The precipitate was washed with ethanol to give the bishydrazide **7** as white solid, which was used to the next step reaction without further purification. The intermediate compound **7** was added to POCl_3 (5 ml), and the resultant solution was refluxed overnight under a nitrogen atmosphere. After the reaction mixture cooled to room temperature, it was poured into ice water and extracted with dichloromethane (3 \times 10 ml). The combined organic layer was washed with water and brine, respectively. Then, the solvent was removed under reduced pressure, and the crude solid was purified by silica gel column chromatography using petroleum ether/ethyl acetate (1:1) as eluent affording the product **1** as white solids. Yield, 35%. Mp: 281–283°C. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 8.0$ Hz, 4H), 7.81 (s, 4H), 7.15 (d, $J = 8.0$ Hz, 4H), 6.93 (s, 2H), 6.72 (d, $J = 8.0$ Hz, 4H), 3.93 (m, 8H), 3.59–3.53 (m, 12H), 3.31 (d, $J = 5.2$ Hz, 4H), 3.26 (d, $J = 5.2$ Hz, 4H), 3.05 (m, 12H), 1.25–1.19 (m, 4H), 0.60 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.80, 163.55, 158.76, 157.10, 152.20, 135.07, 133.83, 129.79, 128.32, 128.13, 122.75, 121.14, 118.35, 111.59, 111.27, 72.43, 72.24, 70.42, 70.14, 69.22, 40.11, 38.05, 22.43, 9.95. HRMS-ESI calculated for $\text{C}_{62}\text{H}_{69}\text{N}_6\text{O}_9$ $[\text{M} + \text{H}]^+$ 1,041.5120, found 1,041.5126. (Supplementary Figure S5, ESI).

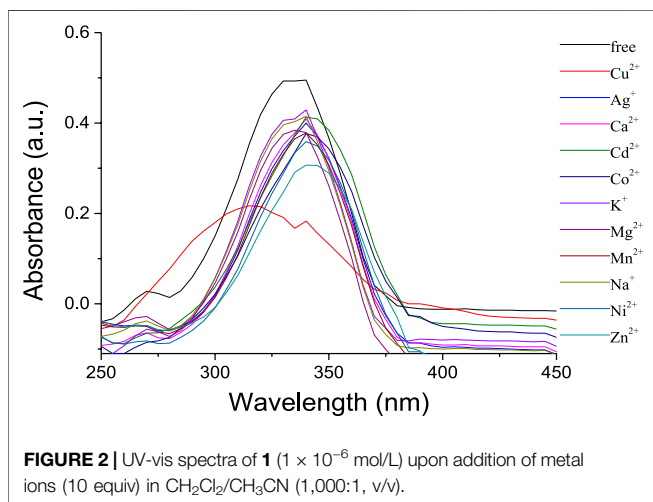
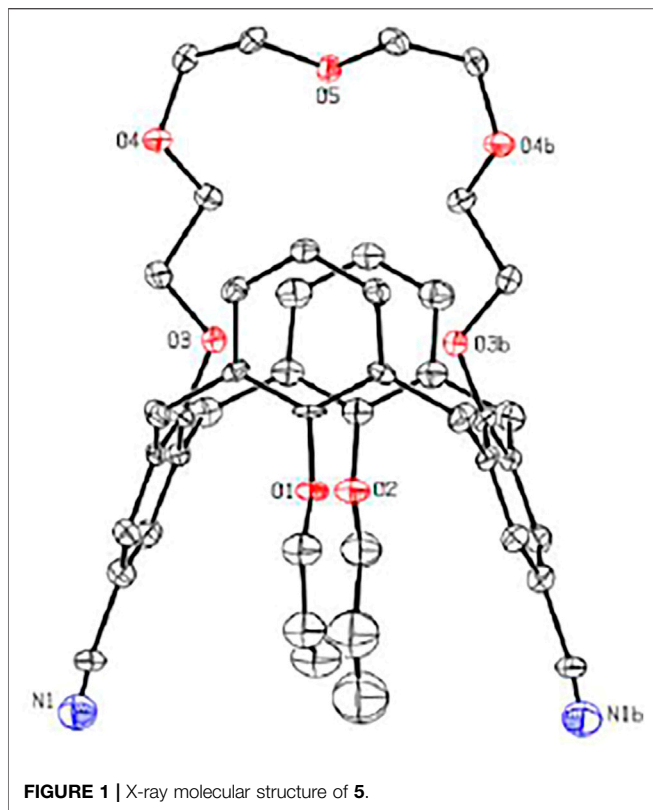
General Procedures for the UV/Vis and Fluorescence Experiments

UV-vis spectra were recorded on a Cary 3,010 spectrophotometer, and the resolution was set at 1 nm. Steady-state emission spectra were recorded on a Varian Cary Eclipse spectrometer. For all measurements of fluorescence spectra, excitation was set at 334 nm for complexation, and the excitation and emission slit width was set to be 2.5 nm. Fluorescence titration experiments were performed with CH_2Cl_2 solutions of compound **1** and varying concentrations of metal perchlorate in CH_3CN solution. During all measurements, the temperature of the quartz sample cell and chamber was kept at 25°C.

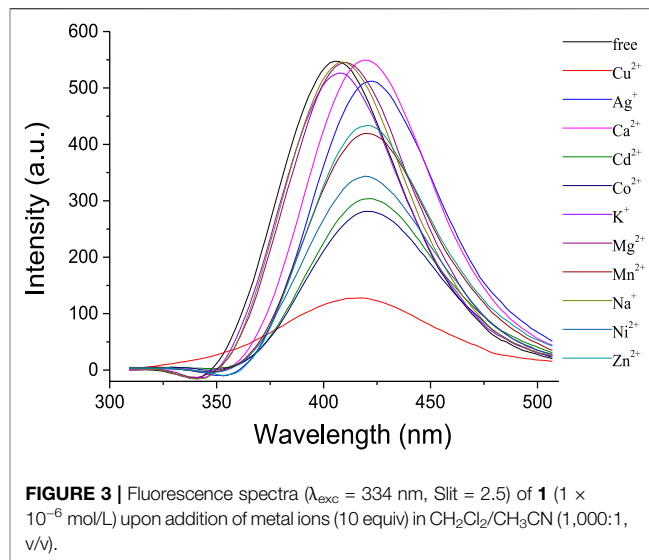
RESULTS AND DISCUSSION

Synthesis and Structural Analysis

As shown in Scheme 1, calix[4]arene **3** was reacted with tetraethylene glycol ditosylate in the presence of Cs_2CO_3 to successfully afford the calix[4]crown **3** in 75% yield. The substitution reaction of **4** with CuCN gave **5** in 62% yield, which was refluxed with KOH in ethanol and treated with hydrochloric acid solution, readily providing the carboxylic



acid **6** in good yield. Then, the carboxylic acid **6** was reacted with thionyl chloride, and treated with benzoyl hydrazine or 4-*N,N'*-dimethylaminobenzoyl hydrazine to generate the intermediate bishydrazide **7**, which was used in the next step without purification and refluxed with phosphorus oxychloride to afford the target products **1**. Except for the calix[4]arene **3**, all of the intermediate calix[4]crowns **3–6** and the chemosensor **1** are in 1,3-alternate conformation, which were well established by ^1H NMR and ^{13}C NMR data (**Supplementary Figures S1–S4**,

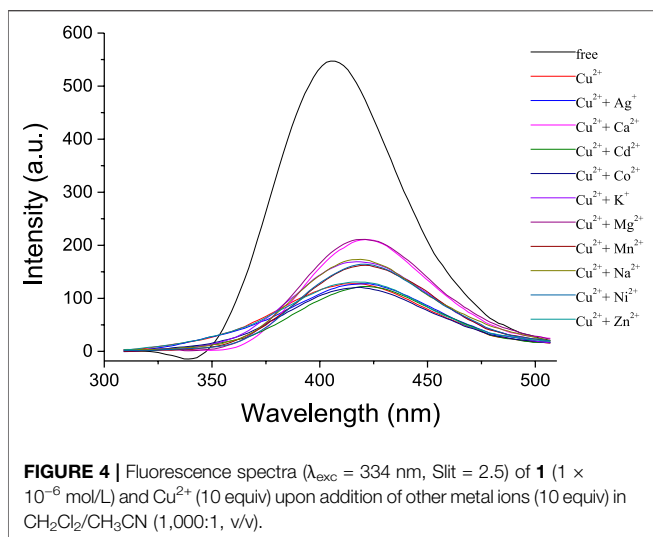


ESI). The 1,3-alternate conformation of **5** was further confirmed unambiguously by x-ray single crystal diffraction as shown in **Figure 1**. The x-ray crystallographic data are collected in **Supplementary Table S1**.

UV-Vis Absorption and Fluorescence Spectra Analysis

The selectivity of the receptor **1** toward different perchlorate salts, including Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Co^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} , Mn^{2+} , Ag^+ , and Cu^{2+} , was first investigated by UV-Vis spectroscopy. The UV-Vis absorption spectra for free **1** in CH_2Cl_2 solution showed an intense and structureless absorption band ($\epsilon = 4.94 \times 10^5$ L/mol·cm) peaking at 340 nm (**Figure 2**), which might have resulted from the spin-allowed $\pi\text{-}\pi^*$ transitions involving the phenyloxadiazole moiety (Han et al., 2006). The addition of Cu^{2+} ions in the solution of **1** resulted in a significant decrease in the absorbance with an appreciable hypochromic shift of 20 nm. In contrast, only a slight decrease was observed upon addition of other metal ions mentioned above, which suggested that the selectivity of **1** toward Cu^{2+} is much higher than the other metal ions.

Ion recognition ability of **1** was further studied by the fluorescence spectra. As shown in **Figure 3**, the receptor **1** exhibited a strong emission with λ_{max} at 405 nm in solution of CH_2Cl_2 . Upon addition of Na^+ , K^+ , and Mg^{2+} , respectively, almost no changes were observed in the intensity and shape of the emission spectra of **1**. It is noted that the addition of Ca^{2+} might slightly increase the intensity with a bathochromic shift of ca. 15 nm, perhaps because the complexation between the Ca^{2+} and the crown ether moiety changed the space distance of the two phenyloxadiazole units and the fluorescence changed consequently. Apparently, the fluorescence response of **1** toward transition metal ions was found to be more pronounced, and the addition of Co^{2+} , Ni^{2+} , Zn^{2+} , and Ag^+ could quench the emission of **1** in a different extent, accompanied by a concomitant red shift of ca. 14–17 nm. In contrast, the addition of Cu^{2+} significantly quenched the



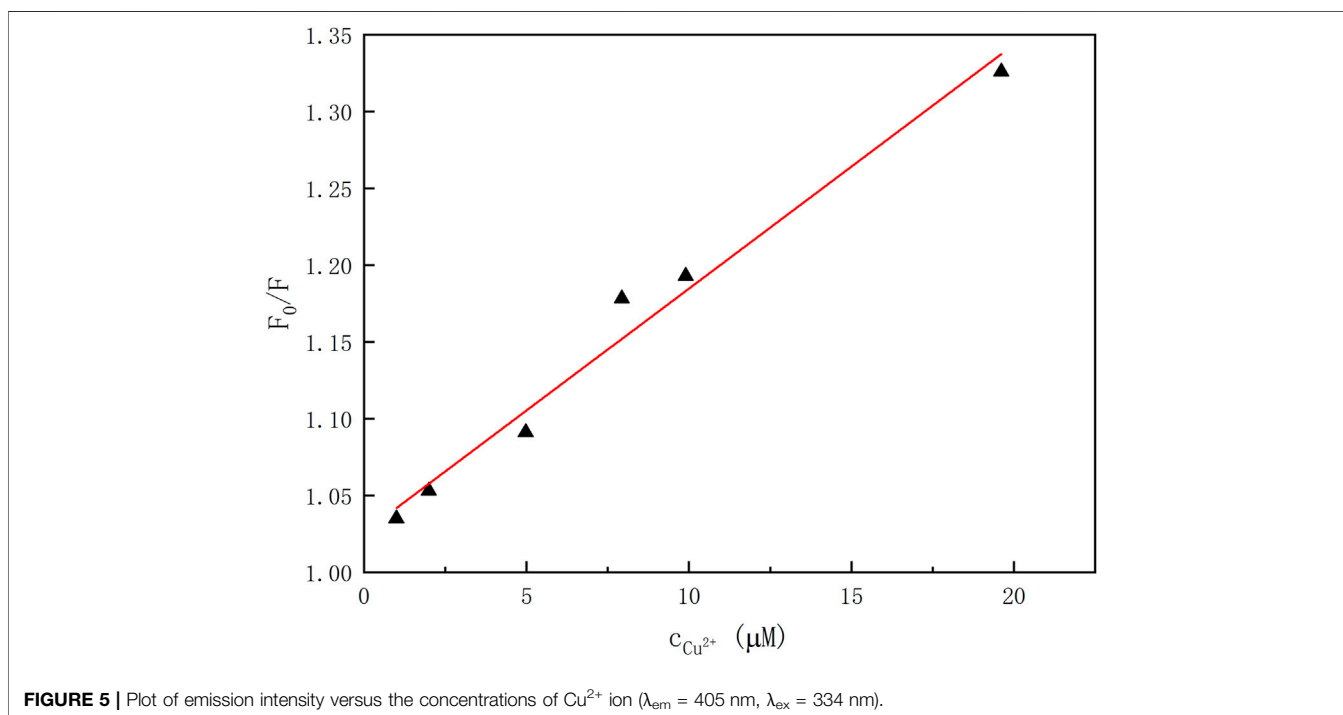
fluorescence of **1** under the same conditions as the aforementioned metal ions, suggesting that there is a strong interaction between 1,3,4-oxadiazole moieties of **1** and Cu^{2+} ion over the other metal ions.

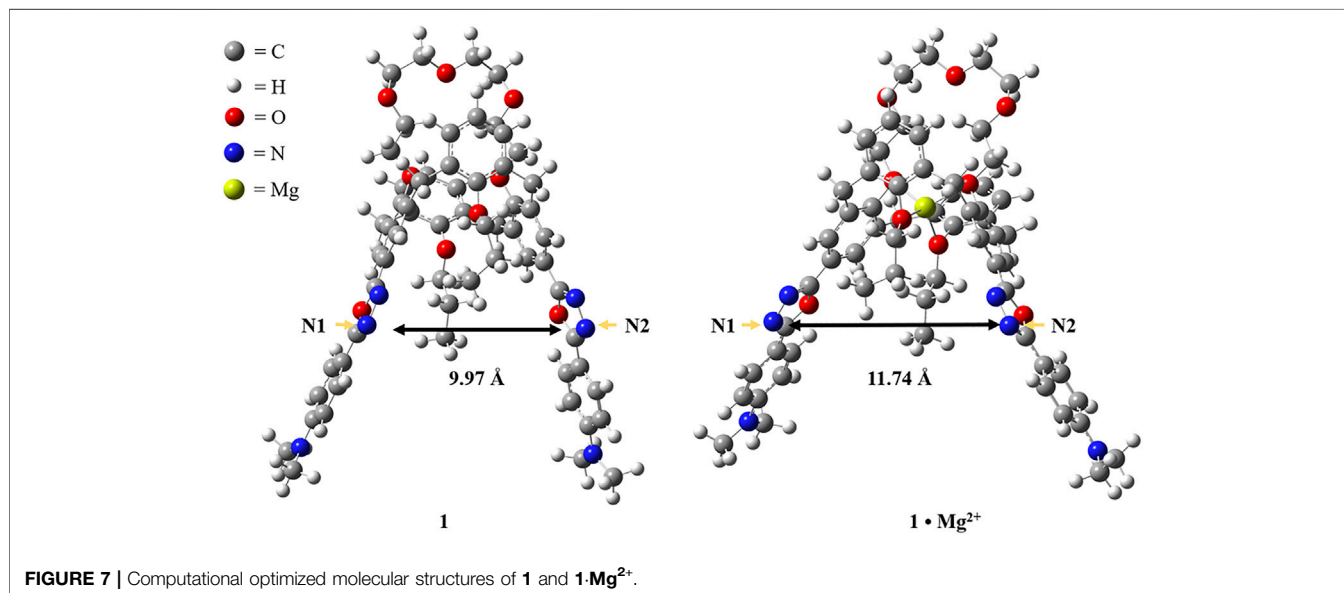
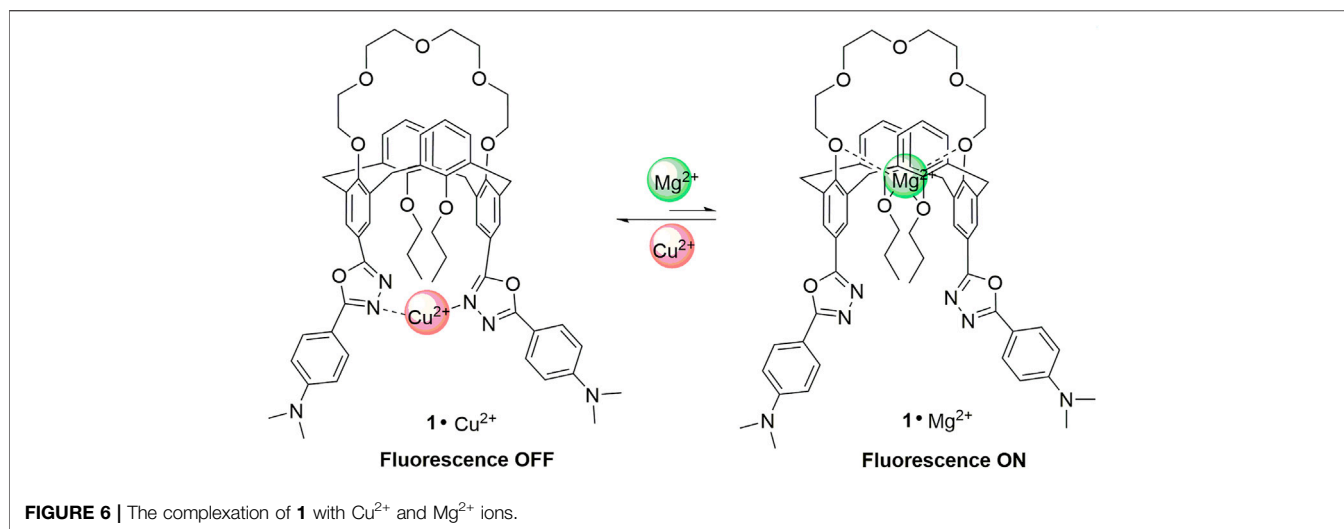
The fluorescence emission properties of **1** in the presence of Cu^{2+} and a competitive metal ion were measured to investigate the selective recognition for Cu^{2+} . As shown in **Figure 4**, no apparent changes were observed in fluorescence intensity when 10 equivalent amounts of transition metal ions (Co^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} , Mn^{2+} , and Ag^+) were added to the solution of **1** and Cu^{2+} (10 equiv). This suggested that the recognition for Cu^{2+} was not interrupted by the competitive

transition metal ions; thus, the receptor **1** might act as a selective fluorescent chemosensor for Cu^{2+} . The addition of alkali metal ions (Na^+ and K^+) to the solution of **1** and Cu^{2+} could increase the fluorescence intensity slightly, while the alkaline earth metal ions (Mg^{2+} and Ca^{2+}) could revive the emission significantly.

In order to elicit the binding property of the chemosensor **1** toward Cu^{2+} ion, fluorescence titration of **1** ($1.0 \times 10^{-5} \text{ mol/L}$) with Cu^{2+} ion (0–2 equiv) was carried out (**Supplementary Figure S6**). According to the fluorescence titration curves of **1** with Cu^{2+} ion at room temperatures, the association constant K_a was calculated as $1.6 \times 10^{-4} \text{ L}\cdot\text{mol}^{-1}$ ($R = 0.97526$) for the **1**– Cu^{2+} complex by the Benesi–Hildebrand plot (Thordarson, 2011) (**Figure 5**). Moreover, the emission intensity of **1** is linearly proportional to the Cu^{2+} concentration in the range of 0–20 μM .

The fluorescence changes of **1** upon addition of Cu^{2+} and Mg^{2+} ions are displayed in **Figure 6**. The nitrogen atoms of the 1,3,4-oxadiazole units can bind with Cu^{2+} to form the complex **1**· Cu^{2+} , and the paramagnetic nature of Cu^{2+} ion could strongly quench the fluorescence of the 1,3,4-oxadiazole units through the electron transfer mechanism, which is consistent to the results reported in literature (Han et al., 2012). In contrast, the polyether ring (crown-5 moiety) and the oxygens from the two propoxyl groups could provide coordination sites with the alkaline earth metal ions to form the complex **1**· Mg^{2+} , which will change the molecular conformation as well as the space distance of the two 1,3,4-oxadiazole units. Consequently, the decomplexations between the 1,3,4-oxadiazoles and Cu^{2+} ions took place and resulted in the increase of the fluorescence. Thus, the receptor **1** might be acted as an on–off–on switchable fluorescent chemosensor triggered by the exchange of Cu^{2+} and Mg^{2+} .





To gain a better understanding about the switchable fluorescence of the chemosensor **1**, DFT calculations with the GAUSSIAN 09 series of programs (Frisch et al., 2013) were carried out to analyze the molecular structures of **1** and **1**• Mg^{2+} , and DFT method B3-LYP with 6-31G(d) basis set was used for geometry optimizations (A. D. Becke, 1993). As shown in **Figure 7**, the distance between N1 and N2 in the free receptor **1** is 9.97 Å, while the corresponding distance is 11.74 Å in the complex **1**• Mg^{2+} , indicating that the molecular conformation changed simultaneously due to the allosteric effect (Kumar et al., 2012; Ni et al., 2013). The conformational change as well as the increase in distance makes it difficult for the chemosensor **1** to coordinate with Cu^{2+} ion to form the stable complex, which reasonably explains the fact that the addition of

Mg^{2+} ions to the solution of **1** and Cu^{2+} can trigger the revival of fluorescence.

CONCLUSION

In summary, we have designed a new type of fluorescent chemosensor based on a 1,3-alternate calix[4]crown with two different cationic binding sites. The 1,3,4-oxadiazole units could bind selectively with Cu^{2+} to form the complexation and resulted in the fluorescence quenching of the chemosensor. The presence of various transition metal ions does not interfere with the quenching process, while the alkaline earth metal ions Mg^{2+} might be entrapped by the crown-5 moiety and revive the fluorescence significantly due to the allosteric effect. As the

chemosensor in this work is not soluble in water, it is difficult to investigate the Cu²⁺ ions' detection under physiological conditions. Devising a water-soluble chemosensor for Cu²⁺ ions is in progress in our lab.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JH designed the work and wrote the manuscript. CS synthesized and characterized the compounds. CS and SD carried out the

UV-Vis absorption and fluorescence studies. TZ carried out the DFT calculations. JH revised and edited the manuscript. All authors contributed to discussion on the results for the manuscript.

FUNDING

This work was financially supported by the National Natural Science Foundation of China (No. 21272130) and the 111 Project (grant no. B12015).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2021.766442/full#supplementary-material>

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