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Synthesis, structural characterization, and fluorescent chemosensory properties of novel molecular clips based on diethoxycarbonyl glycoluril

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Abstract—A pair of novel fluorescent molecular clips was synthesized from diethoxycarbonal glycoluril cyclic ether and 1,2-dihydro-indazol-3-one. Their structures and conformations were confirmed by single crystal X-ray diffraction and chemosensory properties were studied by fluorescent spectroscope. Both of them exhibited selective recognition toward Fe^{3+} over other metal ions examined in DMF/CH_3OH (50:1, v/v).

Recognition and sensing of heavy and transition metal ions via artificial receptors are of current interest in supramolecular chemistry because of their significant importance in chemical, biological, and environmental assays.[1] Of particular interest in this regard are fluorescent sensors, because they have both high sensitivity and ease of signal transduction.[2] Up to now, many fluorescent molecular sensors and switches for heavy and transition metal ions such as Pb^{2+}, Hg^{2+}, Cu^{2+}, and Zn^{2+} have been developed.[3–6] However, examples of specific fluorosensors for Fe^{3+} are still scarce.[7] Iron is an essential element for humans and plays an important role in biochemical and nutritional processes. Many proteins and enzymes contain ferric ions either for structural purposes or as part of a catalytic site.[8] Therefore, the development of selective as well as sensitive fluorescent sensors for ferric ions is still a challenge.

Glycoluril is an important building block for supramolecular chemistry, and its derivatives have been used as the basis for molecular clips,[9] molecular capsules,[10] anion-binding receptors,[11] xerogels,[12] and the cucurbit[*n*]uril (CB[*n*]) family.[13] However, there are few studies having been carried out to explore its utilization as a platform for the synthesis of fluorescent chemosensors for ionic guest in recent years.[14] In this Letter, we report the synthesis and X-ray structure of a pair of novel molecular clips **1a** and **1b** from diethoxycarbonyl glycoluril and 1,2-dihydro-indazol-3-one together with an evaluation of its utility as a new class of fluorescent Fe^{3+} sensor. To the best of our knowledge, this is the first report on fluorescent chemosensors based on glycoluril developed for metal ion recognition.

The new fluorescent clip molecules **1a** and **1b** were synthesized as outlined in Scheme 1. Diethoxycarbonal glycoluril cyclic ether **5** was prepared according to reported procedure.[15] After condensation of **5** with 2 equiv of 1,2-dihydro-indazol-3-one in $MeSO_3H$ at 80 °C according to the previous method,[16] the desired product diastereomers, **1a** and **1b**[17] were obtained in 35% and 26% yields, respectively. Although no obvious difference can be observed for the ^1H NMR spectrum of isomers **1a** and **1b**, assignment of them was possible with help of ^{13}C NMR. Isomer **1a** possesses a C_2 symmetric axis through the molecular plane perpendicularly, causing two carbonyl groups of glycoluril ring with the same chemical environment and only one signal appearing at 154.2 ppm, whereas two carbonyl groups of glycoluril

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Keywords: Diethoxycarbonyl glycoluril; Molecular clip; Fe(III); Fluorescent chemosensor.

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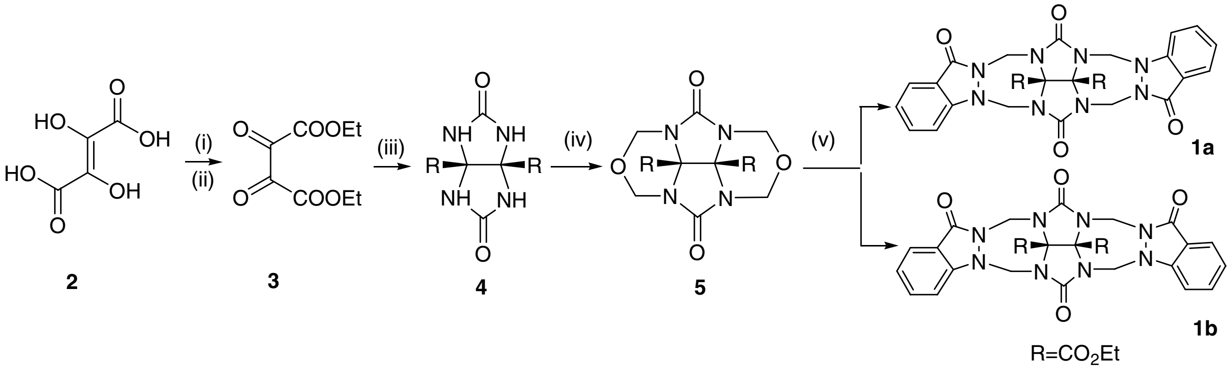

Scheme 1. Reagents and conditions: (i) AcOH, Br_2, H_2O, Na_2CO_3; (ii) EtOH, HCl (g), 0 °C; (iii) PhH, H_2NCONH_2, TFA, reflux; (iv) TFA, $(CH_2O)_n$, reflux; (v) 1,2-dihydro-indazol-3-one, $MeSO_3H$, 80 °C, 3 h, Yield: 35% for **1a** and 26% for **1b**.

ring in **1b** situated in different chemical environments result in two signals at 154.9 and 153.5 ppm. The structures and conformations of **1a** and **1b** were further elucidated by the single crystal X-ray diffraction,[18] as shown in Figures 1 and 2.

The crystals of **1a** and **1b** were obtained by the slow evaporation of solution of them in chloroform/methanol (20:1, v/v) mixture. The crystal structures of **1a** and **1b** clearly reveal that they have well-defined geometry due to the rigidity that the fused rings confer on the molecule. It is easy to disclose the difference in the structures and conformations of **1a** and **1b**. In **1a**, the distance between the two carbonyl oxygen atoms (O_2–O_3) of glycoluril ring amounts to 5.522 Å. The dihedral angle between the two phenyl rings of the sidewalls is 78.70°, and the distance between the centroids of the two phenyl rings of the sidewalls is 9.092 Å; In **1b**, the distance between the two carbonyl oxygen atoms (O_2–O_3) of glycoluril ring amounts to 5.423 Å. The dihedral angle between the two phenyl rings of the sidewalls is 48.99°, and the distance between the centroids of the two phenyl rings of the sidewalls is 7.573 Å. Because of the presence of the polarized carbonyl groups and the electron-rich nitrogen atoms in the cavity, both **1a** and **1b** have the potential to bind guests by means of hydrogen bonding, π–π stacking interactions and a so-called 'cavity-effect'.

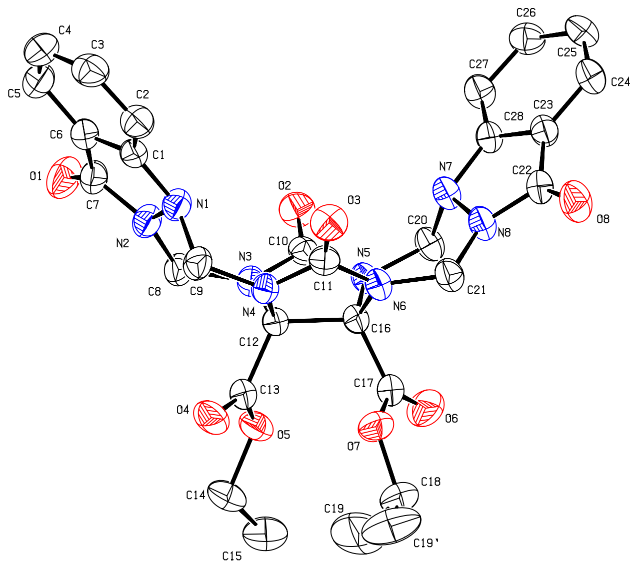

Figure 1. The molecular structure of **1a**. Hydrogen atoms and solvent molecules omitted for clarity.

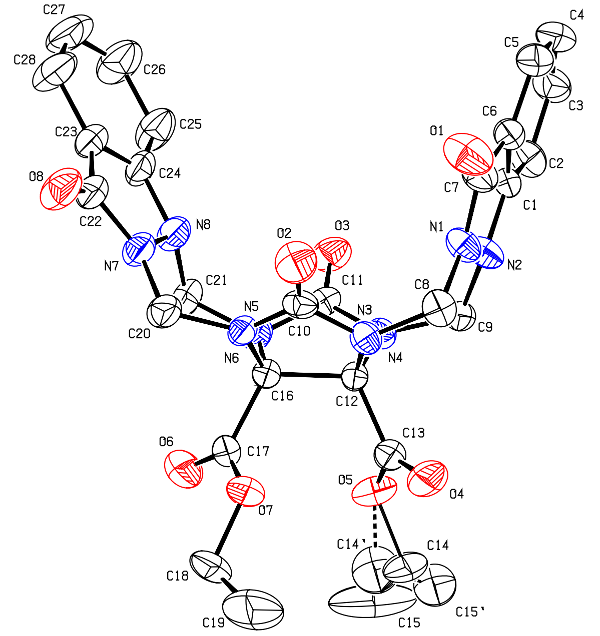

Figure 2. The molecular structure of **1b**. Hydrogen atoms and solvent molecules omitted for clarity.

The chemosensory behavior of isomers **1a** and **1b** were investigated by fluorescence measurements. The changes of the fluorescence properties of 1×10^{-5} M of **1a** and **1b** in DMF/CH_3OH (50:1, v/v) caused by 15 equiv of various metal ions (K^+, Mg^{2+}, Hg^{2+}, Cd^{2+}, Fe^{3+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Pb^{2+}, Cr^{3+}, and Ce^{3+}) were measured once their emission intensity were constant. The results showed Fe^{3+} produced significant quenching in the fluorescent emission of **1a** and **1b**, the other tested metals only show relatively insignificant changes (Figs. 3 and 4). So it can be concluded that **1a** and **1b** have a higher selectivity for recognition of Fe^{3+}. Moreover, since sensors **1a** and **1b** have the same functional groups but different structures and conformations, in the same con-

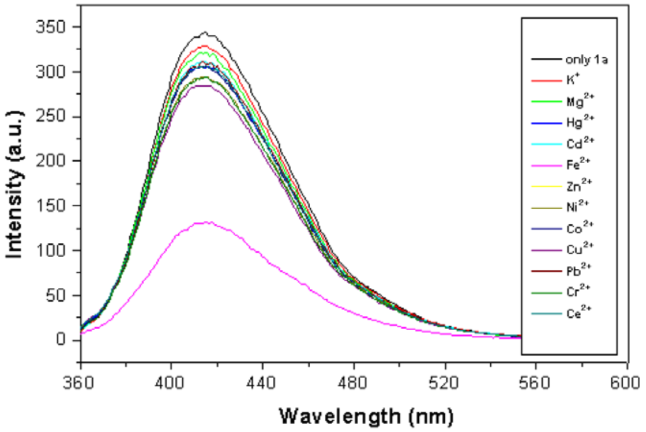

Figure 3. Fluorescence emission changes of **1a** (1×10^{-5} M) in DMF–MeOH (50:1, v/v) in the presence of 15×10^{-5} M various metal ions (excitation at 328 nm).

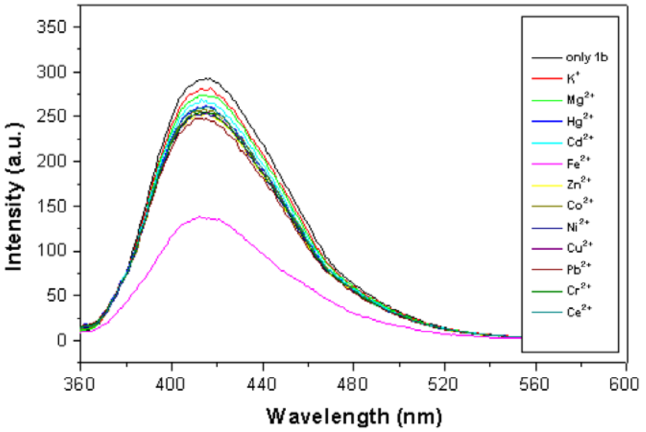

Figure 4. Fluorescence emission changes of **1b** (1×10^{-5} M) in DMF–MeOH (50:1, v/v) in the presence of 15×10^{-5} M various metal ions (excitation at 328 nm).

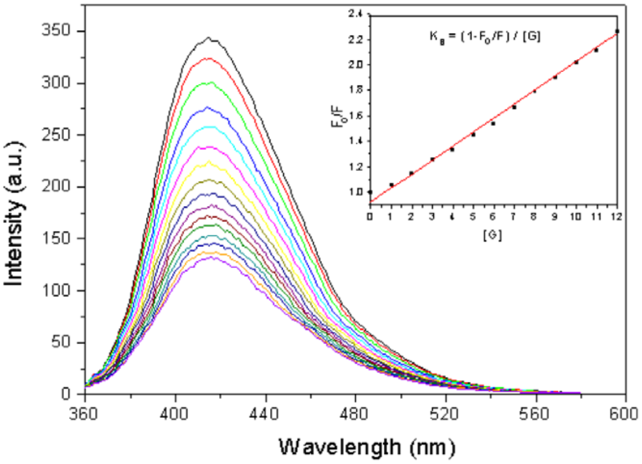

Figure 5. Fluorescence emission spectra (excitation at 328 nm) of **1a** (1×10^{-5} M) in DMF–MeOH (50:1, v/v) in the presence of $Fe(H_2O)_6Cl_3$. The concentration of Fe^{3+}: 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, and 15×10^{-5} M; Inset: Stern–Volmer plot of the emission data.

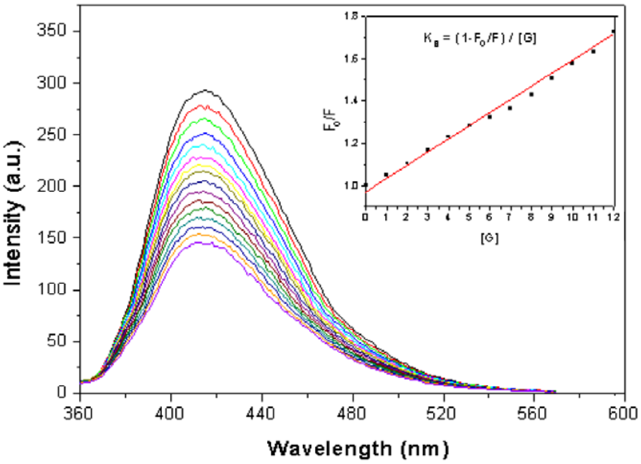

Figure 6. Fluorescence emission spectra (excitation at 328 nm) of **1b** (1×10^{-5} M) in DMF–MeOH (50:1, v/v) in the presence of $Fe(H_2O)_6Cl_3$. The concentration of Fe^{3+}: 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, and 15×10^{-5} M; Inset: Stern–Volmer plot of the emission data.

ditions, the fluorescence emission intensity of **1a** is higher than that of **1b**.

The sensitivity of the fluorescence emission response of **1a** and **1b** toward Fe^{3+} was subsequently examined under the same conditions with various Fe^{3+} concentrations (Figs. 5 and 6). The fluorescence intensity ($\lambda_{em} = 415$ nm) of **1a** and **1b** was decreased continually upon the addition of Fe^{3+} with no significant change in the position of the emission maxima. When the concentration of Fe^{3+} increased to 15 equiv, the fluorescence intensity of **1a** and **1b** were reduced to 39% and 49% of the initial one, respectively. From Stern–Volmer plot (the fluorescence quenching followed the Stern–Volmer equation),[19] both hosts **1a** and **1b** formed 1:1 stoichiometry complex with Fe^{3+}, and the association constants were estimated 1.106×10^4 and 6.227×10^3 M^{-1}, respectively.

To investigate the quench mechanism, for **1a** and **1b**, Fe^{3+} may be easily establish coordinative interactions with the polarized carbonyl groups and the nitrogen atoms in their cavities than other metal ions examined, the capture of Fe^{3+} resulted in the electron or energy transfer from the excited aromatic sidewalls with nitrogen atom conjugated to the benzene ring of them to Fe^{3+}; thus, **1a** and **1b** showed quench fluorescence emission for Fe^{3+} and provided a high selectivity for Fe^{3+} over the other tested metal ions. Moreover, the difference in the structures and conformations of **1a** and **1b** resulted in different association constants of them with Fe^{3+}.

In conclusion, we have described the synthesis and structural characterization of a pair of novel fluorescent clip molecules **1a** and **1b** derived from diethoxycarbonyl glycoluril. The studies of fluorescence emission spectra clearly showed that isomers **1a** and **1b** were two good sensors in the selective recognition for Fe^{3+} over other metal ions examined. Moreover, **1a** and **1b** showed different association constants with Fe^{3+} because of the difference in their structures and conformations. Further studies on their fluorescent quench mechanism toward Fe^{3+} are in progress.

Acknowledgments

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17. To a flask containing 1,2-dihydro-indazol-3-one (0.367 g, 2.74 mmol), was added anhyd $MeSO_3H$ (10 mL) and the mixture were stirred at 80 °C until homogeneous. Compound **5**[15] (0.507 g, 1.37 mmol) was added in one portion and the flask was sealed and heated at 80 °C for 3 h. The reaction mixture was allowed to cool and then poured into water (100 mL). The pale precipitate was collected by filtration over a medium fritted funnel and washed with water (50 mL) and dried under vacuum, flash chromatography gave compound **1a** (0.289 g, yield: 35%) and **1b** (0.214 g, yield: 26%) as a white solid, respectively. Compound **1a**: mp: 266–267 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85–7.75 (m, 2H), 7.65–7.55 (m, 2H), 7.35–7.20 (m, 4H), 5.87 (d, $J = 13.0$ Hz, 2H), 5.71 (d, $J = 14.0$ Hz, 2H), 5.09 (d, $J = 13.0$ Hz, 2H), 4.48 (d, $J = 14.0$ Hz, 2H), 4.40–4.30 (m, 4H), 1.36 (t, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 163.9, 154.2, 148.5, 133.8, 124.6, 123.7, 117.8, 112.4, 79.8, 64.5, 59.9, 53.5, 14.0; IR (KBr, cm^{-1}): 2987, 1766, 1741, 1686, 1659, 1464, 1442, 1253, 1149, 1095, 1016, 939, 759; MS (EI) *m/z*: 603. Compound **1b**: mp: 253–254 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83–7.80 (m, 2H), 7.65–7.6 (m, 2H), 7.35–7.20 (m, 4H), 5.87 (d, $J = 13.2$ Hz, 2H), 5.66 (d, $J = 13.2$ Hz, 2H), 5.11 (d, $J = 13.2$ Hz, 2H), 4.43 (d, $J = 13.2$ Hz, 2H), 4.39–4.30 (m, 4H), 3.69 (t, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.9, 154.9, 153.5, 148.8, 133.8, 124.7, 123.9, 118.3, 112.5, 79.9, 64.5, 60.4, 53.9, 14.0; IR (KBr, cm^{-1}): 3059, 2995, 1748, 1665, 1623, 1485, 1432, 1386, 1295, 1156, 929, 753; MS (EI) *m/z*: 603.
18. *Crystal data for* **1a**. $C_{28}H_{26}N_8O_8$, $M = 602.57$, triclinic, space group $P\bar{1}$, $a = 7.7203(7)$, $b = 11.2070(9)$, $c = 16.6326(14)$ Å, $\alpha = 80.5150(10)$, $\beta = 85.5590(10)$, $\gamma = 74.5300(10)°$, $V = 1367.1(2)$ Å^3, $Z = 2$, $D_c = 1.464$ g cm^{-3}, reflections collected: 12,115, independent reflections: 6026 [$R_{int} = 0.0802$], final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0502$, $wR_2 = 0.1314$. R indices (all data): $R_1 = 0.0683$, $wR_2 = 0.1486$. CCDC 626344. *Crystal data for* **1b**. $C_{29}H_{27}Cl_3N_8O_8$, $M = 721.94$, monoclinic, space group $P2(1)/c$, $a = 7.2518(6)$, $b = 17.9922(14)$, $c = 24.5306(19)$ Å, $\alpha = 90$, $\beta = 94.346(2)$, $\gamma = 90°$, $V = 3191.4(4)$ Å^3, $Z = 4$, $D_c = 1.503$ g cm^{-3}, reflections collected: 30,507, independent reflections: 5605 [$R_{int} = 0.1894$], final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0694$, $wR_2 = 0.1623$. R indices (all data): $R_1 = 0.1161$, $wR_2 = 0.1854$. CCDC 626345.
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