32 **RESEARCH PAPER** JANUARY, 32–34 JOURNAL OF CHEMICAL RESEARCH 2009

Synthesis and binding properties of two new fluorescent molecular clips based on diethoxycarbonyl glycoluril

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Two new fluorescent molecular clips based on diethoxycarbonylglycoluril have been synthesised and their binding properties investigated by fluorescence spectroscopy to show that they can selectively bind Fe^{3+} with fluorescence quenching.

Keywords: diethoxycarbonyl glycoluril, molecular clip, fluorescence quenching, Fe^{3+}

The design of fluorescent chemsensors for the detection of ionic guests is one of the most attractive topics in supramolecular chemistry.[1,2] A chemosensor is a molecule capable of transforming chemical information, such as the presence of a particular metal ion, into an analytically useful signal. In general, chemosensors are composed of two covalently linked components: a recognition site that binds the target substance and a transducer (fluorophore) that signals the binding.[3-5]

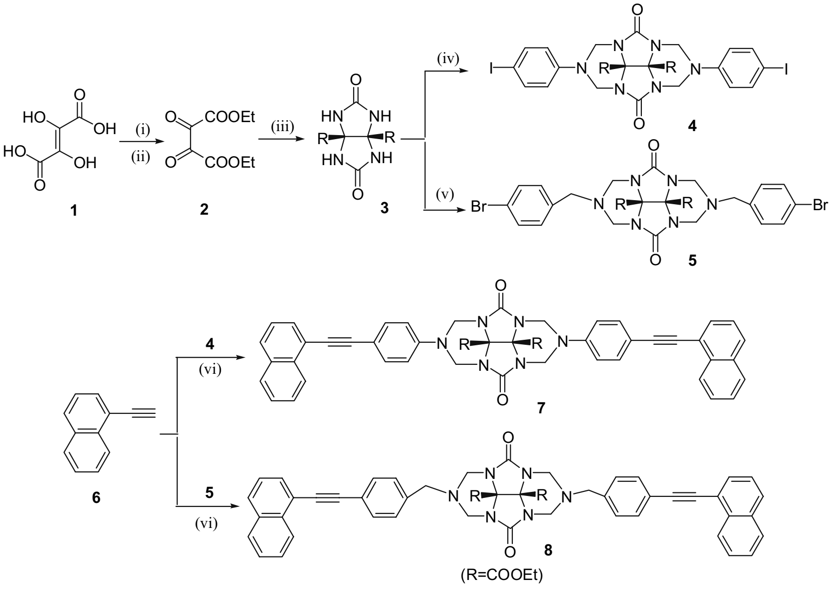
Glycoluril is an important building block for supramolecular chemistry, and its derivatives have been used as the basis for various molecular clips,[6] molecular capsules,[7] anion-binding receptors,[8] and the cucurbit[n]uril (CB[n]) family.[9] However, less attention has been paid to glycoluril and its derivatives as base molecules for constructing fluorescent chemosensors in recent years.[10]

In previous work, we have reported a pair of molecular clips derived from diethoxycarbonyl glycoluril with two 1, 2-dihydro-indazol-3-one moieties as the sidewall and developed their function as selective fluorescent chemsensors for Fe^{3+}.[11] In continuing our research to develop new fluorescent chemsensors based on glycoluril, we have designed two new molecular clips **7** and **8** which have big π-systems that can be used as the signalling subunit in their two sidewalls and two carbonyl oxygen atoms of glycoluril ring and nitrogen atoms in their cavity to be used as the potential binding sites. We now report their synthesis and a binding study with different metal ions.

The synthesis of title clip molecules **7** and **8** is shown in Scheme 1. The structure and conformations of compound **7** was also further elucidated by its single crystal X-ray structure, as shown in Fig. 1.

The crystal structure of **7** clearly reveals that it has a well-defined geometry due to the rigidity that the fused rings confer on the molecule. Interestingly, in the crystal of molecule **7** the two naphthalene rings of the sidewall are fully coplanar. The dihedral angle between two phenyl rings of the sidewalls is 18.2°, and the distance between the centroids of two phenyl rings of the sidewalls is 4.734 Å. The distance between two carbonyl oxygen atoms (O1–O2) of glycoluril ring and two nitrogen atoms (N1–N6) of sidewall amount to 5.261 Å and 5.391 Å, respectively. The polarised carbonyl groups and the electron-rich nitrogen atoms in the cavity give **7** great potential to bind metal ions.

The binding properties of the clip molecules **7** and **8** with various metal ions were investigated by fluorescent spectroscopy titration experiments. Changes of the



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) 4-Iodoaniline, HCHO(37%), MeOH, reflux; (v) (4-bromobenzylamine, HCHO(37%), MeOH, reflux; (vi)$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF,100 °C , Ar.

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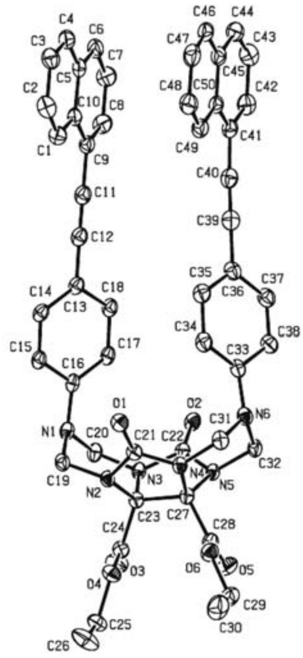

Fig. 1 The crystal structure of **7**.

fluorescence properties of 1 × 10^{-5}M of **7** and **8** in DMF/CH_3OH (50 : 1, v/v) solution caused by 15 equiv. of various metal ions (K^+, Na^+, Ag^+, Mg^{2+}, Hg^{2+}, Cd^{2+}, Fe^{3+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Pb^{2+}, Cr^{3+}, and Mn^{2+}) were measured once their emission intensity were constant. The result showed that Fe^{3+} produced significant quenching in their fluorescent emission. The other metals ion that were tested only show a relatively insignificant change (Figs 2 and 3). It can be concluded that **7** and **8** have a higher selectivity for the recognition of Fe^{3+}

The sensitivity of the fluorescence emission response of **7** and **8** towards Fe^{3+} was also examined under the same conditions with various Fe^{3+} concentrations (Figs 4 and 5). The fluorescence intensity of **7** and **8** decreased continually upon addition of Fe^{3+}. When the concentration of Fe^{3+} increased to 15 equiv, the fluorescence intensity of **7** and **8** was reduced to 47% and 22.5% of the initial value, respectively. From a Stern–Volmer plot (Figs 4 and 5), the quenching constants were estimated 8.34 × 10^3 M^{-1} and 2.447 × 10^4 M^{-1}, respectively.

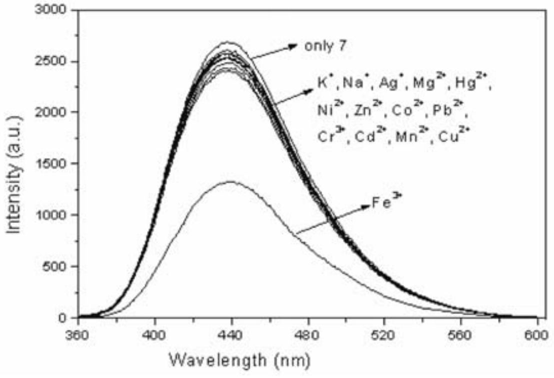

Fig. 2 Fluorescence emission changes of 7 (1 × 10^{-5}M) in DMF–MeOH (50 : 1, v/v) in the presence of 15 × 10^{-5} M various metal ions (excitation at 335 nm).

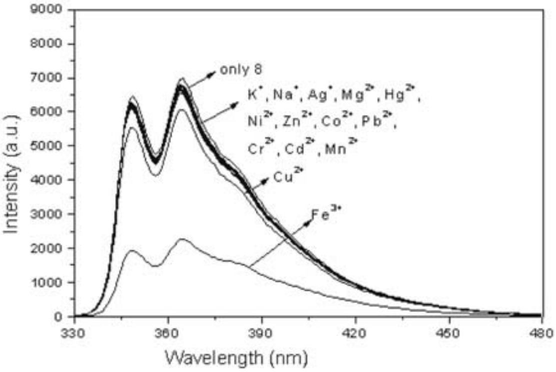

Fig. 3 Fluorescence emission changes of **8** (1 × 10^{-5}M) in DMF–MeOH (50 : 1, v/v) in the presence of 15 × 10^{-5} M various metal ions (excitation at 319 nm).

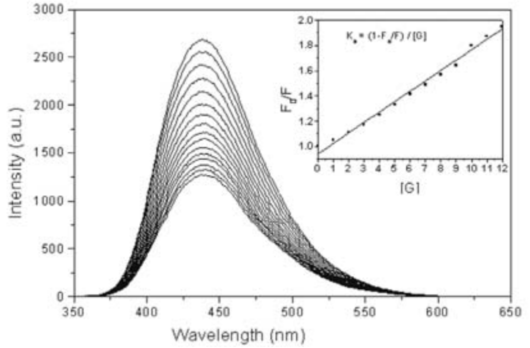

Fig. 4 Fluorescence emission spectra (excitation at 335 nm) of **7** (1 × 10^{-5} M) in DMF–MeOH (50 : 1, v/v) in the presence of different concentration of Fe^{3+}. Inset: Stern–Volmer plot of the emission data.

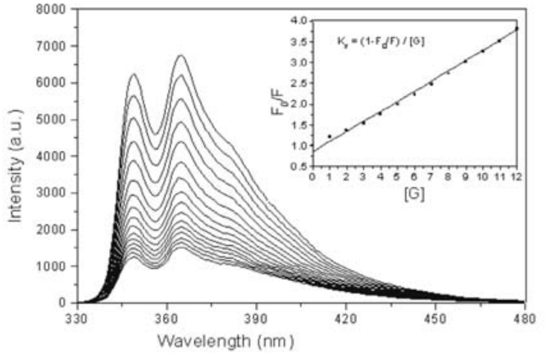

Fig. 5 Fluorescence emission spectra (excitation at 319 nm) of **8** (1 × 10^{-5} M) in DMF–MeOH (50:1, v/v) in the presence of different concentration of Fe^{3+}. Inset: Stern–Volmer plot of the emission data.

The quenching of the electronically excited state of aromatic hydrocarbons by Fe^{3+} chelates is a known phenomenom that has been the subject of extensive investigations. It has been suggested that two main pathways can account for the efficient radiationless deactivation of the singlet excited state, *i.e.* electron transfer from the excited aromatic chromophore to the metal and/or energy transfer from the excited aromatic chromophore to low-lying metal centred energy states.[15,16] Such processes could be particularly effective in the complex of **7** and **8** with Fe^{3+}, due probably to the fact that the chelated metal cation is held very close to two excited aromatic chromophore. In addition, because the molecular clips **7** and **8** have different sidewalls but the same binding properties compared to previously reported molecular clips,[11] we may draw the conclusion that the glycoluril ring plays a crucial role in the recognition of Fe^{3+}.

In conclusion, two new clip molecules derived from diethoxycarbonylglycoluril as fluorescent chemosensors have been designed and synthesised. They display high selectivity for Fe^{3+} revealed by fluorescence quenching. In future work, our efforts will be focused on the elucidation of the detailed mechanisms of these fluorescent chemosensor.

Experimental

General

All reagents obtained from commercial sources were of AR grade. Melting points were determined with XT4A micromelting point apparatus and were uncorrected. NMR spectra were recorded on a Mercury Plus-400 spectrometer with TMS as an internal reference and $CDCl_3$ as the solvent. IR were recorded on a Perkin–Elmer PE–983 IR spectrometer as KBr pellets with absorption in cm^{-1}. MS were obtained with Finnigan Trace MS instrument using EI. Elemental analyses were carried out on a Vario EL III instrument. Fluorescence spectra were determined on a Hitachi F-4500.

Synthesis

Diethoxycarbonyl glycoluril **3**[12], glycoluril derivates **4**[13] and 1-ethynyl-naphthalene **6**[14] were prepared by the literature methods.

2,6-Bis-(4-bromo-benzyl)-4,8-dioxo-tetrahydro-2,3a,4a,6,7a,8a-hexaaza-cyclopenta[def] fluorene-8b,8c-dicarboxylic acid diethyl ester (**5**): A suspension of **3** (1.43 g, 5 mmol) in 37% aq formaldehyde (3.5 mL) and MeOH (30 mL) was brought to reflux under magnetic stirring. (4-Bromobenzylamine (1.85 g, 10 mmol) in MeOH (20 ml) was added slowly, dropwise (over 1 h) to the mixture. The refluxing was continued. The reaction was monitored by TLC. The solvent was removed under reduced pressure and the solid residue was separated by column chromatography (SiO_2, $CHCl_3$–MeOH, 50:1) to give pure compound **5** (2.49 g, 71%)as a white solid. M.p.203–204 °C. IR (KBr, cm^{-1}): 2930w, 2857w, 2967w, 1749 s, 1717 s, 1413 m, 1293 m; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45(d, *J* = 8.4 Hz,4H, ArH), 7.24 (d, *J* = 8.4 Hz, 4H, ArH), 4.83 (d, *J* = 14.0 Hz, 4H, NCH_2N), 3.80 (d, *J* = 14.0 Hz, 4H, NCH_2N), 4.26(q, *J* = 7.2 Hz, 4H, OCH_2CH_3), 1.30 (t, *J* = 7.2 Hz,6H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.3, 158.5, 135.8, 131.6, 130.6, 121.7, 76.2, 63.4, 59.9, 54.7, 13.9; EI-MS: *m/z* 706.0 $[M + 2H]^{2+}$. Anal. Calcd for $C_{28}H_{30}Br_2N_6O_6$ (704.0): C, 47.61; H, 4.28; N, 11.90; Found: C, 47.52; H, 4.20; N, 11.79%.

General procedure for preparation of **7** *and* **8**

To a solution of $Pd(PPh_3)_2Cl_2$ (36 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol) and compound **4**–**5** (0.50 mmol) in freshly distilled Et_3N (15 ml) and DMF (25 ml) under Ar atmosphere at room temperature., were added compound **6** (304 mg, 2 mmol). The mixture was warmed to 100 °C for 14 h, and then the solvent was removed under reduced pressure. The solid residue was separated by flash chromatography (SiO_2, $CHCl_3$–MeOH, 50:1) to give pure compounds **7**–**8** as a yellow solid. The physical and spectroscopic data of the compounds **7** and **8** are as follows.

2,6-Bis-(4-naphthalen-1-ylethynyl-phenyl)-4,8-dioxo-tetrahydro-2,3a,4a,6,7a,8a-hexaaza-cyclopenta[def]fluorene-8b,8c-dicarboxylic acid diethyl ester (**7**): M.p.253–255 °C; IR (KBr, cm^{-1}): 3055w, 2210w, 1751 s, 1727 s, 1606 m, 1516 s, 1414 s, 1237 s, 973 s, 770 s; ^1H NMR ($CDCl_3$, 400 MHz): δ=8.30 (d, *J*=8.4 Hz, 2H, NapH), 7.70 (d, *J*=8.0 Hz, 2H, NapH), 7.59 (d, *J* = 8.4 Hz, 2H, NapH), 7.41 (d, *J* = 8.4 Hz, 4H, ArH), 7.38–7.34(m, 4H, NapH), 7.07–7.03 (m, 2H, NapH), 6.94 (d, *J* = 8.4 Hz, 4H, ArH), 5.61 (d, *J* = 14.0 Hz, 4H, NCH_2N), 4.65 (d, *J* = 14.0 Hz, 4H, NCH_2N), 4.35 (q, *J* = 6.8 Hz, 4H, OCH_2CH_3), 1.36 (m, *J* = 6.8 Hz, 6H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.01, 157.3, 145.6, 133.0, 129.9, 127.9, 126.4, 126.2, 126.0, 125.0, 121.0, 117.1, 116.2, 94.3, 86.7, 76.3, 63.5, 57.7, 14.0; EI-MS: *m/z* = 821.3$[M + H]^+$. Anal. Calcd for $C_{50}H_{40}N_6O_6$ (820.3): C, 73.16; H, 4.91; N, 10.24; Found: C, 73.03; H, 4.81; N, 10.13%.

2,6-Bis-(4-naphthalen-1-ylethynyl-benzyl)-4,8-dioxo-tetrahydro-2,3a,4a,6,7a,8a-hexaaza-cyclopenta[def]fluorene-8b,8c-dicarboxylic acid diethyl ester (**8**): M.p. 210–211 °C; IR (KBr, cm^{-1}): 3044w, 2210w, 1758 s, 1725 s, 1650w, 1461 m, 1413 s, 1293 s, 1034 s, 985 s, 710w. ^1H NMR($CDCl_3$, 400 MHz): δ = 8.43 (d, *J* = 8.0 Hz, 2H, NapH), 7. 83 (t, *J* = 7.2 Hz, 4H, NapH), 7.74 (d, *J* = 7.2 Hz, 2H, NapH), 7.65 (d, *J* = 8.0 Hz, 4H, ArH), 7.56(t, *J* = 6.8 Hz, 2H, NapH), 7.48 (d, *J* = 8.0 Hz, 2H, NapH), 7.44(d, *J* = 8.0 Hz, 4H, ArH), 4.91 (d, *J* = 14.0 Hz, 4H, NCH_2N), 4.30(d, *J* = 14.0 Hz, 4H, NCH_2N), 3.94 (s, 4H, $ArCH_2$), 4.31(q, *J* = 7.2 Hz,4H, OCH_2CH_3), 1.34 (t, *J* = 7.2 Hz, 6H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4, 158.6, 137.3, 133.2, 131.8, 130.3, 129.0, 128.7, 128.2, 126.8, 126.4, 125.2, 122.8, 120.9, 94.2, 87.7, 76.2, 63.4, 60.0, 55.2, 13.9; EI-MS: *m/z* 849.3 $[M + 1]^+$. Anal. Calcd for $C_{52}H_{44}N_6O_6$ (848.3): C, 73.57; H, 5.22; N, 9.90; Found: C, 73.46; H, 5.13; N, 9.79%.

X-ray diffraction study of compound **7**

Crystals were obtained by slow evaporation from chloroform–methanol solution (20 : 1 v/v). A yellow crystal of the title compound **7** having approximate dimensions of 0.20 mm × 0.20 mm × 0.10 mm was mounted on a glass fibre in a random orientation at 295(2) K. The determination of unit cell and the data collection were performed with MoKα radiation (α = 0.71073 Å) on a Bruker Smart Apex-CCD diffactometer with a ψ–ω scan mode. A total of 44378 reflections were collected in the range of $1.60<\theta<25.00^\circ$ at room temperature, and 8149 were independent (R_{int} = 0.0492); 3790 observed reflections with $I>2\sigma(I)$ were used in the structure determination and refinements. The structure was solved by direct methods with SHELXS-97 program and expanded by Fourier technique. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were determined with theoretical calculation. A full-matrix least-squares refinement gave the final R = 0.0878, wR = 0.2459 $[W = 1/[\sigma^2 (Fo^2) + (0.1921P)^2 + 0.0000P]$ where $P = (Fo^2 + 2Fc^2)/3$, $(\Delta/\sigma)_{max}$ = 0.000, S = 0.938, $(\Delta\rho)$max = 0.538, $(\Delta\rho)$min = -0.438 e/Å^3. All calculations were performed on a PC with SHELXS-97 program. *Crystal data*: $C_{51}H_{41}Cl_3N_6O_6$, M = 940.25, Monoclinic, space group $P_2(1)/n$, a = 12.5195(7), b = 25.0264(14), c = 15.5955(8) Å, α = 90, β = 108.0710(10), γ = 90°, V = 4645.3(4) Å^3, Z = 4, D_c = 1.344 g cm^{-3}, μ = 0.088 mm^{-1}. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 681845.

Binding studies

A stock solution of compounds **7** and **8** was prepared by dissolution in DMF/MeOH (50:1, v/v) (1.0×10^{-5}M), respectively. The solutions of metal ions were prepared from $Pb(NO_3)_2$ and the chlorides of K^+, Na^+, Mg^{2+}, Hg^{2+}, Cd^{2+}, Fe^{3+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Pb^{2+}, Cr^{3+}, and Mn^{2+}, respectively, and were dissolved in methanol (3.0×10^{-3} M). Fluorescence titration was performed by filling 3 ml solution of compound **7** or **8** in a quartz cell of 1 cm optical path length, and adding different stock solutions of cations into the quartz cell portionwise using a microsyringe each time. Both excitation and emission bands were set at 2.5 nm.

We thank the Central China Normal University, the National Natural Science Foundation of China (Grant No. 20672042) for financial support.

Received 10 August 2008; accepted 27 October 2008
Paper 08/0105 doi: 10.3184/030823409X396418

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