

A synthetic study of a ditopic homooxalix[3]arene for fluorescence enhanced detection of heavy and transition metal ions

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Abstract: A pyrene-appended ratiometric fluorescent chemosensor **L** based on a ditopic homooxalix[3]arene has been synthesized and characterized. The fluorescence spectrum changes of **L** suggested that chemosensor shows to detect HTM ions ratiometrically and with variable sensitivity according to the substituents. ¹H NMR titration experiment indicated that the three triazole ligands prefer binding with Hg²⁺, Pb²⁺ and Zn²⁺, resulting in a conformational change that produces monomer emission of the pyrene increasing accompany the excimer quenching. However, the addition of Fe³⁺, which may be is suitable accommodated by the cavity of **L**, makes the pyrene units move closer to each other, and a discernible increase in the emission intensity of the static excimer is observed. Therefore, it is believed that the ditopic scaffold of the calix[3]arene as a specific molecular spacer here plays an important role in blocking of the heavy atom effect of HTM ion by insulating the fluorophore from ionophore through a long distance between the metal cation and pyrene moiety.

1. Introduction

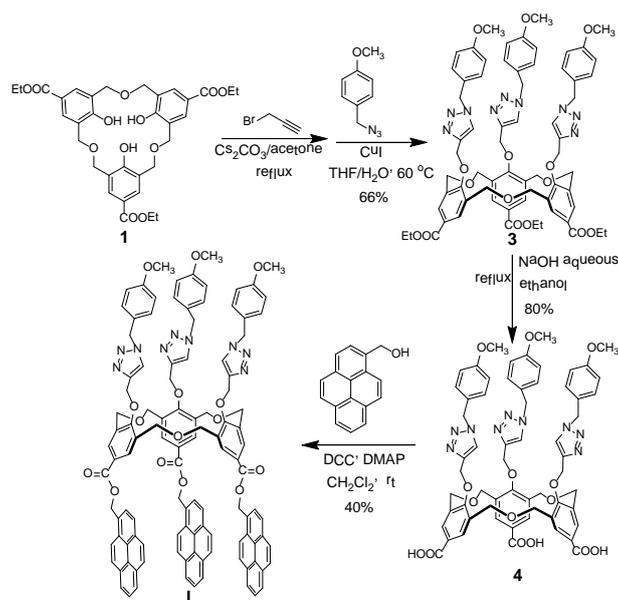
The selective and sensitive detection of heavy and transition metal (HTM) ions has been (and is) of great interest given that such metal ions play an important role in many environmental and biological processes.¹ Methods including atomic absorption, ICP atomic emission, UV-vis absorption, and fluorescence spectroscopy have been utilized to measure such ions. Among these approaches, fluorescence chemosensors are widely used because of their high sensitivity and facile operation. In general, a fluorescence enhancement (FE) response for detecting metal ions is highly preferable in practical applications rather than fluorescence quenching in terms of increased sensitivity and selectivity.² However, due to the heavy atom effect of HTM ions, the fluorescence emission of sensors is usually quenched via enhanced spin-orbital

coupling,³ energy or electron transfer⁴ during the probing process. The development of turn-on fluorescent chemosensors for HTM ions is still a challenge.⁵ In particular, additional synthetic approaches are necessary to be able to drive forward some general aspects of future such probe design. To prevent fluorescence quenching and to preserve the ability for FE to take place upon binding of the HTM ions, the key point is to block the heavy atom effect of the HTM ion. For example, Yoon *et al.* reported that a type of off-on fluorescent probe for HTM ions can be exploited through increasing the oxidation potential of the fluorophore of (1,8-naphthalimide) by introducing a carbonyl group as a sacrificial donor between the analyte binding sites and the fluorophore to inhibited the heavy atom effect of HTM ions.⁶ Meanwhile, our previous studies suggested that chemosensors based on a homooxacalix[3]arene,⁷ which possessing three nitrogen triazole ligands as the ionophore and three pyrene groups as the fluorophore on the lower rim, could isolate the Pb²⁺ ion from the fluorophore and maintain the monomer emission of pyrene. However, fluorescence quenching by the Pb²⁺ ion could be observed if the fluorophore with two triazole moieties incorporated onto a tailored calix[4]arene scaffold was employed.⁸ These results provided unequivocal clues to us that a FE chemosensor for HTM ions could indeed be obtained by rational structure design. In this work, we present a new FE chemosensor through the synthetic approach of insulating the fluorophore from the ionophore by a specific molecular spacer.

2. Results and discussion

Calixarenes are an important class of macrocyclic compounds and have found wide application in molecular recognition and sensing as a result of their utility in rigid scaffolds.⁹ For example, calix[4]arenes and thiacalix[4]arenes are one of the most actively molecular platforms used in molecular recognition of cations,¹⁰ anions,¹¹ and in many biological applications such as enzyme mimics,¹² and in drug delivery systems.¹³ On the other hand, Shinkai *et al.*¹⁴ and our studies¹⁵ suggested that the homooxacalix[3]arene has the ability to create heteroditopic receptors capable of binding cations/anions or fullerene through an allosteric effect by incorporating two different types of ionophore on the upper and lower rims. In other words, use of the homooxacalix[3]arene as the platform has potential application in the development of novel ratiometric chemosensors, typically by introducing an ionophore at the lower rim and a fluorophore at the upper rim, respectively. Furthermore, among the different fluorogenic units, pyrene is one of the most useful for constructing ratiometric sensors due to its novel signal excimer-to-monomer emission (IE/IM). In

particular, the IE/IM parameter is very sensitive to structural change.^{10a,16} It is against this background that the ratiometric chemosensor **L** has been synthesized. As shown in [Scheme 1](#), chemosensor **L** was synthesized in 40 % yield by a series of synthetic steps ([Figures S1-S6](#)). Pyrene was selected as the fluorophore (signal report) at the upper rim, and the 1, 2, 3-triazole moiety was chosen as an ionophore (metal binding site) at the lower rim; triazole was chosen as it can selectively bind various HTM ions.^{7,8,17}



Scheme 1. Synthesis of chemosensor **L**

The fluorescence emission spectrum of **L** was determined in CH_3CN solution ([Fig. 1](#)). The chemosensor **L** itself exhibits a characteristic pyrene excimer band at 482 nm in the absence of metal ions. Upon addition of 6.0 equiv of the various tested metal ions to the solution of **L**, it was found that no significant spectrum changes for **L** were observed in the presence of alkali metal ions. However, the addition of HTM ions caused an obviously increase of monomer emission at the expense of the excimer emission, the extent of which depended on the nature of the ion. The exception was Fe^{3+} , where a fluorescence intensity increase was observed at 465 nm. Most importantly, it should be noted that the addition of HTM ions including both Cu^{2+} and Hg^{2+} , which are the most notorious fluorescence quenchers amongst the HTM ions, clearly increased the monomer emission of pyrene in the present system. Interestingly, both Cu^{2+} and Hg^{2+} were shown to quench the monomer emission of pyrene in a separate homooxalix[3]arene derived chemosensor in CH_3CN solution,⁷ which possessed a similar molecular structure to **L**. Therefore, based on these observations, it can

be concluded that the use of the ditopic scaffold homooxacalix[3]arene in chemosensor **L** here plays a key role in blocking the heavy atom effect of HTM ions.

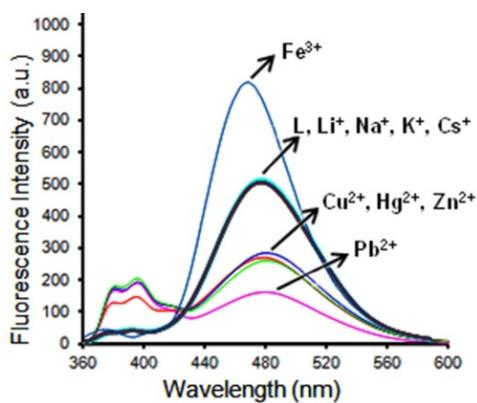


Fig. 1. Fluorescence intensity changes of the Chemosensor **L** (1.0 μM) in CH₃CN at 298 K upon addition of various metal perchlorates (6.0 μM) with an excitation at 343 nm.

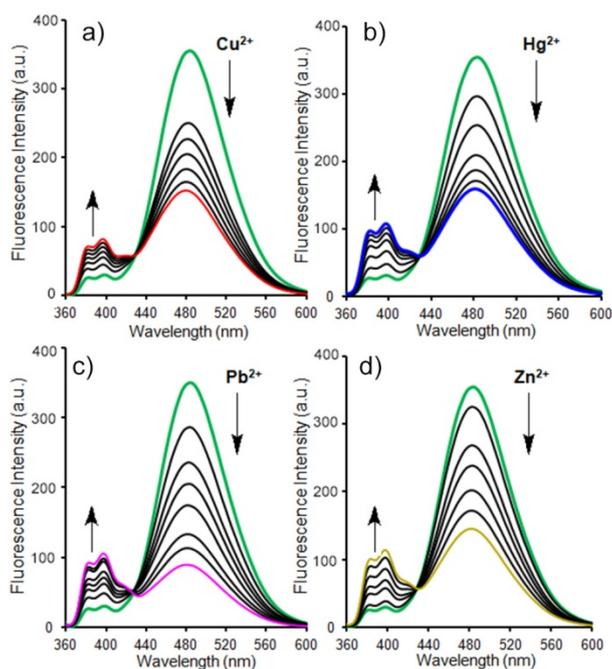


Fig. 2. Fluorescence spectrum of chemosensor **L** (1.0 μM) upon addition of increasing concentrations of (0-6 μM) (a) Cu(ClO₄)₂, (b) Hg(ClO₄)₂, (c) Pb(ClO₄)₂, (d) Zn(ClO₄)₂, in CH₃CN with an excitation at 343 nm.

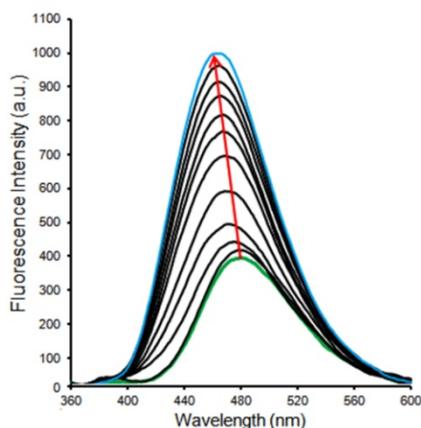


Fig. 3. Fluorescence spectrum of chemosensor **L** ($1.0 \mu\text{M}$) upon addition of increasing concentrations of $\text{Fe}(\text{ClO}_4)_3$ ($0\text{-}6 \mu\text{M}$) in CH_3CN with an excitation at 343 nm .

Fig. 2 shows the fluorescence spectrum changes of **L** upon the addition of increasing concentrations of Cu^{2+} , Hg^{2+} , Pb^{2+} and Zn^{2+} in CH_3CN solution, respectively; it can be seen that the four HTM cations exhibit similar binding behaviour towards **L**. No shift of the maximum of monomer and excimer emissions of the pyrene moiety was observed upon the addition of these cations, but the fluorescence intensity of the excimer emission of **L** markedly decreased and the monomer emission intensity significantly increased. The association constants for complexation¹⁸ were determined to be: $\text{L-Cu}^{2+} = 1.89 \times 10^5 \text{ M}^{-1}$, $\text{L-Hg}^{2+} = 1.67 \times 10^5 \text{ M}^{-1}$, $\text{L-Pb}^{2+} = 6.88 \times 10^5 \text{ M}^{-1}$, $\text{L-Zn}^{2+} = 2.05 \times 10^5 \text{ M}^{-1}$, respectively (**Figure S7**). Interestingly, upon addition of increasing concentrations of Fe^{3+} to the solution **L**, as shown in **Fig. 3**, we observed unusual fluorescence changes, namely the excimer emission of **L** gradually increased with a 17 nm blue shift from 482 nm to 465 nm . This phenomenon is likely to be a consequence of the effect of the formation of a *static* excimer of pyrene in a manner that is similar to that found in examples described by Kim and co-workers.¹⁹ There are two kinds of excimer: a *dynamic* excimer and a *static* excimer which exist depending upon the origin of the pyrene dimer.²⁰ The former results from a pyrene dimer produced in the excited state, whereas the latter arises from a pyrene dimer in the ground state. Formation of a *dynamic* or *static* excimer depends on the distance between the pyrene units, namely the distance between the pyrenes of a *static* excimer is generally shorter than in the *dynamic* excimer.^{19a} This result is thus consistent with complexation of Fe^{3+} to **L** making the distance of the three pyrenes on **L** shorter than in the uncomplexed version of **L**. From the titration, the association constant²¹ of L-Fe^{3+} was calculated to be $1.61 \times 10^5 \text{ M}^{-1}$ (**Figure S8**).

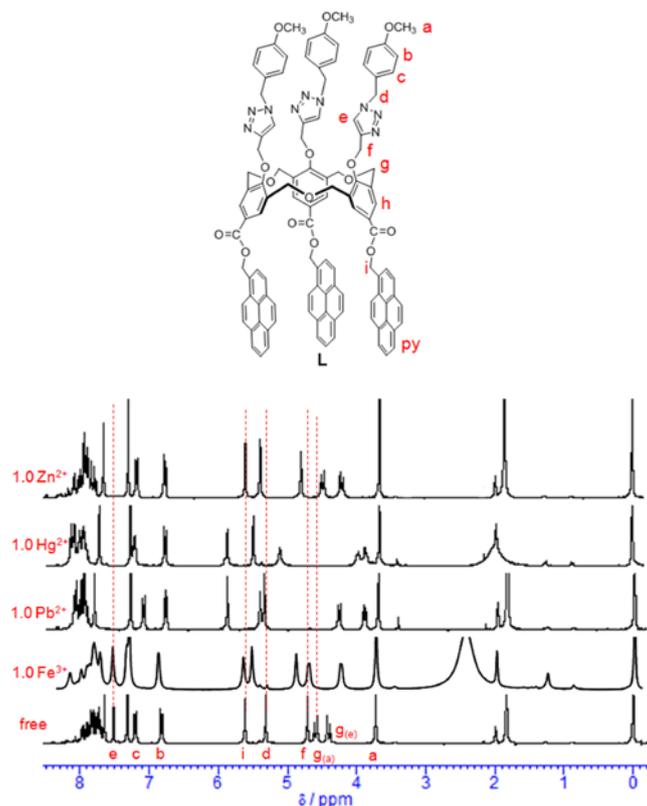


Fig. 4. Partial chemical shifts of **L** (2.0 mM) at 300 MHz in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (v/v, 10:1) solution in the presence of 1.0 equiv of $\text{Fe}(\text{ClO}_4)_3$, $\text{Pb}(\text{ClO}_4)_2$, $\text{Hg}(\text{ClO}_4)_2$, $\text{Zn}(\text{ClO}_4)_2$, respectively.

To seek more detailed information on the binding properties of chemosensor **L** towards Fe^{3+} and other HTM ions, ^1H NMR titration experiments were carried out in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v). The spectrum differences are shown in Fig. 4. For example, in the presence of 1.0 equiv of Fe^{3+} , the peak of the protons on the **L** appeared boarding due to the paramagnetic nature of Fe^{3+} , but we can see that the cluster of peaks of the pyrenyl protons was becoming crowded, in particular, the OCH_2 -bridge linker protons $\text{H}_{\text{g(ax)}}$ and $\text{H}_{\text{g(eq)}}$, which have used to track the complexation behaviour of the calixarene with a guest by measurement of the tilt angle of the parent cavity rings,²² were shifted either downfield by 0.12 ppm or upfield by 0.15 ppm, respectively. In addition, the peak of the OCH_2 -triazole linker proton H_{f} was shifted downfield by 0.19 ppm from δ 4.71 to 4.90 ppm. Furthermore, it should be noted that the protons on the phenol of calix[3]arene parent also experienced a downfield shift and buried in the peaks of pyrene moiety. This result suggested that the cavity of the homooxacalix[3]arene was mainly involved in the complexation of Fe^{3+} . For example, the downfield shift of $\text{H}_{\text{g(ax)}}$ and H_{f} can be attributed to their proximity to the Fe^{3+} ions. The crowded chemical shift of the protons on the pyrenes was due to the deshielding effect of the pyrene excimer moiety, namely, the coordination forces of the Fe^{3+} ion with the parent cavity of the calix[3]arene makes the pyrene moieties

move closer to each other to form the *static* excimer and the shorter distance between the pyrenes thus causes a stronger deshielding effect at the pyrenes compared to that of the *dynamic* excimer.^{19a} Earlier, Kumar *et al.* reported a series of pyrene-appended artificial receptors based on thiacalix[4]arene in *cone*²³ or 1,3-*alternate*²⁴ conformation and which shown selectivity towards Fe^{3+} ions. However, in that case both monomer and excimer emissions of the pyrene on the chemosensors have been quenched by the addition of Fe^{3+} ions. Therefore, these results further indicated that the ditopic homooxalix[3]arene scaffold of **L** here have an advantage in the blocking of heavy atom effect of Fe^{3+} ions.

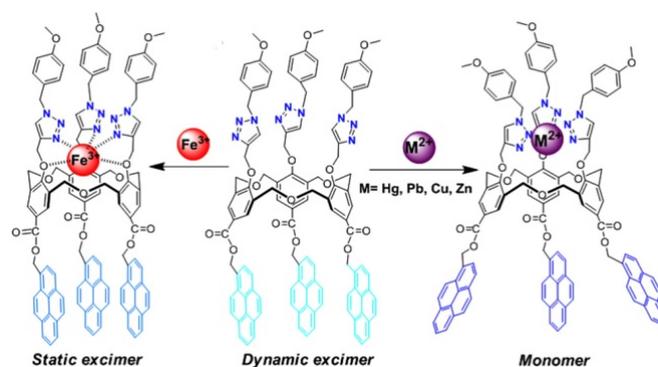


Fig. 5. Proposed binding modes of **L** with different HTM ions.

On the other hand, upon addition of 1.0 equiv of the other HTM ions such as Hg^{2+} , Pb^{2+} and Zn^{2+} ions to the solution of **L**, it was noted that the peaks of the protons on the pyrene, H_i , H_d and H_f were shifted downfield. In particular, the triazole protons H_e undergoes a larger downfield shift, whereas both the OCH_2 -bridge linker protons $\text{H}_{g(\text{ax})}$ and $\text{H}_{g(\text{eq})}$ were shifted upfield, indicating that the three triazole groups are involved in the complexation of these metal ions. In this process, the complexation of the triazole moieties with the HTM ion induces the pyrene groups to move away from each other and thereby inhibits the $\pi \dots \pi$ stacking required for generating the excimer emission. As a result, a characteristic increase of the monomer emission with a concomitant decrease of the excimer emission of the pyrene moiety can be observed in the fluorescence spectrum (Fig. 2). Accordingly, based on the above analysis, the selective binding structure of **L** with HTM ions can be proposed as shown in Fig. 5.

3. Conclusion

In summary, we have developed a new type of fluorescent chemosensor based on a homooxacalix[3]arene scaffold by incorporating with three pyrene fluorophore on the wide rim and three substituted triazole pendants on the other side of the platform. From a structural viewpoint, chemosensor **L** represents a structure complementary to the one reported by us previously,⁷ and it definitely shows distinctive cation sensing behavior. When a HTM ion is bound by **L**, which has two different recognition sites, the cation chooses the more favorable binding location. For example, the three triazole ligands prefer binding with Cu^{2+} , Hg^{2+} , Pb^{2+} and Zn^{2+} , resulting in a conformational change that produces monomer emission of the pyrene increasing accompany the excimer quenching. On the other hand, the addition of Fe^{3+} , which is suitable for accommodation by the cavity of **L**, makes the pyrene units move closer to each other, and a discernible increase in the emission intensity of the *static* excimer is observed. It is believed that the scaffold of the ditopic calix[3]arene as a molecular spacer plays an important role in the blocking of the heavy atom effect of HTM ion by insulating the fluorophore from ionophore through a long distance. Considering there remains increased interest in establishing general concepts for fluorescence ‘turn-on’ chemosensors, this study provides a new approach for the rational design of HTM ion probes.

4. Experimental section

4.1. Instruments

Proton nuclear magnetic resonance (^1H NMR) spectrum was recorded on a Nippon Denshi JEOL FT-300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si . Mass spectrum was obtained on a Nippon Denshi JMS-01SA-2 mass spectrometer at ionization energy of 70 eV; m/z values reported include the parent ion peak. Fluorescence spectrum was recorded on JASCO FP-750 spectrometer. Elemental analyses were performed by Yanaco MT-5.

4.2. Materials

The preparation of compound **1** followed a literature procedure.^{14b} Compound **2** was prepared according to a procedure developed for a related compound.²⁵

Preparation of compound **2**: A solution of compound **1** (0.63 g, 1 mmol) and Cs₂CO₃ (1.96 g, 6 mmol) was refluxed for 1 h in dry acetone (50 ml). 3-bromo-1-propyne (propargyl bromide (0.71 g, 6 mmol) were added and the mixture refluxed for 24 h. The solvent was evaporated and the residue partitioned between 10% HCl and CH₂Cl₂. The organic layer was separated and dried (MgSO₄) and the solvents were evaporated. The residue was dried to afford a mixture of *cone* and *partial-cone* of propargyl substituted compound as a colorless oil (0.47 g, 0.64 mmol, 64%) which was used directly without further purification.

Preparation of compound **3**: Copper iodide (20 mg) and 4-methoxybenzyl azide (0.65 g, 4 mmol) was added to the mixture solution of compound **2** (0.47 g, 0.64 mmol) in 50 mL THF/H₂O (v/v = 10:1). The mixture was heated at 60 °C for 24 h. The resulting solution was cooled and extracted trice with CHCl₃. The organic layer was separated and dried (MgSO₄) and evaporated to give the solid crude product. The residue eluted from a column chromatography of silica gel with hexane/CH₂Cl₂ (v/v =6:1) to give the desired product compound **3** as white solid (520 mg, 66.2%). Mp 179-181°C. ¹H NMR (300 MHz, CDCl₃) δ 1.32 (t, 9H, CH₃), 3.77 (s, 9H, benzene-OMe), 4.26 (q, 6H, -COOCH₂), 4.40 (d, 6H, ether bridge), 4.58 (d, 6H, ether bridge), 4.71 (s, 6H, ArO-CH₂-triazole). 5.35 (s, 6H, triazole-CH₂-benzen), 6.86 (d, 6H, benzen-H), 7.24 (d, 6H, benzen-H), 7.50 (s, 3H, triazole-H), 7.54 (6H, s, Ar-H). MS *m/z* 1228.96 [M⁺]. Anal. Calcd for C₆₆H₆₉N₉O₁₅ (1228.31): C, 64.54; H, 5.66; N, 10.26; Found: C, 64.78; H, 5.81; N, 10.14.

Preparation of compound **4**: Compound **3** (520 mg, 0.42 mmol) was added to a solution of 400 mg NaOH (ethanol/water, 4:1, 25 mL) and refluxed at 50 °C for 4 h. After being cooled to room temperature, the reaction mixture was washed with 20 mL ethylacetate and then the aqueous layer was neutralized with 1N HCl solution and extracted with CH₂Cl₂ (30 mL×3), washed with water (50 mL × 2), and brine (50 mL). After drying with MgSO₄, the solvent was removed under reduced pressure. The residue was recrystallized from CH₂Cl₂/hexane (1:3, v/v) to afford compound **4** as white solid (388 mg, yeald 80.8%). Mp 199–200°C, ¹H NMR (300 MHz, CDCl₃) δ 3.81 (s, 9H, benzene-OMe), 4.56 (d, 6H, ether bridge), 4.64 (d, 6H, ether bridge), 4.85 (s, 6H, ArO-CH₂-triazole). 5.47 (s, 6H, triazole-CH₂-benzen), 6.84 (d, 6H, benzen-H), 7.22 (d, 6H, benzen-H), 7.47 (s, 3H, triazole-H), 7.62 (6H, s, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ 53.59, 55.31, 68.03, 68.34, 114.44, 123.32, 125.29, 126.82, 129.71, 131.84, 132.09, 143.41, 157.65, 159.90, 171.77. MS *m/z* 1144.82 [M⁺]. Anal. Calcd for C₆₀H₅₇N₉O₁₅ (1144.15): C, 62.99; H, 5.02; N, 11.02; Found: C, 62.51; H, 5.09; N, 11.13.

Preparation of compound **L**: Compound **4** (388 mg, 0.34 mmol) and 1-Pyrenemethanol (255 mg, 1.1 mmol) in 15 mL of CH₂Cl₂. The mixture was stirred for 30 min at 0 °C (ice/water bath) under N₂. Then 1,3-dicyclohexylcarbodiimide (DCC) (330 mg, 2 mmol) and 4-(dimethylamino)-pyridine (DMAP) (90 mg, 0.75

mmol) were added, and the mixture was stirred for 30 min at 0 °C. The cooling bath was then removed and the solution was stirred at room temperature. After being stirred for 24 h, the reaction mixture was filtered to yield a clear filtrate and washed with water and brine. The organic layer was dried over MgSO₄, filtered, and evaporated. The residue was washed with hexane and methanol and recrystallized from CH₂Cl₂/hexane (1:4, v/v) to afford the yellow solid **L** (243 mg, 40%). Mp 143-144°C. ¹H NMR (300 MHz, CDCl₃) δ 3.72 (s, 9H, benzene-OMe), 4.38 (d, 6H, ether bridge), 4.59 (d, 6H, ether bridge), 4.70 (s, 6H, ArO-CH₂-triazole), 5.30 (s, 6H, triazole-CH₂-benzen), 5.63 (s, 6H, COO-CH₂- pyrene), 6.82 (d, 6H, benzen-H), 7.19 (d, 6H, benzen-H), 7.46 (s, 3H, triazole-H), 7.65 (6H, s, Ar-H), 7.77-7.94 (m, 27H, pyrene-H). ¹³C NMR (75 MHz, CDCl₃) δ 53.48, 55.25, 64.95, 67.52, 69.00, 114.35, 122.34, 123.33, 124.29, 124.32, 124.37, 124.99, 125.03, 125.60, 126.10, 126.23, 126.88, 127.05, 127.14, 127.67, 128.47, 128.94, 129.69, 130.38, 130.93, 130.99, 131.65, 132.21, 143.63, 158.68, 159.82, 165.29. MS m/z 1787.45 [M⁺]. Anal. Calcd for C₁₁₁H₈₇N₉O₁₅ (1786.93): C, 74.61; H, 4.91; N, 7.05; Found: C, 74.42; H, 4.98; N, 6.94.

Acknowledgements

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Supplementary data

Experimental procedures, ¹H and ¹³C NMR spectral data, associate constant data are available. Supplementary data associated with this article can be found, in the online version.

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