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Turn-on ratiometric fluorescent sensor for Pb^{2+} detection

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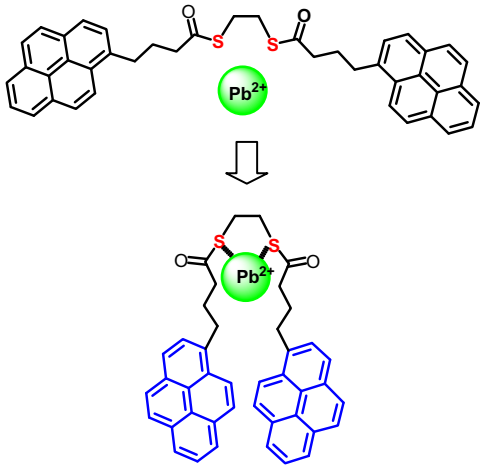
ABSTRACT

We report a ratiometric lead fluorescent sensor (LFS-1) with high affinity to Pb^{2+} that shows considerable selectivity over 12 other physiological related metal cations in aqueous media. Binding induces excimer formation, providing a highly sensitive ratiometric measure of lead concentrations.

As one of the major industrial pollutants, Pb^{2+} causes adverse environmental impacts and human health related problems, particularly for children (where lead poisoning is defined as blood levels above 5 μM).[1] Therefore, developing low-complexity sensing approaches with high affinity for detecting Pb^{2+} remains an active research area.[2] In the past decade, considerable efforts have been devoted to designing and synthesizing fluorescent chemosensors for Pb^{2+} analysis due to their high sensitivity, simplicity, and adaptability to different platforms that facilitate routine screening.[3] Many Pb^{2+}-responsive fluorescent sensors, in which biological molecules, polymers, and small organic scaffolds are utilized as recognition units, have been reported.[4–6] However, compared to other heavy metal ions sensors, the ion specificity and sensitivity of current generation fluorescent sensors for Pb^{2+} limit their utility.[7] Currently, major challenges for Pb^{2+}-responsive fluorescent sensors require increases in both (i) the recognition affinity to Pb^{2+} without interference from other competing metal ions and (ii) the solubility in aqueous media to allow detection of Pb^{2+} in biological samples.[8] Herein, we report the synthesis and properties of a highly soluble turn-on lead fluorescent sensor (LFS-1) that binds Pb^{2+} with high affinity and displays selectivity against other physiological metals in aqueous media. Upon binding Pb^{2+} LFS-1 exhibits a strong excimer peak at 469 nm resulting from contact interactions between pyrene monomers within LFS-1 that are brought together upon metal chelation, which is evident both in model systems and in human blood plasma, indicating the feasibility of using LFS-1 to rapidly screen for Pb^{2+}.

LFS-1 was prepared by using pyrene as the fluorophore, which has been studied extensively because of its strong fluorescence intensity and distinctive excimer emission that results in a large spectral red-shift that facilitates measurements in complex environments.[9] Sensors were designed using the sulfur of a thio-ester moiety as a receptor to recognize Pb^{2+}, thereby facilitating formation of a dimeric interaction between pyrene moieties through a coordinating interaction that is required for excimer formation (Scheme 1). LFS-1 was synthesized by a two-step reaction. 1-Pyrenebutyric acid was refluxed with thionyl chloride for 3 h to give 1-pyrenebutyric chloride. Esterification between 1 equiv 1, 2-ethanedithiol and 2 equiv of 1-pyrenebutyric chloride afforded LFS-1 with 88% yield (Scheme 2). An alternative sensor (i.e., LFS-2) with a shorted linker connecting the thio-ester and pyrene functionalities based on 1-pyrenecarboxylic acid also was prepared



Scheme 1. Fluorescent sensor for Pb^{2+}.

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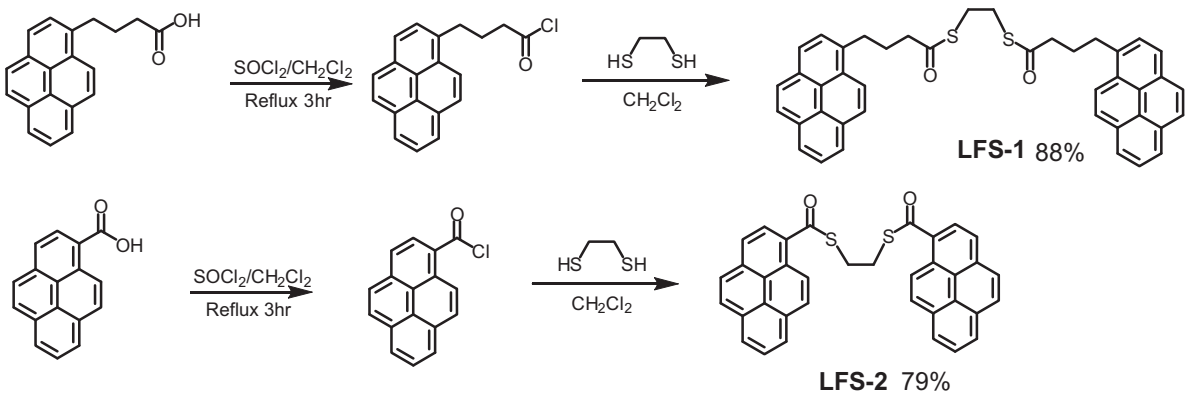

Scheme 2. The synthetic route of LFS-1 and LFS-2.

using the same synthetic route. The structures of LFS-1 and LFS-2 were confirmed by ^{1}H NMR, ^{13}C NMR, and elemental analysis.[10,11]

Spectroscopic measurements were carried out in aqueous buffer (i.e., 10 mM HEPES containing 10% DMSO at pH 7.4). LFS-1 displays characteristic spectral features of pyrene, with absorption bands at 326 and 342 nm and fluorescence emission bands at 375 and 395 nm (λ_{ex} = 355 nm). Upon addition of 10 M equiv of Pb^{2+}, LFS-1(1.0 μM) displays large changes in the absorption spectrum, resulting in decreases in absorption bands at 328 and 342 nm and the appearance of a new peak at 357 nm (Fig. 1A). In the presence of Pb^{2+}, the fluorescence emission spectrum of LFS-1 also exhibits a new band at 469 nm together with a substantial quenching in the 365–425 nm spectral region (Fig. 1B). Observed spectral changes are indicative of the formation of an excimer complex resulting from contact interactions between pyrene monomers in the presence of Pb^{2+} that arise due to π–π stacking interactions. Coupled with the large depletion of fluorescence at 365–425 nm, these results indicate that LFS-1 has the necessary spectral properties to serve as a sensitive ratiometric probe in response to Pb^{2+}.[12] Specifically, as the excimer fluorescence apparent at 469 nm is absent prior to Pb^{2+} binding, it is apparent that the intensity ratio at 469 nm normalized by that at 395 nm (I_{469}/I_{395}) represents a sensitive means to measure Pb^{2+} levels in complex environments using the LFS-1 sensor. While, additional sensitivity is possible by selecting excitation wavelengths that limit excitation of the LFS-1 sensor prior to Pb^{2+} binding, which shifts the absorption spectra toward the red (Fig. 1A), we emphasize the use of LFS-1 under conditions that excite both the free (unbound) and Pb^{2+} chelated species that facilitate ratiometric measurements of the apparent binding affinity.

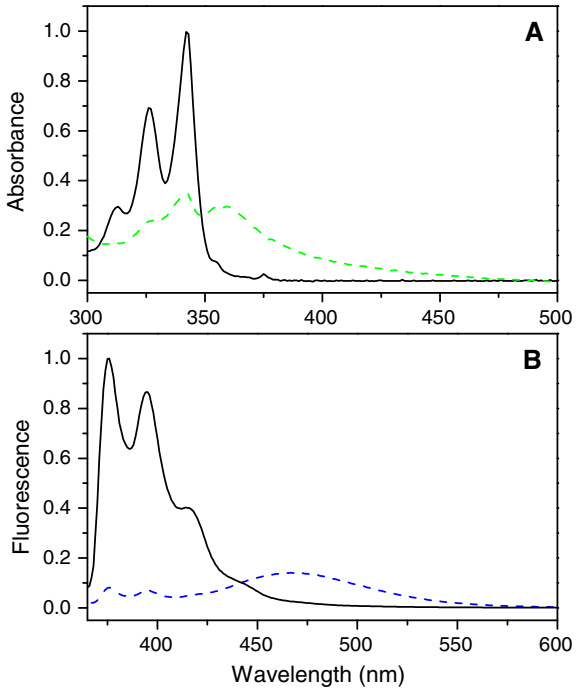

Figure 1. Absorption (A) and fluorescence emission (λ_{ex} = 355 nm) (B) spectra of LFS-1 (1.0 μM) in aqueous buffer (i.e., 10 mM HEPES containing 10% DMSO at pH 7.4), prior to (—) and following addition of 10 μM Pb^{2+} (- - -).

To explore further the binding properties of LFS-1, titration experiments were conducted by using Pb^{2+} with concentrations ranging from 0 to 10 μM (Fig. 2). Upon addition of Pb^{2+} to LFS-1, there is a 92% decrease in the fluorescence of monomer coincident with detection of an excimer fluorescence at 469 nm that provides a high signal-to-noise measurement using 1 μM LFS-1. Based on the titration data, maximal spectral changes are observed upon addition of a near equimolar stoichiometry of Pb^{2+} relative to the LFS-1 (i.e., 1 μM), indicating that the binding affinity of LFS-I for Pb^{2+} is in the submicromolar range needed for practical measurements of Pb^{2+} in drinking water.[13]

The selectivity of LFS-1 to bind Pb^{2+} relative to other common metals was investigated by ratiometric measurements (i.e., I_{469}/I_{395}) in the presence of various biologically and environmentally relevant metal ions. All of measurements were conducted by using the perchlorate of different metal ions (100 μM) and LFS-1(1.0 μM) in aqueous buffer (i.e., 10 mM HEPES containing 10% DMSO at pH 7.4). LFS-1 displayed an extremely selective turn-on response to Pb^{2+} with a maximum I_{469}/I_{395} ratio of 2.1 (no corrections for contributions of scattered light at 469 nm were made). In contrast, upon addition of K^{+}, Na^{+}, Ag^{+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, and Mg^{2+}, LFS-1 exhibited no significant excimer emission at 469 nm; albeit fluorescence quenching at 375 nm leads to small increases in the calculated I_{469}/I_{395} ratio (<0.5) that can be reduced by correcting for scattered light by using suitable blank subtraction or modifying the detection wavelength used to monitor excimer formation toward the red (Fig. 3A). Especially for Ag^{+}, Cu^{2+} and Hg^{2+}, the fluorescence at 395 nm was quenched more than 96%. Fluorescence quenching is possible by two mechanisms involving either excimer formation with concomitant decreases in the fluorescence of the pyrene monomer or through spin-orbital coupling that arises from a coupling between metal ions and pyrene.[14,15] Due to the high I_{469}/I_{395} ratio, the fluorescence quenching trigged by Pb^{2+} binding was attributed mainly to the excimer formation rather than in intrinsic quenching. In comparison, some other metals (e.g., Hg^{2+}) exhibit no excimer fluorescence upon binding LFS-1

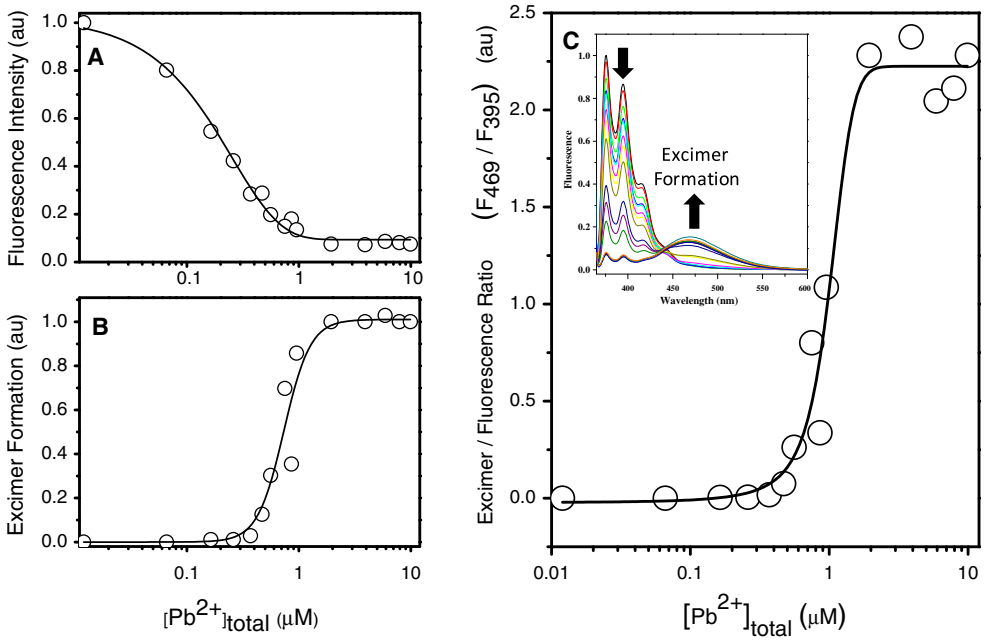

Figure 2. Fluorescence (A), excimer (B), and calculated ratiometric signal (C) of LFS-1 (1.0 μM) in response to increasing amounts of Pb^{2+} (λ_{ex} = 355 nm) in aqueous buffer (i.e., 10 mM HEPES containing 10% DMSO at pH 7.4).

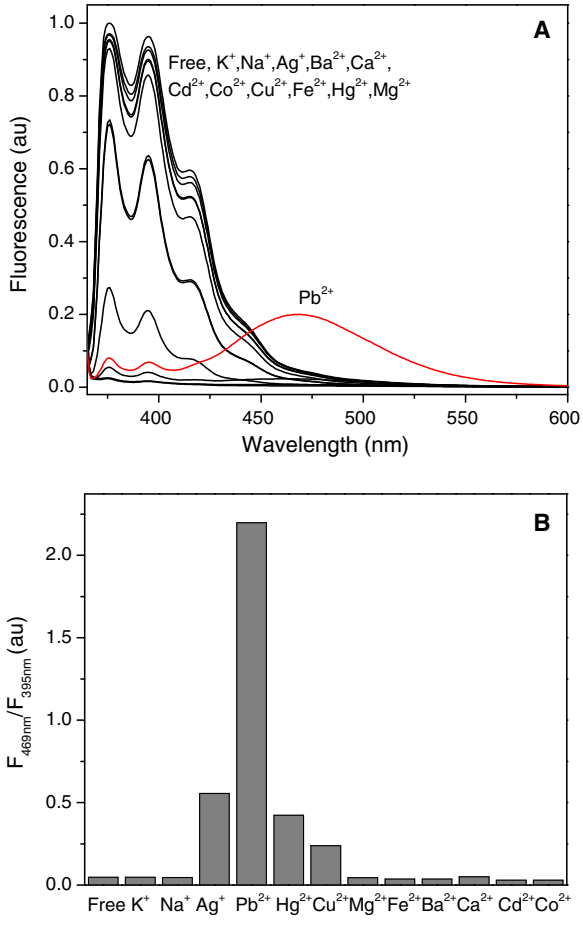

Figure 3. Selective association between LFS-1 and Pb^{2+}. (A) Fluorescence emission spectra of LFS-1 (1.0 μM) upon addition of K^+, Na^+, Ag^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, and Pb^{2+} (100 equiv) in 10 mM HEPES buffer (containing 10% DMSO at pH 7.4) (λ_{ex} = 355 nm). (B) The gray bars represent the ratio of excimer emission fluorescence at 469 nm to monomer emission at 395 nm (I_{469}/I_{395}) in presence of indicated cations.

despite substantial decreases in their fluorescence intensity, which are attributed to spin-orbital coupling (Fig. 3B).

For the practical analysis of Pb^{2+}, it is important that the binding affinity between LFS-1 and Pb^{2+} is not substantially affected by the presence of other cations, such as Ca^{2+}, Cd^{2+}, Fe^{2+}, and Hg^{2+} that commonly cause significant interference. [16] Possible competition between Pb^{2+} and other metals against LFS-1 was measured by using mixed solutions containing 100 μM Pb^{2+} and 100 μM each of K^+, Na^+, Ag^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}. Irrespective of the addition of any of the mixed solution to LFS-1(1.0 μM), the observed pyrene excimer signal was observed at 469 nm with no appreciable changes to the calculated spectroscopic ratio (I_{469}/I_{395}) (Fig. S2). These results indicate that the high-affinity interaction between LFS-1 and Pb^{2+} is selective relative to other cations. Moreover, several anions, including Cl^-, NO_3^-, ClO_4^-, AcO^-, SO_4^{2-}, CO_3^{2-}, and PO_4^{3-}, (obtained by using their sodium salt; 100 μM), also were used to examine possible interference in the binding interaction between LFS-1 and Pb^{2+}. No fluorescence quenching or dimer emission triggered by these anions is observed (Fig. S3, Supplementary data), indicating that LFS-1 represents a robust sensor for high-throughput measurements against Pb^{2+}.

To further explore the possibility of using LFS-1 as a useful reagent for Pb^{2+} analysis in biological systems, LFS-1 was examined in human blood plasma. After incubating with blood plasma diluted 10-fold in an aqueous buffer containing 1.0 μM Pb^{2+} at 37 °C for 5 min, LFS-1 showed fluorescence quenching at 395 nm and a substantial excimer fluorescence emission at 469 nm (Fig. 4). Although the light scattering interference from the plasma contributed to the signal (i.e., I_{469}/I_{395} = 0.1), these results confirm the biocompatibility of LFS-1 for Pb^{2+} detection. The measured signal can be further optimized using more favorable sample geometries and excitation to minimize sample scattering.

As a comparison, LFS-2 was synthesized by 1-pyrencarboxylic acid and 1, 2-ethanedithiol to investigate the influence of distance between pyrene and receptor to forming excimer of pyrene. Compared to LFS-1, the thioester of LFS-2 was appended directly to pyrene without a spacer. Based on our previous results, the decreased distance between thioester acceptor and pyrene fluorophore are

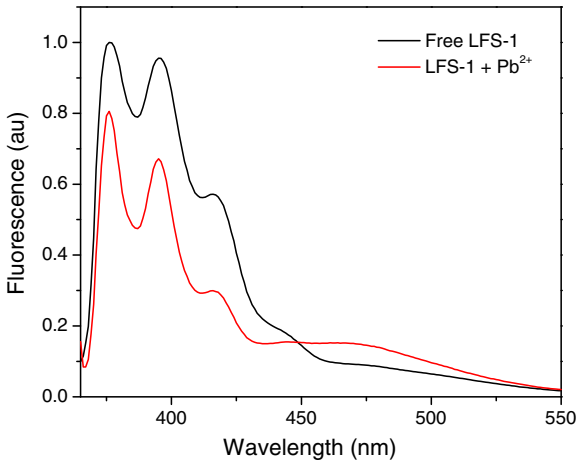

Figure 4. Excimer formation upon chelation of Pb^{2+} by LFS-1 in blood plasma. Fluoresence emission spectra of LFS-1 (1.0 μM) in human blood plasma following a 10-fold dilution to reduce scattering prior to (black line) and following (red line) addition of 1.0 μM Pb^{2+}. Sample conditions are as described in the legend to Figure 2.

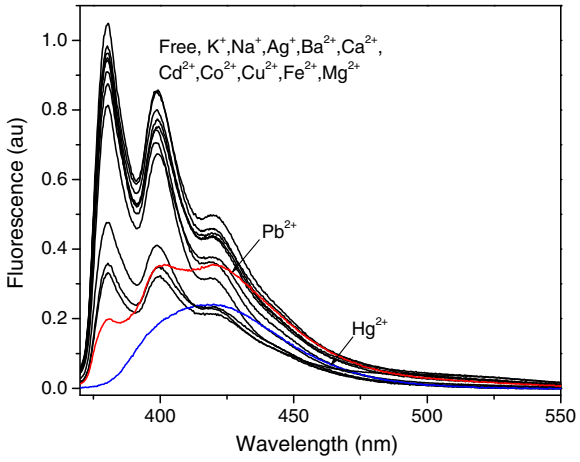

Figure 5. Selective fluorescence quenching of LFS-2 upon metal binding with no excimer formation. Fluorescence emission spectra of LFS-2 (1.0 μM) upon addition of K^+, Na^+, Ag^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, and Pb^{2+} (100 equiv) in 1.0 mM HEPES buffer (pH 7.4) containing 10% DMSO (λ_{ex} = 355 nm).

expected to result in a direct quenching of the pyrene monomer and an inability to form the pyrene dimer upon metal binding due to insufficient scaffold flexibility.[17] Fluorescence titration experiments using different metal ions were performed under the same condition used for LFS-1. Fluorescence quenching was observed without excimer emission upon addition of following metal ions: K^+, Na^+, Ag^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, and Pb^{2+}. While ion binding, particularly apparent in the presence of Hg^{2+}, significantly reduced the fluorescence emission spectra of LFS-2––in no case is there emission of the pyrene excimer (Fig. 5). This result is consistent with our observations using LFS-1, indicating that geometrical considerations associated with the linker between receptor moiety and fluorophore are essential factors that contribute to the sensor design, which requires the formation of the pyrene excimer upon Pb^{2+} binding.

In summary, we report a new pyrene-based sensor that functions as a fluorescent probe for Pb^{2+} sensing with high selectivity. LFS-1 coordinates Pb^{2+} with 1:1 complex stoichiometries. LFS-1 displayed significant pyrene excimer emission as well as the quenching of monomer in the presence of Pb^{2+}. In contrast to LFS-1, LFS-2 showed fluorescence quenching upon addition to Pb^{2+} but without emission of the pyrene excimer, indicating distinct mechanisms underlying fluorescence quenching and the formation of the pyrene dimer necessary for excimer formation. These measurements emphasize a requirement for sufficient flexibility in the probe scaffold in the rational design of fluorescent sensors requiring pyrene–pyrene interactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.075.

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10. A mixture of 1-pyrenebutyric acid (0.504 g, 1.7 mmol) and thionyl chloride (3 mL, 41.0 mmol) in 20 mL dichloromethane was refluxed for 3 h under argon atmosphere. The reaction mixture was distilled to remove excess thionyl chloride and dichlormethane to afford the compound **2** as a white solid, which was used for the next reaction without further purification. To a solution of unpurified **2** in 20 mL of dichloromethane was added 1,2-ethanedithiol (0.072 mL, 0.8 mmol) and the solution was refluxed for 1 h under argon protection. After the reaction mixture was cooled down to room temperature, dichloromethane was removed by rotary evaporation to give the crude product that was purified by column chromatography (silica, 220–400 mesh, hexane/EtOAc = 2:1 v/v). The product is isolated as a pale powder LFS-1 (0.48 g, 88%). ^{1}H NMR (300 MHz, DMSO) δ: 1.21 (m, 4H), 2.03 (m, 4H), 2.39 (m, 4H), 3.45(m, 4H), 7.92–9, 124.6, 124.7, 125.2, 125.5, 126.7, 127.1, 127.7, 127,9, 128.0, 128.7,

129.8, 130.9, 131.4, 136.9, 175.2. MS: m/z $(MH)^+$ 634.29. Anal. calcd for $C_{42}H_{34}O_2S_2$:C, 79.46; H, 5.40. Found: C, 79.68; H, 5.36.

11. A mixture of 1-pyrenecarboxylic acid (0.492 g, 2.0 mmol) and thionyl chloride (3 mL, 41.0 mmol) 20 mL dichloromethane was refluxed for 3 h under argon atmosphere. The reaction mixture was distilled to remove excess thionyl chloride and dichlormethane to afford the compound **4** as a white solid, which was used for the next reaction without further purification. To a solution of unpurified **4** in 20 mL of dichloromethane was added 1,2-ethanedithiol(0.084 mL, 1.0 mmol) and the solution was refluxed for 1 h under argon protection. After the reaction mixture was cooled down to room temperature, dichloromethane was removed by rotary evaporation to give the crude product that was purified by column chromatography (silica, 220–400 mesh, hexane/EtOAc = 2:1 v/v). The product is isolated as a pale powder LFS-2 (0.43 g, 79%). ^1H NMR (300 MHz, DMSO) δ: 1.22 (m, 4H), 8.15 (t, 2H, J = 7.5), 8.18–8.42 (m, 12H), 8.58(d, 2H, J = 7.4), 9.23 (d, 2H, J = 8.4); ^{13}C (75 MHz, DMSO) δ: 28.1, 124.0, 124.5, 124.9, 125.7, 126.3, 126.5, 126.9, 127.8, 128.7, 128.9, 129.3, 130.1, 130.4, 131.2, 133.4, 171.5. MS: m/z $(MH)^+$ 550.18. Anal. calcd for $C_{36}H_{22}O_2S_2$:C, 78.52; H, 4.03. Found: C, 78.34; H, 4.09.
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