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'On–Off' reversible switch for Fe^{3+} and F^{-} mimicking XNOR logic function

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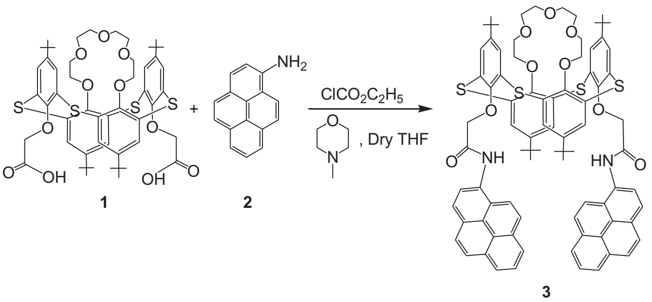
ABSTRACT

A new pyrene-appended chemosensor based on thiacalix[4]arene of 1,3-*alternate* conformation has been synthesised which demonstrates selective optical recognition of Fe^{3+} and F^{-} in two contrasting modes. The chemosensor behaves as a bifunctional fluorescent switch which mimics the performance of an *exclusive*-NOR (XNOR) logic gate with chemical inputs of Fe^{3+} and F^{-} ions.

The development of optical chemosensors for soft transition-metal ions and anions particularly needs attention because of their potential analytical application in many fields such as chemistry, medicine, biology and environment.[1] Among biologically important metal ions, the Fe^{3+} ions[2] have received considerable attention. It plays an important role in many biological processes at cellular level ranging from oxygen metabolism and electron-transfer processes to DNA and RNA synthesis.[3] Iron is essential for most organisms and its deficiency and excess can induce various disorders with iron trafficking and storage, and the balance being tightly regulated in the organism.[4] On the other hand, among anions, fluoride is of particular interest owing to its role in preventing dental caries,[5] and in the treatment for osteoporosis.[6] Furthermore, F^{-} ions are also associated with anaesthetics, hypnotics, psychiatric drugs, nerve gases, in the analysis of drinking water and in the refinement of uranium used in nuclear weapon manufacture.[7] An excess of fluoride can lead to thyroid activity depression and immune system disruption and fluorosis,[8] which is a type of fluoride toxicity that generally manifests itself clinically in terms of an increase in bone density. Thus, the diversity of their functions, both beneficial and otherwise, makes the detection of iron and fluoride important.

Our research programme involves design, synthesis and evaluation of artificial receptors selective for soft metal ions[9] and anions[10] of clinical and environmental interest. Recently, we reported a fluorescent chemosensor based on thiacalix[4]arene of 1,3-*alternate* conformation which behaves as an 'On–Off' reversible switch for two chemical inputs Hg^{2+} and K^{+} ions and mimics a molecular level keypad lock in the presence of F^{-} ions.[9a] Now we have designed and synthesised pyrene-appended chemosensor **3** based on thiacalix[4]arene of 1,3-*alternate* conformation which shows high selectivity towards Fe^{3+} with fluorescence quenching in aqueous media among all the metal ions and towards F^{-} ions in tetrahydrofuran among all anions tested. The in situ prepared **3**·$\mathbf{Fe^{3+}}$ complex showed remarkable affinity for fluoride which revives the fluorescence emission of **3**·$\mathbf{Fe^{3+}}$ complex among all the anions.

The reaction of diacid **1** with 2.0 mol equiv of 1-aminopyrene **2** in the presence of *N*-methylmorpholine (2.6 mol equiv) and ethylchloroformate (2.6 mol equiv) gave thiacalix[4]arene derivative **3** in 41% yield (Scheme 1).[11] The structure of thiacalix[4]arene receptor **3** was confirmed from its spectroscopic and analytical data. The IR spectrum of receptor **3** showed a stretching band at 1674 cm^{-1} due to C=O and no absorption band characteristic of free amino groups indicating that condensation has taken place. The ^1H NMR spectrum of receptor **3** showed two singlets (18H each) for the *tert*-butyl protons at δ 0.45 and 1.49. The upfield shift of one type of *tert*-butyl protons (δ 0.45) was probably due to shielding of the



Scheme 1. Synthesis of receptor **3**.

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tert-butyl protons by pyrene rings. In addition, the compound **3** shows two triplets (4H each) for the OCH_2, two broad singlets (4H each) for the OCH_2, one singlet for OCH_2, two singlets for aromatic protons at δ 7.19 and 7.67, one multiplet for pyrene protons and one singlet (2H) for the amido protons, the magnetic equivalences suggesting a C_{2v}-symmetric structure, that is, in 1,3-*alternate* conformation.

The binding behaviour of compound **3** was investigated towards different cations by UV–vis absorption and fluorescence spectroscopy. All the titration experiments were carried out in ethanol/water/THF (8.85:1:0.15, v/v) by adding aliquots of different guests (cation, anion and amino acids). The UV–vis absorption spectra of the compounds **3** exhibit typical pyrene absorption band at λ 342 nm. The addition of increasing amounts of Fe^{3+} ions from (1.0–50 equiv) resulted in increase in absorption at λ 342 nm (Fig. 1). There was no change in absorption band of compound **3** in the presence of other metal ions.

The fluorescence spectrum of compound **3** gave strong monomer emission at λ 386 nm when excited at λ 344 nm, that is, 'On state' (Fig. 2) and there was no band due to excimer emission which means that the two pyrene units are not in stacked conformation. Among all the metal ions tested, receptor **3** showed high selectivity towards Fe^{3+} ions. Upon addition of increasing amounts of Fe^{3+} as its perchlorate salt (1–100 equiv) to the solution of receptor **3**, there was significant quenching in the fluorescence emission, that is, 'Off state' (Fig. 2). The fluorescence quenching induced by Fe^{3+} is attributed to paramagnetic nature of Fe^{3+} and reverse PET from pyrene units to the nitrogen atom. Under the same conditions as used above for Fe^{3+}, we also tested the fluorescence response of compound **3** to other metal ions such as Li^+, Na^+, K^+, Ba^{2+}, Mg^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Ag^+, Hg^{2+}, Pb^{2+}, Co^{2+} besides Fe^{3+}, no significant fluorescence change of **3** occurred in the presence of (100 equiv) of these cations (Fig. 3).

The method of continuous variation (Job's plot) was used to determine the stoichiometry of the **3**·$\mathbf{Fe^{3+}}$ complex. The total concentration of the compound **3** and $\mathbf{Fe^{3+}}$ was constant (2.5×10^{-6} M), with a continuous variable molar fraction of guest [$\mathbf{Fe^{3+}}$]/([**3**] + [$\mathbf{Fe^{3+}}$]). The **3**·$\mathbf{Fe^{3+}}$ complex concentration approaches a maximum when the molar fraction of $\mathbf{Fe^{3+}}$ is 0.5, which means **3** and $\mathbf{Fe^{3+}}$ formed a 1:1 complex (Fig. 4). The association constant (log β) of compound **3** for Fe^{3+} was calculated from fluorescence titration experiments by means of SPECFIT programme (global analysis system V3.0 for 32-bit Window system), which uses singular value decomposition and non-linear regression modelling by the Leverberg–Marquardt[12] method and was found to be $4.97 \pm 0.13\ M^{-1}$.

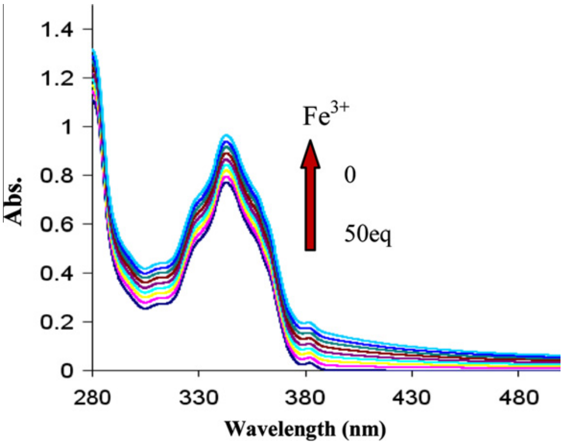

Figure 1. Absorption spectra of receptor **3** (10 μM) on addition of Fe^{3+} (0–50 equiv) in 10% aqueous ethanol.

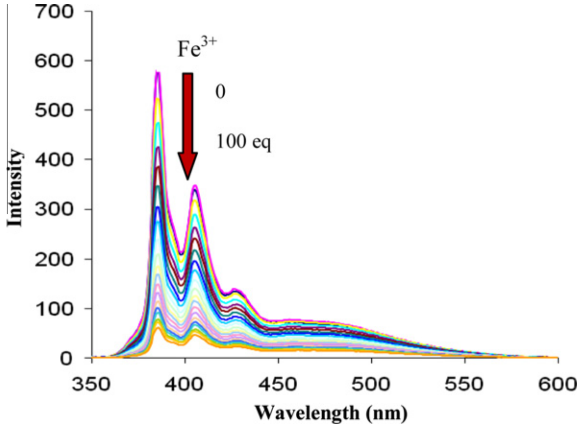

Figure 2. Fluorescence emission spectra of receptor **3** (5.0 μM) upon various addition of Fe^{3+} (0–100 equiv) in 10% aqueous ethanol.

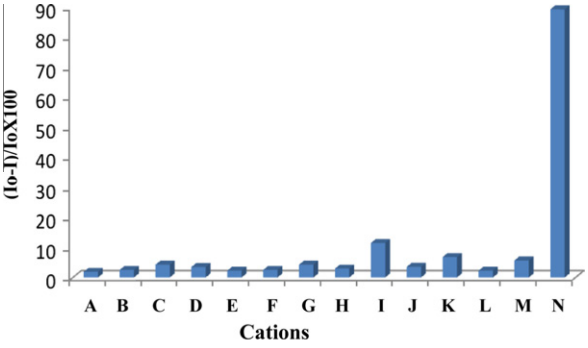

Figure 3. Selectivity of **3** (5.0 μM) upon addition of different cations in 10% aqueous ethanol. A = Li^+, B = Na^+, C = K^+, D = Ba^{2+}, E = Mg^{2+}, F = Ni^{2+}, G = Cu^{2+}, H = Zn^{2+}, I = Ag^+, J = Cd^{2+}, K = Hg^{2+}, L = Pb^{2+}, M = Co^{2+}, N = Fe^{3+}.

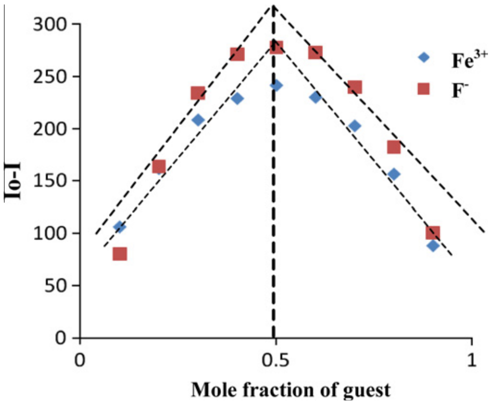

Figure 4. Job's plot of **3** with Fe^{3+} in 10% aqueous ethanol and with F^- in THF (guest = Fe^{3+} or F^-).

The practical applicability of compound **3** as Fe^{3+} selective fluorescent sensor has been addressed by carrying out competitive experiments in the presence of Fe^{3+} at 100 equiv mixed with different cations such as Li^+, Na^+, K^+, Ba^{2+}, Mg^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Ag^+, Hg^{2+}, Pb^{2+} and Co^{2+} at 100 equiv as shown in Figure 5, no significant variation in monomer emission was found by comparison with or without the other metal ions. These results suggest that compound **3** may be used as a potential fluorescent chemosensor for Fe^{3+} ions.

Since, the receptor **3** contains an amide group and amide moiety is known to complex anions through hydrogen bonding between anions and amide NH,[13] we investigated anion binding studies of

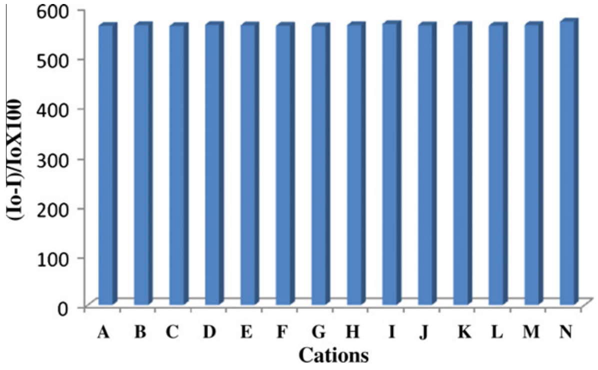

Figure 5. Competitive selectivity of **3** (5.0 μM) towards Fe^{3+} in the presence of different cations in 10% aqueous ethanol. A = Li^+, B = Na^+, C = K^+, D = Ba^{2+}, E = Mg^{2+}, F = Ni^{2+}, G = Cu^{2+}, H = Zn^{2+}, I = Ag^+, J = Cd^{2+}, K = Hg^{2+}, L = Pb^{2+}, M = Co^{2+}, N = Fe^{3+}.

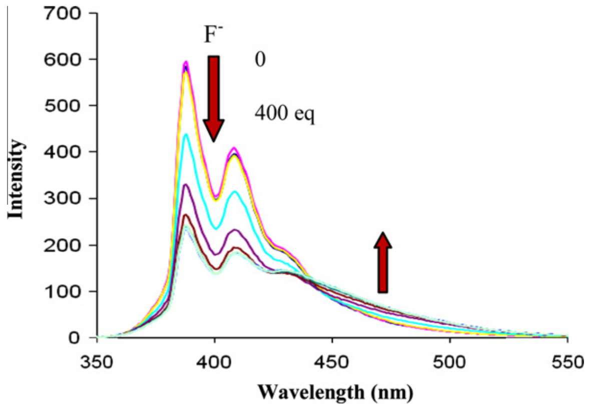

Figure 6. Fluorescence emission spectra of receptor **3** (5.0 μM) upon various addition of F^- (0–400 equiv) in THF.

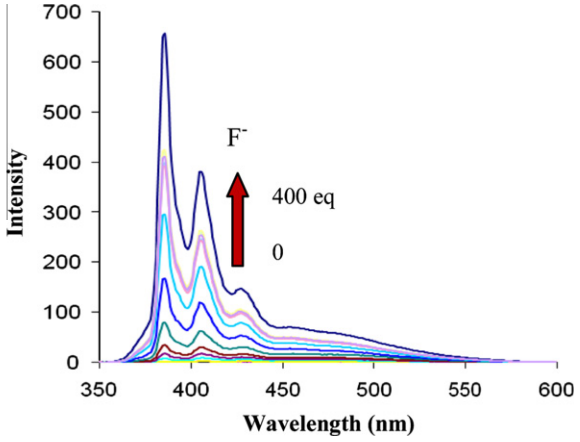

Figure 7. Fluorescence emission spectra of receptor $\mathbf{3{\cdot}Fe^{3+}}$ complex upon various addition of F^- (0–400 equiv) in ethanol.

Table 1
Truth table for reversible 'On–Off' switch for two input signals Fe^{3+} and F^-, where 0 and 1 indicates that the corresponding signals is *off* or *on*

Entry	Input 1 Fe^{3+}	Input 2 F^-	Output at λ 386 nm
1	0	0	1 (High, >250)
2	1	0	0 (Low, <250)
3	0	1	0 (Low, <250)
4	1	1	1 (High, >250)

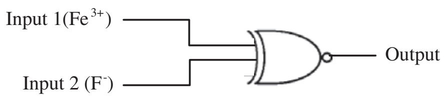

Figure 8. An *exclusive*-NOR (XNOR) gate formed with two chemical inputs.

compound **3** towards different anions such as F^-, Cl^-, Br^-, I^-, CN^- and OAc^-, HSO_4^-, $H_2PO_4^-$ and NO_3^- as their tetrabutylammonium salt in tetrahydrofuran. We did not carry out anion binding studies in alcohol as the protic solvents[14] are known to compete with receptor for anions. The receptor **3** showed high selectivity towards F^- ions among all the anions studied. Upon the addition of F^- (1–400 equiv) to the solution of compound **3**, there was ratiometric response with monomer quenching and small excimer enhancement (Fig. 6). We propose that the fluorescent ratiometric response of compound **3** on the addition of fluoride ions probably occurs by hydrogen bonding of the amide moiety which results in the formation of small excimer band. Earlier, we[10b] reported similar excimer formation between two napthyl moieties and Kim et al., [15] reported static excimer formation between two pyrene moieties due to hydrogen bonding in the presence of fluoride ion.

The method of continuous variation (Job's plot) as used in the case of $\mathbf{3{\cdot}Fe^{3+}}$ complex was used to determine the stoichiometry of the $\mathbf{3F^-}$ complex and it was found to be 1:1 (Fig. 4). The binding constant (log *β*) of compound **3** for F^- ions was calculated from fluorescence titration experiments by means of SPECFIT programme[12] and was found to be $2.18 \pm 0.15\ M^{-1}$.

Since the receptor **3** shows optical sensing towards Fe^{3+} and F^- ions, we investigated the 'On–Off' switching behaviour of receptor **3** between Fe^{3+} and F^- ions. The addition of Fe^{3+} ions to the solution of receptor **3** leads to fluorescence quenching, that is, 'Off state'. The addition of F^- ions to the solution of $\mathbf{3{\cdot}Fe^{3+}}$ complex, that is, 'Off state' results in the revival of fluorescence emission, that is, 'On state' (Fig. 7). The revival in fluorescence emission with the addition of F^- ion indicates that Fe^{3+} has more affinity for F^- ions than with the receptor **3**. The fluorescence was quenched again, that is, 'Off state' when Fe^{3+} was titrated into the solution of $\mathbf{3{\cdot}Fe^{3+}{\cdot}F^-}$ complex. This reversible 'On–Off' switching process of receptor **3** could not be observed with other anions indicating the high selectivity of $\mathbf{3{\cdot}Fe^{3+}}$complex towards fluoride ion.

Thus, depending on the two chemical inputs (Fe^{3+} and F^-), the receptor **3** can switch between different fluorescence emission states, that is, '*on* or off'. The behaviour of this molecular switch can be demonstrated with the help of binary logic.[16] Binary digits (*0* or *1*) can be used to represent the two states '*off* or *on*' of each signal. For reversible 'On–Off' switch of two inputs (Fe^{3+} and F^-), the input and output strings of the molecular switch are illustrated in Table 1. The output signal is '1' (strong monomer emission) when input strings '*00* and *11*' is *on* (in the absence or presence of both Fe^{3+} and F^- ions) and output signal is '0' (quenched monomer emission) when only one of two inputs Fe^{3+} and F^- is *on* in two strings '*10* and *01*' (Fig. 8). Such fluorescence changes upon the actions of two chemical inputs mimic the performance of an *exclusive*-NOR (XNOR) logic gate (Fig. 8). A XNOR logic function is two input device and its output is 'true' if the inputs are same and "false" if the outputs are different.

In conclusion, we synthesised a new pyrene-appended chemosensor **3** based on thiacalix[4]arene of 1,3-*alternate* conformation which demonstrates selective optical recognition of Fe^{3+} and F^- in two contrasting modes. The chemosensor behaves as a bifunctional fluorescent switch which mimics the performance of an *exclusive*-NOR (XNOR) logic gate with chemical inputs of Fe^{3+} and F^- ions.

Acknowledgements

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References and notes

1. (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E.. *Chem. Rev.* **1997**, *97*, 1515; (b) Prodi, L.; Bolletta, F.; Montalti, M.; Zaccheronii, N. *Coord. Chem. Rev.* **2000**, *205*, 59; (c) de Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coord. Chem. Rev.* **2000**, *205*, 41; (d) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3; (e) Harris, H. H.; Pickering, I. J. P.; George, G. N. *Science* **2003**, *301*, 1203.
2. (a) Zhang, M.; Gao, Y. H.; Li, M. Y.; Yu, M. X.; Li, F. Y.; Li, L.; Zhu, M. W.; Zhang, J. P.; Yi, T.; Huang, C. H. *Tetrahedron Lett.* **2007**, *48*, 3709; (b) Xiang, Y.; Tong, J. A. *Org. Lett.* **2006**, *8*, 1549; (c) Oter, O.; Ertekin, K.; Kirilmis, C.; Koca, M.; Ahmedzade, M. *Senors Actuators* **2007**, *122*, 450; (d) Bricks, J. L.; Kovalchuk, A.; Trieflinger, C.; Nofz, M.; Buschel, M.; Tolmachev, A. I.; Daub, J.; Rurack, K. *J. Am. Chem. Soc.* **2005**, *127*, 13522; (e) Fan, L. J.; Jones, W. E. *J. Am. Chem. Soc.* **2006**, *128*, 6784; (f) Mao, J.; Wang, L. N.; Dou, W.; Tang, X. L.; Yan, Y.; Liu, W. S. *Org. Lett.* **2007**, *9*, 4567; (g) Lohani, C. R.; Kim, J. M.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6069; (h) Lohani, C. R.; Lee, K. H. *Sensor Actuators B* **2010**, *143*, 649.
3. (a) Eisenstein, R. S. *Annu. Rev. Nutr.* **2000**, *20*, 627; (b) Winkelmann, G.; van der Helm, D.; Neilands, J. B.. In *Iron Transport in Microbes, Plants, and Animals*; VCH: Weinheim, Germany, 1987; (c) Matzanke, B. F.; Muller-Matzanke, G.; Raymond, K. N.. In *Iron Carriers and Iron Proteins*; VCH: New York, 1989; Vol. 5, (d) Liu, X.; Theil, E. C. *Acc. Chem. Res.* **2005**, *38*, 167; (e) Tezcan, F. A.; Kaiser, J. T.; Mustafi, D.; Walton, M. Y.; Howard, J. B.; Rees, D. C. *Science* **2005**, *309*, 1377; (f) Grinberg, A. V.; Hannemann, F.; Schiffler, B.; Muller, J.; Heinemann, U.; Bernhardt, R. *Proteins* **2000**, *40*, 590; (g) Videira, A.; Duarte, M. *Biochim. Biophys. Acta Bioenerg.* **2002**, *1555*, 187.
4. (a) Andrews, N. C. *N. Eng. J. Med.* **1999**, *341*, 1986; (b) Touati, D. *Arch. Biochem. Biophys.* **2000**, *373*, 1; (c) Cairo, G.; Pietrangelo, A. *Biochem. J.* **2000**, *352*, 241; (d) Beutler, E.; Felitti, V.; Gelbart, T.; Ho, N. *Drug Metab. Dispos.* **2001**, *29*, 495.
5. Kirk, K. L. *Biochemistry of Halogens and Inorganic Halides*; Plenum: New York, NY, 1991. p 58.
6. Kleerekoper, M. *Endocrinol. Metab. Clin. North Am.* **1998**, *27*, 441.
7. (a) Matuso, S.; Kiyomiya, K.; Kurebe, M. *Arch. Toxicol.* **1998**, *72*, 798; (b) Zhang, S.-W.; Swager, T. M. *J. Am. Chem. Soc.* **2003**, *125*, 3420; (c) Laisalmi, M.; Kokki, H.; Soikkeli, A.; Markkanen, H.; Yli-Hankala, A.; Rosenberg, P.; Lindgren, L. *Acta Anaesthesiol. Scand.* **2006**, *50*, 982.
8. (a) Wiseman, A. *Handbook of Experimental Pharmacology XX/2 Part 2*; Springer: Berlin, 1970. p 48; (b) Dreisbuch, R. H. *Handbook of Poisoning*; Lange Medical: Los Altos, CA, 1980.
9. (a) Kumar, M.; Kumar, R.; Bhalla, V. *Chem. Commun.* **2009**, 7384; (b) Kumar, M.; Dhir, A.; Bhalla, V. *Org. Lett.* **2009**, *11*, 2567; (c) Bhalla, V.; Tejpal, R.; Kumar, M.; Sethi, A. *Inorg. Chem.* **2009**, *48*, 11677; (d) Dhir, A.; Bhalla, V.; Kumar, M. *Org. Lett.* **2008**, *10*, 4891; (e) Bhalla, V.; Tejpal, R.; Kumar, M.; Puri, R. K.; Mahajan, R. K. *Tetrahedron Lett.* **2009**, *50*, 2649; (f) Kumar, R.; Bhalla, V.; Kumar, M. *Tetrahedron* **2008**, *64*, 8095.
10. (a) Bhalla, V.; Singh, H.; Kumar, M. *Org. Lett.* **2010**, *12*, 628; (b) Kumar, M.; Kumar, R.; Bhalla, V. *Tetrahedron* **2009**, *65*, 4340; (c) Babu, J. N.; Bhalla, V.; Kumar, M.; Puri, R. K.; Mahajan, R. K. *New J. Chem.* **2009**, *33*, 675.
11. *Synthesis of* **3**: *N*-Methylmorphine (27 mg, 0.26 mmol) was added to a stirred solution of **1** (100 mg, 0.1 mmol) in THF (5 ml) at −12 °C followed by the addition of ethylchloroformate (28 mg, 0.26 mmol). The reaction mixture was stirred for 8 min at −12 °C and then 1-aminopyrene **2** (55 mg, 0.25 mmol) was added. The reaction mixture was stirred for 12 h during which the temperature was allowed to come to room temperature. After completion of reaction (TLC), the solvent was removed in vacuo. The resulting crude was dissolved in 20 ml of ethyl acetate and treated with 5% of citric acid (2×10 ml) and then 5% of Na_2CO_3 (2×10 ml) then with water (2×20 ml). The organic layer was separated and dried over Na_2SO_4 and distilled to get crude solid. Recrystallisation from CH_2Cl_2/CH_3OH (1:1, v/v) gave 60 mg (41%) of **3** as light green solid. mp >240 °C, IR (KBr pallet, cm^{-1}) 1674; ^{1}HNMR (300 MHz, $CDCl_3$): δ 0.45 (18H, s, $C(CH_3)_3 \times 2$), 1.49 (18H, s, $C(CH_3)_3 \times 2$), 3.08 (4H, t, J = 6.6 Hz, $OCH_2 \times 2$), 3.46 (4H, br, $OCH_2 \times 2$), 3.71 (4H, br, $OCH_2 \times 2$), 3.96 (4H, t, J = 7.2 Hz, $OCH_2 \times 2$), 4.12 (4H, s, $OCH_2 \times 2$), 7.19 (4H, s, ArH × 4), 7.67 (4H, s, ArH × 4), 8.00–8.23 (14H, m, ArH × 18, pyrene), 8.44 (2H, d, J = 9.3 Hz, ArH × 2, pyrene), 8.51 (2H, d, J = 8.1 Hz, ArH × 2, pyrene), 9.73 (2H, s, NH × 2). ^{13}CNMR (300 MHz, $CDCl_3$): δ 30.1, 31.4, 32.5, 33.8, 34.5, 66.8, 70.1, 71.7, 72.1, 73.5, 121.6, 122.1, 123.7, 124.9, 125.1, 125.2, 126.0, 126.7, 127.3, 127.7, 127.9, 128.0, 129.0, 130.1, 130.6, 130.9, 131.3, 143.2, 147.3, 148.1, 148.9, 155.0, 156.5, 167.9; FAB-MS: m/z 1393 (M^+); Anal. Calcd for $C_{84}H_{84}N_2O_9S_4$: C, 72.38; H, 6.07; N, 2.01; S, 9.20. Found: C, 72.06; H, 5.89, N, 1.84; S, 9.03.
12. Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbulher, A. D. *Talanta* **1985**, *32*, 95.
13. (a) Ayling, A. J.; Perez-Payan, M. N.; Davis, A. P. *J. Am. Chem. Soc.* **2001**, *123*, 12716; (b) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456; (c) Miyaji, H.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 154; (d) Lio, J.-H.; Chen, C.-T.; Fang, J.-M. *Org. Lett.* **2002**, *4*, 561.
14. Boiocchi, M.; Boca, L. D.; Gomez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507.
15. (a) Kim, S. K.; Bok, J. H.; Bartsch, R. A.; Lee, J. Y.; Kim, J. S. *Org. Lett.* **2005**, *7*, 4839; (b) Kim, H. J.; Kim, S. K.; Lee, J. Y.; Kim, J. S. *J. Org. Chem.* **2006**, *71*, 6611.
16. (a) de Silva, A. P.; McClenaghan, N. D.; McCoy, C. P. Molecular Level Electronics, Imaging and Iinformation, Energy and Environment. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001; Vol. 5, (b)*Molecular Devices and Machines. A Journey into the Nano World*; Balzini, V., Venturi, M., Credi, A., Eds.; Wiley-VCH: Wienheim, 2003.