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Tetrahedron
Tetrahedron 63 (2007) 8825–8830

Cholic acid-based fluorescent sensor for mercuric and methyl mercuric ion in aqueous solutions

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Received 27 April 2007; revised 5 June 2007; accepted 8 June 2007
Available online 15 June 2007

Abstract—Cholic acid-based fluorescent PET sensor probe **1**, bearing a pair of dithiocarbamate pendants as the receptive site and anthracene moiety as the signal displaying unit, was designed and synthesized. The sensor probe not only shows high selectivity and sensitivity to Hg^{2+} in aqueous acetonitrile solution, but also responds moderately to $MeHg^{+}$. A distinctive OFF–ON type signaling of up to 10-fold enhancement was observed for this new sensor probe toward Hg^{2+}.

1. Introduction

Fluoroionophore design based on 'fluorophore–spacer–receptor' motif has been demonstrated to be an effective way of developing both cation and anion chemosensors.[1] With proper incorporation of a receptive site responsible for selectively binding ions and a fluorophore responsible for signal transduction, fluorescent chemosensors are particularly attractive systems for detecting environmentally or biologically significant ions because of their low cost, ability on real time monitoring, and high throughput capability. Upon complexation with a target ion, the built-in transduction mechanisms including photo-induced transfer (PET),[2] photo-induced charge transfer (P-ICT),[3] and excimer/exciplex formation[4] are operative to trigger the chemosensor to undergo photo-physical changes in signifying the binding event. In particular, one area of environmental monitoring is the detection of low levels of heavy metals in aqueous solutions.[5] In this connection, mercury chemosensing has recently attracted considerable interests from the scientific community because of its high toxicity.[6] Bacteria in the sediments of aqueous environments can transform inorganic Hg^{2+} into methylmercury, a potent neurotoxin.[7] However, to our knowledge, most of the literatures on mercury sensing are only confined to the detection of inorganic mercury, the detection of methyl mercury is seldom reported.

To continue our interests in chemosensor development, in this study, we have identified cholic acid as the molecular platform to prepare supramolecular system for mercury ion and methyl mercury detection. The semi-rigid structure and multifunctional nature of cholic acid enable it to be an ideal building block for sensor design. Davis and co-workers reported that the three axially oriented functional groups at the C3, C7, and C12 of cholic acid after proper transformations could be assembled in such a way to confer cooperative binding interactions to chloride ion.[8] We have recently discovered for the first time that the flexible C17 side chain of cholic acid can be exploited to introduce a ligating group onto the C24 as an additional binding site for binding anions.[9] Interestingly, the use of cholic acid as a molecular scaffold for cation chemosensor development is very rare in literature.[10]

In this paper, we report the synthesis and the fluorometric properties of cholic acid-based sensors **1** and **2** (Fig. 1) toward mercuric and organomercuric ions in aqueous solutions.

2. Results and discussion

In our approach, we envisioned that the two axial hydroxyl groups at C7 and C12 could be utilized to append suitable ligating groups so as to create a selective receptive site for binding a cation while the C3 hydroxyl group can provide a handle for the appendage of a fluorophore. To bind soft metals like mercury, we call for the incorporation of a pair of dithiocarbamate pendants onto the C7 and C12. Anthracene moiety chosen as the signal display unit in the sensor design will be connected to the C3 of cholic acid via a suitable spacer group. By manipulating the length of the spacer, the communication between the receptive site and the

Keywords: Cholic acid; Mercury chemosensor; Fluorescence; OFF–ON type signaling.
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doi:10.1016/j.tet.2007.06.026

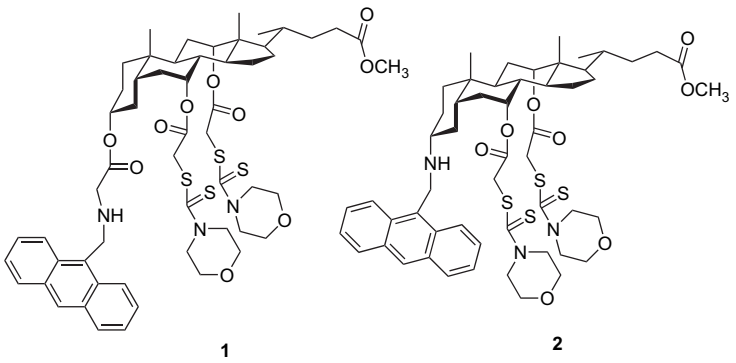
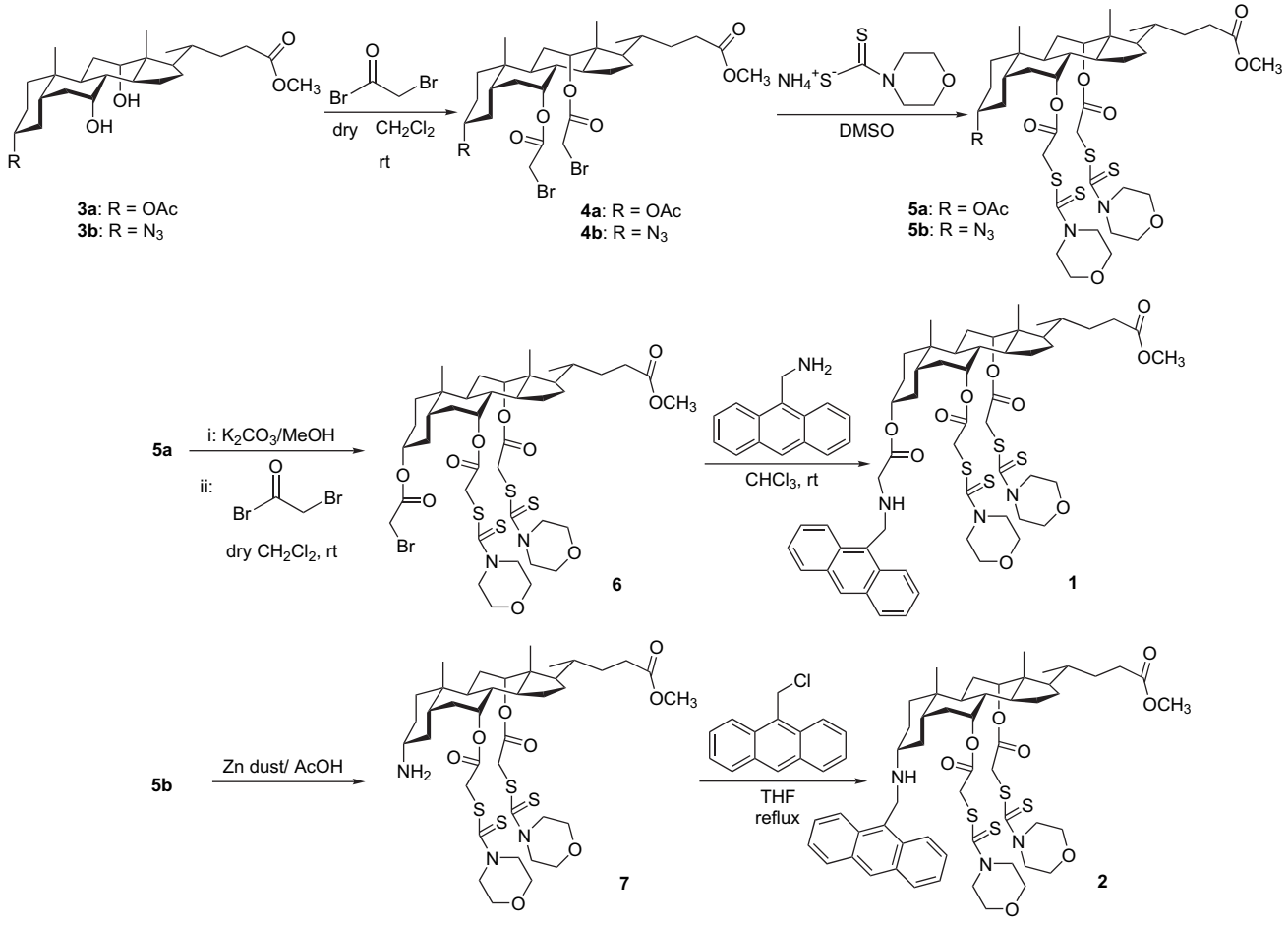


Figure 1. Structures of fluorescent sensors **1** and **2**.

fluorophore can be modulated. Starting from literature known cholic acid derivatives **3a** and **3b**,[11,12] sensors **1** and **2** were assembled in a sequence of high yield reactions outlined in Scheme 1. Condensation of **3a** and **3b** with bromoacetyl bromide followed by substitution with ammonium morpholinyl dithiocarbamate in DMSO afforded **5a** and **5b** in 91% and 89% yield, respectively. Compounds **5a** and **5b** are the precursors for making sensors **1** and **2**. Hydrolysis of acetate **5a** with K_2CO_3 in methanol followed by treatment with bromoacetyl bromide gave **6** in 73% yield. To complete the construction of sensor **1** by introducing the signal display unit, **6** was condensed with 9-aminomethylanthracene in chloroform at room temperature. To prepare sensor **2** for comparative studies, zinc dust reduction of azide **5b** in acetic acid gave 92% yield of the corresponding amine **7**, which underwent facile substitution reaction with 9-chloromethylanthracene to give rise to sensor **2** in 72% yield.

It is noteworthy that the only difference between sensors **1** and **2** is the length of the spacer groups connecting the cholic acid scaffold and the fluorophore. The low quantum yield (QY) discovered for both sensors indicated that photo-induced electron transfer (PET) process took place between the dithiocarbamate pendants and the fluorophore upon



Scheme 1. Synthetic routes for fluorescent chemosensors **1** and **2**.

irradiation at 366 nm. Furthermore, the lower QY observable for sensor **1** (i.e., 0.058) in comparison to that observed for sensor **2** (i.e., 0.092) implicated that the distance between the receptor and the proximate fluorophore is shorter in **1** than that in **2**. Thus, the length of the spacer connecting the C3 of cholic acid scaffold and the fluorophore contributes a significant factor for the sensitivity of the resulting sensors (vide infra).

When **1** and **2** were titrated with mercuric ion in 1:1 aqueous acetonitrile solution, the emission spectra of both sensors were greatly enhanced (Fig. 2). Presumably, the preorganized pair of dithiocarbamate pending groups in the host creates a well-defined binding site for mercury ion. Upon complexation, the electron-donating dithiocarbamate groups were tied up with mercuric ion, the PET process was retarded and this causes the emission of the fluorophore to be switched on from its off-state. The fluorescence of both sensors increased abruptly until the ratio of the host and the guest ion reached 1:1. At the steady state, sensor **1** recorded a 6.62-fold signal enhancement while sensor **2** recorded a 4.00-fold enhancement.

The 1:1 stoichiometric relation between sensor **1** and mercuric ion was confirmed by the Job's method of continuous variation. The non-linear fitting based on the titration data allowed the computation of the binding constant between mercury and sensors **1** and **2** to be $5.27\times10^{6}\ M^{-1}$ and $1.54\times10^{6}\ M^{-1}$, respectively. Apparently, sensor **1** in comparison with sensor **2** is a better mercury sensor. Under optimal conditions, the detection limit for mercuric ion was found to be 5.0×10^{-8} M.

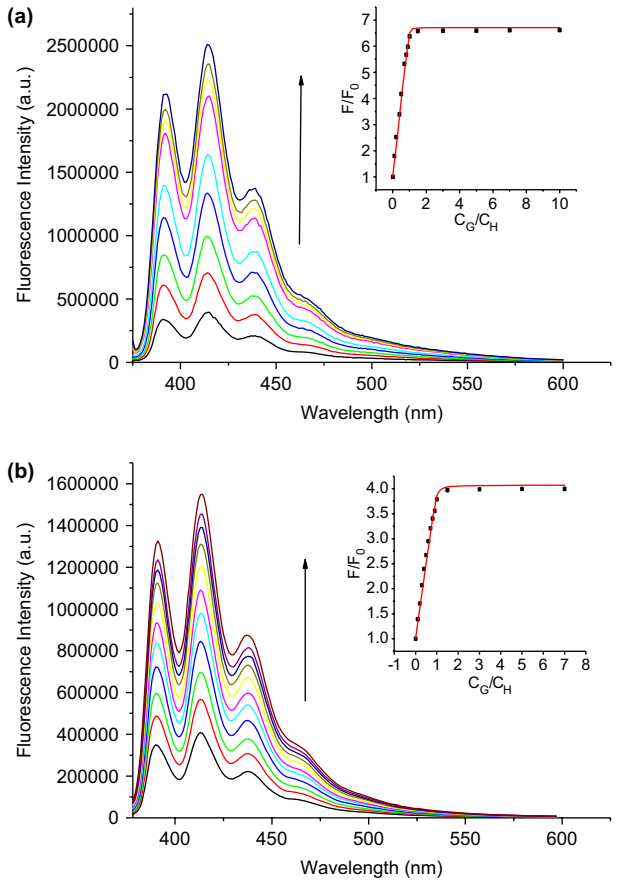


Figure 2. (a) Fluorescence spectra of **1** (1.0 μM) upon addition of Hg^{2+} in CH_3CN/H_2O=1:1. Excitation wavelength was 366 nm and (b) fluorescence spectra of **2** (1.0 μM) upon addition of Hg^{2+} in CH_3CN/H_2O=1:1. Excitation wavelength was 366 nm. Inset is the titration data point and the non-linear least-squares fitting curve.

Metal ion chemosensors are usually sensitive to the pH changes of the system. However, pH fluorescent titration experiments on sensor **1** indicated that there is no cross-response of the sensor to the pH change of the sensor solution. According to Figure 3, emission intensity of the sensor remains constant over a wide pH range from 3 to 13. And this wide working pH range enables our sensor **1** to detect mercury in real samples.

On the other hand, the sensor exhibits an excellent selectivity among common metal ions. With the addition of other metal ions such as Li^{+}, Na^{+}, Ca^{2+}, Mg^{2+}, Ag^{+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} under similar conditions, as shown in Figure 4, we observed negligible changes in fluorescence, indicating thereby their weak interactions with sensor **1**. The lack of interference caused by Cd^{2+} and Pb^{2+}, both are common toxic metals, is particularly noteworthy.

The seemingly perfect selectivity exhibited by sensor **1** could be arising from a combination of both electronic and

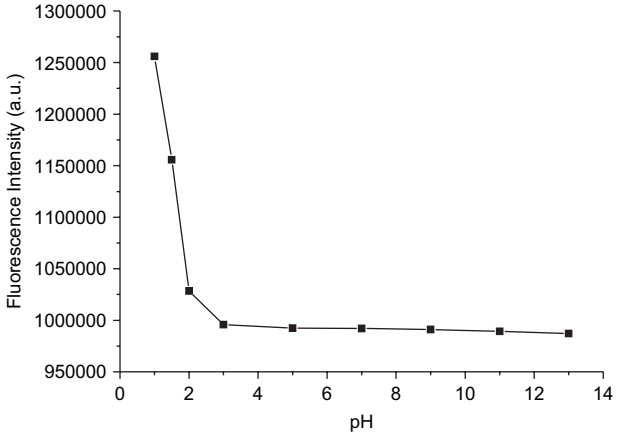


Figure 3. Effect of pH on the emission intensity of sensor **1** in CH_3CN/H_2O=1:1.

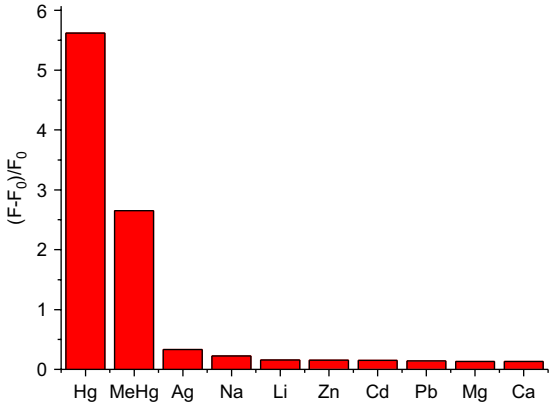


Figure 4. Fluorescence response of **1** to various cations in CH_3CN/H_2O=1:1. The bars represent the emission of **1** in the presence of 30 equiv of the interacting cation.

spatial characteristics of the binding site. The appended dithiocarbamate functionalities can preorganize in such a manner to create a three dimensional semi-rigid cavity with the size matching very well with mercury ion (Fig. 5).

To rule out that the possibility of the fluorescence enhancement observed is not due to a chemical reaction (i.e., chemodosimeter),[13] the reversible binding of Hg^{2+} and the sensor must be established. The reversibility experiment revealed that the 6.62-fold fluorescence enhancement of sensor **1** caused by the addition of 2 equiv of mercuric ion can be removed completely by adding 2 equiv of a mercury chelating agent, ammonium morpholinyl dithiocarbamate.

In a great contrast to many reports on mercury fluorescent sensor development, sensor **1** was found to be also responsive to methyl mercuric ion. A more elaborated study demonstrated that the sensor response to mercuric and methyl mercuric is highly solvent dependent. In general, decreasing the water content in aqueous acetonitrile solution, the presence of mercuric ion/methyl mercuric ion can trigger a greater signal enhancement from the sensor (Fig. 6). When acetonitrile was used as the solvent, $MeHg^+$ as low as 10^{-7} M can be detected by the sensor probe. To shed more light on the nature of binding interaction between methyl mercuric ion and sensor **1**, the ^1H NMR spectrum of sensor **1** was recorded in the absence and presence of $MeHg^+$. In the complex, a clear downfield shift of 0.5 ppm of the methylene group connecting to anthracene moiety was observed.

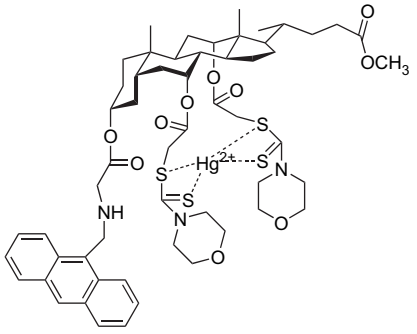


Figure 5. Binding mode of sensor **1** toward Hg^{2+}.

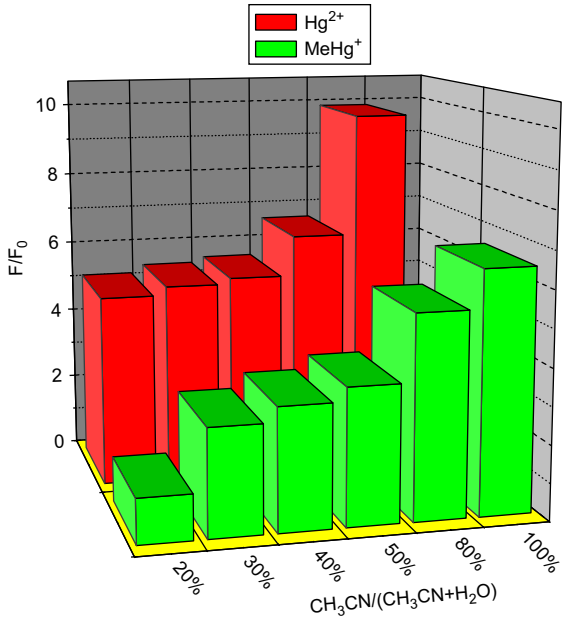


Figure 6. Fluorescence response of **1** to Hg^{2+} and $MeHg^+$ in different solvent systems.

3. Conclusion

In conclusion, we have designed and demonstrated the use of cholic acid-based sensor **1** as a novel fluorescent sensor for the detection of both Hg^{2+} and $MeHg^+$ in aqueous solutions. Sensor **1** exhibits outstanding selectivity toward mercuric ion due to the complementary charge and size factor between the receptive site of the host and the guest ion. A distinctive OFF–ON type signaling of up to 10-fold enhancement was observed for this new sensor probe.

4. Experimental

4.1. General methods

Melting point was determined with a MEL-TEMPII melting point apparatus (uncorrected). ^1H and ^{13}C NMR spectra were recorded on a JOEL AL 270 spectrometer (at 270 and 67.8 MHz, respectively) or VARIAN INOVA 400 spectrometer (at 400 and 100 MHz, respectively) in $CDCl_3$. High-resolution mass spectra were recorded on a Bruker Autoflex mass spectrometer (MALDI TOF) or electrospray ionization high-resolution mass spectra on an API Qstar Pulsari mass spectrometer. Fluorescent emission spectra were collected on a PTI Luminescence Lifetime spectrometer. Unless specified, all fine chemicals were used as received.

4.2. General procedure for the synthesis of compounds 4a and 4b

Bromoacetyl bromide (0.78 ml, 9 mmol) was added to a solution of **3a** (1.40 g, 3 mmol) in 20 ml freshly distilled dry CH_2Cl_2 at room temperature. The reaction mixture was stirred for 5 h. The organic solution was then washed with dilute NaOH solution and dried over $MgSO_4$. After the evaporation of the solvent, the residue was then purified by column chromatography on silica gel using PE/EA (petroleum ether/ethyl acetate)=3:1 as the eluent. Evaporation of the eluent afforded the final product **4a** (1.8 g, 85% yield) as a yellow oil. ^1H NMR (270 MHz, $CDCl_3$): δ 0.70 (s, 3H), 0.78 (d, 3H, J=6.2 Hz), 0.88 (s, 3H), 0.90–2.35 (m, 24H), 1.96 (s, 3H), 3.60 (s, 3H), 3.73–3.88 (m, 4H), 4.51 (s, 1H), 4.94 (s, 1H), 5.11 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 12.0, 17.5, 21.4, 22.3, 22.9, 25.0, 26.0, 26.2, 26.3, 26.3, 26.6, 27.2, 28.5, 30.7, 30.9, 31.2, 34.3, 34.6, 34.8, 37.9, 40.6, 42.7, 45.1, 47.1, 51.5, 73.0, 73.7, 166.0, 166.2, 170.3, 174.2. MALDI TOF HRMS: calcd for $C_{31}H_{46}Br_2O_8Na$, 727.1584; found, 727.1528.

Starting with **3b** (450 mg, 1 mmol), using the above mentioned procedure, **4b** was obtained as a yellow oil in 84% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (s, 3H), 0.81 (d, 3H, J=6.4 Hz), 0.92 (s, 3H), 0.98–2.37 (m, 24H), 3.08 (s,

1H), 3.63 (s, 3H), 3.79–3.88 (m, 4H), 5.00 (s, 1H), 5.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 17.4, 22.4, 22.9, 24.9, 25.8, 26.1, 26.6, 27.1, 28.4, 30.6, 30.8, 31.0, 31.2, 34.3, 34.7, 34.7, 35.1, 37.9, 41.1, 42.7, 45.1, 47.1, 51.5, 60.6, 72.9, 166.4, 166.6, 174.4. MALDI TOF HRMS: calcd for $C_{29}H_{43}Br_2N_3O_6Na$, 710.1497; found, 710.1521.

4.3. General procedure for the synthesis of compounds 5a and 5b

Ammonium morpholinyl dithiocarbamate (388 mg, 2.34 mmol) was added to a solution of **4a** (550 mg, 0.78 mmol) in 10 ml DMSO. After being stirred at room temperature for 2 days, the reaction mixture was poured into 50 ml of H_2O. White precipitate was then filtered out as the crude product. The crude product was then purified by column chromatography eluted using PE/EA=3:2 affording **5a** as a yellow oil (618 mg, 91% yield). ^{1}H NMR (270 MHz, DMSO): δ 0.71 (s, 3H), 0.81 (d, 3H, J=6.0 Hz), 0.89 (s, 3H), 0.90–2.40 (m, 24H), 2.01 (s, 3H), 3.62 (s, 3H), 3.74–3.77 (s, 8H), 3.80–4.38 (m, 12H), 4.54 (s, 1H), 4.98 (s, 1H), 5.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 17.5, 21.5, 22.5, 23.0, 25.4, 26.9, 27.3, 28.7, 30.7, 30.9, 31.2, 34.3, 34.6, 34.9, 34.9, 37.9, 39.1, 39.2, 40.8, 40.9, 43.1, 45.1, 47.1, 50.1, 51.4, 66.04, 72.6, 74.1, 167.7, 167.8, 170.6, 174.5, 195.2, 195.4. MALDI TOF HRMS: calcd for $C_{41}H_{62}N_2O_{10}S_4Na$, 893.3190; found, 893.3202.

Starting with **4b** (1.03 g, 1.50 mmol), using the above mentioned procedure, **5b** was obtained as a yellow oil in 89% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.71 (s, 3H), 0.81 (d, 3H, J=6.2 Hz), 0.90 (s, 3H), 0.95–2.36 (m, 24H), 3.16 (s, 1H), 3.63 (s, 3H), 3.75 (s, 8H), 3.80–4.30 (m, 12H), 5.01 (s, 1H), 5.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 17.7, 22.8, 23.2, 25.5, 27.6, 29.0, 29.7, 31.0, 31.4, 33.6, 34.3, 35.1, 37.8, 38.3, 39.3, 41.5, 43.3, 43.5, 44.0, 45.4, 46.2, 47.3, 50.8, 51.7, 52.9, 66.42, 72.6, 167.9, 168.2, 174.8, 195.4, 195.7. ESI HRMS: calcd for $C_{39}H_{59}N_5O_8S_4$, $[M+H]^+$=854.1038; found, 854.1021.

4.3.1. Compound 6. To a solution of **5a** (435 mg, 0.50 mmol) in MeOH (10 ml) was added K_2CO_3 (69 mg, 0.50 mmol) and stirred for 5 h at room temperature. The reaction was quenched by adding dilute HCl solution. The product was extracted by CH_2Cl_2 (3×10 ml). The combined organic layers were dried over $MgSO_4$. The crude product was dissolved in dry CH_2Cl_2 followed by addition of bromoacetyl bromide (0.13 ml, 1.50 mmol). After stirring for 5 h at room temperature, solvent was removed under reduced pressure. The crude product was purified by column chromatography using PE/EA=1:2 as the eluent to afford product **6** as a yellow oil (355 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.64 (s, 3H), 0.74 (d, 3H, J=6.2 Hz), 0.84 (s, 3H), 0.94–2.37 (m, 24H), 3.55 (s, 3H), 3.62–3.82 (m, 10H), 3.85–4.24 (m, 12H), 4.54 (s, 1H), 4.91 (s, 1H), 5.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 13.9, 17.2, 20.8, 22.2, 22.7, 25.1, 26.3, 26.5, 27.1, 28.4, 30.5, 30.6, 30.9, 34.0, 34.2, 34.5, 37.6, 38.8, 38.9, 40.4, 42.8, 44.8, 46.8, 51.2, 60.0, 65.8, 72.3, 75.9, 166.5, 167.4, 167.5, 174.2, 194.9, 195.0. MALDI TOF HRMS: calcd for $C_{41}H_{61}BrN_2O_{10}S_4Na$, 971.2427; found, 971.2438.

4.3.2. Compound 7. Activated zinc powder (400 mg, 6.20 mmol) was added to a solution of **5b** (256 mg, 0.30 mmol) in glacial acetic acid (10 ml). The mixture was stirred vigorously for 24 h. Acetic acid was then completely removed under reduced pressure by adding toluene several times. The residue, acetate ammonium salt of **7**, was dissolved in saturated sodium chloride solution (10 ml). Basification of the solution by excessive triethylamine and extraction of the product by ethyl acetate gave amine **7** as the pure product. After being dried by sodium sulfate and removal of organic solvent, compound **7** was obtained as a yellow solid (228 mg, 92% yield). Mp: 93–97 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.72 (s, 3H), 0.85 (d, 3H, J=6.0 Hz), 0.92 (s, 3H), 0.94–2.38 (m, 26H), 2.94 (s, 1H), 3.64 (s, 3H), 3.74 (s, 8H), 3.82–4.53 (m, 12H), 5.02 (s, 1H), 5.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 17.5, 22.4, 23.1, 23.2, 23.7, 24.9, 27.4, 28.3, 30.8, 30.9, 31.0, 31.2, 34.3, 34.9, 35.1, 35.5, 35.6, 37.9, 38.9, 41.0, 42.7, 45.1, 47.0, 51.0, 51.4, 66.1, 72.4, 167.9, 168.0, 174.5, 195.6, 195.7. ESI HRMS: calcd for $C_{39}H_{61}N_3O_8S_4$, $[M+H]^+$=828.2216; found, 828.2224.

4.3.3. Sensor 1. A mixture of **6** (190 mg, 0.20 mmol), 9-aminomethylanthracene (41 mg, 0.20 mmol), and K_2CO_3 (55 mg, 0.40 mmol) was stirred in CH_2Cl_2 (15 ml) at room temperature for 1 day. The mixture was then washed with dilute HCl solution and dried over $MgSO_4$. The organic solvent was then removed by rotary evaporation under vacuum. Column chromatography (SiO_2) eluted using PE/EA=1:2 gave the final pure product as a yellow solid (140 mg, 65% yield). Mp: 170–172 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.73 (s, 3H), 0.81–0.94 (m, 6H), 1.00–2.40 (m, 25H), 3.63–3.76 (m, 15H), 3.80–4.21 (m, 10H), 4.74 (s, 3H), 5.01 (s, 1H), 5.18 (s, 1H), 7.44–7.55 (m, 4H), 7.97 (d, 2H, J=8.1 Hz), 8.39–8.46 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 12.2, 14.2, 17.6, 19.2, 19.4, 19.4, 19.9, 21.1, 22.6, 23.1, 25.6, 27.1, 27.4, 28.9, 30.8, 31.0, 31.3, 34.4, 34.7, 34.9, 37.9, 39.1, 39.2, 41.0, 43.2, 45.2, 45.4, 47.2, 51.2, 51.5, 60.3, 66.0, 66.0, 72.6, 74.9, 76.5, 124.1, 124.8, 126.1, 127.3, 128.9, 130.3, 130.5, 131.3, 167.6, 167.6, 172.1, 174.3, 195.0, 195.0. MALDI TOF HRMS: calcd for $C_{56}H_{73}N_3O_{10}S_4Na$, 1098.4082; found, 1098.4101.

4.3.4. Sensor 2. To a mixture of **7** (120 mg, 0.15 mmol) and 9-chloromethyl anthracene (33 mg, 0.15 mmol) in THF (15 ml) were added K_2CO_3 (41 mg, 0.30 mmol) and KI (50 mg, 0.30 mmol). The reaction was stirred at reflux temperature overnight. The mixture was then washed with dilute HCl solution and dried over $MgSO_4$. The organic solvent was then removed by rotary evaporation under vacuum. Column chromatography (SiO_2) eluted using PE/EA=1:1 gave the final pure product as a yellow solid (106 mg, 72% yield). Mp: 106–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (s, 3H), 0.81–0.96 (m, 6H), 1.00–2.60 (m, 25H), 2.94 (s, 1H), 3.62 (s, 3H), 3.74 (s, 8H), 3.82–4.39 (m, 12H), 4.99 (s, 2H), 5.11 (s, 1H), 5.15 (s, 1H), 7.40–7.60 (m, 4H), 8.00 (d, 2H, J=8.4 Hz), 8.30–8.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 17.4, 22.4, 23.0, 24.0, 24.9, 27.3, 28.3, 28.7, 30.7, 30.9, 31.2, 34.2, 34.6, 34.9, 35.3, 37.0, 37.7, 37.9, 39.0, 41.1, 42.7, 45.1, 47.0, 50.4, 51.2, 51.4, 66.1, 72.5, 123.6, 124.9, 126.2, 127.1, 129.2, 129.3, 131.5, 133.5, 167.8, 170.0, 174.5, 195.6, 195.7. MALDI TOF

HRMS: calcd for $C_{54}H_{71}N_3O_8S_4Na$, 1040.4237; found, 1040.4245.

Acknowledgements

A marginally funded studentship provided by the UGC of Hong Kong to H.W. and financial support from the Science Faculty of Hong Kong Baptist University are acknowledged.

Supplementary data

^1H and ^{13}C NMR spectra of sensors **1** and **2**, Job's plot result, and quantum yield measurement table. Supplementary materials associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.026.

References and notes

1. (a) *Fluorescent Chemosensors for Ion and Molecule Recognition*; Czarnik, A. W., Ed.; ACS Symposium Series 538; American Chemical Society: Washington, DC, 1992; (b) *Chemosensors of Ion and Molecule Recognition*; Desvergne, J. P., Czarnik, A. W., Eds.; Kluwer: Dordrecht, 1997.
2. (a) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449–2452; (b) Kim, J. S.; Noh, K. H.; Lee, S. H.; Kim, S. K.; Kim, S. K.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 597–600; (c) Wang, J.; Qian, X. *Chem. Commun.* **2006**, 109–111.
3. (a) Leray, I.; Lefevre, J. P.; Delaire, J.; Valeur, B. *Chem.—Eur. J.* **2001**, *7*, 4590–4598; (b) Xu, Z.; Xiao, Y.; Qian, X.; Cui, J.; Cui, D. *Org. Lett.* **2005**, *7*, 889–892; (c) Cheung, S.-M.; Chan, W.-H. *Tetrahedron* **2006**, *62*, 8379–8383; (d) Wang, J.; Qian, X.; Cui, J. *J. Org. Chem.* **2006**, *71*, 4308–4311.
4. (a) Hamada, F.; Narita, M.; Kinoshita, K.; Makabe, A.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **2001**, 388–394; (b) Roy, B. C.; Chandra, B.; Hromas, D.; Malik, S. *Org. Lett.* **2003**, *5*, 11–14; (c) Yang, R. H.; Chan, W. H.; Lee, A. W. M.; Xia, P. F.; Zhang, H. K.; Li, K. *J. Am. Chem. Soc.* **2003**, *125*, 2884–2885.
5. (a) Klein, G.; Kaufmann, D.; Schurch, S.; Reymond, J.-L. *Chem. Commun.* **2001**, 561–562; (b) Prodi, L.; Bargossi, C.; Montalti, M.; Zaccheroni, N.; Su, N.; Bradshaw, J. S.; Izatt, R. M.; Savage, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 6769–6771.
6. (a) Nolan, E. M.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 14270–14271; (b) Siangfeng, G.; Xuhong, Q.; Lihua, J. *J. Am. Chem. Soc.* **2004**, *126*, 2272–2273; (c) Metivier, R.; Leray, I.; Valeur, B. *Chem.—Eur. J.* **2004**, *10*, 4480–4490; (d) Ono, A.; Togashi, H. *Angew. Chem., Int. Ed.* **2004**, 4300–4302; (e) Yoon, S.; Albers, A. E.; Wong, A. P.; Chang, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 16030–16031; (f) Matsushita, M.; Meijler, M. M.; Wirsching, P.; Lerner, R. A.; Janda, K. D. *Org. Lett.* **2005**, *7*, 4943–4946; (g) Chen, Q.-Y.; Chen, C.-F. *Tetrahedron Lett.* **2005**, *46*, 165–168; (h) Ou, S.; Lin, Z.; Duan, C.; Zhang, H.; Bai, Z. *Chem. Commun.* **2006**, 4392–4394.
7. Clarkson, T. W.; Magos, L.; Myers, G. J. *N. Engl. J. Med.* **2003**, *349*, 1731–1737.
8. (a) Davis, A. P.; Joos, J. P. *Coord. Chem. Rev.* **2003**, *240*, 143–156; (b) Koulov, A. V.; Lambert, T. N.; Shukla, R.; Jain, M.; Boon, J. M.; Smith, B. D.; Li, H.; Sheppard, D. N.; Joos, J.-B.; Clare, J. P.; Davis, A. P. *Angew. Chem., Int. Ed.* **2003**, 4931–4933; (c) McNally, B. A.; Koulov, A. V.; Smith, B. D.; Joos, J.-B.; Davis, A. P. *Chem. Commun.* **2005**, 1087–1089.
9. (a) Fang, L.; Chan, W. H.; He, Y.-B.; Kwong, D. W. J.; Lee, A. W. M. *J. Org. Chem.* **2005**, *70*, 7640–7646; (b) Liu, S. Y.; Fang, L.; He, Y.-B.; Chan, W. H.; Yeung, K. T.; Cheng, Y. K.; Yang, R. H. *Org. Lett.* **2005**, *7*, 5825–5828.
10. Zhao, Y.; Zhong, Z. *J. Am. Chem. Soc.* **2006**, *128*, 9988–9989.
11. Davis, A. P.; Perez-Payan, M. N. *Synlett* **1999**, 991–993.
12. Lawless, L. J.; Blackburn, A. G.; Ayling, A. J.; Perez-Payan, M. N.; Davis, A. P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1329–1341.
13. (a) Yang, Y.-K.; Yook, K.-J.; Tae, J. *J. Am. Chem. Soc.* **2005**, *127*, 16760–16761; (b) Song, K. C.; Kim, J. S.; Park, S. M.; Chung, K.-C.; Ahn, S.; Chang, S.-K. *Org. Lett.* **2006**, *8*, 3413–3416.