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PAPER

Naphthylthiourea-modified permethylcyclodextrin as a highly sensitive and selective "turn-on" fluorescent chemosensor for Hg^{2+} in water and living cells†

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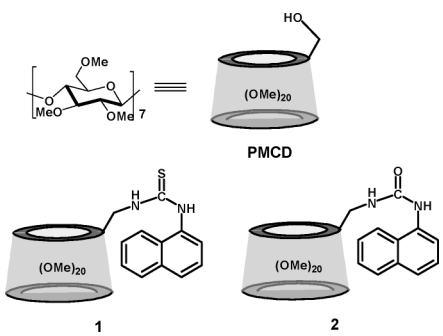
A naphthylthiourea-modified cyclodextrin (**1**) and its urea derivative (**2**) were synthesized, and their fluorescence behaviors in the presence of various metal ions were investigated. Significantly, **1** showed a highly sensitive and selective fluorescence sensing ability for Hg^{2+} over other metal ions in both water and living cells. That is, the addition of Hg^{2+} to an aqueous solution of **1** gave a significantly enhanced fluorescence at ~380 nm. In contrast, the addition of other metal ions induced negligible fluorescence changes. The possible mechanism may be due to the transformation of thiourea to urea by Hg^{2+}-induced desulfurization in water.

Introduction

Mercury is considered highly dangerous and toxic because both elemental and ionic mercury can be converted into methyl mercury by the marine bacteria in the environment, which subsequently bioaccumulates through the food chain and can cause many severely deleterious health effects for human beings, such as damage to the kidneys, skin, respiratory system, central nervous system and other organs.[1] So it is vital to develop highly selective and sensitive chemosensors for the detection of Hg^{2+} ions in the environment, especially in aqueous solutions and living cells. The method based on a fluorescence sensor provides unique advantages in terms of high sensitivity, high selectivity, operational simplicity and short response time.[2] Owing to the enhanced spin–orbit coupling associated with the heavy atom effect, many complexation-based fluorescent sensors for Hg^{2+} often cause "turn-off" (quenching) fluorescence responses.[3] However, a turn-on response is considered to be more effective, so many reaction-based fluorescent indicator systems have been introduced, and plenty of attractive and fascinating chemosensors or chemodosimeters for Hg^{2+} have been elaborately designed and investigated on the basis of a mercury-desulfurization reaction.[4] Czarnik *et al.* reported the first desulfurization reaction-based sensor system to detect Hg^{2+}.[4c] Qian[4e] and Tian[4h–4j] respectively reported a fluorescent chemodosimeter for the selective detection of Hg^{2+}. These sensors, although they were mostly used in organic or organic/water media, presented good Hg^{2+} sensing abilities. More interestingly, some reaction-based sensing systems in pure water and living cells were also reported.[4c,4d,4g,5]

Cyclodextrins (CDs), a class of cyclic oligosaccharides with 6–8 D-glucose units linked by α-1,4-glucose bonds, are widely used as drug carriers and solubilizers.[6] Recently, we prepared an MQAS-β-CD (MQAS = *N*-(2-methyl-8-amino-quinolyl)-*p*-amino-benzene sulfonamide) as a convenient and efficient chemosensor towards Hg^{2+} in both aqueous solution and the thin film.[7] Herein, we wish to report the synthesis and Hg^{2+}-sensing properties of a novel CD derivative **1**, bearing a naphthylthiourea substituent, (Scheme 1) as a highly sensitive and selective fluorescent chemosensor to Hg^{2+}. In this chemosensor, the presence of a CD cavity not only enhances the water solubility to a micromolar concentration level but also enables the location of **1** on the surface of a cell through the interactions of the CD cavity with the acyl chains of phospholipids and the side chains of cholesterol in the cell membrane.[8] This finding would enable **1** as a convenient and highly efficient fluorescence sensor for the detection of Hg^{2+} in water and living cells.



Scheme 1 Chemical Structures of **1** and **2**.

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Results and discussion

Fluorescence sensing to Hg^{2+}

Chemosensor **1** was facilely synthesized in a good yield (85%) by reaction of 6-deoxy-6-amino-permethyl-β-CD[9] with 1-naphthyl isothiocyanate, and its structure was fully characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, HR-MS (ESI), and elemental analysis (see the Experimental section). Owing to the good solubilizing property of the PMCD moiety, **1** showed both a good solubility at a micromolar concentration level in water and a suitable affinity for the biological membrane. Fig. 1 illustrates the fluorescence spectra of **1** with the addition of various metal ions in aqueous solution. Without metal ions, **1** emitted fairly weak fluorescence due to the possible intramolecular photo-induced electron transfer (PET) process between the sulfur atom of the thiourea group and the naphthalene group. Significantly, the addition of Hg^{2+} led to a remarkably enhanced fluorescence of **1**, while the addition of various alkali metal ions (Li^{+}, Na^{+}, and K^{+}), alkaline earth metal ions (Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}), and transition metal ions (Cu^{2+}, Ag^{+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Ce^{2+}, and Pb^{2+}) gave very limited fluorescence changes in **1** under the same conditions. In the control experiment, the comparison of the sensing ability of the fluorophore with and without CD towards Hg^{2+} was also carried out in H_2O–MeCN (v : v = 1 : 1) due to the poor water solubility of free 1-naphthyl isothiocyanate. The results showed that, without CD, the fluorescence intensity of the free 1-naphthyl isothiocyanate increased only 1.3 times, but the fluorescence intensity of **1** increased 3.3 times, with the addition of Hg^{2+} under the same condition (see ESI†). These results indicated a potential application of **1** in the detection of Hg^{2+} in water.

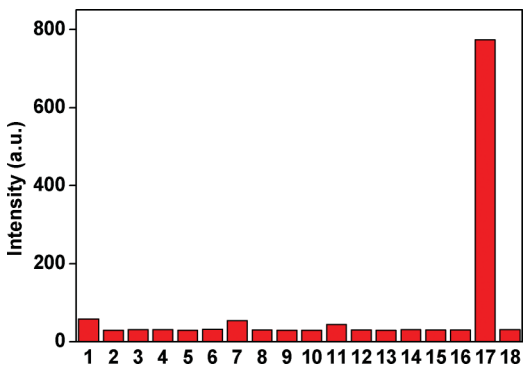


Fig. 1 Fluorescence spectra changes of **1** (5 μM in water) in the presence of various cations, such as 1: Ag^{+}; 2: Ba^{2+}; 3: Ca^{2+}; 4: Cd^{2+}; 5: Ce^{2+}; 6: Co^{2+}; 7: Cu^{2+}; 8: K^{+}; 9: Li^{+}; 10: Mg^{2+}; 11: Mn^{2+}; 12: Na^{+}; 13: Ni^{2+}; 14: Pb^{2+}; 15: Sr^{2+}; 16: Zn^{2+}; 17: Hg^{2+} (200 equiv, respectively) and 18: **1** alone (λ_{ex} = 290 nm, λ_{em} = 380 nm).

To gain more insight into the behavior of **1** towards Hg^{2+}, fluorescence titration experiments in aqueous solution were carried out. As seen from Fig. 2, the fluorescence intensity of **1** gradually increased with the increasing concentrations of Hg^{2+}. Control experiments revealed that the changes in the ion strength resulting from the addition of Hg^{2+} salt was not the main factor leading to the significant fluorescence changes of **1**. In addition, the limit of detection ($3\sigma/K$) of **1** for Hg^{2+} was determined to be 3.7×10^{-7} mol L^{-1} in water.

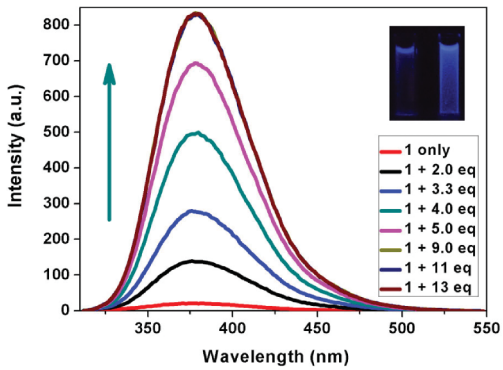


Fig. 2 Fluorescence spectra of **1** (5 μM) with addition of various concentrations of Hg^{2+} ion (λ_{ex} = 290 nm). Inset shows the photographs of **1** (left) and addition of 10 equiv of Hg^{2+} (right) under UV-light irradiation.

Moreover, to explore the possible sensing mechanism of **1** towards Hg^{2+}, some further experiments were performed. When adding an excess of amount of EDTA to a solution of **1**, the obtained **1**/EDTA mixture showed no appreciable fluorescence response to Hg^{2+} under the same conditions. Additionally, the fluorescence changes of the **1**/Hg^{2+} system induced by the addition of an excess of amount of EDTA were also negligible. On the basis of these results, along with the 1 : 1 stoichiometry between Hg^{2+} and **1**, determined by the Job's method (Fig. 3), we deduced that the significant fluorescence response of **1** towards Hg^{2+} may be dependent on a reaction, rather than a simple coordination, between **1** and Hg^{2+}, like the system reported by Chang *et al.*[10] That is, the Hg^{2+} added to the solution of **1** would promote the transformation of the thiourea group of **1** to the urea group. Meanwhile, Hg^{2+} was converted to HgS. Because this conversion was irreversible, the subsequent addition of EDTA could not affect the fluorescence of the **1**/Hg^{2+} system. Whereas, if there existed an excess amount of EDTA in solution, the Hg^{2+} added to the solution would firstly coordinate with EDTA owing to the very strong affinity of EDTA towards Hg^{2+}, which consequently prevented the reaction of Hg^{2+} with **1** and thus led to the low fluorescence response of **1** towards Hg^{2+} in the presence of EDTA.

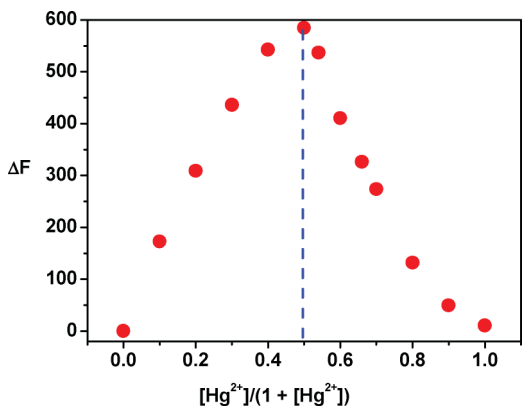


Fig. 3 Job's plot of **1** and Hg^{2+} ions. The total concentration of **1** and Hg^{2+} was kept constant at 50 μM (λ_{ex} = 290 nm, λ_{em} = 380 nm).

This sensing mechanism was further supported by some mass and fluorescence spectral analysis. Firstly, the ESI-MS spectrum clearly showed the peaks of $[M_1]^{+}$ at m/z 1599.58. After the

addition of Hg^{2+}, the peak at m/z 1606.04 corresponding to $[M_2 + Na]^+$ was observed (see ESI†). Secondly, the elemental analysis of the Hg^{2+}-treated **1** showed that, after being treated by Hg^{2+}, the content of S was negligible, which indicated the sulfur atom in **1** was removed by the addition of Hg^{2+}. Thirdly, the fluorescence intensity of **2** was much stronger than that of **1** (Fig. 4a), while the produced HgS was found to be non-fluorescent, indicating that the weak fluorescence of **1** was due to the intramolecular photo-induced electron transfer (PET) process between the sulfur atom of the thiourea group and the naphthalene group. Fourthly, **2** showed comparable fluorescence emission properties but no obvious response to any metal ions studied (Fig. 4b). Based on these observations, a schematic sensing mode of **1** towards Hg^{2+} was proposed (Scheme 2).[11] Without Hg^{2+}, the fluorescence of **1** was fairly weak due to the intramolecular PET. After the addition of Hg^{2+}, the PET process was prevented owing to the transformation of the thiourea group to the urea group with the promotion of Hg^{2+}. As a result, the fluorescence intensity of **1**/Hg^{2+} showed a dramatic enhancement. In another test, the fluorescence intensity of **1** increased only 2.5 times within the initial 5 h and slowly increased to 7.6 times even after 72 h (see ESI†) with the addition of Ag^+.

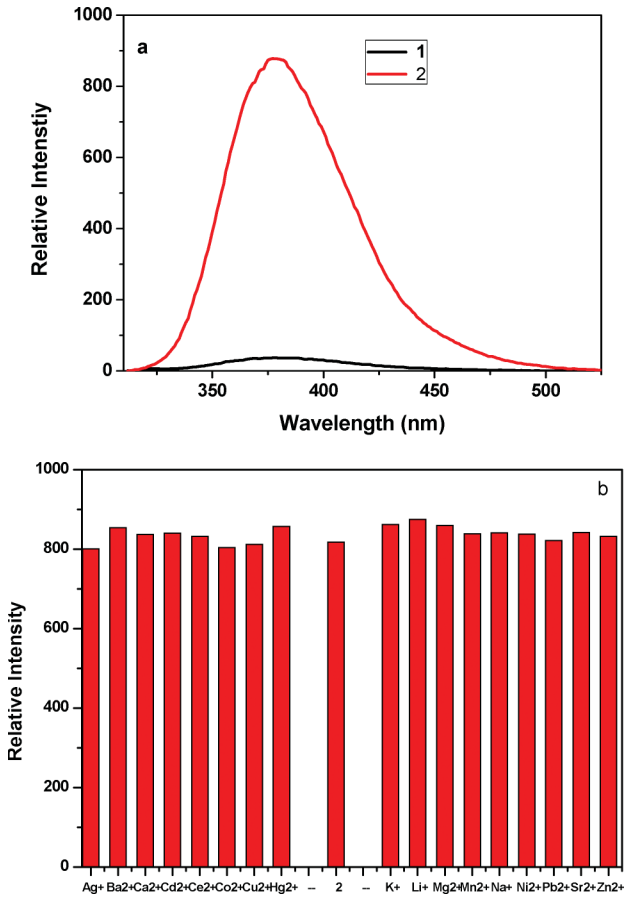
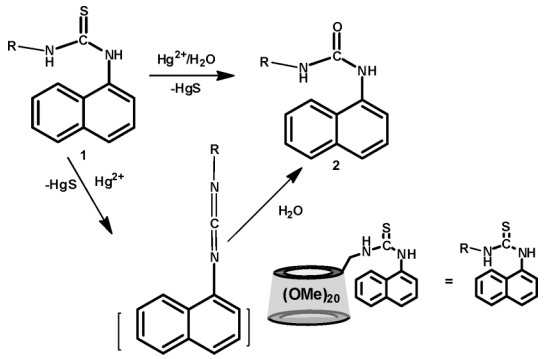


Fig. 4 (a) Fluorescence spectra of **1** and **2** (5 μM in water) and (b) Fluorescence spectral changes of **2** (5 μM in water) in the absence and presence of various cations including Ag^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Ce^{2+}, Co^{2+}, Cu^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Sr^{2+}, Zn^{2+}, Hg^{2+}(200 equiv, respectively). (λ_{ex}= 290 nm, λ_{em} = 380 nm).



Scheme 2 Proposed Hg^{2+}-selective signaling mechanism of chemosensor **1**.

Fluorescence sensing to Hg^{2+}-containing cation mixtures

It is interesting to compare the fluorescence sensing ability of **1** to a Hg^{2+}-containing cation mixtures, because a very important characteristic feature of a sensor is its response to the species to be measured over that to other species also present in the environment. When comparing the fluorescence sensing ability of **1** to the Hg^{2+}-containing cation mixtures, it was found that **1** showed high fluorescence enhancement factors ($F/F_0 > 33.7$), most of which were similar to that for Hg^{2+} alone ($F/F_0 = 35.1$), for the solutions containing Hg^{2+} and various alkali metal ions (Li^+, Na^+, and K^+), alkaline earth metal ions (Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}), or transition metal ions (Ag^+, Cd^{2+}, Ce^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Pb^{2+}, Mn^{2+}, Zn^{2+}) (Fig. 5). This showed that an excess of these competing cations did not obviously influence the detection of Hg^{2+} in water.

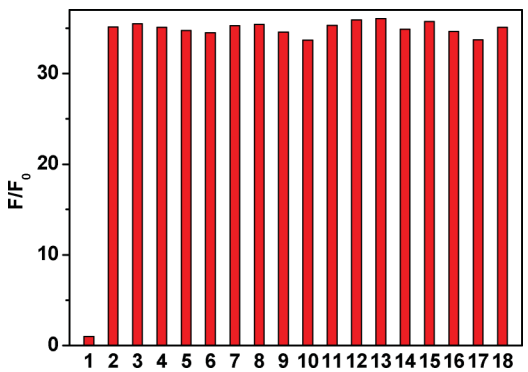


Fig. 5 Signaling of Hg^{2+} ions by **1** in the presence of 200 equiv of possibly interfering ions as background (λ_{ex} = 290 nm, recorded at 380 nm). 20 equiv of Hg^{2+} to the solutions containing **1** and the cations. 1, blank; 2, only Hg^{2+}; 3, Ag^+; 4, Ba^{2+}; 5, Ca^{2+}; 6, Cd^{2+}; 7, Ce^{2+}; 8, Co^{2+}; 9, Cu^{2+}; 10, K^+; 11, Li^+; 12, Mg^{2+}; 13, Mn^{2+}; 14, Na^+; 15, Ni^{2+}; 16, Pb^{2+}; 17, Sr^{2+}; 18, Zn^{2+}.

Effect of pH

For further practical utilization, we studied the effect of different pH on the fluorescence response. Interestingly, **1** also showed good fluorescence sensing ability to Hg^{2+} when the pH was within the 3 to 12 range (Fig. 6). Around pH 7, the F/F_0 value reached its maximum value, indicating that **1** possessed the highest sensing ability in a physiological environment.

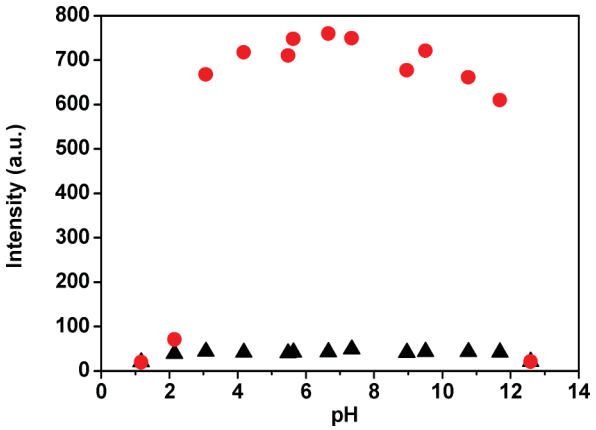


Fig. 6 Fluorescence variation of probe **1** (5 μM) in water without (▲) and with Hg^{2+} ions (100 μM, ●) as a function of pH (λ_{ex} = 290 nm, λ_{em} = 380 nm).

Fluorescence sensing in cells

More interestingly, in a study on the Hg^{2+}-sensing behavior of **1** in a biological system by fluorescence microscopy with yeast cells (*Saccharomyces cerevisiae*) as model cells, **1**-stained yeast cells exhibited a good fluorescence response to Hg^{2+}. After incubation at 35 °C for 30 min in the presence of **1**, yeast cells presented a very weak background fluorescence without the addition of Hg^{2+} (Fig. 7b), but exhibited a strong blue fluorescence, as seen by the fluorescence microscope, upon the addition of Hg^{2+} (Fig. 7d). This result indicated that **1** might be used as a fluorescence probe for studying biological processes involving Hg^{2+} within living cells. In the 2D NMR spectrum of **1** with lecithin liposomes as the cell membrane model (see the ESI†), the cholesterol or lecithin protons in the liposomes showed the obvious NOE correlations with the interior protons (H3/H5/H6) of methylated CDs. These results indicated that the methylated CD cavity of **1** had the capability of associating with the cell membrane. Because the CD unit of **1** was cell-impermeant, we deduced that **1** would be located on the surface of a cell through the interactions of the CD cavity with the acyl chain of the phospholipids and the side chain of cholesterol in the cell membrane.[8] Subsequently, the naphthylthiourea group of **1** could settle in the cell membrane and combine with the intracellular Hg^{2+} to give blue fluorescence.

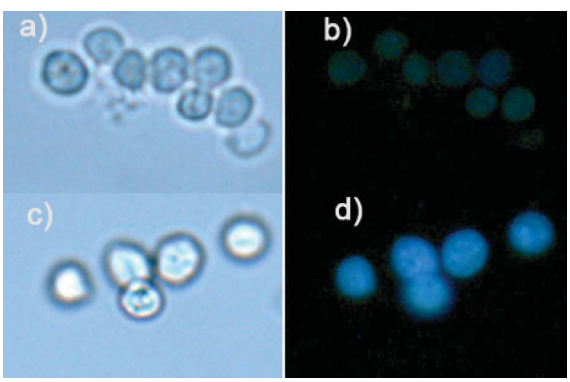


Fig. 7 Optical and fluorescence microscopic images of yeast cells in the absence and presence of Hg^{2+}. (a) Brightfield image of cells in the absence of Hg^{2+}. (b) Fluorescence image of pane a. (c) Brightfield image of yeast cells in the presence of Hg^{2+}. (d) Fluorescence image of pane c.

Conclusions

In conclusion, a "turn-on" chemosensor of Hg^{2+} was synthesized and found to be able to detect Hg^{2+} with high selectivity and sensitivity in water and living cells. Owing to its satisfactory water solubility, convenience in preparation, high sensing specificity for Hg^{2+} over other competing cations, and wide applicable pH range, this sensor system will have an inherent advantage to meet the selectivity requirements of a Hg^{2+} assay in environmental and biological fields.

Experimental

General methods

All the solvents were of analytic grade. ^{1}H-NMR and ^{13}C-NMR were measured on a Bruker AV-400 or AV-600 spectrometer with chemical reported as ppm (in D_2O, and $CDCl_3$ TMS as internal standard). ESI-MS was performed on VG ZAB-HS. Positive-ion matrix-assisted laser desorption ionization (MALDI) mass spectrometry was performed on an IonSpec QFT-MALDI MS. All pH measurements were made with a PHS-3C instrument (Shanghai Rex Instrument Factory). Elemental analyses (C, H and N) were carried out on a Perkin–Elmer-2400C instrument. The Fourier transform infrared (FT-IR) spectrum was recorded on a MAGAN-560 FTIR instrument using KBr pellets in the 4000–400 cm^{-1} regions. Fluorescence spectra were recorded on a Varian Cary Eclipse equipped with a Varian Cary single cell peltier accessory to maintain the temperature.

Yeast cell culture and cell staining. Yeast (*Saccharomyces cerevisiae*) was obtained from the Agronomy and Forestry Department of Huanghuai University and used as a cell model. Before use, it was dispersed on a YPD plate (1.0% yeast extract, 4% peptone, 2.0% glucose, 0.2% $(NH_4)_2SO_4$) and cultured for 2 days at 35 °C. For yeast staining, some colonies were selected and incubated for 30 min at 35 °C in 0.75 mM of **1**. While, some other colonies were selected and incubated for 30 min at 35 °C in 0.75 mM of **1** in the presence of 0.60 mM of $Hg(ClO_4)_2$. Subsequently, cells were washed twice with distilled water to remove uncombined **1** and **1**/Hg^{2+} by centrifugation. Cells for experiments were dropped on glass slides and covered with a glass cover. All imaging experiments were performed on a YZ-2 fluorescence microscope (Beijing Keyi Electro-optic Plant) equipped with a 100 W/DC mercury lamp for UV excitation and a SPC-382B color CCD camera for photo collection. The total magnification was 400×.

Liposome preparation. The mixture of egg phosphatidylcholine (60 wt.%), cholesterol (20%), and sodium deoxycholate (20%), which increased the solubility of lecithin and kept the solution clear, were dissolved in chloroform–methanol (2 : 1). The mixture was placed in a culture tube and the solvent was removed with a stream of nitrogen and then dried under high *vacuum* at room temperature. The solid was dissolved in D_2O to provide a final lecithin concentration of *ca.* 2 g dm^{-3}. The suspensions were sonicated at 60 °C for *ca.* 15 min until the solution became clear.[12]

Synthesis of 1. 6-Deoxy-6-amino-permethyl-β-CD (1414 mg, 1 mmol) and 1-naphthyl isothiocyanate (555 mg, 3 mmol) were dispersed in dry dichloromethane. The mixture was stirred at room temperature under N_2 for 12 h. Then the solvent was evaporated to dryness under *vacuum*. The residue was purified by silica-gel column chromatography with ethyl acetate as eluent and recrystallization from CH_2Cl_2-hexane to yield compound **1** (1360 mg, 85%), as white crystals. ^{1}H NMR (D_2O, 400 MHz, δ): 7.90–7.83 (m, 3H), 7.53–7.50 (m, 4H), 5.33–5.31 (m, 2H), 5.11–4.96 (m, 5H), 3.66–2.90 (m, 102). ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 182.22, 134.76, 134.60, 132.08, 128.55, 122.74, 122.55, 98.94, 98.90, 82.04, 81.83, 81.65, 71.36, 71.06, 70.89, 61.61, 59.10, 58.99, 46.26. FT-IR (KBr, cm^{-1}) 3389.14, 2978.45, 1635.42, 1596.53, 1532.38, 1269.55. ESI-MS: 1599.58 $[M]^+$. Anal. Calcd. for $C_{73}H_{118}N_2O_{34}S$: C 54.81, H 7.43, N 1.75. Found: C 54.74, H 7.57, N 1.62.

Synthesis of 2. 6-Deoxy-6-amino-permethyl-β-CD (707 mg, 0.5 mmol) and 1-naphthyl isocyanate (507 mg, 3 mmol) were dispersed in dry dichloromethane. The mixture was stirred at room temperature for 12 h. Then the solvent was evaporated to dryness under *vacuum* and the residue was purified by column chromatography with ethyl acetate and recrystallization from CH_2Cl_2-hexane to yield compound **2** (395 mg, 50%), as white crystals. ^{1}H NMR (D_2O, 400 MHz) δ 7.72–7.68 (t, 2H), 7.55–7.54 (d, 1H), 7.32–7.25 (m, 4H), 5.12–4.88 (m, 7H), 3.61–2.87 (m, 102). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 156.52, 133.77, 133.34, 128.04, 127.88, 125.53, 125.33, 121.19, 99.06, 98.86, 98.71, 98.57, 98.48, 81.99, 81.88, 81.74, 70.97, 61.57, 61.52, 61.42, 59.12, 59.06, 42.10. FT-IR (KBr, cm^{-1}) 3391.80, 2978.37, 2929.26, 1684.72, 1598.16, 1543.84, 1506.70, 1458.45, 1403.64, 1368.12, 1342.43, 1302.58, 1259.19, 1194.48, 1160.85, 1107.90, 1037.52, 970.33, 856.52, 792.61,705.35, 554.14. HR-MS (MALDI-TOF) Calcd for $[C_{73}H_{118}O_{34}N_2S + Na]^+$ 1605.74. Found, 1605.786, Calcd for $[C_{73}H_{118}O_{34}N_2S + K]^+$, 1621.72, Found, 1621.768. Anal. Calcd. for $C_{73}H_{118}N_2O_{35}$: C 55.36, H 7.51, N 1.77. Found: C 55.24, H 7.69, N 1.50.

Acknowledgements

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