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A water-soluble pillar[5]arene-based chemosensor for highly selective and sensitive fluorescence detection of L-methionine†

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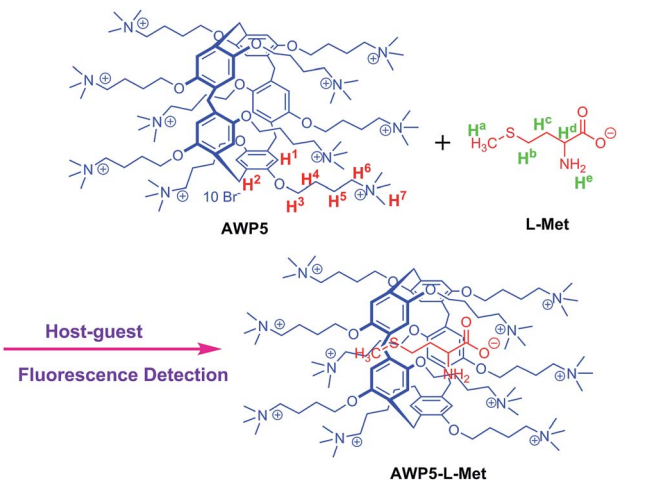
L-Methionine (L-Met) is an essential amino acid for the human body. The detection of L-Met in water solution is very important. Herein, we report an efficient approach for the fluorescent detection of L-Met with high selectivity and sensitivity in water using a cationic pillar[5]arene-based chemosensor (**AWP5**). When various L-amino acids are added to the **AWP5** water solution, only L-Met can induce fluorescence in **AWP5** at λ_{em} = 520 nm, showing dramatic enhancement; thus, other amino acid do not interfere in the L-Met recognition process. **AWP5** also shows high sensitivity for L-Met in water, with the lowest detection limit of **AWP5** for L-Met being 5.46 × 10^{-7} mol L^{-1}.

1. Introduction

L-Amino acids play a significant role in chemistry and biology. In particular, L-Met is one of the most essential amino acid for protein synthesis in the human body, which can promote the growth of hair and nails, enhance muscle activity *etc.* L-Methionine acts as a methyl group donor in many methyltransferase reactions including biosynthesis of phospholipids[1] and bioelectrical activity.[2] Loss of L-methionine in brain cells of aged animals is linked with the loss of dopaminergic β-adrenergic binding sites and changes in cell membrane composition.[3] Therefore, the selective detection of L-Met is very important. To date, there are various useful strategies or methods such as artificial chemosensors, high-performance liquid chromatography, and capillary zone electrophoresis[4–8] that have been applied for the detection of L-amino acids. However, these methods suffer from a number of problems. First, the instrument detection methods often employ expensive equipment. Second, owing to the low water solubility of organic groups, most synthesized chemosensors do not work well in water solution. However, most biological or environmental procedures are carried out in water systems. Therefore, it is still a big challenge and an important task to develop a water soluble chemosensor for the detection L-Met in water.

Recently, pillararene chemistry has undergone rapid development[9–16] and pillararene derivatives have been widely used in the field of molecular recognition,[17–23] drug delivery,[24–30] molecular devices,[31–37] and so on. Note that two kinds of important water-soluble pillararene derivatives have been developed to date: (1) cationic pillararene[38] and (2) anionic pillararene.[39,40] Due to their nice water solubility, inclusion and host–guest properties, these kinds of pillararene derivatives provide a great opportunity for the design of water-soluble chemosensors.

In view of this and based on our research interest in molecule recognition,[41–48] herein, we report a novel and efficient way for the detection of L-Met in water *via* a cationic pillar[5]arene-based chemosensor (**AWP5**). As shown in Scheme 1, the



Scheme 1 The chemical structure of **AWP5** and possible selective detection mechanism of the sensor **AWP5** for L-Met.

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chemosensor **AWP5** possesses high water solubility and can enable fluorescence detection of L-Met in water with high selectivity and sensitivity through a host–guest mechanism.

2. Results and discussion

Cationic pillar[5]arene (**AWP5**) was synthesized according to Scheme S1.† To investigate L-amino acid recognition abilities of the sensor **AWP5** in water, we carried out a series of host–guest recognition experiments. The recognition profiles of the sensor **AWP5** for various L-amino acids, including L-α-Ala, L-Arg, L-Cys, L-Gly, L-Lys, L-Pro, L-Met, L-Thr, L-Ser, L-His, L-Val, L-Tyr, L-Asn, L-Glu, L-Trp, L-Gln, L-Ile, L-Phe, L-Asp, and L-Leu, were primarily investigated using fluorescence spectroscopy in water.

As shown in Fig. 1, when 10 equiv. of L-Met was added to the water solution of sensor **AWP5**, a blue fluorescence emission appeared. Moreover, in the corresponding fluorescence spectrum, the maximum emission peak appeared at 617 nm. However, other L-amino acids such as L-α-Ala, L-Arg, L-Cys, L-Gly, L-Lys, L-Pro, L-Thr, L-Ser, L-His, L-Val, L-Tyr, L-Asn, L-Glu, L-Trp, L-Gln, L-Ile, L-Phe, L-Asp, and L-Leu did not induce similar fluorescence changes (Fig. 2 and S10†). Therefore, in water solution, **AWP5** showed specific fluorescence selectivity for L-Met.

To further investigate the efficiency of the sensor **AWP5** for L-Met detection, we carried out fluorescence titration experiments. As shown in Fig. 3, in the fluorescence spectrum, with an increasing amount of L-Met, emission peak at 594 nm gradually increased. Furthermore, the detection limit of the fluorescent spectrum changes calculated on the basis of $3s/m$ (ref. 49) is 5.46×10^{-7} M for L-Met (Fig. S11, ESI†). Moreover, we carried out similar experiments in the presence of 10 equiv. of L-his (Fig. S12, ESI†). The L-Met detection limit was 2.07×10^{-6} M in the presence of 10 equiv. of L-His, which indicated that **AWP5** showed high sensitivity for L-Met in the presence of other amino acids.

To further exploit the utility of **AWP5** as a selective sensor for L-Met, competitive experiments were carried out in the presence of 10.0 equiv. of L-Met and 2.0 equiv. of various L-amino acids in water. The fluorescence emission spectrum of the sensor **AWP5** with L-Met was not influenced by the subsequent addition of other competing L-amino acids, which indicated that **AWP5** had specific selectivity for L-Met (Fig. 4).

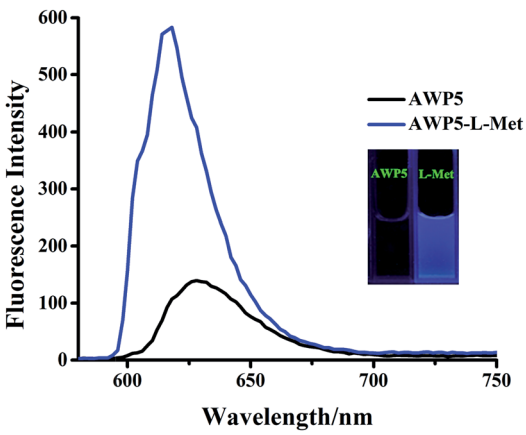

Fig. 1 Fluorescence spectra of AWP5 ($C = 2 \times 10^{-5}$ mol L^{-1} in water) and the AWP5 water solution after the addition of 10 equiv. of L-Met ($\lambda_{ex} = 520$ nm).

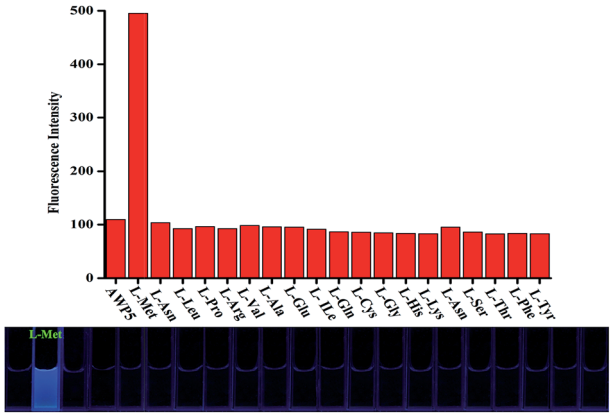

Fig. 2 Fluorescence spectra of the sensor AWP5 in water solution (2×10^{-5} mol L^{-1}) upon the addition of 10 equiv. of L-Ala, L-Arg, L-Asp, L-Cys, L-Gln, L-Glu, L-His, L-Ile, L-Gly, L-Asn, L-Leu, L-Lys, L-Met, L-Phe, L-Pro, L-Ser, L-Thr, L-Trp, L-Tyr, and L-Val ($\lambda_{ex} = 520$ nm).

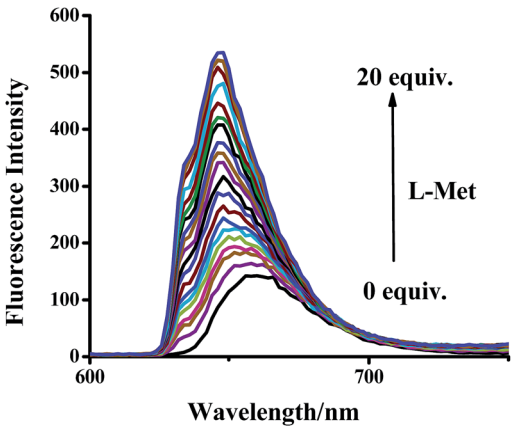

Fig. 3 Fluorescence intensity changes of AWP5 water solution ($C = 1 \times 10^{-5}$ mol L^{-1}) upon the addition of different amounts of L-Met ($\lambda_{ex} = 520$ nm).

The recognition mechanism of **AWP5** towards L-Met was investigated by ^{1}H-NMR titrations, 2D NOESY-NMR, ESI-mass spectrometry, and job plots. As shown in Fig. 5, in ^{1}H-NMR, upon the addition of L-Met to an **AWP5** D_2O solution, proton peaks of **AWP5** and L-Met show obvious shifts. The triplet peaks of H_a, H_b, H_c, and H_d of L-Met show obvious upfield shifts ($\Delta\delta = -0.15, -0.23, -1.54, -0.10, -0.12$ ppm), which indicates that L-Met is located in the cavity of **AWP5**. Simultaneously, the proton peaks of H^1 and H^2 of **AWP5** shift upfield ($\Delta\delta = -0.25$ and -0.40 ppm), which indicate electrostatic interactions between the carboxylic acid groups of L-Met and ammonium salts of **AWP5**. The electrostatic interactions directly lead to charge transfer from the carboxylate groups of L-Met to the **AWP5** ammonium salt groups. By this way, these proton chemical shift changes indicated that the complexation took place between **AWP5** and L-Met in solution.

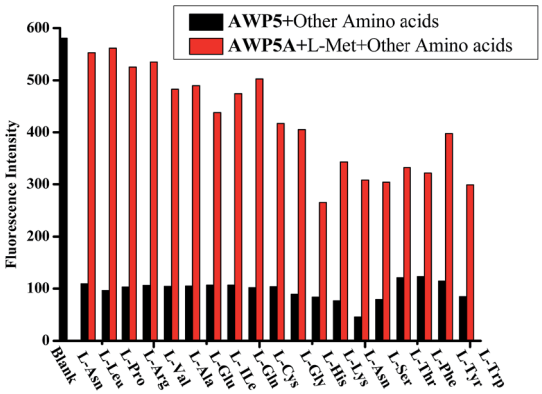

Fig. 4 Fluorescence intensity changes of the sensor **AWP5** water solution (1×10^{-5} mol L^{-1}) ensemble in the presence of other amino acids (2.0 equiv.) ($\lambda_{ex} = 520$ nm).

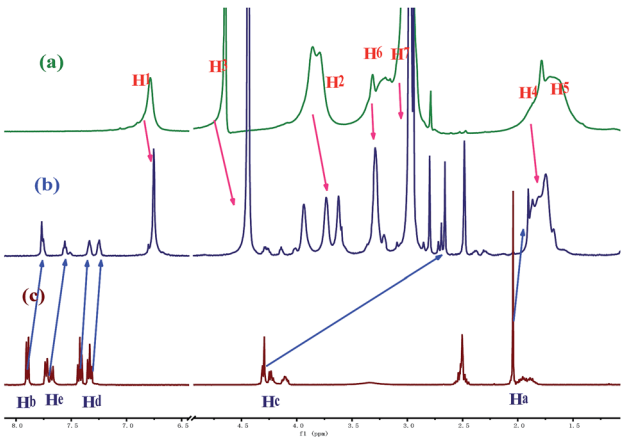

Fig. 5 ^{1}H-NMR spectra (600 MHz, 298 K) of (a) **AWP5** (1×10^{-3} mol L^{-1} in H_2O); (b) equimolar mixture of **AWP5** and L-Met (1 : 1); and (c) L-Met (1×10^{-3} mol L^{-1} in DMSO-d_6).

Furthermore, a 2D NOESY NMR study of a mixture of **AWP5** (10.0 mM) and L-Met (10.0 mM) in D_2O was carried out to investigate the relative spatial positions of this host–guest

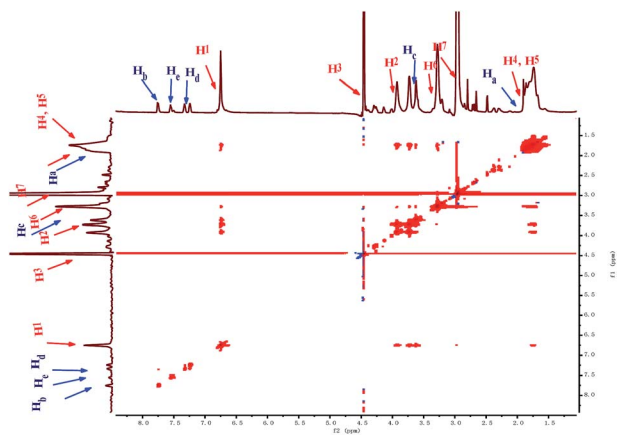

Fig. 6 NOESY-NMR spectra of (600 MHz, D_2O, 298 K) of **AWP5** : L-Met = 1 : 1.

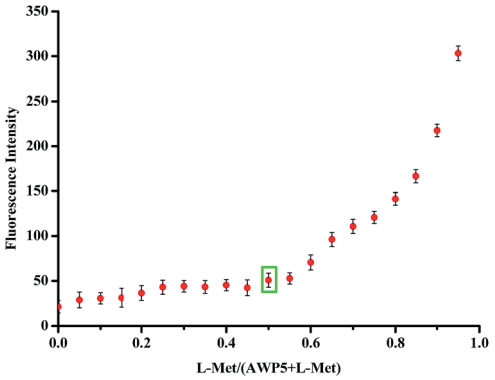

Fig. 7 Job plot for complexation between **AWP5** and L-Met in H_2O.

complex. As shown in Fig. 6, clear correlation signals were observed between proton H^1 of **AWP5** and proton H^a of L-Met, indicating that L-Met penetrated through the cavity of **AWP5**.

To confirm the binding stoichiometry between the sensor **AWP5** and L-Met in H_2O, a job plot was constructed. The results illustrate that L-Met forms a 1 : 1 complex with **AWP5** (Fig. 7). Furthermore, mass spectrometry experiments also support the abovementioned proposed host–guest mechanism. In the ESI-MS of the sensor **AWP5** and L-Met solution, (Fig. S13, ESI†) a peak at $m/z = 444.0376$ for $[\mathbf{AWP5} + \text{L-Met} + 4\text{Br}]^{5+}$ proved the 1 : 1 complexation stoichiometry between **AWP5** and L-Met.

Through the abovementioned phenomena and description, a possible mechanism was proposed (Scheme 1). On addition of L-Met, **AWP5** forms a stable inclusion complex with L-Met in solution because of their multiple interactions. The methylene groups of L-Met can result in C–H$\cdots\pi$ interactions with the pillar[5]arene group, whereas the amino groups of L-Met can form hydrogen bonds with oxygen atoms of the pillar[5]arene group. In addition, electrostatic interactions occur between ammonium groups of **AWP5** and carboxylic acid group of L-Met. These multiple interactions stabilize the resulting inclusion complex between **AWP5** and L-Met.

3. Conclusions

In summary, we employed cationic pillar[5]arene (**AWP5**) as a water-soluble chemosensor for the recognition of amino acids. The chemosensor **AWP5** could fluorescently detect L-Met in water with high selectivity and sensitivity by a host–guest mechanism. Moreover, the detection limit of the sensor **AWP5** for L-Met was 5.46×10^{-7} mol L^{-1}, which indicated that the sensor **AWP5** could be useful as a highly selective and sensitive sensor for detecting L-Met. The chemosensor **AWP5** can thus serve as a practical and convenient fluorescence test kit to detect L-Met.

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