Sensors and Actuators B xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Short Communication

Pillar[6]arene/acridine orange host–guest complexes as colorimetric and fluorescence sensors for choline compounds and further application in monitoring enzymatic reactions

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ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form 16 August 2017
Accepted 17 August 2017
Available online xxx

Keywords:
Pillar[n]arenes
Host–indicator system
Fluorescence indicator displacement

ABSTRACT

A novel pillararene–indicator system between anionic water-soluble pillar[6]arene (WP6) and an aromatic fluorescent dye acridine orange (AO) was constructed. Upon complexation with electron-rich cavity of WP6, AO showed a fluorescence quenching and color change due to the host–guest charge-transfer interactions. The established pillararene–indicator system was further employed in the detection of choline compounds and monitoring enzymatic reactions.

The concept of indicator displacement assay (IDA) has attracted considerable interest with the advancement of supramolecular chemistry, which mainly focused on the exploration of the potential of artificial receptors, in particular macrocyclic hosts, for its promising applications in molecular recognition and analyte sensing [1]. The sensing principle of IDA relies on the competition complex between a test substance and an indicator with the same binding site on the host [2]. When an analyte is added to a solution containing a host–indicator complex, the fluorescent dye will be displaced from the complex and an accompanying change in signal can be observed. To date, IDA has been widely used in a variety of areas, especially in analyte sensing. Furthermore, keeping eyes on potential biological application, Nau utilized IDA to construct a novel approach towards enzyme assays–supramolecular tandem enzyme assays [3]. It is well-known that monitoring enzymatic activity is of significance for academic and industrial research. This method opens up a new possibility for the design of simple and facile systems for real-time monitoring of enzyme activity.

Pillararenes, recognized as the fifth class of macrocyclic host molecules next to crown ethers [4–7], cyclodextrins [8], calixarenes [9] and cucurbiturils [10], have become star receptors because they can form stable host–guest complexes with various organic, inorganic and biological guest molecules [11–15]. In particular, water-soluble pillararenes [16–19], due to their good biocompatibility and simplicity of synthesis, have been widely employed in biological applications such as treatment of paraquat poison [20], cell glue [21], transmembrane channels [22,23] and drug delivery [24–27]. Another important application for water-soluble pillararenes was to fabricate host–indicator complex for analyte sensing through IDA method. However, unlike calixarenes [28], cyclodextrins [29] and cucurbiturils [30], the related work based on pillararene–indicator complexes has been rarely investigated and most of previously published reports have focused on the simple detection of paraquat and its analogues – a class of a pesticide with electron-poor structures [31,32]. In consideration of the limitation of the analytes in such systems, there is great potential unfulfilled with pillararenes–indicator complex in the IDA field. Moreover, further application of pillararenes–based IDA in biological fields needs to be explored.

Herein, a novel pillararene–indicator system between anionic water-soluble pillar[6]arene (**WP6**) and an aromatic fluorescent dye acridine orange (**AO**) was constructed (Scheme 1). Upon complexation with electron-rich cavity of **WP6**, **AO** showed a fluorescence quenching due to the host–guest charge-transfer interactions. Moreover, the color of the solution exhibited an obvious transformation from yellow to red. Upon establishment of this host–guest switch with dual signals, we employed it as sensor for choline compounds through indicator displacement induced color and fluorescence change. After addition of choline, the yellow-green fluorescence of the solution recovered and its color returned to yellow. Furthermore, we utilized supramolecular on-off-on fluorescence assays to construct supramolecular tandem enzyme

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http://dx.doi.org/10.1016/j.snb.2017.08.141
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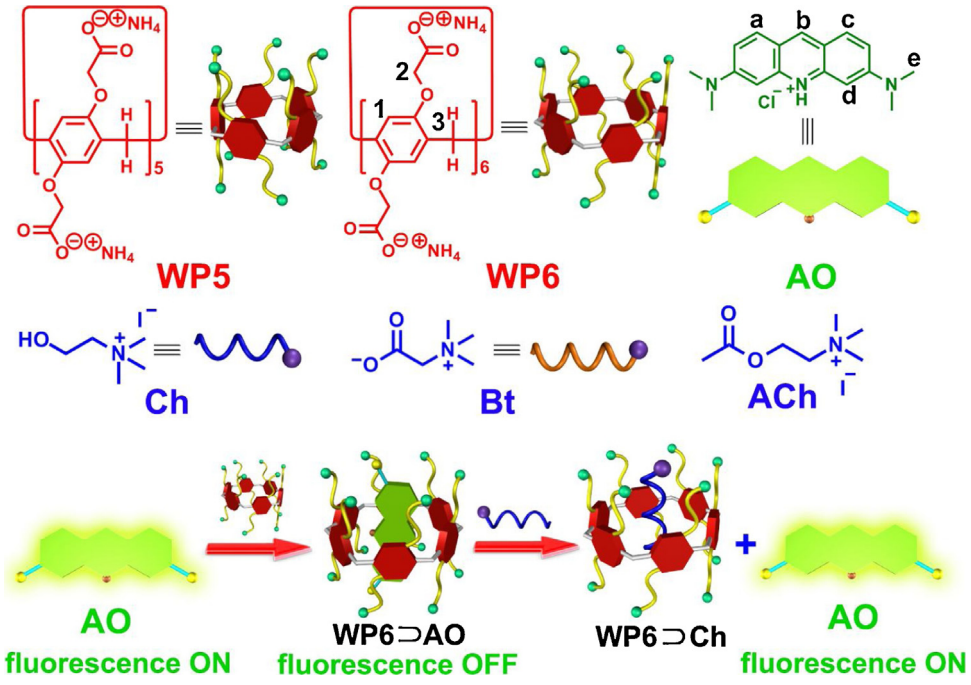

Scheme 1. Chemicals used here and illustration of the turn-on fluorescence detection of choline through indicator displacement process.

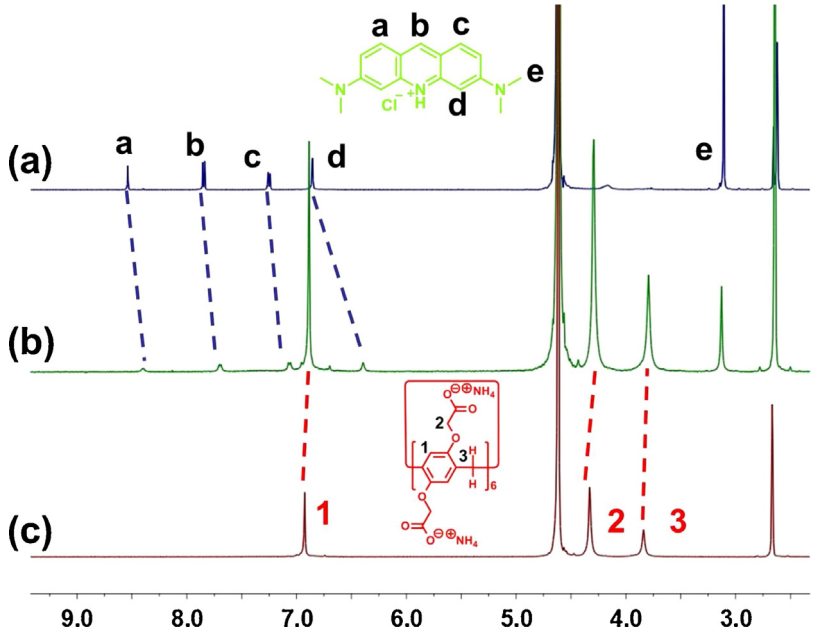

Fig. 1. Partial ^{1}H NMR spectra (500 MHz, D_2O:DMSO-d_6 = 1:1, 293 K): (a) 0.500 mM **AO**; (b) a mixture of 0.500 mM **AO** and 1.00 mM **WP6**; (c) **WP6** (1.00 mM).

assays to monitor the enzyme reaction catalyzed by choline oxidase.

First, ^{1}H NMR spectroscopy was used to study the host–guest complexation between **WP6** and **AO** (Fig. 1). Compared with the spectrum of free **AO**, significant upfield shift changes corresponding to the phenyl proton signals of **AO** occurred in the presence of 2 equiv. **WP6** (Δd = −0.17, −0.19, −0.20 and −0.19 ppm for H_a, H_b, H_c and H_d, respectively). This phenomenon indicated that **AO** was encapsulated by the cavity of **WP6** and the protons on **AO** were shielded by the electron-rich cyclic structure upon formation of an inclusion complex [33]. Meanwhile, broadening effects for the peaks corresponding to the protons on **AO** were observed due to complexation dynamics [34]. On the other hand, peaks related to protons on **WP6** also displayed slight chemical shift changes due to the host–guest interactions between **WP6** and **AO**. [35] Isothermal titration calorimetry (ITC) measurements were further performed to determine the association constant (K_a) of this host–guest complex. The K_a value of **WP6**⊃**AO** was calculated to be $(2.24 \pm 0.10) \times 10^5\ M^{-1}$. The titration data were well fitted by computer simulation using the "one set of binding sites" model, demonstrating 1:1 complexations between **WP6** and **AO** (Fig. S1). Notably, according to the thermodynamic data listed in Fig. S1, the complexation was driven by both enthalpy and entropy changes ($\Delta H^\circ < 0$; $T\Delta S^\circ > 0$) [36].

Further evidence for the complexation between **WP6** and **AO** was obtained from UV–vis absorption spectroscopy. As shown in

Please cite this article in press as: B. Hua, et al., Pillar[6]arene/acridine orange host–guest complexes as colorimetric and fluorescence sensors for choline compounds and further application in monitoring enzymatic reactions, Sens. Actuators B: Chem. (2017), http://dx.doi.org/10.1016/j.snb.2017.08.141