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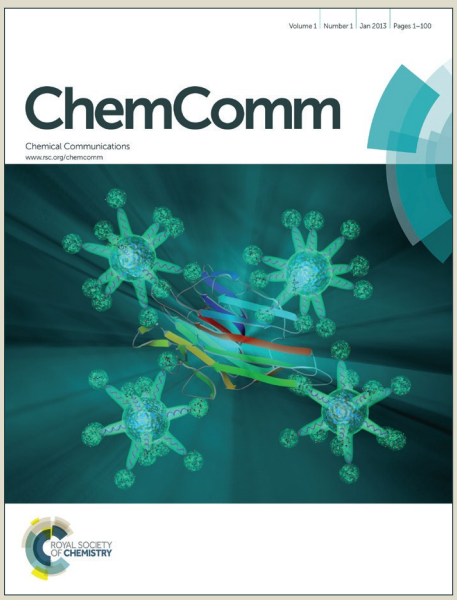

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COMMUNICATION

Host–guest interaction enhanced aggregation-induced emission and its application in cell imaging

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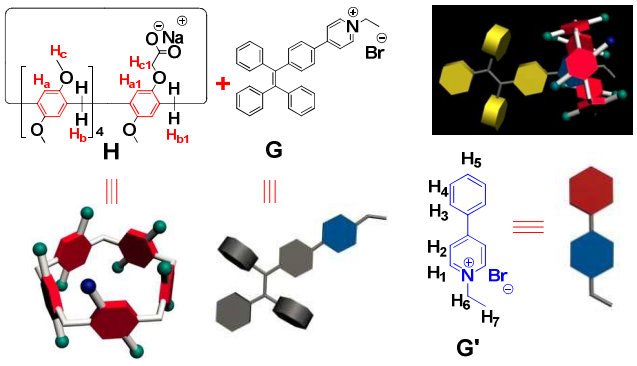
A host–guest inclusion complex based on a monofunctionalized pillar[5]arene and a tetraphenylethene derivative was prepared, resulting in the enhanced emission of the tetraphenylethene-based guest, which was applied in cell imaging.

Fluorescence imaging has appeared as a significant technology for visualizing diverse biological targets due to its highly sensitive and non-invasive properties.[1] Various well-designed fluorescent materials including green fluorescent protein (GFP), inorganic semiconductor quantum dots (QDs) and organic fluorophore-loaded nanoparticles (NPs), have been widely used as fluorescent probes.[2] However, currently available fluorescent probes suffer from some inherent deficiencies, which hamper their future applications in clinical settings. For example, GFP is susceptible to ubiquitination and proteolytic enzymes degradation.[3] The commonly used QDs (e.g., ZnSe, CdS and PdTe) contain heavy metal constituents, which are highly toxic or carcinogenic in oxidative environments.[4] NPs possess low resistance to photobleaching due to photon-induced chemical damage.[5] Moreover, conventional organic fluorophores give high fluorescence quantum yields in dilute solution but lead to weak or quenched emission in concentrated state, which is known as aggregation-caused quenching (ACQ).[6] The ACQ effect has greatly limited the scope of fluorophores for practical applications.[7]

Aggregation-induced emission (AIE), an unusual photophysical phenomenon that is precisely opposite to the ACQ effect, was discovered by Tang and co-workers in 2001.[8a] These fluorogenic molecules are nonluminescent when dissolved in good solvents but become highly emissive upon aggregation. Restriction of intramolecular rotations (RIR) process in aggregated state is rationalized to be responsible for the AIE effect. The free rotations are hindered by intermolecular steric interaction in the aggregates, which block the non-radiative channel and open up the radiative pathway, resulting in strong emission. The novel AIE effect provides a platform for developing new molecular luminogens that can be utilized as biosensors, optoelectronic devices, cell imaging and other advanced functional materials.[8]

Tetraphenylethene (TPE), a typical AIE luminogen, has been widely investigated in the past few years.[9] Various approaches, including covalent and noncovalent functionalization of TPE derivatives, have been applied in restricting the intramolecular rotation of phenyl rings to turn fluorescence on.[8e,9b] Among them, supramolecular methods to modify AIE fluorogens are highly desirable for high emission efficiency and good biocompatibility in biological systems. Host–guest interactions play a significant role in the development of advanced supramolecular aggregates due to their good selectivity and convenient responsiveness.[10] As a new generation of emerging macrocyclic hosts after crown ethers, cyclodextrins, calixarenes, and cucurbiturils,[11] pillar[*n*]arenes, whose repeating units are linked by methylene bridges at *para*-positions, have been extensively studied since they were found in 2008.[12a] The highly symmetrical pillar structures and versatile functionality of pillararenes have endowed them fascinating host–guest properties[12] and intriguing applications in the construction of chemosensors, supramolecular polymers, transmembrane channels, liquid crystals and drug delivery systems.[13] Therefore, we anticipated that the utilization of host–guest interactions to restrict the rotations process of AIE molecules would provide an excellent platform for the development of luminescent materials for biological applications.

Herein, we designed and successfully developed a new supramolecular luminogen through host–guest interactions between a monofunctionalized pillar[5]arene **H** and a tetraphenylethene derivative **G**. The host–guest interactions restricted the intramolecular motion of the aromatic rings, resulting in enhanced fluorescence. Through reprecipitation technique, NPs with an average diameter of about 35 nm were obtained, which was further utilized as imaging agent to light up the cells.



Scheme 1 Compounds used in this study and the cartoon representation of

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the formation of the luminescent host–guest inclusion complex.

^{1}H NMR spectroscopy was utilized to investigate the host–guest complexation between **H** and **G** by using 1-ethylphenylpyridine bromide (**G′**) as a model compound. As shown in Fig. 1a–c, when an equimolar amount of **H** was added into a solution of **G′** (2.00 mM), chemical shift changes of the protons on **G′** were observed, providing evidence for the interactions between **H** and **G′**. The signals corresponding to the protons H_1 and H_2 on the pyridinium ring displayed upfield shifts and broadening effects. The resonance peaks related to protons H_6 and H_7 on alkyl chain shifted upfield as well. The reason was that these protons were located in the cavity of **H** and shielded by the electron-rich cyclic structure upon formation of an inclusion complex between **H** and **G′**. 2D NOESY NMR spectrum of a solution of **H** (10.0 mM) and **G′** (10.0 mM) was also implemented to examine the host–guest interactions. As shown in Fig. 1d, nuclear overhauser effect (NOE) correlation signals were observed between aromatic protons $H_{a–c}$ of **H** and protons $H_{1–5}$ on the pyridinium ring of **G′**. Additionally, there are correlations between the $H_{6,7}$ protons of **G′** and the aromatic protons of **H** (Figs. S10 and S11, ESI†), confirming the formation of the inclusion complex.[14]

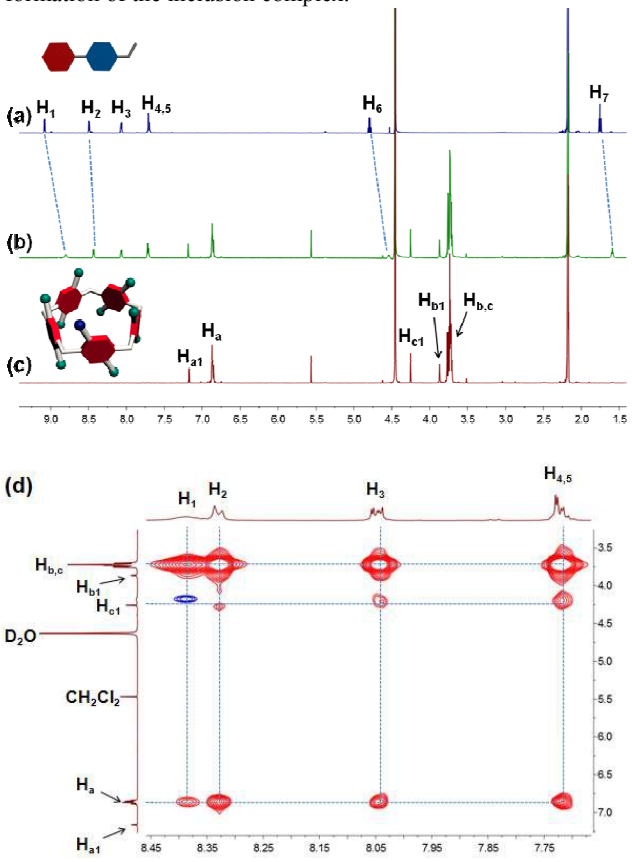

Fig. 1 Partial ^{1}H NMR spectra (600 MHz, acetone-d_6/D_2O = 5:3, 293 K): (a) **G′** (2.00 mM); (b) **H** (2.00 mM) and **G′** (2.00 mM); (c) **H** (2.00 mM). (d) Partial NOESY NMR spectrum (500 MHz, acetone-d_6/D_2O = 5:3, 293 K) of **H** (10.0 mM) and **G′** (10.0 mM).

Isothermal titration calorimetry (ITC) experiment provided the association constant (K_a) and the thermodynamic parameters (enthalpy and entropy changes $\Delta H°$ and $\Delta S°$) for the host–guest complexation between **H** and **G′**. As shown in Fig. 2a, the K_a value of **H**⊃**G′** was calculated to be (1.45 ± 0.78) × 10^4 M^{-1} in 1:1 complexation. In addition, the enthalpy and entropy changes were obtained from the ITC data ($\Delta H°$ = −2.04 kJ·mol^{-1}; $T\Delta S°$ = 21.7 kJ·mol^{-1}), indicating that the complexation was driven by a favorable entropy change with enthalpic assistance.[15]

The fluorescence (FL) behaviors of the complex between **H** and **G** were shown in Figs. 2b and 2c. The FL intensity of **G** was weakened dramatically by increasing the volume fraction of water (f_w) in the THF/H_2O mixture from 0 to 70 vol%. Moreover, upon further enhancement of f_w from 70 to 100 vol%, the FL intensity of **G** was reduced to minimum value (Figs. 2b and S12, ESI†). It was observed that **G** showed relatively good solubility in water due to the presence of the pyridinium bromide salt unit, resulting in the weakening of the AIE effect in water. With increasing the concentration of **H**, the FL intensity of **G** was gradually enhanced (Fig. 2c), because the intramolecular rotations of the phenyl rings of **G** were restricted by the formation of the inclusion complex **H**⊃**G**. The driving forces for the formation of host–guest complex are the cooperativity of electrostatic interactions and the hydrophobic interactions between **H** and **G**. Moreover, the photograph of an enhanced fluorescence of the inclusion complex between **H** and **G** is shown as an inset in Fig. 2c. When **G** (2.00 mM) was excited at 365 nm using a UV lamp in the presence of **H** (2.00 mM), an enhanced yellow fluorescence appeared, further supporting the proposed mechanism.

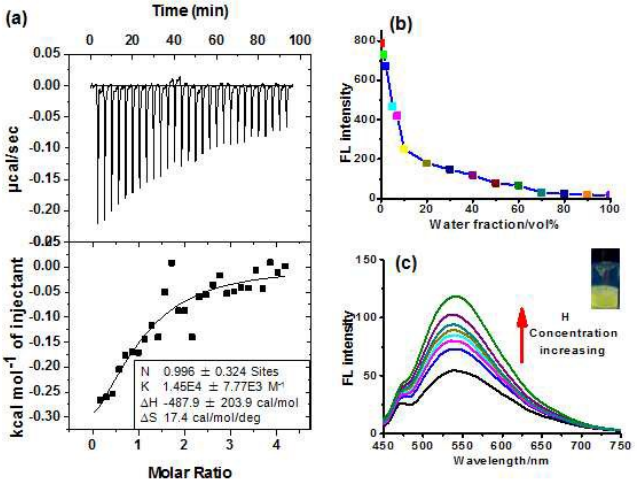

Fig. 2 (a) Microcalorimetric titration of **H** with **G′** in water at 298 K. (Top) Raw ITC data for 28 sequential injections (2 µL per injection) of a **G′** solution (2.00 mM) into a **H** solution (0.100 mM). (Bottom) Net reaction heat obtained from the integration of the calorimetric traces. (b) Plot of emission intensity of **G** at 440 nm *vs*. the composition of THF and THF/water mixtures. The concentration of **G** was 1.00 × 10^{-4} M. (c) Fluorescence spectra of **G** (1.00 × 10^{-6} M) in aqueous solution at room temperature with different concentrations of **H** (from 0 to 2.00 × 10^{-5} M). The inset photograph shows the corresponding enhanced fluorescence (2.00 mM **G** and 2.00 mM **H**) upon excitation at 365 nm using a UV lamp.

To gain further understanding of the self-assembly behaviors of the inclusion complex between **H** and **G** through reprecipitation technique,[13] the sizes and morphologies of these

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microstructures formed from the host–guest system were revealed by dynamic laser scattering (DLS) and transmission electron microscopy (TEM) experiments. The solution of **H⊃G** exhibited a clear Tyndall effect (Fig. S13, ESI†), indicating the existence of plentiful nanoparticles. The DLS result revealed that the **H⊃G** complex formed aggregates with a narrow size distribution, giving an average diameter of 43 nm (Fig. 3a). TEM images showed the solid spherical morphology with a diameter varying from 31 to 48 nm, indicating the formation of NPs (Fig. 3b).

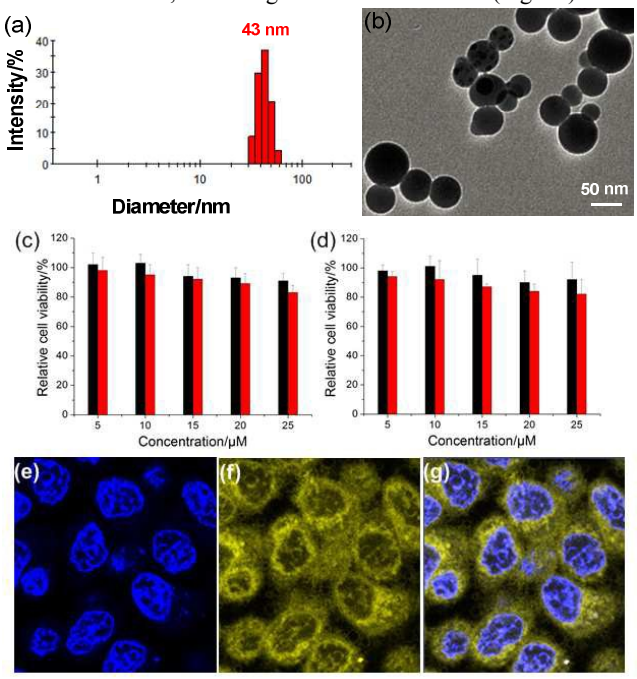

Fig. 3 (a) DLS data of the **H⊃G** aggregates. (b) TEM image of **H⊃G** aggregates (scale bar = 50 nm). Relative cell viabilities of HeLa cells incubated with **H** (black column) and **G** (red column) at different concentrations for (c) 4 h and (d) 24 h. Confocal images of HeLa after incubation with the nanoparticles self-assembled from **H⊃G** for 4 h: (e) DAPI; (f) **H⊃G**; (g) merged image from (e) and (f).

Due to the ACQ effect under the driving forces of intermolecular π–π stacking and hydrophobic interactions, the conventional fluorophores are always used in very dilute states in the imaging process and thus can be photobleached quickly when a harsh laser beam is used as the excitation light source. On account of their superior sensitivity and photostability, fluorescent probes with AIE characteristics have attracted more and more attention in studying the process of translocation, drug release, and excretion of nanomedicines *in vitro* or *in vivo*. The NPs fabricated from the host−guest complex **H⊃G** can be employed as a ideal living cell imaging agent. In order to apply this host−guest system in biologically and pharmaceutically relevant fields, 3-(4',5'-dimethylthiazol-2'-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was carried out to evaluate its cytotoxicity. From Figs. 3c and 3d, we knew that the relative cell viability of HeLa cells kept higher than 80% by culturing with the building blocks (**H** and **G**) for 4 h and 24 h with the concentration ranging from 5 to 25 μM, indicating low cytotoxicity of these two compounds. Moreover, the nanoaggregates self-assembled from electroneutral **H⊃G** could be uptook by the HeLa cells. As depicted by confocal fluorescence microscopy (Fig. 3e−g), strong yellow fluorescence attributed to the aggregates of **H⊃G** was observed mainly in the cytoplasm of the cells with good distribution after culturing HeLa cells with the NPs for 4 h, confirming that the NPs were able to penetrate the cell membrane and worked as a fluorescent visualizer for intracellular imaging.

In summary, we have developed a new supramolecular luminogen through host–guest interactions between a monofunctionalized pillar[5]arene **H** and a tetraphenylethene derivative **G**. Upon formation of the host–guest complex, the fluorescent emission of the TPE-based fluorogen was enhanced effectively, because the intramolecular rotation of the aromatic rings of the TPE group was restricted and the nonradiative decay channels were blocked effectively by forming a [2]pseudorotaxane-type structure. Through the reprecipitation technique, NPs with an average diameter of about 43 nm were obtained, which could be utilized as an imaging agent to light up the cells. These results demonstrated that the combination of the AIE effect and supramolecular chemistry has enormous potential applications in biologically relevant fields, such as biosensors, drug and gene delivery systems, protein-protein interactions and cell imaging.

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