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Endo- and Exo-Functionalized Tetraphenylethylene $M_{12}L_{24}$ Nanospheres: Fluorescence Emission Inside a Confined Space

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Abstract

The intrinsic relationship between the properties of green fluorescent protein (GFP) and its encapsulated small molecular light machine has spurred many biomimicking studies, aiming at revealing the detailed mechanism and further promoting its wide applications in different disciplines. However, how to build a similar confined microenvironment to mimic the cavity of β -barrel and the fluorescence turn-on process is a fundamental challenge for both chemists and biologists. Herein, two distinct *exo*- and *endo*-functionalized tetraphenylethylene (TPE)-based $M_{12}L_{24}$ nanospheres with precise distribution of anchored TPE moieties and unique photophysical properties were constructed by means of a coordination-driven self-assembly strategy. Under dilute conditions, the nanospheres fluoresce stronger than the corresponding TPE subcomponents. Meanwhile, the *endo*-functionalized sphere is able to induce a higher local concentration and more restrained motion of the enclosed 24 TPE units compared with that of *exo*-functionalized counterpart and thus induce much stronger emission due to the restriction of the rotation of the pendant TPE units. The biomimetic methodology developed here represents a promising way to understand and construct artificial GFP materials on the platforms of supramolecular coordination complexes.

Graphical abstract:

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Notes

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Supporting Information Available: Experimental details and additional data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

INTRODUCTION

Green fluorescent protein (GFP) and its derivatives have revolutionized biology through extensive applications including advanced fluorescent markers in live organisms.^{1–3} The active light-emitting molecular unit at the heart of GFP is a conjugated π -system resembling cyanine dyes based on 4-hydroxybenzylidene-2,3-dimethylimidazolinone (HBDI) covalently bonded to the protein, which is buried inside a tight protein barrel that limits its range of motion and accessibility to solvent and other species (ions, oxygen, *etc.*).⁴ However, these isolated chromophores become barely fluorescent upon denaturation of the protein largely ascribed to rapid non-radiative decay, thereby revealing that protection of the barrel is essential for achieving strong fluorescence and photo-stability of the chromophore.^{5–6} Disclosure of the structure-property relationships between the entire protein and its much smaller molecular light machine in GFP facilitates bioinspired investigations, targeting the underlying mechanism and then benefitting its wide applications in various fields.^{7–8} A fundamental challenge herein is how to build a similar confined microenvironment to mimic the cavity of β -barrel and the fluorescence turn-on process.

Non-radiative decay, which is often associated with a geometric distortion in the chromophore, is a process that competes with fluorescence. In the case of GFP, the β -barrel that encapsulates the chromophore in GFP provides a crowded environment to light up fluorescence via suppressing the chromophore twist.^{9–10} At first glance, the criterion to provide confinement to affect fluorescence should consider the following two prerequisites: an organic luminophore with sensitive fluorescence sensing ability and an independent space which can sterically restrain the chromophore motion. In 2001, a phenomenon of aggregation-induced emission (AIE) was first proposed by Tang and co-workers, demonstrating an unprecedented fluorescent phenomenon, which has luminescent features in sharp contrast to the traditional aggregation-caused quenching (ACQ) that is typical for conventional organic fluorophores.¹¹ These luminogens exhibit almost no fluorescence as discrete molecules in good solvents, but become highly luminescent in the aggregated state according to the mechanism of restriction of intramolecular motions (RIM), which suppresses nonradiative relaxation and actuates the energy release through a radiative pathway.^{12–14} Tetraphenylethylene (TPE) is an iconic and readily accessible AIE fluorophore.¹⁵ Recent studies revealed that the formation of aggregates is not the only way to “turn on” the emission of TPEs, while other strategies, including locked in supramolecular hosts,^{16–21} metal–organic frameworks,^{22–25} and host proteins^{26–27} can also be exploited to modulate their intramolecular motions. In biological imaging, TPE derivatives have been used to visualize RNA aptamers and a DNA quadruplex.^{28–29} All these phenomena are similar to the emission behavior of HBDI and match the first criterion of being a bionic GFP chromophore.

Supramolecular coordination complexes (SCCs) are constructed by coordination-driven self-assembly, wherein the spontaneous formation of metal-ligand bonds results in discrete constructs with predetermined shapes and sizes, such as 1D helices, 2D polygons, 3D polyhedral, and other nanoscopic materials, by controlling the size, geometry, and stoichiometry of the rigid precursors.^{30–39} The kinetic reversibility of the self-assembly process allows the system to undergo error correction via a self-repairing processes, leading to the formation of a product that is thermodynamically favorable.⁴⁰ The well-defined internal cavities and versatile peripheral or vertical functional groups of the SCCs make them applicable in molecular flasks,^{41–42} catalysis,^{43–47} supramolecular polymerization,^{48–50} and bioengineering,^{51–52} etc. Among these examples, formation of cage-like architectures draws our attention because of their pre-organized 3D large hollow structure and tunable cavity size, which holds potential for providing a confined space to encapsulate AIEgens with potency and tailored microenvironments and thus activating molecular emission based on the RIM mechanism.^{43, 53–56} Therefore, we conjecture that anchoring AIE-type chromophores, such as TPE, to dipyriddy ligands within a rigid SCC matrix via the coordination-driven self-assembly strategy would provide a platform for the development of AIE-active materials and further mimic the effect of the β -barrel of GFP without tedious covalent synthetic procedures associated with traditional designs.^{22–23, 37, 53, 57–58}

Locking of TPE-based ligands within discrete SCCs and metal-organic frameworks (MOFs) has been demonstrated to efficiently eliminate non-radiative decay pathways and afford luminescent materials.^{59–61} Functionalization of the ditopic ligand is explored widely for both inner- and outer-sphere decoration to deliver various functional $M_{12}L_{24}$ spheres.^{62–63} Fujita has developed an appealing and powerful strategy to generate molecular $Pd_{12}L_{24}$ nanospheres based on the self-assembly of 12 Pd^{2+} ions and 24 ditopic pyridyl ligands.^{64–65} In this work, we employ the coordination-driven self-assembly strategy to functionalize two types of SCC nanospheres ($M_{12}L_{24}(OTf)_{24}$, $M=Pd$ or Pt) exohedrally and endohedrally with up to 24 TPE units, respectively (Figure 1). Although the free TPE subcomponents show weak fluorescent emission under dilute conditions, the Pt-based nanospheres fluoresce strongly. We assume that enclosing 24 TPE units within the sphere would lead to a higher local concentration and more restrained motion compared with that of the *exo*-functionalized counterpart and thus resulting in a much stronger emission due to the restriction of the rotation of the pendant TPE units.

RESULTS AND DISCUSSION

The *exo*- and *endo*-functionalized TPE-based ditopic building blocks **1** and **2** were readily synthesized by linking the 120° dipyriddy ligands with a TPE unit through an alkyl spacer. The two units were characterized by a suite of spectroscopic techniques (Figures S1–S6). Stirring a mixture of 1 equiv. $Pd(CH_3CN)_4(OTf)_2$ with building blocks **1** and **2** (2 equiv.) in DMSO at 80 °C overnight, led to the nearly quantitative formation of the desired self-assembled single $Pd_{12}L_{24}$ species **3a** and **4a**, respectively, as indicated by the proton signals in the 1H NMR spectra with the characteristic downfield shifts for the pyridine protons (H_a , H_b , H_1 and H_2) (Figures 2b, 2d, S7, and S11). This is reasonable considering the electron withdrawing effect from the palladium centers. It should be noted, the chemical shift changes of the H_e and H_f protons on *exo*-functionalized **3a** were not obvious. However, the

shielding effect on the signals corresponding to protons H₅ and H₆ of *endo*-functionalized **4a** revealed that the cavity engulfs the TPE units, leading to high local concentration of TPE in the confined space. This observation was further demonstrated by the 2D NOESY NMR characterization, which clearly showed the NOE signals between the *endo*-functionalized groups (Figure S12). When building block **1** or **2** (2 equiv.) was stirred in DMSO at 80 °C in the presence of 1 equiv. Pt(CH₃CN)₄(OTf)₂, the Pt₁₂L₂₄ species (**3b** or **4b**) formed overnight, as demonstrated by the ¹H NMR spectra, which showed very similar proton chemical shifts to those of the Pd₁₂L₂₄ spheres (Figures 2c, 2e, S9 and S14). According to previous reports, the signals of Pt-nanospheres in the ¹H NMR spectra are much broader compared with those of the Pd-nanospheres because of the restricted tumbling rotation of Pt–pyridine bonds.⁶⁶ The well-defined signals in the ¹H NMR spectra as well as good solubility of these species support the formation of a discrete structure as a sole assembly product.

To further substantiate the formation of the assemblies, 2D diffusion-ordered ¹H NMR spectroscopy (DOSY) was also performed. The measured weight-average diffusion coefficients *D* were 1.37×10^{-10} and 1.40×10^{-10} m² s⁻¹ for free ligands **1** and **2**, respectively (Figure 3a and d). However, upon the formation of Pd₁₂L₂₄ assemblies, the *D* values decreased to 2.97×10^{-11} and 3.20×10^{-11} m² s⁻¹ for *exo*- and *endo*-functionalized **3a** and **4a**, respectively (Figure 3b and e). The observation of a single band confirmed that a single product was formed, which is similar to Fujita's and Reek's previous measurements on the Pd₁₂L₂₄ nanospheres.^{43, 62, 64} The DOSY NMR spectra of Pd₁₂L₂₄ also showed one clear single band at *D* = 2.92×10^{-11} and 3.10×10^{-11} m² s⁻¹ for **3b** and **4b**, respectively (Figure 3c and f). These results are consistent with those observed for the Pd₁₂L₂₄ spheres, indicating that the Pt and Pd spheres (**3** and **4**) have similar sizes. Based on the Stokes-Einstein equation, the radii (nm) of the ligands and spherical particles could be calculated as 0.801 and 0.783 for **1** and **2**, respectively, while, the values of the Pd₁₂L₂₄ and Pt₁₂L₂₄ assemblies were much larger as 3.69 (**3a**), 3.76 (**3b**), 3.43 (**4a**) and 3.54 (**4b**) (Table S1). The molecular size of **3** is somewhat larger than that of **4**, which is reasonable considering the presence of 24 TPE units on the outer surface of the discrete core. The spherical morphologies and sizes of the assemblies were also visualized by atomic force microscope (AFM) and dynamic light scattering (DLS) technologies (Figure S16).

Electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) is a highly reliable tool to provide evidence for the stoichiometry of the multi-charged supramolecular structures. This method oftentimes enables assemblies to remain intact during the ionization process while producing the high resolution desired for isotopic distribution analysis. For the Pd₁₂L₂₄, multiple prominent peaks of [M – *x*(OTf)]^{*x*+} (*x* = 7–15) can be found in the ESI-TOF-MS spectra, *e.g.*, peaks at *m/z* = 1877.7554 corresponding to [**3a** – 11OTf]¹¹⁺ for **3a** and *m/z* = 1565.9816 corresponding to [**4a** – 13OTf]¹³⁺ for **4a** (Figures 4a, 4c, S8 and S13). For the Pt₁₂L₂₄ nanospheres, although the resolution of the peaks were not that high as those in the Pd₁₂L₂₄ assemblies, several peaks corresponded to an intact entity with charge states arising from the loss of counterions can still be identified: *m/z* = 1408.3193 for [**3b** – 15OTf]¹⁵⁺, *m/z* = 1974.0809 for [**4b** – 11OTf]¹¹⁺ (Figures 4b, 4d, S10, and SS15). All the assigned peaks were isotopically resolved and in good agreement with their calculated theoretical distributions, indicating the molecularity of these assembled nanospheres.

In view of the difficulty associated with growing single crystals of these assemblies suitable for X-ray diffraction, molecular simulations were performed to gain further insight into the structural characteristics of these nanospheres (Figure 1). All DFT calculations were performed using Gaussian 09 (G09) with the Becke three-parameter hybrid exchange and the Lee–Yang–Parr correlation functional (B3LYP). All geometry optimizations were performed in the gas phase. The PM6 calculations were also carried out with Gaussian 09. The simulated structures of the four nanospheres possess well-defined cages with a *ca.* $3.5 \times 3.5 \times 3.5$ nm cavities. Molecular simulation indicated that the exohedrally pendent TPEs have more freedom and flexibility than that of the endohedrally decorated TPE units, thereby resulting in different photophysical properties.

The absorption profiles of ligands **1** and **2** and nanospheres **3** and **4** in DMSO are shown in Figure 5a. Both **1** and **2** displayed similar broad absorption bands centered at *ca.* 290 nm with molar absorption coefficients (ϵ) of 4.14×10^4 and 8.02×10^4 M⁻¹ cm⁻¹, respectively. After metal-coordination, all the assemblies showed much higher extinction coefficients for both the endohedral and exohedral nanospheres. Assemblies **3a** and **4a** have an absorption band centered at 290 nm, with $\epsilon = 1.22 \times 10^6$ and 1.20×10^6 M⁻¹ cm⁻¹, respectively. However, a strong and sharp peak centered at 325 nm for **3b** and **4b** with $\epsilon = 1.26 \times 10^6$ and 1.18×10^6 M⁻¹ cm⁻¹, respectively, was also observed. It should be noted that the ϵ values have sharp increases after forming the nanospheres, which can be attributed to the increase of a higher local concentration of TPE units compared with that in a single ligand. It is obvious that only the Pt₁₂L₂₄ self-assemblies have red-shifted (~ 30 nm) lower-energy absorption bands compared with their constituent ligands. This may be attributed to the Pt center coordinating with the pyridyl nitrogen and perturbing the electronic structure of the ligand.⁶⁷ Therefore, we conjecture that π -back bonding from the Pt center to the nitrogen π^* enriches the ligand π -system and lowers the energy required for excitation. The non-obvious absorbance change of the Pd₁₂L₂₄ assemblies compared with those of the corresponding ligands may be due to the comparatively weaker π -back bonding ability.

We then studied the emission of the ligands and assemblies (Figure 5b). Ligands **1** and **2** are non-emissive in DMSO which is attributed to non-radiative decay *via* intramolecular rotations of the pyridyl and phenyl rings. However, partially increased local concentration of TPE units upon the formation of nanospheres induced some fluorescence enhancements. The limited fluorescence enhancement of the Pd₁₂L₂₄ assemblies may be due to insufficient rigidity to remove non-radiative decay pathways and the very strong metal-to-ligand charge-transfer processes to quench the emission. The emission profiles for the Pt₁₂L₂₄ assemblies in DMSO showed much stronger emission centered at *ca.* 465 nm compared with those of Pd₁₂L₂₄ assemblies. The endohedral nanosphere **4b** emits much stronger than the exohedral **3b**. Endohedral functionalization provides a more compact and confined environment to the TPE units than that of *exo*-functionalized counterpart in dilute solution, which imposes more restrictions on their intramolecular motions and thus results in much stronger emission. Interestingly, we are able to utilize the unique light-emitting phenomenon in a confined cavity to dictate the formation of the *endo*-functionalized Pt₁₂L₂₄ assembly.⁶⁸ Reaction time-dependent fluorescent measurements showed that the emission intensity of the mixture of free ligand **2** and Pt(CH₃CN)₄(OTf)₂ reached its highest value and remained stable within

3h, suggesting that the whole metal-coordination process may finish in this time frame (Figure S17).

To gain further insights into the light-emitting behaviors of these assemblies, the fluorescence spectra were recorded in CH₂Cl₂/hexane mixtures (Figure S18). Addition of hexane into the CH₂Cl₂ solutions reduces the solubility of the assemblies and thereby facilitates aggregate formation. With a constant increase of the hexane content, the fluorescence intensities go up chronologically. This is consistent with the expected AIE behavior and indicative of a further suppression of the intramolecular motions of the *exo*- and *endo*-pended TPE units upon aggregation. The life time of the emissive Pt₁₂L₂₄ indicates the emission belongs to fluorescence (Figure S19).

CONCLUSIONS

In summary, the well-established directional-bonding methodology based on the coordination-driven self-assembly of two distinct *exo*- and *endo*-functionalized TPE-based ditopic building block allows the facile construction of two types of M₁₂L₂₄ nanospheres with precise distribution of the TPE moieties with unique photophysical properties. Although the free TPE subcomponents show weak fluorescent emission under dilute conditions, the nanospheres fluoresce strongly. Enclosing 24 TPE units within the *endo*-functionalized spheres leads to a higher local concentration and more restrained motion compared with that of *exo*-functionalized counterparts and thus causes much stronger emission due to the restriction of the rotation of the pendant TPE units. The confined space provides a similar microenvironment to the cavity of a β -barrel and the fluorescence turn-on process. Such bioinspired materials are potentially promising for the fabrication of light-emitting devices and bioimaging agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Molecular structures of building blocks **1**, **2** and PM6 semiempirical molecular orbital method-modelled *exo*- and *endo*-functionalized $M_{12}L_{24}$ nanospheres **3** and **4** with the TPE groups shown in space-filling mode.

Figure 2. Partial ^1H NMR spectra ($\text{DMSO}-d_6$, 300 MHz, 293 K) of free ligand **1** (a), *exo*-functionalized Pd-based nanosphere **3a** (b) and Pt-based nanosphere **3b** (c), and free ligand **2** (d), *endo*-functionalized Pd-based nanosphere **4a** (e) and Pt-based nanosphere **4b** (f).

Figure 3. Partial 2D DOSY NMR spectra (DMSO-*d*₆, 300 MHz, 293 K) of **1** (a), **3a** (b), **3b** (c), **2** (d), **4a** (e), and **4b** (f).

Figure 4.
ESI-TOF-MS spectra of **3a** (a), **3b** (b), **4a** (c), and **4b** (d) with assignment of the observed species.

Figure 5.

(a) Absorption and (b) fluorescence spectra of the ligands and multi-TPE nanospheres in DMSO ($\lambda_{\text{ex}} = 330 \text{ nm}$, $c = 10.0 \mu\text{M}$). Insets: photographs of assemblies of **3b** and **4b** in DMSO upon excitation at 365 nm using an UV lamp at 298 K ($c = 0.43 \text{ mM}$).