Chinese Chemical Letters 35 (2024) 110261

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Editorial

Cucurbituril and cyclodextrin co-confinement-based multilevel assembly for single-molecule phosphorescence resonance energy transfer behavior

Supramolecular assembly strategy has been proved to be an effective way to construct near-infrared (NIR) luminescent materials, especially the host-guest complexation involving macrocycles (such as cyclodextrin, cucurbituril, and pillararene). In particular, the tetraphenylethylene (TPE) derivatives are the most common and easily synthesized and functionalized aggregation-induced emission (AIE) emitters, which can not only overcome the aggregation-caused quenching (ACQ) problem of traditional organic fluorescent molecules, but also have high photobleaching threshold and good biocompatibility showing broad application prospects in the construction of multifunctional luminescent materials. Macrocyclic host compounds can tightly encapsulate the AIE guest chromophore through non-covalent interactions to change the molecular conformation and stacking mode, thereby limiting the molecular rotation to form an assembly with enhanced red-shift emission. In addition, the supramolecular light-harvesting system (SLHS) based on Förster resonance energy transfer (FRET) with NIR luminescence is constructed by assembling with NIR dye molecules at a relatively high donor/acceptor ratio, which could simplify the complex synthesis or modification of covalent chemistry and give the system precise controllability [1–3]. Tang *et al.* prepared a novel AIE covalent organic cages with fluorescence emission around 500 nm based on TPE and assembled with Nile red (NR) for energy transfer to fluorescence emission at 610 nm [1]. Wang *et al.* constructed a highly efficient SLHS with fluorescence emission from 480 nm to 610 nm *via* assembling carboxyl-pillar[5]arene and quaternary ammonium salt TPE with the dye Eosin Y (ESY) and NR continuous energy transfer [2]. Cao *et al.* designed TPE-based octacationic cage in 550 nm fluorescence emission that the fluorescence emission is about 670 nm and 720 nm after energy transfer with rhodamine 700 (R700) and rhodamine 800 (R800), respectively [3]. Although luminescence in the NIR region could be achieved through SLHS, the long-lifetime NIR luminescent materials in aqueous media are still rare. The intrinsic photophysical properties of the long-lived excited state and large Stokes shift of pure organic room temperature phosphorescence (RTP) can solve the above problems.

On the basis of previous work, recently, Professor Yu Liu's group combined the bromo–phenylpyridinium phosphorescence molecule with TPE, and bromo–phenylpyridinium non-conjugatedly on the four-arms TPE (TPE-BrN) form nanofibers with 470 nm weak fluorescence emission (Fig. 1a) [4]. Through the 1:2 inclusion between cucurbit[8]uril (CB[8]) and bromo–phenylpyridinium, two-dimensional network structure with high fluorescence-phosphorescence dual emission at 560 nm and 510 nm was induced. The phosphorescence resonance energy transfer (PRET) of the assembly TPE-BrN/CB[8] with a long-lived NIR emission (675 nm) was given after doping with the organic dye NR (energy transfer efficiency is as high as 99%). Subsequently, in order to red-shift the long-lived luminescence, they non-conjugatedly modified bromo–phenylpyridine on the divinyl-pyridine-derived TPE (TPE-DPY), as shown in Fig. 1b [5]. Interestingly, different topologies were present through different binding modes of cucurbituril (CB[7–8]) and guest molecules, accompanied by different phosphorescence emissions which showed from fluorescent nanoparticles (TPE-DPY, 390 nm), phosphorescent nanorods (TPE-DPY@CB[8], 545 nm), phosphorescent large nanospheres (TPE-DPY@4CB[7], 525 nm), to phosphorescent small nanospheres (TPE-DPY@2CB[7], 525 nm), and then to phosphorescent nanosheets (TPE-DPY@CB[7]@CB[8], 540 nm). More importantly, the TPE-DPY@CB[7]@CB[8] was further assembled with β-cyclodextrin modified hyaluronic acid (HACD) to surprisingly achieve intramolecular PRET, from 540 nm of the phenylpyridine unit to 700 nm of the methoxy–tetraphenylethylene functional group, which was successfully applied to targeted imaging of cancer cell mitochondrion.

In this work, they designed and synthesized a series of guest molecules, including methoxy tetraphenylethylene derivatives containing one (TPE-PY) or two (TPE-DPY) flexible alkyl-bridged phenyl pyridine groups, alkyl-chain-modified bromophenyl pyridine salt (PY-1), one and two vinyl pyridine salt tetraphenylethylene derivatives (TPE-1, TPE-2), alkyl-bridged styrylpyridine-phenylpyridinium (SP-PY). Firstly, the binding mode of the guest molecule TPE-DPY with CB[n] ($n = 7$–8) was explored by using the reference compounds. Nuclear magnetic resonance (NMR) and ultraviolet-visible absorption spectra (UV–vis) revealed the binding ratio of pyridinium salt to CB[7] was 1:1, the binding constant of reference PY-1/CB[7] was 9.17×10^6 L/mol, and the binding constant of TPE-2/CB[7] was 2.72×10^5 L/mol. For TPE-DPY guest molecules, low concentration of CB[7] was preferentially combined with bromo–phenylpyridine, as well as with the increase of concentrations, it was assembled with vinyl-pyridine unit. Different from the CB[7], the binding ratio of CB[8] to pyridinium salt is 2:1,

https://doi.org/10.1016/j.cclet.2024.110261

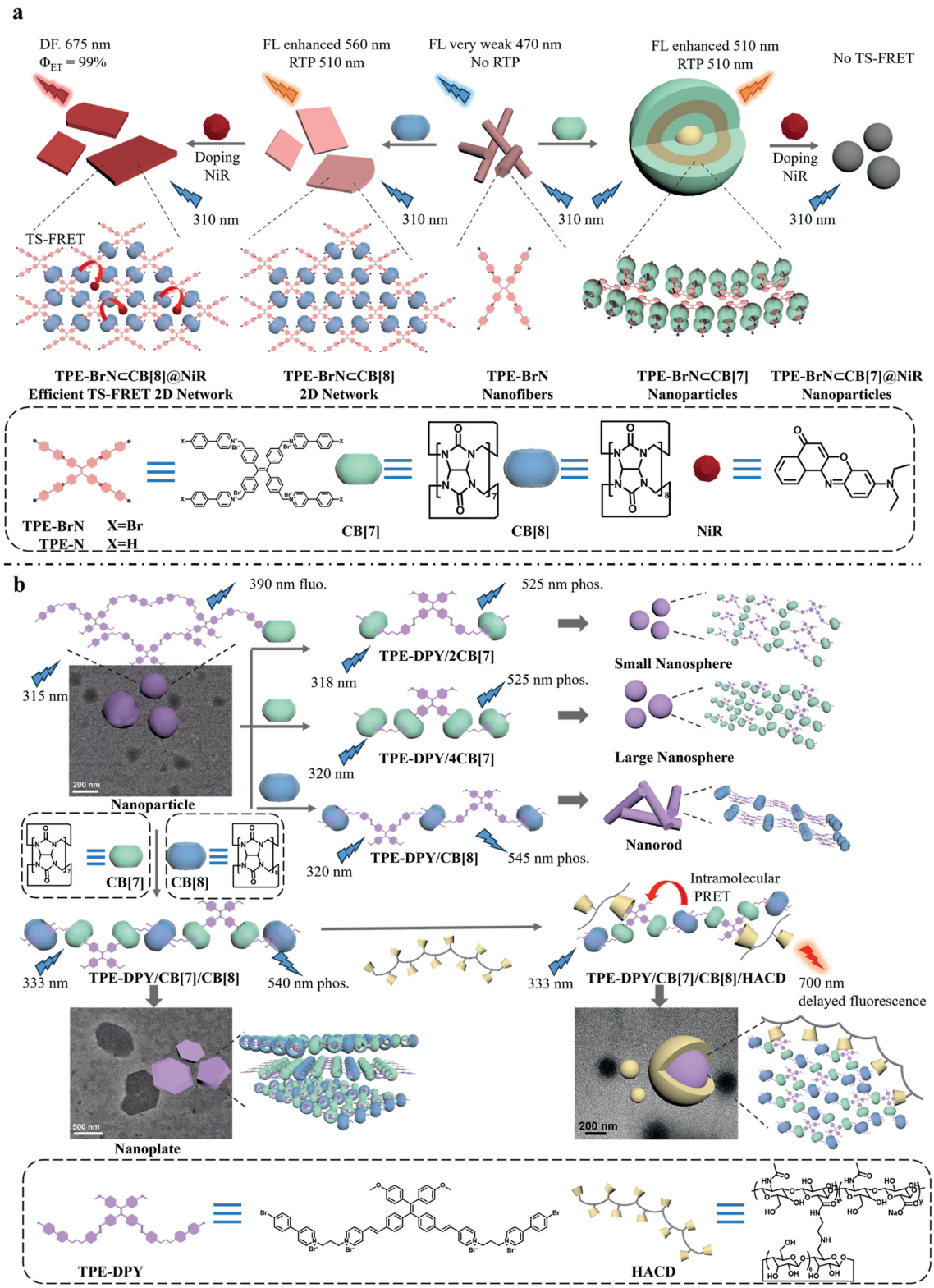

Fig. 1. (a) Scheme illustration of solid-state PRET supramolecular 2D network based on cucurbituril and four-arms bromo–phenylpyridinium TPE. (b) Single-molecule PRET with long-lived NIR luminescence based on cucurbituril, HACD and the bromo–phenylpyridine modified divinyl-pyridine-derived TPE.

and the binding constant is 2.90×10^{12} M^{-2}. Therefore, TPE-DPY was deeply encapsulated by CB[8] in a head-to-tail manner with the stoichiometric ratio of 1:1. Then, the addition of different proportions of CB[7] and CB[8] to the TPE-DPY guest molecule could form a multi-level assembly.

The effects of different hosts on the self-assembly structure of TPE-DPY were studied by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). As shown in Fig. 1b, the individual guest molecule TPE-DPY could form ellipsoidal nanoparticles with a diameter of 50–90 nm. Many nanospheres were ob-

served in the TPE-DPY@CB[7] complex, and the size of 2 equiv. CB[7] and 4 equiv. CB[7] were about 100 nm and 200 nm, respectively, which is due to the increase in the rigidity and stacking arrangement of the guest molecules as the bonding between CB[7] and TPE-DPY increases. In contrast, the TPE-DPY/CB[8] assembly shows linear nanorods with a diameter of about 500 nm, and the 1:2:1 ternary assembly of TPE-DPY/CB[7]/CB[8] is a polyhedral nanoplate due to the side-by-side and layer-by-layer stacking of rigid cores and soft-chain supramolecular assemblies with considerable size.

Interestingly, different configurations of assemblies are accompanied by different photophysical properties. Compared with TPE-DPY, the maximum red-shift of the absorption peak of the ternary assembly TPE-DPY/CB[7]/CB[8] reached 18 nm. The guest molecule TPE-DPY has only 390 nm fluorescence without phosphorescence, while TPE-DPY/2CB[7], TPE-DPY/4CB[7], TPE-DPY/CB[8] and TPE-DPY/CB[7]/CB[8] show obvious long-lifetime phosphorescence emission near 530 nm. The ternary component TPE-DPY/CB[7]/CB[8] has stronger luminescence intensity than the binary component due to the more rigid supramolecular nanostructures formed by the synergistic constraint of CB[7] and CB[8] on the guest molecules, and the lifetime is extended from 29.09 μs to 80.64 μs. More surprisingly, HACD as a polysaccharide targeting agent was introduced into TPE-DPY/CB[7]/CB[8] to further transform hierarchical nanosheets into spherical nanoparticles (about 250 nm) by β-cyclodextrin and methoxybenzene inclusion assembly. The assembly behavior was characterized by dynamic light scattering (DLS), TEM and zeta potential. Notably, the cascade assembly of TPE-DPY/CB[7]/CB[8]@HACD not only changes the topological morphology, but also realizes the macrocycle confined single molecule PRET, in which the electrostatic interaction and inclusion effects of HA and β-CD on the guest molecules are conducive to stabilizing the acceptor singlet excitons and promoting the intramolecular PRET process. After the addition of HACD, the phosphorescence of the TPE-DPY/CB[7]/CB[8] assembly under 333 nm excitation becomes weaker at 530 nm, while it shows a significant emission band at 700 nm with a lifetime of 21.60 μs and Stokes shift of 367 nm. According to the reference experiments and theoretical calculations of TPE-1/CB[7] and PY-1/CB[8], it is confirmed that this is due to the intramolecular PRET derived from the phenylpyridine unit to the methoxytetraphenylethylene part. Due to the specific recognition of HA to overexpressed receptors (such as CD44 and RHAMM) on the surface of cancer cells, the assembly TPE-DPY/CB[7]/CB[8]@HACD is beneficial to become an advanced commercial cancer cell targeted imaging agent. Then, TPE-DPY/CB[7]/CB[8]@HACD assembly was incubated with human cervical carcinoma cells (HeLa cells) and human embryonic kidney cells (293T cells), respectively, and were localized by Hoechst and Mito-Tracker Green. Compared with normal 293T cells, it was found that the assembly TPE-DPY/CB[7]/CB[8]@HACD was preferentially internalized by cancer cells and concentrated in mitochondrion for the bright NIR luminescence (650–750 nm). At the same time. the results of CCK-8 experiments showed the low toxicity of the assemblies. These results confirmed the ability of the assembly to target cancer cell mitochondrion imaging with low cytotoxicity.

In summary, in an aqueous solution, the multi-level assembly of TPE-DPY@CB[7,8]@HACD was successfully prepared by cucurbituril and HACD confinement that the efficient single-molecule PRET system was not only achieved by the adjustment of the topological morphology of the assembly (from nanospheres, rods, to hierarchical self-assembled nanoplates), but also acquired long-lived NIR (700 nm) delayed fluorescence emission. Through the effective restriction of CB[7] and CB[8] on TPE-DPY, the assemblies TPE-DPY/CB[7]/CB[8] displayed significant phosphorescence enhancement, and the harness of HACD assembly activated the PRET of 367 nm large Stokes shift for the TPE-DPY, which exhibited good effect in targeting mitochondrial imaging of cancer cells. The design method of this single-molecule PRET system will provide a simple and feasible method for the construction of NIR luminescent materials. In addition, we believe that more PRET-based in the NIR-II region and stimuli-responsive systems (including mechanical force, light, temperature, redox, enzymes, pH or biomarkers, *etc.*) are also under continuous research in order to further expand their applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Siwei Wang: Writing – original draft. **Wei-Lei Zhou:** Writing – review & editing, Writing – original draft. **Yong Chen:** Writing – review & editing.

Acknowledgments

This work was supported by National Natural Science Foundation of China (Nos. 22101143 and 22361036), the China Postdoctoral Science Foundation (No. 2021M691661), the Program for Young Talents of Science and Technology in Universities of Inner Mongolia Autonomous Region (No. NJYT22050) and the Inner Mongolia Minzu University Doctoral Research Fund (No. BS554).

Siwei Wang
College of Chemistry and Material Science, Inner Mongolia Key Laboratory of Chemistry for Nature Products and Synthesis for Functional Molecules, Innovation Team of Optical Functional Molecular Devices, Inner Mongolia Minzu University, Tongliao 028000, China

Wei-Lei Zhou*
College of Chemistry and Material Science, Inner Mongolia Key Laboratory of Chemistry for Nature Products and Synthesis for Functional Molecules, Innovation Team of Optical Functional Molecular Devices, Inner Mongolia Minzu University, Tongliao 028000, China
College of Chemistry, Nankai University, Tianjin 300071, China

Yong Chen*
College of Chemistry, Nankai University, Tianjin 300071, China

*Corresponding authors.
E-mail addresses: zhouweilei_2011@163.com (W.-L. Zhou), chenyong@nankai.edu.cn (Y. Chen).

Received 22 June 2024
Revised 11 July 2024
Accepted 15 July 2024
Available online 31 August 2024

References

[1] Y. Qin, Q.H. Ling, Y.T. Wang, et al., Angew. Chem. Int. Ed. 62 (2023) e202308210.
[2] M. Hao, G. Sun, M. Zuo, et al., Angew. Chem. Int. Ed. 59 (2020) 10095–10100.
[3] H. Duan, F. Cao, H. Hao, et al., ACS Appl. Mater. Interfaces 13 (2021) 16837–16845.
[4] F.F. Li, M. Huo, J. Kong, et al., Adv. Optical Mater. (2024) 2400453.
[5] X. Zhou, X. Bai, F. Shang, et al., Nat. Commun. 15 (2024) 4787.