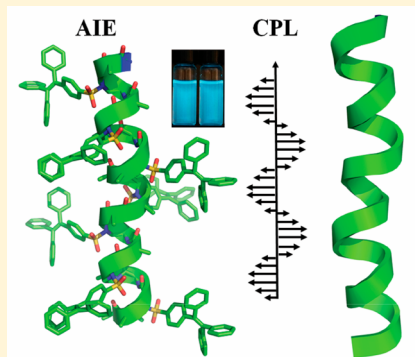


Helical Sulfono- γ -AApeptides with Aggregation-Induced Emission and Circularly Polarized LuminescenceYan Shi,^{†,‡} Guangqiang Yin,^{†,‡} Zhiping Yan,[§] Peng Sang,[†] Minghui Wang,[†] Robert Brzozowski,[‡] Praathees Eswara,[‡] Lukasz Wojtas,[†] Youxuan Zheng,^{*,§,‡} Xiaopeng Li,^{*,†,‡} and Jianfeng Cai^{*,†,‡}[†]Department of Chemistry and [‡]Department of Cell Biology, Microbiology and Molecular Biology, University of South Florida, 4202 East Fowler Avenue, Tampa, Florida 33620, United States[§]State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China

Supporting Information

ABSTRACT: Aggregation-induced emission (AIE) was intensively studied because of packing of small molecules and polymers; however, mid-molecular-weight (1000–3000) molecular scaffold containing a precise number of AIE luminogens is rare. Herein, we report the investigation of three tetraphenylethylene (TPE)-modified sulfono- γ -AApeptides in which multiple TPE moieties are conjugated to the chiral right-handed helical peptidomimetic backbone as functional side chains. The crystal structure of the TPE- α /sulfono- γ -AA peptide 1 demonstrates that because of the rigid helical scaffold of the TPE- α /sulfono- γ -AA peptides, the intramolecular rotations of the TPE with short linker are restricted, therefore leading to the boosted fluorescent emission in solution. Peptides 2 and 3 exhibit aggregation-induced emission enhancement (AIEE), possibly because of the combination of both AIE and rotation restriction. Moreover, because of their preoriented assembly induced by the right-handed helical scaffold, these emissive chiral luminogens show effective circularly polarized luminescence signals with high dissymmetry factor g_{lum} . Finally, the amphiphilic nature of TPE- α /sulfono- γ -AA peptides could enable them to penetrate the bacterial membranes and exhibit strong fluorescence. Their antimicrobial activity and labeling-free character could further augment their potential applications in both materials and biomedical sciences.



INTRODUCTION

The development of aggregation-induced emission (AIE) materials has recently drawn considerable attention because of their applications in organic light-emitting diodes (OLEDs), bioprobes, chemosensors, chiral recognition, and so on.¹ Among the prototypical AIE luminogens (AIEgens), the tetraphenylethylene (TPE) derivatives are the most classic family and have been extensively explored.² In these emissive systems, the TPE derivatives were incorporated into the metal–organic frameworks (MOFs),³ covalent organic frameworks (COFs),⁴ metallomacrocycles,⁵ polymers,⁶ and metallocages.^{2b,7} However, most of the designs are based on the same tactic, that is, the restriction of the intramolecular rotation (RIR) due to aggregation and packing of TPE moieties.^{1b,8} Upon aggregate formation, confinement of the rigid environment weakens the rotation of the four peripheral aromatic rotors against the central olefin stator in TPE, leading to the suppression of nonradiative decay pathways and the activation of the radiative decay in solid state.^{1f} On this basis, much effort has been made to restrict the rotation of the phenyl rings by covalent bond connection^{1g} and coordination networks⁹ so as to enhance fluorescence intensity. Instead of aggregation and packing, it is rare to turn on luminescent properties of TPEs at the single-molecular level, for example, in solution.¹⁰

In parallel to the intensive studies of AIE, circularly polarized luminescence (CPL) materials have also attracted increasing

interests as circularly polarized light would improve the quality of the 3D image and decrease the damage to the eyes in display.¹¹ In the past years, research investigation based on chiral luminescent systems has made significant progress, including metal complexes,¹² small organic luminophores,¹³ conjugated polymers,¹⁴ supramolecules,¹⁵ and liquid crystals.¹⁶ But except for the lanthanide complexes, most reported systems still suffered from the relatively low luminescence dissymmetry factor (g_{lum}) both in solution and solid state, ill-defined structure–property relationship, and chiroptical properties sensitive to the external environments. Therefore, it is still urgent to exploit material which could directly generate CPL, particularly design and synthesis of a single molecule bearing CPL function rather than through the packing of molecules.

To tackle the challenges existing in both AIE and CPL, herein, we report the properties of TPE-modified 1:1 α /sulfono- γ -AApeptides. The γ -AApeptide (oligomers of γ -substituted-*N*-acylated-*N*-aminoethyl amino acids) is a new class of peptidomimetics, the backbone of which was inspired by the chiral peptide nucleic acid (PNA).¹⁷ In the 1:1 α /sulfono- γ -AA peptides, the bulky sulfonamide groups induce a curvature conformation of the backbone, leading to the formation of robust right-handed

Received: May 18, 2019

Published: July 23, 2019

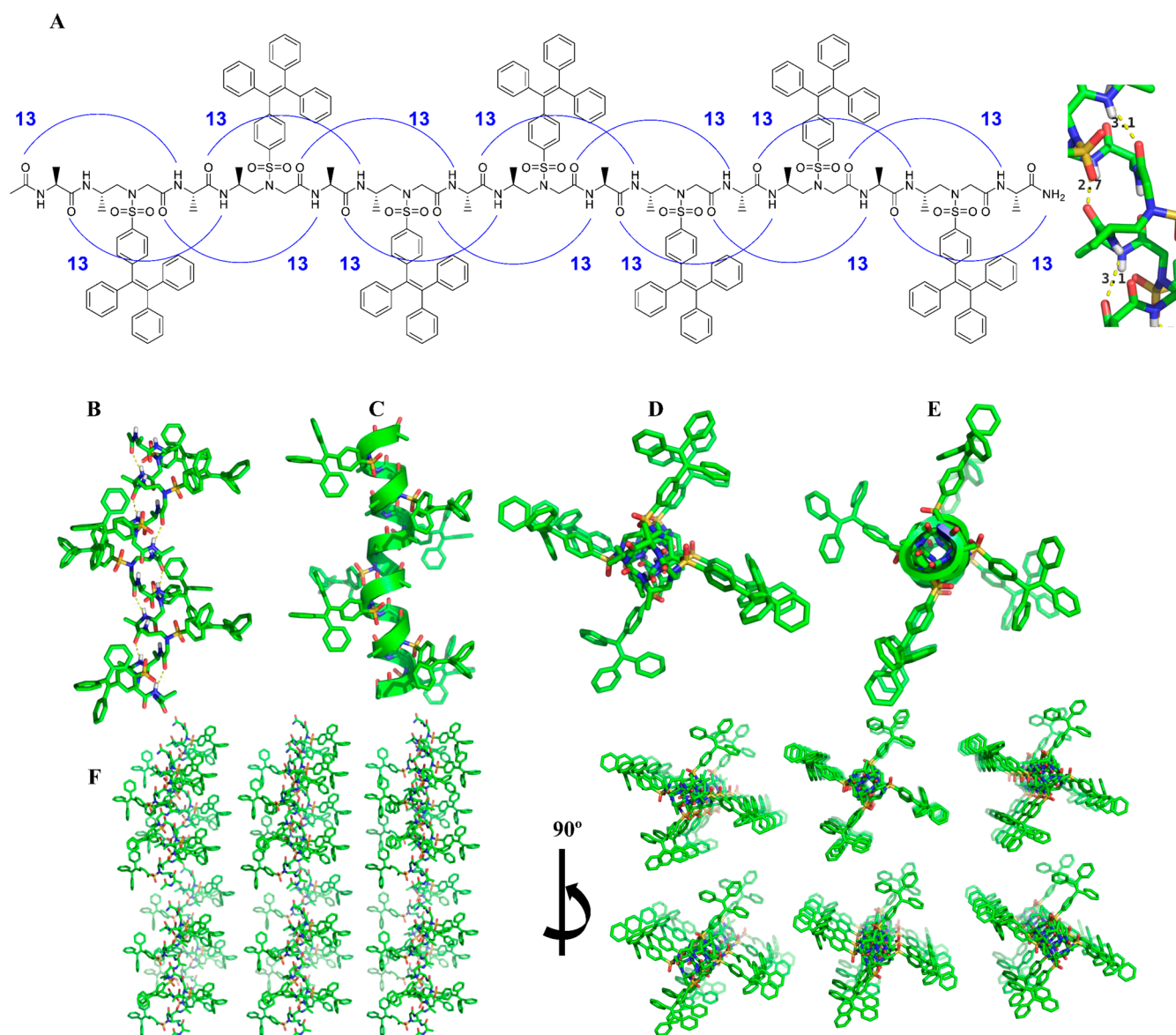


Figure 1. Chemical and crystal structure of TPE- α /sulfonyl- γ -AA peptide **1**; the crystal structures are drawn by PyMol. (A) Chemical structure and the 13-atom-hydrogen-bonding pattern. (B) Crystal structure of the bonding pattern. (C) Helical cartoon of the crystal structure. (D) Crystal packing of **1** along the peptide axis. (E) Cartoon structure of (D). (F) Packing mode of the crystal.

4_{13} windmill-shaped helical structures, which are confirmed by the crystal structure of homo-/heterogeneous sulfonyl- γ -AA peptides as well as solution structures.^{18,19} We hypothesized that when conjugated with the TPE moiety, the constrained helical backbone of the sulfonyl- γ -AA peptide would restrict the intramolecular rotation of the TPE, thereby inducing the fluorescence of these TPE-conjugated sulfonyl- γ -AA peptides even at the single-molecular level in solution. In addition, because of chiral arrangement/assembly of the TPE moieties induced by the right-handed helical sense of the molecular scaffold, these TPE- α /sulfonyl- γ -AA peptides would also be expected to exhibit good CPL properties, which are generated at single-molecule level instead of intermolecular packing.

RESULTS AND DISCUSSION

The first TPE- α /sulfonyl- γ -AA peptide **1** (Figure 1A) was designed by conjugation of TPEs directly onto the backbone of the 1:1 α /sulfonyl- γ -AA hybrid peptide. Particularly, TPE

moieties were incorporated into sulfonyl- γ -AA building blocks and the TPE-conjugated 1:1 α /sulfonyl- γ -AA hybrid peptide **1** was obtained with decent yield by the solid-phase standard Fmoc chemistry based on our previous protocol.¹⁷ The crystal showed a 13-atom-hydrogen-bonding pattern, with 2.7 and 3.1 Å hydrogen-binding distance. The persistent and unified intramolecular H-bond network and organized packing of side chain unambiguously indicates that this class of oligomers, as a 4_{13} helix, could provide a particularly strong stabilization of this novel secondary structure motif (Figure 1A, Figure S1). To our delight, TPE- α /sulfonyl- γ -AA peptide **1** was successfully solved by single-crystal X-ray crystallography with resolutions of 1.5 Å. In the crystal structure, it shows that peptide **1** adopts right-handed helical conformation, with a diameter of 6.0 Å and pitch of 5.8 Å which are consistent with our previously reported related structures.^{18a} There are exactly four side chains per helical turn, and TPE groups are present in a right-handed helical sense (Figure 1B,C). This led to a

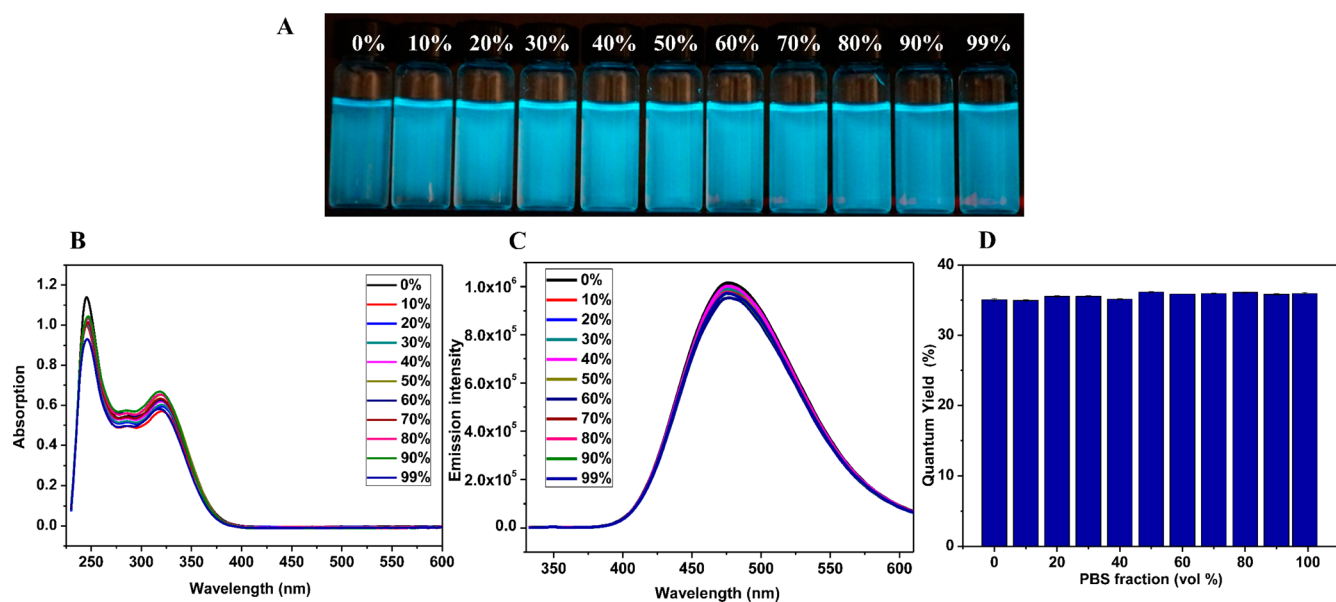


Figure 2. (A) Photographs of **1** in water/PBS with various PBS fractions. (B) UV/vis spectra of **1** in water/PBS with various PBS fractions. (C) Fluorescence spectra ($\lambda_{\text{ex}} = 325 \text{ nm}$, $c = 5.0 \mu\text{M}$). (D) Quantum yields.

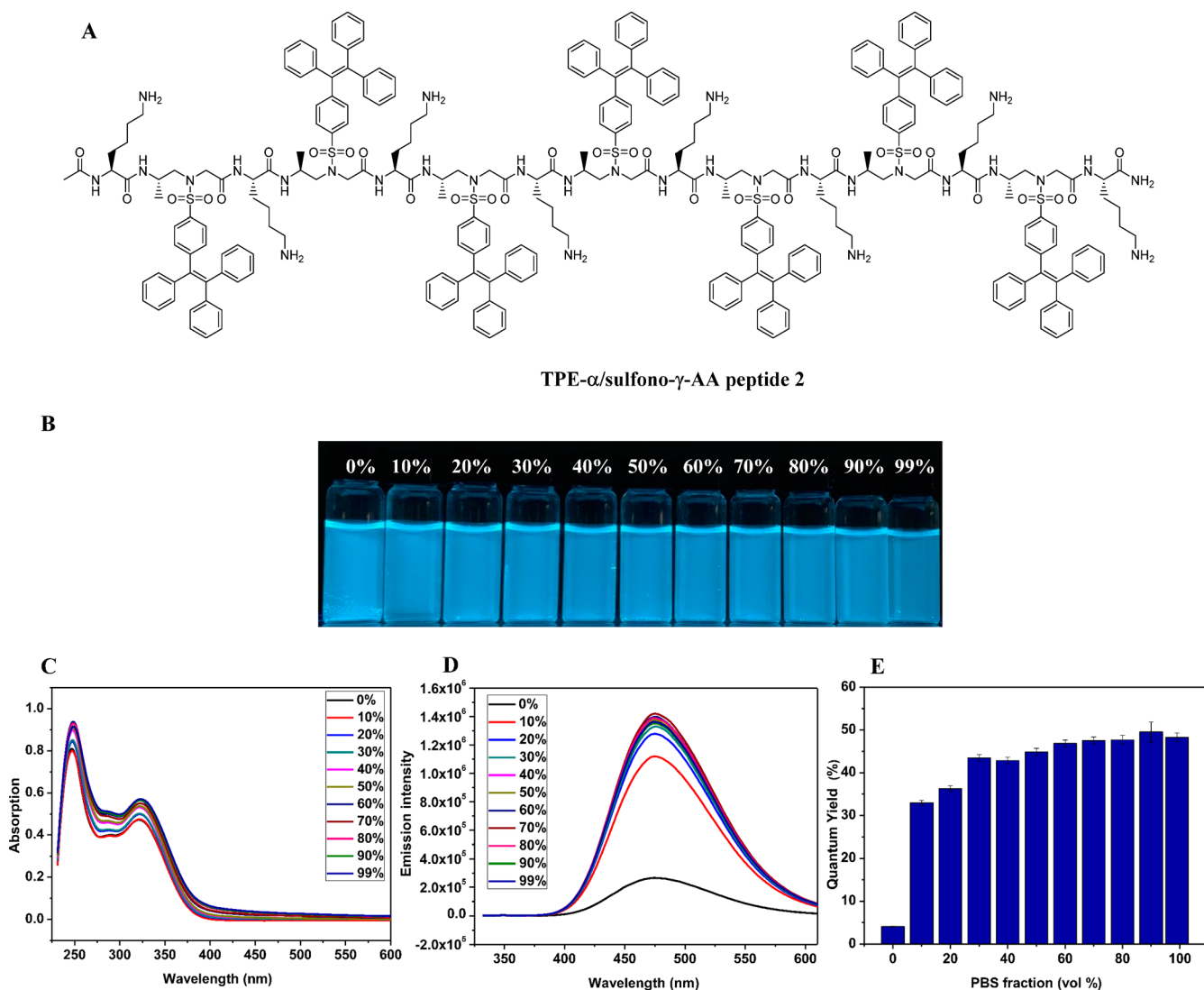


Figure 3. (A) Structure of **2**. (B) Photographs of **2** in water/PBS with various PBS fractions. (C) UV/vis spectra of **2** in water/PBS with various PBS fractions. (D) Fluorescence spectra ($\lambda_{\text{ex}} = 325 \text{ nm}$, $c = 5.0 \mu\text{M}$). (E) Quantum yields.

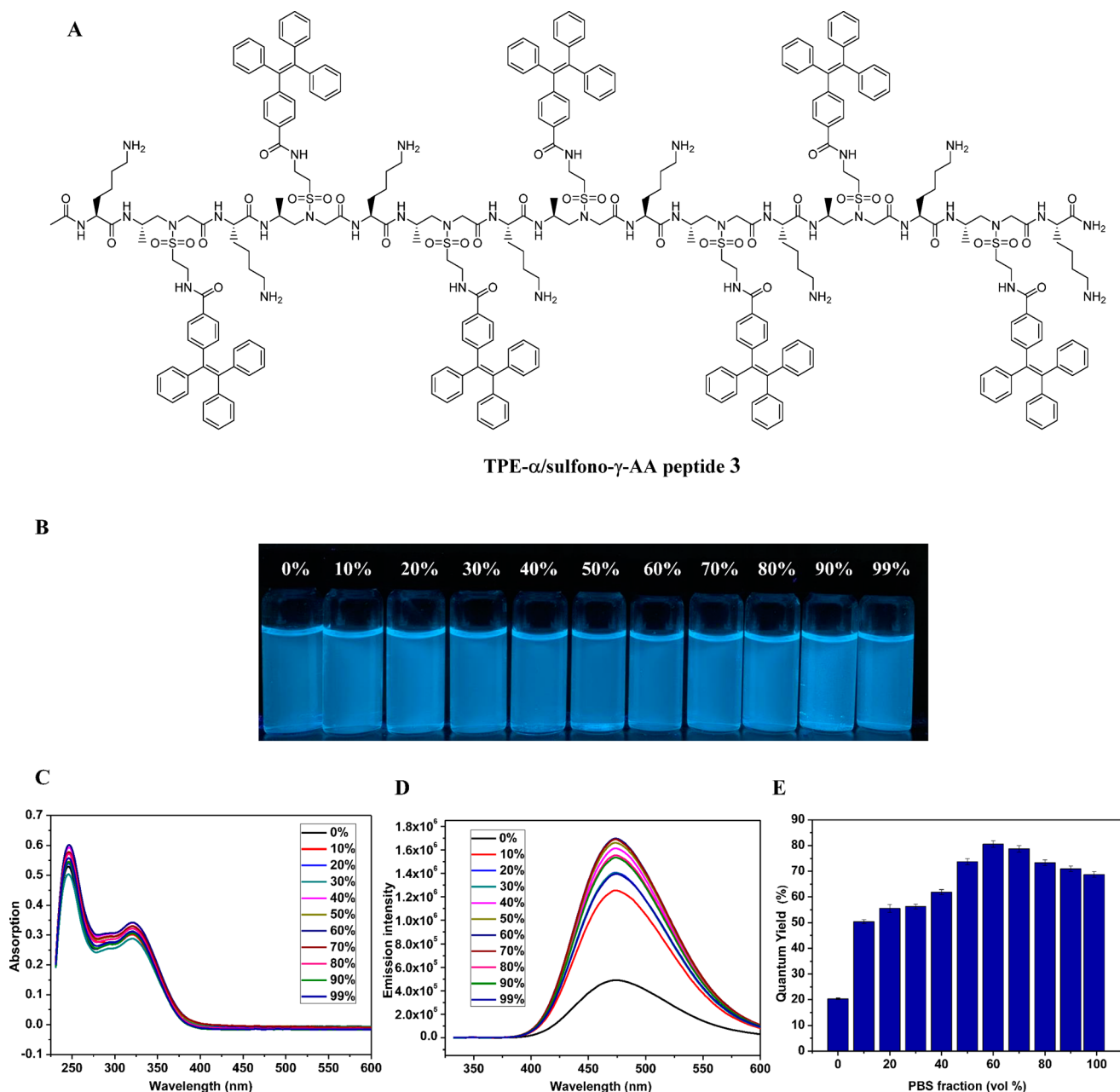


Figure 4. (A) Structure of 3. (B) Photographs of 3 in water/PBS with various PBS fractions. (C) UV/vis spectra of 3 in water/PBS with various PBS fractions. (D) Fluorescence spectra ($\lambda_{\text{ex}} = 325 \text{ nm}$, $c = 5.0 \mu\text{M}$). (E) Quantum yields.

pseudo-4-fold symmetry of windmill shape on the top view (Figure 1D–F).

On the basis of helical structures, we postulated that 1 could exhibit fluorescence at single-molecular level even in solution because the seven TPE moieties are constrained on the helical scaffold. And such fluorescence enhancement is due to their rotation limitation rather than aggregation-induced emission. To test our hypothesis, we next carried out absorption and fluorescence studies. As shown in Figure 2B, two strong peaks (250 and 350 nm) in the UV–vis spectrum of TPE- α /sulfono- γ -AA peptide 1 were observed as the typical absorption peaks of TPE moieties,⁹ indicating that conjugation of TPE moieties to the helical peptide did not alter their intrinsic absorptive property. The result prompted us to move forward to study their potential fluorescent activity. The TPE- α /sulfono- γ -AA peptide 1 (Figure 2C) was found to be soluble in pure water;

however, 99% PBS (phosphate buffered saline) buffer is a poor solvent which led to the precipitation of 1 because of enhanced salt strength. It is very interesting that 1 exhibits strong fluorescence in pure water (Figure 2A), consistent with our postulation that helical molecular scaffold restricts the free rotation of TPE moieties, leading to significantly enhanced fluorescence even in solution. When the percentage of poor solvent PBS buffer fraction (f_{PBS}) is gradually increased from 0% to 99%, the fluorescence intensity shows no significant change (Figure 2A,D), with good quantum yield ($\Phi_{\text{F}} = 35\%$). It suggested that boosted fluorescence was due to restriction on TPE bond rotation instead of AIE.

To understand whether the stability of helical scaffold has impact on the fluorescent behavior of the TPE-modified α /sulfono- γ -AA peptide, a new sequence 2 was also synthesized in which the alanine residues in 1 were replaced with lysine

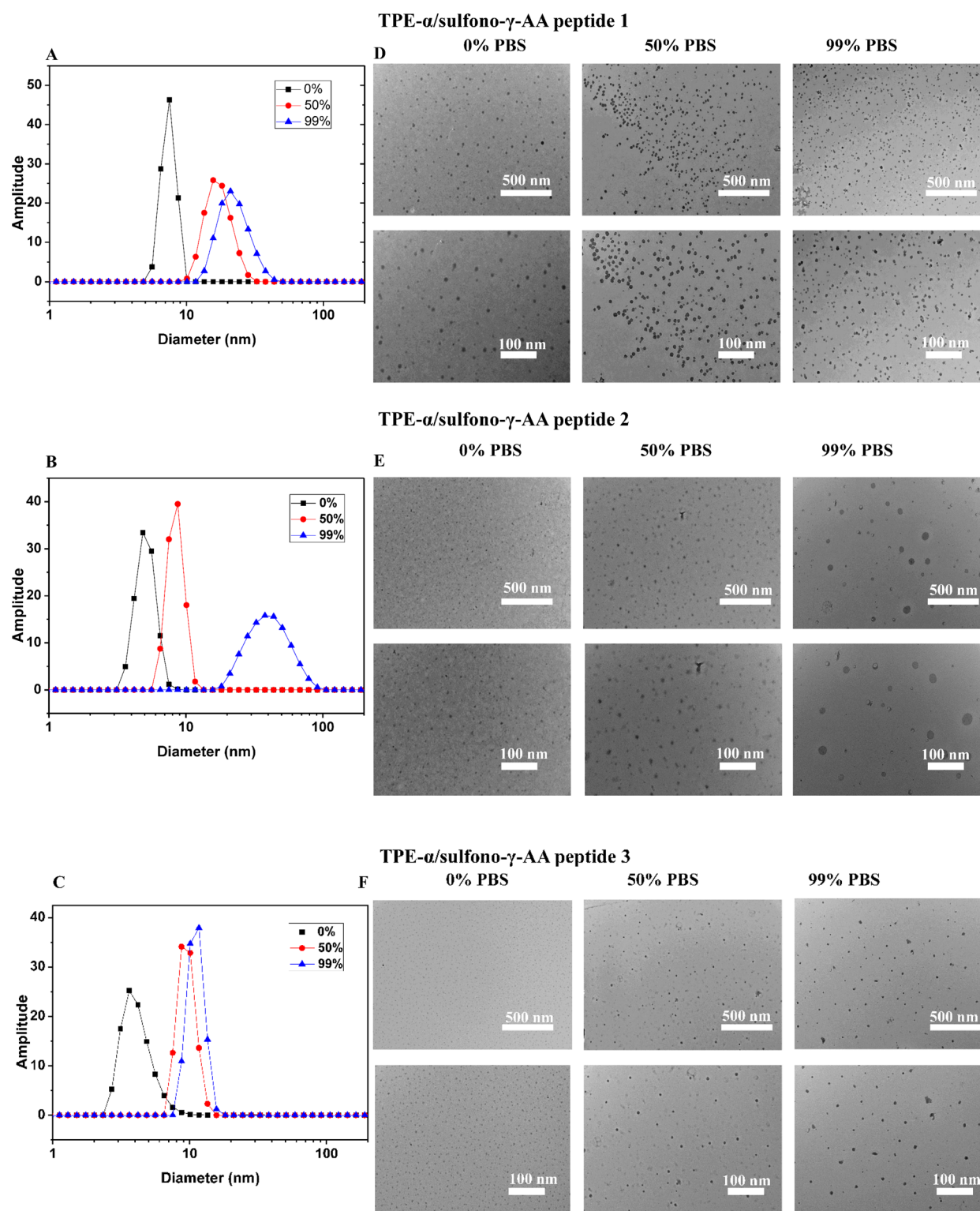


Figure 5. (A–C) DLS data and (D–F) TEM images of TPE- α /sulfonyl- γ -AA peptides 1–3 aggregates in 0% PBS, 50% PBS, and 99% PBS (scale bar, 500 nm for (D), (E), and (F), upper images, and 100 nm for (D), (E), and (F), bottom images, respectively).

residues (Figure 3A). Bearing amino side chains, **2** is expected to destabilize the helical scaffold because of the flexibility of side chains and electrostatic charge repulsion. Thus, we anticipated that the introduction of these amino side chains could confer TPE moieties with increased rotational freedom. Interestingly, although similar absorption and emission wavelengths were found in **2** (Figure 3B–D), Figure 2 displayed different

fluorescent behaviors compared to the steady emission of **1** in both solutions and aggregation states. As shown in Figure 3E, the TPE- α /sulfonyl- γ -AA peptide **2** starts with a low Φ_F value (5%) in pure water, which may be due to the electrostatic repulsion of positively charged side chains that destabilize the helical scaffold. However, when the f_{PBS} increased from 0% to 10%, even though the sequence was still completely soluble,

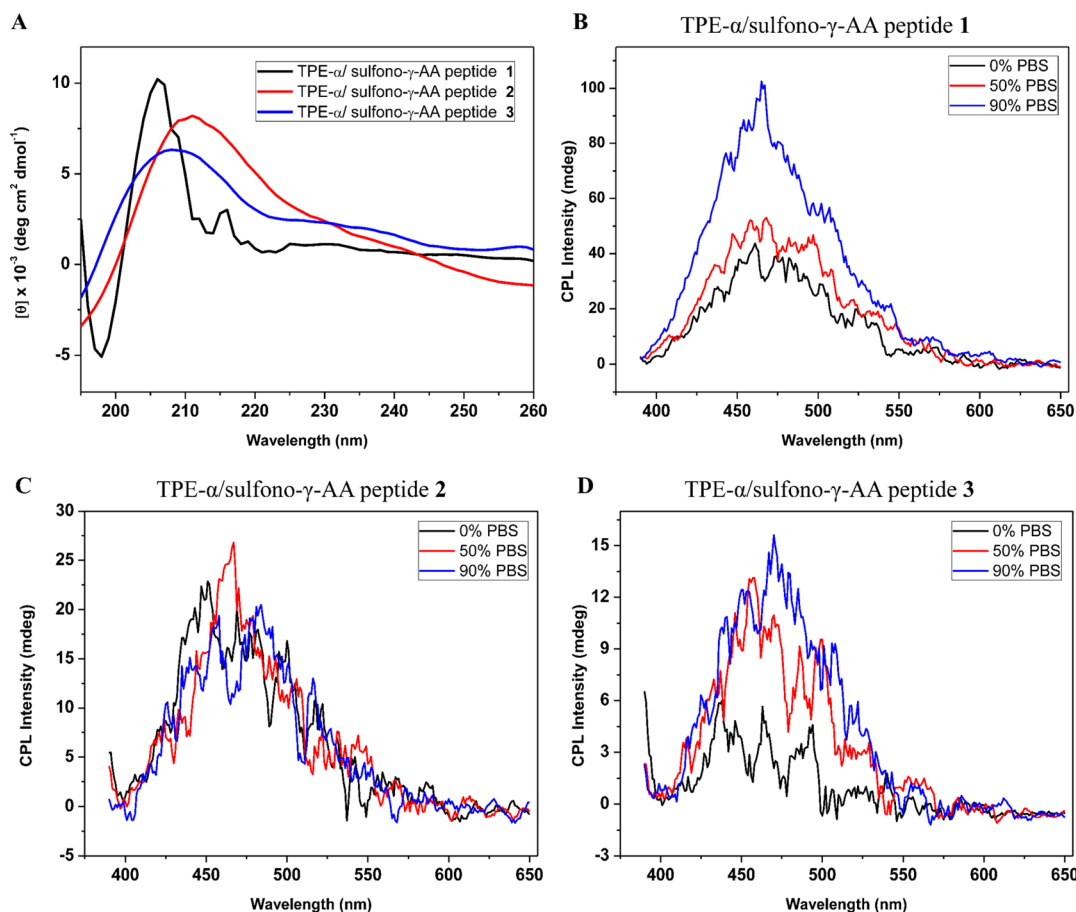


Figure 6. (A) CD spectra of the TPE- α /sulfono- γ -AA peptides 1–3 in H₂O/PBS 1:1. (B–D) CPL spectra of peptides 1–3 in PBS buffer percentage.

the charge repulsion could be shielded by PBS salts, which significantly enhanced the helical stability, leading to sharply increased Φ_F (35%). Further increase of PBS led to gradual aggregation of TPE- α /sulfono- γ -AA peptide 2 with enhanced quantum yield up to 45%. This is a typical AIE effect, by which aggregation further stabilized the helical structure and molecular packing, thereby enhancing fluorescence intensity.

After we explored the impact of helical scaffold on the fluorescence of TPE- α /sulfono- γ -AA peptides, we next asked if further induction of rotational freedom of TPE moieties could tune fluorescence behavior. As shown in Figure 4, a new sequence 3 was prepared. Unlike 1 and 2, in which TPE moieties were conjugated to the backbone via sulfonyl group directly, the TPE moieties in the peptide 3 were attached by the amide bond via an additional flexible ethyl sulfonyl linker (Figure 4A). As anticipated, although a helical molecular scaffold still gave fluorescence at 0% PBS ($\Phi_F = 20\%$), AIE took a more significant role than 2, as seen for the Φ_F values at different f_{PBS} , which demonstrated a gradual increment and reached the maximum ($\Phi_F = 79\%$) at $f_{\text{PBS}} = 60\%$ (Figure 4E). We speculated that when TPE moieties were attached to the helical scaffold via a relatively longer and flexible linker, the restriction from the backbone became weaker, and as such the Φ_F was low when f_{PBS} was close to zero. It is worth noting that as f_{PBS} increased, the fluorescence is boosted up through the combination of both helical scaffold stabilization as well as aggregation-induced emission enhancement (AIEE).²⁰

To further investigate the emission properties of TPE- α /sulfono- γ -AA peptides 1–3, we studied their aggregation

behaviors by dynamic light scattering (DLS) and transmission electron microscopy (TEM). As shown in Figure 5, the TPE- α /sulfono- γ -AA peptides 1–3 were prone to forming nanosphere particles in solution. From the DLS results (Figure 5A–C), the average hydrodynamic diameters (D_h) of the TPE- α /sulfono- γ -AA peptides 1–3 nanospheres increased from 8.5, 5, and 4 nm (0% PBS) to 15, 8, and 7 nm (50% PBS), and then to 18, 25, and 8 nm (99% PBS). TEM was subsequently performed to further investigate the aggregation behavior of peptides. As shown in Figure 5D, the images of peptide 1 revealed that the size of these particles did not increase significantly with the increment of PBS fraction, indicating that the helical structure took the predominant role in emission inducing, which was consistent with the result of the quantum yield, while for TPE- α /sulfono- γ -AA peptides 2 and 3 (Figure 5E,F), at 0% PBS in water, there is no obvious aggregated particle. But along with the increment of the PBS, the size and intensity of the particles became enlarged. These results are in good agreement with the observation that at higher percentage of PBS the emission was enhanced by the aggregation. Furthermore, at each PBS percentage of TPE- α /sulfono- γ -AA peptides 1–3, the size of around 100 particles was measured by ImageJ, and the aggregate diameter distribution data was consistent with the DLS and TEM experiments (Figure S2).

The circular dichroism (CD) spectra were next performed in H₂O/PBS (1:1) in the range of 195–260 nm to evaluate the helical propensity of the three peptides in solution. As shown in Figure 6A, all peptides show strong positive Cotton effects

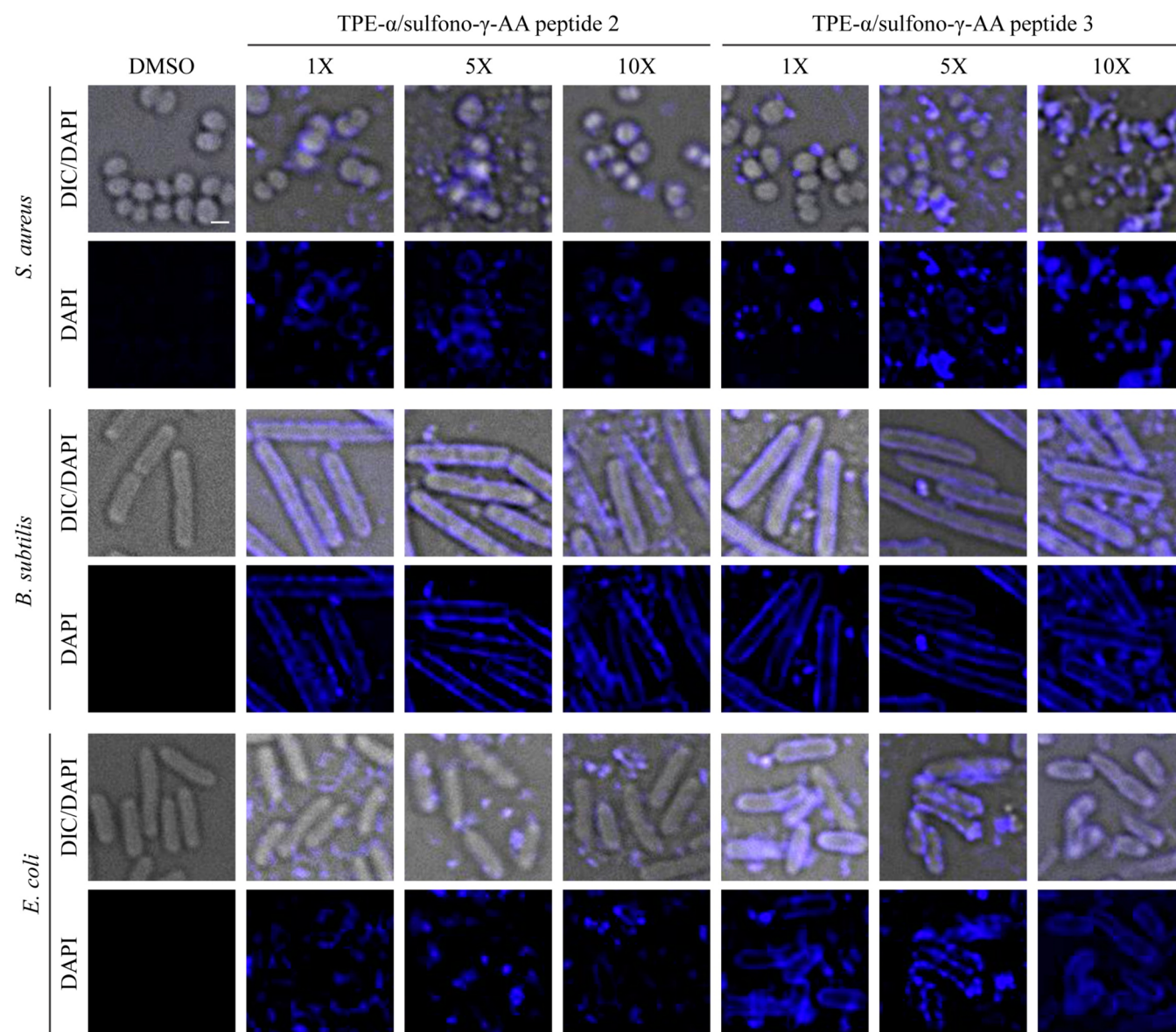


Figure 7. Micrographs of *S. aureus*, *B. subtilis*, and *E. coli* cells treated with 0.05 mg/mL (1×), 0.25 mg/mL (5×), and 0.5 mg/mL (10×) of TPE- α /sulfono- γ -AA peptides 2 or 3. The vehicle for the peptides, DMSO, was used as a control. Differential interference contrast (DIC) and the autofluorescence of peptides obtained through standard DAPI filter are shown. Scale bar, 1 μ m.

between 205 and 215 nm, suggesting that the TPE- α /sulfono- γ -AA peptides 1–3 adopt similar right-handed helical conformations.^{18a} Interestingly, further CD study of peptide 2 at different solvent systems suggested that the sequence retained a good degree of helicity in the presence of water, while in other solvent systems the Cotton effect became relatively weaker (Figure S3).

Given the fact that these TPE moieties are arranged on the right-handed helical scaffold, and the chirality could be transferred from the chiral backbone of the γ -AApeptides, we envision that these luminous TPE- α /sulfono- γ -AA peptides would also generate CPL. To our delight, in the test of three sequences in different ratios of water/PBS buffer, intensive CPL signals were observed in all the samples. The highest calculated value of the dissymmetry factor (g_{lum}) is ca. 1.2×10^{-2} , which is a large g_{lum} value compared to those in the reports ($\sim 10^{-5}$ – 10^{-3} order).²¹ In the TPE- α /sulfono- γ -AA peptide 1, the g_{lum} value is increasing, accompanied by the

increased PBS buffer percentage, while the g_{lum} value does not change dramatically for TPE- α /sulfono- γ -AA peptides 2 and 3 (Figure 6B–D). We speculate that these CPL helical foldamers are superior to known CPL small molecules and polymers since polymers do not have defined structure, whereas it is challenging to precisely control the packing of small chiral molecules.

The peptides 2 and 3 contains both cationic and hydrophobic groups, which satisfy the rationale for developing antimicrobial peptidomimetics mimicking host-defense peptides (HDPs): the cationic functional groups would bind to the negatively charged bacterial membranes, and the hydrophobic groups could subsequently lead to the disruption of the bacterial membranes.²² On the basis of this assumption, we postulated that these two peptides would have antimicrobial activities. Indeed, 2 and 3 show IC_{50} 's of 3.2 and 6.3 μ g/mL in killing Gram-positive bacteria methicillin-resistant *S. aureus* (*Staphylococcus aureus*, MRSA). MRSA is a significant opportunistic

pathogen which is responsible for most hospital-acquired infections in the world.²³ As expected, peptide **1** did not show any antibacterial activity. Compounds bearing both fluorescence and bacteria-killing function could be developed for both diagnostics and antibiotics. Furthermore, as peptides **2** and **3** display strong autofluorescence, we studied their localization and antibacterial activity through three-dimensional, high-resolution, live-cell, fluorescence microscopy. Briefly, we treated the cells of Gram-positive *S. aureus* and *Bacillus subtilis* as well as Gram-negative *Escherichia coli* with the TPE- α /sulfonyl- γ -AA peptides **2** or **3** at the concentration of 0.05 mg/mL (1 $\times$), 0.25 mg/mL (5 $\times$), and 0.5 mg/mL (10 $\times$). Cells treated with the vehicle, dimethyl sulfoxide (DMSO), served as our negative control. As shown in Figure 7, *S. aureus* was sensitive to the treatment of peptides **2** or **3**, as indicated by the loss of cell shape, integrity, and lysis, at the concentrations of 5 $\times$ and higher. At lower concentrations, the localization of both peptides around the cell periphery was evident, suggesting their antimicrobial property likely stems from membrane binding. Similarly, peptides **2** and **3** appeared to localize to the cell membrane in *B. subtilis*, although cells were resistant to the peptide treatment as they were able to retain their cell shape and became sensitive only at 10 $\times$ or higher concentrations. In *E. coli*, TPE- α /sulfonyl- γ -AA peptide **2** did not target the cell surface and peptide **3** weakly associated with the cell periphery. *E. coli* cells were also resistant to peptide **2** treatment and were sensitive to peptide **3** only at higher concentrations. Thus, TPE- α /sulfonyl- γ -AA peptides **2** and **3** are potent antistaphylococcal agents.

CONCLUSION

In this work, we designed and prepared a series of novel chiral and emissive TPE-conjugated sulfonyl- γ -AApeptides. By investigating the structure and the properties, we identified that the helical peptide backbone provides a favorable scaffold to restrict the intramolecular rotations and induce fluorescence. The fluorescence could be synergistically enhanced by AIE effect. In addition, the right-handed helical framework could be used to precisely arrange the distribution of TPE moieties, which lead to the large CPL dissymmetric factor as high as 1.2×10^{-2} , augmenting their great potential in chiral recognition and enantioselective catalysis. The autofluorescence property could be adopted for the investigation of the mechanism of antimicrobial action.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05329.

Synthetic routes, characterization data, X-ray crystallographic data, HPLC traces, and additional figures (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The work was supported by NSF 1708500 (J.C.) and NIH 1R01GM112652-01A1 (J.C.).

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