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Journal

Journal of the American Chemical Society, 145(47)

ISSN

0002-7863

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Publication Date

2023-11-29

DOI

10.1021/jacs.3c08356

Peer reviewed

Self-Assembled Homopolymeric Spherulites from Small Molecules in Solution

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Cite This: *J. Am. Chem. Soc.* 2023, 145, 25664–25672



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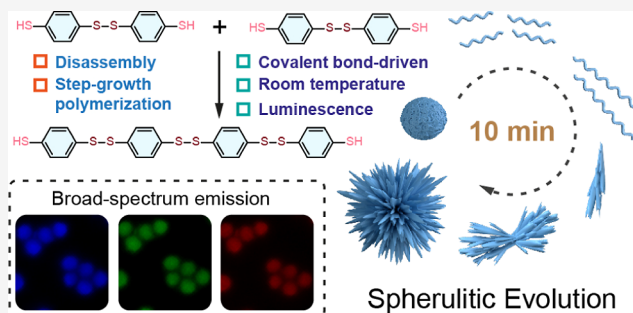


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Supporting Information

ABSTRACT: Polymeric spherulites are typically formed by melt crystallization: spherulitic growth in solution is rare and requires complex polymers and dilute solutions. Here, we report the mild and unique formation of luminescent spherulites at room temperature via the simple molecule benzene-1,4-dithiol (BDT). Specifically, BDT polymerized into oligomers (PBBDT) via disulfide bonds and assembled into uniform supramolecular nanoparticles in aqueous buffer; these nanoparticles were then dissolved back into PBBDT in a good solvent (i.e., dimethylformamide) and underwent chain elongation to form spherulites (rPBBDT) in 10 min. The spherulite geometry was modulated by changing the PBBDT concentration and reaction time. Due to the step-growth polymerization and reorganization of PBBDT, these spherulites not only exhibited robust structure but also showed broad clusterization-triggered emission. The biocompatibility and efficient cellular uptake of the spherulites further underscore their value as traceable drug carriers. This system provides a new pathway for designing versatile superstructures with value for hierarchical assembly of small molecules into a complicated biological system.



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INTRODUCTION

Self-assembly is ubiquitous in nature.^{1–6} Natural molecules such as amino acids, peptides, proteins, and DNA can form cooperative self-assemblies that execute vital biological functions.^{7–11} Such self-assembly can be considered a versatile bottom-up synthesis method and has led to a myriad of functional hierarchical structures in life science and materials engineering.^{12–16} Spherulites are one type of self-assembled systems and polycrystalline structures in which acicular crystals radiate from a common center and grow nearly synchronously, leading to a spherical structure. Indeed, spherulites can be obtained from a wide range of materials (e.g., metals, minerals, organic molecules, proteins, and synthetic polymers) and have garnered extensive attention in drug delivery, tissue engineering, and sensing.^{17–23} Moreover, manipulating the formation of spherulites is an important topic in biological systems. For example, the formation of spherulites by amyloid fibers has been linked to neurodegenerative pathologies (e.g., Alzheimer's diseases).^{24,25} Controlling spherulite morphology and exploring the mechanism of spherulite growth are vital steps in enhancing material performance and achieving effective disease treatment.^{26–28}

The most common method for preparing organic spherulites is cooling crystallization,^{29–31} which involves heating a polymer solution to make it supersaturated and then cooling it rapidly to induce crystallization or directly cooling the polymer melt to

form crystals. The nucleation and growth of spherulites are affected by temperature, concentration, and solvent qualities; therefore, precise control of the annealing process and solution supersaturation is critical in preparing spherulites.^{32–38} For instance, neat poly(1, 6-hexamethylene adipate) spherulites transformed from negative-type spherulites (radial refractive index > tangential refractive index) at low crystallization temperatures to positive-type spherulites (tangential refractive index > radial refractive index) at high crystallization temperatures.³⁹ Porous spherulites were formed with isothermal crystallization of poly(L-lactide) in diethyl phthalate and glycerol tri-*n*-propionate but not in less viscous solvents like dimethyl sulfoxide (DMSO) or dimethylformamide (DMF).⁴⁰ While there are numerous examples of spherulite formation from supersaturated polymer solutions and polymer melts,^{41,42} spherulite formation in dilute solutions remains a rare phenomenon. Recently, Winnik and co-workers reported the first example of spherulite formation via the self-assembly of a block copolymer in a dilute solution. They then investigated the

Received: August 2, 2023

Revised: October 15, 2023

Accepted: October 18, 2023

Published: November 3, 2023



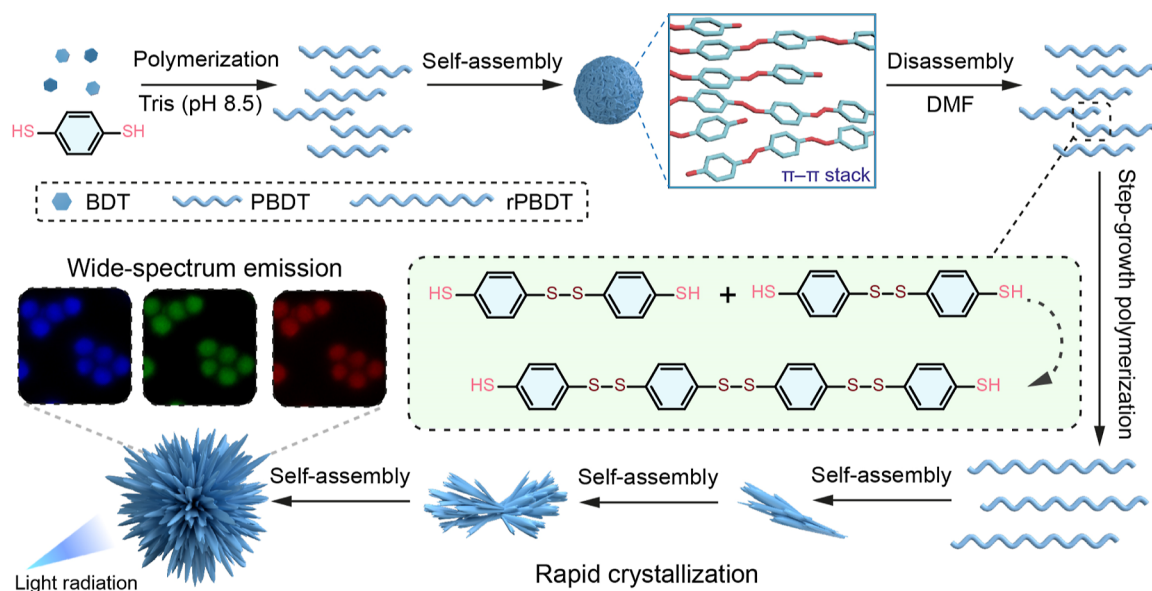


Figure 1. Process of forming rPBDT spherulites from small BDT molecules. BDT molecules form PBDT chains through disulfide bonds under alkaline conditions and then self-assemble into PBDT nanoparticles. PBDT nanoparticles disassemble into PBDT chains in DMF. The formation of disulfide bonds leads to the growth of PBDT chains into rPBDT chains, which gradually assemble to form spherulites.

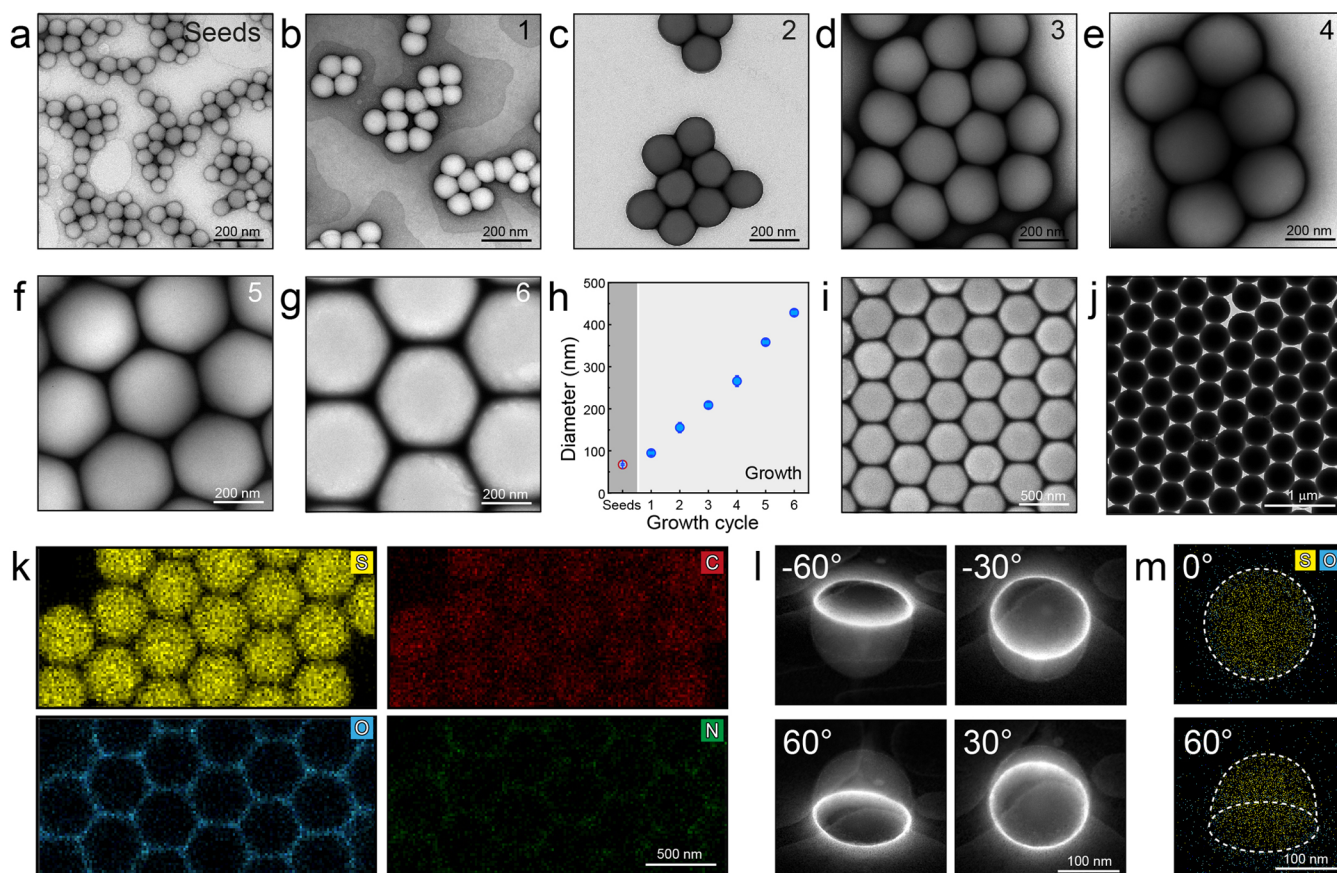


Figure 2. Synthesis of PBDT nanoparticles. (a) TEM image of PBDT nanoparticles. (b–g) TEM images of PBDT nanoparticles of different sizes prepared by seed-mediated growth. The number denoted in the upper right corner indicates the growth cycle. (h) DLS results of PBDT nanoparticles prepared by repeating seed-mediated growth. (i) SEM image of PBDT nanoparticles (450 nm) in a large population. (j) TEM image of PBDT nanoparticles (450 nm) in a large population. (k) Elemental mappings of PBDT nanoparticles. (l) TEM images of PBDT nanoparticles at different angles. (m) EDX elemental mappings of PBDT nanoparticles at different angles.

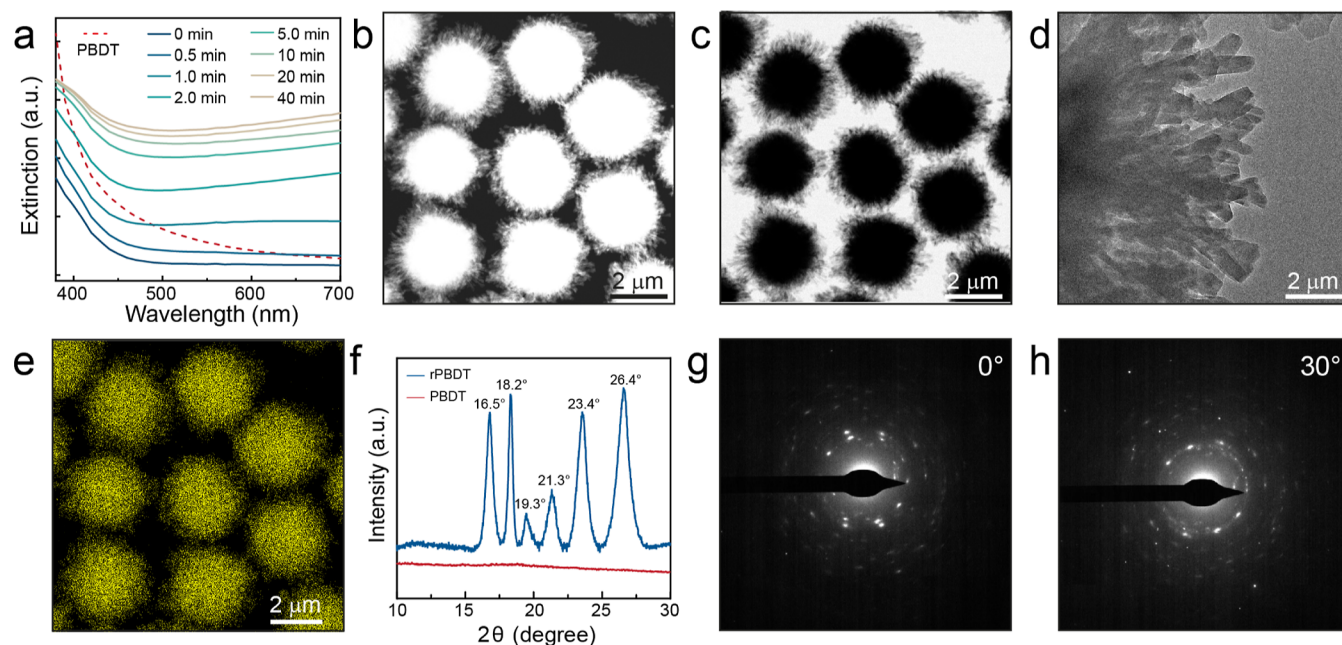


Figure 3. Synthesis of rPBBDT spherulites and crystal structure characterization. (a) Time-dependent UV–vis spectra of rPBBDT spherulites during the spherulitic growth. (b) HAADF image of rPBBDT spherulites. (c) TEM image of rPBBDT spherulites. (d) TEM image of spikes on the surface of rPBBDT spherulites. (e) EDX elemental mapping of S elements in rPBBDT spherulites. (f) XRD patterns of PBBDT nanoparticles and rPBBDT spherulites. (g,h) Cryo-SAED patterns of rPBBDT spherulite at different angles.

assembly mechanism. Of note, this system still required the presynthesized nuclei and delicate control of annealing and aging.^{43,44}

Understanding the morphological changes, structural evolution, and crystallization mechanisms involved in spherulite formation is a challenge due to the demanding conditions required for their growth.^{45,46} We recently found that benzene-1,4-dithiol (BDT) can self-assemble into uniform supramolecular nanoparticles (PBBDT) via π - π stacking with disassembly in organic solvents, e.g., DMF.⁴⁷ Intriguingly, PBBDT nanoparticles rapidly dissolved in DMF and then formed spherulites at room temperature within 1 min. This process did not necessitate intricate temperature control or presynthesized complex polymers. This finding motivated us to further employ this system for spherulite design. Moreover, to the best of our knowledge, the synthesis of homopolymeric spherulites from small molecules in solution remains quite rare.

Here, we report the first example of spherulite formation by the self-assembly of small molecules at room temperature (Figure 1). Specifically, BDT can self-polymerize through disulfide bonds to form polymerized uniform PBBDT nanoparticles with tunable size in aqueous environment. These PBBDT nanoparticles rapidly dissolve in DMF (i.e., generating dispersive PBBDT molecules) and then experience step-growth polymerization via disulfide bonds while assembling into spherulites (rPBBDT) within 10 min. The dynamic growth of the rPBBDT spherulites indicated the unique evolution of this insoluble spherulite: the disulfide-mediated elongation of the chains from PBBDT nanoparticles gives the rPBBDT spherulites a higher molecular weight that then precipitates into a crystal spherulite. The rPBBDT spherulites have broad luminescence performance probably due to the clusterization-triggered emission of PBBDT molecules with different molecular weights. They exhibited obvious fluorescence in various media including at extreme pH conditions (pH 1 or 13). We further validated rPBBDT spherulites as a biocompatible and traceable particle

system. Our findings not only provide a mild fabrication strategy for uniform functional spherulites but also highlight the role of the covalent bond in spherulitic growth which has been largely overlooked.

RESULTS AND DISCUSSION

Homopolymeric PBBDT nanoparticles were first synthesized. In bicine buffer (10 mM, pH 8.5), BDT molecules formed PBBDT molecules via disulfide bonds, and the increased hydrophobicity led to the self-assembly of PBBDT molecules into uniform nanoparticles. Transmission electron microscopy (TEM) result showed that the resulting nanoparticles were ~ 70 nm in diameter (Figure S1) and had a smooth spherical morphology (Figure 2a). Interestingly, the nanoparticle size was tunable via seed-mediated growth,^{48–50} and these PBBDT nanoparticles can be modulated from 90 to 450 nm by repeating this protocol (Figure 2b–h). The PBBDT nanoparticles prepared by seed-mediated growth maintained a smooth spherical morphology and uniform size (Figure 2i,j). It is notable that the size distribution of the products was affected by the quantity of seeds added in the growing step (Figure S2). If a low concentration of seeds (0.1 mL) was used (i.e., high ratio of BDT precursor to seed), then the nucleation and growth of free PBBDT nanoparticles would occur, leading to the poor size distribution of the products. Energy-dispersive X-ray spectroscopy (EDX) results revealed that PBBDT nanoparticles were mainly composed of S and C elements (Figure 2k) confirming that only BDT was involved in the formation of PBBDT nanoparticles. This homogeneous system significantly streamlines this BDT workflow versus our previous system where nanoparticles comprised PBBDT and tannic acid.⁵¹ The PBBDT nanoparticles were a soft material that deformed during drying (Figures 2l,m, and Figure S3).

Next, the assembly process of PBBDT nanoparticles into rPBBDT spherulite was investigated. In a typical process, the as-

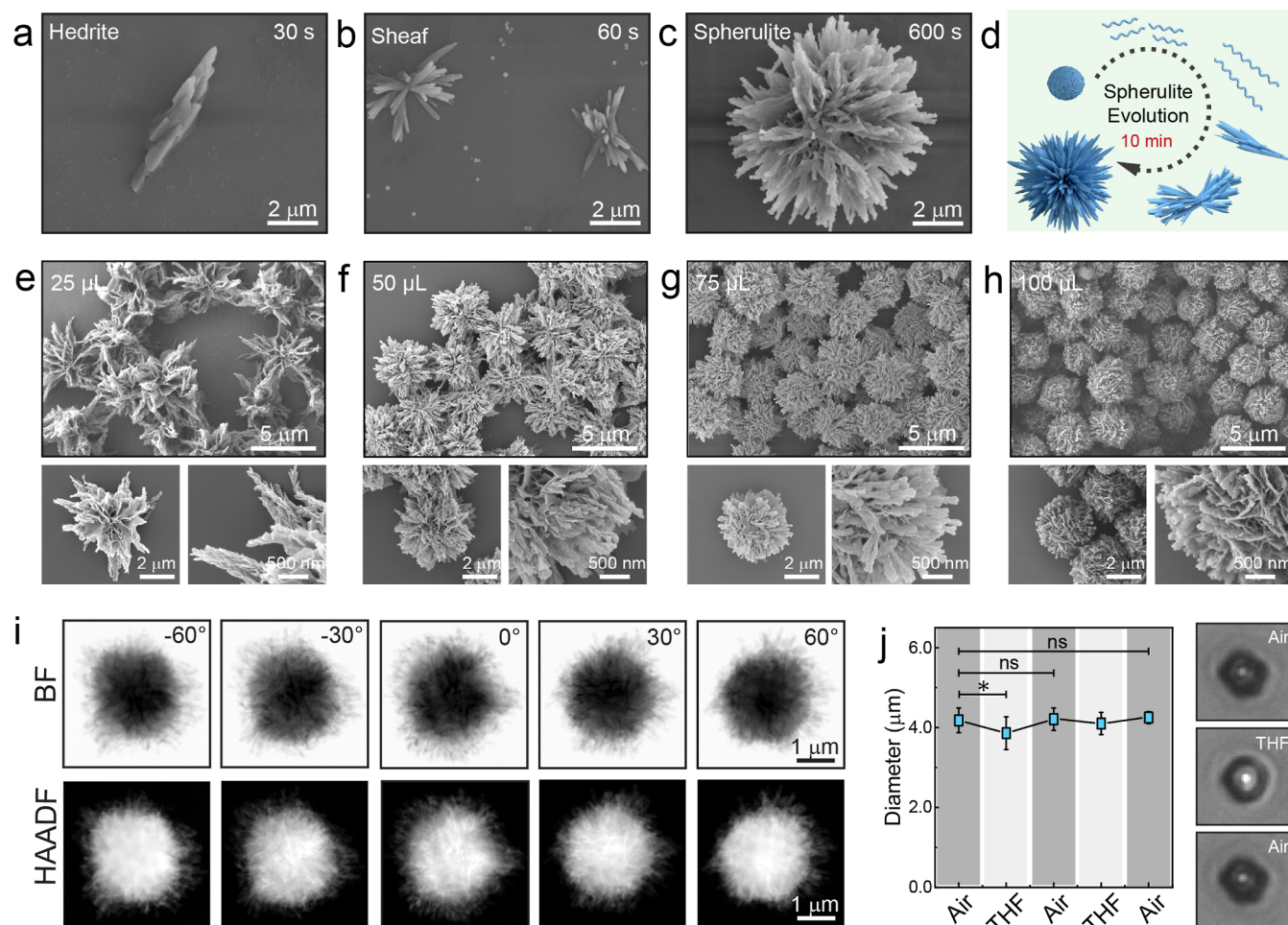


Figure 4. Spherulitic growth of rPBBDT spherulites by dissolution and step-growth polymerization. (a–c) SEM images revealing the self-assembly process of PBBDT into rPBBDT (a: 30, b: 60, c: 600 s). (d) Schematics of rapid self-assembly process from PBBDT nanoparticles. (e–h) SEM images of rPBBDT spherulites prepared with different amounts of PBBDT nanoparticles. (e: 25, f: 50, g: 75, h: 100 μL). (i) Bright field TEM and HAADF images of rPBBDT spherulites at different tilting angles. (j) Size changes of rPBBDT spherulites after soaking in THF for multiple cycles. ns means no significant difference between groups, and * means significant difference between groups.

prepared PBBDT nanoparticles (15 mg mL^{-1}) of $75 \mu\text{L}$ were added into 1 mL of DMF. The initial state of the mixture dispersion was turbid due to the nanoparticle light scattering (i.e., the Tyndall effect). The material became transparent shortly due to the disassembly of nanoparticles into PBBDT molecules. The sample then formed a milky dispersion again in 60 s (Figure 3a and Movie S1), thus indicating the formation of spherulites. High-angle annular dark-field (HAADF) and TEM results showed that rPBBDT formed a branched spherulite with a rough surface topography and radial architecture (Figure 3b–d). Of note, the obtained spherulites were composed of S (Figure 3e), suggestive of the identical composition with PBBDT nanoparticles. In the X-ray diffraction (XRD) patterns (Figure 3f), rPBBDT spherulites showed peaks at $2\theta = 16.5, 18.2, 19.3, 21.3, 23.4,$ and 26.4° , respectively, corresponding to a d -spacing of 0.53, 0.49, 0.45, 0.41, 0.38, and 0.33 nm, while PBBDT nanoparticles did not exhibit obvious peaks. These indicated that the dissolution and step-growth polymerization process transformed amorphous PBBDT nanoparticles into crystalline rPBBDT spherulites. Selected-area electron diffraction (SAED) from spikes on the rPBBDT spherulites surface further confirmed the XRD structural analysis. rPBBDT spherulites were crystalline with a dense core and spiky surface appearing as sharp spots in the SAED pattern (Figure 3g,h).

We further investigated the dynamic assembly of the process. Different morphologies were observed after different reaction times. rPBBDT spherulites grew from hedrite to sheaf and finally became spherulite (Figures 4a–c and S4). The whole process was simple and rapid ($<10 \text{ min}$) without complex temperature control (Figure 4d). The morphology of the spherulites was also modulated by varying the volume of the PBBDT nanoparticle solution (Figures 4e–h and S5–S7). With an increase in the number of PBBDT nanoparticles in the initial solution, rPBBDT spherulites became smaller with denser branches. This is probably due to the generation of more spherulite nuclei at high PBBDT molecules. Spherulites prepared from larger nanoparticles displayed increased dimensions and elongated aciculae, which suggests that fewer nuclei were produced when using large PBBDT nanoparticles (Figure S8). This hierarchy structure endows rPBBDT spherulites with a large specific surface area, which is beneficial for drug delivery application. Notably, rPBBDT spherulites showed improved mechanical and colloidal properties compared to PBBDT nanoparticles (Figure S9). By recording the TEM images at different tilting angles (Figure 4i), the interface between the bottom of spikelike spherulite and the underlying substrate (i.e., TEM grid) clearly showed intact boundary of the spherulites. This indicated that the PBBDT nanoparticles became rigid materials after the spherulitic

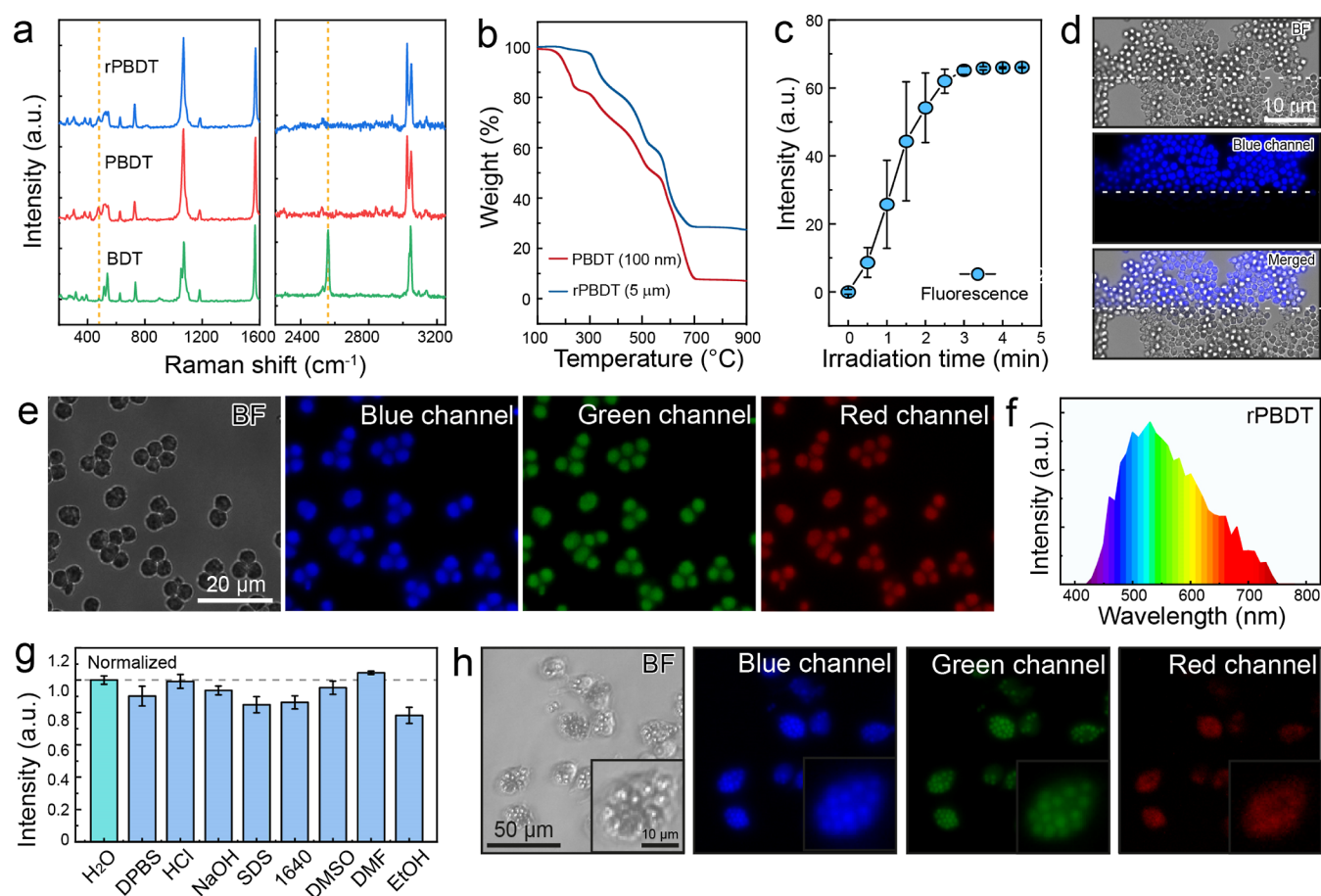


Figure 5. Molecular mechanism and luminescence properties of rPBBD spherulites. (a) Raman spectra of BDT molecules, PBBD nanoparticles, and rPBBD spherulites. (b) Thermogravimetric curves of PBBD nanoparticles and rPBBD spherulites. (c) The luminous intensity of rPBBD spherulites under different irradiation time. (d) Comparison of the luminescence characteristic of rPBBD spherulites irradiated with and without ultraviolet light. (e) Different emission of rPBBD spherulites excited in different channels (i.e., BF, blue channel, green channel, and red channel). BF: bright field; blue channel: channel with excitation wavelength of 405 nm; green channel: channel with excitation wavelength of 480 nm; red channel: channel with excitation wavelength of 560 nm. (f) The emission spectrum of rPBBD spherulites over a wide range of wavelengths (excitation at 405 nm). (g) Luminescence profile of rPBBD spherulites in different solvents (DPBS: Dulbecco's phosphate buffered saline; HCl: hydrochloric acid at pH 1; NaOH: sodium hydroxide at pH 13; sodium dodecyl sulfate buffer; 1640: RPMI-1640; DMSO; EtOH: ethanol). (h) Bright-field and fluorescence microscopy images of the raw cells after the internalization of rPBBD spherulites. Inset: higher-magnification image of a representative cell.

growth. These spherulites also exhibited excellent stability when incubated with tetrahydrofuran (THF) (Figure 4j), where the spherulites retained similar morphology during THF washing cycles, suggesting their poor solubility in THF at the current state.

The key question underneath this system is what drives the dissolved PBBD nanoparticles in DMF to form the rPBBD spherulites. Raman spectra evidenced the formation of disulfide bonds in PBBD nanoparticles and rPBBD spherulites (Figure 5a), with the disappearance of -SH (2590 cm⁻¹) and the formation of disulfide (480 cm⁻¹). Due to the poor solubility of the rPBBD spherulites in common solvent including DMF and THF, we used mass spectrometry to identify PBBD fragments after treating rPBBD with dithiothreitol (Figure S10), which also confirmed the presence of disulfide bonds. Moreover, the thermal stability of rPBBD spherulites was significantly higher than that of PBBD nanoparticles (i.e., 150 vs 300 °C) (Figures 5b and S11), which suggested a higher molecular weight of rPBBD spherulites.^{52,53} We, therefore, hypothesize that the incubation of PBBD nanoparticles in DMF leads to the disruption of π - π stacking and produced PBBD oligomers with active thiol terminal groups in the solution. These free

thiols can form disulfide and bridge two or more oligomers into elongated rPBBD molecules, which makes rPBBD insoluble in DMF and crystallizes into spherulites. This phenomenon suggests that covalent polymerization can be employed for spherulite development, avoiding complicated assembly control (e.g., cooling and aging).

We then attempted to verify this covalent-bond-driven spherulitic formation mechanism. The formation of -S-S- depends on the oxidation of -SH by oxidant (i.e., O₂). The nitrogen atmosphere prevented the solution from becoming cloudy suggesting that the formation of spherulites is linked to the O₂ present in the system (Figure S12a,c). If the -SH groups were oxidized to -SO₃H groups by H₂O₂,⁵⁴ the formation of rPBBD spherulites did not occur, indicating the pivotal role of reactive thiols in the formation of -S-S- for subsequent rPBBD spherulites (Figure S12b,c). Furthermore, we compared the disassembly behavior of rPBBD spherulites to non-cross-linked (low molecular weight) and cross-linked (high molecular weight) polystyrene (PS). The non-cross-linked PS particles, regardless of their size, were immediately dissolved in THF (Figures S13 and S14), while the morphology of the cross-linked PS particles remained basically unchanged (Figure S15). In

contrast, rPBDT spherulites remained intact in THF (Figures S16 and S17). This indicates that the high molecular weight of rPBDT spherulites resists dissolution in organic solvent.

Interestingly, rPBDT spherulites exhibited obvious luminescence (quantum yield: 4.6%) after ultraviolet light irradiation. As the irradiation pretreatment time increases, the luminescence intensity reached a maximum level (Figure 5c and Movie S2). We speculate that the luminescence properties of rPBDT spherulites are related to the formation of rigid disulfide hindering the rotation of benzene rings and the supramolecular structure of molecular chains.^{55–59} The necessity for UV pretreatment can be linked to the insufficiently dense arrangement of PBDT molecules. This lack of density stems from the rapid progression of step-growth polymerization and self-assembly processes, and UV irradiation may disrupt partial disulfide bonds,⁵⁴ which leads to the reorganization of PBDT molecules within the spherulite for a more tightly packed structure. This increased structural rigidity constrains the rotation of the benzene rings within the molecular chains, allowing for the increased release of energy primarily through the fluorescence.⁶⁰ Therefore, the fluorescence intensity of rPBDT increases with prolonged irradiation time and eventually stabilizes. The optical characteristics of rPBDT spherulites without ultraviolet irradiation (Figure 5d) and PS particles (Figure S18) ruled out the potential scattering effects. Notably, these rPBDT spherulites exhibited broad emission from blue, green, to red light as they can be excited in different fluorescence channels (Figures 5e and S19). Specifically, they emitted light ranging from 430 to 750 nm (Figure 5f). We also confirmed that both PBDT nanoparticles (amorphous) and rPBDT spherulites (crystalline) exhibited similar fluorescence while the BDT molecules had no fluorescence properties (Figures S20–S23). These results collectively suggested that the crystalline degree had minor effect on the fluorescence properties. The luminescence characteristics of rPBDT spherulites are stable in diverse media even in various organic solvents (e.g., DMSO, DMF, EtOH, and THF) and harsh conditions (e.g., pH 1 or 13) (Figures 5g and S24). The LUMO and HOMO orbitals of rPBDT spherulites in different media were calculated by Gaussian simulation (Figure S25). Although the values in various solvents are different, the energy band gap is almost the same, which led to a similar luminescence performance. The broad-spectrum, stable, and uniform emission characteristics of the spherulites hold great potential for emerging white-light emission materials.⁶¹

We confirmed the biocompatibility of rPBDT spherulites *in vitro* (Figure S26). Specifically, both PBDT nanoparticles and rPBDT spherulites showed negligible cytotoxicity. This may be because of their inert and robust structure in aqueous media. Significant cellular uptake of spherulites was observed after 24 h incubation with raw cells (Figure 5h). The high cell internalization was ascribed to the spike structure of the spherulites, which facilitates the active engulfment of cells.^{62,63} Moreover, the fluorescence of rPBDT was observed in the cytosol of cells. Collectively, such fluorescent spherulites exhibited great potential for traceable drug delivery due to their good biocompatibility, high porosity, superior cellular uptake, and imaging capability.

CONCLUSIONS

In summary, we report a facile synthesis of homopolymeric luminescent spherulites by a unique dissolution and reaggregation strategy. Specifically, this synthesis relies on the formation

of disulfide bonds, which make shorter PBDT chains into longer rPBDT chains and then precipitate into rPBDT spherulites. The morphology of the spherulites was modulated by varying the reaction time and PBDT concentration at room temperature, avoiding complicated temperature control. The obtained spherulites exhibit excellent structural stability and tolerate various solvents. Moreover, the broad luminescence, good biocompatibility, and branched structures, combined with superior cellular uptake, make these materials attractive for intracellular drug delivery and fluorescence imaging. The simple molecule-driven spherulitic growth not only creates multifunctional hierarchical organic structures but also provides new insights for designing biomimetic architectures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c08356>.

Detailed experimental procedures for PBDT nanoparticles, detailed experimental method for preparing PBDT nanoparticles by seed-mediated growth, characterization of PBDT nanoparticles, detailed preparation of rPBDT spherulites with different sizes and morphologies, and characterization of rPBDT spherulites (PDF)

MP4 (Movie S1): Changes of the solution in 60 s during the preparation of rPBDT spherulites (MP4)

MP4 (Movie S2): Increased fluorescence of rPBDT spherulites in 270 s (MP4)

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Author Contributions

Q.S. and Y.L. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was performed in part at the San Diego Nanotechnology Infrastructure (SDNI) of UCSD, a member of the National Nanotechnology Coordinated Infrastructure, which is supported by the National Science Foundation (grant ECCS-2025752). We thank Dr. Bo Gao from the Analytical & Testing Center of Sichuan University for his assistance with MS characterization, Dr. Yanying Wang from Analytical & Testing Center of Sichuan University for her assistance on steady/transient fluorescence, Qingshuang Song for her assistance with DSC characterizations, and Zhonghui Wang for her assistance with confocal laser scanning microscope. Cryo-SAED patterns were collected at SKLB West China Cryo-EM Center in Sichuan University. We thank Dr. Ying Song from College of Biomass Science and Engineering at Sichuan University for her assistance in fluorescence microscopy. This work made use of the IMSERC Crystallography facility at Northwestern University, which has received support from the Soft and Hybrid Nanotechnology

Experimental (SHyNE) Resource (NSF ECCS-2025633) and Northwestern University. This work made use of the EPIC facility of Northwestern University's NUANCE Center, which has received support from the SHyNE Resource (NSF ECCS-2025633), the IIN, and Northwestern's MRSEC program (NSF DMR-1720139). J.Z. acknowledges the Fundamental Research Funds for the Central Universities. M.N.C. acknowledges NIH T32 CA153915. The authors acknowledge the use of facilities and instrumentation supported by the National Science Foundation through the University of California San Diego Materials Research Science and Engineering Center DMR-2011924.

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