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Anisotropic Synthetic Allomelanin Materials via Solid State Polymerization of Self-Assembled 1,8-Dihydroxynaphthalene Dimers

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Supporting information for this article is given via a link at the end of the document.

Abstract: Melanosomes have diverse morphologies in nature, including spheres, rods, and platelets. By contrast, shapes of synthetic melanins have been almost entirely limited to spherical nanoparticles with few exceptions produced by complex templated synthetic methods. Here, we report a non-templated method to access synthetic melanins with a variety of architectures including spheres, sheets, and platelets. Three 1,8-dihydroxynaphthalene dimers (4-4', 2-4' and 2-2') were used as self-assembling synthons. These dimers pack to form well-defined structures of varying morphologies depending on the isomer. Specifically, distinctive ellipsoidal platelets can be obtained using 4-4' dimers. Solid-state polymerization of the preorganized dimers generates polymeric synthetic melanins while maintaining the initial particle morphologies. This work provides a new route to anisotropic synthetic melanins, where the building blocks are preorganized into specific shapes, followed by solid-state polymerization.

Introduction

Melanin is the term for a class of natural pigments ubiquitously found in most organisms.^[1] Melanin serves a variety of functions, including as a pigment in human skin and hair,^[2] in thermal regulation,^[3] in radiation protection,^[4] in metal ion sequestration,^[5] and in neuroprotection.[6] In nature. melanosomes, or melanin-containing organelles, possess various morphologies and sizes.^[7] Unique melanosome shapes, including rods, disks, and platelets, are ubiquitous across different biological kingdoms, particularly in bird feathers.^[7-8] A wide array of spectacular bird colors emerges as a direct consequence of the diversity of melanosomes morphologies. For example, the green hermit hummingbird (Phaethornis guy) applies densely packed ellipsoidal platelet-like melanosomes in the gorget feathers to generate bright structural color (Figure S1). In contrast to this diversity found in nature, synthetic melanin is mostly produced as spherical nanoparticles. Although some anisotropic structures of polydopamine have been achieved using DNA-origami-based templates,^[9] a more convenient, scalable, and direct route towards non-spherical synthetic melanin materials is desirable.

Allomelanin, the class of melanin targeted in this work, is a heterogeneous group of polymers found mostly in fungi, bacteria, and plants.^[7, 10] These organisms synthesize allomelanins through oxidative polymerization of nitrogen-free precursors, such as 1,8-dihydroxynaphthalene (1,8-DHN) and catechols.[10b, ^{11]} Typically, allomelanin generated by fungi utilizes 1,8-DHN and is referred to as DHN melanin. The existence of DHN melanin may be critical in the survival of fungi in hostile environments, protecting them against ionizing radiation, extreme temperatures, and oxidizing agents.^[12] Previously, we reported a route for the chemical synthesis of artificial allomelanin nanoparticles via oxidative oligomerization of 1,8-DHN.^[13] The resulting nanoparticles showed well-defined spherical nanostructures and free radical scavenging activity. Experimentally, we determined that spherical nanostructures formed upon dimerization of 1,8-DHN, inspiring Kapoor and Jayaraman to probe the self-assembly behavior of the three DHN dimers (4-4', 2-4' and 2-2') (Figure 1) via atomistic molecular dynamics simulations.^[14] These simulations revealed that 4-4' dimers adopt an anisotropic shape as they assemble, as opposed to 2-2' dimers that self-assemble into spherical morphologies.^[14] Inspired by the simulations, we hypothesized that different isomers of DHN dimers would exhibit differences in hierarchical self-assembly behavior that would be reflected in their nanoscale or microscale morphologies. Specifically, 4-4' dimers would have the propensity to generate synthetic allomelanins with anisotropic morphologies. Furthermore, we

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reasoned that once assembled, the DHN dimers would yield to further polymerization and crosslinking.

While DHN dimers have been identified in previous studies as key intermediates and natural products, the dimers have not been individually isolated or used in the preparation of artificial melanin-like materials.^[15] By studying each DHN dimer individually, we aim to gain critical information on the process of nanoparticle formation and to better understand the structure of both natural and synthetic DHN melanins. Here, we describe the synthesis and self-assembly of 4-4', 2-4' and 2-2' DHN dimers in aqueous solution, followed by solid-state oxidative polymerization to generate corresponding synthetic allomelanins.

Results and Discussion

The three dimers were first synthesized as a mixture and isolated by separation using high-performance liquid chromatography (HPLC) (Figure 1A). Specifically, the oxidizing agent KMnO₄ was added to a solution containing 1,8-DHN to generate a mixture of DHN oligomers. By controlling the feed ratio of the oxidizing agent and quenching the reaction early, dimers of DHN were isolated as the main product. Preparatory high-performance liquid chromatography (prep-HPLC) was used to separate and purify each dimer. However, since the oxidative oligomerization process is not well-controlled and regioselective, only 4-4' and 2-4' dimers were obtained in appreciable yields (6% yield for 4-4' dimer, 27% yield for 2-4' dimer). Only trace amounts of the 2-2' dimer was detected. Therefore, a selective multistep synthetic strategy was adopted to synthesize the 2-2' dimer, with the key step being the copper-mediated homocoupling of the boronic acid derivative of 1,8-DHN (Figure 1B). The hydroxy groups of 1,8-DHN were first protected as methyl ethers using methyl iodide, to avoid unwanted side reactions. Regioselective borylation of 1 (1,8dimethoxynaphthalene) was accomplished by treatment at -78 °C with n-BuLi, followed by addition of trimethyl borate. Acidic workup gave the desired boronic acid 2 ((1,8dimethoxynaphthalen-2-yl)boronic acid) in moderate yield. Aerobic homocoupling of the boronic acid 2, catalyzed by copper(I) chloride (CuCl), generated the methylated 2-2' dimer 3 (1,1',8,8'-tetramethoxy-2,2'-binaphthalene),[16] which was subsequently treated with BBr3 to remove the methyl protecting groups to give the desired 2-2' DHN dimer with an overall yield of 14%. A similar synthetic approach was applied to selectively synthesize 4-4' DHN dimer (Figure 1C). Regioselective bromination of 1 was accomplished by treatment with Nbromosuccinamide (NBS), giving rise to the para-substituted compound 4 (1,8-dimethoxy-4-bromo-naphthalene). After borylation, homocoupling and deprotection, the desired 4-4' DHN dimer was obtained with an overall yield of 13%. The structures of all three dimers were identified by nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) (Supporting Information, section 5). Analytical HPLC traces were used to confirm the purity and elution time for each dimer (Figure S2).

The self-assembly of the three DHN dimers was performed via dialysis to leverage this relatively slow process to produce thermodynamically favorable structures (Figure 2). Briefly, self-assembly was performed via dialysis using a slide-A-Lyzer MINI dialysis device. DHN dimers were dissolved in CH₃CN at a concentration of 1.0 mg/mL, and then added to the dialysis device (Figure 2A), which was then placed into a conical tube containing ultrapure water and a stir bar. After stirring for two days at room temperature, the samples were collected by centrifugation and washed with ultrapure water three times to remove unassembled dimers. The resulting self-assembled materials are referred to as 4-4'-DHN-SA, 2-4'-DHN-SA and 2-2'-DHN-SA (SA = self-assembly) (Figure S3).

The DHN-SA samples were first characterized by transmission electron microscopy (TEM) and scanning electron microscopy (SEM) (Figure 2). Interestingly, the 4-4' dimer self-assembled into rectangular structures composed of oriented sheets with well-defined edges. The length of 4-4'-DHN-SA structures

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Figure 2. (A) Dialysis-mediated self-assembly of three DHN dimers. Supramolecular structure of (B) 4-4'-DHN-SA. (i) TEM image, (ii) SEM image. (C) 2-4'-DHN-SA. (i) TEM image, (ii) SEM image. (C) 2-2'-DHN-SA. (i) TEM image, (ii) SEM image, (ii) SEM image. (C) 2-2'-DHN-SA. (i) TEM image, (ii) SEM image. (C) 2-2'-DHN-SA. (i) TEM image. (C) 2-2'-DHN-SA

ranges from 5 to 10 µm, with a width of 1 to 2 µm (Figure 2B). The rectangular sheet structure can also be visualized via optical microscopy (Figure S4). In contrast to the 4-4' dimer, the 2-4' and 2-2' dimers formed well-defined spherical nanoparticles, with diameters ranging from 100 nm to 500 nm for 2-4'-DHN-SA, and 150 nm to 500 nm for 2-2'-DHN-SA based on the TEM images (Figure 2C and Figure 2D). Given the spherical morphology of 2-4'-DHN-SA and 2-2'-DHN-SA structures, dynamic light scattering (DLS) was used to determine the hydrodynamic diameter of the particles and was found to be 244 nm and 342 nm respectively (Figure S5). Considering that phenol and naphthol materials can be slowly oxidized by O₂ from air in solution, we wished to confirm whether the resulting selfassembled structures were composed solely of DHN dimers and not higher molecular weight oligomers generated by aerobic oxidation during the dialysis process. To verify this, DHN-SAs were re-dissolved in CH₃CN and subjected to HPLC analysis (Figure S6). The HPLC traces showed that DHN-SAs had identical elution times compared to the corresponding DHN dimers. Additionally, ESI-MS data of DHN-SAs revealed the DHN dimer peak at m/z 317 [M-H]⁻ (Figure S7). These data confirm that the DHN dimers do not oxidize during the selfassembly process.

To further investigate the atomic structure of DHN-SAs, powder X-ray diffraction (PXRD) and electron diffraction data were collected. The PXRD pattern of 4-4'-DHN-SA displayed many sharp reflections, characteristic of a highly crystalline material (Figure 3A). In contrast, the diffraction patterns of 2-4'-DHN-SA and 2-2'-DHN-SA exhibit broad peaks attributed to a loss of long-range order (Figure S8A and Figure S8B). Specifically, only three features can be located at approximately 14.9, 21.7, and 23.4° in the 2-4'-DHN-SA sample and 15.6, 21.0, and 22.5° in the 2-2'-DHN-SA sample. These values correspond to d spacings of approximately 6.0, 4.2, and 3.9 Å and 5.7, 4.3, and 4.0 Å, respectively. The broadness of these peaks is consistent with the nanoparticle nature of these samples observed in TEM and SEM. Scherrer analysis yields an average crystallite size of 2.56±0.06-3.15±0.08 nm for 2-4'-DHN-SA and 5.1±0.1 nm for 2-2'-DHN-SA (Table S1). The difference of these values from the sizes of the particles determined by electron microscopy underscores the lack of order within these self-assembled structures. Electron diffraction data of DHN-SAs are similar to the powder X-ray diffraction patterns, with electron diffraction of 4-4'-DHN-SA showing specific diffraction patterns (Figure 3B), while for the two spherical structures, no diffraction patterns were observed (Figure S9A and Figure S9B).

To understand the molecular packing and interactions of 4-4'-DHN-SA, the compound was studied using single crystal X-ray diffraction (SCXRD) analysis. Needle-like crystals of 4-4'-DHN-SA suitable for SCXRD were prepared using the solvent switch method described above, without stirring at 4 °C for 2 days (Figure 3C). Analysis of the diffraction data reveals that 4-4'-DHN-SA crystallizes in the P21/c space group, with one 4-4' dimer molecule and two H₂O molecules in the asymmetric unit (Table S2, Figure S10). The other enantiomer of the 4-4' dimer is generated by the symmetry elements of the space group. The dihedral angle of the two naphthalene rings is 108.0(1)°. This value is in reasonable agreement with that calculated in atomistic molecular dynamics simulations,[14] which found a narrow distribution of 90°-100° for the 4-4' dimer, suggesting that its reduced flexibility that could lead to anisotropic packing. Further examination of the crystal structure reveals that aromatic stacking of the naphthalene rings and hydrogen bonding between the hydroxyl groups and co-crystalized water molecules are key driving forces that contribute to this particular packing of the molecules (Figure 3D). The aromatic rings of the DHN dimers form edge-to-face interactions and off-center parallel stacking between neighboring molecules.^[17] The closest carboncarbon distances associated with these two types of interactions are 3.596(2) and 3.533(2) Å, respectively. The oxygen atoms of the hydroxyl groups are located 2.555(1) Å from each other, and 2.590(2) and 2.722(2) Å from the oxygen atoms of the two water molecules in the asymmetric unit. As a result, the DHN dimer molecules orient to create layers of aromatic molecules bridged by regions of hydrogen-bonded water along the [100] direction. These results are also supported by the observation of aromatic stacking and hydrogen bonding with water in simulations.^[14]

The experimental PXRD pattern of 4-4'-DHN-SA displays distinct diffraction peaks that match well in position and relative intensities to the predicted pattern (Figure S11). Similarly, the

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Figure 3. (A) PXRD pattern of 4-4'-DHN-SA. (B) TEM image and electron diffraction pattern of 4-4'-DHN-SA. The dashed yellow circle depicts the region selected for electron diffraction, scale bar 500 nm. (C) SEM image of 4-4'-DHN-SA showing layered structure, scale bar 5 µm. (D) Single crystal structure of 4-4'-DHN-SA. Black, grey, and red spheres represent carbon, hydrogen, and oxygen atoms, respectively. Grey regions represent 4-4' dimer layer. Light blue regions represent hydrogen bonding layer with co-crystallized water molecules. CCDC number and crystallographic details are in the Supporting Information.

simulated electron diffraction pattern was generated from the single crystal structure and compared to experimental electron diffraction data. This comparison revealed that the electron diffraction pattern obtained from TEM was generated from the [100] zone axis, which is perpendicular to the 4-4' dimer 2D layers, and the diffraction spots were indexed (Figure 3B). The d spacings of different planes from experiment and simulation were also compared and found to be in good agreement (Table S3).

The different self-assembly behavior of the DHN dimers can be understood at the molecular level. In the 4-4' dimer, because of its two-fold symmetry, the two pairs of hydroxyl groups face in opposite directions. This conformation allows the hydrophobic and hydrophilic domains to be well-separated, leading to the formation of an organized, anisotropic layered structure that is conducive to the growth of large crystallites. In contrast, the 2-4' and 2-2' dimers do not have hydroxyl groups on opposite sides of the molecule. Rather, the hydroxyl groups would be favored along a particular direction in three dimensions. This preference would likely not allow for the same layered packing as observed in the 4-4' dimer, and as a result, those dimer molecules generate a more spherical amorphous aggregate in adopting optimal packing. Again, these molecular-level insights are consistent with the atomistic simulations which show that the position of the hydroxyl groups plays a vital role in the selfassembly behavior of the dimers.[14]

Since the initial assembly conditions showed that the 4-4' dimer forms anisotropic structures, the morphology of 4-4'-DHN-SA was further investigated through the modification of selfassembly methods (Figure 4). Water was introduced either slowly, by dropwise addition or by rapid injection, to a solution of the 4-4' dimer in CH₃CN (Figure 4A, Supporting Information section 3). Samples were then stirred for 1 hour, followed by centrifugation and washes with water. The resulting selfassembled structures are defined as 4-4'-DHN-SA(S), for assemblies where water was added slowly, and 4-4'-DHN-SA(R), where water was added rapidly (Figure S12).

The self-assembled structures were characterized by TEM and SEM, revealing the formation of ellipsoidal platelets (Figure 4B, Figure S13). Analysis of TEM images of 4-4'-DHN-SA(S) reveals that these samples range from 1.0 to 2.7 µm in length, with a width of 0.25 to 0.65 µm (Table S4). The aspect ratio of 4-4'-DHN-SA(S) is 4.4±0.3, indicating a high uniformity of the morphology (Table S4). The platelets created by rapid injection, 4-4'-DHN-SA(R), consist of thinner ellipsoidal platelets. 4-4'-DHN-SA(R) exhibits lengths ranging from 0.9 to 1.7 µm, with widths of 0.3 to 0.4 µm. The aspect ratios of 4-4'-DHN-SA(R) range widely from 2.7 to 6.4, with an average value of 3.9±0.8 (Table S4). The less uniform shape of 4-4'-DHN-SA(R) can be explained by the fast self-assembly process, where 4-4' dimer molecules are kinetically trapped upon addition of water, resulting in structures with a greater amount of defects compared to 4-4'-DHN-SA(S). The height of individual platelets

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Figure 4. (A) Slow water addition and rapid-injection self-assembly of 4-4' DHN dimer to generate ellipsoidal platelets. (B) Supramolecular structure of 4-4'-DHN-SA(S) (i) TEM image, (ii) SEM image; 4-4'-DHN-SA(R) (iii) TEM image, (iv) SEM image. Scale bars 500 nm. AFM images of (C) 4-4'-DHN-SA(S) and (D) 4-4'-DHN-SA(R); Electron diffraction patterns of (E) 4-4'-DHN-SA(S) and (F) 4-4'-DHN-SA(R); Scale bars 500 nm. The dashed yellow circles are regions selected for electron diffraction.

was measured via AFM. 4-4'-DHN-SA(S) varied in height from 20 nm to 130 nm. (Figure 4C, Figure S14A and Figure S15A) and 4-4'-DHN-SA(R) particles were found that ranged in height between 25 nm and 50 nm, with much rougher surface texture (Figure 4D, Figure S14B, Figure S15B). Both ellipsoidal platelets showed a high degree of crystallinity. The electron diffraction data of 4-4'-DHN-SA(S) and 4-4'-DHN-SA(R) showed similar diffraction patterns (Figure 4E, Figure 4F). The indexed diffraction spots further demonstrate that the planar surface is the [100] zone axis, similar to the predominate surface plane of single crystals of the 4-4' dimer.

Thus, by simply changing how water is introduced to solutions of 4-4' DHN dimers, ranging from dialysis-membrane-mediated diffusion to rapid addition, the morphologies of the resulting 4-4'-DHN-SA is dramatically influenced. The influence of water addition on crystallite morphology is clear when the single crystal structure is considered. The hydrogen bonds present between co-crystallized water molecules and the hydroxyl moieties of the 4-4' DHN dimer likely play a key role in the selfassembly of the dimer into the solid-state. This anisotropic interaction, present along the slow-growing [100] plane of the crystallites, can therefore be tuned by the assembly conditions to form planar sheets and ellipsoidal platelets of different dimensions.

Synthetic melanins are polymeric materials formed by oxidative polymerization.^[18] Therefore, to realize synthetic allomelanins,

the pre-organized DHN dimers self-assembled structures would need to undergo further oxidation and polymerization. The oxidation method used here was ammonia-induced solid-state polymerization (AISSP).^[19] This approach has recently been applied to generate thin films of synthetic DHN melanin with ultrasmooth morphologies.^[19a, 20] Here, spherical nanoparticles (2-4'-DHN-SA, 2-2'-DHN-SA) and ellipsoidal platelets (4-4'-DHN-SA(S)) were used. The DHN-SA powders were enclosed in a glass chamber (e.g. cylindrical TLC chamber) under an ammonia and air atmosphere (Figure 5). Ammonia catalyzes the oxidation reaction, with the oxygen in air serving as the oxidizing agent (Figure 5A). After 24 h, a color change of DHN-SAs from white to black was observed, indicating polymerization and allomelanin formation (Figure 5B). SEM analysis showed that the morphologies of oxidized DHN-SAs were retained after AISSP at the nanoscale (before: Figure 5C, after: Figure 5D). Fourier transform infrared spectrometry (FTIR) was applied to visualize the chemical changes in this process. The spectra showed that 4-4'-DHN-SA(S) and oxidized 4-4'-DHN-SA(S) shared the same characteristic peaks (Figure 5E, Figure S16). However, upon oxidation, the signals of peaks at 759 cm⁻¹ and 1037 cm⁻¹ corresponding to the aromatic C-H bending and the C-OH stretching respectively significantly decreased, suggesting that the C-C oxidative coupling happens as well as the formation of quinone structures from phenol structures (Figure S17). X-ray photoelectron spectroscopy (XPS) analysis shows an increasing VIanus

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Figure 5. (A) AISSP of spherical nanoparticles and ellipsoidal platelets. (B) Photos of DHN-SAs before and after AISSP. (C) SEM images of (i) 4-4'-DHN-SA(S), (ii) 2-4'-DHN-SA and (iii) 2-2'-DHN-SA before AISSP; Scale bars 500 nm. (D) SEM images of (i) 4-4'-DHN-SA(S), (ii) 2-4'-DHN-SA and (iii) 2-2'-DHN-SA after AISSP; Scale bars 500 nm. (E) FTIR spectra of 4-4'-DHN-SA(S) before and after AISSP. (F) XPS O1s spectra of 4-4'-DHN-SA(S) before and after AISSP. (G) PXRD patterns of 4-4'-DHN-SA(S) before and after AISSP. (H) Electron diffraction patterns of 4-4'-DHN-SA(S) after AISSP; Scale bar 500 nm. The dashed yellow circles are regions selected for electron diffraction.

amount of C=O species after AISSP, with the relative ratio changing from 8.17% to 16.76%, which confirms the oxidation of phenol to quinone (Figure 5F, Figure S18). To evaluate the level of crystallinity of 4-4'-DHN-SA(S) after AISSP, PXRD patterns were measured. The sharp peaks of the PXRD pattern of 4-4'-DHN-SA(S) before AISSP convert after solid-state oxidation to broad features with greatly reduced intensity (Figure 5G). Additionally, electron diffraction data of 4-4'-DHN-SA(S) display the loss of specific diffraction patterns (Figure 5H), even though the overall shape of the ellipsoidal platelets remains intact. This route to polymerized, synthetic allomelanins through initial assembly of small molecule building blocks provides a route otherwise inaccessible and potentially generalizable to other types of polymeric melanin including eumelanin and pheomelanin where, again, the majority of known systems are spherical, or amorphous on the nano- and microscale.

Conclusion

In summary, we synthesized three DHN dimers and investigated their assembly and solid-state oxidative polymerization behavior.

We demonstrated that the different connectivity between the two substituted naphthalene rings of the dimers have a tremendous influence on the morphologies and molecular arrangements of the self-assembled structures, which can be used in a selftemplating polymerization strategy to prepare ellipsoidal plateletshaped synthetic melanosomes reminiscent of those found in hummingbirds and other animals.^[21] Specifically, the 4-4' dimer serves as a reliable building block in the generation of structures with anisotropic shape. Subsequent solid-state oxidative polymerization enabled the transition from a pre-organized selfassembled structure to polymerized synthetic allomelanins without changing the overall morphologies. We envision that pre-organization followed by oxidative polymerization will provide a rich route for obtaining synthetic melanins with diverse morphologies. Indeed, the materials prepared here and analogues therein are currently under investigation in structural color and related applications. Finally, although our investigations here relate to allomelanins, this kind of selftemplating may extend to eumelanins, providing an approach to accessing far better chemical mimics of bird feather melanosomes which are eumelanin based in nature.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: melanin • allomelanin • DHN melanin • anisotropic • solid state polymerization

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RESEARCH ARTICLE



A new method to achieve synthetic melanin materials with various well-defined architectures, ranging from spheres to anisotropic sheets and ellipsoidal platelets is described. The specific shapes are obtained through pre-organizing the building blocks of melanins, followed by solid-state oxidative polymerization to render polymeric materials without changing the overall morphology.