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Polydopamine and Eumelanin: From Structure–Property Relationships to a Unified Tailoring Strategy

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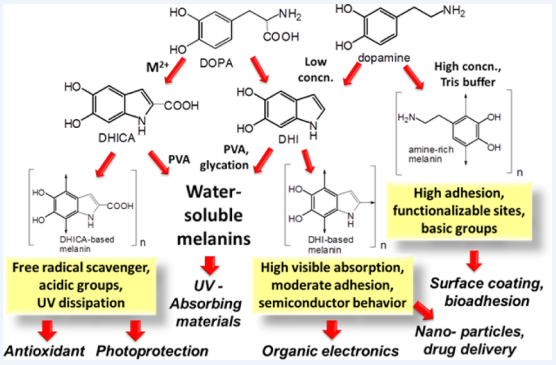
CONSPECTUS: Polydopamine (PDA), a black insoluble biopolymer produced by autoxidation of the catecholamine neurotransmitter dopamine (DA), and synthetic eumelanin polymers modeled to the black functional pigments of human skin, hair, and eyes have burst into the scene of materials science as versatile bioinspired functional systems for a very broad range of applications. PDA is characterized by extraordinary adhesion properties providing efficient and universal surface coating for diverse settings that include drug delivery, microfluidic systems, and water-treatment devices. Synthetic eumelanins from dopa or 5,6-dihydroxyindoles are the focus of increasing interest as UV-absorbing agents, antioxidants, free radical scavengers, and water-dependent hybrid electronic–ionic semiconductors. Because of their peculiar physicochemical properties, eumelanins and PDA hold considerable promise in nanomedicine and bioelectronics, as they are biocompatible, biodegradable, and exhibit suitable mechanical properties for integration with biological tissues. Despite considerable similarities, very few attempts have so far been made to provide an integrated unifying perspective of these two fields of technology-oriented chemical research, and progress toward application has been based more on empirical approaches than on a solid conceptual framework of structure–property relationships. The present Account is an attempt to fill this gap. Following a vis-à-vis of PDA and eumelanin chemistries, it provides an overall view of the various levels of chemical disorder in both systems and draws simple correlations with physicochemical properties based on experimental and computational approaches. The potential of large-scale simulations to capture the macroproperties of eumelanin-like materials and their hierarchical structures, to predict the physicochemical properties of new melanin-inspired materials, to understand the structure–property–function relationships of these materials from the bottom up, and to design and optimize materials to achieve desired properties is illustrated. The impact of synthetic conditions on melanin structure and physicochemical properties is systematically discussed for the first time. Rational tailoring strategies directed to critical control points of the synthetic pathways, such as dopaquinone, DAquinone, and dopachrome, are then proposed, with a view to translating basic chemical knowledge into practical guidelines for material manipulation and tailoring. This key concept is exemplified by the recent demonstration that varying DA concentration, or using Tris instead of phosphate as the buffer, results in PDA materials with quite different structural properties. Realizing that PDA and synthetic eumelanins belong to the same family of functional materials may foster unprecedented synergisms between research fields that have so far been apart in the pursuit of tailorable and marketable materials for energy, biomedical, and environmental applications.



INTRODUCTION

Harnessing Nature's chemical principles and logic for designing efficient, sustainable, and biocompatible multifunctional molecular systems is an important goal in the current quest for innovation-driven strategies and advanced technological solutions in materials science.[1−3] A unique source of inspiration for multifunctional materials is provided by the well-known property of the catecholamine metabolites 3,4-dihydroxyphenylalanine (DOPA) and dopamine (DA) to generate on oxidation a variety of pigments commonly referred to as melanins.[4−6] Melanins include the following: (a) eumelanins, the black insoluble photoprotective pigments of human skin and eyes;[7,8] (b) pheomelanins, the pigments of red-haired individuals with a high propensity to sunburn and skin cancer;[9] and (c) neuromelanin, a dark pigment that accumulates within the dopaminergic neurons of the substantia nigra selectively degenerating in Parkinson's disease. Eumelanins are by far the

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most relevant from a biological and technological perspective and accordingly will be the main focus of this Account. Unlike the vast majority of natural pigments, eumelanins cannot be described in terms of a single well-defined structure, and it is not possible to provide an accurate picture beyond a statistical description of main units and functional groups. The notorious difficulties in the structural investigation of natural eumelanins, due primarily to the amorphous character, the marked insolubility in all solvents, and the close association with the cellular ingredients of the biological matrix, have traditionally dominated the chemists' attitude toward these elusive pigments. Nonetheless, the intriguing physicochemical properties of these polymers,[10] including a broadband UV–vis absorption,[11] an intrinsic free radical character,[12] efficient nonradiative energy dissipation,[13] and a water-dependent, ionic–electronic hybrid conductor behavior,[14] have gradually attracted the interests of scientists from diverse disciplines toward exploitation of synthetic eumelanins as biocompatible multifunctional platforms for application in organic electronics,[3,7] biointerfaces,[15] hybrid materials,[16] and for polymer stabilization[17] (Figure 1).

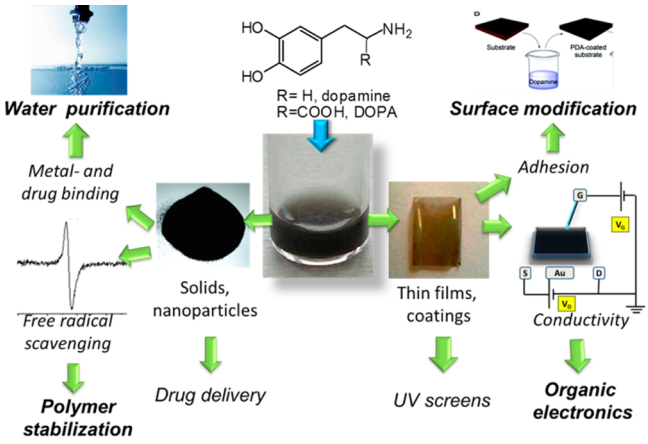


Figure 1. Overview of DOPA and DA as eumelanin precursors: chemical structures and current applications of their polymers.

Paradoxically, most of the impetus to eumelanin research over the past few years derived from studies outside pigment cell research. In an attempt to reproduce the high adhesion properties of mussel byssus,[18] In 2007, Messersmith, Lee, and co-workers described a universal eumelanin-like coating material, polydopamine (PDA), produced by the oxidative polymerization of dopamine (DA) at pH 8.5 in the presence of oxygen.[19] Due to the combination of the functional groups of the amino acids lysine and DOPA of byssus proteins, PDA forms highly adhesive polymeric films which can coat many types of surfaces.

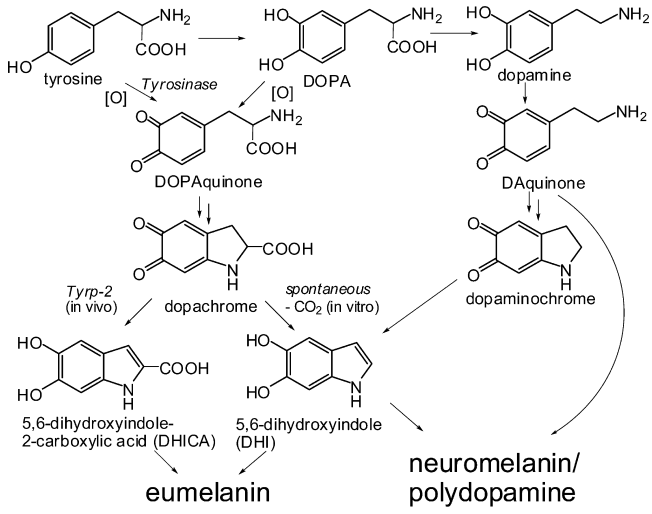
In the most recent few years, the scope of PDA research has rapidly expanded[20−22] to include surface modification,[23,24] interfacing with cells,[25] light-harvesting systems for energy applications,[26] biosensing,[27] and nanomedicine[28] (e.g., to prepare nano- and microparticles,[29−31] and nanocapsules for drug delivery).[32,33]

Thus far, however, progress in the field has been based more on empirical approaches rather than on a solid framework of structure–property relationships. Moreover, only few attempts[34,35] have been made to integrate and assess the rapidly amassing knowledge on PDA structure into the broader context of eumelanin chemistry. The present Account aims at translating for the first time emerging knowledge from eumelanin and PDA research into a common set of structure–property relationships based on an experimental and theoretical background.

BIOSYNTHESIS VERSUS CHEMICAL SYNTHESIS

Eumelanin biosynthesis in epidermal melanocytes involves tyrosinase-catalyzed oxidation of tyrosine or DOPA to DOPAquinone and then to DOPAchrome (Scheme 1). In

Scheme 1. Biosynthetic and Synthetic Pathways for Eumelanin, Neuromelanin, and Polydopamine



vivo, the reaction is assisted by tyrosinase-related protein 2 (Tyrp2), which induces isomerization to DHICA, whereas in the chemically induced polymerization, the isomerization reaction proceeds spontaneously with decarboxylation to give mainly DHI. Oxidative polymerization of DHI and/or DHICA gives rise to the deposition of black insoluble eumelanin polymers.[36] This implies that natural eumelanins contain a high proportion of DHICA-derived units, whereas synthetic melanins from DOPA consist for the most part of DHI-related units.[37]

Scheme 1 shows that neuromelanin derives at least in part from the polymerization of DHI generated by oxidative cyclization of DA,[38] which would warrant inclusion among eumelanins. The same would apply to PDA.

STRUCTURE AND CHEMICAL DISORDER

The general structural properties of DHI and DHICA melanins have been compared[8] and are schematically illustrated in Figure 2.

During biosynthesis, or following polymer buildup, partial breakdown of indole units may occur due to oxidative fission of *o*-quinone moieties, leading to the formation of pyrrolecarboxylic acids (Scheme 2), as demonstrated by MALDI-MS analysis.[39,40]

Until 2012, the structure of PDA was minimally investigated[41,42] In 2012, two studies suggested that PDA is a supramolecular aggregate of monomers (e.g., DAchrome)[43] and contains noncovalent components including a physical trimer of $(dopamine)_2$/DHI derived from a self-assembly mechanism.[44] Subsequent work showed that PDA contains three main types of structural units (i.e., uncyclized amine-

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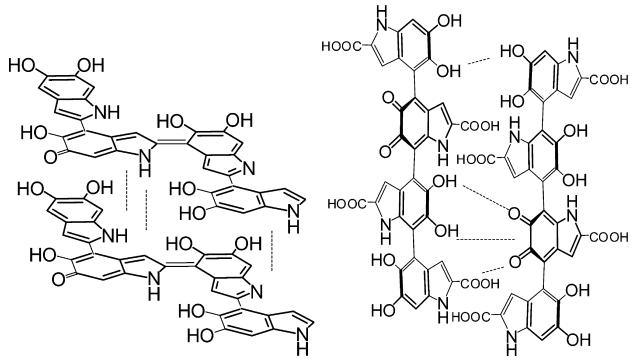
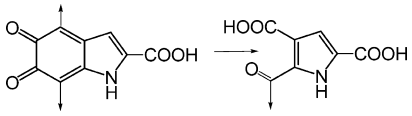


Figure 2. Representative structures of DHI and DHICA melanins. DHI melanin appears to consist of largely planar oligomeric scaffolds, although DHICA melanin is made up of twisted linear oligomer structures featuring atropisomerism caused by slow rotation about interunit bonds.

Scheme 2



containing units and cyclized eumelanin-type indole and pyrrolecarboxylic acid units derived from the oxidative breakdown of indole units,[34] Figure 3). In line with this view,

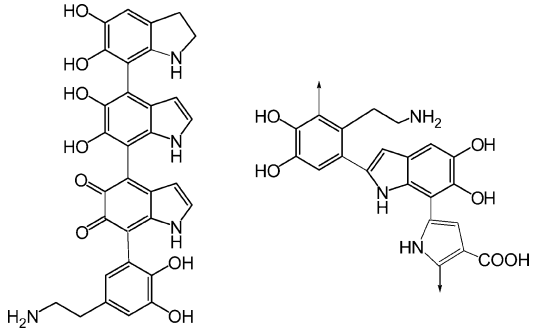


Figure 3. Representative models for PDA structural components based on Liebscher et al.[35] (left) and Della Vecchia et al.[34] (right).

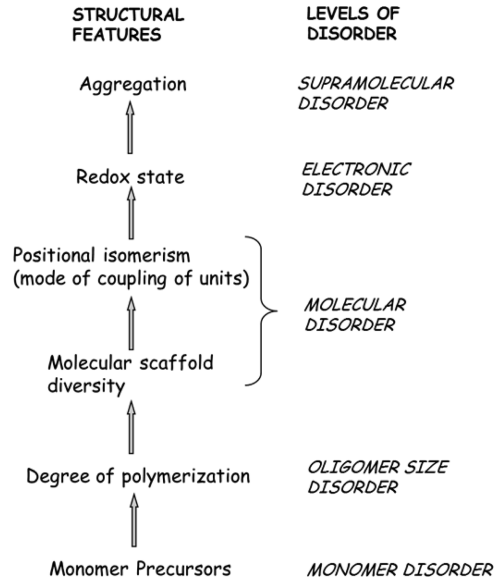
an experimental and computational investigation showed that PDA consists of mixtures of oligomers in which indole units with different degrees of unsaturation and open-chain dopamine units give rise to charge transfer interactions between *o*-quinoid and catechol units.[35]

Raman characterization of carbonized PDA nanoparticles confirmed a layered-stacking graphite-like supramolecular structure.[45] To summarize, natural eumelanins and synthetic DOPA melanins are structurally different because of the enzyme-controlled incorporation in the former of a high proportion of carboxylated DHICA units. Synthetic DOPA melanin, on the other hand, is similar to DHI melanin, though carboxylated units from the amino acid may be incorporated to a detectable extent. PDA differs from DOPA melanin in that it lacks carboxylated units and from DHI melanin for the presence of variable proportions of uncyclized amine-containing units. Finally, PDA is similar to neuromelanin, although the latter also incorporates sulfur-containing units and lipid components.[37,38]

It should be emphasized in this connection that eumelanins are not true polymers or macromolecules and that likewise the term "polydopamine" is misleading, for the following reasons: (a) MALDI-MS analysis has indicated 30−50-mers as the limiting oligomer size for model synthetic 5,6-dihydroxyindole melanins[46] and mixtures of low molecular weight (up to octamers) oligomers for PDA;[34,35] (b) PDA does not arise by dehydrative condensation of DA to form a polymer, as the name could suggest. Thus, the term "dopamine melanin" is more appropriate than "polydopamine" and is strongly recommended by the present authors. Herein, we retain the widespread term "polymer" and the prefix "poly" solely to denote "polymer-like" properties.

The foregoing survey clearly shows that the structure and physicochemical properties of eumelanins imply various levels of chemical disorder,[47] which are schematically illustrated in Scheme 3.

Scheme 3. Simplified Scheme of Chemical Disorder Levels in Eumelanins Realized through Structural Definitions at Multiple Length-Scales in the Hierarchy of the Material



Monomer disorder relates to the variety of monomer building blocks participating in the polymerization process. Size disorder stems from the formation of collections of oligomers of gradationally increasing masses.[46] Molecular disorder denotes the degree of structural diversity based on the variety of scaffolds or positional isomerism due to different coupling modes. Electronic disorder relates to the distribution of redox states (i.e., catechol, semiquinone or quinone) within the oligomeric scaffolds. Supramolecular disorder depends on the variety of aggregates that can be generated by intermolecular interactions between molecular components, for example, π-stacking interactions (DHI units) or bundling aggregations (DHICA units).[8] Thus, whatever the detailed molecular composition and the nature of the supramolecular aggregates, eumelanins and PDA are characterized by a huge chemical disorder, and control of this disorder may allow the shaping of the materials' properties. In turn, control over structural properties is crucial to determine the properties of the final material and its possible functional role or application.

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CHEMICAL CONTROL AND MANIPULATION

Schemes 1 and 3 suggest three different strategies to control chemical disorder, namely, monomer selection, rational structural manipulation at critical control points, and experimental control over polymerization/aggregation.

Monomer Selection and Derivatization

Proper selection, derivatization, or functionalization of monomer substrates is an important means of controlling structure and properties. For example, recent studies provided an explanation as to why nature selected DHICA rather than DHI as the prevalent eumelanin building block,[37] which would be counterintuitive considering that DHI is more oxidizable than DHICA and gives rise on oxidation to black insoluble and compact π-stacked materials. A systematic comparison showed in fact that DHICA melanin is a more efficient free radical scavenger than DHI and DOPA melanins and can induce efficient energy dissipation via excited state intramolecular proton transfer (ESIPT) processes not available to DHI oligomers.[13,48].

In addition, monomer chemistry can be modified by derivatization or installment of specific groups (Figure 4).

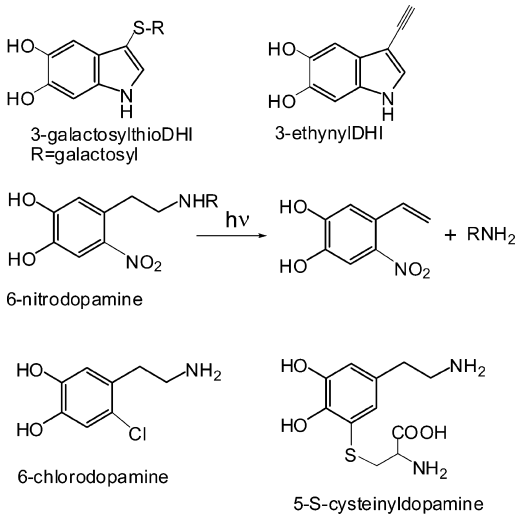

Figure 4. Functionalized eumelanin precursors and DA derivatives for diverse applications. The photochemistry of 6-nitroDA for debonding[53] is highlighted.

Derivatization of DHI with (*S*)-galactosyl groups has been used to develop the first example of water-soluble eumelanin-type polymer.[11] Use of glycated derivatives of DOPA is another promising strategy to produce soluble eumelanins due to the ability of the sugar moiety to prevent polymer precipitation.[49] Manipulation of DHI π-electron system through substitution with alkynyl groups provides a valuable entry to novel eumelanin-like materials for investigation in organic electronic applications.[50] Modification of DA monomer can be carried out at different levels. Norepinephrine (NE) has been shown to produce ultrasmooth coatings of poly norepinephrine (PNE)[51] due to the presence of the beta-OH group accounting for extensive oxidative breakdown of the catecholamine side chain during autoxidation.[52] 6-NitroDA has been successfully used to prepare a photochemically cleavable unit for polymerization reactions and cross-linking with polymeric materials.[53] 6-ChloroDA was used to produce adhesive polymeric films with antibacterial properties.[54] Conjugation of DA with cysteine leads to 5-(*S*)-cysteinylDA which has been shown to enhance the photoresponse of PDA coatings to set up a hybrid photocapacitive/resistive metal−insulator-semiconductor (MIS).[55] Copolymerization of DA with aromatic amines, such as 3-aminotyrosine or *p*-phenylenediamine, has been used to modify the electrical properties of PDA in a metal−insulator−semiconductor device.[56]

Structural Control Points

DOPAquinone is the initial control point of DOPA melanin.[57] It cyclizes at very fast rates to produce DOPAchrome but is a potential target of reactive nucleophilic species and may be useful to modify the properties of DOPA melanin. DOPAchrome rearrangement is the major control point for DOPA melanin: at neutral pH, it gives DHI as main product, but in the presence of metal cations isomerization is deviated toward the nondecarboxylative DHICA-forming pathway[58] (Figure 5). DAquinone is the key control point of PDA and

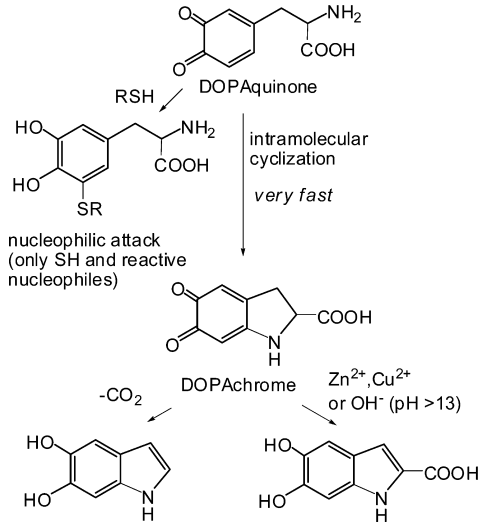

Figure 5. Scheme showing DOPAquinone and DAchrome as the major control points for the chemical manipulation of DOPA melanin.

cyclizes at ca. 100 times slower rate than DOPAquinone:[59] at high DA concentrations, dimerization is the prevalent pathway, at low DA concentrations, intramolecular quinone cyclization or covalent incorporation of Tris buffer are major processes (Figure 6).[34]

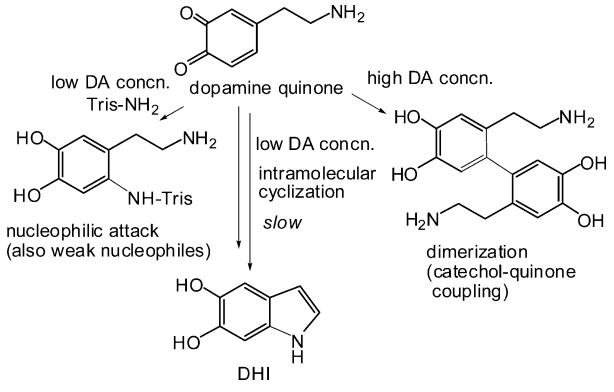

Figure 6. Scheme showing DAquinone as the major control point for chemical manipulation of PDA.

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Control on Polymerization and Aggregation

Tris buffer can be used as an efficient modulator for the control and fine-tuning of PDA properties and aggregate size/morphology.[60] Addition of poly(vinyl alcohol) (PVA) to phosphate buffer is a valuable means of inhibiting eumelanin aggregation and precipitation during oxidative polymerization of DHI and DHICA,[61] leading to water-soluble eumelanins of potential technological relevance. Physical constraint over DHI polymerization can be exerted by insertion into zeolite L.[16] Under conditions of high ionic strength, DOPA also forms good films on a variety of substrates by oxidation in alkali.[62] A new strategy to manipulate the aggregation of PDA with formation of nanobelts and nanofibers is reported on the basis of the addition of folic acid during dopamine oxidation.[63]

IN SILICO MODELING APPROACHES FOR PROPERTY PREDICTION AND TAILORING

The preceding section has shown that experimental control over the structure and composition of eumelanins and related materials are currently yield based on empirical approaches. Nonetheless, the rational design and tailoring of synthetic eumelanins and PDA-based materials may greatly benefit from the current advances of "in silico" modeling approaches which yield considerable insight into eumelanin architecture and properties.

Atomistic simulation methods, such as density functional theory (DFT) simulation and molecular dynamics (MD) simulation, can serve as powerful tools to predict the physicochemical properties of materials.[64−66] Provided that all atom positions and charges are known, atomistic simulation opens the possibility to understand the structure−property−function relationships of materials from the bottom up approach and to design and optimize materials to achieve desired properties. There are several major challenges in computational modeling for PDA and synthetic eumelanin, which may partly explain the limited progress from a computational perspective. Large-scale simulations, which contain at least hundreds of molecules, are necessary in order to capture the macroproperties of eumelanin-like materials due to their amorphous and hierarchical structures. In addition, the lack of well-defined and readily available structures for PDA and eumelanin hindered rapid progress of computational modeling in this field.[7,67]

Computational Modeling Methods

Small-scale simulations with no more than three molecules are less likely to reproduce the macroscopic properties of eumelanin-like materials, since they are believed to be amorphous yet made of hierarchical structures.[68−72] Large-scale simulations for eumelanin-like materials can be simply classified into two different approaches: the monomer-based approach and the molecular-based approach. In the monomer-based approach, the building blocks in a system are DHI and/or DHICA monomers. It might be possible to model the chemical reactions and polymerization of these monomers and to predict the structures of protomolecules of PDA and eumelanin. To-date, there is no appropriate computational modeling method that can address this complex reaction environment, and thus no computational work has successfully and directly modeled the polymerization of DHI and/or DHICA monomers and predicted the structures of protomolecules.[73] Regarding the polymerization pathway, a convenient semiempirical monomer-based approach has been proposed on the basis of the two most possible cross-linking sites of DHI monomers, at 2,4′ and 2,7′ positions.[74] Combined with nonreactive MD simulation techniques, this method can be applied to large-scale simulations containing hundreds or even thousands of molecules. In molecular-based approach, the building blocks in a system are eumelanin protomolecules that do not react further.[75,76] This method is also good for large-scale simulations. The accuracy of this method depends on the structural models of protomolecules used in the simulations since the chemical reactions and polymerization of the monomers do not need to be modeled. DFT calculations had been used previously to propose structural models of eumelanin based on the formation energy.[67] However, it is almost impossible to calculate formation energies for all possible structures of protomolecule due to the chemical disorder. For instance, DHI monomer has four reactive sites and three different oxidation forms (e.g., indolequinone (IQ), quinone-methide (MQ), and quinone-imine (NQ)), implying billions of different possible structures of DHI melanin protomolecule, if the molecular size is considered up to an octamer.

Structural Properties

The hierarchical structures of eumelanin-like materials can be classified into three structural levels (Figure 7). The

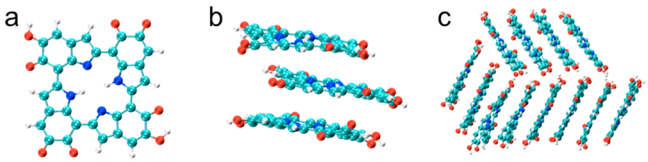

Figure 7. Hierarchical structures of DHI melanin. (a) Primary structures are protomolecules. (b) Secondary structures are formed by stacked protomolecules. (c) Tertiary (aggregate) structures are formed by weak noncovalent interactions between the secondary structures in random-like orientations.

protomolecules are the primary structures and are considered to be made of DHI or DHICA monomers in various redox forms. Protomolecules from DHI are near-planar structures and tend to stack together due to strong noncovalent intermolecular interactions such as van der Waals and $\pi-\pi$ interactions. The stacked structures formed by protomolecules are suggested here to provide the "secondary structures" (see also Meredith and Sarna[10]). Large-scale MD simulation showed that secondary structures of DHI melanin could include a dozen of protomolecules.[75,76] Larger amorphous structures ("aggregate structures") formed by weak noncovalent interactions between the secondary structures in random-like orientations are the tertiary structures. This kind of amorphous structures had been seen in TEM images and MD simulation results (Figure 8).

Mechanical Properties

Large-scale MD simulation results showed that DHI melanin is an isotropic material with the Young's modulus around 5.4−7.8 GPa, calculated from self-assembly of different oligomeric models including tetramers, pentamers, and octamers.[75,76] The isotropic property comes from the random-orientated aggregate structures in the material, and thus, this feature can only be captured in large-scale simulations. The simulated mass densities were in the range of 1.54−1.61 g/cm^3 with different oligomeric models.[75,76] These simulation results were close to

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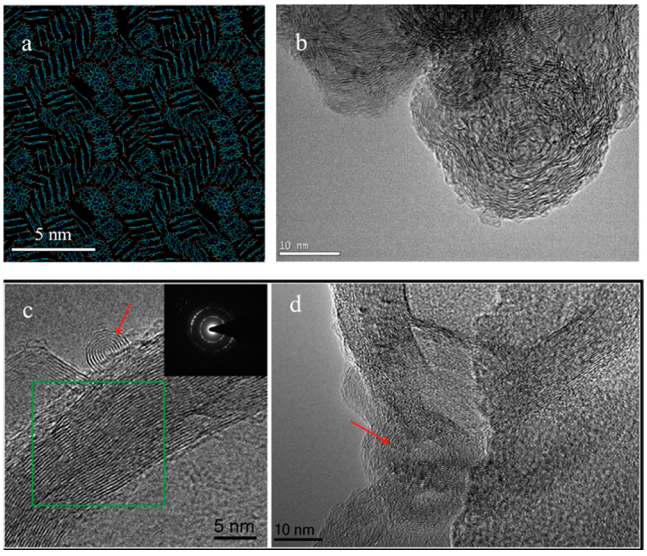


Figure 8. Experimental and computational results of structural models.[75] (a) Snapshot of the simulated aggregate made of 375 DHI melanin protomolecules at the steady state of self-assembly. (b) Typical TEM micrograph of eumelanin produced from the oxidation of dopamine. (c, d) High-resolution TEM images of eumelanin on other locations of the TEM grid. The inset of panel c shows a SAED pattern taken from the green-boxed region. The red arrow in panels c and d indicates that the molecules aggregate and form an onion-like nanostructure composed of stacked planes arranged in concentric rings. Reproduced with permission.

the experimental measurements of eumelanin-like materials, suggesting that the oligomeric models used in the simulations might be similar to the actual protomolecules.

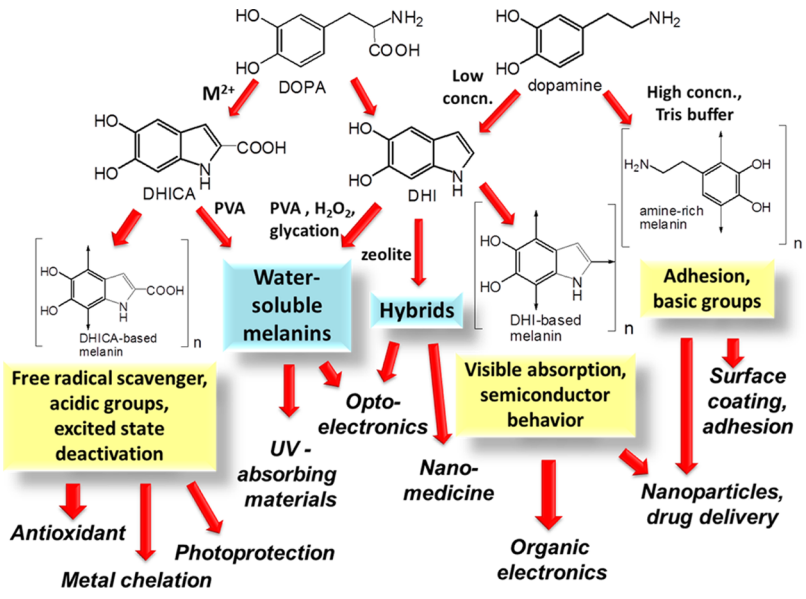
Optical Properties

The broadband UV–vis spectrum monotonically increasing toward the higher-energy end might be a result of chemical disorder in the primary structure and excitonic effects in the secondary and aggregate structures. If the excitonic effects among the protomolecules can be properly calculated in a large-scale system, which is able to capture the hierarchical structures of eumelanin-like material, the broadband absorption spectrum can be reproduced even with few kinds of protomolecules.[10,76] Compared to the mechanical properties, the optical properties of eumelanin-like materials are more sensitive to the structures of protomolecules. It is impossible to determine eumelanin protomolecules from its broadband absorption spectrum. However, a proper computational modeling method, which is able to calculate the optical properties of eumelanin hierarchical structures, can serve as a useful tool to evaluate the structural models. Most importantly, one can use computational modeling techniques to design and optimize the optical properties of eumelanin-like materials to achieve even better optical properties compared to natural eumelanin.

FROM STRUCTURE–PROPERTY–FUNCTION RELATIONSHIPS TO A UNIFYING TAILORING STRATEGY

Most of the studies of synthetic eumelanins have been performed either on commercial materials with ill-defined properties or on DOPA melanins produced under various conditions, and few systematic studies have been reported concerning the effect of synthetic conditions on the properties of eumelanins.[42,44] An important technological goal in PDA research, for example, is the control of film properties and thickness. PDA films of different thickness and roughness on atomic force microscopy (AFM) analysis can be obtained by just changing DA concentration and buffer.[77] Although it is not possible with a single deposition to achieve thickness values beyond a given threshold, it is possible to circumvent this issue by depositing successive stacks of PDA at a given DA concentration (2 mg/mL or 10 mM), by simply putting a fresh catecholamine solution in contact with the previously deposited PDA film. The overall thickness of the PDA coating would then be an integer multiple of the thickness obtained at each deposition step (about 40–45 nm in these experimental conditions and after 20–24 h of deposition in each step).[42,78]

Scheme 4. Unifying Tailoring Strategy for PDA and Eumelanin Synthesis



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The structures of eumelanins may vary significantly depending on such parameters as substrate concentration,[77] nature of the oxidant,[78] reaction medium (e.g., buffer,[78,79] additives,[80] etc.), and postsynthetic processes. Oxidation may be carried out with oxygen (O_2) under alkaline conditions, with chemical oxidants or electrochemically, and depending on conditions material composition and properties may vary.[81,82] Though the medium is usually alkaline, acidic conditions may be used in combination with chemical oxidants to inhibit intramolecular cyclization of the resulting DAquinone.[83,84] Additives that can be used include 3,4-dihydroxybenzaldehyde, to produce smoother PDA films,[51] and metal cations, to affect both DOPA and DA oxidation and structural properties.[58,78] Workup under mild conditions is recommended to prevent breakdown of quinone units, decarboxylation, and degradation.

A unifying picture of the experimental approaches for eumelanin manipulation and tailoring based on the foregoing strategies is illustrated in Scheme 4.

The key concept underlying Scheme 4 is that rational design of experimental protocols based on proper selection of substrates, parameters, and conditions may allow the exertion of efficient control over eumelanin and PDA structure, which in turn may serve to enhance certain properties rather than others finalized to applications (tailoring). The unifying conceptual framework proposed in Scheme 4 shows moreover that it is possible to obtain materials with similar properties using different monomer precursors through proper manipulation at critical control points. The potential of this unifying frame can be exemplified by the possibility of synthesizing a DHI-based eumelanin polymer with efficient visible light absorption and semiconductor properties from three different monomer precursors (i.e., DHI itself, DOPA in the absence of metal ions, and DA at low concentrations). On the other hand, use of Cu^{2+} ions may allow the production of a DOPA melanin with enhanced antioxidant and free radical scavenger properties. Verification, modification, and integration of the unified tailoring scheme based on emerging structure−property−function relationships may stimulate further progress in eumelanin research and technology at multidisciplinary level for energy, biomedical, and environmental applications.

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