

Natural melanin pigments and their interfaces with metal ions and oxides: emerging concepts and technologies

Eduardo Di Mauro, Ri Xu, Guido Soliveri, and Clara Santato, Department of Engineering Physics, Polytechnique Montréal, C.P. 6079, Succ. Centre-ville, Montréal, Québec, H3C 3A7, Canada

Address all correspondence to Clara Santato at clara.santato@polymtl.ca

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Abstract

Melanin (from the Greek μέλας, mélas, black) is a biopigment ubiquitous in flora and fauna, featuring broadband optical absorption, hydration-dependent electrical response, ion-binding affinity as well as antioxidative and radical-scavenging properties. In the human body, photoprotection in the skin and ion flux regulation in the brain are some biofunctional roles played by melanin. Here we discuss the progress in melanin research that underpins emerging technologies in energy storage/conversion, ion separation/water treatment, sunscreens, and bioelectronics. The melanin research aims at developing approaches to explore natural materials, well beyond melanin, which might serve as a prototype benign material for sustainable technologies.

Introduction

The migration of human beings from the tropics to the rest of the globe has been marked by variation in the production of the brown–black melanin pigment of the skin. While hominins near the equator developed dark photoprotective melanin-rich pigmentation due to high ultraviolet (UV) radiation exposure, those settling in low-UVB ($\lambda = 280\text{--}315\text{ nm}$) environments developed depigmented skin with facultative pigmentation (tanning) to sustain the photosynthesis of vitamin D₃. Melanin is thus a key factor in one of the most noticeable human polymorphisms: skin color.^[1]

Humans lacking melanocytes (melanin-producing cells) in the ear and animals with albinism (a deficit or absence of melanin) display hearing conditions as in domestic cats with white fur and blue eyes, thus suggesting a biofunctional role of melanin beyond photoprotection.^[2, 3]

In the melanin biopigments family, eumelanin is a brown–black type found in the human body, other mammals, reptiles, amphibians, and fishes as well as in invertebrates, such as cuttlefish and insects; Sepia melanin is a type of natural eumelanin extracted from the ink sac of cuttlefish. Pheomelanin is a yellowish-red melanin.^[4, 5]

Eumelanin has been intensively studied in recent decades for functional properties, such as UV–vis absorption, metal chelation, and free radical scavenging. It also features an anti-oxidant behavior. The limited solubility of eumelanin in most organic solvents has rendered challenging the understanding of its physicochemical properties.^[4, 6]

Here, after a brief introduction of molecular structural aspects of eumelanin biopigments and their effect on the properties of the pigment, we critically review the binding

properties of eumelanin toward metal cations and eumelanin–metal oxide interfaces. Eumelanin is involved in the accumulation and release of metal cations in the human body.^[7] It is also worthy of note that the interactions between iron and neuromelanin, a pigment made of eumelanin and pheomelanin present in the brain of humans and primates, have been related to Parkinson's disease.^[8] The remarkable adhesion properties of melanin-like materials on surfaces, including metal oxides is the underpinning for emerging applications in the biomedical, water treatment, and energy fields.^[9, 10]

Molecular aspects of eumelanin: building blocks, free radicals, hierarchical development

Eumelanin consists of building blocks of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) (Fig. 1).^[6] The building blocks can polymerize into eumelanin oligomers and polymers at different molecular sites of the monomers (indicated as 2, 3, 4, 7 in Fig. 1). The presence of two building blocks, different polymerization sites, and redox states [the reduced form is the hydroquinone (H2Q), the intermediate form is the semiquinone (SQ), and the oxidized form is the quinone Q and its tautomer (QI)] co-existing in the pigment result in the well-established chemical heterogeneity of eumelanin.^[11]

Hierarchical development characterizes the formation of eumelanin-based materials, generated by supramolecular aggregation. Eumelanin planar oligomers can form from four or more DHI monomers (protomolecules),^[11] possibly stacking via π – π interactions (Fig. 2). Tetramers have been proposed as molecular units to explain a number of functional properties of

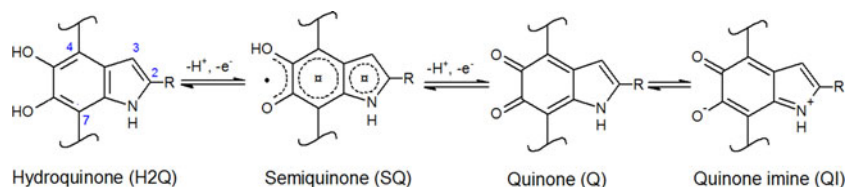


Figure 1. The 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA): R is –H in DHI, whereas it is the –COOH group in DHICA. The scheme also illustrates the redox forms of DHI and DHICA: hydroquinone (H2Q), semiquinone (SQ), and quinone (Q). The quinone imine form (QI) is the tautomer of Q.

eumelanin.^[13–17] The π - π -stacked eumelanin protomolecules with different sizes, randomly oriented, leading to peculiar excitonic interactions among them, have been proposed to explain the broadband optical absorption of eumelanin (see “Photophysical behavior of eumelanin: absorption spectrum, chromophoric species” section and Fig. 3).^[18]

The steric hindrance of the carboxyl groups on the DHICA building blocks causes DHICA to polymerize into non-planar structures, differently from the DHI case. The negative charge, possibly present in the deprotonated carboxyl groups, can induce a further twist in the polymer chain. This leads to rod-shaped assemblies in DHICA polymers (usually referred to as DHICA-melanin, Fig. 2). DHICA-melanin exhibits an absorption peak below 400 nm, which DHI-melanin (solely composed of DHI monomers) does not. In addition, DHICA-melanin has a lower optical absorption in the visible.^[12]

Melanin contains intrinsic stationary-free radicals (observed predominantly in the solid state and likely carbon-centered species associated with defects in the polymer backbone),^[19–21] with additional extrinsic free radicals generated under UV or visible irradiation or in high hydration conditions.^[22–25] The presence of intrinsic radicals is independent of the pH value.^[11, 26, 27] DHICA-melanin exhibits hydroxyl radical-scavenging properties in the Fenton reaction, differently from

DHI-melanin.^[12, 28] DHICA-melanin features relatively homogeneous free-radical species, i.e., spatially confined within restricted segments of the polymer, in contrast to the broader variety of free-radical species generated within the delocalized π -electron systems of the DHI-melanin.

Photophysical behavior of eumelanin: absorption spectrum, chromophoric species

Chemical disorder and geometric disorder models have been proposed to explain the broad optical absorption spectrum of eumelanin. The chemical disorder model posits that eumelanin is made of many chemically distinct species such that its broadband absorption spectrum results from the convolution over the spectra of these species.^[29] However, it has been reported that the spectrum is affected by interactions among eumelanin protomolecules.^[30] Recently, Buehler and co-workers, considering excitonic couplings between eumelanin oligomers (tetramers, pentamers, and octamers), found that the computational spectra with geometric (packing) disorder of a single species of DHI oligomers (Fig. 3) agree with experiments, and that excitonic couplings among eumelanin protomolecules have a considerable role in the increase of the probability of absorption toward the higher energy end of the spectrum.^[18]

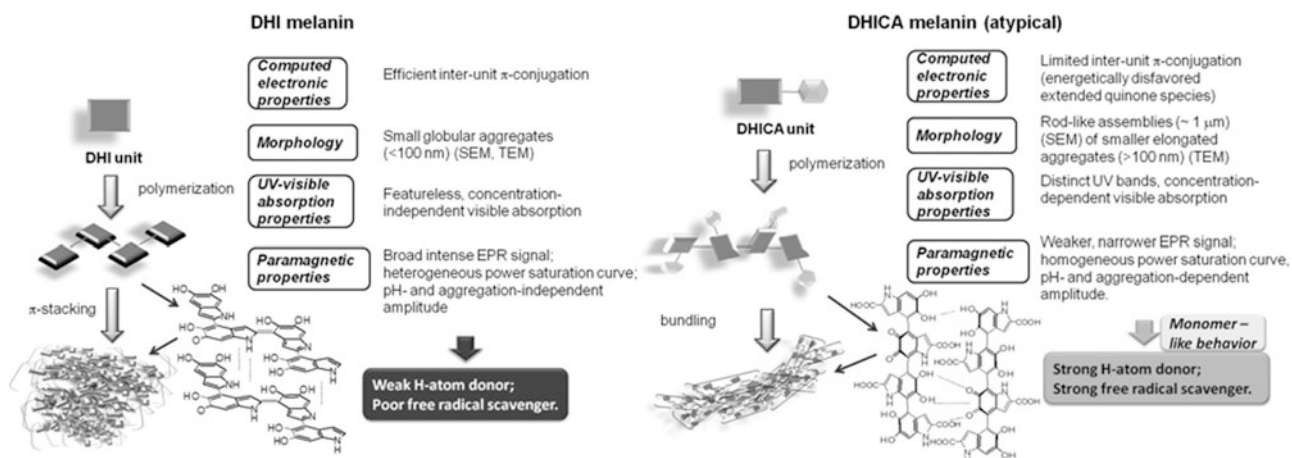


Figure 2. Formation of 5,6-dihydroxyindole (DHI)-melanin [solely composed of DHI monomers, (a)] and 5,6-dihydroxyindole-2-carboxylic acid (DHICA)-melanin [solely composed of DHICA monomers, (b)]. Adapted with permission from Ref. 12. Wiley–VCH, 2013.

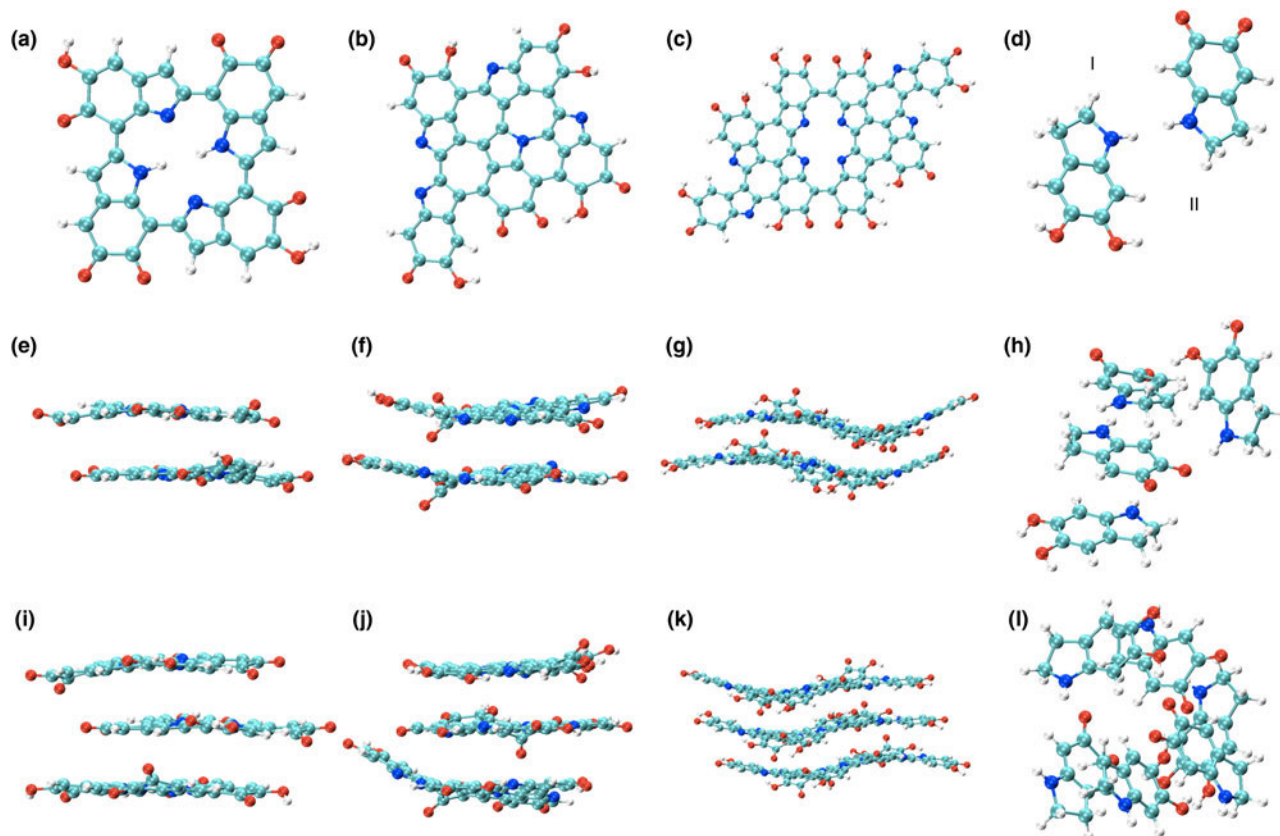


Figure 3. Molecular models and equilibrium structures of small-scale systems in eumelanin. (a) Tetrameric model proposed by Kaxiras et al.;^[14] (b) pentameric model, and (c) octameric models proposed by Chen et al. in Refs. 21 and 22 in Ref. 18 (d) monomeric model proposed by Dreyer et al. in Ref. 33 in Ref. 18. Reduced (I) and oxidized (II) forms of the 5,6-dihydroxyindole (DHI) monomer. Two-layer stacked structure of the (e) tetrameric model, (f) pentameric model, and (g) octameric model, respectively. (h) Two-set (two I monomers and two II monomers) stacked structure of the monomeric model. Three-layer stacked structure of the: (i) tetrameric model, (j) pentameric model, and (k) octameric model, respectively. (l) Three-set (three I monomers and three II monomers) stacked structure of the monomeric model. Reprinted with permission from Ref. 18. Nature Publishing Group, 2014.

Electrical response of eumelanin: amorphous semiconductor model, mixed ionic–electronic conduction, electrochemical interfacial processes, and energy storage

Biologic materials, such as proteins, peptides, and melanin, occur naturally in hydrated environments, such that their electrical response includes an important contribution from water-assisted proton transport.^[31–34] The electrical properties of eumelanin have fascinated scientists since the late 1960s. After the observation of a reversible resistive switching in eumelanin pellets reported in 1974 by McGinness et al.,^[35] the amorphous semiconductor model was adopted to explain the strong hydration dependence of the conductivity. This model considered the increase of the dielectric constant of eumelanin pellets with the increase of the humidity level to explain the decreased activation energy for charge-carrier hopping. Recently, Mostert and co-workers demonstrated that the amorphous semiconductor model does not properly describe the hydration-dependent conductivity of eumelanin pellets. The presence of a comproportionation equilibrium between the reduced (hydroquinone) and oxidized (quinone) forms of

eumelanin to give two semiquinones (intermediate redox species) (Fig. 1) would make eumelanin a mixed ionic–electronic material.^[21, 23, 36] Wünsche et al. proposed an explanation of the charge-carrier transport properties of hydrated eumelanin thin films included between metal electrodes with an interplay between proton migration, interfacial metal electrode/eumelanin charge transfer (redox) processes, and electronic transport^[37, 38] (Fig. 4). The favorable proton conduction properties of eumelanin have been recently used to demonstrate melanin-based supercapacitors, working in slightly acidic aqueous media, in the absence of metal cations with a well-established affinity for melanin.^[39]

Eumelanin and metals: ion chelation in biologic systems, eumelanin/metal electrode interfaces for memory devices, self-assembly on metallic surfaces

The affinity of melanin with pharmaceutical organic compounds has been intensively studied in the past 60 years.^[40] Its role in the accumulation and release of metal cations in vivo, such as

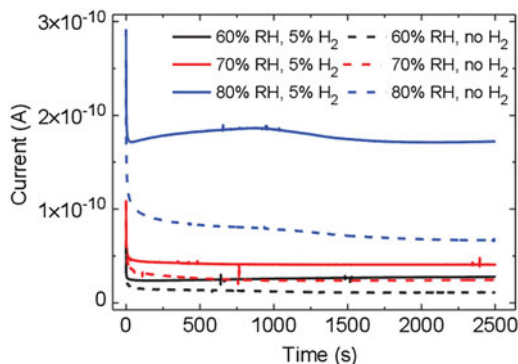


Figure 4. Transient current measurements of a eumelanin film ($d = 50$ nm) with Pd electrodes (electron injecting) and PdHx (proton and electron injecting) contacts ($L = 9$ μm , $W = 20$ μm) at 60, 70, and 80% relative humidity (RH). The applied bias is 0.5 V. Reprinted with permission from Ref. 37. American Chemical Society, 2015.

calcium,^[7, 41] copper,^[42] zinc,^[42, 43] manganese,^[44] iron, and other metals,^[42, 45, 46] has received great attention, too. The uranyl oxycation has been used to reveal, by scanning electron microscopy (SEM), the presence of eumelanin deposited on carbon-based electrodes in supercapacitors.^[39]

The primary binding site for a specific cation with respect to a building block is its most favorable group for binding; if a primary binding site is already occupied, binding will then take place at a secondary binding site.^[47] Ion binding includes coulombic electrostatic interactions as well as coordination, possibly through chelation (multidentate binding, from Greek $\chi\eta\lambda\acute{\eta}$, *chelè*, meaning “claw”). The amine and catechol hydroxyl groups of DHI and DHICA as well as the carboxylic group of DHICA can work as primary or secondary binding sites for metal cations^[11, 48]; factors determining the binding site for each cation are mainly the type of eumelanin (natural or synthetic) and the pH (Table I). Crucial features of melanogenesis, such as the rate of formation of eumelanin^[49] and the relative percentage of the two indolic building blocks present (DHI versus DHICA),^[50, 51] are influenced by the presence of metal ions. Whether their influence on self-assembly and structure is significant^[52, 53] or not^[54] is still a matter of debate.

Neuromelanin, another class of melanins, is a black insoluble pigment found in some (but not all) dopaminergic neurons of three regions of the brain: the “substantia nigra” of the midbrain (where it derives from dopamine), the “locus coeruleus” in the pons and small regions of the “medulla oblongata” (where it derives from noradrenaline) (Fig. 5).^[84] Neuromelanin has been reported to have a dichotomous role (adverse or protective): beneficial when it reduces the oxidative stress in the brain due to its ability to bind cations; detrimental when it exacerbates the oxidative stress releasing H_2O_2 or by reducing redox-active metals to a more reactive state.^[85–87] Particular efforts have been made in understanding the binding of iron to neuromelanin,^[76, 88–95] as iron was reported in dopaminergic neurons of Parkinsonian brains.^[8] Recently, Sepia melanin has

been identified as a suitable model to describe the binding characteristics of neuromelanin.^[84]

Lately, some studies addressed the interactions between melanin and metal electrodes,^[96, 97] after decades of focus on the melanin–metal cation affinity.^[47] Hydrated eumelanin thin films proved able to promote the formation of tree-shaped electrically conductive bridges, dendrites, when in contact with gold electrodes, under electrical bias, in a planar configuration.^[96] Once the dendrites connected one electrode to the other, the resistivity plummeted: a resistive switch took place. The factors playing a determining role are: the chelating groups of indolic building blocks, the electrical bias, the amount of water, and chlorides, whose presence is highly likely in biomaterials. The amount of water in the thin films was proven to determine two types of switches, standard and hybrid, differing by the orders of magnitude of the current increase at the resistive switch as well as by the dendrite composition (pure gold versus gold–eumelanin complexes)^[97] (Fig. 6).

The mechanism of formation of the electrically conductive bridges in hydrated eumelanin thin films is strikingly similar to the working mechanism of resistive switching devices based on electrochemical metallization (electrochemical metallization memory cells).^[98] Here, melanin could be considered as biodegradable ion conductor,^[99] for the development of “green” non-volatile resistive switching memories.

The binding of the biopigment to monovalent and multivalent cations has been recently exploited in melanin-based electrochemical storage devices.^[58, 79]

Polydopamine, a synthetic melanin analog, has been used to selectively extract and separate metal cations from aqueous solutions, leveraging on the different binding affinities of the pigments toward different cations.^[67, 100, 101] Films of polydopamine can reduce Ag^+ cations into Ag nanoparticles, which impart antibacterial properties to the same films.^[83]

Self-assembled molecular networks of indole-2-carboxylic acid (I2CA, i.e., melanin’s monomer DHICA lacking the two hydroxyl phenolic groups) have been investigated on Au (111) surfaces: I2CA showed, both in ultrahigh vacuum and at liquid/solid interfaces, hydrogen-bonded assemblies from molecular dimers,^[102] the next step being the same study with DHI and DHICA. This study represents an important contribution in understanding, at the nanoscale, the process of formation of melanin, from the building blocks to the polymers.

Melanin/metal oxides interfaces: adhesion, biocompatibility, and photosensitization technologies

The underpinning of emerging technologies making use of interfaces between melanin and metal oxides is melanin biocompatibility together with its optical absorption and charge-carrier transport properties. Such interfaces are largely undiscovered since the poor processability of melanin thwarts contact between the pigment and the surface of the oxides. Nevertheless, promising results have been obtained with synthetic melanin-like polymers, e.g., polydopamine.^[10, 103]

Table I. Molecular sites used by the indicated metal cations to bind to the melanin biopigments (synthetic and natural); dopa, 3,4-dihydroxyphenyl-alanine; 5,6-dimethoxyindole-2-carboxylic acid (DMICA)-melanin, synthetic melanin-like material from the oxidative polymerization of DMICA.

Metal cation	Binding site		
	Hydroxyl group	Carboxylic group	Amine
Zn ²⁺	L-dopa ^[43, 55]	Natural (Sepia, ^[48, 56] bovine eye ^[41])	5,6-Dihydroxyindole (DHI)-melanin (QI) ^[57]
Mg ²⁺	Natural (Sepia ^[58])	Natural (bovine eye, ^[41, 45] Sepia, ^[48, 56, 59] squid ^[60]), dopa-melanin ^[45]	
Ca ²⁺		Natural (bovine eye, ^[41, 45] Sepia, ^[48, 56, 59, 61] squid ^[60]), dopa-melanin ^[45]	
Fe ³⁺	Natural (Sepia, ^[56, 59, 62] human hair, ^[63] black rabbit hair ^[64]), neuromelanin, ^[65–67] dopa, ^[68–70] catechols, ^[71] polydopamine, ^[72–74] DHI-melanin, ^[63] melanin from cys-dopamine, ^[75] diethylamine–dopamine–melanin ^[74]	Neuromelanin, ^[76] dopa-melanin, ^[74] natural (Sepia), ^[74] diethylamine–dopamine–melanin ^[74]	Natural (Sepia), ^[56] neuromelanin, ^[76] melanin from cys-dopamine, ^[75] polydopamine, ^[74] diethylamine–dopamine–melanin ^[74]
Cu ²⁺	L-dopa, ^[55] natural (Sepia, ^[48, 56] bovine eye, ^[77] black rabbit hair ^[64]), catechol melanin, ^[25] dopa-melanin ^[25]	Natural [bovine eye, ^[45, 77] Sepia (secondary)], ^[48] dopa-melanin, ^[25, 45, 65, 66] catechol melanin ^[25]	Natural [bovine eye, ^[77] Sepia (secondary)], ^[48] DHI-melanin (QI), ^[57] L-dopa, ^[55] dopa-melanin ^[25, 66]
Ni ²⁺	Natural [bovine eye (secondary)] ^[76]	Natural (bovine eye), ^[45, 76] dopa-melanin ^[45]	L-dopa ^[55]
Co ²⁺	L-dopa, ^[55] natural (black rabbit hair) ^[64]	Dopa-melanin, ^[45] natural (bovine eye) ^[45]	
Pb ²⁺	Natural (squid ^[60])	Dopa-melanin, ^[78] natural (mouse melanoma) ^[78]	Natural (squid) ^[60]
Cs ⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Rb ⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
K ⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	Tyrosine-melanin (Sigma) ^[52]
Na ⁺		Natural (bovine eye, ^[45] squid, ^[60] Sepia ^[79]), dopa-melanin, ^[45] tyrosine–melanin (Sigma), ^[79] DMICA-melanin ^[79, 80]	Tyrosine–melanin (Sigma), ^[79] sepia, ^[79] DMICA-melanin ^[79, 80]
Li ⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Ba ²⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Sr ²⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Tl ⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Mn ²⁺	Dopa-melanin ^[81]	Natural (bovine eye), ^[45] dopa-melanin ^[45, 81]	Dopa-melanin ^[81]
La ³⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Gd ³⁺		Natural (bovine eye), ^[45] dopa-melanin ^[45]	
Cd ²⁺		Natural (squid ^[60])	
Al ³⁺	Dopa-melanin ^[81]	Dopa-melanin ^[81]	Dopa-melanin ^[81]
Uranium (uranyl oxycation)		Dopa-melanin ^[46]	
Vanadium (vanadyl oxycation)	Dopa-melanin ^[66]		

Continued

Table I. Continued

Metal cation	Binding site		
	Hydroxyl group	Carboxylic group	Amine
Au ⁺	Catechol (binding as organometallic complex) ^[82]		
Ag ⁺	Polydopamine ^[83]		

Adhesive proteins (rich in dopa and lysine amino acids) present in *Mytilus edulis* (mussels) inspired a method of making polydopamine coatings, featuring catechol (ortho-hydroquinone of dopa) and amine (lysine) functions, through simple dip coating in aqueous solutions of dopamine on a wide range of materials, including metal oxides.^[9, 104]

Based on its ion-chelating properties, polydopamine has been used as a template to assemble nanoarchitectures^[105, 106] and core (inorganic)-shell (polydopamine) nanoparticles.^[10, 107] Fe₃O₄-polydopamine core-shell nanoparticles have been used for a wide range of technologic applications,^[108, 109] including peroxidase-like catalysis for treatment of industrial waste and environmental monitoring.^[110] Superhydrophobic and superoleophilic particles, obtained by modification with low surface energy materials of Fe₃O₄ on polydopamine particles have been used for oil/water separation.^[111] Iminodiacetic acid-Cu functionalized core-satellite Fe₃O₄/polydopamine/Au magnetic nanocomposites have been used for protein detection.^[112]

Multifunctional nanocomposites can integrate sensing, diagnostic, and therapeutic functions into a single nanostructure. Fe₃O₄-polydopamine core-shell nanocomposites have been fabricated through in situ polymerization. Their ability to act as theranostic agents for intracellular mRNA detection and multimodal imaging-guided photothermal therapy has been reported.^[113, 114] This work exploited polydopamine near-infrared absorption, high fluorescence quenching efficiency and the availability of a surface for further functionalization with biomolecules.

Graeff and co-workers prepared melanin-like/V₂O₅-layered hybrids for application in optoelectronics and electrochemistry, starting from dopa.^[115] The presence of melanin-like units induced the reduction of V⁵⁺ ions to V⁴⁺ ions. The melanin insertion was observed to increase the stability and reproducibility of Li⁺ electrochemical insertion/de-insertion.

Well-investigated metal oxide semiconductors, such as TiO₂, have been coupled to melanin or melanin-like polymers

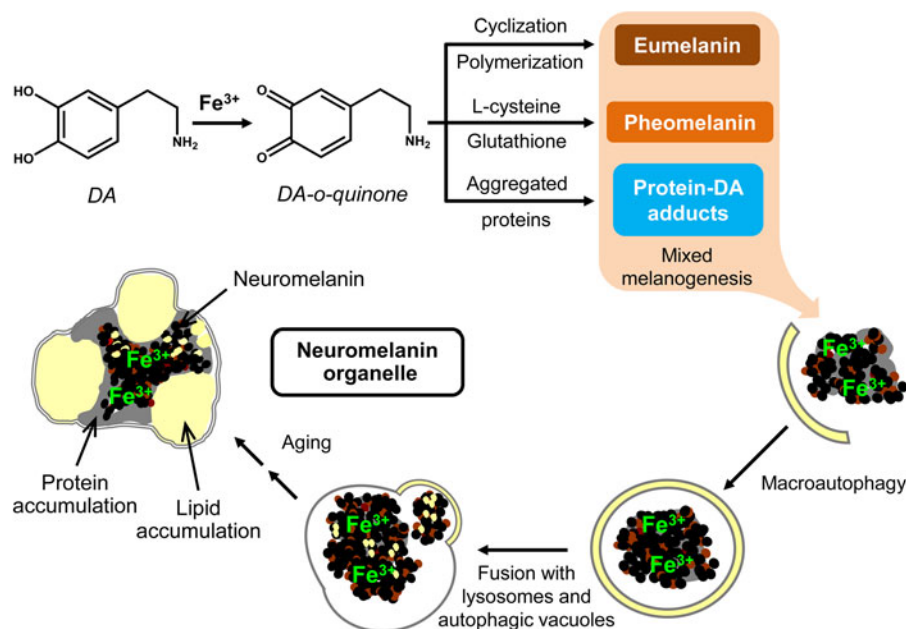


Figure 5. Possible neuromelanin formation mechanism. Reprinted with permission from Ref. 85. Elsevier, 2015.

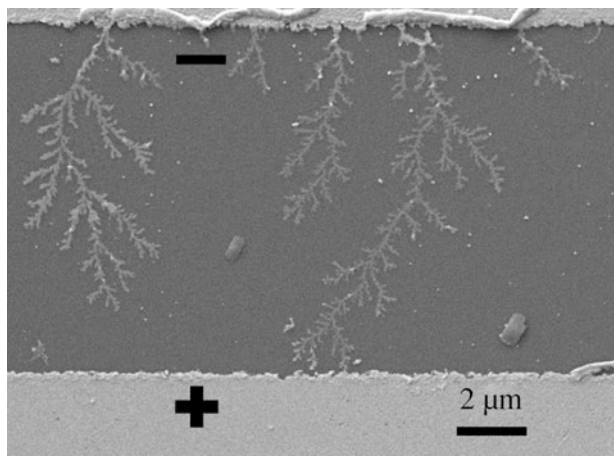


Figure 6. Scanning electron microscopy (SEM) image of dendrites bridging one electrode to the other after 3 h of electrical bias at 1 V in a thin film of *Sepia eumelanin* (7 wt.% Cl^-), hydrated for 1 h at 90% relative humidity (RH), deposited between Au electrodes (10 μm interelectrode distance). The resistive switch took place after 34 min. SEM voltage 5 kV. Reprinted with permission from Ref. 97. Royal Society of Chemistry, 2016.

for applications in solar energy conversion/storage. Purified natural melanin from squid ink and mussel-inspired synthetic polydopamine have been used as dyes in dye-sensitized solar cells.^[103, 116] Polydopamine/ TiO_2 nanocomposites and plasmonic structures fabricated exploiting the reducing properties of polydopamine have been used for photocatalytic applications.^[117–119]

The biocompatibility and optical properties featured by TiO_2 have been used for self-cleaning, self-sterilization, and photolithography purposes^[120, 121] and also in fields such as cosmetics, where TiO_2 has been used as filler and

UV-filter.^[122] To ensure transparency to cosmetic formulations, the average dimension of TiO_2 particles has been typically of the order of 10–20 nm. Safety concerns about nano- TiO_2 -based products have been raised.^[123–125] Reports suggest that TiO_2 nanoparticles do not penetrate the intact epidermal barrier,^[126, 127] with no evidence of significant penetration beyond the stratum corneum.^[128] Melanin is used in cosmetic products, sometimes in combination with photoactive oxides. Melanin (both synthetic and natural)– TiO_2 interactions have been investigated,^[129–131] in particular the photocatalytic activity of TiO_2 on the process of DHICA polymerization (Fig. 7).^[132]

To conclude this Prospective article highlighting the exciting achievements reported in the field of melanin-based materials in recent years, we would like to emphasize the importance of an interdisciplinary approach for melanin research, where materials chemistry, physical chemistry, and materials physics all must be considered to effectively advance both the understanding of fundamental process in electrochemistry, photophysics, and transport physics, and the development of sustainable technologies. We believe this holistic approach will contribute to the advancement of knowledge about the functional properties of melanin-based materials in biologic systems.

At the fundamental level, exciting challenges loom for the melanin research community, such as (i) understanding the electron transfer processes in different electrolytes for sensing (and biosensing) as well as energy conversion/storage; (ii) advancing the knowledge of electron transport and proton transport in quasi-solid state for applications in (bio)electronics, e.g., protonic devices, edible devices, and transient electronics; (iii) gaining further insights into the nature of chromophoric units of melanin for photoprotection and solar energy conversion; (iv) establishing biocompatibility and biodegradability

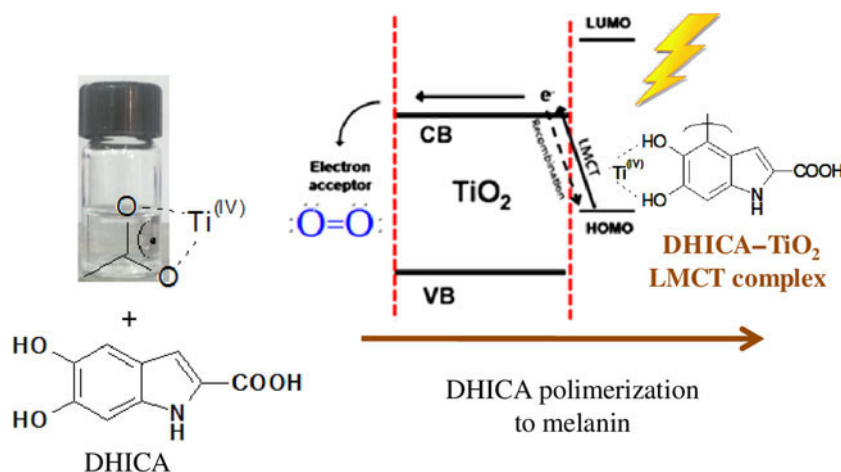


Figure 7. Photocatalytic activity of TiO_2 for 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerization and formation of melanin– TiO_2 hybrid nanostructures with biocide behavior. Adapted with permission from Ref. 132. American Chemical Society, 2016.

according to international standards; and (v) quantifying the physicochemical parameters defining ion binding for ion separation and water treatment.

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