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Elucidating the Structure of Poly(dopamine)

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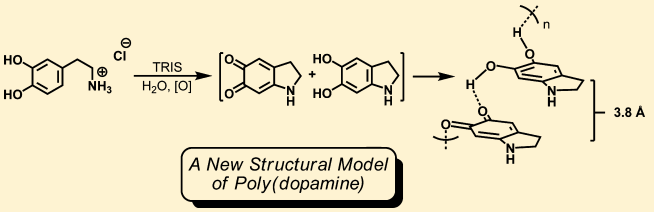
Supporting Information

ABSTRACT: Herein we propose a new structure for poly(dopamine), a synthetic eumelanin that has found broad utility as an antifouling agent. Commercially available 3-hydroxytyramine hydrochloride (dopamine HCl) was polymerized under aerobic, aqueous conditions using tris(hydroxymethyl)aminomethane (TRIS) as a basic polymerization initiator, affording a darkly colored powder product upon isolation. The polymer was analyzed using a variety of solid state spectroscopic and crystallographic techniques. Collectively, the data showed that in contrast to previously proposed models, poly(dopamine) is not a covalent polymer but instead a supramolecular aggregate of monomers (consisting primarily of 5,6-dihydroxyindoline and its dione derivative) that are held together through a combination of charge transfer, π-stacking, and hydrogen bonding interactions.



INTRODUCTION

Poly(dopamine) has drawn interest recently as a universal surface modification agent for use in a broad range of biotechnology,[1−3] electrochemical,[4,5] nanotechnology,[6,7] and membrane[8,9] applications. As elegantly demonstrated by Messersmith and co-workers, diverse substrates, including metals, metal oxides, ceramics, synthetic polymers, and a wide range of other hydrophilic and hydrophobic materials, may be coated with poly(dopamine) via treatment of a surface with a tris(hydroxymethyl)aminomethane hydrochloride (TRIS HCl) buffered dopamine solution.[10,11] The poly(dopamine) coatings obtained from this methodology are typically thin (tens of nm), highly robust and have shown utility as a platform for the conjugation of synthetic polymers[8,11] or biomolecules,[11−13] and for electroless metallization.[10] Unlike other techniques, such as layer-by-layer assembly, monolayer self-assembly, and Langmuir−Blodgett deposition, surface modification with poly(dopamine) requires only a single step.[11]

Despite its remarkable properties and ease of preparation, the molecular structure of poly(dopamine) has yet to be unambiguously determined, making further optimization difficult. In their report on surface modification by dip-coating substrates in dopamine solutions, Messersmith and co-workers suggested a structure (**I**) wherein oxidized and cyclized dopamine monomers were covalently joined via aryl−aryl linkages (Figure 1);[10] similar covalent models (**II**/**III**) have been proposed by others.[14−16] Such structures are not without precedent as similar bonding schemes had been postulated for eumelanins (a class of pigments biosynthesized in melanocytes[17]) derived from various catecholamine monomers.[18−21] Early spectroscopic studies were confounded by the fact that they focused on natural eumelanins, which were often contaminated with proteinaceous materials and other organic impurities.[22] To simplify such experiments, synthetic eumelanins have been employed in lieu of natural samples. HPLC and UV−vis absorption studies of purified tyrosine proposed that cyclization of the catecholamine to the indoline-like cyclodopa was followed by further oxidation to dopachrome (Figure 2), and ultimately covalent coupling to form oligomeric eumelanins, although the precise mechanistic details of the associated processes were not disclosed.[23] Due to the poor solubility of eumelanins, early reports concluded that the presence of these oligomers indicated that the eumelanin product contained mixtures of covalent polymers and noncovalent aggregates.[24] Such a mixed structural model has been supported more recently through DFT calculations, X-ray analyses and mass spectroscopy studies, which have suggested that covalently bound oligomers (such as **IV**) stack through $\pi-\pi$ and other noncovalent interactions to form larger supramolecular complexes rather than traditional, covalently coupled polymers.[17,25]

In contrast to the models described above, scrutiny of the literature reveals that dopamine may polymerize in a manner similar to that of hydroquinone (*p*-benzenediol) and catechol (*o*-benzenediol).[21,30−33] Beyond the structural parallels between benzenediols and catecholamines, such as an aryl core and ortho- or para-substituted diol functionality (meta-substituted benzenediols and catecholamines are unreactive under aqueous, alkaline conditions), monomers in both systems

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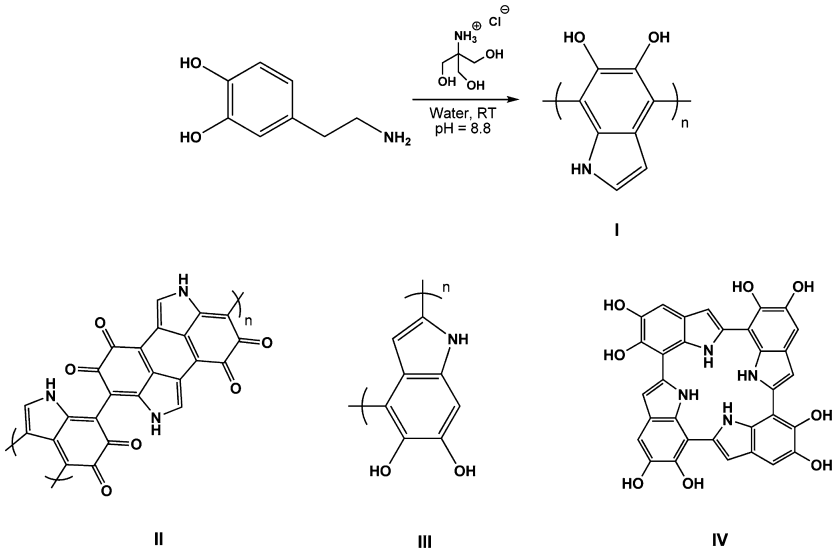

Figure 1. (Top) Synthesis and structure of poly(dopamine) as proposed by Messersmith and others[10,14] and (bottom) additional proposed structures of poly(dopamine).[17,26−29]

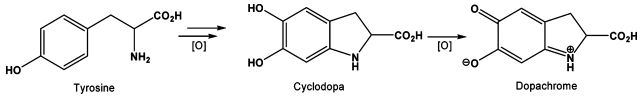

Figure 2. Proposed mechanism for the oxidative cyclization of tyrosine.

can undergo autoxidation. For example, hydroquinone and catechol polymerize under conditions similar to those for the formation of poly(dopamine) and other synthetic eumelanins (alkaline, aqueous media under an aerobic atmosphere) to afford insoluble, polymeric products.[30] Reaction of the two aforementioned diols proceeds via autoxidation, forming *p*-benzoquinone and *o*-benzoquinone, respectively.[33−35] After formation, discrete carbonyl-containing species react with residual diols via charge-transfer, hydrogen bonding, and π-stacking interactions that result in a series of 1:1 complexes commonly referred to as quinhydrones (see Figure 3).[30,36,37] The bimolecular quinhydrone complexes are known to further oligomerize or polymerize via noncovalent interactions that are similar to those described above. Although such supramolecular structures are among the most widely accepted for the quinhydrones, covalent models that feature aryl−aryl linkages have also been proposed.[38,39]

Sharing many of the complexities of quinhydrones, a significant amount of effort has been invested in identifying the structure of poly(dopamine). However, no definitive model exists. Thus, in an effort to provide direction for further optimization of poly(dopamine) for use in surface modifications, we undertook a comprehensive study of the polymer's structure and bonding. Based on a wide range of spectroscopic evidence, we propose herein a structural model for synthetic poly(dopamine) wherein the monomers are linked primarily through noncovalent interactions. Also, because poly(dopamine) is comprised of reactants that are similar to the catecholamine precursors of natural eumelanins, we further propose that poly(dopamine) may serve as a model for broadly understanding structure and bonding patterns of synthetic and naturally occurring eumelanins.[40]

RESULTS AND DISCUSSION

Poly(dopamine) was prepared in one step from commercially available 3-hydroxytyramine hydrochloride (dopamine HCl) by basifying the salt with tris(hydroxymethyl)aminomethane (TRIS; see ESI).[10] The as-prepared poly(dopamine) powder was insoluble in water (both acidic and moderately alkaline) and all common organic solvents. We were therefore restricted to solid state techniques to characterize the structure of the material obtained. Efforts began with solid state nuclear magnetic resonance (ssNMR) spectroscopy. The solid state ^{15}N NMR spectrum of the as-prepared poly(dopamine) showed a resonance at a chemical shift (δ) of −260 ppm (relative to CH_3NO_2; Figure 4), consistent with the presence of cyclized, nitrogenous species such as the indole- or indoline-type structures[41] widely proposed in many eumelanins.[42,43] For comparison, the primary, uncyclized amines of dopamine HCl and TRIS exhibited ^{15}N NMR resonances at −349 and −351 ppm, respectively, in solution (D_2O, relative to CH_3NO_2). The downfield shift of the ^{15}N resonance in poly(dopamine), as well as the absence of signals observed in the region that could be attributed to a primary amine, suggested to us that the

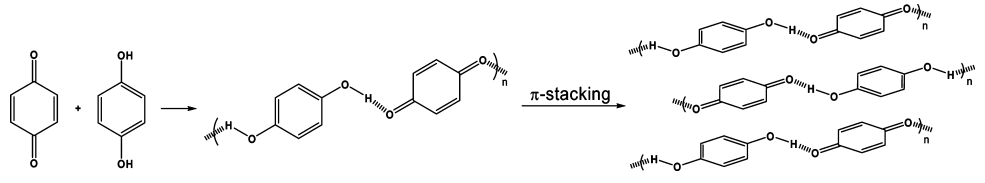

Figure 3. Formation of quinhydrones through the 1:1 complexation of benzoquinone and a diol, and the subsequent π-stacking interactions that lead to the formation of multidimensional polymeric materials.[30]

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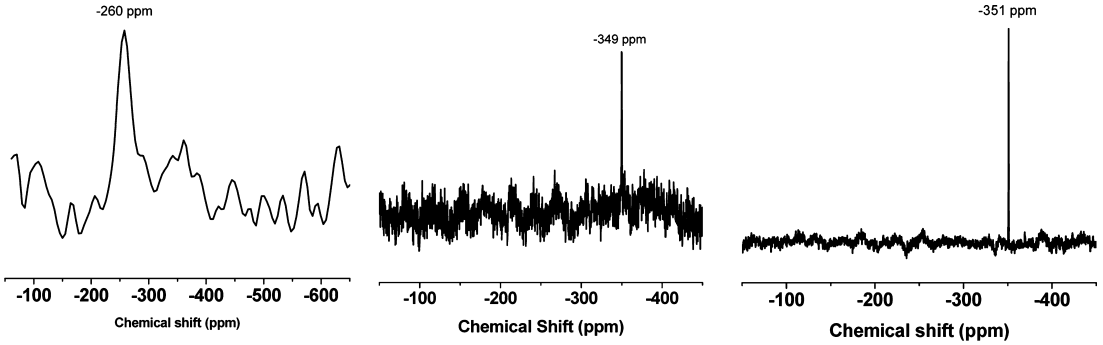

Figure 4. (Left) Solid state ^{15}N NMR spectra of poly(dopamine) (400 MHz, spinning rate: 6 kHz), (middle) solution state ^{15}N NMR of dopamine HCl (D_2O, 400 MHz), and (right) solution state ^{15}N NMR of TRIS (D_2O, 400 MHz). Chemical shifts (δ) reported relative to CH_3NO_2.

dopamine underwent cyclization during the polymerization reaction and that the TRIS reagent was not incorporated into the poly(dopamine) product to a significant extent.

One-dimensional, solid-state ^{13}C NMR spectroscopy was also performed on the as-prepared poly(dopamine) sample described above. As shown in Figure 5, the spectrum showed a pair of resonances spanning from 110 to 150 ppm, characteristic of aromatic species.[44] These signals, which were also present in the solution state spectrum of dopamine HCl (see Figure S2),[45] indicated that the aromatic ring at the core of the molecule was retained. Two other features that were not present in the solution-state spectrum of the dopamine monomer provided additional structural information. First, a resonance observed at 173 ppm indicated that the diol structure present in the starting material underwent partial or complete oxidation to its respective 1,2-dione. The oxidative formation of ketones is a hallmark of quinhydrone assembly and a key step in proposed mechanisms for the oligomerization and polymerization of catecholamines.[30,34] Second, the resonances observed between 30 and 70 ppm were assigned to aliphatic species. The upfield shift of these ^{13}C resonances, relative to unsaturated olefins, was characteristic of the saturated ethylene linker in dopamine; dehydrogenation was not observed upon cyclization, based on these NMR results. Moreover, as the aforementioned ^{15}N NMR data indicated that the nitrogen atom was part of a heterocycle, the chemical shifts of the aliphatic ^{13}C species (30−70 ppm) were consistent with the formation of a saturated indoline product, rather than an unsaturated indole.

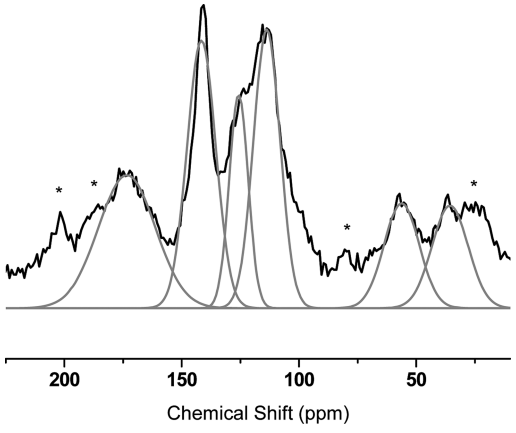

Figure 5. Solid state ^{13}C NMR spectrum of unlabeled poly(dopamine) (black) with peak deconvolutions (gray). Relative integrations of the deconvoluted peaks are given in Table 1 (asterisks denote spinning side bands).

In an effort to confirm the aforementioned NMR assignments, we sought to quantify the peak areas of each of the ^{13}C resonances. Quantitative ^{13}C ssNMR is often challenged by the long spin−lattice relaxation times of carbon nuclei in the solid state.[46−48] The relaxation times of ^{13}C nuclei in poly(dopamine), however, were found to be very short. As shown in Figure S3, ^{13}C NMR spectra collected on a poly(dopamine) sample at three different spin−lattice relaxation times (t_1 = 5, 15, and 20 s) showed no changes in peak shape or intensity, despite the presence of secondary, tertiary, and quaternary carbon centers. Such behavior indicated that the ^{13}C nuclear spin−lattice relaxation times were less than 5 s,[49] which enabled us to deconvolute and integrate the ^{13}C ssNMR resonances. The spectrum shown in Figure 5 was deconvoluted and the relative integrations of the respective signals are summarized in Table 1.

Table 1. Relative Integrations and Proposed Structural Assignments of Deconvoluted Peaks in the ^{13}C ssNMR Spectra Shown in Figure 5

peak maximum (ppm)	proposed structural assignment	relative integration (arbitrary units)
36	cyclized aliphatic carbon	1.0
53	cyclized aliphatic carbon	1.0
114	proteated arene carbons	2.0
126	quaternary bridgehead	1.1
142	quaternary bridgehead	1.2
173	oxygen-bound carbons	2.0

Based on the ssNMR data collected, we were able to identify two possible structures of poly(dopamine) (see Figure 6). These structures, with the carbon centers labeled A−H, were derived largely from the signals observed in the ^{13}C NMR spectrum.[50] The peaks centered at 36 and 53 ppm were assigned to carbons G and H, respectively (see Figure 6),[51] and in agreement with their relative integrations of 1.0 units each. The peak observed at 173 ppm was assigned to the two oxygen-bound carbons (A and B), due to the high downfield shift commonly observed in such deshielded moieties.[52] As mentioned previously, the signals in the 110 to 150 ppm range corresponded to the four remaining carbon centers in the cyclic core. Based on the proposed structure, the most downfield peak at 142 ppm, which integrated to 1.2 units, was attributed to the bridgehead carbon atom (F) that was adjacent to the electronegative nitrogen atom. Such a carbon

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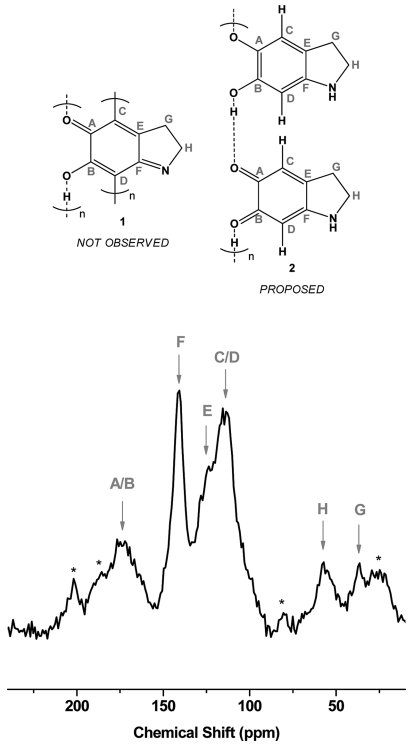

Figure 6. Possible structures of poly(dopamine) (**1** and **2**) derived from the ^{13}C NMR spectrum shown. The proposed peak assignments were based on structure **2**. The relative integrations are summarized in Table 1 and were determined via peak deconvolution. Asterisks denote spinning side bands.

center would be expected to produce a resonance further downfield than the other carbon atoms in the aromatic region. With the signal at 142 ppm assigned, only the large peak centered at 114 ppm (integration of 2.0 units) and the smaller shoulder at 126 ppm (integration of 1.1 units) remained; based on the sum of these resonances, the aforementioned signals were assigned to carbons C, D, and E. Finally, the quaternary bridgehead, carbon E, was assigned to the signal observed at 126 ppm, which left the peak at 114 ppm to be attributed to carbons C and D.

Structures **1** and **2** (Figure 6) are distinguished by the bonding to carbons C and D. In structure **1**, covalent bonds exist between the aryl rings of the monomers; in structure **2**, aryl coupling is absent and carbons C and D are bound to hydrogen atoms. The relatively upfield chemical shift of carbons C and D (114 ppm) suggested to us that these were tertiary, protonated centers rather than quaternary,[53] coupled centers, but further confirmation was desired to conclusively define the polymer's structure.

In order to examine the linkages between repeat units in greater detail, a poly(dopamine) sample was prepared using dopamine HCl that was ^{13}C-labeled (99 atom %) at the six atoms comprising the aromatic core (Figure 7); the aliphatic carbons were not labeled. Poly(dopamine) powder was

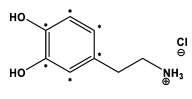

Figure 7. ^{13}C-labeled dopamine HCl used to prepared labeled poly(dopamine) (asterisks denotes the ^{13}C-labeled atoms).

prepared from a mixture of 95:5 (w/w) unlabeled:labeled dopamine HCl using the aforementioned polymerization and purification procedures (see ESI).[54] The use of an enriched sample permitted a one-dimensional cross-polarization (CP) study of the isolated aromatic core to examine the structure and bonding in the aryl moiety, with particular attention given to the presence or absence of aryl–aryl linkages between the repeat units.[55−57] An overlay of the spectra obtained with and without an additional 40 μs evolution period is shown in Figure 8.[58] Inclusion of this evolution period resulted in a diminished

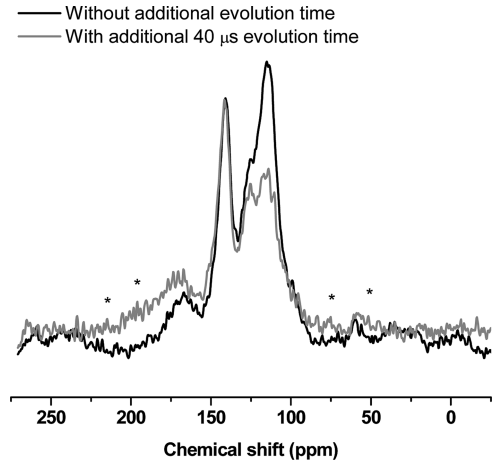

Figure 8. Solid state ^{13}C cross-polarization NMR spectra of 95:5 (w/w) unlabeled/labeled poly(dopamine) with (gray) and without (black) an additional evolution period (40 μs), resulting in perturbation of the resonances of carbons bound to hydrogens. Asterisks denote spinning side bands.

level of magnetization transfer from the hydrogens to the carbons, as partial relaxation had already occurred prior to CP. As expected for carbons free of adjacent hydrogens, the resonances at 173 (carbons A and B), 142 (carbon F), and 126 ppm (carbon E) showed no significant change in intensity. Conversely, the peak at 114 ppm, corresponding to carbons C and D located in the aromatic core, decreased in intensity upon CP. The change in signal intensity, due to diminished magnetization transfer over the extended evolution time, indicated carbons C and D were bound to hydrogen atoms. Since aryl–aryl linkages are not possible with hydrogens bound to carbons C and D, the CP study indicated that **1** was not a dominant structural motif in poly(dopamine).

Aryl–aryl coupling in a fractional amount of the monomer linkages may be ruled out through re-examination of the peak deconvolutions and integrations shown in Figure 5 and Table 1, respectively. Given the comparatively downfield chemical shifts of the other quaternary carbon centers in the polymer's structure (and comparison to model compounds such as biphenyl;[59] $\delta_{4^\circ\ \mathrm{carbon}}$ = 141 ppm), aryl–aryl coupled quaternary centers cannot be contained within the resonance at 114 ppm. Moreover, the peaks observed downfield of 114 ppm did not integrate to higher-than-expected values; likewise, the resonance at 114 ppm did not integrate to a lower-than-expected value, based on structure **2**. Thus, the close agreement of these integrations with structure **2** suggested to us that within the detection limits of the instrument and the software used to deconvolute and integrate the peaks[60] there was no spectroscopic evidence for aryl–aryl coupling between the dopamine monomers.

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Because the NMR studies suggested that covalent bonding between the monomers was not a dominant structural feature, an investigation of the noncovalent forces responsible for poly(dopamine)'s structure and bonding was undertaken. FT-IR spectroscopy of poly(dopamine) powder (KBr), shown in Figure 9, revealed peaks at 1515 and 1605 cm^{-1}, consistent with

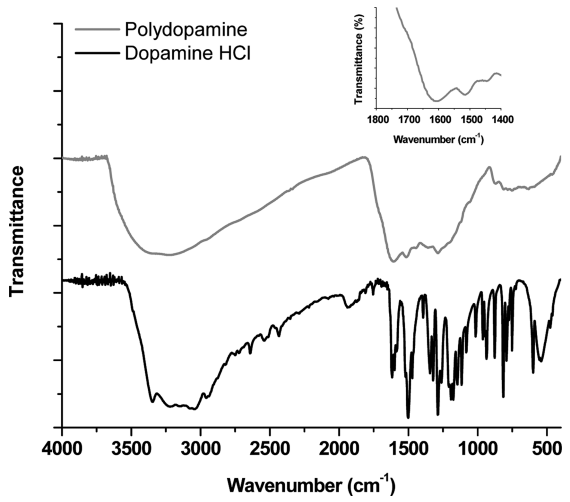

Figure 9. FT-IR spectra (KBr) of poly(dopamine) (gray, top) and dopamine HCl (black, bottom). Expansion of poly(dopamine) spectrum (inset) showing peaks at 1515 and 1605 cm^{-1}, consistent with indole or indoline structures.

the indole or indoline structures proposed earlier.[61] A large, broad peak spanning 3200−3500 cm^{-1} was consistent with the presence of hydroxyl structures as well as water.[62] No carbonyl structures were discernible from this analysis, but these absorbances might be obscured by the broad peak observed between 800 and 1750 cm^{-1}. Nearly identical spectral features were observed in poly(dopamine)-coated KBr samples (see Figure S8). Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry was also performed using a poly(dopamine)-coated steel target. The mass spectrum of the product (see Figure S12) revealed the presence of a polymeric product, as indicated by the broad range of peaks spanning m/z ratios from 888 to more than 3500. However, the separation of these peaks, often used to determine the molecular weight of a polymer's repeat unit,[50] was much lower than expected: 24, as opposed to the 149 or 151 expected for the proposed repeat units (see Figure 6). The low m/z ratios were consistent with previously reported mass spectral data for poly(dopamine) coatings (peak separations ranging from 16−26),[10,63−65] and suggested fragmentation of the monomers under MALDI conditions. Further structural determinations were not possible from these mass spectra.

Because melanin and other similar biopolymers are known to incorporate free-radical species into their structures (present as a result of charge transfer between the repeat units),[66−68] such radical moieties may constitute an important component of poly(dopamine)'s structure. Analysis of the as-prepared poly(dopamine) sample by electron paramagnetic resonance (EPR) spectroscopy revealed a single peak at a g value of 2.0036 (see Figure S9), indicating the presence of stable organic radicals in poly(dopamine)'s structure. Moreover, using a radical standard (diphenylpicrylhydrazyl, DPPH), it was determined that the spin concentration in the polymer was less than 1 spin per 25 repeat units (see ESI); the actual spin concentration may be lower as a result of signal saturation by the DPPH standard.[69] Thus, radicals are evidently present in poly(dopamine) and may play a role in the polymer's formation, structure and bonding.[70] The observation of free radical species in the product may also indicate that the previously described oxidation[71] and cyclization[72,73] processes occur via radical pathways.

The data described above suggested to us that the as-prepared poly(dopamine) samples were composed primarily of noncovalent bonding interactions, including hydrogen bonding and charge transfer, as has been observed in other robust, synthetic or biological, supramolecular polymers and materials.[74−80] To further support such a noncovalent model, poly(dopamine) powder was reacted with aqueous sodium hypochlorite (NaOCl, 5−6%) or potassium periodate (KIO_4, saturated solution), both of which are commonly used for oxidizing alcohols to their corresponding carbonyls.[81−83] We hypothesized that if poly(dopamine) was comprised of monomers bound by charge transfer, hydrogen bonding, or other supramolecular interactions (Figure 10), oxidation of the mixture to the corresponding diones would be expected to degrade the polymer, allowing for analysis of small molecule products. Upon reaction with either of the aforementioned oxidants, the otherwise insoluble powder dissolved into the aqueous medium and transitioned from dark brown to clear and nearly colorless. The material was then extracted from the aqueous solution using THF (a solvent immiscible with the aqueous, hypochlorite solution of the degraded product), and the solvent was removed under vacuum. Analysis of the crude degradation product by FT-IR spectroscopy (see Figure S7) revealed the formation of carbonyl structures as evidenced by the absorbances observed at 1715 and 1770 cm^{-1}, and consistent with the oxidation of the alcohols or semiquinones present in poly(dopamine) to their corresponding carbonyls (Figure 10). Further analysis of the product by ^1H NMR and ESI mass spectroscopy revealed a complex mixture of products, however, possibly as a result of incomplete oxidation of the polymer or over-oxidation of the degradation product(s).

Previous studies have suggested the presence of extended $\pi-\pi$ stacking interactions between oligomeric units in eumelanins and quinhydrones.[84] To investigate the possible existence of such long-range order in poly(dopamine), we performed powder X-ray diffraction (PXRD) on a solid state, as-prepared sample. The resultant spectrum (Figure S5) showed a broad peak centered at 2θ = 23.4°, corresponding

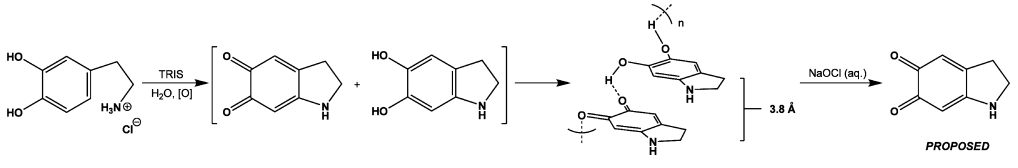

Figure 10. Proposed formation and structure of poly(dopamine), as well as oxidation to the corresponding dione upon exposure to aqueous NaOCl.

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to a *d*-spacing of approximately 3.8 Å. Such spacing was consistent with other π-stacked structures[85] and may facilitate, or be a result of, charge transfer between the faces of the poly(dopamine) monomers.[86] Additionally, in conjunction with the noncovalent interactions provided by the hydrogen bonding between oxidized and unoxidized repeat units (including through the N−H bond of the heterocycle), π-stacking provides a route for the formation of polymeric aggregates (Figure 11). Similar macroscopic ordering through a

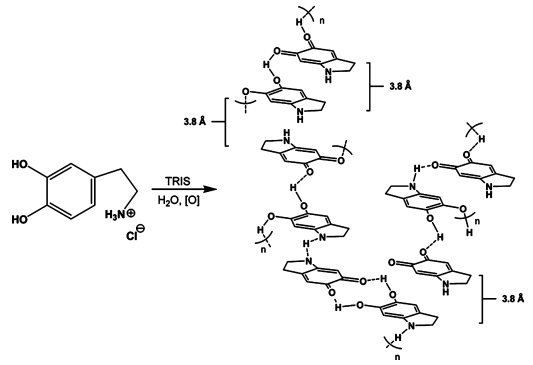

Figure 11. Upon reaction of dopamine HCl with TRIS in aerobic aqueous media, the resultant poly(dopamine) material is proposed to be comprised of intra- and interchain noncovalent interactions, including hydrogen bonding, π-stacking, and charge transfer.

combination of hydrogen bonding and π-stacking has been described previously in a wide range of polymeric and crystalline structures.[87−90] Though noncovalent in nature, these bonding arrangements are strong and in the case of poly(dopamine) explains its insolubility as well as its remarkable stability as a coating.[3,10,15]

CONCLUSIONS

Using a broad range of solid state spectroscopic techniques, we have shown that the repeat units present in poly(dopamine), prepared in powder form under aerobic, alkaline conditions, consist primarily of noncovalent interactions. Such a model is in agreement with many previously reported studies on quinhydrones and other similar macromolecules,[30,34,38,39] but contrasts with contemporary reports proposing covalent bonds between the repeat units in poly(dopamine). Solid state ^{15}N NMR spectroscopy confirmed the formation of a heterocyclic species, and solid state CP ^{13}C NMR experiments indicated the presence of hydrogens bound to the aryl core of the polymer. Additionally, PXRD analysis indicated that the monomers formed stacked structures with a *d*-spacing (3.8 Å) consistent with that observed in other π-stacked materials.[85] Collectively, these results show that poly(dopamine) is not a covalently bound polymer but instead an aggregate of monomers held together by strong, noncovalent forces including charge transfer, π-stacking, and hydrogen bonding. The combination of these noncovalent interactions (all of which have been observed in quinhydrones,[30,36,37] which form similarly robust and insoluble materials) results in the high stability of poly(dopamine) coatings as well as its insolubility.

The similarities between dopamine polymerization and that of eumelanins and quinhydrones are of particular interest, and the insights acquired here may be of broad applicability and provide a deeper fundamental understanding of how these materials are formed. We propose that there are three characteristic steps which govern the formation of eumelanins (synthetic or natural) and quinhydrones: (1) aerobic oxidation of phenolic hydroxyls to carbonyls, (2) cyclization of a pendant amine, if one is present, to form a 5-membered α-hydroxyketone (which may then intermolecularly disproportionate to diol and dione intermediates, as shown in Figure 10), and (3) polymerization *via* charge transfer, hydrogen bonding, and/or π-stacking. In addition to exploring the fundamental structure and reactivity of this ubiquitous class of biopolymers, the spectroscopic results described herein may lead to new and previously unidentified routes toward optimizing the polymers' properties (e.g., biocidal activity, stability to chemical reagents such as halogens, etc.). For example, the use of functionalized derivatives of dopamine (i.e., 3-hydroxytyramine) or other catecholamines may allow for routes to improving the eumelanin's antifouling behavior, while retaining the ability of these monomers to be polymerized. Additionally, derivatives of dopamine that have increased numbers of hydrogen bond donors or acceptors, such as DOPA, which bears a pendant carboxylic acid moiety, may exhibit improved surface adhesion or resistance to chemical degradation.

ASSOCIATED CONTENT

Supporting Information

Synthetic details, optimization studies, and additional spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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