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Photooxidase-Mimicking Nanovesicles with Superior Photocatalytic Activity and Stability Based on Amphiphilic Amino Acid and Phthalocyanine Co-Assembly

Jingjing Han⁺, Kai Liu⁺, Rui Chang, Luyang Zhao, and Xuehai Yan*

Abstract: Enzyme mimics have broad applications in catalysis and can assist elucidation of the catalytic mechanism of natural enzymes. However, challenges arise from the design of catalytic sites, the selection of host molecules, and their integration into active three-dimensional structures. Herein, we describe the development of a photooxidase mimic by synergetic molecular self-assembly. 9-Fluorenylmethoxycarbonyl-L-histidine undergoes efficient co-assembly with phthalocyanine into nanovesicles with tunable particle size and membrane thickness. The obtained nanovesicles can be used as catalysts for reactive-oxygen-mediated photosensitive oxidation with improved efficiency and stability. This work highlights the co-assembly of simple building blocks into a supramolecular photocatalyst, which might give insight into possible evolutionary paths of photocatalytic membrane systems, and might allow facile transfer into photosensitive nanoreactors or artificial organelles.

The superior catalytic activity of natural enzymes has motivated scientists to construct enzyme mimics to overcome their inherently low stability.^[1] The most reasonable design strategy has been suggested to be rather minimalist as only the features of the enzyme that are essential for catalytic efficiency are considered.^[2] For most reported enzyme mimics, the catalytic moiety generally consists of inorganic minerals,^[3] metal complexes,^[4] or organic cofactors,^[5] with a protein,^[6] peptide fiber,^[7] or polymer^[8] acting as the host.

Although great advances have been made, the organization of a catalytic center into a three-dimensional active architecture still remains a great challenge, which heavily depends on the chemical conjunction of the active site and the host molecules.^[9] The assembly of an active site and a host matrix by harnessing non-covalent intermolecular interactions is an efficient approach to fabricate supramolecular catalysts.^[10] The photooxidase in spinach chloroplasts can catalyze the photooxidation of electron donors (e.g., cytochrome c).^[11] The active factor of photooxidase is a chlorophyll-lipoprotein complex (Scheme 1a).^[12] The design and construction of photooxidase mimics will have broad application prospects, including for organic synthesis,^[13] environmental protection,^[14] and photodynamic therapy,^[15] and can help build reaction models to deepen our insight into physiological photooxidation.^[16]

Phthalocyanines are promising photosensitizers owing to their good stability and visible-light responsiveness, as well as high quantum efficiency.^[17] Unfortunately, their inherent hydrophobicity renders them only active in organic solvents, which seriously limits their practical applications. Protein templates have been used to control the architectural

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Scheme 1. Schematic illustration of the nanovesicle fabrication process, and a model of reactive oxygen species mediated photosensitive oxidation. a) The reductionist building blocks were inspired by lipoprotein and chlorophyll, as a representative natural photooxidase. b) Thylakoid membrane structures that host the cytochrome served as inspiration for the design of the enzyme mimics. c) Precisely tuned nanovesicles were applied for the conversion of dopamine into leucodopaminechrome; the co-assembly of phthalocyanine (green) and the amphiphilic amino acid (purple) was enabled by multiple weak intermolecular interactions.

organization of pigments through skilled site-specific mutagenesis/synthesis of the binding site,^[18] but the number of designed binding sites per protein is usually only one, limiting the absolute light harvesting capability. More readily available amino acid derivatives (e.g., Fmoc-modified amino acids) can co-assemble with photoactive molecules (e.g., porphyrins) to enhance their functionality because of nanoscale effects and dynamic and ordered organization.^[19] However, the photosensitization activity of these assemblies is inhibited because of competitive intermolecular photochemical processes (e.g., fluorescence quenching,^[19a] energy transfer,^[19b,c] and charge separation^[19d]). Biological membranes are elegant structures that mediate matter transport and energy transfer, for example, photosynthesis on the thylakoid membrane (Scheme 1b).^[20] Amphiphilic photosensitizers have been proven to be most efficient after partition and insertion into lipids,^[21] suggesting that a membrane structure can facilitate the recovery of their photoactivity. However, the parameters for vesicle-forming amphiphiles are strict, and thus synthetic high-molecular-weight copolymers are mostly used.^[22] Charge-balancing mixtures of cationic and anionic surfactants can generate multicomponent vesicles,^[23] suggesting that membrane structures can be generated by co-assembly.

Herein, we describe the fabrication of photooxidase-mimicking nanovesicles through the co-assembly of an amphiphilic amino acid and phthalocyanine. The nanovesicles can act as a host to precisely tune the organization of phthalocyanine, enabling the arrangement of phthalocyanine molecules into a membrane structure and restricting their serious self-aggregation based on multiple intermolecular interactions with amphiphilic amino acids. This architecture enhances the photosensitization activity and photostability of phthalocyanine compared to the free form in aqueous solution, which was confirmed through the aerobic photo-oxidation of dopamine. The nanovesicles are made up of simplified components of natural photooxidase (amino acid vs. lipoprotein; phthalocyanine vs. chlorophyll), and show an analogous catalytic mechanism in photosensitized oxidation; therefore, they can be regarded as supramolecular photo-oxidase mimics.

Histidine is a natural amino acid with an imidazole functional group bearing a nitrogen lone pair, which provides potential binding sites (e.g., through electrostatic and hydrogen-bonding interactions). Therefore, *N*- α -(9-fluorenylmethoxycarbonyl)-L-histidine (Fmoc-His-OH) was chosen as the amphiphilic amino acid model. With negatively charged peripheral groups and a hydrophobic core, phthalocyanine tetrasulfonic acid (Pc) was used as the amphiphilic phthalocyanine model. After mixing Fmoc-His-OH and Pc at a molar ratio of 1:0.08, oval nanospheres were obtained with an average diameter of 142 nm (Figure 1a). The hydration radius (155.2 nm; PDI: 0.257) is larger than that measured upon vacuum drying because of the solvent effect.^[24] In a high resolution transmission electron microscopy (HRTEM) image, a light center and the periphery contrast with a wall thickness of 15 nm can be clearly observed (Figure 1b), which is indicative of hollow structure. The height-to-diameter ratio is almost 1:10 (horizontal distance: 142 nm; vertical distance:

Figure 1. a) TEM and b) HRTEM images of co-assembled nanovesicles resulting from a mixture of Pc (0.21 mM) and Fmoc-His-OH (2.65 mM) in water at a molar ratio of 1:0.08. A photograph of the green nanovesicle solution and the hydrodynamic radius distribution of the nanovesicles measured by DLS are also shown. c) AFM topography image of nanovesicles on a mica substrate. d) Height profile of a single nanovesicle, suggesting a height of 15 nm. e, f) TEM images of nanovesicles with Fmoc-His-OH/Pc ratios of 1:0.25 and 1:1, respectively.

15 nm) according to atomic force microscopy (AFM) analysis (Figure 1c,d), suggesting a typical vesicular morphology. Additionally, the nanovesicles possess good colloidal stability (see the Supporting Information, Figure S1), which facilitates further catalytic applications.

At an Fmoc-His-OH/Pc molar ratio of 1:0.25, the obtained nanovesicles have a loose periphery and a clear inner periphery with an average diameter of 500 nm and a wall thickness of 62.5 nm (Figure 1e). This increase in particle size and wall thickness at a higher concentration of added Pc is presumably due to the fact that more Pc molecules were integrated into the membranes of the nanovesicles, suggesting that Fmoc-His-OH can be used for the organization of varying amounts of Pc into nanovesicles. After further increasing the proportion of Pc to 1:1, the vesicular structure disappeared, and only solid nanoparticles were observed (Figure 1f). A high concentration of Pc may facilitate their self-aggregation through hydrophobic interactions and π -stacking between planar aromatic macrocycles, resulting in a collapse of the membrane structure. These results suggest that the subtle binary co-assembly of Fmoc-His-OH and Pc controls the formation of nanovesicles.

The surface of the nanovesicles is negatively charged (Figure 2a) because of the deprotonated carboxylic group of Fmoc-His-OH. As the Pc content was increased, the surface charge changed from -33.3 mV to -0.3 mV (Figure 2a),

which is indicative of a charge shielding effect. The nanovesicles strongly absorb in the visible region (620–700 nm), with a red-shift of the Q-band from 628 nm for free Pc to 638 nm, and a weak, broadened peak at 660 nm (Figure 2b),

Figure 2. a) Zeta potentials of assembled nanostructures at different initial Fmoc-His-OH/Pc ratios; the concentration of Fmoc-His was fixed to 2.65 mM and the concentration of Pc was changed from 0 to 2.65 mM. b) UV/Vis absorption spectra of nanovesicles and free Pc in aqueous solution. The concentration of Pc was fixed at 0.21 mM. c) FTIR spectra and d) XRD patterns of nanovesicle, Fmoc-His-OH, and Pc powders.

indicating the heterogeneity of Pc, presumably resulting from the hydrophobic interactions and π -stacking between the Fmoc group and aromatic macrocycles in Pc.^[19a] In the Fourier transform infrared (FTIR) spectra, the ν -NH peak was broadened and shifted from 3290 cm^{-1} to 3313 cm^{-1} (Figure 2c), which was attributed to the formation of hydrogen bonds with a proton receptor,^[19c,f] such as the sulfonic acid group of Pc in the form of $\text{S}-\text{O}\cdots\text{H}-\text{N}$. In the carboxyl vibrational region, the band moved from 1630 cm^{-1} to 1625 cm^{-1} (Figure 2c), which may be due to electrostatic repulsion between the carboxyl and sulfonic acid groups. The molecular assembly mechanism and stacking model were also confirmed by molecular simulation, which showed that a synergy of multiple intermolecular interactions are responsible for nanovesicle formation (Scheme 1c). The X-ray diffraction peaks for the nanovesicles are narrow and strong, and the positions are different from those of pure Pc and Fmoc-His-OH (Figure 2d), suggesting an ordered organized structure. According to Bragg's law, the main peak ($2\theta \approx 12.99^\circ$) indicates a wall thickness of 15 nm.

The fluorescence of the nanovesicles is nearly ten times stronger than that of free Pc (Figure 3a). Generally, the excited states of aggregated luminophores with strong π - π stacking decay or relax back to the ground state via non-radiative channels, resulting in aggregation-caused quenching (ACQ) effects.^[25] Therefore, the increased fluorescence intensity of Pc in the nanovesicles is due to the alleviation of ACQ. Heterogeneous intermolecular interactions (e.g., electrostatic and hydrophobic interactions) can help decrease

Figure 3. a) Fluorescence spectra of the nanovesicles, free Pc, and nanoparticles from Fmoc-His(1-Trp)-OH or Z-His-OBzl tuned self-assembly of Pc in aqueous solution ($\lambda_{\text{ex}} = 660 \text{ nm}$). b) Fluorescence lifetime of the nanovesicles in aqueous solution ($\lambda_{\text{ex}} = 635 \text{ nm}$). c) Time dependence of the leucodopaminechrome production catalyzed by the nanovesicles or Pc in the presence and absence of light. The concentrations of Pc and dopamine were 0.11 mM and 40 mM, respectively. d) Long-term photocatalytic performance of the nanovesicle. On and off represents the light situation.

the degree of Pc aggregation. The absolute fluorescence quantum yield of the nanovesicles is almost five times higher than that of free Pc (1.72% vs. 0.36%; see the Supporting Information, Figure S2). The fluorescence lifetime of Pc in the nanovesicles is much longer than that of free Pc (5.33 ns vs. 1.90 ns; Figure 3b), suggesting the stabilization of excited states in the membrane structure and the potential as an efficient light-harvesting collector.^[26] Fmoc-His(1-Trp)-OH (Figure S3a) or Z-His-OBzl (Figure S3b) can also tune Pc self-assembly into nanoparticles but without vesicular structures (Figure S4). These nanoparticles show severe fluorescence quenching in solution (Figure 3a). These results confirm that the membrane structure in the nanovesicles is pivotal in the fluorescence enhancement (Figure S5 and Figure S6).

The biological oxidation of dopamine has been correlated with psychotic disorders,^[27] and can be applied in materials science.^[28] Therefore, dopamine was chosen as a model substrate to illustrate the photooxidative properties of the nanovesicles. After illumination, dopamine is converted into leucodopaminechrome on the nanovesicles (Figure S7 and Figure S8). The leucodopaminechrome production rate of the nanovesicles was 69.14 $\mu\text{mol L}^{-1}$, which is two times higher than that of free Pc (34.62 $\mu\text{mol L}^{-1}$; Figure 3c). The improved photocatalytic performance is directly related to the increased generation of photoexcited states (Figure S9). Furthermore, the nanovesicles show sustainable leucodopaminechrome production in response to light illumination (Figure 3d), which is indicative of the good photostability of Pc in the nanovesicles (Figure S7 and Figure S10).

The photooxidation of dopamine positively correlates with the oxygen concentration (Figure S11a), suggesting an

aerobic photocatalytic process. We propose that the excited state of Pc in the nanovesicles is first formed after illumination and then converted into the triplet state,^[29] followed by energy transfer to molecular oxygen to generate singlet oxygen (Figure S12),^[30] while Pc returns to the ground state. Reactive oxygen species can attack dopamine to produce semiquinone radicals (Figure S11b), which facilitates leucodopaminechrome generation (Figure S13). Thus the nanovesicles can catalyze the photooxidation of dopamine into leucodopaminechrome in an analogous way to natural photooxidase.^[31]

In summary, we have designed and fabricated photooxidase mimics based on the co-assembly of amino acids and phthalocyanine. Amphiphilic amino acids can be used to precisely tune the organization of phthalocyanine into nanovesicles with a membrane structure through multiple intermolecular interactions. The formation of nanovesicles improved the photosensitization activity and photostability of phthalocyanine, and they exhibited superior and sustainable photocatalytic performance in the conversion of dopamine into leucodopaminechrome. The photooxidation process is based on the photosensitive generation of reactive oxygen. The architectural principles for photooxidase and nanovesicles are both based on molecular templates (proteins or amino acids) for the self-assembly of pigments. The catalytic site is activated by co-assembly with the amino acid host into a membrane structure, which is different from the direct binding of chlorophyll to the hydrophobic area of lipoprotein in photooxidase. The nanovesicles can mediate light harvesting and energy conversion, in analogy to the thylakoid membranes in chloroplasts. In contrast to lipid biomembranes, the nanovesicle membranes are constructed by co-assembly of low-molecular-weight molecules. This co-assembly is a promising strategy to develop supramolecular enzyme mimics with integration of active sites and host molecules in one step. Aside from their use as a photocatalyst for photooxidation, the nanovesicles have potential applications in the design of nanoreactors and artificial organelles after encapsulation of hydrophilic compounds in their aqueous cavities.^[32] This work also provides an inspiration for the creation of function-enhanced materials with flexibly tunable structures by multicomponent synergetic self-assembly.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amino acids · nanovesicles · photooxidases · phthalocyanine · self-assembly

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