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Living supramolecular polymerization realized through a biomimetic approach

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1. Introduction

1.1 Two types of supramolecular polymerization

・ Supramolecular polymers have the intriguing functions and properties that originate from the dynamic behavior and highly ordered molecular organization, and are used in many fields such as electronic and photonic fields.

・ Mechanistic studies on supramolecular polymerization have been well studied and there are two kinds of polymerization: isodesmic model and cooperative model.

→idodesmic model: In this model, every monomer addition to the growing chain is governed by a single equilibrium constant (K_I)

→cooperative model: This model is characterized by nonlinear growth due to two equilibrium constants, one for the nucleation(核生成) process(K_N) and the other for a subsequent elongation(核の生長) step(K_E), where $K_N << K_E$

1.2 Supramolecular polymerization in nature

・ Amyloid fibril(アミロイド繊維) which is the cause of Alzheimer disease and Parkinson's disease, is formed by the aggregation of misfolded abnormal protein.

・ Importantly, this aggregation process is coupled with conversion of normal protein to abnormal one. →The normal protein is kinetically stable and inert, but in the presence of the abnormal protein, the normal one rearranges its conformation to abnormal one as if it is 'infected'.

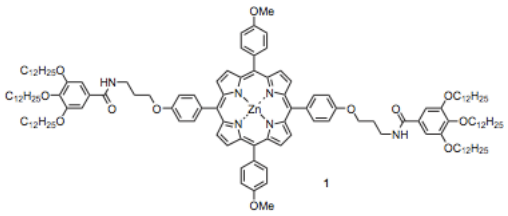
・ However, there have been no successful demonstrations of such 'infection'–like aggregation with supramolecular.

1.3 This work

・ The authors developed supramolecular assemblies that present an 'infection' phenomenon resembling the protein: that is, a porphyrin–based supramolecular assembly that transforms from a nanoparticle to nanofiber upon addition of a small amount of a nanofiber solution as the pathogen(病原体)

2. Results and discussion

2.1 The structure of the compound



- The compound which they synthesized is shown right. This compound aggregates through π–π stacking of the porphyrin andhydrogen bonding of the amide groups.

2.2 'Artificial infection' process in supramolecular polymerization

- Upon cooling a hot methylcyclohexane (MCH) solution of compound 1 ($\mathbf{1}_{mono}$), nanoparticles with a diameter of ～8 nm were formed and confirmed by AFM and DLS (Figure 1).

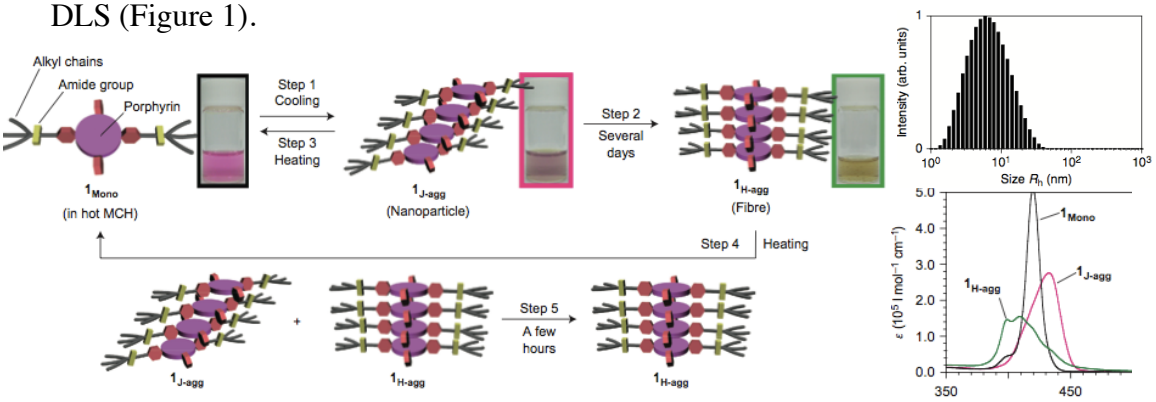


Figure 1. **Transformation, DLS, and absorption spectra of supramolecular polymer**

- The soret bond (ソーレー帯) of the nanoparticles was red–shifted in comparison with that of $\mathbf{1}_{mono}$ (Figure 1)→Porphyrin of $\mathbf{1}_{mono}$ assembles in J-aggregation ($\mathbf{1}_{J\text{-}agg}$).

- $\mathbf{1}_{J\text{-}agg}$ was stable at room temperature for three days, but eventually transformed to the H-aggregation ($\mathbf{1}_{H\text{-}agg}$), as characterized by the blue–shifted soret band. AFM shows that $\mathbf{1}_{H\text{-}agg}$ is fibrous assembly.

- This transformation ($\mathbf{1}_{J\text{-}agg}$→$\mathbf{1}_{H\text{-}agg}$) could be confirmed by a solution color change, or FT–IR which showed rearrangement of the hydrogen bonding of amide groups.

- Transformation ($\mathbf{1}_{J\text{-}agg}$→$\mathbf{1}_{H\text{-}agg}$) was accelerated by mechanical agitation such as shaking or sonication, and $\mathbf{1}_{J\text{-}agg}$ and $\mathbf{1}_{H\text{-}agg}$ can dissociate to $\mathbf{1}_{mono}$ upon heating, which then results in $\mathbf{1}_{J\text{-}agg}$ again after cooling →These processes are reversible.

- When a small amount of $\mathbf{1}_{H\text{-}agg}$ was added to $\mathbf{1}_{J\text{-}agg}$, the $\mathbf{1}_{J\text{-}agg}$ nanoparticles were converted to $\mathbf{1}_{H\text{-}agg}$ within a few hours, as if $\mathbf{1}_{J\text{-}agg}$ had been infected with $\mathbf{1}_{H\text{-}agg}$.

2.3 Investigation of transformation mechanism

- They investigated the transformation of $\mathbf{1}_{\text{J-agg}}$ to $\mathbf{1}_{\text{H-agg}}$ by monitoring changes in the absorption spectrum in detail. The transformation of $\mathbf{1}_{\text{J-agg}}$ to $\mathbf{1}_{\text{H-agg}}$ (Figure 2) exhibited nonlinear transition (i) which is characteristic of autocatalytic process; the formed $\mathbf{1}_{\text{H-agg}}$ accelerates its own propagation (増殖). Hence, the transformation consists of the two kinetics of nucleation and elongation of $\mathbf{1}_{\text{H-agg}}$.

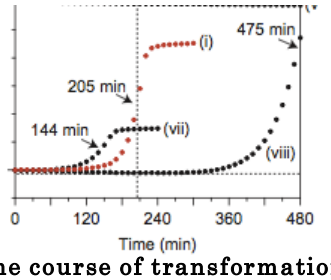


Figure 2. **Time course of transformation**

- The time of the transformation was dependent on the initial concentration of $\mathbf{1}_{\text{mono}}$. The time required for fibril formation to reach 50% completion became shorter as the total concentration of $\mathbf{1}_{\text{mono}}$ decrease ((i) 5×10^{-5} M, (vii) 2×10^{-5} M, (viii) 10×10^{-5} M in Figure 2); this 'inverted' dependence has been observed experimentally in the aggregation of the protein.

- The individual formation mechanisms of $\mathbf{1}_{\text{J-agg}}$ (step 1) and $\mathbf{1}_{\text{H-agg}}$ (step 4) were each investigated by temperature–dependent absorption spectral changes (Figure 3), and each transition curve shapes are characteristic of isodesmic model and cooperative model, respectively.

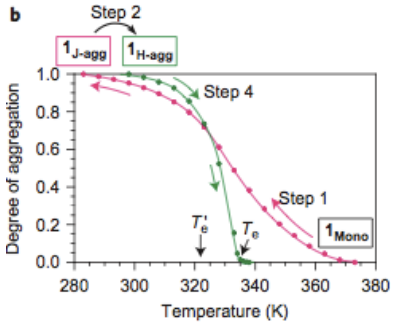


Figure 3. **Temperature–dependent absorption spectral**

- According to the DSC thermogram of **a** ($\mathbf{1}_{\text{H-agg}}$) and **b** ($\mathbf{1}_{\text{J-agg}}$) (Figure 4), $\mathbf{1}_{\text{J-agg}}$ is formed kinetically, even though $\mathbf{1}_{\text{H-agg}}$ is favored thermodynamically.

- These experiments have unveiled the mechanism behind the 'infection–like' transformation. The authors showed Energetic landscape (Figure 5) based on these experiments.

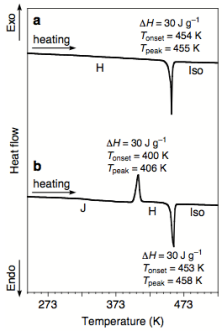


Figure 4. **DSC thermogram**

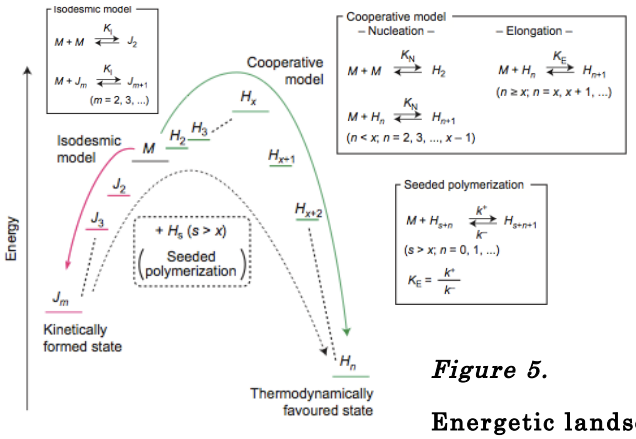


Figure 5. **Energetic landscape**

2.4 'Living' supramolecular polymerization

- The living nature of the supramolecular polymerization of $\mathbf{1}_{\text{H-agg}}$ was investigated by absorption spectroscopy, DLS and AFM (Figure 6).

- The transformation from $\mathbf{1}_{\text{J-agg}}$ to $\mathbf{1}_{\text{H-agg}}$ can be initiated by the addition of 'seed($\mathbf{1}_{\text{H-agg}}$)', as indicated by the black dashed arrow in Figure 5.

- The authors prepared 50 μM solution of $\mathbf{1}_{\text{J-agg}}$ and $\mathbf{1}_{\text{H-agg}}$, and mixed equal volumes of the solutions. Further addition (2nd, 3rd, 4th) of the solution of $\mathbf{1}_{\text{J-agg}}$ to the resulting solution repeated the polymerization with slower rates (Figure 6a).

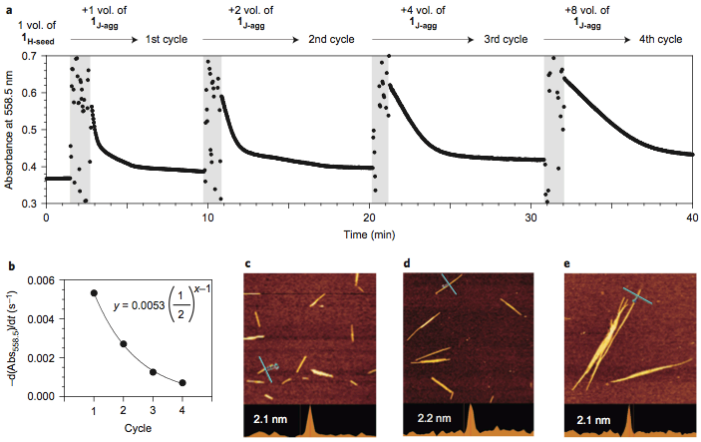


Figure 6. **Living supramolecular polymerization**

- Each cycle reduced the rate by half, which is consistent with the fact that the initial concentration of $\mathbf{1}_{\text{H-agg}}$ was diluted by half, every cycle (Figure 6b).

- The growth in the polymer length was confirmed by AFM (Figure 6c-e), and the authors confirmed that the length of the obtained $\mathbf{1}_{\text{H-agg}}$ was proportional (比例) to the ratio of the total amount of added $\mathbf{1}_{\text{J-agg}}$ by DLS (Figure 7).

- All these experiments indicates the 'living' nature of the supramolecular polymerization.

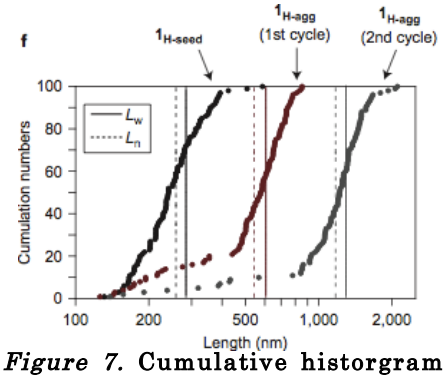


Figure 7. **Cumulative historgram of the length distribution**

3. Conclusion

- The authors presented an 'artificial infection' process in which porphyrin–based monomers assemble into nanoparticles, and then converted into nanofibers, and they presented the first demonstration of 'living' supramolecular polymerization.

- Essence is the fact that the nucleation–elongation process is coupled with a kinetically controlled equilibrium. Accordingly, the spontaneous nucleation is inhibited but dominated by the addition of thermodynamically stable seeds.