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Catalyzed Polymerization in Bio-Nano Cavity of Protein

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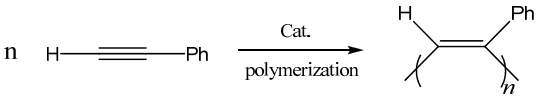
【Introduction】 Proteins are able to form different cavities with size ranging from tens to hundreds of nanometers. One of the significant applications is to make a confined reaction space for catalysis, by encapsulating catalyst into the protein cavity. This application has the potential to become a promising strategy to develop novel catalysis processes in well-defined "matrix". Polyenes with π-conjugated backbones are important materials with potential applications in photoconductivity, optical nonlinear susceptibility, and magnetic susceptibility *etc*. The Rh-catalyzed polymerization is one of the most powerful methods to synthesize polyenes (Scheme 1). Recent experiment reported that a spherical protein, apo-Ferritin, encapsulating rhodium complexes, is able to catalyze the polymerization of phenylacetylene, providing stereospecific polymers with restricted molecular weight and a narrow molecular weight distribution in the reaction space of the protein. Rhodium complexes were immobilized on the interior surface of apo-Ferritin in three types of binding sites. However, it is still unknown which binding site(s) is/are the active site(s) for the polymerization, and how it/they initiate(s) the polymerization. To provide insight into the polymerization behavior in the bio-nano reaction space and to reveal the factors that controlling the polymerization, QM/MM studies were carried out on the Rh-catalyzed polymerization of phenylacetylene in nano-cavity of apo-Ferritin (Fig. 1).

Scheme 1. *Catalyzed Polymerization of Phenylacetylene*



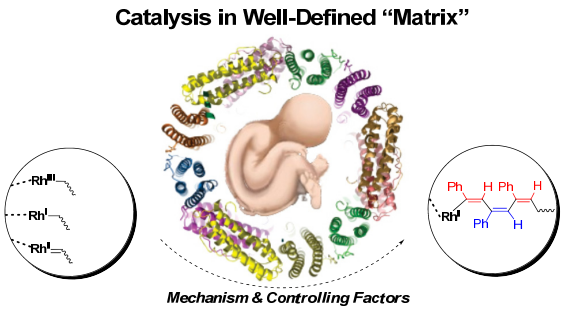


Figure 1. *Rh-Catalyzed Polymerization of Phenylacetylene in Nano-Cavity of apo-Ferritin*

【Computational Method】 For model complexes without apo-Ferritin, density functional theory (DFT), B3LYP (Becke's three-parameter hybrid functional, the LYP correlation functional and VWN), was utilized, in conjunction with the Stevens (SBK) valence basis sets (valence triple-ξ and effective core potentials) for rhodium and 6-31G* basis sets for other main group elements. For polymerization in apo-Ferritin, QM/MM calculations were performed using the two-layer ONIOM scheme. The aforementioned DFT was used for high-level QM method and amber force field was employed as the low-level MM method. In this scheme, the total energy is calculated according to Eq 1. Wherein, $E_{MM,real}$ is the low-level MM energy of the entire system (real system), $E_{QM,model}$ is the high-level QM

energy of the model system (chemical important part in the real system), and $E_{MM,model}$ is the MM energy of the model system.

$$E_{ONIOM} = E_{MM,real} + E_{QM,model} - E_{MM,model} \quad (1)$$

【Results and Discussion】 Different plausible active sites were constructed for the polymerization in binding site C, D and E (Fig. 2). Site C and D should be four-coordinated Rh^{I} or Rh^{I}-carbene centers, Site E should be a six-coordinated Rh^{III} center. Our studies suggested that Site D is the most possible active site for the polymerization. Dissociative Rh^{I}-insertion from site D is the most feasible mechanism with an insertion barrier of ~ 9 kcal/mol. There is no recombination of the active center back to the histidine residue (His49) after the insertion. The abstraction of the Rh^{I}-complex from His49 to a hydrophobic pocket (Phe50, Lys143 and Leu171) nearby plays an important role in the dissociative Rh^{I}-insertion polymerization in site D. The ejection of Rh^{I}-complex from site D after the coordination of phenylacetylene monomer releases a true active site for the polymerization. On the contrary, Rh^{I}-carbene metathesis polymerization in site D has to overcome a barrier of ~ 35 kcal/mol. In Site C, both Rh^{I}-insertion polymerization (barrier, ~ 20 kcal/mol) and Rh^{I}-carbene metathesis polymerization (barrier, ~ 22 kcal/mol) are less favorable than Rh^{I}-insertion polymerization in site D. Rh^{III}-insertion in site E is calculated to be the least possible polymerization mechanism. The coordination of phenylacetylene to the crowded Rh^{III} center is difficult, and the sequent insertion has a barrier calculated to be higher than 45 kcal/mol. Rh^{I}-insertion polymerization in site D favors a 2,1-insertion, producing cis-transoidal polymers.

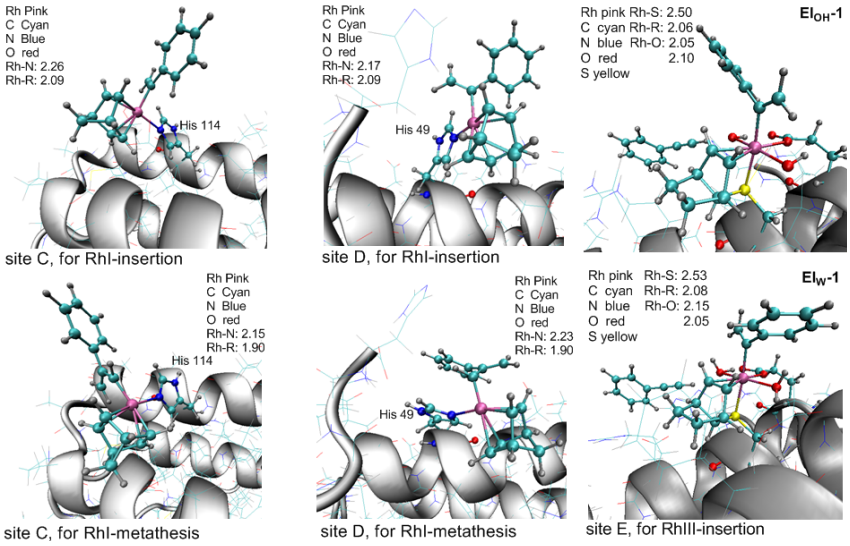


Figure 2. *Rh^{I}, Rh^{III} and Rh^{I}-Carbene Binding Sites in apo-Ferritin*

【Conclusion】QM/MM studies have revealed that apo-Ferritin with encapsulating Rh-complexes can construct unique bio-nano reaction space to perform controllable polymerization of phenylacetylene. Rh^{I} complex in Site D is the most possible active site, and a dissociative Rh^{I}-insertion from site D is suggested to be the most feasible mechanism. Both the electronic effect and steric effect play important roles in controlling the 2,1-insertion and cis-transoidal connection, producing stereospecific polymers, consistent well with the experimental observations.