Structural analysis of amyloid β hydrophobic core in the oligomeric state by encapsulation within an $M_{12}L_{24}$ cage

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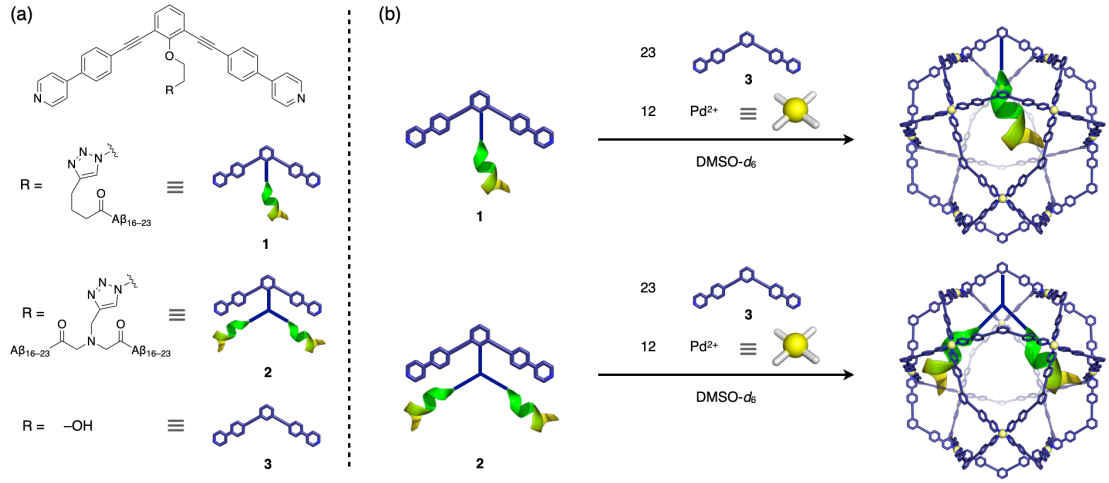
Amyloid β (Aβ) is an aggregative peptide consisting of around 40 amino acids residues. Aβ is the main component of amyloid plaques often found in the brains of Alzheimer's disease patients. Recent studies show the soluble oligomeric state of Aβ exhibits significant neurotoxicity, but the nature of the Aβ oligomer is largely unexplored due to the rapid formation of insoluble Aβ fibril through the uncontrollable aggregation.[1] We previously found that the encapsulation within an $M_{12}L_{24}$ cage, self-assembled from palladium(II) ions (M) and organic bidentate ligands (L), effectively prevents undesired aggregation of proteins including Aβ proteins.[2] In this research, we sought to analyze the oligomeric structure of Aβ by encapsulating a specified number of Aβ fragments into an $M_{12}L_{24}$ cage.

The $Aβ_{16–23}$ fragment (H-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-NH_2), which is the core of the hydrophobic β-strand, was studied to elucidate the Aβ oligomeric structure. One or two molecules of the $Aβ_{16–23}$ fragments were tethered to bis(pyridine) ligands to afford **1** or **2**, respectively (**figure a**). $M_{12}L_{24}$ cages containing only one or two $Aβ_{16–23}$ fragments were self-assembled from **1** or **2** with ligand **3** and palladium(II) ions in DMSO-d_6 (**figure b**). The structures of encapsulated peptides were analyzed by 3D NMR measurements.



1) J. A. Hardy, G. A. Higgins, *Science* **1992**, *256*, 184–185. 2) (a) K. Harris, D. Fujita, M. Fujita, *Chem. Commun.* **2013**, *49*, 6703–6712, (b) D. Fujita, *et al*. *Nat. Commun.* **2012**, *3*, 1093. (c) R. Suzuki, D. Fujita, M. Fujita, the 99th CSJ annual meeting, **2019**, 1G3-49. (d) T. Nomura, R. Suzuki, D. Fujita, M. Yagi, K. Kato, M. Fujita, the 99th CSJ annual meeting, **2019**, 1G3-48.