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Engineering the Geometry of Nanocages Using Proline for Targeted Drug Delivery

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Cisplatin (cis-$Pt(NH_3)_2Cl_2$) has emerged as one of the most potent chemotherapeutics for cancer treatment. Despite its high cure rates, its lack of cellular selectivity causes most of the administered drug dose to either destroy healthy cells or be wasted, with only 1% attacking the cancerous mass. Thus, there is considerable effort being put into the design of biocompatible drug delivery vehicles that can selectively target cancerous tissue. We aim to synthesize precisely shaped nanocages consisting of artificial metallopeptides facilitate selective delivery and unloading of cisplatin. These cages are made of synthetic peptides and have redox-active metal ions such as Cu(I) on the vertices. In highly reducing environments, such as that of a hypoxic tumor, the nanocage is expected to undergo distortions and release the drug cargo. We are studying how the presence of the bent amino acid L--proline in the cage edges affects the cage geometry, which influences the cage topology, size, and redox behavior, and ultimately its binding strength and specificity towards drug cargo. Solid phase synthesis of peptides containing 7, 9 and 11 amino acids with a central L-proline and helix-stabilizing 2-aminoisobutyric acid (Aib) residues has been carried out, followed by metalation with Cu(I) and Cu(II) to induce cage assembly. Structural analysis of these nanocages by NMR, CD and mass spectroscopy indicates the formation of metallopeptide dimers, in which each unit is a helix. Further characterization is underway to determine the three-dimensional kinked geometry of the proline-containing supramolecules. Overall, it is expected that different cage shapes will exhibit selective affinities for different drug molecules. Once we elucidate the relationship between structure and function, these findings will influence the development of chemotherapeutic delivery vehicles and lead to better patient outcomes for cancer treatment.

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