Water helps in the unexpected and ultrafast synthesis of collagen-like synthetic poly-L-proline

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In work published online recently in *National Science Review,* a team led by Prof. Hua Lu from the College of Chemistry and Molecular

Engineering of Peking University reported a surprising finding. In the process of studying the ROP of ProNCA, a type of reaction that would otherwise have been performed in a dry box, the team discovered ultrafast and controlled polymerization in aqueous solutions.

ProNCA monomer is easily hydrolysable and the solubility of the product PLP in organic solvents is very low. Because of this dilemma, the ROP of ProNCA typically took up to a week in dry organic solvents, yielding oligomers with little control on the molecular weight and dispersity. The new method solved the problem by simply replacing the anhydrous organic solvent with a mixed water-acetonitrile solvent, and the polymerization reaction can be completed in 30 seconds to obtain an oligoproline with a degree of polymerization (DP) of 20, or PLP with a DP up to 200 in 5 minutes.

Since the polymerization rate is extremely fast, far exceeding the rate of side reactions such as monomer hydrolysis, the ROP is thus highly controlled, which is manifested in high end group fidelity, chain growth kinetic pattern, predictable molecular weight, and narrow dispersity, and broad scope of initiator. Mechanistic experiments and density functional theory (DFT) calculations together suggest that water acts as a proton shuttle during polymerization, aiding the proton transfer in the rate-determining step, thereby lowering the reaction energy barrier by as much as 7.1 kcal/mol and accelerating the polymerization dramatically.

Due to the mild reaction conditions, simple operation, and easy purification, the researchers also synthesized asparaginase-PLP conjugates using asparaginase, an anticancer drug, as an initiator. By collaboration with the team of Professor Song Yuqin from Peking University Cancer Hospital, the researchers found that the asparaginase-PLP conjugate can significantly prolong the blood circulation time of asparaginase, improve the antitumor efficacy in vivo, and reduce the immunogenicity compared with the wild-type drug protein. The two

research teams are ready to further collaborate to conduct more in-depth preclinical research, and strive to benefit patients with acute lymphoblastic leukemia and NK/T cell lymphoma in the future. In addition, Prof. Lu believes that PLP itself is also potentially useful in food industry, cosmetic, and many other materials applications.

More information: Yali Hu et al, Water-Assisted and Protein-Initiated Fast and Controlled Ring-Opening Polymerization of Proline N-Carboxyanhydride, *National Science Review* (2022). DOI: 10.1093/nsr/nwac033

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