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Well-Defined Polypeptides: Synthesis and Selective Attachment of Poly(ethylene glycol) Functionalities

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Abstract : The synthesis of sequence-controlled polymers has received increasing attention in the last years. Well-defined polyacrylates, polyacrylamides and styrene-maleimide copolymers have been synthesized by sequential or kinetic addition of comonomers. However this approach has not yet been introduced to the synthesis of polypeptides, which are in fact polymers developed by nature in a sequence-controlled way. Polypeptides are natural materials that possess the ability to self-assemble into complex and highly ordered structures. Their folding and properties arise from precisely controlled sequences and compositions in their constituent amino acid monomers. So far, solid-phase peptide synthesis is the only technique that allows preparing short peptide sequences with excellent sequence control, but also requires extensive protection/deprotection steps and it is a difficult technique to scale-up. A new strategy towards sequence control in the synthesis of polypeptides is introduced, based on the sequential addition of α-amino acid-N-carboxyanhydrides (NCAs). The living ring-opening process is conducted to full conversion and no purification or deprotection is needed before addition of a new amino acid. The length of every block is predefined by the NCA:initiator ratio in every step. This method yields polypeptides with a specific sequence and controlled molecular weights. A series of polypeptides with varying block sequences have been synthesized with the aim to identify structure-property relationships. All of them are able to adopt secondary structures similar to natural polypeptides, and display properties in the solid state and in solution that are characteristic of the primary structure. By design the prepared polypeptides allow selective modification of individual block sequences, which has been exploited to introduce functionalities in defined positions along the polypeptide chain. Poly(ethylene glycol)(PEG) was the functionality chosen, as it is known to favor hydrophilicity and also yield thermoresponsive materials. After PEGylation, hydrophilicity of the polypeptides is enhanced, and their thermal response in H2O has been studied. Noteworthy differences in the behavior of the polypeptides having different sequences have been found. Circular dichroism measurements confirmed that the α-helical conformation is stable over the examined temperature range (5-90 °C). It is concluded that PEG units are the main responsible of the changes in H-bonding interactions with H2O upon variation of temperature, and the position of these functional units along the backbone is a factor of utmost importance in the resulting properties of the α-helical polypeptides.

Keywords : α-amino acid N-carboxyanhydrides, multiblock copolymers, poly(ethylene glycol), polypeptides, ring-opening polymerization, sequence control
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