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Conformational and interaction properties of antithrombin binding oligosaccharides obtained by chemo-enzymatic synthesis: An NMR and MD simulation characterization

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Heparin (Hep) is a highly sulfate glycosaminoglycan present as proteoglycan in all cells of the animal body[1]. Hep is the most important anti-coagulant drug, and is extracted by degradation of selected tissues of pigs and bovines. The anti-coagulant properties of heparin is principally based on the binding and activation of antithrombin (AT), one of the major heparin cofactor in the inhibition of several serine proteases of the coagulation system, particularly factors Xa, IXa, and IIa. The mechanism of interaction of heparin and AT involves a specific pentasaccharide sequence GlcNAc/NS,6S-GlcA-GlcNS,3,6S-IdoA2S-GlcNS,6S [AGA*IA] rarely found on the heparin chains[2]. The binding induced allosteric conformational changes in AT promoting the extension of the helix D of AT and the expulsion of the N-terminal portion of the reactive center loop from β-sheet A, exposing the P1 arginine to target proteinase[3]. A key property of this interaction is the conformational plasticity of the IdoA residue, being $^{1}C_{4}$ chair or $^{2}S_{0}$ skew boat conformation, when AGA*IA is in free state or bound to AT respectively. In this work the binding and conformational properties of novel AT active oligosaccharides, systematically prepared by chemo enzymatic approach, are analyzed combining advanced NMR interaction experiments (^{1}H-STD, NOESY/tr-NOESY) and 'state of the art' MD simulation to unravel the structural and dynamic features possibly contributing to the allosteric events.

Biography

Stefano Elli has completed his two year post-degree Master in Polymer Science, and PhD in Material Engineering at the age of 31 and 34 years respectively at politecnico di Milano (Dept. of Chemistry Materials and Chemical Engineering "G. Natta"), visiting scientist at UCD (University College of Dublin, during PhD), and postdoctoral study at Bologna University (dept. Chemistry "G. Ciamician"). He begin as postdoctoral at Istituto di Ricerche Chimiche e Biochimiche "G. Ronzoni" (Milano) in 2009, and in 2012 become researcher at Istituto "G. Ronzoni" being expert in multiscale modeling Monte Carlo and MD simulation, and integration NMR/MD simulation description.

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