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Multiscale Molecular Modelling and Advanced Simulations of Supramolecular Systems

By

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Many biological systems are *de facto* supramolecular materials that possess unique intriguing properties, such as the ability to self-heal, dynamically reconfigure their structure, respond to stimuli, and perform complex functions. These systems are composed of molecular subcomponents that interact and self-assemble, interconnecting with each other through noncovalent interactions. Designing artificial supramolecular systems that possess similar properties and self-assembling principles to those found in nature could lead to the development of a new generation of bioinspired materials that could revolutionize various fields, from biomedical and environmental, to energy and electronics. However, this requires gaining a detailed comprehension of the main molecular factors that control the structure and properties of these supramolecular systems, which is very challenging to attain. Molecular models and computer simulations are fundamental in this field. These tools permit us to investigate supramolecular systems from a privileged point of view and at an unprecedentedly high resolution. In this way, it is possible to reach a molecular-level comprehension of the behaviour and properties of supramolecular systems, which offers unique opportunities toward the design of new materials with bioinspired properties. This PhD Thesis focuses on the computational modelling study of a variety of supramolecular systems via the development of multiscale (atomistic and coarse-grained) molecular models and the use of classical molecular dynamics and advanced molecular simulation approaches (enhanced sampling techniques such as Metadynamics and Umbrella Sampling). Firstly, the chain-capping and supramolecular polymerization of porphyrin-based monomers is investigated. Through the extensive use of Metadynamics simulations and coarse-grained models, we gain a deeper understanding of the interaction between monomers and reveal hidden processes involved in the monomer exchange phenomena. The interaction between isolated nanotubes in solution is then assessed, by employing multiscale modelling. Our approach helps to identify the primary driving forces that lead to the formation of intertwined supramolecular structures, providing a link between experimental observations and the molecular factors that drive the observed phenomena. We then extend the investigation to the interaction of a Benzene-1,3,5-tricarboxamide-based

supramolecular polymer (BTA-OEG_4) with biological structures under physiological conditions to evaluate their potential as biomaterials. Our simulations reveal that the dynamic supramolecular nature of these fibres allows the interaction between BTA-OEG_4 and BSA, and elucidate the mechanism of monomer exchange in this system during the complexation. Finally, we show a flexible computational protocol that allows to reconstruct the thermodynamics and kinetics of different types of mechanically interlocked molecules (MIMs) at atomistic resolution. Though classical molecular dynamics and Metadynamics simulations, we gain deep insights into the free-energy characterization of MIMs and reveal the delicate balance between various intermolecular interactions (*e.g.* H-bonding, solvent effects, conformational entropy) that determine their behaviour. We also demonstrate the impact of changing environmental variables (such as the solvent type) on the dynamical behaviour of the MIMs. Our approach also includes a free-energy decomposition into enthalpy and entropy contributions, and detailed structural and dynamical analyses that provide unprecedented insights into the mechanisms and key transitions ruling the intermolecular movements between metastable states.

Overall, this PhD Thesis makes a significant contribution to the field of supramolecular systems, providing a detailed molecular-level understanding of fundamental processes involved in the self-assembly and dynamic behaviour of supramolecular polymers, and resolving the slow dynamics of rotaxanes and molecular shuttles with sub-molecular resolution. This work demonstrates the power and potential of molecular modelling in this area, paving the way for the rational design of artificial supramolecular systems.