pK_a shifts calculations of encapsulated drugs through a CpHMD approach

Molecular machines have recently been associated with the development of molecular carriers to enhance drug properties, such as solubility or bioavailability. One possible approach is through drug encapsulation by a host molecule, such as cucurbituril (CB) rings, which modifies the environment of the guest molecule. CB rings are able to encapsulate guest molecules providing a hydrophobic cavity and several carbonyl groups that stabilize cationic guests that interact with this region. This results in significant pK_a shifts for drugs with titrable (cationic) groups that can be exploited in order to improve drug bioavailability, whether by enhancing their solubility, stabilizing their active form or by protecting them against external agents.

Computational methods are a powerful way to rationalize the design of CB-guest complexes. In particular, the stochastic titration constant-pH MD (CpHMD) method allows a molecular dynamics simulation to have the pH value as an external parameter and, consequently, obtain full titration curves and pK_a values. Our first step is to develop a strategy to model benzimidazole (BZ) pK_a shifts, which has a well-known shift of ~3.5 pK_a units when encapsulated by a CB ring. The obtained parameters were tested in three different drugs for validation purposes: carbendazim, 2-aminoanthracene and cyclohexylmethylamine. This will be helpful to elucidate the molecular details of these host-guest interactions and to extend this procedure for many other host-guest complexes. Ultimately, we aim to develop a method that predicts the best host which optimizes the drug delivery properties of any chosen drug, enabling the design of multiple complexes with different pK_a shifts. This strategy can be beneficial for novel drug design and medical applications such as cancer therapy, by designing carriers that deliver guest molecules at specific conditions, knowing the specific target properties.

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