Estimating pKa shifts of encapsulated drugs through a CpHMD approach

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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 hosts 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. The aforementioned approach can be used for medical targeting, such as cancer therapy, by designing carriers that deliver guest molecules at specific conditions, knowing the specific target properties [1].

Computational tools are a powerful way to help the rational 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 main goal is to develop a strategy to model benzimidazole (BZ) pK_a shifts, a «proof-of-concept» molecule, and then extrapolate this process to other host-guest complexes. BZ has a well-known shift of ~3.5 pK_a units when encapsulated by a CB ring and, with a CpHMD method, it is possible to elucidate the molecular details of these host-guest interactions.

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References
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