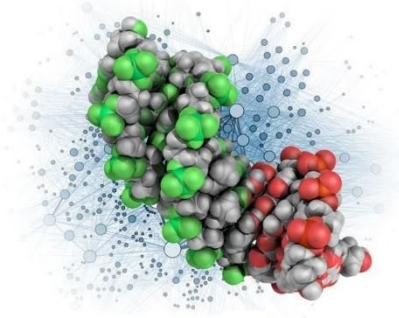

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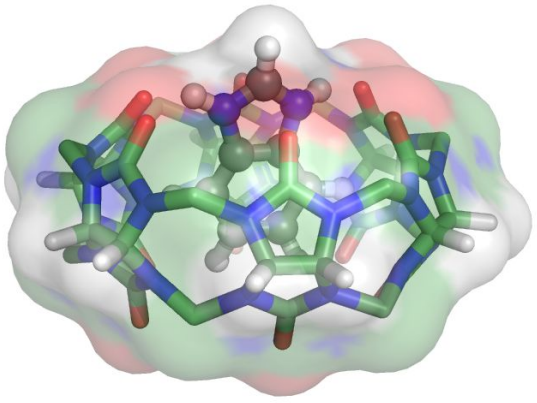
"*In silico*" estimation of encapsulation-induced pK_a shifts in drugs.

Diogo Reis (diogoreis992@gmail.com)[a], Miguel Machuqueiro (machuque@ciencias.ulisboa.pt)[a], Diogo Vila-Viçosa (diogo.vicosa@fc.ul.pt)[a].

[a] *Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal*

Graphical Abstract



Abstract

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 the drug encapsulation by a host molecule, such as cucurbituril (CB) rings, modifying 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 will result 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. This approach can be used for medical targeting, such as cancer therapy, by designing carriers that deliver guest molecules at specific conditions, knowing the target properties.

Computational tools are a powerful way to help the rational design of CB-guest complexes. In particular, the stochastic titrations 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. The main goal

	here is to develop a strategy to model benzimidazole (BZ) pK_a shifts, our «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 the refinement and fine tuning of this process, it is possible to elucidate the molecular details of these host-guest interactions. We acknowledge financial support from FCT through project UID/MULTI/00612/2013 and grant SFRH/BPD/110491/2015.

References *(mandatory)*

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