Extending a CpHMD method to estimate the encapsulation-induced pK_a shifts in drugs

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Introduction:

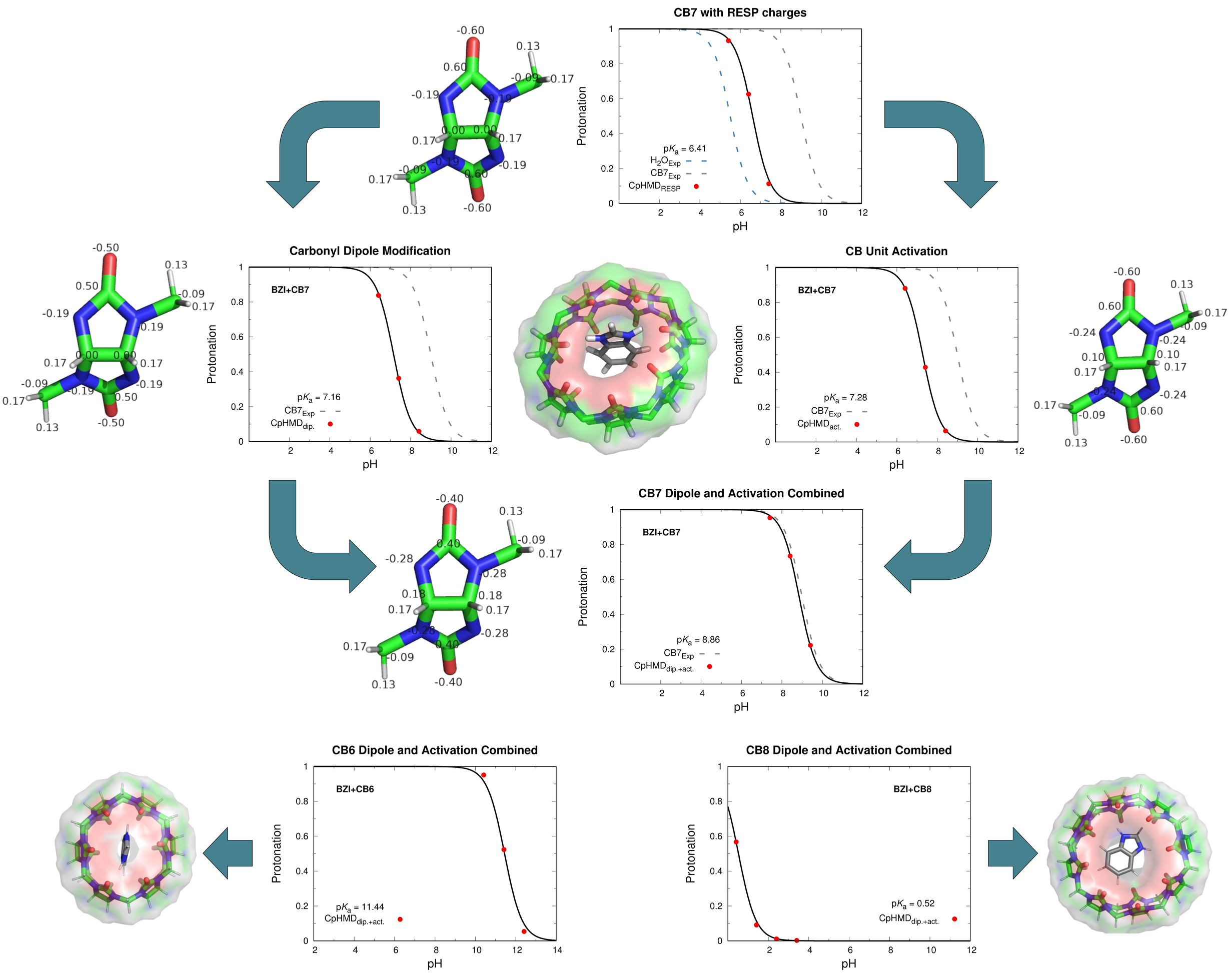
- **Goal**: Enhance drug properties through encapsulation in a cucurbituril (CB) ring.
- Hydrophobic cavity and carbonyl groups in CB ring provide cationic guest stabilization.
- Drug environment changes.
- pK_a shifts for drugs with titrable groups, like benzimidazole (BZI).
- pK_a shifts can be exploited in order to improve properties, such as solubility or bioavailability.

Objectives:

- Develop a strategy to model BZI, our «proof-of-concept» molecule.
- Extrapolate the process to other host-guest complexes.
- Elucidate the molecular details of these host-guest interactions.

Methods:

- All simulations were performed using a CpHMD method, with the GROMOS 54A7 force field and GROMACS v.4.0.7. Long range electrostatics were treated using generalized reaction field (GRF) with an ionic strength of 0.1 M. Poisson-Boltzmann and Monte Carlo calculations were performed using Delphi v. 5.1 and Petit 1.6.1, respectively.



Concluding Remarks:

- **By adjusting some point charges in the CB unit it is possible to reproduce the system's experimental pK_a value.**
- **The final pK_a value obtained is a result from the balance between electrostatic interactions, which increase the pK_a value, and the desolvation effect, which decreases it.**

Acknowledgments:

The authors acknowledge financial support from Fundação para a Ciência e Tecnologia, Portugal, through project UID/MULTI/00612/2013 and grant SFRH/BPD/110491/2015.

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