Halogen Bonds: A Journey Using "Simple" Force Field Methods

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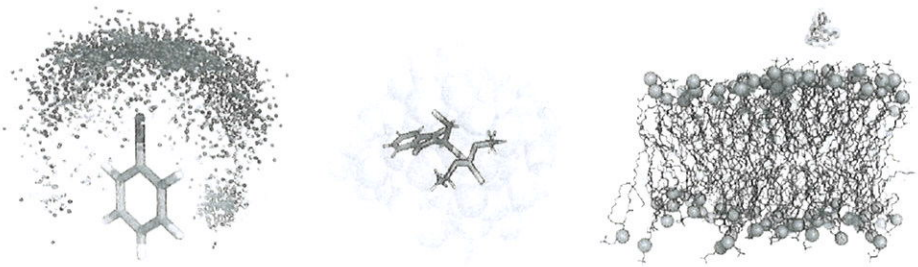
Halogenation, known to enhance drug properties like membrane permeability and pharmacokinetic stability, plays a significant role in drug discovery. Halogenated compounds can also bind biomolecular targets such as proteins, nucleic acids, and biomembranes via halogen bonds.[1-3] Such behavior, due to an anisotropic charge distribution at the halogen leading to a positive region at the tip of this atom known as the σ-hole, is not easy to tackle using force-field-based methods. Indeed, force fields traditionally use point charges, and thus, the anisotropy of the halogen is not commonly considered. In this talk, we will present the latest efforts to tackle these interactions while also disclosing the current caveats of the force field methods based on the assessment of off-center point-charge models using explicit solvent simulations *via* alchemical free energy calculations.[4] Furthermore, we will show how MD simulations can be used to push the boundaries of halogen bond applications, for instance, to study their influence on membrane recognition and drug permeation.[3]



References

[1] Costa, P. J.; Nunes, R.; Vila-Viçosa, D., *Expert Opin. Drug Discovery* **2019**, *14*, 805–820
[2] Frontera, A.; Bauzá, A, *J. Chem. Theory Comput.* **2020**, *16*, 4744–4752
[3] Nunes, R. S.; Vila-Viçosa, D.; Costa, P. J., *J. Am. Chem. Soc.* **2021**, *143*, 4253–4267.
[4] Fortuna, A.; Costa, P. J., *J. Chem. Inf. Model.* **2023**, *63*, 7464–7475.

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