Impact of halogen radii in the prediction of hydration free energies using PBSA calculations

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The estimation of protein-ligand binding energies, which is important for structure-based virtual screening, can be performed over molecular dynamics (MD) trajectories, combining Molecular Mechanics (MM) energies with Poisson-Boltzmann surface area (PBSA) continuum solvation methods. In this context, the PBSA calculations, which estimate hydration free energies, rely on the assignment of atomic radii (PB radii). Several drug and drug-like molecules are halogenated and in force field methods, an off-center point-charge, also called extra point (EP), is often introduced at a given distance from halogen atoms (X) to emulate a positive region of the electrostatic potential of these elements (σ-hole). This simple strategy overcomes the fact that empirical force fields typically consider halogen atoms to carry a negative charge leading to unfavorable interactions halogen bond interactions. However, standard halogen PB radii are often incompatible with typical X-EP distances, placing the EP within the solvent dielectric [1]. To overcome this issue, we previously optimized the halogen PB radii for a single EP implementation taken from the literature in the context of AMBER/GAFF [1]. Given the multitude of EP implementations, herein, we present an extension of the PB radii optimization to other EP approaches in the context of the same (GAFF) and other force fields (e.g. CHARMM) [2]. For that purpose, the performance of PBSA was evaluated for 142 halogenated compounds for which the experimental hydration free energies are known. The optimized values for the halogen PB radii were chosen based on the minimization of the mean absolute error against experimental values. Additionally, the effect of the solute flexibility and nonpolar contributions was also explored.

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[1] Nunes, R.; Vila-Viçosa, D.; Costa, P. J., J. Chem. Theory. Comput. 2019, 15, 4241−4251.
[2] Fortuna, A; Costa, P. J., J. Chem. Inf. Model. 2021, 61, 7, 3361–3375.