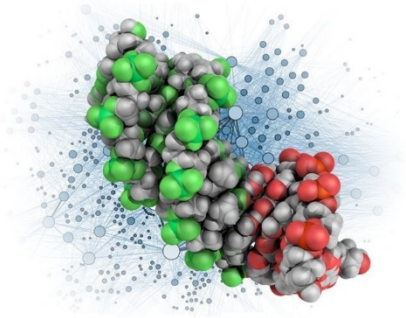

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T4 Lysozyme/Halobenzene: A Test System for Modeling Biomolecular Halogen Bonds

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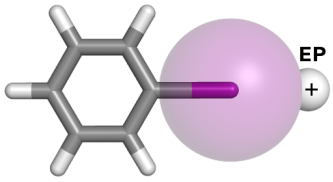
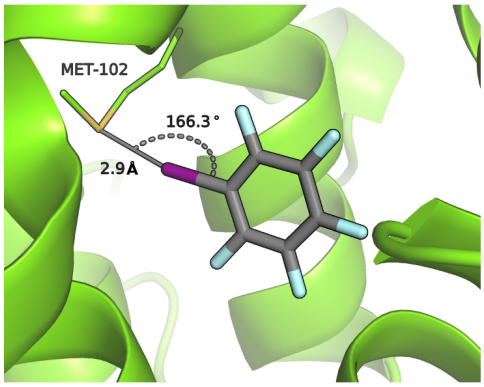
Graphical Abstract





Abstract

Halogen bonds (XBs) are non-covalent R–X···B interactions where heavy halogens (X = Cl, Br, I) act as electrophilic species interacting with Lewis bases (B). This highly directional type of interaction is mostly explained by the existence of a positive region on the molecular electrostatic potential located at the tip of the halogen (called σ-hole), arising from polarization of the R–X covalent bond. Following the recognition of the significance of XBs in biomolecular structures [1], their application in rational drug design, amongst other areas, has been increasingly explored. In this context, the development of computational tools accurately modelling XB is of paramount importance. This is particularly challenging in the case of force field (FF)-based methods, where XBs are typically modelled by introducing a positive extra-point (EP) of charge to mimic the σ-hole [2]. Though different schemes for EP parameterization have been

	proposed for AMBER or other FFs, their application to lengthy molecular dynamics (MD) simulations is still uncommon. In this work, we assessed the performance of distinct EP models and their transferability to the popular united-atom GROMOS FF, using bacteriophage T4 Lysozyme as a prototype system. The L99A mutant of this enzyme contains a large non-polar cavity that binds iodobenzene and related ligands, via XBs [3]. MD simulations were carried out and the network of intermolecular interactions, particularly XBs targeting different acceptors in the protein, was analysed. The results showed the dramatic impact of varying the X–EP distance and the associated sets of charges on the description of XBs. This, together with the implications for computer-aided drug design will be discussed [4].

Acknowledgements

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