How does halogenation change binding affinity of ligands in a protein cavity?

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The purpose of this work is to investigate the effect of halogenation on the binding affinity of ligands and also to consider the effect of substitution pattern (ortho, meta, para) on dynamics and binding of the ligands in a protein. Actually, halogens are widely known to contribute to ligandprotein interactions, thereby received great attention in drug design. A survey of launched drugs showed that 25% are organohalogens of which organochlorines dominate, composing 57% of halogenated drugs [1]. In this work we have studied binding affinity of chlorobenzonitrile (PhClCN) in the nonpolar cavity of T4 lysozyme. All the calculations have been done by CHARMM molecular dynamics simulations package. The CN group in the ligand is a spectroscopic probe (local reporter of the electrostatic environment) for studying the binding, electric field and dynamics of the ligand in the cavity. Theoretical investigations have confirmed that the electrostatic environment in the protein cavity shifts the peak frequency in the linear absorption spectrum of CN group [2]. The shift approximately correlates with the relative binding free energy, which it means the stronger the binding the larger, the red shift. In this work three different ortho, meta and para isomers of chlorobenzonitrile have been chosen to study the frequency shifts of CN group in different ligands and correlate the changes to the binding modes of the ligands. After 10 ns of production run, it was realized that 4-chlorobenzonitrile leaves the cavity after 5ns of simulation. On the contrary, 2-chlorobenzonitrile (both isomers), and 3-chlorobenzonitrile stay in the protein pocket. The binding free energies of PhClCN ligands in lysozyme have been calculated using umbrellasampling method (see figure(1)).

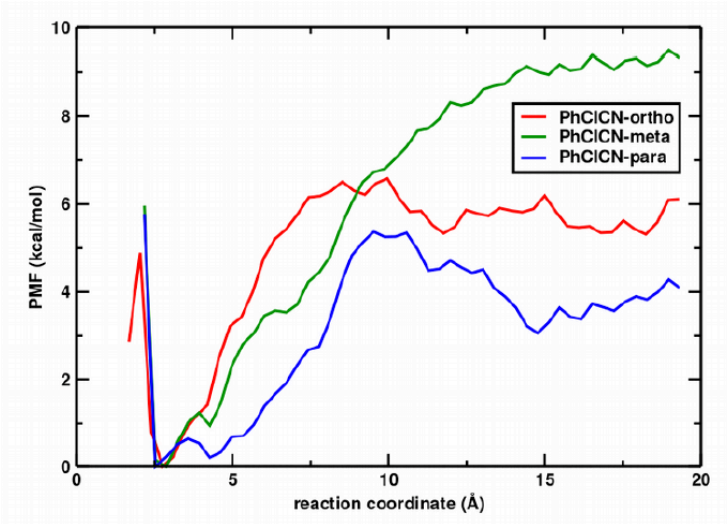

Figure1. Potential of mean force (PMF) profiles vs reaction coordinate for PhClCN ligands in lysozyme.

[1] Xu, Z.; Yang, Z.; Liu, Y.; Lu, Y.; Chen, K.; Zhu, W. J. Chem. Inf. Model. **2014**, 54 (1), 69−78.
[2] P. Mondal and M. Meuwly. Phys. Chem. Chem. Phys, **2017**,19, 16131-16143