Probing Aromatic- Heteroaromatic Interactions for Ligand Optimization

M.A.Margreiter[#], K.R. Liedl[#], R.G. Huber[#], J.E. Fuchs[#], S. von Grafenstein[#],
H.G.Wallnöfer[#], C.S. Tautermann[⊥], T. Fox[⊥]
[⊥]Computational Chemistry, Dept. of Lead Identification, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[#]Institute of
General, Inorganic and Theoretical Chemistry, Faculty of Chemistry and Pharmacy, University of Innsbruck, Austria

The interactions within biomolecular systems as well as between protein and ligands can be divided into contributions from H-bonding, dipole-dipole, covalent and ionic forces. Another, much less well studied interaction results from dispersion. Nevertheless, estimated 60% of all natural occurring aromatic amino acids are believed to be involved in pi-pi interactions; and it is also important for drug recognition or protein-ligand binding.
Here we report on our first steps towards a more thorough understanding of dispersion interaction in aromatic model systems by in-silico methods. As a starting point, the Protein Database (PDB) was searched to yield information about preferred interaction geometries between aromatic amino acid side chains (Phe, Tyr, Trp) and between proteins and ligands can be divided into contributions from H-bonding, dipole-dipole, covalent and ionic forces. Another, much less well studied interaction results from dispersion.
Also, we investigate how well several fast DFT functionals can reproduce expensive CCSD(T) calculations to scan the potential energy surface of the benzene dimer, and how well quantum-chemical calculations match with the experimental geometry distribution.
We conduct rigid Potential Energy Surface (PES) scans of various aromatic- heteroaromatic dimers. The results are confirmed by a follow-up full geometry optimization. These insights allow a rough comparison of different scaffolds, when performing a Lead Optimization.