Thermodynamics of halogen bonding in the bio-molecular cage

A still increasing number of halogenated compounds are becoming drug or drug candidates. A large number of drugs already available in the marked also contain fluorine, chlorine, bromine or iodine. Most of these compounds are strongly hydrophobic, which implies that they are very poorly soluble in water. It is therefore very difficult to investigate their interaction with potential molecular targets.

The screening for new drugs is usually done virtually using computer aided drug design approach. This method is much more efficient, and thus cheaper, than blindly testing of millions of available chemicals. However, in all drug design methods the accurate description of all interactions contributing to interaction of a ligand with a target protein are absolutely required.

In 1996, a new type of intermolecular interactions that involve halogen atoms (chlorine, bromine or iodine) and proximal electronegative atoms or groups (e.g. oxygen or benzene ring) was identified in the Cambridge Structural Database, and further in 2004 the presence of this type of interactions was also confirmed in Protein Data Bank. These interactions were named halogen bond. So far, the scientific community agree on their preferred geometry, albeit there are still disagreement concerning the estimation of their strength, and therefore their contribution to the free energy of ligand binding. The project being proposed will address this problem.

Not only the choice of the analyzed compounds screened from hundreds of others by appropriate methods, but also the selection of a protein partner, whose rational modifications will form a series of molecular cages in which the halogen bonding properties can be studied in detail, are unique features of the project. The range of experimental methods used, which in addition to the standard methods of structural and thermodynamics analyses (e.g. Crystallography, Titration Calorimetry, Microscale Thermophoresis), has been extended by studies of the effect of ligand on the internal protein dynamics (e.g. fluorescence anisotropy, analysis of nuclear relaxation of ^{15}N backbone amide groups), is also extremely wide. The collected data should then allow to build not only a static model of interactions (e.g. structure, energy, entropy, enthalpy), but also a dynamic one that describes the balance between halogen bonding and all other types of interactions contributing in protein complexes.

All these data will improve understanding of the interactions of potential drugs with their molecular targets, and will also improve reliability of computer aided drug design procedures.