

## Multipolar Interactions in Structural Chemistry and Biology

François Diederich<sup>a</sup>, Klaus Müller<sup>b</sup>, Ralph Paulini<sup>a</sup>, <sup>a</sup>*Department of Chemistry and Applied Biosciences, ETH Zürich.* <sup>b</sup>*Pharma Research, F. Hoffmann-La Roche, Basel.* E-mail: [diederich@org.chem.ethz.ch](mailto:diederich@org.chem.ethz.ch)

The past decades of molecular recognition studies have greatly enhanced our knowledge on apolar, ion-dipole, and H-bonding interactions. However, much less attention has been given to the role that multipolar interactions, in particular those with orthogonal dipolar alignment, adopt in organizing a crystal lattice or stabilizing complexes involving biological receptors.

In a recent fluorine scan of thrombin inhibitors to map the fluorophilicity/fluorophobicity of an enzyme active site, we discovered favorable C–F<sub>(ligand)</sub>···C=O<sub>(protein)</sub> interactions, with the F-atom approaching the electrophilic C-atom in a nearly orthogonal way, along the pseudotrigonal axis of the carbonyl unit. The attractive nature of such contacts was subsequently established in model studies.

Using Cambridge structural database (CSD) and protein database (PDB) mining tools, we now have established the generality of these previously rather overlooked interactions. A number of illustrative examples of these interactions found in X-ray crystal structures of small molecules and protein-ligand complexes will be shown to demonstrate their propensity and thus potential importance for both, chemical and biological molecular recognition processes. [1]

[1] Paulini R., Müller K., Diederich F., *Angew. Chem. Int. Ed.*, 2005, *in press*.

**Keywords:** nonbonded interactions, databases, x-ray crystal structure analysis