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Molecular recognition enrichment rules in crystals and protein/ligand complexes

C. Jelsch[1], B. Guillot[1], K. Ejsmont[3]

[1]CNRS, CRM2, Université de Lorraine, Vandoeuvre les Nancy, France, [2]Chemistry dept. Opole University, Poland.

To analyze the propensity of chemical species to interact with each other, we have developed the concept of enrichment ratios. The ratios are derived from the decomposition of the contact surface between pairs of interacting chemical species. The actual contacts are compared with those computed as if all types of contacts had the same probability to form. As expected, several polar contacts, which can be hydrogen bonds and show electrostatic complementarity, show enrichment values larger than unity. Among other results, O···O and N···N contacts are impoverished while H···H interactions appear very slightly disfavored. We have also investigated the directionality and stereochemistry of hydrogen bonds with an oxygen acceptor including in the Cambridge Structural Database [1]. The results obtained through this survey are correlated with the charge density of these different chemical groups. The electron density of these different oxygen atoms types show striking dissimilarities in the electron lone pairs configuration. As previously observed, the directional attraction of hydrogen bond donors towards the lone pairs is much more pronounced for strong H-bonds. Van der Waals and solvent accessible surfaces are widely used representations in protein modelling and drug design. We propose in the software MoproViewer [2] a revisited definition of the molecular surface based on flattened atoms when strong hydrogen bonding is possible. These stereochemical relationships found in molecular recognition within crystal structures of small compounds have implications in drug design and were investigated in some protein/ligand cases. Finally protein/ligand electrostatic calculations are compared using two different charge density models: multipoles vs spherical dummy charges on bonds and lone pairs[3].

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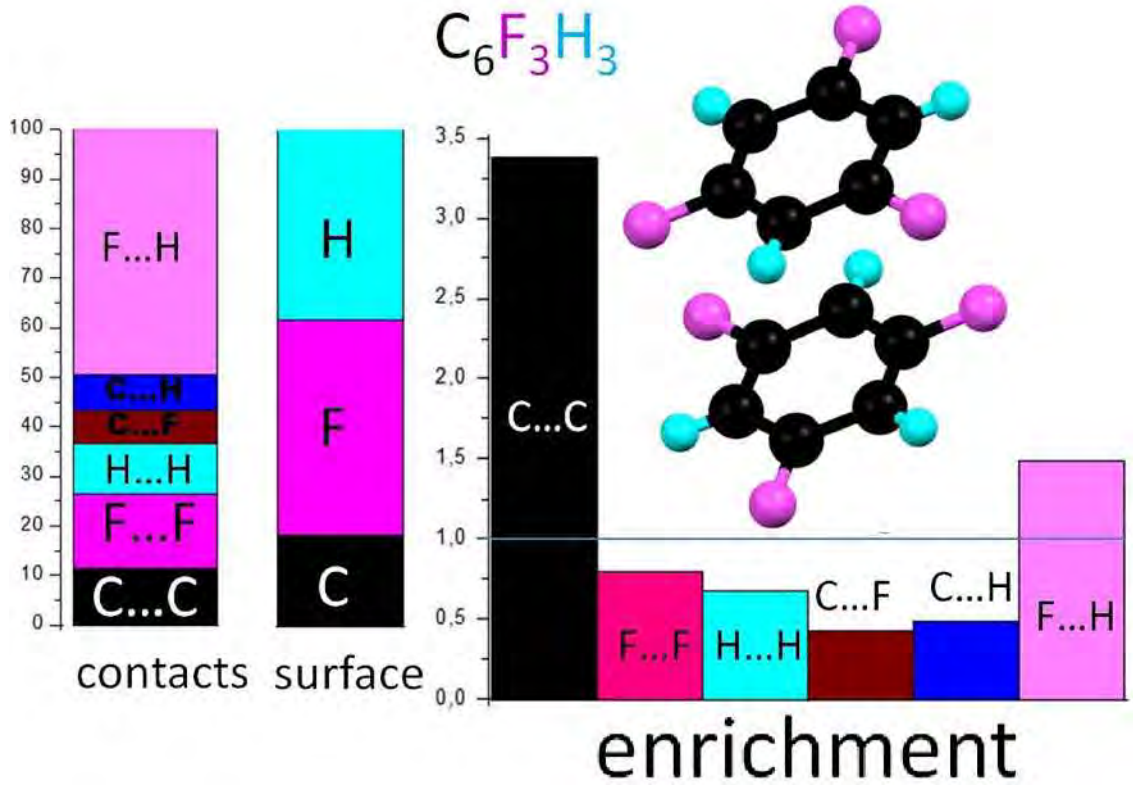

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