

"Organic fluorine" in stabilizing crystal structures: Does it matter?

Angshuman Roychoudhury¹, Gurpreet Kaur², Hare Ram Yadav¹, Maheshwararao Karanam¹, Sudeep Maheshwari³, Sagarika Dev⁴
¹Department Of Chemical Sciences, IISER Mohali, Mohali, India, ²Department of Chemistry, DAV University, Jalandhar,, Jalandhar, India, ³Department of Chemical Engineering, Delft University of Technology, Delft, Delft, Netherlands, ⁴Department of Chemistry, MCM DAV College for Women,, Chandigarh, India
E-mail: angshurc@iisermohali.ac.in

Intermolecular interactions involving fluorine in the solid-state chemistry of small organic molecules have attracted several research groups simultaneously due to its debatable behaviour in an organic environment. The influence of a C-F group in building supramolecular assemblies were ignored and used to be refuted as very weak and insignificant. Based on limited number of fluorinated compounds in the Cambridge Structural Database, it was concluded that the fluorine mediated interactions are insignificant in number and are non-directional and hence not important for stabilization of the crystal structures. But it was also observed that a number of drugs contain one or more F atom and their non-fluorinated analogue were biologically inactive. Therefore, it was conceived that fluorine substitution in small organic molecule may have a significant role in controlling the physicochemical properties of drugs and pharmaceuticals; but the exact role was not clear. Since then, many active research groups have structurally characterized many molecules containing one or more C-F bond(s) in a systematic way to understand the role of "organic fluorine" in crystal engineering. Early studies indicated that a CF bond present in a molecule is capable of forming weak interactions of the types C-H...F-C, C-F...F-C and C-F...pi (Aromatic) interactions. Guru Row and co-workers, have shown that the weak C-H...F-C hydrogen bonds in association with weak C-F...F-C interactions are capable of forming highly stable crystalline architecture in a series of mono and difluorinated isoquinolines, difluorinated benzamides etc. Polymorphism through different C-H...F-C interaction was also observed by them. Ozala and co-workers and Merz and co-workers have also shown that organic fluorine in the absence of other strong hydrogen bonds are capable of forming various supramolecular synthons involving C-H...F-C interactions. Our long endeavour in this area proved that the C-H...F-C interactions have characteristics similar to hydrogen bonds and hence it should be considered as a weak hydrogen bond, which provides 3-6 kcal/mol of stabilization to the crystal structures. We established the existence of a number of supramolecular synthons based on C-H...F-C hydrogen bonds and have shown that these hydrogen bonds though very weak compared to the traditional strong hydrogen bonds are capable to alter the crystal packing of small organic molecules both in the presence of strong hydrogen bonds in a series of fluorinated amides and weaker hydrogen bonds in fluorinated anilides. In the absence of any strong hydrogen bonds, in addition to C-H...F-C hydrogen bonds, C-F...F-C interactions are encountered more frequently and the versatility of C-F...F-C interactions were prominent. A combination of experimental structural analysis [1], gas-phase computational study [2] experimental and theoretical charge density analysis on these interactions lead to the fact that the organic fluorine offers significant stabilization to crystalline architecture. A recent reviews indicates the importance of the field [3]

[1] Kaur. G. et al. (2012) *Crystal Growth Des.* 12, 5096-5110.

[2] Dev. S. et al. (2015) *RSC Adv.* 5, 26932-26940.

[3] Chopra. D. and Guru Row. T. N. (2011) *CrystEngComm.* 13, 2175-2186.

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