

Crystal engineering underlies the essence of natural affiliation between the molecule on the one side and the crystal as a supramolecular assembly on the other. Molecular recognition is the fundamental cause for this efficient transformation and if we consider the crystal as a supramolecular entity then it is not at all difficult to conceive crystallization as an outstanding example of molecular recognition. In general, organic compounds often facilitate closed packed crystal structures as described by A. I. Kitaigorodskii in the form of the close packing principle but based on chemical features, there is still a small window to understand, to rationalize and to fashion new crystal structures. Extending the chemical viewpoint as first proposed by J. M. Robertson, the supramolecular synthon model as a descriptor of collective crystal structures has been invoked that enables one to trail the molecular behaviour from an entropy dominated situation in solution to an enthalpy driven progression in the solid state. After 20 years, the concept of the supramolecular synthon has stood the test of time because of its simplicity and effectiveness towards the implementation in complex crystal structures and has led the scientific community to further handle complex and interesting ideas in structural chemistry and supramolecular synthesis.

The complexity of dynamic and progressive behavior of molecules during crystallization may be understood by the analogous argument of protein folding; both these complex phenomena decode the emergence of multiple metastable forms before the final structures are attained. These intermediate kinetically driven species may be high energy polymorphs and pseudopolymorphs of the compound in question or semicompact random globules for proteins. Understanding the role of these species in their respective processes is of critical importance in elucidating mechanisms. As an alternative approach, crystal structure prediction (CSP) is also of fundamental importance in the context of understanding the crystallization process. All energy based computational methods of CSP address this problem by scanning the multi-dimensional energy hypersurface. This is performed by computing lattice energy changes with respect to parameters like unit cell dimensions, space group symmetry and the positional coordinates of atoms in the asymmetric unit. Further, the computational prediction of the crystal structure of an

organic compound results in several choices, and it is possible that a collection of some of these when taken together forms a pattern that mimics the course of the crystallization process very much in the manner that structure correlation mimics covalent bond breaking and making. With all these developments, one is truly at the stage today when any experimental or computed crystal structure is just that, *a crystal structure* of the molecule in question and it is part of a complex and dynamic structural space which may include a part of the supramolecular reaction trajectory for crystallization itself.

Accordingly, this thesis emphasizes the importance of kinetic events during crystallization and proposes some strategies to access the inaccessible domains of this structural space of a given compound. I have exploited the supramolecular synthon model to understand the kinetics of the crystallization process and have further extended this understanding towards the isolation of stoichiometric ternary solids. The synthon model also helps one to provide a logical step to explore these remote domains of the complex hyperenergy surface that have collectively been termed as the *crystal structure landscape* of the compound in question. The precise descriptions of the chapters are mentioned below.

Chapter 2 describes fluorosubstitution as a unique chemical probe to explore the high energy crystal structures of benzoic acid in ambient conditions. This landscape exploration of benzoic acid is based on the robust (kinetically favoured) supramolecular homosynthon as well as consistent fluorosubstitution in native compound. This analysis is also supported by synthon based crystal structure prediction which is one of the best ways of monitoring high energy virtual crystal structures.

Chapter 3 extends the idea of landscape exploration towards multicomponent systems. The incorporation of an additional compound during crystallization facilitates even complex kinetic environments but using fluorosubstitution as a chemical probe, it again helps to analyse the high energy virtual domains of the given multicomponent system. Similar to chapter 2, the landscape exploration of multicomponent system is also based on the robust (kinetically favoured) supramolecular heterosynthon as well as consistent fluorosubstitution in the native multicomponent system.

Chapter 4 emphasizes the importance of synthon modularity as a chemical probe to traverse in the crystal structure landscape of the given multicomponent system. Here, I have quantified the role of the definitive synthon, by using the supramolecular synthon based fragment approach (SBFA), in the emergence of polymorphism in cocrystals. In latter part of this chapter, I utilized this collective kinetic information in order to realize the combinatorial nature of the crystallization process and showed the complex combinatorial synthesis of ternary solids which itself is considered to be an arduous exercise.

Chapter 5 discusses the importance of kinetic information which were fetched from the corresponding multicomponent landscapes and were further utilized for combinatorial synthesis of ternary solids. Although the combinatorial idea is well established in solution, this chapter highlights the first experimental evidence of this idea in the solid state and shows preferred amplification of certain supramolecular synthons from corresponding libraries in the supersaturated crystallizing medium.

Chapter 6 extends the combinatorial idea of crystallization even further by using highly flexible organic compounds that collectively provide larger structural space during crystallization. Using the delicate kinetic information about the molecular and supramolecular features, this chapter describes the preferential selection of molecular conformation and supramolecular synthons from the supersaturated solution during the molecule→crystal pathway.

In summary, the idea of the *crystal structure landscape* provides an extended interpretation about some of the complex ideas namely, *crystal energy landscape* and *polymorphism* in modern crystal engineering. The crystallization of an organic compound often depends upon intrinsic chemical features and accordingly one selects optimized crystallization routes in the corresponding landscape through decisive experimental conditions. As a final note, the idea of the *crystal structure landscape* enables one to (at least qualitatively) understand the importance of crystallization kinetics which is understandably a difficult task.