Synopsis (For figures refer the Main PDF file)

Supramolecular chemistry, aptly termed by Lehn as the study of molecular sociology, is the chemistry of the intermolecular bond, focusing on the structures and functions of “supermolecules” – chemical system formed by the association between two or more molecular components. While interrelated, this discipline forges beyond the domain of traditional molecular chemistry, which seeks to master the manipulation of the covalent bond between atoms and uncover the principle that governs the structures and properties of molecular species. Supramolecular chemistry assays to blend the comprehensive resources of molecular chemistry with designed control of the intermolecular interactions to engineer supramolecular with features as well defined as those of the constituent molecular themselves. Not surprisingly, it has been stated that supramolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond. In the realm of molecular crystals, the focus of supramolecular chemistry and indeed, the scope of the present thesis coverings with that of a rather recent, but rapidly emerging scientific discipline, namely crystal engineering. Coined nearly four decades ago in connection with photodimerization reaction in crystalline cinnamic acids, the term “crystal engineering” has since then broadened its expanse considerably and is, at present, most appropriately defined as “the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties”.

It would be befitting to remark that it is very pursuit (and more often than not, the elusive target) of being able to make functional solids by design that has allowed crystal engineering to evolve from an object of mere scientific curiosity to a subject of tremendous utilization value. No proof for this assertion might be greater than that which lies in the fervent efforts put forth by pharmaceutical companies in understanding and controlling drug polymorphism, especially in the wake of the contemporary legal implications attendant with observing such a phenomenon. Polymorphism in molecular crystals results from the possibility of at least two different arrangements of the molecular of a given compound in the solid state and has therefore often been regarded as the “dark side” of crystal engineering. On one hand, polymorphism presents itself as an important probe in the study of structure-property relationship and allows elucidation of the varied macroscopic properties of the same molecule self-assembled in different crystalline environments. On the other hand, the phenomenon poses an implicit complication when predicating the product of a crystallization process forms the goal of a crystal engineering project. This is particularly true in case of crystal structure prediction (CSP) from the molecular structure of a given compound, where the experimentally obtained polymorphic modification may be a kinetic form and therefore, need not correspond to the one ranked lowest in energy from the computational studies.

Indeed, this dichotomy between a thermodynamically controlled and a kinetically controlled crystallization process reflects the underlying uncertainty associated with judging the outcome of a crystallization event. In this concept of a supramolecular synthon has been postulated to assimilate both thermodynamic and kinetic alternative, and therefore provide a working model for heuristic crystal design. By analogy with Corey’s definition of a molecular synthon, a supramolecular synthon has been described “a structural unit within a supramolecule which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions”.

Being entirely probabilistic in nature, the robustness and thus, the transferability of a
A brief overview of each chapter is presented below.

**Chapter 1.** Relating intramolecular O-H…O hydrogen bonds to conformational locking: Design and self-assemblies of crystalline polycyclitols.

**Chapter 2.** Preferences of supramolecular assemblies towards competing inter- and intramolecular O-H…O hydrogen bonds: A case study in crystalline acyl derivatives of conformationally locked polycyclitols.

**Chapter 3.** Synthesis of novel polyhydroxylated flustrates: Probing fluorine interactions in a conformationally constructed environment.

**Chapter 4.** Strength vs. accessibility: Universe the patterns of self-recognition in designer conformationally locked aminoacohols.

The first chapter of the thesis investigates the supramolecular chemistry of an O-H…O Hydrogen Bond formed between hydroxyl groups that have been constrained to occupy spatially invariant position in the crystal structure of a polycyclitol (a portmanteau word derived from *polycyclic cyclitol*). Having been constructed on a grid trans-decalin carbocyclic backbone, the polycyclitols under study 1-6 are conformationally locked and destined to exhibit an axial rich disposition of the hydroxyl groups, so that the OH functionalities in 1,3-relationship are automatically brought into a favorable geometry for the formation of intramolecular O-H…O hydrogen bonds. Working within this paradigm, which was formulated both logically and on the basis of the observed H-bonding patterns in the crystal structures of several conformationally locked polyols, we were able to demonstrate that intramolecular H-bonding between 1,3-syndisxial OH groups can be used as a tool to preordain the position of the intermolecular O-H…O bond donors and accepts in the specially crafted polycyclitolol 1-3. This observation not only simplified a qualitative visualization of the various packing patterns in 1-3, but also allowed us to propose, based on previously reported CSD analysis, the packing motifs most likely to converge with the experimental results. Despite its qualitative nature, the O-H…O hydrogen bonding pattern, proposed for 1-3 were found to conform well with those observed experimentally for the tetrolys 1 and 3, and even for the two polymorphic modifications of the hexol 2.[Figure 1]
The determination role played by intramolecular O-H…O bonding in the supramolecular assembly of 2, a novel bicycle C$_{2h}$ symmetric hexol having an all axial disposition of the six hydroxyl functionalities, prompted us to study the crystal packing of the three diastereomeric perhydro-2,3,4q,6,6,8a-naphthalenehexols 4-6, the end-to-end co-operative intramolecular O-H…O-H hydrogen bonding chain on both faces of the molecule, as observed in case of 2, through an axial-equatorial.

**Figure 1.** (left) one of the packing modes proposed for the hexol 2. Note that the H-bonding pattern involves all donor/acceptor oxygen and incorporates infinite chains of O-H…O bonds of O-H…O bonds; (right) Molecular packing observed experimentally in the polymorph of the hexol 2. Transposition of one or more of the peripheral hydroxyl groups. With increased freedom now allowed to the OH groups in the choice of their H-bonding partners, as a compared to 2 crystal packing in the polycyclitols 4-6 evolved from the simplistic model of hydrogen bonding proposed and observed for 2, to invoke more complex patterns of self-assembly mediated through O-H…O-bonds.

In the second chapter, the crystal structures of four conformationally locked esters, namely tetraacetate 7/tetrabenzoate 8 of hexol 2 and the diacetate9/dibenzoate 10 of tetrol1, have been analyzed in order to examine the preference of their supramolecular assemblies towards competing inter and intramolecular O-H…O hydrogen bonds. To this end, all the four esters under study were specially crafted on a trans-decalin backbone with the objective of relegating the O-H…O H-bond donors (in form of the 3° OH groups) to the molecular interior and having the peripheral H-bond accepters (in form of the 2° acylgroups) in 1,3-syndiaxial relationship. It was anticipated that this common design element would allow the supramolecular assembly of the esters to evolve along two possible pathway, namely one which employs intermoleculars O-H…O H-bonds (pathway 1) and the other that sacrifices those for intramolecular O-H…O H-bonds and settles for a crystal packing dictated by weak intermolecular interactions alone (pathway 2).

A pure sample of 7 crystallized along pathway 1 in two enantiotropic modifications, one obtained at room temperature (form) and the other at 20°C (form) [Figure 2]. Behaving much like a temperature guided molecular switch, the tetraacetate 7 could be shifted reversibly between the forms response to changes in the ambient temperature. Thus, the form converted at -4°C to the denser form, which displayed an unusual kinetic stability till 67°C and transformed back to the form beyond this temperature. Subsequently, the close similarity between the self-assembly of the two dimorphs of 7 and the diastereomer 11 was exploited in order to stimulated 7 to follow the pathway 2 through preferential inhibition of pathway 1[Figure 3]. Interestingly, the nucleation inhibition 11 was obtained serendipitously a route 7 via an apparent breakdown of first-platter rule.

Unlike the tetracetate 7, crystal packing in the tetrabenzoate 8 preferred to follow exclusively pathway 2. The individualistic nature of the self-assembly of 7 and 8 found to be in contrast commonalities noted in the mode of molecular assembly in 9 and 10 both of which conformed to a combination of pathway 1 and 2. A rationale for the preferred crystallization pathway of the four estes 7-10 as well as probable mechanism for the observed reversible transformation between the forms the tetracetate 7 will be put forth in this chapter.

**Figure 2.** (Model for pathway 1) Molecular packing in the forms of the tetraacetate 7. The non-interacting hydrogen atoms have been omitted for clarity.
**Figure 3.** (Model for pathway 2) The nucleation inhibitor 11 and form of the tetraacetate 7. The non-interacting hydrogen atoms have been omitted in the molecular packing diagram for clarity.

In light of the wide ranging application of organofluorine compounds and the ambiguity that resides over the disposition of fluorine as a H-bond accepter, the **third chapter** utilizes three specially designed fluorinated polycyclitols 12-14 investigate the role of covalently bonded fluorine in crystal structures of lesser studied aliphatic fluorous substracts and probe its capacity to engage itself in C(sp\(^3\))-F…H-X(sp\(^3\))(X=O and/or C) H-bounding, in presence of its isostere, the hydroxyl group. Conformationality locked with well defined spatial disposition of functional groups, all the fluorinated polycyclitols 12-14 bear a fluorohydrin moiety, embedded in a rigid trans-decalin framework. In 12 and 14, it was conceived that the presence of a hydroxyl donor in a favorable 1, 3-syndiaxial relationship to a fluoro group on one side and a hydroxyl group on the other would allow an unambiguous comparison between the two isoteric functionalities (C-OH and C-F) to serve as acceptors for intramolecular hydrogen bonds (O-H…O and purported O-H…F respectively) The difluorodiol 13 was sought to serve as a control to assess the change in the C-F…H-X interactions (if any) which might be observed upon incorporating the peripheral secondary hydroxyl groups in 14. The result presented in this chapter will revel, in particular, that C(sp\(^3\)) –F…H-C(sp\(^3\)) hydrogen bonds, though weak and lesser investigated, can indeed be observed and supramolecular recognition motifs, involving such interactions, can be conserved even in crystal structures laden with stronger O-H…O hydrogen bonds [Figure 4].

**Figure 4. (Left)** Molecular packing in the difluorodiol 13, showing how four intermolecular C-H…F hydrogen bonds forms a part of a R\(_2^2\) H-bonding motif (encircled). This centrosymmetric supramolecular recognition unit is observed even in the molecular packing in the difluorohexol 14 (right). Non-interacting H atoms have been omitted in both diagrams for the sake of clarity.

The **forth chapter** details an in-depth study carried out on the self-assembly of a conformationally locked aminoalchohol 15, in which the amino protons serve as mere spectators, the molecular packing in the crystal being realized through the cooperativity between O-H…N H-bonds and weak \(\pi\)-\(\pi\) stacking interaction (Figure 5b). The crystal structure of 15 was quite intriguing on three sailet grounds (a) previous studies on the supramolecular assemblies in the aminols have shown that both amino and hydroxyl protons participate in H-bonding in the crystal structures of such compounds; (b) the fact that the hydrogen atoms of the NH\(_2\) group remain as mere bystanders in anomalous if one were to abide by the Etter’s rule; (c) the rather well-defined \(\pi\)-\(\pi\) stacking interactions in crystal structure of the aminoalcohol occurs between isolated olefinic bonds-a rarely encountered form of non-covalent interaction. Charge destiny analysis was carried out on the aminoalchohol 15 not only to catheterize the non-covalent interactions existing in the supramolecular assembly in terms of topological features of electrol destiny at their bond critical points, but also to confirm the non-involvement of the amino H-atoms in any form of either intra- or intermolecular hydrogen bonds beyond the criteria of mere geometry (Figure a,c,d). The maverick nature of the self-assembly of 15 was elucidated as resulting from the preference of the
molecules to assemble with O-H…N H-bonds. This automatically relegated the hydrogen atoms of the tertiary amine to the interior of the conformationally locked cabocyclic scaffold, thereby making them far less accessible than the peripheral C=C bonds.