

**Supramolecular Chemistry of Thiazole Based Urea/Thiourea and
Imine/Amine Derivatives: Polymorphism, Molecular/ion recognition**



Synopsis of the PhD Thesis

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Title of the thesis

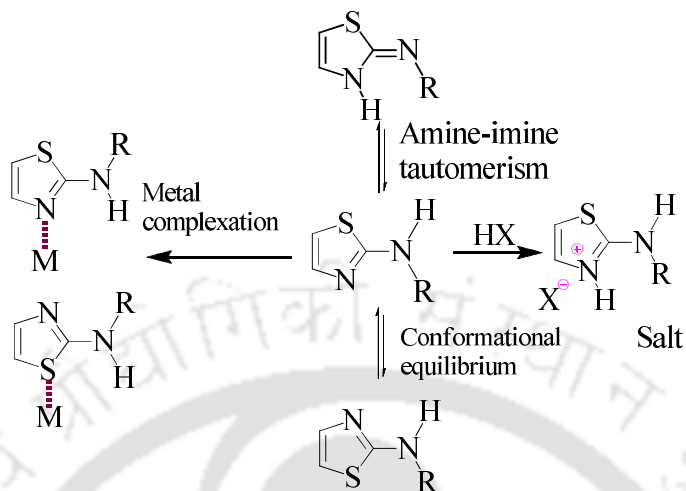
Supramolecular Chemistry of Thiazole Based Urea/Thiourea and Imine/Amine Derivatives: Polymorphism, Molecular/ion recognition

Synopsis

Self-assembly, guided by non-covalent interactions is one of the fundamental features associated with biological systems. Inspired by this biological phenomenon, self-assembly has become a key step for miniaturization of functional devices and the development of future nanotechnology.^{1,2} Self-assemblies of small organic heterocyclic molecules generates interest in modern supramolecular chemistry for developing molecular devices and machines, molecular/ion recognition processes.³ Hydrogen bonds play the major role to control architecture self-assemblies of small molecules.⁴ Many small molecules act as supramolecular catalyst.⁵ and served as template to control chemical reactivity by forming host-guest complexes.⁶ Challenges in small molecule self-assemblies is to understand the reasons why a molecule selectively adopts a particular conformation in the crystal lattice. Molecular conformation is a subtle but important property in the chemistry of organic solid state⁷. Material properties associated with many molecules are controlled by conformations, for which self assemblies of small molecules can provide the basis for understanding. Due to the importance of predesigned non-covalent synthesis, understandings of different types of synthons that are present in self-assemblies of small molecules are important.⁸ Multi-component cocrystals build up in systematic manner by small molecules provides avenue for non-covalent synthesis.⁹ Small molecules have contributed significantly to understand anion-guided assemblies, and some of which finds important applications in material chemistry and in ion detection.¹⁰ On the other hand, study on cocrystals of small organic molecules helps in establishing the solute-solvate interactions and nucleation process.

Among small organic molecules thiazole functional units are found within many natural products and biologically active compounds such as thiamine (Vitamin B₁)¹¹ and D-Firefly luciferin.¹² responsible for bioluminescence properties of Fireflies. Thiazoles are used as neuroprotectors¹³ and antioxidants.¹⁴ Some thiazole derivatives are used as valuable medicines.¹⁵ Thiazoles can be derivatised with wide range of functional groups.¹⁶ Presence of multifunctional groups on thiazole ring makes them versatile to enhance their bioactivity. They also form biologically potent metal complexes.¹⁷ Aminothiazoles have supramolecular properties and can act as hosts.¹⁸ There are several possibilities to cause slight structural modifications in aminothiazoles. Structural changes can be as a result of (a) amine-imine

equilibrium, (b) rotation around the C–N bond, (c) salt formation, and (d) binding to metal ions, which are illustrated in Scheme 1.



Scheme 1: Possibilities to cause structural modification in aminothiazole

Due to practical applications of thiazole derivatives and ease of introducing function groups to such unit, there are definite scopes to study supramolecular aspects. Such study can include structure-property relationship, biological activity and molecular recognition etc. This thesis deals with studies on synthesis, characterization, polymorphic behavior and ion/s recognition properties of thiazole derivatives. The contents of the thesis are divided into six chapters.

Chapter 1:

The content of this chapter is on a general introduction of thiazole derivatives to bring out the necessity for study of supramolecular aspects of them. To bring a general outlook on pharmaceutical applications, molecular and ion recognition properties associated with thiazole derivatives are discussed. Scope of the work with thiazole derivatives is presented as the last part of this particular chapter.

Chapter 2: Polymorphs and Anion-Assisted Assemblies of Thiourea tethered Thiazole

It is a well known fact that thiourea derivatives are good host for anions.¹⁹ and also act as anion transporters.²⁰ This chapter deals with the polymorphic behavior as well as various anion assisted assemblies formed by thiourea group containing two positional isomeric thiazole derivatives **2.1** and **2.2**.

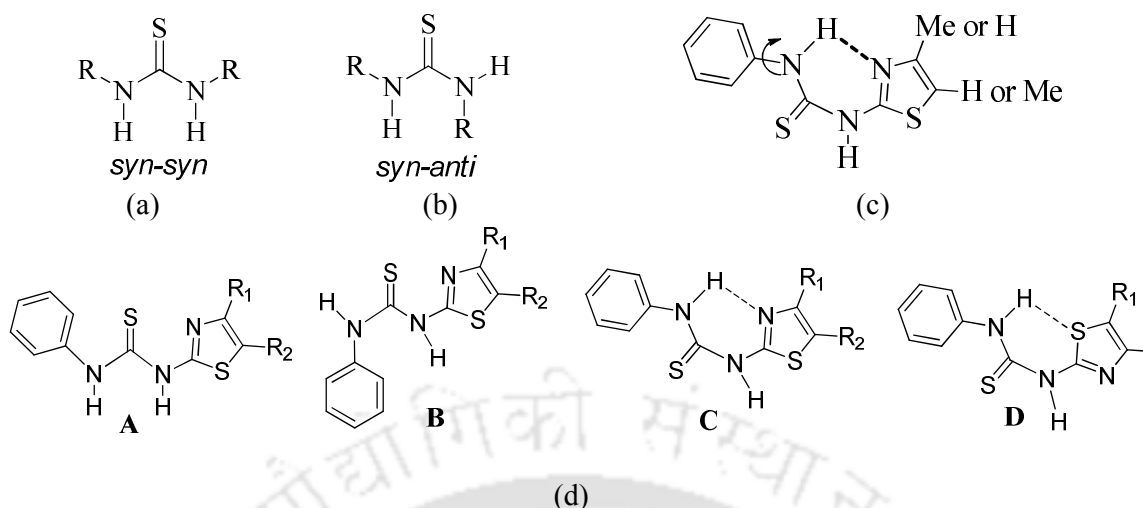


Figure. 2.1: Two different geometries of a symmetric thiourea (a) *syn-syn* and (b) *syn-anti*; (c) Showing the rotation of the phenyl group in **2.1** and **2.2** (d) Some conformers of **2.1** and **2.2**.

Based on the orientation of phenyl-group and intramolecular hydrogen-bond (Figure 2.1c), we isolated three conformational polymorphs of **2.1** named as polymorph **I**, polymorph **II** and polymorph **III**. These three polymorphs belong to $P2_1/c$, $P1$ and $C2/c$ respectively. The self-assembly of each polymorph is comprised of hydrogen-bonded dimeric motifs held together in head to tail arrangement but are packed in different manners. The positional isomer **2.2** is monomorphic as there is an intermolecular C-H \cdots S interaction between a C-H bond of phenyl-ring with sulphur atom of neighboring thiocarbonyl moiety, which locks the orientation of phenyl group in solid state.

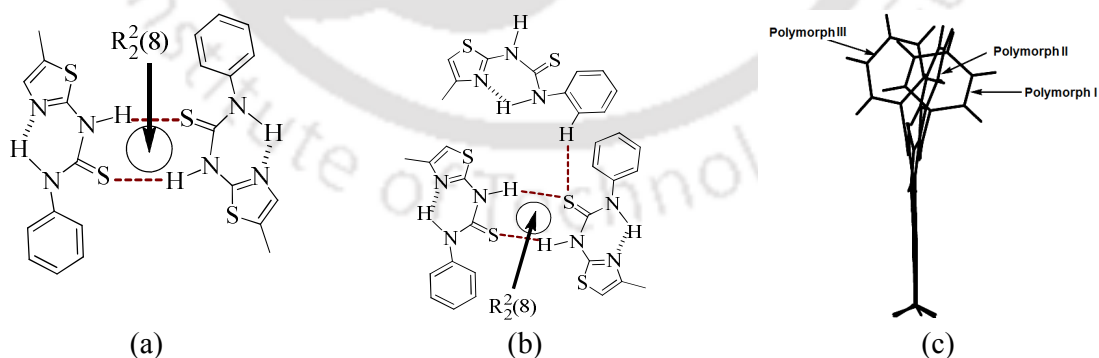
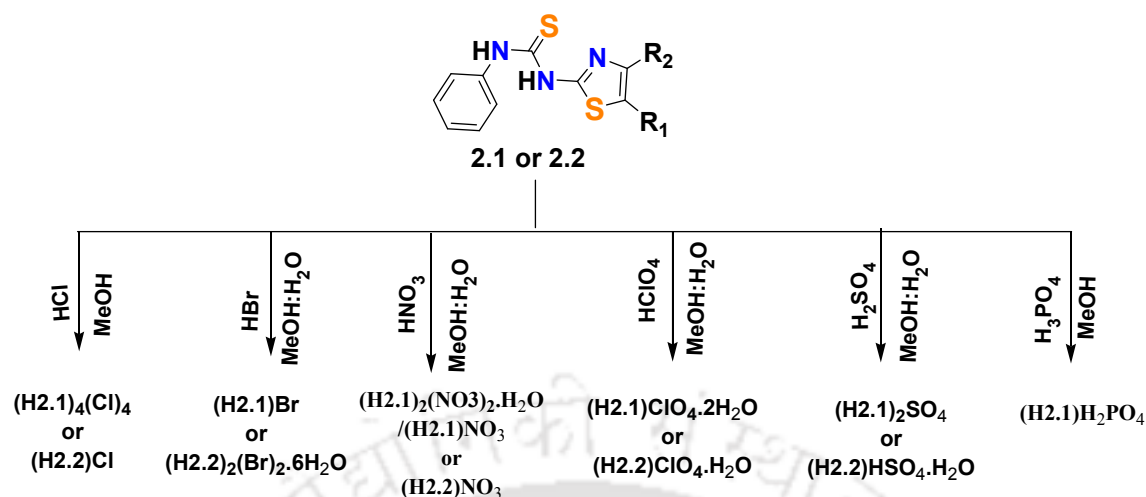


Figure 2.2: (a) Dimeric assembly within the three polymorphs of **2.1** (b) The hydrogen-bonds in the structure of **2.2** showing intermolecular C-H \cdots S interaction. (c) Overlay diagram showing orientations of the phenyl group of three polymorphs of **2.1** (drawn by fixing the 5-methylthiazole planes in one direction).



Scheme 2.2: Schematic diagram showing the synthesis of different salts.

A series of inorganic salts are prepared by treating **2.1** and **2.2** with different mineral acids. It is found that the structure of these salts are influenced by type of host and mainly dependent on the shape and charge on the anions. Here, each salt is composed of protonated host/s that protonated at the nitrogen atom of methylthiazole unit and corresponding hydrated or anhydrous anion/s. The *syn-anti* conformation across the thiourea group originally present in the positional isomers **2.1** and **2.2** are invariably transformed to *syn-syn* conformation in their salts. The anhydrous chloride salt of **2.1** has large difference in packing patterns with corresponding anhydrous chloride salt of **2.2**; they also differ in the numbers of symmetry non-equivalent molecules in their respective unit cells. The bromide salt **2.1b** is a one-dimensional polymeric chain, while **2.2b** provided platform for stabilization of a bromide-water cluster having composition $\{\text{H}^+(\text{2.2})\}_2(\text{Br})_2 \cdot 6\text{H}_2\text{O}$ as shown in Figure. 2.3a.

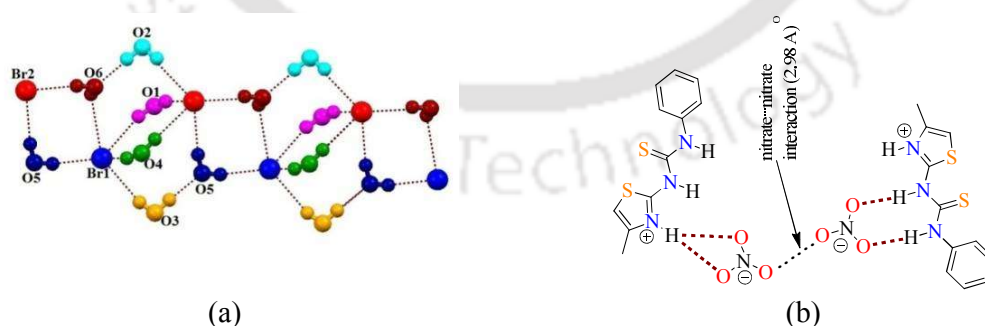


Figure 2.3: (a) Two units of bromide-water cluster present in 2.2b. (b) Hydrogen-bonds in the anhydrous nitrate salts 2.2c.

We obtained hydrated and anhydrous form of nitrate salts of **2.1**, namely, $\{H^+(2.1)_2\}(NO_3)_2 \cdot H_2O$ (**2.1c**) and $\{H^+(2.1)\}NO_3$ (**2.1c'**), but only anhydrous form in case of **2.2**, namely $\{H^+(2.2)\}NO_3$ (**2.2c**). The anhydrous nitrate salts **2.1c'** and **2.2c** have structural similarities by having nitrate...nitrate interactions (Figure 2.3b), which is lost in hydrated form **2.1c** by a water molecule of hydration.

The ability to abstract proton from sulphuric acid to form crystalline salts by the **2.1** and **2.2** differs. The sulphate salt $\{H^+(2.1)\}_2(SO_4)$ (**2.1e**) is formed by reaction of sulphuric acid with **2.1**, but **2.2** forms bisulphate salt $\{H^+(2.2)\}HSO_4 \cdot H_2O$ (**2.2e**). The lattice water molecules bridges the bisulphate ions and form a $R_4^4(12)$ hydrogen-bond motifs in **2.2e** as shown in Figure 2.4a.

The **2.1** forms corresponding dihydrogenphosphate salt, namely $\{H^+(2.1)\}H_2PO_4$ (**2.1f**). On reaction with orthophosphoric acid; the dihydrogenphosphate anions are held together in the form cyclic hexameric hydrogen-bonded assemblies in the lattice as shown in Figure 2.4b. To the best of our knowledge, it is a new type of hexameric assembly of dihydrogenphosphate. Whereas, we could not obtain crystalline salt from the reaction of orthophosphoric acid with **2.2**.



Figure 2.4: (a) $R_4^4(12)$ hydrogen-bond motif in bisulphate-(water)₂-bisulphate assembly formed within **2.2e** (b) Cyclic-hexameric assembly of the dihydrogenphosphate ion of **2.1f**.

The detail synthetic procedure, spectroscopic characterization and thermal analysis of polymorphs and salts are available in the experimental section which is included at the end of the chapter.

Chapter 3: Conformational adjustments over hydrogen bonded synthons of urea and thiourea derived Thiazole.

In this chapter, conformational adjustments of rotatable group acting like a top over hydrogen bonded motifs is studied in multi-component crystals.

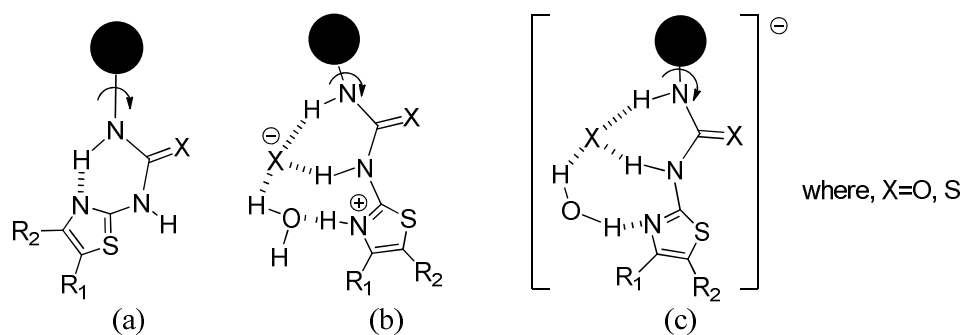


Figure 3.1: Models to show rotation of a top over (a) thiazole derived six-member intramolecular hydrogen bonded hetero synthon, (b) Protonated thiazole locked by anion and water, (c) Neutral thiazole derived urea/thiourea derivative holding an anion and water.

We have chosen a set of molecules shown in chart 3.1 to understand generality of conformational adjustment across hydrogen bonded cyclic motifs. Polymorphs of compound **3.1** are designated as **3.1a** and **3.1b** while **3.2a** and **3.2b** for compound **3.2**. Due to the presence of intramolecular hydrogen bonds all the polymorphic forms adopt *syn-anti* orientation across the thiourea unit. In each case, dimeric hydrogen bonded assemblies are observed.

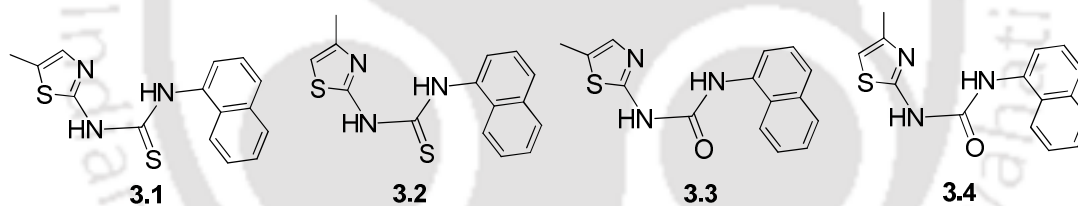


Chart 3.1: Different *n*-methylthiazole (*n*=5,4) containing positional isomers of urea and thiourea derivatives.

Crystallization of **3.3** and **3.4** from various solvents did not yield polymorphs of any of these compounds. Structures elucidation of **3.3** and **3.4** have showed similar conformations across the urea moiety as that found in the corresponding thiourea derivatives. The packing patterns of the compounds **3.3** and **3.4** showed that one -NH of urea is involved in intramolecular N-H⁺⋯N with N-atom of the methylthiazole unit.

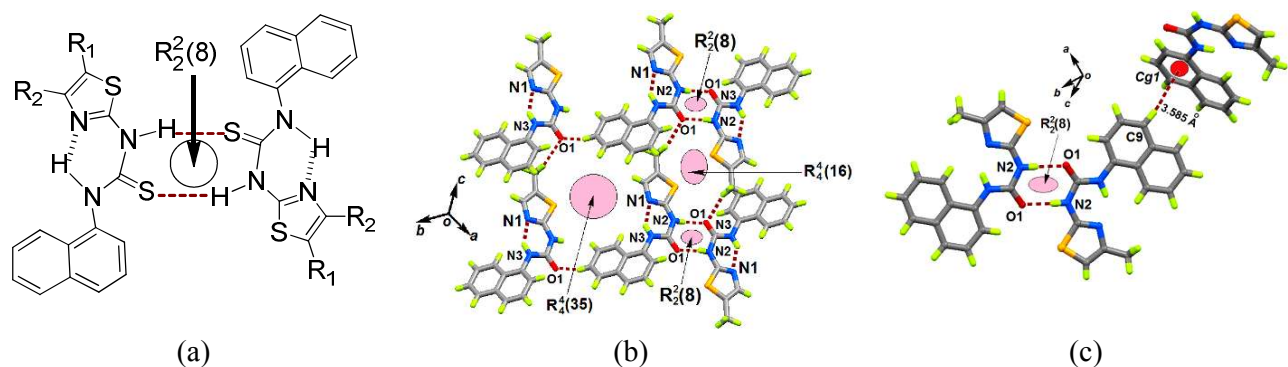
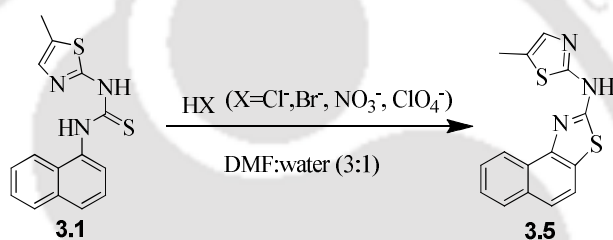


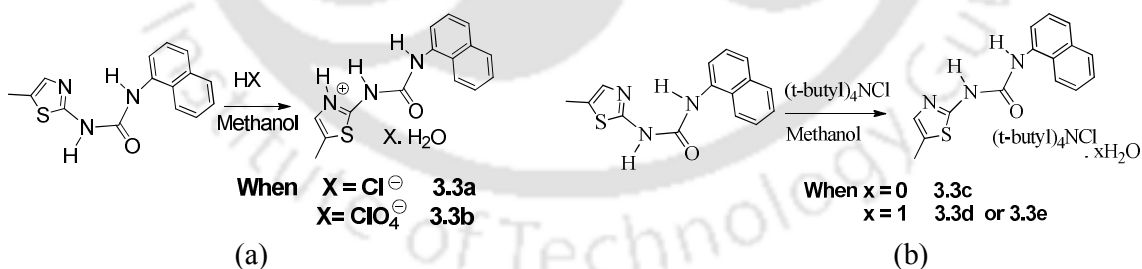
Figure 3.2: (a) Dimeric assemblies of polymorphs of **3.1** and **3.2**. Hydrogen-bonded assembly within the crystal lattice of (b) **3.3** and (c) **3.4**.

Compound **3.1** underwent cyclization reaction in presence of different acid such as HCl, HBr, HNO₃, HClO₄, and H₃PO₄. In each case the compound **3.5** (Equation 3.1) was formed.



Equation 3.1: Acid catalysed cyclization of compound **3.1**

Two crystalline salts of urea derivatives **3.1** were prepared by reacting **3.1** with hydrochloric or perchloric acid as shown in Equation 3.2. Chloride salt **3.3a** and perchlorate salt **3.3b** were obtained as hydrate.



Equation 3.2: (a) Crystalline salts of urea derivative **3.3**; (b) Cocrystallization of **3.3** with tetrabutylammonium chloride.

Overall packing pattern shows that the chloride ions are involved in trifurcated hydrogen bond acceptor. Due to protonation of the thiazole nitrogen, the intramolecular N-H...N hydrogen bond present in the parent compound is lost and new motifs as shown in Figure 3.4a is formed. Within the crystal lattice of salt **3.4b**, perchlorate anion did not participate in

bifurcated hydrogen bonds despite of having a negative charge on the oxygen atom but chloride ion are part of bifurcated hydrogen bond with -NH of urea.

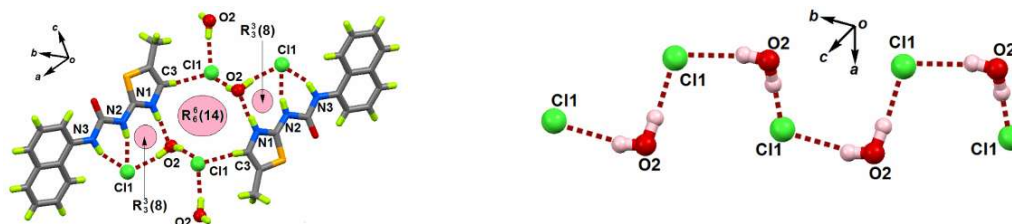


Figure 3.4: (a) Various weak interactions in salt **3.2a** (b) Aquated chloride ions in **3.2b**.

Three different cocrystals of **3.3** with tetrabutylammonium chloride (TBACl) were crystallized concomitantly. One type of crystals was identified as simple 1:1 cocrystal with TBACl **3.3c** and other two were polymorphs of hydrated cocrystals designated as **3.3d** and **3.3e** (Equation 3.2b). The cocrystals of urea with tetrabutylammonium chloride provided us the basis to explore neutral urea interacting with chloride ion in different supramolecular environments. Due to coordination of urea to the anion, the two rings across the urea moiety are organized *syn* to each other. Hydrated cocrystals crystallized as concomitant polymorphs; one crystallized in triclinic *P*-1 and another in monoclinic *P*2₁/*c* space group.

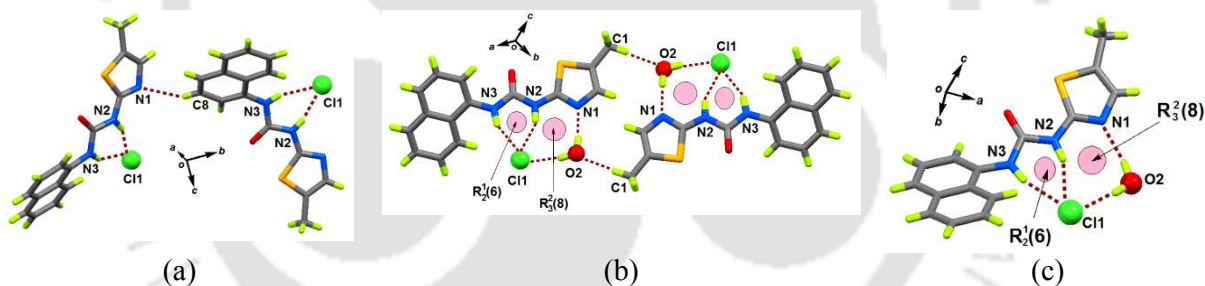


Figure 3.5: (a) Interaction between different components of cocrystal **3.3c** having bifurcated hydrogen bonds. (b) Dimeric motif formed by hydrogen bonds among Cl^- ions, host and water in cocrystal **3.3d**. (c) Structure of cocrystal **3.3e**.

Both the polymorph have water molecule serving as bridge to connect chloride ion with nitrogen atom of thiazole. The major differences in structures of the two polymorphs arise from the orientations of the naphthalene groups.

Thus, a general approach on polymorphism by rotation over intramolecular hydrogen bonded synthon possessing cyclic structure of thiourea derivatives has been established.

Chapter 4: Imine-tautomers of Aminothiazole Derivatives: Intriguing aspects of Chemical Reactivities

Several solvent and ion guided crystallization and signal transduction processes of 1-(5-methylthiazol-2-yl)-3-(4-nitrophenyl)thiourea (**4.1**) and 1-(4-methylthiazol-2-yl)-3-(4-nitrophenyl)thiourea (**4.2**) are presented in this chapter. Structural elucidation shows that **4.1** and **4.2** adopt imine form in solid state (Figure 4.1c) reflected in the bond parameters of C4-N1 and C4=N2.

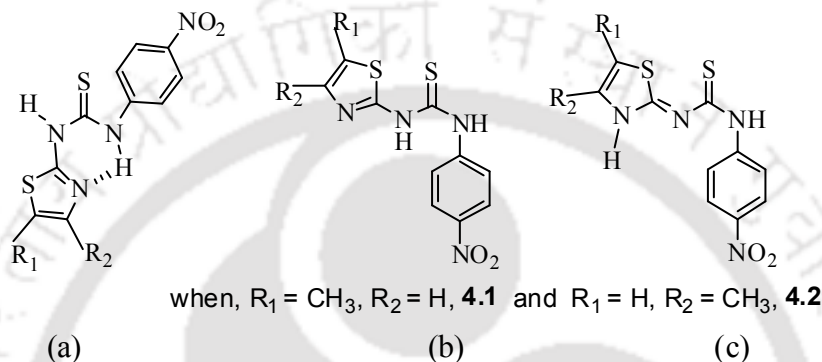
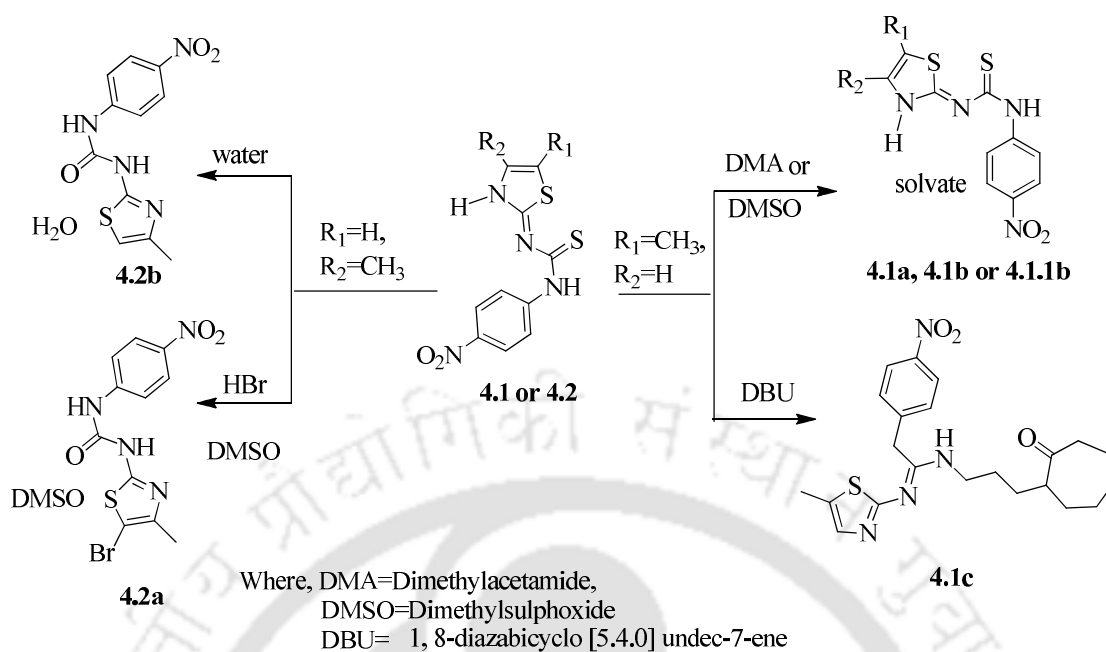


Figure 4.1: (a-b) Conformers of amine form and (c) imine form of **4.1** or **4.2**.

Solvent play a crucial role in catalytic reactions of thiourea derivatives. With such an anticipation we attempted preparation of solvates of **4.1** and **4.2** with dimethylformamide or dimethylacetamide having C=O as acceptor for hydrogen bond and dimethylsulfoxide which has S=O as the acceptor to form hydrogen bond. But, we find that the isomers **4.1** and **4.2** showed distinguishable reactivities in solution (Scheme 4.1).

Solvate **4.1b** has R₂²(8) and R₂²(24) type dimeric assembly of host molecules formed through N-H...S and N-H...O interactions as shown in Figure 4.2a. The metastable form **4.1.1b** has only one type of cyclic hydrogen bonded motif that is R₂²(8), guided by N-H...S interactions. In this case the dimethyl formamide molecules are present as discrete unit (Figure 4.2b) but in a disordered manner by sharing of the carbon atoms as well as the nitrogen atoms at two equivalent positions.



Scheme 4.1: Reactivity of the 4.1 and 4.2 towards different solvents.

Upon heating the mixture of the two forms (4.1b and 4.1.1b) under mild condition at 50 °C for about 10 minutes the metastable form 4.1.1b transforms to stable form 4.1b, which was confirmed by comparing the samples before heating and after heating as illustrated in Figure 4.2c.

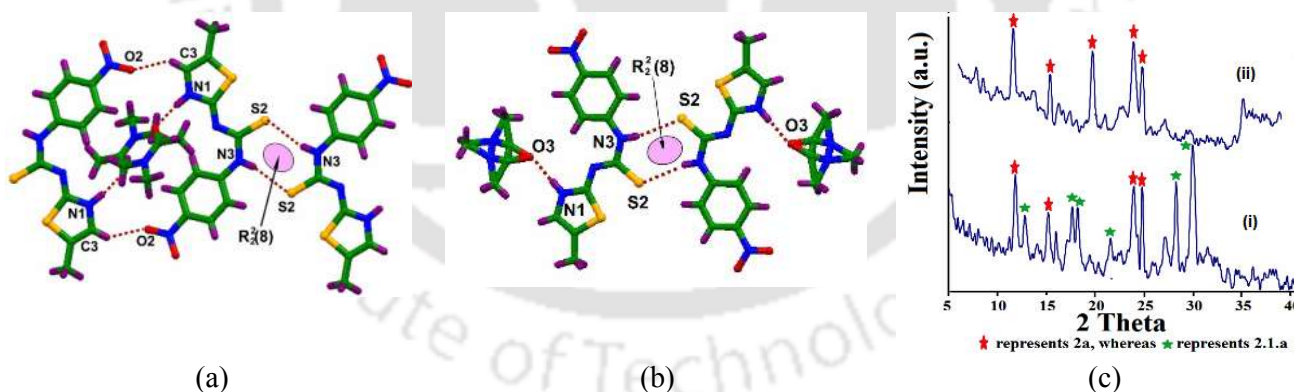
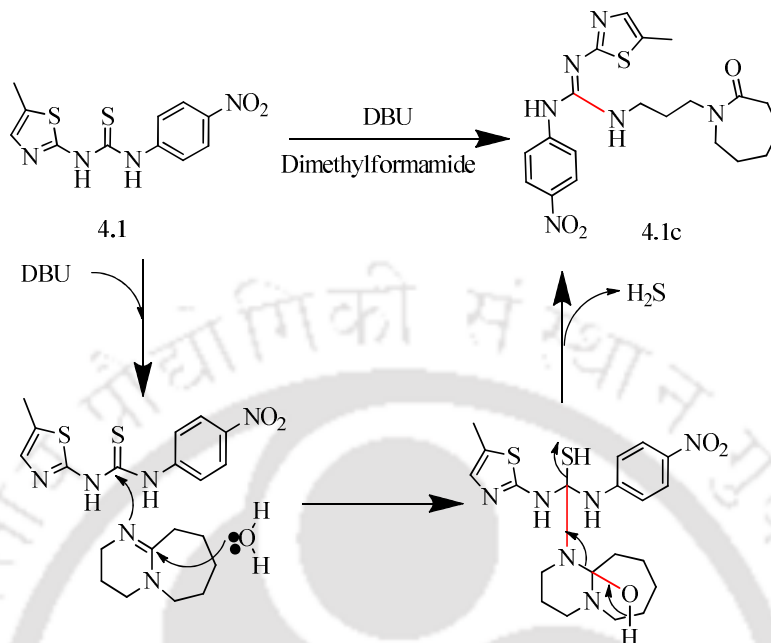


Figure 4.2: Hydrogen bonded cyclic motifs in the self-assemblies of the solvates (a) 4.1b (b) 4.1.1b; (c) Powder X-ray diffraction patterns of a mixture of 2a and 2.1a (i) as obtained, (ii) after heating mixed crystal of 2a and 2.1a at 50 °C for 10 mins.

The compound 4.1 reacted with 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) to give ring opened product (4.1c) illustrated in Scheme 4.2. This observation is significant from the point

that it cautions on the limitation of using DBU as a solvent while performing a reaction with a thiourea derivative.



Scheme 4.2: A plausible mechanism on formation of 4.1c.

Small heterocyclic organic molecules are useful for selective detection of ions. Selective interactions of **4.1** and **4.2** were checked with chloride salts of various metal ions Na⁺, K⁺, Ca²⁺, Mg²⁺, Cr³⁺, Hg²⁺, Cu²⁺, Pb²⁺, Zn²⁺, Fe³⁺, Al³⁺, Co²⁺, Ni²⁺, Cd²⁺ and Ag⁺. Among these only interactions of Hg²⁺ ions with **4.1** and **4.2** resulted in characteristic colorimetric change. The selective colorimetric change induced by Hg²⁺ ions is attributed to easy hydrolysis of thiourea to urea. Incremental addition of Hg²⁺ to **4.1** rendered a systematic growth of the absorbance maxima at 355 nm with a simultaneous decrease of the peak at 400 nm. To confirm the binding mechanism ¹H-NMR spectra of **4.1** and **4.2** were recorded in absence of Hg²⁺ and at different Hg²⁺ concentrations (Figure 4.4).

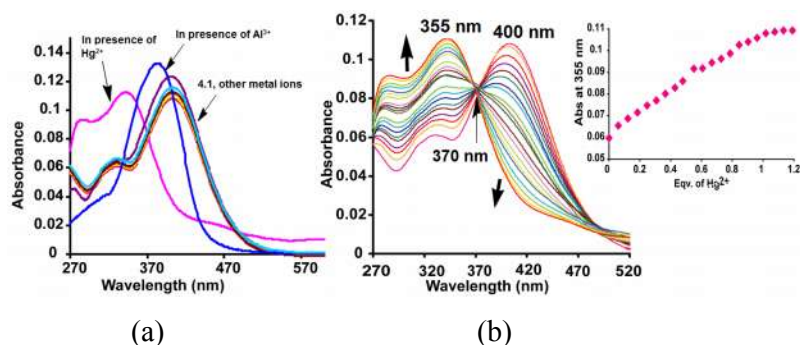


Figure 4.3: UV-Visible spectra of (a) **4.1** ($5 \mu\text{M}$) in the presence of 10 equivalents of various metal ions in dimethylformamide solution. (b) **4.1** ($5 \mu\text{M}$, 4.0 mL) with incremental addition of the Hg^{2+} in dimethylformamide solution. inset: change in absorbance at 355 nm with the equivalents of Hg^{2+} added into the solution.

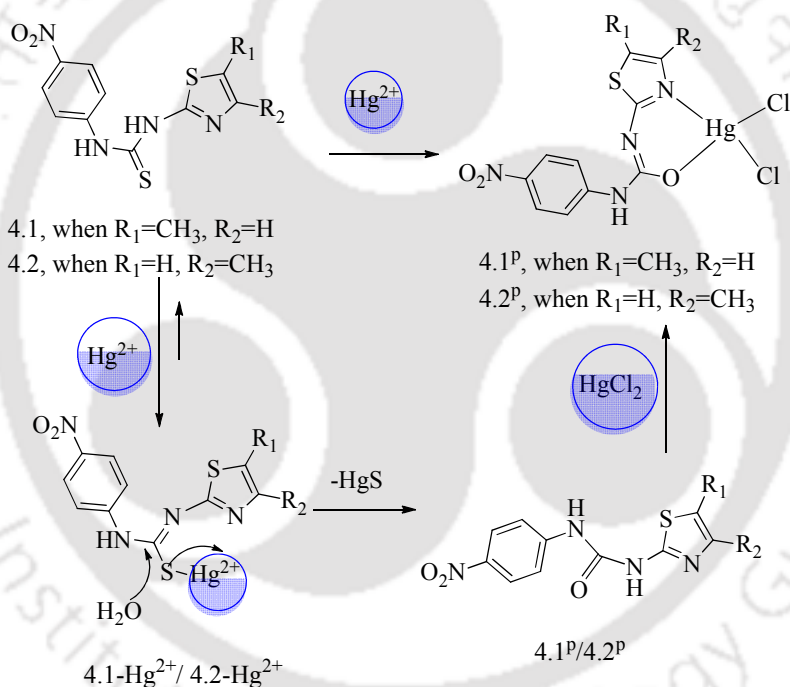


Figure 4.4: Schematic representation of mechanism of Hydrolysis of **4.1** and **4.2** and complexation with Hg^{2+} .

The binding selectivity of **4.1** and **4.2** was checked with various anions such as, F^- , Br^- , Cl^- , I^- , SO_4^{2-} , HSO_4^- , PF_6^- , NO_3^- , HPO_4^- , H_2PO_4^- , OAc^- , ClO_4^- etc by taking the respective tetrabutylammonium salts. Only tetrabutylammonium fluoride able to induce a significant colorimetric response in dimethylformamide as well as in dimethylsulphoxide. These changes caused visual color change from yellow to orange red (Figure 4.5a inset).

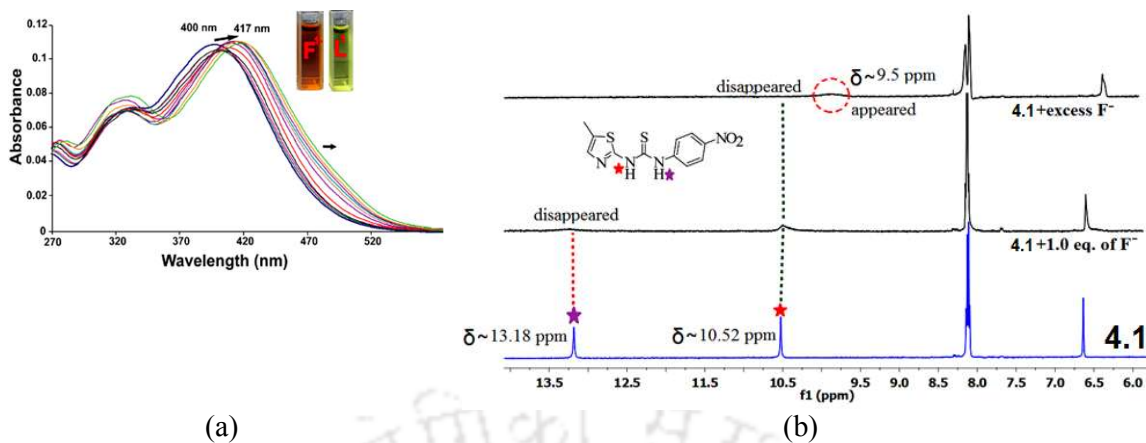
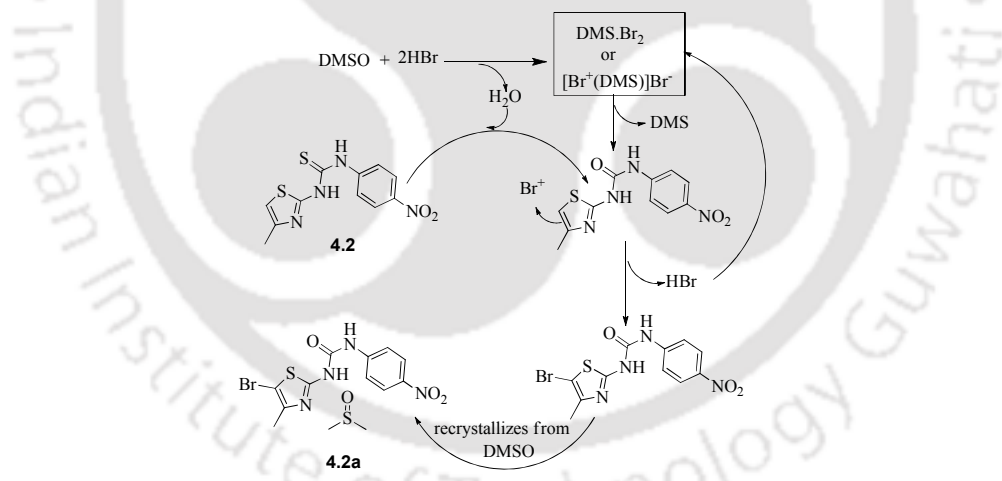


Figure 4.5: (a) Absorption spectra of **4.1** ($5 \mu\text{M}$) in DMF. (b) $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 600MHz) spectra in the region of 6-14 ppm of **4.1** during titration with tetrabutylammonium fluoride.

We found that between the two positional isomers, **4.2** reacted with hydrobromic acid and it yielded a very selective bromo derivative **4.2a** as illustrated in Scheme 4.3. Though this reaction was slow and yet this was an interesting reaction as it was specific to compound **4.2**. The compound **4.2** underwent hydrolysis and reacted with hydrobromic acid to form the brominated product **4.2a**.



Scheme 4.3: Proposed mechanistic path on the formation of **4.2a**.

We addressed here the need for a robust and holistic approach to investigate the intrinsic reactivities of two positional isomers.

Chapter 5: Part A: Polymorphs of Thiazole-Derived Imines Tethered Hydroxyaromatics.

This chapter deals with the role of intramolecular and self-assembling properties of thiazole derivatives connected to aromatic hydroxy compounds. For this purpose, we synthesized two thiazole tethered imine derivatives namely (E)-2-(((5-methylthiazol-2-yl)imino)methyl)phenol (**5.1**) and (E)-1-(((5-methylthiazol-2-yl)imino)methyl)naphthalen-2-ol (**5.2**).

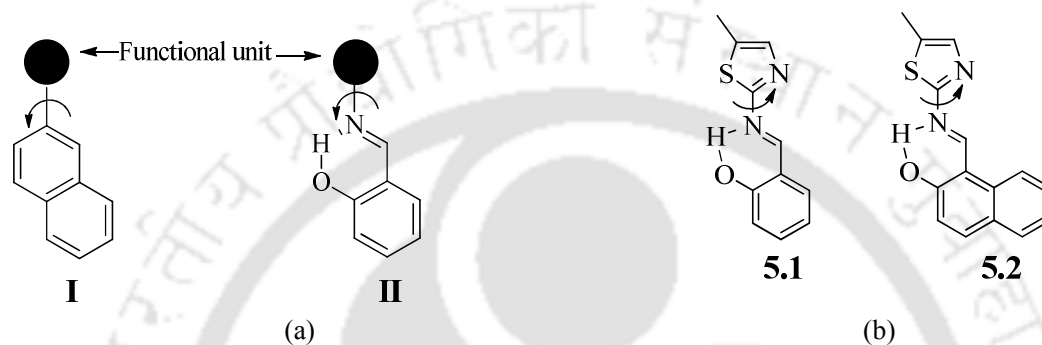


Figure 5.1: (a) Possible rotation of functional unit attached to (I) naphthyl ring, (II) intramolecular hydrogen bonded six-member ring above a phenyl ring. (b) Thiazole-tethered hydroxyaromatic imines **5.1** and **5.2**, with arrows showing possible rotations.

Thioimidazole has N- and S-atoms in a five-membered planar ring separated by an intervening carbon; thus, the orientation of such a planar unit across an unsymmetrical planar unit, like **5.1** and **5.2** in Figure 5.2b, would lead to conformational polymorphs. Presence of a methyl group at 5-positions of thiazole in these compounds would contribute a steric factor to stabilize or destabilize a particular conformer(s) generated through C–N rotation. A series of crystallization from different solvents were carried out leading to different types of crystals Morphologies of each polymorph was different. The polymorphs are designated as polymorphs **5.1a** and **5.1b** for compound **5.1** whereas **5.2a** and **5.2b** for compound **5.2**.

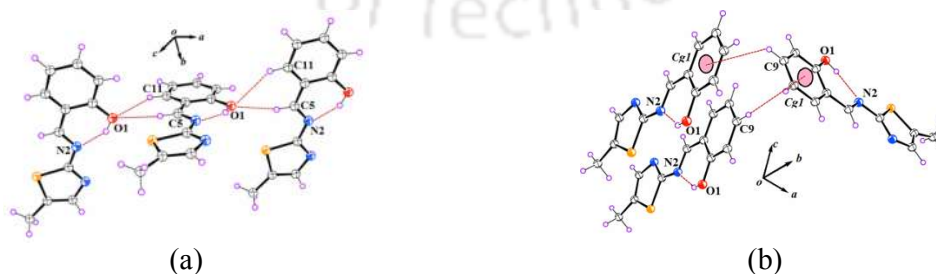


Figure 5.2: (a) Hydrogen bonds in polymorph **5.1a**. (b) C-H... π interactions in **5.1b** (d) C9-H... π = 3.531 Å, where π is the centroid of the phenyl ring).

Polymorph **5.2a** exists as dimeric assemblies in its crystal lattice through very weak C-H···O interactions, as shown in Figure 5.3(b). The structure also shows the presence of an intramolecular O-H···N hydrogen bond. Polymorph **5.2b** contains two symmetry-equivalent molecules in its asymmetric unit ($Z' = 2$). The two symmetry independent molecules are connected to each other through C-H···N interactions via a C-H of the naphthyl ring interacting with the N-atom of the thiazole unit of a neighboring molecule of **5.2b**, as shown in Figure 5.3(c).

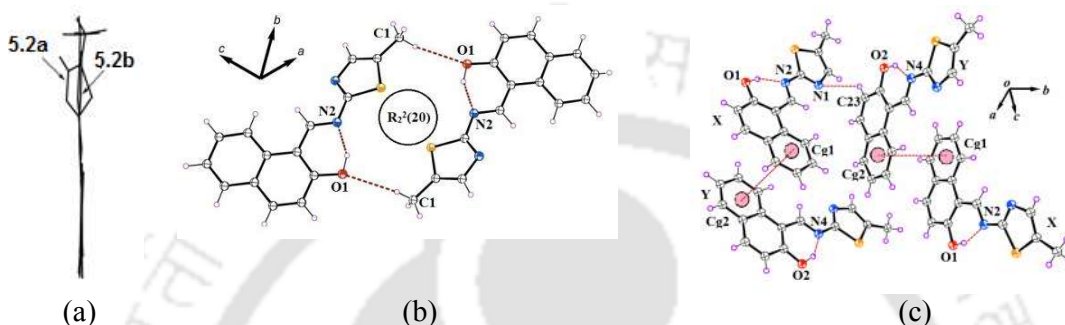
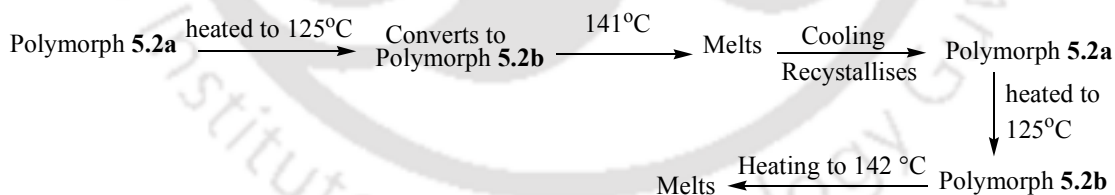
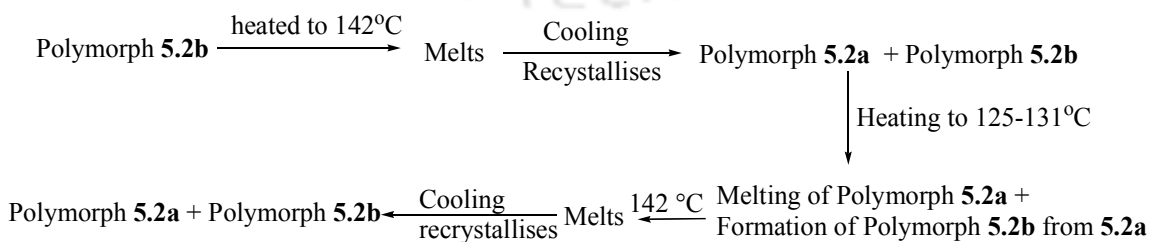


Figure 5.3: (a) Overlay diagram of molecules from polymorphs **5.2a** and **5.2b** shown by fixing hydroxynaphthyl unit in one plane. (b) Hydrogen bonds in polymorph **5.2a**. (c) π - π Stacking interactions in lattice of **5.2b**.

DSC plots of **5.1a** and **5.1b** showed conventional features of melting, with their respective melting points at 118 and 117 °C. However, DSC of polymorphs **5.2a** and **5.2b** revealed several interesting features. Schematic representations of the thermal events occurring in polymorphs **5.2a** and **5.2b** are shown in Schemes 5.1 and 5.2 respectively.



Scheme 5.1: Thermal events of Polymorph **5.2a**



Scheme 5.2: Thermal events of polymorph **5.2b**

Thus, conformational polymorphs arising due to different orientations of thiazole ring via C-N bond rotation over intramolecular hydrogen bonded six member ring have been established.

Chapter 5: Part B: Detection of Al³⁺ and Zn²⁺ ions by 2-(5-methylthiazol-2-yliminomethyl)phenol

In this chapter, we have studied Al³⁺ catalyzed hydrolysis of 2-(5-methylthiazol-2-yliminomethyl)phenol (**5.1**). This reaction can be specifically used for detection of Al³⁺ ions in the presence of various other ions from the characteristic emission at 446 nm (λ_{ex} =365 nm). We have observed that compound **5.1** undergoes fast catalytic hydrolysis by Al³⁺ ions to form 2-hydroxybenzaldehyde and 2-amino-5-methylthiazole which can be monitored by fluorescence spectroscopy.

On the other hand, addition of Zn²⁺ ions to a solution of **5.1** leads to a strong emission peak at 490nm (Figure 5.7c). This peak is attributed to 1:1 complex formation with **5.1**. Such emission peak was not observed with other metal ions. The characteristic emission at 490nm shown by Zn²⁺ ions with **5.1**, was not interfered by the other metal ions such as Zn²⁺, Ni²⁺, Cu²⁺, Hg²⁺, In³⁺, Na⁺, and Li⁺. However, Al³⁺ ion is an exception to this, upon addition of catalytic amount of Al³⁺ ions under neutral condition to a solution containing equimolar amount of **5.1** and Zn²⁺ ions, the fluorescence emission at 490 nm decreases and a new emission peak at 446 nm develops. The new emission peak at 446nm grows due to formation of 2-hydroxybenzaldehyde that interacts with Al³⁺ ions as well as Zn²⁺ ions. The intensity of the new emission peak at 446 nm enhances until the hydrolysis of the **5.1** is completed.

Chapter 6: Part A: Anion Guided Conformational Adjustments by Protonation Leading to Conformation Reversal

In this chapter, anion guided conformational adjustments of an uncommon conformer found in self-assembly of 2-[(5-methylthiazol-2-ylamino)-methyl]-phenol (**6.1**) and subsequent protonation leading to reversal of conformer is shown. *Syn* or *anti* forms A and B illustrated in Figure 6.1 of thiazole derivatives. These derivatives are prone towards protonation hence the protonated forms also can have similar conformers (C and D in Figure 6.1) and one may utilize the hydrogen bonding ability of aminothiazole to stabilize any of such forms by hydrogen bonds.

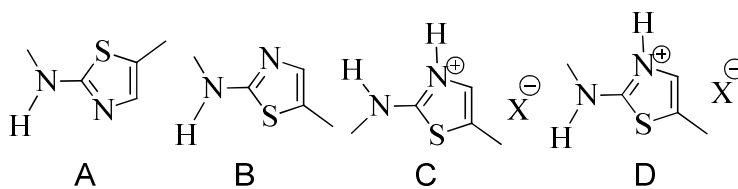


Figure 6.1: Syn and anti conformers of aminothiazole (A and B) and aminothiazolium salt (C and D).

Structural elucidation of **6.1** showed that, it possesses an overall twisted geometry in which the aminothiazole ring has NH and the sulphur atom of the ring *syn* to each other across the C-N bond (Figure 6.2a) to form an *anti* conformer. The stabilization of the uncommon conformer can be explained by considering self-assembly of the compound illustrated in Figure 6.2b.

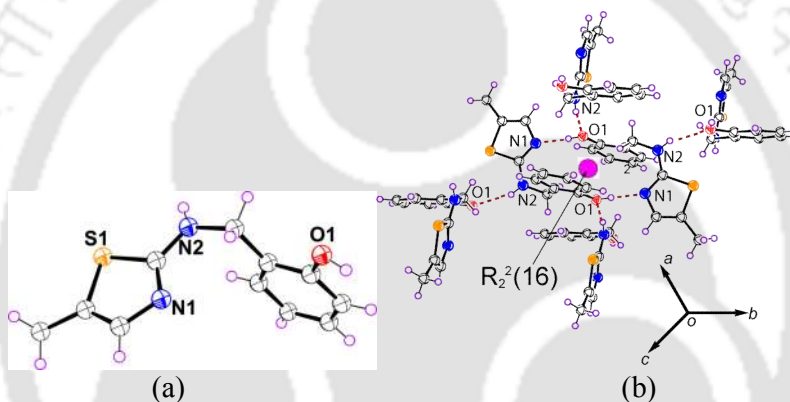
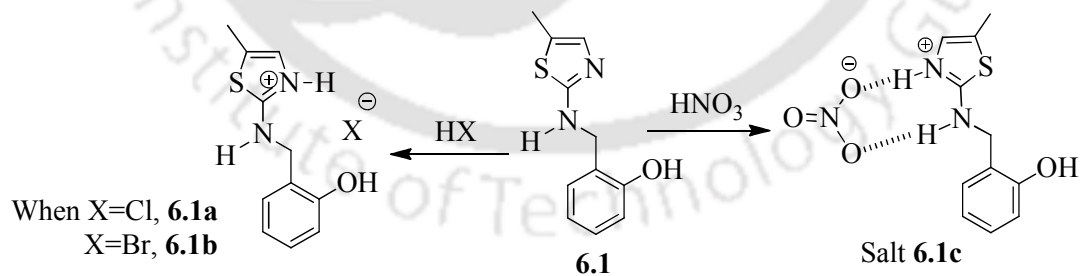


Figure 6.2: (a) The structure of the compound **6.1** (with 50% thermal ellipsoids) (b) hydrogen bonded self-assembly of **6.1**.



Scheme 6.1: Synthesis of salts of compound **6.1**.

Generally self-assembly of a salt is different from the parent compound. Accordingly the chloride (**6.1a**) (Figure 6.3a) or bromide (**6.1b**) salt forms self-assembly which has the orientation of the thiazole ring across C-NH bond similar to the parent compound **6.1**.

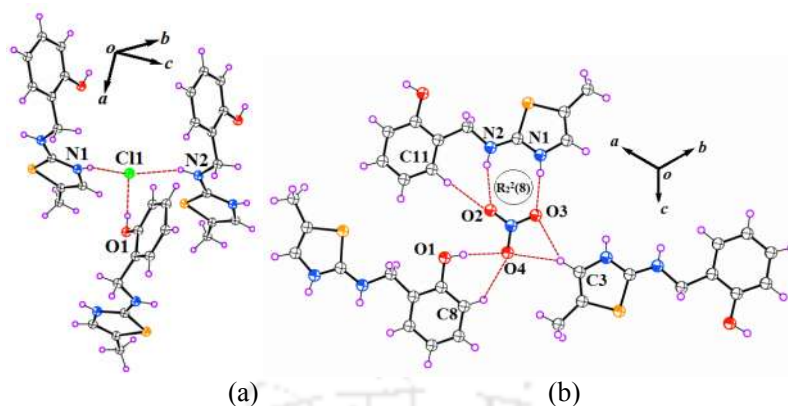


Figure 6.3: T-shaped hydrogen bond environment in self-assembly of chloride salt **6.1a**. (b) Nitrate holding three cationic units through hydrogen bonds within the lattice of salt **6.1c**. (c) The cyclic hydrogen bonded motif of nitrate to lock a rotamer.

Nitrate ion being planar, three oxygen atoms of each nitrate is associated with three neighboring cations of **6.1** in the lattice of nitrate salt **6.1c** as illustrated in Figure 6.3b. The N⁺-H and N-H bonds and phenolic OH of cationic part act as hydrogen bond donors to nitrate anions (Figure 6.3c). In the present salt the cyclic hydrogen bonded R₂²(8) type motif formed between the cation and anion. The phenolic OH group participates in hydrogen bond formation on the other face of the nitrate ion, hence the nitrate ions remain segregated in the self-assembly within the hydrogen bond environment created by the cations. Accordingly, nitrate ions contribute to form layers comprising of cations and anions. While forming such a layer the cations adopt a planar structure.

Importantly, the nitrate salt has the opposite conformer of the thiazole across the C-NH bond as that of the one found in the parent compound. In a nutshell, with an example of thiazole derivative we have shown the importance of conformation adjustments to get reversal of orientations of a functional unit.

Chapter 6: Part B: Solvent and Anion Facilitated Conformational changes in Benzylamine substituted Thiazolamine

In this chapter, solvent and anion facilitated conformational adjustments in the solid state structures of of *syn-anti-syn* form of N,N'-(1,4-phenylenebis(methylene)-bis(5-methylthiazol-2-amine) (**6.2**) are studied. Crystallisation of **6.2** from different solvents resulted in two polymorphic forms abbreviated as **6.2a** and **6.2b**.

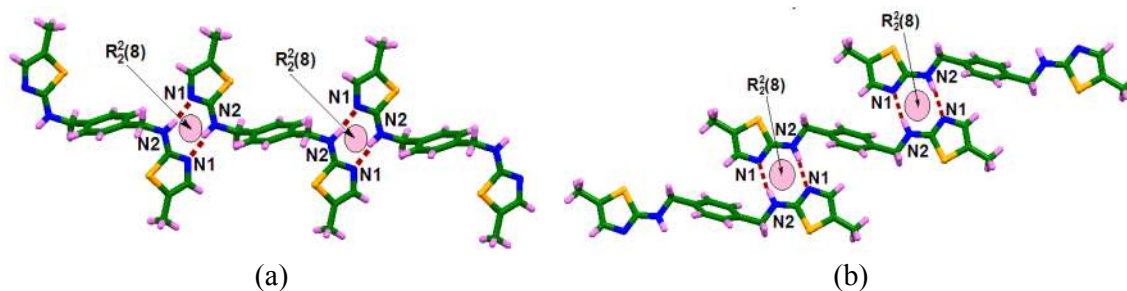


Figure 6.4: Assembly of (a) **6.2a** and (b) **6.2b** showing intermolecular N-H...N interactions.

The assembly of the both the polymorphs are guided by $R_2^2(8)$ motif with N-H...N type interactions as shown in the Figure 6.4a and Figure 6.4b. Hence, there are two types of geometrical arrangements of *syn-anti-syn* conformers one resembling S-geometry and another l-geometry leading to the conformational polymorphs. Such orientations arise from the adjustments on rotations through two C-N bonds.

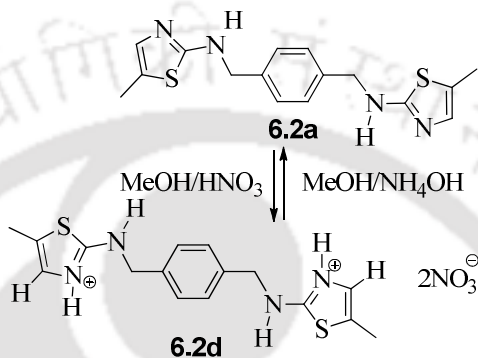
Generally conformational flexible pre-organized cationic host molecules undergo reorganisation to provide a platform for anion, we find that the crystalline salts **6.2c**, **6.2d**, and **6.2e** have doubly protonated cationic host but other than nitrate salt (**6.2d**) in other two salt (**6.2c**, **6.2e**), anions are in the form of assemblies. In the self-assembly of the salt **6.2c**, the spherical Br^- ions were hydrated by forming anionic hydrogen-bonded cluster $[\text{Br}_2(\text{H}_2\text{O})_2]^{2-}$. These motifs have two water molecules providing four O-H bond as hydrogen bond donors to two bromide ions forming cyclic motif which has $R_4^2(8)$ graph-set notation (Figure 6.5a). Interestingly, each H_2PO_4^- anion interacts concurrently with another H_2PO_4^- anion and one H_3PO_4 molecule which, in turn, interacts with another H_3PO_4 moiety generating an infinite tetrameric anion-acid $[(\text{H}_2\text{PO}_4^- \cdot \text{H}_3\text{PO}_4)_2]_n$ cluster with a tetragonal planar arrangement (Figure 6.6b).



Figure 6.5: (a) Bromide-water tetrameric $[(\text{H}_2\text{O})_2\text{Br}_2]^{2-}$ cluster in **6.2a**. (b) Hydrogen bonded cyclic motifs within the $(\text{H}_2\text{PO}_4^- \cdot \text{H}_3\text{PO}_4)_2$ cluster.

Structural analysis of the salt **6.2d** revealed that each NO_3^- ion interacts with two cationic hosts involving strong N⁺-H...O interaction and also through additional C-H...O interaction with another cationic host. Intriguing aspect of the nitrate salt is the orientation of the amino-

thiazolinium cations, which are *anti-anti-anti* as shown in Scheme 6.2. The reversal of the conformer is due to the participation of the N⁺-H in hydrogen bonds with nitrate anions. To check the reversal of the conformation to parent conformer, we recrystallized the salt by adjusting pH to a neutral condition by adding ammonium hydroxide to a methanol solution of **6.2**. Needle shaped crystals of **6.2a** were obtained (Scheme 6.2). This information clearly indicated that the inter-conversion of *syn-anti-syn* to *anti-anti-anti* conformer by crystallization from solution with nitric acid and subsequent neutralization.



Scheme 6.2: Conformational change from *syn-anti-syn* to *anti-anti-anti* of protonated **6.2**.

In a nutshell, the change from *syn-anti-syn* to *anti-anti-anti* was observed when the nitrate salt was formed whereas *syn-anti-syn* conformer was observed in all other cases. Thus, the planar nitrate ion is capable of stabilizes the *anti* form of aminothiazole.

A conclusion section is given at the thesis underlying the major overall findings from the present work, this is done to complement the conclusions that are given at the discussion of each chapter. Relevant literatures and experimental sections of each chapter is compiled after results and discussion in each chapter. The crystallographic parameters are given as an appendix and corresponding crystallographic information files are provided as soft copy attached to the thesis.

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