

What Triggers Supramolecular Isomerism in Nonmolecular Solids? A case study of Copper Pyridazine Halides

JENCY THOMAS^{a,*} and ARUNACHALAM RAMANAN^{b,*}

^aResearch and P G Department of Chemistry, St. Thomas' College (Autonomous),
Thrissur, Kerala 680 001, India

^bDepartment of Chemistry, Indian Institute of Technology Delhi, Hauz Khas, New Delhi 110 016, India
e-mail: jencyiitd@yahoo.co.in; aramanan@chemistry.iitd.ac.in

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Abstract. Molecular recognition and aggregation occurring in solution are critical events towards the nucleation and growth of a crystal. However, controlling aggregation towards a particular supramolecular assembly is difficult due to lack of information on its thermodynamics and kinetics. Hence, the occurrence of supramolecular isomers is hardly recognized. In this paper, therefore, we demonstrate a retrosynthetic analysis to interpret the occurrence of isostructures and supramolecular isomers and predict the possibility of new phases in copper halide-pyridazine-H₂O system. A significant feature of this paper is the use of crystal engineering tools, namely, synthons and tectons to interpret the phase diagram of a system. The structure-synthesis correlation discussed here provides chemical insight to evolve a synthetic protocol to interpret and predict the possibility of supramolecular isomers in metal organic solids.

Keywords. Crystallization; nucleation; supramolecular isomerism; coordination polymer; non-molecular.

1. Introduction

Polymorphism in molecular solids, wherein discrete molecules are held together by noncovalent interactions, has been well-addressed by several groups.^{1–4} The occurrence of polymorphs i.e., compositionally similar solids with different crystal structures, is more frequent in compounds containing conformationally flexible molecules and functional groups like –OH, –NH₂, –COOH and –CONH₂ that can participate in strong hydrogen bonding.⁵ The fact that these groups are commonly found in drug molecules makes it attractive in pharmaceutical development.⁶ However, the definition of polymorphism as given by Bernstein¹ suffers in the context of non-molecular solids characterized by the occurrence of extended metal ligand interaction in one or more dimensions. In contrast to crystallization of organic molecules wherein only groups like –OH, –NH₂, –COOH and –CONH₂ that can participate in strong hydrogen bonding dictate the self-assembly; the crystallization of metal organic solids is dynamic.⁷ Moreover metal complexes with different metal to ligand ratio can participate in supramolecular aggregation leading to compositionally different metal organic

solids.⁸ Zaworotko and co-workers have coined the term ‘supramolecular isomerism’ for describing the occurrence of such solids with the same composition but different networks in the case of coordination polymers and MOFs.⁹

Crystallization is a supramolecular reaction that is conceived to occur in two steps, nucleation and growth.¹⁰ Nucleation of a crystal can be understood to occur *via* a high energy intermediate or supramolecular aggregate (analogue of a transition state). The structure of the aggregate enforced by entropy-enthalpy balance thus provides a link between the molecules aggregating in the solution phase and the supramolecular assembly observable in the solid state. In other words, this can represent a supramolecular reaction pathway wherein chemically reasonable molecules (henceforth referred as tectons;¹¹ tectons are chemically reasonable molecules that induce assembly of aggregates with controlled geometries. These vary from simple molecules such as H₂O to robust units like metal complexes) aggregate and condense into a crystal at the phase transition through appropriate bonding and non-bonding interactions.^{12,13} Molecular solids result when only nonbonding interactions facilitate condensation between self assembling tectons. In contrast, dehydration or desolvation between appropriate tectons causes covalent or coordinate bonding either in one or more

*For correspondence

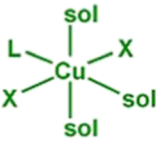
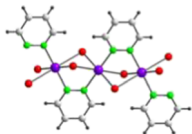
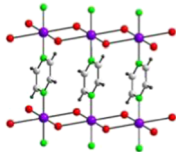
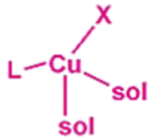
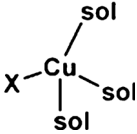
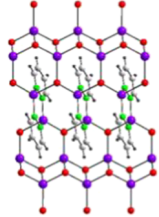
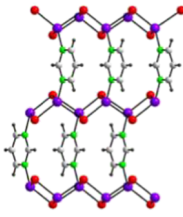
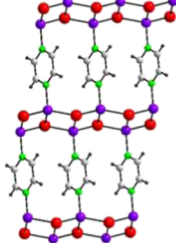
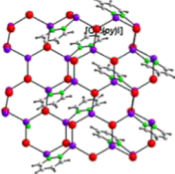
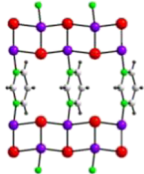
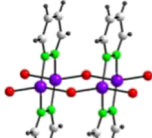
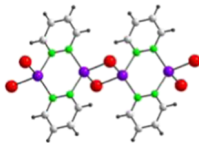
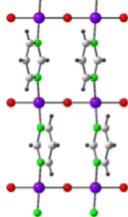
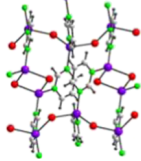
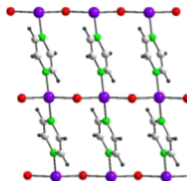
dimensions forming nonmolecular or extended networks. Where necessary, additional water (or solvent molecules) mediate leading to unusual water clusters or extended arrays.¹⁴ Etter's principle of H-bonding¹⁵ and the concept of supramolecular synthons by Desiraju¹⁶ can be readily extended to recognize the supramolecular interaction in the formation of the intermediate and hence the nucleation of a metal organic crystal. Also, one can readily interpret the occurrence of

supramolecular isomerism in metal organic solids and probably a way to control and predict new phases.

2. Identification of tectons and its role in crystal engineering

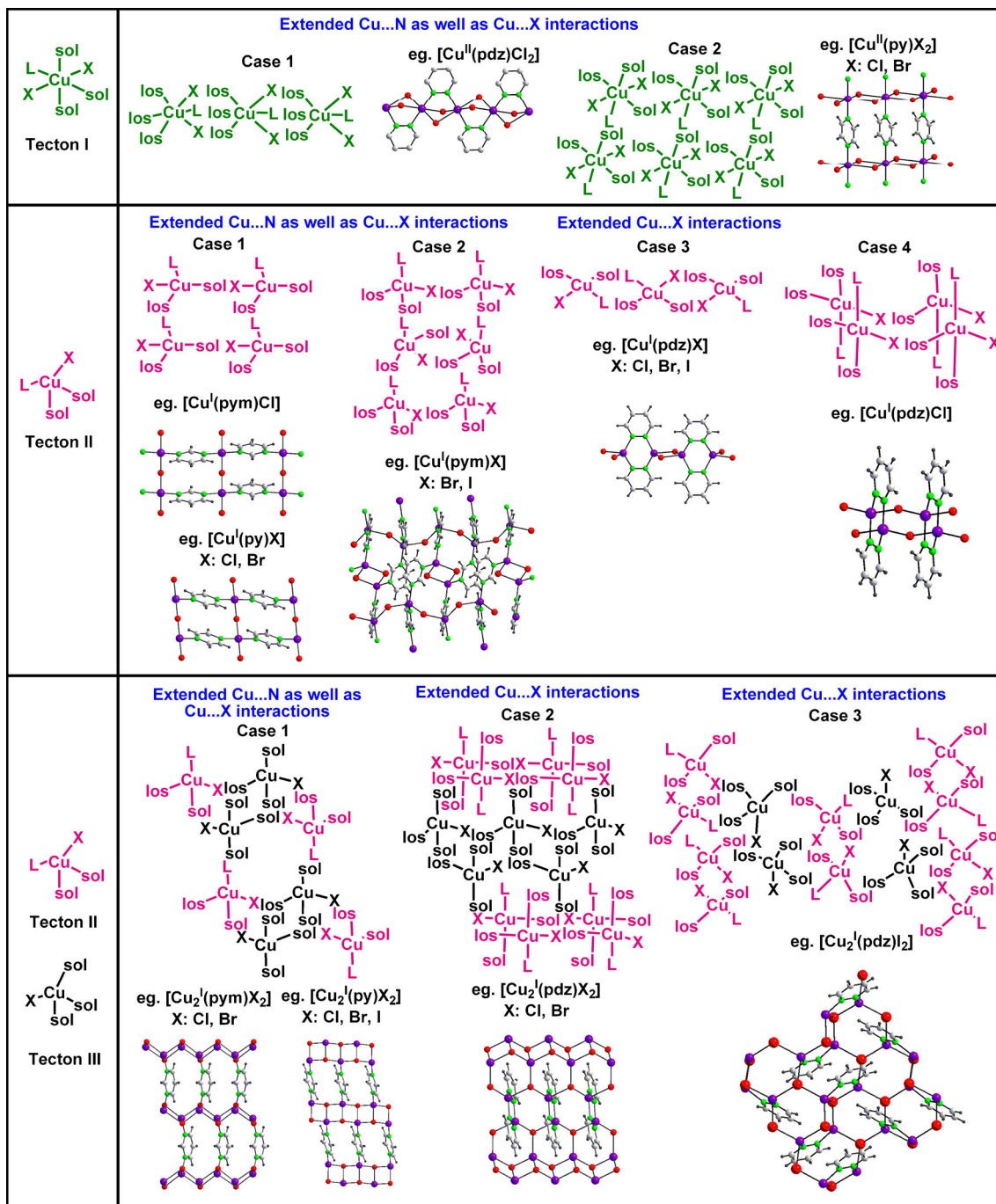
Crystal structure prediction of nonmolecular or organic/inorganic solids such as MOFs remains an

Table 1. A summary of the diazine mediated copper halide based solids reported in literature. The table shows the occurrence and absence of isostructures of different halides. All the solids can be rationalized in terms of aggregation induced by three tectons, octahedral $[\text{Cu}^{\text{II}}\text{L}(\text{sol})_3\text{X}_2]$ and tetrahedral $[\text{Cu}^{\text{I}}\text{L}(\text{sol})_2\text{X}]$ and $[\text{Cu}^{\text{I}}(\text{sol})_3\text{X}]$ (sol: water, methanol, acetonitrile, etc.).

Tecton	Composition	Pyridazine	Pyrimidine	Pyrazine
<p>Tecton I</p> 	$[\text{Cu}^{\text{II}}\text{LX}_2]$	<p>$[\text{Cu}^{\text{II}}(\text{pdz})\text{Cl}_2]$</p>  <p>Br and I analogues are not known</p>	Unknown	<p>$[\text{Cu}^{\text{II}}(\text{py})\text{X}_2]$ X: Cl, Br</p> 
<p>Tecton II</p>  <p>and</p> <p>Tecton III</p> 	$[\text{Cu}_2^{\text{I}}\text{LX}_2]$	<p>$[\text{Cu}_2^{\text{I}}(\text{pdz})\text{X}_2]$ X: Cl, Br</p> 	<p>$[\text{Cu}_2^{\text{I}}(\text{pym})\text{X}_2]$ X: Cl, Br</p> 	<p>$[\text{Cu}_2^{\text{I}}(\text{py})\text{X}_2]$ X: Cl, Br, I</p> 
		<p>$[\text{Cu}_2^{\text{I}}(\text{pdz})\text{I}_2]$</p> 	<p>$[\text{Cu}_2^{\text{I}}(\text{pym})\text{I}_2]$</p> 	
		<p>$[\text{Cu}^{\text{I}}(\text{pdz})\text{Cl}]$</p>  <p>Br and I analogues are not known</p> <p>$[\text{Cu}^{\text{I}}(\text{pdz})\text{X}]$ X: Cl, Br, I</p> 	<p>$[\text{Cu}^{\text{I}}(\text{pym})\text{Cl}]$</p>  <p>$[\text{Cu}^{\text{I}}(\text{pym})\text{X}]$ X: Br, I</p> 	<p>$[\text{Cu}^{\text{I}}(\text{py})\text{X}]$ X: Cl, Br</p>  <p>$[\text{Cu}^{\text{I}}(\text{py})\text{I}]$ Unknown</p>

elusive dream. Almost a decade ago, Davey *et al.*, have highlighted the necessity to understand the link between molecular assemblies found in liquid phase and their solid state counterparts.¹⁷ Thus, recognizing the molecular assemblies found in liquid phase i.e., the tectons and the nature of nonbonding interactions between the tectons can provide better insights towards achieving

'designed materials'. Clearly, the choice of tecton or tectons is critical. In this context, the perspective by Ramanan and Whittingham is quite significant.¹⁸ The authors employed an *á posteriori* approach to provide chemical insights into the building of solids in terms of aggregation of tectons. By carefully analysing a large number of MOFs reported in the literature, they have



Scheme 1. The scheme represents the different ways in which tectons can supramolecularly aggregate to favor intermolecular interactions that can result in extended or alternating coordination bonds –Cu–X–Cu– or –Cu–org–Cu–. The scheme shows how the composition of a solid is decided by the system at the molecular level.

also postulated the possible chemical events that can result in the nucleation of a particular crystal.

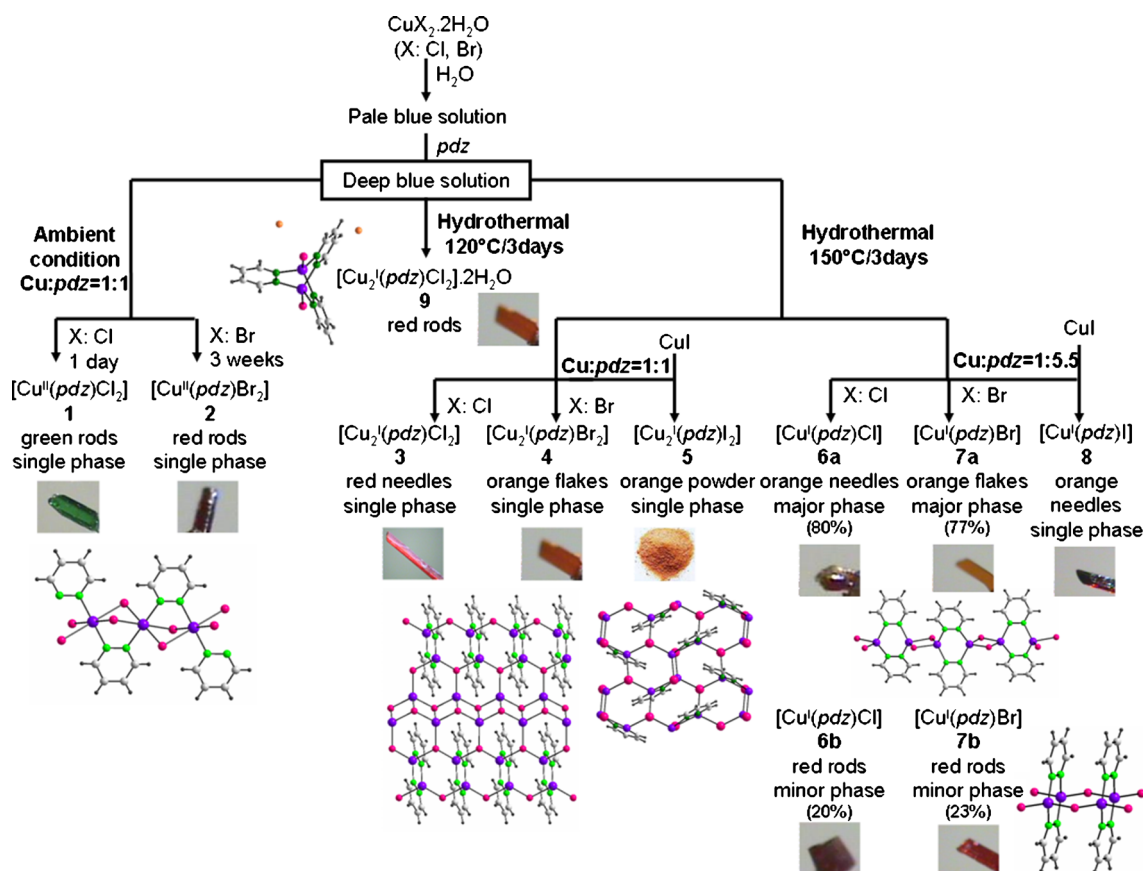
A crystal is not built molecule by molecule but through supramolecular assembly. Crystallization of solids, molecular or non-molecular from solution is a supramolecular reaction. A significant feature of this supramolecular reaction is the perceived nonbonding interactions (e.g., H-bonding in aqueous systems) in dictating a particular arrangement and the presence of symmetry. Symmetry is an important structural director as it influences the assembly of reacting molecules in the specific orientation which is a critical step leading to the growth a solid. Solvent, temperature, *etc.* are external factors that can alter the nature of forces operating between the assembling molecules, and hence a different crystal growth. Thus, one can realize the crystallization of more than one phase or supramolecular isomerism once the nature of non-bonding interactions between the tectons is established.

3. Special case of copper-pyridazine-halide system

Non-bonding interactions play a crucial role in crystal packing. Therefore, crystal engineering of supramolecular

isomers requires careful kinetic control during the synthesis. In this context, retrosynthesis discussed here provides better chemical insights into the crystal packing of metal organic solids – molecular or non-molecular. We have taken the example of self assembly of all the solids of the type $[\text{CuL}_m\text{X}_2]$ where L is N-based diazine (pyrazine, pyrimidine and pyridazine) reported in the literature as well as by our group. The self assembly of all the solids can be rationalized in terms of aggregation between three supramolecular tectons, octahedral $[\text{Cu}^{\text{II}}\text{L}(\text{sol})_3\text{X}_2]$ and tetrahedral $[\text{Cu}^{\text{I}}\text{L}(\text{sol})_2\text{X}]$ and $[\text{Cu}^{\text{I}}(\text{sol})_3\text{X}]$, where sol is a solvent such as water, methanol, acetonitrile, *etc.* (refer Table 1).

A close inspection of the Scheme 1 revealed that several supramolecular isomers are possible for copper halide-pyridazine- H_2O system but not all members are known. Since different groups (in the literature) adopted a myriad of reagents and solvents, rationalization of the solids becomes difficult. Hence, we employed a systematic approach to understand the growth of different members and those hitherto unknown. We preferred that pyridazine (*pdz*) as N atoms on adjacent positions of the six-membered ring facilitates different self assembly (refer Scheme 1). Reaction under ambient condition



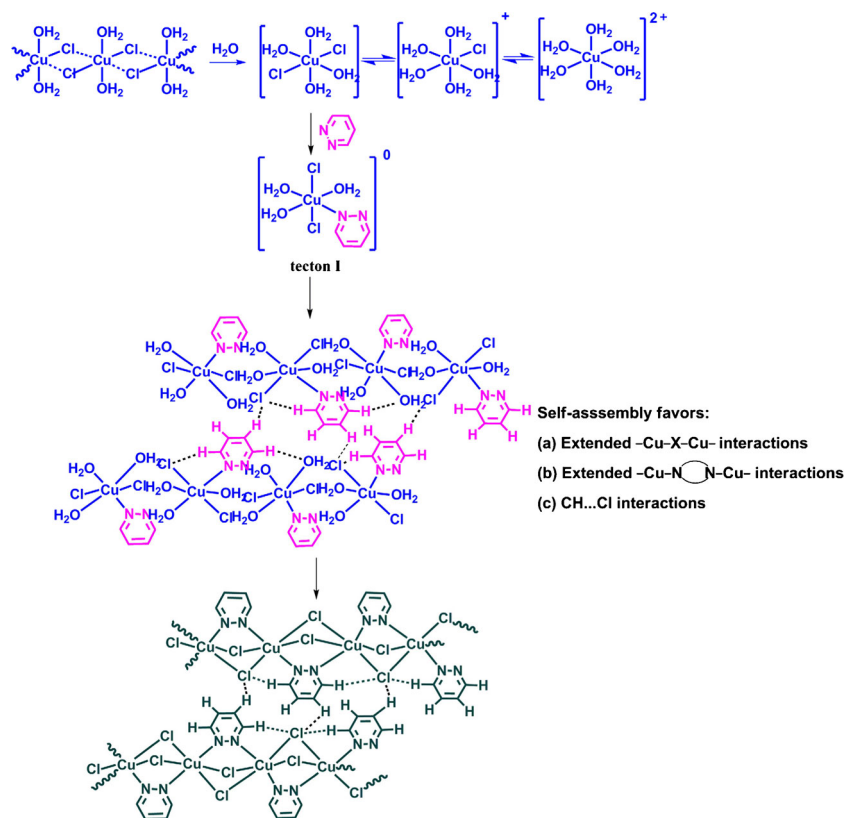
Scheme 2. A summary of the synthetic protocol employed for the preparation of the solids 1–9. The % given in brackets for solids 6 and 7 are estimated from Rietveld analysis of the PXRD patterns (refer Figure S24 in Supplementary Information).

favored the crystallization of fully oxidized solids, $[\text{Cu}^{\text{II}}(\text{pdz})\text{X}_2]$, X: Cl, **1** and Br, **2**. Under hydrothermal condition, the organic amine effected the reduction of copper(II) to copper(I) and yielded two sets of compositionally different solids, $[\text{Cu}^{\text{I}}(\text{pdz})\text{X}]$ and $[\text{Cu}_2^{\text{I}}(\text{pdz})\text{X}_2]$ depending on the ligand to metal molar ratio: (i) Lower ligand concentration led to the formation of $[\text{Cu}_2^{\text{I}}(\text{pdz})\text{X}_2]$, X: Cl, Br and I, **3–5**. (ii) Large excess of ligand resulted in $[\text{Cu}^{\text{I}}(\text{pdz})\text{X}]$, X: Cl, Br and I. Two supramolecular isomers were identified for Cl (**6a**, **6b**) and Br (**7a**, **7b**) analogues, whereas only one was isolated for $[\text{Cu}^{\text{I}}(\text{pdz})\text{I}]$, **8**. A hitherto unknown molecular solid, $[\text{Cu}_2^{\text{I}}(\text{pdz})_3\text{Cl}_2] \cdot 3\text{H}_2\text{O}$, **9** was isolated under hydrothermal condition (refer Scheme 2). A significant feature of this paper is how retrosynthesis can address the occurrence of supramolecular isomers with same or different composition in terms of aggregation of tectons (copper aqua complex, copper diazine complex and water) thus providing a basis for rational structure-synthesis correlation and predict the possibility of isostructures. Also, the approach enables one to highlight the effect of chemical (composition) and

external (temperature and solvent) variables in altering the recognition and aggregation.

4. Chemistry of formation of copper halide based solids

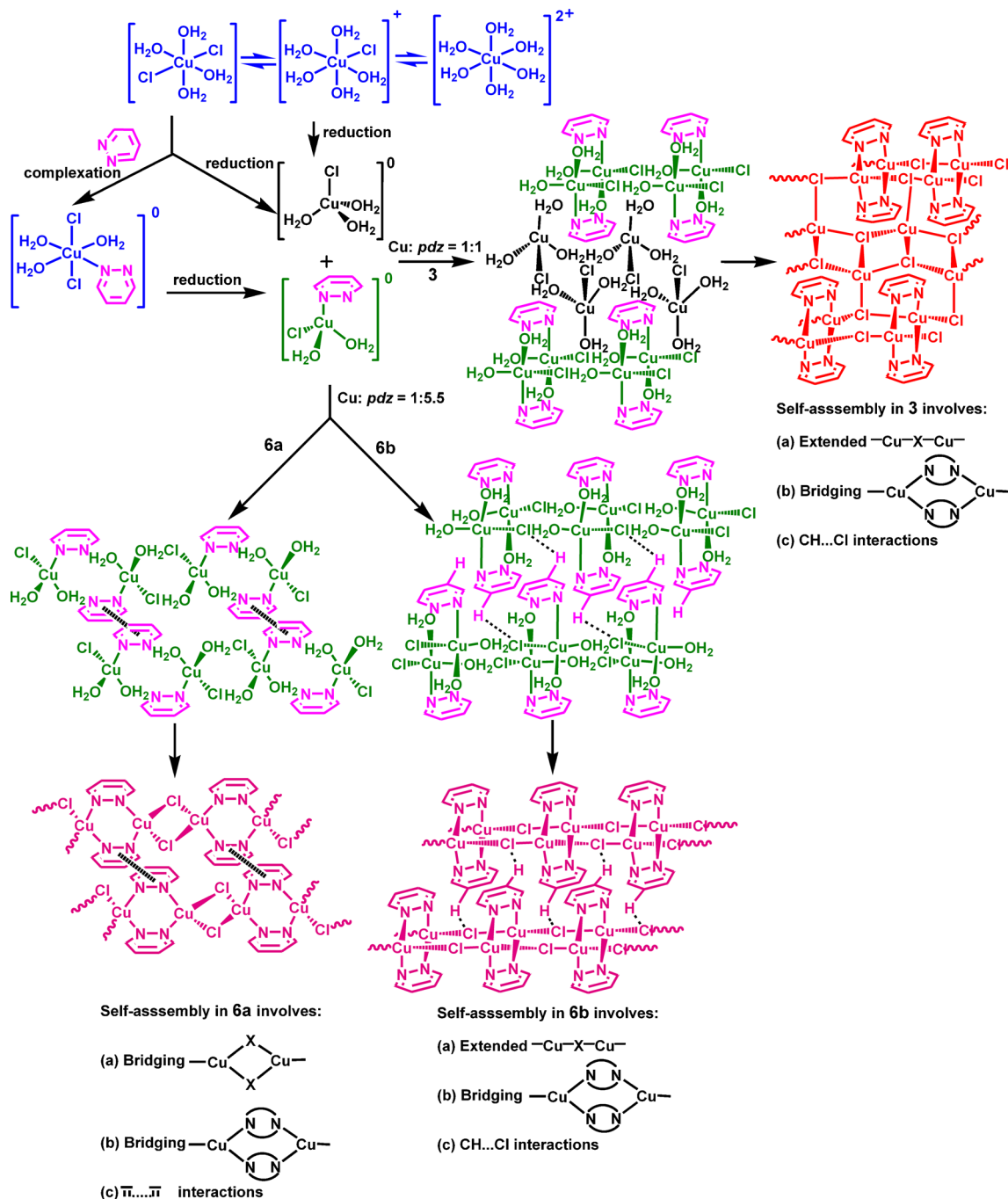
An examination of the literature on the occurrence of copper halide based metal organic solids (refer Tables S2–S4 in Supplementary Information) suggests that the chemistry issues related to the crystallization of these phases appear confusing due to arbitrary condition employed by several groups. Our reactions as well as those described in literature clearly suggest that hydrothermal/solvothermal condition assists the solubility of Cu(I) salts or facilitates *in situ* reduction of Cu(II) into Cu(I). Reduction of Cu(II) to Cu(I) by organic ligands under hydrothermal condition is well-known.¹⁹ Growth of the crystals **1–9** can be readily interpreted in terms of self-assembly between the tectons *viz.*, copper complex units with solvent and/or ligand molecules leading to spontaneous aggregation dictated through non-bonding interactions. If the assembly favors long range coop-



Scheme 3. Dissolution of the solid $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in water results in soluble molecular precursors. These undergo complexation with *pdz* to form a metal complex of 1:1 stoichiometry. The tectons represent chemically reasonable molecules that eventually aggregate supramolecularly just before the onset of nucleation. H-bonding interactions are shown in dashed black lines. The formation of **2** can be interpreted similarly.

erative interactions (coordinate or covalent $\text{Cu}\cdots\text{X}$ bonds) by the elimination of water or solvent, the result will be an extended nonmolecular solid. When copper salt is dissolved in water, the species $[\text{Cu}(\text{H}_2\text{O})_4\text{X}_2]^0$, $[\text{Cu}(\text{H}_2\text{O})_5\text{X}]^+$ and $[\text{Cu}(\text{H}_2\text{O})_6]^{2+}$ are formed (where X: Cl or Br). In the presence of pyridazine, cupric ions

immediately form the complex, $[\text{Cu}(\text{H}_2\text{O})_3(\text{pdz})\text{X}_2]^0$ which can be considered as building block or tecton (tecton I). In the absence of reduction, tecton I dominates the supramolecular assembly as a consequence of two directing forces: (i) Tendency to form 1D ribbons through strongly interacting $\text{Cu}\cdots\text{X}$. This has been



Scheme 4. Supramolecular reaction pathways for the formation of compositionally same and different supramolecular isomers **3**, **6a** and **6b** from the aggregation of appropriate tectons. The scheme highlights how a single tecton (tecton II) dictates different intermolecular interactions, and hence different pathways leading to supramolecular isomers. The pathways represent how the system optimizes the varying weak forces for an efficient crystal packing through metal coordination and nonbonding interactions. Bonding in various solids thus become obvious in interpreting the occurrence of **4**, **7a** and **7b** as well.

observed earlier in a large number of Cu(II) halides (refer Tables S2–S4 in Supplementary Information). (ii) Extended Cu...organic...Cu coordination bonds. In addition, $\pi \cdots \pi$ or H-bonding interaction stabilizes the structure further. The crystallization of **1** and **2** from aqueous solution under ambient condition thus becomes obvious (refer Scheme 3). **1** and **2** are examples of 1D coordination polymers.^{20,21}

However, when copper undergoes reduction two possibilities arise. If the ligand to metal ratio is less, then aqueous solution contains two copper tectons, {Cu(pdz)(H₂O)₂X}, tecton II and {Cu(H₂O)₃X}, tecton III in equilibrium and hence, supramolecular assembly is influenced by both. However, when the ligand concentration is quite high in comparison to copper, only tecton II dominates. While the former arrangement results in a solid with the composition [Cu₂(pdz)X₂] (X: Cl, **3**; X: Br, **4**), the latter arrangement yields the composition [Cu(pdz)X]. The solids of the compositions [Cu₂(pdz)X₂] and [Cu(pdz)X] may be considered as compositionally different supramolecular isomers as the building blocks have similar origin. It should be noted that powder XRD pattern of the orange powder, **5** indicated the formation of [Cu₂(pdz)I₂] reported by Kromp and Sheldrick.²² The chloride and bromide analogues of [Cu(pdz)X] were found to be concomitant supramolecular isomers. The occurrence of **6a** along with **6b** (**7a** along with **7b**) is quite evident from the mechanism shown in Scheme 4. **7b** has been isolated for the first time under our reaction condition. The co-existence of **6a** and **6b**; **7a** and **7b** in the same reaction indicates that the energy difference between the two phases is not very significant because they are formed from the same tecton {Cu(pdz)(H₂O)₂X}. Since **6a** and **7a** are major phases, the additional stability probably comes from the occurrence of extended coordination interaction in these solids. Several reports have earlier observed the occurrence of the crystals **6a** and **7a**, under arbitrary condition but could not analyze the presence or absence of these two supramolecular isomers. The fact that crystals **6a** and **7a** could be grown from aqueous as well as non-aqueous medium and varying temperature confirms that the stability of the phases is unaffected by the solvent or temperature. In compounds **6–8**, the tecton II readily self-assembles. Nather and Jess²³ have also isolated compounds **6a**, **6b** and **7a** under solvothermal conditions starting from CuX (X: Cl, Br). It should be noted that an iodide analogue, isostructural to **6b** and **7b** is yet to be isolated. In the case of **6b** and **7b**, C–H...X interactions are quite dominant. It is possible that the much weaker C–H...I interactions (due to lesser electro-negativity of iodide as compared to chloride and bromide) make the supramolecular

assembly less probable for the crystallization of the unknown supramolecular isomer (**8b**).

5. Effect of temperature

It is well-known that organic ligands can effect reduction of Cu(II) to Cu(I) under hydrothermal condition. Therefore, the effect of temperature in the case of chloro and bromo solids was investigated using high ligand to metal ratio. While at 100°C Cu(II) did not undergo reduction, at 150°C it was completely reduced. On the other hand, at 120°C, both reduced and oxidized molecular units were present in the reaction medium. In the case of chloride, a new hydrated solid, **9** crystallized along with **1** (Figure S7 in Supplementary Information). The formation of **9** seems to be favorable owing to firstly, the tendency of Cu^I ions to dimerize; secondly, the two {Cu(pdz)(H₂O)₂Cl} units along with a pdz moiety (freely available due to its high concentration in the medium) undergo condensation to form the new molecule observed in **9**. Further, favorable strong H-bonding interactions between chloride and mediating water molecules provide additional stability to the crystal packing (Figure S7d). We did not succeed in obtaining **9** as a single phase. Our inability to isolate a bromo analogue of **9** under similar reaction conditions is probably due to the weaker Br...O interactions.

6. Conclusions

Crystal engineering of supramolecular isomers especially metaphases requires careful kinetic control during the synthesis. A close inspection of systematic synthetic protocols can provide clues to understand the occurrence of supramolecular isomerism in various extended solids. A significant feature of this paper is how retrosynthesis can address the occurrence of supramolecular isomers with same or different composition in terms of aggregation of tectons (copper aqua complex, copper diazine complex and water as examples), thus providing a basis for rational structure-synthesis correlation and predict the possibility of isostructures. Also, the approach enables one to highlight the effect of chemical (composition) and external (temperature and solvent) variables in altering the recognition and aggregation.

Supplementary Information (SI)

Crystallographic information files (CIF) for **1–9**; crystal structure description of **1–9**; figures showing weak interactions in **1–9**; simulated and experimental powder XRD (Figures S8–S15); *á posteriori* analysis of

solids reported in literature with pyridazine, pyrimidine and pyrazine (Figures S16–S23); results of rietveld refinement for phase quantification of orthorhombic and triclinic phases in **6** and **7** (Figure S24); results of vibrational and thermal analysis (Figures S25–S28); crystallographic details for solids **1–9** (Table S5) are given in the Supplementary Information available at www.ias.ac.in/chemsci.

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