# Growing crystals from solution: By design or by default?

Crystallization is a self-assembly process. Understanding the nucleation of a crystal from liquid or solution is a pertinent theme for producing designed materials. Thanks to the advancement in single-crystal diffractometers attached with CCD, the past few years have seen an unprecedented number of papers in leading chemistry journals, describing several crystal structures exhibiting interesting topologies. Almost every day a couple of papers appear with tall claims that new structures with potential applications have been designed. Interestingly, few have analysed the growth of a particular crystal from a solvent medium. In almost all the reports, the crystals tend to occur by default!

A convenient definition of a crystal is to refer it as a super molecule or an emergent property of molecules[1,2]. Describing the crystal structure of a solid, be it molecular or nonmolecular, in terms of chemically reasonable molecular units as building blocks is quite advantageous. Such an approach enables one to derive chemical insights into the growth of a crystal in terms of reacting molecules in a supramolecular reaction, paving the way for a rational synthetic methodology. In this context, the recent paper by Ramanan and Whittingham[3] is significant. By carefully analysing a large number of metal organic frameworks (MOFs) reported in the literature, they postulated possible chemical events that result in the nucleation of a particular crystal. Soluble molecular species (supramolecular synthons) organize into a supramolecular assembly dictated through nonbonding interactions mediated by the solvent. A significant feature of this supramolecular reaction is the choice of supramolecular synthons, the perceived nonbonding interactions (e.g. H-bonding in aqueous systems) in dictating a particular arrangement and above all the presence of symmetry. Remember, symmetry is an important structural director in many natural systems. Initially, they rationalized the formation of neutral MOFs in terms of supramolecular reaction occurring between neutral species, commonly referred as 'point zero charge' (pzc) units, widely employed in colloidal chemistry literature[4]. The strategy was further extended by us to understand the crystallization of ionic MOFs and molybdates in addition to the occurrence of water clusters in crystal hydrates[5–7]. Crystallization of ionic framework solids with appropriate counter ions will be quite evident when we consider the assembly between
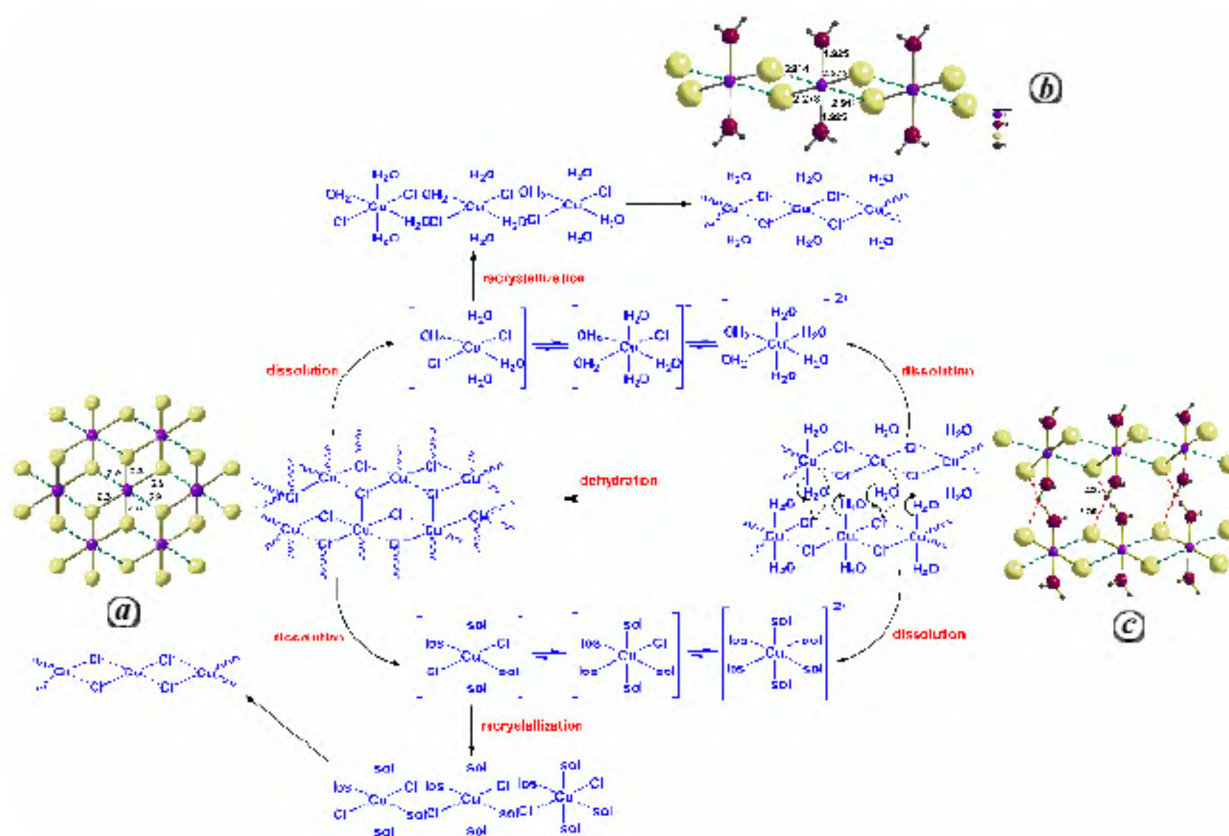
Figure 1. Sequence of dissolution of the solid, $CuCl_2 \cdot 2H_2O$ and then reassembling into the dihydrate or anhydrous copper chloride. *a*, Crystal structure of anhydrous copper chloride[15]. Dashed lines indicate non-bonding interactions. The structure resembles 'rutile' if we consider 2.9 Å as bonding distance. *b*, Crystal structure[16] of $CuCl_2 \cdot 2H_2O$. The figure shows how discrete square planar $[CuCl_2(H_2O)_2]$ units interact through nonbonding interactions (denoted by dashed lines) appearing as chains. *c*, Adjacent chains are further linked through H-bonding between water and chloride molecules. Topotactic dehydration of $CuCl_2 \cdot 2H_2O$ into anhydrous $CuCl_2$ is obvious in the structures.
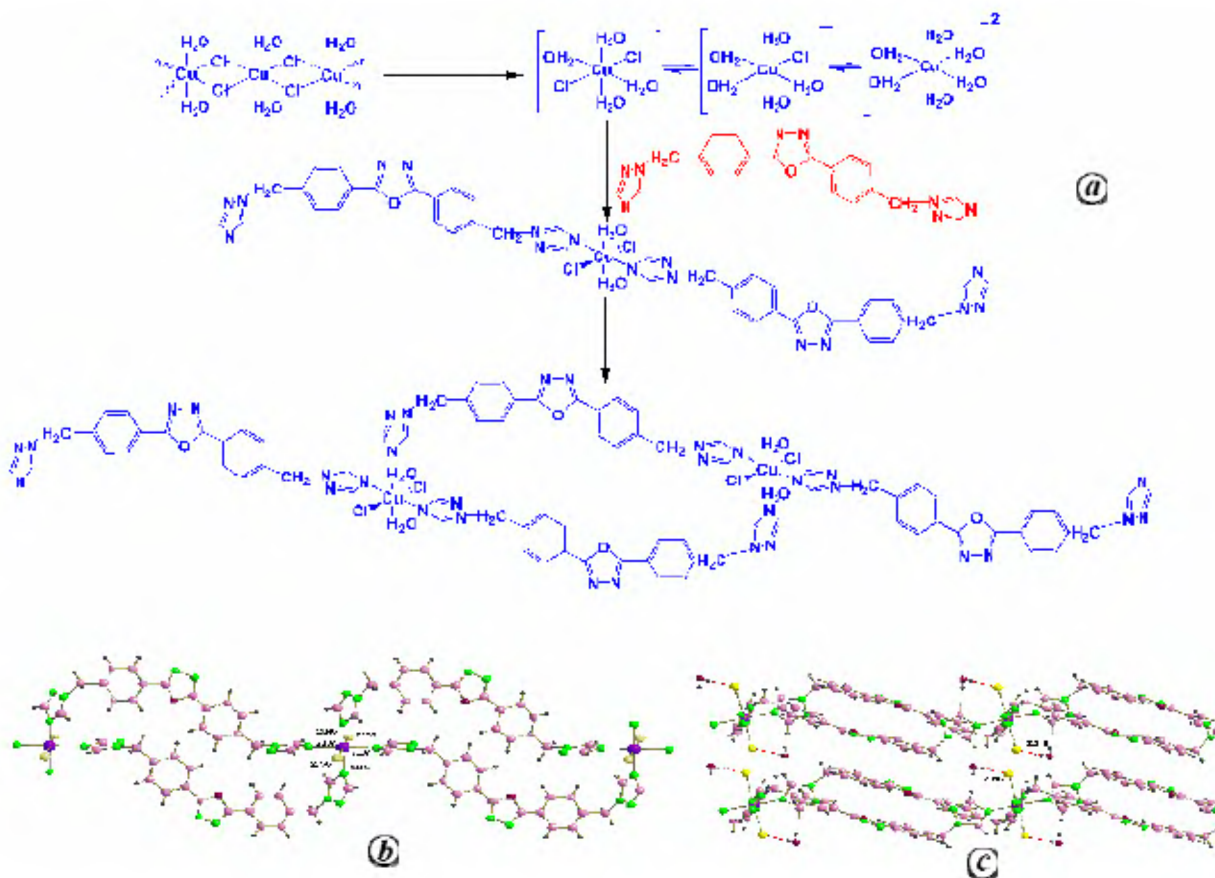
Figure 2. *a*, Copper chloride dihydrate forms soluble molecular species (pzc as well as ionic) in solution that are in equilibrium with each other. The pzc, i.e. $[CuCl_2(H_2O)_4]$ complexes with ligand through the most basic nitrogen atom. Choice of the building blocks is unique. Assembly of *bis*-complexes is essentially driven by the additional Cu–N bonding. Any other choice of building complexes will be random. Also, observe the symmetry between assembling units in the supramolecular reaction. *b*, A fragment of the crystal structure in correspondence with the mechanism given. *c*, A strong H-bonding interaction between Cl…H_2O in the self-assembly facilitates the occurrence of water molecules between the chains as it further stabilizes the structure through H-bonding.

ion-pairs as well as other pzcs. This intuitive *á posteriori* approach provides chemical insights into the building of a nonmolecular solid as well as hybrid solid. Occurrence of oxide, hydroxyl or halide linkages in oxyhydroxides/oxyhalides, intercalation of ions, interpenetration of layers, water clusters in crystal hydrates, etc. can be readily recognized in terms of reacting molecular units.

In the crystallization of molecular solids, intermolecular interactions influence their assembly and hence the crystal packing. Researchers have pioneered the role of nonbonding interactions in the formation of several molecular solids[8–10]. However, rationalization of network structures involving covalent bonds is difficult to interpret. In this context, the concept of 'secondary building units' (SBU) has been popular to describe MOF structures[11]. In a recent article, Davey *et al.*[12]

have highlighted the necessity to understand the link between molecular assemblies (crystal growth units) found in liquid phase and their solid state counterparts, the supramolecular synthons. While supramolecular chemistry is reasonably developed in dealing with molecular solids, crystal structure prediction of nonmolecular or organic/inorganic solids such as MOFs remains an elusive dream as one has to deal with changing covalent to non-covalent bonding. How do we recognize 'the true building blocks' – the chemically reasonable molecular units that are dynamic in solution and eventually lead to the growth of 'the desired crystal'?

This correspondence is an attempt, mainly targeted to synthetic chemists to perceive the crystal structure of a solid in terms of building molecular units. Self-assembly is widely used in the literature,

but no chemical insights are provided for it in terms of assembling units. Taking copper chloride as an example, we have shown how different organically templated copper chlorides (MOFs, organic/inorganic salts or inorganic complexes) are crystallized from a suitable solvent. In traditional inorganic chemistry, we are taught that a reaction occurs between ions in the solution. For example, when cupric ions are reacted with chloride ions, copper chloride precipitates. However, the chemistry becomes almost magical if we attempt crystallization from a solvent containing one or more organic molecules.

When $CuCl_2·2H_2O$ or anhydrous $CuCl_2$ is dissolved in water/solvent, soluble molecular species are formed (Figure 1). In nonaqueous solvent, it is convenient to consider the metal complex coordinated by the solvent. However, in predominantly water-containing medium (mixed
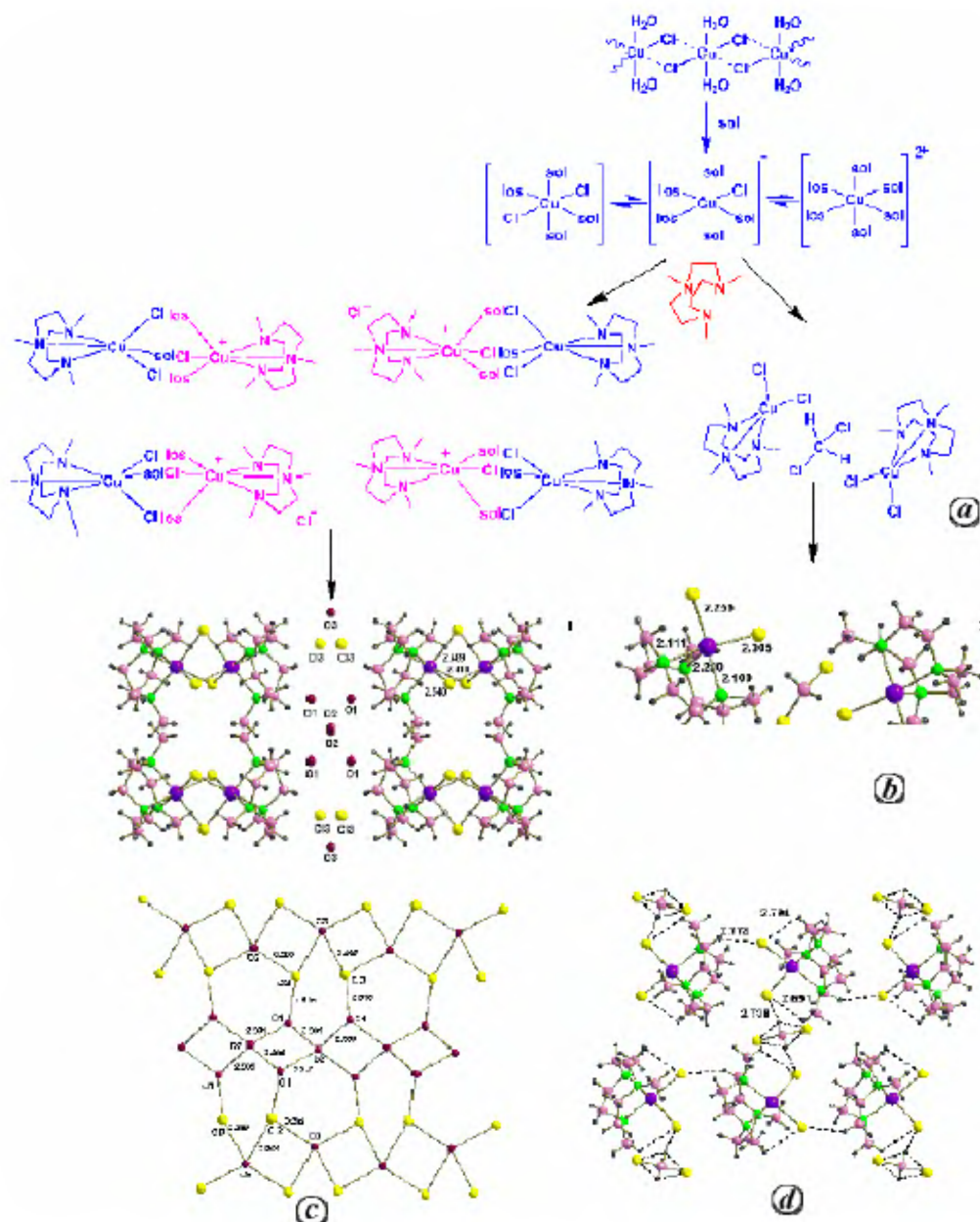
Figure 3. *a*, While the reaction of copper chloride solution with the ligand, L in ethanol/THF yields a mixture of (**1**) with the dimeric cationic molecule, $[Cu_2Cl_3L_2]^+$ and (**2**) (monomeric complex, $[CuCl_2L]$); in CH_2Cl_2 crystals of (**1**) are grown. In ethanol/THF, the dominant species are ionic as well as neutral, and hence both readily complex with the tridentate ligand. In (**1**) self-assembly is favoured between neutral (blue), ionic (pink) and the counter anion (hence the ion-pair, the synthon) leading to (**1**) (solvent mixture is more polar), while CH_2Cl_2 (less polar) forces the assembly only between the neutral molecules. However, here favourable C–H...Cl facilitates aggregation of two molecules in *b*, through the mediating solvent forming the synthon. This also explains the stoichiometry of (**2**). Occurrence of the solvent in (**2**) is not arbitrary but with a purpose. Assembly of (**1**) is initially dominated by Cu...Cl forming the triply Cl-bridged dimer. Notice in the solid state, the difference between the cation (pink) and neutral (blue) molecules disappears as charge is being redistributed in the condensed state. The overall assembly of these molecules is triggered by two other dominant interactions. While C–H...Cl between dimers favours the columnar arrangement (appearing as chains) in one dimension, an unusual H-bonding influences the ordering of the atoms in the other dimension. The occurrence of counter anion (Cl^-) on either side of these molecular chains (notice the symmetry in the assembly) necessitates participation of water molecules (solvent mediation) to stabilize the structure (*c*). The result is a remarkable two-dimensional sheet. The mediating water molecules occur as tetramers linked together as infinite chains. These chains are further stitched to one another by a different tetrameric chain made of H_2O and Cl. The whole assembly appears as a 2D sheet lying between molecular columns. *d*, The environment of copper in (**2**) is essentially due to crystal packing where different forces operating between reacting molecules are compromised. Solubility of (**1**) and (**2**) in a particular solvent decides the fate of a crystal grown in a medium and the assembly signals the solubility (stability of a phase). The fact that both (**1**) and (**2**) can occur in the same reaction clearly indicates the complexity of the process. It is difficult at this stage to predict which molecules will participate in a particular assembly. Moreover, the occurrence of water clusters observed here is not a novelty (see Upreti and Ramanan[7] for other examples), but simply a consequence of the molecular assembly between interacting molecules in the supramolecular reaction.

solvent like methanol/water), it is appropriate to consider the metal aqua complex. As long as the two Cl atoms are linked to the metal, the charge on the complex is zero (pzc). If one or both the Cl atoms are replaced by water (or solvent), then the complex thus formed will be ionic species like $[CuCl(H_2O)_5]^+$ or $[Cu(H_2O)_6]^{+2}$; these species are susceptible to hydrolysis forming other pzc, $[CuCl(OH)(H_2O)_4]^0$ or $[Cu(OH)_2(H_2O)_6]^0$, which facilitate the occurrence of Cu–O–Cu or Cu–(OH)–Cu bonds during the assembly. The overall charge of all the species present in the supramolecular reaction (i.e. supramolecular assembly that eventually results in the nucleation of a particular crystal) will be neutral. If the molecules participating in the supramolecular reaction are only neutral, then crystallization will result in a molecular solid (crystal packing is influenced only by nonbonding interactions) or a neutral framework solid (where extended –Cu–X–Cu–, X = F, Cl, Br, OH, O, etc. are permitted by the geometry of the complex). Otherwise, one ends up only with discrete molecular solid (monomer, dimer, trimer or any other oligomer) influenced by the weak nonbonding interactions. The molecular species or the extended framework can also be ionic; here the position of the counter cations in the solid state will be decided by the overall assembly. In many instances, 'anion templating' is also misleading. The examples cited here, clearly demonstrate the chemistry issues. In Figure 2, the copper complex favours the extended assembly through Cu–N and hence a MOF, $CuCl_2L_2 \cdot 2H_2O$ where L: 2,5-bis(4-(1H-1,2,4-triazol-1-ylmethyl)phenyl)-1,3,4-oxadiazole is formed[13].

In Figure 3, formation of the complex $[Cu_2Cl_3L_2]Cl \cdot 4H_2O$, (1) (where L = N,N', N''-trimethyltriazacyclononane) is restricted only to molecular solids, but it also varies with the reaction conditions[14].

We can presume that the rate of formation of the self-assembly (the assembly of reacting molecules in the correct orientation) leading to an activated supramolecular complex is a critical step.

Solvent, temperature, etc. are external factors that can alter the nature of forces operating between the assembling molecules, and hence a different crystal growth. The equilibrium constant of this activated supramolecular complex is probably related to the solubility product of a crystal (in terms of the concentration of interacting molecules – neutral as well as ions) and hence signals the nucleation of a particular structure. Calculation of the equilibrium constant of the activated supramolecular complex can reveal the magical chemistry occurring between reacting molecules.

We have demonstrated this á posteriori approach choosing eight other examples found in recent literature (supporting information can be obtained from authors), wherein crystals were grown from copper chloride solution. In each example, we have reproduced the synthetic procedure as given in the cited paper and interpreted their crystal structures (refer comments given for each example) in terms of molecular recognition and self-assembly occurring in the supramolecular reaction. All the examples clearly show how the varying nonbonding interactions between Cu...Cl, C–H...Cl and Cl...H₂O mediated by the solvent play a significant role in stabilizing the structure.

The rationale provided here shows how composition and structure of each solid becomes obvious in terms of chemically reasonable molecular bricks. Recognizing supramolecular synthons and how nonbonding interactions facilitate a supramolecular assembly in a supramolecular reaction occurring closer to the saturation point (nucleation) will provide better insights towards achieving 'designed materials'. Until then synthetic chemists will continue to employ 'crystal growing' as alchemy and continue to impose 'design' on solids obtained 'by default'.

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