

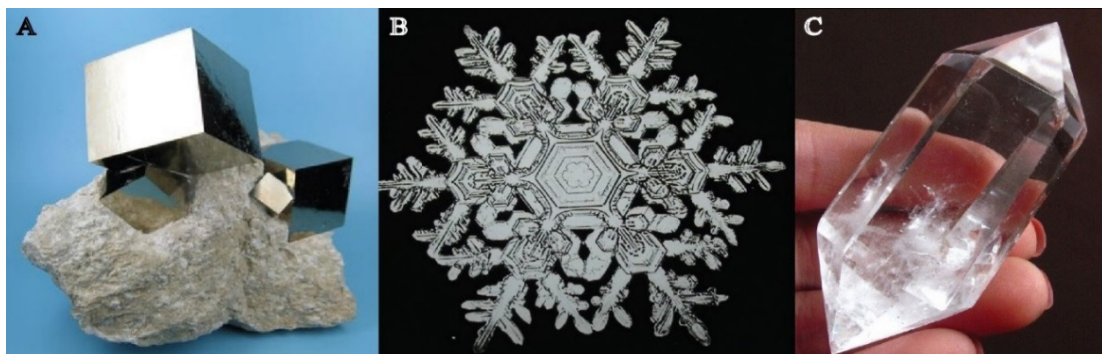
Designer Crystals

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“Simplicity is the ultimate sophistication.”

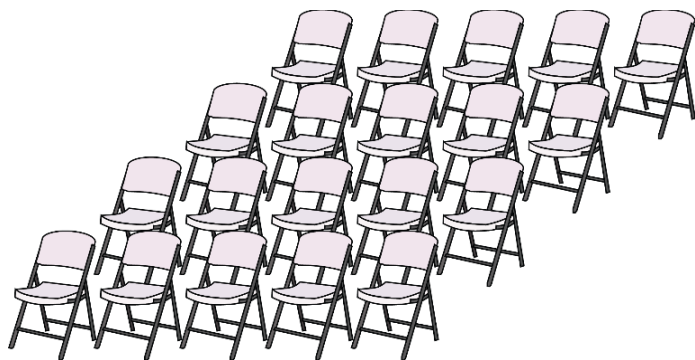
– Leonardo da Vinci

And who has greater mastery over sophistication than Nature herself? One finds it hard to believe that the golden cubes in panel A can be natural formations of something as mundane as iron and sulphur, that simple water can freeze into something as intricate as the snowflake in panel B, or that the shapely prism in panel C – despite how it looks – is not carved out of ice. The ancient Greeks made exactly this mistake, describing blocks of quartz as *Krustallos* (*Kruos* =



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icy cold) out of the mistaken belief that they were looking at everlasting ice sent from Heaven. Thence came the word crystal, which in every day vocabulary is any stone which, irrespective of its colour, is clear and symmetric. A crystal is an object of purity and beauty with a very special place in ancient lore – be it as a conduit into the afterlife or as the cure for various physical and metaphysical imbalances.



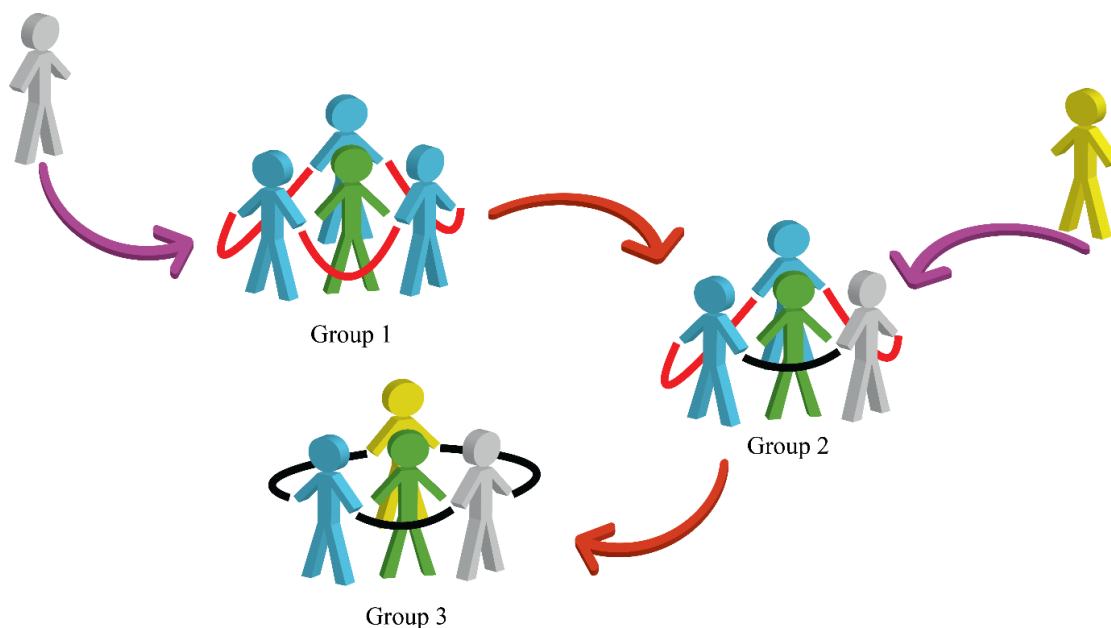
What a crystal really is, however, is a highly ordered arrangement of atoms or molecules much like a large classroom with a regular array of chairs, each of which is occupied by an atom or a molecule. These atoms and molecules are always of the same chemical substance. They have an uncanny knack for locating each

other in the chaos of a solution and crystallising, mostly because they fit each other like the pieces of a jigsaw. Anything that is a mismatch gets unceremoniously thrown out, making crystallisation a highly efficient purification process.

Man has made use of this fact since the earliest recorded history: salt crystallised from sea water has always been an indispensable part of our food. The art of crystallisation has over the years evolved into a science capable of producing remarkable results ranging from the hardness of steel to the deliciousness of chocolates. Attempts are currently underway to develop protocols for incorporating different molecules into the same crystal. The idea is perhaps a bit counterintuitive considering what has been said till now, but imagine if the two different medicines prescribed by your doctor could be punched into one single pill! Not only would you have to take them in smaller doses, but also at considerably less expense because of simpler production protocols. This is but one of the facets of the subject of crystal engineering, which can be loosely said to be concerned with the crafting of designer crystals. It sometimes takes strategising at Machiavellian levels, as I found out when I teamed up with one of my colleagues to persuade six different molecules to enter the same crystal.

Molecules are very pragmatic, always making the best of their surroundings to have the lowest possible energy. Naturally, they crystallise with only those molecules that can bind them strongly enough to effect a lowering of energy for both. The present state of the art is the making of binary cocrystals – crystals with two different molecules. Cocrystals with even three different components are achievable, albeit with considerable brainstorming, but raising the number of components any higher is impossible. At least it was, until very recently, when my colleague Mithun Paul noticed something strange in the way molecules of tetramethylpyrazine (TMP) were arranged in its cocrystal with 2-chlororesorcinol (CRES). He realised that some TMPs were held more loosely than the others and guessed that they can be replaced with molecules that would be held tighter, because of the resulting energy advantage to the whole system. The idea worked: progress

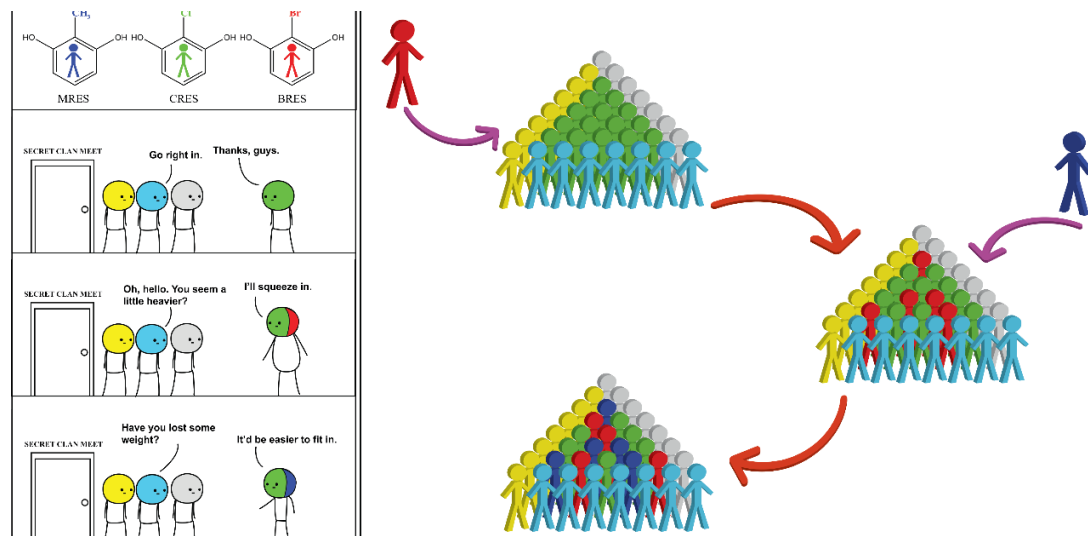
could be made to a three-component cocrystal, but *it too had a loose molecule!* This meant that one could incorporate a fourth component into a three-component cocrystal with the same logic. The situation closely resembles the one shown below: One of the blue men holding the slack red ropes in Group 1 is replaced by a grey man who brings a stronger black bond into Group 2. This leaves one blue man whose bonds to the rest of the group are not as strong. The yellow man relieves him to form Group 3. The green man watches all the fun from the bleachers. But not for long...



Molecules in a crystal can be tricked into accepting other molecules as one of themselves. The great crystallographer Alexander Kitaigorodskii wrote in 1973 that if the most important bonds in a crystal are left undisturbed, random molecules in it can be replaced by others that look very similar. The internal structure of the crystal remains essentially unchanged. The phenomenon is called doping and the result is a substance called a solid solution, in which the constituents are present in ratios of fractions (eg., 0.33:0.67) rather than whole numbers (e.g., 1:4) as in the case of chemical compounds. The energy-lowering in solid solutions happens not by forming strong bonds, but rather by an increase in randomness in the crystal. The greater the disorder, the more stable the system is. Objects crumble away, gases leak out of cylinders and spread everywhere – disorder is the natural order of things.

This is relatively easy in metallic crystals, which consist entirely of spherical atoms. A metal atom which is slightly bigger can squeeze into the site of a smaller one with a nominal effort, while a smaller atom can easily slip into the site of a larger one. However, one must factor in the asymmetric shapes of molecules when conducting a doping experiment with molecular crystals. Typically, exchangeable molecules should have essentially the same chemical diagrams, differing perhaps in only one atom or so. I had had some experience in this from my doctoral research,

and visualised the following scenario involving 2-methylresorcinol (MRES), 2-chlororesorcinol (CRES) and 2-bromoresorcinol (BRES):



Suppose a secret meeting is underway in the above-mentioned classroom and the blue, yellow and grey men stand guard at the door with strict instructions to let *only* green men (CRES) in. The first man gains entry without any trouble, but the second and the third have the bouncers confused. One of them looks exactly like the average green man but seems to be heavier. The bouncers accept that he will squeeze in somehow. The third also looks exactly like a green man but is thinner. The bouncers agree that he can quietly slip in without jostling other people. Little do they know that the second man is really BRES and is heavier because he has a bromine atom (the B of BRES) in place of a chlorine atom (the C of CRES); and that the third man is MRES, who is lighter because he has a methyl group (a carbon with three hydrogens; the M of MRES) where CRES has chlorine. The bromine and the chlorine atoms and the methyl group (B, C and M) have very similar volumes. It is as if MRES and BRES have put on green masks to slip past the bouncers. So, if either MRES or BRES enter separately and blend into the crowd of CRES in the four-component cocrystal, the resulting crystals would have five components. Similarly, if the two of them enter together the number of components would be six.

The initial X-ray photographs of the supposedly five-component cocrystals were somewhat misleading – they were rather like the four-component cocrystal containing CRES, meaning that they were NOT five-component cocrystals and the theory that the fifth molecule (MRES) could get into the structure without disturbing it was incorrect. A closer look at the photographs, however, put wide grins on our faces. We had caught the MRES lurking at random positions in the crowd of CRES. The theory of minimal structural disturbance was correct. It worked for the CRES-BRES and BRES-MRES mixtures as well, producing a total of three different types of five-component

cocrystals with essentially the same structures. But what if CRES, BRES and MRES were taken all together? Considering the sheer gain in randomness, a six-component cocrystal was perhaps even more feasible. Indeed, a CRES could sit next to another CRES or a BRES or a MRES in this case, whereas in a five-component cocrystal with say a CRES-MRES mixture, it could sit next to either another CRES or a MRES. It worked. We could isolate a six-component cocrystal in quite large quantities.

One can only wonder at the raw genius of Willard Gibbs, whose 1873 equation for predicting the feasibility of such a process holds true even today. What we had done on our way to the six-component cocrystal was to simply manipulate the two parts of his equation concerning energy and randomness. First, we had lowered the energy by replacing the loose bonds by strong ones and when that resource had been exhausted, we had upped the randomness in the system by bringing in molecules with similar shapes. This simple logic had lowered the overall energy, making the incorporation of half a dozen molecules into the same crystal possible. Seeing the textbook principles work in real life was humbling, and yet a lot of fun.