

What is a co-crystal – and does it matter?

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Abstract. The debate about the definition of the term co-crystal is a distraction from the quality of molecular solid-state science being published.

During the 1990s the term “co-crystal” gradually gained scientific acceptance, first among the crystal engineering community, and then among the crystallographic community at large. Despite its widespread usage, there were – and still are – some scientists who believe the term is too vague, or even scientifically suspect. One of the most prominent of these, Desiraju, ignited much of the current debate about the definition of the term co-crystal [1], when he recommended the abandonment of the term altogether, although he admits that if its usage is too common then we may be forced to accept it. Others have also expressed an opinion on how the term should be used. Dunitz offered a second opinion [2] that suggested that even if it is not perfect the term co-crystal is as good as any currently available, and that it should also be used inclusively; as the prefix *co-* is used to indicate togetherness, then any two compounds crystallised together can be termed a co-crystal. Aakeröy and Salmon wrote a review article that defined a co-crystal [3] as being “made from reactants that are solids at ambient conditions”, although this definition was made principally to limit the scope of their review. A need to limit their scope is particularly understandable when one considers that a Web of Science search for articles published between 1st January 2007 and 21st January 2008 gives a total of 168 articles contained the term “co-crystal” in either the title or the abstract of the paper [4]. Bond has suggested a more precise definition [5], stating that co-crystal should only be used as a synonym for the term “multi-component molecular crystal”, as he highlights a few awkward examples that might be regarded by many people as co-crystals, but where the reactants are not solids at ambient conditions. It seems that there are as many definitions as there are people who use the term, and many of these are subtly different!

Although the definition of Bond seems sensible and inclusive, it relies on being able to tell the difference between molecular and ionic species; in the case of poor quality crystals containing hydrogen bonds it may be difficult to locate the hydrogen atoms even using modern equipment, and it may thus be impossible to determine whether the product is a co-crystal or a salt. This is clearly undesirable.

The boundary between multi-component molecular crystal and an ionic crystal can also be blurred in other ways. There are many examples of hydrogen atoms that can change

position across the hydrogen bond with temperature; one example is the co-crystal of urea with phosphoric acid [6, 7]. Although at low temperature the compound is clearly ionic (and therefore best termed uronium phosphate), at higher temperatures the hydrogen atom is centred in the hydrogen bond, and therefore difficult to define as either molecular or ionic. Even more awkward is the example of the co-crystal of 4-methylpyridine with pentachlorophenol, which contains a short O...H...N hydrogen bond between the two components [8]. At room temperature the hydrogen atom is closer to the pentachlorophenol and so the crystal can be regarded as a multi-component molecular crystal, while at lower temperatures the proton migrates across the hydrogen bond to form an ionic complex! The proton is exactly centred between the two components at approximately 90 K. At room temperature, this system clearly meets Bond’s criteria for a multi-component molecular crystal, but at low temperature it does not. It seems that if we are to use the definition of Bond, then it may be necessary to include a specific temperature at which the definition applies; however if this is necessary then it may turn out to be necessary to specify all other physical conditions. There is therefore not only a great deal of ambiguity in the definition of the term co-crystal, but also in the defining of a crystal structure as a molecular or an ionic species. In reality, it seems that the divide between molecular and ionic in crystal structures is more appropriately described as a “salt-co-crystal continuum” [9].

Perhaps the most important question is therefore, does it matter what the definition of a co-crystal is? Considering what Desiraju termed the “easy way” that we as scientists have used the term co-crystal over the past 15 years, it is likely that the many articles published in 2007 containing the term co-crystal correspond to no particular definition, other than one that encompasses all possible definitions! Clearly this ambiguous usage makes literature searching more difficult if, say, a neutral multi-component molecular species is of greater interest than a charged ionic species, but other than this it has no effect on the science in the articles. Given these difficulties, there seems no reason to be pedantic about a definition, so long as each article is consistent within its own definition. Perhaps this debate over definition of the term co-crystal is simply a distraction from the most important issue; the quality of the solid-state science being published.

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