

Perspective

Redefining the Term of Cocrystal and Broadening Its Intension

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Cryst. Growth Des., **Just Accepted Manuscript** • DOI: 10.1021/acs.cgd.8b01537 • Publication Date (Web): 23 Jan 2019Downloaded from <http://pubs.acs.org> on January 26, 2019

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1 2 3 **Redefining the Term of *Cocrystal* and Broadening Its Intension**

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14 **Abstract:** *Cocrystal* is currently a more and more popular term in the crystal community, as it has already
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16 been verified that, the cocrystallization to form new crystals can serve as a promising strategy and an
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18 efficient technology to modulate and improve properties and performances of materials in the fields of
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20 pharmaceuticals and others. Nevertheless, the definition and intension of *cocrystal* remain still debatable.
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22 In this *Perspective*, we redefine *cocrystal* with a broadened intension as *a cocrystal is a single phase*
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24 *crystalline solid composed of two or multiple components in a stoichiometric ratio, and the components*
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26 *of a cocrystal can be atoms, molecules, anions and cations in pairs, and/or metallic cations with free*
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28 *electrons shared.* Thereby, cocrystals are classified into five types in terms of the kinds of the components
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30 and their interactions in crystal entity, including *atomic cocrystal, molecular cocrystal, ionic cocrystal,*
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32 *metallic cocrystal* and *mixed-type cocrystal.* The reasserted definition and broadened intension of
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34 *cocrystal* present a uniform term for all crystalline solids with two or multiple components, and facilitate
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36 to avoid confusion of numerous existing terms of these solids. Thereby, some terms with narrow
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38 intensions are expected to be updated and applied less and less as time proceeds.
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■ INTRODUCTION

It becomes more and more popular to cocrystallize two or multiple components to create new materials with modulated or improved performances and properties in comparison to those composed of pure components. For example, the important physicochemical properties of pharmaceutical materials, such as solubility, stability, or bioavailability, can be modulated by cocrystallization. Beyond pharmaceutical materials, cocrystallization has also been or is being developed to a common and efficient technique in other fields.¹⁻⁸

With respect to the scientific term of the products of cocrystallization, it may naturally be named *cocrystal*, as that of crystallization is named *crystal*. However, the definition of cocrystal and its intension remain still debatable, which have caused much ambiguity, confusion and puzzle. As stated by Seddon, *it is our duty as scientists to avoid ambiguity, and to be as clear in our expositions as possible, especially when terms are likely to become visible to the general public.*⁹ This duty provokes us to redefine cocrystal with a much broader intension and do our best to reduce the ambiguity, confusion and puzzle. Our simple intention in this *Perspective* is to highlight what is the components in a cocrystal, and that a cocrystal is mainly distinguished by the heterogeneousness of its components and the classification criterion of cocrystals should be that of crystals.

■ INSUFFICIENCY OF THE PRESENT DEFINITIONS AND CLASSIFICATIONS

There have been many definitions of cocrystals, and the most possibly accepted one defined in a recent perspective authored by 46 scientists in the pharmaceutical field as *cocrystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.*¹⁰ Regarding the classification, cocrystal referred to *molecular cocrystal* only until both *molecular cocrystal* and *ionic*

cocrystal were clearly stressed very recently.¹¹ Practically, many insufficiencies of present definitions and classifications of cocrystals exist as follows.

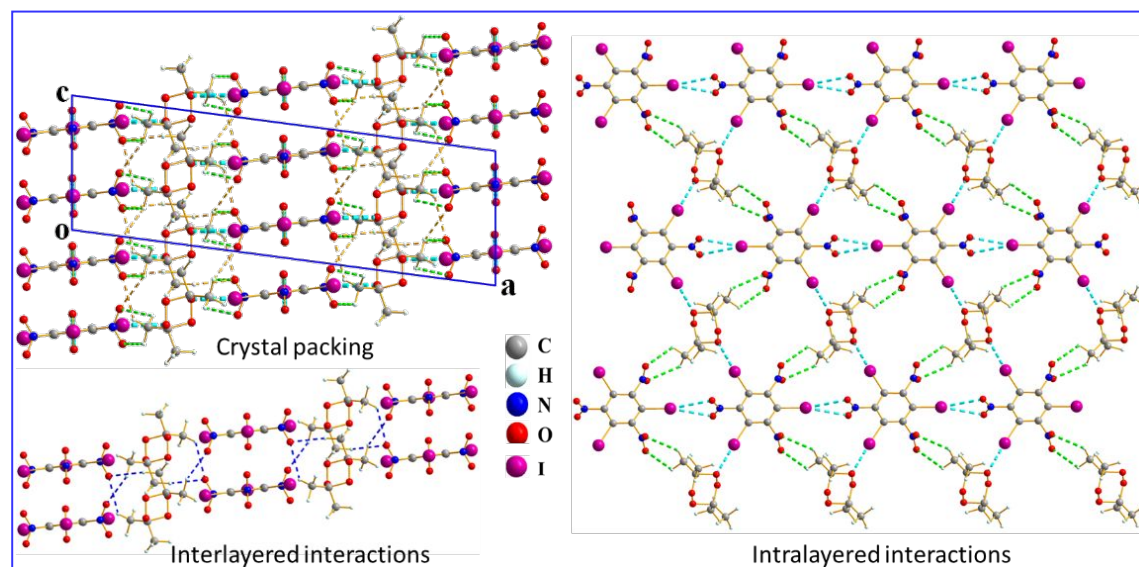


Figure 1. Crystal packing and inter/intra-layered intermolecular interactions of the energetic cocrystal of diacetone diperoxide (DADP)/1,3,5-triiodo-2,4,6-trinitrobenzene (TITNB).

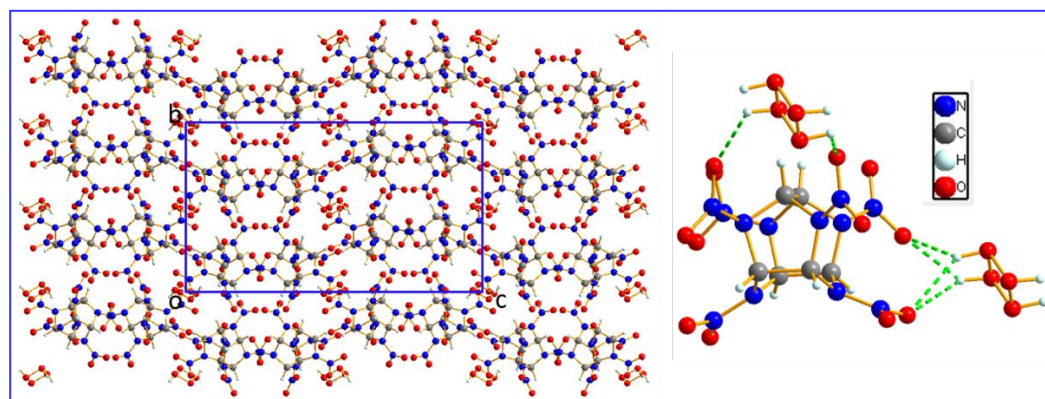


Figure 2. Crystal packing and intermolecular hydrogen bonding of the energetic cocrystal of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20)/H₂O₂.

- Too much pharmaceutical sense and influence on the definition of *cocrystal*. Besides pharmaceutical cocrystals, a distinct example is that energetic cocrystals appear with a promising perspective. In comparison, a pharmaceutical cocrystal contains at least one active pharmaceutical ingredient (API); while, at least one energetic component should be included in an energetic cocrystal. Energetic cocrystals can not only modulate some key properties of energetic materials like density,

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2 energy and safety between their pure components, but also outperform their pure components in these
3 properties. For example, the diacetone diperoxide (DADP)/1,3,5-triiodo-2,4,6-trinitrobenzene (TITNB)
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energy and safety between their pure components, but also outperform their pure components in these properties. For example, the diacetone diperoxide (DADP)/1,3,5-triiodo-2,4,6-trinitrobenzene (TITNB) cocrystal with intermolecular halogen bonding and hydrogen bonding (Figure 1) possesses remarkably decreased impact sensitivity in comparison to its pure components of DADP and TITNB,¹² due to much enhancement of intermolecular interactions and their anisotropy;¹³ the orthorhombic 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20)/H₂O₂ cocrystal with intermolecular hydrogen bonding (Figure 2) is more powerful than either of its pure components of CL-20 and H₂O₂, by improving oxygen balance and maintaining a high density close to that of ϵ -CL-20, i.e., 2.03 vs. 2.04 g/cm³;¹⁴ and the packing density of 2,4,6-trinitrotoluene (TNT)/1-bromonaphthalene cocrystal (1.737 g/cm³) is higher than those of both TNT (1.704 g/cm³) and 1-bromonaphthalene (1.489 g/cm³).¹⁵ It shows a benefit of energetic cocrystals, as the higher energy, safety and density are usually highly desired for energetic materials. In fact, cocrystallization has been taken as a means of crystal engineering to create new energetic materials.¹⁶ Also, like pharmaceutical cocrystal, energetic cocrystal is a subset of cocrystal. While, this classification is carried out in terms of the applicable function of a cocrystal, lack of a sense of scientific terminology.

Given the significance of cocrystals in the pharmaceutical field, the definition of cocrystals is not only a question of correct scientific terminology, but has also regulatory implications. Recently, United States Food and Drug Administration (FDA) proposed a definition of cocrystals in the draft guidance as *crystalline materials composed of two or more different molecules within the same crystal lattice that are associated by nonionic and noncovalent bonds*.¹⁷ This FDA proposed definition possesses much restriction on the component of molecules and the interaction among the components of nonchemical bonds, and it seems to be specified for pharmaceutical industry, as APIs are usually composed of

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2 molecules. Actually, pharmaceutical ionic cocrystals have come into being with a large quantity.
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4 Scientifically and terminologically, it requires a broader and clearer definition for *cocrystal*, as stressed
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6 in a recent perspective.¹⁰
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10 ● Too much weakening of the physical nature for classifying crystals in defining and classifying
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12 cocrystals. Note, cocrystals are crystal. The physical nature lies in the components and the interactions
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14 among the components involved in crystal. It is also the criterion for classifying crystals. Because the
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16 use of the prefix co- is to indicate togetherness here, cocrystals are distinguished from crystals by their
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18 two or multiple components only, i.e., by the amount of the components, instead of the kinds of both the
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20 components and the interactions among the components. Now that it is, ionic cocrystals belong in
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22 principle to ionic crystals; and how *ionic cocrystals* can be defined as *which are comprised of at least*
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24 *one ionic coformer that is a salt*¹⁸ in comparison to the definition of *ionic crystal* as *An ionic crystal is*
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26 *a crystal consisting of ions bound together by their electrostatic attraction* (Wikipedia)? Besides, now
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28 that *crystal* can be classified into *molecular crystal*, *ionic crystal*, *atomic crystal* and *metallic crystal*,
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30 why *cocrystal* can't correspondingly be classified into such four kinds? Currently, there are only
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32 *molecular cocrystal* and *ionic cocrystal*.¹¹ Why we can't define two or multi-component atomic crystals
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34 and metallic crystals as *atomic cocrystals* and *metallic cocrystals*, respectively? Indeed, they have existed
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36 for a long time.
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40 ● Too much terms that are essentially subsets of *cocrystal* existing. It seems that there are many
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42 terms for describing a chemical phenomenon, and a large quantity of terms or concepts with unclear
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44 physical meanings are presented as a usual situation in chemistry. For example, with respect to
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46 *intermolecular interaction*, it may be described as *nonchemical interaction*, *nonbonded interaction*,
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48 *noncovalently bonding*, *noncovalent interaction*, *van der Waals and electrostatic interactions*, *hydrogen*
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3 *bonding, halogen bonding, π - π stacking, p - π interaction, cation- π interaction, anion- π interaction, H- π*
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5 *interaction* or others. It usually confuses and dazzles me, as some of them are termed conditionally,
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7 without physical origin instead. Actually, most of these terms are perceptual and phenomenological
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9 without exact physical origin, and further are difficult to be exactly described or calculated. In principle,
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11 they are the van der Waals and electrostatic interactions with a simple and clear physical meaning.
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15 Similarly, too many terms of *molecular compound, molecular complex, molecular organic*
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17 *compounds, organic molecular compounds, hydrate, solvate, pseudopolymorph, inclusion compound,*
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19 *channel compound, clathrate compound, complex molecule, complex salts, additional complex, addition*
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21 *compounds, metal salt complex, heteromolecular crystals, mixed crystals, complexes, hydrogen bonded*
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23 *complexes,* and others all represent a two or multicomponent crystal, i.e., actually, a cocrystal. These
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25 terms are usually conditional and phenomenological as aforementioned ones of intermolecular
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27 interactions. For example, solvates (hydrates) are named *solvates* because they are resulted from
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29 cocrystallization with solvents; then, what are their names if they are produced by another means of
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31 which the solvents don't serve as solvents any longer? It shows an evident sense of a manufacture process
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33 in naming *solvates* or *hydrates*, which is a term absent from a clear physical meaning. As a matter of
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35 fact, due to the unclear physical meaning for the existing definitions of *cocrystal* and its relatives, most
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37 of them are overlapped in use, together with debates. Robust historic inertia of the existing definitions
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39 should partly be responsible for the debates. In the most cases, new chemical terms or new definitions
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41 were proposed and specified for given cases, without sufficiently refinement and clarification. Once they
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43 keep in mind, it can hardly be varied. Usually, it usually costs a long time to extensively accept an updated
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45 and more scientific term.
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57 Science is to understand and reveal the origin of the objective world, and it requires and tends to
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3 simplicity and unification. For instance, lots of aforementioned terms that are originally cocrystals can
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5 be simplified or unified as one, *cocrystals*. A scientific term of cocrystals with a clear physical meaning
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7 facilitates us to understand and create this kind of substances or materials that become more and more
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9 important currently, to benefit our human. Owing to the aforementioned insufficiency in the present
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11 definitions of cocrystals, a redefinition and a scientifically clear classification are required.
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15 ■ HISTORY OF COCRYSTAL AND ITS RELATIVES

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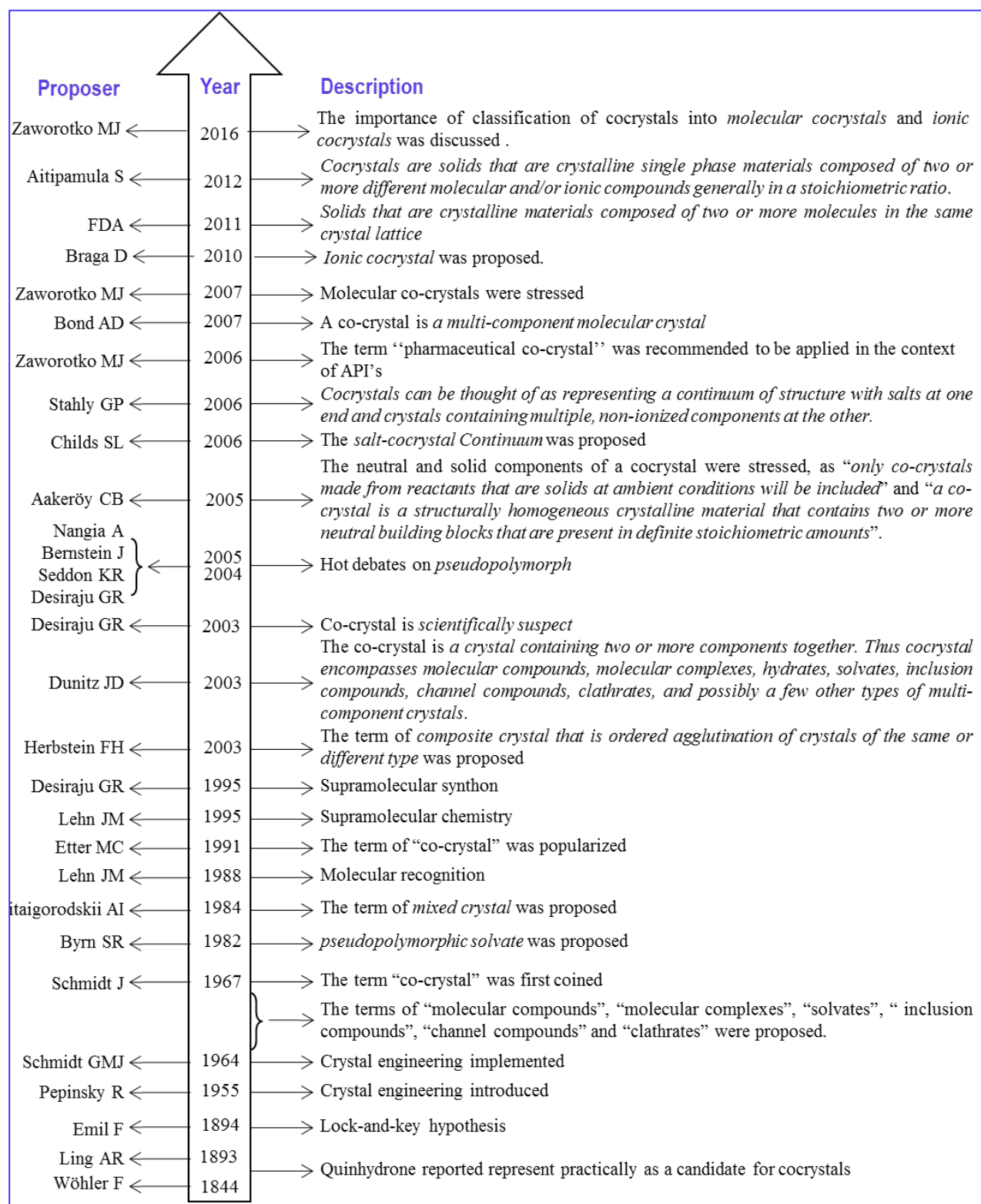


Figure 3. Historic diagram of the term of *cocrystal* and its relatives. The words in italic are directly cited for the original literatures.

Prior to redefining *cocrystal*, it is necessary to look back its evolution, as we summarize the historic

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3 proposals or descriptions for the terms of *cocrystal* and its relatives in Figure 3. Cocrystals represent a
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5 long known class of compounds, like quinchrydron as a prototypal example, which was reported at least
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7 as early as 1844¹⁹ and 1893²⁰. In 1894, the lock-and-key hypothesis was proposed as the earliest ones
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9 of supramolecular chemistry.²¹ Afterwards, the term of crystal engineering was introduced by Fischer
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11 firstly²² and implemented by Schmidt^{23,24}. During this period, various terms of *molecular compound*,
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13 *molecular complex*, *solvate*, *inclusion compound*, *channel compound*, and *clathrate compound* appeared.
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15 In 1967, the term of *cocrystal* was firstly coined by Schmidt and Snipes²⁵, and subsequently popularized
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17 by Etter²⁶. Prior to 2000, some known terms or concepts like *pseudopolymorph*²⁷, *molecular recognition*
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19 ²⁸, *supramolecular chemistry*²⁹ and *supramolecular synthon*^{30,31} were proposed. After a period of about
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21 20 years of silence till 2003, the debates on the term of *cocrystal* became hot during 2003-2007, even on
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23 the difference in a hyphen between the terms of *cocrystal* and *co-crystal*. As illustrated in Figure 1,
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25 among the debates, few people don't suggest to use the term of *cocrystal*³², while most scholars support
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27 its usage more or less³³⁻³⁹. At this stage, a term of *pseudopolymorph*, representing solvates, was hotly
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29 debated^{9,40-42}. It makes indeed much confusion because this term does not possess a new physical
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31 meaning, relative to an existing term of *solvate*. Recently, *ionic cocrystal* was proposed, as another type
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33 of cocrystal in comparison to *molecular cocrystal* in the pharmaceutical field. It should be progress in
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35 terming *cocrystal*, as it refers no longer to *molecular cocrystal* only. In combination with the proposals
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37 of *mixed crystal*⁴³, *composite crystal*⁴⁴, *salt-cocrystal continuum*³⁶ and *pharmaceutical cocrystal*⁴⁵,
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39 more and more people accept that *a cocrystal is a two or multi-component crystal*.

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41 Overall, there are indeed too many terms of *cocrystal* and its relatives, with more or less scientific
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43 merits in the long river of history. Nevertheless, with the scientific improvement and development, some
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45 of these terms become ambiguous, overlapped, or even out of date. Thereby, it is timely to clarify the
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definition and intension of cocrystal, as a scientific term.

■ REFERRING *COCRYSTAL* WITH A BROADER INTENSION

It has extensively been accepted that a *cocrystal* is a *two or multi-component crystal*, in comparison to a single-component crystal. That is to say, a cocrystal is in principle the same as a single-component crystal, only with a difference in the amount of the components. So, what is the component? This issue was also raised by other scholars, and should be clarified in the redefinition to be distinguished from the existing definitions. A definition of crystal, *A homogenous solid formed by a repeating, three-dimensional pattern of atoms, ions, or molecules and having fixed distances between constituent parts* (*The American Heritage Dictionary, AHD*), may enlighten us to think that the component refer to atoms, ions, or molecules, as *constituent part* is literally equal to *component*. Someone also thought so.³⁷ Nevertheless, that the component refers to atoms, ions, or molecules could be rough and primary, with some explanations required as following:

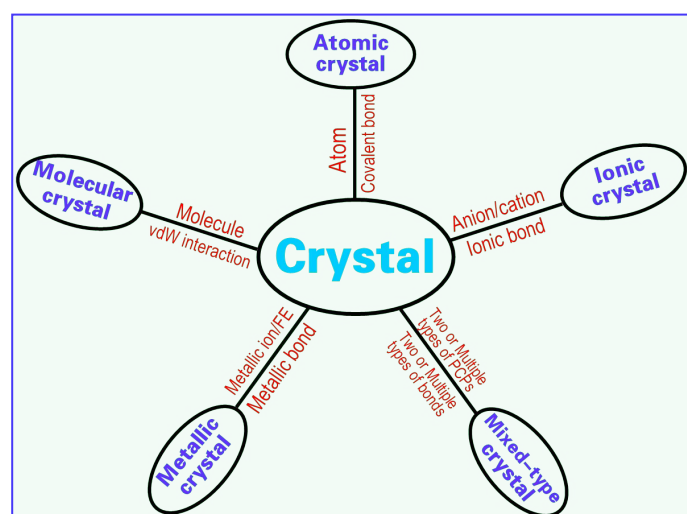


Figure 4. Crystal classification by means of primary constituent parts (PCPs) and the nature of PCP interactions. FE is the abbreviation of free electron.

- On the crystal level, atoms, ions, or molecules should be specified as *primary constituent parts* (PCPs), which are the closest substructures to crystal. Figure 4 demonstrates five kinds of crystals, which

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3 possess different PCPs from one another. For atomic crystal, molecular crystal, ionic crystal and metallic
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5 crystal, their PCPs are atoms, molecules, cations/anions, and metallic ions/free electrons, respectively.
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7 Besides, a crystal is named a *mixed-type crystal*, which contains two or multiple types of PCPs in it. The
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10 mix-typed crystal is distinguished from the former four kinds of crystal by the amount of the PCP types.
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12 For example, the PCPs of ions and molecules can coexist in a same lattice. It should be noted that we
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14 have to use a term of *mixed-type crystal* to be distinguished from that of *mixed crystal*, representing a
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16 solid solution with a wide acceptance. In fact, we hope that the term of *mixed crystal* possesses just the
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18 intension of that of *mixed-type crystal*, instead of that as it is, because the crystalline solid solution can
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20 be classified into any type of the five shown in [Figure 4](#). For example, the ordered mixed crystals of
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22 AuCu and AuCu₃ are in fact the metallic crystals or metallic cocrystals.⁴⁶ Meanwhile, a mixed crystal
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24 can also represent a disordered solid solution (an amorphous solid). That is, a mixed crystal can't always
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26 be a crystal. Now that it is, we think that it should replace the proposed *mixed-type crystal* by *mixed*
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28 *crystal*, with an intension of that proposed for the former, instead of solid solution as it is now. Thereby,
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30 a mixed crystal only represents a crystal in name.
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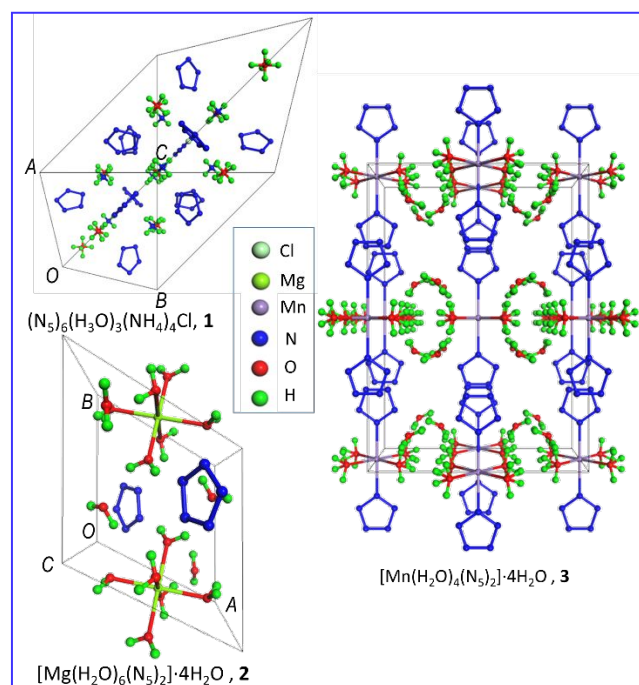


Figure 5. Crystal packing of three cyclo- N_5^- contained crystals.

It is necessary to clarify the PCP in some substantial crystals. To do this, three salts, including $(N_5)_6(H_3O)_3(NH_4)_4Cl$ (**1**)⁴⁷, $[Mg(H_2O)_6(N_5)_2] \cdot 4H_2O$ (**2**) and $[Mn(H_2O)_4(N_5)_2] \cdot 4H_2O$ (**3**)⁴⁸, are adopted to exemplify what is the PCP. As illustrated in Figure 5, N_5^- , H_3O^+ , NH_4^+ and Cl^- , $Mg(H_2O)_6^{2+}$, N_5^- and H_2O , and $Mn(H_2O)_4(N_5)_2$ and H_2O are the closest substructures of **1**, **2** and **3**, and therefore their PCPs, respectively. It should be noted that the coordinated H_2O in **2** and **3**, and the coordinated N_5^- in **3** are all not the PCP, because they are not the closest substructures to crystal, despite that they are the substructures too. Even though N_5^- and H_2O are the substructures of the three crystals, they are on the different levels.

- The types of the PCPs and their interactions reflect the physical nature of crystal, and they are the criterion for the crystal classifications, as illustrated in Figure 4. Atomic crystals are a class of crystals in which the atoms are held in the lattice by covalent bonds, therefore they also called as covalent crystals. Molecular crystals are a group of crystals consisting of discrete molecules and held by weak

intermolecular interactions. An ionic crystal is a crystal consisting of ions bound together by their electrostatic attraction. A metallic crystal is composed of metallic ions and free electrons, and the metallic bonds are present in all metals, in which the outer electrons are shared by the crystals as a gas of valence electrons which are free to move throughout the metal lattice. And a mixed-type crystal is a crystal held by two types of the interactions among the PCPs at least. For **1**, **2**, and **3** in Figure 3, their PCPs are N_5^- , H_3O^+ , NH_4^+ and Cl^- , $Mg(H_2O)_6^{2+}$, N_5^- and H_2O , and $Mn(H_2O)_4(N_5)_2$ and H_2O , belonging to ions, ions and molecules, and molecules, respectively. The interactions among the PCPs are in turn ionic bonds, ionic bonds and intermolecular interactions, and intermolecular interactions. Accordingly, they fall into ionic crystal, mixed-type crystal and molecular crystal, respectively. In the original literature, **3** was roughly regarded salts,⁴⁸ it may be questionable.

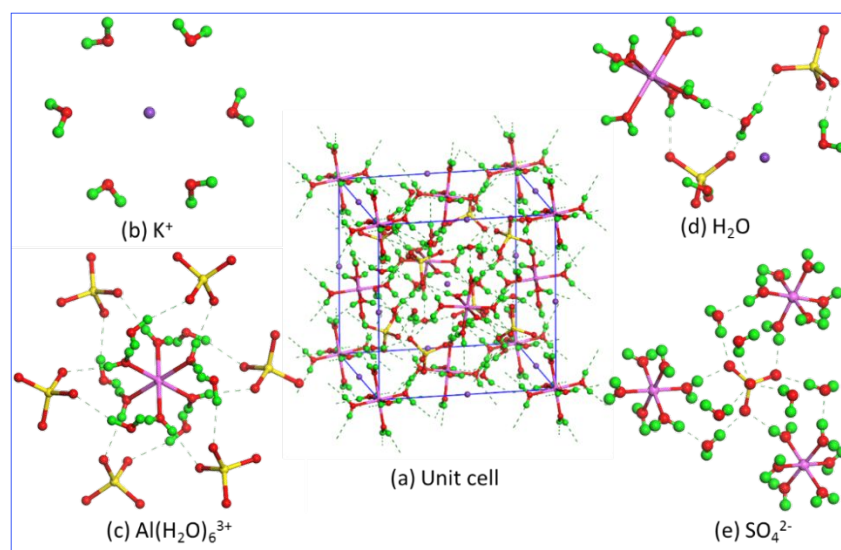


Figure 6. Crystal structure and PCS interactions in alum. O, H, S, Al and K atom are represented in red, green, yellow, purple and scarlet, respectively.

Alum is employed as another example to clarify the PCPs and their determination in crystal type. All illustrated in Figures 6a to 6e, there are four kinds of PCPs in the alum crystal, including K^+ , $Al(H_2O)_6^{3+}$, H_2O and SO_4^{2-} . Note, one Al^{3+} and six coordinated H_2O in one $Al(H_2O)_6^{3+}$ just compose of

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3 Al(H₂O)₆³⁺, and are not the PCPs of the alum crystal, similar to the aforementioned coordinated N₅⁻ and
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5 H₂O. and. As to the interactions among the PCPs, those around one K⁺ (Figure 6b) and around a free
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7 H₂O (Figure 6d) belong to intermolecular interactions, while those around one Al(H₂O)₆³⁺ (Figure 6c)
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9 and one SO₄²⁻ (Figure 6e) belong to the combination of intermolecular interactions and interionic
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11 attraction. That is to say, two types of interactions among the PCPs exist in alum, suggesting that alum
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13 is a mixed-type crystal.
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18 ● The PCP is not completely identical to the component. As aforementioned, what is the
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20 component is the mostly concerned by scholars, and possibly the root for the long-time debate on the
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22 term of *cocrystal*. *AHD* explains *component* as *Any of the minimum number of substances required to*
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24 *specify completely the composition of all phases of a chemical system*. The explanation shows ambiguity
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26 with an *Any* in it. Looking back into the aforementioned history of *cocrystal*, we can find that it requires
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28 two different components that each exists alone to synthesize a *cocrystal*. In this case, *the components*
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30 *for an atomic crystal, a molecular crystal, an ionic crystal and a metallic crystal are clarified as atoms,*
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32 *molecules, anions and cations in pairs, and metallic cations with free electrons shared, respectively*. The
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34 pairing of anions and cations or metallic cations with free electrons is requested for electric neutrality. If
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36 these components are classified into four types according to the crystal types, two or more types of
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38 components will be involved in a mixed-type crystal. In a complex case exemplified by alum in Figure
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40 6, the components are accordingly K₂SO₄ and [Al(H₂O)₆]₂(SO₄)₃, and H₂O, belonging to two types. It
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42 should be sympathized that, even though the *existing-alone* is considered in the clarification of
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44 component, it doesn't suggest a necessary *existing-alone*. It is the same as that a two-component *cocrystal*
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46 should not necessarily be prepared by the two components. It is just for the clarification.
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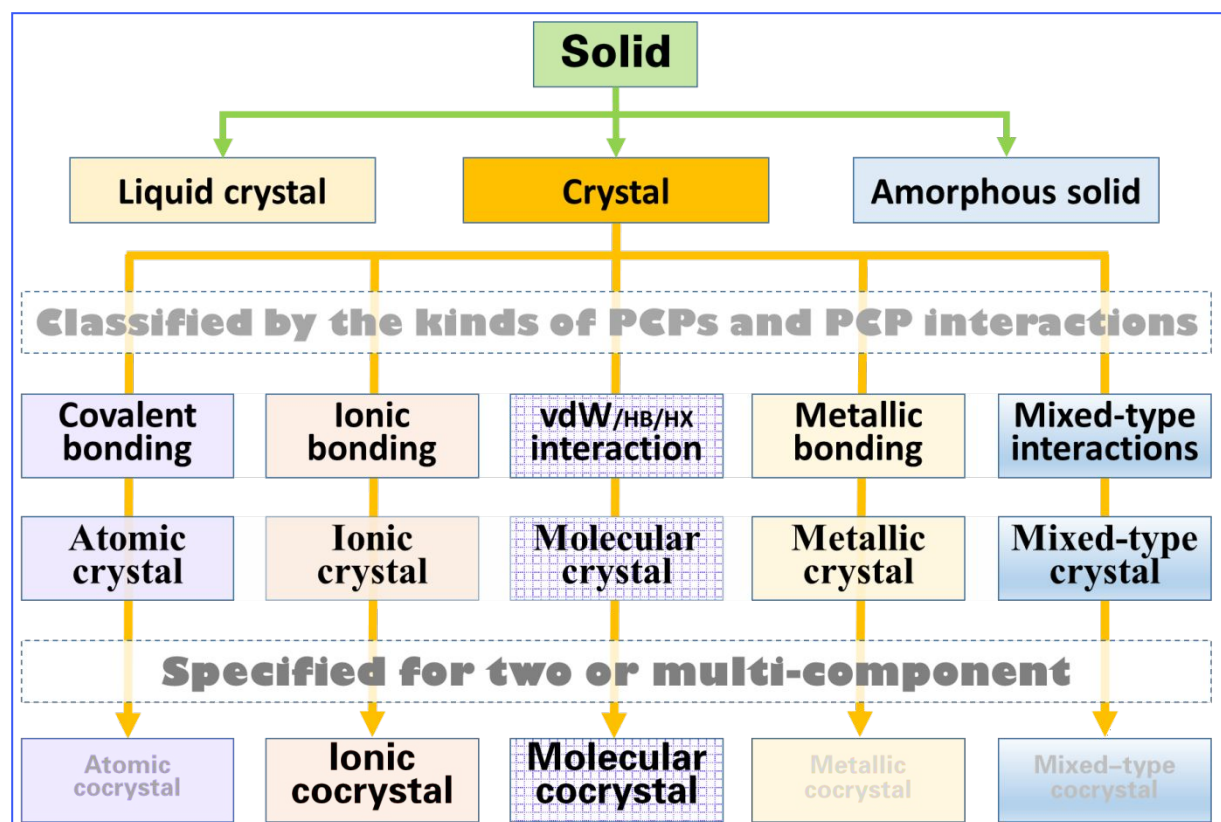


Figure 7. Crystal and cocrystal classification by means of the types of PCPs and the nature of their interactions. Terms in dark are firstly proposed.

Based on the aforementioned clarification of component, we redefine the term of *cocrystal* as *a cocrystal is a single phase crystalline solid composed of two or multiple components in a stoichiometric ratio, and the components of a cocrystal can be atoms, molecules, anions and cations in pairs, and/or metallic cations with free electrons shared.* Corresponding to the classification of crystals in terms of the kinds of PCPs and their interactions, the cocrystals are classified into five types, including *atomic cocrystal, molecular cocrystal, ionic cocrystal, metallic cocrystal* and *mixed-type cocrystal* (it is expected to be accepted as *mixed cocrystal* someday), as illustrated in [Figure 7](#). That is, *an atomic cocrystal is an atomic crystal with at least two kinds of atoms, such as crystalline SiC and Si₃N₄; a molecular cocrystal is a molecular crystal with at least two kinds of molecules, and molecular cocrystals occupy a large population in cocrystals; an ionic cocrystal is an ionic crystal with at least two kinds of same*

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3 *electronically signed ions*, such as crystalline anhydrous $\text{KAl}(\text{SO}_4)_2$ and $(\text{NH}_4)_4\text{Fe}(\text{SO}_4)_3$; a metallic
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all mixed-type crystals are mixed-type cocrystals as they should be composed of at least two kinds of components, such as aforementioned **2** and alum.

Up to the present, only the terms of *molecular cocrystal* and *ionic cocrystal* were introduced.^{11,49,50} In comparison, a new proposal of *atomic cocrystal*, *metallic cocrystal* and *mixed-type cocrystal* will broaden the intension of *cocrystals*. It is understandable that our proposal of the term of *cocrystal* may be radical and cause new debates; after all, it is dominant thriving in the field of pharmaceuticals, mainly composed of organic molecules. Modestly, these firstly introduced terms of *atomic cocrystal*, *metallic cocrystal* and *mixed type cocrystal* are darkened in [Figure 7](#). However, I strongly believe they will be accepted more and more widely in future, because they full of a scientific sense. When we use the broadened definition, some clarifications or advantages should be accounted as follows.

- We agree with Stahly's suggestion³⁷ to remove the hyphen in term of *co-crystal*, according to the guide of *The Columbia Guide to Standard American English*.⁵¹ That is, it is expected to use *cocrystal* uniformly to avoid the confusion of the term of *co-crystal*.

- The stoichiometric ratio of the components in a cocrystal should strictly be required for a crystal including a cocrystal, as it is well known that, crystals are distinguished from solids by the regular, periodic order of their components.

- Multiple terms of crystalline *double salt*, *molecular compound*, *molecular complex*, *solvate*, *inclusion compound*, *channel compound*, *clathrate compound*, *pseudopolymorphs*, *intermetallic compound*, *double salt*, *composite crystal*, *salt-cocrystal continuum*, etc. that contain at least two components and refer to *cocrystal* can be unified to a single one of *cocrystal* by broadening the intension

of *cocrystal* to avoid scientific suspects. In particular, as a common term of *solvate (hydrate)*, it can fall in the category of *molecular cocrystal* when all components are molecules, such as aforementioned CL-20/H₂O₂; and it can be mixed-type cocrystal, such as above mentioned alum and 2.

■ CONCLUSIONS

Summarily, we redefine the term of *cocrystal* according to the types of the PCPs and their interactions, and broaden its intension to all two or multiple component crystals. Accordingly, cocrystals can be classified into five types, including *atomic cocrystal*, *molecular cocrystal*, *ionic cocrystal*, *metallic cocrystal* and *mixed-type cocrystal*. The redefinition with a broadened intension, based on the PCPs and physical origins of interactions that build and support crystalline solids, is expected to be more popular and extensively accepted, as time runs.

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Notes

The views expressed herein are those of the individual signatories and do not necessarily represent the views of the institutions with which they are affiliated.

The authors declare no competing financial interest.

■ ACKNOWLEDGMENT

The authors thank a lot for the support of the Science Challenge Project (TZ-2018004) and the National Natural Science Foundation of China (U1530262).

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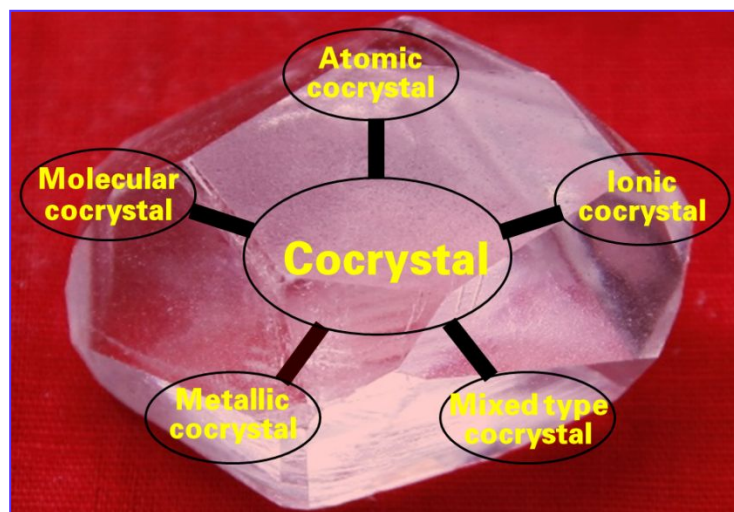
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Redefining the Term of *Cocrystal* and Broadening Its Intension

Chaoyang Zhang, Ying Xiong, Fangbao Jiao, Minmin Wang, and Hongzhen Li



We redefine the term of cocrystal as *a cocrystal is a single phase crystalline solid composed of two or multiple components in a stoichiometric ratio, and the components of a cocrystal can be atoms, molecules, anions and cations in pairs, and/or metallic cations with free electrons shared.* And cocrystals can be classified into five kinds, including atomic cocrystal, molecular cocrystal, ionic cocrystal, metallic cocrystal and mixed cocrystal.