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Cocrystals Definitions

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Cocrystals may be stabilized by different types of interactions, besides that of hydrogen bonding—the only type of stabilization specified in the current definitions. There are, for instance, van der Waals forces, $\pi-\pi$ interactions, and halogen bonding, among others. The current definitions of cocrystals do not describe these types of interactions, which may be crucial in determining cocrystal formation in diverse compounds. Herein, we attempt to propose a more universal definition of cocrystals, considering all of the various forces involved, and to place more emphasis on the characterization of cocrystals. Moreover, we highlight some examples of cocrystals that are very clearly stabilized by forces other than hydrogen bonds.

Keywords: Cocrystals; Synthons; Heterosynthons; Hydrogen bond; Halogen binding

INTRODUCTION

Molecular cocrystals have been known for a long time, but they have yet to be studied in sufficient detail, in spite of the growing interest in polymorphism, pharmaceutical compositions, crystal growth design, and related areas. Furthermore, the definition of cocrystals remains a matter of discussion, independent of the great number of recent articles on cocrystal applications. Desiraju [1] was the first to ask: "co- is co- to what?". Dunitz [2] answered that "co-" means togetherness, and that this is its function in the term cocrystals. Furthermore, he cited Glasstone, who defined *lattice compounds* as: "those substances formed between definite stoichiometric amounts of two molecular species, which owe their stability to packing in the crystal lattice, and not to ordinary valency forces," and proposed that the word "two" should be changed to "two or more" to provide a definition of cocrystals. This generality has been lost more recently, and we find new definitions claiming, for instance, that: "cocrystals are crystalline materials comprised by two or more unique solids at room temperature, in a stoichiometric ratio ... and where the dominant interactions in the formation of the cocrystal are hydrogen bonds..." [3]. Alternatively, a cocrystal has been defined as: "a formation of a molecular complex of an active pharmaceutical ingredient and a second molecule typically requiring complementary hydrogen bonding between the two components" [4]. A further definition is that cocrystals are "crystalline entities with at least two different components constituting the unit cell and interacting by hydrogen bonds" [5]. The previous definition was appended with several exception cases (for other exception cases, see reference [6]), such as that they are not "salts, where the strength of the interaction is so strong that the linkage is between two oppositely-charged ions (electrovalent bond; r^{-1} dependence)." Another exception case to be added to the proposed definition was that cocrystallization should be understood as being different to coprecipitation, to eutectic formation, to a solid solution, or to dispersion.

In the light of the above-mentioned definitions and incorporated exception cases, and to show their vagueness, we can mention several cases that may generate uncertainties or ambiguities. In a first approach, let us consider solvated polymorphs that have specific crystalline arrays, and in which a solvate participates as a structural part of the unit cell. Crystals of this type, which are also designated as pseudopolymorphs [1], are constituted by at least two components, and involve interactions with the solutes through hydrogen bonds, therefore conforming to the above definition of cocrystals. As a second case, we may consider solid pharmaceutical

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formulations, in which a crystalline mixture of inert excipients frequently establishes strong interactions with the crystalline active ingredient, modifying its solubility and other properties [7–11]. This also conforms to the main elements of the above definitions.

On the other hand, crystalline compounds that do not conform to the above definitions are those in which two or more components are stabilized in a crystalline array by van der Waals interactions (r^{-6} dependence) (see Fig. 1), by $\pi-\pi$ stacking interactions (see Fig. 2), or by halogen bonding (see Fig. 3), among others. That is to say, in the current definitions, the non-ordinary valency forces mentioned above are restricted to hydrogen bonds as the principal type of interaction involved in cocrystal formation, ignoring the role played by the other mentioned nonbonding forces, which, in many cases, are solely responsible for the lattice stabilization.

More recently, Zaworotko *et al*. [5,12,13] generalized the definition and proposed a cocrystal to be: "a multiple-component crystal, in which all components are solid under ambient conditions when in their pure form. These components consist of a target molecule or ion and a molecular cocrystal former(s); when in a cocrystal, they coexist at the molecular level within a single crystal." This last definition by Zaworotko *et al.*, includes all of the elements proposed in Dunitz's definition. However, it does not establish the type of interaction responsible for stabilizing the cocrystals. Nonetheless, this definition of cocrystals encompasses molecular entities interacting with ionic entities (see, however, reference [6]). The other above-mentioned definitions ascribe the decisive influence in cocrystal array stabilization to hydrogen bonds alone, which is far from being true. To support this claim, we highlight three examples of cocrystals stabilized by non-ordinary valency forces other than hydrogen bonds, from among the many such examples that exist in the literature. See for instance [14–22]

$\pi-\pi$-INTERACTIONS AND VAN DER WALLS FORCES

A trimer of the heterosynthon [(C_{60})(calix[5]arene)] reported for a cocrystal [23] was calculated by the PM3 semiempirical quantum chemical method, using the Spartan 04 package for Windows [24,25]. The coordinates were taken from X-ray determined data [23]. The obtained calculations showed an energy of 12.662 kcal mol^{-1} for the calixarene(fullerene interaction, which corresponds to the sum of all of the $\pi-\pi$ aromatic interactions established by the two cocrystal components (Fig. 1). To establish the interaction energy between the different heterosynthons, we followed two approximations. First, we calculated the interaction energy between three individual fullerenes, which gave a value of 3.677 kcal mol^{-1} for each fullerene(fullerene interaction, clearly corresponding to the order of a van der Waals-type of interaction [26]. The second approximation was to calculate the interaction energy between the three heterosynthons [(C_{60})(calix[5]arene)], which yielded an interaction energy between two fullerenes of 3.283 kcal mol^{-1}. These two values are very similar, and the small difference between them may possibly be attributed to steric hindrance arising from the presence of the calixarene basket when the second strategy is used. In this discussion, we define the synthon as the fullerene and calixarene molecules that make up the cocrystal,

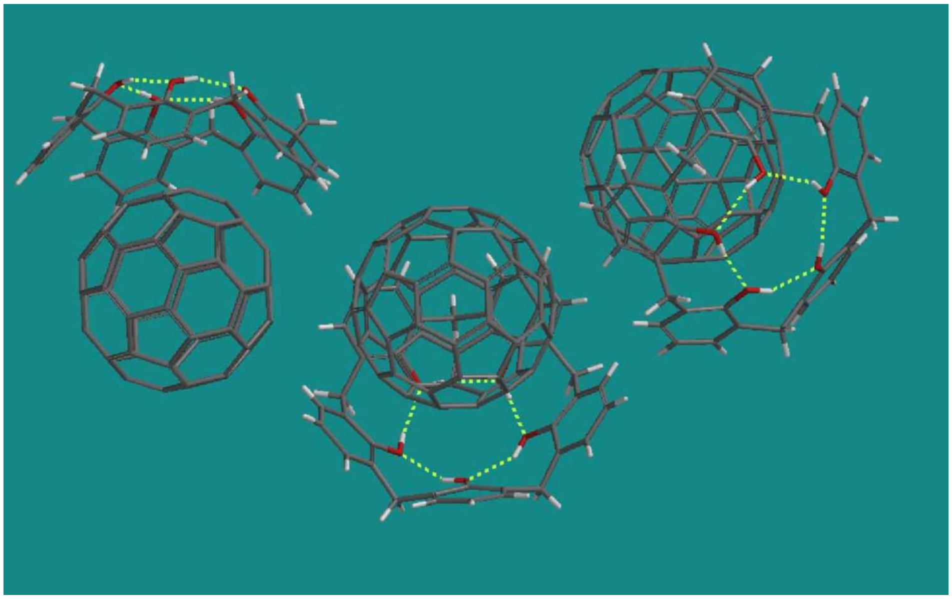

FIGURE 1 Trimer of the heterosynthon [(C_{60})(calix[5]arene)] [23].

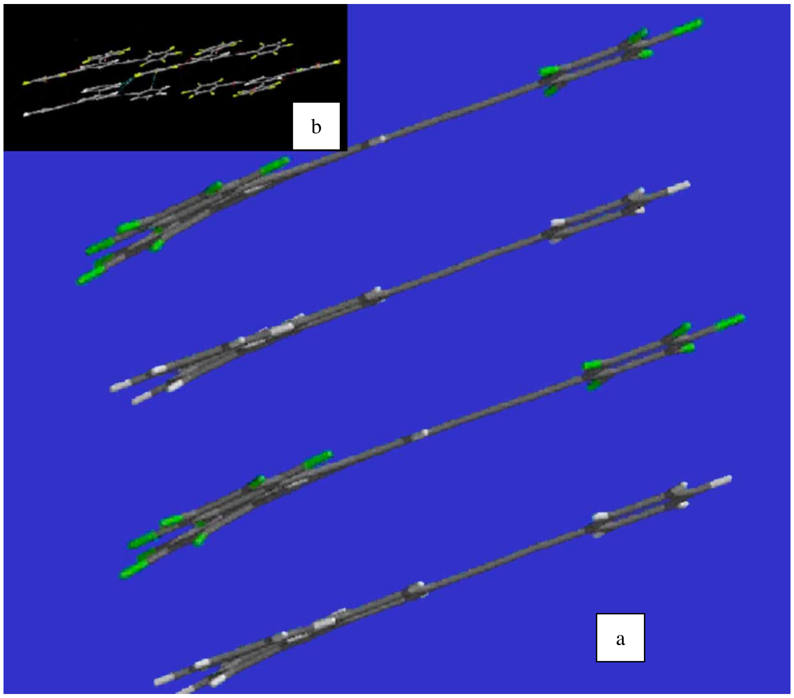

FIGURE 2 Dimer of the hetherosynthon 1:1 *sym*-triphenethynylbenzene: *sym*-tris(perfluorophenethynyl)benzene [28].

constituted by the heterosynthon [(C_{60})(calix[5]arene)] [27], the crystalline array of which is stabilized by two types of forces, namely π−π aromatic interactions and van der Waals forces.

π−π STACKING INTERACTIONS

A dimer of the heterosynthon 1:1 *sym*-triphenethynylbenzene/*sym*-tris(perfluorophenethynyl)benzene

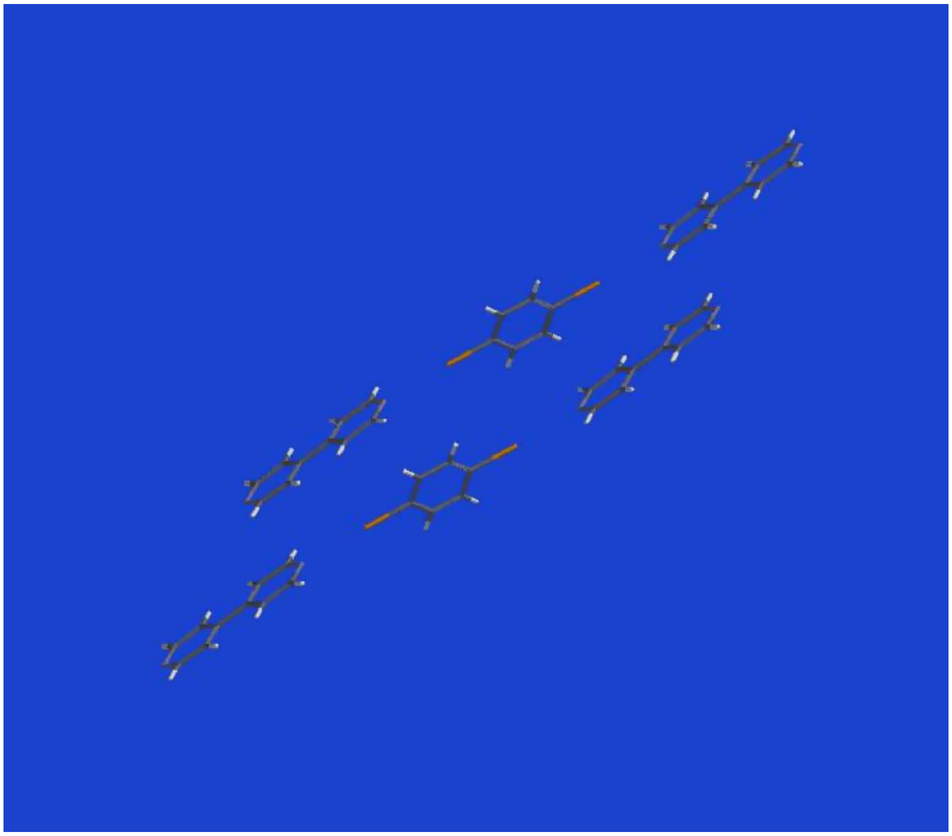

FIGURE 3 Six synthons of the heterosynthon 4,4Çbipyridine: 1,4-diiodobenzene [29].

reported for a cocrystal was calculated by the Hartree–Fock *ab initio* quantum chemical method with 6-31G* basis function, using the Spartan 04 package for Windows [24,25]. The coordinates were taken from X-ray determined data [28]. The calculated energy values for the $\pi-\pi$ stacking interaction were of the order of 1.3 kcal mol^{-1} for each synthon (Fig. 2). However, when we superimposed two synthons (Fig. 2a), a repulsive effect of approximately 0.6 kcal mol^{-1} was obtained. The balance of forces to stabilize the crystalline lattice is achieved through halogen binding present in the heterosynthon 1:1 *sym*-triphenethynylbenzene/*sym*-tris(perfluorophenethynyl) benzene and formed by mutually displaced molecules in very close planes with an energy of the order of 7 kcal mol^{-1} (see Fig. 2b)

HALOGEN BINDING

Six synthons that constitute the heterosynthon 4,4′-bipyridine/1,4-diiodobenzene reported for a cocrystal [29] were calculated by the Hartree–Fock *ab initio* method with 6-31G* basis functions, using the Spartan 04 package for Windows [24,25]. Calculations were performed from one to six molecules in one supramolecular plane and in two parallel planes (Fig. 3). The results indicate that there is a principal halogen–nitrogen interaction. Moreover, the calculations show that the stabilization energy for one heterosynthon, considering only one plane, is of the order of 5.5 kcal mol^{-1}, and that this is additive as the molecule size is increased. Furthermore, there are two additional types of interactions. A slipped stacking between the diiodo compounds of two different planes of the order of 1 kcal mol^{-1} and a repulsive force between bipyridine molecules of neighboring planes of the order of 0.74 kcal mol^{-1} may possibly be ascribed to steric hindrance (Fig. 3). Previous calculations in the literature were not attempted with more than one heterosynthon, making it impossible to identify the interactions that exist between planes that play a crucial role in determining the equilibrium of forces that stabilize the crystalline lattice.

CONCLUSIONS

The results obtained from the calculations on the above-mentioned cocrystals show that different types of interactions besides that of hydrogen bonds—the only type of stabilization specified in the current definition of cocrystals—may participate in the crystalline array formation. There are, for instance, van der Waals forces, $\pi-\pi$ interactions, $\pi-\pi$ stacking interactions, and halogen binding, among others. The current definition of cocrystals does not include these types of interactions, which may play a crucial role in determining cocrystal formation. A definition must describe the distinctive features that characterize the object, without having to include the origin of the object, and should not need to be appended with a set of exception cases as is the case with some of the current definitions.

In the light of the above discussion, we suggest that a definition that may reflect in a more appropriate way the features of a cocrystal may be: "a crystal constituted by heterosynthons, stabilized by hydrogen bonds or other types of non-valency intermolecular interactions, and in which all the component synthons are solid under ambient conditions, when in their pure form." This definition may cover the characteristics of all types of cocrystals, not only those stabilized by hydrogen bonds. Optionally, one can include in the above definition that the types of non-ordinary valency forces are halogen binding, $\pi-\pi$ interactions, stacking interactions, and van der Waals forces, among others, or otherwise one may omit the generality of saying non-valency intermolecular interactions and just mention the types of forces involved in stabilizing the cocrystal array (other references, published almost at the same time that the present paper was evaluated, proposing similar modifications to the current definition of cocrystal, are due to Professor Ashwini Nangia [30,31], and that proposed in [32]). On the other hand, the vagueness of the current definitions may perpetuate the erroneous practice of continuing to designate some cocrystals as adducts [6], molecular complexes [1], or multi-component crystalline materials [13], if they are stabilized by forces other than hydrogen bonds, as has frequently been the case in the literature [1].

As a corollary of trying to set definitions, there is additionally the case in which the cocrystal is stabilized by the presence of a solvent [33]. The question then is how to designate these hydrates and solvates of cocrystals. In analogy with the nomenclature of polymorphs [1], it is possible to imagine referring to such solvated heterosynthons as *pseudococrystals*, nomenclature that has raised objections from various authors (see, for instance, [34,35]; see, however, [36] and [37]) who prefer to simply refer to these crystalline arrays as solvates and, consequently, in the present case, should be called *cocrystal solvates*.

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