

What is a co-crystal?

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What might very well be classified as a revolution in chemical crystallography is the emergence of *crystal engineering* as a discipline and the pivotal role X-ray crystallography plays in this [1]. Although dating back to the 1950's, the field has exploded in the last decade or so, and now is at the forefront of contemporary chemical and cognisant research. One of the areas in crystal engineering of greatest potential impact relates to the pharmaceutical industry – drug formulation and intellectual property – where issues relating to crystallisation, polymorphism, *etc.* are paramount [2]. A focus of these crystal engineering studies relates to the preparation of multi-component crystals, often referred to as co-crystals, where, for example utilizing hydrogen bonding synthons, active pharmaceutical ingredients are co-crystallised with other molecules [2]. The motivation for such studies is to improve stability (*e.g.* shelf-life), bioavailability (*e.g.* solubility), *etc.* [3]. Over and above these considerations, a pharmaceutical crystallised with some other species, is no longer the original pharmaceutical and accordingly, brings forth intellectual property issues [4]. The idea of co-crystal formation is not restricted to applications in the pharmaceutical industry alone but also finds utility in synthetic chemistry [5], in the generation of optical materials [6], even in epi-

taxial growth, where a crystal is grown upon another crystal. But, what is in fact a co-crystal?

As scientists, precise terminology is essential in the communication of ideas and this dictate is compounded by litigation issues, alluded to above. We conducted two searches on the term “co-crystal” or in American English, “cocrystal”. The first, utilising Google Scholar, resulted in over 12,600 “hits” (January 23rd, 2008). A cursory perusal of a small fraction of these hits quite plainly indicated that the term co-crystal is applied widely in biomacromolecular crystallography. The prevalence of the term “co-crystal”, in the Web of Science is evident from the data collected in Table 1. An examination of these hits again showed wide usage in biomacromolecular crystallography as well as in polymer science. It is probably too much of a challenge to get an all encompassing definition for “co-crystal” to serve the needs of these different disciplines – our focus is definitely upon small molecule chemistry.

A co-crystal might be the expected outcome of a co-crystallisation experiment in which the final crystal contains at least two distinct species connected by intermolecular forces. In previous times, such crystals might have been termed a molecular complex, a molecular adduct, a lattice adduct or other cognate terms included in Table 1. Apparently, the term “co-crystal” was first used in 1967 to describe a multi-component crystal containing pyrimidine and purine [7]. The use of “molecular complex” in the crystallographic literature predates this by two decades [8].

One of the founders of organic crystal engineering, G. R. Desiraju has expressed concern over the use of the term “co-crystal” and has argued that such multi-component crystals with clearly defined intermolecular, *i.e.* non-covalent, interactions between the component molecules, be termed “molecular complex” [9]. J. D. Dunitz suggested that the term “co-crystal” is inelegant and pointed out that the term encompasses the full range of multi-component crystals including solvates, channel compounds, clathrates, *etc.* [10]. Dunitz further argued that using terms such as “molecular complex” might be open to misinterpretation as these can apply equally to the non-crystalline phase [10]. More recently, Bond [11], challenged an ear-

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Table 1. The occurrence of the term “co-crystal (or cocrystal)” and related terms included in the title and/or abstract of papers included in the Web of Science as at January 21st, 2008.

Years	Co-crystal (Cocrystal)	Molecular complex	Molecular adduct	Lattice adduct	Inclusion compound	Channel compound	Multi component molecular crystal	Solid-state complex	Hetero-molecular crystal	Organic molecular crystal	Pharmaceutical co-crystal
1945–1964	1	23	–	–	4	–	–	–	–	–	–
1965–1976	2	123	5	–	13	2	–	1	–	1	–
1977–1986	3	142	7	–	55	2	5	–	2	–	–
1987–1996	122	510	26	1	265	4	3	4	1	3	–
1997–2006	680	1034	55	1	504	7	3	26	5	2	11
2007–2008	168	88	6	–	59	1	–	2	2	–	6

lier contribution by Aakeröy and Salmon [12], delineating the parameters for their review article, who suggested that “co-crystals” are composed of multi-component, stoichiometric and neutral molecular species, that themselves each exists as a solid under ambient conditions. Using this criterion, the crystal comprising stoichiometric amounts of 1-phenyl-3,5-dimethylpyrazole, a liquid under ambient conditions, and oxalic acid would not be classified as a “co-crystal” [13]. Neither would the crystal formed by 1-phenyl-3,5-dimethylpyrazole and nitric acid [14] where both components are liquids under ambient conditions. In the latter case, proton transfer has occurred and so the solid is strictly formulated as a salt.

In keeping with the spirit of *Zeitschrift für Kristallographie*'s Discussion series, which recently deliberated upon the question “What is a crystal?” [15], we now invite responses to the question: “what is a co-crystal?”

References

- [1] Desiraju, G. R.: Crystal engineering: a holistic view. *Angew. Chemie. Int. Ed.* **46** (2007) 8342–8356.
- [2] Vishweshwar, P.; McMahon, J. A.; Bis, J. A.; Zaworotko, M.: Pharmaceutical co-crystals. *J. Pharm. Sci.* **95** (2006) 499–516.
- [3] Almarsson, Ö.; Zaworotko, M.: Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem. Commun.* (2004) 1889–1896.
- [4] Trask, A. V.: An overview of pharmaceutical cocrystals as intellectual property. *Molec. Pharm.* **4** (2007) 301–309.
- [5] Friščić, T.; MacGillivray, L. R.: Reversing the code of a template-directed solid-state synthesis: a bipyridine template that directs a single-crystal-to-single-crystal [2 + 2] photodimerisation of a dicarboxylic acid. *Chem. Commun.* (2005) 5748–5750.
- [6] Friščić, T.; MacGillivray, L. R.: Single-crystal-to-single-crystal [2 + 2] photodimerizations: from discovery to design. *Z. Kristallogr.* **220** (2005) 351–363.
- [7] Schmidt, J.; Snipes, W.: Free radical formation in a gamma-irradiated pyrimidine-purine co-crystal complex. *Int. J. Rad. Biol. Rel. Stud. Phys., Chem. & Med.* **13** (1967) 101–109.
- [8] van Niekerk, J. N.; Saunderson, D. H.: The crystal structure of the molecular complex of 4:4'-dinitrodiphenyl with diphenyl. *Acta Crystallogr.* **1** (1948) 44.
- [9] Desiraju, G. R.: Crystal and co-crystal. *CrystEngComm* **5** (2003) 466–467.
- [10] Dunitz, J. D.: Crystal and co-crystal: a second opinion. *CrystEngComm* **5** (2003) 506.
- [11] Bond, A. D.: What is a co-crystal? *CrystEngComm* **9** (2007) 833–834.
- [12] Aakeröy, C. B.; Salmon, D. J.: Building co-crystals with molecular sense and supramolecular sensibility. *CrystEngComm* **7** (2005) 439–448.
- [13] Zukerman-Schpector, J.; Castellano, E. E.; Oliva, G.; Massabni, A. C.; Pinto, A. D.: Hydrogen bonding in the crystal structures of the adducts between 1-phenyl-3,5-dimethylpyrazole with oxalic and perchloric acids. *Can. J. Chem.* **62** (1984) 725–728.
- [14] Zukerman-Schpector, J.; Castellano, E. E.; Massabni, A. C.; Pinto, A. D.: The crystal structure of 1-phenyl-3,5-dimethyl pyrazolium nitrate. *Can. J. Chem.* **60** (1982) 97–99.
- [15] Steurer, W.: What is a crystal? Introductory remarks to an ongoing discussion. *Z. Kristallogr.* **222** (2007) 308–309.