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Polymorphism in molecular crystals

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BOOK REVIEW

Polymorphism in molecular crystals, by Joel Bernstein, 2nd Edition, New York, Oxford University Press, 2020, 575 pp., e-book US $ 59.99, hardcover US $ 135.00, Hardcover ISBN: 9780199655441

The first time I heard about the idea of writing a second edition of the legendary book Polymorphism in Molecular Crystals (Oxford University Press, New York, 2002. ISBN 0198506058) was in 2017, and the source was Joel Bernstein himself. I had the pleasure of spending the breakfasts with Joel, one of the most entertaining discussion partners one could hope for, while we were both in attendance at the 23rd International Conference on the Chemistry of the Organic Solid State in Stellenbosch (South Africa). He was enthusiastic about the possibility of writing an updated version of the first edition, which is undoubtedly a classic, being a prime source of information for anybody interested in polymorphism, the formation of different crystal structures when the same compound crystallises.

Professor Bernstein's untimely death in January 2019 shocked the solid state community, and our anticipation for the new edition was replaced by grief. But as a year passed, in May 2020, the second edition of Polymorphism in Molecular Crystals (Oxford University Press, New York, 2020; ISBN: 9780199655441) was released. Because of the strict lockdowns imposed by the COVID-19 pandemic at the time, which forced people to find alternatives to their usual activities, the timing was actually ideal. After all, what could be better to do than lose ourselves in a book of this calibre? Admittedly, the reality was very different, and by 2021, most of us were worn out from navigating this new world. In 2022, I had the chance to review the second edition while we adjusted to the 'new normal'. I immediately enthusiastically concurred and impatiently awaited the delivery of the book. After waiting for several months, it was evident that the postal services had not yet returned to their pre-COVID levels of dependability, and the hard copy of the book didn't arrive for a few more months, but I have to say it was worth the wait! I almost forgot how satisfying it was to read a hard copy of a book because I became accustomed to reading e-books over the past decade. First, the book's hard cover instantly generates high expectations and suggests substantial content. The 608 pages printed on soft-textured matte-coated paper give off an exceptional sense of quality. Even though the majority of the figures are line diagrams representing molecular structures, high-resolution coloured figures were used when necessary, such as to show a phase transformation when observed under a hot stage microscope or displaying the Hirshfeld surfaces of molecules. After my sensory feelings were satisfied, I dived into reading the book!

The second edition is ca. 200 pages longer than the first. Most of the chapters are updated versions of the first edition with the addition of the most important recent developments, but some chapters were extended significantly, e.g., Chapter 3 (Exploring the crystal form landscape), Chapter 5 (Computational aspects of polymorphism) and Chapter 7 (Polymorphism of pharmaceuticals).

I must admit, the second edition gets off to a great start! Regarding terms that have recently gained popularity in the solid state community to describe some unique cases of polymorphism, Bernstein poses some provocative questions (see Chapter 1.2.2 Some additional adjectival polymorphism: pros and cons).

Based on McCrone's original definition of a polymorph, i.e. 'a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the

molecules of that compound in the solid state', the use of the terms *structural*, *packing*, or *synthon polymorphism* is redundant, Bernstein argues. He also disagrees with using the phrase *pharmaceutical polymorph* because potentially any compound could become an active pharmaceutical ingredient in the future, or any currently used pharmaceutical could be taken off the market for unforeseen reasons, and this subsequently would suggest that the name would not be applicable anymore, despite dealing with the same structure. Contrary, Bernstein accepts the name *isotopomeric polymorphism* to describe different structures of compounds which differ only in the nature of one or more atoms' isotopic identity. However, *isotopomeric* is not the right term to use in this case, in my opinion. IUPAC defines isotopomers as 'isomers having the same number of each isotopic atom but differing in their positions' [1]. A well-known example of isotopomers is the two forms of monodeuterated methanol (CH_3OD and CH_2DOH). The two examples that Bernstein mentions describe *isotopic polymorphism*, in which different isotopes are affixed to the same position in molecules, i.e., isotopic substitution, the least possible change of the molecular structure is carried out and results in different crystal structures. Nevertheless, this field of polymorphism is expanding steadily, and examples of both isotopomeric and isotopic polymorphism have recently been published in the literature. As a result, the need for the clarification of the two terms is increasing.

The newly added Chapter 3.5, The polymorph (solid form) screen provides a summary of how to look for new solid forms and polymorphs. Bernstein emphasizes the importance of solid form screening and gives practical guidance about the steps to take when planning the screening process. While traditional solution crystallisation and its variations are still the most frequently used crystallisation technique (and this chapter focuses on discussing these), some non-traditional solution techniques are also mentioned, e.g., *capillary crystallisation, templating* (using surfaces or seeding), *electrochemical crystallisation,* or *physical or chemical perturbation* of the solution. Bernstein highlights two methods, *nanoscopic confinement* and the application of *supercritical carbon dioxide* as a solvent, as these are very likely to become crucial in the solid form screening process. The former creates a unique environment between microscopic and molecular levels in which the thermodynamic properties of polymorphs can differ from those observed on the macroscopic scale, whereas the latter—in addition to its many benefits, such as its suitability for thermolabile compounds and good control of the crystallisation conditions—most importantly eliminates the use of solvents and thereby decreases the crystallisation process' negative effects on the environment. The moderate emphasis placed on non-solution crystallisation methods in this chapter was slightly disappointing, but it should be noted that some crystallisation methods were revisited in Chapter 7, thus, my disappointment was somewhat mitigated. Nonetheless, I feel that mechanochemistry—probably the fastest-growing method for forming new or desired solid forms—should have received more attention because it not only minimizes or eliminates the use of solvents but also permits the modification of compounds that are inaccessible in solution at the supramolecular or even at the molecular level. To illustrate the theoretical discussion of solid form screening with a practical example, Bernstein concludes the chapter with a case study of axitinib, a small molecule tyrosine kinase inhibitor which fascinatingly has 78 known solid forms (solvates or polymorphs).

The subchapters of Polymorphism of pharmaceuticals, Chapters 7.4 - 7.6, are excellent extensions of the topics discussed in general terms in Chapter 3.5, as they list and discuss briefly several pharmaceutical examples from recent literature. Unfortunately, the application of mechanochemical methods when screening pharmaceutical solid forms was again neglected. The last two subchapters are certainly thought-provoking. One addresses the issue of the assumed link between chemical similarity of molecular structures of two compounds and their likelihood of having similar polymorphic behaviour, while the final chapter focuses on excipients and their potential influence on formulation, a particularly important topic that receives less attention than anticipated.

The largest expansion was made to Chapter 5 by adding a subchapter entitled 'The computational comparison of polymorphs' (5.10). The question of differentiating between polymorphs was already raised in 4.12 (*Are two samples polymorphs of the same compound?*), which describes McCrone's technique used to determine whether two samples are polymorphs. As a continuation, Bernstein summarizes recent computational methods applied to comparing structures in section 5.10. Comparing the XRPD patterns of solids serves as the first step in identifying polymorphs. While judgement is frequently based on visual, i.e. subjective comparison, Bernstein notes that the recently developed computational methods also have limitations. The other computational methods mentioned are the analysis of the Hirshfeld surface of a molecule mapped with selected properties or the 2D representation of these as fingerprint plots. Importantly, through the *CrystalExplorer* package, researchers can access these valuable and freely accessible tools. The significance of these techniques is demonstrated by the detection of identical structures of terephthalic acid and the clarification of the number of crystallographically unique molecules in high *Z*' value structures. The newly added function of the software, which is based on lattice energy partitioning, is the calculation of energy frameworks that serve as an 'energy fingerprint' when comparing polymorphs. The chapter also discusses how to differentiate between *conformational change* and *conformational adjustment*. Providing numerical limits (or more accurately, approximations) of changes in selected geometrical parameters, such as the minimum *rms* deviations between atomic positions and the maximum difference in torsion angles between two molecules, is essential for identifying conformational polymorphism.

There are many more gems in the revised chapters; Chapter 10, which addresses the complexity of the overlap between chemistry and the law by presenting some patent litigations, is just one example. I leave the reader the pleasure of discovering others!

In summary, the objective of the first edition was straightforward: to summarize the knowledge of polymorphism in molecular crystals in a single reference that serves as a starting point for anyone from novices to experts in solid state chemistry. The aim of the second edition is more refined because the evolution of the field over the past two decades necessitated a revision of the topics based on the most recent literature. The addition of more than a thousand new references and their discussion, along with the author's attempt to provide representative examples, is a true reflection of the enormous effort that went into the second edition and evidence that Bernstein's goal was accomplished without any doubt. I believe that this book should be on the shelf of every solid state chemist, not only because it is undeniably a testament to Bernstein's legacy in the field of solid state chemistry, but also because the nature of the discussions makes it an excellent catalyst for future research.

Reference

[1] IUPAC. Compendium of Chemical Terminology, 2nd ed. (the 'Gold Book'). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). Online version (2019-) created by S. J. Chalk. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook.

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