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RADIATION DECAY - A NEW TOOL IN MACROMOLECULAR CRYSTALLOGRAPHY

Z. Otwinowski[1] D. Borek[1] W. Minor[2]
[1]UT Southwestern Medical Center, Dallas, Texas 75390- USA 903
[2]Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA 22908-073

The radiation damage that results from high brilliance synchrotron beam lines severely limits the quality and quantity of information that can be measured from a single crystal. For small, marginally diffracting crystals the main issue is to find the minimal amount of experimental information that allows phasing, and also to use appropriate phase improvement methods to produce interpretable results. The synergism amongst experimental protocol, phasing methods, and scaling show the need to re-develop all of these methods simultaneously. Improvement of any one step generates an improvement in the final result, but due to the nonlinear nature of the problem the impact of improving all the steps together is larger than the sum of individual improvements.

Radiation decay introduces substantial non-isomorphism that can be considered as the sum of consecutive changes. These include localized structural changes in a protein structure, rotations and translations of whole molecules in a crystal lattice and eventually total destruction of the protein tertiary structure.

The localized structural changes introduce non-isomorphism that may be used as a source of phasing signal in a manner similar to the MIR method. So, an old enemy of the MIR method may be turned into a powerful phasing technique, assuming that the non-isomorphism introduced by radiation decay can be correctly modeled, at least within some reasonable accuracy. The newly developed scaling algorithms that exploit data redundancy allow for simultaneous correction of absorption, experimental system imperfections and radiation decay. The application of these algorithms resulted in the solution of new protein structures.

Keywords: RADIATION DECAY, SCALING, PHASING

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POLYMORPHISM: A BRIEF OVERVIEW

G. R. Desiraju
University of Hyderabad School of Chemistry P.O. Central University Hyderabad 500046 INDIA

Polymorphism is the phenomenon wherein the same chemical substance exists in different crystalline forms. There is much interest in this well known though little understood phenomenon. Polymorphism is a very complex issue, and this complexity relates not only to causes for its occurrence but also to criteria that can judge as to whether it is present at all. There is still no consensus on the exact definition of the term. How common is polymorphism? Considering that crystallization is a very efficient process, and given the complementary nature of molecular recognition, it would appear that the likelihood of polymorphism should generally be low. On the other hand, the intermolecular interactions in molecular crystals are feeble, and the possibility of polymorphism would appear to be high.

Crystallization is a supramolecular reaction. Like all chemical reactions it is controlled by kinetic and thermodynamic factors. In such a context, polymorphism is a multi-path reaction and may therefore be central to our understanding of the events that take place during crystallization.

Polymorphism is of outstanding importance in pharmaceutical development because its occurrence is more common in drug molecules. These molecules contain functional groups that are good hydrogen bond donors and acceptors and are also conformationally flexible. This combination makes for a good drug but it also leads to polymorphism.

In this talk some of the following aspects of this subject will be discussed: (i) conformational polymorphism; (ii) concomitant polymorphism; (iii) supramolecular synthons and polymorphism; (iv) pseudopolymorphism; (v) additive mediated polymorphism; (v) crystal structure prediction.

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TWO CLOSELY RELATED POLYMORPHS (Z'=1/2 AND Z'=10) THAT SEEM TO CO-EXIST

C. P. Brock X. Hao S. Parkin
University of Kentucky Department of Chemistry Rose Street at Funkhouser Drive LEXINGTON KY 40506-0055 USA

The compound $[Cu(H_2O)_2(15\text{-crown-}5)](NO_3)_2$ (CSD refcode GAVPEY) is reported to have two polymorphs: one with Z'=10 (1) and a second with Z'=1/2 (2). If the former is transformed from *Pc* to *Pn*. The larger *Pn* cell is related to the smaller $P2_1/c$ cell by the transformation 200/010/005. The dimensions near 295 K of the two cells are indistinguishable if *a* and *c* for the larger cell are divided by 2 and 5, respectively. In the Z'=1/2 polymorph the cations are disordered around inversion centers, but in the Z'=10 structure the cations are ordered.

A partially disordered Z'=5 structure in $P2_1/n$ seems reasonable, but preliminary results suggest that the noncentrosymmetric *Pn* description is preferable. Phase transitions from disordered to ordered structures are usually associated with a decrease in molar volume, but this one is not. Careful examination of diffraction patterns suggests that most 'single' crystals contain more than one phase. The diffraction patterns for most crystals are best indexed using the larger cell, but the relative intensities of the substructure and superstructure reflections are highly variable. For some crystals the superstructure reflections (h.ne.2n and l.ne.5m) are only ca. 10x weaker than the reflections that correspond to the smaller cell, but for other crystals the superstructure reflections are too weak to measure reliably.

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COCRYSTALS WITH AT LEAST ONE PHARMACEUTICAL COMPONENT

M.J. Zaworotko[1] B. Moulton[1] R. Walsh[1] L. Morales[1] S. Fleischman[1]
University of South Florida Chemistry SCA400, 4202 East Fowler Avenue TAMPA 33620 USA

The design of binary crystalline compounds, co-crystals, relies upon understanding how complementary supramolecular synthons influence composition and structure in the solid state. In this paper we shall present details concerning a range of new binary co-crystals that involve carboxylic acid (e.g. aspirin, tylenol, profens), amide (e.g. carbamazepine) or ether moieties. The molecular components generate the expected stoichiometry and, in some cases, predictable crystal packing motifs.

An analysis of the structures and physical properties of the new binary co-crystals will be presented. The results will be discussed in the context of how one might generally exploit our results in order to generate novel pharmaceutical phases.

Keywords: CRYSTAL ENGINEERING POLYMORPH COCRYSTAL