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Sulfur-SAD phasing becomes a routine approach to solve *de novo* structures

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The recent application of softer X-ray radiation provides an alternative path to solve protein crystal structures in high throughput pace. In-house chromium Kα radiation (λ = 2.29 Å) is one of the most commonly used softer X-ray radiation wavelengths in macromolecular crystallography. Chromium radiation increases the anomalous signal of many intrinsic elements or often used heavy atoms in derivatization. For example, compared to Cu radiation, the contribution to the anomalous term of sulfur and selenium atom doubles to 1.14 e and 2.28 e, respectively. These enhanced anomalous signals are sufficient to be routinely collected and processed with modern instrumentation and software packages. This work reports several examples of protein structures solved using sulfur-SAD phasing. For these proteins it was difficult to produce or crystallize the selenium-methionine substituted form, or to reproduce more of the original crystals. In other words, the native forms of these crystals had to be used to solve their structures. A single data set was collected with an in-house Cr X-ray radiation source for each protein crystal and was phased by the S-SAD phasing approach. These examples demonstrate that Cr radiation has become a routine phasing approach in the crystallographer's toolkit, which makes it possible to solve a crystal structure with native crystals only or before synchrotron data collection when selenium-methionine substituted protein is not available. This method clearly improves the productivity of macromolecular structure determination, usage of synchrotron beam time and helps enhance high throughput structure determination.

Keywords: SAD, sulfur-SAD, Cr radiation

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Scientific inquiry and inference in macromolecular crystallography

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A number of recent retractions of protein structures published in high impact journals shows that not all is well in the way macromolecular crystallography is taught to students. The negative impact of severely incorrect structures extends beyond mere nuisance: crystallographic structure models carry great persuasive power - a wrong structure in a leading journal contradicting correct experimental findings makes it quite impossible for others to obtain funding for their work. With great power of modern crystallography comes great responsibility for its appropriate use, and the mistaken idea that crystallography is just a basic analytical technique only amplifies the risk of uncritical use of increasingly powerful crystallographic methods and its propagation to the next generation. The complexity of teaching a science that encompasses fundamentals of mathematics, physics, and probability theory in addition to the biological knowledge necessary to analyze and interpret the results with an array of bioinformatics tools should not be underestimated. A closer inspection of incorrect structures shows that an even deeper and more concerning general misconception of the process of scientific inquiry lead to wrong structures and misinterpretations. These findings should be taken as an encouragement to teach crystallography in a larger framework consistently emphasizing the role of evidence and probability in inference methods. Examples range from crystallization propensities to maximum likelihood in phasing and refinement to evidence-based examination of ligand structures. In such a curriculum, even if the details of crystallographic theory are long forgotten, the fundamentals of proper inquiry and inference will remain invariably useful for the students.

Keywords: teaching, likleihood, Bayesian inference

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Metal-organic networks designed by combination of hydrogen bonds and halogen bonds

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The electronic properties of inorganic halogens (M-X) differ markedly from those of organic halogens (C-X). The former are directional nucleophiles in interactions with typical hydrogen bond donors (N-H, O-H, etc.). By contrast, organic halides (C-X) can be tuned to serve as directional electrophiles; they can participate in halogen bonds, wherein the C-X group plays a Lewis acidic role, viz...X-C. Recently we have combined these two complementary environments of halogens in order to create a new type of supramolecular synthon, M-X…X-C halogen bonds, based on attractive interactions that are highly directional at both halogens. Complementary experimental and theoretical studies demonstrate that M...X-C interactions are predominantly electrostatic in nature rather than dominated by the charge transfer as might have been anticipated. These studies suggest an electronic description of halogen bonds ranging from weakest to strongest that parallels the description of hydrogen bonds. Competition between halogen bonds and hydrogen bonds has been studied in a series of compounds which are propagated by N-H...X_2M hydrogen bonds and M-X...X-C halogen bonds. The hierarchy of the interactions has been rationally modified by tuning the strength of the halogen bonds from weak isotropic to moderately strong attractive interactions and consequently the crystal packing changes depending on their strength. Finally, it has been shown that the application of isotropic perturbations such as changes in temperature or pressure produces an anisotropic response in the crystal structures due to the different behavior of non-covalent interactions, providing useful information on the intermolecular interaction potentials in molecular crystals containing hydrogen bodns and halogen bonds.

Keywords: halogen bond, hydrogen bond, high-pressure structures

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A journey through the rational design of molecular solids with halogen bonding

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Halogen atoms are typically located at the periphery of organic molecules and are thus ideally positioned to be involved in intermolecular interactions. Halogen bonding (XB) describes any interaction where halogen atoms function as electrophilic species. XB can be described by the general scheme D•••X-Y where X is the electrophilic halogen atom (Lewis acid, XB donor), D is a donor of electron density (Lewis base, XB acceptor), and Y is carbon, nitrogen, halogen, etc. (Scheme 1)[1]. The main features of the interaction will be given and the close similarity with hydrogen bonding will become apparent. Some heuristic principles will be presented in order to develop a rational crystal engineering based on XB. The potential of the interaction will be shown by useful applications in different fields spanning synthetic chemistry, material science, and bioorganic chemistry.

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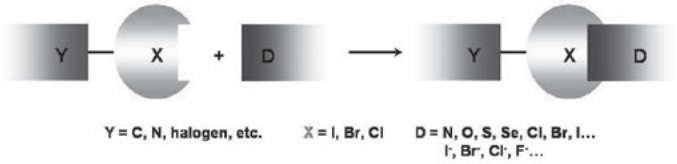

Keywords: halogen bonding, intermolecular interactions, supramolecular chemistry

MS.45.3

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Structural systematic studies of fluoro(pyridinyl) benzamide derivatives

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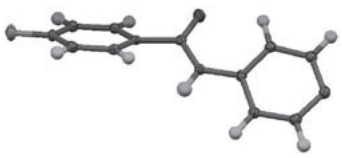
We are currently studying the crystal structures of a series of Fluoro(pyridinyl)benzamides. Several isomers will be presented including the following:
Isomers (I)-(III) $C_{12}H_9FN_2O$, Monoclinic, $P2_1/c$, $Z = 4$, $T = 150$K.
(I) (4-F), $a = 5.6506(3)$, $b = 11.3882(8)$, $c = 15.4314(8)$ Å, $\beta = 95.602(3)°$ $V = 988.27(10)$Å^3, $D_x = 1.453$ Mg.m^{-3}, $R = 0.051$.
(II) (3-F), $a = 5.7537(3)$, $b = 11.2421(4)$, $c = 15.1672(7)$ Å, $\beta = 94.188(2)°$ $V = 978.45(8)$Å^3, $D_x = 1.468$ Mg.m^{-3}, $R = 0.048$.
(III) (2-F), $a = 5.9832(3)$, $b = 11.1508(5)$, $c = 14.8921(7)$ Å, $\beta = 94.986(3)°$ $V = 989.80(8)$ Å^3, $D_x = 1.451$ Mg.m^{-3}, $R = 0.044$.
An ORTEP diagram of the molecular structure of (I)



Keywords: isomers, structural systematics, fluorine compounds

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Crystal engineering using the thiourea moeity

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Crystal engineering[1] is a form of supramolecular synthesis, where discrete molecules use molecular recognition to form supramolecular entities. We aim to identify robust H-bonding synthons that behave predictably in different chemical environments. In studies[2,3] of a variety of derivatives of monopodal and bipodal acylthioureas with varying side chains R_1, R_2 and R_3, we have observed apparently predictable intra- and intermolecular H-bond patterns (Scheme 1) In addition to the H-bonding synthons, these compounds can coordinate to metals through the thiourea moiety. This presentation will consider our own results, together with an analysis of reported structures[4] to address the following questions:
1. How robust is the H-bonding motif for differing R_2?
2. Is the same pattern observed in the monopodal and bipodal cases?
3. What is the influence of the R group or the coordinated metal on the H-bonding motif?

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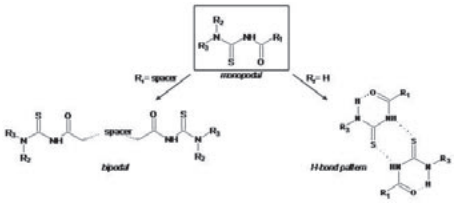

Keywords: crystal engineering, hydrogen bonding, thiourea

MS.45.5

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Electrostatic complementarity: A universal theme in molecular crystal structures?

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The nature of protein-protein and protein-ligand interactions has long been discussed on the basis of electrostatic complementarity, where complementary electronegative and electropositive regions are observed to pack adjacent to one-another. Although modern research in crystal engineering, crystal structure prediction and rationalization is overwhelmingly discussed in terms of specific intermolecular interactions, with special reference to the electrostatic properties of molecules, the concept of electrostatic complementarity is yet to be widely exploited in the context of molecular crystal structures. We have recently demonstrated how the graphical representation of ab initio electrostatic potentials mapped on Hirshfeld surfaces can be used to rationalize patterns of intermolecular interactions in molecular crystals, with application to small cyclic molecules such as alloxan, benzonitrile and fluorobenzene [1]. Through application to a much wider range of molecular crystals incorporating weak and strong hydrogen bonds, halogen bonds, and C-H...pi and other weak interactions, we explore the extent to which electrostatic