

Teaching crystallography to undergraduate physical chemistry students

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Teaching goals, laboratory experiments and homework assignments are described for teaching crystallography as part of two undergraduate physical chemistry courses. A two-week teaching module is suggested for introductory physical chemistry, including six to eight classroom sessions, several laboratory experiences and a 3 h computer-based session, to acquaint undergraduate physical chemistry students with crystals, diffraction patterns, the mathematics of structure determination by X-ray diffraction, data collection, structure solution and the chemical insights available from crystal structure information. Student projects and laboratory work for three to four weeks of an advanced physical chemistry course are presented. Topics such as symmetry operators, space groups, systematic extinctions, methods of solving the phase problem, the Patterson map, anomalous scattering, synchrotron radiation, crystallographic refinement, hydrogen bonding and neutron diffraction all lead to the goal of understanding and evaluating a crystallographic journal article. Many of the ideas presented here could also be adapted for inorganic chemistry courses.

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1. Introduction

Structure analysis by X-ray diffraction has been the fundamental empirical method for determining the geometry of chemical bonding in molecules larger than a few atoms. However, there is little or no emphasis in the traditional United States undergraduate chemistry curriculum on the methodology of X-ray crystallography or how to evaluate the results of a typical structure determination (American Crystallographic Association and United States National Committee for Crystallography, 2006). The organic chemistry course typically taught in the second year of the undergraduate chemistry curriculum relies on the valence bond approach to predict the structure and bonding of organic molecules. Students learn fundamental principles of structure, such as the tetrahedral C atom, the planar benzene ring, the conformation of organic molecules and the role of intermolecular interactions in stabilizing structure. Unfortunately, the experimental method that enabled scientists to discover or verify these principles often remains a 'black box' to students.

In the United States the introductory physical chemistry sequence, typically a two-semester course for third-year chemistry majors, emphasizes infrared spectroscopy for structure determination of diatomic molecules, such as HCl, and quantum mechanical calculations for structure determination of small molecules. Because X-ray crystallography is the important method for determining the three-dimensional structure of organic molecules larger than a few atoms, it is likewise appropriate to teach physical chemistry students the mathematical basis of X-ray diffraction, as well as giving students opportunities in the laboratory to examine a crystal,

to measure a diffraction pattern and to obtain chemical information from a completed structure determination. In the context of an actual molecular structure, principles of covalent bonding and intermolecular forces become real – and intriguing!

For a three- or four-week section of an advanced physical chemistry course, appropriate topics are symmetry operators, space groups, systematic extinctions, methods of solving the phase problem (including the Patterson method, anomalous scattering and direct methods), crystallographic refinement, hydrogen bonding, neutron diffraction and synchrotron radiation, with the higher-order goal for students to understand and evaluate an experimental crystallographic journal article.

At some institutions crystallography is taught in inorganic chemistry courses rather than in physical chemistry courses. Many of the ideas presented here may also be adapted for introductory and advanced inorganic courses. The topics presented here are consistent with the recommendations for undergraduates in the physical sciences by the American Crystallographic Association and United States National Committee for Crystallography (2006).

2. Crystallography in the introductory two-semester physical chemistry sequence

The two-week module, including six to eight classroom sessions, several laboratory experiences and a 3 h computer-based session, may be included in either semester of the typical United States introductory physical chemistry sequence. An auxiliary textbook that goes beyond the infor-

mation available in most physical chemistry textbooks is helpful to students. The 84-page *Crystal Structure Determination* (Clegg, 1998) is detailed enough to be useful as well as understandable for undergraduates. For the instructor, useful references are Glusker & Trueblood (2010), Glusker *et al.* (1994) and Stout & Jensen (1989). The fundamental concepts for this introductory physical chemistry course are as follows: diffraction requires an orderly crystal; real space *versus* reciprocal space; the nature of the diffraction pattern; the mathematical expressions for structure factors and electron density; the phase problem; and solving the phase problem by the 'heavy atom' method or probability methods. Most important, students should understand that the molecular model obtained from a crystallographic determination allows us to measure bond distances, bond angles and torsion angles; to visualize the conformation of a molecule; and, in some instances, to predict the reactivity of the molecule.

In addition to classroom instruction, demonstrations and laboratory experiences reinforce the topics listed above. (See the supplementary information to this paper¹ for detailed student handouts used at The College of Wooster.)

2.1. Bragg's law classroom demonstration

With two geological sieves (of different mesh size) and two laser pointers (red and green) one can show four different diffraction patterns on a projection screen in a darkened room. (Safety precaution: look only at the diffraction pattern on the projection screen, never at the laser.) In these experiments the sieves, with their regularly spaced wires, represent the crystalline solid with regular interplanar spacing d ; the two lasers represent X-ray sources with two different wavelengths. First, with the red laser, point out the reciprocal relationship between crystal lattice spacing (the two sieves) and the diffraction pattern; the diffraction spots are farther apart for the sieve with smaller spacing. Therefore, the diffraction angle ($\sin\theta$) must be inversely proportional to the interplanar spacing in the crystal (d). Second, because the diffraction spots from the same sieve are farther apart with red light than with green light, the diffraction angle must be directly proportional to the wavelength (λ) of the X-rays. Together, these experiments allow students to deduce that $n\lambda = 2d \sin\theta$. Students can then understand why Cu radiation (1.5418 Å) might be more appropriate for large unit cells and Mo radiation (0.7107 Å) for small unit cells. The fact that synchrotron radiation can be 'tuned' to a selected wavelength makes it very convenient for crystallographers.

2.2. View an X-ray tube and learn how X-rays are generated

A no longer functioning X-ray tube is passed around to the class while diagrams of an X-ray tube are shown on the overhead projector. The instructor gives the quantum explanation for X-ray production and discusses the relationship

between atomic number of the target and the wavelength of the emitted X-rays.

2.3. Examine a crystal with polarized light

Students examine a crystal under a polarizing stereomicroscope, determine whether it is a single crystal and measure its size. It is best to mount the crystal on a goniometer head that is on a spindle stage or optical analyzer (Fig. 1), in order to manipulate and measure the crystal under the stereomicroscope. Students are often surprised at the small size of the crystal suitable for X-ray diffraction. The idea that a crystal is an orderly arrangement of atoms is reinforced by seeing that a crystal can extinguish polarized light at certain angles of rotation. If different parts of the crystal extinguish at different rotation angles, we can diagnose a twinned crystal. In some cases, we can cut the twinned crystal to obtain two single crystals, each suitable for a diffraction experiment.

2.4. Obtain a zero-level photograph of a diffraction pattern

Students are shown how to align a crystal and to obtain zero-level photographs with an X-ray camera or a diffractometer. Here we point out the distinction between real space and reciprocal space, and the fact that the spots on the photograph or computer display are not atoms – each spot represents the sum of the diffraction from a plane in the crystal. The instructor demonstrates the technique for groups of students larger than three, and the photograph or diffractometer image may be copied to a file and disseminated to the students electronically.

2.5. Measure the diffraction pattern

Students measure the zero-level diffraction pattern to calculate lattice constants. (Orthogonal space groups are the easiest for students.) Previously obtained diffractometer data, precession photographs or Weissenberg photographs may be used. The reciprocal relationship between real space (crystal) and the diffraction pattern is shown by the mathematical relationship between the measurements on the diffraction pattern and the sides of the unit cell. [For a tutorial on measuring precession photographs, see Kastner *et al.* (2000); see the supplementary materials for this paper for a student



Figure 1

A crystal mounted on a goniometer head and spindle stage for measurement and viewing in polarized light.

¹ Supplementary teaching materials are available from the IUCr electronic archives (Reference: KK5059). Services for accessing these materials are described at the back of the journal.

Table 1

Lattice constants for 3-thiabicyclo[3.2.0]heptane-6,7-dicarboxylic acid 3,3-dioxide.

The chemical formula is $C_8H_{10}O_6S$ and the formula weight is $234.22 \text{ g mol}^{-1}$. The crystal size was $0.36 \times 0.11 \times 0.05 \text{ mm}$. The 4458 independent diffraction data were collected on an area detector to a maximum angle of 57.0° at 103 K with molybdenum radiation ($\lambda = 0.71073 \text{ \AA}$). The final residual error ($R1$) is 0.052.†

$a = 18.497 (3) \text{ \AA}$	$\alpha = 90^\circ$
$b = 6.1203 (8) \text{ \AA}$	$\beta = 112.051 (2)^\circ$
$c = 17.188 (2) \text{ \AA}$	$\gamma = 90^\circ$
Volume = $1803.4 (4) \text{ \AA}^3$	$Z = 8$ molecules in the unit cell

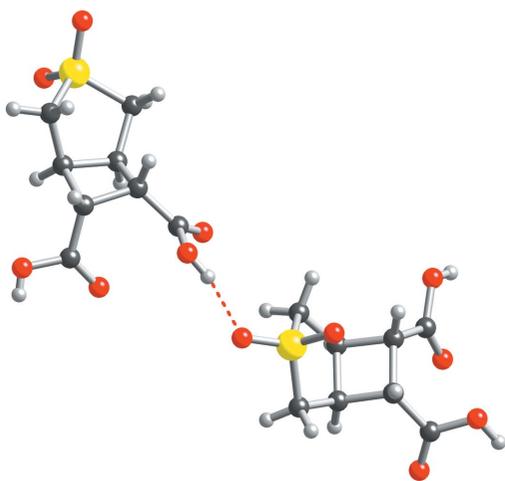
† CSD refcode HOFVAA (Pett & Haynes, 2008).

handout used at The College of Wooster on analyzing Weissenberg photographs.]

2.6. Examine a crystal structure and its diffraction pattern

The high point of this teaching module is a 3 h laboratory experiment in which students use computer software to examine a small-molecule structure. While they explore an actual molecular structure, students come to understand the power of X-ray diffraction as a method, learn more about the diffraction experiment and see how a molecular structure leads to chemical insights. (See the supplementary materials for this paper for a CIF and a student handout relating to 3-thiabicyclo[3.2.0]heptane-6,7-dicarboxylic acid 3,3-dioxide used at The College of Wooster.)

The instructor obtains a CIF, either from the Cambridge Structural Database (CSD; Allen, 2002) or from the journal in which the determination was published, in order to display the structure. The suggested software is *CrystalMaker* and *SingleCrystal* (CrystalMaker Software, Yarnton, Oxfordshire, UK; <http://www.crystallmaker.com>). *Mercury* (Macrae *et al.*, 2008) could be used for the first part of the tutorial; it is freely available, displays the packing diagram and the asymmetric unit in a user-friendly manner, enables students to measure

**Figure 2**

The asymmetric unit of the bicyclic compound 3-thiabicyclo[3.2.0]heptane-6,7-dicarboxylic acid 3,3-dioxide, showing the intermolecular hydrogen bond as a dashed line (Pett & Haynes, 2008).

distances and angles, and displays hydrogen bonds. Using the instructor-supplied handout, students collaborate in pairs to obtain data from the structure. They record their observations in their laboratory notebooks and prepare a laboratory report, reporting data in tabular form, answering questions posed in the handout, and drawing conclusions about bonding, conformation and reactivity.

It is important to show students what the CIF contains – lattice constants, symmetry operators, structure factors for the *hkl* planes, atom types, atomic coordinates and displacement parameters. Using this information, the computer software displays the molecule.

The handout given to students summarizes how the organic chemist synthesized the molecule and why the structure is of interest. A table of information about the molecule and the crystal is presented (Table 1), and the students are asked to calculate the maximum resolution of the crystal and the density of the crystal. Obviously, far more information is given in the table than is needed to carry out the two calculations, making it necessary for students to do more than memorize equations and plug in numbers.

The students begin their exploration by viewing a packing diagram of the unit cell, the repeating unit in the crystal lattice. Here there is opportunity to discuss the unit cell, asymmetric unit, symmetry operations and number of molecules. Students are challenged to find molecules related to each other by the inversion center. The instructor may choose to provide a file or give instructions about how to use the software in order to display only whole molecules in the unit cell, noting that the actual unit cell usually contains both whole molecules and parts of molecules, and is indeed packed full of atoms in van der Waals contact. Although introductory chemistry textbooks typically show unit-cell diagrams with atoms at the vertices of the unit cell, in organic structures there may not be any atoms at the vertices.

Next, the students examine the asymmetric unit, which in the case of 3-thiabicyclo[3.2.0]heptane-6,7-dicarboxylic acid 3,3-dioxide contains two molecules – two ‘snapshots’ of low-energy conformations of this bicyclic molecule. They are asked, ‘Why are the C–S, C–C and C–H single-bond distances different?’, ‘Why are the C–O bonds in the carboxylic acid group different lengths?’ and ‘Do the measured angles correlate with hybridization ideas from organic chemistry?’ These questions require students to apply concepts such as atomic size and bond order that they learned in earlier courses. Students observe that the bond angles and torsion angles in the four- and five-membered rings differ from those of ‘straight chain’ hydrocarbons, stimulating the students to think about the relationship between angle strain and reactivity. As they view and rotate the two molecules on the computer display, students typically conclude that the five-membered sulfolane rings in the two molecules have different conformations.

In their final exploration of crystal space, the students are asked to find hydrogen bonds, both in the asymmetric unit and in the packing diagram (see Fig. 2). Here we emphasize that hydrogen bonds are usually intermolecular bonds, with char-

characteristic bond distance and bond angle, quite different from covalent bonds involving hydrogen.

While scrutinizing all these aspects of an actual crystal structure, students see how the structural principles they previously studied are embodied in the experimentally determined molecular structure. Students are more likely to retain the ideas because they worked actively to deduce structural principles from experimental evidence. Other aspects of this part of the exercise – studying hydrogen-bonding patterns and comparing molecular conformations – go beyond what is normally taught in organic chemistry and are appropriate for an upper-level physical chemistry course.

In order to explore reciprocal space, students may use the auxiliary software *SingleCrystal* to display a diffraction pattern that shows intensities and Miller indices for the crystal structure examined above. The *hkl* indices are the coordinate system for the diffraction spots in reciprocal space, just as fractional *xyz* coordinates give the position of atoms in real space. The geometry of the diffraction pattern gives information about the size and shape of the unit cell, while the intensities of the reflection spots contain the information for atomic positions and type of atom. Students examine the zero-level diffraction pattern and measure the spacing along the *b** axis to calculate the length of the *b* axis in real space. They search for systematic absences of reflections, which are evidence for symmetry in the unit cell. They note that reflections at high angle are generally less intense than reflections at low angle; however, the high-angle reflections provide the high-resolution data needed for accurate structure determination. This experimental difficulty is particularly troublesome for macromolecular structure determination of proteins and DNA. Students identify particularly intense reflections and then display the corresponding crystal planes in real space. They find that these planes, which diffract X-rays best, contain many atoms, usually the atoms with the greatest number of electrons in the structure. This is a very impressive and concrete demonstration of an idea that flows from the mathematical form of the structure factor series.

With *SingleCrystal* the diffraction pattern can be displayed in color, to denote the phase of the reflections. The computer software calculates structure factors and the phase from the known atomic positions. Unfortunately, we need the phase to calculate electron density, find the atoms and solve the structure. This circular dilemma is the essence of the phase problem in crystallography. By presenting the mathematical equations for structure factor and electron density in class, and then reinforcing these ideas graphically in the laboratory, we can teach physical chemistry students sophisticated ideas about the diffraction experiment in the context of a real crystal structure.

3. Crystallography in an advanced physical chemistry course

Crystallography has been included as part of an advanced topics course at The College of Wooster that comprises materials science, solid-state chemistry and surface chemistry. Appropriate textbooks for the crystallography part of this

course include Glusker & Trueblood (2010), Clegg (1998), Smart & Moore (1998) and Rhodes (2009). Besides the resources suggested in §2, resources by Allen & Motherwell (2002), Loehlin & Norton (1988), Kastner *et al.* (2000), Szalay *et al.* (2005) and Taylor (2000) give additional teaching ideas for the instructor. Because physical chemistry stresses a mathematical approach to chemistry, in this advanced course we include more about symmetry operators, the matrix representation of symmetry operators, symmetry groups, space groups and the mathematics of systematic extinctions; the books by Julian (2008) and Sands (1994) are particularly helpful for this topic. We delve more deeply into the phase problem and discuss methods of solving it. The students use the Patterson method to locate the position of the ‘heavy atom’ during a laboratory period. In class the instructor shows examples of probability relationships that are effective in solving the phase problem for small molecules. For large structures such as proteins, the instructor points out that the intensity of synchrotron radiation and the ability to select the wavelength of radiation maximizes the anomalous scattering of a heavy atom and enables crystallographers to determine phases. Based upon the knowledge they attained during the course, students are able to read, understand and assess a crystallographic journal article.

3.1. Homework assignments on symmetry operators

Using *International Tables for Crystallography* (2005), *Brief Teaching Edition of Volume A: Space-Group Symmetry*, students independently browse the monoclinic space groups to become familiar with the possible symmetry operators. Then they find a crystal structure in the CSD that exhibits interesting symmetry. They present the packing diagram of the structure to the class, pointing out how each symmetry operator gives rise to a symmetry-related copy of the molecule or ion. (Two homework assignments, a list of interesting structures in the CSD for teaching symmetry ideas and a sample exam are included in the supplementary material for this article.)

3.2. Homework assignment on hydrogen bonds

Using such sources as Glusker (1998) and Steiner (2002) students learn about less common types of hydrogen bonds, such as the bonds with C–H donors or with π acceptors. They find examples of unusual or interesting hydrogen-bond patterns in the CSD and present the structure to the class. The software to search the database and the convenient link to display the structure with *Mercury* (Macrae *et al.*, 2008) are ‘user friendly’ and can be used by students in other inquiry-based assignments to learn about molecular structure. In connection with this topic, the instructor should compare neutron diffraction with X-ray diffraction. While H atoms diffract X-rays weakly, H atoms diffract neutrons extremely well. Neutron diffraction would more clearly show the positions of the H atoms and verify the hydrogen-bonding scheme.

3.3. Systematic absences demonstration

Lisensky *et al.* (1991) devised an Optical Transform Kit (available from the Institute for Chemical Education; <http://>

ice.chem.wisc.edu) that includes slides of diffraction patterns with handouts that compare direct space and reciprocal space. This demonstration clearly illustrates that translational symmetry operations such as a glide plane extinguish certain classes of reflections, and is most useful in conjunction with a mathematical proof that, when a glide plane is present, certain classes of reflections are systematically absent.

3.4. Solve the phase problem with Patterson vectors

The instructor selects a monoclinic crystal structure that includes a single atom (such as a Co atom in an organic structure) with significantly higher atomic number than the other atoms in the structure, and downloads a CIF from the CSD or from supplementary material for the journal article. Before coming to the laboratory, the students have been asked to generate the possible Patterson vectors from the symmetry operators in the space group. The *XTAL* (Hall *et al.*, 2000), *PLATON* (Spek, 2009) or *SHELX* (Sheldrick, 2008) software is used to calculate a list of the Patterson vectors. It is important to emphasize that electrons diffract X-rays, and thus we expect the vectors between symmetry-related atoms with the highest number of electrons to have the greatest intensity in the Patterson map. Usually the expected vectors are found at or near the top of the list. The students collaborate in groups to choose the correct Patterson vectors and calculate the position of the atom. The 'heavy' atom dominates the structure factor series to such an extent that many of the reflections are correctly phased when the students input the single atomic position, and the ensuing graphical display shows most of the other non-H atoms in the structure. The students locate as many other atoms as possible and turn in the computer-generated drawing of their structure at the end of the laboratory period.

3.5. Present a crystal structure to the class

As future scientists, students in the advanced physical chemistry course need to become sophisticated users of crystallographic information. As a capstone or culminating assignment, students select an experimental crystal structure determination from the literature, assess the quality of the data and discern the chemical implications of the structure. They summarize the experimental procedure and present the results graphically to the class. As part of the assignment, they learn about statistical measures for the precision of the X-ray experiment and compare the results with expected structural parameters. This assignment calls upon students to synthesize all the knowledge they have gained about crystallography in order to evaluate experimental results, as they will need to do when they are practicing scientists.

4. Concluding remarks

The course modules outlined above emphasize practical understanding of X-ray crystallographic methods using homework assignments, demonstrations and laboratory investigations. Rotation of polarized light by a crystal clearly

demonstrates the internal order of a crystal. That we can determine the size of a unit cell on an ångström scale by measuring a diffraction pattern in millimetres is fascinating to students. Real crystal structures from journal articles or from the CSD engage students with the chemical ideas that flow from a three-dimensional structure. Ideas such as symmetry, molecular conformation, hydrogen bonding and reciprocal space become concrete when students examine a crystal structure and its diffraction pattern. In these assignments students collaborate in small groups to investigate, discover, discuss and then present their conclusions to other students. Open-ended assignments and communication with other students lead to learning and understanding of the concepts rather than superficial memorization.

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