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Integrating fundamental concepts with practical skills: consolidating small-molecule crystallography education

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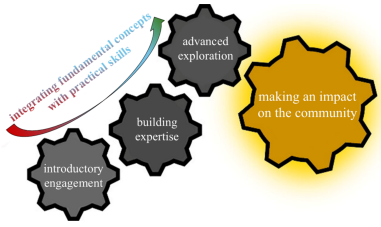
A comprehensive educational strategy designed to make small-molecule crystallography more accessible for students at various academic levels is described. By integrating hands-on laboratory visits, structured courses and advanced application training, we cultivate a deep understanding of fundamental crystallographic concepts while fostering practical skills. This strategy also aims to inspire novice learners, building their confidence and interest in structural science. Our approach demystifies complex concepts through real-world examples and interactive case-learning modules, enabling students to proficiently apply crystallography in their research. The resulting educational impact is evident in numerous publications from undergraduates, scholarship awards to graduates and successful independent research projects, highlighting the effectiveness of our programme in inspiring the next generation of chemical crystallographers.

1. Introduction

X-ray crystallography stands as a cornerstone technique for structure determination in chemical research (Bond, 2014). Recent technological advancements have vastly increased its accessibility, enabling researchers to routinely collect, process and interpret crystallographic data without reliance on a dedicated 'professional crystallographer' (Clegg, 2005). Although the increased availability of crystallography is exciting for the field of chemical research, this ease of access comes at the cost of understanding many fundamental concepts in crystallography. Consequently, many chemistry students who routinely perform single-crystal X-ray diffraction studies often approach experiments with a 'black box' mentality, which may lead to significant errors in their results (Girolami, 2015; Campbell *et al.*, 2016; Dong & Zheng, 2021; Raymond & Girolami, 2023; Thompson *et al.*, 2024).

Advancements in software have facilitated the integration of X-ray crystallography experiments into undergraduate curricula (Brannon *et al.*, 2020; Beauparlant *et al.*, 2023; Caro *et al.*, 2023), yet access to instrumentation remains limited (Zheng & Campbell, 2018). Our university hosts researchers from a variety of academic backgrounds, ranging from high schoolers (Chaudhry, 2024) and undergraduate students beginning their first research endeavours to graduates and post-graduates, many of whom may lack prior crystallographic experience. Our facility, the Centre for Crystallographic Studies, is devoted to engaging and training the next generation of chemical crystallographers, including researchers at



both expert and amateur levels (Jung, 2019; Zheng, 2022*b*). This mission requires accommodating a wide range of skill levels, ensuring that all students can grasp basic yet fundamental concepts and develop essential skills, ultimately enabling them to employ small-molecule crystallography in their future research and contribute meaningfully to the scientific community (Zheng & Campbell, 2018; Dong & Zheng, 2021).

To address these challenges, we have implemented a comprehensive three-part plan aimed at attracting and training students to become critical and independent crystallographic users. Instead of starting with a formal lecture on diffraction physics, we introduce novice learners to the field by inviting them to the crystallography laboratory, where they have an opportunity to measure the crystals they have brought in and make connections between the crystallographic concepts and practice. Such a hands-on approach ensures that students gain a lasting memory of what they learned, while obtaining a three-dimensional model of their molecule can ignite their excitement about the capabilities of structural science. For those interested in continuing their education in crystallography, we offer a formal course in the subject that follows the case study approach (Campbell *et al.*, 2016; Dong & Zheng, 2021). The case studies presented in the course address many of the key concepts in the field and require active engagement from all students. After completing this course, our students are not only equipped to obtain their own crystallographic data for publications but also prepared to explore more advanced techniques such as photocrystallography (Powers *et al.*, 2014; Hwang *et al.*, 2015; Nascimento *et al.*, 2024) and anomalous X-ray diffraction (Powers *et al.*, 2013; Hernández-Sánchez, 2015; Bartholomew *et al.*, 2019; Juda *et al.*, 2024).

2. Development of the crystallography education strategy

One of the main educational missions of our facility is to ensure that students at various educational levels can engage with crystallographic concepts and develop the skill sets they need to use crystallography effectively in their future research. To achieve this, we tailor our educational strategies to meet the diverse needs of our students, from secondary school beginners to advanced graduate researchers.

Given the varied academic backgrounds of our students, our educational plan has accounted for individual learning levels. For instance, complex topics like structure factors and atomic scattering components are essential for graduate students aiming to perform advanced applications, such as anomalous X-ray diffraction on polymetallic clusters (Hernández-Sánchez, 2015; Bartholomew *et al.*, 2019; Juda *et al.*, 2024). In contrast, a straightforward demonstration using a simple crystal, such as cane sugar, is more appropriate for high school or undergraduate students as an introduction to the utility of single-crystal X-ray diffraction (Abrahams *et al.*, 2023; Beauparlant *et al.*, 2023).

Although the appropriate teaching methods required to accommodate the skill levels of our students may vary, the overall objective remains consistent: to instil a deep understanding of crystallographic concepts, enabling students to grasp the techniques' strengths, limitations and potential pitfalls (Campbell *et al.*, 2016; Dong & Zheng, 2021).

2.1. Introductory engagement: integrating crystallography into undergraduate courses and community outreach

To inspire students with crystallography, we have developed a laboratory-visit module that can incorporate crystallography laboratory practice into various advanced undergraduate experimental chemistry courses. This module extends to our outreach programmes, inviting undergraduates from local institutions to engage with small-molecule crystallography through hands-on activities. The aim is to provide students with a practical experience rather than overwhelming them with theoretical lectures.

During these visits, students bring their crystals and follow a demonstration–experiment–lecture format. They practice crystal picking and mounting, solve a crystal structure using data collected during the demonstration, and visualize their results (Fig. S1 in the supporting information). Details of the guidelines, including schedule and format, were discussed in our 2018 paper (Zheng & Campbell, 2018).

To support the local secondary school students who may not yet be aware of the exciting possibilities within science, technology, engineering and mathematics, we have engaged with the Boston public school community (Chaudhry, 2024). By carefully choosing the reading list (Foxman, 2006), we were able to expand our outreach programme using a similar strategy and provide a guided tour with hands-on activities for secondary school students. The tutorial's style, which incorporates inquiry-based instruction, occasional humour and bundled reference links, effectively prepares students to complete activities and actively participate in discussions.

The visiting students are encouraged to bring their own samples, which makes the laboratory visit more fun and engaging for both students and instructors. The undergraduates usually bring samples from the projects they are

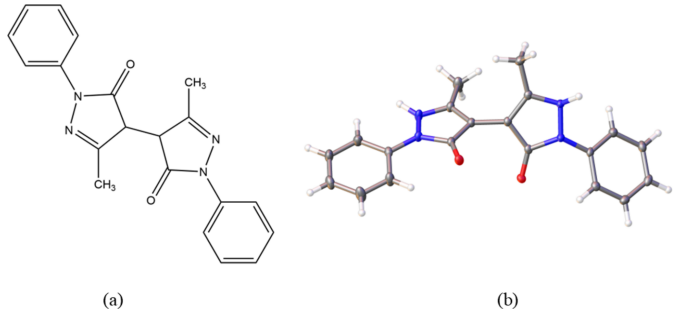


Figure 1
(*a*) Proposed structure of bispyrazolone as listed on the Thermo Scientific Chemicals website (https://www.thermofisher.com/order/catalog/product/A14308.14); (*b*) crystal structure CCDC 2389208 determined through X-ray crystallography in 2019.

Table 1
Representative crystalline samples from secondary school students' visits.

Sample	Crystal structure identifiers (CSD refcodes, CCDC or ICSD numbers)
Cane sugar from a coffee store	SUCROS01
Epsom salt for the soaking solution	ICSD16595†
Crystallized lemonade from TURE LEMON package	CITARC‡
Potassium bitartrate from wine cork§	CCDC2389207¶

† Baur (1964). ‡ Roelofsen & Kanters (1972). § Potassium bitartrate crystals form due to the compound's low solubility. In this specific case, the crystals probably appeared on the cork because some wine had soaked into it while the bottle was moved. When the bottle was subsequently placed upright or on its side, the wine no longer reached the cork. As the wine evaporated back into the bottle, the concentration of potassium bitartrate increased until it reached saturation, leading to crystal formation. These crystals dissolve very slowly once formed and can persist even if the wine contacts the cork again (Coulter *et al.*, 2015). ¶ When we completed our 2022 paper (Zheng, 2022*b*), we found that the only potassium bitartrate structure in the CSD (refcode XIJXAS) was from 2018, with a Flack parameter of 0.98 (3). This structure later became a new case for determining the correct absolute configuration (Dong & Zheng, 2021; Zheng, 2022*a*). Therefore, the structure from a laboratory-visit data set with the correct configuration has been deposited.

working on. In this case, the data they obtain from this trip may become the last piece of data they need before submitting their research for publication (Table S1). We will further interact with the students and course instructors, help complete the X-ray components of experiments, and aid in manuscript preparation and review. If the students' samples do not work out, we usually turn to a reliable commercial compound, bispyrazolone, allowing practice in obtaining diffraction-quality crystals without recrystallization. The most interesting part is that the actual structure of this compound is different from the proposed structure on the label (Ruf & Noll, 2019; Powell & Rix, 2020) (Fig. 1). The follow-up discussion allows students to reflect on why X-ray crystallography has been called the 'gold standard', on the basis of the reading list (Bond, 2014) provided before the laboratory visit (Table S2).

The secondary school students always surprise us with creative choices of crystals from everyday sources. For example, we have run crystallography experiments and determined the structures of sucrose from a coffee shop's cane sugar, magnesium sulfate from Epsom salt, the citric acid from a store-bought crystallized lemonade package and even the deposited potassium bitartrate from a wine cork (Table 1). These real-world examples and the ability to understand these materials from an atomistic perspective help demystify science (Brown *et al.*, 2014; Svinicki & McKeachie, 2015) and encourage participation in every step of a single-crystal X-ray diffraction experiment, often eliciting 'wows' and 'oohs' when the three-dimensional models of their crystals are revealed.

2.2. Building expertise: practical training through a structured course

To foster deep learning and critical thinking rather than mere information transfer (Eilks & Byers, 2009), we designed a one-semester practical crystallography course that combines both lectures and complementary laboratory sessions. The course covers a range of topics, from crystal symmetry and space groups to the geometry of diffraction (Helliwell, 2021), structure factors and problematic structure refinement. This course is designed to ensure that everyone who has learned molecular symmetry, regardless of their crystallographic starting point, can develop the necessary skills to use crystallography in their future research, and have the confidence to independently perform small-molecule crystallography experiments and publish their results. This course is aimed at graduate and upper-level undergraduate students, although it has attracted post-graduate students and participants from other institutions as well.

In the laboratory session, students practice crystal picking and mounting and instrument operation in a setup like the laboratory-visit module; however, these sessions extend over multiple weeks, providing more extensive practice opportunities. They also perform data integration, data reduction and structure solution and attend refinement lessons with preplanned examples, including complicated cases such as disorder and twinning, similar to crystallography workshops. In the lecture setting, we focus on basic yet fundamental crystallography concepts and integrate them into student-centred active learning methods, such as interactive case studies, chalk talks and team presentations (Campbell *et al.*, 2016; Dong & Zheng, 2021; Zheng & Campbell, 2021). For example, assigning small groups of students to assess high-profile publications containing problematic crystal structure refinements directly related to their fields of research creates a comprehensive and immersive learning environment. This connection between the case study and their academic interests becomes a memorable experience, embedding key educational messages within a relatable story (Herreid, 2013; Svinicki & McKeachie, 2015). A series of case-based learning modules have been designed to address some common misconceptions in chemical crystallography and resolve the space-group-choice dilemmas that students may have encountered in structure refinement (Table S3). The details of the guidelines, including the examples, have been discussed in our previous publications (Campbell *et al.*, 2016; Dong & Zheng, 2021).

By incorporating case-based learning modules into the crystallography curriculum, students gain a profound understanding of the strengths and limitations of crystallography as an experimental science. Through hands-on analysis of crystallographic data in contemporary chemistry research, they learn how to navigate potential errors and misconceptions. Initially apprehensive, students quickly develop the skills to identify and avoid common pitfalls. By the end of the course, they confidently integrate crystallography into their research efforts.

2.3. Advanced exploration: developing new methodology in crystallography applications

To inspire students to pursue their interest in structural science and further expand the frontiers of this important field, we have covered advanced crystallography applications in our formal crystallography course (Malbrecht *et al.*, 2016;

Table 2
Representative advanced crystallography topics.

Advanced crystallography topic	Themed project
Photocrystallography	Determination of structures for metastable intermediates
Crystalline sponge method	Structure elucidation of target organic molecules in liquid or amorphous solid states
Anomalous X-ray diffraction	Distinguishing atoms in proximity on the periodic table and differentiating valence states
Neutron single-crystal diffraction	Precision location of atoms that are near on the periodic table and accurate hydrogen-atom placement
X-ray charge density modelling	Electron population variations across crystallographic independent metal centres
Modulated structures and their solution	Resolving incommensurately modulated crystal structures
Data processing and structure determination for 3DED using dynamical diffraction theory	Enhancing structure models and achieving reliable absolute structure determination for small molecules

Zheng *et al.*, 2018), as well as in a monthly crystallography seminar. Depending on the faculty research demand, we have covered many advanced topics in the past decade (Table 2). The students appreciate the importance of 'knowing what is possible', although some of them may not use these techniques in their current research. Despite these topics being considered as an advanced level, we emphasize that the same basic, but fundamental, crystallography concepts still apply.

For example, several research groups here have worked on isolating highly reactive intermediates such as metallonitrenoids. If these compounds are produced in solution, they immediately decompose through a reaction with the solvent or self-immolation. The only hope of observing these compounds is to generate them *in crystallo* and utilize the crystal matrix to preserve the reactive motif (Zheng *et al.*, 2009; Reid & Powers, 2021). The guiding questions (Fig. S2) allow students to reflect on what they have learned from the class (Coppens *et al.*, 2010; Coppens & Zheng, 2011).

Observing the execution of advanced crystallography experiments in our facility has inspired students to apply similar techniques to characterize their reactive compounds. The training and knowledge gained from these experiences equip them with the skills needed not only for their research at Harvard (Powers *et al.*, 2014; Hernández-Sánchez, 2015; Ramadhar *et al.*, 2015) but also for future opportunities beyond (Hernández-Sánchez *et al.*, 2018), including their independent academic careers (Reid & Powers, 2021; Cardenal & Ramadhar, 2021).

3. Bridging concepts and practice

Teaching students to solve chemistry problems is not the same as teaching them about the nature of matter (Novak, 1984; Nurrenbern & Pickering, 1987). In our crystallography educational programmes, we consistently focus on fundamental concepts. However, we emphasize different aspects of these concepts in varying learning settings (Brown *et al.*, 2014).

In the laboratory-visit modules for novice learners, students get their first introduction to the concept that 'a careful crystal structure determination is at best a measure of the precision of the fit of the model used to the experimental data obtained' (Zheng & Campbell, 2018), not a measure of the accuracy (Cruickshank, 1999). A follow-up question, 'How can you obtain better experimental data or refine your model to improve the final result?', anchors their reflections on their laboratory practice (Fig. 2). Each student's perspective may be unique, shaped by their own experience during the hands-on activities. However, group discussions help to collectively shape their understanding of crystallography concepts and best practices. Students gain insights into the importance of growing high-quality crystals, accurately mounting well diffracting crystals and correctly assigning atom types. This methodology also aids in grasping more advanced crystallography concepts, such as disorder and twinning. Through learning these basic concepts, students are motivated to further their education in formal crystallography courses, especially if they plan to use crystallography in their future research.

In the formal course, we continue to emphasize that structure refinement is fundamentally about fitting the model to the data. For a problematic structure refinement, refining *disorder* involves improving the model to better fit the data, while handling *twinning* focuses on obtaining detwinned data for a better fit of the model (Zheng & Campbell, 2018; Dong & Zheng, 2021). We use the case study method to explore situations where crystallography has led to ambiguous or incorrect results. To improve results, it is essential to either enhance the model or obtain better data, which may necessitate redesigning the experiment. Students learn that, during problematic small-molecule structure refinements, X-ray crystallography alone may not provide an unequivocal result. Mistakes in refinement can occur, leading to incorrect conclusions, and additional data from other experimental techniques may be needed to model the crystallography data correctly. A common question that we encourage students to ask during structure determination is 'Does my model make chemical and physical sense?' They recognize that in their research it is crucial to gather additional information about

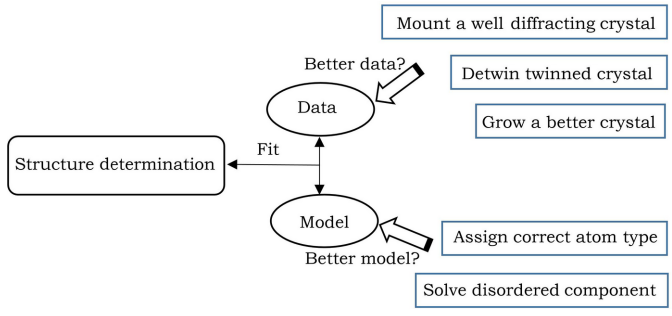


Figure 2
Schematic illustration highlighting fundamental concepts for students to consider for improving results in crystallography experiments. Adapted with permission from Zheng & Campbell (2018). Copyright 2018 American Chemical Society.

the chemical structure of the analysed molecule by using other techniques. As the adage goes, 'What you see (from the Fourier difference map) + What you believe (the geometry of your structure) = What you get' (Campbell *et al.*, 2016).

Recapping key concepts and incorporating various related topics in a one-semester-long course is crucial. This approach helps students visualize the connections between different course materials and understand the course content within the 'big picture' of experimental science (Brown *et al.*, 2014).

While advanced techniques and technologies are exciting, a strong foundation in the basic yet fundamental crystallography concepts is still crucial. For example, three-dimensional electron diffraction [3DED (Gemmi *et al.*, 2019), also known as MicroED (Clabbers *et al.*, 2022)] expands the scope of analysis to materials that are too small for conventional X-ray crystallography, such as those under 1 μm in size. However, interpreting electron diffraction data is more complex due to multiple scattering effects, also known as dynamical diffraction effects (Klar *et al.*, 2023). Students understand that achieving an accurate structure model and reliable absolute structure determination for small-molecule compounds requires data processing and structure determination using dynamical diffraction theory. This understanding enables them to refine their data more effectively.

We encourage students wishing to use advanced crystallographic techniques to keep key concepts in mind when facing challenges. For example, in our lecture on scattering factors, we provide guiding questions (Fig. S3). With a good data set, routine small-molecule crystallography experiments can determine atom types between C/N/O due to a significant difference in their scattering factors, which is greater than 10% (Girolami, 2015). Although distinguishing two transition metals that are close on the periodic table, such as Zn^{2+}/Co^{2+} or Zn^{2+}/Ni^{2+}, has been considered much more challenging, it could be achieved with tuneable synchrotron radiation by considering anomalous scattering, where the atomic scattering factor shows wavelength dependence near the absorption edge of the atom (Powers *et al.*, 2013; Juda *et al.*, 2024). By designing specific strategies for data collection and refinement, even with in-house Mo/Cu DUO source diffractometers (Liu *et al.*, 2021), students can determine metal occupancies in mixed-metal metal–organic frameworks and polynuclear clusters, which has been crucial for several research projects. Mastering these fundamentals will enable students to tackle more sophisticated challenges and innovate within the field.

4. Impact and conclusion

Our crystallography education strategy has fostered a profound and long-lasting interest in crystallography among our students and researchers, ensuring the growth and evolution of this vital scientific field. The laboratory-visit modules have provided invaluable opportunities for both course instructors unfamiliar with crystallography and institutions lacking access to single-crystal X-ray diffractometers. Numerous papers from undergraduate courses (Table S1) and outreach programmes (Huang *et al.*, 2017; Wang *et al.*, 2019; Norman *et al.*, 2022) have been published, with the crystallography result obtained during visits making significant contributions. We encourage interested faculty members to approach nearby crystallographic facilities to arrange similar visits.

Our philosophy centres on serving, educating and enabling. Through comprehensive educational programmes, we have empowered our students to independently perform over 95% of routine crystallography experiments, fostering a hands-on learning environment. After utilizing our facility, students gain a nuanced understanding of the advantages and limitations of crystallography. The case studies incorporated into our curriculum create memorable learning experiences. They enable students to develop critical skills for analysing scientific literature (Dong & Zheng, 2021). Past students have applied these skills in their own research, identifying crystallographic errors that have subsequently served as case studies in future courses (see the supporting information). In some instances, these observations have led to corrections or even retractions of published papers, emphasizing the real-world impact of the training (Kaysser *et al.*, 2014; Du *et al.*, 2016).

By making the learning process interactive and reflective of actual scientific practice, we not only enhance students' crystallographic knowledge but also inspire a lasting interest in crystallography and its applications in chemistry and materials science. Our students frequently use crystallography in their research projects independently and have published peer-reviewed academic papers, demonstrating their proficiency. Remarkably, three of our students have been awarded the Ludo Frevel Crystallography Scholarship (Table S4), reflecting their interest in incorporating crystallography as a critical component of their research workflow. Additionally, some students have continued their crystallography education by learning and applying advanced techniques to their research projects at Harvard (Table S5) and to their independent academic careers, significantly contributing to various fields (Hernández-Sánchez *et al.*, 2018, Reid & Powers, 2021; Cardenal & Ramadhar, 2021).

By fostering an interactive and practical learning environment, we not only empower students to become proficient users of small-molecule crystallography in their scientific studies but also inspire them to pursue further advancements in this crucial field. The success of our educational programmes underscores the importance of a strong foundational understanding of crystallography concepts, paired with hands-on experience and the ability to critically navigate complex scientific challenges. As we continue to refine and expand our programmes, we anticipate that our approach will serve as both a framework and a guide for modern crystallography education, driving innovation and excellence in research and academia.

5. Related literature

The following references are cited in the supporting information: Cao *et al.* (2023), Mukherjee *et al.* (2023), Marks *et al.* (2024), Mi *et al.* (2019), Dash *et al.* (2024), Brown *et al.*

(2023), Bass *et al.* (2023), Crisp *et al.* (2022), Aigeldinger *et al.* (2022), Chou *et al.* (2022), Carsch *et al.* (2021*a*, 2021*b*), Duckett *et al.* (2015), Glazer (2016), Kastner *et al.* (http://www.crystallographiccourseware.com/), Clegg (2016), Zheng *et al.* (2008), Coppens (2017), Glusker *et al.* (1996), Li *et al.* (2001), Fout *et al.* (2011), Basu *et al.* (2021), Liu *et al.* (2021), Ethan (http://skuld.bmsc.washington.edu/scatter/).

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Conflict of interest

The authors declare no competing financial interest.

Data availability

CCDC entries 2389207–2389208 contain the supporting crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/ or by emailing data_request@ccdc.cam.ac.uk or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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