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Review

Dynamic single-crystal diffraction studies using synchrotron radiation

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ABSTRACT

The methods that have been developed to determine the three-dimensional crystal and molecular structures while they are in metastable or short-lived photoactivated states are described. The structural science of photocrystallography has developed over the last two decades because of the use of synchrotron radiation, coupled with advances in cryogenics, computer hardware and software, and laser technology. Initial studies have been carried out on metastable linkage isomers and LIESST-generated metastable structures and, more recently, by using the synchronisation of laser pulses with X-ray pulses, it has been possible to determine the structures of complexes with microsecond lifetimes. In the future X-ray Laue techniques and one-shot XFEL studies applied to molecular systems promise to make the study of sub-microsecond species a reality.

1. Introduction

X-ray crystallography has always been the preferred method for determining the three-dimensional structure of a crystalline starting material or of a reaction product. What the method does not generally provide is the route by which the starting material is converted into the product [1]. Over the last two decades, however, developments in synchrotron radiation, X-ray detectors, cryogenics, laser technology, computing power and data storage capacity have all supported the development of new methodologies that have allowed the chemical and biological processes occurring in the solid-state to be monitored in "real time" [2,3]. Thus, the dimension of "time" has been introduced into the crystallographic experiment and the discipline of "dynamic" crystallography has evolved.

When crystalline materials are being investigated, the routes by which external media can be applied to promote a chemical reaction are limited; two or more reagents cannot be mixed readily as in solution chemistry. In spite of this difficulty a number of different stimuli have been reported to induce changes in the single-crystal; including temperature [4–6], pressure [7–9] and light. Photochemical reactions can be particularly advantageous because they can be easily controlled and manipulated: the size, shape and direction of the incident beam can be controlled using widely available optical equipment and, when using a tunable source, the excitation

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wavelength can be easily varied to suit the process under study. Additionally, the majority of light-induced solid-state reactions are clean and efficient, producing few or no waste products or unwanted side-reactions. As such, it is perhaps unsurprising that the majority of dynamic crystallographic experiments have involved the activation of the crystalline sample with light, either from a laser, a flash lamp or a LED source [10–15]. In line with the technological developments enjoyed by the field, in recent decades there has been a dramatic reduction in the time needed to collect and process single-crystal X-ray data, opening up the technique to a wide new range of feasible experiments. It is now possible to study a variety of photoinduced processes in the single-crystal, obtaining a full, three-dimensional picture of the photoactivated species obtained. As such, the phrase "photocrystallography" is now commonly applied to this diverse area of crystallographic research [16].

The type of photocrystallographic experiment conducted is necessarily dictated by the lifetime of the photoactive species, as this excited state (ES) must exist for longer than the required data collection period. It is necessary that both the experiment and the process under study be brought onto a common timescale and this can be achieved either by slowing the photoreaction down to the timeframe of the crystallographic experiment, or speeding up the experiment to match the lifetime of the transient species. The former approach is often achieved *via* trapping methods, for example chemical- or cryo-trapping, which involve a sudden change in the reaction conditions in order to "freeze" the reactant in an intermediate state for a period long enough to allow its analysis. While there are advantages to this approach, it is possible that the chosen trapping method will change the natural progress of the solid-state reaction. To be sure of observing the true reaction pathway it may be preferable to adopt the latter approach, speeding up the data collection procedure so that the photoinduced process can be followed in real time.

The shorter the lifetime of the photoactive species, the more complicated the photocrystallographic procedure that is required for its study.

(i) At the longer end of the scale, "steady-state" and "pseudo-steady-state" experiments can be conducted using standard, single-crystal X-ray diffraction techniques. Steady-state methods are typically used to study metastable ES, with lifetimes ranging from hours up to infinity at low temperature. The experiment consists of an irradiation period to induce maximum conversion to the metastable arrangement. The irradiation is then stopped and a standard, single-crystal X-ray data collection is performed (Fig. 1(a)). Pseudo-steady-state experiments are used to study slightly shorter-lived species, existing for periods between minutes and milliseconds, which can achieve a stable, constant ES occupancy with continued irradiation (Fig. 1(b)). These methods require an effective means of illuminating the crystal throughout the experiment, without impeding the single-crystal X-ray data collection.

(ii) For the study of transient photoinduced species, "stroboscopic" or "pump-probe" photocrystallographic methods have been developed. These experiments require short duration light and X-ray pulses to be generated, which must then be synchronised to arrive at the sample position in a specified time sequence (Fig. 1(c)). While light pulses are achieved using ultra-fast lasers, pulsing of the X-ray probe source is more complicated. For species with lifetimes in the millisecond to nanosecond range pulses are usually generated by a mechanical chopper that is placed into the incident X-ray beam [17,18]. When these short probe pulses are used, the amount of X-ray flux that is incident on the crystal is severely limited. As such, pump-probe experiments have typically required the use of high intensity synchrotron radiation sources. Even so, it is usually the case that a number of pump-probe cycles are required per frame to build up sufficient X-ray intensity on the diffraction image. The electrons moving around a synchrotron storage ring are accelerated to speeds approaching the speed of light and are therefore subject to relativistic effects, causing them to orbit the ring in discrete bunches [19]. As such, the synchrotron radiation produced is naturally pulsed, with a repetition rate dictated by the period of the electron orbit about the ring. This is typically in the nanosecond to picosecond range for most Third Generation synchrotron sources. Pump-probe experiments involving photoactive species with lifetimes in this range can therefore be conducted without the need for mechanical X-ray pulse generation, as the laser repetition rate is instead synchronised with that of the storage ring [20].

(iii) Access to sub-picosecond timescales requires the development of "single-shot" diffraction methods, *via* a "diffract-and-destroy" approach [21]. These require the whole diffraction pattern to be obtained in a single X-ray image and, as such, single-shot methods are also strongly affected by X-ray flux limitations. Attempts to counteract these issues are now being made: either by the use of Laue diffraction for molecular systems [22], or additionally by accessing of even higher levels of X-ray flux at X-ray Free Electron Laser (X-FEL) facilities.

2. The beginnings of time-resolved crystallography

2.1. Macromolecular photocrystallography

The methodology for time-resolved crystallography was first developed for macromolecular systems because of interest in many key biological processes. This need gave the impetus for faster data collection and processing procedures than those hitherto required for studies on molecular systems. Biological crystals are also typically less stable and so are more susceptible to degradation problems, such as radiation damage when exposed to the X-ray beam [23]. As such, shorter data collection times are also desirable as they can help to circumvent such issues. Macromolecular crystallography makes use of the Laue diffraction method, in which the crystal is subject to a continuum of X-ray wavelengths from a polychromatic, or "white" beam [24]. Laue methods therefore make more efficient use of the X-ray beam, allowing many more reflections to be collected in a single image than are obtained with a monochromatic source. This can help to reduce the time needed for data collection, however further improvements were still required to approach timescales comparable to the biological processes under study.

The first reported nanosecond-resolved diffraction study was conducted by Moffat et al. in 1996, investigating the photodissociation mechanism of carbon dioxide (CO) in carbon monoxy-myoglobin (MbCO) [25]. MbCO had previously been studied extensively *via* ultra-fast spectroscopic methods and, as a result, the photoactivity of the complex in solution was well-documented [26,27]. In their photocrystallographic study conducted at the European Synchrotron Radiation Facility (ESRF), Moffat et al. were able to obtain diffraction data that correlated well with these solution studies. They employed a pump-probe strategy consisting of an initial 7.5 nm-wide laser pump pulse at $\lambda = 630$ nm, followed by an X-ray probe pulse timed to arrive after a specified delay (τ). This pump-probe delay was varied such that six different datasets were recorded at intervals between $\tau = 4$ ns and 1.9 ms. With the earliest delays of $\tau = 4$ ns and 1 μs, the resulting diffraction data revealed there to be regions of negative electron density present at the expected position of the CO ligand. These observations confirmed the conclusion of the earlier solution-based studies that photolysis of the Fe—CO bond is induced and indicate that a similar process is