Virtual issue on absolute structure

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It should come as no surprise, following after the first virtual issue on **polymorphism** (http://journals.iucr.org/special_issues/2011/polymorphism/), that the Editor has chosen **absolute structure** (http://journals.iucr.org/special_issues/2012/absolutestructure/) as the topic for this year's effort. The unambiguous determination of absolute structure, particularly where the absolute configuration of an enantiomerically pure chiral molecule is needed, is important not only for synthetic and natural-product chemists, who wish to fully characterize their products, but can be a critical step for the pharmaceutical industry, where opposite enantiomers of a drug can have quite different biological properties. One should also mention those crystal engineers endeavouring to prepare non-centrosymmetric crystals for applications such as second-harmonic generation.

A major impetus in enabling the study of absolute structure has been the advent of dual radiation CCD diffractometers. This means that more laboratories have routine access to Cu $K\alpha$ radiation with the potential to successfully study light-atom structures. The latter have been viewed as one of the remaining difficulties in this field. This virtual issue has the ambition to present the results of crystal-structure determinations which demonstrate new successes and remaining limitations in absolute-structure evaluation.

Historically, the determination of absolute structure started on the wrong foot with Friedel (1913) who, by a false argument using optics and crystal symmetry, managed to prove that the intensities of the reflections hkl and $\overline{hkl}$ are always identical, regardless of the point group of the crystal. The effects of this unfortunate mistake are still felt today in the teaching of diffraction by crystals, as Friedel's Law is often presented and used as a fundamental principle whereas it is no more than an approximation, which often does not need to be invoked. Resonant scattering was predicted theoretically by Waller (1928). The first determination of absolute structure by X-ray diffraction appeared as a by-product of a carefully contrived experiment by Coster *et al.* (1930) to demonstrate the existence of resonant scattering. Coster *et al.* (1930) used a crystal of hexagonal ZnS (zincblende), which is non-centrosymmetric and achiral, in an experiment with Au L radiation. The latter has a wavelength corresponding to the K absorption edge of Zn which falls between the Au $L\alpha_1$ and Au $L\alpha_2$ lines. The first chemical application of absolute-structure determination by X-ray diffraction was published by Peerdeman *et al.* (1951) and Bijvoet *et al.* (1951). They deduced the absolute configuration of the (2*R*,3*R*)-tartrate anion in its Na Rb salt. The modern developments of absolute-structure determination by least-squares refinement find their source in a paper by Rogers (1981). In 1984, Jones coined the term absolute structure. Your editorialist has published extensively in this field starting with the oft-quoted paper of Flack (1983).

One has no choice in this editorial but to make some comments on the thorny subject of the validation of absolute-structure determinations. It has become standard practice over the years to rely on the values and standard uncertainties of derived parameters or something equivalent. This is very much in line with the technique of comparing bond distances and angles from one particular crystal-structure determination with those given in tables of standard values. However, Dr David Watkin of the University of Oxford had the inspiration of looking at the fit of the observed to the model (calculated) intensities (Flack *et al.*, 2011). It is customary to plot $|F_{\mathrm{obs}}|^2$ against $|F_{\mathrm{model}}|^2$. However, Watkin found great value in plotting $2A_{\mathrm{obs}}$ against $2A_{\mathrm{model}}$ and D_{obs} against D_{model} on the same $2AD$ graph. $A(hkl)$ and $D(hkl)$ are respectively the average and the difference of the intensities of Friedel opposites; $A(hkl) = \frac{1}{2}[|F(hkl)|^2 + |F(\overline{hkl})|^2]$ and $D(hkl) = |F(hkl)|^2 - |F(\overline{hkl})|^2$. Fig. 1 shows the $2AD$ plot of one of the crystal-structure determinations in the virtual issue. A good fit between $2A_{\mathrm{obs}}$ and $2A_{\mathrm{model}}$, and D_{obs} and D_{model} shows up as a distribution of data points spread around the straight line of slope 1 passing through the
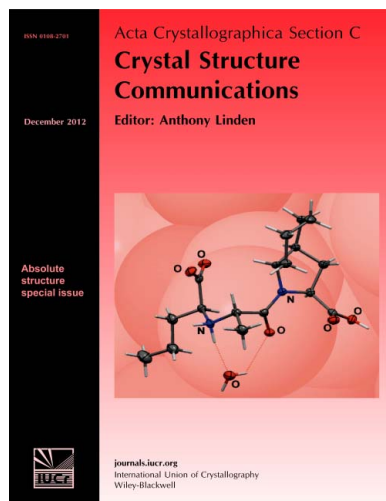
origin. Various R values can also be calculated. Flack *et al.* (2011) prepared $2AD$ plots from 31 crystal structures published in 2007. The publications in the virtual issue show exactly the same trend. One third of the structures showed a reasonable fit between D_{obs} and D_{model}. Another third showed no fit between D_{obs} and D_{model}, with all D_{model} values being near to zero. For these structures, the D_{obs} values were interpreted as being dominated by random uncertainty and systematic error. The remaining one third of structures had intermediate results.

It would seem appropriate to make some remarks based on personal experience, concerning crystallographers' understanding of the subject area of absolute structure and absolute configuration. In general, there is a deep rift in the comprehension of the subject between:

(*a*) chiral (necessarily non-centrosymmetric) crystal structures and the deduction of the absolute configuration of molecules (this is of a high level), and

(*b*) achiral non-centrosymmetric crystal structures, where there is a great deal of confusion apparent in people's minds.

This is a problem that writers of text books on crystallography and organizers of schools on crystallography need to address. As an aperitif in such an effort, here are the definitions of absolute configuration and absolute structure.

Absolute configuration: The spatial arrangement of the atoms of a physically identified chiral molecular entity (or group) and its stereochemical description [*e.g.* (*R*) or (*S*), (*P*) or (*M*), D or L *etc.*).

Absolute structure: The spatial arrangement of the atoms of a physically identified noncentrosymmetric crystal and its description by way of unit-cell dimensions, space group, and representative coordinates of all atoms.

In short, for the validation of absolute-structure determination, over the years there has been a heavy reliance on the statistics (values and standard uncertainties) of derived parameters or something equivalent, and little study of the fit of the model to the observed quantities. There has been little questioning of the quality of crystals, data collection and
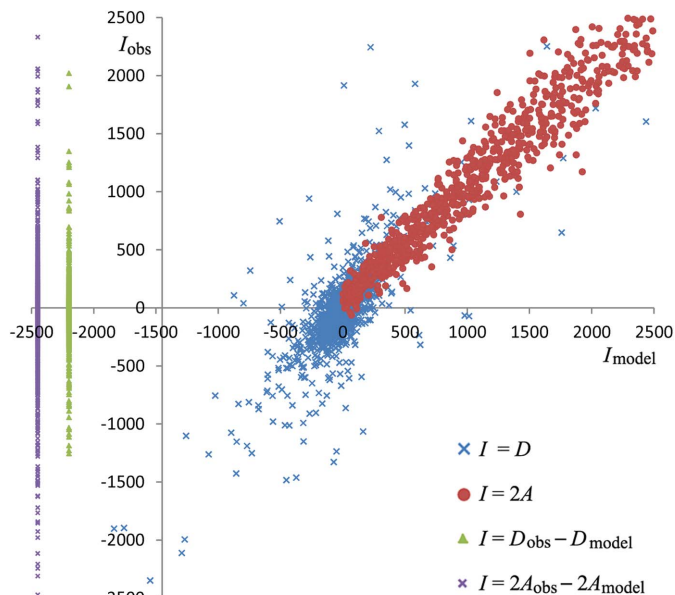

Figure 1

$2AD$ plot of one of the crystal-structure determinations in the virtual issue. This determination shows a good fit of D_{obs} and D_{model}, with $R_A = 5.9\%$, $R_D = 67.2\%$ and $R_{A\text{weak}} = 9.6\%$.

correction methodologies. Clearly, absolute-structure determination is still a rich field, wide open for development, especially for light-atom compounds of great importance to the pharmaceutical and chemical industries.

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