Absolute Structure

Simon Parsons

School of Chemistry and Centre for Science at Extreme Conditions,
The University of Edinburgh, Edinburgh, UK.
S.Parsons@ed.ac.uk

Introduction

The term *absolute configuration*, which is used widely in organic chemistry, refers to the arrangement of atoms in an individual chiral molecule. For example, *'naturally-occurring alanine adopts a structure which has the S configuration at the α-carbon atom'* is a statement about absolute configuration.

Absolute configuration needs to be carefully distinguished from *absolute structure*, which refers to the spatial arrangement of the atoms of a physically identified non-centrosymmetric **crystal** and its description by way of unit-cell dimensions, space group and representative coordinates of all atoms.[1, 2]

Since inverted images of a non-centrosymmetric crystal structure are non-superimposable, the question of absolute structure arises during analysis of any non-centrosymmetric crystal structure regardless of its composition. Although the most important practical application of absolute structure analysis is in the crystallographic determination of the absolute configuration of chiral molecules, the concept is still relevant to those crystals which consist of achiral compounds crystallising in non-centrosymmetric space groups.

Details of the nomenclature used for classification of chiral and achiral crystal structures and the space group restrictions imposed by enantiopurity have been discussed by Flack.[3]

Diffraction Patterns of Crystals with Non-Centrosymmetric Space Groups

Friedel's famous 'law' states that reflections with indices **h** (*i.e.* hkl) and $\mathbf{h}^-$ ($\overline{hkl}$) have the same intensity. If this 'law' held rigorously it would be impossible to distinguish two non-centrosymmetric crystal structures related by inversion. That is, absolute structure determination by X-ray diffraction would be impossible.

The fact that absolute structure can be derived in a crystal structure determination is the result of resonant scattering, also known as anomalous scattering or anomalous dispersion. The effect introduces small differences in intensity between reflections **h** and $\mathbf{h}^-$ in contravention of Friedel's 'law'. These differences carry information on absolute structure, and the larger they are, the more confident we can be in absolute structure assignment. An important feature of experimental absolute structure determination is in finding methods to maximise the effects of dispersion while minimising systematic errors and maintaining atomic resolution.

If dispersion effects are large enough be observable, the point group of a diffraction pattern is the same as the point group related to the space group of the crystal structure. Thus for a crystal structure in the centrosymmetric space group $P2_1/c$, the relevant point group is $2/m$ and reflections hkl, $\overline{h}kl$, $h\overline{k}l$ and $\overline{hk}l$ are all equivalent even if dispersion is substantial. However, if the space group is $P2_1$ the point group is 2 and only the reflections and hkl and $\overline{hk}\overline{l}$ are equivalent; reflections $h\overline{k}l$ and $\overline{h}k\overline{l}$ also form an equivalent pair.

The reflections hkl and $\overline{hk}\overline{l}$ are referred to as a *Friedel pair*. Bijvoet pairs are pairs of reflections which are related to the Friedel pair by symmetry. For example, in point group

2 the Friedel pair is equivalent to hkl and $h\bar{k}l$, and this would be referred to as a *Bijvoet pair*. In practice, however, the two terms *Friedel pair* and *Bijvoet pair* are often used interchangeably. We shall refer to the difference in intensities between reflections hkl and $\overline{hkl}$ (or symmetry equivalents) as a *Bijvoet difference.*

Flack's method of absolute structure refinement

The method for absolute structure determination most commonly used today is based on a formulation first described by Flack,[4] in which the crystal under investigation is considered to be an inversion twin in which the reference domain has the absolute structure of the current refinement model, and the other domain is inverted. Following the methods outlined in the lecture on Twinning, measured intensities are then modelled according to

$$| F_{\text{twin}}(\mathbf{h}) |^2 = (1-x) | F_{\text{single}}(\mathbf{h}) |^2 + x | F_{\text{single}}(\bar{\mathbf{h}}) |^2$$

$|F_{\text{single}}(\mathbf{h})|^2$ and $|F_{\text{single}}(\mathbf{h},\bar{})|^2$ are model quantities based on a single crystal comprised of the reference domain. The two alternative absolute structures can be refined competitively against one another by refining the twin scale factor, x, which in this application is referred to as the *Flack parameter*.

The Flack parameter has a physically meaningful value in the range of 0 to 1, and represents the fraction of the inverted structure present in the crystal. A value of $x = 0$ implies that none of the crystal is in the inverted form and the model has the correct absolute structure; if $x = 1$ then all of the crystal is in the inverted form. Intermediate values of x point to inversion twinning.

The Precision of the Flack Parameter

It is important to interpret the value of the Flack parameter in the context of its standard uncertainty. From a statistical point of view, a value of 0.2(8) has such a large standard uncertainty (0.8) that one neither knows whether the crystal is twinned by inversion or not, nor whether it is inverted or not. Further analysis shows that before any conclusions regarding absolute structure can be made, the standard uncertainty of the Flack parameter should be less than 0.1, even if a material is known to be enantiopure.[5]

The ability to achieve a low standard uncertainty for the Flack parameter depends on the resonant scattering effects having sufficient magnitude to lead to measurable Bijvoet differences. This depends on the chemical elements present in the crystal and the wavelength of the X-rays used to collect the diffraction data. The magnitude of resonant scattering effects in a given experiment can be conveniently quantified by the *FRIEDIF* parameter.[6]

If *FRIEDIF* has a value of about 80 or more, absolute structure determination presents little problem.[7] However, resonant scattering effects for elements such as C, N and O are small in comparison to the non-resonant scattering factors (f) even for Cu $K\alpha$ radiation, making it difficult to determine the Flack parameter with sufficient precision to establish absolute structure for many organic compounds. For example, the value of *FRIEDIF* for the amino acid *L*-alanine with Cu $K\alpha$ radiation is only 34. Accordingly, the value of the Flack parameter obtained from a conventional least squares refinement of *L*-alanine was -0.04(27).[8] The data set was of excellent quality, yielding low merging and refinement residuals, yet the precision of the Flack parameter is too low to enable a definitive statement to be made regarding the absolute structure.[5]

Precise absolute structure determination for light-atom crystal structures

There is a long-standing interest in finding ways to improve the precision of the Flack parameter in light-atom structures. One 'work-around' solution is to form a chemical derivative for which *FRIEDIF* is larger, *e.g.* a heavy-atom derivative, such as a chloride salt. Alternatively, since there is no ambiguity between diastereomers, derivatisation using a group of known absolute configuration fixes the absolute configuration at the asymmetric centre of interest. Nevertheless, it is usually preferable to characterise the absolute structure of a material without going to the trouble of making new derivatives, and two methods which enable this have recently been developed.[9, 10] Both methods have been shown to yield acceptable precision for *x* with data-sets with *FRIEDIF* of 10 or even lower.[11]

A post-refinement Bayesian statistical procedure based on Bijvoet differences has been described by Hooft *et al.*[9, 12] which can be used either to define a probability that a refined absolute structure is correct, or to obtain an estimate of the Flack parameter. The Flack parameter estimated in this way is sometimes referred to as the Hooft parameter and given the symbol *y*. The method depends on assumptions about the random error distribution the Bijvoet differences. According to the central limit theorem, this would be expected to be a Gaussian distribution, and statistical validation procedures usually show that this is a reasonable assumption for data sets derived from well-diffracting crystals measured at low temperature with high redundancy. However, an advantage of the method is that it can readily accommodate other error distributions, such as the Student-*t* distribution, making it applicable to lower quality data.[12] The procedure is available in BIJVOET routine in PLATON.[13]

A procedure used in SHELXL[14] is based on comparison of observed and calculated differences or quotients defined in terms of Friedel pair intensities.[10] For Bijvoet differences, *D*,

$$D_{obs}(\mathbf{h}) = (1-2x)[|F_{single}(\mathbf{h})|^2 - |F_{single}(\bar{\mathbf{h}})|^2] = (1-2x)D_{single}(\mathbf{h})$$

so that a plot of experimentally observed values of $D_{obs}(\mathbf{h})$ in a data set against values of $D_{single}(\mathbf{h})$ calculated from the reference domain of the model should be a straight line which passes through the origin. The gradient of the plot yields *x*. Quotients, *Q*,

$$Q_{obs}(\mathbf{h}) = (1-2x)\frac{|F_{single}(\mathbf{h})|^2 - |F_{single}(\bar{\mathbf{h}})|^2}{|F_{single}(\mathbf{h})|^2 + |F_{single}(\bar{\mathbf{h}})|^2} = (1-2x)Q_{single}(\mathbf{h})$$

can be used in a similar way, their use exemplified for L-alanine in Fig. 1. The quotient method has the advantage that *Q* is independent of scale and, in principle at least, suffers from reduced absorption and extinction effects. Like the Bayesian procedure described above the difference or quotient plots can be applied as a post-refinement procedure, but they can also be incorporated into a refinement so that *x* can correlate with the other parameters of the model.[15] Recent work has shown that iterative reweighting of the straight-line fitting can help to reduce the effect of outliers in lower-quality data-sets.[16]
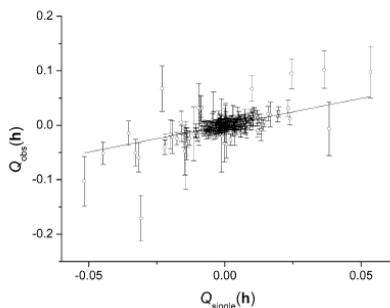
Figure 1. A plot of Q_{obs} against Q_{single} for *L*-alanine. The gradient is 0.95(7) giving x = 0.03(3).

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