The use of X-ray Crystallography to Determine Absolute Configuration (II)

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Dedicated to the memory of Professor Ljubo Golič

Abstract

An update is provided to H. D. Flack and G. Bernardinelli, *Chirality*, **2008**, *20*, 681–690 on *The use of X-ray Crystallography to determine absolute configuration.* In particular, comments are made about optical rotation, powder diffraction, the Bijvoet ratio and intensity measurements for single-crystal X-ray diffractometry.

Keywords: Absolute configuration, absolute structure, crystal structure, resonant scattering, X-ray crystallography

1. Introduction

A recent special issue of the journal *Chirality*[1] deals with the topic of the determination of absolute configuration. All techniques are covered in articles written by internationally acknowledged experts in the field. Flack and Bernardinelli have contributed an article on *The use of X-ray Crystallography to determine absolute configuration*[2]. The article gives essential background on the determination of absolute configuration by way of single-crystal X-ray diffraction and explains in detail: the use and limitations of an internal chiral reference, the physical model underlying the Flack parameter, the definitions of *absolute structure* and *absolute configuration* with their similarities and differences being highlighted, the necessary conditions on the Flack parameter for satisfactory absolute-structure determination, the symmetry and purity conditions for absolute-configuration determination, the physical basis of resonant scattering, the requirements for satisfactory least-squares refinement, the need for right-handed axes, the requirements on intensity measurement and software, crystal-structure evaluation, and errors in crystal structures. Characterization of the compounds and crystals by the physico-chemical measurement of optical rotation, CD spectra, and enantioselective chromatography are presented with some simple and some complex examples of absolute-configuration determination using X-ray diffraction combined with CD or enantioselective chromatography measurements.

2. Comments and Discussion

In this short article the attention of the reader is directed to some information that was not available to us previously and to the applications of some of our own recent work[3,4,5] in this field.

2. 1. Optical Rotation (OR) and Optical Rotatory Dispersion (ORD)

It is stated[2] that measurement of the specific rotation in solution is not feasible for microgram quantities of material (*i.e.* the mass of a typical single crystal used for X-ray diffraction measurements). In fact, modern polarimeters do allow the measurement of the specific rotation of microgram quantities of material in solution. Moreover with the more advanced polarimeters it is also possible to obtain the specific rotation as a function of wavelength in an ORD measurement. Moreover ORD overcomes the difficulty of impurities inherent to the single-wavelength OR technique.

2. 2. Powder Diffraction

No mention was made of the potential use of X-ray powder diffraction for absolute-configuration determination[2]. In principle it is entirely possible to do this by using an internal enantiopure reference group or molecule within the crystal structure but we know of no reported case of such a determination.

As concerns absolute-configuration determination using resonant- scattering effects, this is clearly impossible from a powder. The rings or lines in the powder pattern due to the *hkl* and *–h–k–l* reflections (Friedel opposites) necessarily overlap completely. It is thus only possible at best to obtain a value for the average intensity of each Friedel pair, their difference intensity engendered by resonant scattering being totally obscured by their mutual overlap.

2. 3. Bijvoet Ratio

In the section *Resonant scattering and its effects on the diffraction intensities*[2] we made a preliminary description of the properties and applications of the Bijvoet ratio of a compound, this being formulated as the ratio of the root mean square of the intensity differences between Friedel opposites to that of the mean value of their averages. In practice we use a value called *Friedif* which may be calculated from a knowledge of the chemical composition of the compound and the wavelength of the X-radiation. A spreadsheet application is available for this calculation[5]. We have now completed the analysis of a considerable number of crystal-structure determinations from the literature[5] to establish an empirical relationship between the standard uncertainty of the Flack parameter, *i.e.* the *u* in *x(u)*, and the value of *Friedif*. It was found that *u* is inversely proportional to *Friedif* giving $u = m / Friedif$. *u.Friedif* takes values in the range from 8 to 12 for ordinary crystal structure determinations. Suspect determinations take larger or even very much larger values of *u.Friedif*.

One of the conditions necessary for absolute-configuration determination is that the standard uncertainty *u* on the Flack parameter should be less than 0.04 in the general case and less than 0.1 if the compound has been established to be enantiomerically pure. Using a value $m = 8$ we may translate these *u* values into *Friedif* values. One finds that $u = 0.04$ corresponds to *Friedif* = 200 and $u = 0.1$ corresponds to *Friedif* = 80. We may use these values of *Friedif* in two ways. Prior to experimentation, the value of *Friedif* of the compound to be studied indicates whether an absolute-configuration determination may be achieved. If *Friedif* is smaller than the appropriate limit, one has the choice of using a different radiation, of making a suitable chemical derivative or of making a cocrystal of suitable composition. Following experimentation the value of *u . Friedif* may be calculated and if it is much larger than 10 the structure analysis should be considered to be suspicious and should be examined very carefully indeed.

2. 4. XRD Intensity Measurements

Our examination[5] of ~30 crystal structures published in 2007 in *Acta Crystallographica* **B**, **C** and **E** has revealed several undesirable features in the intensity data presented for these compounds. Firstly we observe that in many cases, although a reasonable number of Friedel opposites have been measured, there are nevertheless a considerable number of acentric reflections for which the Friedel opposites have not been measured. There is no indication in the publications either why a measurement strategy of this nature has been employed or what algorithm is in operation to decide for the acentric reflections which Friedel opposites are to be measured. Secondly it is very frequent indeed that one of the Friedel opposites of a pair is measured with considerably greater precision than the other[5]. Why the measurements should have been undertaken in this way is very far from clear. Further clarification of these unusual choices of measurement strategy needs to be undertaken.

2. 5. Experimental Values of the Flack Parameter

In the section of the above name[2], didactical examples of the interpretation of experimental results from such information as the value of the Flack parameter, the space group, the enantiopurity of the compound, *etc* were given. In view of the comments made above we wish to add a few further examples as follows. Indeed it might well be advisable to include the chemical composition and radiation in more of the published examples2. $x(u) = 0.05(2)$, space group *C2*, enantiomerically-pure bulk compound, x-ray diffraction measurements made on a powder sample: This report is complete rubbish as in a powder diffraction experiment the overlap of the *hkl* and *–h –k –l* reflections obscures the difference in their intensities necessary for determining the Flack parameter.

Can one determine the absolute configuration of D-glucose $C_6H_{12}O_6$ with either Mo*Kα* or Cu*Kα* radiations? The *Friedif* values are 7 and 36 respectively for these two radiations. D-glucose is enantiomerically pure so the appropriate limit on *Friedif* is 80. The value for Mo*Kα* is so much smaller than 80 that an absolute-configuration determination would not be achieved routinely. With Cu*Kα* although 36 < 80 nevertheless by measurement of selected reflections with large calculated Friedel difference intensities perhaps at low temperature it might be possible to achieve an absolute-configuration determination. Otherwise the synthesis of a derivative or the formation of a cocrystal containing a suitable chemical element with a high imaginary resonant-scattering component should be considered.

$x(u) = 0.05(7)$, space group C2 for a compound of composition $C_{35}H_{36}FeO_2P$ measured with Mo*Kα*. *Friedif* for this compound and radiation evaluates to 405. *u. Friedif* = 28 which is far above the normal range of values 8 to 12 which one finds for standard compounds. The crystal-structure analysis needs to be examined very carefully.

2. 6. Explaining Chirality in Molecules and Crystals

Over the past ten years the author has created and continuously improved a short series of lectures on the to-

pic of chirality in molecules and crystals. The lectures are intended for chemists who need instruction in the material of our recent review[2] coupled with other appropriate background information such as the phase diagrams of binary mixtures of enantiomers. In general the lectures cover three sessions of two hours followed by a further section of exercises, and questions and answers.

As part of this lecture course time is taken to expose the very useful classification of crystal structures into the three classes CA (centrosymmetric achiral), NC (non-centrosymmetric chiral and NA (non-centrosymmetric achiral)[6]. Whereas the first two classes, *i.e.* CA and NC, give little difficulty to students and authors, the structural and transformation properties of the NA class are more tricky to communicate and one frequently finds fallacious statements of fact concerning it in the literature (*e.g.* antiwurtzite[7]). The difficulty is that in the NA class a pure rotation is equivalent to inversion in a point *i.e.* one can invert such an object by rotating it. To make the message clear the author has taken to using a pair of children's teddy bears of symmetry *m*. For the demonstration of the NC class the teddy bears are each dressed with a pirate's eye patch, one on the right eye of one teddy bear and one on the left eye of the other. For the demonstration of the NA class, the eye patches are removed.

The following colour photograph shows the author doing this demonstration.

3. In Memoriam

From 1990 to 1994 H. D. Flack was the secretary of the European Crystallographic Committee, an organization which was later to become the European Crystallographic Association. In this capacity he came in close contact with Ljubo Golič during the very difficult situation which developed surrounding the 13th European Crystallographic Meeting. ECM13 was being organized by L. Golič to take place in Ljubljana in August 1991. In the event the painful decision was taken to hold ECM13 in Trieste. Subsequently L. Golič invited H. D. Flack to give a presentation on 'Mastering Least-Squares' at the 5th Slovenian-Croatian Meeting in Zreče in 1996. From these and other contacts I treasure the memory of a very friendly, amusing, efficient and decisive man.

4. References

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Povzetek

V prispevku je dodatek k originalnemu članku H. D. Flacka in G. Bernardinellija, Chirality, 2008, 20, 681–690, ki obravnava uporabo rentgenske difrakcije pri določanju absolutne konfiguracije (The use of X-ray Crystallography to Determine Absolute Configuration). Posebej je dodan komentar o optični rotaciji, praškovni difrakciji, Bijvoetem količniku in o postopku merjenja intenzitet pri rentgenski difrakciji na monokristalih.