

## 1.6. METHODS OF SPACE-GROUP DETERMINATION

## 1.6.2.4. Restrictions on space groups

The values of certain chemical and physical properties of a bulk compound, or its crystals, have implications for the assignment of the space group of a crystal structure. In the chemical domain, notably in proteins and small-molecule natural products, information concerning the enantiomeric purity of the bulk compound or of its individual crystals is most useful. Further, all physical properties of a crystal are limited by the point group of the crystal structure in ways that depend on the individual nature of the physical property.

It is very well established that the crystal structure of an enantiomerically pure compound will be chiral (see Flack, 2003). By an enantiomerically pure compound one means a compound whose molecules are all chiral and all these molecules possess the same chirality. The space group of a chiral crystal structure will only contain the following types of symmetry operation: translations, pure rotations and screw rotations. Inversion in a point, mirror reflection or rotoinversion do not occur in the space group of a chiral crystal structure. Taking all this together means that the crystal structure of an enantiomerically pure compound will show one of 65 space groups (known as the Sohncke space groups), all noncentrosymmetric, containing only translations, rotations and screw rotations. As a consequence, the point group of a chiral crystal structure is limited to the 11 point groups containing only pure rotations (*i.e.* 1, 2, 222, 4, 422, 3, 32, 6, 622, 23 and 432). Particular attention must be paid as to whether a measurement of enantiomeric purity of a compound applies to the bulk material or to the single crystal used for the diffraction experiment. Clearly, a compound whose bulk is enantiomerically pure will produce crystals which are enantiomerically pure. The converse is not necessarily true (*i.e.* enantiomerically pure crystals do not necessarily come from an enantiomerically pure bulk). For example, a bulk compound which is a racemate (*i.e.* an enantiomeric mixture containing 50% each of the opposite enantiomers) may produce either (*a*) crystals of the racemic compound (*i.e.* crystals containing 50% each of the opposite enantiomers) or (*b*) a racemic conglomerate (*i.e.* a mixture of enantiomerically pure crystals in a proportion of 50% of each pure enantiomer) or (*c*) some other rarer crystallization modes. Consequently, as part of a single-crystal structure analysis, it is highly recommended to make a measurement of the enantiomeric purity of the single crystal used for the diffraction experiment.

Much information on methods of establishing the enantiomeric purity of a compound can be found in a special issue of *Chirality* devoted to the determination of absolute configuration (Allenmark *et al.*, 2007). Measurements in the fluid state of optical activity, optical rotatory dispersion (ORD), circular dichroism (CD) and enantioselective chromatography are of prime importance. Many of these are sufficiently sensitive to be applicable not only to the bulk compound but also to the single crystal used for the diffraction experiment taken into solution. CD may also be applied in the solid state.

Many physical properties of a crystalline solid are anisotropic and the symmetry of a physical property of a crystal is limited both by the point-group symmetry of the crystal and by symmetries inherent to the physical property under study. For further information on this topic see Part 1 of Volume D (Authier *et al.*, 2014). Unfortunately, many of these physical properties are intrinsically centrosymmetric, so few of them are of use in distinguishing between the subgroups of a Laue group, a common problem in space-group determination. In Chapter 3.2 of the

present volume, Hahn & Klapper show to which point groups a crystal must belong to be capable of displaying some of the principal physical properties of crystals (Table 3.2.2.1). Measurement of morphology, pyroelectricity, piezoelectricity, second harmonic generation and optical activity of a crystalline sample can be of use.

## 1.6.2.5. Pitfalls in space-group determination

The methods described in Sections 1.6.2 and 1.6.5.1 rely on the crystal measured being a single-domain crystal, *i.e.* it should not be twinned. Nevertheless, some types of twin are easily identified at the measurement stage as they give rise to split reflections. Powerful data-reduction techniques may be applied to data from such crystals to produce a reasonably complete single-domain intensity data set. Consequently, the multi-domain twinned crystals that give rise to difficulties in space-group determination are those for which the reciprocal lattices of the individual domains overlap exactly without generating any splitting of the Bragg reflections. A study of the intensity data from such a crystal may display two anomalies. Firstly, the intensity distribution, as described and analysed in Section 1.6.2.2, will be broader than that of the monodomain crystal. Secondly, one may obtain a set of conditions for reflections that does not correspond to any entry in Section 1.6.4. In this chapter we give no further information on the determination of the space group for such twinned crystals. For further information on this topic see Part 3 of Volume D (Boček *et al.*, 2006) and Chapter 1.3 on twinning in Volume C (Koch, 2006). A supplement (Flack, 2015) to the current section deals with the determination of the space group from twinned crystals and those displaying a specialized metric. However, it is apposite to note that the existence of twins with overlapping reciprocal lattices can be identified by recording atomic resolution transmission electron-microscope images.

In order to obtain reliable results from space-group determination, the coverage of the reciprocal space by the intensity measurements should be as complete as possible. One should attempt to attain full-sphere data coverage, *i.e.* a complete set of intensity measurements in the point group 1. All Friedel opposites should be measured. The validity and reliability of the intensity statistics described in Section 1.6.2.2 rest on a full coverage of reciprocal lattice. Any systematic omission by resolution, azimuth and declination, intensity *etc.* of part of the asymmetric region of the reciprocal lattice has an adverse effect. In particular, reflections of weak intensity should not be omitted or deleted.

There are a few other common difficulties in space-group determination due either to the nature of the crystal or the experimental setup:

- The crystal may display a pseudo-periodicity leading to systematic series of weak or very weak reflections that can be mistaken for systematic absences.
- The physical effect of multiple reflections can lead to diffraction intensity appearing at the place of systematic absences. However, the shape of these multiple-reflection intensities is usually much sharper than a normal Bragg reflection.
- Contamination of the incident radiation by a  $\lambda/2$  component may also cause intensity due to the  $2h\ 2k\ 2l$  reflection to appear at the place of the  $hkl$  one. Kirschbaum *et al.* (1997) and Macchi *et al.* (1998) have studied this problem and describe ways of circumventing it.