

## Chiral and Achiral Crystal Structures

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Dedicated to Professor *Jack D. Dunitz* on the occasion of his 80th birthday

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An extensive study and analysis of the concepts, classification, presentation, and nomenclature of chirality and lack of chirality in crystal structures and their constituents is presented. Oriented crystal structures are classified. The chirality rules for existence of molecular crystal structures are examined and the relation to segmentation and latent symmetry highlighted. The nomenclature of chirality and related terms, and the relationship of chirality to optical activity is covered. The uses and limitations of the Euclidean normalizer are treated. An improved glossary of terms is included.

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**1. Introduction.** – In dealing with chirality in relation to crystal structures it is essential to distinguish between three different objects that may be either chiral or achiral. These three are 1) the molecular components of the crystal, 2) the crystal structure itself and 3) the symmetry group of the crystal structure, *viz.*, its space group. The interrelationship between these chiral or achiral objects is the main theme of this paper. Some consideration will also be given to physical properties and nomenclature in their relationship to chirality. An improved glossary of appropriate terms is presented in *Appendix A*.

Whether an object is chiral or achiral depends on its symmetry group. Restricting all considerations in this paper to three-dimensional physical space (but see *Sect. 4.1*), the symmetry group of a chiral object contains symmetry operations of only the first kind (*viz.*, rotations and translations) and none of the second kind (*viz.*, roto-inversions), whereas that of an achiral object contains symmetry operations of both kinds in equal numbers. These statements are formalized and proven below. The symmetry group of a molecule is its point group, that of a crystal structure is its space group, and that of a space group is its Euclidean normalizer [1].

The origin of the distinction of enantiomorphs is physical. Rigid-body motions of an object are isometries of the first kind. The interconversion of an object between enantiomorphs requires an isometry of the second kind, but there is no corresponding physical action for a rigid body. Although the energies of the enantiomorphs are identical, the energy barrier to interconversion is excessive for a rigid body. In the presence of parity violation mitigated through the weak neutral current, an energy difference between the two enantiomorphs appears but this is many orders of magnitude ( $10^{-17}$ ) smaller than  $kT$  at room temperature. Differences in the activation energies for forward and backward enantiomerisation reactions are possible, even when the energies of the end states are identical [2–4].

Molecules and crystals may be present in the form of mixtures. Enantiomeric mixtures of particular importance are those of compositions 100:0% and 0:100%, described as enantiomerically pure, and the equimolar one of 50:50% described as a racemate or as being racemic. By definition, all the molecules in an enantiomeric mixture, be it enantiomerically pure, racemic, or of intermediate composition, are chiral. With regard to crystals, the special name *racemic conglomerate* is given to the crop of crystals grown under equilibrium conditions from a racemate undergoing spontaneous resolution. This solid-state mixture is characterised as having individual crystals that are enantiomerically pure, but where the overall molecular composition of the crop is that of a racemate. A 50:50% mixture of crystals of D- and L-NaClO<sub>3</sub> (cubic  $P2_13$ ) is not a racemic conglomerate. The ClO<sub>3</sub><sup>-</sup> anion is achiral (pyramidal, symmetry:  $3m, C_{3v}$ ) and the enantiomorphic composition of a crop of NaClO<sub>3</sub> crystals is not dictated by the molecular enantiomer composition of the bulk from which the crystals are grown. Crystal growth and phase transitions may lead to multidomain samples known as twins. These may be thought of as a special kind of agglomerated mixture in which the translation lattice (or a sublattice) is (approximately) invariant throughout the whole sample, but where the crystal structure takes an integral number of different orientations with respect to the lattice.

The chirality sense of a molecule is specified by its absolute configuration. The chirality sense of a chiral crystal structure is specified by its absolute structure, but the later term has a wider definition than the mere distinction of enantiomorphs (see below, [5–7]). Once again, the origin of this dichotomy of definitions is physical. Many experiments on molecules are undertaken under conditions where they are free to rotate and are detected in arbitrary orientations. Consequently, orientation is hidden for molecules, and only enantiomers can be distinguished. Crystals are studied as oriented single crystals where they are detected in controlled orientations, leading, as a side product, to the distinction of enantiomorphs if the crystal is chiral.

**2. Classification of Oriented Crystal Structures.** – Consider the effect of inversion through a point on an oriented single crystal and its oriented crystal structure. Let  $X$  represent the oriented crystal structure. Inversion through a point  $\bar{1}$  generates the oriented inverted crystal structure  $\bar{X} = \bar{1} X$ . Let the point symmetry group of  $X$  be  $P$ . Then  $X =_p X$  for all  $p \in P$ . It is easy to show that  $P$  is composed of symmetry operations, which are either all of the first kind, or one half are of the first kind and the other half are of the second kind. The product of two symmetry operations of the same or opposite kind gives a symmetry operation of the first or second kind respectively. Clearly  $\bar{X} = \bar{1} X = \bar{1} p X$  for  $p \in P$  so the coset  $\bar{1} P$  contains all of those isometries equivalent to the inversion that transform  $X$  into  $\bar{X}$ . The coset  $\bar{1} P$  is composed of symmetry operations that are either entirely of the second kind, when  $P$  contains only those of the first kind, or half each of the first and second kinds, when  $P$  contains symmetry operations of both kinds. The properties of the transformation  $X \rightarrow \bar{X}$  will now be classified according to chirality and centrosymmetry.

Suppose that  $X$  is achiral. It follows by definition (see *Appendix A*) that there exists an isometry  $f$  of the first kind such that  $\bar{X} = fX$ . So  $\bar{X} = \bar{1} X = fX = f p X$  for  $p \in P$ . Multiplying by  $\bar{1}$  one obtains  $X = \bar{1} f p X$  and so  $\bar{1} f p \in P$ . For argument, assume that  $P$  contains only symmetry operations of the first kind. Then as  $f$  and  $p$  are of the first kind

and  $\bar{1}$  of the second kind, so  $\bar{1}fp \in P$  must be of the second kind in contradiction to the hypothesis that  $P$  contains only symmetry operations of the first kind. Thus,  $P$  contains symmetry operations of the second kind, and the symmetry group of an achiral crystal structure contains symmetry operations of the second kind. Conversely, let the symmetry group  $P$  of  $X$  contain symmetry operations of the second kind  $s$  for  $s \in P$ . One may always write  $s = f\bar{1}$  where  $f$  is of the first kind. So,  $X = sX = f\bar{1}X = f\bar{X}$ .  $X$  is achiral as  $X$  and  $\bar{X}$  may be superimposed by a pure rotation. So, the symmetry group of an oriented achiral crystal structure contains symmetry operations of the second kind, and, conversely, an oriented crystal structure whose symmetry group contains symmetry operations of the second kind is achiral. By exclusion, since crystal structures are either chiral or achiral, and symmetry groups are composed either entirely of operations of the first kind or of equal numbers of the first and second kinds, the symmetry group of a chiral crystal structure contains only symmetry operations of the first kind and, conversely, a crystal structure whose symmetry group contains only symmetry operations of the first kind is chiral.

Suppose that  $X$  is centrosymmetric, so  $\bar{1} \in P$ . It follows that  $\bar{X} = \bar{1}X = X$  since  $X = pX$  for  $p \in P$ . The oriented crystal structure and its inverse are identical and, hence, achiral. Conversely, if  $\bar{X} = X$ , then  $\bar{X} = \bar{1}X = X$  and  $\bar{1} \in P$ . The crystal structure is centrosymmetric. So, if  $X$  is centrosymmetric, then  $\bar{X}$  and  $X$  are identical, and, conversely, if  $\bar{X}$  and  $X$  are identical, then  $X$  is centrosymmetric. By exclusion, one sees that if  $X$  is non-centrosymmetric, then  $\bar{X}$  and  $X$  are not identical, and, conversely, if  $\bar{X}$  and  $X$  are not identical, then  $X$  is non-centrosymmetric.

Oriented crystal structures  $X$  are usefully classified into three crystal-structure types NA, NC, CA as follows, each of which is illustrated by an example for a crystal structure in the orthorhombic crystal system:

*Crystal-Structure Type NA.* The non-centrosymmetric achiral crystal-structure type in which the point symmetry group  $P$  of  $X$  contains symmetry operations of the second kind.  $\bar{X}$  and  $X$  are not identical but may be brought into coincidence by a pure rotation taken from the coset  $\bar{1}P$ . Clearly  $X$  and  $\bar{X}$  are not enantiomorphs. Crystal structures in the point group  $mm2$  are an illustration of this type. An oriented crystal structure and its image produced by inversion through a point are not enantiomorphs and may be brought into coincidence by the equivalent operations  $\bar{1}$ ,  $2_x$ ,  $2_y$ , or  $m_z$ , two of which are pure rotations by  $\pi$  and the other two are roto-inversions, *viz.*, inversion through a point and reflection in a plane.

*Crystal-Structure Type NC.* The non-centrosymmetric chiral crystal-structure type for which the point symmetry group  $P$  of  $X$  contains only symmetry operations of the first kind.  $\bar{X}$  and  $X$  are not identical and may not be brought into coincidence by a pure rotation.  $X$  and  $\bar{X}$  are enantiomorphs. Crystal structures in the point group  $222$  are an illustration of this type. An oriented crystal structure and its image produced by inversion through a point are enantiomorphs and may be brought into coincidence by the equivalent operations  $\bar{1}$ ,  $m_x$ ,  $m_y$ , or  $m_z$ , all of which are roto-inversions *viz.*, inversion through a point and reflections in three mutually perpendicular planes.

*Crystal-Structure Type CA.* The centrosymmetric achiral crystal-structure type where  $\bar{X} = X$ . Clearly,  $X$  and  $\bar{X}$  are not enantiomorphs. Crystal structures in the point group  $mmm$  are an illustration of this type. An oriented crystal structure and its image produced by inversion through a point are identical.

X-Ray-diffraction measurements on single crystals are treated by way of the *Flack* parameter [8] (see also [5][6][9–11]). The macroscopic crystal  $C$  is treated as a mixture of an oriented crystal structure  $X$  and its inverted structure  $\bar{X}$  in variable proportion defined by  $C = (1 - x) X + x \bar{X}$ . In non-centrosymmetric crystal structures (types NA and NC),  $x$  describes the proportions of the oriented crystal structures  $X$  and  $\bar{X}$  in the sample. When the crystal structure is non-centrosymmetric and achiral (type NA),  $x$  describes the proportions of two inversion-related orientations of the crystal structure whose relationship may also be described by a rotation. When the crystal structure is chiral (type NC),  $x$  measures the proportion of the two enantiomorphs present in the sample. For a multi-domain twin of a chiral crystal structure (type NC), *Flack* and *Bernardinelli* [5] show how to calculate an equivalent *Flack* parameter. For centrosymmetric crystal structures (type CA),  $X = \bar{X}$  and the *Flack* parameter  $x$  is undefined.

**3. Molecular Crystal Structures.** – The upper part of *Table 1* tabulates the collation of observations of *Jacques et al.* [12] concerning the existence of chiral and achiral crystal structures formed of chiral (enantiomerically pure or racemate) or achiral molecules. The lower part of *Table 1* deals with non-racemic enantiomeric mixtures. *Jacques et al.* [12] do not provide collated information on the latter, of which presumably few have been reported in the literature. Applying the reasoning developed below in this section, we come to the conclusion that, for non-racemic enantiomeric mixtures, chiral crystal structures should be permitted whereas achiral crystal structures should be forbidden, thus following the same rules as in the enantiomerically pure case. In the upper part of *Table 1*, every possible combination except one has been observed in practice. These include the counter-intuitive case of a chiral crystal structure formed from a racemate. In this case, supposing, for example, the molecule to be rigid, an isometry must relate the two enantiomers of opposite chirality, but this isometry is not part of the symmetry operations of the space group but rather a ‘local’ or ‘pseudo-symmetry’ operation. It is thought that *ca.* 50 of these chiral crystal structures of racemates are known at present from 250000 structures in the CSD, although it is not possible to give an authoritative and citable reference for this number. For various technical reasons associated with nomenclature and self-consistency, a direct search on the CSD does not produce reliable results, and one must critically consult the primary literature to identify those racemates with chiral crystal structures (see, *e.g.*, [13]).

Table 1. *Restrictions on the Formation of Chiral and Achiral Crystal Structures from Chiral or Achiral Molecules.* Numerous examples are given in [12][63].

	Achiral crystal structure	Chiral crystal structure
Achiral molecules	Permitted	Permitted
Chiral molecules – enantiomerically pure	Forbidden	Permitted
Chiral molecules – racemate	Permitted	Permitted
Chiral molecules – non-racemic mixture (enantiomeric mixture)	See text	See text

The one forbidden case in the upper part of *Table 1* is that of an achiral crystal structure formed from enantiomerically pure chiral molecules. It follows that all known

crystal structures formed from enantiomerically pure chiral molecules are chiral. *Jacques et al.* [12] offer no explanation for this observation, but a commonly formulated proof, based entirely on considerations of symmetry, runs as follows. In an achiral crystal structure, symmetry operations of the second kind are in action. When these operate intramolecularly, the molecules are achiral, whereas, when they operate intermolecularly, a racemate is present. An achiral crystal structure is, thus, formed either from achiral molecules or from a racemate but never from enantiomerically pure chiral molecules. Consequently, the latter must form a chiral crystal structure. We now investigate this observation and proof in more detail in an attempt to uncover its true nature. This is carried out first with a visual illustration and then with a more technical example. The illustration is inspired from *La Coupe du Roi* [14], which is a neat way of cutting an apple into two identical chiral halves. Consider building up an apple crystal structure from an enantiomerically pure load of identical chiral apple halves. Pairs of apple halves are assembled to form complete achiral apples (it is assumed that the interior boundaries of the apple between the half apples disappear as they stick together), and these complete achiral apples are then arranged with a cubic close packing to form an achiral apple crystal structure. We have, thus, managed to construct an achiral crystal structure out of an enantiomerically pure load of chiral entities. On the other hand, *Jacques et al.* [12] do not find achiral crystal structures formed by crystallization of enantiomerically pure chiral molecules.

*Figure.a* shows the representation in projection of two identical chiral sets each of four points [15]. Each four-point set has point symmetry 2, the three nearest-neighbour distances are equal, and the three angles, two nearest-neighbour and one torsion, are  $90^\circ$ . The two four-point sets are so placed that the point symmetry of the combined set of eight points is 2 and they are allowed to approach each other (*Fig.,b*), until at one particular position (*Fig.,c*), the point symmetry of the ensemble jumps up to  $m\bar{3}m$ , making the combined set of eight points achiral. The essential difference between the four-point-set objects and real molecules is in their interaction. In the special high-symmetry arrangement, the points of the four-point-set objects have approached each other to distances identical to the intraset ones. This leads to a singular change in symmetry. However, if these points are now taken to represent atoms in a molecule, one would say that the two molecules have reacted to form a compound molecule whose symmetry and chirality is quite different from that of the reactants. According to the usual procedure, a crystal pattern derived from these interacting molecular reactants would be described as that of the compound molecule rather than that of the reactants. Real molecules are identified by the distinct differences in intra- and intermolecular geometries they display. A molecule has its own identity and interacts only weakly with its neighbours. Moreover, it is not customary to describe real crystal structures as being composed of partial molecules obtained by the arbitrary and imaginary segmentation of real molecules. The origin of the restriction described by *Jacques et al.* [12] is physical and chemical, not symmetrical. For completeness, in *Appendix B* is a comparison presented point by point of experimental observations on molecular crystal structures collated principally by *Jacques et al.* [12], and the conclusions of the molecular segmentation theory of *Anet et al.* [14].

Such sudden jumps in symmetry as occur in the above examples are known in related problems in comprehending the domain structure of crystals caused by phase

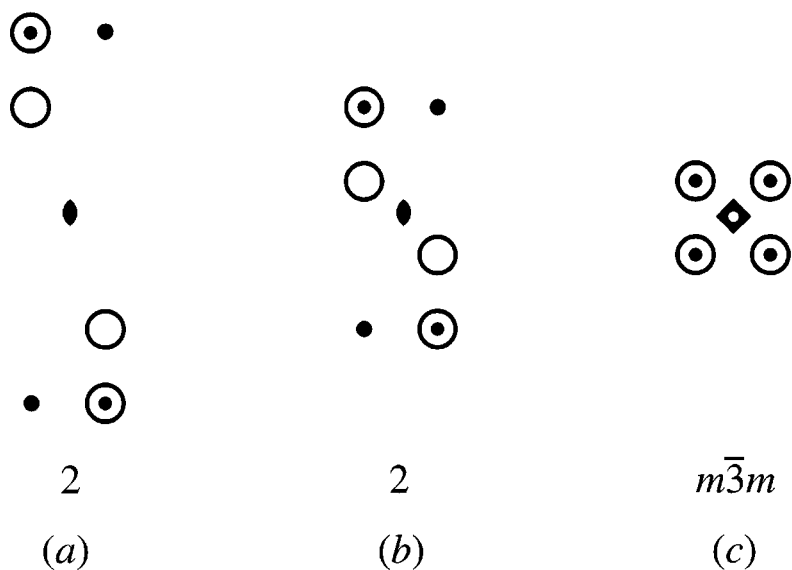


Fig. 1. A representation in projection of two four-point-set objects of individual symmetry 2 forming an eight-point-set object of symmetry 2 in a) and b), and  $m\bar{3}m$  in c). The points marked by a dot are above and those marked by an open circle below the plane of the figure. Within each four-point set the three nearest-neighbour distances are equal, and the three angles, two nearest-neighbour and one torsion, are  $90^\circ$ .

transitions. Under the name of *latent symmetry*, Litvin and Wadhawan [16] used modulo-normalizers in the study of a composite object formed of basic units that can be further subdivided into subunits. This approach predicts some but not all of the symmetries of the composite object. In a following paper, Litvin and Wadhawan [17] then derived a sufficient condition that an isometry is a symmetry of a composite. However, the condition is not necessary, and the theorem has no general converse.

The example cited above for searching the CSD for chiral crystal structures of racemates draws our attention to the importance of correctly naming molecular compounds in reporting their crystal structures. Specific nomenclatures (see *Appendix A*) exist for naming enantiomerically pure compounds of known absolute configuration, enantiomerically pure compounds of unknown absolute configuration or relative configuration, and racemates. Moreover, the name to be given is that of the molecular compound in the crystal structure and not that in the bulk from which it was crystallized. The molecular enantiomer composition of the liquid and crystalline phases may well be different.

**4. Nomenclature.** – Towards the end of the 19th century, there was a great deal of work on the properties and characterisation of mixtures of enantiomers in the solid and liquid states [12][18–20]. Inevitably, terms were invented before the phenomena were fully understood. This has led to the use of some clearly unsuitable terms being used commonly even to this day. In the subsections below we give examples that are of relevance to crystallography with suggestions for improved terminology.

A persistent idea of the scientists of the end of the 19th century who were studying enantiomorphs and racemates was the notion that crystallization of an equimolar mixture of opposite enantiomers to form an homogeneous structure necessarily involved compound formation or association (e.g., [18][20]). In this view, this equimolar mixture was a compound, a *racemic compound*. The current view is, of course, that the forces controlling intermolecular packing of an enantiomerically pure sample are very similar to those at work in the equimolar mixture of enantiomers (see, e.g., Brock *et al.* [21] on *Liebisch's Law* [22]). What is nowadays known as a racemic conglomerate [23], Kipping and Pope [18] called an *externally compensated mixture of non-racemic molecules*. Wisely, in modern-day parlance, racemic and racemate refer to an equimolar mixture of opposite enantiomers rather than to any notion of some specific interaction between opposite enantiomers. The term racemate applies only to the equimolar mixture of opposite enantiomers. Mixtures in other proportions are referred to as *enantiomeric mixtures* (see [24–26]).

The classical analysis of the phase equilibria of binary mixtures of enantiomers was written in 1899 by Roozeboom [27] and is treated in detail, together with that of ternary systems, in Jacques *et al.* [12]. Coquerel [28] has published an authoritative modern review on the heterogeneous equilibria between condensed phases in binary systems of enantiomers, presenting many possible phase diagrams. Unfortunately a review of ternary phases is not yet available. Of interest in the current context is the marked similarity between some of the phase diagrams near to the racemic composition in situations where, on the one hand, one has the formation of an homogeneous phase of the racemate (racemic compound) that is miscible with the pure enantiomers, and, on the other hand, no homogeneous phase of the racemate is formed although the enantiomers mix to form solid solutions. Consequently the topology and topography of the phase diagram, if available, may not be a reliable guide to crystal structure. In particular, a maximum in the liquidus curve at the racemic composition should not be taken to indicate an ordered crystal structure. One also notes that Coquerel [28] does not qualify the phase transitions between the homogeneous phase of the racemate (racemic compound) and the racemic conglomerate as polymorphic in the manner of Jacques *et al.* [12] but uses the terms *eutectoid* and *peritectoid*.

4.1 *Chirality*. Throughout this paper we have used a geometric definition of chirality, derived from the classical one of Lord Kelvin [29] as given in the *Basic Terminology of Stereochemistry* [23], but which is based on inversion through a point followed by an arbitrary pure rotation and translation rather than mirror reflection. This definition is entirely satisfactory for the needs of three-dimensional stereochemistry and crystal chemistry. The choice of inversion through a point rather than mirror reflection is guided by the special importance of the inversion operation in crystallography and its commutative properties. The equivalence of these two descriptions of chirality may be readily established. Let  $Rm$  represent a mirror reflection  $m$  followed by an arbitrary pure rotation  $R$ . As  $m = 2 \bar{1}$ , where 2 is a rotation of  $\pi$  about the normal to the mirror plane and  $\bar{1}$  represents the operation of inversion through a point, one obtains  $Rm = R 2 \bar{1} = S \bar{1}$  where  $S$  is a pure rotation. This establishes the required equivalence. In general, mirror reflection and inversion through a point are not equivalent for oriented objects where the arbitrary pure rotations are not permitted. The entire treatment in this paper is limited to three-dimensional structures, because inversion is important in

the definition, and needs to be an isometry of the second kind and have a determinant of  $-1$ . In spaces of even dimension, the inversion is an isometry of the first kind. Enantiomorphism occurs also in two-, four-, and higher-dimensional spaces.

In situations where one is dealing with electric and magnetic fields interacting with bodies in motion, the geometric definition of chirality is unsatisfactory. Moreover the fine effects of the nucleus have also to be taken into account. The approach taken is to consider the invariance of the laws of nature under certain very general transformations. To a very good degree of approximation, it is known that these are invariant under the transformations C, P, and T, where C stands for charge conjugation (changing a particle into its antimatter particle of opposite electric charge), P for parity (space inversion or inversion through a point), and T for time reversal (reversal of the directions of motion). Currently it is known that P and C can be independently violated under very special conditions but, as yet, no case of CPT violation has been observed. One of the major objectives of the production of cold anti-hydrogen at CERN is to allow comparison of the fine atomic spectra of hydrogen and anti-hydrogen in a search for CPT violation. Very clear presentations of how chirality should be dealt with in these situations are to be found in the works of *Barron* [2–4], where one finds the following new definition of chirality: ‘*True chirality is exhibited by systems that exist in two distinct enantiomorphic states that are interconverted by space inversion but not by time reversal combined with any proper spatial rotation.*’

4.2 *Racemic Compound and Anomalous Racemates.* What is dubbed [21] a racemic compound is an ordered crystal structure of a racemate. This crystal structure can be either chiral or achiral, and may be arranged in any one of the 230 space-group types. In place of *racemic compound*, it would be clearer to call this arrangement, in full, an *ordered racemic crystal structure*, or in short, a *racemic structure*. A few cases are known where the composition of an ordered crystal structure is that of a mixture of enantiomers in rational proportions other than the 1:1 of the racemate. These have been called anomalous racemates [12], a choice of name that makes it difficult to distinguish them from pseudoracemates and quasiracemates. Perhaps it would be clearer to use, in full, an *M:N mixed enantiomeric crystal structure* or, in short, an *M:N enantiomeric structure*, where *M* and *N* are integers giving the proportion of the two enantiomers. Such nomenclature fits in nicely with the existing IUPAC system for naming racemates, e.g., for an *M:N* enantiomeric mixture of (2*R*,3*R*)- and (2*S*,3*S*)-tartrate ions one would write {*M:N*} (2*RS*,3*RS*)-tartrate. An extension of this system even allows the naming of mixtures of diastereoisomers, e.g., {*M:N:L*} (2*RSR*, 3*RSS*)-tartrate names a mixture containing proportions *M* of (2*R*,3*R*)-tartrate, *N* of (2*S*,3*S*) tartrate, and *L* of (2*R*,3*S*) tartrate (*meso*-tartrate).

4.3. *Pseudoracemate.* *Kipping* and *Pope* [18] identified crystalline solids of equimolar proportions of enantiomers that were clearly different from those of the corresponding ordered racemic crystal structures. They called them *pseudoracemates*. *Kipping* and *Pope*'s [18] physical model of these solids was that of multi-domain crystals where individual domains are enantiomerically pure and the crystal is twinned by inversion. This ingenious proposition, drawn on their considerable knowledge of classical crystallography, but limited by the state of science at the time, is, unfortunately, wrong. What they had identified turned out to be crystals of a solid solution of enantiomers in which any molecular location in the crystal structure may happily be



occupied by either enantiomer. A suitable name would, thus, be a *disordered racemic (crystal) structure*, but an essential characteristic of these solid solutions is the wide range of compositions over which the structure occurs. Consequently, it seems unnecessary to have a specific name for the racemate and the generic name *disordered mixed enantiomeric (crystal) structure* would have more-general application. To specify the structure, one needs to indicate the composition(s) at which a structure analysis has been undertaken and the composition range of the phase at a given temperature.

4.4. *Racemic Twinning*. No definition of *racemic twinning* is to be found in the literature, although the term is widely used. Like the term *data mining*, recently criticised by Allen [30], *racemic twinning* is semantically questionable. Its meaning cannot easily be construed from its component words, one of which, 'racemic', refers to the fixed molecular composition of the crystal and the other, 'twinning', to the existence of variously orientated homogeneous domains within the crystal. So the term specifies the molecular composition of the crystal but does not specify the orientational relationship between the domains. Since it is known that racemates may crystallize in any one of the 230 space groups, there seems to be no restriction on space group for the incidence of *racemic twinning*, so that it may occur in crystals with either a centrosymmetric or a non-centrosymmetric structure. On the other hand, *racemic twinning* cannot occur in NaClO<sub>3</sub>, which, although it has a chiral crystal structure, is composed of achiral molecules and is not a racemate. Even if an extended interpretation of 'racemic' to objects of larger scale than molecules, such as domains, were to be allowed, one still has to accept the implicit fixed proportions of the chiral domains. For these reasons, we have never used the term *racemic twinning* and thoroughly discourage its use. On the other hand, in our contributions to the study of non-centrosymmetric crystals, we have found the term *twinning by inversion*, defined in *Appendix A*, to be both clear and useful.

4.5. *Fixing the Enantiomorph*. In direct methods of structure solution, a few phases may be forced to take a restricted range of values for what are called, according to the tradition of the literature on direct methods, *fixing the origin* and *fixing the enantiomorph* [31][32]. While the process of restricting a single phase to *fix the enantiomorph* is not applicable to centrosymmetric crystal structures, neither is it restricted only to chiral crystal structures (crystal-structure type NC) [1]. For all non-centrosymmetric achiral crystal structures (crystal-structure type NA), one has also to *fix the enantiomorph*, although the choice is not one of choosing an enantiomorph but, in fact, of choosing between two inversion-related orientations. To make matters even more complicated, for structures with a chiral space group, the process of *fixing the enantiomorph* is determined not by restricting a phase but by choosing one of two enantiomorphically-related space groups. All in all, it seems that what is called *fixing the enantiomorph* would be better called *fixing the absolute structure*. Authors of publications dealing with the experimental determination of triplet phases by multiple-beam X-ray diffraction have also used the term enantiomorph in the manner of the direct-methods literature [33–36] but, more recently, use also the term absolute structure [37].

4.6. *Optical Activity*. There is no one-to-one correspondence between optical activity and chirality. The situation concerning natural optical activity (see Table 10.2.1.1 of Hahn and Klapper [38], and Barron [39]) can be seen by examination of

*Table 2.* The natural optical rotation observable is a time-even pseudoscalar [4]. It was well known to *Faraday* and *Lord Kelvin*, but perhaps not to *Pasteur*, that magnetic optical rotation (*Faraday* rotation) is not chiral, as the magnetic optical rotation observable is a time-odd axial vector. Natural optical activity (see [40] for a comprehensive review of optical-activity measurements on crystals) has, indeed, been observed in particular achiral single crystals belonging to the four geometric crystal classes listed in *Table 2*: in class *m*,  $\text{LiH}_3(\text{SeO}_3)_2$  [41] and  $\text{K}_2\text{ZnCl}_4$  [43]; in class *mm2*,  $\text{KTiOPO}_4$ ,  $(\text{NH}_3(\text{CH}_3))_5\text{Bi}_2\text{Br}_{11}$  [44],  $\text{NaNO}_2$  [42]; in class  $\bar{4}$ ,  $\text{CdGa}_2\text{S}_4$  [45]; in class  $\bar{4}2m$ ,  $\text{NH}_4\text{H}_2\text{PO}_4$  [46] and  $\text{AgGaS}_2$  [47–49]. Molecules with symmetries *m*, *mm2*,  $\bar{4}$ , and  $\bar{4}2m$  do not show optical activity in solution since directions within the molecule occur in enantiomorphic pairs with optical activities of equal magnitude but opposite sign, and thermal tumbling of the molecules ensures a spatial and temporal average of zero. In much the same way, albeit with the individual directions of enantiomorphic pairs residing in opposite enantiomers, a racemate in solution does not show optical activity.

*Table 2. Restrictions on Natural Optical Activity for Crystals and Molecules both Chiral and Achiral.* The row title qualifies the column titles.

	Single crystal	Molecules in solution or as liquid
Achiral	Permitted only in <i>m</i> , <i>mm2</i> , $\bar{4}$ , $\bar{4}2m$	Forbidden
Chiral	Permitted	Enantiopure: Permitted
		Racemate: Forbidden
		Non-racemic mixture: (enantiomeric mixture) Permitted

A partial examination of *Table 2* limited to molecules in solution, these being enantiomerically pure when chiral, leads to a false one-to-one correspondence between chirality and optical activity as a potential source of confusion. Thus, the 1930 edition of the *Oxford English Dictionary* contained a definition of chirality that identified it with optical activity. *Whyte* [50][51] made a very strong case in opposition to this usage, and subsequent versions of the *Oxford English Dictionary* define chirality in the way of *Lord Kelvin* [29]. *Barron* [4] is able to state ‘... that the hallmark of a chiral system is that it can support time-even pseudoscalar observables’. Isotropic natural optical rotation is such an observable, but anisotropic optical rotation from achiral crystals is not. One should, thus, be aware that *Glazer* and *Stadnicka* [52], in their classification of physical properties of crystals and directions within a crystal, have implicitly chosen to retain the 1930 *Oxford English Dictionary* definition identifying chirality with optical activity and chiral with optically active. With this choice of definition, they come to identify ‘absolute chirality’ as being permissible for crystals in the geometric crystal classes *m*, *mm2*,  $\bar{4}$ , and  $\bar{4}2m$ .

**5. Chiral and Achiral Space Groups.** – *Many objects of our three-dimensional perceptual world are not only chiral but appear in nature in two versions, related at least ideally, as a chiral object and its mirror image. Such objects are called enantiomorphous, or simply enantiomorphs* [53]. The eleven pairs of enantiomorphous space groups [54]

are a familiar set containing the 22 chiral space groups. Within each pair, inversion through a point transforms one space group into the other, *e.g.*,  $P6_1$  transforms into  $P6_5$  and *vice versa*. These 22 space groups are the only ones of the 230 that are chiral. All of the other 208 are achiral. For example, inversion through a point transforms space group  $P2_1$  into  $P2_1$  itself. Space group  $P2_1$  is, thus, achiral. Let us be clear: a crystal structure in space group  $P2_1$  is chiral but the space group itself is achiral since it does not form one member of an enantiomorphous pair. This point was overlooked by many authors of contributions to the field of small-molecule crystallography and, more recently, crystal engineering, who used expressions such as ‘chiral space group’ to mean the space group of a chiral crystal structure or ‘structures in a chiral space group’ to mean chiral crystal structures.

As a consequence of the above clarification of the term ‘chiral space group’, one is confronted with the problem of giving a suitable name to the class of those space groups that are compatible with chiral crystal structures. There are 65 such space groups and these contain only symmetry operations of the first kind. It is of relevance to note that, in his very early development of space groups, predating those of *Schoenflies* and *Fedorov, Sohncke* (1879) correctly derived the 65 containing only symmetry operations of the first kind since he did not consider isometries of the second kind to be symmetry operations [55][56]. One may, thus, refer to the *Sohncke* space group (type)s as the class of the 65 containing only symmetry operations of the first kind.

5.1. *Symmetry Elements and Their Graphical Representation.* The methodology that has been used above for space groups may also be applied to isolated symmetry operations and their representative symmetry elements [57–59]. On inversion, a screw rotation  $N_m$  is transformed into a screw rotation  $N_n$ , where  $m + n = N$ . Consequently the following four pairs of enantiomorphic screw rotations exist:  $\{3_1, 3_2\}$ ,  $\{4_1, 4_3\}$ ,  $\{6_1, 6_5\}$ , and  $\{6_2, 6_4\}$ , and each of these eight screw rotations is chiral. The three screw rotations  $2_1$ ,  $4_2$ , and  $6_3$  are invariant on transformation by inversion and do not fall into enantiomorphic pairs. Clearly  $2_1$ ,  $4_2$ , and  $6_3$  are achiral, although an atomic distribution around any one of these eleven isolated screw axes is chiral. In the *International Tables for Crystallography*, Vol. A [60], the three achiral screw rotations are described as ‘neutral’, but the term is not used elsewhere in the literature.

When one holds the symmetry-element diagram of space group  $P6_1$  as drawn in [60] up to a mirror one observes that the graphical symbol for the  $6_1$  symmetry element has been transformed into that of the  $6_5$  symmetry element, as, indeed, it should be. Likewise the graphical symbol for the  $3_1$  symmetry element becomes correctly that of the  $3_2$  symmetry element. However, the graphical symbol of the  $2_1$  symmetry element is transformed into a symbol which is undefined in [60]. A similar problem arises with the graphical symbols of the other achiral symmetry elements  $4_2$  and  $6_3$ . Moreover, the graphical symbols of some other symmetry elements do not transform in the same way as the symmetry operations they represent. Consider the graphical symbol of the  $6_1$  symmetry element. As we have seen, mirror reflection transforms this correctly into the graphical symbol of the  $6_5$  symmetry element. However, rotation by  $180^\circ$  about a direction perpendicular to the axis of the  $6_1$  symmetry element also transforms a  $6_1$  graphical symbol into a  $6_5$  graphical symbol, contrary to the transformation properties of the  $6_1$  symmetry operation it represents, and for which such a rotation leaves the symmetry operation invariant. Moreover, the  $6_1$  graphical symbol is centrosymmetric.

Designers of 3D graphical representation systems of the 230 space groups will have to pay great attention to the transformation properties of the graphical objects used to represent symmetry elements. The 3D graphical objects chosen need both to have the same transformation and symmetry properties of the symmetry operation represented, and, in section/(limited-)projection, to resemble as nearly as possible the well-accepted but unsatisfactory 2D graphical symbols used in [60]. No doubt the Euclidean centralizer of the symmetry operation [58] has a key role to play in the analysis. One also notes that, in the report of the sub-committee on symmetry elements [57–59], no mention is to be found concerning the symmetry of a symmetry element.

*5.2. Euclidean Normalizers.* A powerful technique in symmetry-group theory is that of the Euclidean normalizer, which is fully described, with examples of its use, in [1]. This section has the double objective of drawing the attention of structure analysts to the practical value of the Euclidean normalizer in their work and to point out to theoreticians the shortcomings of the current state of development of Euclidean normalizers as they apply to chiral and achiral space groups.

One observes on examination of Tables 15.2.1.2–4 in [1], that the Euclidean normalizers of 208 space groups are centrosymmetric. Each of these space groups is, thus, achiral. These are exactly the same 208 space groups identified above as being achiral. The Euclidean normalizers of the remaining 22 space groups contain only isometries of the first kind. The space groups themselves are, thus, chiral. They are, indeed, the 11 pairs of enantiomorphic space groups mentioned above. However, the concept of the Euclidean normalizer, which refers to individual groups, does not lead to the classification of the chiral space groups into enantiomorphic pairs.

A space group is mapped onto itself by any symmetry operation of its Euclidean normalizer. But what happens to the crystal structure under the effect of an operation of the corresponding Euclidean normalizer? One finds the crystal structure or its enantiomorph in a different setting or orientation with a space group that remains totally unaltered. First, let us concentrate our attention on the 208 space groups with a centrosymmetric Euclidean normalizer and consider the action of the Euclidean normalizer's centre of inversion. Its position is tabulated in Tables 15.2.1.3 and 4 in [1]. If the initial crystal structure and its inverted image are not identical, the coordinates of the centre of inversion are precisely the ones to use to invert the crystal structure model without change of the space group setting [6][9], making Tables 15.2.1.3 and 4 of great practical use. For example, for space group *Fdd2*, the coordinates of the inversion point are given as  $1/8, 1/8, 0$ . For completeness, within these 208 space groups, the initial crystal structure, and its invert are: (crystal-structure type NA) inverted one with respect to the other for the non-centrosymmetric achiral structures; (crystal-structure type NC) enantiomorphs for chiral crystal structures; and (crystal-structure type CA) identical for centrosymmetric crystal structures. If we now turn to the remaining 22 space groups, forming the 11 enantiomorphic pairs, for which the Euclidean normalizers contain only symmetry operations of the first kind and for which the crystal structure is chiral. The operations of the Euclidean normalizer only rotate or translate the crystal structure, meaning that the enantiomorph of the crystal structure is NOT generated. Tables 15.2.1.3 and 4, thus, lack the coordinates of the centre of inversion to form the enantiomorph. As detailed in [9], the origin suffices for space groups in the conventional setting.

Further examination of Tables 15.2.1.3 and 4 shows that some space groups have Euclidean normalizers containing continuous translations. These are identified by a numerical superscript on the upper case cell-centring symbol as well as by one or more of the cell basis vectors containing a multiplicative factor  $\epsilon$ . For example, for space group  $Fdd2$ , the Euclidean normalizer is given as  $P^1ban$  with basis vectors  $1/2\mathbf{a}$ ,  $1/2\mathbf{b}$ ,  $\epsilon\mathbf{c}$ . These are space groups for which the origin cannot be fixed on a symmetry element in one or more directions. Tables 15.2.1.3 and 4 allows the number and direction of these continuous translations to be readily identified for space groups in conventional settings. The section of *International Tables for Crystallography*, Vol. A in [60] does not give a specific collective name to these space groups, but, in the literature, they are called *polar*, and *Flack* and *Schwarzenbach* [11] sometimes use the term *origin-free*. Neither *polar* nor *origin-free* are really satisfactory. With the automation provided by the *Flack* and *Schwarzenbach* [11] origin-fixing algorithm, it is so infrequently necessary to speak collectively about these space groups that the editors of *International Tables for Crystallography*, Vol. A [60], were wise to not have coined or defined a specific term.

The shortcomings of the Euclidean normalizer as detailed above are not really surprising, as the normalizer is based on group-theoretical rather than physical concepts. One is reminded of the classification of space groups into 219 isomorphism or affine-equivalence classes, which proves to be of limited practical value. Structure analysis makes use of a space-group classification into 230 special affine-equivalence classes engendered by the addition of physical concepts connected to inversion through a point [61]. It would seem, then, that an extension of the Euclidean-normalizer formalism permitting mapping of a space group both onto itself and onto its enantiomorph should lead naturally within this framework to the identification of enantiomorphic pairs of space groups and the identification of inversion points. One notes that *Billiet* and *Bertaut* [62], in their study of isomorphic subgroups of space groups, specifically allow the subgroup to be of the same or enantiomorphic type to that of the space-group type.

**6. Concluding Remarks.** – As the structure analyst must deal with and write about three chiral or achiral objects *viz.*, the molecules, the crystal structure, and the space group, it is of paramount importance that clear nomenclature be adhered to in order to limit misunderstanding and confusion. It is essential to separate the chiralities of these objects and ensure that the qualifier ‘chiral’ is applied correctly to the appropriate object. The space group of a chiral crystal structure is not necessarily chiral, although it will always be one of the *Sohncke* space groups. Furthermore, in circumstances where the molecular enantiomer composition of an enantiomeric mixture, be it in solution or the solid state, is being specified, it is highly advisable to use only the terms enantiomerically pure and racemic. Applying the term chiral in these circumstances, while not necessarily wrong, is certainly open to misinterpretation.

This paper describes a work that is much more of scholarship and analysis than of discovery and invention. Nevertheless, its content is pertinent to modern-day crystallography. *Brock* and *Dunitz* [63] have contributed towards a grammar of crystal packing. The current work adds a concise, useful and well-defined vocabulary specific to chirality.

**Appendix A: Glossary of Terms.** – Many of the definitions of terms given in this glossary are drawn or inspired from the IUPAC *Basic Terminology of Stereochemistry* [23]. Only where the definition of a term is identical to that in [23] is the source cited.

*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 non-centrosymmetric crystal and its description by way of unit-cell dimensions, space group, and representative coordinates of all atoms.

*Chiral:* Having the property of chirality [23].

*Chirality:* The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable by pure rotation and translation on its image formed by inversion through a point; the symmetry group of such an object contains no symmetry operations of the second kind (inversion through a point,  $\bar{1}$ ; reflection through a plane, *m*; roto-inversion,  $\bar{N}$ ). When the object is superposable by pure rotation and translation on its inverted image, the object is described as being achiral; the symmetry group of such an object contains symmetry operations of the second kind. *Barron* [4] provides a more-general definition of chirality: ‘True chirality is exhibited by systems that exist in two distinct enantiomorphic states that are interconverted by space inversion but not by time reversal combined with any proper spatial rotation’.

*Chirality sense:* The property that distinguishes enantiomorphs. The specification of two enantiomorphic forms by reference to an oriented space, e.g., of a screw, a right threaded one or a left threaded one. The expression opposite chirality is short for opposite chirality sense [23].

*Enantiomer:* One of a pair of chiral molecular entities of opposite chirality sense.

*Enantiomerically pure:* A sample in which all molecules have (within limits of detection) the same chirality sense. *Use of homochiral as a synonym is strongly discouraged* [23].

*Enantiomorph:* One of a pair of chiral objects or models of opposite chirality sense.

*Flack parameter:* The *Flack* parameter [8] is the molar fraction *x* in the defining equation  $C = (1 - x)X + x\bar{X}$ , where *C* represents an oriented two-domain-structure crystal, twinned by inversion, consisting of an oriented domain structure *X* and an oriented inverted domain structure  $\bar{X}$ . In reciprocal space, the *Flack* parameter [8] *x* is defined by the structure-amplitude equation  $G^2(h, k, l, x) = (1 - x) |F(h, k, l)|^2 + x |F(\bar{h}, \bar{k}, \bar{l})|^2$ . For a multi-domain-structure twin of a chiral crystal structure, an equivalent *Flack* parameter [8] may be calculated according to the method of *Flack* and *Bernardinelli* [5].

*Racemate:* An equimolar mixture of a pair of enantiomers. It does not exhibit optical activity in solution. The chemical name or formula of a racemate is distinguished from those of the enantiomers by the prefix ( $\pm$ ) or *rac* or by the symbols (*RS*) or (*SR*).

*Racemic:* Pertaining to a racemate [23].

*Racemic conglomerate:* An equimolar mechanical mixture of crystals, each one of which contains only one of the two enantiomers present in a racemate. The process of its formation on crystallization of a racemate is called spontaneous resolution, since pure or nearly pure enantiomers can often be obtained from the conglomerate by sorting [23].

*Relative configuration:* The configuration of any stereogenic centre with respect to any other stereogenic centre contained within the same molecular entity. Unlike absolute configuration, relative configuration is reflection-invariant. Relative configuration, distinguishing diastereoisomers, may be denoted by the configurational descriptors (*R\**, *R\**) (or *l*) and (*R\**, *S\**) (or *u*) meaning, respectively, that the two centres have identical or opposite configurations. For molecules with more than two asymmetric centres the prefix *rel* may be used in front of the name of one enantiomer where (*R*) and (*S*) have been used. If any centres, have known absolute configuration then only (*R\**) and (*S\**) can be used for the relative configuration [23].

*Twinning by inversion:* The symmetry operation relating pairs of domain structures twinned by inversion may be represented by inversion through a point or by some other isometry equivalent to inversion under the point symmetry group of the domain structure. A two-domain-structure twin that is twinned by inversion is called an *inversion twin*, but this term is not appropriate when there are more than two domain structures.

**Appendix B: Segmentation of Molecular Crystal Structures.** – A comparison is made here point by point of experimental observations on molecular crystal structures collated principally by *Jacques et al.* [12], labelled *Obs*, and the conclusions of the molecular segmentation theory of *Anet et al.* [14], labelled *Seg*. The findings of *Anet et al.* [14] are presented as direct quotes (in italics) from their paper apart from the explanatory comments given between square brackets [ ]. There are five points of comparison. The theory of *Anet et al.* [14] seeks to partition a finite object (i.e., a molecule) into a set of isometric segments from which the whole molecule can be

built up in the way that a crystallographic asymmetric unit builds up a whole crystal structure (although these molecular segments are not necessarily completely lacking in symmetry). From the derived segmentation of the molecule, a comparison is then made of one particular aspect of the symmetry of the object and the segments of much concern to these chemists *viz.*, the chirality. A major difference between molecules and crystal structures is that the symmetry group of the former is finite and that of the latter is infinite. Nevertheless, in our opinion the methodology and results of *Anet et al.* [14], which we make no attempt to describe here, may be extended to space groups and molecular crystal structures by the pragmatic use of a cyclic boundary condition applied to a finite object.

*Obs 1:* There are hundreds of known chiral crystal structures formed of achiral molecules.

*Seg 1:* It is not possible to dissect chiral molecular models into achiral isometric segments.

*Obs 2:* There are tens of known chiral crystal structures composed of racemates.

*Seg 2:* It is not possible to dissect chiral molecular models into heterochiral isometric segments.

*Obs 3:* All known crystal structures of enantiomerically pure substances are chiral.

*Seg 3:* Indeed, among the myriad combinations of objects and segments in three dimensions, only five types are disallowed. [Among the allowed combinations is the segmentation of an achiral molecular model into homochiral isometric segments.]

*Obs 4:* There are hundreds of crystal structures in which the number of independent (crystallographically independent but chemically identical) molecules in the asymmetric region  $Z' > 1$ .

*Seg 4:* The segments must be related by a symmetry operation of the cut object.

*Obs 5:* Many molecules have non-crystallographic symmetry in the crystal structure.

*Seg 5:* Accordingly, the segments may not contain any symmetry element that does not belong to the object.

The understanding of the relationship between the symmetry of the molecules that build a crystal structure and the crystal's own symmetry is an important objective of structural crystallography. Whilst appreciating the inventiveness, effort, and scholarship of *Anet et al.* [14] one is forced to admit that that particular approach has not yielded useful results for molecular crystal structures. What is most probably lacking in their approach is a physical and chemically meaningful basis for the segmentation.

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