

Chirality, a never-ending source of confusion

Carl-Johan Wallentin^I, Edvinas Orentas^{II},
Kenneth Wärnmark^{*,I} and Ola F. Wendt^{*,I}

^I Organic Chemistry, Department of Chemistry, Lund University,
P.O. Box 124, 221 00 Lund, Sweden

^{II} Department of Organic Chemistry, Vilnius University, Naugarduko
24, 03225 Vilnius, Lithuania

Received October 19, 2009; accepted October 20, 2009

*Chiral / Chirodescriptive / Enantiomorphism /
Racemorphism / Chirogenic*

Abstract. In this Discussion a few points of confusion concerning chirality are clarified. The term chirodescriptive is proposed for such space groups that lack inversion centres, reflection planes, glide planes or rotary-inversion axes and thus can contain enantiopure, chiral objects. It is pointed out that chiral compounds can (and often do) crystallise in non-chirodescriptive space group when they occur as racemates and in such cases there is no incompatibility between chirality and mirror planes or centres of inversions. We also propose the term racemorphism to describe the relationship between a conglomerate and a collection of racemic crystals of the same compound.

In the last couple of decades X-ray crystallography has become a method routinely employed also outside the fields of inorganic and structural chemistry. Due to the fast development of instrumentation and software, X-ray data collection and data treatment can readily be performed by others than trained crystallographers, in particular if the crystal structure can be obtained from the collected data without complications. However, often an experienced crystallographer needs to supervise/overlook/aid in the process since disorder, twinning and other problems can cause the refinement to become quite complex. In addition, interpretation of the solid state structure often requires rigid experience, unless only the molecular structure is the target. Many departments of organic chemistry now routinely use X-ray diffraction to determine structure. One outcome of this development is that concepts commonly used by structural chemists as well as organic chemists in different contexts may have different meanings; this might cause confusion. One such concept is chirality. Both the concept and especially the associated terminology has been the subject of misunderstanding and debate ever since the term was coined by Lord Kelvin in 1894 [1]. Naturally, the discussion has mainly taken place in organic chemistry forums since stereochemistry is a cornerstone of this chemistry.

* Correspondence author (e-mail:
kenneth.warnmark@organic.lu.se and ola.wendt@organic.lu.se)

This debate and the awareness of the “necessity to purify the available vocabulary” has been mainly absent from the structural chemistry community [2].

This insight was revealed to the present authors during the submission of a structural report to *Acta Crystallographica* describing the crystal structure of a racemate of a chiral molecule, where the referee concluded that the compound was not chiral due to the presence of improper symmetry operations in the unit cell. A subsequent survey of the related crystallographic literature convinced us that the terminology describing chirality is different in crystallography and organic chemistry; *e.g.* in many crystallography textbooks the term *chiral* is used where an organic chemist would say *enantiomerically pure* [3]. In this letter we would like to highlight the nature of this confusion by exemplifying some specific errors regarding the nomenclature of stereochemistry. The intention is not to criticise certain authors but to promote an awareness of the necessity of rigour in the use of terminology as well as promoting easy communication between structural and synthetic chemists. To aid this communication we also suggest a clarifying nomenclature.

A chiral molecule cannot be superimposed on its mirror image. Hence, chiral molecules cannot have internal mirror planes or centres of inversions (improper symmetry operations). A chiral molecule and its mirror image constitute an enantiomeric pair and an equimolar mixture of the two forms a racemate. These statements define molecular chirality¹ and this description includes not only molecules but all physical objects such as crystals [4].

Central to this discussion are also the terms enantiomorphism and enantiomer. In *Elemente der Theoretischen Kristallographie* (Elements of Theoretical Crystallography) published in 1856, Carl Friedrich Naumann proposed that the term enantiomorphism (enantiomorphie) should describe the relationship between nonsuperimposable-mirror-image crystals (expressed as right and left handed bodies). The historic development is excellently described in a review by Gal [5]. In modern usage, Naumann’s terminology (*i.e.* enantiomorphism) is confined to macroscopic objects such as crystals whilst the term enantiomerism is used to describe the corresponding relationships for individual molecules. In line with these definitions and in an attempt to circumvent misapprehensions we propose that the relationship between racemic crystals and a conglomerate should be referred to as *racemorphism*. Hence, a conglomerate and a collection of racemic crystals (of the same chiral molecule) are *racemorphs*.

There are three common misunderstandings regarding the actual meaning of the term chiral even though, in

¹ There is also a more general definition of chirality proposed by Barron: “True chirality is shown by systems existing in two distinct enantiomeric states that are interconverted by space inversion, but not by time reversal combined with any proper spatial rotation.” See Barron, L. D.: <http://www.chem.gla.ac.uk/~laurence/Chirality.htm>. For the chirality of objects and molecules the original definition is more appealing to the present authors.

every context, it is accurately defined (*vide supra*). Firstly, we often associate chirality with objects although abstract things such as symmetry operations also can be chiral. However, the use of chiral in the context of unit cells is often incorrect, see for example the following article by Palusiak *et al.* [6]. As pointed out by Flack there are 22 chiral space groups which appear as enantiomorphic pairs (*e.g.* $P6_1$ vs. $P6_5$) [7]. However, there are a total of 65 space groups (including the 22 chiral ones) that lack inversion centres, reflection planes, glide planes or rotary-inversion axes and thus can contain enantiopure, chiral objects; these are all often improperly referred to as chiral. Flack [7] suggests that these be called Sohnke space groups but this term is not widely spread, probably because it is not self-explanatory. We instead propose that they be called *chirodescriptive*. With this terminology the remaining 165 space groups can then collectively be known as *non-chirodescriptive* (including both centrosymmetric and non-centrosymmetric ones). Our term is also an adjective which makes it easy to use in the same way as we do with *e.g.* centrosymmetric, polar and chiral space groups.

Secondly, chiral does not mean enantiomerically pure. A chiral molecule can exist in an enantiomerically enriched form or as a racemate; in both cases the molecule remains chiral. In the crystallographic literature there are many examples of statements like “Neither can chiral molecules crystallize in space groups that contain [symmetry elements of the second kind] [...]. Thus, proteins, which are chiral, cannot crystallize in space groups that contain these types of symmetry operations, and, as a result, the number of possible space groups for them is reduced from 230 (for both chiral and achiral objects) to only 65 (for chiral objects)” or “Crystals of pure chiral objects, such as protein or nucleic acids, cannot crystallize in space groups that contains mirror planes, glide planes, or inversion centers” [8]. This is not true. Chiral compounds in racemic mixtures (a mixture of pure chiral objects with opposite handedness) can crystallise with an achiral arrangement of the molecules in the unit cell. However, enantiomerically pure compounds are restricted to the 65 chirodescriptive unit cells. Another example states that “As the synthesis has produced a 1:1 mixture of the two enantiomers, the presence of the both [sic!] enantiomers precludes a chiral description for the compound. The supposed chirality of the molecule does not appear to be relevant to the discussion of the crystal structure either” [9]. Chirality is an inherent property of the molecule not of the bulk composition of the synthesised material which can contain both enantiomers. Here the word compound is used in an ambiguous way and it is not clear if it refers to the molecule or the crystal (which of course is racemic)². In addition, it

² For historical reasons, it is unfortunately often seen that the phrase racemic compound is used to describe a racemic crystal (see for example: Bredikhin, A. A.; Eliseenkova, R. M.; Bredikhina, Z. A.; Dobrynin, A. B.; Kostyanovsky, R. G.: Racemic compound against racemic conglomerate formation: The crystal properties of allylbenzylmethylphenylphosphonium iodide as compared with the nitrogen analogue. *Chirality* **21** (2009) 637–641. Eliel, E. L.; Wilen, S. H.: *Stereochemistry of Organic Compounds*. John Wiley & Sons, inc., New York, 1994). Here, the word compound is used to describe the fact that the racemate is of one homogeneous phase and not in the

should be mentioned that the structure of racemic crystals necessarily must differ from the structure of enantiomerically pure crystals. Hence, whether the molecule is chiral or not often has a great impact on the crystal structure and is an important piece of information when it comes to rationalising a crystal structure.

Finally, an atom cannot be chiral³. It is often said that a molecule is chiral if it contains a chiral atom such as a carbon. These “chiral carbons” are often referred to as “chiral centres” since it is from these atoms the chirality stems. A single atom or point in a molecule is not chiral, rather it is the object itself that is chiral. Within the society of organic chemistry the term stereogenic centre has come to describe atoms (or points) that have the geometric features that can generate stereoisomers by means of an interchanging of any two connected groups. To be more descriptive, chirogenic centre should be used when the two isomers generated are enantiomers⁴.

To conclude, herein we wanted to clarify a few points of confusion concerning chirality. Specifically, we have pointed out that chiral compounds can (and often do) crystallise in non-chirodescriptive space group when they occur as racemates and in such cases there is no incompatibility between chirality and mirror planes or centres of inversions. Only in cases of enantiomerically pure compounds are we restricted to the 65 chirodescriptive space groups. Finally, we propose the term raceomorphism to describe the relationship between a conglomerate and a collection of racemic crystals of the same compound.

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general sense which usually refers to a well-defined molecular composition.

³ Strictly speaking, atoms can be chiral, however only in the context of nuclear chemistry, see Ref. [2].

⁴ Chirogenic was initially used to denote enantioselective reactions (Drenkard, S.; Ferris, J.; Eschenmoser, A.: *Chemie von Aminonitrilen. Aziridin-2-carbonitril photochemische Bildung aus 2-Aminopropennitril*. *Helv. Chim. Acta* **73** (1990) 1373–1390) but is presently used as described in the text. For an example, see Miura, T.; Yamada, H.; Kikuchi, S.; Imamoto, T.: Synthesis and Reactions of Optically Active Secondary Dialkylphosphine-Boranes. *J. Org. Chem.* **65** (2000) 1877–1880.