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The Mirror of Galadriel: looking at chiral and achiral crystal structures

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Abstract

Illustrative examples are provided of infrequent situations arising in the chiral or achiral crystal structures formed of chiral or achiral molecules. For absolute-configuration determination by way of structure analysis, it is demonstrated how powerful characterization of enantiomers by way of CD spectra and enantioselective chromatography can be when working on the single crystal used in the diffraction analysis. Common misunderstandings in the description of non-centrosymmetric achiral crystal structures are clarified. Further attention is given to questions of nomenclature.

Keywords: Chiral; Crystal structure; Absolute configuration; Dimorphism

With water from the stream Galadriel filled the basin to the brim, and breathed on it, and when the water was still again she spoke. 'Here is the Mirror of Galadriel,' she said. 'I have brought you here so that you may look in it, if you will'.

The air was very still, and the dell was dark, and the Elf-lady beside him was tall and pale. 'What shall we look for, and what shall we see?' asked Frodo, filled with awe.

'Many things I can command the Mirror to reveal', she answered, 'and to some I can show what they desire to see. But the Mirror will also show things unbidden, and those are often stranger and more profitable than things which we wish to behold. What you will see, if you leave the Mirror free to work, I cannot tell. For

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it shows things that were, and things that are, and things that yet may be. But which it is that he sees, even the wisest cannot always tell. Do you wish to look?'

Frodo did not answer [27].

1. Introduction

This paper was written as accompanying notes to a presentation entitled *Chirality and achirality in crystal structures* made at Indaba IV, Skukuza, South Africa, 17th–22nd August 2003. The presentation consisted of a selection of topics which are of importance for the understanding of the relationship between the chirality or achirality of the molecules forming a crystal structure, the chirality or achirality of the crystal structure itself and the chirality or achirality of the symmetry group of the crystal structure. To a lesser extent time was spent on experimental techniques for the characterization of enantiomers. The notes are entirely complementary to the presentation and do not follow its form. The major sources of written material on the topics of the presentation are the papers *Absolute structure and absolute configuration* [8], *Reporting and evaluating absolute-structure and absolute-configuration determination* [9] and *Chiral and achiral crystal structures* [7], the book *Enantiomers, Racemates and Resolutions* [13] and the *Basic Terminology of Stereochemistry, IUPAC Recommendations* [18]. The reader is presumed to be familiar with their content which will not be reproduced here. The space available in the current article is used to highlight some examples unknown to us previously, to describe some examples of the way in which modern physico-chemical techniques can be essential in absolute-configuration determination, to clarify some of our previous writings and to draw conclusions on how structure reporting can be still further improved.

2. Solid solutions of enantiomers

2.1. Dimorphism in solid solutions

An instructive example, which seems not to have attracted the attention which it merits, is that of the structural properties of the compound 3,3-diethyl-5-methylpiperidine-2,4-dione (methyprylon) whose chemical diagram is shown in Fig. 1. Ther-

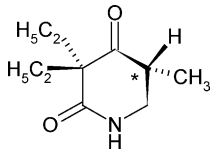

Fig. 1. Chemical diagram of methyprylon. The chiral C atom is marked with a ∗.

mochemical, DSC, contact-method [15,25] and crystallographic [20] measurements have been made. The work on this compound was highlighted in the review on *Structural Chemistry in Helvetica Chimica Acta, 1917–1992* [3]. The atoms forming the ring, with the exception of the chiral C atom marked by a $*$, the two ketonic O atoms and the C atom of the equatorial methyl group lie approximately in a plane. This same plane acts as a mirror plane for the two ethyl groups and the molecule thus presents an approximate mirror symmetry although it is chiral. The space-filling diagrams [20] show that the shapes of the two opposite enantiomers are very similar indeed and it comes as no surprise that the opposite enantiomers form a continuous range of solid solutions (mixed crystals) from enantiomerically pure *S*-methyprylon to enantiomerically pure *R*-methyprylon. A further significant observation is that the enantiomerically pure samples are dimorphic. Both of the solid phases crystallize in the space group type $P2_12_12_1$ (Modification I: $a = 13.12$, $b = 11.69$, $c = 6.83$ Å; Modification II: $a = 12.35$, $b = 12.30$, $c = 6.83$ Å) with essentially the same cell parameter c whilst a and b vary linearly as a function of composition as determined by the optical rotation of a crop of crystals ($a = 12.738 + 0.00310\ [\alpha]_D^{20}$, $b = 11.996 - 0.00247\ [\alpha]_D^{20}$ Å). As pointed out in [3], the dimorphism seems inevitable in such a case. Consider the crystal structure of the enantiomerically pure *S*-methyprylon in the solid phase I. Let us call this the *L* crystal structure or to be precise *L decorated by S*. As this crystal structure is formed of enantiomerically pure molecules it must be chiral (but see Section 3.2). The enantiomorph of the *L decorated by S* crystal structure is the *D* crystal structure formed of pure *R*-methyprylon molecules i.e. the *D decorated by R* crystal structure. Now in the *L decorated by S* crystal structure consider gradually replacing the *S*-methyprylon by *R*-methyprylon molecules. As end-point of this replacement, we will obtain the *L decorated by R* crystal structure composed entirely of *R*-methyprylon molecules. Clearly this new structure, *L decorated by R* is not the enantiomorph of the starting structure *L decorated by S*. The enantiomorph of *L decorated by R* is *D decorated by S* and the enantiomorph of *L decorated by S* is *D decorated by R*. Clearly for the enantiomerically pure *S*-methyprylon molecules there are two crystal structures *L decorated by S* and *D decorated by S* each with its own enantiomorph formed of enantiomerically pure *R*-methyprylon molecules.

From the above considerations it seems inescapable that if opposite enantiomers form a continuous range of solid solutions over the full domain of composition, then the enantiomerically pure substance must be dimorphic. Roozeboom's type 1 solid-solution curve [23] not only looks highly idealized but contrary to structural chirality principles. The only way for the dimorphism not to appear is for the crystal structures of the enantiomerically pure substances to be achiral. However, no achiral crystal structure of an enantiopure compound is known at present although under the unusual conditions discussed below in Section 3.2 such a structure may in fact exist. In passing, Coquerel [5] presents a very interesting review on the heterogeneous equilibria between condensed phases in binary systems of enantiomers but none of those concerned with solid solutions without formation of a stable

homogeneous structure at the racemic composition have the topological and topographical characteristics of that of methyprylon.

2.2. Pseudoracemates

As discussed in [7], solid solutions of enantiomers are currently known under the unsuitable name of *pseudoracemates*. However, at the outset [14], this term was used to describe unusual crystals of some camphor derivatives which did not appear to be either racemic conglomerates or homogeneous crystals of the racemate. Although X-ray crystallography was unknown at that time, and Roozeboom's classic paper [23] on binary phases of enantiomers appeared two years later, Kipping and Pope [14] had an ingenious structural model of their pseudoracemates which was *not* that of a solid solution of enantiomers. Kipping was an organic chemist with an acknowledged reputation of being green-fingered at crystallization [28]. Apparently, the urban legend was that he kept seeds of all his crystals in his beard, and in cases of difficult crystallizations, he would give his beard a shake and hope that something would fall out and start nucleation [29]. However, he had a profound knowledge of classical crystallography and was well aware of the discovery of the 230 space groups by Fedorov and Schönflies. He was also well acquainted with the existence in mineralogical samples of crystals twinned by inversion. Kipping and Pope [14] had observed striations on their crystals and came to the conclusion that their pseudoracemate crystals of organic molecules grown from a racemic solution were twinned by inversion, although the morphology of the crystals was unable to confirm this hypothesis as the all-important hemihedral faces did not develop. It was thus supposed that these crystals grow from a racemic solution by spontaneous resolution to give a racemic conglomerate in which the macroscopic enantiopure regions are not separate crystals but form an agglomeration of homogeneous domains of opposite chirality with perfectly oriented lattices. So the unsuitable term *pseudoracemate* has stuck for solid solutions of enantiomers, a state of matter which it was not intended to describe. This twist of changed nomenclature led to the assumption [7] that Kipping and Pope [14] had necessarily postulated a wrong structural model for their crystals [7].

3. Crystal structures of enantiomers

3.1. Twins by inversion

A very nice demonstration that Kipping's model [14] does appear in nature, is afforded by a study of crystals of the resolvable compound hexahelicene [10]. Crystals grown either from an enantiopure or a racemic solution have the same chiral crystal structure displaying space group $P2_12_12_1$. However, taken back into solution, the crystals from the enantiopure solution are optically active whereas those grown from the racemate are either optically inactive or only very weakly so. Crystals from the two batches were etched by solvent. The ones from the enantiopure solution showed no particular macroscopic structure whereas those from the

racemate display lamellae of thickness 10–30 μm. Green and Knossow [10] were able to cut out individual lamellae and from the measurement of optical activity in solution to confirm that the lamellae are enantiopure. These observations reveal that the crystals of hexahelicene grown from the racemic solution are twinned by inversion. A further example is given in Section 4.2.

3.2. Achiral crystal structures of disordered enantiopure molecules

The compilation [13] shows that there is no known achiral crystal structure formed of enantiopure molecules and the standard explanation of this observation has already been presented [7]. However, from an examination of the intriguing *La Coupe du Roi*, a way of dissecting an apple into two identical chiral halves, we came to the conclusion that the origin of the lack of achiral crystal structures formed of enantiopure chiral molecules was physical and chemical, and not symmetrical. The reason is that one relies on the property of molecules keeping their own identity in the crystal structure, intermolecular interactions being clearly distinct from intramolecular ones. A very important contribution [21] has been made pointing out that our arguments, and the observations [13], apply correctly to fully ordered enantiopure crystal structures but one may expect to find exceptions in the case of the average crystal structure of disordered enantiopure crystal structures, for in the average unit cell of a disordered structure, average atoms may approach each other in ways that real atoms do not. Consequently, a close approach in the manner of *La Coupe du Roi* as displayed in Fig. 1 of [7] becomes possible with its capacity for making a jump in symmetry, especially from a chiral to an achiral arrangement of average atoms. Despite some effort, we have been unable to identify a known crystal structure for which the well-characterized average crystal structure is achiral but which is composed of disordered enantiopure molecules. The CSD does not allow a direct search for such structures. Moreover to qualify according to these criteria, there must be concrete evidence of the enantiopurity of the compound in the crystal structure and such information is frequently lacking in the older literature. It is essential to prove the enantiopurity, as disordered crystal structures of racemates are commonplace. It may be that one of the crystal structures presented during the poster session at Indaba IV may qualify as being the first authenticated crystal structure of this type. Further investigations are being undertaken.

3.3. Dimorphism in enantiopure crystals

In the literature one finds only infrequent reports of crystal structure analyses carried out on opposite enantiomers. Perhaps, it is supposed a priori that the crystal structure of an opposite enantiomer will be the opposite enantiomorph of the crystal structure of the enantiomer and the extra work involved is not worthwhile. Recently, there has been a renewed interest in polymorphism due to the needs of the pharmaceutical industry [2]. The results [1,30] on the enantiopure opposite enantiomers of a planar chiral ortho-chloropalladated 2-[tricarbonyl(η^6-phenyl)-chromium]pyridine complex come as somewhat of a surprise. (For information on

planar chirality see [18].) The synthesis proceeded by forming an approximately equimolar mixture of two diastereoisomers. These diastereoisomers contain a planar chirality of opposite sense and a chiral centre of identical sense, the latter coming from an enantiopure starting reagent. Following separation of the diastereoisomers by low-temperature chromatography, the chiral centre was removed by chemical reaction resulting in separate products which were essentially enantiopure ($ee > 96\%$) opposite enantiomers, albeit of slightly different purity. Crystals were grown under the same conditions of high supersaturation using dichloromethane as solvent and the crystal structures of these opposite enantiomers were determined. The crystals of the (+) enantiomer displayed the space group $P2_1$ with approximate cell dimensions $a = 6.47$, $b = 12.43$, $c = 14.09$ Å, $\beta = 96.1^\circ$, Flack's parameter $x = -0.04(5)$. The complex is in the R_p configuration, one disordered dichloromethane in the asymmetric unit and the planes of the aryl rings are perpendicular, forming a herring-bone pattern. The crystals of the (−) enantiomer displayed the space group $P2_12_12_1$ with approximate cell dimensions $a = 18.03$, $b = 18.06$, $c = 6.60$ Å, Flack's parameter $x = -0.05(5)$. The complex is in the S_p configuration, one ordered molecule of dichloromethane in the asymmetric unit and the planes of the aryl rings are approximately parallel. There is no metrical nor any structural relation between these two crystal structures which are clearly not enantiomorphs. The complexes in them are indeed opposite enantiomers but in different conformations characterised by the orientation of the pyridine ligand bonded to the Pd(II). On recrystallizing the opposite enantiomers by slow diffusion of *n*-hexane into a solution of the appropriate enantiomer in acetone, crystals were produced which are enantiomorphs. The crystals of the (+) enantiomer displayed the space group $P2_1$ with approximate cell dimensions $a = 6.31$, $b = 12.87$, $c = 13.77$ Å, $\beta = 97.5^\circ$, Flack's parameter $x = -0.01(3)$. The complex is in the R_p configuration. The crystals of the (−) enantiomer displayed the space group $P2_1$ with approximate cell dimensions $a = 6.30$, $b = 12.88$, $c = 13.77$ Å, $\beta = 97.4^\circ$, Flack's parameter $x = 0.01(4)$. The complex is in the S_p configuration. The complexes in these two structures are opposite enantiomers of the same conformation whilst the two crystal structures are very similar to the herring-bone arrangement of the (+) enantiomer obtained from dichloromethane but contain one ordered molecule of acetone in the asymmetric unit.

We know of no report where crystallization of a racemate undergoing spontaneous resolution produces crystals of the opposite enantiomers which are not enantiomorphs. This may be due to rareness or to shyness!

4. Characterization of enantiomers

For the determination of the absolute configuration of an enantiomer to be complete in itself, and hence useful to others, characterization of the substance measured is necessary. In absolute-configuration determination carried out by single-crystal X-ray diffraction, it is the single crystal used for the diffraction experi-

ments which needs to be characterized. Notwithstanding that in many cases characterization of the bulk in solution is adequate if sufficient attention is paid to detail, in the following we give consideration to, and present examples of, the characterization of a single crystal. The mass of a single crystal of an organic compound, containing no heavy atoms, as used for diffraction experiments is of the order of 1 μg.

4.1. Optical activity

Optical rotation is the classic method of characterizing the chirality of a bulk product in solution or in the melt. It suffers, however, from several limitations. Being a single-wavelength technique, the effect of impurities is difficult to identify. For the structure analyst, this is especially important as the glue used to adhere the crystal to a fibre may be optically active and act as a source of impurity. Moreover, a quantity of material orders of magnitude greater than the mass of a typical diffraction crystal is necessary for measurements of the optical rotation.

4.2. Circular dichroism

CD is the name given to the difference absorption spectrum of a compound in solution, the difference being between left- and right-circularly polarized light. For this spectrum to show absorption bands, the compound must contain a chromophore. The CD-spectra of enantiopure opposite enantiomers in solutions of identical concentration are mirror images of one another. Only a small quantity of material, of about the mass of one single crystal, is sufficient to obtain a CD-spectrum. Moreover, as CD is a dispersive technique measured over a range of wavelengths, the effect of impurities is easier to estimate. In an early unpublished work [24], CD spectra had been successfully used to characterize a pharmaceutical product in an absolute-configuration determination and Hareda [11] had also later proned the use of CD to characterize enantiomers in absolute-configuration determinations. As an example, we quote a recent case from our laboratories in Geneva. A new chiral chromium complex (η^6 hexamethylbenzene)Cr(CO)$_2$(*exo*-η^2-methylacrylate) [16] was synthesised, and crystals were grown from a solution of the racemate. The crystal structure is chiral displaying the space group $P2_12_12_1$. One would suspect that the crystallization had proceeded by spontaneous resolution giving rise to a racemic conglomerate. The chromium in the complex is a significant resonant scatterer for X-rays (anomalous dispersion) which suggested that one might be able to determine the absolute structure of the crystals and the absolute configuration of the molecules *if* the enantiomers could be characterized satisfactorily. Two different crystals were measured by X-ray diffraction and gave values for the Flack parameter [6] x of 0.36(4) [$ee = 28(8)\%$] and 0.90(3) [$ee = -80(6)\%$]. Both crystals are thus twinned by inversion, being in effect oriented agglomerations of enantiopure domains containing molecules of opposite chirality in the manner of the model [14] as further witnessed in hexahelicene [10]. Moreover, the second crystal shows a higher enantiomeric excess than the first but contains a majority of the enantiomer opposite to that present as majority component in the first crystal.

The two crystals were put into separate solutions and the CD-spectra of these were measured and normalized to equal crystal volume. The CD-spectrum of the solution from crystal 1 is indeed weaker and in form the mirror image of that from crystal 2. The ratio of the enantiomeric excesses from the X-ray diffraction gives a value of −0.35(10) whereas the ratio of the normalized peak heights at 350 nm of the CD spectra is −0.42. The agreement is very good indeed. So long as a CD-spectrum of a solution of the crystal used for the diffraction experiment is published with the results of the structure analysis, it will be justifiable to claim that the absolute configuration has been determined. This is very satisfactory considering that one is working from a racemate in solution.

4.3. Enantioselective chromatography

The synthesis of an N-sulphonated aziridine, *N*-tricyclo[2.2.1.$0^{2,6}$]hept-3-yl-*p*-toluenesulfonamide, resulted in an enantiomeric mixture which was found to have an *ee* of 43% of the (1*R*,3*R*,6*S*) enantiomer [19,31]. The enantiomers were separated by semi-preparative HPLC on *Chiracel OD H* using hexane/isopropanol 9:1 at 0.5 ml/min giving retention times of 15.3 and 16.3 min. The product from the minority component (retention time 15.3 min) was used to make crystals. Their crystal structure is chiral displaying space group $P2_1$, Flack parameter [6] $x = -0.03(12)$, and the molecular conformation was determined to be (1*S*,3*S*,6*R*). The retention time and experimental conditions provide a sufficient characterisation of the enantiomer in the absolute-configuration determination. In this case, it would not have been possible to use optical activity or CD as these effects are far too weak: $[\alpha]_D = 0.7^\circ$ for 43% *ee* and the CD spectrum is flat.

5. Non-centrosymmetric achiral crystal structures

Crystal structures which are non-centrosymmetric and achiral (NA) are a rich source of misunderstanding and misinterpretation. A general consideration to this topic is given in [7] followed by a detailed explanation of the *anti-wurtzite* case in [12]. The space groups of NA crystal structures belong to the following geometric crystal classes: *m*, *mm*2, $\bar{4}$, $\bar{4}2m$, 4*mm*, 3*m*, $\bar{6}$, $\bar{6}m2$, 6*mm* and $\bar{4}3m$, all of which are non-centrosymmetric but contain symmetry operations of the second kind.

Misunderstandings arise in part because the symmetry conditions for a crystal structure to be chiral (i.e. the symmetry group must only contain symmetry operations of the first kind) are not the same as for the possible appearance of intensity differences between Friedel opposites in an X-ray diffraction pattern (i.e. the symmetry group must be non-centrosymmetric). So the NA crystal structures have the peculiarity of possibly displaying X-ray diffraction intensity differences between Friedel opposites without being capable of distinguishing the chirality of the crystal structure because it is in fact achiral. Unfortunately in the minds of many structure analysts differences in intensity between Friedel opposites are automatically and invariably associated with chirality. In the NA crystal structures this association is false. (For intensity differences between Friedel opposites to be observable one

necessary, but not sufficient, condition is that the crystal must contain atoms which are significant resonant scatterers.)

Of a more fundamental nature in this misunderstanding is the precise definition of chirality and achirality (see [7]). It is not required that an achiral object be *identical* to its mirror image or image in a point but only that this image may be brought into congruence with the initial object after some suitable pure rotation and translation. The pure rotation and translation are crucial here and find a correspondence in the chemist's world of working in the liquid and gaseous phases where molecules are continuously tumbling around by pure rotation and translation. In this world the orientation of the molecules is random or hidden, and may not be determined. All that may be achieved by suitable experimentation is to distinguish between opposite enantiomers. On the other hand crystallographers work in the solid state where the orientation of crystals and the molecules that compose them can be detected. As a side-product one also determines the chirality of the crystal, if it is chiral, and if that is achieved the chirality of the molecules composing the crystal, if they are chiral. What is determined by the intensity differences of the Friedel opposites of an NA crystal structure is not its chirality, since it is achiral, but its complete orientation. These intensity differences resolve an orientation ambiguity which may be represented as the choice between two orientations of the crystal structure related one to another by inversion through a point. According to the symmetry of the NA crystal structure, this orientation has other representations and in every case this orientation ambiguity may be represented as a pure rotation. Any NA object has the slightly curious property that its image in a point can be produced by a pure rotation.

6. Concluding remarks

The database CSDsymmetry [26] created from the entries in the Cambridge Structural Database (CSD) using an algorithm which perceives molecular symmetry is an important contribution to the study of molecular crystal structures. However, the algorithm does not permit the assignment of absolute configuration to chiral molecules and this is a particular handicap in the study of those structures containing more than one molecule in the asymmetric region of the unit cell. Information on molecular symmetry and chirality should be included as an integral part of a primary publication of a crystal structure. Unfortunately, no complete nomenclature has yet been devised for reporting this information and for its encoding in a standardized form such as CIF. In our opinion, the nomenclature [4] is likely to prove the most suitable as a basis for generalization and standardization.

On reading Section 4, it is evident that the techniques of CD spectra and enantioselective chromatography are very powerful in the characterization of the enantiomers composing a crystal used for diffraction studies. The measurement and subsequent reporting of such information in a standardized encoding such as CIF needs to be actively encouraged in publications of crystal structures.

Some preliminary results [22] show significant progress in the use of measurements of selected pairs of Friedel opposites to determine the absolute configuration of light-atom structures. Further work is in progress. The selection and experimental techniques come from an earlier publication [17] but the new method has a sounder statistical basis and is not limited to enantiopure compounds.

It is becoming more frequent nowadays to use the terms *resonant scattering* and *resonant scatterer* in place of the phenomenological terms *anomalous dispersion*, *anomalous scattering*, *anomalous scatterer* and *dispersive scatterer*. These latter terms made good sense at the time of the experimental proof of this type of scattering event with X-rays, stressing the discontinuous nature of the scattering phenomenon as a function of wavelength. However, *anomalous* may also be used to mean *deviant* leading to the impression that the physical basis of the phenomenon is not well understood. Moreover, *dispersion* implies correctly that the scattering is wavelength dependent but gives no hint as to the physical process which gives rise to this dependency. At a time when this type of scattering is exploited so often and so successfully, and its physical basis is so well established, it seems natural to use terms which stress the physical basis of the scattering process rather than its phenomenological behaviour.

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