

On Chiral Space Groups and Chiral Molecules

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ABSTRACT This note explains the relationship (as well as the absence of a relationship) between chiral space groups and chiral molecules (which have absolute configurations). For a *chiral molecule*, which must crystallize in a *chiral space group*, the outcome of the absolute configuration determination must be linked to some other properties of the *chiral crystal* such as its optical activity for the observation to the relevant.

As chemical nomenclature was originally developed for compounds in the solution state, there is some confusion in the proper use of the term 'chiral' for describing certain crystal structures. This has led to a number of compounds being incorrectly categorized as being chiral although they belong to centrosymmetric space groups or those having mirror planes. A chiral compound that separates from solution as a crystalline material must necessarily pack in a motif such that other molecules in the unit cell are not superimposable on their own mirror images.

The condition for *optical activity* (in solution) is governed by the general condition of the absence of a *rotary-inversion axis*^[1] (in the solid state). In crystals, this stipulation for *chirality* excludes both the center-of-inversion (one-fold rotary-inversion) and the mirror-plane (two-fold rotary-inversion) symmetry elements. As a glide plane consists of a reflection across the plane followed by a translation parallel to the plane, chiral molecules can not belong to the space groups having this symmetry element either; in fact, chiral compounds can only belong to 65 space groups^[2].

The compound [h^5 -C₅H₄C(O)CH₂CH₂C(O)O-CH₃]RuCoW(m_3 -Se)(CO)₈ crystallizes in the centrosymmetric *P2₁/c* space group^[3]. As the synthesis

has produced a 1:1 mixture of the two enantiomers, the presence of the both 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. (An exception has been noted in a cobalt-aminoacid complex; although DL-isoleucine was used in the reaction, the product consists of the enantiomers in a ratio other than 1:1, which necessitates its tenure in a chiral space group^[4].) Another report describes a tetrahedral phosphorus compound whose synthesis yielded a pair of diastereomers that were separated by partial crystallization; their identities were separately confirmed by solution ³¹P NMR spectroscopy. The crystal structure determination was performed on one of the diastereomers, which was refined in $\hat{P}1$ to $R = 0.071$ for the 2176 of the 3031 $I > 3S(I)$ reflections^[5]. However, the centrosymmetric $\hat{P}1$ space group can not hold only chiral molecules; most likely, the authors had inadvertently selected a specimen from the racemic batch. If they were certain that they had not unintentionally measured the racemate, they should have refined the structure in *P1* instead of $\hat{P}1$.

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Although chiral molecules must necessarily pack in chiral space groups, a chiral space group does not always have to accommodate only chiral objects. For example, 3-methyl-4-nitropyridine *N*-oxide, an organic compound that shows an extremely large non-linear effect, belongs to $P2_12_12_1$ ^[6], and lacks a chiral carbon center. This space group is the most common space group for small, irregularly shaped chiral molecules^[2] as well as achiral molecules as it possesses three two-fold screw axes. On the other hand, although second-harmonic-generation activity is not possible for all centrosymmetric space groups (as well as for chiral No. 207 to No. 214)^[7], the mirror and glide planes are not excluded for the manifestation of SHG activity.

The 230 space groups are classified into non-centrosymmetric/chiral space groups (those without rotary-inversion axes), non-centrosymmetric space groups (those without a center-of-inversion but with mirror and/or glide planes) and centrosymmetric space groups (those with a center-of-inversion). The 65 chiral space groups can be found from the *Space Group Explorer* in the *WinGX* suite^[8] or in the *XPREP*^[9] program in the *SHELXTL* package. In the crystal structure analysis of compounds belonging to chiral space groups, the refinements should report on whether the chirality of the *crystal*

could be established from the Flack parameter^[10]. As a chiral crystal can accommodate either chiral or achiral molecules, if it does not contain chiral molecules, the absolute structure (Flack) parameter has no general significance.

The 65 chiral space groups include 11 enantiomeric pairs^[2]; if an enantiomer crystallizes in one of the pair, the other enantiomer will crystallize in the enantiomorphous space group. 1,6-Anhydo-4-deoxy-4-diphenylphosphino-D-glycopyranose was described in the monoclinic $P2_1$ space group ($a = 11.575$, $b = 12.521$, $c = 11.573$ Å, $\beta = 89.89^\circ$; $Z = 4$)^[11]. As this space group is not an enantiomorphous space group, the chirality of the molecule must be determined by the refinement of Flack parameter. However, as the *a* and *c* axes are almost identical and the *b* angle is almost a right angle, the space group is better described in the tetragonal crystal class. When the space group is revised^[12] from $P2_1$ to $P4_1$ ^[13], the higher-symmetry unit cell contains only one independent molecule. The D-configuration dictates that the molecule must be described in $P4_1$ rather than $P4_3$.

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