Achiral molecules in non-centrosymmetric space groups

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A database survey of molecules with and without a chiral centre indicates molecular flexibility plays a role in space group choice.

Chiral molecules, if crystallised from an enantiomerically pure solution, must have a structure belonging to a Sohncke space group, that is a space group without mirror or inversion symmetry. Two of the five most popular space groups are the Sohncke space groups $P2_12_12_1$ and $P2_1$. An important question, however, for those interested in crystal structure prediction, crystal engineering or non-linear optics is how often does an achiral molecule crystallise in a Sohncke space group? In this paper, statistics concerning the distribution of molecules with and without a chiral centre over the popular space groups are presented. An indication that molecular flexibility plays a role in space group choice is observed.

An algorithm has been written that identifies whether a molecule contains a chiral centre.† For an atom to be identified as a chiral centre it must be a carbon, silicon, sulfur or phosphorus atom, be four coordinate and the substituents of the atom must be in topographically different environments. All the coordinates of all non-hydrogen atoms were required to be present in the entry and a maximum of one molecule in the asymmetric unit was allowed. The first 200,000 entries of the Cambridge Structural Database[1] (henceforth CSD) were interrogated by the algorithm. Only structures belonging to the six most popular space groups were included. These space groups and their presence in the latest release (v5.26) of the CSD are as follows: $P2_1/c$ (35.3%), $P\bar{1}$ (22.0%), $P2_12_12_1$ (8.3%), $C2/c$ (7.8%), $P2_1$ (5.6%) and $Pbca$ (3.6%). Of the first 200,000 molecules of the database 92,670 structures matched the criteria above and 80,032 belonged to the six space groups chosen. The resulting lists of molecules with and without a chiral centre, were processed by ConQuest[2] to select only organic structures for which $Z' = 1$.[3] Metal-containing complexes were excluded as the metal atom is not assessed for chirality. Table 1 presents a summary of the number of organic molecules with and without a chiral centre, where $Z' = 1$, found in the top 6 space groups.

As can be seen from Table 1, approximately 80% of the structures found in the Sohncke space groups $P2_12_12_1$ and $P2_1$ are built from molecules that contain a chiral centre. The space group $P2_12_12_1$ is one of the top five most populated space groups in the database but it is popular, predominantly, with molecules containing a chiral centre. Only 11.3% of the molecules in the above dataset, with no chiral centre, are found in space groups $P2_12_12_1$ and $P2_1$. The most popular space groups with molecules with no chiral centre, belonging to the above dataset are, in descending order, $P2_1/c$ (55.6%), $P\bar{1}$ (18.9%), $Pbca$ (7.9%) $P2_12_12_1$ (7.8%), $C2/c$ (6.4%) and $P2_1$ (3.4%). This distribution is quite different from the statistics calculated for the space groups listed, from the CSD (see Table 1). Therefore in exercises of crystal structure prediction, for example, if the molecule does not contain a chiral centre then common centrosymmetric space groups are significantly more likely hosts than the Sohncke space groups $P2_12_12_1$ and $P2_1$ by a factor of 8:1.

From Table 1, the space groups most popular with molecules containing a chiral centre are, in descending order, $P2_12_12_1$ (34.1%), $P2_1/c$ (29.3%) $P2_1$ (18.2%) $P\bar{1}$ (11.7%), $Pbca$ (3.7%) and $C2/c$ (3.1%). Unfortunately since it is not known how many of the structures contributing to the chiral centre dataset were crystallised from enantiomerically pure solutions (though it is likely to be the majority) it is not possible to draw any meaningful conclusions from the above data. Racemic structures (those crystallising in centrosymmetric space groups), however, are not uncommon, accounting for 47.8% of the dataset.

Since the work of Kitaigorodskii[4] it has been conjectured that inversion centres in space groups are "good" for the close-packing of molecules. Certainly centrosymmetric space groups are very popular. In a study of the symmetry operators that mediate strong intermolecular interactions it was found that the inversion centre was the most popular mediator of the strongest interactions, when available.[5] Furthermore, the phenomenon of spontaneous resolution, where a racemic solution crystallises into enantiomerically pure structures, though not unheard of, is not common[6] and perhaps indicates that centrosymmetric space groups offer better opportunities for close-packing.[7] Given this body of empirical evidence, why do molecules with no chiral centre crystallise in non-centrosymmetric space groups $P2_12_12_1$ or $P2_1$?

Four possible scenarios describing the crystallisation of an molecule with no chiral centre in a Sohncke space group are as follows:

1) The molecule is rigid and is of a molecular point group symmetry which contains only rotational symmetry elements. The

Table 1 Distribution of a sample of 34,946 organic molecules, with and without chiral centres over six of the most common space groups[a]

Space group	Chiral centre	Percentage of dataset	No chiral centre	Percentage of dataset	Total	CSD (%)[b]
$P2_1/c$	5130	29.3	9687	55.6	14 817	42.7
$P\bar{1}$	2042	11.7	3293	18.9	5335	26.6
$P2_12_12_1$	5963	34.1	1364	7.8	7327	10.1
$C2/c$	540	3.1	1113	6.4	1653	9.4
$P2_1$	3194	18.2	600	3.4	3794	6.8
$Pbca$	640	3.7	1380	7.9	2020	4.4
Total	17509		17437		34946	

[a] Only $Z' = 1$ structures. [b] Statistics calculated from structures only in space groups listed.

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point group symmetry of the molecule means that it cannot be superimposed on its mirror image and the lack of torsional flexibility means that the molecule cannot convert to its mirror image through internal degrees of freedom. Thus a crystal structure built from this type of molecule in one of the Sohncke groups represents either an example of spontaneous resolution from a "racemic" solution, or the result from a crystallisation performed from a solution of just one of the "enantiomers". An example of a such a molecule is shown in Fig. 1.

2) The molecule is rigid and is of point group symmetry that contains the inversion symmetry element or mirror symmetry elements. A molecule of this type can be superimposed on its mirror image and therefore is achiral. It has no flexible torsion angles and its conformation is fixed.

3) The molecule is conformationally flexible but there are high steric energy barriers to the conversion of the structure to the mirror image. Thus the molecule is conformationally-locked and so is effectively chiral as it cannot convert to its mirror image. A structure of this type of molecule displaying a Sohncke group represents an example of spontaneous resolution if both the molecule and its mirror image were present in solution. An example of a molecule with a conformation which may be hindered from interconverting to its mirror image is given in Fig. 2. Hexahelicene is a known example of a molecule which does not interconvert with its mirror image in solution.[9]

4) The molecule is conformationally flexible and there are low steric energy barriers to interconversion between the molecule and its mirror image. Thus a chiral crystal structure results from a molecule which displays no chirality.

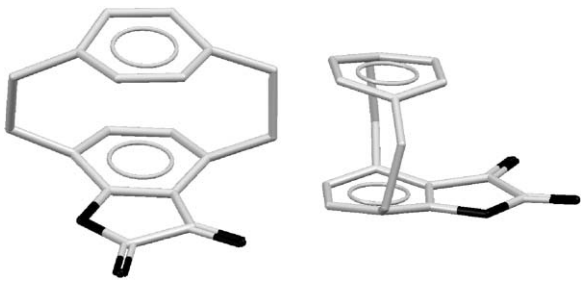

Fig. 1 (*R*)-2,3-Dioxo-2,3-dihydrofurano(4,5-*d*)(2.2)paracyclophane (MEYCUO[8]), a molecule with C_1 symmetry and no flexible torsion angles. Hydrogen atoms are omitted for clarity; oxygen atoms are coloured black.

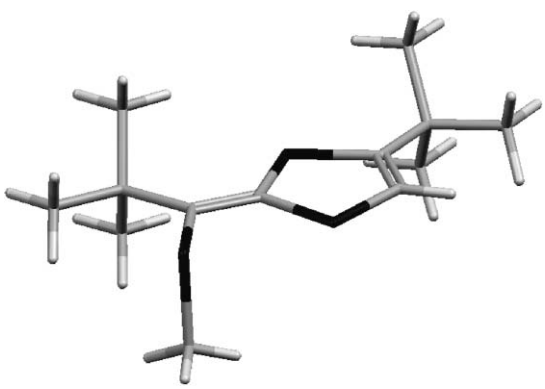

Fig. 2 4-*tert*-Butyl-2-(2,2-dimethyl-1-methylthiopropylidene)-1,3-dithiole (BMTPRD,[10] sulfur atoms coloured black). The S–Me group is hindered from free rotation by the dithiole ring and the *tert*-butyl group.

In the above categorisation of molecules with no chiral centres the path of conversion between molecules and their mirror images through bond-breaking events have been ignored. In order to assess whether there are observable differences between the molecules with no chiral centres in Sohncke space groups and those in centrosymmetric space groups a simple algorithm has been written to assess the flexibility of a molecule.

Each molecule is examined and torsion angles are counted. Torsion angles describing the orientation of terminal, hydrogen saturated groups such as $-CH_3$ or $-NH_2$ are not counted and torsion angles within rings are ignored. Only acyclic single bonds are regarded as flexible torsion angles. The next step established how many, if any, of the flexible torsion angles were adjacent to one another and a count was kept of torsion angles contributing to a "chain" of torsion angles. A molecule with three adjacent torsion angles, for example, is extremely flexible in the conformations it can adopt. Conversely a molecule with three non-adjacent torsion angles has a much more restricted conformational space. These simple torsion angle counts form the basis of the assessment of molecular flexibility. In terms of how sterically hindered a molecule is, for the purposes of this study it is assumed that if a molecule has a chain of three or more adjacent torsion angles then it can rotate to its mirror image and is regarded as fully flexible. When a molecule has torsion angles not included in a torsion chain, rotations, both clockwise and anticlockwise are performed around each torsion angle individually until the mirror image value is reached. The other torsion angles of the molecule remain fixed during this process. If the rotations both clockwise and anticlockwise can be performed with no non-bonded atoms coming to within 1.5 Å of each other, the torsion angle is deemed not to cause bumps. If all torsion angles within the molecule can be rotated with no bumps then the molecule is regarded as flexible, *i.e.* capable of converting to its mirror image through internal degrees of freedom. If the rotation of any torsion angle causes a bump, then the molecule is regarded as conformationally locked, or conformationally chiral. This approach is a starting point for looking at the complex issues surrounding chirality and space group choice. Table 2 presents the results of the classification of molecules with and without chiral centres in terms of flexibility.

It can be seen from Table 2 that the distribution of structures over the categories of molecular flexibility show some variation depending on the space group. However for molecules, with or without a chiral centre crystallising in the centrosymmetric space groups, the ratio of rigid and conformationally-locked molecules to conformationally flexible molecules remains remarkably consistent. Thus the proportion of molecules which are conformationally flexible in $P2_1/c$ is the same whether the molecule contains a chiral centre or not. The same is true for molecules crystallising in $P\bar{1}$, $C2/c$ or $Pbca$. However, there are significant differences between the populations for molecules belonging to the Sohncke space groups. For example the proportion of molecules categorised as rigid or conformationally locked (*i.e.* those which cannot rotate to the mirror image conformation) is greatest for molecules without a chiral centre in $P2_12_12_1$ and $P2_1$, at 40.5 and 35.0% respectively. Molecules with a chiral centre in $P2_12_12_1$ and $P2_1$, on the other hand are the least likely to be rigid or to have torsion angles which cause bumps, accounting for only 29.8% and 23.9%

Table 2 Distribution of structures over flexibility categories[a]

No chiral centre Space group	Rigid + bump	%	Flexible + no bump	%
$P2_1/c$	1553 + 1705	33.6	3180 + 3249	66.4
$P2_12_12_1$	319 + 234	40.5	345 + 466	59.5
$P\bar{1}$	327 + 648	29.6	1407 + 912	70.4
$P2_1$	118 + 92	35.0	180 + 210	65.0
Pbca	215 + 246	33.4	398 + 521	66.6
$C2/c$	142 + 230	33.4	382 + 359	66.6
Chiral centre Space group	Rigid + bump	%	Flexible + no bump	%
$P2_1/c$	730 + 1030	34.3	1604 + 1766	65.7
$P2_12_12_1$	759 + 1020	29.8	2549 + 1635	70.2
$P\bar{1}$	187 + 444	30.9	835 + 576	69.1
$P2_1$	279 + 484	23.9	1651 + 780	76.1
Pbca	87 + 119	32.2	196 + 238	67.8
$C2/c$	65 + 109	32.2	199 + 167	67.8

[a] Rigid: no flexible torsion angles; bump: molecule contains a torsion angle that cannot be rotated to mirror image value without contact between non-bonded atoms; flexible: molecule contains at least 3 adjacent torsion angles; no bump: molecule contains no torsion angles that cannot be rotated to mirror image values.

of the datasets respectively. Thus a conformationally flexible molecule with no chiral centre is 7.9 times more likely to be found in $P2_1/c$ than $P2_12_12_1$ but molecules categorised as rigid or conformationally locked with no chiral centre are only 5.9 times more likely to be found in $P2_1/c$ than $P2_12_12_1$. The presence of conformationally locked molecules in the Sohncke space groups is perhaps evidence of "spontaneous resolution" by molecules with no chiral centre. Since the conditions of synthesis and crystallisation of these molecules is not known it is not possible to estimate the degree of spontaneous resolution exhibited by conformationally locked molecules. However, for molecules where interconversion with the mirror image can be achieved through internal degrees of freedom, centrosymmetric space groups are greatly preferred.

For molecules that are rigid and which have mirror symmetry (as determined by the symmetry detection algorithm[11] available in RPluto[12]), the "appeal" of a centrosymmetric space group appears to be lessened, perhaps because an inversion operation performed on a molecule with mirror symmetry is equivalent to performing a rotation. A rigid molecule with mirror symmetry is only 4.3 times more likely to be found in $P2_1/c$ (500 molecules) than $P2_12_12_1$ (115 molecules). Both $P2_1/c$ and $P2_12_12_1$ are maximal non-isomorphic subgroups of *Pnma* and so it is perhaps not surprising that mirror-symmetric molecules discriminate less between $P2_1/c$ and $P2_12_12_1$. However, not a single structure out of the 115 rigid, mirror-symmetric molecules displaying space group $P2_12_12_1$ can be described as a *Pnma* structure.

Therefore, despite the crude measurement of the conformational flexibility of the molecules performed in this study, trends are observed which indicate there are differences between molecules with no chiral centre that crystallise in Sohncke space groups and those that crystallise in centrosymmetric space groups. This paper represents an initial attempt at quantifying what makes a molecule with no chiral centre crystallise in a Sohncke space group. Currently it appears that rigid molecules, particularly if they have mirror symmetry, have an increased chance of crystallisation in a Sohncke space group. This result is perhaps of interest to the non-linear optics community where non-centrosymmetric space groups are a requirement for second-harmonic generation.

The subset of structures that are conformationally flexible (and which are assumed to be capable of converting to the mirror image through internal degrees of freedom) but which crystallise in the Sohncke space groups are particularly interesting since there are no obvious barriers to their crystallisation in, for example, $P2_1/c$. Thus, the molecular packing offered by the Sohncke groups must be, in some way, preferable to the more commonly used centrosymmetric space groups. This will be an area of future research: is there any feature of these molecules that causes a preference for molecular packing *via* screw axes rather than the inversion centres and glide planes present in $P2_1/c$? The measurement of molecular flexibility used in this study is too crude to prove that conformationally locked molecules (not including rigid molecules) have an increased presence in Sohncke space groups. The more accurate assessment of molecular flexibility planned will provide a more rigorous assessment of this question. However, it is clear from the data of Table 1 that molecules with no chiral centre strongly prefer crystallisation in centrosymmetric space groups. Attempting to overcome this preference for centrosymmetric space groups (without introducing chirality) appears to have, at best, a 1 in 4 chance.

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Notes and references

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