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Studies in Crystal Chirality. I. Chiral Hydrogen-Bonded Structures

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This study is concerned with the possible formation of chiral crystal structures from small chiral and non-chiral molecules whose packing is primarily governed by hydrogen bonding. Chirality is discussed in terms of chiral H-bonded arrays in one, two and three dimensions. The formation of a chiral one-dimensional array is a necessary but not sufficient condition for the generation of a chiral crystal. Molecules which are capable of forming more than a single chiral one-dimensional H-bond array may form either a chiral layer structure or a chiral three-dimensional network. The first arrangement will lead to a chiral crystal structure if the layers are related by chiral symmetry elements only. This classification is aimed at a better understanding of spontaneous resolution.

Introduction

The factors which lead molecules, chiral or non-chiral, to crystallize in chiral structures are of interest, particularly because of the close relationship to the phenomenon of spontaneous resolution. While certain classes of molecules are known not to crystallize in chiral structures, there seem to be no rules by which we are able to predict whether or not molecules of other classes can crystallize in a chiral arrangement. This question arises sharply in consideration of the modes of crystallization of enantiomeric mixtures. Collet, Brienne & Jacques (1972) have recently listed most of the compounds known to undergo spontaneous resolution and tried to systematize the structural information on them. This review has been followed by a number of crystallographic analyses of optical isomers which undergo such resolution (Cesario & Guilhem, 1974*a–e*).

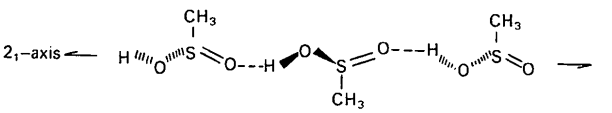
Many factors are involved in determining the crystal structure which an arbitrary chiral, or non-chiral, molecule selects: the ones commonly encountered are the molecular shape, van der Waals forces, the need for close packing, and more specific interactions such as dipole–dipole and H-bonding. In this communication we concentrate on H-bonding interactions which have the advantage that they are readily recognised from their geometric properties and are rather insensitive to variations in molecular structure.

We shall discuss the H-bonding arrangement in terms of those crystallographic symmetry elements necessary for obtaining crystal chirality, *i.e.* translation and two- or threefold screw axes (four- and sixfold axes are rarely encountered in organic crystals). Twofold rotation symmetry may be excluded on the following grounds. This *space*-symmetry element would generate a cyclic H-bonded system, *e.g.* the cyclic H-bonded carboxydimer (–  –), which is more easily obtained *via* a centre of inversion as this *point*-symmetry element imposes less constraints on the overall crystal structure than would a twofold axis.

One-dimensional hydrogen-bonded arrays

Molecules containing only one H-bonding function, *i.e.* one H-donor and one H-acceptor, may interlink in one dimension only. These include hydroxyl-containing molecules, carboxylic acids, secondary amides, sulphinic acids, *etc.* The formation of such a one-dimensional array in whose generation only chiral symmetry elements are involved, is a necessary but not sufficient condition for the crystal structure to be chiral. These chiral one-dimensional arrays may constitute a chiral three-dimensional structure provided they are interrelated by chiral symmetry elements only.

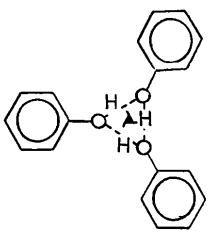
This principle is illustrated by methanesulphinic acid (Seff, Heidner, Meyers & Trueblood, 1969) which crystallizes in space group $P2_1$. The molecules form one-dimensional H-bonded chains (I) along twofold screw axes. The neighbouring chains are held together principally by van der Waals interactions and are interrelated by translation. Thus the full structure is chiral.



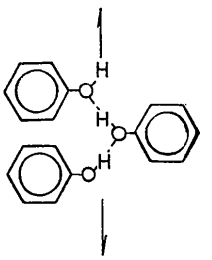
(I)

While it may be expected that other sulphinic acids form similar H-bonded arrays, their crystal structures are not necessarily chiral. This argument is clearly demonstrated by reference to the structural properties of phenols. Phenol itself (Scheringer, 1963; Gillier-Pandraud, 1967) crystallizes in space group $P2_1$ in which the molecules form helical H-bonded networks (II*a*) along a pseudo-threefold screw axis with repeat

distance 5·97 Å. *o*-Cresol (Bois, 1972) crystallizes in the chiral space group $P3_1$, the molecules forming a helical H-bonded array along a threefold screw axis of 5·94 Å. On the other hand, *m*-cresol (Bois, 1973), while forming a similar array along a 6·2 Å axis, crystallizes in the centrosymmetric space group $P2_1/c$. Most other phenols thus far described (Bavoux & Perrin, 1973; Bavoux & Thozet, 1973; Neuman & Gillier-Pandraud, 1973) appear with an H-bond motif (II*b*) in which the molecules are interlinked about the twofold screw axis of $4{\cdot}6 \pm 0{\cdot}3$ Å, and crystallize in either chiral or non-chiral structures.

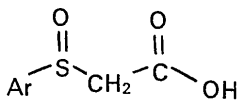


(II*a*)



(II*b*)

The carboxylic acids, with a few exceptions, form centrosymmetric H-bonded pairs. However, the monocarboxylic acids formic (Holtzberg, Post & Fankuchen, 1953), acetic (Nahringbauer, 1970) and β-tetrolic (Benghiat & Leiserowitz, 1972) each form one-dimensional H-bonded chains, the first two along a glide plane whereas β-tetrolic acid forms a H-bonded array along a twofold screw axis. Carboxylic acids tend to form translation-related stacks as a result of dipole–dipole forces. This tendency together with the chiral H-bonded array leads to a chiral structure ($P2_1$) of the tetrolic acid.



(*a*) Ar=phenyl
(*b*) Ar=1-naphthyl
(*c*) Ar=4-chlorophenyl

(III)

In the course of our studies on spontaneous resolution we have investigated the packing characteristics of some chiral arylsulphinyl acetic acids (III). These molecules differ from the carboxylic acids mentioned above insofar as they contain a second potential H-bond acceptor (S=O). Thus the molecules may interlink either *via* the commonly observed H-bonded carboxy-dimers or *via* H-bonds involving OH as donor and S=O as acceptor (O–H···O=S). The latter linkage results in an extended one-dimensional array. The cell constants of a number of arylsulphinyl acetic acids are listed in Table 1. The phenyl derivative (III*a*) crystallizes in space group $P2_12_12$. Thus these molecules certainly do not form H bonds *via* cyclic carboxy-pairs, but link by O–H···O=S bonds along a twofold screw axis (see below). The 1-naphthyl derivative (III*b*) crystallizes in the non-centrosymmetric space group *Aba*2 with a twofold screw axis of 9·3 Å. We have performed a structure analysis of this material (Leiserowitz, Salem & Weinstein, 1975) and find that the molecules are indeed linked by O–H···O=S bonds along the twofold screw axis (Fig. 1).

The phenyl derivative has a twofold screw axis of length almost equal to the 1-naphthyl derivative and we conclude that the H-bonding geometries are similar. The formation of a chiral crystal from the phenyl compound must be due, as in methanesulfinic acid, to a combination of H-bonding and van der Waals forces.

The 4-chlorophenyl derivative (III*c*) crystallizes in the centrosymmetric space group $C2/c$, the structure having a twofold screw axis of 7·3 Å (*cf.* the 9·3 Å axis

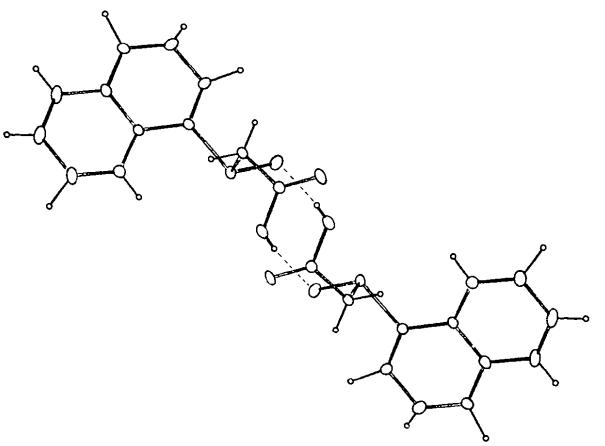


Fig. 1. 1-Naphthylsulphinylacetic acid. Hydrogen-bonding arrangement seen along the twofold screw axis.

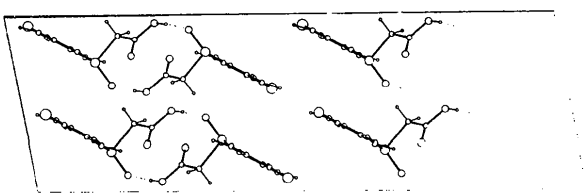


Fig. 2. 4-Chlorosulphinylacetic acid. Packing arrangement seen along [010].

Table 1. *Cell constants*

Compound	*a* (Å)	*b* (Å)	*c* (Å)	β (°)	Space group	*Z*
Phenylsulphinylacetic acid	10·21	10·07	8·47	—	$P2_12_12_1$	4
1-Naphthylsulphinylacetic acid	17·75	13·38	9·35	—	*Aba*2	8
4-Chlorophenylsulphinylacetic acid	27·98	7·37	9·23	100·07	$C2/c$	8
Phenylsulphinylacetamide	4·91	12·77	13·54	96·29	$P2_1/c$	4

above). Nevertheless the molecules choose to form an O–H···O=S H-bond motif *via* the (relatively) short 7·3 Å axis. However, the H-bonding motif (Leiserowitz, Salem, Tang & Weinstein, 1975) (Fig. 2) is rather different in this case, involving a conformation of the $-SO-CH_2-CO_2H$ moiety different from that of the 1-naphthyl derivative.

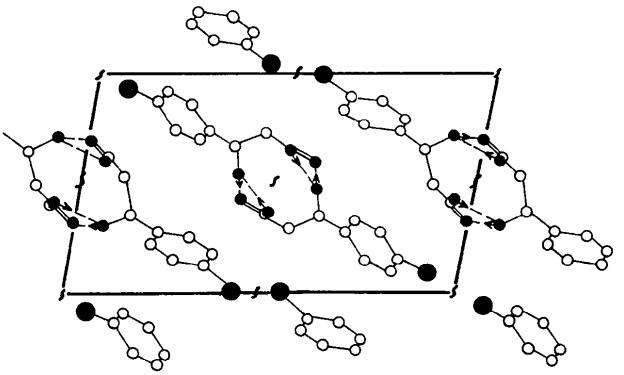


Fig. 3. 3-(4-Bromophenyl)-3-hydroxypropionic acid (after Cesario & Guilhem, 1974*d*). Packing arrangement seen along [010]. The O–H proton donors are denoted by arrows (→).

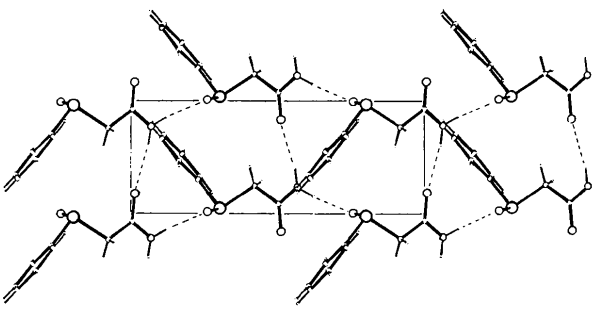


Fig. 4. Phenylsulphinylacetamide. Packing arrangement seen along [001], showing the two-dimensional hydrogen-bonded layer.

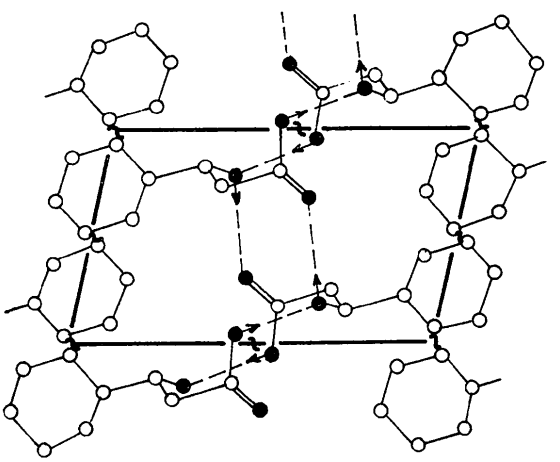
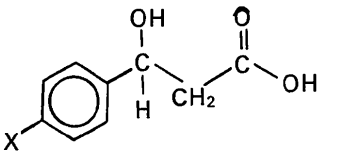


Fig. 5. 3-Phenyl-3-hydroxypropionic acid (after Cesario & Guilhem, 1974*b*). Packing arrangement seen along [010]. The O–H proton donors are denoted by arrows (→).

The crystal structure of the 4-chlorophenyl derivative (III*c*) also shows Cl···Cl interactions, the Cl atoms making 4 Å contacts along the 7·3 Å axis about centres of inversion. It is probable that these Cl···Cl interactions are responsible for the ability of the 4-chlorophenyl derivative to H-bond along the 7·3 Å rather than along a 9·3 Å axis as in the 1-naphthyl derivative (III*b*). This explanation is supported by consideration of the crystal structures of 3-(4-bromophenyl)- and 3-(4-chlorophenyl)-3-hydroxypropionic acids (IV*b*,*c*), (Cesario & Guilhem, 1974*d*,*e*).



(IV)

(*a*) x = H
(*b*) x = Br
(*c*) x = Cl
(*d*) x = F

These molecules (IV*b*,*c*) both contain two proton-donor and two proton-acceptor functions, (*i.e.* one proton-donor more than the arylsulphinyl acetic acids) yet do not form two-dimensional H-bonded arrays as does 3-phenyl-3-hydroxypropionic acid (IV*a*) which is discussed below; rather, they are H-bonded to form a helix about a twofold screw axis of 5·7 Å (Fig. 3). Both structures show halogen–halogen contacts of 4 Å along a twofold screw axis similar to those observed in 4-chlorophenylsulphinylacetic acid (III*c*) except that the latter span centres of inversion. Thus, even though the 3-(4-halophenyl)-3-hydroxypropionic acids do resolve spontaneously (they crystallize in space group $P2_1$) we could imagine these molecules to be arranged in a hypothetical centrosymmetric structure involving halogen···halogen contacts across an inversion centre as in the crystal structure of (III*c*) (Fig. 2).

Two-dimensional H-bonded networks

We extend the analysis to crystal structures containing two different H-bonded arrays which may be achieved if the molecule possesses at least two H-bonding groups. These two arrays may be generated by a combination of the chiral symmetry elements of translation and twofold screw axis. Possible combinations are: (*a*) two translations; (*b*) a translation plus a twofold screw axis; (*c*) two parallel twofold screw axes; and (*d*) two mutually perpendicular twofold screw axes. The last-mentioned combination generates a chiral crystal structure. The first three combinations listed yield a chiral plane which may or may not result in a chiral crystal structure. This depends on whether these planes are related by chiral or non-chiral symmetry elements.

We have not come across any crystal structures in which the molecules link to give a chiral plane by combination (*a*), *i.e.* by H-bonding along two translation axes. Fumaramic acid (Benghiat, Kaufman,

Leiserowitz & Schmidt, 1972) is an example of combination (*b*), in which a chiral layer is formed by H-bonding of the molecules along a translation and a twofold screw axis. Since amides, and in particular carboxy-groups, show a tendency to form translationally related stacks to achieve maximum dipole–dipole interactions as in β-tetrolic acid these fumaramic acid layers are related by translation yielding a chiral ($P2_1$) crystal structure.

Phenylsulphinylacetamide possesses two proton donors (NH_2), unlike the acetic acid analogue discussed above, as well as two proton acceptor groups (C=O, S=O). The crystal structure (Leiserowitz, Berkovitch-Yellin & Weinstein, 1975) contains two different H-bonded arrays consisting of amide groups H-bonded to each other along a translation axis (N–H···O=C), and an N–H···O=S bond along a twofold screw axis resulting in a chiral layer (Fig. 4). Since these layers are related to each other *via* centres of inversion, the overall structure is centrosymmetric ($P2_1/c$).

3-Phenyl-3-hydroxypropionic acid (IV*a*) (Cesario & Guilhem, 1974*a*), as well as the optically active 4-fluorophenyl derivative (IV*d*) (Cesario & Guilhem, 1974*b*), unlike the other halogenated derivatives, form extended two-dimensional H-bond networks. It involves two sets of H-bonds between the carboxy–OH and the hydroxyl oxygen

(O=C–OH···O–CH–), as well as between the hydroxyl OH and the carbonyl oxygen of the carboxy-group (CH–OH···O=C). Both sets are H-bonded *via* two parallel twofold screw axes yielding a chiral layer (Fig. 5). These layers are related to one another by translation, thus generating a chiral structure ($P2_1$).

As mentioned above, H-bonding along two perpendicular twofold screw axes generates a chiral crystal. The crystal structure of hippuric acid (Ringertz, 1971; Harrison, Rettig & Trotter, 1972) represents an excellent example of such a network. The molecules form N–H···O=C(carbonamide) and O–H···O=C-(carbonamide) H-bonded chains along two orthogonal twofold screw axes. To achieve such a H-bond network both proton donors (NH, OH) are linked to the carbonamide O, whereas the carbonyl O of the carboxy-group does not participate in the H-bonding. *A priori*, we might have expected both carbonyl O atoms to participate in H-bonding thus generating a more evenly distributed H-bond network, as exemplified by the analogous *N*-acetylglycine (Donohue & Marsh, 1962). The crystal structure of *N*-acetylglycine is centrosymmetric ($P2_1/c$) containing a motif in which both carbonyl O atoms participate in the H-bond network.

We hope that this classification of H-bonding in chiral crystals may provide further insight into the phenomenon of spontaneous resolution.

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