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COMMUNICATION

Helix-helix interactions – homochirality and heterochirality†

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The relatively simple molecule 2-amino-4-(thiazolin-2-yl)phenol, 1, as its acetonitrile solvate crystallises such that the lattice can be considered to contain heterochiral sheets of helical, N···HO H-bonded polymers which are linked within their sheets by weaker N···HN H-bonds between adjacent helices of opposite chirality. Weaker interactions of the CH···π type can be discerned as linking helices of the same chirality between these sheets, these interactions being reinforced by weaker interactions still involving the acetonitrile solvent molecules. A similar analysis can be conducted of the helical structures found within the lattice of the related compound 4-(methoxycarbonyl)-2-aminophenol, 2, although here it is more difficult to define the hierarchy of the weak interactions observed.

Introduction

Helicity is a common aspect of molecular structure in both the liquid and solid states, with the composition of the species involved varying from that as simple as SiO_2 to one as complex as DNA.[1] While the issue of which forces give rise to helical structures is of fundamental importance,[2–7] the interactions between helices are also critical in determining properties as diverse as the aggregation of proteins[8] and the crystallisation of a solid either as a racemic mixture or a racemic compound.[9] They may also be important in mixed synthetic and natural systems of medical potential.[10] Since such association is usually the result of weak interactions, its analysis must involve a dissection of forces which are not necessarily easily placed in a hierarchy.[11] While sophisticated tools are available for the analysis of helix-helix interactions in proteins,[12] for example, such systems involve not only numerous types of weak interaction but also numerous variations in any particular type of interaction, as well as being subject to the chirality bias of all natural materials. Hence, synthetic small molecule crystals, where helical assemblies may be identified in the lattice,[13] are of interest because of the possibility of establishing the hierarchy of a small number of separate interactions between helices of both the same chirality and of the opposite, as well as being of interest for the understanding of chiral interactions in general.[14] In the present instance, the molecule **1** (Fig. 1), 2-amino-4-(thiazolin-2-yl)phenol, has been found to crystallise, solvated, in a form where there are both right- and left-handed helical polymer entities resulting from N···O H-bonding present in the lattice and where these helices can be regarded as segregated into domains on the basis of different types of interactions occurring within these domains. It may be noted in general that the properties of chiral materials are of increasing interest in numerous sophisticated domains of science.[15]

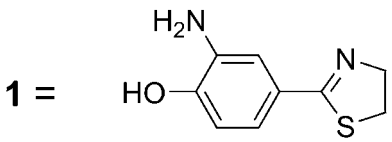

Fig. 1 Molecule **1**, studied as its crystalline acetonitrile solvate.

Results and discussion

Within the lattice of the mono-acetonitrile solvate of **1**, the closest intermolecular contact indicative of an H-bonding interaction is that between phenolic-O and –N of 2.688(3) Å. This interaction leads to the formation of helical polymer chains where the helix axis lies parallel to the crystallographic *b* axis (Fig. 2).

In viewing the lattice down *b*, the impression gained is that it has a layered form in which homochiral sheets of $\mathbf{1}_n$ helices alternate in planes parallel to *ab* (Fig. 3(a)). Acetonitrile molecules lie largely within these sheets and not between them, although from a view of the lattice down *c* (Fig. 3(b)) it is apparent that they lie in what would otherwise be voids formed through the molecular packing. Thus, there is clearly a degree of segregation of Δ and Λ forms of the helices within the lattice, though this segregation is incomplete in terms of the complete lattice since both forms are present.

Within a homochiral sheet, the shortest intermolecular contacts other than those of the H-bonds are those between the methylene groups of the thiazoline ring and the aromatic phenyl ring. Since these are presumably multi-centre CH···π interactions,[16] they are difficult to represent and only the shortest aliphatic-C···aromatic-C contacts of 3.367(3) Å are shown in Fig. 4. Three of the four H-atoms of the two methylene groups lie between 3.0 and 3.1 Å of aromatic carbons, a separation which is essentially that of van der Waals contact,[16] so that the interaction energy must be small, although they are interactions which occur with neighbours to each side of a given helix within the sheet.

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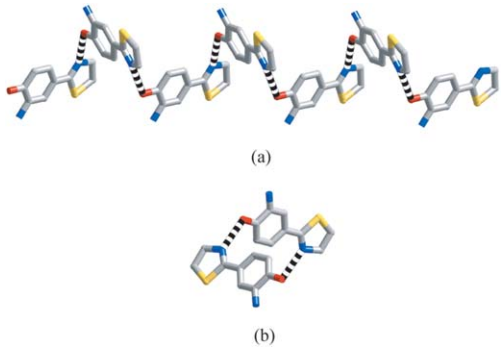

Fig. 2 Stick representations of one of the right-handed helices formed (along with the same number of left-handed) by thiazoline-N···phenol-O H-bonding (dashed lines) (a) perpendicular to the helix axis (which is parallel to b) and (b) down this axis. H-atoms are not shown but the phenolic H-atoms lie close to the dashed lines; N···H–O 174.7°.

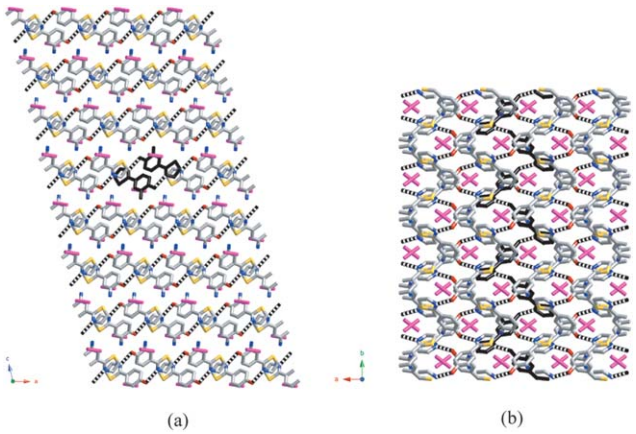

Fig. 3 Partial views of the crystal lattice of $\mathbf{1}\cdot CH_3CN$ (a) down b and (b) down c. For clarity, all atoms in the acetonitrile molecules are shown in pink and one H-bonded $\mathbf{1}_n$ helix is shown with all atoms in black.

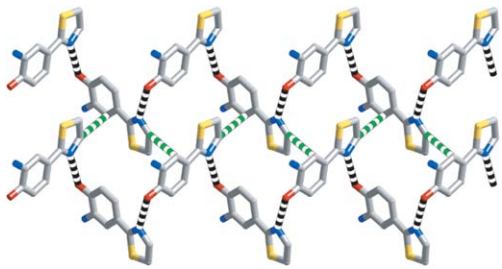

Fig. 4 A partial view of two adjacent left-handed helices present in a homochiral sheet (parallel to the ab plane) of the lattice of $\mathbf{1}\cdot CH_3CN$, showing the shortest methylene-C···aromatic-C contacts (3.367(3) Å) as green and white dashed lines (and the H-bonding contacts within the helices as black and white dashed lines).

Every helix within a given homochiral sheet has neighbours of opposite chirality to both sides in the adjacent sheets. The shortest intermolecular atomic contacts here (3.139(3) Å) are between the anilino-N and phenolic-O and are taken to be indicative of H-bonding which must be considerably weaker than that within the helical chains. However, as indicated in Fig. 5, these interactions are

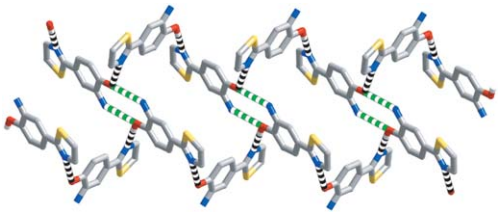

Fig. 5 A partial view of two adjacent helices of opposite chirality with the double H-bonding interactions between anilino-N and phenolic-O (3.139(3) Å) shown as green and white dashed lines.

reciprocal, that is, each can be regarded as double, thus possibly enhancing their influence. In combination, the two forms of N···HO H-bonding observed in the lattice can be regarded as defining an array (Fig. 6) which is a heterochiral sheet of helices lying parallel to the *bc* plane. As with the homochiral sheets, the acetonitrile molecules can also be considered to lie within these sheets.

A final issue to be considered in the analysis of the lattice structure of $\mathbf{1}\cdot CH_3CN$ is that of the reason for the presence of acetonitrile molecules. It is indeed difficult to find any evidence for strong, specific interactions, since all contacts to any of the three atoms in the solvent molecule are remote. The shortest, 3.266(3) Å, is that between acetonitrile-N and anilino-N and can be described as N···HN bonding but interestingly it is an interaction which serves to bind the heterochiral sheets together, since the anilino-N is in the sheet adjacent to that which can be considered to « contain » the acetonitrile. Within a *bc* (heterochiral) sheet, the shortest contact, of 3.470(3) Å, is that between the central acetonitrile-C and phenolic-O (incipient

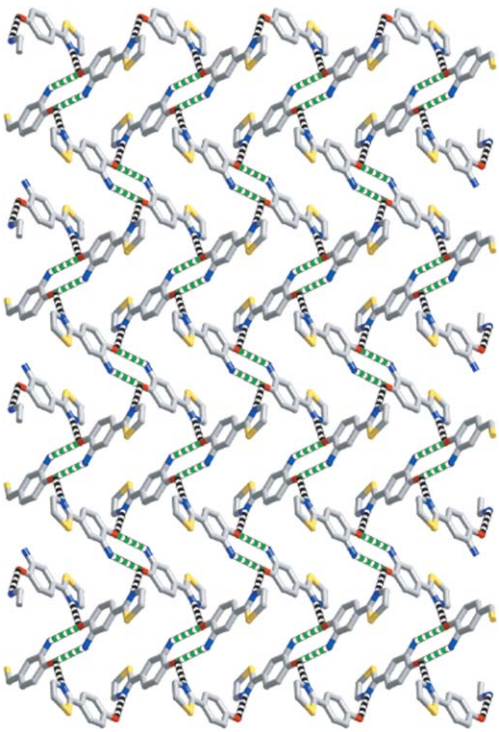

Fig. 6 A partial view of a heterochiral (*i.e.* overall achiral) sheet parallel to the bc plane within the lattice of $\mathbf{1}\cdot CH_3CN$ involving strong (black and white) and weak (green and white) hydrogen bonds, the former being considered to define the helices.

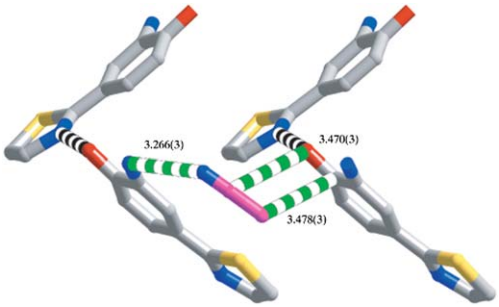

Fig. 7 The bridging contacts, shown as green and white dashed lines, of an acetonitrile molecule (C atoms pink, N atom blue) between two helices of the same chirality in different heterochiral sheets parallel to the bc plane.

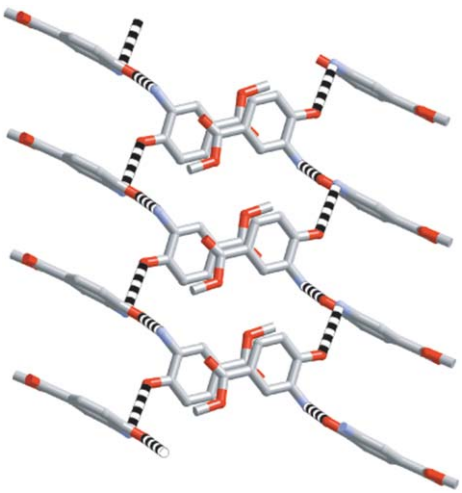

Fig. 8 A partial view of two adjacent helices formed by strong H-bonds (black and white dashed lines) and of opposite chirality, found within the lattice of unsolvated 4-(methoxycarbonyl)-2-amino phenol, **2**, showing the stacking of the methoxycarbonylphenyl units from separate helices.

nucleophilic addition?), although it is perhaps not significantly different from the contact, 3.478(3) Å, between the methyl-C and the aromatic-C to which the phenolic-O is attached, and which is presumably indicative of a CH···π interaction (and not, for example, a dipole–dipole interaction, since the two dipoles are parallel). These three interactions, shown in a perspective view in Fig. 7, link helices of the same chirality in adjacent *bc* sheets.

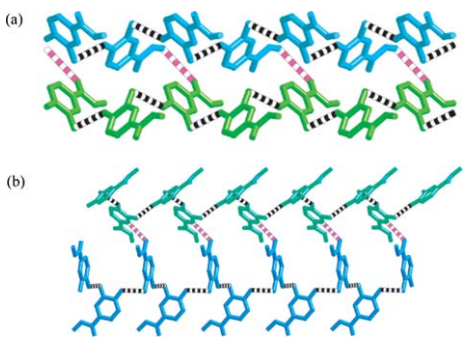

Fig. 9 Partial views of adjacent helices within the lattice of **2**, showing (a) CH_3···O contacts (3.488(8) Å; pink and white dashed lines) between helices of opposite chirality and (b) carbonyl-O···HC(aromatic) contacts (3.228(8) Å; pink and white dashed lines) between helices of the same chirality (here, left-handed).

The importance of the nature of the substituents on a 2-amino-phenol ring is nicely illustrated by a comparison of the structure of **1**·CH_3CN with that of 4-(methoxycarbonyl)-2-aminophenol, **2** obtained by recrytallisation from DCM. The latter forms a crystal lattice in which the dominant H-bonding motif (that is, the one involving the shortest OH···N contact, here 2.735(6) Å), is typical of 2-aminophenols[17] in that it involves the amino and hydroxyl groups and generates a helical polymer, although it may be noted that with a substituent as large as a difluorobora-azaindacene (« Bodipy »),[18] the H-bonded polymer is not helical. Once again, in the lattice of **2**, helical polymers of alternating chirality may be considered to lie in sheets (parallel to the *bc* plane) with inter-helix interactions seemingly mediated by stacking of the (methoxycarbonyl)phenyl groups (Fig. 8). In the *a* direction these sheets stack in such a way that helices of alternating chirality form sheets parallel to the *ab* plane, with interactions involving the methoxycarbonyl substituents in CH_3···O contacts (3.488(8) Å) (Fig. 9(a)). While the impression thus given is that heterochiral contacts are the more important in this lattice, there are in fact homochiral contacts (3.228(8) Å), again involving carbonyl-O but to an aromatic-CH and linking helices along a direction parallel to the *ac* diagonal (Fig. 9(b)). As well, there is an additional interaction of the amino group, apparently an NH···O (carbonyl) interaction (at 3.125(8) Å), linking homochiral helices. It is difficult to place a quantitative ordering on these various observations but since the lattice is heterochiral, the numerous close atom contacts (the shortest being carbonyl-O···C(2) of 3.346(8) Å, while C(4)···C (4′) is 3.500(8) Å) involved in the stacking parallel to the *bc* plane must presumably outweigh the simple pairs involved otherwise.

Conclusions

Contrary to the visual impression gained from the view of the lattice of **1**·CH_3CN down *b* that it might be considered as being built up from homochiral sheets of helical H-bond polymers of **1** lying parallel to the *ab* plane, if additional H-bonding interactions between the helical chains are more important than rather long contacts indicative of CH···π interactions, then the lattice is better regarded as being built up from heterochiral sheets lying parallel to the *bc* plane. This structure allows acetonitrile molecules to form links between the sheets involving a third and presumably weaker form of H-bonding along with probably extremely weak interactions, one of which might be termed electrostatic, the other CH···π. As has long been recognised in the search for weak interactions in crystal lattices,[19] there are many situations where it is difficult to establish whether or not a particular contact is simply enforced by the existence of others and thus it is possible than one or the other (or even both) of the non-H-bonding interactions of the acetonitrile molecule should be ignored. Nonetheless, at least one attractive interaction must be found to explain the presence of the solvent!

Overall, if the simple criterion of the distance of atom···atom separation for a given pair is taken as an index of the strength of an attractive interaction, the nature of the lattice of **1**·CH_3CN can be readily rationalised. In this case, interactions between helices of opposite chirality dominate those between helices of the same chirality, giving rise to a lattice which is overall achiral. While it is

observed that chiral (but racemic) compounds crystallise far more frequently as racemic compounds than as racemic mixtures,[1] this applies to many systems which do not involve extended helices in their crystal lattices. The present study is nonetheless informative in that it suggest various ways in which hetero- *versus* homo-chiral interactions might be controlled. Thus, methylation of the aromatic amino group, for example, should serve to block the principal interactions favoring heterochiral contacts. While numerous structures of 2-aminophenol derivatives may be found in the Cambridge data base, nearly all have such elaborate or particular functionalisation that no direct comparison with the present systems is possible. In the case of the relatively simple derivative N(2-hydroxy-5-methylphenyl)-imidazole,[24] for example, the lattice contains helical polymer units due to phenolic-OH interactions with the unalkylated imidazole-N and contacts (CH$\cdots\pi$) between homochiral helices appear to be shorter than those between heterochiral, with no obvious contacts involving the N-atom bound to the phenyl ring, but obviously the incorporation of this N-atom into an imidazole ring must alter its properties rather greatly.

Experimental

Synthesis

a) molecule 1. To a solution of 3-amino-4-hydroxybenzoic acid (1 g, 6.52 mmol) in dry DMF (20 ml) 1-hydroxybenzotriazole (HOBt, 0.88 g, 6.52 mmol) and N,N′- diisopropylcarbodiimide (DIC, 0.82 g, 6.52 mmol) were added under an N_2 atmosphere. After 30 min. stirring, 2-aminoethanethiol hydrochloride (0.74 g, 6.52 mmol) was added and the mixture was stirred at room temperature under N_2 for 24 h. After removal of the solvent, H_2O (50 ml) was added to the residue and the mixture was extracted with DCM (3 × 50 ml). The combined organic phases were dried over Na_2SO_4, filtered and taken to dryness. The colourless residue was recrystallised from acetonitrile to give the pure product as a colourless crystals. Yield: 0.31g (1.57 mmol, 24%). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ (ppm) = 3.12 (m, 2H), 4.02 (s, 1H), 4.53 (s, 2H), 6.52 (d, J = 8.4, 1H), 6.57 (d, J = 6.4 Hz, 1H), 6.71 (s, 1H), 7.58 (t, 1H) 9.46 (s, 1H). ^{13}C NMR ([D$_6$] DMSO, 100 MHz): δ = 54.7, 75.6, 113.2, 116.4, 119.6, 132.3, 137.2, 142.0, 159.2. HR-MS (ES): calcd for $C_9H_{13}N_2OS$: m/z = 197.0739, found m/z = 197.0522 $[M + H]^+$. Microanalysis: calcd (%) for $C_9H_{12}N_2OS\cdot$2MeCN: C 56.09, H 6.52, N 20.13; found C 56.38, H 6.42, N 20.05.

b) molecule 2. Commercial 3-amino-4-hydroxybenzoic acid (1 g, 6.52 mmol) was suspended in methanol (40 ml) under N_2. Sulfuric acid (0.7 ml, 13.1 mmol) was added slowly *via* syringe, and the mixture was heated under reflux for 24 h. On cooling, it was neutralized with saturated $NaHCO_3$ solution to pH = 7 and extracted with DCM (3 × 50 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. A brown solid was isolated and recrystallized from DCM. The crystals obtained were suitable for X-ray crystallography. Yield: 0.52g (3.11mmol, 47%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.86 (s, 3 H, CH_3), 6.79 (d, J = 8 Hz, 1H, H_2), 7.43 (dd, J = 8 Hz and 1.6 Hz 1H, H_1), 7.46 (s, 1H, H_5). ^{13}C-NMR ($CDCl_3$, 100 MHz): 52.0, 114.5, 117.8, 122.3, 122.4, 133.9, 148.9, 167.7. HR-MS (ES): calcd for $C_8H_{10}N_1O_3$: m/z = 168.0655, found m/z = 168.0661 $[M + H]^+$.

Table 1 Crystal data and structure refinement details

Compound	**1**·CH$_3$CN	**2**
Chemical formula	$C_9H_{11}N_2OS\cdots CH_3CN$	$C_8H_9NO_3$
M/g mol^{-1}	235.31	167.16
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$Pbca$
a/Å	8.0960(2)	10.1980(8)
b/Å	9.8380(2)	8.7310(12)
c/Å	15.2620(5)	17.664(2)
α/°	90.00	90.00
β/°	103.0690(9)	90.00
γ/°	90.00	90.00
V/Å^3	1184.11(5)	1572.8(3)
Z	2	8
D_c/g cm^{-3}	1.320	1.412
μ/mm^{-1}	0.256	0.109
F(000)	496	704
T/K	173(2)	173(2)
Reflections collected	5856	3185
Independent reflections	3443	1774
"Observed" reflections ($I > 2\sigma(I)$)	2720	868
R_{int}	0.017	0.091
Parameters refined	146	119
R_1	0.047	0.077
wR_2	0.134	0.1672
S	1.046	1.050

Crystallography

X-Ray diffraction data collection was carried out at 173(2) K on a Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ = 0.71073 Å). COLLECT software[20] was used for the data measurement and DENZO-SMN[21] for the processing. The structures were solved by direct methods using the program SHELXS-97.[22] The refinement and all further calculations were carried out using SHELXL-97.[23] The H-atoms of the OH, NH and NH_2 groups were located from Fourier difference maps and refined isotropically. The other H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2 (Table 1).

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