

Pseudopolymorphs of 3,5-dinitrosalicylic acid

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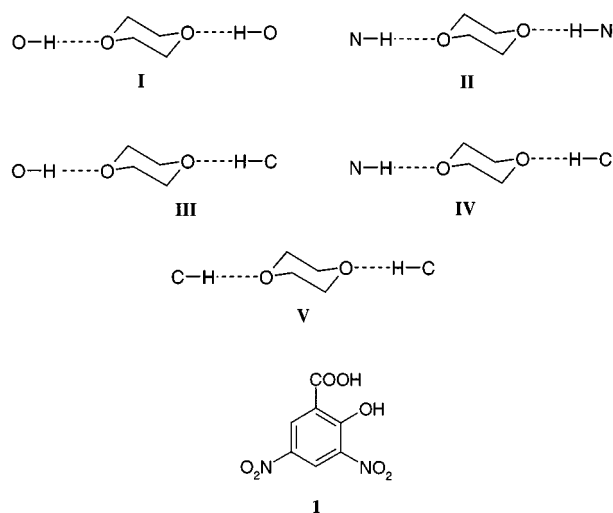
Seven pseudopolymorphs of 3,5-dinitrosalicylic acid are studied. Four of these (A–D) are obtained from dioxane and their formation is rationalised on the basis of simultaneous O–H...O and C–H...O bond formation between the donor-rich solute molecule and the multiple-acceptor solvent. A fifth (E) is a previously reported centrosymmetric hydrate. The sixth and seventh (F and G) are a non-centrosymmetric hydrate and a *tert*-butyl alcoholate whose structures are related to that of form E, in that hydrogen bonds are both donated and accepted between solute and solvent. The formation of this rich diversity of pseudopolymorphs with hydrogen bonding solvents follows from the nature of the title acid while the similarities between the structures of the pseudopolymorphs may be accounted for in terms of a permutation of a small number of solute–solvent supramolecular synthons. All this indicates that this interesting phenomenon may be both anticipated and also studied systematically. The scope of the term *pseudopolymorph* has been extended a little, in the expectation that such a definition would be of more general utility.

Introduction

Solvent is generally not included in crystals when organic compounds are recrystallised. A recent survey of the Cambridge Structural Database (CSD) shows that fully 85% of all organic crystals do not contain solvent of crystallisation.¹ This observation may be rationalised by assuming that crystallisation begins with solute–solvent aggregates that contain solute–solute, solute–solvent and solvent–solvent interactions. The entropic gain in eliminating solvent molecules from these aggregates into the bulk solution, and the simultaneous enthalpic gain in forming stable solute species that contain robust supramolecular synthons provides an adequate driving force for nucleation and crystallisation leading to solvent-free crystals. When solvent is included, however, one needs to consider the formation of pseudopolymorphs, that is crystalline forms of a compound that differ in the nature or stoichiometry of the included solvent.^{2,3} Pseudopolymorphism is an important phenomenon for both fundamental and applied reasons^{4,5} but it has not been the subject of much systematic study.

There are many reasons for the inclusion of solvent in organic crystals and these depend on the nature of both solute and solvent. The formation of a solvated crystal may be considered with reference to the mechanism for crystallisation sketched above. If solute–solvent interactions are unusually important, say because of multipoint recognition, the entropic advantage associated with solvent expulsion into the bulk may be overridden by these additional enthalpic factors resulting in retention of some solvent in the crystal. Indeed, multi-point recognition between solvent and solute appears to be a critical factor that determines ease of solvation, especially for organic solvents capable of strong and/or weak hydrogen bonding. For instance, the CSD study referred to above¹ showed that the likelihood of solvation by 1,4-dioxane is unusually high because it is able to act as a double acceptor of strong and/or weak hydrogen bonds. It was found that of the 83 ordered dioxane solvates in the CSD, there were 12, 5, 13, 8 and 40 hits that contained respectively the doubly hydrogen bonded synthons I–V. It appears then that whenever dioxane is included in an organic crystal, it is almost always hydrogen bonded and more importantly, to more than one donor.

With this background, we considered 3,5-dinitrosalicylic acid, C₇H₄N₂O₇, **1**. This molecule contains a number of hydrogen bond donors (two O–H and two acidic C–H groups), and accordingly it was expected that it would be a good candidate



for the observation of dioxane pseudopolymorphs. Acid **1** proved to be an unusually serendipitous choice for this purpose and this paper describes the structural chemistry of seven pseudopolymorphs formed by this acid, of which an unprecedented four are with dioxane.

Experimental

Acid **1** was prepared by nitration of salicylic acid (HNO₃–H₂SO₄). Two successive precipitations from Na₂CO₃ solution followed by two recrystallisations from water gave the raw material (mp 171 °C) which was used for all further experiments. This procedure removes all traces of the mononitro derivative (mp 229 °C) obtained in the reaction. All the crystal forms reported in this work were obtained from material that originated from a single nitration batch.

Crystals obtained for data collection were recrystallised from the appropriate solvent. A particular crystallisation from dioxane resulted in any (but only one) of forms B, C and D. X-Ray diffraction data were collected on capillary sealed crystals on an Enraf-Nonius MACH-3 diffractometer at 293 K, using Mo-K α X-rays, in the ω scan mode. Structure solution and refinement was carried out with SHELX-97.⁶ All structure solutions, refinements and auxiliary computations were carried out on a Silicon Graphics Indigo2 workstation.

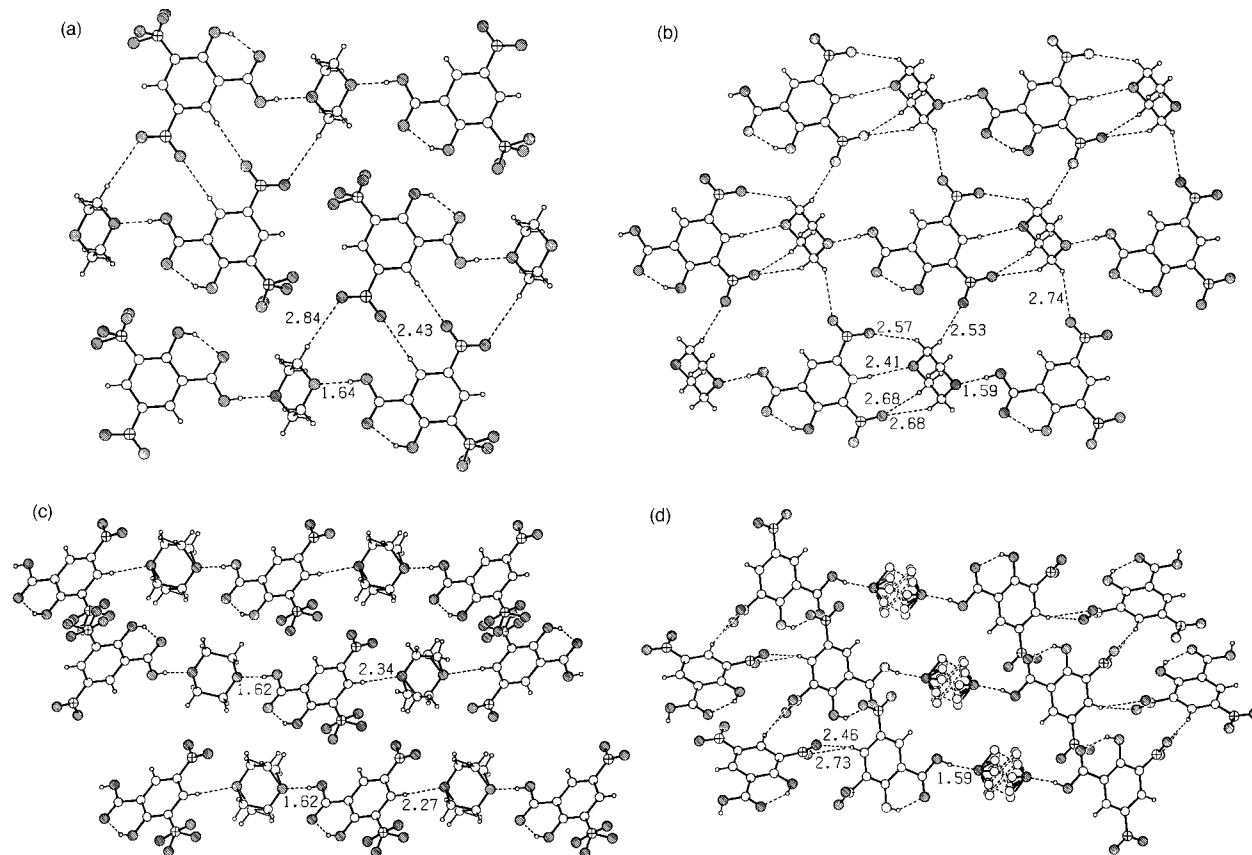


Fig. 1 (a)–(d) Crystal structures of pseudopolymorphs A–D in the 1,4-dioxane–3,5-dinitrosalicylic acid system. All disordered atomic positions are shown. H-atom positions are normalised. Some hydrogen bond metrics are shown. In all the cases, the two-dimensional structure is constituted with rows of acid and solvent molecules arranged according to synthons **VI**, **VIII** and/or **IX**.

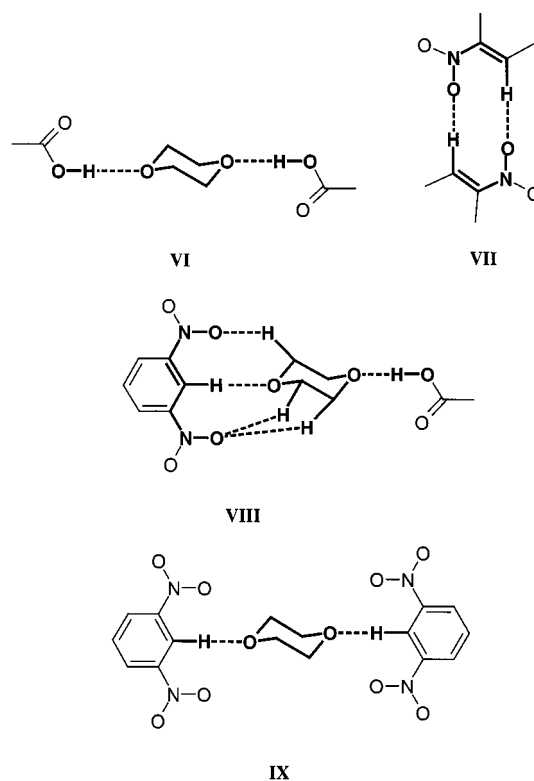
Table 1 contains pertinent crystallographic details for the structures determined in this study.†

Results and discussion

Acid **1** is extremely soluble in dioxane. The very first recrystallisation experiment yielded large crystals of a 2:1 acid–dioxane solvate **A** ($P\bar{1}$), in the presence of excess mother liquor. These crystals were moderately stable when kept in the open (*ca.* 2 h) and in the X-ray beam (40% decay in 5 h). Subsequent experiments (saturated solutions, 2–3 days) never resulted in form **A**,^{7,8} but rather in one of three other crystal forms. These are the 1:1 solvate **B** ($P\bar{1}$), the 1:1 solvate **C** ($P\bar{1}$) and the 2:1 solvate **D** ($P2_1/m$). Forms **B–D** were invariably obtained when almost all the solvent had evaporated, as small needles or tablets. In contrast to **A**, these forms are very unstable with respect to solvent loss. Though they were obtained easily enough, any particular crystallisation batch contained curiously only one of the three forms **B**, **C** or **D**.

Figs. 1(a)–(d) show respectively the crystal structures of solvates **A–D**. In every case, the carboxylic acid group has the *syn* conformation and is ordered and the phenolic H-atom is intramolecularly hydrogen bonded. The nitro groups that do not accept O–H or C–H groups in hydrogen bonds are generally disordered. The dioxane molecules are located in channels accounting for their easy loss from the crystals. The existence of four such solvates for a simple compound like **1** is quite unusual, even unprecedented.‡

The structures of pseudopolymorphs **A–D** may be rational-



ised in terms of alternative arrangements of a small number of robust multi-point supramolecular synthons. The most important synthon in form **A** is **VI** which links two molecules of **1** via a dioxane molecule with O–H...O hydrogen bonds. The unfulfilled C–H...O bond forming capability of **1** is satisfied by dimer synthon **VII** while the solvent acts as an additional weak

† CCDC reference number 188/164. See: <http://www.rsc.org/suppdata/p2/1999/1069> for crystallographic files in .cif format.

‡ For three monohydrates of 3,4-dihydroxybenzoic acid, see CSD refcodes BIJDON, BIJDON01, BIJDON02 (I. Agmon and F. H. Herbstein, *Eur. Cryst. Meeting*, 1982, 7, 50).

Table 1 Crystallographic data for the pseudopolymorphs of acid **1** in this study

Form	A	B	C	D	E ^a	F	G
Empirical formula	C ₇ H ₄ N ₂ O ₇ ·(C ₄ H ₈ O ₂) _{0.5}	C ₇ H ₄ N ₂ O ₇ ·C ₄ H ₈ O ₂	C ₇ H ₄ N ₂ O ₇ ·C ₄ H ₈ O ₂	C ₇ H ₄ N ₂ O ₇ ·(C ₄ H ₈ O ₂) _{0.5}	C ₇ H ₄ N ₂ O ₇ ·H ₂ O	C ₇ H ₄ N ₂ O ₇ ·H ₂ O	C ₇ H ₄ N ₂ O ₇ ·C ₄ H ₁₀ O
Crystal system	triclinic	triclinic	triclinic	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2/ <i>c</i>	<i>C</i> 2	<i>Pca</i> 2 ₁
<i>a</i> /Å	6.006(4)	6.6852(8)	9.149(15)	11.3053(10)	25.373(7)	16.487(4)	10.290(4)
<i>b</i> /Å	9.517(4)	9.7347(18)	11.912(3)	6.0266(5)	6.529(8)	5.8204(16)	5.972(3)
<i>c</i> /Å	10.396(5)	10.5534(18)	13.318(4)	16.9126(2)	12.495(4)	13.462(4)	22.928(7)
<i>α</i> ^o	78.99(3)	79.468(17)	111.22(3)	90	90	90	90
<i>β</i> ^o	73.84(5)	80.152(14)	90.13(6)	97.921(9)	111.90(1)	132.58(2)	90
<i>γ</i> ^o	85.86(5)	82.990(12)	101.12(4)	90	90	90	90
<i>Z</i>	2	2	4	4	8	4	4
<i>V</i> /Å ³	560.1(5)	662.35(18)	1323.0(2)	1141.30(14)	1921(3)	951.2(5)	1409.1(10)
<i>D</i> _{calc} /g cm ⁻³	1.614	1.586	1.587	1.561	1.702	1.719	1.425
<i>R</i> ₁	0.0578	0.0568	0.0630	0.0704		0.0592	0.0499
<i>wR</i> ₂	0.1469	0.1368	0.1642	0.2114		0.1143	0.1191
GOF	0.991	1.030	1.049	1.045		1.012	0.984
<i>θ</i> range/ ^o	1.5–25	1.5–30	1.5–28	1.5–28		1.5–32.5	1.5–28
Unique reflections	1924	3851	6384	2734		1867	1738
Observed reflections	932	2088	3316	1446		1057	1082
Variables	178	190	436	184		150	181
Solvent	dioxane	dioxane	dioxane	dioxane	ethanol	water	<i>tert</i> -butyl alcohol

^a See reference 11.

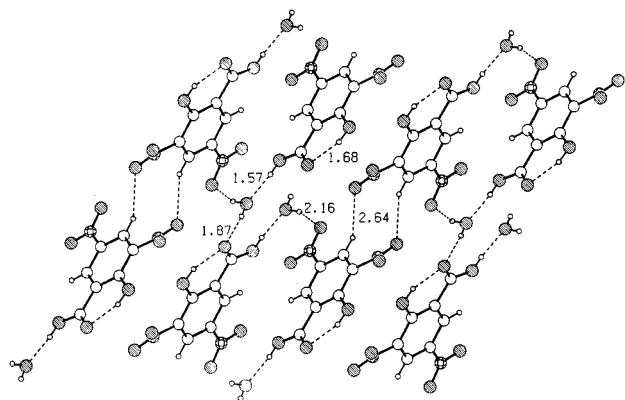
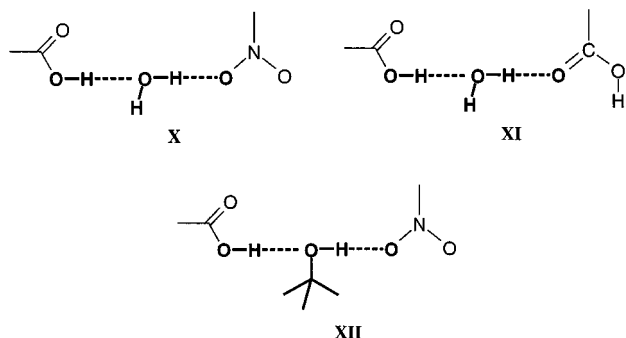


Fig. 2 Crystal structure of form F, the non-centrosymmetric hydrate of acid **1**. Notice the donor and acceptor roles of the water molecules and the formation of synthon **XI**. There is additional hydrogen bonding between the water and the nitro groups.

C–H donor. Form B is more interesting in that the main synthon **VIII** is a composite motif that includes both strong and weak hydrogen bonds. The O–H...O hydrogen bond pattern resembles synthon **VI**, while the C–H...O bonds assemble into a multi-point recognition pattern similar to that found in complexes of *sym*-trinitrobenzene.⁹ Form C contains elements of both forms A and B. The structure consists of rows of acid and dioxane molecules. One set contains synthon **VIII** almost as in form B while the alternating set contains synthon **VI** linked together through the C–H...O hydrogen bonded synthon **IX**.¹⁰ In both sets, the dioxane molecules are slightly disordered. In form D, the C–H and C–C groups of the dioxane are heavily disordered but the O-atoms are ordered presumably because of the hydrogen bonded synthon **VI**. All four structures are closely related and can be understood in terms of the similarities between the synthons **VI**, **VIII** and **IX** that are characteristic of this solvent. Needless to say, we made several attempts to isolate more dioxane solvates of acid **1** and even used additives like dithiane and 5-nitrosalicylic acid in some of these experiments. No other forms could be obtained, but their existence cannot be completely ruled out.

Observing the structural variety and richness of these dioxane pseudopolymorphs, we turned our attention to other solvents. A centrosymmetric 1:1 hydrate (space group *C2/c*) from EtOH has been previously reported¹¹ (form E) and contains synthon **X**. Water contains good hydrogen bond donor



and acceptor groups, and consequently it can both accept from and donate hydrogen bonds to acid **1**. Accordingly the solvent is held to the solute here too in a multi-point manner. We were able to isolate a different 1:1 hydrate (form F) from water. This was invariably obtained when acid **1** was recrystallised from water (rather than EtOH) and is non-centrosymmetric (space group *C2*). The crystal structure of pseudopolymorph F is shown in Fig. 2 and is seen to contain the multi-point synthon **XI** that is related to **X**. The crystal structures of the centrosymmetric form E and the non-centrosymmetric form F are

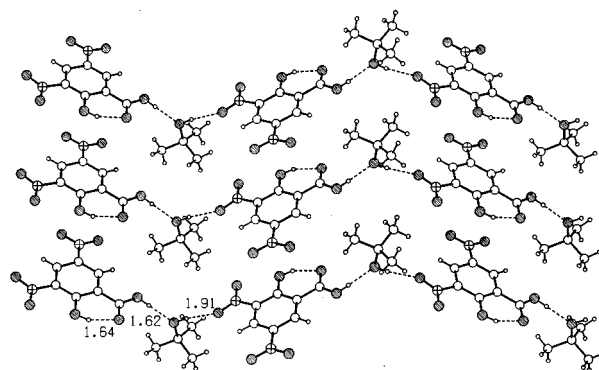


Fig. 3 Crystal structure of form G, the *tert*-butyl alcohol solvate of acid **1**. Notice the formation of synthon **XII** and its relationship to synthon **X**.

similar with respect to the hydrogen bond patterns; this led to the hypothesis that other related pseudopolymorphs could be obtained from alcoholic solvents. Accordingly, when material was crystallised from *tert*-butyl alcohol, a 1:1 solvate (form G, space group *Pca2*₁) was obtained (Fig. 3). This contains synthon **XII**, that closely resembles synthon **X**.

Conclusions

These results show that: (i) a compound like acid **1** with different hydrogen bonding donor groups can form a permutation of supramolecular synthons with a solvent like dioxane which has multiple accepting capability; (ii) the multi-point nature of these synthons leads to retention of solvent in the crystal; (iii) the structural variety of the possible supramolecular synthons results in the formation of pseudopolymorphs; (iv) other hydrogen bonding solvents like water and *tert*-butyl alcohol with dual donor–acceptor capability may also lead to pseudopolymorphic structures; (v) the classification of crystal forms as polymorphs or pseudopolymorphs could be subjective. Pairs A,D and B,C are stoichiometrically identical and may be termed polymorphs. Pairs A,B and A,C or B,D and C,D may be termed pseudopolymorphs. Alternatively all the seven forms A–G could be termed pseudopolymorphs.

In this last context, it may be noted that the terms *polymorph* and *polymorphism* should be used with caution for crystals which contain more than one chemical entity. We would also like to expand the definition of the term *pseudopolymorph* to cover those cases of solvation where different crystal structures are obtained in forms which have the same solvent and solute: solvent ratio. So, *pseudopolymorphs are solvated forms of a compound which have different crystal structures and/or differ in the nature of the included solvent*. The term *polymorph* should preferably be confined to single-component crystals. According to these definitions and conventions, the legal implications of the terms *polymorph* and *pseudopolymorph* are the same. Finally, it should also be appreciated that the scope of terms such as *pseudopolymorph*, *solvate*, *inclusion compound* and *clathrate* are intersecting and that one term may be more appropriate than another, depending on the particular chemical situation.

The derivation of the structures of pseudopolymorphs A–G from a few hydrogen bonded synthons argues in favour of crystallisation proceeding through these sub-structural units.¹² The formation of these closely-related solvates of acid **1** re-emphasises the importance of structure-defining interactions and the enthalpic and electrostatic basis of crystal engineering.¹³ Strong O–H...O and weak C–H...O hydrogen bonds are of utmost importance here and one can interchange equivalent synthons to obtain these seven crystal structures. The formation of just one pseudopolymorph in a particular crystallisation batch and the non-appearance of form A in subsequent

crystallisations hint that kinetic factors also need to be considered.^{7,8} However, they probably operate within an overall framework provided by the thermodynamic factors.¹³

Acknowledgements

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References

- 1 A. Nangia and G. R. Desiraju, *Chem. Commun.*, 1999, 605.
- 2 J. Bernstein, in *Organic Solid State Chemistry*, Ed. G. R. Desiraju, *Studies in Organic Chemistry*, vol. 32, Elsevier, Amsterdam, 1987, pp. 471–518.
- 3 T. L. Threlfall, *Analyst*, 1995, **120**, 2435.
- 4 R. David and D. Giron, *Handb. Powder Technol.*, 1994, **9**, 193.
- 5 S. R. Byrn, *Solid-State Chemistry of Drugs*, Academic Press, 1982, New York.
- 6 G. M. Sheldrick, SHELX-97, Program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.
- 7 J. D. Dunitz and J. Bernstein, *Acc. Chem. Res.*, 1995, **28**, 193.
- 8 J. Bernstein and J.-O. Henck, *Cryst. Eng.*, 1998, **1**, 119.
- 9 K. Biradha, A. Nangia, G. R. Desiraju, C. J. Carrell and H. L. Carrell, *J. Mater. Chem.*, 1997, **7**, 1111.
- 10 H. Bock, R. Dienelt, H. Schödel and Z. Havlas, *J. Chem. Soc., Chem. Commun.*, 1993, 1792.
- 11 G. Smith, D. E. Lynch, K. A. Byriel and C. H. L. Kennard, *Aust. J. Chem.*, 1995, **48**, 1133.
- 12 G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
- 13 G. R. Desiraju, *Science*, 1997, **278**, 404.

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