ELSEVIER

International Journal of Pharmaceutics 194 (2000) 147–153

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Studies of polymorphism in three compounds by single crystal X-ray diffraction

Philip J. Cox [a,*], James L. Wardell [b]

[a] *School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen AB10 1FR, UK*
[b] *Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen, Aberdeen AB24 3UE, UK*

Received 10 March 1999; accepted 12 October 1999

Abstract

The role of single crystal diffraction in the quantitative determination of polymorphism is demonstrated by the examination of three compounds. Two polymorphs were found for each of the compounds bis(2-nitrophenyl) trisulphide (1), 2-amino-5-nitrobenzophenone (2) and bis(2-nitrophenyl) sulphide (3). Only in one polymorph of (1) does molecular symmetry correspond with crystallographic symmetry. In (2) the polymorphs arise in the same crystal class and in the same crystallographic space group whereas in (3) the two polymorphs exist in different crystal classes and hence in different space groups. Crystallographic space group transformation is also discussed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Crystals; Polymorphism; X-ray crystal structure; Transformations; Symmetry

1. Introduction

The search for polymorphic crystals is part of any preformulation study on a new drug candidate as different crystal structures of the same drug may lead to different bioavailabilities. This fact is certainly relevant for chloramphenicol palmitate and novobiocin, but perhaps less so for many other drugs. Polymorphism can be problematic in the advanced stages of product development. For example, the unexpected appearance of a new polymorph of the HIV protease inhibitor ritonavir, recently caused problems with manufacture and batch release of the capsule formulation (1998). The possibility that metastable polymorphs may be kinetically stabilised is therefore worthy of study (Blagden and Davey, 1999). For financial reasons it is not unusual to find physical form patenting in support of a product, e.g. Glaxo's ranitdine Form 2 patent, SmithKline Beecham's cimetidine Form A patent and Fison's support of salbutamol with patents claiming particle size and moisture content ranges (Steele, 1994). Theoretical considerations involving polymorph prediction methods (Gavezzotti, 1991; Gdanitz, 1992; Karfunkel and Gdanitz, 1992; Chaka et al., 1996; Verwer and Leusen, 1998; Hofmann and Lengauer, 1999) and computer

* Corresponding author. Tel.: +44-1224-262535; fax: +44-1224-262555.
E-mail address: p.j.cox@rgu.ac.uk (P.J. Cox)

PII: S0378-5173(99)00364-6

software such as C^2-polymorph (Leusen, 1998) attempt to find polymorphs by fitting organic molecules into possible crystallographic space groups.

Numerous reviews on crystal polymorphism have been published (Borka and Haleblian, 1990; Borka, 1991; Bernstein, 1993; Threlfall, 1995; Brittain, 1997; Caira, 1998).

Apart from systematic searches, polymorphs may also be discovered by chance when their presence has not been sought — for example in intermediate compounds formed in multi-step reaction sequences. This can be related to differences in physical properties of polymorphs which may be assigned — erroneously — to different compounds. When suitable crystals can be found the principal arbiter in these considerations is the practical technique of X-ray single crystal diffraction which leads to a definition of the crystal structure from a set of 3-dimensional atomic coordinates expressed as fractions of unit cell lengths associated with the symmetry of a specific crystallographic space group. When a sample is crystalline but suitable single crystals are unobtainable, then the technique of X-ray powder diffraction for structure solution is meeting with increasing success.

2. Methods and experiment

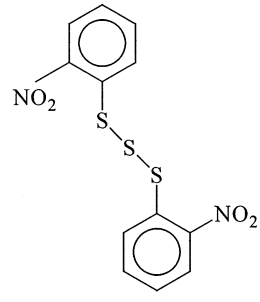
Single-crystal studies using various X-ray diffractometers have been performed by various authors on all six polymorphs (1a, 1b, 2a, 2b, 3a, 3b). Comparison of these structures plus, previously unpublished data relating to the redetermination of the molecular structure of (2a) and the novel structure solution of (3b) are presented here.

For the redetermination of (2a) X-ray data were collected on a Rigaku AFC7S four-circle diffractometer. For (3b). X-ray data were collected on a Delft Instruments FAST diffractometer using an area detector. The structures of (2a) and (3b) were solved by direct methods using SIR92 (Altomare et al., 1994) and refined with SHELX-97 (Sheldrick, 1998). The non-hydrogen atoms were refined with anisotropic displacement parameters and the hydrogen atoms with isotropic displacement parameters. The hydrogen atoms coordinates were allowed to ride on their attached carbon atom coordinates.

3. The three compounds

3.1. Bis(2-nitrophenyl) trisulphide (1)

The important consideration for this molecule is the presence of a twofold molecular symmetry axis.



The first report of the crystal structure of this molecule (Howie and Wardell, 1996) showed the molecule in a triclinic space group, (1a) whereas a polymorphic form, (1b), was found in an orthorhombic space group (Cox and Wardell, 1997). In the triclinic form (1a) the molecular twofold axis is not related to the crystallographic symme-

Table 1
Unit cell dimensions of (2a) and (2b)

	Space group	Unit cell dimensions	Cell volume (Å^3)
(2a)	$P2_1/b$	$a = 7.851$, $b = 12.686$, $c = 11.121$; $\alpha = 90°$, $\beta = 90°$, $\gamma = 95.5°$	1102
(2a)	$P2_1/c$	$a = 7.851$, $b = 11.121$, $c = 12.686$; $\alpha = 90°$, $\beta = 95.5°$, $\gamma = 90°$	1102
(2b)	$P2_1/c$	$a = 5.736(2)$, $b = 14.693(2)$, $c = 13.112(1)$ Å; $\alpha = 90°$, $\beta = 98.87(4)°$, $\gamma = 90°$	1091.8(3)

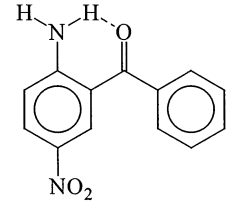
Table 2
Redetermined crystal data and structure refinement for (2a)

Final weighting scheme:	Calc $w=1/[\sigma^2(F_o^2)+(0.0588P)^2+$
Empirical formula	$C_{13}H_{10}N_2O_3$
Formula weight	242.23
Temperature	123(2) K
Colour	Yellow
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a=7.701(2)$ Å $b=11.120(2)$ Å $c=12.7066(10)$ Å $\alpha=90°$ $\beta=96.749(13)°$ $\gamma=90°$
Volume	1080.5(4) Å^3
Z	4
Density (calculated)	1.489 Mg/m^3
Absorption coefficient	0.108 mm^{-1}
$F(000)$	504
Crystal habit	Prism
Crystal size	$0.40\times0.30\times0.30$ mm
θ range for data collection	2.66–27.00°
No. standard reflections	3 (every 150 reflections)
Scan type	$\omega-2\theta$
No. reflections used for cell	18 (in 9–22° θ range)
Scan widths A,B,M. Speed	1.21, 0.35, 0.50°·12°/min
Decay	none
Index ranges	$0\le h\le9$ $0\le k\le14$ $-16\le l\le16$
Reflections collected	2529
Independent reflections	2356 [R(int) = 0.0244]
Observed reflections [$(I>2\sigma(I)$]	1796
Refinement method	Full-matrix l.s. on F^2
Number of parameters	165
Goodness-of-fit on F^2 (S)	1.052
Final R indices [$I>2\sigma(I)$]	$R^1=0.0376$, $wR^2=0.1037$
R indices (all data)	$R^1=0.0617$, $wR^2=0.1153$
Final weighting scheme:	Calc $w=1/[\sigma^2(F_o^2)+(0.0588P)^2+$ 0.2884P] where $P=(F_o^2+2F_c^2)/3$
Residual diffraction max	0.336 e/Å^3
Residual diffraction min	−0.299 e/Å^3

try whereas in (1b) the relationship is present. In the crystals of (1b) the twofold axis passing through the central S atom enables the coordinates of symmetry-related atoms to be generated by the operation $(1-x,\ 1-y,\ z)$. Hence the asymmetric unit in (1b) is only half the molecule, whereas, in (1a) the asymmetric unit is the whole molecule. These are clearly different crystal forms of the same compound.

3.2. 2-Amino-5-nitrobenzophenone (2)

This compound contains no molecular symmetry but possesses both intra and inter-molecular H-bonding. Differences in H-bonding can lead to different molecular packing arrangements in crystals resulting in polymorphism.



The first report of the crystal structure of this molecule (Dvorkin et al., 1985) showed the molecule in the monoclinic space group, $P2_1/b$, (2a) and a subsequent polymorphic form was found (Cox et al., 1998) in the monoclinic space group $P2_1/c$, (2b). The two structures are polymorphic but the difference in these two space groups is not relevant as $P2_1/b$ can be transformed into $P2_1/c$ as shown in Section 3.2.1. Only small differences in the H-bonding in (2a) and (2b) were observed.

3.2.1. Crystal unit cell transformations

It is possible to obtain a crystallographic data set for a given polymorph which can be interpreted in a number of different space groups. Computer programs such as LePage (Spek, 1998) are available which perform these mathematical transformations prior to structure solution. On completion of structure solution and refinement the geometry program, Platon, (Spek, 1999) will also alert the user to possible higher symmetry space groups. For a given data set the space

Table 3
Atomic coordinates ($\times 10^4$) and equivalent isotropicdisplacement parameters ($Å^2 \times 10^3$) for (2a)[a]

Atom	x	y	z	U_{eq}
O(1)	6920(1)	−543(1)	10 335(1)	19(1)
O(2)	12 236(2)	4296(1)	9083(1)	26(1)
O(3)	11 333(2)	4097(1)	10 625(1)	24(1)
N(1)	7655(2)	−350(1)	8300(1)	20(1)
N(2)	11 357(2)	3770(1)	9699(1)	18(1)
C(1)	8407(2)	1120(1)	9689(1)	15(1)
C(2)	8482(2)	662(1)	8646(1)	16(1)
C(3)	9456(2)	1313(1)	7952(1)	17(1)
C(4)	10 373(2)	2322(1)	8280(1)	18(1)
C(5)	10 339(2)	2732(1)	9322(1)	16(1)
C(6)	9353(2)	2151(1)	10 009(1)	15(1)
C(7)	7339(2)	517(1)	10 432(1)	15(1)
C(8)	6716(2)	1246(1)	11 309(1)	15(1)
C(9)	5901(2)	2353(1)	11 101(1)	18(1)
C(10)	5156(2)	2953(1)	11 896(1)	21(1)
C(11)	5254(2)	2464(1)	12 909(1)	20(1)
C(12)	6105(2)	1367(1)	13 124(1)	19(1)
C(13)	6817(2)	756(1)	12 326(1)	17(1)

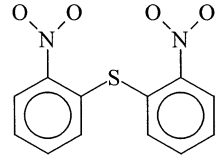
[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

group which should be chosen is the one of highest symmetry in which the structure can be solved and successfully refined. Table 1 shows the published unit cell dimensions of (2a) in space group $P2_1/b$ and the simple transformation to the more conventional space group $P2_1/c$, together with the unit cell dimensions of (2b).

The space groups of (2a) and (2b) are now the same, i.e. $P2_1/c$, and the cell volumes are essentially the same, but the unit cell dimensions are different. Furthermore, we have not been able to transform the cell dimensions of (2a) into the cell dimensions of (2b). To fully establish (2b) as a polymorphic form of (2a) crystals of (2a) were obtained and subjected to an independent structure determination by X-ray crystallography. The crystal data from this determination are presented in Table 2 and the atomic coordinates are shown in Table 3. Further details (bond lengths, valency angles, torsion angles, anisotropic thermal displacements and hydrogen positions) are available as supplementary material. The new data for (2a) corresponds to the original published form by Dvorkin but may be of a higher quality whereas (2b) is a polymorphic form of (2a).

3.3. Bis (2-nitrophenyl) sulphide (3)

The diagram of this molecule presented below appears to show a mirror plane containing the central S atom but this is misleading as the aryl rings are not parallel but inclined to each other to reduce unfavourable interactions.



The first crystal structure of (3a) was reported in the triclinic space group $P\bar{1}$ (Kucsman et al., 1984) and a different form (3b) in the monoclinic space group Cc is presented here. In both forms, the coordinates of the atoms in the molecules are independent, i.e. there are no mathematical relationships between any of them. This demonstrates that there is no correspondence between any apparent molecular symmetry and the crystallographic symmetry of the two space groups. The triclinic unit cell dimensions cannot be transformed into the monoclinic cell dimensions so two different crystal forms are present. Some of the conformational differences between the molecules in the two structures are

Table 4
Conformational differences between (3a) and (3b)

Structure	Angle between planes of -NO_2 group and attached aryl ring (°)	Shortest intra S...O distances (Å)	Inclination of aryl rings (°)
(3a)	50.5, 76.6	2.656(1), 2.900(2)	69.1
(3b)	35.5(6), 5.1(9)	2.606(5), 2.992(5)	59.2(2)

Table 5
Crystal data and structure refinement for (3b)

Empirical formula	$C_{12}H_8N_2O_4S$
Formula weight	552.53
Temperature	293(2) K
Colour	Colourless
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions	$a = 11.759(3)$ Å $b = 9.809(4)$ Å $c = 10.917(6)$ Å $\alpha = 90°$ $\beta = 114.940(2)°$ $\gamma = 90°$
Volume	1141.8(8) Å^3
Z	4
Density (calculated)	1.607 Mg/m^3
Absorption coefficient	0.296 mm^{-1}
$F(000)$	568
Crystal size	$0.3 \times 0.4 \times 0.1$ mm
θ range for data collection	2.82–24.88°
Index ranges	$-13 \le h \le 11$ $-10 \le k \le 10$ $0 \le l \le 12$
Reflections collected	1551
Independent reflections	920 (R(int) = 0.0944)
Observed reflections	[($I > 2\sigma(I)$]864
Refinement method	Full-matrix l.s. on F^2
Number of parameters	173
Goodness-of-fit on F^2 (S)	1.123
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0569$, $wR_2 = 0.1344$
R indices (all data)	$R_1 = 0.0603$, $wR_2 = 0.1363$
Final weighting scheme	calc $w = 1/[\sigma^2(F_o^2) + (0.1092P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
Absolute structure parameter	0.08(16)
Residual diffraction max	0.535 e/Å^3
Residual diffraction min	−0.404 e/Å^3

Table 6
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for (3b)[a]

Atom	x	y	z	U_{eq}
S(1)	8920(1)	−381(1)	3568(1)	22(1)
O(1)	8270(4)	2014(4)	4847(5)	29(1)
O(2)	9731(4)	3500(4)	5826(5)	37(1)
O(3)	6882(4)	−960(4)	1432(4)	30(1)
O(4)	6077(4)	−25(6)	−562(5)	39(1)
N(1)	9385(4)	2341(5)	5497(5)	23(1)
N(2)	6851(4)	−64(6)	620(5)	23(1)
C(1)	10232(5)	102(7)	5081(6)	23(1)
C(2)	11193(6)	−875(7)	5595(6)	24(1)
C(3)	12183(6)	−715(7)	6863(7)	29(1)
C(4)	12271(6)	423(6)	7645(7)	28(2)
C(5)	11331(5)	1427(7)	7144(6)	25(1)
C(6)	10335(5)	1238(6)	5893(6)	20(1)
C(7)	8772(5)	967(6)	2441(5)	19(1)
C(8)	7790(5)	1011(5)	1119(5)	18(1)
C(9)	7715(5)	2094(6)	263(6)	22(1)
C(10)	8600(5)	3104(6)	719(6)	24(1)
C(11)	9534(5)	2992(6)	2011(6)	23(1)
C(12)	9620(4)	1960(5)	2872(5)	11(1)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

shown in Table 4. (Errors associated with some geometrical features of (3a) are unavailable.)

Full crystal data for (3b) is given in Table 5 and atom coordinates for (3b) are listed in Table 6. Further details (bond lengths, valency angles, torsion angles, anisotropic thermal dis-

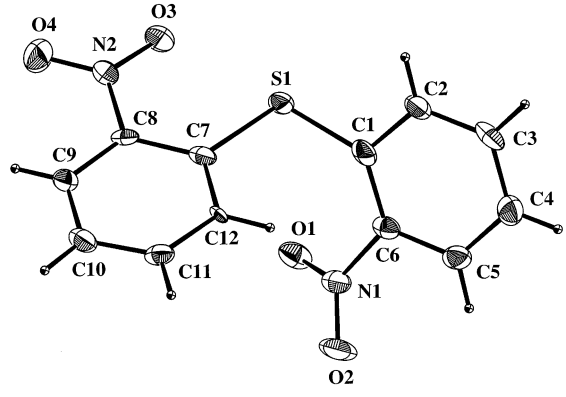


Fig. 1. The atomic arrangement in 3(b). Thermal ellipsoids shown at he 50% probability level.

placements and hydrogen positions) are available as supplementary material.

The atomic arrangement in (3b) was obtained with program ZORTEP (Zsolnai, 1997) and is shown in Fig. 1.

The three compounds each contain nitro groups and polymorphism in other molecules containing nitro groups has been previously reported, e.g. the active compounds chloramphenicol palmitate (Szulzewsky et al., 1982) and nitrofurantoin (Pienaar et al., 1993). However, there was no intention in the present studies to direct investigations solely towards nitro compounds and no evidence is presented to suggest that such compounds produce more polymorphic structures than any other class of compounds.

4. Conclusion

In general, the role of single crystal diffraction in the determination of polymorphism has been shown to give quantitative information on the different crystal structures of the molecules. Crystalline polymorphs can occur for a variety of reasons and their presence is related to the conformations adopted by molecules and the packing forces between molecules within crystals. Polymorphism can occur not only within the same crystal class but also within the same space group. During the examination of single crystal X-ray data sets, care should be taken to ensure that the most appropriate space group is chosen.

Acknowledgements

We thank the EPSRC X-ray crystallography service at the University of Wales, Cardiff (now based in Southampton, England) for collecting the X-ray data on compound (3b) and Norman Shankland and Alan Kennedy of the University of Strathclyde for providing X-ray data on compound (2a).

References

Altomare, A., Burla, M.C., Camalli, M.C., et al., 1994. SIR92' A program for automatic solution of crystal structures by direct methods. J. Appl Crystallogr. 27, 435.

Bernstein, J., 1993. Crystal-growth, polymorphism and structure-property relationships in organic crystals. J. Phys. D-Appl. Phys. 26, 66–76.

Blagden, N., Davey, R., 1999. Polymorphs take shape. Chem. in Britain 3 (35), 44–47.

Borka, L., 1991. Review on crystal polymorphism of substances in The European Pharmacopeia. Pharm. Acta Helvet. 66, 16–22.

Borka, L., Haleblian, J.K., 1990. Crystal polymorphism of pharmaceuticals. Acta Pharm. Jugo. 40, 71–94.

Brittain, H.G., 1997. Spectral methods for the characterization of polymorphs and solvates. J. Pharm. Sci. 86, 405–412.

Caira, M.R., 1998. Crystalline polymorphism of organic compounds. Top. Curr. Chem. 198, 163–208.

Chaka, A.E., Zaniewski, R., Youngs, W., Tessier, C., Klopman, G., 1996. Predicting the crystal structure of organic molecular materials. Acta Crystallogr. B (52), 165–183.

Cox, P.J., Wardell, J.L., 1997. A polymorph of bis(2-nitrophenyl) trisulphide. Acta Crystallogr. C (53), 122–124.

Cox, P.J., Anisuzzman, A.T., Pyrce-Jones, R.H., et al., 1998. 2-Amino-5-nitrobenzophenone and 2′-fluoro-2-methylamino-5-nitrobenzophenone. Acta Crystallogr. C (54), 856–859.

Dvorkin, A.A., Andronati, S.A., Gifeisman, et al., 1985. The structure of 5-nitro-amino-benzophenone. Dopovidi Akad. Nauk Ukr. RSR. Ser. B-Geol. Khim. Biol. Nauk. 8, 34–37.

Gavezzotti, A., 1991. Generation of possible crystal structures from the molecular structure for low-polarity compounds. J. Am. Chem. Soc. 113, 4622–4629.

Gdanitz, R.J., 1992. Prediction of molecular crystal structures by monte carlo simulated annealing without reference to diffraction data. Chem. Phys. Lett. 190, 391–396.

Karfunkel, H.R., Gdanitz, R.L., 1992. Ab initio prediction of possible crystal structures for general organic molecules. J. Comput. Chem. 13, 1171–1183.

Hofmann, D.W.M., Lengauer, T., 1999. Prediction of crystal structures of organic molecules. J. Mol. Struct. 474, 13–23.

Howie, R.A., Wardell, J.L., 1996. Bis(2-nitrophenyl)trisulphide. Acta Crystallogr. C (52), 1533–1534.

Kucsman, Á., Kapovits, I., Párkányi, L., Argay, G.Y., Kálmán, A., 1984. Intramolecular sulphur(II)-oxygen interaction in sulphides and disulphides with 2-methyloxycarbonylphenyl and 2-nitrophenyl groups: an X-ray study. J. Mol. Struct. 125, 331–347.

Leusen, F., 1998. C2-Polymorph Module. Molecular Simulations, Barnwell Road, Cambridge, CB5 8RE, UK.

Pienaar, E.W., Caira, M.R., Lotter, A.P., 1993. Polymorphs of nitrofurantoin 2: preparation and X-ray crystal structures of 2 anhydrous forms of nitrofurantoin. J. Crystallogr. Spec. Res. 23, 785–790.

Sheldrick, G.M., 24 March 1998. SHELX-97. Program for the Refinement of Crystal Structures. University of Göttingen, Germany.

Spek, A.L., 1998. LEPAGE. An MS-DOS program for the determination of the metrical symmetry of a translation lattice. J. Appl. Crystallogr. 21, 578–579.

Spek, A.L., 1999. PLATON-A Multipurpose Crystallographic Tool. Utrecht University, Utrecht, The Netherlands.

Steele, P., 1994. Ranitidine — The Patent Story. Scrip Magazine, April, PJB Publications, pp. 12–14.

Szulzewsky, K., Kulpe, S., Schulz, B., Fichtner-Scmitter, H., 1982. Crystallographic results on the polymorphism of chloramphenicol palmitate. Acta Pharm. Suec. 19, 457–470.

Threlfall, T.L., 1995. Analysis of organic polymorphs. Analyst 120, 2435–2460.

Verwer, P., Leusen, F.J.J., 1998. Computer Simulation to Predict Possible Crystal Polymorphs. In: Reviews in Computational Chemistry, vol. 12. Wiley-VCH, New York, pp. 327–365.

Zsolnai, L., 1997. ZORTEP, An Interactive ORTEP Program. University of Heidelberg, Germany.