Abundant Polymorphism in a System with Multiple Hydrogen-Bonding Opportunities: Oxalyl Dihydrazide

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Abstract: To date, only one crystal structure has been reported in the literature for oxalyl dihydrazide [$H_2N \cdot NH \cdot CO \cdot CO \cdot NH \cdot NH_2$]. In the present paper, we report the discovery of four new polymorphs of oxalyl dihydrazide, obtained by crystallization from solution under different conditions, including the use of different crystallization solvents. All polymorphs have the trans-trans-trans conformation of the N−N−C−C−N−N backbone, but the positions of the hydrogen atoms of the NH_2 groups relative to this backbone differ between the different polymorphs through variation of the torsion angle around each NH−NH_2 bond. The different polymorphs display a range of different hydrogen-bonding arrangements, constructed from different types of hydrogen-bonded array. The existence of several different potential hydrogen-bond donor and hydrogen-bond acceptor groups in the oxalyl dihydrazide molecule, together with the fact that the N−H bonds of the NH_2 groups adopt different orientations with respect to the molecular plane, leads to several possible geometric permutations for hydrogen-bonding arrangements in the solid state. It would not be surprising if even more polymorphs of oxalyl dihydrazide are discovered in the future.

1. Introduction

In the case of molecular solids, polymorphism arises when a given type of molecule is able to form different crystal structures.[1−8] Although the different polymorphs have the same chemical composition,[9] their solid-state properties are generally different as a consequence of their different crystal structures. Clearly, several issues of fundamental scientific interest devolve upon the issue of polymorphism, not least of which is the fact that studies of polymorphic systems represent an ideal opportunity for understanding structure−property relationships. Furthermore, in recent years, there has been considerable interest[10,11] within industrial sectors in being able to find and

characterize as many polymorphs as possible of the active molecule of interest (such as a drug substance or pigment), so that the polymorph with the most desirable properties for the targeted application can be selected.

A relevant question to pose in relation to polymorphism, although one that is virtually impossible to answer at the present time, is how many polymorphic forms is a given molecule able to form? In recent years, the application of computational techniques for crystal structure prediction[12−16] has played an important role in advancing our understanding of the underlying issues, as well as revealing the enormity of the challenges that are involved in addressing this question. In most cases, the number of computationally predicted polymorphs within an accessible energy range far exceeds the number of polymorphs that are observed experimentally for the same molecule; indeed, examples of molecules that yield a large number of experimentally verified polymorphs are relatively rare. The currently accepted record for the highest number of polymorphs for a given molecule (considering only those cases in which the polymorphs have been subjected to an adequate level of structural characterization) is nine, for 5-methyl-2-[(2-nitrophenyl)amino]-

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(9) Throughout this paper, we adhere strictly to the requirement that polymorphic forms have identical chemical composition: in the case of molecular crystals, they must contain the same type(s) of molecule(s) with the same stoichiometry. A given type of molecule may exist in different crystalline phases, such as (i) "pure" crystals containing only the given type of molecule or (ii) cocrystals containing the given type of molecule and one or more other types of molecule (which encompasses also solvate phases in which the "other molecule" is the solvent used in crystal growth). Crystalline phases *within* a given category, provided they have the same chemical composition, may be classified as polymorphic forms. Crystalline phases in different categories cannot be classified as polymorphic forms. We note that the present paper considers only crystalline phases of the type covered by category (i).

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Scheme 1

ODH
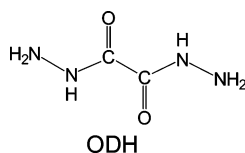
3-thiophenecarbonitrile (often called "ROY").[17−19] And while examples of trimorphic systems are not uncommon within organic solid-state chemistry, cases of molecules that have four or more experimentally verified polymorphic forms are certainly quite rare.

In the present paper, we focus on studies of polymorphism of oxalyl dihydrazide [$H_2N\cdot NH\cdot CO\cdot CO\cdot NH\cdot NH_2$ (ODH), Scheme 1], the underlying motivations for which are elaborated below. To date, only one crystal structure[20] has been reported in the literature for this molecule,[21] and here we report the discovery and structural characterization of four new polymorphs. Our initial studies[22] of ODH focused on the formation of hydrogen-bonded cocrystals with cyanuric acid, and the structural properties of a cocrystal containing cyanuric acid, ODH, and water (in 1:1:2 ratio) were reported. In following up this work, we explored the possible formation of cocrystals between trithiocyanuric acid and ODH. Although no cocrystals were obtained, we observed that the samples of pure ODH obtained in these crystallization experiments comprised crystals with two different morphologies, which were subsequently separated by hand. One set of crystals gave a powder X-ray diffraction pattern corresponding to the previously reported structure of ODH (α polymorph), whereas the other set of crystals represented a new polymorph of ODH (here denoted the β polymorph). The structural properties of this new polymorph, determined from single-crystal X-ray diffraction, are reported here.

Following this accidental discovery of a new polymorph of ODH, we anticipated that there may be scope for ODH to exhibit more extensive polymorphism, based on the fact that the molecule may exist in a number of different plausible (energetically accessible) conformations with respect to the orientations of the terminal NH_2 groups (rotation of the NH_2 group around the $NH-NH_2$ bond is associated with a relatively low energy barrier, and thus a range of different conformations of the $NHNH_2$ end groups should be accessible in the solid state). In principle, this feature of the molecular structure should create the opportunity for ODH to form several different, energetically accessible, geometrical arrangements for hydrogen-bonded arrays in the solid state involving the potential hydrogen-bond donors (N−H bonds of the NH and NH_2 groups) and hydrogen-bond acceptors (oxygen atoms of the C=O groups and the nitrogen atoms of the NH_2 groups) in the ODH molecule. With this motivation, an extensive series of crystallization experiments (see Table 1) has been carried out, yielding three further

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polymorphic forms (denoted the γ, δ, and ε polymorphs). The structural properties of these new polymorphs have also been determined by single-crystal X-ray diffraction and are reported here. Issues relating to the behavior of the polymorphs of ODH at elevated temperature are also discussed.

2. Experimental Section

2.1. Preparation and Characterization. The sample of ODH used in this work was purchased from Aldrich. Initial identification of the materials obtained from all crystallization experiments was carried out using powder X-ray diffraction (Siemens D5000 and D8 diffractometers; transmission mode; Cu Kα₁ radiation (Ge-monochromated)), which confirmed that, of the five polymorphs of ODH obtained, one polymorph (α polymorph) was the same as the previously reported structure,[20] and that the other polymorphs (β, γ, δ, and ε polymorphs) represented new polymorphs. Differential scanning calorimetry (DSC) was performed using a TA Instruments Q100 differential scanning calorimeter.

As discussed above, following the accidental discovery of the β polymorph of ODH, crystallization of ODH was carried out under a wide range of different sets of conditions to explore the possible formation of further polymorphic forms. The different conditions comprised the use of a range of different solvents, crystallization with a number of other cosolute molecules, and (to a lesser extent) altering the temperature range of the crystallization experiments (which were carried out by systematic cooling). The results of all crystallization experiments are summarized in Table 1. We focus now on describing the crystallization conditions that we have found to be the most reliable and reproducible for obtaining a monophasic sample of each polymorphic form.

The α polymorph of ODH is obtained from a wide variety of crystallization conditions (Table 1), including cooling a solution of ODH in water. Crystals of the α polymorph are colorless, and are typically block-shaped or needlelike, depending on the crystallization conditions employed.

The β polymorph (colorless crystals) was obtained (as a mixture with the α polymorph) by crystallization from a solution containing ODH and an equimolar amount of trithiocyanuric acid in DMSO/water (2:1) at 10 °C. The crystals of the β polymorph were prismatic needles, which were separated from the α polymorph by hand under a polarizing optical microscope. Thus far, this crystallization procedure is the only one that has produced the β polymorph, but the outcome is not readily reproducible. Therefore, after initially obtaining a mixture of the α and β polymorphs by this method, subsequent attempts to repeat the same procedure were found to produce only the α polymorph.

A monophasic sample of the γ polymorph (colorless, long-needle crystals) was prepared by cooling a solution of ODH in DMSO/water (2:1). Monophasic samples of the γ polymorph were also formed in preparations involving a variety of cosolute molecules in addition to ODH (see Table 1), and the γ polymorph was also obtained in biphasic mixtures with the α polymorph under other sets of conditions (see Table 1).

A monophasic sample of the δ polymorph (colorless, flat-plate crystals) was prepared by cooling a solution of ODH in 1,4-dioxane/water (2:1) (see Table 1).

A monophasic sample of the ε polymorph (colorless, needle-shaped crystals) was prepared by cooling a solution of ODH in DMSO (although we note that the same crystallization procedure over a different temperature range tends to yield the α polymorph instead). The ε polymorph was also obtained in biphasic mixtures with the α polymorph under other sets of conditions (see Table 1).

It is relevant to note that crystallization from a solution containing ODH and trithiocyanuric acid (1:1) in DMSO/water (2:1) appears to give a monophasic sample of the δ polymorph on some occasions and to give a monophasic sample of the ε polymorph on other occasions.

Table 1. Details of Crystallization Experiments for ODH under Different Sets of Conditions[a]

solute	solvent	initial temperature (°C)	final temperature (°C)
	experiments producing the α polymorph		
ODH	water	70−80	10
ODH	DMSO	70−80	10
ODH	DMSO/methanol (2:1)	70−80	ambient
ODH	DMSO/THF (2:1)	70−80	10
ODH	DMSO/acetonitrile (2:1)	70−80	10
ODH	DMSO/acetylacetone (2:1)	70−80	10
ODH	DMF/water (2:1)	70−80	10
ODH	water/1,4-dioxane (2:1)	70−80	ambient
ODH	water/acetonitrile (2:1)	70−80	ambient
ODH + biuret (1:1)	DMSO	70−80	10
	DMSO/water (2:1)	70−80	10
	DMF	70−80	10
ODH + cyanuric acid (1:1)	DMSO	70−80	10
	DMSO/water (2:1)	70−80	10
ODH + phthalic acid (1:1)	DMSO	70−80	ambient
	DMF	70−80	ambient
ODH + urea (1:1)	DMSO	70−80	10
	DMSO/water (2:1)	70−80	10
	DMF	70−80	10
ODH + benzene-1,3,5-tricarboxylic acid (1:1)	DMSO	70−80	10
	DMSO/water (2:1)	70−80	10
ODH + 5-amino-1,2,3,4-tetrazole monohydrate (1:1)	DMSO	70−80	ambient
	DMSO/water (2:1)	70−80	10
ODH + trithiocyanuric acid (1:1)	DMSO	70−80	10
	DMSO/water (2:1)	70−80	10
	DMSO/water (2:1)	45	10
	experiments producing a mixture of α and β polymorphs		
ODH + trithiocyanuric acid (1:1)[b]	DMSO/water (2:1)	ambient	10
	experiments producing the γ polymorph		
ODH + cyanuric acid (1:1)	DMF	70−80	10
ODH + benzene-1,3,5-tricarboxylic acid (1:1)	DMF	70−80	10
ODH + 5-amino-1,2,3,4-tetrazole monohydrate (1:1)	DMF	70−80	10
ODH	DMSO/water(2:1)	160	ambient
	experiments producing the δ polymorph		
ODH	1,4-dioxane/water (2:1)	160	ambient
ODH + trithiocyanuric acid (1:1)	DMSO/water (2:1)	70−80	ambient
	experiments producing the ε polymorph		
ODH	DMSO	70−80	ambient
ODH[c]	methanol/water (3:1 v/v)	60	ambient
ODH + trithiocyanuric acid (1:1)	DMSO/water (2:1)	70−80	ambient
	experiments producing a mixture of α and ε polymorphs		
ODH	DMSO/1,4-dioxane (1:1)	70−80	10
ODH	DMSO/DMF (1:1)	70−80	ambient
ODH	water/2-butanone (2:1)	70−80	10
ODH	DMSO/water (1:3 v/v)	60	ambient
	experiments producing a mixture of α and γ polymorphs		
ODH	DMF	70−80	10
ODH	DMF/1,4-dioxane (2:1)	70−80	10

[a] In all cases, crystal growth was carried out by cooling the solutions between the initial and final temperatures indicated. All ratios indicated are molar ratios. [b] As discussed in section 2.1, this preparation method is not readily reproducible. [c] As reported in ref 22 and discussed in section 4 of this paper.

This observation is a reflection of the fact, often observed in studies of polymorphic systems[3], that the outcome of crystallization experiments can often be influenced by factors that are (apparently) outside the direct control of the experimenter.

Powder X-ray diffraction patterns (Figure 1, left side) of each polymorph confirm clearly that they represent different crystalline phases. Infrared spectra (recorded in KBr disks) also indicate clear differences between the different polymorphic forms (see Supporting Information), arising from the structural differences (e.g., the different hydrogen-bonding arrangements) discussed below. Results from melting point analysis and other aspects of the behavior of the different polymorphs above ambient temperature are discussed in section 3.8.

2.2. Crystal Structure Determination. The crystal structures of all five polymorphs of ODH were determined from single-crystal X-ray

diffraction data, including a redetermination of the structure of the α polymorph. For the α, γ, δ, and ε polymorphs, data collection was carried out at ambient temperature on a Bruker SMART 6000 diffractometer (CCD detector; Cu Kα radiation (graphite monochromated)). For the β polymorph, single-crystal X-ray diffraction data were recorded on a Rigaku R-axis IIc diffractometer equipped with a molybdenum rotating anode source and an image plate detector system. We note that the quality of the available single crystals for the β polymorph was comparatively poor, which is reflected in the relative accuracy of the structural information obtained.

The crystal structures were solved and refined using the SHELX97 program.[23] Hydrogen atoms were located in difference Fourier maps,

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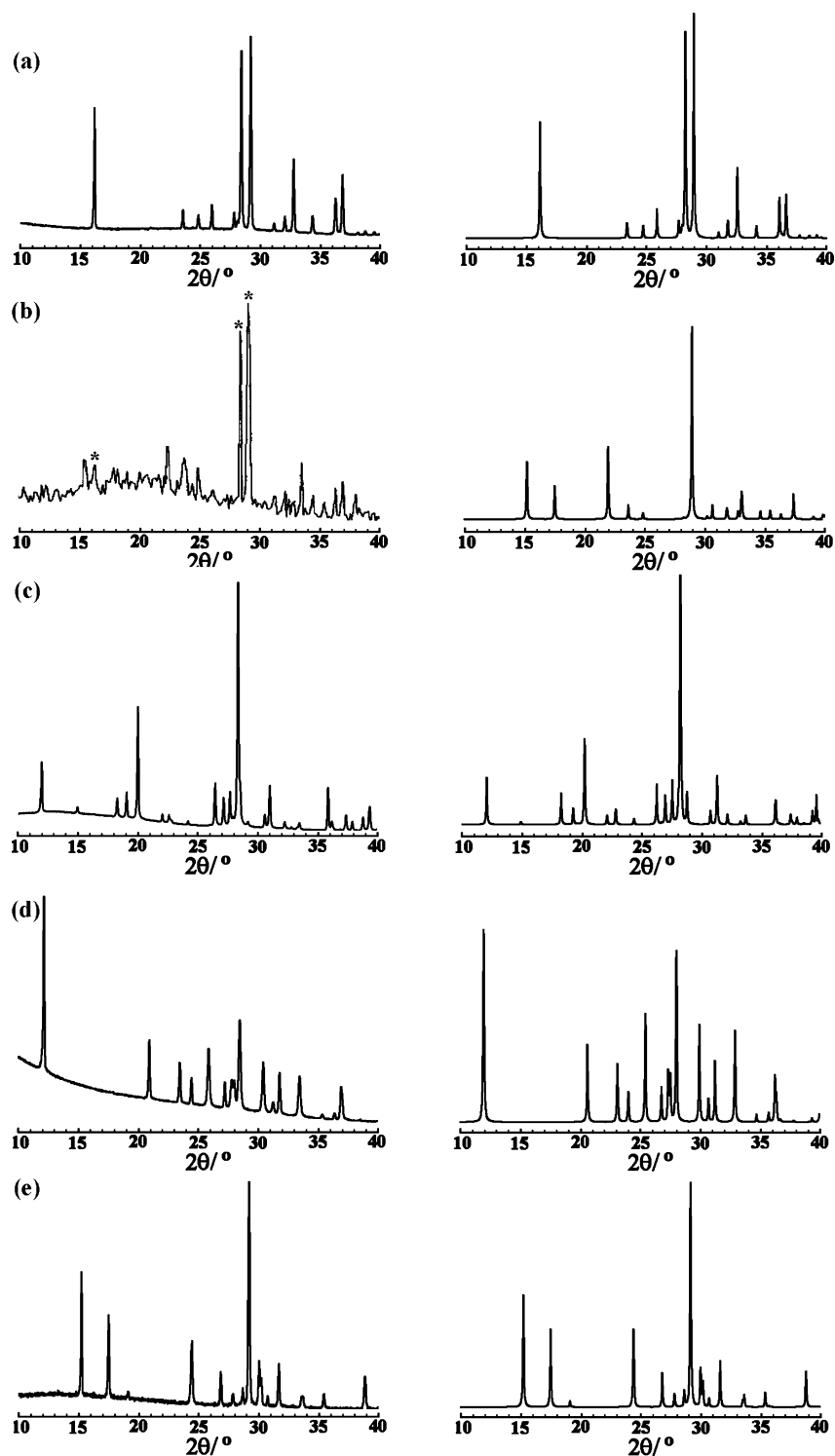
Figure 1. Powder X-ray diffraction patterns for (a) the α polymorph, (b) the β polymorph, (c) the γ polymorph, (d) the δ polymorph and (e) the ε polymorph of ODH. Left side: *experimental* powder X-ray diffraction pattern. Right side: the powder X-ray diffraction pattern *calculated* for the crystal structure determined from the single-crystal X-ray diffraction data. As discussed in the text, the β polymorph was obtained only as a mixture with the α polymorph, and the experimental powder X-ray diffraction pattern shown in (b) is for this mixture—the major peaks due to the α polymorph in this powder X-ray diffraction pattern are indicated with an asterisk. We note that slight discrepancies in relative peak intensities between the experimental and calculated powder X-ray diffraction patterns are observed in some cases, and arise due to the effects of preferred orientation in the experimental sample.

and were included in the final structure refinement calculations. The positions of all non-hydrogen atoms were refined freely using anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms of the NH_2 groups were refined freely, and hydrogen atoms of the NH groups were refined using a riding model, with isotropic displacement parameters in both cases.

3. Results and Discussion

3.1. General Considerations. Structural data relating to the five polymorphs of ODH are summarized in Table 2, and CIF files containing full structural details are available as Supporting Information. All polymorphs are monoclinic with space group

Table 2. Crystallographic Data for Polymorphs of ODH

polymorph	α	β	γ	δ	ϵ
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a/Å	3.6221(4)	3.762(4)	5.0795(4)	3.6608(5)	5.3642(3)
b/Å	6.8322(7)	11.652(5)	14.6679(14)	14.550(2)	3.8412(2)
c/Å	9.1294(10)	5.619(2)	7.0345(7)	5.0646(8)	12.3191(6)
β/°	99.298(9)	92.793(5)	114.160(6)	119.006(9)	108.999(3)
Z	2	2	4	2	2
V/Å³	222.96(4)	246.0(3)	478.20(8)	235.93(6)	240.01(2)
D_{calc}/Mg m⁻³	1.759	1.594	1.641	1.663	1.634
no. of reflections	1340	1037	3013	1344	1411
no. of unique data	414	412	838	412	433
data with $I > 2\sigma(I)$	394	330	593	339	392
R_f	0.0306	0.0890	0.0436	0.0374	0.0360
wR2	0.0884	0.2045	0.1029	0.0884	0.0967
s	1.152	1.245	1.022	1.101	1.102

$P2_1/c$. In the α, β, δ, and ϵ polymorphs, the molecule is located on a crystallographic inversion center, and the molecular conformation is therefore strictly centrosymmetric (in these polymorphs, the asymmetric unit comprises half the molecule). For the γ polymorph, on the other hand, the asymmetric unit comprises one complete molecule, and the conformation is noncentrosymmetric (although the backbone of the molecule, comprising the non-hydrogen atoms, is essentially centrosymmetric). As there are six potential hydrogen-bond donors and four potential hydrogen-bond acceptors, one may expect to have 12 hydrogen bonds per molecule if each donor is involved in one hydrogen-bonding interaction and if some of the acceptors (in particular the two C=O groups) are involved in more than one hydrogen-bonding interaction.

For each polymorph, the *experimental* powder X-ray diffraction pattern and the powder X-ray diffraction pattern *calculated* for the crystal structure determined from single-crystal X-ray diffraction data are shown in Figure 1. In each case, the *calculated* powder X-ray diffraction pattern clearly matches the *experimental* powder X-ray diffraction pattern, thus confirming that, in each case, the single crystal used in the single-crystal X-ray diffraction experiment was representative of the bulk polycrystalline sample from which it was selected. We emphasize (as also discussed elsewhere[24]) the importance of carrying out this test in making structural assignments of polymorphic systems from single-crystal X-ray diffraction data.

3.2. Conformation of the ODH Molecule. First we consider the conformation of the ODH molecule in the different polymorphs. In all polymorphs, the N−N−C−C−N−N backbone of the molecule is planar and adopts the trans-trans-trans conformation. The oxygen atoms of the O=C groups and the hydrogen atoms of the NH groups lie within this plane. In the α, β, δ, and ϵ polymorphs, the molecule is located on a crystallographic inversion center, and the molecular conformation is therefore strictly centrosymmetric. In all polymorphs, the NH₂ group is pyramidal, consistent with sp³ hybridization of the nitrogen atom, which enhances the capacity for the nitrogen atom to serve as a hydrogen-bond acceptor.

The only significant difference in the conformations of the ODH molecule in the different polymorphs concerns the positions of the hydrogen atoms of the NH₂ groups, corresponding to variation of the torsion angle around the NH−NH₂ bonds. Details of the H−N−N−C torsion angles for the five polymorphs are given in Table 3. In the α, δ, and ϵ polymorphs,

Table 3. Torsion Angles Defining the Molecular Conformation in the Polymorphs of ODH[a]

polymorph	H–N–N–C torsion angles/°	
α	166.2	−84.1
β	55.8	−70.7
γ	34.6	−73.5
	35.2	−79.1
δ	11.5	−104.6
ϵ	12.5	−95.8

[a] Note that the ODH molecule is centrosymmetric in the α, β, δ, and ϵ polymorphs and the pair of H−N−N−C torsion angles is therefore the same for both H₂N−N(H)−C(O)− groups.

one N−H bond of the NH₂ group lies close to the molecular plane (H−N−N−C torsion angle relatively close to 0° or 180°), whereas the other N−H bond points outward from this plane (H−N−N−C torsion angle relatively close to 90° or −90°). For the α polymorph, the "in-plane" N−H bond of the NH₂ group has a cis orientation with respect to the N−H bond of the NH group (H−N−N−C torsion angle close to 180°), whereas for the δ and ϵ polymorphs, the "in-plane" N−H bond of the NH₂ group has a trans orientation with respect to the N−H bond of the NH group (H−N−N−C torsion angle close to 0°).

For the β and γ polymorphs, both hydrogen atoms of the NH₂ group lie significantly out of the molecular plane. In the β polymorph, the two hydrogen atoms lie above and below the molecular plane approximately equally, whereas in the γ polymorph, one hydrogen atom (H−N−N−C torsion angle ca. 35°) still lies appreciably closer to the molecular plane than the other. For the γ polymorph, although the two NH−NH₂ groups in the molecule are not related by symmetry, they nevertheless have similar conformations.

3.3. Structural Properties of the α Polymorph. The crystal structure of the α polymorph has been reported previously.[20] We have redetermined this structure as part of the present work, allowing comparison of the structures of the different polymorphs using data of comparable quality. However, we emphasize that there are no significant differences between the structure of the α polymorph determined in the present work and the structure reported previously. The crystal structure is monoclinic with space group $P2_1/c$ and is shown in Figure 2. The α polymorph has the highest calculated density of all the polymorphs of ODH (Table 2).

In the crystal structure, the ODH molecule lies on a crystallographic inversion center. In the molecular conformation, one N−H bond of the NH₂ group lies close to the molecular plane, and this "in-plane" N−H bond has a cis orientation with respect to the N−H bond of the NH group. The α polymorph is the only polymorph that has this conformational feature (see Table 3).

As shown in Figure 2a, the molecules are arranged in two-dimensional sheets parallel to the (1 0 −2) plane, although the sheets are not perfectly flat (the molecular plane is not parallel to the plane of the sheet). The molecules within the sheets are linked by hydrogen-bonded rings (designated $R_2^2(8)$ in graph set notation[25−27]) involving one N−H···O hydrogen bond and

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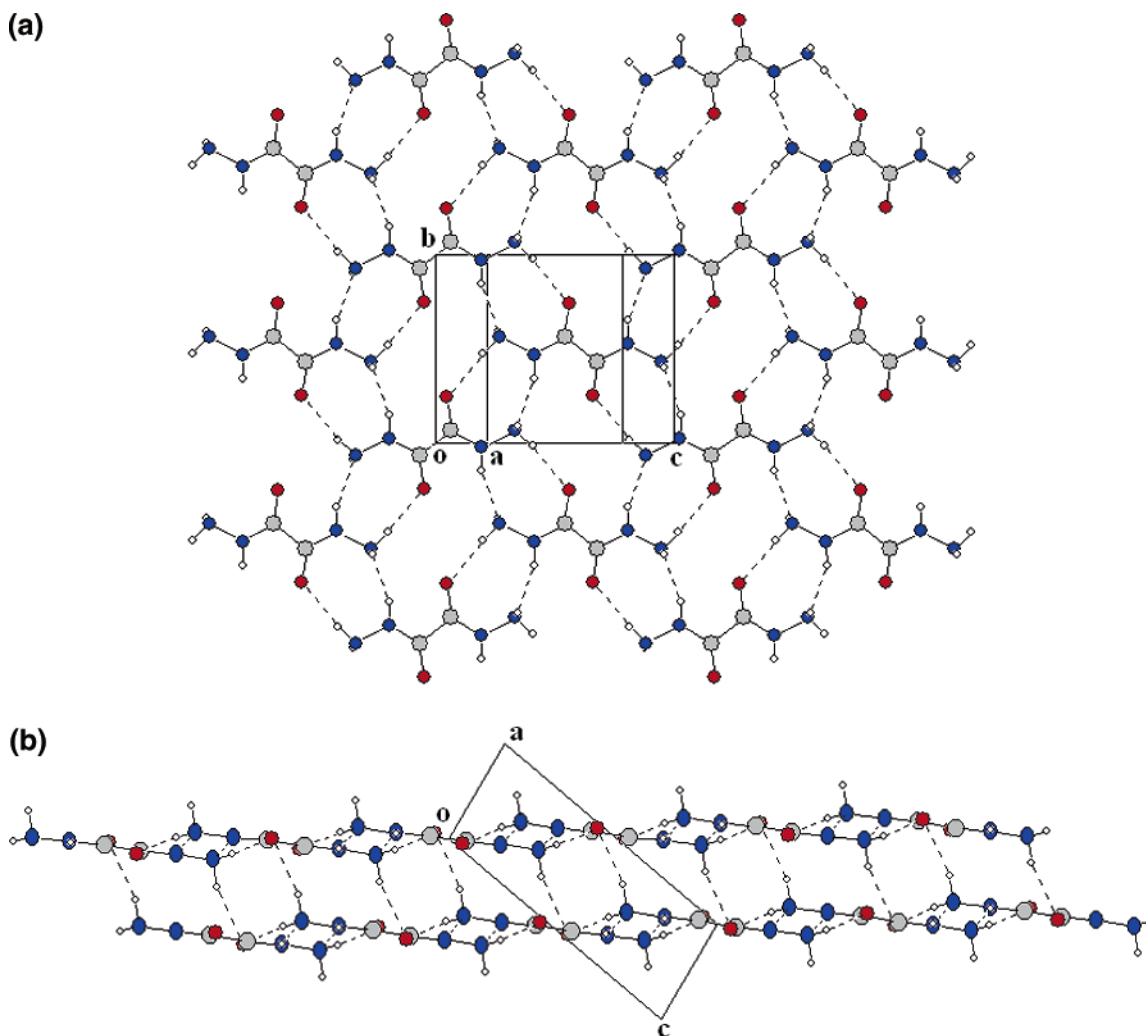
(a)

(b)

Figure 2. Crystal structure of the α polymorph of ODH showing (a) an individual hydrogen-bonded sheet (viewed perpendicular to the sheet), and (b) the relationship between adjacent sheets (viewed parallel to the plane of the sheets).

one N−H···N hydrogen bond (both N−H donors are on the same molecule). Each molecule is involved in four cyclic hydrogen-bonded arrays of this type.

For each molecule, the "out-of-plane" N−H bond of one NH_2 group points above the plane of the sheet, and the "out-of-plane" N−H bond of the other NH_2 group points below the plane of the sheet (Figure 2b). These "out-of-plane" N−H bonds form N−H···O hydrogen bonds with the oxygen atoms of O=C groups in adjacent sheets. Each oxygen atom is engaged in one N−H···O hydrogen bond with an adjacent sheet in this manner.

The structural properties determined here for the α polymorph are in agreement with the previously reported crystal structure determination of this polymorph,[20] and in agreement with conclusions from earlier studies using vibrational spectroscopies.[20]

3.4. Structural Properties of the β Polymorph. The crystal structure of the β polymorph is monoclinic with space group $P2_1/c$ and is shown in Figure 3. The molecule lies on a crystallographic inversion center. Both N−H bonds of the NH_2 group lie significantly out of the plane of the remainder of the molecule.

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The structure comprises planar one-dimensional molecular ribbons that run parallel to the [1 0 1] direction. Each molecule in the ribbon is linked to each adjacent molecule by a cyclic $R_2^2(6)$ hydrogen-bonded array, as shown in Figure 3a. This $R_2^2(6)$ hydrogen-bonded array comprises two N−H···N hydrogen bonds involving an NH−NH_2 group of each molecule; the hydrogen-bond donors are the N−H bonds of the NH groups and the hydrogen-bond acceptors are the nitrogen atoms of the NH_2 groups.

The N−H bonds of the NH_2 groups do not lie in the plane of the ribbons; instead, they are involved in N−H···O interactions with O=C groups in adjacent ribbons (Figure 3b). However, we note that some of these N−H···O interactions are rather long and nonlinear. One N−H bond of the NH_2 group forms a single N−H···O interaction (N···O distance, N−H···O angle: 3.07 Å, 146°), whereas the other N−H bond forms two relatively long N−H···O interactions (3.21 Å, 147°; 3.21 Å, 117°). In total, each O=C group is involved in three N−H···O interactions of this type. We note that the β polymorph is the only one in which the O=C group is not involved in any N−H···O interactions with neighboring molecules that lie within (or close to) the same plane. Overall, the hydrogen bonding (particularly the hydrogen bonding involving the O=C group) appears to be less optimal geometrically than that in the other poly-
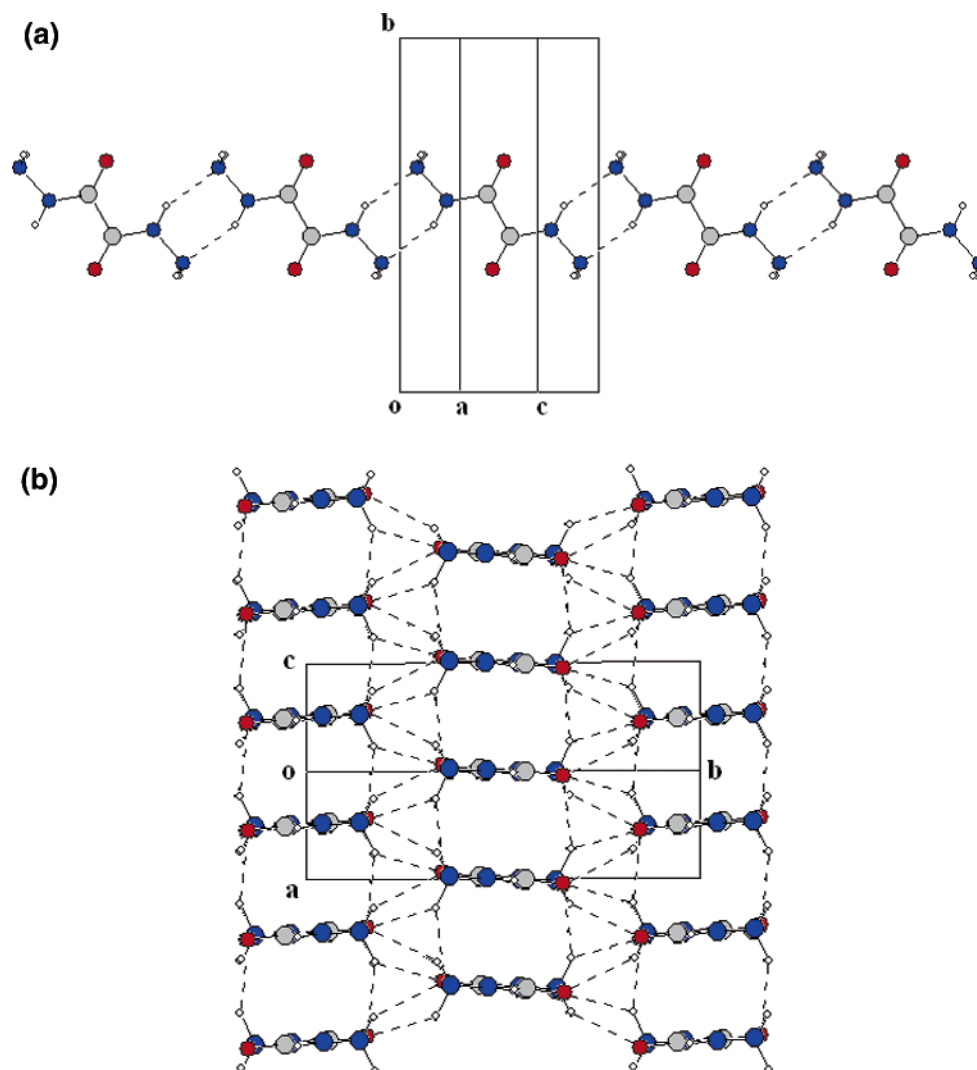
(a)

(b)

Figure 3. (a) An individual hydrogen-bonded ribbon in the crystal structure of the β polymorph of ODH, and (b) the crystal structure of the β polymorph viewed along the direction of propagation of the hydrogen-bonded ribbons, showing the relationship between adjacent ribbons.

morphs, which may suggest that the β polymorph is of lower stability.

3.5. Structural Properties of the γ Polymorph. The crystal structure of the γ polymorph is monoclinic with space group $P2_1/c$ and is shown in Figure 4. In this case, the molecule is noncentrosymmetric, and the asymmetric unit comprises the whole molecule. As discussed in section 3.2, both hydrogen atoms of the NH$_2$ groups lie significantly out of the molecular plane, although one hydrogen atom lies closer to the molecular plane than the other. Significantly, both of the "out-of-plane" N—H bonds point outward from the *same* side of the molecular plane (in contrast, the "out-of-plane" N—H bonds of the α, δ, and ϵ polymorphs point outward from opposite sides of the molecular plane, consistent with the fact that the molecular conformation in these polymorphs is centrosymmetric).

As shown in Figure 4a, the crystal structure comprises molecular ribbons in which adjacent molecules are linked by a cyclic $R_2^2(10)$ hydrogen-bonded array, involving two N—H···O hydrogen bonds (both N—H bonds are from NH groups). Adjacent molecules in these ribbons are related by the unit cell translation along the 5.1 Å axis (*a* axis). Adjacent ribbons within the *ab* plane are linked by N—H···N hydrogen bonds involving the NH$_2$ groups at the periphery of each ribbon,

and leading to ···N—H···N—H···N—H··· chains that also run along the 5.1 Å axis. For each NH$_2$ group, these N—H···N interactions involve the N—H bond that lies closer to the molecular plane (H—N—N—C torsion angle ca. 35°). There are two N—H···N hydrogen bonds within the 5.1 Å repeat unit along this axis. The two NH$_2$ groups of a given molecule are involved in chains of this type with adjacent ribbons, with the two ···N—H···N—H···N—H··· chains running in opposite directions (as defined by the N—H bond vectors) along the 5.1 Å axis. The network of N—H···N hydrogen bonds that link adjacent ribbons leads to a sheetlike hydrogen-bonded network, although this sheet is not completely flat (Figure 4b); the planes of all ribbons in the sheet are nearly parallel to each other, but the planes of adjacent ribbons are slightly displaced from each other. The average plane of the sheet is parallel to the *ab* plane.

For each NH$_2$ group, the N—H bond that points outward from the molecular plane forms an N—H···O hydrogen bond with an O=C group in the adjacent sheet. For a given ribbon, all of these N—H bonds point outward from the same side of the plane of the ribbon, whereas for the adjacent ribbon in the same sheet, all of these N—H bonds point outward from the opposite side of the plane.
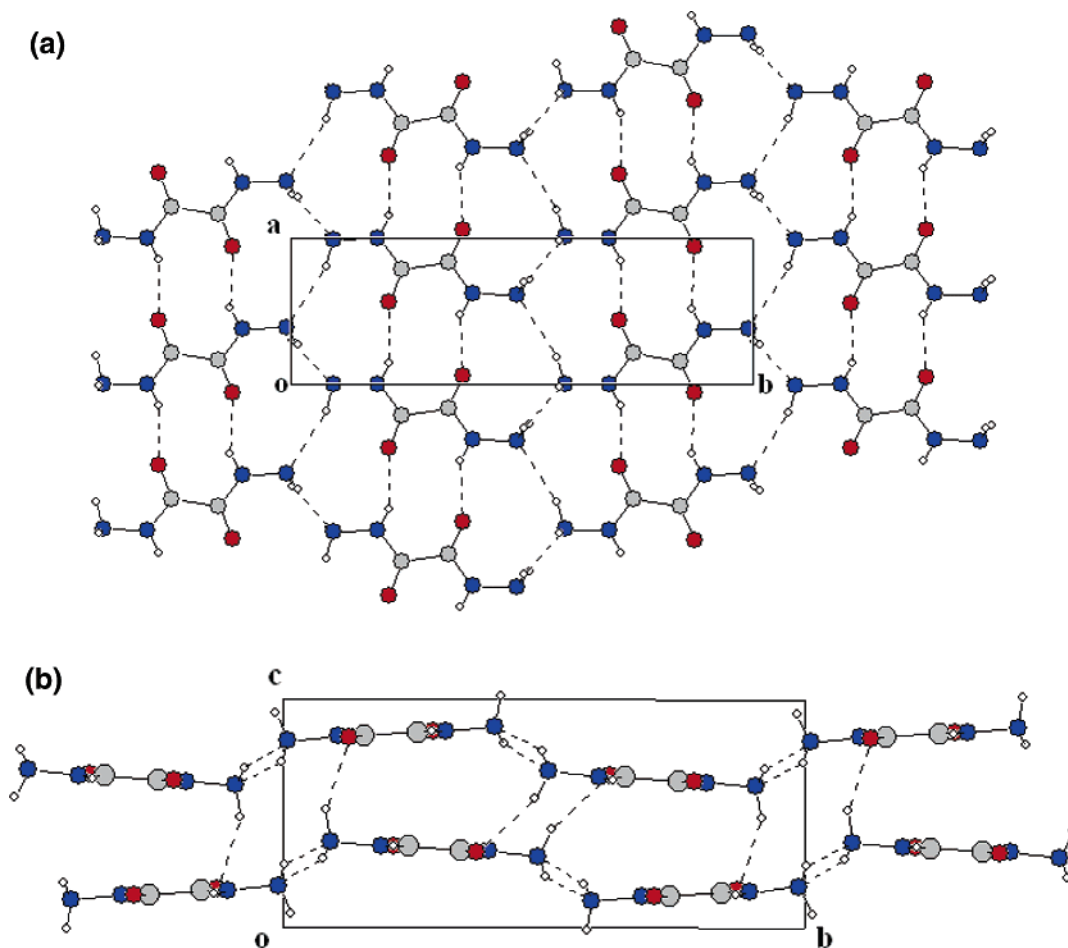
(a)

(b)

Figure 4. Crystal structure of the γ polymorph of ODH viewed (a) along the *c* axis, showing an individual hydrogen bonded sheet, and (b) along the *a* axis, showing the relationship between adjacent sheets.

3.6. Structural Properties of the δ Polymorph. The crystal structure of the δ polymorph is monoclinic with space group $P2_1/c$ and is shown in Figure 5. The molecule lies on a crystallographic inversion center. One N—H bond of the NH$_2$ group lies close to the molecular plane, whereas the other N—H bond of the NH$_2$ group points outward from this plane.

The structure of the δ polymorph bears some similarity to the γ polymorph in terms of the hydrogen-bonding connectivity *within* (but not between) the sheets. Thus, the δ polymorph contains one-dimensional ribbons (Figure 5a) that are similar to those discussed above for the γ polymorph; in these ribbons, adjacent molecules are linked by a cyclic $R_2^2(10)$ hydrogen-bonded array, involving two N—H···O hydrogen bonds, and adjacent molecules are related by the unit cell translation along the 5.1 Å axis (*c* axis). Furthermore, the NH$_2$ groups at the periphery of adjacent ribbons form N—H···N hydrogen bonds (involving the "in-plane" N—H bond as the hydrogen-bond donor), leading to the formation of ···N—H···N—H···N—H··· chains that also run along the 5.1 Å axis.

In the γ polymorph, the planes of adjacent ribbons are parallel to each other, although displaced slightly along the direction of the normal to the plane. In the δ polymorph, on the other hand, the planes of adjacent ribbons are not parallel to each other and are tilted such that they give rise to an undulating sheet (Figure 5b). Nevertheless, the *connectivity* between molecules within the sheet is the same as that in the γ polymorph. Thus, when viewed in projection along the normal

to the plane of the sheet, the structures of the γ and δ polymorphs appear very similar. However, as elaborated above, the three-dimensional architecture of the sheets in the γ and δ polymorphs differs significantly.

In the δ polymorph, the molecule is centrosymmetric and the "out-of-plane" N—H bonds of the two NH$_2$ groups point outward from opposite sides of the molecular plane. Each of these N—H bonds forms an N—H···O interaction with an O=C group in an adjacent sheet, although we note that this N—H···O interaction is somewhat longer and less linear (N···O distance, 3.15 Å; N—H···O angle, 134°) than would normally be considered to represent strong N—H···O hydrogen bonding.

3.7. Structural Properties of the ϵ Polymorph. The crystal structure of the ϵ polymorph is monoclinic with space group $P2_1/c$ and is shown in Figure 6. The molecule lies on a crystallographic inversion center. One N—H bond of the NH$_2$ group lies close to the molecular plane, whereas the other N—H bond of the NH$_2$ group points outward from this plane.

As shown in Figure 6a, the ϵ polymorph comprises planar ribbons that run approximately along the [1 1 0] and [1−1 0] directions (the periodic repeat distance within these ribbons is ca. 6.6 Å). In the ribbon, adjacent molecules are linked by a cyclic $R_2^2(10)$ hydrogen-bonded array involving two N—H···O hydrogen bonds; in each hydrogen bond, the donor is the "in-plane" N—H bond of an NH$_2$ group. In contrast, in the $R_2^2(10)$ arrays in the γ and δ polymorphs, the N—H hydrogen bond
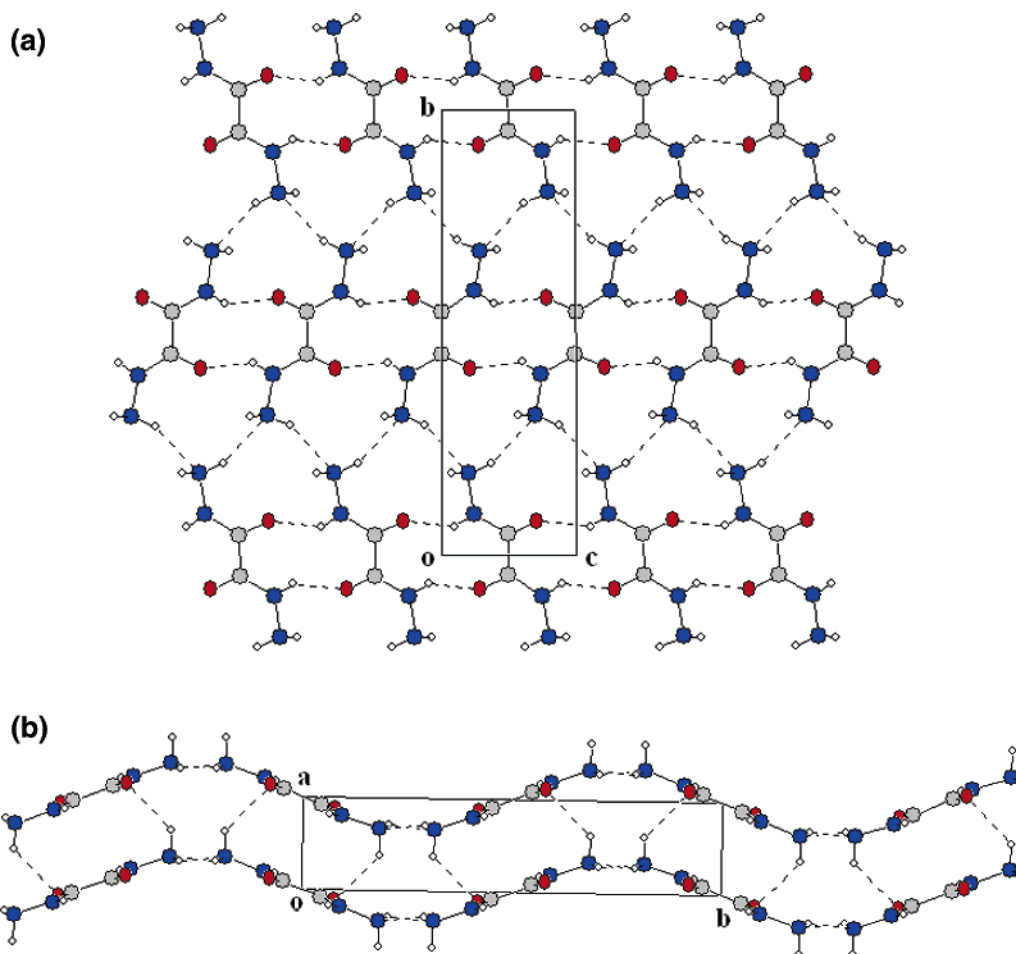
Figure 5. Crystal structure of the δ polymorph of ODH viewed (a) along the *a* axis, showing an individual hydrogen-bonded sheet, and (b) along the *c* axis, showing the relationship between adjacent sheets.

donors are from NH groups. Indeed, in the ε polymorph, the N−H bonds of the NH groups are not involved in hydrogen bonding within the ribbons, and the nitrogen atoms of the NH_2 groups are not involved as hydrogen-bond acceptors within these ribbons. Instead, the N−H bond of each NH group and the nitrogen atom of each NH_2 group are involved in an N−H⋯N hydrogen bond that links adjacent ribbons that run in directions that are almost perpendicular to each other. The "out-of-plane" N−H bond of the NH_2 group also forms an N−H⋯O interaction to the O=C group of a molecule in an adjacent ribbon that runs in a parallel direction.

In many respects, the structure of the ε polymorph differs significantly from the other polymorphs, as it contains ribbons that run in essentially perpendicular directions, leading to a "grid-like" pattern when viewed in projection along the *c* axis (see Figure 6b). On the other hand, the structures of the α, γ, and δ polymorphs are substantially sheetlike, whereas the β polymorph has parallel ribbons that are offset from each other and not arranged in a sheetlike manner.

3.8. Behavior of ODH Polymorphs above Ambient Temperature. Following the discovery and structural characterization of the polymorphs of ODH discussed above, it is relevant to consider issues relating to the relative stability of the polymorphs. As discussed elsewhere,[6,29−32] melting point de-

termination provides a convenient means of assessing relative stabilities of the different polymorphic forms of a substance. Accordingly, we have carried out DSC measurements to investigate melting behavior in the α, γ, δ, and ε polymorphs (as discussed above, following the initial discovery of the β polymorph as a mixture with the α polymorph, we were unable subsequently to obtain the β polymorph again, and thus at the present time further studies of the β polymorph have not been possible). However, we have found that on heating, the α, γ, δ, and ε polymorphs of ODH undergo a solid-state reaction (Scheme 2) prior to melting, to produce solid *N,N′*-dioxalylhydrazidylhydrazine (abbreviated DOHH) and hydrazine (which is gaseous at the temperatures at which the reaction occurs (see below)). Powder X-ray diffraction studies of the solid reaction product show that the same solid phase of DOHH is obtained irrespective of which polymorph of ODH is used as the staring material. We are currently carrying out detailed investigations of this solid-state reaction using time-resolved high-temperature powder X-ray diffraction and time-resolved isothermal TGA, focusing inter alia on detailed kinetic and mechanistic aspects of the solid-state reaction. The results from these investigations will be reported in detail in a future paper.[33] Within the context of the present paper, it is relevant to highlight those aspects of

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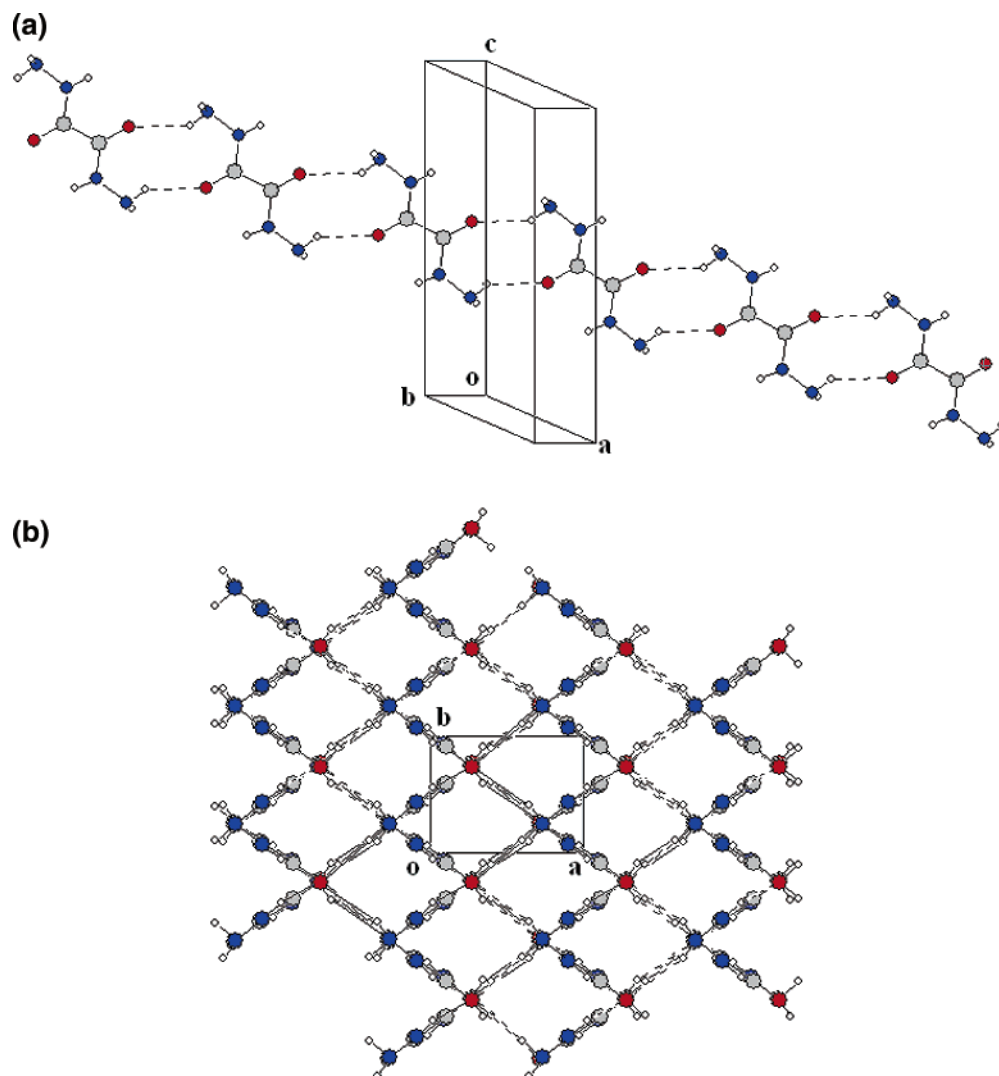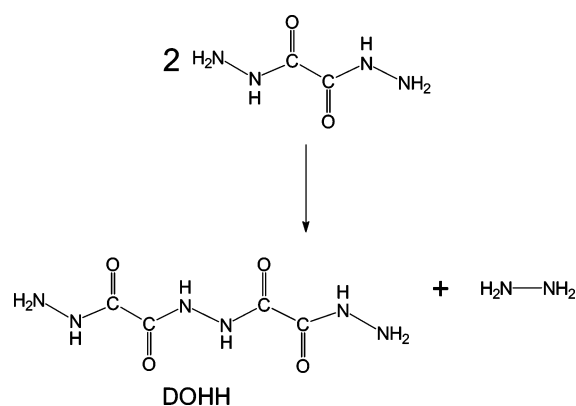(33) Guo, F.; Ahn, S.; Kariuki, B. M.; Harris, K. D. M. Manuscript to be submitted.

Figure 6. (a) An individual hydrogen-bonded ribbon in the crystal structure of the ϵ polymorph of ODH, and (b) the crystal structure of the ϵ polymorph viewed along the c axis, showing the "grid-like" arrangement of ribbons running in essentially perpendicular directions.

Scheme 2

Figure 7. DSC results for (a) the α polymorph, (b) the γ polymorph, (c) the δ polymorph, and (d) the ϵ polymorph of ODH. All DSC data shown were recorded at a heating rate of 20 °C min^{-1}.

the DSC data that relate to possible transformations between the polymorphs of ODH, and thus we focus here on thermal events that occur in the temperature range below that of the solid-state reaction.

DSC data for the α, γ, δ, and ϵ polymorphs of ODH are shown in Figure 7. In each case, the solid-state reaction corresponds to the large endothermic peak in the region of ca. 250 °C in Figure 7 (assignment of this peak as the solid-state
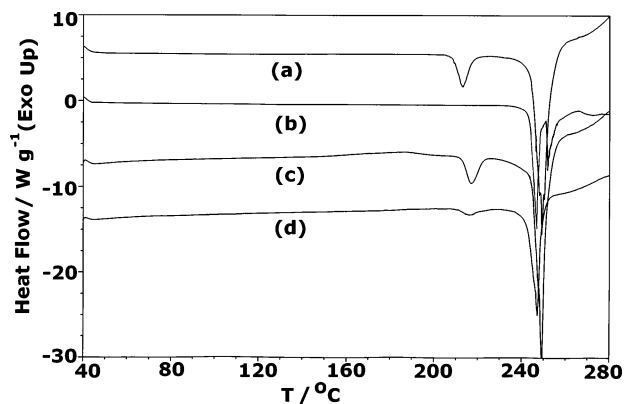
reaction is confirmed from TGA studies, which show a sharp mass loss, corresponding to the loss of gaseous hydrazine, at the same temperature). On heating the γ polymorph, it is clear (from Figure 7b) that no thermal event occurs prior to the solid-state reaction. On heating the α, δ, and ϵ polymorphs, on the other hand, an endothermic peak is observed in each case below

the temperature (ca. 250 °C) of the endotherm due to the solid-state reaction. The onset temperatures[34] (recorded at 20 °C min^{-1}) for these endotherms are: α polymorph, 208.0 °C; δ polymorph, 212.0 °C; ϵ polymorph, 210.3 °C. In each case, the thermal event is *irreversible*; thus, on heating the sample to 220 °C (i.e. below the temperature of the endotherm corresponding to the solid-state reaction) followed by cooling to ambient temperature, no thermal event is observed to occur during the cooling cycle. In each case, powder X-ray diffraction analysis of the material recovered from the DSC sample holder following the cooling cycle indicates that it is a monophasic sample of the γ polymorph of ODH. Thus, we conclude that the endotherms observed at around 200−210 °C on heating the α, δ, and ϵ polymorphs result in the formation of the γ polymorph of ODH. The fact that these polymorphic transformations are endothermic suggests that (under the assumptions specified by Burger and Ramberger in enunciating their "heat of transition rule"[29,30]) each of the α, δ, and ϵ polymorphs has an enantiotropic relationship to the γ polymorph and that the γ polymorph is the stable form among these polymorphs at high temperature. The DSC data, however, do not allow detailed insights to be established on other aspects of polymorph stability, such as the question of whether pairs of the α, δ, and ϵ polymorphs are monotropically or enantiotropically related. Nevertheless, we note that, from the crystal structures determined here (Table 2), the density of the α polymorph is significantly higher than the density of any of the other polymorphs at ambient temperature. Thus, provided the assumptions underlying the "density rule" of Burger and Ramberger[29,30] are valid in the present case, this observation suggests that the α polymorph should be the thermodynamically stable form of ODH at sufficiently low temperature (at least at absolute zero).

Although the endotherm due to the solid-state reaction is observed to occur at ca. 250 °C in the DSC data shown in Figure 7, it is important to emphasize that this does not necessarily imply that the solid-state reaction can only occur at this temperature. Rather, under the conditions of rapid heating in the DSC experiment, the endotherm due to the solid-state reaction is observed at a temperature at which the reaction rate is such that detectable heat absorption occurs on the time scale of the heating process. From experiments[33,35] in which the polymorphs of ODH are maintained for periods of time (typically several hours) at temperatures (e.g., 170 °C for the α and γ polymorphs) *below* the temperature (ca. 250 °C) of the endotherm for the solid-state reaction in the DSC data, followed by characterization of the resulting material by powder X-ray diffraction, it is clear that the solid-state reaction can indeed proceed to completion, albeit over a period of several hours, at substantially lower temperatures. Furthermore, the fact that the solid-state reaction is observed to occur in the α polymorph at temperatures (e.g., 170 °C) below the temperature of the polymorphic transformation to the γ polymorph (ca. 208 °C, see above) suggests that the polymorphic transformation to the γ polymorph is not a prerequisite for the solid-state reaction to

occur. Indeed, on heating the sample in the DSC experiment shown in Figure 7a, some amount of solid-state reaction presumably occurs *before* the polymorphic transformation, and therefore the onset temperature measured for the polymorphic transformation is not strictly that for a monophasic sample of the α polymorph, but rather for the α polymorph plus some amount of the solid-state reaction product (DOHH).

As discussed above, a comprehensive series of experiments to explore kinetic aspects of the solid-state reaction in each polymorphic form as a detailed function of temperature (including temperatures above and below the temperatures [ca. 200−210 °C] of the polymorphic transformation to the γ polymorph), are in progress, and will be reported in due course.[33]

4. Concluding Remarks

The work reported here reveals a number of issues of interest within the polymorphism field. Among these issues is the observation of an "elusive" polymorph (the β polymorph) that was obtained in early preparations but could never be prepared again (despite extensive attempts to repeat the preparation procedure). More importantly, however, the work reported here supports the view that a class of molecules that may be particularly susceptible to polymorphism are those for which low-energy conformational changes (in the case of ODH, reorientation of the NH$_2$ group about the NH−NH$_2$ bond) lead to significantly different orientational characteristics of the potential hydrogen-bond donor (N−H bonds) and/or hydrogen-bond acceptor (nitrogen atom) groups, which in turn creates the opportunity for significantly different modes of molecular aggregation to be formed in the crystalline state. Although a wide range of experimental conditions for producing polymorphs of ODH have been considered in the present work, it would not be surprising if further polymorphs of ODH are found in the future. Indeed, our attempts to search for polymorphs have been confined only to conventional crystallization procedures from solution. A wide range of other strategies provide the potential to generate further polymorphic forms, some of which are currently being explored in our ongoing research.

It is also relevant to note that all polymorphs of ODH discussed in this paper have the trans-trans-trans conformation of the N−N−C−C−N−N backbone, and a further range of conformational polymorphs may be envisaged in which the ODH molecule adopts a trans-trans-cis or cis-trans-cis conformation (although the latter is perhaps less likely on account of its higher intramolecular potential energy). Indeed, the earlier paper[20] that reported the crystal structure of the α polymorph (denoted "Structure A" in ref 20) also reported evidence for two additional polymorphs of ODH (denoted "Structure B" and "Structure C" in ref 20) from vibrational (Raman and infrared) spectroscopies, although the crystal structures were not determined and no results from X-ray diffraction experiments were presented or discussed. From the vibrational spectra, it was deduced that these additional crystal forms contained CO·NH·NH$_2$ units with the C−N bond in the cis conformation, leading to the suggestion in ref 20 that they probably contain ODH molecules in the trans-trans-cis conformation. However, it is clear from comparison of the infrared spectra recorded in the present work (see Supporting Information) and those reported in ref 20 that the material denoted "Structure B" in ref 20 is actually the δ polymorph of ODH and the material denoted

(34) We note that the onset temperatures exhibit an appreciable dependence on heating rate (e.g. for the transformation from the α polymorph to the γ polymorph, the onset temperatures at different heating rates are: 202.3 °C at 5 °C min^{-1}, 204.8 °C at 10 °C min^{-1} and 208.0 °C at 20 °C min^{-1}).

(35) These experiments have so far been carried out for the α and γ polymorphs, as these polymorphic forms are generally easier to prepare as monophasic samples in large quantities.

"Structure C" in ref 20 is actually the γ polymorph of ODH. As all the polymorphs of ODH reported in the present paper contain ODH molecules exclusively in the trans-trans-trans conformation, it is apparent that the assignment in ref 20 that "Structure B" and "Structure C" contain CO·NH·NH$_2$ units with the C−N bond in the cis conformation is incorrect.

Finally, we note that, in the course of our previous study of the formation of cocrystals containing ODH and cyanuric acid, we observed[22] from powder X-ray diffraction evidence that a new phase of ODH (different from the known α polymorph, which was the only polymorph that had been structurally characterized at that time) was obtained by crystallization from a methanol/water (3:1 v/v) solution. Structural characterization of this new phase was not carried out at that time. However, it is now clear from comparison of powder X-ray diffraction patterns that this new phase was the ϵ polymorph of ODH, the structure of which is reported in the present paper.

Note Added after ASAP Publication. After this paper was published ASAP on June 9, 2006, a typographical error was corrected in one of the subheadings in Table 1. The corrected version was published ASAP on June 19, 2006.

Supporting Information Available: Structural data (CIF files) and other information referred to in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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