An Exploration of Polymorphism in Molecular Compounds Using High Pressure

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Abstract

A novel technique for the study of organic compounds under high pressure has been developed. This involves recrystallisation from solution under high-pressure conditions. Crystals grown using this technique have been characterised in situ by single-crystal X-ray diffraction.

This novel high-pressure crystallisation technique has been demonstrated to be successful by growth of a single crystal of a new high-pressure polymorph of the polycyclic aromatic compound phenanthrene, from a dichloromethane solution at 0.6 GPa. A new polymorph of pyrene is also reported at 0.5 GPa. Structural analysis of the new high-pressure polymorphs of these two compounds shows that intermolecular interactions are substantially different from those found in the ambient-pressure structures and do not fit a previously established packing model. Recrystallisation of naphthalene in the 0.2-0.6 GPa pressure range did not result in the formation of a new polymorph, and its crystal structure is reported to be stable to compression to 2.1 GPa.

A new monoclinic polymorph of acetamide has been prepared and structurally characterised from an aqueous solution at 0.8 GPa. Comparison of densities of this new polymorph with those of the known orthorhombic and rhombohedral forms, strongly suggests that the high-pressure phase corresponds to a phase previously identified in volumetric experiments by Bridgman. This is corroborated by the results of powder neutron diffraction studies, which show that direct compression of polycrystalline acetamide-$d_5$ also results in the formation of the new monoclinic phase at a pressure of ca. 1.0 GPa. The effect of different pressure-transmitting media for inducing the phase transition has also been investigated.

The first 1:1 solvate of paracetamol with methanol has been crystallised from a methanolic solution at 0.6 GPa. The hydrogen-bonding pattern in this new structure has been compared and contrasted with patterns found in other solvates and polymorphs of paracetamol. The first dihydrate of paracetamol at 1.1 GPa is also reported. Interestingly, a solvate has not been obtained from ethanol. Instead the metastable orthorhombic polymorph of paracetamol has been prepared at 1.0 GPa.
and a single crystal was recovered to ambient pressure. The orthorhombic polymorph can also be crystallised from acetone at 0.2 GPa and subsequently recovered to ambient pressure. The structure of a new paracetamol/acetone solvate crystallised at 0.6 GPa remains unsolved.

It has been demonstrated how the systematic variation of pressure in combination with ambient-pressure polymorph screening can be used not only to identify rapidly all of the known polymorphs of the nootropic drug piracetam, but also to identify and characterise new polymorphs and hydrates. High-pressure recrystallisation of aqueous and methanolic solutions of piracetam contained in a diamond-anvil cell at pressures of 0.07-0.40 GPa has resulted in the formation of a new high-pressure polymorph of piracetam, form IV. Depressurisation to ambient pressure results in the formation of form II via a single-crystal to single-crystal transition. Compression studies of form II have afforded a reversible, single-crystal to single-crystal shear transition to a new polymorph, form V. The transition occurs between pressures of 0.45-0.70 GPa. Crystallisation from a dilute aqueous solution of piracetam at pressures of 0.6 GPa results in the formation of a previously unreported dihydrate. By contrast, ambient pressure crystallisation of piracetam from water affords a new monohydrate of piracetam, irrespective of concentration.
Declaration

I declare that this thesis was written by myself and that the work detailed in this thesis is my own, or I have contributed substantially to such work, except where specific reference is made to the work of another.

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Chapter 1

Introduction: Polymorphism and High-Pressure Studies of Molecular Compounds
1.1 Polymorphism

1.1.1 General concepts: introducing polymorphism and metastability

Polymorphism (from the Greek meaning "existing in multiple forms") is a term that is used in many disciplines. In chemistry it refers to a substance that can adopt more than one crystal structure in the solid state; these different crystalline forms are termed polymorphs. Many substances can exist as multiple solid-state forms, which vary in their physical properties: these forms include polymorphs, hydrates and solvates in the crystalline state, and amorphous forms. The expression pseudo-polymorphism is sometimes applied to hydrates and solvates and is widely used in the literature. However, in a recent comment on the use of this term, Bernstein (2005) suggested that "... it is a misnomer that should be abandoned."

Polymorphs are different in the crystal structure but are identical in the liquid or vapour states. The crystal form can influence the physical and chemical properties of a material: the main properties affected by polymorphism are melting and sublimation temperature, heat capacity, conductivity, solubility, density, dissolution rate, stability (to temperature and pressure), hygroscopicty and solid-state chemistry (Bernstein, 2002; Giron, 1998a).

Many compounds are known to crystallise in polymorphic forms. A classical example of polymorphism in nature is represented by carbon and two of its allotropes, graphite and diamond (Figure 1.1). The term allotropy is more appropriate when the substance in question is an element. Graphite is a black, soft, electrically conductive and chemically reactive material, whilst diamond is transparent, hard (it is the hardest material), electrically insulating and relatively inert.

![Figure 1.1 Structures of (a) diamond, (b) graphite and (c) Buckminster fullerene C60.](image)
The phase and reaction diagram of carbon is depicted in Figure 1.2. There are two principal crystallographic forms of both graphite and diamond (Tonkov & Ponyatovsky, 2005): hexagonal (several polytypes are known) and rhombohedral graphite and hexagonal (lonsdaleite) and cubic (gem stone) diamond (the stability domains of the various polytypes are not shown in Figure 1.2). Under normal conditions, the thermodynamically stable form of carbon is hexagonal graphite. Carbon modifications typically exist well into pressure-temperature regions where a different solid phase is thermodynamically stable. For this reason, diamond survives indefinitely under normal conditions, although graphite is the thermodynamically stable form. Graphite persists at pressures far into the stability range of diamond, except at very high temperatures. The same is true of buckminsterfullerene $C_{60}$ (Figure 1.1), another allotrope of carbon. Only graphite and diamond have stability regions in the pressure-temperature diagram of carbon; all $C_{60}$ phases should be considered as metastable.

Figure 1.2 Pressure-temperature phase and reaction diagram of elemental carbon, reproduced from Bundy (1980).
Crystallisation is determined by a complex interplay between kinetics and thermodynamics. Thermodynamics governs the order of stability of each form through the free energy differences between these forms, whilst kinetic factors influence the appearance of thermodynamically less stable forms. The transformation to the thermodynamically stable form can occur rapidly, but some metastable forms are known to exhibit apparent stability for years, depending on the environment surrounding the crystal (temperature, humidity, solvation, etc.). For example, at normal temperature and pressure, the transformation of diamond to graphite would require the carbon atoms to change their location and this is an immeasurably slow process in the solid state, except at very high temperatures. In this case the rate of attainment of equilibrium is a kinetic problem.

The example of carbon highlights the sensitivity of physical and chemical properties to a specific crystal structure. This reinforces the concept that the occurrence of polymorphs provides an opportunity to explore structure-property relationships of particular structures.

Ostwald’s Rule of Stages (Ostwald, 1897) is often cited in the case of molecular polymorphism. According to this rule, the most soluble, metastable form will often crystallise first (which recognises the dominance of kinetic factors) and given time, the metastable form will transform to a more stable metastable or stable form (depending on the thermodynamic energy differences between these forms). In the remainder of this section, the attention will be focussed on polymorphism of organic molecular crystals.

1.1.2 Polymorphism, molecular design and crystal engineering

Crystal engineering is the synthesis of new materials with desirable functions and properties that can be adjusted in a controllable manner through molecular design (Desiraju, 1989, 2003, 2005). This is achieved by modifying various supramolecular assemblies through changes in intermolecular interactions, e.g. hydrogen bonds, i.e. by modification of crystal packing. The phenomenon of polymorphism has its basis in the ability of molecules to pack in different arrangements. Thus, an understanding of polymorphism (its control, prediction and rationalisation) is crucial if crystal engineering is to be effective.
The search for polymorphs is therefore an area of intense activity. The phenomenon of polymorphism (and solvate formation) in the crystallisation of compounds is of fundamental interest to experimental and theoretical chemists, and is also of crucial importance to industry for a wide range of materials that includes pharmaceuticals, pigments, optoelectronic materials and explosives (Bernstein, 2002). Examples of polymorphism for various classes of compounds are given in the following paragraphs.

- **Piezoelectric materials.** Quartz (SiO₂) exists as at least ten polymorphs (Greenwood & Earnshaw, 1997). The most familiar and technologically important form is the α-form, which exhibits the piezoelectric effect. Quartz crystals are used in clocks, watches and computers, as a frequency standard (e.g. in stereo tuners) and for ultrasonic imaging. If the α-quartz is heated above 846 K, the β-form is formed, and its piezoelectric properties are lost.

- **Organic conductors.** The charge-transfer salt TMTSeF-TCNQ (tetramethyltetraselenafulvalene-7,7',8,8'-tetracyanoquinodimethane) is dimorphic. Both forms crystallise in space group P-1. One is metallic and forms black crystals with segregated stack of donors and acceptors. The other is semiconducting and forms red crystals with mixed stacks of donors and acceptors (Beckgaard et al., 1977; Kistenmacher et al., 1987).

- **Molecular magnets.** The sensitivity of magnetic properties to changes in polymorphic structures is demonstrated by the trimorphic system of the charge transfer complex of decamethycyclopentadienylferricium and TCNQ, [Cp₂*Fe]⁺[TCNQ]₂⁻. Form I crystallises as purple plates and the compound is paramagnetic because of the Cp*₂Fe⁺ ions, but the S = ½ spins on the adjacent TCNQ anions are antiferromagnetically coupled. Form II crystallises as green blocks and the material is metamagnetic, whereby the occurrence of ferromagnetism depends upon the magnitude of the external magnetic field. Form III crystallises as purple parallelepipeds and the material is a ferromagnet. Changes in magnetic properties arise from the different stacking of the cations and anions (Miller et al., 1987; Broderick et al., 1995).

- **Pigments.** Different packing arrangements of CuPhthalocyanine give rise to at least 10 polymorphs (Bernstein, 2002; Erk, 2005). The β-form (the
thermodynamically stable form) has become the standard letter-press printing ink pigment and more than 80,000 tons are produced annually. Different polymorphs have different shades of blue (from green to red) and are primarily used as printing inks, paints, plastics and automotive finishes. The ε-form is used as a colour filter for liquid-crystals displays.

- **Energetic materials.** Polymorphism can alter the sensitivity and performance of energetic materials such as explosives, propellants, pyrotechnics and gas generators (Bernstein, 2002). For example, different polymorphs may have substantially different densities. This can be important because to a first approximation the detonation velocity of an explosive is proportional to its density. The widely used explosive HMX (cyclotetramethylene tetranitramine) exists as three modifications and the sensitivity to impact is in the order γ > α > β. The high sensitivity of the γ and α-forms and associated risk of accidental detonation mean that only the β-form can be safely used in munitions. Because energetic materials are subject to pressure-induced stress, there is also considerable interest in the pressure dependence of phase transformations in this class of compounds (Piermarini et al., 1990).

- **Proteins.** The most well-known example of polymorphism in proteins is given by the complex polymorphism of lysozyme, a small enzyme that attacks the protective cell walls of bacteria. At least six different modifications are known (Bernstein, 2002) and structural variety can be increased by varying the degree of hydration and nature of the anions during crystallisation (Vaney et al., 2001).

- **Pharmaceuticals.** Polymorphism in pharmaceutical compounds is discussed in more detail in the following section.

1.1.3 **Polymorphism in the pharmaceutical industry**

Within the pharmaceutical industry, the identification of polymorphic forms of drug compounds is of crucial importance. Aside from the impact on drug quality and patient risk, two polymorphs of the same drug compound may have very different physical properties that affect bioavailability or processibility (e.g. tabletting) (Vippagunta et al., 2001). Polymorphs, hydrates, solvates and amorphous solids can be produced by a variety of standard pharmaceutical processes, such as
crystallisation, milling, freeze drying, wet granulation, tabletting and many more (Yu et al., 1998). A range of techniques, often used in combination, is available for the characterisation of polymorphs (Gilon, 1998b):

- Thermal techniques such as Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA).
- Diffraction techniques for long-range order (X-ray powder and single-crystal methods).
- Spectroscopic techniques for short-range order (infrared, Raman, NMR).
- Optical microscopy techniques to distinguish polymorphs through optical and morphological properties (light microscopy, hot stage microscopy).

“Regulations aside, pharmaceutical companies are becoming increasingly aware that different polymorphs can translate into more or less profit.” (Goho, 2004). Drug regulators such as the FDA demand detailed information about drug polymorphs (polymorph types, reproducibility of manufacturing and purity levels) before granting licenses for product distribution. Intellectual property associated with different polymorphs and solvates can be worth billions of dollars and challenges to patents made on the basis of polymorphism are becoming increasingly frequent and very expensive.

In the pharmaceutical industry, the widely used analgesic drug paracetamol is perhaps the most studied case of polymorphism (see Chapter 5). Under ambient conditions the thermodynamically most stable form is the monoclinic form and this is used commercially. This modification is not suitable for direct compression and requires mixing with binding agents before tabletting. The metastable orthorhombic form is suitable for direct compression, but scaling up of the crystallisation of this form is a difficult task and drug companies are usually reluctant to market metastable forms.

Perhaps the most striking example of the potential impact of polymorphism in the pharmaceutical industry to date is represented by the case of Ritonavir, Abbott’s protease inhibitor for HIV, currently marketed as Norvir (Chemburkar, 2000). Discovered in 1992 and brought into market in 1996 as a semi-solid capsule in liquid formulation, in 1998 many final product lots failed a dissolution test, which revealed the existence of a new, much less soluble and more stable polymorph. This caused major problems for the processing plant and for the biological uptake of the drug in
capsule form. A new formulation to accommodate the new form was designed and a controlled process was established to generate consistently the initial form. Abbott lost an estimated $250 million in the sales during the year that the drug was withdrawn for reformulation.

The case of ranitidine hydrochloride, the anti-ulcer drug sold by GlaxoSmithKline and known as Zantac, provides an example of patent litigation. In the mid-1990s, the patent on a polymorph, form I, of the drug was about to expire and a patent on a second polymorph, form II, was still in force. Generic drug companies were interested in manufacturing and selling form I. The problem of making form I is that contamination by form II inevitably occurs. One of these companies, Novopharm, was repeatedly sued by GlaxoSmithKline for infringing the patents on both forms. After several court cases and appeals, Novopharm was allowed to market mixtures of form I and form II and GlaxoSmithKline lost profits on the largest-selling drug in the world.

The cases of Ritonavir and Zantac reinforce the concept that polymorphism is not predictable and that polymorphs apparently come and go in unpredictable ways and new ones appear when least expected. The cases of Ritonavir and Zantac emphasise the need for an effective and rapid means of identification, characterisation and mapping of drug polymorphs in the lengthy and expensive process of drug development. Thus pharmaceutical companies deploy substantial effort and resource (either in-house or contracted out) for the identification and characterisation of polymorphs and solvates of every drug that reaches the market. Indeed, polymorph/solvate screening is now regarded so important that it is often conducted very early on in the drug development process. These techniques typically involve recrystallisation (increasingly via high-throughput robotic screening) by varying parameters such as temperature, concentration, solvent, and relative humidity, with subsequent analysis by calorimetric, spectroscopic, and diffraction techniques. Even after these exhaustive tests, a new polymorph may remain undetected for many years, or a sample of a new polymorph may be obtained once but never again, the phenomenon of so-called “disappearing polymorphs”. (Dunitz & Bernstein, 1995).

At a more fundamental level, the area of polymorphism is fascinating to structural chemists and substantial research effort is being directed at developing methods for its control (Davey et al., 1997; Meidong et al., 2002). Polymorphism remains one of the major challenges for those involved in the theoretical ab initio
prediction of equilibrium crystal structures. Invariably, the results from even the most favourable ab initio studies result in the generation of many plausible structures that have similar absolute energies, making it difficult to identify the structure that would have the lowest free energy (Motherwell et al., 2002). Almost all studies that seek to explore polymorphism and solvate formation are performed under ambient pressure, yet it is well known that pressure is an unrivalled method for inducing phase transitions in a wide range of materials, as it will be illustrated in Section 1.2. The only exceptions are a few processes that use supercritical liquids (such as carbon dioxide) as solvents, but the pressures rarely exceed 0.01 GPa and the pressure ranges are narrow (Tozuka et al., 2003). Furthermore, the range of easily accessible supercritical solvent systems is limited to only a small number of solvents.

The development of complementary methods for efficient exploration of polymorphism and solvate formation would therefore be highly desirable and would enhance the understanding of the factors that are responsible for the observed packing arrangements of organic molecules in the solid state. Applied to the pharmaceutical industry, a better control of polymorphism could ultimately improve the preparation and control of dosage forms.

The effect of pressure on solid drugs is currently of great interest (Boldyreva, 2003), and there are two main reasons for this. First, many solid drugs are subjected to mechanical action during processing and, for example in tablet production. It is important to know if any phase transition during such processing is possible, in order to control the properties and production of drugs selectively and consistently. Second, the study of the response of a crystal structure to hydrostatic pressure provides important knowledge on the intermolecular interactions in the crystals, in particular, on the hydrogen bonds as these interactions are important in understanding some of the properties of solid drugs, including crystallisation, dissolution and bioavailability, as well as for improving potentials used for structure and polymorph predictions.
1.2 High Pressure Research

1.2.1 General concepts

One of the most fundamental properties of a material is its structure in the solid state. This tells us about the connectivity of its component atoms and their packing as well as allowing the calculation, or at least the estimation, of most of its physico-chemical properties.

A novel approach as a possible answer to the need of a rapid and effective means of identifying, characterising and mapping polymorphs in industry is presented in this thesis. This involves exploiting high pressure as an additional dimension in the search for new polymorphs and solvates of organic molecules. This allows a much wider range of conditions to be explored and also improves the knowledge of intermolecular interactions in the crystalline state. The rationale for this is that the structure of matter in the solid state is governed by interatomic and intermolecular interactions. These interactions depend critically upon distance and so they are strongly affected by the application of pressure. This phenomenon has been widely studied within the Physics and Geosciences communities, where the use of pressure has reached a relatively high degree of maturity and has been shown to be an unrivalled means of inducing phase transitions and substantial changes in electrical, optical, or magnetic properties in elements, semiconductors, minerals, and ceramics, as briefly reviewed in Section 1.2.2. Typical experiments achieve pressures in the order of several GPa and temperatures of several thousand K.

Until recently, however, there have been very few studies of the effects of high pressures on small organic molecules: these are reviewed in Section 1.2.3.

1.2.2 High-pressure research: a short review on elements, materials and some industrial applications

Pressure-temperature phase diagrams of the elements have been reviewed in a recent book by Tonkov and Ponyatovsky (2005), which also contains references of the earlier work carried out by Bridgman in the five decades of the 20th century. P. W. Bridgman was a pioneer in high-pressure research on materials and their thermodynamic properties. In his volumetric experiments conducted up to 10 GPa, he carried out extensive investigations on the properties of matter, including a study
of the compressibility, electric and thermal conductivity, tensile strength and viscosity of more than 100 different compounds. He won the Nobel Prize in Physics 1946 “for the invention of an apparatus to produce extremely high pressures, and for the discoveries he made therewith in the field of high pressure physics” (Nobel Lectures, Physics 1942-1962, 1964).

An entire volume of Reviews in Mineralogy and Geochemistry (Volume 41, Hazen & Downs, 2000) is dedicated to high-temperature and high-pressure crystal chemistry and is the basis of numerous excellent reviews on the variation of structures with temperature and pressure, as well as on experimental and analytical techniques for high-pressure crystallography. Silicate structures, dense oxide minerals, framework structures, hydrous phases and molecular crystals are covered in detail in part II of this volume. Another reference work available in the literature (Katrusiak & McMillan, 2004), covers further aspects of high-pressure crystallography and further classes of compounds (e.g. superconductors, metals and alloys and quasicrystals). These materials are typically studied using small-volume diamond-anvil cells or larger volumes presses.

- **Actinides.** High-pressure studies on actinides (Lindbaum et al., 2003) illustrate the difference between the earlier metals and those following plutonium (trans-plutonium elements). The complex structures at atmospheric pressure of the lighter actinides are a consequence of delocalised (“itinerant”) 5f electrons, and these metals show less compressibility (i.e. exhibit larger bulk moduli) and few (if any) phase transitions under pressure. In contrast, the trans-plutonium metals do not have 5f electrons contributing to their cohesive energies at atmospheric pressure. They are therefore relatively ‘soft’ (have lower bulk moduli), and show multiple phase transitions. After delocalization of their 5f electrons due to pressure, they adopt structures displayed by the light actinides.

- **Synchrotron experiments.** Technological advances in the field of high-pressure research make it now possible to conduct experiments on materials under extreme high-pressure conditions, including pressures in excess of those found at the centre of the earth (363 GPa). An increasing number of methods are based on synchrotron radiation, the use of which has shed a new light on materials under extreme conditions (Hemley et al., 2004). The application of powder diffraction techniques has for example resolved the long-standing controversies with respect
to the high-pressure structures of sulfur (Degtyareva et al., 2005a, 2005b). The eight-member ring of form I transforms at 1.5 GPa into a non-metallic form II characterised by triangular chains. At higher pressures, a transition to a non-metallic, square-chain structure, form III, occurs. An incommensurate superconducting phase, form IV, is found above 86 GPa and form V, a \( \beta \)-Po structure is found above 162 GPa. A similar sequence is found in Se.

- Neutron experiments. Neutron experiments for the study of lattice dynamics and magnetic ordering in materials were in the past limited in high-pressure experiments due to the poor penetration through high-pressure apparatus and to small sample size. With the advent of tailor-made large-volume apparatus and sample assemblies, such as the Paris-Edinburgh cell (Besson et al., 1992), they are now performed routinely at pressures into the 10-20 GPa range (Loveday et al., 2001). High-pressure neutron diffraction experiments are particularly suited for the study of hydrogen-containing systems, e.g. ammonia, ices and various clathrates.

- Incommensurate crystals in the metallic elements. The structures of high-pressure incommensurate crystals in the metallic elements have been discussed in a recent review by McMahon and Nelmes (2004). Composite host-guest structures have been found for Ba, Sr, Bi, Sn, As, Rb and K, whilst incommensurately modulated structures have been reported for Te and Se and commensurately modulated structures have been found for Rb, Cs and Ga.

- Group 14, 13-15, and 12-16 compounds. The high-pressure phases of group 14, 13-15, and 12-16 compounds have also been reviewed (Mujica et al., 2003; Ackland, 2001). At high pressure, these compounds usually adopt high-symmetry structures of increasing coordination number. However, recent experiments have shown that previously unexpected lower-symmetry phases are formed at intermediate pressures. At low pressures (10 GPa), group 14, 13-15, and 12-16 materials tend to adopt open crystal structures and are mostly covalently-bonded semiconductors. At higher pressures (20 GPa) more compact metallic structures are formed. For example, at pressures a little above 20 GPa, the low-pressure zinc-blende phase of GaP undergoes a structural transition to a metallic phase II (Onodera et al., 1974). The review by Mujica et al. (2003) also gives a good
introduction to some general concepts in high-pressure techniques, model calculations, and solid-solid phase transitions.

- **Synthesis of new materials.** The synthesis of new materials under conditions of high pressures has also been recently reviewed (McMillan, 2002, 2003). Silicate minerals are usually based on tetrahedrally-coordinated SiO₄, but the discovery of a new polymorph of SiO₂ based on the rutile structure, provided evidence of octahedrally-coordinated Si at pressures above 9 GPa (Stishov & Popova, 1961). Another example of a high-pressure structure containing octahedral silicon is represented by the MgSiO₃-pyroxene silicate-perovskite phase formed above 24 GPa. The results of the high-pressure phase transitions of this material revolutionised the understanding of seismic wave propagation and of the layered structure of the Earth. Selected recent studies of major planet-forming minerals are also reported in a review by Hemley & Mao (2002). These include the silicate perovskites that form the bulk of the Earth's lower mantle and high-pressure studies on Fe-Ni alloys. Materials with technological applications are also discussed by McMillan, *e.g.* high-pressure synthesis on an industrial scale of super-hard abrasives synthetic diamonds and cubic boron nitride, wide-bandgap semiconductors, ferroelectrics as BaTiO₃ and (Pb,Zr)(Zr,Ti)O₃. Introducing small Si⁴⁺, Ge⁴⁺ or V⁵⁺ cations into the metal sites of ferroelectrics at high pressure has been shown to enhance the dielectric and non-linear optical properties of the materials, both at high pressure and following decompression to ambient conditions.

- **Condensed gases, water and clathrates.** Condensed gases such H₂, CH₄ and NH₃, that are important components of giant gas planets such as Neptune, Saturn and Jupiter and their moons, have been extensively studied at high pressure (McMillan, 2003 and references therein). Metallic conductivity was recorded in dense fluid hydrogen under extreme conditions of pressure and temperature, during shock-wave studies. Perhaps one of the most studied molecules under pressure is water, mainly because of its relevance to the origin of life on our planet. The numerous structures and rich phase diagram of water are reviewed in Hemley & Dera (2000) and in references therein. In addition to the various studies on ices, hydrogen-bonded H₂O-‘clathrates’ containing trapped ‘guest’
species (Xe, CH₄, CO₂) have been characterised and stabilised at lower pressures (Hemley & Mao, 2002). In particular, CH₄-H₂O clathrates are found on the deep ocean floor and could have fuel storage applications, whereas CO₂-H₂O clathrates are being investigated for CO₂ sequestration strategies. Ammonia hydrates are amongst the simplest systems to exhibit N-H...O and O-H...N hydrogen bonds. In addition, the planets Uranus and Neptune, and Saturn’s largest moon, Titan, contain large amounts of ammonia and water and the study of ammonia hydrates might be important for planetary modelling.

• **Amorphous solids and liquids.** Amorphous solids and liquids form a large class of condensed materials. Application of high pressure usually promotes crystallisation of amorphous substances (McMillan, 2003). However, the ‘reverse’ phenomenon of ‘pressure-induced amorphisation’ (PIA) is now also well known (Mishima et al., 1984). Compressing solids at low temperatures to avoid transformation into dense crystalline phases results in ‘metastable melting’ to a solid amorphous material. PIA can be applied to many different substances, and it provides a useful method for producing amorphous materials without passing through the liquid state (e.g. in the formation of high-density amorphous Si).

• **Pressure and the origin of life.** In an article by Hazen et al. (2002) it was highlighted that high pressure may have played a significant role in the origin of life. The discovery of life in high-pressure aqueous environment has led to the study of microbes and biomolecules. For example, cultures of microbes at high pressure have displayed both barotolerant and barophilic behaviour. Hazen et al. (2002) have investigated the stability and reaction pathways of key organic molecules under high-pressure hydrothermal conditions. For example, the hydrothermal organic chemistry of pyruvic acid was studied from 423 to 573 K at pressures to 0.5 GPa. It was found that in all high-pressure hydrothermal experiments, pressure significantly expands the temperature stability of the aqueous phase. At higher temperatures, the physical and chemical properties of water are more suitable to a variety of organic reactions. In addition, pressure appears to favour certain reactions. In the case of pyruvic acid, enhanced yields of the cyclic aromatic compounds through Diels-Alder cyclo-addition reactions at
0.2 and 0.5 GPa were observed. Decarboxylation to acetic acid and carbon dioxide through aldol condensation and decarboxylation of dimers to yield methyl succinate were also monitored.

- **Pressure and chemical reactions.** Whilst a number of chemical reactions occur spontaneously, most require activation. Heat is traditionally employed to increase molecular agitation as well as the frequency of collision between molecules. The role of high pressure as an activation mode in organic synthesis was reviewed by Jenner (2002), where high-pressure techniques have the potential to further the understanding of reaction pathways. Compared to temperature, pressure is a mild non-destructive mode, generally respecting the molecular structure by limiting decomposition or additional evolution of the products. The use of high pressure has been shown to activate the cyano group in nitriles for Diels-Alder reactions. In addition, pressure activation achieves more negative activation volumes and therefore minimises or removes steric inhibition. Pressure activation also provides an alternative for the synthesis of heat-sensitive molecules by lowering the synthetic temperature, *e.g.* in the synthesis of β-lactams.

- **Pressure as a food-processing technique.** Applications and advances in the use of high pressure as a food-processing technique have been reviewed by O’Reilly *et al.*, (2001). In contrast to thermal processing, the application of high pressure to food does not significantly reduce the nutritional value, taste, colour, flavour or vitamin content. This is because it is generally believed that mainly non-covalent bonds within biological matter are affected by pressure. Thus, small molecules such as amino acids, vitamins and flavour compounds remain unaffected by high pressure, whilst the structure of large molecules such as proteins and enzymes can be altered. This means that processes as denaturation or aggregation of food macromolecules or (in)activation of enzymes can occur. In the late 19th century Bert Hite and his co-workers examined the pressure sensitivity of microorganisms in milk (Hite, 1899), fruit and vegetables (Hite *et al.*, 1914) and a range of other foods and beverages, and demonstrated that the shelf life of foods could be extended by high-pressure treatment. The technique of high-pressure freezing and thawing of food that mainly contain water has been reviewed by Le Bail *et al.*, 2002.
• Pressure in medicine and pharmacology. The applications of high pressure in medicine and pharmacology have been reviewed in an article by Silva et al. (2004). The study of misfolded proteins, aggregates and amyloids can potentially improve scientists’ understanding of protein misfolding diseases (e.g. amyloidosis, Alzheimer’s, Parkinson’s and the prion diseases CJD and BSE) and has attracted considerable attention from pharmaceutical and biotechnology companies. High pressure has also been used to study viruses and other infectious agents for the purpose of sterilization and in the development of vaccines.

• Cold denaturation of proteins. Experiments on the cold denaturation of proteins under high pressure have been reviewed by Kunugi & Tanaka (2002). It was found that the structure of a protein can be destabilised and the protein can be denatured. The transition pressure can vary from a very low value (< 0.2 GPa) to a very high value (> 0.7 GPa), depending on the structure and the nature of each protein. The molar volume change of melting water is positive and the freezing point of water decreases as pressure is increased up to 0.2 GPa, where water freezes at about 251 K. Hence pressure is simultaneously employed as a destabiliser and as an antifreeze.

• The effect of pressure on proteins. Pressure affects the equilibrium between denatured or dissociated and native forms of a protein in the direction of the form that occupies a smaller volume (Silva et al., 2004 and references therein). The structural region of the protein that is most sensitive to pressure is the hydrophobic core, especially when cavities are present. Experimental and theoretical approaches have shown that pressure induces the disruption of the hydrophobic core, leading to partially or fully unfolded states that are more hydrated and with smaller volumes than the native state. The decrease in the volume of proteins upon partial or complete disruption of the native structure can be explained by hydration of exposed non-polar amino acid residues, electrostriction of exposed charges, and the loss of free volume arising from packing defects in the completely folded structure (Foguel & Silva, 2004). High pressure (< 0.1 GPa) has been shown to affect the kinetics of gating but not the conductance of ion channels, which are distinctive membrane proteins which provide a gated pathway for diffusing ions (MacDonald, 2002). Other recent
observations point to systematic effects of pressure on protein folding, as well as
on protein interactions with various substrates. However, the experimental study
of biomolecules at high pressure is in its infancy and this field represents an
important area for future research.

- **Pressure in protein crystallisation.** The topic of protein crystallisation under high
  pressure has been reviewed by Suzuki *et al.* (2002). Pressure is expected to be an
  important parameter to control protein crystallisation, since hydrostatic pressure
  affects the whole system uniformly and can be readily controlled. In addition,
  protein solubility depends on pressure. For instance, the solubility of the
tetragonal form of lysozyme increases with increasing pressure, whilst that of
orthorhombic from decreases. Pressure also influences crystal growth rates of
proteins. For example, the growth rate of crystals of glucose isomerase is
significantly enhanced with increasing pressure, whilst the growth rate of
tetragonal lysozyme crystal and subtilisin decreases with increasing pressure.
These studies give some insight into surface growth kinetics.

**1.2.3 High-pressure structural research of molecular organic compounds**

The study of the structural response to external action, such as increasing
pressure or decreasing temperature, is an effective way of probing intermolecular
interactions. Pressure, with temperature, is a means of inducing phase transitions and
the application of pressure can therefore be used to induce the formation of new
d polymorphs, as mentioned earlier. In order to develop a systematic understanding of
interactions, bonding characteristics and packing motifs of specific classes of
compounds (e.g. compounds containing a particular functional group) it is imperative
to start by studying some of the simplest derivatives.

Compression of molecular organic crystals (to < 10 GPa) affects the weaker
and more compressible/longer ("softer") interactions between the constituent
molecules (e.g. hydrogen bonds, C-H...π and van der Waals interactions). The
directional character of intermolecular interactions such as hydrogen bonds and the
general appreciable asphericity found in organic molecules induce significant
anisotropy in the response of these crystals to pressure (and temperature). It is
generally accepted that the effect of increasing pressure is comparable and correlated
to that of decreasing temperature (Hazen & Finger, 1982). However, this is strictly true only for isotropic distortions in cubic crystals, and for crystals of lower symmetry the distortion is usually anisotropic and not necessarily the same. There are a number of examples in the literature that indicate that the responses can be qualitatively and quantitatively quite different. These include charge-transfer complexes and other molecular compounds such as paracetamol and Co(III)-nitropentaammines (Hemley & Dera, 2000; Boldyreva, 2003, 2004b). Variable-pressure studies are much less common than variable-temperature studies, and this is largely due to the greater difficulty of conducting a high-pressure experiment, caused by the requirements for specialised high-pressure equipment and the non-routine treatment of data.

Comparative studies of different polymorphs of the same compound can provide a better understanding of intermolecular interactions and of the factors that influence phase transitions between them. The effects of pressure on molecular crystals have been recently reviewed in the literature by Hemley & Dera (2000) and by Boldyreva (2004b).

Crystallographic high-pressure studies on molecular organic compounds available in the literature can be broadly divided into two main categories, depending on the physical nature of the sample and consequently on the method of loading in a high-pressure cell, as explained below. A further class is represented by substances that are normally gases under ambient conditions and require more specialised loading. These are not reported here, but a comprehensive review is available in Hemley & Dera (2000). Research on molecular organic compounds has been pioneered by the groups at the University of Edinburgh, UK and at the Adam Mickiewicz University, Poland, at the Novosibirsk State University, Russia and at the Geophysical Lab of the Carnegie Institution of Washington, USA.

- **Liquid samples at ambient pressure and temperature.** These samples are straightforward to load because they are in the liquid state and crystallisation can be induced by the application of pressure. The loading procedure involves placing a small drop on the edge of the gasket hole. The cell is then rapidly assembled and the screws tightened to induce crystallisation. This results in the formation of a polycrystalline solid, which is not suitable for single-crystal X-ray diffraction.
single crystal is grown by heating the sample, thereby reducing the number of
crystallites, until a single crystal remains. The sample is then allowed to cool and
grow into a single crystal, which ideally fills the entire gasket hole, and which can be
analysed by single-crystal X-ray diffraction, and in situ Raman and IR spectroscopy.

- **Solid samples at ambient pressure and temperature**: these can be further divided
in two subclasses.

  - **Low-melting sample** (melting point typically < 313-323 K). These samples
require more careful loading. The sample can be gently heated until liquid and
a small drop is placed on the edge of the gasket hole. A single crystal is then
grown as explained above. For samples that crystallise rapidly, gentle heating
of the cell components and of any apparatus used to handle the sample ensures
that the sample remains liquid. It is important that crystallisation is induced by
application of pressure rather than by cooling at ambient pressure, as the
purpose of the experiment is to study structural changes induced by pressure.

  - **High-melting samples** (melting point typically > 323 K). These samples are
usually loaded as powders or as single crystals previously grown at ambient
pressure. The evolution of structural changes can then be followed by means of
compression studies as a function of pressure. The pressure-temperature curve
is often very steep and it can therefore be extremely difficult to melt and grow
crystals under pressure. In addition, overheating should be avoided to prevent
sample decomposition, especially for organic compounds. This causes severe
limitations to the study of phase transitions, as described in more detail in
Section 1.3 and in Chapter 2.

1.2.3.1 **Liquid samples at ambient pressure and temperature**

Amongst van der Waals compounds that are liquids at ambient pressure and
temperature and which have been studied by high-pressure techniques are benzene
[the high-pressure phases on this compound are reviewed by Hemley & Dera (2000)]
and cyclohexane. For the latter, a phase observed for the deuterated compound has
been observed at low temperatures between 0.15 GPa and 0.3 GPa (Wilding et al.,
1993), but not for the hydrogen-containing isotopomer.

At the University of Edinburgh, pressures in the range of 0.1-10.0 GPa have
been used to investigate small organic molecules such as simple amines, ketones,
carboxylic acids and alcohols. Almost all of the compounds studied have undergone one or more phase changes to give polymorphs, some of which were new, others of which were known, but are metastable at ambient pressure. A concise review of the compounds studied is given in the remainder of this section.

One representative example is provided by acetone (Allan et al., 1999a). The two distinct low-temperature and high-pressure phases exhibit all three of the archetypal packing motifs identified in an important recent survey of dipolar carbonyl-carbonyl interactions in more complex molecules (Allen et al., 1998). This is a significant example that illustrates the usefulness of studying small, simple molecules under a range of pressures and temperatures.

The behaviour of the alkyl mono alcohols has also been investigated by the group at Edinburgh, whereby the effect of pressure on the O-H...O hydrogen bond has been studied in a range of chemically similar molecules. Common packing motifs on the basis of different packing requirements of the alkyl R-groups and the hydroxyl groups have been identified in the crystal structures of this class of compounds at low temperature (Brock & Duncan, 1994). Molecules with a “small” or “thin” R-group have a tendency to form hydrogen-bonded chains where the molecules are related by a 2_1 screw axis or a glide plane. Molecules with bulky R-groups tend to form 3-fold or higher helical chains.

Methanol (Allan et al., 1998), ethanol (Allan & Clark, 1999b; Allan et al., 2001), phenol (Allan et al., 2002), its halogenated derivatives 2-fluorophenol and 4-chlorophenol (Oswald et al., 2005a), 2-chlorophenol and 4-fluorophenol (Oswald et al., 2005b), _t_-butanol (McGregor 2003), cyclobutanol (McGregor et al., 2005) and cyclopentanol (Moggach et al., 2005a) have been studied in this series and showed polymorphic behaviour under pressure. 3-fluorophenol, 3-chlorophenol gave the same polymorph under recrystallisation conditions of high pressure and low temperature (Oswald et al., 2005a).

Methanol crystallises at 3.5 GPa in space group _P_1 with _Z_ = 3. The liquid can be easily super-pressed and vitrification at high pressure is not uncommon. The molecules pack in a strained environment (compared to the two low-temperature polymorphs) giving rise to a “2-1-2-1” arrangement (Allan et al., 1998), according to which two molecules sit on one side of the hydrogen-bonded chain. At 3.0 GPa
ethanol is unstrained with respect to the low-temperature form and this might explain why it crystallises more readily than methanol under conditions of high pressure.

At ambient pressure, 2-chlorophenol and 4-fluorophenol crystallise in high-symmetry space groups with the molecules disposed about $3_2$ and $-3$ symmetry operators, whilst phenol packs via a pseudo 3-fold axis in $P2_1$. All three systems crystallise under pressure in low-symmetry space groups with the molecules disposed about $2_1$ screw axes. At high pressure, 2-chlorophenol, 4-fluorophenol and phenol crystallise in low-symmetry space groups at 0.12, 0.10 and 0.16 GPa, respectively, and all three systems exhibit packing motifs that are typical of alcohols with small or “thin” R-groups (with the molecules disposed about $2_1$ screw axes). Hence, for these systems, the effect of pressure is to overcome the steric effect of the bulky groups, forcing them to act as “thin” R-groups at high pressure.

In contrast to these observations, pressures up to 0.35 GPa are not sufficient to overcome the steric hindrance of the R-group in $t$-butanol. The high-pressure structure forms hexameric rings, whilst the ambient-pressure polymorph forms pseudo 3-fold helices, characteristic of large R-groups.

2-fluorophenol gives different polymorphs at low temperature (260 K) and high pressure (0.36 GPa). Whilst C-H...F interactions are very significant in the high-pressure form, they are completely absent in the low-temperature form. 4-chlorophenol (solid at conditions of ambient pressure) gives two modifications when crystallised from the melt or from benzene. Recrystallisation from the melt at 0.02 GPa has been shown to afford the same polymorph as that obtained from benzene at ambient pressure, and which exhibits more extensive C-H...π interactions. The observation of this form at high pressure has been attributed to the more efficient packing of phenyl groups in this form. Transition to structures typical of small alcohols were not observed for the bulky alcohols 3-chlorophenol, 3-fluorophenol, 4-chlorophenol and 2-fluorophenol.

At temperatures below 220 K, the structure of cyclobutanol is characterised by hydrogen-bonded chains in which catemers form a pseudo 3-fold molecular arrangement (McGregor et al., 2005). At pressures about 1.3 GPa, a wave-like topological arrangement is observed, where molecular catemers adopt pseudo 2-fold packing, which is typically exhibited by compounds with a “thin” R-group.
Cyclopentanol is a relatively simple example of a molecular compound that forms plastic crystalline phases on initial cooling. A previously unobserved, fully ordered phase has been crystallised at pressures above 1.5 GPa (Moggach et al., 2005a), where molecules adopt a 4-fold molecular arrangement. The bulkier R-group of cyclopentanol compared to cyclobutanol might account for the absence of a polymorph in the former compound with crystal packing typical of a “thin” R-group.

The monocarboxylic acids acetic acid (Allan & Clark, 1999a; Allan et al., 1999b), formic acid (Allan & Clark, 1999c) and propionic acid (Allan et al., 2000) have been studied using a combination of single-crystal X-ray diffraction and density functional calculation techniques. Both formic acid and acetic acid form infinite hydrogen-bonded chains rather than the isolated dimers that are observed in the longer chain monocarboxylic acids. Both low-temperature structures are essentially identical. In the high-pressure phase of formic acid at 0.8 GPa molecules were found to adopt both the cis and trans conformers (relative to the two hydrogen atoms) rather than only the trans conformer characteristic of the low-temperature phase. The molecules form “near dimers” arranged on symmetrically flat layers, but the required bond lengths for “true dimer” formation are significantly shorter than those observed.

The hydrogen-bonded molecular chains found in the high-pressure polymorph of acetic acid at 0.2 GPa are essentially identical to those of the low-temperature phase, although the relative orientations of the chains are noticeably different. A more efficient molecular packing is formed through puckering of molecular layers.

Propionic acid is the first in the series of monocarboxylic acids to form isolated dimer pairs linked by hydrogen bonding. The high-pressure polymorph (the structure has been determined at 1.4 GPa) is also characterised by dimers (here two types of dimers are observed, dimers formed about an inversion centre and about a point of inversion), but at high pressure a herringbone-type of packing rather than flat dimer stacking is observed.

High-pressure crystallisation of CS₂ (Dziubek & Katrusiak, 2004), 1,2-dichloroethane (Bujak et al., 2004) and 1,1,2,2-tetrachloroethane (Bujak & Katrusiak, 2004), afforded the same polymorph observed at low temperature.
Thiocarbonyl and carbonyl bonds have been observed to elongate as pressure increases (Katrusiak, 1991b).

### 1.2.3.2 Solid samples at ambient pressure and temperature

General phenomena that have been observed on compression of molecular crystals include the tendency of collapse of structural voids, ordering of disordered molecules/moieties, and changes in the conformation of flexible molecules, which adjust to the strain of the surroundings (Boldyreva, 2004a).

A wide range of aromatic compounds have been investigated by compression experiments, starting with the volumetric experiments performed by Bridgman (1914, 1941). These include naphthalene, phenanthrene and anthracene. High-pressure polymorphism in some aromatic compounds is discussed in more detail in Chapter 3.

High-pressure compression studies at the University of Edinburgh have focussed on the amino acids glycine (Dawson et al., 2005), L-cysteine (Moggach et al., 2005b), L-serine (Moggach et al., 2005c) and L-cystine (Moggach et al., 2005d). L-glutamine, L-β-glutamic acid, L-asparagine monohydrate and L-α-aspartic acid (Lozano-Casal, 2005). Of these, L-cysteine, L-glutamine, L-β-glutamic acid, L-asparagine monohydrate and L-α-aspartic acid did not show polymorphic transformations up to pressures of ca. 6.0 GPa. In all structures, closure of voids as pressure was increased was observed. The structure of L-cysteine was investigated from 0.4 GPa to 3.7 GPa and changes in the unit cell parameters were monitored up to 6.4 GPa. The C-S-S-C torsion angle was observed to change so that the molecule could act as a spring in response to the applied pressure. The length of N-H...O hydrogen bonds was found to decrease by 0.10-0.60 Å over the 0.4-3.7 GPa pressure range. Interestingly, L-α-aspartic acid compressed by ca. 19% at 5.8 GPa.

The three ambient-pressure polymorphs of glycine, α, β and γ, have also been investigated at high pressure (Dawson et al., 2005; Boldyreva et al., 2005b). α-glycine undergoes a single-crystal to single-crystal transition between ambient pressure and 0.8 GPa (Dawson et al., 2005) to afford a new polymorph, δ-glycine. The driving force for the transition to this new phase is an increase in number and strength of C-H...O interactions and in closure of structural voids. γ-glycine
undergoes a destructive transition at 1.9 GPa to a new polymorph, denoted ε. Structural information on this phase was obtained by powder X-ray diffraction. The transition is complete at 4.3 GPa and the structure is characterised by similar layers found in the α-form. An alternative structural model for the ε-form has been proposed by Boldyreva et al. (2005). The main difference between the two models lies in the orientation of the molecules: the shortest N-H...O hydrogen bond in the model proposed by Dawson et al. has an N...O separation of ca. 2.60 Å (which is at the lower limit of such distances observed under ambient conditions) and a shortest O...O contact of 3.22 Å. In the model suggested by Boldyreva et al., these distances are considerably shorter at 2.37 Å and 2.65 Å, respectively. The α-form is stable to the application of pressure up to 6.2 GPa, and no “super-short” N-H...O hydrogen bonds have been observed. Instead, the effect of pressure manifests itself in the closure of voids and the formation of strong C-H...O interactions.

Two new polymorphs have been characterised for L-cysteine. The first single-crystal to single-crystal phase transition was observed on compressing form I at pressures above 1.8 GPa. The resulting new polymorph, form III is reported to be stable to at least 4.2 GPa; no S...S contacts within 3.6 Å are observed in this modification. A second transition was observed on decompression of form III to 1.7 GPa to afford a new polymorph denoted form IV, which is not observed on increasing pressure. The structure of form IV separates into zones with motifs that are alternately phase-I-like and phase-III-like. Form IV can therefore be thought of as an unusual example of an intermediate phase.

Compression studies on L-serine were performed on a powder sample by Boldyreva et al. (2005b) and no transition was observed up to pressures of 4.4 GPa. The anisotropic effects of cooling a single crystal of the compound were compared to the anisotropic effects of applying pressure to a polycrystalline sample and were correlated with the different responses of intermolecular hydrogen bonds. On cooling, the a axis was observed to expand and the b and c axes compressed in a similar manner. This was contrasted to the different behaviour at high pressure, where all axes compressed with the c axis experiencing the largest compression and the a axis the least compression. This comparative study clearly illustrates the need to take into account conformational transformations in molecular geometry as well as...
changes in individual intermolecular interactions for a meaningful structural analysis. A single-crystal to single-crystal polymorphic transition in L-serine was observed above 4.8 GPa (Moggach et al., 2005c) with structural data collected at 5.4 GPa. The transition occurred with no change in space group via a change from the gauche to anti conformation of the hydroxyl groups and a significant change in the NC\textsubscript{4}CO torsion angle from -178.1(2)° at 4.8 GPa to -156.3(10)° at 5.4 GPa, with no other major molecular reorientation. This explains why during the transition the single crystal remained intact. In the new high-pressure structure, OH...O(H) hydrogen bonds are replaced by stronger and shorter OH...O=C interactions.

The anisotropy of structural distortions arising from the application of pressures up to ca. 4.0 GPa has also been investigated for paracetamol and phenacetin, whilst p-benzoquinone has been studied up to 3.0 GPa (Boldyreva, 2003 and references therein). These compounds have been studied by X-ray powder diffraction. Single-crystal experiments have also been performed in the case of paracetamol. Phase transitions were not observed in these compounds, apart from the irreversible and poorly reproducible monoclinic to orthorhombic phase transition in polycrystalline samples of paracetamol. This is discussed in more detail in Chapter 5.

From the high-pressure compression studies performed on the compounds mentioned above and on other systems (e.g. Co(III)-nitro and nitrito-pentaammine complexes and sodium oxalate), it has been possible to make some generalisations about the effects of pressure. For example, the directions of maximum compression usually correlates with the orientation of molecular layers (i.e. it is perpendicular to the layers) or with the direction of the “softer” hydrogen bonds. In general, the direction of medium and minimum compression correlate with the different strength of the various types of intermolecular interactions. It is also clear that the behaviour of hydrogen bonds under high pressure depends not only on the bonds themselves, but also on their relationship to other features of a structure, such as other intermolecular interactions and crystal packing. The anisotropy of structural distortion should be analysed by considering the cooperative movement of molecules or changes in intramolecular geometry, where flexible fragments are available.

\(\beta\)-diketoalkanes as 1,3-cyclohexanedione (Katrusiak, 1990a) have been extensively studied. As the enolic tautomer they exhibit interesting properties on
account of their alternating π-electron bond system HO-C=C-C=O. In this form the hydroxyl group can potentially lose its hydrogen atom and the carbonyl oxygen atom can accept another hydrogen atom from a neighbouring molecule. The result of this exchange is to produce an alternate sequence of single and double bonds in the conjugated bond system, which changes the polarisation of the molecule. 1,3-cyclohexanedione undergoes a single-crystal to single-crystal phase transition at 0.3 GPa. The transition is associated with a visible change in the appearance of the crystal, due to the large anisotropy of compression. After the transition, the sequence of double and single bonds is reversed, indicating that the donor and acceptor parts of the molecule have interchanged and a new tautomer has been formed. In addition, with increasing pressure the disorder over two positions of one of the carbon atoms is reduced. Similar structural changes were observed on cooling below 287 K (Katrusiak, 1991a).

A phase transition of 1,3-cyclopentanedione was also observed at pressures below 0.3 GPa, but the transition resulted in crystal damage and the structure was not solved by single-crystal or by powder diffraction (Katrusiak, 1990b). The compressibilities and pressure-induced structural changes of other β-diketoalkanes have been reviewed by Katrusiak (1991b).

Studies on the compressibilities of hydrogen bonds have shown that different types of molecular packing involving the same type of hydrogen bond can have profound effects on compressibility. Thus, the compressibility of O-H...O hydrogen bonds that bridge molecules into chains or layers in 1,3-cyclohexanedione (Katrusiak, 1990a), 2-methyl-1,3-cyclopentanedione (Katrusiak, 1991c), squaric acid (Katrusiak, 1993) and paracetamol (Boldyreva et al., 2000) was similar (Boldyreva, 2004). On the other hand the same hydrogen bond in dimedone (Katrusiak, 1991d), where spiral chains are formed, was much higher (Katrusiak, 1991e). Hydrogen bonds have also been observed to elongate as a function of pressure. For example, in the [Co(NH₃)₅NO₂]Cl₂ nitroligands, NO...H intermolecular hydrogen bonds lengthen by 0.01 Å with an increase of 3.5 GPa.
1.3 General aims and outline of research

Aims:

- To develop a high-pressure methodology for in situ crystallisation.
- To study under high pressure more complex, pharmaceutically relevant compounds.
- To study different solvent systems.
- To compare and rationalise high-pressure polymorphs, solvates and hydrates and mechanisms of interconversion.

To date, most success with accessing new polymorphs has been achieved with compounds that are liquids at or near ambient temperature and pressure. Attempts to induce polymorphism in more complex compounds, such as pharmaceuticals, that have high melting points, have been much less successful. This is because thermal decomposition of the compound usually occurs long before the melting temperature is reached. This is exacerbated by the increase in melting point with increasing pressure. An alternative method is direct compression of the material (either as a single crystal or as a powder) contained in a diamond-anvil cell. Whilst this method can be effective for inducing phase transitions in some materials (see Section 1.2.3.2), experience has shown that the method is less effective for solids containing larger, more complex molecules. It is clear that even though the application of pressure to these larger organic molecules may thermodynamically favour the adoption of a new polymorphic form, there is often a substantial kinetic barrier to be overcome before the molecules can rearrange. A polymorphic transition in the solid state requires the breaking and reforming of many intermolecular hydrogen bonds and reorientation of many molecules simultaneously. This is difficult to obtain unless there is considerable structural affinity between the low- and high-pressure polymorphs.

In this PhD a new experimental technique to overcome the difficulties mentioned above has been developed. This involves growing single crystals from solution at high pressures. The principles of this technique and experimental procedures for sample preparation and structural characterisation are illustrated in

Chapter 1 – Introduction: Polymorphism and High-Pressure Studies of Molecular Compounds
Chapter 2. In the remainder of the thesis it is demonstrated that recrystallisation from solution at high pressure is an unrivalled method for preparing new polymorphs and solvates of molecular organic compounds. The structures of new polymorphs of phenanthrene and pyrene, alongside a compression study of naphthalene, are presented in Chapter 3. The attention is then focussed on a small molecule with an amide functional group, and a new polymorph of acetamide, characterised by X-ray single-crystal and powder neutron diffraction, is the attention of Chapter 4. The pharmaceutically active compounds paracetamol and piracetam are investigated in Chapter 5 and 6, respectively. As well as characterising a new dihydrate and the first methanol solvate of paracetamol, it has been demonstrated that the orthorhombic polymorph of this drug, generated using high pressures, is sufficiently metastable that it can be recovered under ambient conditions. It is also illustrated that systematic variation of pressure and temperature can be used not only to identify rapidly all of the known polymorphs of the nootropic drug piracetam, but is also able to identify and characterise two completely new polymorphs and two completely new hydrates. Conclusions and possible future directions are described in Chapter 7.

1.4 References


Chapter 2

Single-Crystal High-Pressure Crystallography:
Experimental Techniques, Data Collection, Data
Processing and Structural Analysis
2.1 Experimental Techniques

2.1.1 The Merrill-Bassett diamond-anvil cell

The development of high-pressure apparatus is an active area of research (Miletich et al., 2000). Until the 1960s most types of devices were based on the large hydraulic-driven Bridgman anvil and piston-cylinder presses (Bridgman, 1971). With the advent of the gasketed diamond-anvil cell in the mid 1960s, high-pressure research became accessible to non-specialised laboratories. Diamond is the hardest natural material, it is one of the most infusible substances known and it is relatively transparent to X-rays and visible light. The assembly of the gasketed diamond-anvil cell is illustrated in Figure 2.1. A force is applied to the large table faces of two parallel, opposing gem-quality diamonds. This force is multiplied at the small culet faces, penetrating and sealing a metal gasket that contains the sample and pressure is generated in the sample chamber.

![Diagram of gasketed diamond-anvil cell]

**Figure 2.1** Assembly of the gasketed diamond-anvil cell.

The Merrill-Bassett gasketed diamond-anvil cell (Merrill & Bassett, 1974) was the standard tool employed for the high-pressure studies presented in this thesis. A schematic representation is depicted in Figure 2.2.
The choice of materials, the preparation of the various cell components and their function have been described in detail elsewhere (Miletich et al., 2000). A concise summary of the general procedure for the cell preparation carried out for the experiments reported in this thesis is presented in the following paragraphs.

Two flawless gem-cut diamonds mounted on two beryllium discs were placed opposite each other and aligned. With the design of the diamond-anvil cell used at The University of Edinburgh the culets can be corrected for lateral but not for parallel alignment; parallelism can only be controlled during the mounting of the diamonds on the beryllium backing plates with epoxy glue. Diamond alignment is a crucial step in the cell preparation and misalignment is the most common reason for diamond failure. Type I diamonds were used for most of the experiments presented in this thesis, with the exception of experiments which involved Raman spectroscopic measurements, for which type II diamonds, that have low fluorescence, were used. All diamond pairs used had a culet diameter of 600 μm or 800 μm. Smaller culets are available for work that requires very high pressures.

Beryllium is the material used for the backing plates because of its low absorption cross-section for X-rays and its good tensile strength. The beryllium discs were mounted on two triangular steel plates.
A hole of 200 µm or 300 µm diameter was drilled through a pre-indented 250 µm thick tungsten gasket by spark erosion to create the sample chamber. The gasket was then placed in between the two diamonds by aligning the hole with the diamonds’ thrust axis. This system ensures that as the three screws are tightened, a sealed space is formed and pressure is generated.

Very high pressures can easily be reached because the force is applied to a very small area —pressure is defined as force divided by the area over which the force is applied— and the design makes the cell itself easy to use. Every material used influences the maximum pressures that can be obtained with a diamond-anvil cell; the cells used at the University of Edinburgh are capable of attaining pressures of ca. 12 GPa. These are modest compared to the pressures routinely employed in other areas of research (e.g. pressures in the 100 GPa range for the study of planetary interiors), but more than sufficient for the high-pressure recrystallisation experiments presented in this thesis. Indeed, 12 GPa is well in excess of the working range of high-pressure recrystallisation experiments, which rarely exceed 2 GPa. Since the upper limit required for these experiments is significantly lower than the one that can be theoretically achieved, and since it is difficult to control the pressure and make small adjustments with the cells currently used, cell design tailored for high-pressure recrystallisation experiments is an area that should be explored in the future.

2.1.2 Sample Loading

The technique of pressure-induced crystallisation of simple organic compounds from the pure liquid for the generation of new polymorphs was briefly discussed in Section 1.2.3.1. Whilst this technique is particularly effective when the compounds under study have normal melting points that lie below or close to room temperature, attempts to induce polymorphism in more complex compounds —such as pharmaceuticals— that have higher melting points have been much less successful. This is because thermal decomposition of such compounds usually occurs long before the pressure-elevated melting temperature is reached.

An alternative method for inducing phase transitions in organic compounds under high pressure is direct compression of the material in a diamond-anvil cell, also briefly discussed in Section 1.2.3.1: this is effective for compounds containing...
small molecules that have some conformational flexibility, but is not so effective for larger molecules such as pharmaceuticals. This is because the kinetic barrier associated with molecular rearrangement is usually very large. This is illustrated in Chapter 5 with the example of the conversion of the monoclinic to the orthorhombic polymorph of paracetamol.

To overcome the difficulties mentioned above, a different technique has been developed instead. A schematic procedure for the technique is summarised in Figure 2.3. This involves growing single crystals from solution at high pressure by recrystallisation from solution at high pressure.

Figure 2.3 Schematic procedure for a high-pressure recrystallisation from solution experiment.

The technique removes the need for excessively high temperatures, overcomes the barrier to molecular rearrangement (lattice energy is overcome by solvation energy) and also provides an opportunity to study high-pressure crystallisation from different solvent systems. Of course, this is not a new concept and it has been widely applied in hydrothermal growth of inorganic materials such as quartz and other minerals (Hervey & Foise, 2001), but there is no indication in the literature that the technique has been applied to the growth of single crystals of organic compounds contained in a diamond-anvil cell.

Cell loading and crystal growth are performed under an optical microscope. The procedure consists of the following: a small drop of the solution is placed on the edge of the gasket hole. The cell is then rapidly assembled and the screws tightened to induce the precipitation of polycrystalline material —this corresponds to the crystallisation step—, which is not suitable for single-crystal X-ray diffraction.
single crystal is grown by heating—and therefore dissolving—the sample with a hot-air gun, thereby reducing the number of crystallites, until a single crystal remains. The sample is then allowed to cool and the temperature is cycled in an iterative process until a single crystal is grown, which ideally fills as much of the gasket hole as possible.

Several variables can be controlled prior to and during a high-pressure recrystallisation experiment, and these are discussed in more detail in the following paragraphs.

**Choice of solvent**

Several factors are taken into consideration whilst preparing a solution of the compound of interest. The solvent is chosen so that the compound has a reasonable solubility. This ensures that the resulting single crystal grown at high pressure is of reasonable size for X-ray diffraction. Concentrations in the range 0.5-6.0 M have been tested and have been shown to give crystals of good size. The problems associated with data collection from small crystals can be reduced when synchrotron facilities are accessible.

Ideally, the solvent itself crystallises at reasonably high pressures. This ensures a good working range for the high-pressure recrystallisation of the solute before the pressure at which the solvent freezes is reached. No severe restrictions have been encountered so far and all the solvents used provide an upper limit of at least 1.3 GPa [1.33 GPa is the freezing pressure of dichloromethane, Podsiadlo *et al.*, (2005)]. The solvents that were used in the experiments presented in this thesis were water, dichloromethane, acetone, methanol and ethanol. Ideally, the solute exhibits a steep solubility vs. pressure curve with a negative slope, and a steep solubility vs. temperature curve with a positive slope. The first ensures that precipitation of polycrystalline material occurs at low applied pressures and therefore reduces the temperature needed for dissolving it, whilst the second determines the temperature required for dissolution. In an ideal case, precipitation occurs at low pressures and minimum temperatures are then required to dissolve the polycrystalline material.

Intuitively, it is not difficult to see why the application of pressure is likely to induce the precipitation of the solute (or a solvate). The volume of the sample chamber decreases as pressure is applied. The system can then respond either by increasing the solubility of the solute, or by decreasing it, thereby inducing
precipitation. In practice, the system considered is a very complicated one and there are several contributing factors that should be taken into account, *e.g.* the effect of pressure on the free energy, enthalpy and entropy of the solute, the solvent and the solvated species to name but a few. The ultimately complex interplay between these effects arises because of the large number of different contributions and because of the subtle changes that occur at the molecular level. From a qualitative and simple point of view, if one considers a solution and the equation:

$$\Delta G = \Delta U + P\Delta V + T\Delta S$$

then, if the $\Delta V$ term increases as a solute is added and $P$ increases, the $P\Delta V$ term also increases and so will $\Delta G$, making the process less favourable (assuming the $T\Delta S$ term is negligible). In this case, solubility will decrease. The question arises whether the $\Delta V$ term will increase or decrease as the solute is added. This will depend on the partial molar volume at a certain composition, which reflects how various forces act between molecules, *i.e.* whether the partial molar volume is positive (the overall volume increases as the solute is added) or negative (the overall volume decreases as the solute is added).

All systems studied in this thesis afforded precipitation of polycrystalline material, indicating that solubility did decrease with increasing pressure. However, it would be incorrect to state that it will always be the case. Research at The University of Edinburgh has in fact shown that there are examples for which this is not the case, *e.g.* the sodium formate-water system, (Allan, 2005).

A final requirement for the choice of solvent is that it is not likely to react with the solute under high-pressure conditions at the temperatures reached during heating (typically 313-423 K). The possibility of high-pressure reactions is an interesting area of high-pressure research in its own right (Jenner, 2004), but it is not explored in this thesis.

In the course of this research it has been found that at higher pressures the increased solvent viscosity induced by application of pressure can in some cases hinder the crystallisation process by preventing nucleation. The role of the medium in high-pressure organic reactions has been explored by Jenner (2004) and viscosity is reported to be a parameter that is greatly affected by pressure—exponential dependence—and so influences the rates of chemical reactions. During the course of the research presented in this thesis, it has been found that when this occurred, crystallisation could sometimes be induced by decreasing the pressure inside the
diamond-anvil cell. Alternatively, in the case of a solvent with a low freezing pressure, the pressure could be increased to induce the crystallisation of the solvent itself, thereby creating a range of nucleation points. The latter is discussed in more detail in Section 6.5.2 with the example of piracetam. Nucleation can also be prevented in the case where few or no seeds are present in a vessel, e.g. where there is an absence of specks of dust combined with a particularly smooth vessel. This is unlikely in the diamond-anvil cell where there are numerous surfaces available for nucleation (e.g. ruby chip, gasket walls, diamond surface). However, the type of nucleating surface may be important. For example, the use of tailor-made additives has been shown to control the nucleation and growth of molecular crystals (Weissbuch, et al., 2001).

Concentration

The role played by concentration in a high-pressure recrystallisation from solution experiment should not be underestimated. First of all, concentration plays a role in determining the size of the crystal that can be grown in a pressure cell. Secondly, concentration might influence whether an unsolvated or a solvated species is crystallised (this is illustrated in Chapter 6 with the example of piracetam). Concentration also affects the pressure at which precipitation occurs: the higher the concentration, the lower the pressure, provided solubility decreases with increasing pressure.

For these reasons, there is a scope for loading the high-pressure cell with a solution of the compound of interest together with a few crystallites of the compound. Once the cell is assembled, the pressure is increased to a minimum to form a sealed system and the cell is then heated gently to dissolve all of the material. This is a crucial step, since all seeds of an ambient-pressure polymorph should be dissolved to avoid crystallisation of the same polymorph at high pressure. The pressure inside the cell is subsequently increased while the cell is still warm, the cell is then allowed to cool and precipitation is observed. The main advantage of this procedure is that on cooling a large single crystal can be recovered at ambient pressure.
General remarks

By growing a single crystal of the compound of interest from solution at high pressure, phase transitions of any type of compound can be studied, provided a suitable solvent system can be found. This method is therefore particularly attractive for those organic compounds that exhibit high melting points, e.g. drug molecules. Not only are the risks of overheating minimised, but also crystallisation in a variety of solvent systems can be explored, thereby highlighting the versatility of the technique, and single crystals can be grown at moderate pressures. Since pressure is a true thermodynamic variable and recrystallisation from solution overcomes the kinetic barrier to molecular rearrangement, this technique offers a potential and useful application to complement current polymorph screening experiments that are carried out in industry, e.g. for pharmaceuticals, as mentioned in Section 1.1.3.

Possible reasons why pressure is so effective at generating new polymorphs and solvates, and the question of whether recrystallisation from solution at high pressure is likely to give an unsolvated or a solvated form will be considered in Chapter 7.

2.1.3 Pressure measurement

When loading the sample into a diamond-anvil cell a small piece of ruby is also added in order to allow the determination of the pressure by laser fluorescence spectroscopy. Ruby has two distinct fluorescent emission lines, which shift linearly with pressure up to 25.0 GPa (Piermarini et al., 1975). The fluorescence was measured using excitation with the 441.4 nm line from a Hg-Cd laser. The ruby fluorescence was dispersed and detected by a Jobin-Yvon LabRam 300 spectrometer, with a measurement precision of ± 0.05 GPa.

2.1.4 Raman spectroscopy

Raman spectroscopy involves shining an intense monochromatic light source, i.e. a laser beam, on a sample and detecting the scattered light. The majority of the scattered light is of the same frequency as the excitation source: this is known as Rayleigh or elastic scattering. Generally, Raman spectra are plotted with respect to the laser frequency such that the Rayleigh band lies at 0 cm\(^{-1}\). A very small amount of the scattered light, ca. 1-5% of the incident light intensity, is shifted in energy to the left-hand side (Stokes) and right-hand side (anti-Stokes) with respect to the laser...
frequency due to interactions between the incident electromagnetic waves and the discrete vibrational energy levels of the molecules in the sample. On this scale, the band positions will lie at wavenumbers that correspond to the energy levels of different functional group vibrations. The Raman spectrum can thus be interpreted in a similar way to an infrared absorption spectrum.

Selection rules for vibrational modes that are Raman active state that there must be a change in the polarisability tensor during the vibration. This requirement is best pictured as the ease with which the electron cloud is distorted, i.e. polarised. For a detailed discussion on Raman spectroscopy, the reader is advised to consult one of the many available textbooks on the topic, e.g. the one by Svanberg (2005).

One aspect that makes Raman spectroscopy attractive is that because monochromatic light is used, any material which is transparent to light can be used as sample holder (e.g. thin-walled glass tubes, diamond-anvil cells). In addition, the sample can be examined spatially by focusing the incident beam with a confocal microscope.

Raman spectroscopy is very useful for detecting phase transitions in the crystalline state because the active vibrational modes of molecules are strongly dependent on molecular symmetry. The general shift in wavenumber (either increase or decrease) with increasing pressure is primarily due to changes in the environment, solvation and the intramolecular potential. If a crystal subjected to increasing pressure remains in the same phase, bands will therefore tend to shift constantly and a plot of the relative change in wavenumber vs. the relative change in pressure will have a constant gradient. If a phase transformation occurs, new spectral features characteristic of the new lattice may appear. In the spectrum, the position of some of the bands may change more dramatically and a plot of wavenumber vs. pressure will have a change in the gradient. Raman spectra presented in this thesis were collected using a LabRam instrument equipped with a 50 mW He-Cd laser of wavelength 441.6 nm.

2.1.5 Neutron powder diffraction

A neutron is an electrically neutral subatomic particle with mass 1,839 times that of an electron. Neutrons are used as a powerful tool for the determination of the structures of crystalline materials as well as to determine magnetic structures. They are also employed to study pair distribution functions in amorphous solids, liquids
An important difference between X-rays and neutrons is in the nature of the interaction between the radiation and the sample. Whilst X-rays interact with the electron cloud of atoms, neutrons interact with nuclei. There are two important consequences of this: firstly, the neutron scattering power of an atom does not fall off with increasing angle because the interaction between the neutron and the nucleus occurs over a much shorter distance than the neutron's wavelength. Secondly, the neutron scattering power of an atom is not strongly related to its atomic number: this is in marked contrast to X-rays, where the scattering power of an atom is proportional to $Z^2$. This has some advantages. Firstly, it is easier to sense light atoms in the presence of heavier ones; secondly, neighbouring elements in the periodic table generally have substantially different scattering cross sections and can be distinguished. Finally, the nuclear dependence of scattering allows isotopes of the same element to have substantially different scattering lengths for neutrons (Windsor, 1981). In addition, neutrons are spin-$\frac{1}{2}$ particles: magnetic scattering for the study of magnetism in materials arises from the coupling of the neutron magnetic moment that can couple with atomic magnetic moments due to unpaired electrons.

The interaction of a neutron with the nucleus of an atom is weak, making it a highly penetrating, non-destructive probe. As well as enabling the investigation of the interior of materials, complex sample environments such as cryostats, furnaces and pressure cells can be used quite routinely.

In the case of a polycrystalline material, the sample to be analysed consists of a large number of small, randomly oriented single crystals and for any reflection $hkl$ there will always be a finite number of planes inclined at the correct Bragg angle. Because of the random orientation of the crystallites, the radiation is scattered simultaneously for all reflections $hkl$ as continuous cones of intensity—rather than as single, narrow beams as in single-crystal diffraction—, the axis of which lie along the incident beam direction.

Most elements are predominantly coherent scatterers. The most important exceptions are hydrogen and vanadium. The spin-incoherent scattering cross section of hydrogen is a nuisance in neutron diffraction studies, since it contributes a large constant background to the measured intensity. This is the reason why deuterated samples are preferably used for powder diffraction experiments.

High-pressure time-of-flight powder neutron experiments were recorded on
the Polaris diffractometer at the ISIS pulsed source in the UK, as detailed in Chapter 3. Neutrons at ISIS are produced by the spallation process, whereby a heavy metal target (tantalum) is bombarded with pulses of highly energetic protons from a powerful accelerator, driving neutrons from the nuclei of the target atoms. Time-of-flight techniques are used on the generated polychromatic neutron beams. The neutrons strike the sample and are scattered in various directions, arriving at the detector(s) at times that depend on their wavelengths. This enables a direct determination of the energy and wavelength of each neutron and allows fixed scattering geometries to be used. Given a detector's scattering angle and its distance from the source, each peak in the time-of-flight spectrum is uniquely associated with one or more Bragg reflections.

The results of the neutron powder diffraction experiment presented in this thesis (Chapter 4) were analysed by Rietveld refinement, according to which model parameters are fit to the measured pattern, resulting from a plot of the intensity measured as a function of scattering angle $2\theta$. The Rietveld technique is discussed by Young (1993). Model parameters include the unit cell constants, which determine the positions of the Bragg peaks, and atom positions within the unit cell, which, together with site occupancies and displacement parameters, collectively determine integrated intensities. The background and the shapes of the peaks are also modelled.

2.2 Data Collection and Processing

2.2.1 Data collection

It is beyond the scope of this thesis to give a comprehensive and complete background on such a vast topic as X-ray crystallography and the reader is advised to consult one of the many excellent textbooks available (Giacovazzo et al., 1992; Massa, 2000 and references therein).

Single-crystal X-ray diffraction is the best method for determining the positions of atoms in molecules in a crystalline solid. When a beam of X-rays is directed towards a crystalline sample, it is scattered in various directions by the electrons associated with the atoms. Distances between atoms or ions are typically in the order of a few Å, which is comparable to the X-ray wavelength produced by bombardment of metals by electrons (e.g. Mo-Kα radiation, $\lambda = 0.71073$ Å). In a crystal, this causes interference between the X-rays scattered from particular electron
centres to occur, giving rise to a characteristic pattern of intensities. Intensities are directly proportional to the square of the amplitude of the scattered radiation, but the relative phases are lost, giving rise to the so-called phase problem, one of the fundamental challenges in X-ray crystallography. Both phases and intensities of the X-rays scattered by a crystal are required in order to obtain information about its molecular structure. Subsequent to structure solution (e.g. by Patterson or direct methods), the development of a structural model enables the determination of approximate phases. Calculated phases can then be combined with observed amplitudes and the resulting Fourier synthesis affords a better model (and a new set of calculated phases). Missing atoms can then be located by a difference Fourier synthesis. Structural refinement is then performed, whereby the differences between observed and calculated amplitudes—or intensities—are minimised, thereby leading to the determination of the crystal structure.

In all experiments presented in this thesis, the diamond-anvil cell was mounted and centred on a Bruker SMART APEX diffractometer according to an established procedure (Dawson et al., 2004). Diffraction data were collected at 293(2) K with Mo-Kα radiation, λ = 0.71073 Å, in a sequence of eight scans (Dawson et al., 2004), as detailed in Table 2.1. This sequence has been optimised for the type of diamond-anvil cell used at The University of Edinburgh with an opening angle of 40°. The basic diffraction geometry for a diamond-anvil cell is illustrated in Figure 2.4.

<table>
<thead>
<tr>
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<th>2θ (°)</th>
<th>ω range (°)</th>
<th>φ (°)</th>
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<tbody>
<tr>
<td>1</td>
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<td>-10 to -40</td>
<td>90</td>
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<tr>
<td>2</td>
<td>28.0</td>
<td>40 to -25</td>
<td>90</td>
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<tr>
<td>3</td>
<td>-28.0</td>
<td>-155 to -220</td>
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<tr>
<td>4</td>
<td>28.0</td>
<td>-140 to -170</td>
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<tr>
<td>5</td>
<td>-28.0</td>
<td>-155 to -220</td>
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<td>6</td>
<td>28.0</td>
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<tr>
<td>7</td>
<td>-28.0</td>
<td>-10 to -40</td>
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<tr>
<td>8</td>
<td>28.0</td>
<td>40 to -25</td>
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* Each frame had a range of 0.3° in ω. Exposure time for each experiment varied between 30 s to 60 s.

Table 2.1 Sequence of eight scans used for high-pressure single-crystal X-ray diffraction experiments for a diamond-anvil cell with 40° opening angle.

Chapter 2 - Single-Crystal High-Pressure Crystallography: Experimental Techniques, Data Collection, Data Processing and Structural Analysis
These settings, in conjunction with a camera distance of 70 mm, ensured maximum coverage of the reciprocal space, limited by enclosure of the sample in steel which absorbs X-rays, whilst avoiding interception of the primary beam and ensuring minimal absorption of the diamond-anvil cell components.

2.2.2 Data processing

All single-crystal data were processed according to the procedure described by Dawson et al. (2004), which is here summarised, and detailed and implemented in each chapter, where appropriate.

Diffraction of the X-ray beam by the diamonds and the beryllium windows of the cell contributed to the reduction of useful reflections, as only spots with intensities above those of beryllium rings were used when harvesting reflections. Figure 2.5 shows a copy of a SMART CCD frame contaminated by an intense diamond reflection and by beryllium powder rings. The contamination of the diffraction pattern make the indexing, integration and solution steps more difficult compared to ambient-pressure studies.
The sample reflections were found by using the thresholding algorithm in the SMART code or harvested manually. Orientation matrix and unit cell geometry were determined using the program GEMINI (Sparks, 2000), unless otherwise specified. Data integration and global-cell refinement were performed using the program SAINT (Bruker, 2003). The use of dynamic masks during data integration has been shown to considerably improve integration results and these were used throughout this thesis; dynamic masks ensure that intensity data are not harvested from the regions of the detector that are shaded by the body of the diamond-anvil cell.

The number of reflections was then reduced as various corrections were applied, as detailed by Dawson et al. (2004): an analytical absorption correction was performed using the program SHADE (Parsons, 2004): this rejected reflections that lay within 2° of the high-pressure cell opening angle (40°) and had poorly fitting profiles. In a second step, a multi-scan absorption correction was applied using the program SADABS (Sheldrick, 2004) to correct for differences in path lengths of X-rays through the crystal, which varied as the crystal orientation changed, and to cure other systematic errors. “In spite of the corrections described above, data collected using pressure cells still suffer from substantial systematic errors. These arise, for example, from overlap of reflections with beryllium powder rings, but a few reflections may be wildly in error if they overlap with reflections from the diamonds.” (Dawson et al., 2004).
Data were subsequently merged using the program `SORTAV` (Blessing, 1995), as incorporated in the `WinGX` suite (Farrugia, 1999). The use of robust-resistant weights during merging was described by Blessing (1995). Their application to high-pressure data has been shown to correct further for outliers and yield superior refinement results (i.e. a lower R-factor) when compared with allowing the refinement program to perform the merging itself (Dawson et al., 2004).

**Structure solution**

The structures were solved either by reciprocal-space methods [direct methods: `SHELXS` (Sheldick, 1997a), `SIR92` (Altomare et al., 1994), `SIR2002` (Burla et al., 2003)] or by direct-space methods [global optimisation methods: `DASH` (David, et al., 1998), `FOX` (Favre-Nicolin, & Černý, 2002)], as detailed in each section. The main reason why structure solution of high-pressure data by direct methods is at times not straightforward is due to the experimental set-up that limits the possible coverage of the reciprocal space, resulting in a limited amount of data. This can be exacerbated by an unfortunate orientation of the crystal (Merrill & Bassett, 1974). The low resolution of the data, from which discrete clumps of electron density can be difficult to extract, can cause further difficulties.

These are common problems that can be experienced with high-pressure data, but fortunately they may be overcome by using direct-space methods originally devised for structure solution from powder data. This is an area that has developed rapidly in recent years with the advent of global optimisation methods (David et al., 2002). The success of these methods results from the fact that the structure solution problem is reduced to determining only molecular position, orientation and internal conformation. However, there is a caveat, which is that the molecular contents (and the molecular connectivity) of the crystal structure must be well known beforehand.

Fortunately, for these high-pressure recrystallisation studies the principal molecular contents are already known. The sole uncertainties are associated with the nature of any potential solvate structure. However, maximum likelihood techniques have been developed to overcome this problem and salt and solvate structures have successfully been solved using this approach (Markvardsen et al., 2002). Global optimisation techniques such as those used by the powerful programs `DASH` (David
et al., 1998) and FOX (Favre-Nicolin, & Černý, 2002) effectively reduce the number of parameters that must be determined for a successful structure solution and are thus well suited to relatively poor or incomplete crystallographic data. These structure solution programs are able to solve structures from high-pressure single-crystal data sets collected on a range of small molecule structures.

Global optimisation methods search for a global minimum by selectively altering the positions, orientations, and conformations (by varying torsion angles) of the molecules, until a good match is obtained between calculated and observed intensities. Several algorithms are available to achieve this. The program DASH uses a simulated annealing algorithm in combination with a Monte Carlo search, whereby a single chain of configurations is optimised by slowly decreasing the “temperature” (high “temperature” = high number of configurations) according to an established law. Careful choice of the temperature regime and a slow decrease in “temperature” are necessary to avoid becoming trapped in a local minimum. In addition to simulated annealing, the program FOX offers a parallel tempering algorithm. In this algorithm, all “temperatures” are optimised in parallel and exchange between the configurations obtained by the optimisation process is evaluated so that a local minimum can in theory be avoided at all times.

It is foreseen that the outcome of high-pressure research will be heavily dependent on the increased level of sophistication of these methods, in particular as the molecules under study become larger and more flexible.

Once solved, the structures were refined using either the program SHELXL (Sheldrick, 1997b), or the program CRYSTALS (Betteridge et al., 2003), as detailed in each section. The various strategies used during refinement (e.g. the use of restraints to increase the data to parameter ratio) are also detailed in each section.

2.3 Structural Analysis

Two approaches not commonly encountered in the literature for comparison or polymorphs are described in this section, namely topological analysis and Hirshfeld surfaces. These are particularly useful to visually and rapidly compare
ambient-pressure and high-pressure polymorphs, whose structures and intermolecular interactions (hydrogen bonding, π...π interactions, etc.) are profoundly different (and/or complex) or are subtly related.

2.3.1 Topology

The effects of pressure on the structure of molecular compounds can be monitored by topological analysis. The topological approach described by Blatov (Blatov & Peresypkina, 2000) provides a useful tool for the comparison of polymorphs. For example, the higher density of high-pressure phases with respect to ambient-pressure forms can be illustrated by analysis of the local environment around a central molecule, whereby molecules are replaced with their geometric centroids. Throughout this thesis, centroids of neighbouring molecules arranged around the centroid of a central molecule were considered. Centroids were calculated using the program TOPOS 4.0 Professional (Blatov et al., 2000).

The shortest contacts between centroids can be used to partition 3-D space into Voronoi-Dirichlet domains. Voronoi-Dirichlet analysis is a versatile method for partitioning space amongst points occupying that space. A 2-D illustration of this analysis is shown in Figure 2.6. A 2-D space filled by a random set of points is divided into cells containing one point, where each point is separated from a neighbouring point by a line bisecting the vector between them.

![Figure 2.6 Partition of 2-D space into Voronoi-Dirichlet cells (Byers, 1992).](image)

This construction in 3-D space gives rise to polyhedra, which are formed by intersecting planes that bisect perpendicularly the lines joining atomic centres. Blatov
distinguishes between the construction of molecular, smoothed molecular and lattice Voronoi-Dirichlet Polyhedra (VDPs) (Peresypkina & Blatov, 2000a).

*Molecular* VDPs are defined by constructing VDPs around each atom, taking into account both intra- and intermolecular contacts. If the interior structure of contacting molecules is ignored and only their centroids are taken into consideration, VDPs whose shape characterises the arrangement of molecules around the central one are obtained: these are termed smoothed molecular VDPs and are indicative of the *local* topology of molecular packing. By taking into account only those molecules directly connected, smoothed molecular VDPs do not always give rise to a partition of space, but the number of faces of a smoothed molecular VDP equals the Molecular Coordination Number (MCN). An alternative way of constructing a VDP that describes the *global* topology of packing entails considering a sublattice of molecular centroids, where molecules are nearest neighbours but are not necessarily directly connected: these give rise to lattice VDPs. Only analysis of lattice VDPs is presented in this thesis: this is because lattice VDPs represent a true partition of space, whereas smoothed molecular VDPs do not. However, it should be noted that the number of faces of lattice VDPs does not always give the MCN: instead, it gives rise to another quantity, termed Molecular Packing Number (MPN). Smoothed molecular and lattice VDPs may suggest different coordination numbers, but the more spherical the molecule, the closer is the match between the two.

In many cases, the topological parameters of these domains and the number of centroids in successive coordination spheres can be used to relate molecular crystal structures to the well-known packing of spheres [Cubic Close Packing (CCP), Hexagonal Close Packing (HCP) and Body-Centred Cubic (BCC)]. By consideration of coordination sequences, identification of molecular packing by topology is possible, irrespective of the degree of distortion from ideal packing. The Reduced Graph of Molecular Lattice (RGML, Blatov & Peresypkina, 2000b) of the corresponding lattice VDP gives the number of neighbours in the first, second and third coordination spheres; this sequence can then be checked against the sequences of known packing topologies. The coordination sequences for HCP, CCP and BCC are 12-44-96, 12-42-92 and 14-50-110, respectively. Their corresponding lattice VDPs are depicted in Figure 2.7.
Peresypkina & Blatov (2000b) have suggested construction of VDPs that take into account all contacts and to compare them against those constructed by only taking into account “strong” contacts, defined as contacts that subtend lattice VDP faces with a value for the solid angle > 1.5%. This procedure has the main effect of assessing whether small faces appearing or disappearing are a result of errors in the determination of atomic coordinates, or are a true feature of the VDP.

The idea of applying the principles of close-packing topology to molecular crystals was first introduced by Kitaigorodskii (1973). On analysis of 150 structures, he demonstrated that packing coefficients tend to fall into the range 0.65-0.77 and that the most common coordination number was 12.12 12 is the coordination number of HCP and CCP, whilst 14 is the coordination number of the slightly less efficient BCC.

A more extensive survey of the crystal structures of 33,575 organic compounds, showed that within the first coordination sphere most of the molecules tend to arrange with MCN = 14, obeying the model of the thinnest covering of space, but molecular packings as a whole tend to be constructed according to one of the close-packing models, and that other coordination numbers are far from uncommon (Peresypkina & Blatov, 2000b).

The packing coefficient, $k$, is defined as $k = V_0/V$, where $V_0$ denotes the intrinsic volume of the molecule of the compound, calculated from its internuclear dimensions and the van der Waals radii of its peripheral atoms, and $V$ denotes the average volume per molecule in the crystal. In order to form a close packing, molecules tend to be occupied so that the ‘bumps’ of one molecule interact with the ‘hollows’ of another. Kitaigorodskii used $k$ to characterize the density of molecular packing.
2.3.2 Hirshfeld surfaces

The Hirshfeld surface, named in honour of F. L. Hirshfeld's "stockholder partitioning" scheme (Hirshfeld, 1977), was devised by Spackman & Byrom (1997) at the University of New England, Australia, as an entirely novel way of defining molecules in molecular crystals.

"Hirshfeld surfaces divide the crystal into regions where the electron distribution of a sum of spherical atoms for the molecule (the promolecule) dominates the corresponding sum over the crystal (the procrystal)." (McKinnon et al., 2004). More precisely, the Hirshfeld surface of a molecule in a crystal is defined so that for every point on the Hirshfeld surface, exactly half of the electron density is due to the spherically averaged non-interacting atoms comprising the molecule, and the other half is due to those comprising the rest of the crystal.

Detailed information on how Hirshfeld surfaces are obtained computationally are given by McKinnon et al. (2004).

**Important properties of a Hirshfeld surface**

- Hirshfeld surfaces are unique for a given crystal structure and set of spherical atomic electron densities.
- Hirshfeld surfaces partition crystal space into smooth, non-overlapping, interlocking molecular regions.
- The size and shape of a Hirshfeld surface reflect the interplay between different atoms and intermolecular contacts in a crystal, and hence reflect different intermolecular interactions. This is in marked contrast to van der Waals volumes, which depend entirely on molecular geometry.
- Hirshfeld surfaces and volumes generally fill at least 95% of the crystal volume. This is in marked contrast to more conventional packing coefficients that range between 0.65 and 0.80 (Kitaigorodskii, 1973) and is a direct consequence of taking into account both molecular geometry and crystal environment.
- Hirshfeld surface pack very tightly in the crystal but, quite unlike any other partitioning or packing scheme, they leave small intermolecular voids (usually less than 5% of the total space), which can be regarded as regions where the crystalline electron density is not dominated by any single molecule.
- Properties of a Hirshfeld surface can be encoded and mapped in colour on the surface itself, as described in the following paragraphs. Quantitative analysis of this partitioning scheme is also possible, as detailed by McKinnon et al. (2004), but is not described or employed in this thesis.

**Properties that can be mapped on a Hirshfeld surface**

For each point on the surface, two distance properties are defined, as illustrated in Figure 2.8:
- $d_e$ is the distance to the nearest nucleus outside (external to) the surface.
- $d_i$ is distance to the nearest nucleus inside (internal to) the surface.

![Figure 2.8 Schematic representation of $d_e$ and $d_i$.](image)

In addition, two properties based on the curvature of the surface can be specified:
- The *curvedness* is a measure of "how much shape". Flat areas of the surface have a low curvedness and areas of sharp curvature have a high curvedness. Regions with high curvedness tend to divide the surface into contact areas with each neighbouring molecule: curvedness of the Hirshfeld surface could therefore be used to define a coordination number in the crystal.
- The *shape index* is a measure of "which shape". It can be sensitive to very subtle changes in surface shape, particularly in areas where the total curvature (or the curvedness) is very low. One important attribute of this property is that where the shape index of two areas differs only by a sign, complementary "stamp" and "mould" pairs can be identified.

The properties of Hirshfeld surfaces discussed above are depicted in Figure 2.9 with the example of naphthalene, which will be discussed in detail in Chapter 3.
Figure 2.9 Hirshfeld surfaces and fingerprint plot for naphthalene at ambient pressure and 293 K (CSD reference code NAPHTAI1). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

Throughout this thesis Hirshfeld surfaces and fingerprint plots were generated using the program *Crystal Explorer* (Grimwood et al., 2004). Curvedness was always mapped on the Hirshfeld surfaces between -4.0 (red) and +0.4 (blue), and shape index between -1.0 (red) and +1.0 (blue). $d_e$ was mapped on the most appropriate scale for each group of compounds investigated to maximise the information derived from this distance property and to enable direct comparison between related structures. For the polycyclic aromatic hydrocarbons investigated in Chapter 3 a range of 1.0 (red) and 2.5 (blue) was employed, whilst a range of 0.4 (red) and 2.6 (blue) was applied for piracetam in Chapter 6.

**Fingerprint plots**

A particularly striking method developed by Spackman & McKinnon (2002) for comparison of polymorphs is the use of graphical fingerprint plots derived from the corresponding Hirshfeld surfaces. Fingerprint plots map and summarise quantitatively in a convenient 2-D colour plot the types of intermolecular contacts experienced by molecules in a crystal, and are also unique for any given crystal structure. These plots map the fraction of points on the corresponding Hirshfeld surface as a function of the closest distances from the point to nuclei interior ($d_i$) and

---

For the generation of Hirshfeld surfaces the program *Crystal Explorer* automatically fixes bond lengths to hydrogen atoms to typical neutron values.
exterior \((d_e)\) to the surface. Each point on the 2-D graph represents a bin formed by discrete intervals of \(d_i\) and \(d_e\) (0.01 Å × 0.01 Å). The colour of each point is a function of the fraction of surface points in that bin ranging from blue (relatively few points) through green (moderate fraction) to red (many points). An example of a fingerprint plot is given in Figure 2.9.

Fingerprint plots show several common features: the pseudo-symmetry about the diagonal arises because of the close packing of the Hirshfeld surfaces, which guarantees that where surfaces touch one another (and provided that there is only one molecule in the asymmetric unit) both of the points \((d_i, d_e)\) and \((d_e, d_i)\) are plotted on the 2-D graph. Several intermolecular interactions manifest themselves clearly on these plots, e.g. hydrogen bonding, \(\pi...\pi\) interactions, and \(H...H\) contacts. Each gives rise to characteristic and readily identifiable features on the plots. These will be illustrated in more detailed with appropriate examples throughout this thesis.

Fingerprint plots have been found to be useful for distinguishing between different densities of polymorphic compounds, since values at large \(d_e\) and \(d_i\) correspond to regions on the Hirshfeld surface without close contacts to neighbouring molecules, where the close packing of the surfaces results in the formation of small cavities.

The uniqueness of Hirshfeld surfaces and the corresponding fingerprint plots for any crystal structure makes them a powerful tool for elucidating and comparing intermolecular interactions, particularly when comparing the same molecule in different crystal environments, as well as for spotting common features/trends in specific classes of compounds. In particular, fingerprint plots summarise the complex information on intermolecular interactions present in molecular crystals into one, single colour plot, thereby providing a major practical advance in the description of crystal structures and complementing other tools currently available for the systematic description and analysis of organic molecular crystal structures, e.g. graph-set analysis (Etter et al., 1990; Bernstein et al., 1995) and topological analysis (Section 2.3.1).
2.4 References


Chapter 2 - Single-Crystal High-Pressure Crystallography: Experimental Techniques, Data Collection, Data Processing and Structural Analysis


Chapter 3

High-Pressure Studies of Polycyclic Aromatic Hydrocarbons
A.1 High-Pressure Recrystallisation of Phenanthrene

3.1 Introduction

Phenanthrene is a tricyclic aromatic hydrocarbon and is a major component of the total content of Polycyclic Aromatic Hydrocarbons (PAHs) that are commonly found as pollutants in the environment (Harvey, R. G., 1991). It is a component of coal tar used in the production of dyes, explosives, and in the synthesis of drugs (Harvey, R. G., 1991).

Solid phenanthrene is readily obtained by recrystallisation from solutions of organic solvents (typically dichloromethane) at ambient temperature and pressure in the form of colourless plates that melt at ca. 373 K. The molecular structure of phenanthrene and numbering scheme used for structural discussion are depicted in Figure 3.1

![Molecular structure of phenanthrene with numbering scheme.](image)

The structure of the ambient-temperature phase was first determined by Basak (1950). At 295 K phenanthrene crystallises in the monoclinic crystal system, space group \(P2_1\) with \(a = 8.441(2)\), \(b = 6.140(1)\), \(c = 9.438(1)\) Å, and \(\beta = 97.96(1)\)°, and a calculated density of 1.222 g cm\(^{-3}\) (Pettíček et al., 1990). This phase is here denoted as form II. The crystal packing of phenanthrene follows a herringbone motif, which is dominated by C-H...\(\pi\) interactions (Figure 3.2).

Phenanthrene undergoes a reversible phase transition at 339-344 K that was first discovered by Ueberreiter & Orthmann (1950) and subsequently studied by Kroupa et al. (1988) by measurements of several physicochemical properties. The structure of the high-temperature phase, here denoted as form I, was elucidated by
Petříček et al. (1990), who showed that the transition gives an orientationally disordered phase with approximately equal occupancies (55:45) of the two orientations. In the high-temperature phase, monoclinic, space group $P2_1/a$, with lattice parameters $a = 8.506(2)$, $b = 6.215(2)$, $c = 9.525(2)$ Å, and $\beta = 98.73(2)^\circ$, each phenanthrene molecule can occupy two possible positions (one in addition to the “room-temperature” position), thereby generating a new symmetry element (an inversion centre). The high-temperature phase can be quenched by rapid cooling to below 260 K. Gloistein et al. (2000) have shown that it is possible to stabilise the high-temperature phase of phenanthrene by doping it with compounds of similar structure such as anthracene. This study emphasises the importance of controlling the behaviour of molecular crystals, a factor of high relevance for crystal engineering.

Fluorescence spectra of phenanthrene measured as a function of pressure (Jones & Nicol, 1968) showed changes in the region 2.5-3.5 GPa and the authors suggested that these observations might be consistent with a sluggish phase transition. Infrared studies of phenanthrene also indicated a phase change near 2.0 GPa (Hamann, 1978).

Phenanthrene/dichloromethane was selected as a test-system for the high-pressure in situ recrystallisation technique from solution described in Section 2.1.2 for the following reasons: (i) phenanthrene has a high solubility in dichloromethane and also a high solubility dependence with temperature: these are important factors that affect the size of crystal that can be grown in the diamond-anvil cell; (ii) dichloromethane has a low melting point (183 K), thereby providing a good range of working pressure without incurring into the risk of recrystallising the solvent itself; (iii) under ambient conditions phenanthrene readily grows large single crystals and it
was anticipated that this would also be the case when at pressure; (iv) the molecule is planar and rigid, and so, if structure solution by direct methods were to fail, global optimisation methods would provide an alternative method for structure solution.

3.2 Experimental Procedure

3.2.1 Recrystallisation at 0.35 GPa

Phenanthrene (BDH) was purified by recrystallisation from dichloromethane (Fischer) under ambient conditions. A ca. 1 M solution of phenanthrene in dichloromethane was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 µm culet diamonds and a tungsten gasket with a 300 µm gasket hole. On sealing the cell and pressurising to ca. 0.30 GPa precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 353 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 80% of the gasket hole (Figure 3.3). The pressure within the gasket hole was determined as ca. 0.35 GPa by measuring the fluorescence from a small piece of ruby, as detailed in Section 2.1.3.

![Figure 3.3](image)

**Figure 3.3** Optical image of a single crystal of phenanthrene-II in a diamond-anvil cell at 0.35 GPa.

Diffraction data were collected as described in Section 2.2.1. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions similar to those found for the ambient-temperature phase of phenanthrene, form II, corresponding to a volume decrease of ca. 5.4%.
Fractional coordinates for the structure determined at 295 K by Petříček et al. (1990) were employed for the refinement of the structure at 0.35 GPa using the program SHELXL (Sheldrick, 1997a). Whilst not ideal, the R-factor of 15 % is typical for refinement of high-pressure data sets and is sufficient to identify the main changes in crystal packing as a result of increased pressure.

### 3.2.2 Recrystallisation at 0.7 GPa

Subsequent to the identification of the ambient-pressure phase, the pressure inside the diamond-anvil cell was increased to ca. 0.6 GPa. The single crystal of this phase was redissolved by gentle heating, and on cooling precipitation of polycrystalline material was observed. The temperature was then cycled near ca. 353 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill almost 50 % of the gasket hole (Figure 3.4). The pressure within the gasket hole was determined as ca. 0.7 GPa.

![Figure 3.4 Optical image of a single crystal of phenanthrene-III in a diamond-anvil cell at 0.7 GPa.](image)

Diffraction data were collected as described in Section 2.2.1. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions substantially different from either of the two known polymorphs of phenanthrene. Solution and refinement of the structure were not straightforward using direct methods owing to the limited amount of data that can be collected using the diamond-anvil cell on account of shading by the body of the pressure cell. This is a common problem with high-pressure data, but fortunately the problem may be overcome by using methods originally devised for structure solution from powders. This is an area that has developed rapidly in recent years with the
advent of global optimisation methods incorporated in programs such as DASH (David et al., 1998) and FOX (Favre-Nicolin & Černý, 2002).

**DASH** (David et al., 1998) rapidly identified a global minimum by simulated annealing corresponding to the structure of a new polymorph of phenanthrene, here denoted as form III. The structure was subsequently refined using the program SHELXL (Sheldrick, 1997a). Whilst not ideal, the $R$-factor of 11.3% is typical for refinement of high-pressure data and is sufficient to identify the main structural features of the new polymorph.

### 3.3 Results

#### 3.3.1 Form II at 0.35 GPa

Data reduction was performed according to procedures described by Dawson et al. (2004), detailed in Section 2.2.2, up to the absorption correction step. Known coordinates were taken from the literature (Petříček et al., 1990). Full-matrix least-squares structure refinement against $F^2$ was performed using SHELXL (Sheldrick, 1997b) and the phenanthrene molecule was refined as a rigid group; Friedel opposites were merged during refinement since no reliable information on anomalous scattering was obtained for this light-atom molecule. A $\theta$ cut-off of 20.82° was applied during the refinement. All non-hydrogen atoms were refined isotropically and hydrogen atoms were placed in calculated positions and allowed to ride on their parent atoms. Full refinement details are shown in Table 3.1. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

#### 3.3.2 Form III at 0.7 GPa

Data reduction was performed according to procedures described by Dawson et al. (2004) up to the absorption correction step. Structure solution in space group $P2_1/n$ was performed using the program DASH (David et al., 1998). Full-matrix least-squares structure refinement against $F^2$ was performed using SHELXL (Sheldrick, 1997b) and the phenanthrene molecule was refined as a rigid group. All
non-hydrogen atoms were refined isotropically and hydrogen atoms were placed in calculated positions and allowed to ride on their parent atoms. Full refinement details are shown in Table 3.1. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Phenanthrene-II at 0.35 GPa</th>
<th>Phenanthrene-III at 0.7 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>$C_{14}H_{10}$</td>
<td>$C_{14}H_{10}$</td>
</tr>
<tr>
<td>$M_r$</td>
<td>178.22</td>
<td>178.22</td>
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<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, $P2_1$</td>
<td>Monoclinic, $P2_1/n$</td>
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<tr>
<td>$a$, $b$, $c$ (Å)</td>
<td>8.289 (8), 6.012 (2), 9.303 (9)</td>
<td>12.937 (3), 3.8218 (5), 17.693 (6)</td>
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<tr>
<td>$\beta$ (°)</td>
<td>97.72 (5)</td>
<td>99.13 (2)</td>
</tr>
<tr>
<td>$V$ (Å$^3$)</td>
<td>459.4 (6)</td>
<td>863.7 (4)</td>
</tr>
<tr>
<td>$Z$</td>
<td>2</td>
<td>4</td>
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<tr>
<td>$D_x$ (Mg m$^{-3}$)</td>
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<td>1.371</td>
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<td>$T_{\min}$</td>
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<tr>
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<td>1938, 451, 197</td>
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<tr>
<td>Criterion for observed reflections</td>
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<td>$I &gt; 2\sigma(I)$</td>
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<tr>
<td>$R_{int}$</td>
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<tr>
<td>$\theta_{max}$ (°)</td>
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<td>23.2</td>
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Table 3.1 Crystal, collection and refinement details for phenanthrene at 0.35 and 0.7 GPa.
### Table 3.1 (cont.) Crystal, collection and refinement details for phenanthrene at 0.35 and 0.7 GPa.

<table>
<thead>
<tr>
<th>Phenanthrene-II at 0.35 GPa</th>
<th>Phenanthrene-III at 0.7 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range of $h, k, l$</strong></td>
<td>$-4 \rightarrow h \rightarrow 4$</td>
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<td></td>
<td>$-5 \rightarrow k \rightarrow 5$</td>
</tr>
<tr>
<td></td>
<td>$-6 \rightarrow l \rightarrow 5$</td>
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#### Refinement

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<th>$F^2$</th>
<th>$F^2$</th>
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<td><strong>Refinement on</strong></td>
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<td>451 reflections</td>
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<td>No. of parameters</td>
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<td>21</td>
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<tr>
<td>H-atom treatment</td>
<td>Riding</td>
<td>Riding</td>
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<td>Weighting scheme</td>
<td>Calculated $w = 1/[\sigma^2(F_o^2) + (0.0595P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$</td>
<td>Calculated $w = 1/[\sigma^2(F_o^2) + (0.1319P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$</td>
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<td>$&lt;0.0001$</td>
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<td>$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ $(\text{e} \text{Å}^{-3})$</td>
<td>$0.17, -0.20$</td>
<td>$0.24, -0.18$</td>
</tr>
</tbody>
</table>

#### 3.4 Discussion

Unit-cell parameters for the polymorphic forms of phenanthrene are summarised in Table 3.2. As phenanthrene is a rigid molecule, it was possible to build a reasonably full molecular model by application of rigid-body constraints: this reduced the number of parameters to be refined, a desirable situation when refining against a dataset of low completeness, as often found with high-pressure data. Rigid-body refinement does not allow comparison of primary bond lengths of the phenanthrene molecules with those of the two ambient pressure phases, but at these relatively low pressures it would be expected that they would be almost unchanged. Instead, the effect of pressure manifests itself in changes in the molecular packing and intermolecular distances.
<table>
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<th>CSD reference code</th>
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<th>High-temperature Form I</th>
<th>High-pressure (0.35 GPa) Form II</th>
<th>High-pressure (0.7 GPa) Form III</th>
</tr>
</thead>
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<tr>
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<td>-</td>
<td>-</td>
<td>PHENAN14</td>
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<table>
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<th>Monoclinic</th>
<th>Monoclinic</th>
<th>Monoclinic</th>
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<td>$P2_1$</td>
<td>$P2_1/n$</td>
</tr>
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<td>$a/\text{Å}$</td>
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<td>8.506(2)</td>
<td>8.289(8)</td>
<td>12.937(3)</td>
</tr>
<tr>
<td>$b/\text{Å}$</td>
<td>6.140(1)</td>
<td>6.215(2)</td>
<td>6.012(2)</td>
<td>3.8218(5)</td>
</tr>
<tr>
<td>$c/\text{Å}$</td>
<td>9.438(1)</td>
<td>9.525(2)</td>
<td>9.303(9)</td>
<td>17.693(6)</td>
</tr>
<tr>
<td>$\beta/^\circ$</td>
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<td>98.73(2)</td>
<td>97.72(5)</td>
<td>99.13(6)</td>
</tr>
<tr>
<td>$V/\text{Å}^3$</td>
<td>484.4(1)</td>
<td>497.7(2)</td>
<td>459.4(6)</td>
<td>863.7(4)</td>
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<td>$Z$</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>$D_\text{o}/\text{g cm}^{-3}$</td>
<td>1.222</td>
<td>1.189</td>
<td>1.288</td>
<td>1.371</td>
</tr>
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<td>$T/K$</td>
<td>295</td>
<td>344</td>
<td>293(2)</td>
<td>293(2)</td>
</tr>
</tbody>
</table>

Table 3.2 Unit-cell parameters for polymorphs of phenanthrene.

3.4.1 Description of the structure of the new polymorph

Inspection of the crystal packing of form III, depicted in Figure 3.5, shows layers held together by $\pi...\pi$ interactions with a small contribution from C-H...$\pi$ interactions. This is also confirmed on analysis of Hirshfeld surfaces and fingerprint plots (Section 3.9.1).

**Figure 3.5** Crystal packing of phenanthrene-III viewed perpendicular to the $ab$ plane.
3.4.2 Topological analysis

In comparison with form II at ambient pressure, form III at 0.7 GPa is 12% denser, indicating a more efficient packing of the molecules. This is illustrated in Figure 3.6, which shows selected layers of the two structures. Two effects are seen in the high-pressure phase: firstly, the distance between parallel planes of molecules (\(\pi\ldots\pi\) stacking) is substantially reduced; secondly, molecules between these planes overlap to a greater extent, \(i.e.\) the offset between molecules in neighbouring planes is reduced. In each structure there are two distances between parallel planes involved in \(\pi\ldots\pi\) stacking: one shorter distance of ca. 2.8 and 2.3 Å for the ambient and high-pressure phases, respectively, and one longer distance of ca. 4.4 and 3.5 Å for the ambient and high-pressure phases, respectively.

Figure 3.6 Packing motif of phenanthrene (a) at ambient pressure and (b) at 0.7 GPa [some layers have been omitted for clarity].

The topological approach described by Peresypkina & Blatov (2000a, 2000b) provides a further tool for polymorph comparison. Analysis of the local environment around a central molecule is a useful tool to illustrate the higher density of the high-pressure phase, and comparison between two polymorphs is achieved by replacing molecules with their geometric centroids. In this instance, centroids of neighbouring
phenanthrene molecules arranged around the centroid of a central molecule have been considered (Figure 3.7). Centroids were calculated using the program *TOPOS 4.0 Professional* (Blatov et al., 2000). In the ambient phase, each molecule has six near neighbours ranging between 5.1 Å and 6.1 Å, the centroids of which form a slightly irregular hexagon and lie in an almost exact plane (with a mean deviation from the best least-squares plane of 0.05 Å), and a further eight neighbours lying within a radius of 11.3 Å. The effect of pressure on the structure of form II at 0.35 GPa is to decrease the distance between these contacts (the structure is 5.4 % denser): the six nearest neighbours are now found between 5.0 and 6.0 Å and the remaining eight are within 11.1 Å.

In the high-pressure phase, each molecule has two nearest neighbours and four further neighbours that give rise to a distorted hexagon with a substantial deviation from coplanarity (the mean deviation from the best least-squares plane is 0.53 Å); eight further neighbours lie within a radius of 10.6 Å and are arranged around the distorted hexagon.

![Figure 3.7 Distribution of the six nearest neighbour centroids around the centroid of a central molecule of phenanthrene for (a) the ambient-pressure phase, and (b) the high-pressure phase at 0.7 GPa.](image)

The shortest contacts between centroids can be used to partition the structures into Voronoi-Dirichlet domains and construct *molecular* and *lattice* Voronoi-Dirichlet Polyhedra (VDPs), indicative of the *local* topology of molecular packing and of the *global* topology of packing, respectively. Only analysis of *lattice* VDPs is

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Chapter 3 – High-Pressure Studies of Polycyclic Aromatic Hydrocarbons

A.1 High-Pressure Recrystallisation of Phenanthrene
presented here (see Section 2.3.1). In many cases the topological parameters of these
domains and the number of centroids in successive coordination spheres can be used
to relate molecular crystal structures to the well-known sphere packings (BCC, CCP
and HCP). The Reduced Graph of Molecular Lattice (RGML, Peresypkina & Blatov,
2000b) of the corresponding lattice VDP gives the number of neighbours in the first,
second and third coordination spheres; this sequence can then be checked against the
ones of known packing topologies, and for phenanthrene form II at ambient pressure
this is 12-42-92, which is based on CCP topology. The same sequence is found for
phenanthrene form II at 0.35 GPa, although taking into account only "strong"
contacts, defined by Blatov as contacts that subtend lattice VDP faces with a value
for the solid angle > 1.5 % (Blatov & Peresypkina, 2000b), the sequence is reduced
to 10-34-74, which does not correspond to any of the known packing types.

For the new high-pressure phase of phenanthrene, form III, the RGML is 14-
52-114, which does not correspond to any of the known structure types, and the
modified sequence that considers only "strong" contacts is 10-36-79, and so is also
not characteristic of any of the well-known packing types. This is perhaps not
surprising given the distorted hexagonal array illustrated in Figure 3.7b.

3.4.3 Decompression studies

The question as to whether high-pressure phases are sufficiently metastable
that they can be recovered at ambient conditions is of great interest, particularly if
such recovered phases have industrial or technological applications. On progressive
decompression from ca. 0.7 GPa at 293 K, optical observation of the crystal showed
that it shattered after only a small reduction in pressure, suggesting that a
reconstructive phase change had occurred, presumably to give the ambient-pressure
polymorph. Further spectroscopic and diffraction experiments could be envisaged to
confirm this. Cooling of the cell to ca. 230 K delayed the onset of the
decompression-induced phase change until ca. 0.15 GPa, suggesting that it may be
possible to recover the high-pressure phase at ambient pressure by decompression at
much lower temperatures, and this is an area that merits future exploration.
A.2 High-Pressure Studies of Pyrene

3.5 Introduction

Pyrene is a colourless to yellow solid (the yellow colour is given by the presence of tetracene, a common contaminant) of high toxicity and a suspected human carcinogen (Harvey, R. G., 1991). Pyrene is derived from incomplete combustion of organic material and can be isolated from coal tar together with a broad range of related compounds. There is currently no commercial production or use of this compound.

Pyrene is almost insoluble in water, but can be recrystallised at room temperature and pressure from solutions of a variety of organic solvents, including dichloromethane, benzene and ethanol, in the form of colourless plates that melt at ca. 429 K. The molecular structure of pyrene is depicted in Figure 3.8.

![Figure 3.8 Molecular structure of pyrene with numbering scheme.](image)

At conditions of ambient temperature and pressure, pyrene exists in two solid modifications, a stable form I and a metastable form II. The first X-ray crystal structure of form I was reported by Robertson and White (1947) and was subsequently re-investigated by X-ray (Camerman & Trotter, 1965; Allmann, 1970; Kai et al., 1978) and neutron diffraction (Hazell et al., 1972). Crystals of form I transform to form II on cooling below 110 K and the transition is accompanied by the shattering of the crystal. A structure of form II was postulated from potential energy calculations and Transmission Electron Microscopy (TEM) by Jones et al. (1978) and this was confirmed by structure solution from high-resolution neutron powder diffraction data collected on a deuterated sample at 4.2 K (Knight, et al., 1996). Single-crystal X-ray diffraction data have been obtained fairly recently.
(Frampton et al., 2000) by cooling a single crystal of form I slowly through the phase transition and by collecting data at 93 K on a single-crystal fragment that was preserved after crystal shattering. Fluorescence (Mansour & Weinreb, 1974) and TEM (Jones & Cohen, 1977) measurements indicated the existence of a third phase, but no structural details have ever been published.

Volumetric measurements by Vaidya & Kennedy (1971) pointed towards a pressure-induced phase transition in pyrene at an equilibrium transition pressure of 0.26 GPa. A transition was also observed at the slightly different pressure of 0.4 GPa by analysis of Raman lattice modes (Zallen et al., 1976). Infrared spectra (Hamann, 1978) collected in a diamond-anvil cell at ambient temperature showed subtle and weak changes in the ring-stretching bands corresponding to a first transition at 0.3 GPa and marked changes in the ring- and C-H deformations bands, as well as a discontinuous shift of the main C-H stretching band, associated to a second transition between 3.0 GPa and 4.5 GPa. Spectroscopic studies at pressures below 0.4 GPa are consistent with the I \(\rightarrow\) II phase transition that has also been observed in a variable temperature and pressure neutron powder diffraction study of pyrene-\(d_{10}\) (Knight et al., 1999), which showed that at ambient temperature form I undergoes a phase transition to the denser polymorph II at ca. 0.4 GPa (Figure 3.9).

![Figure 3.9 Pressure-temperature phase diagram of pyrene-\(d_{10}\) (Knight, 1999).](image)

The known polymorphism of pyrene and its solubility in dichloromethane were deciding factors for choosing this compound for high-pressure recrystallisation studies.
3.6 Experimental Procedure

3.6.1 Recrystallisation at 0.3 GPa

A ca. 0.5 M solution of pyrene (BDH, used as received) in dichloromethane (Fischer) was loaded at 293 K into a Merrill–Bassett diamond-anvil cell equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm gasket hole. On sealing the cell and pressurising to ca. 0.3 GPa precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 303 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 50 % of the gasket hole (Figure 3.10). Several temperature-annealing cycles were necessary to grow a single crystal of reasonably large size and prevent the growth of a large number of smaller single crystals nucleating from the edge of the gasket. Notwithstanding this, two smaller single crystals were allowed to grow in the pressure cell, and these are visible in Figure 3.10. The pressure within the gasket hole was determined as ca. 0.3 GPa.

Diffraction data were collected on a Bruker SMART APEX CCD diffractometer at 293(2) K using Mo Kα radiation (λ = 0.71073 Å). Data collection was performed according to procedures described by Dawson et al. (2004) and detailed in Section 2.2.1. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions substantially different from either of the two known polymorphs of pyrene corresponding to a volume decrease of ca. 6 % with respect to the structure of form II at ambient pressure and temperature.

Figure 3.10 Optical image of a single crystal of pyrene-III in a diamond-anvil cell at 0.3 GPa.
The structure of this new polymorph, which has been denoted as form III, was solved by direct methods (SHELXS, Sheldrick, 1997b) and refined with the program SHELXL (Sheldrick, 1997a). Whilst not ideal, the $R$-factor of 11.9% is typical for refinement of high-pressure data and is sufficient to identify the main changes in crystal packing of the new high-pressure polymorph.

**Unit cell determination with CAD4**

The single crystal grown at 0.3 GPa proved to be weakly diffracting and refinement of the unit-cell parameters in the integration step was based on merely 80 reflections. This is a low number of reflections for obtaining accurate unit-cell parameters from a diffractometer equipped with an area detector. Different data/integration parameters were varied, but the number of strong reflections was not found to increase significantly. It is well known that unit cells obtained from data collected with point detectors are more accurate. A more accurate unit cell for pyrene recrystallised at 0.3 GPa was obtained by determining the setting angles of 10 strong reflections on an Enraf-Nonius CAD4 diffractometer equipped with Mo Kα radiation ($\lambda = 0.71073$ Å). A least-squares fit gave monoclinic unit-cell parameters in good agreement with the ones found with the Bruker SMART Apex CCD diffractometer, confirming that the correct unit cell had been identified, and these parameters were used during structure refinement.

3.6.2 Recrystallisation at 1.0 GPa

Subsequent to the identification of a new high-pressure phase at 0.3 GPa and the observation that the application of pressure did not seem to reduce significantly the high solubility with temperature, our attention focussed on whether further new phases could be accessed at higher pressures. A new loading with the same solution employed in the 0.3 GPa experiment was performed. On sealing the cell and pressurising to ca. 1.0 GPa precipitation of polycrystalline material occurred. Despite the fact that dissolution of the polycrystalline material at this pressure required a modest temperature of ca. 313 K, the growth of multiple single crystals could not be inhibited and a single crystal suitable for X-ray diffraction could not be obtained. A possible explanation for this observation is that there is little or no control over the number of nucleation sites inside the high-pressure cell: indeed, it is worth
emphasising that the lack or presence of nucleation sites in a diamond-anvil cell can be a crucial factor in determining the outcome and success of a high-pressure recrystallisation experiment, since these may affect the kinetics of the crystallisation process. On the other hand, similar although less severe problems were encountered when growing a crystal at 0.3 GPa and it could therefore be argued that this is an intrinsic property of pyrene-III under these conditions.

### 3.6.3 Recrystallisation at 0.5 GPa

The pressure inside the cell was reduced from 1.0 to 0.5 GPa and four temperature-annealing cycles near \( \text{ca. 303 K} \) were needed to dissolve the multiple single crystals originally recrystallised at 1.0 GPa, and grow one single crystal that filled \( \text{ca. 50\%} \) of the gasket hole (Figure 3.11). The pressure within the gasket hole was determined as \( \text{ca. 0.5 GPa} \).

![Diagram of a single crystal in a diamond-anvil cell at 0.5 GPa](image)

**Figure 3.11** Optical image of a single crystal of pyrene-III in a diamond-anvil cell at 0.5 GPa.

Diffraction data were collected on a Bruker SMART APEX CCD diffractometer at 293(2) in the same manner as for the single crystal grown at 0.3 GPa. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions similar to those found for the new high-pressure polymorph, form III, and corresponding to a volume decrease of \( \text{ca. 4\%} \) compared to form I.
3.7 Results

3.7.1 Form III at 0.3 GPa

Data indexing was performed using the indexing program CELL_NOW (Sheldrick, 2002), which confirmed the presence of two further single-crystal domains in addition to the main one visible in Figure 3.10. The twin laws relating these domains indicated essentially no reflections overlap with the principal domain. Reflections from these additional two domains were too weak to be integrated. Had that not been the case, an improvement in the data completeness would have been expected. However, it should be noted that reasonably good completeness (ca. 60 \% to $\theta_{\text{max}} = 20.8^\circ$) for the data collected on this low-symmetry monoclinic crystal was nevertheless achieved.

Data processing was performed according to procedures described by Dawson et al. (2004) and detailed in Section 2.2.2. The structure was solved in $P2_1/c$ using direct methods (SHELXS, Sheldrick, 1997b) with a pyrene molecule sitting on an inversion centre, giving half a crystallographically independent molecule in the asymmetric unit. Full-matrix least-squares structure refinement against $F^2$ was performed using SHELXL (Sheldrick, 1997a) in the non-standard $P2_1/a$ setting in order to facilitate structure comparison with the known polymorphs. Due to the paucity of the data, a $\theta$ cut-off of 20.8° was applied during data merging. The pyrene molecule was refined as a rigid group. Distance restraints were applied for the two 1,2 distances and for three of the 1,3 distances generated by symmetry about the inversion centre. One common isotropic thermal parameter was refined for non-hydrogen atoms and hydrogen atoms were placed in calculated positions and allowed to ride on their parent atom.

Full refinement details are shown in Table 3.3. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

3.7.2 Form III at 0.5 GPa

Data indexing was performed using the indexing program CELL_NOW (Sheldrick, 2002), which identified the presence of one principal single-crystal domain and a further, smaller one that had not been identified by optical microscopy.
As for the 0.3 GPa data, no overlap of reflections was identified. Data processing was performed on the principal domain according to procedures described by Dawson et al. (2004). Full-matrix least-squares structure refinement against $R^2$ was performed using SHELXL (Sheldrick, 1997a) using the coordinates of the structure obtained at 0.3 GPa. Due to the paucity of the data, a $\theta$ cut-off of 20.8° was applied during data merging and this resulted in a considerable reduction of measured data, although not in a significant reduction in the number of strong data. Data were refined using the same refinement strategy employed for the structure obtained at 0.3 GPa. A considerably lower completeness of 34.4% was obtained for this data set due to an unfortunate orientation of the crystal, and this is reflected in the higher $R$-factor.

Full refinement details are shown in Table 3.3. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Pyrene III at 0.3 GPa</th>
<th>Pyrene III at 0.5 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C$<em>{16}$H$</em>{10}$</td>
<td>C$<em>{16}$H$</em>{10}$</td>
</tr>
<tr>
<td>$M_r$</td>
<td>202.24</td>
<td>202.24</td>
</tr>
<tr>
<td>Cell setting, space group</td>
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<td>Monoclinic, $P2_1/a$</td>
</tr>
<tr>
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<td>15.309 (4), 3.8375 (5), 8.3341 (16)</td>
</tr>
<tr>
<td>$\beta$ (°)</td>
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<td>102.606 (19)</td>
</tr>
<tr>
<td>$V$ (Å³)</td>
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<td>477.81 (18)</td>
</tr>
<tr>
<td>$Z$</td>
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<td>2</td>
</tr>
<tr>
<td>$D_t$ (Mg m$^{-3}$)</td>
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<td>1.406</td>
</tr>
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<td>Mo Kα</td>
</tr>
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<td>209</td>
</tr>
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<td>298 (2)</td>
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<td>Crystal form, colour</td>
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<td>Block, colourless</td>
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<tr>
<td>Crystal size (mm)</td>
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<td>0.3 × 0.15 × 0.15</td>
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Table 3.3 Crystal, collection and refinement details for pyrene-III at 0.3 and 0.5 GPa.
<table>
<thead>
<tr>
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<th>Pyrene form III at 0.5 GPa</th>
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</thead>
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<td>Bruker SMART</td>
</tr>
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<td>$\omega$ scans</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Empirical &amp; multi-scan (based on symmetry-related measurements)</td>
<td>Empirical &amp; multi-scan (based on symmetry-related measurements)</td>
</tr>
<tr>
<td>$T_{\text{min}}$</td>
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<td>0.308</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>No. of measured, independent and observed reflections</td>
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<td>671, 172, 80</td>
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<tr>
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<td>$I &gt; 2\sigma(I)$</td>
</tr>
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<td>$R_{\text{int}}$</td>
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<td>$\theta_{\text{max}}$ ($^\circ$)</td>
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<td>20.8</td>
</tr>
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<td>Range of $h, k, l$</td>
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<td>$-9 \rightarrow h \rightarrow 10$</td>
</tr>
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<td></td>
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<td>$-6 \rightarrow l \rightarrow 6$</td>
<td>$-7 \rightarrow l \rightarrow 7$</td>
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<table>
<thead>
<tr>
<th>Refinement</th>
<th>F$^2$</th>
<th>F$^2$</th>
</tr>
</thead>
<tbody>
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<td>$R[F^2 &gt; 2\sigma(F^2)], wR(F^2), S$</td>
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<td>0.134, 0.401, 1.11</td>
</tr>
<tr>
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<td>172 reflections</td>
</tr>
<tr>
<td>No. of parameters</td>
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<td>8</td>
</tr>
<tr>
<td>H-atom treatment</td>
<td>Riding</td>
<td>Riding</td>
</tr>
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<td>Weighting scheme</td>
<td>Calculated $w = 1/[\sigma^2(F_o^2) + (0.2P)^2]$ where $P = (F_o^2 + 2F_e^2)/3$</td>
<td>Calculated $w = 1/[\sigma^2(F_o^2) + (0.1514P)^2 + 6.3887P]$ where $P = (F_o^2 + 2F_e^2)/3$</td>
</tr>
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<td>$(\Delta\sigma)_{\text{max}}$</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
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<td>$\Delta P_{\text{max}}, \Delta P_{\text{min}}$ ($\text{e} ,\text{Å}^{-3}$)</td>
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<td>0.28, -0.32</td>
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<td>Extinction method</td>
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<td>Extinction coefficient</td>
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**Table 3.3 (cont.)** Crystal, collection and refinement details for pyrene-III at 0.3 and 0.5 GPa.
3.8 Discussion

Crystallographic data for the polymorphic forms of pyrene are summarised in Table 3.4. In the case of form I, both low-temperature and ambient-temperature cell parameters are reported.

<table>
<thead>
<tr>
<th>CSD reference code</th>
<th>Crystal system</th>
<th>Space group</th>
<th>Ambient-pressure Form I&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ambient-pressure Form I&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Low-temperature phase Form II&lt;sup&gt;c&lt;/sup&gt;</th>
<th>High-pressure phase at 0.3 GPa Form III&lt;sup&gt;d&lt;/sup&gt;</th>
<th>High-pressure phase at 0.5 GPa Form III&lt;sup&gt;d&lt;/sup&gt;</th>
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</thead>
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<td>12.358(6)</td>
<td>15.35(9)</td>
<td>15.309(4)</td>
</tr>
<tr>
<td>PYRENE01&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Monoclinic</td>
<td>P2&lt;sub&gt;1&lt;/sub&gt;/a</td>
<td>9.159(1)</td>
<td>9.267(1)</td>
<td>10.020(4)</td>
<td>3.852(3)</td>
<td>3.8375(5)</td>
</tr>
<tr>
<td>PYRENE07&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Monoclinic</td>
<td>P2&lt;sub&gt;1&lt;/sub&gt;/a</td>
<td>8.387(1)</td>
<td>8.479(2)</td>
<td>8.260(4)</td>
<td>8.65(7)</td>
<td>8.3341(16)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Kai et al., 1978.
<sup>b</sup> Camerman & Trotter, 1965.
<sup>c</sup> Frampton et al., 2000.
<sup>d</sup> This work.

Table 3.4 Unit-cell parameters for the polymorphs of pyrene.

As pyrene is a rigid molecule, it was possible to build a reasonably full molecular model by application of rigid-body constraints for the refinement of the new high-pressure polymorph. This reduced the number of parameters to be refined, and is desirable when refining against a dataset of low completeness, or, as in this
case, a weak dataset of poor refinement statistics due to the low precision of measured intensities. Rigid-body refinement does not allow comparison of primary bond lengths of the pyrene molecules with those of the two ambient-pressure phases, but at these relatively low pressures it would be expected that they would be almost unchanged. Instead, the effect of pressure manifests itself in changes in the molecular packing and intermolecular distances.

3.8.1 Description of the structures of forms I and II

A previously unreported detailed structural analysis of forms I and II is reported in Section 3.8.3. This will prove useful for the discussion of the structure of the new high-pressure polymorph, form III. Both forms I and II belong to the sandwich-herringbone class (Desiraju & Gavezzotti, 1989a, 1989b): two parallel molecules (in the case of pyrene these are related by an inversion centre) are arranged in a sandwich motif via π...π stacking interactions, and each motif is arranged in a herringbone fashion favouring C-H...π interactions, as depicted in Figure 3.12.

Figure 3.12 (a) Form I and (b) form II viewed along the crystallographic c axis.
3.8.2 Description of the structure of the new polymorph, form III

Direct inspection of the crystal packing of this form, depicted in Figure 3.13, shows layers held together by \( \pi \ldots \pi \) interactions with a small contribution from C-H...\( \pi \) interactions. This is also confirmed by analysis of Hirshfeld surfaces and fingerprint plots (Section 3.9.1).

![Figure 3.13 Form III viewed along the crystallographic c axis.](image)

3.8.3 Topological analysis

The effects of pressure on the structure of pyrene can be monitored by topological analysis using the program *TOPOS 4.0 Professional* (Blatov *et al.*, 2000).

Forms I and II

Jones *et al.* (1978) have pointed out that a small rotation of molecules around the \( c \) axis of the unit cell of pyrene I generates a new structure that is very close in terms of cell dimensions and packing motif to form II. The small rotation around the \( c \) axis can be illustrated by considering the angles that the least-squares plane through a pyrene molecule make with each of the unit-cell axes. Thus, for form I, the angles of this plane with the \( a, b \) and \( c \) axes are 39.9, 48.6 and 15.8°, respectively, and for form II the corresponding angles are 49.5, 38.3 and 16.3°, respectively. This tilt is largely responsible for the noticeable change in the interplanar angle between nearest neighbours, (82.8° for form I and 103.5° for form II, illustrated in Figure 3.14). Interestingly, the largest changes in unit-cell dimensions are associated with the \( a \) and \( b \) axes, along which the sandwich-herringbone motif has strong components. Thus, the \( a \) axis decreases by 7.3 % on going from form I to form II, the \( b \) axis lengthens by 9.4 % and the \( c \) axis increases by 1.5 %. The \( \beta \) angle decreases by ca.
3.8 %, so that overall the density of form II is only slightly higher than that of form I (1.322 for form II at 93 K and 1.313 g cm\(^{-3}\) form I at 113 K).

![Figure 3.14 Geometrical parameters for pyrene: (a) form I (PYRENE03) and (b) form II (PYRENE07).](image)

Distances between parallel molecules remain essentially unchanged at ca. 3.5 Å, although the offset for π...π stacking is slightly reduced, as shown by the shorter distance between molecular centroids of parallel molecules (3.889 Å for form I and 3.747 Å for form II). Distances between the centroids of molecules related by a screw axis and involved in the herringbone motif are 7.148 Å for form I and 6.611 Å for form II: the geometrical parameters between these molecules (see Figure 3.14) define the tilt of the herringbone motif.

When reduced to an array of molecular centroids, forms I and II are surrounded by six closest neighbours forming a highly distorted hexagonal planar array around the central molecule (the mean deviation from best least-squares plane is 0.37 Å for form I and 0.34 Å for form II). The spatial arrangement of these centroids is depicted in Figures 3.15 and 3.16 and values for centroids distances are given in Table 3.5. Seven further neighbours (that lie within a distance of 10.062 Å for form I and of 10.021 Å for form II) give a total of thirteen atoms in the first coordination sphere.
Figure 3.15 Arrangement of the six nearest molecular centroids around a central centroid for pyrene: (a) form I (PYRENE03) and (b) form II (PYRENE07).

Centroid separation for the six nearest neighbours of forms I and II / Å

<table>
<thead>
<tr>
<th>Centroid</th>
<th>Form I(^1)</th>
<th>Form II(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.889</td>
<td>3.747</td>
</tr>
<tr>
<td>2</td>
<td>6.004</td>
<td>6.226</td>
</tr>
<tr>
<td>3</td>
<td>6.004</td>
<td>6.226</td>
</tr>
<tr>
<td>4</td>
<td>7.148</td>
<td>6.611</td>
</tr>
<tr>
<td>5</td>
<td>7.148</td>
<td>6.611</td>
</tr>
<tr>
<td>6</td>
<td>7.574</td>
<td>7.821</td>
</tr>
</tbody>
</table>

\(^1\)CSD reference code PYRENE03
\(^2\)CSD reference code PYRENE07

Table 3.5 Separations of the centroids of a central pyrene molecule and its six nearest neighbours.

Figure 3.16 Packing arrangement of the six closest neighbouring pyrene molecules around a central molecule.

The overall tilting and compression of the sandwich-herringbone motif is depicted in Figure 3.17, which shows an overlay of the two structures.

Figure 3.17 Overlay of the structures of forms I and II.
Peresypkina & Blatov (2000b) have defined the Reduced Graph of Molecular Lattice (RGML), as a useful parameter for topological analysis that gives the number of neighbours in the first, second and third coordination spheres. This sequence can then be checked against the ones of known packing topologies. For forms I and II, the RGML is 14-50-110 (it was previously noted that the molecular coordination number is thirteen, but this does not necessarily equal the molecular packing number, as discussed in Section 2.3.1), which is related to the coordination sequences of body-centred cubic packing (see Section 2.3.1). Taking into account only “strong” contacts, defined by Blatov as contacts that subtend lattice VDP faces with a value for the solid angle $> 1.5\%$ (Peresypkina & Blatov, 2000b), the coordination sequence is reduced to 11-40-88, which is not related to the coordination sequence of any of the well-known packing of spheres. Comparison of lattice VDPs of pyrene-I and pyrene-II with those for perfect BCC (not shown here) shows that there is very little resemblance between the two topologies. This is to be expected since the packing of a disk-like shape molecule like pyrene is likely to be very different from the packing of hard spheres such as found in BCC iron.

**Form III at 0.3 and 0.5 GPa**

The new polymorph of pyrene at 0.3 GPa has a density that is ca. 6.1\% higher than that of form I at ambient pressure and temperature (CSD reference code PYRENE01); at 0.5 GPa the increase is found to be ca. 10.6\%. The substantial increase in density is comparable to the increase observed for the high-pressure polymorph of phenanthrene (see Section 3.4.2), where the increase in density between form I and III at 0.6 GPa was ca. 12\%.

As in the case of phenanthrene, the increase in the density of the high-pressure phase of pyrene is indicative of more efficient packing of the molecules. Analysis of the local environment around a central molecule is a useful tool to illustrate the higher density of the high-pressure phase.

In the high-pressure phase, each molecule has two nearest neighbours and four further neighbours that give rise to a distorted hexagonal planar array (Figures 3.18 and 3.19); distances between these six centroids at 0.3 GPa and 0.5 GPa are given in Table 3.6.
Centroid separation for the six nearest neighbours of pyrene-III / Å

<table>
<thead>
<tr>
<th>Centroid</th>
<th>0.3 GPa</th>
<th>0.5 GPa</th>
<th>Centroid</th>
<th>0.3 GPa</th>
<th>0.5 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.852</td>
<td>3.838</td>
<td>4</td>
<td>7.913</td>
<td>7.891</td>
</tr>
<tr>
<td>2</td>
<td>3.852</td>
<td>3.838</td>
<td>5</td>
<td>7.913</td>
<td>7.891</td>
</tr>
<tr>
<td>3</td>
<td>7.913</td>
<td>7.891</td>
<td>6</td>
<td>7.913</td>
<td>7.891</td>
</tr>
</tbody>
</table>

Table 3.6 Separations of the centroids of a central pyrene-III molecule and its six nearest neighbours at 0.3 and 0.5 GPa.

Centroids 1 and 2 correspond to pyrene molecules involved in $\pi...\pi$ stacking related by translation along the $b$ axis and therefore show the same trend of compression as the $b$ axis, i.e. a modest 0.4 % decrease over the narrow pressure 0.3-0.5 GPa pressure range. No significant change in the offset to $\pi...\pi$ stacking is observed on increasing pressure from 0.3 to 0.5 GPa. Centroid distances of molecules involved in $\pi...\pi$ stacking are slightly shorter than those found in form I and slightly longer than in form II, although distances between parallel planes are unchanged at ca. 3.47 Å. Although the distances are the same, slightly different types of offsets to $\pi...\pi$ stacking are observed for the three polymorphs (see Section 3.9.1). Centroids 3 to 6 correspond to molecules related to a central one via a 2$_{1}$-screw rotation and an $a$-glide reflection and these distances decrease by ca. 0.3 % on increasing pressure. The direction of the maximum strain tensor was found to lie approximately along the $c$ axis. This compresses by ca. 3.7 % from 0.3 to 0.5 GPa and corresponds to the compression of the hexagonal layers of closest molecules.
related by translational symmetry along this axis, which ultimately results in a reduction of voids in the structure.

In form III, eight further neighbours lie within a distance of 10.339 Å at 0.3 GPa and of 10.192 Å at 0.5 GPa, and are arranged around the distorted hexagon shown in Figure 3.18. Overall, the topology resembles a distorted CCP arrangement (not shown here). This is confirmed by the fact that the RGML is 12-42-92, which is based on CCP topology. Similar discrepancies between molecular coordination and packing numbers apply, as discussed for forms II and I; in addition, it should be noted that the RGML contains four “weak” contacts. Deviation from perfect hard-sphere topology can be explained on consideration of molecular shape, as discussed earlier for pyrene and for phenanthrene (Section 3.4.2).

3.8.4 Decompression studies

On progressive decompression from 0.5 GPa at 293 K, optical observation showed that the crystal of form III gradually dissolved. This was in marked contrast to the disintegration of the high-pressure form of phenanthrene (Section 3.4.3). This might suggest that pyrene-III does not undergo a reconstructive phase transition, although at this stage it is not possible to rule out a non-reconstructive phase transition taking place prior to dissolution. Cooling of the cell to low temperatures may delay the onset of the decompression-induced dissolution, and may ultimately lead to the recovery the high-pressure phase at ambient pressure, and this is an area that is currently being explored.
A.3 Overall Discussion of the Structures of Phenanthrene and Pyrene

3.9 Classification of the crystal structures of the new polymorphs

Desiraju & Gavezzotti (1989a, 1989b) divided PAHs into four structural types: $\beta$, $\gamma$, herringbone and sandwich-herringbone structures. According to the work by Desiraju & Gavezzotti, the key parameters to discern between the four structure types are the shortest cell axis and the interplanar angle (Figure 3.20), defined as the angle between the mean plane of one molecule and that of its nearest neighbours (this model shall be referred to as the “geometrical model”); in particular, the authors stated “the shortest axis is in fact crystal structure defining while the two other cell axes are merely a function of individual molecular geometries.”. They found that the overwhelming majority of crystal structures of PAHs are monoclinic, with the shortest axis coinciding with the unique axis. This statement will be challenged in this section.

Figure 3.20 Intermolecular interplanar angle vs. shortest cell axis in the crystal structures of 27 of the 32 PAHs analysed by Desiraju & Gavezzotti (1989b) and their Classification into four-structure types: $\beta$, $\gamma$, herringbone (HB) and sandwich-herringbone (SHB) structures. The black dots are the orthorhombic structures of benzene and triphenylene. The black triangle is the high-pressure monoclinic phase of benzene. Reproduced from Figure 3 in Desiraju & Gavezzotti (1989b).
The ambient-pressure ambient-temperature polymorph of phenanthrene, phase II is no exception, and with a $b$ axis of 6.140 Å and an interplanar angle of 58°, it belongs to the herringbone-type of structures, dominated by C-H...$\pi$ interactions (Desiraju & Gavezzotti, 1989b). According to the geometrical model, the new high-pressure phase of phenanthrene, form III, with a $b$ axis of 3.8218 Å, would belong to the $\beta$-type structures, characterised by layered structures made of “graphitic” planes. On the other hand, this would make form III a distinct “outlier” in this class, as shown in Figure 3.20: an interplanar angle of 52° is atypical for this class of structures, which typically exhibit values below 30° and in fact falls in the region of herringbone-type structures (Figure 3.20).

As mentioned earlier, Desiraju & Gavezzotti found that the overwhelming majority of crystal structures of PAIs are monoclinic, and stated: “...the shortest crystallographic axis is always a screw-axis direction. This axis is, therefore, a key parameter in separating packing types and defines the crystal structure.” (Desiraju & Gavezzotti, 1989a). The authors have always quoted the correct values for the shortest unit-cell axis, but it is here noted that in the case of pyrene this axis does not coincide with the unique axis (where the shortest axis is in fact the $c$ axis) and this would appear to contradict their statement. On analysis of other PAH structures reported in their papers, perylene was also found not follow this rule. It is concluded that the monoclinic $b$ axis is always crystal defining but not necessarily always the shortest one. In the case of pyrene, two types of analysis could therefore be envisaged, based on the consideration of the length of the shortest axis or of the unique axis. The shortest ($c$) axis and interplanar angles are 8.387 Å and 82.8° for form I (CSD reference code PYRENE03) and 8.260 Å and 103.8° for form II (CSD reference code PYRENE07). The unique ($b$) axis is 9.159 Å for form I and 10.020 Å for form II. According to both types of analysis both structures belong to the sandwich-herringbone class, a hybrid between herringbone and $\gamma$ structures (in which both C-H...$\pi$ and $\pi$...$\pi$ interactions are present), as shown in Figure 3.12.

With a $b$ axis of 3.852 Å, pyrene-III falls into the region of $\beta$-type structures characterised by layered structures made of “graphitic” planes. It should however be noted that, similarly to phenanthrene-III, an interplanar angle of 60° makes form III an “outlier”, since $\beta$ structures typically exhibit values below 30°. In fact, from an
angular point of view pyrene falls in the region of herringbone-type structures (Figure 3.20).

It is here noted that there seem to be further outliers within the structures analysed by Desiraju & Gavezzotti with respect to the plot presented in Figure 3.20. The high-pressure monoclinic form of benzene (depicted as a black triangle in the \(\gamma\)-type structures in Figure 3.20) is an example. At ambient pressure, the structures of diperinaphthyleneanthracene (CSD reference code NAPANT01) and tetrabenzoperylene (TBZPER), which do not seem to be depicted in Figure 3.20 (but are referred to in the original paper), are classified as \(\beta\)-type on virtue of their small interplanar angles of 9 and 3°, respectively, but values for the shortest axis of 7.83 and 7.65 Å, are atypical for this class of compounds. However, tetrabenzoperylene crystallises in the orthorhombic crystal system and the authors had already mentioned some shortcomings of the geometrical model when applied to this type of system.

It therefore appears that both new high-pressure polymorphs of phenanthrene and pyrene are outliers in the class of \(\beta\) structures, when considering the shortest cell axis, as suggested by Desiraju & Gavezzotti, as the key parameter for discerning between the four packing types. Both forms are classified as \(\beta\) structures according to the values for the shortest unit-cell axis, but values for the interplanar angle are higher than normally found for this class and would in fact point more towards herringbone structures. In both cases, features characteristic of both structural types would therefore be expected, as confirmed by direct investigation of the crystal packing, of the molecular topology and of Hirshfeld surfaces and fingerprint plots (Section 3.9.1). The high-pressure monoclinic polymorph of benzene also stands out from its structure class, as seen in Figure 3.20. Although three outliers are a too small number to draw any decisive conclusion, the fact that the two new high-pressure polymorphs of PAHs reported in this thesis are outliers with respect to the model by Desiraju & Gavezzotti may be ascribed to the observation that the trends they observed relied on geometrical parameters and interactions found at conditions of ambient pressure. It is perhaps not surprising that high-pressure polymorphs partially deviate from this model, and this may be a direct consequence of the ability of pressure to modify and combine intermolecular interaction in ways that are not
usually found at ambient pressure. Further high-pressure studies on a wider range of PAHs could be envisaged, in order to test not only whether new polymorphs can be produced, but also to discover if there is a trend in the favoured mode of packing of the high-pressure structures.

3.9.1 Decoding intermolecular interactions: Hirshfeld surfaces and fingerprint plots

A comparison of Hirshfeld surfaces and fingerprint plots (discussed in Section 2.3.2) produced with CRYSTAL EXPLORER (Grimwood et al., 2004) is undertaken in this section for forms II and III of phenanthrene and for forms I, II and III of pyrene. Particular attention is given to fingerprint plots, which provide a concise summary of the intermolecular interactions occurring in the crystal. These plots have been shown (Spackman & McKinnon, 2002; McKinnon et al., 2004) to provide a rapid visual tool for discriminating between the four PAHs structure types and to identify examples where molecules exhibit features characteristic of more than one structural type.

Phenanthrene-II: ambient pressure and 0.35 GPa structures

Hirshfeld surfaces for phenanthrene at conditions of ambient temperature and pressure (PHENAN08) with the curvature, shape index and \( d_e \) properties mapped onto them are shown in Figure 3.21. These have recently been discussed in a paper by McKinnon et al. (2004) and their salient features are summarised here. The herringbone structure of phenanthrene is dominated by C-H...π contacts and these manifest themselves as characteristic “wings” on the corresponding fingerprint plot and broad red depressions on the \( d_e \) surface. In general, the presence of more than one type of these contacts leads to the distinct “sawtooth” shape on the lower right of the plot. The double “sawtooth” visible for phase II at ambient pressure in Figure 3.21 arises from different C-H...π interactions on both sides of the planar molecule. Head-to-head H...H contact (the pointed feature on the diagonal at the bottom left) are also visible on the plot: a spike at \( d_e \approx d_i = 1.15 \) Å indicates a short contact, whilst longer contacts are responsible for the broadening of the plot at \( d_e \approx d_i = 1.25 \) Å.
Figure 3.21 Fingerprint plot and Hirshfeld surfaces for phenanthrene-II at ambient pressure. The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

Hirshfeld surfaces and fingerprint plots for form II at 0.35 GPa are depicted in Figure 3.22.

Figure 3.22 Fingerprint plot and Hirshfeld surfaces for phenanthrene-II at 0.35 GPa. The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

Investigation of the fingerprint plots reveals several trends. Since a new polymorph was not observed at 0.35 GPa, it is not surprising that comparison with the ambient-pressure structure shows that the overall shape of the plot is maintained. The most visible effect of the application of pressure is the "shift" of the entire plot to lower $d_e$ and $d_1$ values, and this confirms the higher density (6.1 %) of the structure at 0.35 GPa. The increase in density is also apparent at higher $d_e$ and $d_1$ values with the "void" regions (where $d_e$ is larger than $d_1$ and where data points are scarce) decreasing in size.
Another noticeable difference between the two plots lies at low $d_e$ and $d_i$ values, with shorter H...H contacts (reduced from $d_e = d_i \approx 1.15 \text{ Å}$ to $1.05 \text{ Å}$) and thinner H...H fingerprint region found for the structure at 0.35 GPa. On the basis that the accepted value of the van der Waals radius for the hydrogen atom is 1.20 Å (Bondi, 1964), it could be argued that a contact of 1.05 Å is unrealistically short. On the other hand, unusually short but real H...H contacts have for example been reported for the ambient-pressure structures of pyrene (1.02 Å), coronene (1.09 Å) and dipheninaphtyleneanthracene (1.00 Å) (Spackman & McKinnon, 2002). The short H...H contact in the case of phenanthrene-II at 0.35 GPa is likely to be primarily the result of pressure bringing molecules closer together, coupled with an uncertainty in the accuracy of the structure determination that is reflected by a high $R$-factor of 15%.

It has been suggested that Hirshfeld surfaces and fingerprint plots may provide a crystallographic tool for assessing the reliability of structure determination (Spackman & McKinnon, 2002). For example, unrealistically short H...H contacts may be indicative of orientational disorder or of an average orientation of the hydrogen atoms, or simply of poor structure determination. An example of the latter is presented here: initial refinement of phenanthrene-II at 0.35 GPa afforded a structure for which the fingerprint plots was considerably different from the one depicted in Figure 3.22 and reproduced in Figure 3.23c, and this is shown in Figure 3.23b.

![Figure 3.23](image)

**Figure 3.23** Fingerprint plots for phenanthrene form II at ambient pressure (a) and at 0.35 GPa obtained for structures refined with different strategies: (b) wrong refinement and (c) optimal refinement.
In the initial refinement strategy, isotropic thermal parameters for carbon atoms were freely refined, but the majority of these converged to meaningless small values. This resulted in a poorly determined structure, as confirmed by the fingerprint plot showing unusually short H...H contacts at $d_e = d_l \approx 0.93$ Å and elongated fingerprint. An improved model was obtained by refining a common isotropic thermal parameter for all the carbon atoms and a more reliable structure was consequently obtained. This is also confirmed by visual inspection of the fingerprint plot depicted in Figure 3.23c, which appears now to be more realistic.

**Phenanthrene-III: 0.7 GPa structure**

Fingerprint plot and Hirshfeld surfaces for phenanthrene-III at 0.7 GPa are shown in Figure 3.24.

![Fingerprint plot and Hirshfeld surfaces for phenanthrene-III at 0.7 GPa.](image)

**Figure 3.24** Fingerprint plot and Hirshfeld surfaces for phenanthrene-III at 0.7 GPa. The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

In Section 3.9 the mode of packing of form III was contrasted to the herringbone-type of packing of form II. It was postulated that the new high-pressure, form III, would belong to the $\beta$-type structures with some limited contribution from C-H...$\pi$ contacts due to the larger than average value of the interplanar angle. These different modes of packing are clearly illustrated in Figure 3.25.
Hirshfeld surfaces and fingerprint plots shown in Figure 3.24 are remarkably different from those illustrated for the herringbone structures in Figures 3.21 and 3.22. Fingerprint plots for \( \beta \)-type structures are overall noticeably different from those of the other structure types: the prominent "wings" indicative of C-H...\( \pi \) contacts are absent and the dominant contact between molecules is \( \pi \)...\( \pi \) stacking, shown as a red area around \( d_e = d_l \approx 1.8 \text{ Å} \). In Figure 3.24, the "wings" indicative of C-H...\( \pi \) contacts on the fingerprint plot are absent and the broad depressions above and below the aromatic ring in the shape index surface and \( d_e \) surfaces are moved to the edges of the surface, thereby indicating the presence of limited C-H...\( \pi \) (peripheral) interactions. The dominant contact between molecules is now \( \pi \)...\( \pi \) stacking, visible as a red/green area on the fingerprint plot diagonal around \( d_e = d_l \approx 1.78 \text{ Å} \) and corresponding to a C...C contact around the van der Waals radius for carbon (1.7 Å; Bondi, 1964) and to an interlayer distance of ca. 3.5 Å. \( \pi \)...\( \pi \) stacking is evident on the Hirshfeld surface as a large flat region across the molecule, and is most clearly visible on the curvedness surface. On the \( d_e \) surface this feature appears as a relatively flat green region, where the contact distances are all very similar. The pattern of red and blue triangles on the same region of the shape index surface is characteristic of \( \pi \)...\( \pi \) stacking (McKinnon et al., 2004).

The significantly higher density of form III is reflected by the compaction of the fingerprint plot to lower \( d_e \) and \( d_l \) values in comparison with plots of form II at ambient pressure and 0.35 GPa shown in Figure 3.23.
Pyrene-I and pyrene-II

Fingerprint plots and Hirshfeld surfaces for pyrene-I have been reported and discussed in a recent paper by McKinnon et al. (2004). A summary of their investigation is here reported and the analysis is extended to form II.

Both forms I and II belong to the sandwich-herringbone type of structures and this is clearly visible in the corresponding Hirshfeld surfaces and fingerprint plots (Figure 3.26 for form I at 113 K, and Figure 3.27 for form II at 93 K). One side of the molecule is involved in \( \pi \ldots \pi \) stacking and shows a corresponding flat Hirshfeld surface, whilst the other has a prevalence of C-H...\( \pi \) interactions.

**Figure 3.26** Hirshfeld surfaces and fingerprint plot for pyrene-I at 113 K (CSD reference code PYRENE03). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) \( d_e \).

**Figure 3.27** Hirshfeld surfaces and fingerprint plot for pyrene-II at 93 K (CSD reference code PYRENE07). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) \( d_e \).
McKinnon et al. (2004) have observed that "...the colour of the shape index is exactly complementary where two molecular surfaces touch each other, and this feature can be used to establish the precise relationship between molecules in the crystal without viewing a packing diagram." For forms I and II the pattern of alternating red and blue triangles with local three-fold symmetry on the same region of the shape-index surface is indicative of offset $\pi ... \pi$ stacking interactions characteristic of graphite-like layers. Blue triangles represent ring carbon atoms of the molecule around which the surface is constructed, whilst red triangles represent those of the $\pi$-stacked molecule above it. The change in the orientation of these triangles in form II is indicative of the slight change in the offset discussed in Section 3.8.3.

$\pi ... \pi$ interactions are also clearly visible from the fingerprint plot as a green region at $d_e = d_i = 1.75 \text{Å}$, corresponding to an interlayer distance of 3.5 Å, and as noted earlier C-H...$\pi$ contacts are characterised by "wings" on the fingerprint plots. The presence of more than one type of these contacts leads to the distinct "sawtooth" shape on the lower right of the plots. These wings are well separated on the plot of form I, whilst they are almost overlapping for form II and this is mirrored by the four large depressions on the $d_e$ surfaces being more evenly coloured. The fact that similar distances are associated with these two contacts in form II is a direct consequence of the change in the tilt of the herringbone motif.

For form I head-to-head H...H contacts at $d_e = d_i = 1.02 \text{Å}$ give rise to the pointed feature on the diagonal at the bottom left: this contact for form II is at a longer distance of 1.16 Å and appears to be split on the fingerprint, indicating that the shortest contact is between three atoms, rather than between two.

**Pyrene-III**

In Section 3.9, it was postulated that the new high-pressure polymorph of pyrene, form III, would exhibit packing features typical of both $\beta$ and herringbone structures. These criteria are met in the fingerprint plots and Hirshfeld surfaces for pyrene-III at 0.3 and 0.5 GPa, shown in Figures 3.28 and 3.29, respectively (only one side of the surfaces is shown as the molecule resides on an inversion centre). Both $\pi ... \pi$ stacking at around $d_e = d_i = 1.8 \text{Å}$ and a limited contribution from C-H...$\pi$
(peripheral) interactions around $d_e = 1.1 \AA - d_i = 1.6 \AA$ and $d_e = 1.6 \AA - d_i = 1.1 \AA$ are observed in the fingerprint plots. Both features are also visible on the Hirshfeld surface, as discussed earlier for the high-pressure polymorph of phenanthrene.

![Figure 3.28 Hirshfeld surfaces and fingerprint plot for pyrene-III at 0.3 GPa. The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.](image)

![Figure 3.29 Hirshfeld surfaces and fingerprint plot for pyrene-III at 0.5 GPa. The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.](image)

The offset to perfect $\pi...\pi$ stacking produces an alternating rhomboidal pattern of blue and red regions of the shape index. This type of stacking, also found in the $\gamma$-type structure of hexabenzocoronone (McKinnon et al., 2004) is indicative of a reduced offset in comparison with graphite-like stacking, where projection of ring carbon atoms of one layer is offset to the centres of the rings of an adjacent layer. The centres of the four rings of pyrene are shown as deep blue spots on the upper part of the $d_e$ surface.

Comparison between the fingerprint plots of forms I, II and III of pyrene, shows very clearly the highest density of form III, with the plot being spread over lower $d_e$ and $d_i$ values. The increase in density from 0.3 to 0.5 GPa is also apparent at
higher $d_e$ and $d_i$ values. At 0.5 GPa, "void" regions (exemplified in the plot at 0.3 GPa by the sharp feature at $d_e = 2.2 \text{ Å}$ and $d_i = 1.55 \text{ Å}$, and on the right hand side of the plot where data points are scarce and $d_e = 1.8 \text{ Å}$ and $d_i = 2.2 \text{ Å}$) are noticeably reduced in number and in size. In addition, the region around $d_e = 1.1 \text{ Å} - d_i = 1.6 \text{ Å}$ and $d_e = 1.6 \text{ Å} - d_i = 1.1 \text{ Å}$, corresponding to C-H...π (peripheral) interactions, is also reduced at the higher pressure. One other difference is that H...H contacts for form III occur at a longer distance of 1.17 Å, compared to form I and form II.

**Phenanthrene-III and pyrene-III**

Overall, the fingerprint plots of phenanthrene-III and pyrene-III (Figures 3.30a and 3.30b, respectively) show features that are typical of β-type structures (an example of which is given in Figure 3.30c for anthrabenzonaphthopentacene), with only some limited contributions from C-H...π interactions.

![Figure 3.30 Fingerprint plots for (a) phenanthrene-III at 0.7 GPa, (b) pyrene-III at 0.5 GPa, (c) anthrabenzonaphthopentacene (CSD reference code BOXGAW01) and (d) benzodicoronene (CSD reference code YOFCUR).](image)
The fingerprint plots of phenanthrene-III and pyrene-III are remarkably similar to that of benzodicoronene, depicted in Figure 3.30d. Benzodicoronene also represents an outlier with respect to the geometrical model by Desiraju and Gavezzotti reported in Figure 3.20. In fact, similarly to phenanthrene-III and pyrene-III, benzodicoronene also exhibits a short axis whose value is typical of \( \beta \)-type structures but an interplanar angle that is larger than normally found for this structural class.

Interestingly, the crystal structure of benzodicoronene was not available at the time of publication of the papers by Desiraju & Gavezzotti (1989a: 1989b). The authors predicted its structure to be \( \gamma \)-type by analysis of the ratio of the total stacking and glide-forming surfaces vs. the total molecular surface. \( \gamma \) structures exhibit a "flattened" herringbone motif, where \( \pi...\pi \) interactions are dominant but a significant contribution from C-H...\( \pi \) interactions is also found. The crystal structure of benzodicoronene was later published in 1995 by Goddard, et al. (1995) (CSD reference code YOFCUR), who assigned the structure type to \( \beta \)-type according to the value of the shortest axis: with a value of 3.83 Å for the shortest axis and a value of 50.2° for the interplanar angle, a similar "outlier" case (see Figure 3.20) to the one described for the high-pressure forms of phenanthrene and pyrene arises. This was also pointed out by McKinnon et al. (2004), who classified benzodicoronene as a \( \gamma \)-type structure but noted that "...the fingerprint plot for benzodicoronene is set apart from all previous fused aromatic hydrocarbons in this section (\( \gamma \)-structures) in that it shows almost no contribution from the C-H...\( \pi \) fingerprint...". With these considerations in mind, the structures of the high-pressure phases of phenanthrene and pyrene are here classified as \( \beta \)-type structures that exhibit a small contribution of C-H...\( \pi \) interactions as confirmed by a larger than average value for the interplanar angle to be expected for this structural type.

Another example where an ambient-pressure structure shows features typical of more than one structure type on analysis of fingerprint plots and Hirshfeld surfaces is given by diperinaphthaleneanthracene. Diperinaphthaleneanthracene is classified as a \( \beta \)-type structure by Desiraju and Gavezzotti, but its corresponding fingerprinting plot shows \( \pi...\pi \) stacking as well as C-H...\( \pi \) contacts (McKinnon et
al., 2004). This “anomaly” is supported by the fact that the value of its shortest cell axis is larger than usually found for \( \beta \)-type structure, as noted in Section 3.9.

Hirshfeld surfaces and fingerprint plots have been successful in providing a visual tool to describe the “outlier” status of phenanthrene-III and pyrene-III with respect to the geometrical model by Desiraju and Gavezzotti.

It is expected that new high-pressure polymorphs of PAHs may provide further outliers in this model. This should perhaps not come to a surprise since it is a general observation that high pressure provides a thorough means of exploring combinations of intermolecular interactions that are not encountered under ambient conditions. This is achieved by modifying in the relative orientations of molecules and by encouraging the formation of denser structures in which molecules pack together more efficiently.

3.10 Overall Conclusions

A denser structure of phenanthrene-II has been recrystallised from a dichloromethane solution at 0.35 GPa. A new polymorph, here denoted as form III, has been recrystallised at a higher pressure of 0.7 GPa.

A new polymorph of pyrene, here denoted as form III, has been recrystallised from a dichloromethane solution at pressures of 0.3 GPa and 0.5 GPa.

By investigation of the topology of molecular centroids and in particular of Hirshfeld surfaces and fingerprint plots, the mode of packing of the two new high-pressure polymorphs has been found to be profoundly different when compared to the ambient pressure modifications. At ambient pressure, the crystal structure of phenanthrene-II exhibits a herringbone motif (C-H...\( \pi \) interactions), and the structures of pyrene-I and pyrene-II are characterised by a sandwich-herringbone motif (C-H...\( \pi \) and \( \pi \)...\( \pi \) contacts). This is in marked contrast to the high-pressure modifications of both compounds, which have been classified as \( \beta \) structures (where \( \pi \)...\( \pi \) contacts are dominant) with a small contribution from C-H...\( \pi \) interactions.

High-pressure studies on a wider range of PAHs are envisaged to discover whether a trend in the favoured mode of packing of high-pressure structures exists.
B. High-Pressure Recrystallisation and Compression Studies of Naphthalene

3.11 Introduction

Naphthalene is a bicyclic aromatic hydrocarbon; it is a natural constituent of coal tar and it is present in gasoline and diesel fuels (Harvey, R. G., 1991). The principal use of naphthalene is as an intermediate in the production of phthalic anhydride, which is used as an intermediate in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellents (e.g. mothballs), and other materials (Harvey, R. G., 1991). Naphthalene is readily obtained by recrystallisation from solutions of organic solvents (typically methanol or dichloromethane) at room temperature and pressure in the form of white plates that have a strong smell and melt at ca. 253 K. The structure of naphthalene is depicted in Figure 3.31.

![Molecular structure of naphthalene with numbering scheme.](image)

_Naphthalene has been extensively studied both at low temperatures and at high pressures._

**Variable temperature studies**

The first published crystal structure of naphthalene is that of Abrahams et al. (1949), who reported that naphthalene crystallises at ambient pressure in the monoclinic space group \( P2_1/a \) with the molecule residing on an inversion centre to give half a crystallographically independent molecule in the asymmetric unit. According to the classification of Desiraju & Gavezzotti (1989a), the crystal packing
of naphthalene follows a herringbone motif, which is dominated by C-H...π interactions (Figure 3.32). Diffraction data of Abrahams et al. (1949) were later refined in detail by Cruickshank (1957), who also analysed thermal motion. Thermal motion was also investigated by Brock & Dunitz (1982) in a series of single-crystal experiments at five different temperatures between 92 and 239 K. More recently, Oddershede & Larsen (2004) published a charge density study based on X-ray diffraction data collected at multiple temperatures between 100 and 205 K and demonstrated that it is possible to deconvolute thermal motion and static electron density in crystalline naphthalene at temperatures below 200 K. Perdeuteronaphthalene has also been studied by neutron diffraction by Pawley & Yeats (1969) and later by Natkaniec et al. (1983).

Figure 3.32 Herringbone packing motif of naphthalene viewed along the c axis.

**Pressure studies**

Bridgman (1938) found with his volumetric apparatus an "unmistakable transition" in naphthalene at ca. 3.0 GPa. The volume change associated with this transition was very small and the transition was sluggish and showed hysteresis. The transition was subsequently detected at about 2.6 GPa in shearing experiments (Gonikberg et al., 1966). Jones & Nicol (1968) suggested that changes they observed in the fluorescence spectra of a single crystal of naphthalene below 4.0 GPa may have arisen from a phase transition. Block et al. (1970) observed the transformation by optical microscopy in a diamond anvil cell at about 3.0 GPa, but Vaidya & Kennedy (1971) failed to detect it in their volumetric measurements to 4.0 GPa. Infrared studies in a diamond anvil cell (Hamann, 1978) indicated that the transition is first detected at an average pressure of 2.0 GPa, although traces of the original
spectrum were still present at 4.5 GPa, in line with Bridgman’s observation of a sluggish transition.

In contrast to some spectroscopic evidence, X-ray powder diffraction experiments at room temperature up to 0.51 GPa (Alt & Kalus, 1982) gave no indication of a phase transition. It was found that the angles between the long axis of the molecule at the origin and the monoclinic \( b \) and \( c \) axes remain nearly unchanged, whereas the angle between the molecular plane and the \( bc \) plane showed a decrease of about 1.4(1)°. These results are in agreement with Raman studies indicating that the naphthalene crystal makes no structural phase transition, at least up to 3.6 GPa (Nicol, Vernon & Woo, 1975) and 450 K.

The apparently contradictory results of these studies were intriguing and suggested that the compound is an ideal candidate for study by high-pressure recrystallisation from solution. In addition, naphthalene is one of the “very widely studied compounds have shown no evidence of polymorphic behavior, even though they have been crystallized and handled for many years under a far-ranging variety of conditions” (Dunitz & Bernstein, 1995) (the two other most cited examples are sucrose and Pigment Red 179) and stimulated some curiosity as to whether the new high-pressure technique could challenge this statement.

### 3.12 Experimental Procedure

#### 3.12.1 Recrystallisation at 0.4 GPa

A ca. 2.2 M solution of naphthalene (BDH, used as received) in dichloromethane was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 µm culet diamonds and a tungsten gasket with a 300 µm gasket hole. On sealing the cell and pressurising to ca. 0.4 GPa precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 343 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 70 % of the gasket hole (Figure 3.33).

Diffraction data were collected as described in Section 2.2.1. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit
cell with dimensions similar to those found for the ambient-temperature and pressure phase of naphthalene, form I (Cruickshank, 1957) (CSD reference code NAPHTA11), corresponding to a volume decrease of ca. 6%.

![Diagram of a diamond-anvil cell](image)

**Figure 3.33** Optical image of a single crystal of naphthalene in a diamond-anvil cell at 0.4 GPa.

### 3.12.2 Recrystallisation at 0.6 GPa

Subsequent to the identification of the ambient-pressure phase, the pressure inside the diamond-anvil cell was increased from 0.4 GPa to ca. 0.6 GPa. The single crystal grown previously was redissolved by gentle heating, and on cooling precipitation of polycrystalline material was observed. The temperature was then cycled near ca. 353 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill almost 50% of the gasket hole. The pressure within the gasket hole was determined as ca. 0.6 GPa.

Diffraction data were collected in the same manner as for the crystal grown at 0.4 GPa. Data indexing gave a unit cell with dimensions similar to those found for the ambient-temperature and pressure phase of naphthalene, form I, corresponding to a volume decrease of ca. 7%.

### 3.12.3 Compression studies

Crystallisation of naphthalene from dichloromethane at pressures higher than 0.6 GPa could not be induced because the pressure inside the cell was too high to allow for dissolution of the single crystal by heating with a hot-air gun under a microscope. With a maximum attainable temperature of ca. 423 K, this heating method is currently imposing a limit on the highest pressures at which a compound...
can be recrystallised from solution. Alternative heating methods are in place for Merrill-Bassett diamond-anvil cells, for example, resistance heating, high-temperature ovens, or laser heating, but these methods were not attempted in this series of experiments. If these methods were to be attempted, it would be essential to observe visually the contents of the cell in order to ensure that all crystallites dissolved and to monitor the growth of any new phases.

High-pressure recrystallisation of naphthalene from a more diluted methanol (ca. 1.5 M solution) did not increase the working range of pressure for successful dissolution and so further studies of naphthalene were performed by compression of the single crystal grown at 0.6 GPa from dichloromethane. Limitations of this technique to induce polymorphic transformations were discussed in Section 1.3

Single-crystal diffraction data were collected at 1.0 GPa and 2.1 GPa. Broad ruby fluorescence lines indicated that at 1.0 GPa the quality of the crystal was deteriorating and that the conditions inside the cell were non-hydrostatic (the freezing pressure of dichloromethane is 1.33 GPa, Podsiadlo et al., 2005). This is not necessarily an undesirable situation for inducing phase transformations for although non-hydrostatic stresses can in some cases suppress a phase transition (Angel et al., 2001), on other occasions uneven compression can also cause structural strain that can ultimate lead to a phase transition (Resel et al., 2004). No transition for naphthalene was observed up to 2.1 GPa. Above this pressure the super-pressed dichloromethane solvent froze and no single-crystal data suitable for analysis could be collected.

### 3.13 Results

Indexing of reflections was performed using the indexing program \textit{CELL\_NOW} (Sheldrick, 2002). Data processing was performed according to procedures described by Dawson et al. (2004) and discussed in Section 2.2.2. Fractional coordinates for the structure determined at 92 K by Brock & Dunitz (1982) (CSD reference code NAPHTA06) were employed for the full-matrix least-squares rigid-group refinement of the structure at each pressure using the program \textit{SHELXL} (Sheldrick, 1997a). Distance restraints were applied for the two bonds.
generated by symmetry about the inversion centre. All non-hydrogen atoms were refined isotropically and hydrogen atoms were placed in calculated positions and allowed to ride on their parent atom.

The lower quality of the data collected at 1.0 and 2.1 GPa was reflected in the broader reflection profiles observed and higher R-factors obtained.

Full refinement details are shown in Table 3.7. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Naphthalene 0.4 GPa</th>
<th>Naphthalene 0.6 GPa</th>
<th>Naphthalene 1.0 GPa</th>
<th>Naphthalene 2.2 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crystal data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C_{10}H_{8}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M_r)</td>
<td>128.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, (P2(1)/a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a, b, c (\text{\AA}))</td>
<td>8.0348 (15), 5.8899 (8), 8.565 (3)</td>
<td>7.9948 (12), 5.8726 (8), 8.542 (2)</td>
<td>7.8523 (11), 5.8106 (9), 8.474 (2)</td>
<td>7.6778 (17), 5.7210 (10), 8.395 (3)</td>
</tr>
<tr>
<td>(\beta (^\circ))</td>
<td>123.59 (2)</td>
<td>123.677 (16)</td>
<td>124.027 (16)</td>
<td>124.55 (2)</td>
</tr>
<tr>
<td>(V (\text{\AA}^3))</td>
<td>337.66 (13)</td>
<td>333.72 (12)</td>
<td>320.42 (11)</td>
<td>303.73 (14)</td>
</tr>
<tr>
<td>(Z)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(D_x (\text{Mg m}^{-3}))</td>
<td>1.261</td>
<td>1.275</td>
<td>1.328</td>
<td>1.401</td>
</tr>
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<td>Radiation type</td>
<td>Mo Ka</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>No. of reflections for cell parameters</td>
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<td>317</td>
<td>262</td>
<td>207</td>
</tr>
<tr>
<td>(\theta) range ((^\circ))</td>
<td>4.5–25.7</td>
<td>4.5–22.9</td>
<td>4.5–26.2</td>
<td>4.6–26.0</td>
</tr>
<tr>
<td>(\mu (\text{mm}^{-1}))</td>
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<td>0.07</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Temperature (K)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Crystal form, colour</td>
<td>Block, colourless</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.25 x 0.20 x 0.15</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.7** Crystal, collection and refinement details for naphthalene at 0.4, 0.6, 1.0 and 2.1 GPa.

Chapter 3 – High-Pressure Studies of Polycyclic Aromatic Hydrocarbons

B. High-Pressure Recrystallisation and Compression Studies of Naphthalene
### Table 3.7 (cont.) Crystal, collection and refinement details for naphthalene at 0.4, 0.6, 1.0 and 2.1 GPa.

<table>
<thead>
<tr>
<th>Absorption correction</th>
<th>Naphthalene 0.4 GPa</th>
<th>Naphthalene 0.6 GPa</th>
<th>Naphthalene 1.0 GPa</th>
<th>Naphthalene 2.2 GPa</th>
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</thead>
<tbody>
<tr>
<td>Empirical + multiscan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{\text{min}}$</td>
<td>0.795</td>
<td>0.551</td>
<td>0.522</td>
<td>0.504</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>No. of measured, independent and observed reflections</td>
<td>1115, 208, 141</td>
<td>1119, 286, 199</td>
<td>1037, 262, 188</td>
<td>803, 264, 153</td>
</tr>
<tr>
<td>Criterion for observed reflections</td>
<td>$I &gt; 2\sigma(I)$</td>
<td>$I &gt; 2\sigma(I)$</td>
<td>$I &gt; 2\sigma(I)$</td>
<td>$I &gt; 2\sigma(I)$</td>
</tr>
<tr>
<td>$R_{\text{int}}$</td>
<td>0.046</td>
<td>0.045</td>
<td>0.082</td>
<td>0.078</td>
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<tr>
<td>$\theta_{\text{max}}$ (°)</td>
<td>25.8</td>
<td>26.0</td>
<td>25.9</td>
<td>26.2</td>
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<tr>
<td>Range of $h, k, l$</td>
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<td>$-9 \rightarrow h \rightarrow 9$</td>
<td>$-9 \rightarrow h \rightarrow 9$</td>
<td>$-9 \rightarrow h \rightarrow 9$</td>
</tr>
<tr>
<td></td>
<td>$-7 \rightarrow k \rightarrow 7$</td>
<td>$-6 \rightarrow k \rightarrow 6$</td>
<td>$-6 \rightarrow k \rightarrow 6$</td>
<td>$-6 \rightarrow k \rightarrow 6$</td>
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<td></td>
<td>$-6 \rightarrow l \rightarrow 6$</td>
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**Refinement**

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<tr>
<th>Refinement on</th>
<th>$F^2$</th>
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</thead>
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<tr>
<td>$R[F^2 &gt; 2\sigma(F^2)]$, $wR(F^2), S$</td>
<td>0.071, 0.181, 1.23</td>
</tr>
<tr>
<td>No. of reflections</td>
<td>208 reflections</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>12</td>
</tr>
<tr>
<td>H-atom treatment</td>
<td>Riding</td>
</tr>
<tr>
<td>Weighting scheme</td>
<td>Calculated $w = 1/\sigma^2(F_o^2) + (0.0688P)^2 + 0.3068P]$</td>
</tr>
</tbody>
</table>

where $P = (F_o^2 + 2F_c^2)/3$

| $(\Delta / \sigma)_{\text{max}}$ | <0.0001 |
| $\Delta \rho_{\text{max}}, \Delta \rho_{\text{min}}$ (e Å⁻³) | 0.11, -0.15 | 0.19, -0.20 | 0.23, -0.23 | 0.34, -0.36 |

### Chapter 3 – High-Pressure Studies of Polycyclic Aromatic Hydrocarbons

#### B. High-Pressure Recrystallisation and Compression Studies of Naphthalene
3.14 Discussion

3.14.1 Compressibility

Table 3.8 summarises the values for the unit-cell parameters of naphthalene at ambient pressure and temperature (Cruickshank, 1957, CSD reference code NAPHTA11), at pressures between 0.01 and 0.51 GPa in the study conducted by Alt & Kalus (1982, CSD reference code for the structure at 0.51 GPa NAPHTA12) and at pressures between 0.4 and 2.1 GPa of the work of this thesis. Overall, the values for lattice parameters obtained in this study are in good agreement with those of Alt & Kalus (1982), as can be seen in the plots of Figures 3.34 and 3.35 that show variation of unit-cell volume, density and cell parameters with pressure. Their structure determined at 0.51 GPa is confirmed to be correct: similar values for the angles between the a, b and c axes and the naphthalene molecule were obtained in the structure at 0.4 GPa reported here. Changes in lattice parameters are fairly linear at lower pressure; deviation from linearity is visible from 1.0 GPa and this could be attributed to the non-hydrostatic conditions present in the high-pressure cell above this pressure, or could be an indication that the structure is reaching the limit of compression.

<table>
<thead>
<tr>
<th>P/GPa</th>
<th>a/Å</th>
<th>b/Å</th>
<th>c/Å</th>
<th>β°</th>
<th>V/Å³</th>
<th>D&lt;sub&gt;f&lt;/sub&gt; g cm⁻³</th>
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</thead>
<tbody>
<tr>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.235(5)</td>
<td>6.003(10)</td>
<td>8.658(10)</td>
<td>122.92(8)</td>
<td>359.3(8)</td>
<td>1.185</td>
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<tr>
<td>0.01&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.245(4)</td>
<td>5.987(4)</td>
<td>8.649(7)</td>
<td>122.50(5)</td>
<td>360.1(5)</td>
<td>1.182</td>
</tr>
<tr>
<td>0.22&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.127(3)</td>
<td>5.932(4)</td>
<td>8.595(5)</td>
<td>123.01(5)</td>
<td>347.5(4)</td>
<td>1.225</td>
</tr>
<tr>
<td>0.42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.042(2)</td>
<td>5.898(4)</td>
<td>8.549(5)</td>
<td>123.36(3)</td>
<td>338.7(3)</td>
<td>1.257</td>
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<tr>
<td>0.51&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>5.884(3)</td>
<td>8.536(4)</td>
<td>123.45(3)</td>
<td>335.7(3)</td>
<td>1.268</td>
</tr>
<tr>
<td>0.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.0348 (15)</td>
<td>5.8899 (8)</td>
<td>8.565 (3)</td>
<td>123.59 (2)</td>
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<td>0.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.9948 (12)</td>
<td>5.8726 (8)</td>
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<td>123.677 (16)</td>
<td>333.72 (12)</td>
<td>1.275</td>
</tr>
<tr>
<td>1.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.8523 (11)</td>
<td>5.8106 (9)</td>
<td>8.474 (2)</td>
<td>124.027 (16)</td>
<td>320.42 (11)</td>
<td>1.328</td>
</tr>
<tr>
<td>2.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.7677 (17)</td>
<td>5.7210 (10)</td>
<td>8.395 (3)</td>
<td>124.55 (2)</td>
<td>303.73 (14)</td>
<td>1.401</td>
</tr>
</tbody>
</table>

<sup>a</sup> Abrahams et al. (1949) and Cruickshank (1957).
<sup>b</sup> Alt & Kalus (1982).
<sup>c</sup> This work.

Table 3.8 Changes in unit-cell parameters of naphthalene with increasing pressure.
Figure 3.34 Change in unit-cell volume and density of naphthalene with applied pressure. The estimated standard deviations are smaller than the plotted symbols.

Figure 3.35 Change in unit-cell parameters of naphthalene with applied pressure. The estimated standard deviations are smaller than the plotted symbols.
With an increase in density of 6.4 % with respect to the ambient-pressure structure, the structure of naphthalene at 0.4 GPa, is slightly more compressible than that of phenanthrene-II at 0.35 GPa, which exhibits a density increase of 5.4 %. The overall 18.2 % increase in density over the pressure range 0.0-2.1 GPa of naphthalene is comparable to the increase in density of anthracene, a tricyclic aromatic molecule, which shows a ca. 20 % density increase over the 0.0-2.45 GPa pressure range (Oehzelt & Resel, 2002).

Compression of the crystallographic axes from ambient pressure to 2.1 GPa are 6.8 %, 4.7 % and 3.0 % for \(a\), \(b\) and \(c\), respectively. The value for the monoclinic \(\beta\) angle increases by 1.3 % over the same pressure range. Rationalisation of changes at a structural level as a function of pressure should be related to the linear strain in the directions of the principal axes of the strain ellipsoid rather than to the compressibilities of lattice parameters. This is because the unit cell is monoclinic and so two of the strain tensor axes do not necessarily lie along the unit-cell axes. Linear strain in the directions of the principal axes of strain ellipsoids vs. pressure was calculated using the program STRAIN (Parsons, 2003) and is shown in Figure 3.36.

![Plot of linear strain in the directions of the principal axes of strain ellipsoids vs. pressure for naphthalene](image)

**Figure 3.36** Plot of linear strain in the directions of the principal axes of strain ellipsoids vs. pressure for naphthalene. Colouring scheme: blue, minimum strain; red, medium strain; green, maximum strain.
The directions of the minimum, medium and maximum compression with respect to the cell axes are shown in Figure 3.37. The same colouring scheme as in Figure 3.36 was used to differentiate between the three directions. The direction of medium compression coincides with the [010] direction in direct space (i.e. the b axis), whereas the directions of minimum and maximum compression lie approximately along the [001] (i.e. the c axis) and the [201] directions, respectively. Figure 3.37 shows that minimum strain occurs for molecules related by translational symmetry along the c axis. Maximum strain is applied to the herringbone motif, which becomes "tighter" with the application of pressure, as will be illustrated by topological analysis in Section 3.14.2.

Figure 3.37 Orientation of the principal directions of the strain tensors in naphthalene at 2.2 GPa viewed along: (a) the minimum (~ [001]), (b) medium ([010]) and (c) maximum (~ [201]) direction of compression. Colouring scheme: blue, minimum strain; red, medium strain; green, maximum strain.
3.14.2 Topological analysis

The effects of pressure on the structure of naphthalene can be monitored by topological analysis using the program TOPOS 4.0 Professional (Blatov et al., 2000).

When reduced to an array of molecular centroids, at ambient temperature and pressure naphthalene (NAPHTA11) is surrounded by six closest neighbours forming a distorted hexagonal planar array around the central molecule: four neighbours are at a distance of 5.095 Å and two are at a longer distance of 6.003 Å. Eight further neighbours lie within a distance of 10.536 Å. The distances between the centroids of the resulting fourteen closest neighbours belonging to the first coordination sphere of one naphthalene molecule at ambient temperature and at 2.1 GPa are listed in Table 3.9. Spatial arrangement of these centroids and packing arrangement of the corresponding molecules are shown in Figures 3.38 and 3.39, respectively.

Distortion from the ideal classical packing geometry of spheres arises from the flat rod-like shape of the naphthalene molecule. The presence of fourteen closest neighbours and the overlap (in projection) of the layers would point towards BCC packing, but qualitatively the arrangement of the twelve nearest neighbours resembles CCP, with the strongest distortion arising from the arrangement of the layers above and below the hexagonal-like array of the six closest contacts.

Molecular centroids can be used to construct molecular and lattice Voronoi-Dirichlet Polyhedra (VDPs), indicative of the local topology of molecular packing, and of the global topology of packing, respectively. Only analysis of lattice VDPs is presented here (see Section 2.3.1). The Reduced Graph of Molecular Lattice (RGML, Peresypkina & Blatov, 2000b) of the corresponding lattice VDP gives the number of neighbours in the first, second and third coordination spheres. This sequence can then be checked against the ones of known packing topologies, and for naphthalene this is 14-50-110, which is based on BCC topology. Taking into account only “strong” contacts, defined by Blatov as contacts that subtend lattice VDP faces with a value for the solid angle > 1.5 % (Peresypkina & Blatov, 2000b), the coordination sequence for the lattice VDP is reduced to 12-42-92 (this ignores contacts 13 and 14), which is based on CCP topology.
<table>
<thead>
<tr>
<th>Molecule</th>
<th>0.0 GPa</th>
<th>2.1 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.095</td>
<td>4.787</td>
</tr>
<tr>
<td>2</td>
<td>5.095</td>
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<tr>
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<tr>
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<td>8.658</td>
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<tr>
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<td>10.159</td>
</tr>
<tr>
<td>14</td>
<td>10.536</td>
<td>10.159</td>
</tr>
</tbody>
</table>

**Table 3.9** Separations of the centroids of a central naphthalene molecule and its fourteen nearest neighbours at ambient pressure and 2.1 GPa.

**Figure 3.38** Arrangement of the molecular centroids in the first coordination sphere in naphthalene. The six closest neighbours (in yellow) form a distorted hexagonal planar array around the central molecule.

**Figure 3.39** (a) Packing arrangement of the six closest neighbouring molecules (in yellow) around a central molecule viewed along the crystallographic c axis; (b) the arrangement viewed along the b axis, with the closest neighbours in yellow and further neighbours in blue.
The distortion from perfect CCP topology is even more evident when comparing visually lattice VDPs for naphthalene and for copper (Figure 3.40). Application of pressure has the effect of “regularising” some VDP faces, making them more equal in size. In contrast to smaller, more spherical-like molecules as glycine (Dawson et al., 2005), L-alanine or formamide (Dawson, 2003), symmetrisation of the lattice VDP of naphthalene is not likely to occur even at higher pressures mainly because of the flat rod-like shape of this rigid molecule.

Figure 3.40 Lattice VDPs for naphthalene at (a) ambient pressure, (b) 2.1 GPa and (c) copper. RGML 12-42-92, indicative of CCP topology.

3.14.3 Correlating structural changes with topological analysis and strain tensors

It is clear from Figures 3.38 and 3.39 that distances 5 and 6 correspond to distances between parallel molecules where C-H groups interact with the periphery of the π-electron cloud and distances 1 to 4 to distances between the stacked columns that give rise to the herringbone motif and where C-H groups interact with the centre of the π-electron cloud around the central molecule.

The distances between the four closest neighbours decrease by ca. 6 % over the pressure range 0.0-2.1 GPa. Trends in compression of strain tensors can now be correlated with changes at the structural level. The distances between the four closest neighbours that are involved in the formation of the herringbone motif have a strong component along the direction of maximum strain and consequently the motif is made “tighter”. The second effect of pressure is to “flatten out” the herringbone...
motif: the dihedral angle between pairs of molecules decreases from 52.49° to 48.17° over the same pressure range (Figure 3.41 and Table 3.10).

Figure 3.41 Geometric parameters of naphthalene molecules involved in the herringbone motif.

<table>
<thead>
<tr>
<th>0.0 GPa</th>
<th>2.1 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance 1/Å</td>
<td>5.095</td>
</tr>
<tr>
<td>Distance 2/Å</td>
<td>3.911</td>
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<tr>
<td>Distance 3/Å</td>
<td>6.423</td>
</tr>
<tr>
<td>Angle 2 ∘</td>
<td>52.49</td>
</tr>
</tbody>
</table>

Table 3.10 Values for the geometric parameters of naphthalene molecules involved in the herringbone motif shown in Figure 3.41.

The distance between centroids of parallel molecules related by translational symmetry along the b axis (contacts 5 and 6 in Table 3.9 and Figure 3.38) represents the offset of the C-H...π- interactions. This distance decreases by 4.7 % (i.e. it corresponds to the compression of the b axis and medium strain tensor) over the 0.0-2.1 GPa pressure range. The distance between parallel planes through these molecules has a strong component along the direction of maximum strain and decreases from 2.66 Å to 2.33 Å over the same pressure range.

Distances involving centroids 9 and 10 in Table 3.9 and Figure 3.38 correspond to the distances between the parallel herringbone motifs related by translational symmetry along the c axis. A decrease of 3.0 % corresponds to the compression of this axis (which is approximately parallel to the direction of minimum strain) over the 0.0-2.1 GPa pressure range. In addition, the distance between the parallel planes is decreased from 1.67 to 1.47 Å, with the effect of bringing H...H contacts closer together (see Section 3.14.4 on Hirshfeld surfaces).

It is not surprising that the overall response of the various intermolecular interactions is to work cooperatively to maximise packing efficiency, increase structural density and minimise voids in the structure, as shown in Figure 3.42.
Figure 3.42 Space filling plots for naphthalene at (a) ambient pressure and (b) 2.1 GPa. Examples of reduction in structural voids are shown in the circled area.

3.14.4 Decoding intermolecular interactions: Hirshfeld surfaces and fingerprint plots

The use of Hirshfeld surfaces and fingerprint plots as a tool for decoding intermolecular interactions was introduced in Section 2.3.2 and was successfully applied for elucidation of the structures of phenanthrene and pyrene in Section 3.9.1. Hirshfeld surfaces and fingerprint plots were created with the program CRYSTAL EXPLORER (Grimwood et al., 2004).

Naphthalene belongs to class of aromatic molecules packing with a herringbone structure (Desiraju & Gavezzotti, 1989a, 1989b), where C-H...π contacts are the dominant interactions. Hirshfeld surfaces for naphthalene at conditions of ambient temperature and pressure (NAPHTA11) are shown in Figures 3.43; these have been recently described by McKinnon et al. (2004). Only one side of the surfaces is shown as the molecule resides on an inversion centre. The authors showed how C-H...π interactions manifest themselves most visibly as a broad red depression on the $d_e$ surface; its position to the right of the centre of the surface is indicative of the offset of this interaction onto the right-hand ring of the molecule.
These interactions give rise to characteristic “wings” on the corresponding fingerprint plot around $d_e = 1.2 \, \text{Å} - d_i = 1.8 \, \text{Å}$ and $d_e = 1.8 \, \text{Å} - d_i = 1.2 \, \text{Å}$.

Figure 3.43 Hirshfeld surfaces and fingerprint plot for naphthalene at ambient pressure and 293 K (CSD reference code NAPHTA11). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

Hirshfeld surfaces and fingerprint plot for naphthalene at 2.1 GPa and 293 K are shown in Figure 3.44.

Figure 3.44 Hirshfeld surfaces and fingerprint plot for naphthalene at 2.1 GPa and 293 K. The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

Comparison of the ambient-pressure and high-pressure structures is made on the basis of fingerprint plots since these summarise the differences most visibly. A series of fingerprint plots ranging from ambient pressure to 2.1 GPa is shown in Figure 3.45. As expected, the plots maintain their overall shape and features, since no drastic structural change, e.g. a change associated with a phase transition, is encountered over this pressure range. The finding that increasing structural density is observed with increasing pressure manifests itself in the progressive shift of the plots.
to lower $d_c$ and $d_i$ values. This shift can be deconvoluted for various interactions in turn: for example, C-H...π interactions become shorter, as indicated by the position of the characteristic “wings” mentioned earlier, and this mirrors the results of the topological analysis of Section 3.14.2. H...H contacts (corresponding to the pointed feature at the bottom left of the plots) also become considerably shorter, from just below 1.2 Å at ambient pressure to just above 1.0 Å at 2.2 GPa. The splitting of the H...H fingerprint has been ascribed to a three-atom short contact (McKinnon et al., 2004). The upper part of the plots, where data points are scarce and $d_c$ is larger than $d_i$, is representative of voids in the structure: these voids also follow the general trend of contraction, as it was shown in Figure 3.42. The reduction in voids is also visible on comparison of the $d_c$ surfaces at ambient pressure and 2.1 GPa: blue regions on the upper part of the plots, indicative of areas of non-contact between adjacent surfaces, are less extended at 2.1 GPa. On closer analysis of interactions between neighbouring surfaces, these voids are revealed to arise principally from interaction between the closest neighbouring molecules involved in the formation of the herringbone motif, thus confirming the results of the topological analysis conducted in Section 3.14.2.

![Fingerprint plots for naphthalene at different pressures](image)

**Figure 3.45** Fingerprint plots for naphthalene at (a) ambient pressure, (b) 0.4 GPa, (c) 0.6 GPa, (d) 1.1 GPa and (e) 2.1 GPa.
3.15 Conclusions

Naphthalene form I has been recrystallised from dichloromethane at 0.4 and 0.6 GPa and. Owing to the limitations of the heating methods employed in this study, it has not been possible to grow a single crystal at higher pressures. No phase transition has been observed on application of pressure to the single crystal initially grown at 0.6 GPa, up to a maximum pressure of 2.1 GPa. Crystallisation of the solvent at 2.1 GPa prevented collection of X-ray diffraction data at higher pressures.

Structural analysis has been found to correlate changes in compression of cell dimensions and strain tensors with changes at a structural level. Through topological analysis and construction of Hirshfeld surfaces it is concluded that the main effect of the externally applied pressure is to minimise voids in the structure, in particular those between molecules forming the herringbone motif.

Some volumetric and spectroscopic pressure studies on both single crystals and polycrystalline samples suggested that a transition takes place between 2.0 and 4.0 GPa, while others failed to detect it. The effects of non-hydrostatic conditions and choice of pressure transmitting medium might have an influence on the reliability of these results, especially in the case of spectroscopic data, which is often prone to over-interpretation. Our high-pressure structural studies to 2.1 GPa have not identified a new modification of naphthalene, which remains for the moment one of the few extensively studied systems at conditions of ambient pressure for which no other polymorphs have been found.

Further structural investigations in the search for a high-pressure phase transition in naphthalene are envisaged to encompass direct compression of a single crystal using a higher working-pressure hydrostatic medium (e.g. methanol/ethanol), direct compression of a polycrystalline sample and high-pressure recrystallisation from solution coupled with laser heating or resistive heating. The latter is more likely to afford a new polymorph, if one indeed exists, at much lower pressures than compression experiments would give. As an illustrative example, which will be discussed in more detail in Chapter 5, it is here recalled that orthorhombic paracetamol can be recrystallised from ethanol at 1.0 GPa, whilst compression of a powder sample of monoclinic paracetamol only affords incomplete conversion to the orthorhombic form at much higher pressures of 4.0 GPa (Boldyreva et al., 2002).
3.16 References

Chapter 3 – High-Pressure Studies of Polycyclic Aromatic Hydrocarbons

B. High-Pressure Recrystallisation and Compression Studies of Naphthalene


Sheldrick, G. M. (2002). *CELL_NOW*: a program for indexing diffraction patterns from multiple or twinned crystals. University of Göttingen, Germany.


Chapter 3 – High-Pressure Studies of Polycyclic Aromatic Hydrocarbons

B. High-Pressure Recrystallisation and Compression Studies of Naphthalene
Chapter 4

Polymorphism of Acetamide at High Pressure
4.1 Introduction

Acetamide, CH$_3$CONH$_2$, is the second member of the homologous series of amides of the type RCONH$_2$ containing the biologically important amide linkage. Solid acetamide exists in two crystal forms under ambient conditions. The structure of the most stable modification, form I, was first determined by Senti & Harker (1940). The structure is rhombohedral, space group $R3c$; crystals of this modification are obtained by crystallisation from solutions of organic solvents and have a melting point of ca. 353 K. The structure of form I has been determined at 23 K by single-crystal X-ray (Zobel et al., 1992) and neutron diffraction (Jeffrey et al., 1980). A metastable orthorhombic form, form II, was first reported by Senti & Harker (1940) and its structure was later determined by Hamilton (1965). This orthorhombic phase, space group $Pccn$, is typically obtained by crystallisation of molten acetamide and has a lower melting point of ca. 346 K (Watanabe et al., 1986). A recent publication reports the facile recrystallisation of the orthorhombic form from a mixture of ethyl acetate and aqueous ammonia solution (Bats et al., 2003). The molecular structure of the compound is shown in Figure 4.1. The description of the crystal structure of the two forms given in Section 4.4.1.

![Molecular structure of acetamide with numbering scheme.](image)

Figure 4.1 Molecular structure of acetamide with numbering scheme.

The high-pressure phase equilibria of acetamide have been studied by Bridgman using volumetric measurements as a function of pressure (Bridgman, 1916, 1938). Bridgman found the existence of four modifications, but these have not been structurally characterised. In accordance with his numbering scheme, the I-II transition occurred at 0.59 GPa and 293 K; the II-III transition was observed at 1.8 GPa/323 K, at 1.95 GPa/423 K and at 2.3 GPa/473 K, whilst the III-IV transition occurred at 2.22 GPa/323 K and at 2.46 GPa/473 K. The I-II phase transition is associated with $\Delta V = 1.7$ cm$^{-3}$ mol$^{-1}$, the II-III transition with $\Delta V = 1.0$ cm$^{-3}$ mol$^{-1}$ and
the III-IV transition with $\Delta V = 1.47 \text{ cm}^{-3} \text{ mol}^{-1}$. The phase diagram determined by Bridgman is shown in Figure 4.2.

![Phase diagram of acetamide determined by Bridgman.](image)

**Figure 4.2** Phase diagram of acetamide determined by Bridgman.

To avoid confusion, the numbering scheme for the polymorphs presented in this chapter follows the one denoted in the literature based on the available crystal structures (according to which form I is rhombohedral acetamide and form II is the orthorhombic modification) and reference to the numbering scheme used by Bridgman is explicitly made where appropriate.

Recrystallisation of acetamide in the presence of HCl affords acetamide hemihydrochloride (Speakman et al., 1981); a hemihydrobromide is obtained from HBr (Groth, 1977). Acetamide is soluble in a wide range of solvents and is therefore an ideal candidate for the technique of high-pressure recrystallisation from solution. In addition, the presence of four modifications suggested by Bridgman, only one of which has been structurally characterised, prompted an exploration and clarification of the polymorphic behaviour of this compound.
4.2 Experimental Procedure

4.2.1 High-pressure recrystallisation from water at 0.8 GPa: a new monoclinic polymorph of acetamide characterised by X-ray diffraction

Acetamide (BDH reagents) was purified by recrystallisation from deionised water under ambient conditions to give the rhombohedral form (checked by single-crystal X-ray diffraction). An equimolar solution of acetamide and water was loaded at 293 K into a Merrill-Bassett diamond-anvil cell (Merrill & Bassett, 1974) equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole. On sealing the cell and pressurising to ca. 0.8 GPa precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 333 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution, which filled almost 50% of the gasket hole (Figure 4.3). The pressure within the gasket hole was determined as ca. 0.8 GPa.

During experimental work, it was noted that the crystal was relatively short lived and redissolved fairly rapidly. At present, it is not known whether this was due to the effects of stability, temperature, or solubility or a combination of all three. The crystal instability precluded collection of good quality high-pressure X-ray diffraction data and merging of two datasets collected on two different crystals was required for structure solution. The second crystal was grown at ca. 0.8 GPa in a similar manner to that described above.

Figure 4.3 Optical image of a single crystal of acetamide recrystallised from water at 0.8 GPa in a diamond-anvil cell.
Indexing of the reflections obtained from these single-crystal X-ray diffraction experiments gave a monoclinic unit cell with dimensions substantially different from either of the two known polymorphs of acetamide. Initial estimation of the unit-cell volume suggested the presence of a new polymorph. Structure solution using global optimisation methods with subsequent full-matrix least-squares structure refinement identified the crystal as a new polymorph of acetamide.

Single-crystal X-ray diffraction data were collected at 293(2) K according to the procedures described by Dawson et al. (2004) summarised in Section 2.2.

4.2.2 High-pressure powder neutron diffraction study on acetamide-d$_5$

Loading 1

A mixed phase of rhombohedral acetamide-d$_5$ (Aldrich) (ca. 100 mg) was lightly ground with NaCl as a pressure standard (ca. 30% by volume, judged by eye) and was then loaded into an encapsulated TiZr gasket (Figure 4.4) (Marshall & Francis, 2002) together with a small quantity of isopropyl alcohol-d$_8$ as a pressure-transmitting fluid. The gasket was then loaded into a Paris-Edinburgh cell (Figure 4.5) (Besson et al., 1992; Nelmes et al., 1993) at the ISIS Neutron Facility, Rutherford Appleton Laboratory, UK. Time-of-flight neutron powder diffraction patterns were then recorded at incremental pressure steps between 0.03 GPa and 5.62 GPa using the $2\theta = 90^\circ$ detectors of the PEARL diffractometer with a ‘transverse’ (through-anvil) scattering geometry.

Loading 2

A 2:1 mix (by volume) of isopropyl alcohol-d$_8$: methanol-d$_4$ was used as a pressure-transmitting medium and neutron diffraction data were collected between 0.22 GPa and 4.64 GPa.

Sample pressures for the mixed-phase loading were determined from the refined value for the NaCl lattice parameter by reference to the room-temperature equation-of-state for NaCl (Decker, 1971).
Figure 4.4 Diagrammatic procedure for the sample loading into a Paris-Edinburgh cell. (a) sample preparation and loading into an encapsulated TiZr gasket; (b) top view of an open cell loaded with gasket; (c) side view of the sealed cell; (d) PEARL support scientist Mr. Duncan Francis supervises the lowering of the Paris-Edinburgh cell into the PEARL aluminium tank. The assembly is subsequently loaded into the PEARL diffractometer (not shown here).
4.3 Results

4.3.1 High-pressure recrystallisation from water at 0.8 GPa: a new monoclinic polymorph characterised by X-ray diffraction

Data processing was performed according to the procedures described by Dawson et al. (2004) and detailed in Section 2.2. Both datasets were treated separately up to the absorption correction step. The two unmerged reflection files were then scaled and merged in SORTAV (Blessing, 1995) applying a 2θ cut-off of 42.5° in the manner described by Dawson et al. (2004). Unit-cell dimensions and systematic absences indicated the presence of a monoclinic crystal in space group $P2_1/n$ with two molecules in the asymmetric unit.

Solution and refinement of the structure was not straightforward using direct methods owing to the limited amount of data be collected using the diamond-anvil cell. Hence the incomplete data set was input into the global optimisation program, FOX (Favre-Nicolin & Černý, 2002). This program rapidly identified a global minimum by simulated annealing thereby allowing subsequent refinement of the new polymorph in $P2_1/n$, here denoted as form III.

Full-matrix least-squares structure refinement was then performed using CRYSTALS (Betteridge et al., 2003). All non-hydrogen atoms were refined isotropically subject to rigid-bond restraints, distance and angle restraints. Hydrogen atoms were placed in calculated positions and not refined. Whilst not ideal, the $R$-factor of 8.8 % is typical for refinement of high-pressure data sets and is sufficient to identify the main structural features of the new polymorph.

Full refinement details are shown in Table 4.1. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

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<th>Crystal data</th>
<th>Form III at 0.8 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
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</tr>
<tr>
<td>$M_r$</td>
<td>59.07</td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, $P2_1/n$</td>
</tr>
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<td>$a$, $b$, $c$ (Å)</td>
<td>5.036 (2), 18.211 (7), 6.9456 (16)</td>
</tr>
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</table>

*Table 4.1* Crystal, collection and refinement details for form III at 0.8 GPa.
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<th>Value</th>
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**Data collection**

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<td>Bruker SMART APEX CCD'</td>
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<td>No. of measured, independent and observed reflections</td>
<td>2160, 314, 172</td>
</tr>
<tr>
<td>Criterion for observed reflections</td>
<td>$I &gt; 2\sigma(I)$</td>
</tr>
<tr>
<td>$R_{\text{int}}$</td>
<td>0.20</td>
</tr>
<tr>
<td>$\theta_{\text{max}}$ (°)</td>
<td>19.9</td>
</tr>
<tr>
<td>Range of $h$, $k$, $l$</td>
<td>$-6 \rightarrow h \rightarrow 4$</td>
</tr>
<tr>
<td></td>
<td>$-9 \rightarrow k \rightarrow 9$</td>
</tr>
<tr>
<td></td>
<td>$-6 \rightarrow l \rightarrow 6$</td>
</tr>
</tbody>
</table>

**Refinement**

<table>
<thead>
<tr>
<th>Details</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refinement on</td>
<td>$F^2$</td>
</tr>
<tr>
<td>$R[F^2 &gt; 2\sigma(F^2)]$, $wR(F^2)$, $S$</td>
<td>0.088, 0.209, 0.99</td>
</tr>
<tr>
<td>No. of reflections</td>
<td>303 reflections</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>33</td>
</tr>
<tr>
<td>H-atom treatment</td>
<td>Not refined</td>
</tr>
<tr>
<td>Weighting scheme</td>
<td>$W = 1 / [\Sigma a^2(F^2) + (P(1)p^2)]$, where $P(i)$ are: 0.492E-01 3.88 and $P = (F_r^2 + 2F_i^2)/3$</td>
</tr>
<tr>
<td>$(\Delta\sigma/\sigma)_{\text{max}}$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å$^{-3}$)</td>
<td>0.28, -0.31</td>
</tr>
</tbody>
</table>

**Table 4.1 (cont.)** Crystal, collection and refinement details for form III at 0.8 GPa.
4.3.2 **High-pressure powder neutron diffraction study on acetamide-d$_5$**

The refined diffraction patterns were obtained after focusing the individual detector element spectra to a common time-of-flight scale, normalisation of the summed data with respect to the incident beam monitor and the scattering from a standard vanadium sample, and then correcting the normalised pattern for the nominal wavelength and scattering angle dependence of the neutron attenuation by the anvil (WC) and gasket (TiZr) materials.

Data analysis was performed by the Rietveld method using the GSAS suite of programs (Larson & Von Dreele, 1987). *All structural refinements were carried out at the ISIS Facility by Dr. Bill Marshall.* All atoms were refined with isotropic displacement parameters and 1,2 distances were restrained to the values observed in the structure of rhombohedral acetamide refined using single-crystal neutron diffraction data at 23 K. (Zobel *et al.*, 1992, CSD reference code ACEMID05). Bond angle restraints for the methyl group and planar group restraints for the C, N and O atoms were employed in the refinements.

**Loading 1 with isopropyl alcohol-d$_8$ as the pressure-transmitting medium**

No phase transition was observed up to pressures of 4.99 GPa. Peak broadening associated with the freezing of the pressure-transmitting medium was observed from 4.72 GPa; the refinement of the data collected at 4.99 GPa did not give a satisfactory model and hence is not presented here. Further data were collected at 5.19 GPa and 5.62 GPa: these were not refined due to significant broadening, as illustrated in Figure 4.5. On depressurisation a clean pattern of the rhombohedral phase was obtained at 3.6 GPa. No further phase transitions were observed on depressurising to ambient pressure. Crystallographic details are shown in Table 4.2. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.
Figure 4.5 Powder patterns of rhombohedral acetamide-$d_5$ as a function of pressure.
<table>
<thead>
<tr>
<th>Pressure (GPa)</th>
<th>0.03</th>
<th>0.45</th>
<th>0.77</th>
<th>1.06</th>
<th>1.25</th>
<th>1.60</th>
<th>1.90</th>
<th>2.24</th>
<th>2.58</th>
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<tr>
<td>Chemical formula</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C\textsubscript{3}D\textsubscript{3}NO</td>
</tr>
<tr>
<td>( M_r )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64.08</td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Rhombohedral, ( R\bar{3}c )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( a (\text{\AA}) )</td>
<td>11.510(13)</td>
<td>11.4400(10)</td>
<td>11.3928(11)</td>
<td>11.3615(12)</td>
<td>11.3374(16)</td>
<td>11.2995(8)</td>
<td>11.2693(9)</td>
<td>11.2382(8)</td>
<td>11.2091(9)</td>
</tr>
<tr>
<td>( c (\text{\AA}) )</td>
<td>13.531(2)</td>
<td>13.0164(14)</td>
<td>12.7457(16)</td>
<td>12.5357(15)</td>
<td>12.428(2)</td>
<td>12.2394(10)</td>
<td>12.1008(11)</td>
<td>11.9683(10)</td>
<td>11.8461(13)</td>
</tr>
<tr>
<td>( V (\text{\AA}^3) )</td>
<td>1552.4(3)</td>
<td>1475.3(2)</td>
<td>1432.7(3)</td>
<td>1401.4(3)</td>
<td>1383.5(4)</td>
<td>1353.35(17)</td>
<td>1330.88(19)</td>
<td>1309.05(17)</td>
<td>1289.0(2)</td>
</tr>
<tr>
<td>( Z )</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( D_s (\text{Mg m}^{-3}) )</td>
<td>1.234</td>
<td>1.298</td>
<td>1.337</td>
<td>1.367</td>
<td>1.384</td>
<td>1.415</td>
<td>1.439</td>
<td>1.463</td>
<td>1.486</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( R_{wp} )</td>
<td>0.0505</td>
<td>0.0458</td>
<td>0.0512</td>
<td>0.0519</td>
<td>0.0730</td>
<td>0.0335</td>
<td>0.0393</td>
<td>0.0336</td>
<td>0.0393</td>
</tr>
<tr>
<td>Parameters</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Restraints</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.2** Crystallographic details for powder neutron diffraction of rhombohedral acetamide-\( d_5 \).
<table>
<thead>
<tr>
<th>Pressure (GPa)</th>
<th>2.94</th>
<th>3.25</th>
<th>3.50</th>
<th>3.78</th>
<th>4.11</th>
<th>4.38</th>
<th>4.72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>( \text{C}_2\text{D}_5\text{NO} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( M_r )</td>
<td>64.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Rhombohedral, ( R3c )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( c ) (Å)</td>
<td>11.7309(11)</td>
<td>11.6455(14)</td>
<td>11.5735(13)</td>
<td>11.5022(14)</td>
<td>11.4335(13)</td>
<td>11.3784(19)</td>
<td>11.3149(17)</td>
</tr>
<tr>
<td>( V ) (Å³)</td>
<td>1269.94(19)</td>
<td>1255.5(2)</td>
<td>1243.1(2)</td>
<td>1230.3(2)</td>
<td>1215.9(2)</td>
<td>1203.3(3)</td>
<td>1188.5(3)</td>
</tr>
<tr>
<td>( Z )</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( D_\text{r} ) (Mg m(^{-3}))</td>
<td>1.508</td>
<td>1.526</td>
<td>1.541</td>
<td>1.557</td>
<td>1.575</td>
<td>1.592</td>
<td>1.612</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( R_{\text{wp}} )</td>
<td>0.0327</td>
<td>0.0380</td>
<td>0.0382</td>
<td>0.0382</td>
<td>0.0295</td>
<td>0.0378</td>
<td>0.0270</td>
</tr>
</tbody>
</table>

| Parameters | 65 |
| Restraints | 15 |

**Table 4.2** (cont.) Crystallographic details for powder neutron diffraction of rhombohedral acetamide-\( d_5 \).
Loading 2 with isopropyl alcohol-d₆: methanol-d₄ mix (2:1) as the pressure-transmitting medium

The rhombohedral to monoclinic phase transition was observed at 1.04 GPa. On increasing the pressure to 1.56 GPa new peaks were observed to grow in the diffraction pattern (Figure 4.6). Data were collected up to 4.64 GPa, at which point significant broadening prevented further data collection. The patterns of the new phase could not be indexed. However, it seemed that the structure of the new phase is closely related to the monoclinic structure. Indexing efforts were badly hampered by the presence of the NaCl peaks and it is therefore envisaged that further experiments without a pressure marker could circumvent this problem.

Figure 4.6 Powder patterns of monoclinic acetamide-d₅ (at 1.04 GPa) and evidence of a phase transition at higher pressures.

On depressurisation, the monoclinic to rhombohedral transition was observed at 0.82 GPa. This is somewhat less than that observed for the transition (1.04 GPa)
on increasing pressure, and can be attributed to hysteresis. On depressurisation to ambient pressure the rhombohedral modification, form I, was recovered. Crystallographic details for the monoclinic structure at 1.04 GPa are shown in Table 4.3. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

<table>
<thead>
<tr>
<th>Monoclinic acetamide-(d_5) at 1.04 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
</tr>
<tr>
<td>(M_r)</td>
</tr>
<tr>
<td>Cell setting, space group</td>
</tr>
<tr>
<td>(a, b, c) (Å)</td>
</tr>
<tr>
<td>(\beta) (^\circ)</td>
</tr>
<tr>
<td>(V) (Å(^3))</td>
</tr>
<tr>
<td>(Z)</td>
</tr>
<tr>
<td>(D_\text{s}) (Mg m(^{-3}))</td>
</tr>
<tr>
<td>Temperature (K)</td>
</tr>
<tr>
<td>(R_{wp})</td>
</tr>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>Restraints</td>
</tr>
</tbody>
</table>

**Table 4.3** Crystallographic details for powder neutron diffraction of monoclinic acetamide-\(d_5\) at 1.04 GPa
4.4 Discussion

4.4.1 High-pressure recrystallisation from water at 0.8 GPa: a new monoclinic polymorph of acetamide characterised by X-ray diffraction

Unit-cell parameters for the polymorphs of acetamide characterised by single-crystal X-ray diffraction are summarised in Table 4.4.

<table>
<thead>
<tr>
<th>Form I</th>
<th>Form II</th>
<th>Form III</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSD reference code</td>
<td>ACEMID05</td>
<td>ACEMID06</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Rhombohedral</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>R3c</td>
<td>Pccn</td>
</tr>
<tr>
<td>a/Å</td>
<td>11.492(2)</td>
<td>19.021(4)</td>
</tr>
<tr>
<td>b/Å</td>
<td>11.492(2)</td>
<td>7.5084(14)</td>
</tr>
<tr>
<td>c/Å</td>
<td>12.892(2)</td>
<td>9.4038(16)</td>
</tr>
<tr>
<td>β°</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>V/Å³</td>
<td>1474.5(12)</td>
<td>1343.0(4)</td>
</tr>
<tr>
<td>Z</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>D₀/g cm⁻³</td>
<td>1.197</td>
<td>1.169</td>
</tr>
<tr>
<td>T/K</td>
<td>23(2)</td>
<td>146(2)</td>
</tr>
</tbody>
</table>

* Zobel et al., 1992. b Bats et al., 2003. c This work.

| Table 4.4 Crystallographic data for polymorphs of acetamide. |

The structure of form I is dominated by a three-dimensional hydrogen-bonded network, where every molecule in the crystal is connected to every other one through a continuous series of hydrogen bonds. Every molecule accepts and donates two hydrogen bonds. Adjacent molecules are arranged in rings of six, the ring being held together by N-H…O hydrogen bonds and forming pseudo hexagons in the ab-plane, where alternating molecules are related by 3-fold rotation axes (Figure 4.7a).
The structure of form II is also dominated by hydrogen bonding. In contrast to form I, the structure of form II is characterised by hydrogen-bonded “dimers”. Each molecule is hydrogen bonded to two of its neighbours in chains parallel to the $c$ axis: this results in a four-stringed column (where hydrophilic regions are found), which runs through the lattice in the $c$ direction, creating essentially a one-dimensional hydrogen-bonding motif (Figure 4.7b). This is a striking difference with respect to the hydrogen bonding in the rhombohedral modification, which is best described as a three-dimensional network and perhaps accounts for the enhanced stability of this form.

![Figure 4.7](image)

**Figure 4.7** Hydrogen-bonding motifs in (a) form I viewed along the $c$ axis (some layers have been omitted for clarity) and (b) form II viewed along the $c$ axis.

The hydrogen bonding in acetamide is best described with the aid of graph-set analysis. Graph-set analysis is a very useful tool to reduce complicated networks to combinations of simple patterns (Etter, 1990; Bernstein *et al.*, 1995). The descriptions of the hydrogen-bond pattern according to graph-set notation at a first-level graph set are $N_1 = C(4)C(4)$ and $N_1 = C(4)C(4)DD$ for forms I and II, respectively. There are two $C(4)$ and $D$ motifs in form II since there are two molecules in the asymmetric unit. The hydrogen bonds in form I arranged around the three-fold axis give rise to a $R_6^3(12)$ ring at the second-level graph set; the basic second-level graph set for form II is obtained by combining the two $D$ motifs,
leading to $R_2^2(8)$. Graph-set motifs for the two modifications are illustrated in Figure 4.8.

![Graph-set motifs for the two modifications](image)

**Figure 4.8** Graph set analysis for (a) form I and (b) form II (here molecules are coloured according to symmetry equivalence). Methyl hydrogen atoms have been omitted for clarity.

The new high-pressure monoclinic phase, here denoted as form III, has a calculated density of 1.274 g cm$^{-3}$, which represents an increase in density of 6.4% compared with the rhombohedral phase at ambient pressure and 23 K (CSD reference code ACEMID05) and 11.8% at 293 K (Zobel *et al.*, 1992). This initially suggested that the new high-pressure phase is Bridgman's phase II. This is corroborated by the results of powder neutron diffraction studies, as discussed in Section 4.4.2.

Not surprisingly, the crystal structure of form III is also dominated by hydrogen bonding. This polymorph is another example of structure with $Z' = 2$, but in contrast to the orthorhombic form the two independent molecules are not hydrogen-bonded to each other to form a dimer. Let us name these two independent molecules A and B. Molecules A (coloured in blue in Figure 4.9) are involved in the formation of centrosymmetric dimers perpendicular to the (101) planes, whilst molecules B (coloured in green in Figure 4.8) are connected via C(4) chains that run parallel to (101) planes. Dimers stack along the $a$ axis and are linked by the $C(4)$
chains. These chains also link dimers along the $b$ and $c$ axes to give rise to a three-dimensional hydrogen-bonded motif that exhibits large hydrophobic regions (c.f. hydrophilic regions observed in form II and depicted in Figure 4.7b).

Figure 4.9 Hydrogen-bond motifs of form III at 0.8 GPa (a) viewed along the $a$ axis and (b) viewed along the $b$ axis. Molecules are coloured according to symmetry equivalence, as described in the main text. Methyl hydrogen atoms have been omitted for clarity.

First-level graph-set analysis for form III gives $N_1 = C(4)DDR_2^2(8)$. This is shown in Figure 4.10. Combination of D motifs gives rise to $R_2^2(16)$ at the second level graph set.

Figure 4.10 Graph-set analysis for form III at 0.8 GPa. The molecular arrangement is viewed perpendicular to the $ab$ plane.
4.4.2 High-pressure powder neutron diffraction study on acetamide-d$_5$

**Loading 1 with isopropyl alcohol-d$_8$ as the pressure-transmitting medium**

The plots of unit-cell parameters for rhombohedral acetamide vs. pressure are given in Figure 4.111.

**Figure 4.11** Plot of (a) unit-cell volume and (b) lattice parameters vs. pressure for rhombohedral acetamide. The solid curves for the volume and for the lattice parameters $a$ and $c$ represent a fit to a third-order polynomial. The estimated standard deviations on $a$, $c$ and $V$ are smaller than the plotted symbols.

The $c$ axis decreases by 16.2 % and the $a$ and $b$ axes by 4.3 % over the 0.03-4.72 GPa pressure range. The unit-cell volume decreases by 23.4 % over the same pressure range. This is a very significant reduction in volume and represents to our knowledge a most remarkable example of an exceedingly compressible hydrogen-bonded, small, organic molecular system. For comparison, the unit-cell volume of (non-deuterated) $\alpha$-glycine decreases by 16.1 % over the pressure range ambient- to 6.2 GPa (Dawson et al., 2005), (non-deuterated) L-serine form I reduces by 10.6 % over the 0.3-4.8 GPa pressure range (Moggach, et al., 2005) and L-$\alpha$-aspartic acid reduces by ca. 19 % over the 0.0-5.8 GPa pressure range (Lozano-Casal, 2005). The unit-cell volume of deuterated acetamide at 0.03 GPa and ambient temperature is 1552.4(3) Å$^3$, whilst the volume of non-deuterated acetamide at conditions of ambient pressure and temperature is 1549.7(4) Å$^3$ (Zobel et al., 1992). This close similarity indicates that the effect of deuteration on the unit-cell volume at ambient
pressure and temperature is negligible, although the same is not necessarily true under high-pressure conditions.

Changes in unit-cell parameters with pressure provide important information on structural changes. As hydrostatic pressure is applied to a crystal, a spherical volume element of the original crystal will, in general, deform to an ellipsoid (Hazen et al., 2000). Symmetry constraints govern the shape of this ellipsoid for every crystal system. In cubic crystals, the ellipsoid must have a spherical shape. In uniaxial crystals (trigonal, hexagonal and tetragonal) this strain ellipsoid must also be uniaxial and be aligned with the unique crystallographic axis. The strain ellipsoid’s maximum and minimum directions of compression are parallel to the crystallographic axes and can be calculated directly from the unit-cell parameters. The direction of maximum strain corresponds to the \( c \) direction in the case of rhombohedral acetamide.

The effect of pressure is to reduce the available space in the unit cell through minimisation of voids and cooperative rotation of methyl groups, as discussed in the following paragraphs. It is here recalled that the \( c \) axis is the direction perpendicular to the hydrogen-bonded hexagons discussed in Section 4.4.1. Figure 4.12 illustrates the closing up of voids on going from 0.03 GPa to 4.72 GPa.

![Figure 4.12](image)

**Figure 4.12** Space-filling plots of rhombohedral-\( d_5 \) acetamide at (a) 0.03 GPa and (b) 4.72 GPa. The plots are drawn to the same scale.

One important application of neutron diffraction is the accurate location of hydrogen atoms. In the 23 K single-crystal neutron diffraction experiment conducted by Jeffrey et al. (1980), it was shown that the orientation of the methyl group is such...
that one C-H bond is normal to the plane of the non-hydrogen atoms (the torsion angle is 92.4°). The authors also performed ab initio MO calculations that showed that the lowest energy conformation for the isolated molecule is different from that observed in the crystal, namely with one C-H bond eclipsed to the carbonyl bond. The conformation in the crystal structure was calculated to be 1.7 kJ mol⁻¹ higher in energy. In addition, the authors observed experimentally that the amide group is slightly pyramidal and that H(1) is significantly out of the N-C=O plane [O C(2) N H(1) torsion angle = -8.2°]. The structure obtained by neutron powder refinement of acetamide-d₅ at 0.03 GPa shows that one C-D bond is nearly eclipsed with the C(1)-N bond [D(4)-C(1)-C(2)-N torsion angle = 12(2)°] and that D(1) and D(2) lie significantly out of the N-C=O plane [O-C(2)-N-D(1) torsion angle = -8(5)°; O-C(2)-N-D(2) torsion angle = 25(5)°]. This may be attributed to the effect of deuteration and of data collection at room temperature; the relatively large standard uncertainty associated with positional parameters of deuterium atoms, mainly due to their large thermal vibration, should also be taken into consideration when performing structural analysis.

Figure 4.13 shows the sequence of conformational changes for rhombohedral acetamide as a function of pressure.

![Figure 4.13](image)

**Figure 4.13** Molecular conformations in rhombohedral acetamide-d₅ as a function of pressure.
Figure 4.14 Variation of D(4)-C(1)-C(2)-N torsion angle in rhombohedral acetamide-d₅ as a function of pressure. All standard uncertainties were estimated with PLATON (Spek, 2005).

Figure 4.15 Variation of hydrogen-bond lengths and angles in rhombohedral acetamide-d₅ as a function of pressure. (a) and (b) parameters involving D(1); (c) and (d) parameters involving D(2). All standard uncertainties were estimated with PLATON (Spek, 2005).

Symmetry codes: O': 1/3-x+y,-1/3+y,1/6+z; O'': 1/3+x,-1/3+x-y,1/6+z.
The reorientation of amide and methyl deuterium atoms as pressure is increased is depicted in Figure 4.13. This reorientation is depicted quantitatively in Figures 4.14 and 4.15 as a function of pressure. Figure 4.14 illustrates the variation of the D(4)-C(1)-C(2)-N torsion angle, whilst Figure 4.15 illustrates the change in hydrogen-bonded distances and angles involving D(1) and D(2).

Let us first consider the change in the D(4)-C(1)-C(2)-N torsion angle. Interestingly, methyl deuterium atoms rotate overall by ca. 43° over the 0.03-4.72 GPa pressure range, and whilst at 0.03 GPa the C(1)-D(4) bond is almost eclipsed with the C(2)-N bond [D(4)-C(1)-C(2)-N torsion angle = 12(2)°], at 4.72 GPa the same bond has changed its orientation considerably [D(4)-C(1)-C(2)-N torsion angle = 55.6(17)] and C(1)-D(5) is now eclipsed with the C(2)-O bond. The large variation of this torsion angle is perhaps not surprising on accounting for the low energy barrier to rotation about the C(1)-C(2) bond, as explained by Jeffrey et al. (1980) and Hagler et al. (1976). As illustrated in Figure 4.14, the change in the D(4)-C(1)-C(2)-N torsion angle is not smooth and monotonic: the standard uncertainties on this angle are sufficiently small that there does appear to be a real cyclic variation. As far as the available literature is concerned, this type of trend has never been observed before. The driving force for this change must be the reduction of void spaces, which is dependent on several intermolecular (and intramolecular) interactions. Unlike the case of an isolated molecule containing a methyl group with local $C_3$ symmetry, where a smooth variation in energy would be observed, a smooth variation is not necessarily to be expected for the methyl group in acetamide, since in the solid state the symmetry will be broken. In addition, a series of C-D...N and C-D...O interactions are formed in the rhombohedral modification from pressures above 1.06 GPa: these contribute to the stabilisation of the denser structures and these are likely to influence the behaviour of the CD$_3$ group.

Trends in hydrogen-bond distances and angles are depicted in Figure 4.15. Overall, despite the large standard uncertainty associated with the hydrogen-bonding parameters, both D(1)...O' and D(2)...O'' hydrogen-bond lengths decrease. D(1)...O' compresses the most over the 0.03-4.72 GPa pressure range (by ca. 8.5 %), whilst D(2)...O'' experiences a larger variation in length at lower pressures, but overall compresses to a lesser extent over the same pressure range (by ca. 3 %). Cyclical
variations can also be noticed in the trends of the two hydrogen-bond lengths. Furthermore, the variations appear to be out of phase: this is perhaps not surprising since the same oxygen atom is involved in the hydrogen bonding. These variations are also indicative of a cooperative change in hydrogen bonds for the preservation of the hydrogen-bonded pattern as pressure is applied to the system. A cyclical trend is also apparent in the hydrogen-bond angles. N-D(2)...O acquires a more linear character over the 0.03-4.72 GPa pressure range (from 139° to 162°), whilst N-D(1)...O also fluctuates substantially, but values for 0.03 GPa and 4.72 GPa are very similar. Overall, it can be concluded that both hydrogen bonds become stronger as pressure is increased. The “cyclic” trends observed in hydrogen-bond parameters correlate very well with the change in the rotation of the methyl group, as illustrated by comparison of Figures 4.14 and 4.15. This strongly suggests that the reorientation of the methyl group and of hydrogen bonding occurs via a concerted process that minimises steric repulsion forces, whilst ensuring that the voids in the crystal structure are reduced as pressure is applied.

It was noted earlier that the direction of maximum compression of form I is along the c axis. Both hydrogen bonds do not lie along this axis, although they have a component along it. As pressure is applied to the system, maximum compression occurs in the direction that is more normal to them, reducing the size of the voids and flattening the three-dimensional hydrogen-bond motif, as illustrated in Figure 4.16.

**Figure 4.16** Hydrogen-bond motif of rhombohedral-$d_5$ acetamide viewed along a at (a) 0.03 GPa and (b) 4.72 GPa. The plots are drawn to the same scale. The corresponding space-filling plots are shown in Figure 4.10.
The structure of monoclinic acetamide-\textit{d}_5 at 1.03 GPa is in good agreement with the one found by X-rays at 0.8 GPa. It was found that the deuterium atoms of the amide group in molecule A (see Section 4.4.1), involved in the formation of centrosymmetric hydrogen-bonded dimers, deviate substantially from planarity [the torsion angle defined by D(1)-N(1)-C(1)-C(2) is 14(5)° and the angle defined by D(2)-N(1)-C(1)-C(2) is -23(5)°]. Deuterium atoms in molecule B do so to a lesser extent and the corresponding torsion angles are 14(4)° and -6(3)°, respectively. The methyl group of molecule B adopts a conformation with one C-D bond almost in the plane of the non-hydrogen atoms and eclipsed with the C-N bond. The methyl group of molecule A adopts a similar conformation. The same conformation is observed in the metastable (non-deuterated) orthorhombic polymorph at 146 K. As noted earlier, the energy barrier for the orientation of the methyl group is low and the orientation is therefore principally determined by crystal packing forces, as observed by Bats \textit{et al.} (2003).

At 1.414 g cm\textsuperscript{-3} the structure of the monoclinic-\textit{d}_5 polymorph at 1.03 GPa is considerably denser (3.4 \%) than that of the rhombohedral one at a similar pressure. (1.367 g cm\textsuperscript{-3}), and it is 14.6 \% denser with respect to the rhombohedral structure at 0.03 GPa (1.234 g cm\textsuperscript{-3}). The rhombohedral-to-monoclinic reconstructive phase transition was observed to take place at 1.03 GPa on increasing pressure, whilst the reverse transformation occurred at a lower pressure of 0.83 GPa on decreasing pressure. This effect is attributed to hysteresis and is far from uncommon in first-order phase transitions.

In his volumetric experiments, Bridgman observed a first transition at 0.59 GPa and 293 K associated with a $\Delta V = 1.6$ cm\textsuperscript{3} mol\textsuperscript{-1} in a non-deuterated sample of acetamide. This correlates very well with a $\Delta V = 1.56$ cm\textsuperscript{3} mol\textsuperscript{-1} obtained from comparison of molar volumes of rhombohedral acetamide-\textit{d}_5 at 1.03 GPa (using isopropyl alcohol-\textit{d}_8 as a pressure-transmitting medium) and monoclinic acetamide-\textit{d}_5 at 1.04 GPa (using isopropyl alcohol-\textit{d}_8 and methanol-\textit{d}_4 as a pressure-transmitting medium). It also correlates very well with a $\Delta V = 1.46$ cm\textsuperscript{3} mol\textsuperscript{-1} obtained from comparison of molar volumes of rhombohedral acetamide-\textit{d}_5 and
monoclinic acetamide-$d_5$ from a mixed-phase refinement of powder data collected during the transition (when isopropyl alcohol-$d_8$ and methanol-$d_4$ was used) that occurred at 1.04 GPa and was complete within 50 min. Even though the relative amounts of each phase in the sample were different over the same time period, the pressure should have remained constant. This is because the pressure system is designed to maintain fixed the pressure. Of the transitions identified by Bridgman, the II-III transition was observed at 1.8 GPa/323 K and at 2.3 GPa/473 K with a $\Delta V = 1.0 \text{ cm}^3 \text{ mol}^{-1}$. The III-IV transition had a $\Delta V = 1.46 \text{ cm}^3 \text{ mol}^{-1}$ associated with it, but was observed at the higher pressure and temperature of 2.22 GPa/323 K and of 2.46 GPa/473 K.

It is therefore believed that the monoclinic polymorph corresponds to Bridgman’s form II and that the rhombohedral form (form I in the crystallographic literature) corresponds to Bridgman’s form I. In a previous powder neutron diffraction experiment, in which a 4:1 mix of deuterated methanol:ethanol was used as the pressure-transmitting medium, the rhombohedral to monoclinic phase transition was also observed at ca. 1.0 GPa. The observation that the transition occurs at a higher pressure than that determined by Bridgman might be a consequence of the differences in the phase behaviour of the deuterated and non-deuterated samples. Alternatively, it may be caused by different pressurisation regimes and pressure-transmitting fluids used in the experiments. (e.g. if Bridgman conducted the experiment under non-hydrostatic conditions, a phase change could have initiated at a lower pressure).

It is also believed that the transition observed in the deuterated sample between 1.56-2.21 GPa (Figure 4.6), for which a structure has not been determined yet, is likely to correspond to Bridgman’s form III. The similarity in powder patterns suggests that the structure of the new phase is closely related to the monoclinic structure. This would also provide evidence in support of Bridgman’s form III since the II-III transition is characterised by a low molar $\Delta V$. It is possible that Bridgman’s form III is the orthorhombic polymorph of acetamide, but molar $\Delta V$ values and structural differences mitigate against this. The same transition had also been detected at ca. 1.6 GPa in a previous experiment that used a deuterated methanol:ethanol mixture as the pressure-transmitting medium. A thorough
exploration of the phase diagram of acetamide-\textit{d}_5 will be the subject of future investigations.

4.4.3 The influence of pressure-transmitting media on the transitions of acetamide-\textit{d}_5

The results presented in this chapter on compression of powder samples of rhombohedral acetamide-\textit{d}_5 indicate that the choice of pressure-transmitting medium has a profound influence on the phase transition to the monoclinic form. No transition was observed up to 4.99 GPa using isopropyl alcohol, whilst use of a 2:1 mixture of deuterated isopropyl alcohol and methanol resulted in a clean transition to the monoclinic form at 1.04 GPa.

A clean transition from form I to form III was also observed when a 4:1 mixture of deuterated methanol and ethanol was used as the pressure-transmitting medium. In this case, though, it was clear that a proportion of the sample had dissolved at ambient pressure during loading, and precipitated from solution with increasing pressure. The evidence for this came from the appearance of a highly textured pattern of form I consistent with precipitation of large crystallites in pressurisation. This severe textured pattern persisted through the phase transition and therefore precluded extraction of structural information.

By contrast, when Fluorinert FC-75 was used as the pressure-transmitting fluid, no phase transition was observed up to and beyond the freezing pressure of the medium (1.8 GPa). Instead the pattern broadened severely, and at \textit{ca.} 2.5 GPa no diffraction peaks were observed. On \textit{reducing} the pressure to \textit{ca.} 1.0 GPa, the pattern sharpened up to give the monoclinic phase. A further transition to the rhombohedral phase was observed on depressurisation to ambient pressure.

In order to overcome these problems, isopropanol-\textit{d}_8 was selected on the basis that this has a higher freezing pressure than FC-75. As described earlier, no transition was observed up to the freezing pressure. At this point, it was suggested that doping of isopropanol-\textit{d}_8 with methanol-\textit{d}_4 might be an effective method of changing the properties of the pressure-transmitting fluid. In particular, it was anticipated that the small amount of methanol would partially dissolve some of the acetamide and this promote the phase transition but without affecting the texture of
the pattern. Indeed, this proved to be the case and lends weight to the hypothesis that the choice of hydrostatic medium depends on the degree to which the sample has some solubility in the fluid. The physical basis for such a hypothesis lies in the mechanism of phase transitions in powder samples. In many cases, transitions are initiated by defects on the surfaces of small particles of the sample. Dynamic dissolution and reprecipitation of sample at the surface is likely to increase the number of defects at the surface, thereby promoting the phase change. An additional factor is that precipitation of material from solution at pressures above the transition pressure is likely to result in precipitation of the high-pressure phase, and so one can imagine a process by which the relative amount of the high-pressure phase is selectively increased or further nucleation is encouraged.

It is therefore concluded that some degree of solubility in the pressure-transmitting medium is a desired property to kinetically encourage a phase transition and it is believed that this knowledge can be extended to general studies of high-pressure phase transitions on polycrystalline materials. On the other hand, the use of an inert pressure-transmitting fluid, in which the compound is not soluble, might promote the study of anisotropic compressibility and avoid the occurrence of a phase transition.

For example, it would explain why observation of the monoclinic-to-orthorhombic phase transition of paracetamol on a powder sample (Boldyreva et al., 2002) only occurred at high pressures, was not reproducible or complete and only occurred on depressurisation. In these experiments a 1:1 mixture of pentane-isopentane was used and paracetamol is practically insoluble in this mixture. It is foreseen that the use of a methanol:ethanol mixture might facilitate the transition and future experiments are planned to verify this. The observation that a transition to monoclinic acetamide was observed on decompression using Fluorinert FC-75, but none was observed when isopropyl alcohol was used, is also due to kinetic factors: a conjecture is that the transition goes via an amorphous phase. The reproducibility of these results should be tested by performing a larger number of experiments using these two different media. As an example, the transition in CBr₄ (Bridgman, 1946) represents another example of a kinetically hindered transformation, which occurs on decreasing pressure (although the molar volume decreases during the transition).
The concept of solute-solvent interaction in the context of polymorph interconversion is not new. At conditions of ambient pressure, interconversion of monoclinic and orthorhombic paracetamol often takes place in contact of the crystals with a saturated solution (Nichols & Frampton, 1998) or in the melt, where nucleation can be assisted by the liquid phase. The observation that polymorphic transformations can be sensitive to the choice of pressure-transmitting medium was also noted by Boldyreva (2000), who noted a phase transition in \([\text{Co(NH}_3)_6\text{NO}_2]_2\) when a water-ethanol-methanol mixture was substituted to poly(chlorotrifluoroethylene) oil. However, as far as is known, the connection of these effects with solubility has been never made and this concept is entirely new.

### 4.4.4 Topological analysis

Topological analysis of the three structurally characterised modifications of acetamide revealed packing topologies different from any of the known sequences for the packing of hard spheres (see Section 2.3.1) and no further analysis is presented here.

### 4.4.5 Hirshfeld surfaces and fingerprint plots

The use of Hirshfeld surfaces and fingerprint plots (Spackman & McKinnon, 2002; McKinnon et al., 2004) for comparison of polymorphs was discussed in Section 2.3.2. Since Hirshfeld surfaces and the corresponding fingerprint plots are unique for any crystal structure (and consequently for any polymorph), they provide a powerful visual tool for elucidating and comparing intermolecular interactions, as well as for spotting common features and trends in specific classes of compounds. Hirshfeld surfaces and fingerprint plots for each of the polymorphs of acetamide are shown in Figures 4.17 to 4.23. In the case of orthorhombic and monoclinic acetamide there are two molecules in the asymmetric unit, and therefore two distinct sets of surfaces and fingerprint plots. All fingerprint plots show two sharp “tails” corresponding to N-H...O=C hydrogen bonds extending down to around \(d_e + d_i = 1.9-2.0\) Å, the upper one corresponding to the hydrogen-bond donor and the lower one to the hydrogen-bond acceptor.
The fingerprint plot in Figure 4.17 for rhombohedral acetamide (non-deuterated) at ambient pressure and 23 K shows a large number of values at large $d_e$ and $d_i$ corresponding to regions on the Hirshfeld surface without close contacts to neighbouring molecules and where the close packing of the surfaces results in the formation of small cavities (these were discussed in Section 4.4.1). Values around $d_e + d_i = 2.2-2.4$Å correspond to a larger void created about the 3-fold rotation axes, clearly depicted in Figure 4.18.

**Figure 4.17** Hirshfeld surfaces and fingerprint plot for rhombohedral acetamide at ambient pressure and 23 K (CSD reference code ACEMID05). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$.

**Figure 4.18** (a) Hirshfeld surfaces for rhombohedral acetamide illustrating the 3-fold symmetry in the packing arrangement and the formation of structural voids; (b) corresponding molecular structure. The colouring scheme highlights the 3-fold symmetry.
Figure 4.19 illustrates the sequence the fingerprint plots of rhombohedral acetamide-$d_5$ at selected increasing pressures.

Figure 4.19 Fingerprint plots for rhombohedral acetamide-$d_5$ at (a) 0.03 GPa, (b) 1.25 GPa, (c) 2.58 GPa, (d) 3.78 GPa and (e) 4.72 GPa.

The most prominent features in these plots are the progressive shift and contraction to lower $d_c$ and $d_l$ as structural density increases: hydrogen-bond tails become shorter, as do D...D contacts (the pointed features across the diagonal at low $d_c$ and $d_l$) and the number of voids is reduced (the regions at high values of $d_c$ and $d_l$).

In orthorhombic acetamide (Figures 4.20 and 4.21) at ambient pressure and 146 K there are two molecules in the asymmetric unit and therefore all intermolecular contacts are reflected in two Hirshfeld surfaces, and hence in two fingerprint plots.
Figure 4.20 Hirshfeld surfaces and fingerprint plot for one of the two molecules in the asymmetric unit of orthorhombic acetamide at ambient pressure and 146 K (CSD reference code ACEMID06). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$. The highlighted region is referred to in the text.

Figure 4.21 Hirshfeld surfaces and fingerprint plot for the second molecule in the asymmetric unit of orthorhombic acetamide at ambient pressure and 146 K (CSD reference code ACEMID06). The molecule is shown with the Hirshfeld surface mapped with (a) curvedness, (b) shape index and (c) $d_e$. The highlighted region is referred to in the text.

Since there are contact regions between the Hirshfeld surfaces of these two molecules (various intermolecular interactions link the two molecules), it is possible to identify complementary regions in the fingerprint plots, where one molecule acts as a donor part and the other one as an acceptor part. The most striking complementary features are the regions highlighted in Figures 4.20 and 4.21. These correspond to interactions of methyl hydrogen atoms with the amide bond and are reminiscent of the donor and acceptor regions described earlier for hydrogen bonds.
Hence, the molecule in Figure 4.20 is the acceptor part of this interaction and the molecule in Figure 4.21 is the donating part. In Section 4.4.1 it was discussed how the two independent molecules are hydrogen-bonded to each other to form a cyclic motif that leads to a $R_2^2(8)$ dimer. Dimer formation is evident in the fingerprint plots of both molecules and appears as a diffuse set of points in between the “tails” indicative of hydrogen bonding.

Monoclinic acetamide is another example of a $Z' = 2$ structure. Hirshfeld surfaces and fingerprint plots for the structure obtained by high-pressure recrystallisation from water at 0.8 GPa are shown in Figure 4.22 and 4.23. Fingerprint plots convey the different molecular environments very clearly. The denser packing of this form with respect to the rhombohedral and orthorhombic modifications at ambient pressure is most prominently illustrated by the observation that the fingerprint plot of molecule A (see Section 4.4.1 for the notation) is shifted to lower values of $d_e$ and $d_i$. In addition, within the asymmetric unit, molecule A has a more “crowded” environment and this is apparent in the fingerprint plots by the number of points at quite large distances for molecule B (Figure 4.23), compared with the relatively compact pattern for molecule A (Figure 4.22).

Molecule B is involved in C-H...amide interactions to neighbouring symmetry equivalent molecules and this is evident from the fact that complementary donor and acceptor regions are visible on the same fingerprint plot between 1.4-1.8 Å in $d_e$ and $d_i$.

As discussed in Section 4.4.1, each molecule donates one hydrogen bond to a symmetry equivalent molecule and one to a symmetry independent molecule. This has the effect of creating a subtle asymmetry in the hydrogen-bond “tails” in Figures 4.22 and 4.23, evidence that the donor and acceptor molecules are not the same for this interaction. This asymmetry is less obvious than in $Z' > 1$ structures where the molecule under consideration donates a single hydrogen bond (e.g. aziridine, McKinnon et al., 2002). Each acetamide molecule donates two hydrogen bonds and the two hydrogen-bond “tails” overlap, making it more difficult to distinguish between the two interactions on the plots. The broadening of the “tails” at higher $d_e$ and $d_i$ are an indication of the presence of two contacts.
In both plots, the region between the hydrogen-bond "tails" shows features characteristic of H...H contacts. The complexity of this region, where N-H...H-N and N-H...H-C contacts are found between symmetry equivalent and symmetry inequivalent molecules, masks other features, most notably the distinction between molecule A and molecule B in terms of dimer-forming ability. From structural analysis, it is in fact known that molecule A is involved in the formation of a $R_2^2(8)$ centrosymmetric dimer, but the diffuse set of points that was a striking feature for the plots of the orthorhombic polymorph is now not easily deconvoluted without manual inspection of the fingerprint plot and corresponding $d_e$ Hirshfeld surface.
Hirshfeld surfaces and fingerprint plots for monoclinic acetamide at 0.8 GPa were generated from a structure where hydrogen atoms were placed in calculated positions. Comparison of these plots with the ones calculated for the deuterated structure obtained by powder neutron diffraction at 1.04 GPa is shown in Figure 4.24. The experimentally observed positions of deuterium atoms are different from calculated positions mentioned above, and the fingerprint plots illustrate the profound difference in the regions where hydrogen and deuterium atoms are involved in the formation of intermolecular contacts.

![Fingerprint plots for neutron and X-ray structures of monoclinic acetamide at (left) 1.04 GPa and (right) 0.8 GPa, respectively.](image)

**Figure 4.24** Fingerprint plots for neutron and X-ray structures of monoclinic acetamide at (left) 1.04 GPa and (right) 0.8 GPa, respectively.

Close examination of the fingerprint plot of acetamide-$d_5$ in molecule A reveals that the diffuse set of points between the hydrogen-bond spikes do not arise from very close contacts across the centrosymmetric hydrogen-bonded dimer, as observed in orthorhombic acetamide and in monoclinic acetamide at 0.8 GPa (X-ray structure). Since in this case the hydrogen-bond $R_2^2(8)$ ring is twisted out of the plane of the N-C(1)-O plane, D...D contacts are now found at a longer distance than when
the ring is planar. A similar observation was made for the case of benzamide (McKinnon et al., 2002).

Void regions in the structure are significantly affected by the orientation of the methyl groups. Methyl hydrogen atoms in the X-ray crystal structure at 0.8 GPa were placed so that one C-H bond was eclipsed with the carbonyl bond. The deuterated sample at 1.04 GPa showed these to be differently oriented (see Section 4.4.2) and the sizes and shapes of voids are consequently different, as illustrated in the plots.

4.4.6 Decompression experiments

Optical observation on progressive decompression at 293 K of the monoclinic single crystal grown at 0.8 GPa from water showed gradual dissolution of the crystal. Powder samples of monoclinic acetamide-\(d_5\) obtained by compression experiments at the neutron ISIS facilities reverted to the rhombohedral form on decompression to ambient pressure at 293 K. It is not possible at this stage to rule out that monoclinic acetamide may be sufficiently metastable to exist at ambient pressure, provided that the temperature is sufficiently low. Methods for the recovery at ambient pressure of new polymorphs prepared at high pressure are currently being investigated.

4.5 Conclusions

The use of the technique of high-pressure recrystallisation from solution of acetamide afforded a new, denser polymorph of acetamide, recrystallised from water at 0.8 GPa. This polymorph was characterised by single-crystal X-ray diffraction and its hydrogen-bonding motif was shown to be profoundly different from that of the known rhombohedral or orthorhombic modifications.

Future experiments on acetamide include high-pressure recrystallisation from solution using other solvents for the identification of new polymorphs and solvates. The use of different aqueous concentrations may lead to the formation of a hydrate: the remarkable solubility of acetamide in water parallels the case of piracetam, for which two hydrates have been successfully isolated (see Chapter 6). No hydrates of acetamide are yet known and preliminary results on low-temperature crystallisation
of acetamide from an equimolar aqueous solution of acetamide have produced the metastable orthorhombic polymorph.

Compression studies by neutron powder diffraction on the rhombohedral modification showed that a first-order transition to the monoclinic polymorph occurs at 1.04 GPa; the reverse transition was observed at 0.8 GPa. A second transition occurred at 1.56 GPa. The structure of this new phase remains as yet unsolved due to severe peak overlap with the pressure marker. Further experiments without the use of a pressure marker (or with the use of a marker, whose diffraction peaks do not give rise to overlap) are needed in order to collect data of better quality. On the basis of comparison of molar volumes, the rhombohedral and monoclinic polymorphs have been assigned to the modifications denoted by Bridgman from volumetric experiments as forms I and II, respectively. The second transition observed at 1.56 GPa could correspond to Bridgman’s form III. Further compression studies (coupled with the use of high temperatures) are envisaged for the exploration of the phase diagram of acetamide and possible structural identification of the modifications reported by Bridgman.

The use of different pressure-transmitting fluids was shown to have a profound influence on the observation of a phase transition and it was concluded that some solubility in the medium is a desired property for inducing phase transitions that are kinetically hindered. This knowledge can be extended to the study of a large variety of polycrystalline compounds and further experiments are envisaged to support this. By using isopropyl alcohol, in which acetamide is not soluble, the volume of rhombohedral-$d_5$ acetamide was reduced by 23.4 %, which represents a remarkable compressibility. This illustrates how the choice of medium can also be tailored to perform anisotropic compression studies and minimise the occurrence of a phase transition.
4.6 References


Chapter 5

The influence of Pressure on the Formation of Polymorphs, Solvates and Hydrates of Paracetamol
5.1 Introduction

Paracetamol (acetaminophen or p-hydroxyacetanilide) is an analgesic drug that is used widely throughout the world. The molecular structure of the compound is shown in Figure 5.1.

![Molecular structure of paracetamol with numbering scheme.](image)

Figure 5.1 Molecular structure of paracetamol with numbering scheme.

To date, there have been several studies that have identified and structurally characterised two polymorphs. The monoclinic form (form I, melting point 442 K) was first described by Haisa et al. (1976), followed more recently by more precise structural determinations at low temperature (Naumov et al., 1998; Nichols & Frampton, 1998) and by single crystal neutron diffraction (Wilson et al., 1997; Wilson, 2000). It has been shown to be the thermodynamically stable form under normal conditions and is also the form used commercially. Because of its inability to undergo plastic deformation, monoclinic paracetamol needs to be mixed with binding agents prior to tabletting (Fachaux et al., 2002).

The orthorhombic form (form II, melting point 430 K) was also first described by Haisa et al. (1974) but subsequent attempts by other workers to obtain single crystals of this form using Haisa's method were unsuccessful (Naumov et al., 1998; Di Martino, 1997; Sohn, 1990), although polycrystalline material in this phase can be grown from the melt (Sohn, 1990). An elegant study by Nichols & Frampton (1998) showed that single crystals of the orthorhombic polymorph can be grown by seeding a super-saturated solution of paracetamol with a micro-crystal of the orthorhombic form derived from melt-crystallised paracetamol. The authors also described the thermochemical and optical properties of both polymorphs. The interest in the orthorhombic polymorph stems from its property of undergoing plastic deformation upon compaction, thereby presenting some processing advantages over the monoclinic form (Di Martino, 1996). The orthorhombic form of paracetamol has
also been crystallised preferentially in the presence of selected polymers (Lang et al. 2002), and also from water via a process that involves pre-treatment of the recrystallisation vessel with a concentrated alkaline solution (Mikhailenko, 2004).

Packing in both polymorphs is dominated by the formation of N-H…OH and O-H…O=C hydrogen bonds that give rise to layered 2-D networks. These are depicted in Figure 5.2.

![Figure 5.2 Hydrogen-bonded layers in (a) monoclinic paracetamol (form I) viewed along the b axis and (b) orthorhombic paracetamol (form II) viewed along the c axis.](image)

Both polymorphs have identical graph sets (Bernstein et al., 1995), in which OH…O=C and N-H…OH hydrogen bonds form first-level graph set C(9) and C(7) motifs, respectively. In the monoclinic form, the hydrogen-bonded layers are arranged parallel to the (010) planes: these give rise to polar layers, shown in Figure 5.2a, where all the molecules have the methyl group on the left. In the orthorhombic polymorph, glide planes run perpendicular to the layers: methyl groups lie on the left- and right-hand sides of the molecules to form non-polar layers depicted in Figure 5.2b.

Boldyreva et al. (2000, 2002, 2003) studied the anisotropic compressibility of both forms and showed that the direction of maximum compressibility correlates with the orientation of molecular layers (this being normal to the layers) and with the “softness” of the hydrogen bonds involved. Whilst the bulk compressibility of the two forms is similar (ca. 20 % decrease in volume from ambient pressure to 4.0 GPa), linear strain results are very different. For form I, expansion of the layers in some directions due to cooperative rotation of molecules and flattening of the
hydrogen-bonded layers is observed. For form II, isotropic compression in the planes of hydrogen-bonded layers due to cooperative movement of molecules occurs, which can be explained on account of the layers being already flat at ambient pressure. Boldyreva et al. (2002) have demonstrated that the application of pressures in excess of 4 GPa to powder samples of paracetamol results in conversion of form I into form II, but for kinetic reasons the conversion is incomplete and poorly reproducible and no conversion is observed in a single crystal. This transition would require the breaking/reforming of many intermolecular hydrogen bonds and reorientation of every other chain in a layer and it is therefore expected to be kinetically hindered. This is thus unlikely to occur within the bulk of the crystal, as it must be limited by nucleation and explains why this transition is not observed in a single crystal. In addition, the authors observed a partial transformation of form II into I during grinding and a complete and irreversible transformation to form I when this sample was compressed to 0.6 GPa.

A third polymorph of paracetamol (form III) has been identified by calorimetric measurements (Di Martino et al., 1997). More recently, a powder X-ray diffraction pattern of form III was reported (Peterson et al., 2002) and the authors claimed that the pattern was consistent with one of the structures calculated by Beyer et al. (2001). However, inspection of the supplementary data shows quite clearly that this claim is not justified and therefore the structure of form III remains unsolved.

Despite extensive studies on the crystallisation of the compound from a wide range of solvents, it is only very recently that the first of its solvates or adducts have been isolated and structurally characterised. These include a monohydrate (Parkin et al., 2002) and a trihydrate (McGregor et al., 2002) five hemiadducts of paracetamol with 1,4- dioxane, N-methylmorpholine, morpholine, N,N-dimethylpiperazine and piperazine, and a related 1:1 adduct of paracetamol with 4,4'-bipyridine (Oswald et al., 2002a, 2002b). Whilst the thermal stabilities of the paracetamol adducts containing amines and dioxane are generally relatively high, this is not the case for the two hydrates and both compounds dehydrate within minutes at temperatures greater than 273 K to give the monoclinic polymorph of paracetamol (Parkin et al., 2002; McGregor et al., 2002).
All previous attempts to obtain solvates of paracetamol with simple alcohols have been unsuccessful (Fachaux et al., 1995). We were therefore interested in investigating the ability of paracetamol to form new solvates and hydrates by high-pressure recrystallisation from solution and whether this technique would overcome kinetic barriers to molecular rearrangement so that new polymorphs could be obtained.

5.2 Experimental Procedure

For each experiment the pressure within the gasket hole was determined as described in Section 2.1.3. Unless otherwise stated, all diffraction data were collected on a Bruker SMART APEX CCD diffractometer at 293(2) K using Mo Kα radiation (\( \lambda = 0.71073 \) Å). Each data collection consisted of \( \omega \) scans at two different \( \phi \) values (90° and 270°). Data collection was performed according to procedures described by Dawson et al. (2004) and detailed in Section 2.2.1.

Raman spectra were recorded using a Jobin-Yvon LabRam 300 instrument with excitation by a He-Cd laser operating at 441.6 nm, as explained in Section 2.1.4.

5.2.1 High-pressure recrystallisation from methanol at 0.6 GPa: methanol solvate

A ca. 1 M methanolic solution of paracetamol (Sigma-Aldrich) was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole. By varying the pressure in the range 0.1-1.0 GPa, a pressure of 0.6 GPa was found to be the optimum. At this pressure and at ambient temperature, precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 333 K in order to dissolve all but one of the crystallites. On slow cooling to 293 K a single crystal grew from solution to fill ca. 50% of the gasket hole (Figure 5.3). The pressure within the gasket hole was determined as ca. 0.6 GPa.
Figure 5.3 Optical image of a single crystal of the high-pressure methanol solvate of paracetamol at 0.6 GPa in a diamond-anvil cell.

The Raman spectrum of the crystal recrystallised from methanol at 0.6 GPa and contained within the diamond-anvil cell showed a substantially different pattern of bands in the regions associated with the stretching modes of C=O and aryl C-C bonds, and with the deformation mode of the N-H bond (Moynihan & O’Hare, 2002), when compared to the spectrum of paracetamol form I or II, thereby indicating the formation of either a new polymorph of paracetamol or a solvate.

Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions substantially different from either of the two known polymorphs of paracetamol. Initial estimation of the unit-cell volume suggested the presence of a solvate. Structure solution using global optimisation methods with subsequent full-matrix least-squares structure refinement identified the crystal as the first methanol solvate of paracetamol.

5.2.2 High-pressure recrystallisation of paracetamol from water at 1.1 GPa:
paracetamol dihydrate

An aqueous solution of paracetamol (Sigma-Aldrich) of concentration ca. 0.06 M was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole. By varying the pressure in the range 0.1-1.5 GPa, a pressure of 1.1 GPa was found to be the optimum. At this pressure and at ambient temperature, precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 343 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single
crystal grew from solution. The optical image of the crystal contained within the gasket aperture is shown in Figure 5.4.

![Optical image of a single crystal of the high-pressure dihydrate of paracetamol at 1.1 GPa in a diamond-anvil cell.](image)

**Figure 5.4** Optical image of a single crystal of the high-pressure dihydrate of paracetamol at 1.1 GPa in a diamond-anvil cell.

A single-crystal X-ray diffraction experiment gave unit-cell dimensions that were significantly different from either of the known polymorphs or hydrates of paracetamol and initial estimation of the unit-cell volume suggested the presence of a dihydrate species.

Diffraction data were collected on a Bruker APEX CCD diffractometer at 293(2) K using synchrotron radiation ($\lambda = 0.6889 \text{ Å}$) on Beamline 9.8 at the Synchrotron Radiation Source, Daresbury Laboratory, Warrington, UK. Data collection was performed according to an established 16-runs 1-second $\omega$ scans procedure (Moggach et al., 2005). Data were collected with the diamond-anvil cell in two orientations (glued onto the goniometer head on two different sides of the cell) to simulate two different values of $\chi$ in order to improve data completeness.

### 5.2.3 High-pressure recrystallisation from ethanol

A *ca.* 1.5 M ethanolic solution of paracetamol (Sigma-Aldrich) was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 600 $\mu$m culet diamonds and a tungsten gasket with a 300 $\mu$m hole together with a few small crystallites of monoclinic paracetamol (previously identified by single-crystal X-ray diffraction). The cell was sealed and pressurised to *ca.* 0.8 GPa, and then heated to *ca.* 323 K to dissolve all of the solid. Precipitation of polycrystalline material was
observed on cooling to 293 K. The temperature was then cycled near ca. 323 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution. The pressure within the gasket hole was determined as ca. 1.0 GPa.

Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions similar to those found for the orthorhombic polymorph of paracetamol corresponding to a volume decrease of ca. 6% compared with the structure at ambient pressure. A partial dataset was collected to extract qualitative structural information in order to identify unambiguously the crystalline form.

5.2.4 High-pressure recrystallisation from acetone

In order to explore the effect of a different solvent on the outcome of a high-pressure recrystallisation experiment of paracetamol, a ca. 0.7 M solution of paracetamol in acetone was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 µm culet diamonds and a tungsten gasket with a 300 µm hole together with a few small crystallites of monoclinic paracetamol (previously identified by single-crystal X-ray diffraction). The cell was sealed and pressurised to ca. 0.1 GPa, and then heated to ca. 313-323 K to dissolve all of the solid. Precipitation of polycrystalline material was observed on cooling to 293 K. The temperature was then cycled near ca. 323 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution. The pressure within the gasket hole was determined as ca. 0.2 GPa. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions similar to those found for orthorhombic paracetamol and no further X-ray data were collected.

The crystal of form II was redissolved by gentle heating and the pressure was increased to ca. 0.6 GPa. A single crystal was grown in the cell in the manner described previously. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions substantially different from either of the two known polymorphs of paracetamol. Initial estimation of the unit-cell volume suggested the presence of a monoclinic acetone solvate. Data were collected
with the diamond-anvil cell in three orientations (glued onto the goniometer head on three different sides of the cell) to simulate three different values of $\chi$ in order to improve data completeness.

5.3 Results

Data processing was performed according to the procedures described by Dawson et al. (2004) and detailed in Section 2.2.2. Where appropriate, some details are given in the following sections.

5.3.1 High-pressure recrystallisation from methanol at 0.6 GPa: methanol solvate

5.3.1.1 Raman spectroscopy

Raman spectroscopy is unfortunately not a useful tool to distinguish between the orthorhombic and monoclinic forms of paracetamol, as the Raman spectra are almost identical, but the two polymorphs have been distinguished using IR spectroscopy (Moynihan & O’Hare, 2002; Boldyreva, 2003).

The 1350-1850 cm$^{-1}$ region of the Raman spectrum collected on the solvate in the high-pressure cell at 0.6 GPa is shown in Figure 5.5a. Comparison with the spectrum of a polycrystalline sample of monoclinic paracetamol collected at ambient pressure (Figure 5.5b) illustrates significant differences in the 1450-1800 cm$^{-1}$ region associated with the stretching modes of C=O and aryl C-C bonds, and the deformation mode of the N-H bond (Moynihan & O’Hare, 2002). It is of course possible that these differences are caused by the effects of pressure on monoclinic paracetamol.

In the high-pressure solvate these bands exhibit a different pattern. Due to the limited resolution and sensitivity in this region, it was difficult to draw any definitive conclusion by comparison of these two spectra alone. This is mainly due to small-sized sample and the rather weak scattering of the crystal.
Figure 5.5 Raman spectra of (a) paracetamol methanolate at 0.6 GPa, (b) monoclinic paracetamol at ambient pressure and (c) monoclinic paracetamol at 1.0 GPa.
The difficulty lies in establishing whether the apparent differences were genuinely new, or they were due to changes in different relative band positions and changes in relative intensities, attributable to the effect of pressure. This difficulty was overcome by comparison of the same region with the Raman spectrum of monoclinic paracetamol at 1.0 GPa (Figure 5.5c). It is known that N-H in-plane deformations and C=O stretches are well resolved and that the changes in frequencies are due to pressure effects that can be monitored at least up to 4.0 GPa (Boldyreva, 2003). The Raman spectrum of monoclinic paracetamol at 1.0 GPa (Figure 5.5c) indicated that although the broader bands move to higher energies by varying amounts, the pattern of bands observed at ambient pressure is preserved. Thus the crystal obtained from methanol is definitely not the monoclinic form of paracetamol, and so suggests a new polymorph or a solvate.

5.3.1.2 X-ray diffraction

The low completeness of this dataset (ca. 24 % to \( \theta_{\text{max}} = 20.8^\circ \) in terms of symmetry-independent reflections) arises from the restricted volume of reciprocal space that can be accessed on account of the 40° opening angle of the high-pressure cell (Merrill & Bassett, 1974, Dawson et al., 2004) coupled with an unfortunate orientation of the sample in the cell. This made it difficult to assign the space group on the basis of systematic absences alone. The crystal system was known to be monoclinic, with a primitive lattice; no reflections in the 0k0 domain were collected and only one reflection in the h0l zone, \( l \equiv 2n \) was flagged as weak. Based on this single systematic absence the choice of space group \( P2_1/c \) was presented and chosen, supported by the fact that this space group is one of the most common space group for organic crystals (14 % of the CSD, version 5.24).

Solution of the structure was not straightforward using direct methods. Hence the incomplete data set was input into the global optimisation program DASH (David et al., 1998), that has recently been modified to solve structures from high-pressure single-crystal datasets collected on a range of small molecule structures (Markvardsen, et al., 2002). This program rapidly identified a global minimum by simulated annealing thereby allowing subsequent refinement of the 1:1 solvate in \( P2_1/c \).
Full-matrix least-squares structure refinement was then performed using CRYSTALS (Betteridge et al., 2003). The positional coordinates of methanol and paracetamol atoms were refined as two separate rigid groups. All non-hydrogen atoms were refined isotropically and hydrogen atoms were placed in calculated positions. A 2θ cut-off of 36.3° was used during structural refinement. Whilst not ideal, the R-factor of 13.4 % is typical for refinement of high-pressure data sets and is sufficient to identify the main structural features of the solvate.

Full refinement details are shown in Table 5.1. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Paracetamol methanolate at 0.6 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₈H₉NO₂.CH₄O</td>
</tr>
<tr>
<td>$M_r$</td>
<td>183.21</td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, $P2_1/c$</td>
</tr>
<tr>
<td>$a$, $b$, $c$ (Å)</td>
<td>7.630 (2), 17.209 (3), 7.3710 (11)</td>
</tr>
<tr>
<td>$\beta$ (°)</td>
<td>115.52 (3)</td>
</tr>
<tr>
<td>$V$ ($Å^3$)</td>
<td>873.4 (4)</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>$D_x$ (Mg m$^{-3}$)</td>
<td>1.393</td>
</tr>
<tr>
<td>Radiation type</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>No. of reflections for cell parameters</td>
<td>285</td>
</tr>
<tr>
<td>$\theta$ range (°)</td>
<td>4–18</td>
</tr>
<tr>
<td>$\mu$ (mm$^{-1}$)</td>
<td>0.11</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293 (2)</td>
</tr>
<tr>
<td>Crystal form, colour</td>
<td>Block, colourless</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.20 × 0.20 × 0.10</td>
</tr>
</tbody>
</table>

| Data collection | |
| Diffractometer | Bruker SMART |
| Data collection method | $\omega$ scans |
| Absorption correction | Empirical & multi-scan (based on symmetry-related measurements) |
| $T_{\text{min}}$ | 0.29 |
| $T_{\text{max}}$ | 0.99 |

Table 5.1 Crystal, collection and refinement details for paracetamol methanolate at 0.6 GPa.
Table 5.1 (cont.) Crystal, collection and refinement details for paracetamol methanolate at 0.6 GPa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of measured, independent and observed reflections</td>
<td>801, 223, 118</td>
</tr>
<tr>
<td>Criterion for observed reflections</td>
<td>$I &gt; 2\sigma(I)$</td>
</tr>
<tr>
<td>$R_{\text{int}}$</td>
<td>0.046</td>
</tr>
<tr>
<td>$\theta_{\text{max}}$ ($^\circ$)</td>
<td>18.1</td>
</tr>
<tr>
<td>Range of $h, k, l$</td>
<td>$-4 \rightarrow h \rightarrow 4$</td>
</tr>
<tr>
<td></td>
<td>$-17 \rightarrow k \rightarrow 16$</td>
</tr>
<tr>
<td></td>
<td>$-7 \rightarrow l \rightarrow 7$</td>
</tr>
<tr>
<td>Refinement</td>
<td></td>
</tr>
<tr>
<td>Refinement on</td>
<td>$F^2$</td>
</tr>
<tr>
<td>$R[F^2 &gt; 2\sigma(F^2)], wR(F^3), S$</td>
<td>0.135, 0.216, 0.93</td>
</tr>
<tr>
<td>No. of reflections</td>
<td>172 reflections</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>14</td>
</tr>
<tr>
<td>H-atom treatment</td>
<td>Not refined</td>
</tr>
<tr>
<td>Weighting scheme</td>
<td>Chebychev polynomial, $[\text{weight}] = 1.0/[A_0 + A_1(x) + \cdots + A_{n-1} + x]$</td>
</tr>
<tr>
<td></td>
<td>where $A_i$ are the Chebychev coefficients listed below and $x = F/F_{\text{max}}$</td>
</tr>
<tr>
<td></td>
<td>$A_i$: 9.45, 10.7, 2.51</td>
</tr>
<tr>
<td>$(\Delta \sigma)_{\text{max}}$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\Delta V_{\text{max}}, \Delta V_{\text{min}}$ (Å$^3$)</td>
<td>0.33, -0.42</td>
</tr>
</tbody>
</table>

5.3.2 **High-pressure recrystallisation of paracetamol from water at 1.1 GPa:**

**paracetamol dihydrate**

Diffraction data were collected with the diamond-anvil cell in two orientations (glued onto the goniometer head by two different sides of the cell) to simulate three different values of $\chi$ in order to improve data completeness. The two datasets were treated separately up to the absorption correction step. The two unmerged reflection files were then scaled and merged in **SORTAV** (Blessing, 1995) applying a 20 cut-off of 39.4° in the manner described by Dawson et al. (2004).

Solution of the structure was not straightforward using direct methods owing to the limited amount of data and structure solution was therefore performed using the global optimisation program **FOX** (Favre-Nicolin & Černý, 2002). Since it was
not known at this stage whether this crystal represented either a new polymorph or a
new hydrate of paracetamol, the number of water molecules per paracetamol
molecule was varied from 0-3 in a series of optimisations. The program rapidly
identified a dihydrate as the most likely composition and successfully solved the
structure in space group $P2_1/c$.

Full-matrix least-squares structure refinement was then performed using the
program CRYSTALS (Betteridge et al., 2003). All non-hydrogen atom bond distances
were restrained to be equal to those of monoclinic paracetamol at 123 K (CSD
reference code HXACAN07). All non-hydrogen atoms were refined isotropically
(the isotropic thermal parameters of non-hydrogen atoms of the paracetamol
molecule were restrained to be similar to the average sum of all such parameters) and
hydrogen atoms on the paracetamol molecule were placed in calculated positions,
with the exception of the hydrogen atom of the hydroxyl group, which was located in
a slant-plane difference-Fourier map. The positions of hydrogen atoms were fixed
during refinement. Some plausible hydrogen atoms positions were similarly located
on the water molecules; these appeared to imply orientational disorder of the water
molecules and since alternative positions were not located these atoms have been
omitted from the model presented here, but have been included for the calculation of
$F(000)$, $\mu$ and density.

Full refinement details are shown in Table 5.2. Crystallographic data in CIF
format are available in the attached CD at the back of the thesis.

| Table 5.2 Crystal, collection and refinement details for paracetamol dihydrate at 1.1 GPa. |
| --- | --- |
| **Crystal data** | **Paracetamol dihydrate at 1.1 GPa** |
| Chemical formula | $C_8H_9NO_2 \cdot 2(H_2O)$ |
| $M_r$ | 187.20 |
| Cell setting, space group | Monoclinic, $P2_1/c$ |
| $a$, $b$, $c$ (Å) | $6.6840 \pm 12$, $12.475 \pm 7$, $10.736 \pm 4$ |
| $\beta$ (°) | 107.387 (19) |
| $V$ ($Å^3$) | $854.3 \pm 6$ |
| $Z$ | 4 |
| $D_\text{c}$ (Mg $m^{-3}$) | 1.455 |

Chapter 5 - The influence of Pressure on the Formation of Polymorphs, Solvates and Hydrates of Paracetamol
<table>
<thead>
<tr>
<th><strong>Radiation type</strong></th>
<th>Synchrotron radiation, λ = 0.68890 Å</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of reflections for cell parameters</strong></td>
<td>139</td>
</tr>
<tr>
<td><strong>θ range (°)</strong></td>
<td>3–23</td>
</tr>
<tr>
<td><strong>μ (mm⁻¹)</strong></td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Temperature (K)</strong></td>
<td>293 (2)</td>
</tr>
<tr>
<td><strong>Crystal form, colour</strong></td>
<td>Block, colourless</td>
</tr>
<tr>
<td><strong>Crystal size (mm)</strong></td>
<td>0.18 × 0.10 × 0.05</td>
</tr>
</tbody>
</table>

**Data collection**

<table>
<thead>
<tr>
<th><strong>Diffractometer</strong></th>
<th>Bruker SMART Apex 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data collection method</strong></td>
<td>ω scans</td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
<td>Empirical &amp; multi-scan (based on symmetry-related measurements)</td>
</tr>
<tr>
<td><strong>imin</strong></td>
<td>0.108</td>
</tr>
<tr>
<td><strong>imax</strong></td>
<td>1.000</td>
</tr>
<tr>
<td><strong>No. of measured, independent and observed reflections</strong></td>
<td>895, 339, 180</td>
</tr>
<tr>
<td><strong>Criterion for observed reflections</strong></td>
<td>I &gt; 2σ(I)</td>
</tr>
<tr>
<td><strong>Rint</strong></td>
<td>0.088</td>
</tr>
<tr>
<td><strong>θmax (°)</strong></td>
<td>19.3</td>
</tr>
<tr>
<td><strong>Range of h, k, l</strong></td>
<td>-6 → h → 6, 0 → k → 9, 0 → l → 9</td>
</tr>
</tbody>
</table>

**Refinement**

<table>
<thead>
<tr>
<th><strong>Refinement on</strong></th>
<th>F²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R[F² &gt; 2σ(F²)], wR(F²), S</strong></td>
<td>0.086, 0.242, 1.00</td>
</tr>
<tr>
<td><strong>No. of reflections</strong></td>
<td>334 reflections</td>
</tr>
<tr>
<td><strong>No. of parameters</strong></td>
<td>53</td>
</tr>
<tr>
<td><strong>H-atom treatment</strong></td>
<td>Not refined</td>
</tr>
<tr>
<td><strong>Weighting scheme</strong></td>
<td>W = 1 / [Sigma²(F²) + (P(1)p)² + P(2)p + P(4) + P(5)Sin(theta)]</td>
</tr>
<tr>
<td><strong>(Δ/σ)max</strong></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Δρmax, Δρmin (e Å⁻³)</strong></td>
<td>0.22, -0.24</td>
</tr>
</tbody>
</table>

Table 5.2 (cont.) Crystal, collection and refinement details for paracetamol dihydrate at 1.1 GPa.

Chapter 5 – The Influence of Pressure on the Formation of Polymorphs, Solvates and Hydrates of Paracetamol
5.3.3 High-pressure recrystallisation from ethanol

Data collection was interrupted after identification of the known orthorhombic form. A high-pressure structure of orthorhombic paracetamol at 1.0 GPa has already been reported in the literature by Boldyreva et al. (2002) and no further structural information is presented here.

5.3.4 High-pressure recrystallisation from acetone

A partial dataset was collected at 0.2 GPa in order to extract qualitative structural information, namely for the assignment of the orthorhombic form and no further structural information is presented here.

The three datasets collected on the crystal grown at 0.6 GPa were treated separately up to the absorption correction step. The two unmerged reflection files were then scaled and merged in SORTAV (Blessing, 1995) in the manner described by Dawson et al. (2004). Results from the data integration step are shown in Table 5.3.

<table>
<thead>
<tr>
<th>Paracetamol/acetone at 0.6 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell setting</td>
</tr>
<tr>
<td>$a$/Å</td>
</tr>
<tr>
<td>$b$/Å</td>
</tr>
<tr>
<td>$c$/Å</td>
</tr>
<tr>
<td>$\alpha^o$</td>
</tr>
<tr>
<td>$\beta^o$</td>
</tr>
<tr>
<td>$\gamma^o$</td>
</tr>
<tr>
<td>$V$/Å³</td>
</tr>
<tr>
<td>Number of reflections for cell</td>
</tr>
<tr>
<td>$\theta$ range (°)</td>
</tr>
</tbody>
</table>

Table 5.3 Results from data integration paracetamol/acetone at 0.6 GPa.

By using "the 18 Å³ rule" (Kempster & Lipston, 1972), according to which all non-hydrogen atoms occupy a volume of 18 Å³, and knowledge that this volume can often be reduced to 15 Å³ for high-pressure structures of molecular crystals [(ca. 15 Å³ per non-hydrogen atom for monoclinic paracetamol at 0.5 GPa (Boldyreva et
the unit-cell dimensions of this monoclinic structure at 0.6 GPa pointed either towards an acetone hemisolvate (*ca.* 16 Å³ per non-hydrogen atom) or a 1:1 solvate (*ca.* 14 Å³ per non-hydrogen atom) of paracetamol. This is supported by consideration that the volume occupied by non-hydrogen atoms in the methanolate isolated at 0.6 GPa was also *ca.* 16 Å³; the possibility of a 1:1 solvate was nevertheless taken into account in the structure solution step.

A 2₁-screw axis was not identified on the basis of systematic absences since no reflections in the 0k0 domain were collected. Systematic absences clearly indicated the presence of a c-glide perpendicular to the b axis. The structure failed to solve by direct methods.

Structure solution with the global optimisation methods programs FOX (Favre-Nicolin & Černý, 2002) and DASH (David, *et al.*, 1998) was attempted in a range of space groups, as detailed in Table 5.4. Various approaches were employed. These included different data resolution cut-offs, different merging strategies, the use of different datasets (three were available since data were collected with the diamond-anvil cell glued on three different orientations on the goniometer head), and the use of different structure flexibility models. No plausible solutions were found. However, a consistent feature from the global optimisation solutions was the head-to-tail chain of paracetamol molecules. This may be correct, with the wrong position for the acetone molecule; further, the orientation may be correct, but the position within the unit cell wrong. To date, this structure remains unsolved.

<table>
<thead>
<tr>
<th>Space group</th>
<th>Number of molecules in the asymmetric unit</th>
<th>Paracetamol</th>
<th>Acetone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemisolvate</td>
<td><em>Pc</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>P2/c</em></td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>1:1 solvate</td>
<td><em>Pc</em></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>P2/c</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>P2₁/c</em></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5.4 Space groups attempted for the structure solution by global optimisation methods of single-crystal data of paracetamol/acetone at 0.6 GPa.
5.4 Discussion

Unit-cell parameters for the two characterised polymorphs of paracetamol are summarised in Table 5.5. Their crystal structures were briefly described in Section 2.3.

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<th>Form II</th>
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</tr>
<tr>
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Table 5.6 Crystallographic data for the monoclinic and orthorhombic polymorphs of paracetamol.

5.4.1 High-pressure recrystallisation from methanol at 0.6 GPa: methanol solvate

The crystal packing of the methanol solvate (CSD reference code OMISIM) is dominated by hydrogen bonding giving rise to layered 2-D networks (Figure 5.6a). One of the two layers is also found in the monoclinic and orthorhombic polymorphs of paracetamol: the NH...OH hydrogen bond forms C(7) motifs at the unitary level of graph set analysis (Bernstein et al., 1995). However, it should be noted that the
conformation of the paracetamol molecules in the solvate is different from that of the monoclinic and orthorhombic forms, i.e. the H-N...O-H dihedral angle is close to 180° for the solvate, but is close to 0° for the monoclinic and orthorhombic forms. These chains are linked via methanol molecules giving an overall layered structure that closely resembles that of paracetamol monohydrate (Figure 5.6b), although in the monohydrate the additional O-H bonds of water molecules link layers together to form a 3-D network (Parkin et al., 2002). It is therefore not surprising that the two structures can in part be described by the same graph-set analysis with the formation of small R4(22) rings and larger R8(30) rings between four of the smaller rings. One striking feature of the structure of the methanol solvate is the presence of large hydrophobic regions within the R8(30) rings.

Figure 5.6 2-D hydrogen-bonded network of paracetamol-methanol at 0.6 GPa (a) and paracetamol monohydrate at 150 K (b).

The methanol solvate exhibits corrugated sheets (Figure 5.7). Similar sheets are also found in the monoclinic polymorph of paracetamol (Figure 5.8a), whereas the orthorhombic form is characterised by parallel planar layers (Figure 5.8b).
Figure 5.7 Corrugated layers in paracetamol-methanol at 0.6 GPa viewed perpendicular to the \( bc \) plane.

Figure 5.8 Corrugated layers in monoclinic paracetamol (a) and flat layers in orthorhombic paracetamol (b).

Given the paucity of the data, it is not possible to discuss the detailed aspects of the hydrogen bonding in the structure. Nevertheless, it is possible to rationalise the pattern of Donor...Acceptor (D...A) interactions found in the structure by examining the relative strengths of hydrogen-bonding interactions using the assumption that hydrogen-bond strength is related to the average D...A distance.
A search of the Cambridge Structural Database (version 5.24) for ArOH...O(H)R, Ar-OH...ONC(amide) and ROH...ONC(amide) mean hydrogen-bond lengths is summarised in Table 5.7.°

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<td>1.86</td>
<td>2.20</td>
<td>1.83</td>
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</table>

Table 5.7 Mean hydrogen-bond lengths obtained from searches of the CSD for typical distances in hydrogen-bonded systems containing specified functional groups. Distances to hydrogen atoms were normalised to typical neutron distances (N-H 1.009 and O-H 0.983 Å).

For both the monoclinic and orthorhombic polymorphs of paracetamol, the two interactions are NH...O(H)Ar and Ar-OH...ONC(amide), and on the basis of Table 5.5 the latter is the stronger of the two. Rather surprisingly, in the methanol

° All searches were performed in the CSD version 5.24 according to the following criteria. Distances to H atoms were normalised to typical neutron distances (C-H to 1.803 Å, N-H to 1.009 Å and O-H to 0.983 Å) to enable direct comparison. The carbon atoms attached to the amine moiety and aliphatic alcohol were specified to be tertiary. The H...A distance was specified to be 1.5-2.20 Å. The search was restricted to organic structures, not disordered, ionic or polymeric for which 3-D coordinates were determined and with an R-factor less than 5 %.

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solvate the former interaction persists, whilst the latter interaction is not present, but is replaced by two new interactions ROH...ONC(amide) and ArOH...O(H)R. One way of rationalising this observation is to identify from the table the strongest ROH...O interaction, which is ROH...ONC(amide). Given this, it is then a competition between either the combination NH...O(H)Ar and ArOH...O(H)R or the combination NH...O(H)R or ArOH...O(H)Ar. At 1.78 Å the strongest interaction is ArOH...O(H)R, thereby favouring the former combination.

The angle between the mean planes of the amide and phenyl group is known to be very susceptible to the degree of protonation/deprotonation of the OH and NH groups (Binev et al., 1998) and at 11.2° is close to that found in the monohydrate (10.3°), but significantly different from the corresponding angles in the monoclinic and orthorhombic polymorphs of paracetamol (20.5° and 17.7°, respectively). Analogous angles observed in a series of co-crystals of paracetamol (Oswald, et al., 2002a) range from 3.03 to 41.72°.  

5.4.2 High-pressure recrystallisation of paracetamol from water at 1.1 GPa: 

Unit-cell parameters for the hydrates of paracetamol are summarised in Table 5.8. Various combinations of hydrogen atoms positions associated with disordered water molecules were found to give plausible hydrogen-bonding patterns. Given the paucity of data no disorder was modelled and hydrogen atoms on the oxygen atoms of water molecules were omitted. The presence of disorder makes the description of hydrogen bonding and comparison with other hydrates of paracetamol less straightforward.

Chapter 5 – The influence of Pressure on the Formation of Polymorphs, Solvates and Hydrates of Paracetamol
<table>
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<tr>
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<td><em>P</em>2&lt;sub&gt;1&lt;/sub&gt;/n</td>
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<td>7.3324(16)</td>
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<td>12.590(3)</td>
</tr>
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<td>10.736(4)</td>
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<td>273(2)</td>
<td>150(2)</td>
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<sup>a</sup> Parkin <i>et al.</i>, 2002. <sup>b</sup> This work. <sup>c</sup> McGregor <i>et al.</i>, 2002.

**Table 5.8** Crystallographic data for paracetamol hydrates.

The crystal packing of the dihydrate is dominated by hydrogen bonding, giving rise to 3-D networks. One of the layers in this network is also found in the monoclinic and orthorhombic polymorphs of paracetamol, namely the OH...O=C hydrogen bonds that form C(9) zig-zag chains at the unitary level of graph-set analysis (Bernstein <i>et al.</i>, 1995) that run along the crystallographic *b* axis (Figure 5.9). However, it should be noted that the conformation of the paracetamol molecules is different from that of the monoclinic or orthorhombic forms, i.e. the dihedral angle between the N-H and O-H bonds angle is close to 150° for the dihydrate, but is close to 0° for the two anhydrous polymorphs. These angles have values of 180° and 30° for the monohydrate and dihydrate species, respectively. Each C(9) chain is linked to two further chains via NH...O(water)...O=C hydrogen bonds running along the crystallographic *c* axis, giving an overall 3-D hydrogen-bonded pattern (Figures 5.10 and 5.11). These chains are linked to adjacent chains via water molecules, whose
Oxygen atoms are arranged in a square-like fashion. These "squares" are linked directly to each other, and give rise to an unusual "tape" motif (Infantes et al., 2003) that runs along the $a$ axis.

Figure 5.9 View of C(9) chains perpendicular to the $bc$ plane (the chains run along the $b$ axis).

Figure 5.10 View perpendicular to the $ac$ plane of C(9) chains (represented here by molecules of the same colour) linked via NH...O(water)...O=O hydrogen bonds.

Figure 5.11 View of the motif illustrated in Figure 5.10 (here represented by molecules of the same colour) (a) perpendicular to the $ac$ plane and (b) along the crystallographic $c$ axis, showing water-oxygen "square" motifs.
The angle between the mean planes of the amide and phenyl group is known to be very susceptible to the degree of protonation/deprotonation of the OH and NH groups (Binev et al., 1998). At 7.6° it is close to those found in the monohydrate (10.3°) (Parkin et al., 2002) and the methanol solvate (11.2°), but significantly different from the corresponding angles in the monoclinic and orthorhombic polymorphs of paracetamol (20.5° and 17.7°, respectively) (Nichols & Frampton, 1998), and very different from the corresponding angle in the trihydrate (45.9°) (McGregor et al., 2002).

5.4.2.1 Decompression experiments

Optical observation of the crystal on progressive decompression at 293 K showed gradual dissolution of the crystal rather than a catastrophic phase change as observed in the case of phenanthrene (Chapter 3). This suggests that the dihydrate may be sufficiently metastable to exist at ambient pressure provided that the temperature is sufficiently low. Given the existence of a monohydrate and trihydrate of paracetamol at ambient pressure, albeit stable under a narrow range of temperatures, it would not be too surprising to discover that other hydrates may be stable at ambient pressure.

5.4.3 Recrystallisation from ethanol at 1.0 GPa and from acetone at 0.2 GPa

In an attempt to explore whether other paracetamol solvates could be prepared by high-pressure recrystallisation, paracetamol was recrystallised from ethanol at a pressure of 1.0 GPa. However, instead of a solvate, a single crystal of the orthorhombic polymorph of paracetamol was obtained. This is perhaps not unexpected given that Boldyreva et al. (2002) have shown that direct compression of the monoclinic form as a powder results in the formation of the orthorhombic form, in line with the higher density of this form measured to 4.0 GPa. However, it is noteworthy that those experiments required pressures of 4.0 GPa and even then conversion was incomplete. In the current recrystallisation study, much more modest pressures are required and conversion is complete, thereby indicating very convincingly that the high-pressure recrystallisation technique is able to overcome the kinetic barriers associated with interconversion of polymorphs in the solid state.
This is a significant result in that it demonstrates the feasibility of crystallising at high pressure a polymorph that is metastable at ambient temperature and pressure. Furthermore, it has been demonstrated that the metastable polymorph can be prepared at relatively modest pressures. The significant example is represented by the recrystallisation of paracetamol from acetone at 0.2 GPa: instead of a solvate, a single crystal of the orthorhombic form was obtained. These results open up the possibility of preparing much larger quantities by seeding solutions at ambient pressure. The use of larger volume hydraulic high-pressure cells for the precipitation and isolation of larger quantities of polycrystalline material is an area that is currently being explored.

With the limited number of high-pressure experiments performed so far, it would be premature to rule out the existence of a 1:1 ethanol solvate of paracetamol analogous to the 1:1 methanol solvate reported in Section 5.4.1. However, a possible reason for failing to observe this solvate is suggested by inspection of the structure of the 1:1 methanol solvate (Figure 5.6a). In this structure, the methyl groups of paracetamol and methanol molecules are arranged to form hydrophobic regions. Given the larger steric requirement of an ethyl group compared to a methyl group, such regions would be required to be larger in an ethanol solvate, thereby weakening or disrupting the hydrogen-bonding arrangement in the remainder of the structure. Of course, there is no obvious reason why an ethanol solvate with a different structure could not be prepared and this is an area that deserves exploration.

Despite the good quality of the data collected on the single-crystal of paracetamol/acetone at 0.6 GPa, its structure has not been solved so far. There seems to be no obvious reason as to why this should be the case, but it is likely that the range and number of reflections collected was insufficient, most likely because of the orientation of the crystal in the diamond-anvil cell. It is possible that the crystal was twinned, although this was not apparent from the diffraction pattern or data merging statistics; the presence of disorder may also contribute to the difficulty in structure solution. Further single-crystal and powder diffraction experiments are therefore planned to obtain more structural data.
5.5 Conclusions

By extending the general technique of high pressure to include high-pressure recrystallisation from solution, we have demonstrated that high-pressure crystallisation is no longer restricted to compounds that have melting points near or below ambient temperature. With a relatively high melting point of 442 K (form I), any attempt of heating the material and growing crystals from the melt at high pressure would inevitably have resulted in its chemical decomposition. Furthermore, the use of different solvents allows access to new solvates: high-pressure recrystallisation of paracetamol from methanol and from water afforded a new methanolate and a dihydrate, respectively.

This work has demonstrated that high-pressure recrystallisation can be used to prepare a polymorph that is metastable under ambient conditions. Although this is only the first example, it seems likely that other high-pressure polymorphs and solvates will be found that can subsequently be recovered under ambient conditions. This is because the phenomenon of polymorphism relies on the existence of kinetic barriers to prevent interconversion of polymorphs. Thus, in future high-pressure recrystallisation experiments, it is inevitable that occasionally new polymorphs/solvates will be formed, for which there is no facile molecular rearrangement pathway available to regenerate the ambient-pressure phase.

Given that almost all conventional polymorph/solvate screening procedures in both the academic and pharmaceutical sectors are currently performed at or near ambient pressure, the high-pressure recrystallisation technique has the potential to complement and enhance existing methods by providing another dimension for exploration.

The work presented in this chapter also highlights the challenges associated with high-pressure single-crystal X-ray diffraction, one of the most important being the restricted reciprocal space that can be accessed using diamond-anvil cells. The resulting low completeness of data often causes structure solution to fail by direct methods. Advances in structure solution from powder diffraction methods have so far enabled to overcome this problem. These techniques will be further tested and challenged in the future, as high-pressure single-crystal and powder studies will be extended to more complex systems with more degrees of freedom. Development of
new cells and data-collection strategies are areas that should also be explored in order to increase the number and the quality of reflections that can be collected in a single-crystal X-ray diffraction experiment.

5.6 References


Chapter 5 - The influence of Pressure on the Formation of Polymorphs, Solvates and Hydrates of Paracetamol
Chapter 6

An Exploration of the Polymorphism of Piracetam Using High Pressure
6.1 Introduction

Piracetam (2-oxo-pyrrolidineacetamide) is a nootropic agent, currently marketed by UCB Pharma as Nootropil®, that is used to treat conditions of age-associated mental decline and disorders of the nervous system (see Figure 6.1 for the molecular structure). Three polymorphs of piracetam have been identified and structurally characterised. Forms II (triclinic, $P\overline{1}$) and III (monoclinic, $P2_1/n$) can be prepared by recrystallisation from various solvents (e.g. methanol, propan-2-ol) under ambient conditions, and crystal structures for both forms have been reported (Bandoli et al., 1981; Admiraal et al., 1982). Both forms transform above 400 K into the high-temperature phase denoted as form I (triclinic, $P\overline{1}$). This can be recovered to ambient temperature by quenching, but transforms within a few hours at 298 K into form II. Its crystal structure has been determined from X-ray powder diffraction in combination with minimisation of the crystal-lattice potential energy (Louër et al., 1995).

![Figure 6.1 Molecular structure of piracetam with numbering scheme.](image)

All three polymorphs have been studied by thermochemical methods and shown to be enantiotropically related (Toscani, 1998; Kühnert-Brandstätter et al., 1994; Céolin et al., 1996). The hierarchical stability of these polymorphs was studied by relating sublimation vapour pressures to measurements made by differential scanning calorimetry (Toscani, 1998). These studies concluded that at ambient temperatures the stability order is II > III > I, whilst above 399 K the stability order is I > II > III (Toscani, 1998). However, these results are in disagreement with those obtained from studies using thermomicroscopy and DSC measurements, which
showed that at ambient temperature form III is more stable than form II (Kühnert-Brandstätter et al., 1994).

The III → I phase change has also been studied at high pressure. After compression of a sample of form III to ca. 0.2 GPa at 443 K followed by decompression, the III → I transition was recorded at 0.156 GPa (Ter-Minassian & Milliou, 1992). Form III has been identified as the stable form at higher pressures on the basis of these observations and because it is the densest of the three forms under ambient conditions (Toscani, 1998). Lattice energy calculations using the atom-atom potential method (Pertsin & Kitaigorodskii, 1987) have been performed to give values of -87.29, -97.30, and -99.44 kJ mol\(^{-1}\) for phases I, III, and II, respectively (Louër et al., 1995). These calculations also located another distinct minimum at -100.78 kJ mol\(^{-1}\), but this structure has never been observed experimentally. Three further polymorphs have been postulated on the basis of morphological changes and differences in optical polarisation observed on cooling from the melt, but in all cases transformation into form II occurred very rapidly at room temperature (Kühnert-Brandstätter et al., 1994).

The approach presented in this chapter has been to explore how the recrystallisation of piracetam from various solvents under high pressures might lead to the formation of different polymorphs. This interest was also corroborated by the intriguing observation that although piracetam has been extensively studied in a range of solvents, no hydrates or other solvates have ever been reported in the academic literature. Hence the use of high-pressure methods might be expected to change this situation.
6.2 Experimental procedure – anhydrous piracetam

6.2.1 High-pressure recrystallisation from water at 0.4 GPa: form IV

A ca. 6 M aqueous solution of piracetam (Sigma-Aldrich) was loaded at 293 K into a Merrill-Bassett diamond-anvil cell (Merrill & Bassett, 1974) equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole. On sealing the cell and pressurising to ca. 0.4 GPa precipitation of polycrystalline material occurred. The temperature was then cycled near ca. 323 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 75 % of the gasket hole (Figure 6.2). The pressure within the gasket hole was determined as ca. 0.4 GPa in the manner describer in Section 2.1.3. During manipulation of the cell it was observed that the crystal dissolved slightly and became free to move within the gasket hole. It is suspected that this may have been caused by slight variations in temperature and/or pressure, which therefore affected solubility.

Figure 6.2 Optical image of a single crystal of the high-pressure polymorph of piracetam, form IV, at 0.4 GPa in a diamond-anvil cell.

Diffraction data were collected according to procedures described by Dawson et al. (2004) detailed in Section 2.2.1. Each data collection consisted of ω scans at two different Φ values (90° and 270°) and, as a consequence of the crystal moving within the gasket, two orientation matrices were identified for the two Φ settings. Diffraction data were collected with the diamond-anvil cell in two orientations (glued onto the goniometer head by two different sides of the cell) to simulate two different values of χ in order to improve data completeness.
Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions substantially different from any of the three known polymorphs of piracetam. Structure solution using direct methods with subsequent full-matrix least-squares structure refinement identified the crystal as a new polymorph of piracetam, which has here been denoted as form IV.

6.2.2 High-pressure recrystallisation from methanol: forms II, III and IV

In order to explore the effect of a different solvent on the high-pressure recrystallisation of piracetam, a ca. 1.6 M methanolic solution of piracetam was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole together with a few small crystallites of form III (previously identified by single-crystal X-ray diffraction). The cell was sealed and pressurised to ca. 0.5 GPa, and then heated to ca. 313-323 K to dissolve all of the solid. The cell was then depressurised to 0.15 GPa and cooled to 293 K, at which point precipitation of small crystallites occurred. The temperature was then cycled near ca. 323 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 50% of the gasket hole (Figure 6.3). The pressure within the gasket hole was determined as ca. 0.1 GPa. Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a unit cell with dimensions similar to those found for form III corresponding to a volume decrease of ca. 2.5% compared with the volume at ambient pressure.

The crystal of form III was redissolved by gentle heating and the pressure was reduced to ca. 0.07 GPa. Over a period of 48 hours at 293 K, a single crystal grew in the cell and this was subsequently identified by single-crystal X-ray diffraction as the new form IV (Figure 6.3), but with a density reduced by ca. 2.5% compared with the structure previously obtained at 0.4 GPa. On depressurising the crystal of form IV to ambient pressure at 293 K, partial dissolution occurred, but a single crystal remained clearly visible (Figure 6.3). Single-crystal X-ray diffraction showed this to be form II.
All diffraction data were collected according to procedures described by Dawson et al. (2004) detailed in Section 2.2.1. Partial datasets were collected in order to extract qualitative structural information, i.e. for polymorph identification.

![Image of optical images of successive high-pressure recrystallisation of piracetam from methanol in a diamond-anvil cell.]

**Figure 6.3** Optical images of successive high-pressure recrystallisation of piracetam from methanol in a diamond-anvil cell.

6.2.3 **Polymorph screening at ambient pressure: form I**

The structure of form I had previously been solved from powder diffraction data (Louër et al., 1995). It is not difficult to produce form I: heating form II or form III to 400 K induces rapid transformation. However, the conversion has always been reported for polycrystalline material and no single-crystal structure has ever been published.

The high-temperature polymorph form I was not identified in the preliminary high-pressure screening reported in Section 6.2.2. However, single-crystal X-ray diffraction data from a single crystal of form I were successfully obtained by heating single crystals of form III to 400 K, cooling to 298 K, and then after coating with oil, cooling rapidly to 150 K.

Diffraction data were collected on a Bruker APEX CCD diffractometer equipped with an Oxford Cryosystems low-temperature device at 150(2) K using Mo Kα radiation (\(\lambda = 0.71073\) Å). Data collection (\(\omega\) and \(\phi\) scans) was optimised with the program COSMO (Bruker 2004).
No significant worsening of the diffraction pattern was observed as data collection progressed and at the end of the 12 h run the single crystal remained intact, as shown in Figure 6.4.

![Figure 6.4](image)

*Figure 6.4* Optical image of a single crystal of form I on a glass fibre mounted on a goniometer head (a) before and (b) after 12 h of data collection at 150 K.

### 6.2.4 Compression studies of piracetam form II: the transition to form V

Intrigued by the observation that form IV had transformed to form II on depressurising to ambient pressure via a single-crystal to single-crystal phase transition, the interest focussed on probing whether the reverse transition could be induced by compression of form II.

Single crystals of form II were grown at ambient pressure by slow evaporation of saturated solutions (at 323 K) of piracetam (Sigma-Aldrich) in 2-propanol and 1,4-dioxane, respectively. The correct polymorph was identified by checking the unit cell prior to loading into the diamond-anvil cell. All attempts to cut the crystals to the required size for loading resulted in damage, as confirmed by visual inspection with an optical microscope (the crystals exhibited shear damage irrespective of the direction of cleavage), or by checking the quality of the X-ray diffraction pattern (crystals that were cut did not diffract using either laboratory or synchrotron sources).

Instead, recrystallisation from solution at high pressure was attempted. A saturated solution (at 293 K) of piracetam and 2-propanol was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole together with a few small crystallites (obtained
by cutting larger crystals) of form II. The cell was sealed and pressurised to ca. 0.2 GPa and the temperature was cycled between 313-323 K to grow a single crystal. A unit cell check performed on the diffractometer revealed this to be a crystal of form III. This could either suggest that the crystals of form II had transformed to form III on cutting at ambient pressure, or on cycling the temperature in solution under these high-pressure conditions, indicating that form III is the stable form at high pressure, as previously noted by Toscani (1998).

In a second attempt, the cell was reloaded as described above and was sealed under a very minimum of pressure such that a small air bubble remained visible in the gasket. The cell was then heated to ca. 313 K to dissolve all of the solid and then pressurised while warm to ca. 0.1 GPa. On cooling to 293 K, precipitation of small crystallites occurred. The temperature was then cycled near ca. 313 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 50% of the gasket hole. Dissolution of all crystalline material proved to be the key step to successfully obtain crystals of the desired form II and prevent nucleation of form III. The cell was then pressurised to ca. 0.9 GPa. Indexing of the reflections gave a triclinic unit cell with reduced cell dimensions related to those of form II, but with a significant increase of ca. 10° of the β angle. Diffraction data were collected with the diamond-anvil cell in two orientations (glued onto the goniometer head by two different sides of the cell) to simulate two different values of χ in order to improve data completeness and obtain good quality structural data on this new polymorph, here denoted as form V.

The pressure inside the cell was subsequently decreased to 0.45 GPa and indexing of reflections indicated that a single-crystal to single-crystal transition to form II had occurred: a full dataset was collected at this pressure. The pressure inside the cell was then increased to ca. 0.7 GPa and a reversible transition to form V was observed. Two further datasets in this compression study were subsequently collected at 2.5 and 4.0 GPa.

All diffraction data were collected at Station 9.8 at the CCLRC Daresbury Laboratory with a Bruker APEX 2 CCD diffractometer at 293(2) K using synchrotron radiation (λ = 0.6765 Å). Data collection was performed according to an established 1-second ω-scans procedure (Moggach et al., 2005).
6.3 Results – anhydrous piracetam

6.3.1 High-pressure recrystallisation from water at 0.4 GPa: form IV

Data processing was performed according to the procedures described by Dawson et al. (2004) and detailed in Section 2.2.2. Owing to the freedom of movement of the single crystal in the sample chamber, the strategy of collecting data with the diamond-anvil cell in two orientations resulted in only a poor improvement of the overall data completeness (ca. 43%). Each data collection consisted of \( \omega \) scans at two different \( \varphi \) values (90° and 270°) and as a result of the crystal moving within the sample chamber, two orientation matrices were identified for the two \( \varphi \) settings, giving a total of four datasets. All datasets were treated separately up to the absorption correction step. The four unmerged reflection files were then scaled and merged with \textit{SORTAV} (Blessing, 1995) in the manner described by Dawson et al. (2004). The structure was solved by direct methods using \textit{SIR92} (Altomare et al., 1993) and full-matrix least-squares structure refinement was performed using \textit{CRYSTALS} (Watkin et al., 2003). Thirteen reflections were treated as outliers and were omitted in the refinement after close investigation revealed they were either partially overlapping with diamond reflections, or with intense beryllium powder rings. All non-hydrogen atoms were refined anisotropically; rigid-bond and thermal similarity restraints were employed to obtain a satisfactory model. All hydrogen atoms were placed in calculated positions and fixed during refinement.

A final \( R \)-factor of 5.3 % was obtained, which represents a good refinement of high-pressure data collected for a monoclinic crystal system and allows reliable comparison with the structural features of the three known polymorphs.

Full refinement details are shown in Table 6.1. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

### Form IV at 0.4 GPa

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Form IV at 0.4 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C71H10N2O2</td>
</tr>
<tr>
<td>( M_r )</td>
<td>142.16</td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, ( P2_1/c )</td>
</tr>
</tbody>
</table>

Table 6.1 Crystal, collection and refinement details for form IV at 0.4 GPa.
### Table 6.1 (cont.) Crystal, collection and refinement details for form IV at 0.4 GPa.

<table>
<thead>
<tr>
<th>Form IV at 0.4 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a, b, c$ (Å)</td>
</tr>
<tr>
<td>$\beta (^\circ)$</td>
</tr>
<tr>
<td>$V$ (Å$^3$)</td>
</tr>
<tr>
<td>$Z$</td>
</tr>
<tr>
<td>$D_x$ (Mg m$^{-3}$)</td>
</tr>
<tr>
<td>Radiation type</td>
</tr>
<tr>
<td>No. of reflections for cell parameters</td>
</tr>
<tr>
<td>$\theta$ range ($^\circ$)</td>
</tr>
<tr>
<td>$\mu$ (mm$^{-1}$)</td>
</tr>
<tr>
<td>Temperature (K)</td>
</tr>
<tr>
<td>Crystal form, colour</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
</tr>
<tr>
<td>Data collection</td>
</tr>
<tr>
<td>Diffractometer</td>
</tr>
<tr>
<td>Data collection method</td>
</tr>
<tr>
<td>Absorption correction</td>
</tr>
<tr>
<td>$T_{\text{min}}$</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
</tr>
<tr>
<td>No. of measured, independent and observed reflections</td>
</tr>
<tr>
<td>Criterion for observed reflections</td>
</tr>
<tr>
<td>$R_{\text{int}}$</td>
</tr>
<tr>
<td>$\theta_{\text{max}}$ ($^\circ$)</td>
</tr>
</tbody>
</table>
| Range of $h, k, l$ | $-11 \rightarrow h \rightarrow 11$  
|                       | $-6 \rightarrow k \rightarrow 6$  
|                       | $-8 \rightarrow l \rightarrow 9$  |
| Refinement         | |
| Refinement on      | $F^2$ |
| $R(F^2 > 2\sigma(F^2)), wR(F^2), S$ | 0.053, 0.103, 1.09 |
| No. of reflections | 457 reflections |
| No. of parameters  | 92 |
| H-atom treatment  | Not refined |
| Weighting scheme   | $W = 1/[\Sigma\sigma^2(F^*) + (P(1)p^2 + P(2)p + P(3)p + P(4) + P(5)\sin(\theta))]$  
| $P(0)$ are: | 0.247 1.0 0.610 0.000 0.000 0.000 0.333 |

Chapter 6 – An Exploration of the Polymorphism of Piracetam using High Pressure
### Table 6.1 (cont.) Crystal, collection and refinement details for form IV at 0.4 GPa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(\Delta c)_{\text{max}}$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\Delta p_{\text{max}}$, $\Delta p_{\text{min}}$ (e Å$^{-3}$)</td>
<td>0.20, -0.24</td>
</tr>
<tr>
<td>Extinction method</td>
<td>Larson, 1970</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>57 (17)</td>
</tr>
</tbody>
</table>

#### 6.3.2 High-pressure recrystallisation of piracetam from methanol: forms II, III and IV

Partial datasets were collected in order to extract qualitative structural information, namely for polymorph identification of this screening experiment. Results from data integration are shown in Table 6.2. Due to the low number of data collected, the structures were not refined and no further structural information is presented here.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Form III at 0.1 GPa</th>
<th>Form IV at 0.07 GPa</th>
<th>Form II at ambient pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>$C_6H_{17}N_2O_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M_r.$</td>
<td>142.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, $P2_1/n$</td>
<td>Monoclinic, $P2_1/c$</td>
<td>Triclinic, $P-1$</td>
</tr>
<tr>
<td>$a$, $b$, $c$ (Å)</td>
<td>6.4823 (9), 6.3897 (9), 16.283 (4)</td>
<td>9.0240 (16), 5.5335 (12), 13.719 (4)</td>
<td>6.387 (2), 6.605 (2), 8.531 (5)</td>
</tr>
<tr>
<td>$\alpha$, $\beta$, $\gamma$ (°)</td>
<td>90, 92.33 (2), 90</td>
<td>90, 105.32(3), 90</td>
<td>80.00 (5), 102.46 (5), 91.20 (3)</td>
</tr>
<tr>
<td>$V$ (Å$^3$)</td>
<td>673.9(2)</td>
<td>660.7(3)</td>
<td>346.0(3)</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>$D_c$ (Mg m$^{-3}$)</td>
<td>1.401</td>
<td>1.429</td>
<td>1.364</td>
</tr>
<tr>
<td>Radiation type</td>
<td>Mo Kα</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of reflections for cell parameters</td>
<td>364</td>
<td>94</td>
<td>111</td>
</tr>
<tr>
<td>$\theta$ range (°)</td>
<td>3–26</td>
<td>4–12</td>
<td>4–18</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal form, colour</td>
<td>Block, colourless</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal size (nm)</td>
<td>$0.25 \times 0.15 \times 0.15$</td>
<td>$0.25 \times 0.20 \times 0.15$</td>
<td>$0.20 \times 0.15 \times 0.15$</td>
</tr>
</tbody>
</table>

Table 6.2 Crystal data for form III at 0.1 GPa, form IV at 0.07 GPa and form II at ambient pressure.
6.3.3 Polymorph screening at ambient pressure: form I

Data integration and reduction were performed using the program SAINT (Bruker, 2003). Known fractional coordinates of form I were taken from the literature (CSD reference code BISMEV03) and full-matrix least-squares structure refinement was performed using CRYSTALS (Watkin et al., 2003). The carbon atom C(3) was disordered about two sites and the occupancies of the two components refined to 0.66(1) and 0.34(1), respectively. All non-hydrogen atoms were refined anisotropically: the disordered carbon atoms were constrained to have the same anisotropic displacement parameters and bond distances to adjacent carbon atoms were refined subject to restraints. Hydrogen atoms attached to carbon were placed in calculated positions and their position fixed during refinement, with disorder modelled for the appropriate atoms. Hydrogen atoms involved in hydrogen bonding were located on a difference-Fourier map and refined freely. A θ cut-off of 27° was applied during refinement.

Full refinement details are shown in Table 6.3. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Form I at 150 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C₆H₁₀N₂O₂</td>
</tr>
<tr>
<td>M,</td>
<td>142.16</td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Monoclinic, P2₁/n</td>
</tr>
<tr>
<td>a, b, c (Å)</td>
<td>6.7254 (2), 13.2572 (4), 8.0529 (2)</td>
</tr>
<tr>
<td>β (°)</td>
<td>98.603 (2)</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>709.92 (4)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>D₄ (Mg m⁻³)</td>
<td>1.330</td>
</tr>
<tr>
<td>Radiation type</td>
<td>Mo Kα</td>
</tr>
<tr>
<td>No. of reflections for cell parameters</td>
<td>2057</td>
</tr>
<tr>
<td>θ range (°)</td>
<td>3-30</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
<td>0.10</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>150 (2)</td>
</tr>
<tr>
<td>Crystal form, colour</td>
<td>Block, colourless</td>
</tr>
</tbody>
</table>

Table 6.3 Crystal, collection and refinement details for form I at 150 K.
### Form I at 150 K

<table>
<thead>
<tr>
<th>Data collection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal size (mm)</td>
<td>$0.41 \times 0.25 \times 0.19$</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Bruker SMART</td>
</tr>
<tr>
<td>Data collection method</td>
<td>$\phi$ &amp; $\omega$ scans</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Multi-scan (based on symmetry-related measurements)</td>
</tr>
<tr>
<td>$T_{\text{min}}$</td>
<td>0.81</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>1.00</td>
</tr>
<tr>
<td>No. of measured, independent and observed reflections</td>
<td>8349, 2123, 1215</td>
</tr>
<tr>
<td>Criterion for observed reflections</td>
<td>$I &gt; 2\sigma(I)$</td>
</tr>
<tr>
<td>$R_{\text{int}}$</td>
<td>0.026</td>
</tr>
<tr>
<td>$\theta_{\text{max}}$ ($^\circ$)</td>
<td>30.6</td>
</tr>
<tr>
<td>Range of $h$, $k$, $l$</td>
<td>$-9 \rightarrow h \rightarrow 9$</td>
</tr>
<tr>
<td></td>
<td>$-18 \rightarrow k \rightarrow 13$</td>
</tr>
<tr>
<td></td>
<td>$-11 \rightarrow l \rightarrow 11$</td>
</tr>
</tbody>
</table>

### Refinement

<table>
<thead>
<tr>
<th>Refinement</th>
<th>$F^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R[F^2 &gt; 2\sigma(F^2)]$, $wR(F^2)$, $S$</td>
<td>0.042, 0.091, 0.97</td>
</tr>
<tr>
<td>No. of reflections</td>
<td>1545 reflections</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>103</td>
</tr>
<tr>
<td>H-atom treatment</td>
<td>Mixture of independent and constrained refinement</td>
</tr>
<tr>
<td>Weighting scheme</td>
<td>$W = 1 / [\Sigma^2(F^*P) + (P(1)p)^2 + P(2)p + P(4) + P(5)\sin(\theta)]$</td>
</tr>
<tr>
<td>$P(i)$ are: 0.297 - 0.00 0.00 0.00 0.00 0.333</td>
<td></td>
</tr>
<tr>
<td>$(\Delta\sigma)^{\text{max}}$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å$^{-3}$)</td>
<td>0.24, −0.24</td>
</tr>
</tbody>
</table>

Table 6.3 (cont.) Crystal, collection and refinement details for form I at 150 K.

### 6.3.4 Compression studies of piracetam form II: the transition to form V

Data processing was performed according to procedures described by Dawson et al. (2004) and detailed in Section 2.2.2.

The structural transition of form II to form V was first identified in the data collected at 0.9 GPa. The strategy of collecting data with the diamond-anvil cell in two orientations resulted in only a poor improvement of the overall data completeness (ca. 33 % to $\theta_{\text{max}} = 25^\circ$). Both datasets were treated separately up to the absorption correction step. The two unmerged reflection files were then scaled...
and merged in SORTAV (Blessing, 1995) in the manner described by Dawson et al. (2004). The structure of form V was solved by direct methods using SIR92 (Altomare et al., 1993) and full-matrix least-squares structure refinement was performed using CRYSTALS (Watkin et al., 2003). Despite the low data completeness, the good quality of the data allowed a satisfactory model to be obtained by refining all non-hydrogen atoms anisotropically in conjunction with rigid-bond and thermal similarity restraints, with the exception of carbon atom C(1), which was refined with an isotropic displacement parameter. However, all non-hydrogen atoms were later refined isotropically for a consistent and meaningful comparison with the structures of form II at 0.45 GPa (obtained by decompression of form V at 0.9 GPa) and of form V at 0.7, 2.5 and 4.0 GPa (obtained by compression of form II at 0.45 GPa). These were refined with isotropic displacement parameters owing to the low completeness of the datasets (a maximum completeness of ca. 28% to \( \theta_{\text{max}} = 25^\circ \) was observed; data were collected with the diamond-anvil cell in only one orientation and this accounts for the lower completeness compared with the 0.9 GPa data). All hydrogen atoms were placed in calculated positions and fixed during refinement.

Full refinement details are shown in Table 6.4. Crystallographic data in CIF format are available in the attached CD at the back of the thesis; details for the anisotropic refinement of the structure at 0.9 GPa are also available in the CD.

### Table 6.4 Crystal, collection and refinement details for forms II and V at increasing pressures.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Form II 0.45 GPa</th>
<th>Form V 0.7 GPa</th>
<th>Form V 0.9 GPa</th>
<th>Form V 2.5 GPa</th>
<th>Form V 4.0 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td></td>
<td>C(<em>4)H(</em>{19})N(_2)O(_2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( M_r )</td>
<td>142.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Triclinic, P-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( a, b, c (\text{Å}) )</td>
<td>6.321 (2), 6.5597 (11), 8.380 (4)</td>
<td>6.442 (2), 6.3530 (11), 8.737 (3)</td>
<td>6.3903 (7), 6.2932 (11), 8.6450 (16)</td>
<td>6.263 (2), 6.2063 (10), 8.412 (3)</td>
<td>6.169 (2), 6.1602 (11), 8.287 (3)</td>
</tr>
</tbody>
</table>

Chapter 6 – An Exploration of the Polymorphism of Piracetam using High Pressure
<table>
<thead>
<tr>
<th>Form II</th>
<th>Form V 0.45 GPa</th>
<th>Form V 0.7 GPa</th>
<th>Form V 0.9 GPa</th>
<th>Form V 2.5 GPa</th>
<th>Form V 4.0 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>α, β, γ (°)</td>
<td>79.82 (3), 102.34 (3), 90.94 (2)</td>
<td>81.43 (3), 112.88 (2), 91.38 (2)</td>
<td>81.106 (12), 113.680 (12), 91.295 (11)</td>
<td>80.77 (3), 114.69 (2), 91.12 (2)</td>
<td>80.41 (3), 115.33 (3), 91.15 (2)</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>334.0 (2)</td>
<td>325.49 (19)</td>
<td>314.26 (9)</td>
<td>292.81 (17)</td>
<td>280.23 (17)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>D₂ (Mg m⁻³)</td>
<td>1.413</td>
<td>1.450</td>
<td>1.502</td>
<td>1.612</td>
<td>1.685</td>
</tr>
<tr>
<td>Radiation type</td>
<td>Synchrotron radiation, λ = 0.6765 Å</td>
<td>Synchrotron radiation, λ = 0.6765 Å</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of reflections for cell parameters</td>
<td>484</td>
<td>531</td>
<td>531</td>
<td>524</td>
<td>492</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293 (2)</td>
<td>293 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal form, colour</td>
<td>Block, colourless</td>
<td>Block, colourless</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.20 × 0.15 × 0.15</td>
<td>0.20 × 0.15 × 0.15</td>
<td>0.20 × 0.15 × 0.15</td>
<td>0.20 × 0.15 × 0.10</td>
<td>0.20 × 0.15 × 0.10</td>
</tr>
</tbody>
</table>

**Data collection**

<table>
<thead>
<tr>
<th>Diffractometer</th>
<th>Bruker SMART Apex 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection method</td>
<td>ω scans</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Empirical &amp; multi-scan (based on symmetry-related measurements)</td>
</tr>
<tr>
<td>T_min</td>
<td>0.07</td>
</tr>
<tr>
<td>T_max</td>
<td>1.00</td>
</tr>
<tr>
<td>No. of measured, independent and observed reflections</td>
<td>1016, 363, 222</td>
</tr>
<tr>
<td>Criterion for observed reflections</td>
<td>I &gt; 2σ(I)</td>
</tr>
<tr>
<td>R(int)</td>
<td>0.0712</td>
</tr>
<tr>
<td>θ_max (°)</td>
<td>25.0</td>
</tr>
</tbody>
</table>

**Table 6.4 (cont.)** Crystal, collection and refinement details for forms II and V at increasing pressures.
<table>
<thead>
<tr>
<th>Piracetam form II at 0.45 GPa</th>
<th>Piracetam form V at 0.72 GPa</th>
<th>Piracetam form V at 0.9 GPa</th>
<th>Piracetam form V at 2.5 GPa</th>
<th>Piracetam form V at 4.0 GPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of h, k, l</td>
<td>-6 → h → 6</td>
<td>-7 → h → 7</td>
<td>-7 → h → 6</td>
<td>-7 → h → 6</td>
</tr>
<tr>
<td></td>
<td>-7 → k → 8</td>
<td>-7 → k → 7</td>
<td>-7 → k → 6</td>
<td>-7 → k → 7</td>
</tr>
<tr>
<td></td>
<td>0 → l → 7</td>
<td>0 → l → 5</td>
<td>0 → l → 8</td>
<td>0 → l → 4</td>
</tr>
</tbody>
</table>

**Refinement**

Refinement on $F^2$

<table>
<thead>
<tr>
<th>$R(F^2 &gt; 2\sigma(F^2))$, $wR(F^2)$, $S$</th>
<th>0.110, 0.284, 1.10</th>
<th>0.083, 0.229, 1.06</th>
<th>0.079, 0.208, 1.07</th>
<th>0.082, 0.205, 1.10</th>
<th>0.091, 0.239, 1.07</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of reflections</td>
<td>323 reflections</td>
<td>332 reflections</td>
<td>410 reflections</td>
<td>321 reflections</td>
<td>292 reflections</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>42</td>
<td>42</td>
<td>41</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>H-atom treatment</td>
<td>Not refined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighting scheme</td>
<td>Calculated $w = 1/[\sigma^2(F^2) + 0.13 + 0.88P]$</td>
<td>Calculated $w = 1/[\sigma^2(F^2) + 0.11 + 0.82P]$</td>
<td>Calculated $w = 1/[\sigma^2(F^2) + 0.09 + 0.66P]$</td>
<td>Calculated $w = 1/[\sigma^2(F^2) + 0.08 + 1.03P]$</td>
<td>Calculated $w = 1/[\sigma^2(F^2) + 0.14 + 0.65P]$</td>
</tr>
</tbody>
</table>

where $P = (\max(F^2, 0) + 2F_e^2)/3$

<table>
<thead>
<tr>
<th>$(\Delta/\sigma)_{\text{max}}$</th>
<th>&lt;0.0001</th>
<th>&lt;0.0001</th>
<th>&lt;0.0001</th>
<th>&lt;0.0001</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta \rho_{\text{max}}, \Delta \rho_{\text{min}}$ (e Å$^{-3}$)</td>
<td>0.27, -0.23</td>
<td>0.19, -0.24</td>
<td>0.29, -0.31</td>
<td>0.32, -0.25</td>
<td>0.23, -0.26</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>771 (78)</td>
<td>430 (150)</td>
<td>-</td>
<td>210 (80)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 6.4 (cont.)** Crystal, collection and refinement details for forms II and V as a function of pressure.
6.4 Discussion - anhydrous piracetam

Unit-cell parameters for the polymorphic forms of piracetam are summarised in Table 6.5.

<table>
<thead>
<tr>
<th>CSD reference code</th>
<th>Crystal system</th>
<th>Space group</th>
<th>a/Å</th>
<th>b/Å</th>
<th>c/Å</th>
<th>α/°</th>
<th>β/°</th>
<th>γ/°</th>
<th>V/Å³</th>
<th>Z</th>
<th>D₀/g cm⁻³</th>
<th>T/K</th>
</tr>
</thead>
<tbody>
<tr>
<td>BISMEV03</td>
<td>Monoclinic</td>
<td>P2₁/n</td>
<td>6.747(2)</td>
<td>13.418(3)</td>
<td>8.090(2)</td>
<td>90.0</td>
<td>99.01(3)</td>
<td>90.0</td>
<td>723.4(3)</td>
<td>4</td>
<td>1.306</td>
<td>283-303</td>
</tr>
<tr>
<td>BISMEV05</td>
<td>Monoclinic</td>
<td>P2₁/n</td>
<td>6.7250(2)</td>
<td>13.2570(4)</td>
<td>8.0530(2)</td>
<td>90.0</td>
<td>98.603(2)</td>
<td>90.0</td>
<td>709.87(4)</td>
<td>4</td>
<td>1.330</td>
<td>150(2)</td>
</tr>
<tr>
<td>BISMEV</td>
<td>Triclinic</td>
<td>P-1</td>
<td>6.403(3)</td>
<td>6.618(4)</td>
<td>8.556(6)</td>
<td>79.85(3)</td>
<td>102.39(3)</td>
<td>91.09(3)</td>
<td>348.5(4)</td>
<td>2</td>
<td>1.355</td>
<td>283-303</td>
</tr>
<tr>
<td>BISMEV01</td>
<td>Monoclinic</td>
<td>P2₁/n</td>
<td>6.525(2)</td>
<td>6.440(2)</td>
<td>16.463(5)</td>
<td>92.19(3)</td>
<td>92.19(3)</td>
<td>90.0</td>
<td>691.3(4)</td>
<td>4</td>
<td>1.366</td>
<td>283-303</td>
</tr>
<tr>
<td>BISMEV04</td>
<td>Triclinic</td>
<td>P₂₁/c</td>
<td>8.9537(11)</td>
<td>5.4541(6)</td>
<td>13.610(4)</td>
<td>90.0</td>
<td>102.39(3)</td>
<td>90.0</td>
<td>642.2(2)</td>
<td>4</td>
<td>1.470</td>
<td>293(2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Form I (powder)</th>
<th>Form I (single crystal)</th>
<th>Form II</th>
<th>Form III</th>
<th>High-pressure phase Form IV</th>
<th>High-pressure phase Form V</th>
</tr>
</thead>
<tbody>
<tr>
<td>BISMEV03</td>
<td>BISMEV05</td>
<td>BISMEV</td>
<td>BISMEV01</td>
<td>BISMEV04</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.5 Crystallographic data for polymorphs of piracetam.

a Louër et al., 1995.
b This work.
c Admiraal & Eikelenboom, 1982.
6.4.1 High-pressure recrystallisation from water at 0.4 GPa: form IV

The molecular packing arrangements in the crystal structures of forms II and III (Figure 6.5) are very similar and exhibit networks constructed of centrosymmetric hydrogen-bonded dimers of piracetam molecules, a motif commonly found in primary amides (Hagler & Leiserowitz, 1978).

![Figure 6.5 Hydrogen-bonding motif found in forms II and III.](image)

The descriptions of the hydrogen-bond pattern according to graph-set notation (Etter, 1990; Etter et al., 1990), are a first-level graph set $N_1 = C(7)R_2^2(8)$ formed by cyclic dimerisation of the two acetamide groups about the centre of inversion, and a second-level graph set, $N_2 = R_4^4(18)$ that is a product of hydrogen-bond interactions between the primary amide and pyrrolidone groups. The rings and chains form infinite ribbons connected by van der Waals interactions that pack differently in the two forms.

In the crystal structure of form I (Figure 6.6), piracetam molecules are linked by two types of hydrogen bonds in two types of perpendicular infinite chains, giving rise to a two-dimensional network. No cyclic hydrogen-bonded dimers of piracetam molecules are present in this structure. Graph-set analysis reveals a first-level graph set, $N_1 = C(4)C(7)$ and a second-level graph set, $N_2 = R_4^4(18)R_4^4(22)$. 

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The molecular packing in the crystal structure of the new high-pressure polymorph form IV (Figure 6.7) does not contain the centrosymmetric hydrogen-bonded dimers as found in forms II and III. Instead, dimers are formed by interactions between one of the N-H bonds of the primary amide of one molecule and the carbonyl oxygen of the pyrrolidone of an adjacent molecule to form a unitary ring motif denoted as $R_{2}^{2}(14)$ by graph-set analysis. These dimers are linked by infinite $C(4)$ chains that run along the $b$ axis. These are formed by the interaction between the other N-H bond of the primary amide and the primary amide oxygen of an adjacent molecule. The combination of these two hydrogen bonds results in a binary graph set that can be described as $R_{6}^{6}(26)$. Overall the hydrogen-bonded graph set for form IV is $N_{1} = C(4)R_{2}^{2}(14)$ and $N_{2} = R_{6}^{6}(26)$. These motifs form a two-dimensional layer that runs perpendicular to the $ac$ plane. Successive layers are related by glide planes that run parallel to the $ac$ plane.
This mode of dimer formation in form IV is unusual, but not unknown. A search of the Cambridge Structural Database (version 5.25) revealed 91 structures containing both a tertiary and a secondary amide group. Of these, 21 structures contain the centrosymmetric hydrogen-bonded amide dimers \([R_2^2(8)]\) that are found in forms II and III, and 12 structures exhibit the type of hydrogen-bonded dimer \([R_2^2(14)]\) found in form IV. A second search revealed 13 structures containing both a tertiary and primary amide group. Of these, 7 structures contain the amide dimers found in forms II and III and a further 2 structures exhibit both this motif and the type of dimer found in form IV (CEDJIE and QICXEF).

\(^1\) All searches were performed in the CSD version 5.25 (November 2003, with updates from January, April and July 2004) according to the following criteria: for the search of structures containing the type of tertiary amide group found in the pyrrole ring of piracetam, a restriction of a general formula: \(C_{13.30}O_{3.9}N_{2.8}H_{1.89}\) was applied to limit the number and type of functional groups containing oxygen and nitrogen atoms. The tertiary amide group was described as a nitrogen atom bonded to three non-hydrogen atoms, of which one carbonyl carbon and a further \(sp^3\) hybridised carbon with no hydrogens. Secondary amides were described as a nitrogen atom bonded to three atoms, of which one hydrogen atom and a carbonyl carbon were specified. Similarly, primary amides were described as a nitrogen atom bonded to two hydrogen atoms and one carbonyl carbon atom. All searches were restricted to crystal structures containing one residue. The search was further restricted to organic structures, not disordered, ionic or polymeric for which 3-D coordinates were determined and with an \(R\)-factor less than 10\%.
During structural refinement of form IV, hydrogen atoms were placed geometrically and their position fixed during refinement. It is therefore not possible to discuss the detailed aspects of the hydrogen bonding in the structure, but the comparison of Donor...Acceptor (D...A) distances with respect to the other known polymorphs is meaningful. At 3.017(5) Å, the D...A distance of the hydrogen bond involved in the formation of the dimer of form IV is longer than the one found in the dimer of forms II and III [2.942(3) and 2.945(2) Å, respectively]. Analysis of the structure retrieved from the CSD search detailed earlier shows that mean values for D...A distances in centrosymmetric dimers are 2.863 Å for structures containing a tertiary and a secondary amide and 2.939 Å for structures containing a tertiary and a primary amide.

Experimental bond lengths for the piracetam molecule are overall in good agreement with those observed for forms I, II, and III. The major differences lie in the conformations of both the acetamide group and the ring (Figure 6.8). In previous work, two torsional angles φ and ω, arising from the rotational freedom around C(5)-N(1) and C(5)-C(6), were defined by C(6)-C(5)-N(1)-C(1) and N(1)-C(5)-C(6)-N(2), respectively. Conformational energy maps calculated for an isolated molecule by means of semi-empirical calculations (Céolin et al., 1996) and by ab initio calculations (Bandoli et al., 1981) showed that the energy minimum is found at φ = 74° and ω = 298°. In the crystal structures of forms I, II, and III, higher energy conformations are observed (Table 6.6) and the authors speculated that although the conformations in both forms II and III are higher in energy than that of form I, it is the formation of hydrogen-bonded dimers in forms II and III that contributes to the stabilisation of these structures (Céolin et al., 1996). The values of φ and ω for form IV (115.4° and 32.0°, respectively) are substantially different from those for the other three forms and so lie on a different region of the energy contour map (in fact in a different potential energy well), but nevertheless this conformation appears to have a similar energy to those of forms II and III.
Table 6.6 Selected torsional angles for polymorphs of piracetam: the same numbering scheme was adopted throughout the analysis.

The conformations of the pyrrolidone rings in forms I, II, and III are all similar and a conformational analysis using methods developed by Pople & Cremer (1975) and Evans & Boeyens (1989), which have been incorporated into the program PLATON (Speck, 2000), reveals that they are best described as twisted (Table 6.7). By contrast, in form IV the ring adopts an envelope conformation with the fold running from C(2) to C(4) and with C(3) at the apex (see Table 6.7).
Cremer & Pople coefficients of primitive and normalized forms descriptor

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>$Q_2$/Å</th>
<th>$\phi_2$°</th>
<th>Cos form</th>
<th>Sin form</th>
<th>Closest pucker descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.152(14)</td>
<td>89(5)</td>
<td>0.056</td>
<td>0.944</td>
<td>Twist on C(2)-C(3)</td>
</tr>
<tr>
<td>Ic</td>
<td>0.213(4)</td>
<td>107.4(7)</td>
<td>0.966</td>
<td>0.034</td>
<td>Envelope on C(3)</td>
</tr>
<tr>
<td>II</td>
<td>0.1634(14)</td>
<td>299.6(5)</td>
<td>0.356</td>
<td>0.644</td>
<td>Twist on C(3)-C(4)</td>
</tr>
<tr>
<td>III</td>
<td>0.106(5)</td>
<td>309(2)</td>
<td>0.148</td>
<td>0.852</td>
<td>Twist on C(3)-C(4)</td>
</tr>
<tr>
<td>IVc</td>
<td>0.216(6)</td>
<td>282.7(16)</td>
<td>0.704</td>
<td>0.296</td>
<td>Envelope on C(3)</td>
</tr>
</tbody>
</table>

All standard uncertainties calculated with PLATON. 

Table 6.7 Ring puckering parameters for pyrrolidone rings of piracetam polymorphs, the same numbering scheme was adopted throughout the analysis and rings were defined as N(1)-C(1)-C(2)-C(3)-C(4).

6.4.2 High-pressure recrystallisation of piracetam from methanol: forms II, III and IV

The results obtained from the high-pressure recrystallisation of piracetam from methanol offer several interesting points of discussion. First of all, both forms III and IV can be recrystallised from methanol at very similar pressures. This may suggest that the two polymorphs have similar thermodynamic stabilities under these conditions, and/or that nucleation, growth processes and kinetic factors control which polymorph crystallises in the cell. It should in fact be noted that within the diamond-anvil cell there is a range of potential surfaces on which nucleation can occur, e.g. the ruby chip, the edge of the tungsten gasket, or the faces of the diamond, and these may also have an important influence in determining which polymorph is produced. For example, it is possible that a very small crystallite of form III persisted during the initial dissolution and was responsible for seeding the crystallisation of form III in the first recrystallisation experiment at 0.1 GPa. In the second recrystallisation at 0.07 GPa, dissolution removed all traces of form III, thereby allowing growth of form IV.

Lattice parameters obtained for form IV at 0.07 GPa are based on merely 94 reflections and are therefore less precise that might be desirable, but they

Chapter 6 – An Exploration of the Polymorphism of Piracetam using High Pressure
nevertheless point towards a *ca.* 3.1% lower density (1.426 g cm\(^{-3}\)) with respect to form IV crystallised from water at 0.4 GPa (1.470 g cm\(^{-3}\)). The density of form III increases by *ca.* 2.5% from 1.366 g cm\(^{-3}\) at ambient pressure to 1.401 g cm\(^{-3}\) at 0.1 GPa and this is a significant increase over a relatively small pressure range. It is also interesting to note that the density of form IV at 0.07 GPa appears to be higher than that of form III at the slightly higher pressure of 0.1 GPa. The paucity of the data and the uncertainty on the pressure measurement (*ca.* ±0.05 GPa) do not allow quantitative conclusions to be drawn. Form IV would be expected to crystallise on the basis of density (which is higher than the density of form II or III at similar conditions of pressure and temperature), but in fact form III is observed at 0.1 GPa. This may be attributed to the presence of seeds of form III in the pressure cell or to kinetic factors; alternatively, this could indicate that density may not govern the outcome of the crystallisation process.

The existence of form IV has been suggested by a computational study of piracetam (Price *et al.*, 2005). With no prior knowledge of the experimental results presented here, this study successfully predicted by lattice energy minimisation methods the existence of a low-energy polymorph (within 5 kJmol\(^{-1}\) of the total global energy minimum) that has the same structure as form IV. In addition to locating forms I, II and III, of the low-energy structures predicted in this study, form IV was identified as the most favourable new crystal structure based on density and most plausible hydrogen bonding. In particular, computed lattice parameters for form IV at ambient pressure and 0 K are in good agreement with experimental lattice parameters at 0.07 GPa and 0.4 GPa, *i.e.* they exhibit the trend expected with decompression. Overall, this result highlights the synergy between experimental and theoretical work. Although it is currently not possible to energy-minimise structures under applied pressure, initial investigations have shown that high-pressure polymorphs tend to appear amongst the lowest energy predicted structures, even in exotic cases of \(Z' = 3\) structures (Oswald *et al.*, 2005). The mutual benefit is clear from consideration that experimental structures observed at high pressure may help to rule out proposed computational structures, in conjunction with more traditional methods of structure comparison (*e.g.* through data mining in the CSD). Conversely, computed structures may help in the structure solution step of high-pressure data
processing, which is anticipated to become less straightforward for larger and more flexible molecular systems.

The direct transformation of form IV to form II on release of pressure at ambient temperature is an interesting result because such pressure-mediated single-crystal to single-crystal transformations that proceed without destruction (or dissolution) of the crystal are rare, and usually require the molecules to have some degree of conformational flexibility, e.g. the pressure-induced transformation of β-glycine to δ-glycine (Dawson et al., 2005). Such conformational flexibility is present in the piracetam molecule and at ambient temperature there will be sufficient thermal energy available to overcome any conformational barrier. At low temperatures, however, the available thermal energy may be too low and recovery of form IV at ambient pressure may yet be possible. In this system, depressurisation is expected to have two main effects: an increase in the solubility of piracetam and a change in the free energies of each of the possible polymorphs of piracetam. The change in solubility, and hence degree of supersaturation, might in some cases be expected to influence which polymorph is formed, particularly when polymorphs interchange via dissolution and re-precipitation, but in this case visual observation shows that although some dissolution of the crystal of form IV does occur, the bulk of the crystal remains intact, thereby suggesting that release of pressure changes the relative thermodynamic stabilities of forms II and IV.

6.4.3 Polymorph screening at ambient pressure: form I

Form I is reported to transform to form II within a few hours at ambient temperature (Louër et al., 1995; Céolin et al., 1996); the experiment reported in this thesis demonstrates quite clearly that the rate of this transformation can be dramatically reduced at low temperatures: the single crystal persisted with no apparent sign of degradation for over 12 hours at 150 K, although on warming back to ambient temperature it disintegrated completely within two hours.

This is the first reported single-crystal structure for form I. One of the major advantages of collecting low-temperature single-crystal data lies in the improved precision of refined structural parameters as well as in the ability to locate and refine hydrogen atoms that may be involved in hydrogen bonding. The crystal structure of
form I reported here is in very good agreement with the structure obtained from the previous powder diffraction study (Louër et al., 1995) thereby highlighting not only the high quality of the study by Louër et al., but also the growing power of structure solution methods from powder diffraction data. Bond lengths and angles in the two structures are not significantly different (within 3σ). The only difference is a slight variation in the torsion angle C(6)–C(5)–N(1)–C(1) (see Tables 6.6 and 6.7) that has the effect of causing the pyrrolidone ring to adopt an envelope rather than a twisted conformation. This may be a direct effect of the disorder observed in the structure that is likely to have arisen from the way the single crystal was obtained in the first place.

6.4.4 Compression studies of piracetam form II: the transition to form V

The structure of form V is very closely related to that of form II: the geometrical parameters of the molecules in the two forms are very similar, and the molecules are essentially superimposable, as shown in Figure 6.9. The phase transition is of a shear nature, as illustrated in Figure 6.9, which shows an overlay of form II at 0.45 GPa and form V at 0.7 GPa. The most striking difference between the lattice parameters of the two forms is the increase of the β angle by ca. 10° associated with the II → V transition.

Figure 6.9 Overlay of form II at 0.45 GPa and form V at 0.7 GPa.

Shear phase transitions are unusual, but not unknown in organic crystals. For example, the monoclinic polymorph (form II) of the pigment Indigo is related to another monoclinic modification (form I) by a shear transition that is accompanied by an increase in the β angle of ca. 13° (Eller-Pandraud, 1958). Another notable
example is represented by the hypnotic drug Zopiclone, in which slipping of bilayer sheets by 6.61 Å along the c axis and 1.48 Å along the a axis facilitate the dehydration of the monoclinic dihydrate (form I) to the monoclinic anhydrous species (form II) (Shankland et al., 2001).

The plots of Figures 6.10, 6.11 and 6.12 illustrate the variation of unit-cell parameters, cell volume and density with increasing pressure. Ambient pressure values for form II were taken from the literature (Admiraal & Eikelenboom, 1982; CSD reference code BISMEV).

![Graphs showing the variation of unit-cell parameters](image)

**Figure 6.10** Variation of a, b and c cell parameters of forms II and V as a function of pressure. The lines indicate the discontinuity referred to in the text and are guides to the eye.

A discontinuity between 0.4 and 0.7 GPa is apparent in the plots of Figure 6.10 and 6.11. The discontinuity is less obvious in the plot of volume vs. pressure (Figure 6.12), which could be interpreted as a smooth decrease in volume through the phase change. A subtle discontinuity could nevertheless be present and not be visible from the limited amount of data points sampled in this experiment. From the clear discontinuity observed in the plots of lattice parameters and in the absence of more data it is here postulated that the single-crystal to single-crystal reversible phase
transition between form II and form V occurs via a first-order transition between 0.45 and 0.7 GPa.

Figure 6.11 Variation of $\alpha$, $\beta$ and $\gamma$ cell parameters of forms II and V as a function of pressure. The lines indicate the discontinuity referred to in the text and are guides to the eye.

Figure 6.12 Variation of unit-cell volume and percentage density increase of forms II and V as a function of pressure. The lines indicate the discontinuity referred to in the text and are guides to the eye.
Compression of the crystallographic axes of form V from 0.7 to 4.0 GPa are 4.2, 3.0 and 5.1 % for $a$, $b$ and $c$, respectively. Over the same pressure range, the value of the triclinic $\alpha$ angle decreases by ca. 1.2 %, $\beta$ increases by 2.2 % and with a decrease of 0.2 % $\gamma$ remains almost unchanged.

Rationalisation of changes at the structural level as a function of pressure should be related to the linear strain in the directions of the principal axes of the strain ellipsoid rather than to the compressibilities of lattice parameters. This is because the unit cell is triclinic and so none of the three strain tensor vectors are expected to lie along the unit-cell axes.

Linear strain in the directions of the principal axes of strain ellipsoids vs. pressure was calculated using the program $STRAIN$ (Parsons, 2003) and is shown in Figure 6.13.

![Plot of linear strain in the directions of the principal axes of strain ellipsoids vs. pressure for piracetam-V](image)

Figure 6.13 Plot of linear strain in the directions of the principal axes of strain ellipsoids vs. pressure for piracetam-V. Colouring scheme: blue, minimum strain; red, medium strain; green, maximum strain.

The directions of the minimum, medium and maximum compression with respect to the cell axes are shown in Figure 6.14: the same colouring scheme as in Figure 6.13 was used to differentiate between the three directions. As it will be discussed in the following paragraphs, the medium and maximum directions of
compression correlate well with the directions of hydrogen bonding, whilst the minimum direction parallels the minimisation of sterically unfavourable CH₂...H₂C contacts.

Figure 6.14 Orientation of the principal directions of the strain tensors in piracetam form V at 4.0 GPa viewed along the medium direction of compression. Colouring scheme: blue, minimum strain; red, medium strain; green, maximum strain

Comparison of hydrogen-bonded patterns of forms II and V

Four scalar quantities are necessary to define the geometry of a hydrogen bond. These are the D-H covalent bond length, the H...A hydrogen-bond length, the D...A hydrogen-bond distance and the D-H...A angle (Jeffrey, 1997). These quantities are also indicative of the strength of the hydrogen bond considered. Since hydrogen atoms were placed geometrically and fixed during structure refinement, a discussion of hydrogen bonding should only be made on the basis of D...A distances. On this basis, the assignment of the strength of the hydrogen bonding has been made from the guideline values of strong, moderate and weak hydrogen bonding as detailed by Jeffrey (1997).

The hydrogen bond motif of form II is retained in form V and both polymorphs have a first-level graph set $N_1 = C(7)R_2^2(8)$ and a second-level graph set
$N_2 = R_4^4(18)$ arising from two distinct "normal" (i.e. two-atoms; Steiner, 2002) hydrogen bonds, as discussed in Section 6.4.1. Due to the large uncertainties associated with the D...A distances of the high-pressure data, only discussion of overall trends is possible. These are not significantly different within adjacent pressure measurements, but the D...A distances of both hydrogen bonds decrease over the 0.7-2.5 GPa pressure range (Table 6.8 and Figure 6.15).

<table>
<thead>
<tr>
<th>D...A distance/Å</th>
<th>Form II ambient pressure</th>
<th>Form II</th>
<th>Form V</th>
<th>Form V</th>
<th>Form V</th>
<th>Form V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Form II</td>
<td>0.45 GPa</td>
<td>0.7 GPa</td>
<td>0.9 GPa</td>
<td>2.5 GPa</td>
<td>4.0 GPa</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>D-H...A</td>
<td></td>
<td></td>
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<tr>
<td>N(2)...O(2)$^b$</td>
<td>2.942(2)</td>
<td>2.921(15)</td>
<td>2.891(15)</td>
<td>2.874(14)</td>
<td>2.812(16)</td>
<td>2.786(16)</td>
</tr>
<tr>
<td>Bifurcated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N(2)...O(1)$^c$</td>
<td>2.963(2)</td>
<td>2.90(3)</td>
<td>2.95(2)</td>
<td>2.963(11)</td>
<td>2.85(2)</td>
<td>2.86(2)</td>
</tr>
<tr>
<td>N(2)...O(1)$^d$</td>
<td>4.022(2)$^e$</td>
<td>3.905(15)$^e$</td>
<td>3.384(17)</td>
<td>3.283(8)</td>
<td>3.073(16)</td>
<td>2.950(18)</td>
</tr>
</tbody>
</table>

$^a$ Admiraal & Eikelenboom, 1982.
Symmetry codes: $^b$ -1+x, -1+y, -z; $^c$ -1+x, y, z; $^d$ -x, -1-y, 1-z.
$^e$ Long contact.

**Table 6.8** D...A distances for atoms involved in normal and bifurcated hydrogen bonds.

The distance involved in the formation of the hydrogen-bonded centrosymmetric dimer [N(2)...O(2)$^b$] decreases by *ca.* 5.3 % on going from form II at ambient pressure to form V at 4.0 GPa and the distance involved in the hydrogen bond that links these dimers [N(2)...O(1)$^c$] decreases by *ca* 3.5 %. For form V, in the pressure range 0.7-4.0 GPa the same distances decrease by 3.6 % and 3.0 %, respectively. The plots of Figure 6.15 show the discontinuity that was discussed earlier, indicative of a phase transition, and is most visible for the N(2)...O(1) distance.
Figure 6.15 Variation of hydrogen-bonded D...A distances in form II and V as a function of pressure. The lines indicate the discontinuity referred to in the text and are guides to the eye.

The shear phase transition to form V is associated with the formation of a new close contact (Table 6.8 and Figure 6.16). Investigation revealed this to be a new D...A contact at 0.7 GPa involving N(2) and O(1). This contact is significantly reduced to 3.384 Å (c.f. 4.022 Å at ambient pressure for form II) and can now be classified as a weak hydrogen bond. This results in the overall formation of a bifurcated hydrogen bond (Steiner, 2002) from N(2)-H(9) (Figure 6.16) that satisfies the double-acceptor capability of the carbonyl oxygen, O(1). At 4.0 GPa this intermolecular interaction is considerably shortened by ca. 12%. Assuming geometrical placement of the hydrogen atoms belonging to the amide group is a relatively good approximation of true hydrogen-bonding geometry, and that no disorder is involved, a D-H...A angle of 107.2(5)° at 0.4 GPa makes this new hydrogen bond considerably weaker than the other [155.0(5)°]. No conclusions can be drawn at present since hydrogen atom positions could not be observed experimentally.

Not surprisingly, the directions of hydrogen bonding correlate well with the directions of medium and maximum compression (Figure 6.17). In particular, the direction of maximum strain has a strong component along the direction of the longest hydrogen bond (see Table 6.8), thereby confirming the “soft” nature of this interaction.
Symmetry codes: (1) -x, 1-y, -1-z; (2) 1-x, 1-y, -z; (3) -x, -1-y, -z.

**Figure 6.16** Crystal structures of (a) form II and (b) form V viewed along the b axis. Normal hydrogen bonds are shown in blue colour, bifurcated ones in magenta. The figures are drawn to the same scale.

**Figure 6.17** (a) Orientation of the principal directions of the strain tensors in form V at 4.0 GPa viewed along the b axis. Colouring scheme: blue, minimum strain; red, medium strain; green, maximum strain. (b) Hydrogen-bonded network viewed along the b axis; the same colouring scheme as in Figure 6.16 is used.
6.4.5 Polymorph comparison using fingerprint plots derived from Hirshfeld surfaces

Form IV

A particularly striking method recently developed by Spackman & McKinnon (2002) for comparison of polymorphs is the use of graphical fingerprint plots derived from the corresponding Hirshfeld surfaces (McKinnon et al., 2004). These were discussed in Section 2.3.2. Here it is recollected that the Hirshfeld surfaces and the corresponding fingerprint plot are unique for any crystal structure and consequently for any polymorph, and that they therefore provide a powerful tool for elucidating and comparing intermolecular interactions, as well as for spotting common features/trends in specific classes of compounds. Hirshfeld surfaces and fingerprint plots were obtained for each of the polymorphs of piracetam using the program Crystal Explorer (Grimwood et al., 2004) and the fingerprint plots are shown in Figure 6.18. These graphs show several common features: the pseudo-symmetry about the diagonal arises because of the close packing of the Hirshfeld surfaces, which guarantees that where surfaces touch one another (and provided that there is only one molecule in the asymmetric unit) both of the points \((d_1, d_e)\) and \((d_e, d_1)\) are plotted on the 2-D graph. All four plots show two sharp ‘tails’ corresponding to N-H...O=C hydrogen bonds extending down to around \(d_e + d_1 = 1.9-2.0\) Å, the upper one corresponding to the hydrogen-bond donor and the lower one to the hydrogen-bond acceptor. Each of forms I, II and IV exhibit a feature running along the plot diagonal that extends down to \(d_e + d_1 = 2.2\) Å in form I, 2.4 Å in form II, and 2.3 Å in form IV. These features correspond to aliphatic H...H contacts and for forms I and II they are attributed to the interactions between ring hydrogen atoms of adjacent molecules. In form IV the shortest contacts around 2.3 Å are now attributed to interactions between hydrogen atoms on the ring and hydrogen atoms of C(5). The

§ For the generation of Hirshfeld surfaces and the corresponding fingerprint plots, coordinates were obtained from the CIF files of the CSD reference codes of the ambient temperature structures listed in Table 6.7. In the case of form I hydrogen atoms on the primary amide group, although originally placed in calculated positions, were found to deviate considerably from an ideal geometry: these were therefore placed along the hydrogen-bond donor-acceptor axis, resulting in a more reasonable geometry. For the generation of Hirshfeld surfaces the program Crystal Explorer automatically fixes bond lengths to hydrogen atoms to typical values obtained from neutron diffraction.
different densities of the four polymorphs are also illustrated in the plots. Thus form I
has the lowest density and this is reflected in the plot by the large number of values
at large $d_e$ and $d_l$ corresponding to regions on the Hirshfeld surface where close
contacts to neighbouring molecules are absent and where the close packing of the
surfaces results in the formation of small cavities. The diffuse feature off the plot
diagonal, where $d_c$ is greater than $d_c$ corresponds to a larger void created in the
proximity of the ring groups. For form IV, the points in the fingerprint plot are
shifted to smaller values of $d_c$ and $d_n$, illustrating the denser packing in this form.

Although close examination of the molecular packing arrangements in forms
IV and II shows no obvious route for some form of concerted molecular motion that
would allow interconversion, it is perhaps significant that the two Hirshfeld
fingerprint plots that resemble each other most closely are those of forms II and IV.

![Form I](image1)
![Form II](image2)
![Form III](image3)
![Form IV](image4)

**Figure 6.18** 2-D fingerprint plots derived from Hirshfeld surfaces for form I, II, III and IV of
piracetam.
Fingerprint plots obtained from the compression experiment of form II are depicted in Figure 6.19. The fingerprint plot of form II at ambient pressure (CSD reference code BISMEV) is also given to facilitate comparison.

At 0.45 GPa the plot of form II shows the expected contraction to lower $d_e$ and $d_i$ values with respect to the ambient pressure structure. In particular, shorter H...H contacts are visible, with the splitting indicating the presence of one distinct short H...H contact between one hydrogen atom of the pyrrolidone ring methylene group and one hydrogen atom of C(5) (belonging to the pendant group), reminiscent of the donor and acceptor "upper and lower" tails observed for hydrogen-bonded interactions.

Whilst structural differences between forms II and V are not immediately obvious on initial inspection and would require detailed structural analysis, fingerprint plots provide a rapid visual means for distinguishing the two polymorphs. The plot of form V at 0.7 GPa is significantly different from that of form II at 0.45 GPa. The most striking differences are visible in the region of H...H contacts and in the upper part of the plots at large $d_e$ and $d_i$. In the fingerprint plot of form V at 0.7 GPa, three distinct regions involving H...H contacts are visible. Region 1 corresponds to contacts between methylene hydrogen atoms in the pyrrolidone ring; region 2 to contacts between methylene hydrogen atoms attached to C(5), and region 3 to contacts between methylene hydrogen atoms belonging to the pyrrolidone ring and pendant group. Over the 0.7-4.0 GPa pressure range, these three regions "merge", i.e. they all decrease to a limiting value and the distinction between the different types of contacts becomes less clear. The increase in density associated with increasing pressure is evident in the contraction of the plots to lower $d_e$ and $d_i$ values and in the decrease in the number of points at large $d_e$ and $d_i$ - this correlates with a reduction in the number of voids in the structure. For example, the short H...H contact decreases from 1.084 Å to 1.011 Å.
Figure 6.19 2-D fingerprint plots derived from Hirshfeld surfaces for forms II and V at different pressures. The numbering of the regions is discussed in the main text.
6.5 Experimental procedure - piracetam hydrates

6.5.1 Piracetam monohydrate

Since high-pressure polymorphs can often be stabilised kinetically by depressurising at low temperature, the interest of the high-pressure research on piracetam focussed to discover whether a single crystal of the high-pressure form IV could be recovered using this technique.

A diamond-anvil cell containing a single crystal of form IV grown from aqueous solution was cooled to ca. 243 K. Optical observation of the crystal showed that it maintained its morphology even when the surrounding aqueous solution froze. The diamond-anvil cell was disassembled whilst still cold and the crystal appeared to remain intact within the tungsten gasket. The cold gasket was then rapidly transferred to a supersaturated aqueous solution (saturated at 293 K) of piracetam maintained at a temperature of 275 K and rapid precipitation of powder material was observed. After maintaining the solution at 277 K for a period of a month, single crystals (blocks) suitable for X-ray diffraction were obtained. These were identified by single-crystal X-ray diffraction as a new monohydrate of piracetam.

Whilst it would be very satisfying to suggest that the formation of this new hydrate was as a consequence of seeding with a high-pressure form, it was not possible at this stage to rule out that it was formed simply by crystallisation of an aqueous solution of piracetam at low temperature. Hydrate formation under such conditions has also been observed for other compounds such as paracetamol (Parkin et al., 2002; McGregor et al., 2002). Hence, experiments were performed to discover whether flash-cooling of aqueous solutions of piracetam to near 273 K resulted in the formation of the monohydrate. The rapid cooling of a ca. 6 M aqueous solution to 273 K resulted in the precipitation of polycrystalline material that on standing at 275 K for a few days produced single crystals that were subsequently identified as piracetam monohydrate. The crystals in the solution were indefinitely stable at this temperature, but dissolved on warming to ambient temperature. In another experiment, a saturated aqueous solution of piracetam at 323 K was rapidly cooled to just below 273 K so that ice formed on the walls of the flask. On warming above 273 K, the ice melted but a white polycrystalline powder was produced, which was
identified by powder X-ray diffraction to be the monohydrate and persisted at ambient temperature. Indeed it also became clear that low temperatures were not always necessary, since slow evaporation of a saturated aqueous solution of piracetam at 293 K also produced crystals of the monohydrate.

Diffraction data were collected as described in Section 6.2.3.

6.5.2 High-pressure recrystallisation of piracetam from water at 0.6 GPa: piracetam dihydrate

As discussed in Section 6.2.1, high-pressure recrystallisation of a ca. 6 M aqueous solution of piracetam afforded a new polymorph, form IV. On the other hand, in Section 6.5.1 it was reported that at conditions of ambient pressure and irrespective of the concentration used, recrystallisation from water resulted in the formation of the first hydrate of piracetam, a monohydrate. It therefore became interesting to probe whether concentration had an effect on the outcome of a high-pressure recrystallisation experiment and, in particular, whether using a lower concentration could induce the formation of a hydrated species.

A ca. 0.7 M aqueous solution of piracetam (Sigma-Aldrich) was loaded at 293 K into a Merrill-Bassett diamond-anvil cell equipped with 800 μm culet diamonds and a tungsten gasket with a 300 μm hole. The cell was sealed and pressurised in incremental steps but no precipitation of polycrystalline material was observed up to pressures of 1.0 GPa. The cell was subsequently pressurised to 1.6 GPa to induce the crystallisation of the aqueous solvent. The success of this procedure in encouraging the precipitation of polycrystalline material was discussed in more detail in Section 2.1.2. The cell was depressurised in incremental steps and at 0.6 GPa ice crystals were observed to melt under a microscope, revealing the presence of finely divided powder. The temperature was then cycled near ca. 303 K in order to dissolve all but one of the crystallites and on slow cooling to 293 K a single crystal grew from solution to fill ca. 40 % of the gasket hole (Figure 6.20).
Indexing of the reflections obtained from a single-crystal X-ray diffraction experiment gave a triclinic unit cell with dimensions substantially different from any of the three known polymorphs of piracetam or of the recently discovered monohydrate. Structure solution using direct methods with subsequent full-matrix least-squares structure refinement identified the crystal as a new hydrate of piracetam (dihydrate).

Single-crystal diffraction data were collected as described in Section 6.2.4. Data were collected with the diamond-anvil cell in three orientations (glued onto the goniometer head on three different sides of the cell) to simulate three different values of $\chi$ in order to improve data completeness.

6.6 Results - piracetam hydrates

6.6.1 Piracetam monohydrate

Data integration and reduction were performed using the program SAINT (Bruker, 2003). The structure was solved by direct methods with SHELXS (Sheldrick, 1997) and full-matrix least-squares structure refinement was performed using CRYSTALS (Watkin et al., 2003). All non-hydrogen atoms were refined anisotropically, hydrogen atoms attached to carbon were placed in calculated positions and their position fixed during refinement. Hydrogen atoms involved in
hydrogen bonding were located on a difference-Fourier map and refined freely. Inspection of a plot of \( F_o \) vs. \( F_c \) showed a poor fit of the six strongest reflections, due to a substantially higher \( F_c \) than \( F_o \), for which no extinction correction resulted in a satisfactory model. It is known that for high-quality single crystals, such as the one analysed in this case, extinction can introduce systematic errors. The fit of weaker reflections was deemed compromised by the high leverage of these strong, outlying reflections, which were ultimately omitted in the refinement, resulting in an improvement of the R-factor of 0.5%.

Full refinement details are shown in Table 6.9. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

---

**Table 6.9** Crystal, collection and refinement details for piracetam monohydrate at 150 K.

<table>
<thead>
<tr>
<th>Crystal data</th>
<th>Piracetam monohydrate at 150 K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>( \text{C}<em>6\text{H}</em>{10}\text{N}_2\text{O}_2\cdot\text{H}_2\text{O} )</td>
</tr>
<tr>
<td>( M_r )</td>
<td>160.17</td>
</tr>
<tr>
<td>Cell setting, space group</td>
<td>Triclinic, ( P\bar{1} )</td>
</tr>
<tr>
<td>( a, b, c ) (Å)</td>
<td>6.9376 (2), 7.4450 (2), 9.1267 (2)</td>
</tr>
<tr>
<td>( \alpha, \beta, \gamma ) (°)</td>
<td>97.732 (2), 103.958 (2), 115.766 (2)</td>
</tr>
<tr>
<td>( V ) (Å³)</td>
<td>396.24 (2)</td>
</tr>
<tr>
<td>( Z )</td>
<td>2</td>
</tr>
<tr>
<td>( D_x ) (Mg m⁻³)</td>
<td>1.342</td>
</tr>
<tr>
<td>Radiation type</td>
<td>Mo ( K\alpha )</td>
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<tr>
<td>No. of reflections for cell parameters</td>
<td>4605</td>
</tr>
<tr>
<td>( \theta ) range (°)</td>
<td>2-30</td>
</tr>
<tr>
<td>( \mu ) (mm⁻¹)</td>
<td>0.11</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>150 (2)</td>
</tr>
<tr>
<td>Crystal form, colour</td>
<td>Block, colourless</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.45 x 0.35 x 0.26</td>
</tr>
</tbody>
</table>

| Data collection               | Bruker SMART                    |
| Data collection method        | \( \omega \) scans              |
| Absorption correction        | Multi-scan (based on symmetry-related measurements) |
| \( T_{\min} \)               | 0.86                            |
| \( T_{\max} \)               | 1.00                            |

---

Chapter 6 – An Exploration of the Polymorphism of Piracetam using High Pressure
Piracetam monohydrate at 150 K

| No. of measured, independent and observed reflections | 9556, 2297, 1876 |
| Criterion for observed reflections | \( I > 2\sigma(I) \) |
| \( R_{\text{int}} \) | 0.039 |
| \( \theta_{\text{max}} \) (°) | 30.5 |
| Range of \( h, k, l \) | \(-9 \rightarrow h \rightarrow 9\) |
| | \(-10 \rightarrow k \rightarrow 10\) |
| | \(-12 \rightarrow l \rightarrow 13\) |

**Refinement**

| Refinement on | \( F^2 \) |
| \( R[F^2 > 2\sigma(F^2)], wR(F^2), S \) | 0.041, 0.117, 0.99 |
| No. of reflections | 2291 reflections |
| No. of parameters | 116 |
| H-atom treatment | Mixture of independent and constrained refinement |
| Weighting scheme | \( W = 1/[(\Sigma a^2(F^4) + P(1)p^2 + P(2)p + P(4) + P(5)\sin(\theta))] \) |
| \( P(i) \) are: | 0.728 1 0.288 0 0.00 0.00 0.00 0.333 |
| \( (\Delta/\sigma)_{\text{max}} \) | <0.0001 |
| \( \Delta P_{\text{max}}, \Delta P_{\text{min}} \) (e Å\(^{-3}\)) | 0.37, -0.21 |

**Table 6.9 (cont.)** Crystal, collection and refinement details for piracetam monohydrate at 150 K

**6.6.2 High-pressure recrystallisation of piracetam from water at 0.6 GPa: piracetam dihydrate**

Data processing was performed according to procedures described by Dawson *et al.* (2004) and detailed in Section 2.2.2. The three datasets were treated separately up to the absorption correction step and then scaled and merged with SORTAV (Blessing, 1995) in the manner described by Dawson *et al.* (2004). The structure was solved by direct methods using SIR92 (Altomare *et al.*, 1993) and full-matrix least-squares structure refinement was then performed using CRYSTALS (Watkin *et al.*, 2003). All non-hydrogen atoms were refined anisotropically and rigid-bond and thermal similarity restraints were employed to obtain a satisfactory model. Hydrogen atoms attached to carbon were placed in calculated positions and their positions fixed during refinement. Hydrogen atoms involved in hydrogen bonding were located on a difference-Fourier map and refined subject to distance restraints. A final R-factor of 3.5 % was obtained, which represents an excellent...
refinement result of high-pressure data collected for a triclinic crystal system and allows reliable comparison with the structural features of the anhydrous and monohydrate forms.

Full refinement details are shown in Table 6.10. Crystallographic data in CIF format are available in the attached CD at the back of the thesis.

**Piracetam dihydrate at 0.6 GPa**

<table>
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<th>Crystal data</th>
<th></th>
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<tbody>
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<tr>
<td>Mr</td>
<td>178.19</td>
</tr>
<tr>
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<td>Triclinic, P-1</td>
</tr>
<tr>
<td>a, b, c (Å)</td>
<td>6.217 (2), 7.0356 (9), 10.0593 (13)</td>
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<td>α, β, γ (°)</td>
<td>84.711 (12), 76.83 (2), 75.77 (2)</td>
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<td>V (Å³)</td>
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<tr>
<td>Temperature (K)</td>
<td>293 (2)</td>
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<td>Block, colourless</td>
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<tr>
<td>Crystal size (mm)</td>
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**Data collection**

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<th>Diffractometer</th>
<th>Bruker SMART Apex 2</th>
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<tbody>
<tr>
<td>Data collection method</td>
<td>θ scans</td>
</tr>
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<td>Absorption correction</td>
<td>Empirical &amp; multi-scan (based on symmetry-related measurements)</td>
</tr>
<tr>
<td>T_min</td>
<td>0.30</td>
</tr>
<tr>
<td>T_max</td>
<td>0.98</td>
</tr>
<tr>
<td>No. of measured, independent and observed reflections</td>
<td>5183, 611, 493</td>
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<tr>
<td>Criterion for observed reflections</td>
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<tr>
<td>R_in</td>
<td>0.047</td>
</tr>
<tr>
<td>θ_max (°)</td>
<td>25.1</td>
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</table>

**Table 6.10** Crystal, collection and refinement details for piracetam dihydrate at 0.7 GPa.
Piracetam dihydrate at 0.6 GPa

<table>
<thead>
<tr>
<th>Range of h, k, l</th>
<th>-3 → h → 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-8 → k → 8</td>
</tr>
<tr>
<td></td>
<td>0 → l → 12</td>
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</tbody>
</table>

**Refinement**

- Refinement on $F^2$
- $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ 0.035, 0.091, 1.06
- No. of reflections 608 reflections
- No. of parameters 127
- H-atom treatment Mixture of independent and constrained refinement
- Weighting scheme $w = 1/[\sigma^2(F^2) + 0.04 + 0.13P]$, where $P = (\text{max}(F_o^2,0) + 2F_c^2)/3$
- $(\Delta/\sigma)_{\text{max}}$ <0.0001
- $\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å⁻³) 0.10, -0.11

**Table 6.10 (cont.)** Crystal, collection and refinement details for piracetam dihydrate at 0.7 GPa.

### 6.7 Discussion - piracetam hydrates

#### 6.7.1 Piracetam Monohydrate

Bond lengths and angles are similar to those found for the anhydrous polymorphs. The torsion angles of 92.3° for C(6)--C(5)--N(1)--C(1) and 170.4° for N(1)--C(5)--C(6)--N(2) are similar to those found for the forms I, II, and III of anhydrous piracetam. The crystal structure of the monohydrate is characterised by two-dimensional hydrogen-bonded networks (see Figure 6.21) that run along the $b$ and $c$ axes. These networks can be viewed as corrugated motifs that run perpendicular to the (1 0 1) planes and that are related by translational symmetry and linked by van der Waals interactions (Figure 6.21). In each network, there are four distinct intermolecular hydrogen bonds and a total of five hydrogen bonds per piracetam molecule, where the carbonyl oxygen atom of the primary amide fulfils its double-acceptor ability. Two of the latter hydrogen bonds are involved in the formation of the sole direct contacts between piracetam molecules, in the form of centrosymmetric dimers, giving an $R_2^2(8)$ ring at the first-level of graph-set analysis.
These contacts are also observed in forms II and III. The remaining three hydrogen bonds are involved in contacts with water to give two distinct $R_4^4(18)$ rings at a binary level, which have one type of hydrogen bond in common.

Combination of the three hydrogen bonds which are unique to the three rings described so far gives one $R_4^6(12)$ ring at the ternary level. The overall first-level and second-level graph sets for piracetam monohydrate are $N_1 = DDDR_2^2(8)$ and $N_2 = D_3^3[15][R_2^2(8)] D_3^2(7)[R_2^2(8)] D_3^3(9)[R_2^2(8)] C_2^2(6) R_4^4(18) R_4^4(18)$, respectively. A matrix representation of these graph sets is given in Table 6.11. Graph-set assignments were confirmed using the GSET routine in RPLUTO (Motherwell et al., 1999). Geometrical parameters for hydrogen bonding are given in Table 6.12.

![Figure 6.21 Hydrogen-bonding motif found in piracetam monohydrate viewed along the (a) a and (b) b axes (the blue, brown and green colours indicate parallel chains that run perpendicular to the (101) planes.](image)

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>$R_4^4(18)$</td>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>$D_3^3[15][R_2^2(8)]$</td>
<td>$D_3^2(7)[R_2^2(8)]$</td>
<td>$R_2^2(8)$</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>$R_4^4(18)$</td>
<td>$C_2^2(6)$</td>
<td>$D_3^3(9)[R_2^2(8)]$</td>
<td>D</td>
</tr>
</tbody>
</table>

Table 6.11 Graph-set matrix with unitary motifs (on-diagonal) and binary graph sets (off-diagonal) for piracetam monohydrate. At the ternary level, $N_3(bcd) = R_6^4(12)$. 

Chapter 6 – An Exploration of the Polymorphism of Piracetam using High Pressure
D-H...A/Å | Notation from Figure 6.21 and Table 6.11 | D-H/Å | H...A/Å | D...A/Å | D-H...A/°
---|---|---|---|---|---
O(11)-H(111)...O(1)\(^b\) | a | 0.98 | 1.76 | 2.735(1) | 173.5(19)
O(11)-H(112)...O(2) | b | 0.98 | 1.79 | 2.774(1) | 174.9(17)
N(2)-H(9)...O(2)\(^c\) | c | 1.01 | 1.97 | 2.956(1) | 167.5(13)
N(2)-H(10)...O(11)\(^d\) | d | 1.01 | 1.87 | 2.857(1) | 165.8(13)

\(^a\) The distances to hydrogen have been normalized in PLATON (Speck, 2000) to mimic those that might be obtained by neutron diffraction.

Symmetry codes: \(^b\) 1-x, 1-y, 1-z; \(^c\) -x, 1-y, -z; \(^d\) \(x, 1+y, z\).

Table 6.12 Hydrogen-bonding parameters in piracetam monohydrate.

### 6.7.1.1 Stability of piracetam monohydrate

Visual inspection of crystals that remained exposed to air at ambient temperature showed that they completely transformed to polycrystalline powder over a period of 12 hours. By contrast, crystals immersed in perfluoropolyether oil on a microscope slide at ambient temperature appeared to survive over this period. As a further indication of the stability of the hydrate towards dehydration, it was observed that a single crystal coated with oil and mounted on the diffractometer maintained its crystallinity up to a temperature of 320 K before dehydration occurred. Variable-temperature powder X-ray diffraction (using a Bruker D8 diffractometer equipped with a variable temperature stage) showed that a polycrystalline sample of the monohydrate began to dehydrate in vacuo at 293 K, and by 333 K dehydration was complete, leading to the formation of anhydrous form II.

Given that piracetam has been extensively studied over the years, the discovery of a new monohydrate of piracetam that crystallised under ambient conditions was surprising. There appear to be no reports of such a hydrate in either the academic literature or the easily accessible patent literature. The monohydrate loses water relatively easily under ambient conditions if not protected from the atmosphere and so is perhaps not a particularly desirable form for a pharmaceutical formulation, although its facile dehydration to anhydrous form II might offer some processing advantages.
6.7.2 **Piracetam Dihydrate**

Bond lengths and angles are similar to those found for the anhydrous polymorphs and monohydrate species. The torsion angle of $118.0(5)^\circ$ for C(6)–C(5)–N(1)–C(1) is similar to that found for the form IV of anhydrous piracetam, while the angle of $153.0(5)^\circ$ for N(1)–C(5)–C(6)–N(2) is similar to that for forms II and III.

The crystal structure of the high-pressure dihydrate is characterised by a three-dimensional hydrogen-bonded network (see Figure 6.22) that involves a total of six distinct hydrogen bonds. The three-dimensional network can be decomposed into a principal hydrogen-bonded chain motif that runs along the $a$ axis and is then translated along $b$ (Figure 6.22a). The motif is extended along $c$ by application of inversion symmetry (Figure 6.22b).

![Figure 6.22](image)

**Figure 6.22** Hydrogen-bond motif of piracetam dihydrate viewed along the (a) $c$ and (b) $a$ crystallographic axes. Some layers have been omitted for clarity in (a). The labels refer to the types of hydrogen bonds described in Tables 6.13 and 6.14.

In contrast to the monohydrate, no dimers or other hydrogen-bonded contacts are found between piracetam molecules, which are instead linked via hydrogen bonds to and from water molecules. Within the piracetam moiety, the primary amide nitrogen atom N(2) donates two hydrogen bonds to two crystallographically
independent water oxygen atoms. The primary amide oxygen atom O(2) fulfils its
double acceptor capability, accepting two hydrogen bonds from two
crystallographically independent water molecules, while the tertiary amide oxygen
atom O(1) accepts only one hydrogen bond. One water oxygen atom, O(11), fulfils
its double acceptor capability through involvement in a further hydrogen bond from a
crystallographically distinct water molecule. This scheme, along with hydrogen-
bonding parameters, is summarised in Table 6.13, with the atom labelling depicted in
Figure 6.23.

According to the classification of the strength of hydrogen bonding based on
geometrical parameters by Jeffrey (1997), all six hydrogen bonds are of “medium”
strength, with values for the D-H...A angle approaching linearity.

<table>
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<td>N(2)-H(10)...O(12)b</td>
<td>a</td>
<td>1.01</td>
<td>1.91</td>
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<td>1.92</td>
<td>2.921(3)</td>
<td>177(6)</td>
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<td>O(11)-H(111)...O(2)</td>
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<td>158(5)</td>
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<td>2.902(4)</td>
<td>163(4)</td>
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<tr>
<td>O(12)-H(122)...O(11)f</td>
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<td>0.98</td>
<td>1.82</td>
<td>2.788(8)</td>
<td>168(6)</td>
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</tbody>
</table>

*aThe distances to hydrogen have been normalized in PLATON (Speck, 2000) neutron values to mimic those that might be obtained by neutron diffraction.

Symmetry codes: b x, 1+y, z; c -x, -y, -z; d -x, y, l-z; e -l+x, y, z.

**Table 6.13 Hydrogen-bonding parameters in piracetam dihydrate.**

![Figure 6.23 Atom labelling for the hydrogen-bond scheme in Table 6.13.](image-url)
Combination of the six hydrogen bonds gives an overall first-level and second-level graph sets for piracetam dihydrate $N_1 = \text{DDDD}$ and $N_2 = D_2^2(5)D_2^2(6)R_4^4(12)D_2^2(9)C_2^2(9)R_4^4(18)C_2^2(6)D_2^2(6)D_2^1(3)D_2^2(4)D_2^1(3)D_2^2(4)D_2^2(4)D_2^2(5)$, respectively. A matrix representation of these graph sets is given in Table 6.14. Graph-set assignments were confirmed using the GSET routine in RPLUTO (Motherwell et al., 1999).

<table>
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<tr>
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<th>a</th>
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<td>b</td>
<td>$D_2^2(5)$</td>
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<td>$C_2^2(9)$</td>
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<tr>
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<td>$D_2^2(6)$</td>
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<tr>
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<td>$D_2^1(3)$</td>
<td>$D_2^2(4)$</td>
<td>$D_2^2(4)$</td>
<td>$D_2^2(5)$</td>
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</tbody>
</table>

Table 6.14 Graph-set matrix with unitary motifs (on-diagonal) and binary graph sets (off-diagonal) for piracetam dihydrate.

6.7.2.1 Stability of piracetam dihydrate

The pressure range for the stability of the dihydrate was investigated by compression and recrystallisation from solution at high pressure. The pressure inside the diamond-anvil cell was increased from 0.6 to 1.0 GPa. The single crystal was subsequently identified by single-crystal X-ray diffraction as the dihydrate, but with a ca. 4.3% increase in density with respect to the structure at 0.6 GPa. The pressure inside the cell was then increased to ca. 1.3 GPa. On heating the cell, the single crystal of the dihydrate was observed to dissolve and new block-like crystals (in contrast with the finely divided powder crystallised at 0.6 GPa) simultaneously grew, after nucleating from the side of the gasket. All crystallites were accidentally dissolved while attempting to grow a single crystal at this pressure. Crystallisation of morphologically similar, block-like crystals was induced by lowering the pressure inside the gasket, and single crystals were successfully grown at ca. 0.7 GPa and 0.4 GPa in two separate experiments. X-ray diffraction revealed these to be anhydrous form IV. On the assumption that the block-like crystals that appeared on heating at
1.3 GPa were in fact form IV, it is postulated that the dihydrate transformed to form IV as a response to heating at high pressure by dehydration. A possible mechanism of dehydration might involve the breaking of the hydrogen-bonded network and cooperative rotation of piracetam molecules to form dimers. Support for such a mechanism is provided by comparison of the two structures. Both structures contain neighbouring molecules that lie at similar separations, as illustrated in Figure 6.24.

Figure 6.24 A potential mechanism for the dehydration of the dihydrate of piracetam to anhydrous form IV involving the collapse of the hydrogen-bonded network and the cooperative rotation of molecules. The values refer to distances between C(1) atoms of neighbouring molecules. Circled molecules are involved in dimer formation by cooperative rotation.

In the first experiment, piracetam dihydrate was obtained by first pressurising to 1.6 GPa to induce the crystallisation of the aqueous solvent, and then by subsequent decompression to 0.6 GPa, whilst observing ice crystals melting. Such a procedure appeared to be very successful during the course of this research in encouraging the precipitation of polycrystalline material when all other attempts failed. This is presumably because polycrystalline ice provides numerous nucleation sites. At ambient temperature, compression of liquid water leads to the formation of tetragonal ice-VI at pressures greater that 1.05 GPa (Kamb, 1965) and to cubic ice-VII above 2.1 GPa (Kamb & Davis, 1964). Furthermore, crystallisation of solid ice must change the concentration of the aqueous solution, thereby encouraging crystallisation. This process may also encourage the formation of host-guest species. The reason why subsequent recrystallisation at 0.7 and 0.4 GPa afforded form IV instead, might be because the procedure did not involve the crystallisation of ice first. Alternatively, it might be a direct consequence of seeds of this form still present in
solution subsequent to the transformation that was observed to take place at 1.3 GPa. In support of the first hypothesis it is recalled that paracetamol trihydrate (McGregor et al., 2002) and monohydrate (Parkin et al., 2002) are obtained by rapid cooling of aqueous solutions of paracetamol at ambient pressure to 273 K. On warming, ice crystals are observed to melt leaving behind crystals of the hydrated species that eventually dehydrate to orthorhombic paracetamol. This opens up a new line of research, whereby crystallisation of organic molecules is studied by inducing crystallisation of different ice forms (e.g. ice-Ih, II, V, VI and VII) and where different ice forms may preferentially induce the precipitation of specific polymorphs or hydrates.

6.8 Conclusions

The transformations between the polymorphs and hydrates of piracetam are summarised in Scheme 6.1.

Scheme 6.1 Transformations of polymorphs and hydrates of piracetam.
High-pressure recrystallisation of aqueous and methanolic solutions (ca. 6 M and 1.6 M, respectively) of piracetam contained in a diamond-anvil cell at pressures of 0.07-0.4 GPa resulted in the formation of a new high-pressure polymorph of piracetam, form IV, that has been characterised by in situ X-ray diffraction. The molecular packing arrangement of the new form is very different from those of forms I, II, and III, and the piracetam molecules also adopt a very different conformation in this new phase. Depressurisation to ambient pressure resulted in the formation of form II via a single-crystal to single-crystal transition.

Compression of form II resulted in a reversible, single-crystal to single-crystal shear transition to a new polymorph, form V. The transition occurred between pressures of 0.45-0.7 GPa pressure and was monitored by X-ray diffraction.

Crystallisation from an aqueous solution (ca. 0.7 M) of piracetam at pressures of 0.6 GPa resulted in the formation of a previously unreported dihydrate species. By contrast, crystallisation of piracetam from water at ambient pressure, irrespective of concentration, afforded a new monohydrate of piracetam. Both hydrates have been characterised by single crystal X-ray diffraction. Given that piracetam has been extensively studied over the years, the discovery of a monohydrate of piracetam that crystallised under ambient conditions was surprising.

The first low-temperature single-crystal data on form I have been reported here, thereby demonstrating that the rate of the I \( \rightarrow \) II transformation can be dramatically reduced at low temperatures. The crystal structure observed in this work is in very good agreement with the structure obtained by the previous powder-diffraction study and benefits from improved precision of structural parameters.

It is clear from the results of this study that recrystallisation of piracetam under a range of pressure conditions allows one to tune readily which polymorph is produced. The technique can therefore be regarded as a method of crystal engineering and has the potential to provide an efficient and possibly more comprehensive method for exploring polymorphism.

Further work on piracetam is envisaged to encompass the study of new solvent systems (of various concentrations) in the search of new polymorphs and solvates; in addition, the role of ice for triggering nucleation should be explored and in particular, whether different forms of ice can lead to controlled crystallisation of a
desired polymorph. Further efforts in the recovery at ambient pressure of new polymorphs and solvates prepared at high pressure are foreseen to rely on a thorough investigation of the pressure-temperature-concentration space and on the use of large volume presses to recrystallise powders in bulk.

6.9 References


Chapter 7

Conclusions, General Remarks and Future Directions
7.1 Conclusions

The novel technique of high-pressure recrystallisation from solution has been described in detail and has been demonstrated to be a very successful means of preparing new polymorphs, solvates and hydrates of molecular compounds. The method is particularly attractive for those compounds that exhibit high melting points, e.g. pharmaceutical substances.

New polymorphs have been obtained for the rigid molecules phenanthrene and pyrene, and for the more flexible molecules acetamide and piracetam. A novel methanol solvate has been characterised for paracetamol, whilst new hydrates have been prepared for paracetamol and piracetam. These have been characterised by single-crystal X-ray diffraction in situ in a diamond-anvil cell, and, on occasion, by powder neutron diffraction and Raman spectroscopy. The structures of polymorphs, solvates and hydrates have been analysed using a combination of topological and graph-set analysis and comparison of Hirshfeld surfaces and fingerprint plots.

The metastable form of orthorhombic paracetamol has been crystallised at high pressure from acetone and methanol. This is a significant result in that it demonstrates the feasibility of crystallising at high pressure a polymorph that is metastable at ambient temperature and pressure. Even more interestingly, this form can be recovered at ambient pressure. Although this is only the first example, it seems likely that other high-pressure polymorphs and solvates will be found that can subsequently be recovered under ambient conditions. Further efforts in the recovery at ambient pressure of new polymorphs and solvates prepared at high pressure are expected to rely on a thorough investigation of the parameter-space pressure, temperature and concentration, and on the use of large volume presses to recrystallise powders in bulk.

It is clear from the results presented in this thesis, in particular from the study of the recrystallisation of piracetam, that the variation of pressure conditions allows one to tune readily which polymorph is produced. In this respect, the technique can therefore be regarded as a method of crystal engineering. Given that almost all conventional polymorph/solvate screening procedures in both the academic and pharmaceutical sectors are currently performed at or near ambient pressure, the high-
pressure recrystallisation technique has the potential to complement and enhance existing methods by providing another dimension for exploration.

A new polymorph has not yet been identified for naphthalene and a similar situation might be encountered again in the future as the number of systems investigated will increase. Further structural investigations in the search for a high-pressure phase transition in this and future compounds are envisaged to encompass complementary direct compression studies and high-pressure recrystallisation from solution experiments coupled with laser heating or resistive heating.

7.2 General Remarks and Future Directions

Recrystallisation from solution

It should be emphasised that high-pressure recrystallisation from solution, like recrystallisation from a pure liquid, is fundamentally different from a pressure-induced solid-solid transformation, even though on occasions both techniques may result in the same phase. In the latter case, a phase transition is influenced by whether there is a facile rearrangement pathway that allows the molecules to reorient themselves, and so there is frequently a direct structural relationship between the ambient and high-pressure phases that allows some insight into the mechanism of the interconversion. By contrast, in a high-pressure recrystallisation from solution (or from the melt) the kinetic barriers for molecular reorientation are greatly reduced and the structure of the high-pressure phase may bear little relationship to that of the ambient phase and is governed mainly by the thermodynamic parameters of the system.

There are several reasons why pressure is so effective at generating new polymorphs and solvates, particularly when combined with recrystallisation from solution or from the melt. High pressure encourages denser structures in which molecules must pack together more efficiently. This means that changes in the relative orientations of molecules in a solid are very likely to occur, therefore giving rise to different motifs of intermolecular interactions. The strengths of these interactions are themselves sensitive to distance and hence to the effects of pressure. For recrystallisation experiments conducted in solution, the interactions between
solute and solvent molecules will also be modified by pressure thereby changing the solubility of a given polymorph. In some cases the solubility differences between two or more polymorphs might also be expected to change, thereby encouraging recrystallisation of one polymorph at the expense of another. The modification of solute-solvent interactions by pressure would also be expected to alter the relative stabilities and solubilities of potential solvates. In practice, this translates into the possibility of crystallising solvates using this technique. The outcome of crystallisation may therefore give an insight into possible solvent-solute interactions, perhaps accounting for the crystallisation of particular forms at ambient pressure.

Given the comparatively few compounds that have so far been recrystallised under high pressure, it is difficult at this point to predict the types of structure that might be expected in future studies or whether a particular system is likely to give an unsolvated or a solvated form. So far, it has been established that when compared with ambient-pressure structures, high-pressure polymorphs are likely to be denser, to approximate more closely to close-packed arrangements, and, in the case of hydrogen-bonded compounds, to exhibit more extensive hydrogen-bonding motifs. This has significance for the theoretical \textit{ab initio} prediction of equilibrium crystal structures \citep{Motherwell2002}. In addition to the correct identification of the experimentally observed structure, these calculations sometimes identify potential structures with similar energies that have higher densities and which exhibit a more extensive network of hydrogen bonding \citep{Price2005}. It is therefore possible that these structures represent high-pressure polymorphs that have yet to be discovered. With regards to the question of whether high pressure encourages the formation of a polymorph over a solvate, it has not been possible so far to devise general rules. Principles usually employed in crystal engineering, such as analysis of potential hydrogen bonding, can be useful and it is foreseen that as the number of experiments performed will increase, it may be possible to observe particular trends. At present, it is speculated that when a non-coordinating solvent is used, it is perhaps more likely to obtain an unsolvated polymorph, although the possibility of host-guest structures should not be overlooked.
Single-crystal data collection and structure solution

The work presented in this thesis also highlights the challenges associated with high-pressure single-crystal X-ray diffraction, one of the most important being the restricted reciprocal space access limited by diamond-anvil cells. The design of high-pressure cells that will improve the access of X-rays to the sample chamber is an area of current interest at the University of Edinburgh, e.g. the development of beryllium-free diamond-anvil cells. New strategies for the collection of single-crystal high-pressure data are also expected to attract considerable attention, e.g. data collection of twinned or multiple crystals to improve data completeness and the use of shorter X-ray wavelengths to improve resolution.

Global optimisation methods for structure solution have so far overcome the problem of data of low completeness and it is foreseen that these techniques will be challenged still further for more complex systems with more degrees of freedom. Advances in refinement strategies, e.g. the use of a Z-matrix description of the structure, are also expected to facilitate the refinement of larger molecules.

7.3 References


Appendix
A. Conferences and lecture courses attended

Year 1

Poster presentation:


Lecture courses:

- Organised by the University of Edinburgh: Unix 1 and Unix 2, Introduction to HTML, Fortran, X-Ray Diffraction, Computational Methods, Postgraduate NMR Course.

Year 2

Poster presentation:


Lecture courses:

Oral presentation:


Invited talk:


Year 3

Poster presentation:

Invited talk:

- F. P. A. Fabbiani. Probing polymorphism with high pressure. BASF, Ludwigshafen, Germany, June 2005.

Workshop:


Lecture courses:

- Organised by the University of Edinburgh: Procter&Gamble Business Game.
B. Publications

Publications are included as an electronic copy in the attached CD at the back of the thesis


Appendix
### C. Abbreviations

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<td>Differential Scanning Calorimetry</td>
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<td>TGA</td>
<td>Thermal Gravimetric Analysis</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>VDP</td>
<td>Voronoi-Dirichlet Polyhedron</td>
</tr>
<tr>
<td>HCP</td>
<td>Hexagonal Close Packed</td>
</tr>
<tr>
<td>BCC</td>
<td>Body-Centred Cubic</td>
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<td>CCP</td>
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<td>MCN</td>
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