Experimental and theoretical studies on molecular geometry and polymorphism in crystalline drug substances

By

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Summary

The phenomena of polymorphism and pseudo-polymorphism are introduced, together with their pharmaceutical importance. Some basic knowledge about crystallization is introduced as well as the methods of experimental structure determination. The information about H-bonds and prediction of polymorphic forms is also given in the first chapter. The pharmaceutical role of Temozolomide and 5,5-diphenylhydantoin is introduced in the second chapter.

Using aqueous acetic acid as solvent, we crystallized a hydrate of Temozolomide, and the same hydrate also grows in the water: acetone 1:1 mixed solvent. This hydrate has a space group of $P2_1/m$ in a cell of dimensions a = 7.5158(9), b = 6.3044(13), c = 9.5324(16) Å, β = 92.907(12), V = 451.09(13) $Å^3$, Z = 2. Its crystal structure was determined by direct methods and refined by full-matrix least squares.

A twinned crystal of hydantoin grew from an aqueous medium. The crystal structure was determined, which revealed a space group of C2/c in a cell of dimensions a = 9.339(2), b = 12.1866(17), c = 7.304(4) Å, β = 104.91(2), V = 803.3(5) $Å^3$, Z = 4.

Two kinds of solvent were used to grow the crystal of 5,5-diphenylhydantoin, however the better quality is from acetone: N-methylformamide = 1: 1 mixed solvent. In space group $Pna2_1$ the crystal data are a = 6.2280(10), b = 13.5680(10), c =

15.520(2) Å, $\beta = 90$, V = 1311.5(3) $Å^3$, Z = 4.

Keywords: Polymorphism

Pseudo-polymorphism

Crystallization

Temozolomide

Hydantoin

5,5-diphenylhydantoin

To my parents and wife

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Symbols and Abbreviations

a	The width of each of series of (or single) diffracting slits.
a, b, c	Unit cell axial lengths.
d	The distance between two diffracting slits
Dx	Calculated density
F	The structure factor for the unit cell, for the reflection *hkl*.
hkl	Indices of the reflection from a set of parallel planes; also the coordinates of a reciprocal lattice point.
(hkl)	Indices of a crystal face, or of a single plane, or of a set of parallel planes.
I	Intensity for each reflection.
R	Discrepancy index.
X, Y, Z	Coordinates of any one of a series of systematically spaced points, expressed as fraction of *a*, *b*, *c* filling the unit cell at regular intervals.
Z	The number of molecules in one unit cell.
α, β, γ	Interaxial angles between *b* and *c*, *a* and *c*, and *a* and *b* respectively (alpha, beta, gamma).
λ	Wavelength, usually that of the radiation used in the diffraction experiment (lambda).
θ	The angle of incidence of the X-ray beam to the 'reflecting plane.' 2θ is the deviation of the diffracted beam from the direct X-ray beam (theta).
$\sigma(F)$	The estimated error in measuring the structure factor *F*.

μ	Absorption coefficient.
DSC	Differential scanning calorimetry.
NMR	Nuclear magnetic resonance.

Chapter 1 Introduction

1.1 Polymorphism

Isomorphism and polymorphism are two reversed and common phenomena in the crystalline state. [1]

1.1.1 Isomorphs

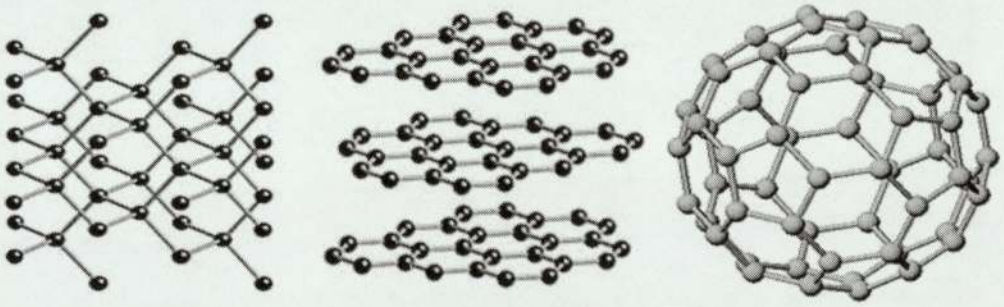
Two or more substances that crystallize in almost identical forms are said to be isomorphous, which, in Greek, means 'of equal form'. These crystals do show small, but quite definite differences in their respective interfacial angles, so this is not a contradiction of Haüy's law (See section **1.2 Crystallization**). Isomorphs are often chemically similar and can then be represented by similar chemical formulae. Sometimes isomorphous substances can crystallize together out of a solution to form a 'mixed crystal'. In such cases the composition of the homogeneous solid phase that is deposited follows no fixed pattern; it depends largely on the relative concentration and solubility of the substances in the original solvent. Another phenomenon often shown by isomorphs is the formation of overgrowth crystals. For example, if a crystal of chrome alum is placed in a saturated solution of potash alum, it will grow in a regular manner such that the purple core is covered with a continuous colourless overgrowth. There have been many 'rules' and 'tests' proposed for the phenomenon of isomorphism, but in view of the large number of known exceptions to these it is now recognized that the only general property of isomorphism is that crystals of the different substances shall show very close similarity.

1.1.2 Polymorphism

Since Klaproth's discovery of the calcium carbonate polymorphs calcite and aragonite in 1798, the phenomenon of polymorphism has been known. [2] Polymorphism is the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. [3] The molecule in two polymorphs may be of different shape, but this is not necessary, and indeed, the shape changing which because of dynamic isomerism or tautomerism, involves formation of different molecules does not belong to the concept of polymorphism. Dynamic isomers, like polymorphs, will melt at different temperatures; however, they will give melts of different composition. Some chemists have reported examples of polymorphism which are really dynamic isomerism, since they have quite similar behaviour, especially if the equilibrium between the two isomers can be established rapidly. Geometrical isomers or tautomers, even those are interconvertible and reversible, cannot be called polymorphs although they display a confusingly similar manner. Shape changes are permitted in the molecule crystallizing as two or more polymorphic forms, including resonance structures, rotation of parts of the molecule around certain bonds, and minor distortions of bond distances and angles. [4]

The safe criterion for identifying polymorphs is: two polymorphs will be different in crystal structure but identical in the liquid and vapour states.

For understanding the term of polymorphism is that any element or compound to crystallize as more than one crystal species, we use the most widely known example - the element carbon, which can exist in the form of graphite (hexagonal), diamond (cubic) or as fullerenes (C_{60} and C_{70}). [5] Different polymorphs of a certain compound are as different as the crystals of different compounds in structure and properties. Properties such as solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapour pressure and so on, are all different. In general, it is possible to get different crystal forms of a drug and then modify the performance of the drug.



a. diamond b. graphite c. fullereneC_{60}

Figure 1 Three polymorphic forms of carbon

1.1.3 The polymorphism in pharmaceutical sciences

Because different polymorphs have different properties, the subject of polymorphism plays an important role in the pharmaceutical sciences.

1. Polymorphism can influence the chemical stability. It means different crystalline phases of the same compound have different chemical stabilities. One author [4] has

observed this when he was working with aqueous suspensions of an experimental corticosteroid, which developed chemical instability in some batches. The original material batches were checked with X-ray diffraction and it was found there were two different polymorphs in this compound, one of which is light-sensitive. Batches containing this crystal form would decompose with time and would be assayed lower than the other batches. This chemical sensitivity may be because of solvents occluded in one of the polymorphs or absorbed mother liquor, where the latter could affect chemical stability, or maybe the polymorphs themselves due to different light absorption patterns. The patterns would be slightly different and one must absorb a wavelength that causes a photochemical decomposition. In another instance, Macek [6] has reported that the amorphous forms of the sodium and potassium salts of penicillin G obtained by evaporation from solution, are less stable chemically than their crystalline counterparts. For example, crystalline potassium penicillin can withstand dry heat for several hours without significant decomposition; while under similar conditions, the amorphous forms lose considerable activity. In such cases where chemical stability is a problem, we need to be careful to control during chemical manufacture the desired polymorphic form.

2. Polymorphism will affect generically equivalent dosage forms. If the rate of absorption of the active ingredient in an oral preparation is dissolution-rate dependent, the use of a compound exhibiting polymorphism may lead to good or bad consequences. The successful use of a polymorph of significantly greater thermodynamic activity than the stable modification may provide, in some instances,

therapeutic blood levels from otherwise inactive drugs. On the other hand, when the existence of multiple crystalline modifications goes unrecognized in a particular formulation, this may possibly result in unacceptable dose-to-dose variations in drug availability to the patient. [7]

3. Polymorphism can decide the tabletting behaviour of powders. Polymorphs of the same compound can crystallize in different habits (outer appearance of a crystal). [8] When the drug is a large portion of the tabletting mixture, it will exhibit similar problems. Even if all other conditions are the same, the choice of the right polymorph will make the tabletting easier because of its special habit.

4. Miscellaneous applications of polymorphism. Different polymorphs of the same compound have different densities. Because of this phenomenon, when one polymorph is heated to the temperature which is higher than its conversion temperature (to another polymorph), and then cooled to room temperature, strains can be developed in the crystal which cause fracturing into finer particles. This operation needs the suitable polymorphic forms and that the repeat temperature cycle would not produce chemical degradation. This mechanism of particle size reduction might prove to be more efficient than present methods of micronization.

As we can see above, polymorphism is a common chemical phenomenon existing in most compounds, and we should study it further as it is very important to the pharmaceutical science.

1.1.4 Pseudo-polymorphism

With some crystalline solids, solvent in the surrounding medium may become incorporated into the crystal lattice of the compound in stoichiometric proportions. These molecular adducts are termed solvates. [9] Hydrates are formed when water is the solvent of crystallization. In hydrates water occupies definite positions in the crystal lattice usually by forming hydrogen bonds or coordinate covalent bonds with the anhydrate drug molecules. Incorporation of the solvent molecules into the crystal lattice produces a new unit cell different from that of the anhydrate and, consequently, the physical properties of the solvate may differ from those of the anhydrate. This effect is analogous to polymorphism, which is mentioned in section **1.1.2**, although solvates are strictly molecular adducts. To distinguish solvates from polymorphs, the term of pseudo-polymorphs has been applied to solvates. [10] Of course, we also can tell, like other chemical compounds, some exactly solvate may exhibit polymorphism by itself. [11]

1.1.5 How the water molecules exist in hydrate?

The water molecule H_2O behaves as if it consists of a tetrahedral distribution of two positive and two negative regions of charge. On each negatively charged region, the water molecule interacts with its neighbours via a covalent bond or by accepting a hydrogen bond. (The knowledge of hydrogen bonding will be introduced in section **1.4**) On each positively charged region the water molecule interacts with its neighbours via a donated hydrogen bond. Thus, the neighbours of a water molecule in

a hydrate include electron acceptor groups and electron donor groups.

1.1.6 Why the physical properties of hydrates are different?

Incorporation of the water molecule in the crystal lattice of the anhydrate changes the dimensions, shape, symmetry and capacity of the unit cell. As a result, the anhydrate and each hydrate of a given chemical compound exhibit different physical properties. The hydration changes the volume of the unit cell, which changes the molar volume, so the density of the substance is changed. Because the incorporated water molecule interacts with the anhydrate in the crystal lattice, the refractive index, thermal conductivity and electrical conductivity changes as result. Formation of additional bonding between the host molecules and the water molecules and changes in the bonding between the host molecules themselves change the cooperativity of the molecules in the crystal lattice and hence change the melting point.

1.1.7 The effect of pseudo-polymorphism in pharmaceutical sciences

The change in the thermodynamic activity of the solid due to hydration alters its pharmaceutically important properties. For example, the solubility and the physical and chemical stability, and the change in the solubility of a drug will change the dissolution rate. If the dissolution rate and the stability of a drug change, then its bioavailability and product performance will be modified as a result.

To the solubility, there is a rule: the anhydrous form of a substance is always more soluble in water than the corresponding hydrate which crystallized from water at the

same temperature. [12] (We will discuss the reason in the chapter of discussion.) As the result of this phenomenon, under the same transport rate-controlled conditions, the dissolution rate of the anhydrate is great than that of the corresponding hydrate. [13] Although the differences in bioavailability are related to the formulation factors, we still need to consider the effect of the solubility and dissolution rate to the bioavailability. [14] Solvent of crystallization may occupy a position where it can easily attack nearby molecules. However, some solid-state oxidation reactions of crystal solvates require prior desolvation, so some drug substances are found to be more stable to light and heat in their hydrated forms. [3]

1.2 Crystallization

1.2.1 The crystalline state

The three general states of matter- gas, liquid and solid- represent different degrees of atomic or molecular mobility. In the gaseous state, the motion of molecules is constant, vigorous and random; a mass of gas takes the shape of its container, is readily compressed and exhibits a low viscosity. In the liquid state, random molecular motion is much restricted. A liquid occupy the volume limitedly, i.e., it only takes the shape of the occupied part of its container, and its free surface is flat, except in those regions where it contacts the container walls. Comparing with a gas, a liquid exhibits a much higher viscosity and is less easily compressed. In the solid state, molecular motion is confined to an oscillation about a fixed position, and the rigid structure

generally resists compression very strongly; in fact it will often fracture when it is subjected to a deforming force.

Some substances, such as wax, which possess the outward appearance of being in the solid state, yield and flow under pressure, and they are sometimes regarded as highly viscous liquids. Solids may be crystalline or amorphous. In the regular arrangement of the constituent molecules, the crystalline state differs from the amorphous state, atoms or ions into some fixed and rigid pattern known as a lattice. Actually, many of the substances that were once considered to be amorphous have now been proved, by X-ray analysis, to exhibit some degree of regular molecular arrangement, but the term 'crystalline' is the most frequently used to indicate a high degree of internal regularity, resulting in the development of definite external crystal faces.

As molecular motion in a gas or liquid is free and random, the physical properties of these fluids are the same no matter in what direction they are measured. In other words, they are isotropic. True amorphous solids, because of the random arrangement of their constituent molecules, are also isotropic. However, most crystals are anisotropic; their mechanical, electrical, magnetic and optical properties can vary according to the direction in which they are measured. The exception to this rule is crystals belonging to the cubic system, whose highly symmetrical internal arrangement makes them optically isotropic. Anisotropy is readily detected by refractive index measurements.

1.2.1.1 Crystalline solid

The type of crystal that everyone is familiar with is a solid crystalline body (there is a state of matter which possesses the flow properties of a liquid yet exhibits some of the properties of the crystalline state, namely liquid crystal); the solid crystal comprises a rigid lattice of molecules, atoms or ions, the locations of which are characteristic of the substance. The regularity of the internal structure of this solid body results in the crystal having a characteristic shape; smooth surfaces develop as a crystal grows, and the planes of these faces are parallel to atomic planes in the lattice. However, any two crystals of a given substance very rarely look identical; in fact, any two given crystals often look quite different in both size and external shape. This is due to the fact that crystals have grown under different conditions. This state of affairs prevented the general classification of crystals for centuries. In 1784 Haüy proposed his law of constant interfacial angles: the angles between corresponding faces of all crystals of a given substance are constant. The crystals may be different in size, and the development of various faces (the crystal habit) may vary considerably, but the interfacial angles do not vary; they are characteristic of the substance. It should be noted, however, that substances can often crystallize in more than one structural arrangement (The phenomenon of polymorphism which has been mentioned in the first section **1.1**) in which case Haüy's law applies only to the crystals of a given polymorph. Interfacial angles on centimeter-sized crystals may be measured with a contact goniometer or even the reflecting goniometer, and the modern techniques of X-ray crystallography enable lattice dimensions and interfacial angles to be measured

with high precision on milligram samples of crystal powder specimens.

1.2.1.2 Crystal symmetry

Many of the geometric shapes appearing in the crystalline state are easily recognized as being to some degree symmetrical, and there are three types of symmetry generally:

1. Symmetry about a point. A crystal possesses a centre of symmetry when every point on the surface of the crystal has an identical point on the opposite side of the centre, equidistant from it.

2. Symmetry about a line. If a crystal appears to have reached its original position more than once during its complete rotation, the chosen axis is an axis of symmetry. If the crystal has to be rotated through 180° (360/2) before coming into coincidence with its original position, the axis is one of twofold symmetry (diad axis). If it has to be rotated through 120° (360/3), 90° (360/4) or even 60° (360/6), the axes are of the threefold symmetry (triad axis), fourfold symmetry (tetrad axis) and sixfold symmetry (hexad axis), respectively.

3. Symmetry about a plane. A plane of symmetry bisects a solid object in such a manner that one half becomes the mirror image of the other half in the given plane. However, we should bear in mind that, some crystals may possess a centre and several different axes and planes of symmetry, and some other crystal may have no element of symmetry at all.

1.2.1.3 Crystal systems

There are only 32 possible combinations of the above-mentioned elements of symmetry, including the asymmetric state (no element of symmetry), and these are called the 32 point groups or classes. These 32 classes are grouped into seven systems, they are cubic, tetragonal, orthorhombic, monoclinic, triclinic, trigonal and hexagonal, respectively. The first six of these systems can be described with reference to three axes, x, y, and z. The z axis is vertical, and the x axis is directed from front to back and the y axis from right to left. The angle between the axes y and z is denoted by α, that between x and z by β, and that between x and y by γ. Four axes are required to describe the hexagonal system: The z axis is vertical and perpendicular to the other three axes (x, y and u), which are coplanar and inclined at 60° (or 120°) to one another.

Table 1 The seven crystal systems

System	Angles between axes	Length of axes
Cubic	$\alpha = \beta = \gamma = 90°$	$x = y = z$
Tetragonal	$\alpha = \beta = \gamma = 90°$	$x = y \neq z$
Orthorhombic	$\alpha = \beta = \gamma = 90°$	$x \neq y \neq z$
Monoclinic	$\alpha = \gamma = 90° \neq \beta$	$x \neq y \neq z$
Triclinic	$\alpha \neq \beta \neq \gamma \neq 90°$	$x \neq y \neq z$
Trigonal	$\alpha = \beta = \gamma \neq 90°$	$x = y = z$
Hexagonal	z axis is perpendicular to the x, y and u axes, which are inclined at 60°	$x = y = u \neq z$

1.2.1.4 Miller indices

There are always lots of faces in a crystal and all the faces of a crystal can be described and numbered in terms of their axial intercepts. The axes referred to here are the crystallographic axes which are chosen to fit the symmetry; one or more of these axes may be axes of symmetry or parallel to them; however three convenient crystal edges can be used if needed. If three crystallographic axes have been decided, a plane that is inclined to all three axes is chosen as the parametral plane. Sometimes, it is possible to choose one of the crystal faces to act as the parametral plane. The intercepts X, Y and Z of this plane on the axes x, y and z are called parameters a, b and c. W. H. Miller suggested that each face of a crystal could be represented by the indices h, k and l, defined by:

$h = a / X$, $k = b / Y$, and $l = c / Z$

To the parametral plane, the axial intercepts X, Y and Z are equal to the parameters a, b and c, then the indices h, k and l are a/a, b/b and c/c, i.e. 1, 1 and 1; this is usually written (111). The indices for the other faces of the crystal are calculated form the values of their respective intercepts X, Y and Z, and these intercepts can always be represented by ma, nb and pc, where m, n and p are small whole numbers.

1.2.1.5 Space lattices

Hooke and Haüy gave a conclusion that all crystals are built up from a large number of minute units, which shape is similar to the larger crystal. This hypothesis in fact is a very important step forward in the science of crystallography because its logical

extension led to the modern concept of the space lattice. A space lattice is a regular arrangement of points with three dimensions, each point referring to a structural unit, e.g. an ion, atom or a molecule. The whole structure is homogeneous, in another words, every point in the lattice has an environment which is identical with other point's environment. To proving that, we can draw a line between any two points, when produced in both directions, the line will pass through other points in the lattice whose spacing is identical with that of the chosen pair. We also can imagine that we look at the structure within the structure; then we can get the same view of the surroundings from any of the points in the lattice. In 1848 Bravais postulated that there were only 14 possible basic types of lattice that could give the environmental identity which mentioned above. These 14 lattices can be classified into seven groups due to their symmetry. The 14 Bravais lattices are given in **Table 2**.

Table 2 The fourteen Bravais lattices

Type of symmetry	Lattice	Corresponding crystal system
Cubic	Cube Body-centred cube Face-centred cube	Regular
Tetragonal	Square prism Body-centred square prism	Tetragonal
Orthorhombic	Rectangular prism Body-centred rectangular prism Rhombic prism Body-centred rhombic prism	Orthorhombic

Monoclinic	Monoclinic parallelepiped Clinorhombic prism	monoclinic
Triclinic	Triclinic parallelepiped	Triclinic
Rhomboidal	Rhombohedron	Trigonal
Hexagonal	Hexagonal prism	Hexagonal

Although there are only 14 basic lattices, combination of lattices can occur in actual crystals. Till now, it has been deduced, to any given point, 230 combinations are possible which still may result in the identity of environment. These 230 combinations are named space groups, which are divided into the 32 point groups, or classes.

1.2.1.6 Solid state bonding

According to the method of bonding in the solid state, we can specify the crystalline solid in four types, which are ionic, covalent, molecular and metallic, respectively. Some materials contain more than one type of bond within them, but most crystalline solids can be classified as mainly one of the basic types. The ionic crystals are composed of charged ions held in place in the lattice by electrostatic forces, and separated from the oppositely charged ions by regions of negligible electron density. Covalent crystals composed of atoms which do not carry effective charges, instead they are connected by a framework of covalent bonds, the atoms sharing their outer electrons with each other. Molecular crystals are composed of discrete molecules held together by weak attractive forces, e.g. interaction of π – electrons or hydrogen bonds.

Metallic crystals comprise ordered arrays of identical cations. The constituent atoms share their outer electrons, but these are too loosely held to force them to stay in one crystal lattice, so that they are free to move through the crystal lattice and offer 'metallic' properties to the solid.

1.2.1.7 Crystal habit

As has been introduced in the last paragraphs (**1.2.1.3**), crystals can be classified according to the seven general systems; however, the relative sizes of the faces of a particular crystal can vary greatly. This variation is called a modification of habit. The crystals may grow more rapidly, or be stunted, in one direction; then an elongated growth of the prismatic habit gives a needle-shaped crystal and a stunted growth gives a flat plate-like crystal. Almost all the crystals, no matter whether their source is from manufacture or nature, are distorted to some degree, and this fact always leads to a misunderstanding of the meaning of 'symmetry'. Perfect geometric symmetry is rarely observed in crystals, but crystallographic symmetry is easily detected by means of a goniometer. The relative growths of the faces of a crystal may be altered, and often controlled by a number of factors. Rapid crystallization, for example, the crystallization produced by the sudden cooling or seeding of a supersaturated solution, may result in the formation of needle crystals; impurities in the crystallizing solution can stunt the growth of a crystal in some directions; and a change of habit is frequently caused by the use of different solvents in the crystallization. The degree of supersaturation or supercooling of a solution or melt also often gives a considerable

influence on the crystal habit, and the degree of agitation of the system can make a considerable influence too.

1.2.1.8 Composite crystals and twins

A lot of crystals, especially the crystalline natural minerals, exhibit some aggregation or intergrowth, and one of the important problems of large-scale crystallization is how to prevent the formation of these composite crystals. The presence of aggregates in a crystalline mass injures the appearance of the product and interferes with its free-flowing nature. At the same time, aggregation often implies the presence of impurities because crystal clusters readily retain impure mother liquor and resist efficient washing. Composite crystals may occur in simple symmetrical forms or in random clusters. The phenomenon known as parallel growth can form the simplest form of aggregate; individual forms of the same substance grow on the top of one another in such a manner that all corresponding faces and edges of the individuals are parallel. Another composite crystal frequently encountered is known as a twin or a macle; it appears to be composed of two intergrown individuals, similar in form, joined symmetrically about an axis (a twin axis) or a plane (a twin plane). A twin axis is possibly a crystal edge, the twin plane is possibly a crystal face. Many types of twins may be formed in simple shapes, or they may show an interpenetration giving the appearance of one individual having passed completely through the other; partial interpenetration can also occur. The phenomenon of twinning occurs most frequently when the crystals belong to the orthorhombic or monoclinic systems although twins of

individuals belonging to most of the seven crystal systems may form. Parallel growth and twinning are usually encountered when crystallization has been allowed to take place in an undisturbed solution; however some impurities in the crystallizing medium can cause twin formation even under agitated conditions.

1.2.2 Nucleation

In order to make a system to begin to crystallize, we need two conditions at least: the first condition is supersaturation or supercooling, and another one is, there must exist in the solution a number of minute solid bodies, embryos, nuclei or seeds, which act as centres of crystallization. The nucleation may occur spontaneously or it may be induced artificially. A significantly effective method to induce nucleation is cavitation. Hunt and Jackson (1966) demonstrated that nucleation occurs when a cavity collapses rather than when it expands. Very high pressure (~ 10^5 bars) can be generated by the collapse of a cavity; the change in pressure lowers the crystallization temperature of the liquid and nucleation results. There are two main kinds of nucleation: the first, primary nucleation, means the nucleation in the systems that do not already contain crystalline matter. On the other hand, secondary nucleation refers to the cases that the nuclei are generated in the vicinity of crystals present in a supersaturated system.

1.2.2.1 Primary nucleation

The formation of crystal nuclei in a homogeneous fluid is a difficult process to envisage. It is a kinetic process: firstly, there is the coagulation of the constituent

molecules, on the other hand, they must resist the tendency to redissolve; however, as the result, they also have to become orientated into a fixed lattice. The number of molecules in a stable crystal nucleus can vary from about ten to several thousands. As we recognized, the stable nucleus could arise from a sequence of bimolecular additions according to the scheme:

$A + A \leftrightarrow A_2$

$A_2 + A \leftrightarrow A_3$

.....

$A_{n-1} + A \leftrightarrow A_n$ (critical cluster)

Further molecular additions to the critical cluster would result in nucleation and subsequent growth of the nucleus. Initially, short chains or flat monolayers may be formed, and eventually a crystalline lattice structure is built up.

There is a fact that we should mention here: indeed, it is generally accepted that true homogeneous nucleation is not a common event as it is virtually impossible to achieve a solution completely free of foreign bodies, so we should pay attention to the impurity in the system. However, an impurity that acts as a nucleation inhibitor in one case may not necessarily be effective in another; indeed it may even act as an accelerator, so we can see, no general rule applies and each case must be considered separately. And there is evidence to suggest that the most active heteronuclei in liquid solution lie in the range 0.1 to 1 μm.

1.2.2.2 Secondary nucleation

Secondary nucleation means the supersaturated solution nucleates when crystals of the solute are already present or deliberately added. There are several possible mechanisms of secondary nucleation described by Strickland-Constable. [1] They are initial breeding, needle breeding, polycrystalline breeding and collision breeding.

Now, we introduce two methods on secondary nucleation, contact nucleation and seeding. Collisions in a liquid medium can initiate complex behaviors. Fracture may occur at the point of contact, but substantial hydrodynamic force can operate over the surfaces in the vicinity of the point of contact, giving rise to plastic and elastic deformation in the parent crystal. Due to energy absorption, a small fragment broken off a crystal by collision could be in a considerably disordered state, with many dislocations and mismatch surfaces, so that the small crystalline fragments often grow much more slowly than macrocrystals. Till now, the method of seeding a supersaturated solution with small particles of the material to be crystallized is probably the best one. There are several uses of this method. For example, deliberate seeding is frequently employed in industrial crystallization to effect a control over the product size and size distribution. And from Ostwald's rule of stages, we know an unstable system does not necessarily transform directly into the most stable state, but into one which most closely resembles it own, in another words, into another transient state whose formation from the original is accompanied by smallest loss of energy. However, fortuitous seeding from atmospheric dust (which may contain particles of the crystalline product itself) can serve to prevent the crystallization of

thermodynamically unstable phases, e.g., hydrates or polymorphs. And there is a common phenomenon that some crystals grow up on some particular spot on the vessel wall, which is because the minute cracks and crevices in the surface retain tiny crystals from a previous batch that act as the seeds for the supercooled solution, and the cracks and crevices also supply the nucleation site for the solution.

1.2.3 Crystal growth

There is a large variety of methods available for growing crystals. The choice of method depends greatly upon the physical and chemical properties of the sample. Here, we introduce several most frequently used methods.

1.2.3.1 Solution methods

Solution methods of crystallization are probably the most popular. The main mechanism of these methods is for most substances, the variation of the solubility with the temperature, so when the saturated solution of the sample at one exact temperature be cooled (or heated) to another temperature, the crystallization will take place from the supersaturated solution. The rate of crystal growth can be controlled by controlling the rate of temperature change. Taking advantage of the variation of solute solubility with solution temperature, a well-known temperature reduction crystallizer has been designed, which has many good features. [15] Furthermore, some substances can be dissolved in acidic solvent; however some substances can be dissolved in basic solvent. In other words, the solubility of these substances varies with the pH value, so,

when the pH value of one saturated solution is changed, the crystallization may take place.

1.2.3.2 Evaporation

Evaporation is one of the easiest methods for crystallizing organic and organometallic small molecule compounds. The choice of solvent is very important for these methods because it can greatly influence the mechanism of crystal growth and because the solvent may be incorporated into the crystalline lattice. It is necessary to try a large number of solvents or solvent mixtures to find the best conditions for crystal growth. The rate of crystal growth can be slowed either by reducing the rate of evaporation of the solvent or by cooling the solution. Formation of rosette-shaped masses is an indication of an insufficient number of nucleation sites. The number of nucleation sites may be increased either by seeding the solution or by scratching the exposed surfaces of the glass vessel.

1.2.3.3 Vapor and Liquid Diffusion

Liquid and vapor diffusion methods are often tried when evaporation methods do not immediately succeed. Both methods require finding two solvents or solvent mixtures in which the compound is soluble in one system but insoluble in the other. The two solvent systems should be immiscible or nearly immiscible for liquid diffusion and should be miscible for vapor diffusion. Crystal growth may be slowed somewhat by cooling the apparatus.

Liquid diffusion usually requires that the less dense solvent system be carefully layered on top of the more dense system. The sample can be dissolved in either solvent system. Crystals grow at the interface between the solutions. When compounds precipitate immediately upon being formed, it is possible to slow down the reaction and thus grow larger crystals by putting the reactants in different liquid layers which are separated by a third solvent layer which is not miscible with either of the layers with reactants.

Vapor diffusion is carried out by dissolving a small amount of the sample in one vial, then sealing this inner vial inside a larger vial that contains a small volume of another solvent system. Vapor from the solvent of the outer vial then diffuses into the solution in the inner vial, causing the compound to precipitate. The vertical surfaces of the inner vial should not touch the outer vial to keep the outer solution from rising by capillary action and entering the inner vial.

1.2.3.4 Thermal Gradient

Thermal gradient methods usually produce very high quality crystals. Such methods include slow cooling of sealed, saturated solutions, refluxing of saturated solutions, sublimation, and zonal heating. Zonal heating is used primarily for crystallizing solid solutions or mixtures. Small crystals may sometimes be grown larger by zonal refluxing of a supersaturated solution. Sublimation may be carried out in a variety of tubes or vessels. Sealed vessels offer an advantage for sublimation in that the chamber may be evacuated or a partial pressure of some inert gas may be introduced before

sealing the sample in the apparatus. Sublimation methods consistently produce very high quality crystals. Larger crystals may be grown either by decreasing the thermal gradient or by cyclic heating and cooling of the sample.

There are still some other methods can be used in crystal growth, we have not mentioned every one here. However, among them, the first two methods are the most frequently used because they are suitable for a great number of substances and the rate of crystal growth is easy to control by these two methods.

There are a few general points that apply to all crystallization methods. First, it is important that the sample be as pure as possible. When crystallization attempts consistently yield oils, the sample is probably not pure. Second, the solvents or co-crystallizing materials should be as pure as possible too. Contaminants may often break down the desired sample. Third, it is important for most solution methods that the glassware be thoroughly clean and "old" or "used". New glassware is so smooth that there are no nucleation sites available on the exposed surfaces (See **1.2.2.2**). Also, new glassware from the manufacturer usually has a variety of dusty contaminants. A final point about the crystallization process is that if a sample only yields small crystals, the method should be altered so as to slow down the growth step.

1.3 Experimental determination of structures

In previous section of this chapter, we discussed how the crystals can grow. Then after we have grown the crystal, the next important question is how we can obtain a trial

structure from the crystal.

1.3.1 The methods that can be used in structure analysis

In recent years, in addition to the many polymorphs isolated, the more sophisticated isolation techniques now available have extended the capabilities of exploring biological molecules heretofore thought too complex to understand or investigate. The chemist thus is faced with the task of identifying the chemical structure of a large number of complex materials in order to understand their biological functions.

For many of the compounds the chemist may rely on standard spectrometric methods (i.e., IR, UV, NMR), together with other chemical measurements, to elucidate molecular structure. Newer methods, especially mass spectrometry, have emerged as useful means of elucidating the structures of complex organic materials. In many instances these approaches have shortcomings, as they provide only fragmentary evidence about various portions of the molecule, which must be pieced together to get the picture of the whole compound. [16]

As we mentioned in section **1.1.2** and **1.1.4**, polymorphism and pseudo-polymorphism are frequent phenomena in pharmaceutical compounds; therefore several techniques are currently used for the study of this field. Thermoanalytical techniques combining differential scanning calorimetry, microcalorimetry and thermogravimetry with microscopy, spectroscopy, mass spectrometry or X-ray diffraction are state of the art

techniques. [17] We will introduce the method of X-ray diffraction especially in the next section.

Neutrons, electron beams and X-rays capable of giving atomic resolution (1 Å or less) exist, while the maximum resolution that can be obtained through an ordinary light microscope under the best conditions is about 2000 Å. Lenses have been constructed only for the second of these kinds of radiation, and at best they have a resolving power of about 6 Å. This resolution is insufficient to measure the distances between atoms. It is possible to study the details of molecules without lenses, by means of diffraction experiments. Of the three types of radiation, X-rays have proved to be the most useful and fruitful for studying molecular structure. [16] When it is applicable, X-ray crystallographic analysis is both convenient and precise. Using this method, the three-dimensional structure of a molecule can be determined without relying on any chemical information.

1.3.2 X-ray crystallography

Crystallography grew up as a branch of mineralogy, and involved mainly the recognition, description, and classification of naturally occurring crystal species. As a subject in its own right, crystallography is a relatively new discipline, dating from the discovery of the diffraction of X-rays by crystals in 1912. [18] The primary aim of X-ray crystallography is to obtain a detailed picture of the contents of the crystal at the atomic level. Once this information is available, the positions of the individual atoms

are therefore known precisely; one can calculate interatomic distances, bond angles etc, and even a molecular formula and geometrical details which are completely unknown can be established through the resulting full three-dimensional representation of the atomic contents of the crystal.

1.3.2.1 The nature of X-rays

The X-rays are a form of electromagnetic radiation, a part of the great range which extends from the waves used for radio whose length is measured in meters to the waves a million million times shorter, which come from radioactive bodies or reach us from space as cosmic rays. [19]

1.3.2.2 Diffraction

As we all know, light travels in a straight line, so when the object is a big one (much bigger than the wavelength of the light), we can get a sharply defined shadow; however, when light from a point source passes through a narrow slit or a very fine pinhole, we can see the light exists in the region that we thought should be shadow. This phenomenon is named diffraction.

Diffraction pattern is the pattern comes from the phenomenon of diffraction. The width of the pattern is related to the ratio of the wavelength of the radiation- λ, to the minimum dimension of the scattering object- a; the larger the value of λ/a, the greater the spread of the pattern. [20]

The light has the character of waves, so it also can undergo the phenomenon of interference. The distance between two slits- d, has an inverse relationship with the spacing of the sampling region. In other words, when there is a relatively narrow spacing between slits, the distance between sampling regions is relatively large, and vice versa.

If we increase the number of the equidistant slits, the radiation is concentrated in increasingly narrower regions, and then the diffraction pattern become sharp.

The character of diffraction mentioned above may be extended to three dimensions and to crystals. In the instance of diffraction of X-rays by a crystal, we can imagine the electrons in the atoms act as the edges of the slits in a grating. And the sources of X-rays may be regarded as sources of visible light. We can do this because there is an analogy between atoms in a crystal, arranged in a regular array, and slits in a grating, arranged in a regular array. In diffraction by crystals, as by slits, the intensities of the diffraction maxima show a variation in different directions and also vary significantly with angle of scattering. The X-ray photography is merely a scaled-up 'sampling' of the diffraction pattern of a single unit cell, with the 'envelope' being the diffraction pattern produces by scattering from the electrons in the atoms of the unit cell, and the 'sampling regions' arranged on the lattice reciprocal to crystal lattice.

1.3.2.3 The experimental measurements

After understanding the principle of the X-ray diffraction, then we proceed to the experimental measurements. Before we can use the diffractometer to collect the X-ray diffraction data about the crystal which comes from our previous experimental work, we should do some preparatory steps. They include crystal selection and crystal mounting. About the crystal selection, we should keep the following points in mind: ideal crystals for diffraction studies are well-ordered single crystals of suitable size. And crystals should be examined under low power (10X to 40X) magnification to determine their overall quality, size and, if possible, point group symmetry. Good crystals usually have smooth flat faces, sharp edges, no inclusions, no striations and no obvious dislocations. Careful notes should be made if the bulk sample is not visibly homogeneous. The selected crystal should show no obvious external twinning. Transparent crystals should be checked with a polarizing microscope to verify that the crystals are single. The typical morphology and point group symmetry should be noted. The crystal chosen for analysis needs to be large enough to produce an adequate diffraction pattern, at the same time, as small as possible to minimize absorption problems. The calculation of structure factor amplitudes assumes that the crystal is being completely bathed in a uniform beam of X-rays. Since the uniform region of the X-ray beam is about 0.5 mm in diameter, this is taken as the maximum dimension of any crystal. For most samples, a minimum dimension of 0.1 mm is needed to produce adequate X-ray scattering. Compounds with few atoms or very heavy atoms can have all three dimensions toward the small end of this 0.1 to 0.5 mm

range. The best crystals for compounds with many light atoms should have all three dimensions toward the large end (0.5 mm) of this range. As most of our experimental substances are composed with light atoms, so we always choose a relatively big crystal. Crystals that are too large can be cut with a razor blade, scalpel, or solvent saw. We used the scalpel in our experiments. In other cases, if the crystals are strongly absorbing (contain heavy atoms), it is worthwhile to reshape the crystal to make it as nearly spherical as possible. This reshaping may be done by cutting, grinding or dipping the crystal in solvent.

About the crystal mounting, we should notice that crystal mountings must be rigid to hold the sample in the same orientation and must minimize the amount of extraneous material that is in the incident and diffracted beam paths. The sample support is usually made from an amorphous material such as glass which is held in a metal pin and clamped on a goniometer head. For different samples, we should adopt different methods according their stability. There are three methods that are frequently used in the laboratory. Air stable crystals are usually glued (using epoxy, Elmers, Duco/amyl acetate, etc.) to the end of a glass fiber. The sample should be mounted with its smallest surface toward the fiber. Fibers pulled from glass tubing are actually small capillary tubes and are more rigid than fibers made from solid glass. For mildly air unstable compounds, we can coat them with epoxy or an inert viscous material such as paratone N or Krytox oil. These mountings are usually carried out in an inert atmosphere such as a dish filled with argon gas. The crystal is further kept from reacting during data collection by cooling the sample in a chilled nitrogen gas stream.

Very reactive crystals must be mounted in a glove bag or glove box and sealed in capillary tubes. And some compounds must be mounted in glass capillary tubes because they are unstable or lose solvent easily. Crystals that lose solvent easily (such as proteins) are wedged in capillary tubes with a drop of mother liquor on or near the crystal. These mounts are typically sealed only with beeswax. Unstable crystals are usually wedged in the capillary tubes or are held in place by a small amount of grease. Capillary tubes containing unstable compounds must be usually sealed by melting the ends of the glass tube. Capillaries do introduce problems related to a distorted optical image of the sample during centering on the instrument and to increased background scattering and absorption of the diffracted X-ray beam. It is crucial that the capillaries be made out of thin glass similar to that found in commercially available capillaries. Thick glass capillaries absorb X-rays so much that very little scattered radiation will leave the capillary.

Then the diffraction data can be collected by the diffractometer. From the measurements on the diffraction pattern, we may collect two types of data. First, the angle of scattering (2θ, the angular deviation from the direct undeviating beam); this data can be used to determine the spacing of the reciprocal lattice and hence the spacing of the crystal lattice, which may be used to measure the size and shape of the unit cell. Second, the intensities of the diffracted beams; by analyzing this data, we can get the positions of the atoms within the unit cell. These positions are usually expressed as fractions of the unit cell edges.

1.3.2.4 The remaining steps

After we get the relative intensity- I, for each reflection with indices, h, k, l, together with the corresponding value of the scattering angle-2θ, we can deduce a suggested atomic arrangement, i.e. a trial structure, by some method. Direct methods are most frequently used in small-molecule crystallography to generate the required information. In the work reported here, the direct methods program SHELX-S provided the trial structures. The intensities of the diffraction maxima corresponding to this arrangement can be calculated and compared with those observed. After the approximate positions have been determined for most of the atoms, the refinement of the structure can be started. In this process the atomic parameters are varied systematically so as to give the best possible agreement of the observed structure factor amplitudes with those calculated for the proposed structure. Because there are many parameters in the crystal structure problem, many continuous refinement cycles are needed so that the structure converges to the stage at which shifts in the atomic parameters from cycle to cycle are negligible with respect to the expected experimental errors.

By now, we have finished the whole process of crystal structure analysis, and a clear structure pattern is in front of our faces. Here, it is necessary to introduce two computer programs which are used in our experiment. They are SHELXL-97 for refinement and ORTEP-III for crystal structure illustrations.

1.4 Identification and naming of hydrogen bond patterns

Hydrogen bonding is a subset of intermolecular interactions. [21] There are several kinds of intermolecular interactions that are useful for directing molecular self-assembly, such as electrostatic attractions, Van der Waals interactions, and charge-transfer interactions; however the hydrogen bonds are the most popular among them.

Pauling [22] gave the definition of the hydrogen bond: Hydrogen bond is an interaction that directs the association of a covalently bound hydrogen atom with one or more other atoms, groups of atoms, or molecules into an aggregate structure that is sufficiently stable to make it convenient for the chemist to consider it as an independent chemical species.

In the solid state, hydrogen-bond patterns are usually well defined and often involve infinite chains or arrays. In dilute solution, the dimer patterns are preferred; in concentrated solutions or melts, the chains are always shown; and high-dielectric solvent might favour more polar conformers.[23] Such considerations cause some trouble for making empirical predictions of hydrogen-bond patterns. Theoretical methods have been proven useful in solving some of these problems. It is shown that empirical hydrogen-bond rules useful for determining preferred modes of hydrogen bonding can be developed by using the huge Cambridge Crystallographic Database. Development of empirical hydrogen-bond rules is based on the frequency of

occurrence of specific graph sets with a functional group class and the observations about stereo electronic hydrogen-bond preference and hydrogen-bond selectivity. Several empirical hydrogen-bond rules have been obtained; we just list three general rules here. The first rule, all good proton donors and acceptors are used in hydrogen bonding. The second rule, six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds. The third rule, the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another. There are still other specific hydrogen-bond rules which can be derived for other functional-group classes; they are available in the literature. [24]

As it became obvious that the hydrogen bonds occurred in many kinds of materials, and were important for determining the properties and activities of most bio chemicals, hydrogen bond classifications were developed. [25] The purpose of graph-set notation is to define the morphology of hydrogen-bonded arrays. Here, real molecules rather than points are used as nodes, and the hydrogen bonds are distinguished by the type of donors and acceptors. The set of molecules that are hydrogen bonded to one another by repetition of just one of these types of hydrogen bonds is named a motif. In order to indicate whether the motif is infinite or finite, and cyclic or not, the motif is separated into four types, namely C (chain), R (ring), D (dimer), and S (intramolecular hydrogen bond). The number of donors (d) and acceptors (a) that are used in a motif is assigned as subscripts and superscripts, respectively. The number in

the repeat unit is indicated in parentheses.[6] Examples are given in **Figure 2**.

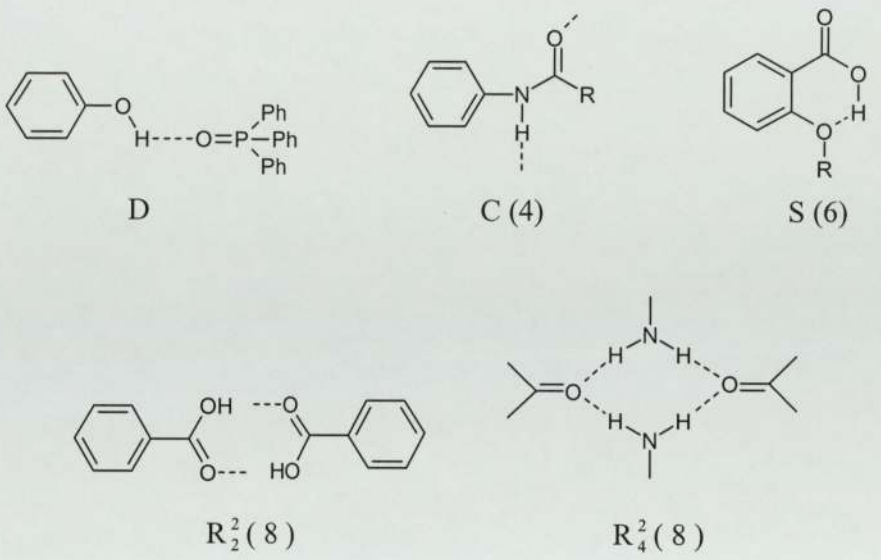


Figure 2 Graph-set assignment for representative hydrogen-bond motifs

1.5 Prediction of polymorphic forms

One of the most fundamental unsolved problems in chemistry is to predict how a molecule will pack in the solid state solely on the basis of its molecular structure. [26] This is a very interesting problem, because the crystal packing affects many physical properties of the solid, such as solubility, bioavailability and colour, which is useful in the fields of pigments, pharmaceuticals, magnets, conductors, and photosensitive or optoelectronic materials. [27]

But the crystal structure prediction is not easy work, because of the existence of a large number of local minima in the high dimensional potential energy surface of the crystal, which make it very difficult to locate the most stable structure. [28] Till now, we still cannot predict *ab initio* the complete structure of any organic crystal: space group,

cell parameters, and atomic positions, much in the same style as in X-ray single-crystal structure analysis. We can see it objectively from the blind test organized by the Cambridge Crystallographic Data Centre, in which several computational chemistry groups tried their hand at the truly *ab initio* prediction of the crystal structures of some compounds for which only a molecular diagram was supplied. At the same time, the crystal was separately analyzed by X-ray diffraction. At last, the results showed that genuine success was achieved only in a handful of cases, the number of hits not exceeding 3% of the total number of submitted trial structures. [29] So we have to ask 'why it is so difficult to achieve the aim of crystal structure prediction?' In 1994, Angelo Gavezzotti said no true prediction in the above sense can be accomplished without calculating the crystal potential energy, but one fundamental point is the choice of the best coordinates for the energy space. [27] Nowadays it is not great problem to calculate the potential energy of a crystal built from small to medium-sized organic molecules by pairwise addition of atom-atom potentials, such as, $E = \sum_i \sum_j A \exp(-BR_{ij}) - CR_{ij}^{-6}$. [30] In usually logical thought, if given a molecular structure, we assume it to be rigid at one moment, we can simply calculate E for very many hypothetical crystalline arrangements and find the one with the lowest potential energy. Thousands or even more of possible structures can be generated by grid search or random search techniques, or by systematic generation of dimers or strings of molecules over crystal space group symmetry elements, and we can choose some of them to be used as starting points for energy minimization calculations. However, as we know, there are lots of polymorphic forms of closely

similar energy, so even after we carry out the calculations mentioned above, we always get many possible crystal structures within a very small energy range, instead of a single crystal structure. That is the problem! Furthermore, the question of *how* crystals form is even more problematic; in fact, there are many cases showing that the crystals first formed from solution or from a melt are not the thermodynamically stable crystal under normal laboratory conditions, which makes the crystal structure prediction more unrealistic and unreliable.

Even so, occasionally some method can make the problem to be solved feasible. Sometimes the X-ray powder diffraction pattern is available, but the structure cannot be solved from the diffraction data due to the phase problem, which means that the orientation of the molecule inside the cell cannot be calculated directly from the diffraction. However the predicted structures can be used as good starting points for refinement procedures based on diffraction comparison and minimizing procedures with a highly accurate intermolecular force field.[31] The work of refinement can be separated into two steps: the first step using a Monte-Carlo procedure to generate some random structure, and the second step refining the initial structure by energy minimization with a steepest descent or a simulated annealing procedure.[32,33] However, because the initially chosen structure tends to be far away from a local energy minimum, it will take the existing algorithms a long time to run the procedure.[34]

Detlef W. M. Hofmann *et al* developed a new algorithm named FlexCryst to solve the problem of crystal structure prediction, which takes a conformer of an organic molecule assumed to be rigid and produces a number of candidates of crystal structures for this molecule; it can also give out the approximate energy of the respective crystal structure. However, this algorithm is currently implemented only for the four space groups $P1$, $P\text{-}1$, $P2_1$, and $P2_12_12_1$. The three latter space groups are widespread in nature. [34] The packing calculations can be based only on molecular shape without consideration of atomic charges, or electrostatic effects can be included by input of the calculated partial charge on each atom.

Chapter 2 Experimental Work and Results

General: In our search for useful crystals of previously unknown or ambiguously described polymorphs and solvates, the test compounds were crystallized from a variety of solvents differing in polarity and acid-base properties. ^{1}H NMR spectra were recorded on a Bruker AC-250 spectrometer at (250.1 MHz) with positive chemical shifts downfield of TMS. Infra-red spectra were recorded on a Mattson 3000 instrument. DSC traces were recorded on a Perkin-Elmer DSC-4 differential scanning calorimeter. And the crystal data were collected from an Enraf-Nonius CAD4 diffractometer with monochromated Mo-K_a radiation, $\lambda = 0.71069$ Å.

Material: There are in total five substances investigated in my research, they are Temozolomide, Hydantoin, 5,5-diphenylhydantoin, 5,5-dimethylhydantoin and allantoin. As successful results were only obtained from the former three substances, I list the experimental procedure and results of Temozolomide, Hydantoin and 5,5-diphenylhydantoin below only. Numerous attempts were made to prepare polymorphs of 5,5-dimethylhydantoin and allantoin, but the only crystals obtained duplicated already published structures. Only the result of crystal structure prediction is obtained from 5,5-dimethylhydantoin.

2.1 Temozolomide

2.1.1 Introduction

a. Bioactivity

Gliomas are the most common primary intracerebral tumours and over 60% of these are malignant. [35] Malignant gliomas (MG) are difficult to eradicate and surgical morbidity and mortality are high. [36] Recurrence rates following surgery and radiotherapy are of the order of 90% and the 6-month survival in this group is less than 30%.[37] Over 90% of recurrences occur within 2cm of the original tumour. Many chemotherapy drugs have very poor response rates in these tumours. Standard treatment in the UK for patients with a good performance status consists of surgery and postoperative radiotherapy, however, recurrence is almost inevitable. Treatment of recurrent malignant gliomas is limited to further surgery, chemotherapy and novel biological therapies. The response rate to standard chemotherapy protocols for recurrent malignant gliomas is less than 30%.[35]

8-Carbamoyl-3-methylimidazo-[5,1-d]-1,2,3,5-tetrazin-4(3*H*)-one (temozolomide) is one of a series of imidazotetrazinone derivatives. [38] Temozolomide (Temodar–US, Temodal–Rest of World) was developed by the UK Cancer Research Campaign in the 1980s. [39] It is an orally active alkylating agent with a similar chemical structure to dacarbazine; however, it has some advantages over dacarbazine, with which it shares the active metabolite 5-(3-methyl)-1-triazen-1-yl-imidazole-4-carboxamide (MTIC). Temozolomide has revealed good bioavailability after oral administration and spontaneously converts into the active metabolite without the need for enzymatic

demethylation in the liver and has recently been licensed in the UK for second line treatment of recurrent malignant gliomas. [40] Temozolomide has excellent penetration into all body tissues, including the brain. One mechanism of resistance to this agent is mediated through the enzyme O6-alkylguanine transferase (AGT). Many brain tumours express low concentrations of this enzyme. [41] Temozolomide has shown a broad spectrum of antineoplastic activity. In patients with malignant glioma, the objective response (complete or partial response) rate ranged from 11 to 47% in noncompetitive studies, especially in newly diagnosed patients. The progression-free survival (PFS) at 6 months was consistently more than 20%.[42] Preclinical studies also proved that the temozolomide has some appropriate activity against high-grade glioma: The main benefit in patients with glioblastoma multiforme (GBM, designated grade IV in high grade gliomas), demonstrated in one randomized controlled trial (RCT) and one relatively large uncontrolled study, is an increase (13%) in the estimated proportion of patients remaining progression-free at 6 months and a significant increase in median PFS of approximately 4 weeks. However, there was no significant overall survival advantage. For patients with anaplastic astrocytomas (AA, classified as grade III in high grade gliomas), one large uncontrolled study suggests favourable PFS and possibly increased overall survival. [43] And it also has shown activity in relapsed oligodendroglioma after nitrosourea chemotherapy.

There are lots of future developments in the use of temozolomide to be explored, for example, there may be synergy when temozolomide is concomitantly combined with radiotherapy. Temozolomide is a radiosensitising agent and may help to eliminate

residual microscopic disease outside the radiation field. [44] Temozolomide may be more effective in combination with other drugs such as procarbazine or irinotecan.[45,46]

Like all the other anti-tumour drugs, temozolomide also has adverse effect. Myelosuppression is the most serious adverse effect of temozolomide and is dose limiting; however, it does not appear to be cumulative and is relatively easily treated. Between 6 and 10% of patients suffered grade 3 or 4 thrombocytopenia, less than 5% suffered each of grade 3 or 4 neutropenia, leukopenia or anaemia. [43] A wide range of other grade 3 or 4 adverse effects were noted in one study, most commonly asthenia (6%), headache (6%), nausea (10%) and vomiting (6%).[47]

b. Former crystal structure

The U.S. patent for temozolomide[48] (Examples 4 and 9) describes crystals grown from four different solvents, namely acetone:water (3:1 and 1:3), the former giving high-quality laths that were used for structure determination; [49] hot water, yielding a granular solid; and acetonitrile, producing "a polymorphic form". The previously reported crystal structure of temozolomide contains no solvent. The two independent molecules in the asymmetric unit of that form of temozolomide are illustrated below, showing the hydrogen-bonded dimer and possible intra-molecular hydrogen bonding (**Figure 3**). [49]

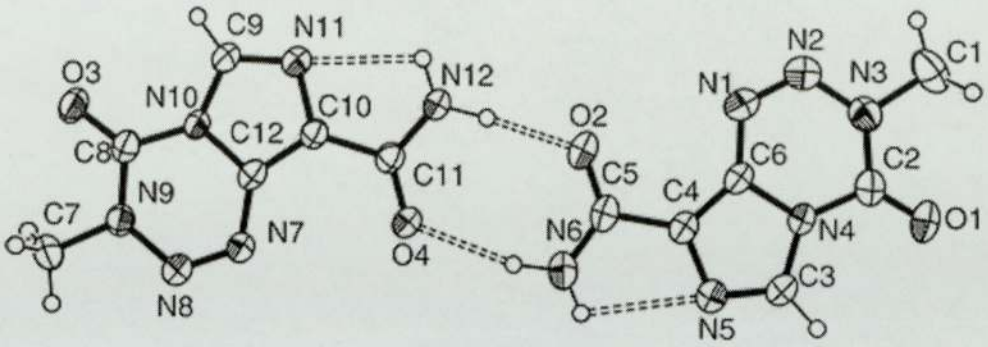


Figure 3 Crystal Structure of Temozolomide

In an attempt to get different polymorphs or solvates of temozolomide, we used three different kinds of solvent in our experiments. The first one is aqueous acetic acid; we choose this solvent because water is a polar solvent which can dissolve polar compounds well, such as the temozolomide, and the acetic acid can help dissolution because of the base functionality on temozolomide. The second kind of solvent is acetone: water (1:1) mixed solvent; this kind of solvent has been used in Example 4 on page 8 of the U.S. patent, however in different proportions. We wanted to investigate any change in structure through changing the proportions. The third solvent is acetonitrile, used as solvent without water to guarantee an anhydrous form.

2.1.2 Method 1.

Crystal growing

To the temozolomide (0.044g) in a 25 ml flask was added water 2 ml as solvent, then shaken in the 40°C water bath. At this time, there was still some undissolved

temozolomide. Three drops of acetic acid were added into the solution, with continued shaking in the 40°C water bath, until the solid was completely dissolved. Then the solution was gradually cooled to room temperature, while keeping the solution in darkness (with kitchen foil). Five hours later, several pink planar square crystals could be found in the flask bottom; one day later, more such crystals grew; one additional day later, no more crystals appeared.

Crystal data

Temozolomide monohydrate, $C_6H_6N_6O_2 \cdot H_2O$, M = 212.18. Crystals exhibit monoclinic symmetry, space group $P2_1/m$, with a = 7.5158(9), b = 6.3044(13), c = 9.5324(16) Å, β = 92.907(12), V = 451.09(13) $Å^3$, Z = 2, D_x = 1.562 Mg/m^3, F (000) = 220, μ = 0.13 mm^{-1}.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angles of 25 reflections, $7.76 \leq \theta \leq 13.96°$. Intensity data were collected by the ω-2θ scan technique with ω scan range 0.96 + 0.35 tan θ and ω scan speed 0.83 to 3.33 degree per minute. The 1815 reflections were measured for $-8 \leq h \leq 8$, $-7 \leq k \leq 3$, $-11 \leq l \leq 11$, in the range of $2 \leq \theta \leq 25^{\circ}$ and were merged to give 871 independent reflections (R_{int} = 0.0346) of which 767 were deemed observed with $F > 4\ \sigma(F)$, R(obs) = 0.0334, wR2(all data) = 0.0967, largest peak and hole on difference map are 0.240 and -0.176 $e.Å^{-3}$. Direct-phase determinations and full-matrix least-squares refinement were

carried out with the SHELXS-97 and SHELXL-97 programmes.

Table 3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for temozolomide hydrate. U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
N(1)	94(2)	2500	4517(2)	44(1)
N(2)	-707(2)	2500	3308(2)	48(1)
N(3)	259(2)	2500	2114(2)	43(1)
C(4)	2075(3)	2500	2070(2)	41(1)
O(4)	2909(2)	2500	1028(2)	61(1)
N(5)	2881(2)	2500	3418(2)	37(1)
C(6)	4626(3)	2500	3837(2)	41(1)
N(7)	4841(2)	2500	5209(2)	40(1)
C(8)	3159(2)	2500	5714(2)	36(1)
C(8A)	1911(3)	2500	4613(2)	36(1)
C(31)	-870(4)	2500	813(2)	55(1)
C(81)	2835(3)	2500	7241(2)	40(1)
O(82)	1313(2)	2500	7632(2)	62(1)
N(82)	4239(3)	2500	8122(2)	58(1)
OW	7798(2)	2500	7231(2)	74(1)

Table 4 Bond lengths [Å] for temozolomide hydrate.

Bond	Bond Distance
N(1)-N(2)	1.272(2)
N(1)-C(8A)	1.364(3)
N(2)-N(3)	1.381(2)
N(3)-C(4)	1.368(3)
N(3)-C(31)	1.467(3)
C(4)-O(4)	1.201(2)
C(4)-N(5)	1.393(2)
N(5)-C(6)	1.351(3)
N(5)-C(8A)	1.384(2)
C(6)-N(7)	1.310(3)
N(7)-C(8)	1.375(2)
C(8)-C(8A)	1.371(3)
C(8)-C(81)	1.488(3)
C(81)-O(82)	1.221(2)
C(81)-N(82)	1.315(3)

Table 5 Bond angles (°) for temozolomide hydrate

Atoms	Bond Angle
N(2)-N(1)-C(8A)	119.14(17)
N(1)-N(2)-N(3)	120.15(17)
C(4)-N(3)-N(2)	126.35(16)
C(4)-N(3)-C(31)	120.60(18)
N(2)-N(3)-C(31)	113.05(17)
O(4)-C(4)-N(3)	126.10(19)
O(4)-C(4)-N(5)	122.83(19)
N(3)-C(4)-N(5)	111.07(16)
C(6)-N(5)-C(8A)	107.49(15)
C(6)-N(5)-C(4)	130.01(17)
C(8A)-N(5)-C(4)	122.50(16)
N(7)-C(6)-N(5)	111.34(17)
C(6)-N(7)-C(8)	106.28(17)
C(8A)-C(8)-N(7)	109.73(16)
C(8A)-C(8)-C(81)	127.49(18)
N(7)-C(8)-C(81)	122.78(17)
N(1)-C(8A)-C(8)	134.05(17)
N(1)-C(8A)-N(5)	120.79(16)
C(8)-C(8A)-N(5)	105.16(16)

O(82)-C(81)-N(82)	122.60(18)
O(82)-C(81)-C(8)	120.10(17)
N(82)-C(81)-C(8)	117.30(18)

Table 6 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for temozolomide hydrate.

	X	Y	Z	U(eq)
H(6)	5570(30)	2500	3210(30)	49(6)
H(31A)	-130(50)	2500	70(40)	80(9)
H(31B)	-1580(30)	1290(30)	770(20)	77(6)
H(82A)	5400(40)	2500	7840(30)	65(7)
H(82B)	4080(40)	2500	8990(40)	79(9)
HWA	8920(40)	2500	7240(30)	72(8)
HWB	7340(50)	2500	6410(40)	91(11)

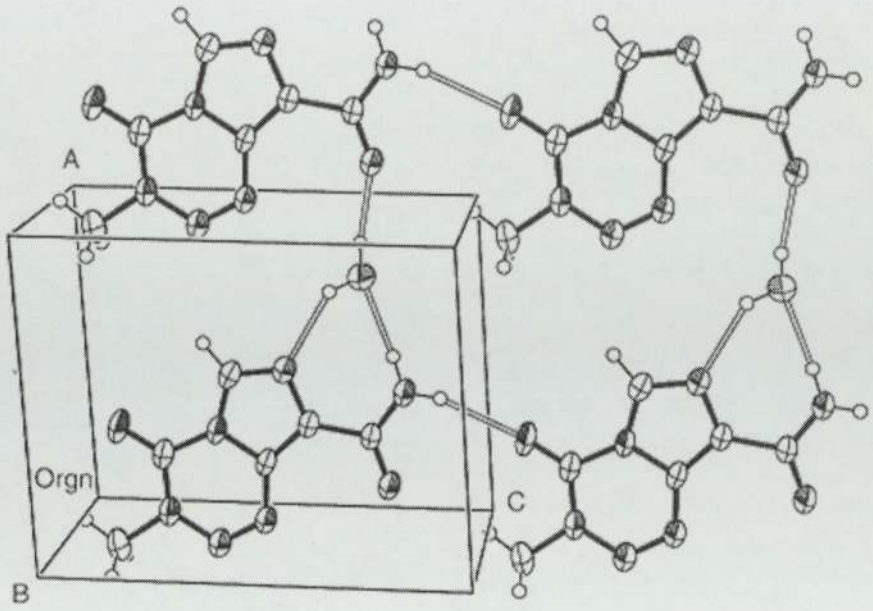


Figure 4 Crystal structure for new hydrate of the Temozolomide

2.1.3 Method 2.

Crystal growing

To the temozolomide (0.092g) in a 25 ml flask was added Acetone: Water (1:1) mixed solvent. The flask was shaken in the 30°C water bath, then more acetone and water mixed solvent was added until the temozolomide solid was completely dissolved. Altogether 4.2 ml acetone and water mixed solvent was added.

Then the solution was cooled to room temperature gradually, keeping the solution in darkness (with kitchen foil). Some pink micro crystals came out after standing about ten hours; two days later, some bigger crystals appeared which are pink and look like square plates.

Crystal data

Temozolomide monohydrate, $C_6H_6N_6O_2 \cdot H_2O$, M = 212.18. Crystals exhibit monoclinic symmetry, space group $P2_1/m$, with a = 7.5160(10), b = 6.3040(13), c = 9.5328(17) Å, β = 92.910(13), V = 451.09(14) $Å^3$, Z = 2, D_x = 1.562 Mg/m^3, F (000) = 220, μ = 0.13 mm^{-1}.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angles of 25 reflections, $7.01 \leq \theta \leq 13.39°$. Intensity data were collected by the ω-2θ scan technique with ω scan range 1.20 + 0.35 tan θ and ω scan speed 0.83 to 3.33 degree per minute. The 2969 reflections were measured for $-9 \leq h \leq 8$, $-7 \leq k \leq 0$, $-11 \leq l \leq 11$, in the range of $2 \leq \theta \leq 26.5°$ and were merged to give 1024 independent reflections (R_{int} = 0.0332) of which 754 were deemed observed with $F > 4\ \sigma(F)$, R (obs) = 0.0388, wR2 (all data) = 0.1089, largest peak and hole on difference map are 0.243 and -0.250 $e.Å^{-3}$. Direct-phase determinations and full-matrix least-squares refinement were carried out with SHELXS-97 and SHELXL-97 programmes.

2.1.4 Method 3.

Crystal growing

To the temozolomide (0.025g) in a 25 ml flask was added acetonitrile, the flask was shaken in the 30°C water bath, and more acetonitrile was added until the temozolomide solid was dissolved completely. Altogether 2.6 ml acetonitrile was

added.

The solution was cooled to room temperature and then concentrated until all the acetonitrile evaporated completely, keeping the solution in darkness. Some beautiful pink-yellow square crystals came out after standing about two days.

Crystal data

Temozolomide, $C_6H_6N_6O_2$, M = 194.17. Crystals exhibit monoclinic symmetry, space group $P2_1/c$. with a = 17.3303(16), b = 7.346(3), c = 13.241(3), Å, β = 109.544(12), V = 1588.6(8) $Å^3$, Z = 8, D_x = 1.624 Mg/m^3, F (000) = 800, μ = 0.129 mm^{-1}.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angles of 25 reflections, $7.72 \leq \theta \leq 12.86°$. Intensity data were collected by the ω-2θ scan technique with ω scan range 1.20 + 0.35 tan θ and ω scan speed 0.83 to 3.33 degree per minute. The 6757 reflections were measured for $-20 \leq h \leq 20$, $-8 \leq k \leq 8$, $-15 \leq l \leq 3$, in the range of $2.5 \leq \theta \leq 25°$ and were merged to give 2800 independent reflections (R_{int} = 0.0348) of which 1991 were deemed observed with $F > 4\sigma(F)$. R (obs) = 0.0625, wR2 (all data) = 0.1025, largest peak and hole on difference map are 0.214 and -0.156 e.$Å^{-3}$. Direct-phase determinations and full-matrix least-squares refinement were carried out with SHELXS-97 and SHELXL-97 programmes.

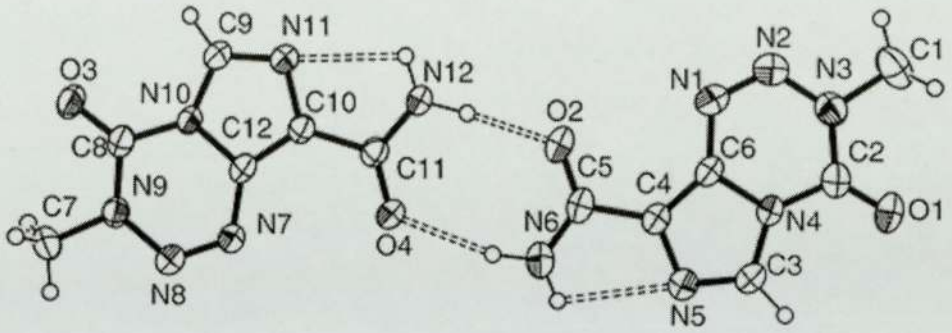


Figure 5 The same crystal structure as the one previously determined for the anhydrous form.

2.1.5 Decomposition Study of Temozolomide

In order to find out whether this hydrate is more stable than the anhydrous form or not, we need some way to monitor the decomposition process, which probably will take place gradually over time. The method we use is to expose a number of small samples to identical conditions, and at suitable time intervals take out one of these samples and subject it to analysis. With NMR we can check the disappearance of a reactant peak and appearance of a product peak for the partially decomposed solid.

We separated the samples into four groups: I Hydrate of Temozolomide in hot environment (37°C), II Hydrate of Temozolomide in light and temperature 16°C, III Anhydrous form of Temozolomide in hot environment (37°C), IV Anhydrous form of Temozolomide in light and temperature 16°C. Then at time intervals of 0 day, 3 days,

1 week, and 2 weeks some sample was taken from every part to run NMR. The spectrum is displayed in the Appendix II.

2.2 Hydantoin

2.2.1 Introduction

The hydantoin ring contains two hydrogen bond donor groups (NH) and two acceptors (O=C). Various modes of hydrogen-bonded association can be envisaged, including dimers and chains. Surprisingly, no structure of hydantoin exists in the Cambridge Structural Database. The structure of 5,5-diphenylhydantoin, a pharmaceutically important derivative, has been reported; but its quality was impaired by disorder. The present studies were undertaken in an attempt to determine the structure of hydantoin for the first time, improve the structure of 5,5-diphenylhydantoin, and grow polymorphs with different hydrogen bonding motifs by variation of solvent.

2.2.2 Method 1.

Crystal growing

To the hydantoin (0.407g) in a 25 ml flask was added water 2 ml as solvent first, and shaken in the 80°C water bath. Since at this time there was still some hydantoin solid that could not be dissolved completely, more water was dropped into the solution, with continued shaking in the 80°C water bath, until the solid was completely dissolved. Altogether 4.4 ml water was added. Then the flask which contained the hot

solution was put in a ' thermos cup' which had already contained the 80°C water in order to make the solution be cooled very slowly.

It took almost four days to cool the solution to room temperature. A lot of white crystals appeared, which looked like needles, but not very long. They were filtered out and dried.

Crystal data

Hydantoin, $C_6H_8N_4O_4$, M = 200.16. Crystals exhibit monoclinic symmetry, space group C2/c, with a = 9.339(2), b = 12.1866(17), c = 7.304(4) Å, β = 104.91(2), V = 803.3(5) $Å^3$, Z = 4, D_x = 1.655 Mg/m^3, F (000) = 416, μ = 0.14 mm^{-1}.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angles of 25 reflections, $6.69 \leq \theta \leq 13.59°$. Intensity data were collected by the ω-2θ scan technique with ω scan range 1.20 + 0.35 tan θ and ω scan speed 0.83 to 3.33 degree per minute. The original measurement of the *a* axis yielded a length of 28.016(7) Å, but reflections were systematically weak unless h = 3n. Pairs of reflections (h,k,l; -h-2l,k,l) could be identified, for which the Bragg angles were nearly identical and the intensity of the first was about 8 times that of the second. The cause was identified as non-merohedral twinning, which apparently tripled the length of the *a* axis by interleaving lattice rows from the minor twin component. Division of h values by 3 and rejection of reflections with a non-integral index left a complete data set from the

major twin component. However, reflections with l = 3n could still be contaminated by reflections from the minor component, so these too were removed. The 962 remaining reflections covered the range $-11 \leq h \leq 10$, $-14 \leq k \leq 14$, $1 \leq l \leq 8$, $2 \leq \theta \leq 25°$. They were merged to give 476 independent reflections (R_{int} = 0.0678) of which 328 were deemed observed with $F > 4\sigma(F)$. Direct-phase determinations and full-matrix least-squares refinement were carried out with SHELXS-97 and SHELXL-97 programmes, leading to R(obs) = 0.0387, wR2(all data) = 0.1151; largest peak and hole on the difference map are 0.151 and -0.170 e.$Å^{-3}$.

Table 7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for hydantoin. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	*Y*	*Z*	*U(eq)*
N(1)	8502(3)	3923(2)	3661(4)	45(1)
C(2)	7974(3)	4952(2)	3208(4)	33(1)
O(2)	8516(2)	5820(2)	3861(3)	47(1)
N(3)	6644(3)	4843(2)	1857(3)	33(1)
C(4)	6330(3)	3782(2)	1347(4)	33(1)
O(4)	5246(2)	3461(2)	150(3)	47(1)
C(5)	7533(3)	3123(2)	2511(4)	36(1)

Table 8 Bond lengths [Å] for hydantoin.

Bond	Bond Distance
N(1)-C(2)	1.357(3)
N(1)-C(5)	1.444(4)
C(2)-O(2)	1.216(3)
C(2)-N(3)	1.379(4)
N(3)-C(4)	1.357(3)
C(4)-O(4)	1.219(3)
C(4)-C(5)	1.463(4)

Table 9 Bond angles (°) for hydantoin.

Atoms	Bond Angle
C(2)-N(1)-C(5)	110.4(2)
O(2)-C(2)-N(1)	128.3(3)
O(2)-C(2)-N(3)	124.8(2)
N(1)-C(2)-N(3)	106.8(2)
C(4)-N(3)-C(2)	112.3(2)
O(4)-C(4)-N(3)	125.7(3)
O(4)-C(4)-C(5)	127.8(3)
N(3)-C(4)-C(5)	106.5(2)
N(1)-C(5)-C(4)	103.9(2)

Table 10 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for hydantoin.

	X	Y	Z	U(eq)
H(1)	9301	3769	4513	54
H(3)	6079	5386	1391	39
H(5A)	7161	2610	3295	43
H(5B)	8044	2717	1728	43

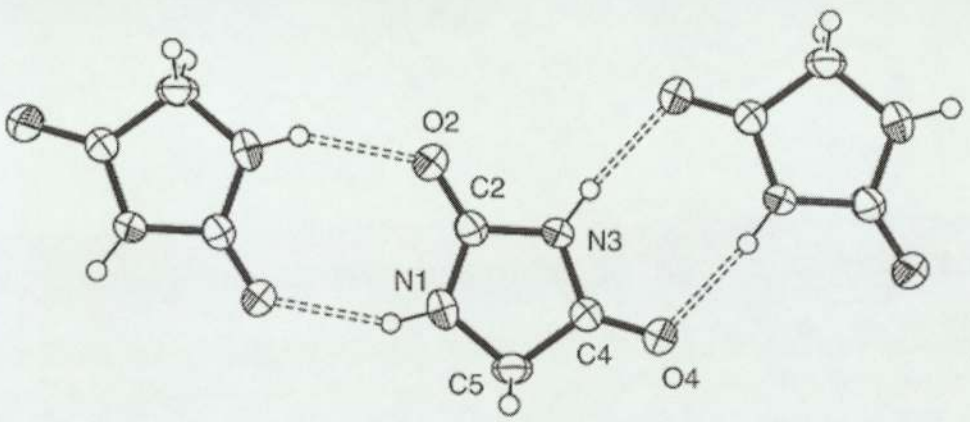


Figure 6 Crystal Structure of Hydantoin.

2.2.3 Method 2.

Crystal growing

The hydantoin powder was dissolved in sodium hydroxide (12.5 %) solution in a small beaker. The beaker was placed into a glass basin with another small beaker

which containing the acetic acid next to it. Then the glass basin was covered with a glass plate. This procedure was adopted in order to make the pH value of the hydantoin solution drop gradually through the reaction between the sodium hydroxide and acetic acid (vapour).

Two days later, there were many white crystals floating on the surface of the solution; however, the crystals stuck together and became a conglomerate like a piece of ice. With some difficulty a suitable specimen was picked out.

Crystal data

Hydantoin, $C_3H_4N_2O_2$, M = 100.08. Crystals exhibit monoclinic symmetry, space group C2/c with a = 9.3745(12), b = 12.1938(14), c = 7.311(2) Å, β = 105.01(2), V = 807.2(3) $Å^3$, Z = 8, D_x = 1.655 Mg/m^3, F (000) = 416, μ = 0.14 mm^{-1}.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angle of 25 reflections, $8.06 \leq \theta \leq 14.01°$. The same twinning was found as before, and the initially determined value for a was 28.124(4) Å. Intensity data were collected by the ω-2θ scan technique with ω scan range 1.20 + 0.35 tan θ and ω scan speed 0.83 to 3.33 degree per minute. The 1253 reflections from the major twin component alone were measured for $-11 \leq h \leq 10$, $-14 \leq k \leq 14$, $1 \leq l \leq 8$, in the range of $2 \leq \theta \leq 25°$ and were merged to give 481 independent reflections (R_{int} = 0.0678) of which 371 were deemed observed with $F > 4\sigma(F)$, R(obs) = 0.0407, wR2(all data) = 0.1289, largest

peak and hole on difference map are 0.174 and -0.190 e.Å^{-3}. Direct-phase determinations and full-matrix least-squares refinement were carried out with SHELXS-97 and SHELXL-97 programmes.

2.2.4 Method 3.

Crystal growing

To the hydantoin (0.507g) in a 25 ml flask was added 2 ml of water: acetic acid = 3 : 2.5 mixed solvent followed by shaking in the 40°C water bath. At this time the hydantoin solid could not be dissolved completely, but more water : acetic acid mixed solvent was dropped into the solution, with continued shaking in the 40°C water bath, until the solid was completely dissolved. Altogether 3.4 ml water: acetic acid mixed solvent was added.

Then the solution was cooled to room temperature gradually. Two days later, some white crystals appeared, which looked like needles. They were filtered out and dried.

Crystal data

Hydantoin, $C_3H_4N_2O_2$, M = 100.08. Crystals exhibit monoclinic symmetry, space group C2/c with a = 9.341(2), b = 12.195(2), c = 7.326(2) Å, β = 105.05(4), V = 805.9(5) Å^3, Z = 8, D_x = 1.655 Mg/m^3, F (000) = 416, μ = 0.14 mm^{-1}.

Structural analysis

The very strong -2 0 2 reflection (-6 0 2 in the original indexing system) provides guidance on extent of twinning. Its counterpart from the other twin component (2 0 2 in the original system) had only 1/8 as much intensity with the original crystal but 1/5 the intensity here. With little prospect of improved accuracy, data collection was stopped and structural analysis not attempted.

2.2.5 Theoretical studies on hydantoin

As the hydantoin does not appear in the Cambridge Structural Database (CSD), in which about 5500 crystal structures of polymorphic forms with coordinates determined, we survey the molecular geometry, patterns of hydrogen bonding in hydantoins with coordinates and their occurrence in the Cambridge Structure Database. We also did the molecular orbital calculation for hydantoin with the programme of CAChe.

2.3 5,5–Diphenylhydantoin

2.3.1 Introduction

a. Bioactivity

5,5-Diphenylhydantoin (phenytoin) has been used for 60 years as an important antiepileptic drug. Its primary mechanism of action is modulation of the sustained repetitive firing of neurones by direct inhibition and blockage of voltage-gated sodium channels in the neuronal cell membrane, and by delay of cellular reactivation.

The drug is rapidly distributed from the blood to the tissues and is almost completely metabolized in the liver. Phenytoin is effective for treating generalized tonic-clonic seizures, partial seizures with or without generalization. [50]

b. Former crystal structure

Two crystal structure determinations (PHYDAN[51] and PHYDAN01[52]) appear in the CSD; however, the first one reports no standard uncertainty values for coordinates and the second admits to disorder in the phenyl groups. We therefore attempted to obtain better-quality crystals.

2.3.2 Method 1.

Crystal growing

The 5,5-diphenylhydantoin powder was dissolved with the sodium hydroxide (12.5 %) solution in a small beaker, which was placed into a glass basin with another small beaker containing HCl (37.5%) next to it. Then the glass basin was covered with a glass plate. This was done in order to make the pH of the 5,5-diphenylhydantoin solution drop gradually through the reaction between the sodium hydroxide and HCl (vapour). This is the same strategy that was followed by previous workers, but with maximum opportunity for undisturbed slow crystal growth.

After a day, there were some white crystals floating on the surface of the solution, which looked like fur (very thin), however, some crystals big enough for

crystallographic analysis were still found.

Crystal data

5,5-diphenylhydantoin, $C_{15}H_{12}N_2O_2$, M = 252.27. Crystals exhibit orthorhombic symmetry, space group $Pna2_1$ with a = 6.2249(10), b = 13.581(2), c = 15.536(2) Å, β = 90, V = 1313.4(3) $Å^3$, Z = 4, D_x = 1.278 Mg/m^3, F(000) = 528, μ = 0.087 mm^{-1}. This unit cell was obviously the same as the one stored in the CSD under refcode PHYDAN01, a = 6.228(1), b = 13.568(1), c = 15.520(2) Å. Because the estimated standard deviations were slightly smaller for the values in the CSD, those cell dimensions were used in the present study.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angles of 25 reflections, $5.15 \leq \theta \leq 13.20°$. Intensity data were collected by the ω-2θ scan technique with ω scan range 0.80 + 0.35 tan θ and ω scan speed 0.83 to 3.33 degree per minute. The 2363 reflections were measured for $-7 \leq h \leq 0$, $0 \leq k \leq 16$, $-18 \leq l \leq 18$, in the range of $2.6 \leq \theta \leq 25°$ and were merged to give 1205 independent reflections (R_{int} = 0.1393) of which 457 were deemed observed with $F > 4\sigma(F)$. R(obs) = 0.0481, wR2(all data) = 0.1805, largest peak and hole on difference map are 0.189 and -0.195 $e.Å^{-3}$. Direct-phase determinations and full-matrix least-squares refinement were carried out with SHELXS-97 and SHELXL-97 programmes.

2.3.3 Method 2.

Crystal growing

To the 5,5-diphenylhydantoin (0.605g) in a 25 ml flask was added acetone: N-methylformamide = 1 : 1 mixed solvent 2 ml and shaken in the 30°C water bath. At this time, some 5,5-diphenylhydantoin solid could still not be dissolved completely; then more acetone: N-methylformamide mixed solvent was dropped into the solution, with continued shaking in the 30°C water bath, until the solid was completely dissolved. Altogether 3.6 ml acetone: N-methylformamide mixed solvent was added.

Then the solution was cooled to room temperature and gradually made more concentrated. Two days later, some colourless hexagonal crystals appeared in the bottom of the flask, which were filtered and dried.

Crystal data

5,5-diphenylhydantoin, $C_{15}H_{12}N_2O_2$, M = 252.27. Crystals exhibit orthorhombic symmetry, space group $Pna2_1$, with a = 6.2252(12), b = 13.548 (6), c = 15.5245(15) Å, β = 90, V = 1309.3(3) $Å^3$, Z = 4, D_x = 1.278 Mg/m^3, F (000) = 528, μ = 0.087 mm^{-1}. Although the *c* axis is more precisely measured than it was in PHYDAN01, the other axes are not, and therefore the values from the CSD are used in further calculations.

Structural analysis

Unit cell dimensions were obtained from least squares analysis of setting angles of 25 reflections, $9.50 \leq \theta \leq 12.22°$. Intensity data were collected by the ω-2θ scan technique with ω scan range $0.80 + 0.35 \tan \theta$ and ω scan speed 0.83 to 3.33 degree per minute. The 4968 reflections were measured for $-7 \leq h \leq 7$, $-1 \leq k \leq 16$, $-18 \leq l \leq 18$, in the range of $2 \leq \theta \leq 25°$ and were merged to give 1314 independent reflections (R_{int} = 0.0272) of which 1259 were deemed observed with $F > 4\sigma(F)$. R(obs) = 0.0429, wR2(all data) = 0.1224, largest peak and hole on difference map are 0.176 and -0.169 e.$Å^{-3}$. Direct-phase determinations and full-matrix least-squares refinement were carried out with SHELXS-97 and SHELXL-97 programmes.

Table 11 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for diphyd-n. U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
N(1)	970(3)	2693(2)	575(1)	42(1)
C(1)	4641(3)	2788(3)	493(1)	37(1)
C(2)	1726(4)	2743(3)	1374(1)	40(1)
N(2)	3971(3)	2782(3)	1315(1)	42(1)
C(3)	2625(3)	2740(3)	-86(1)	35(1)
O(1)	6498(2)	2816(2)	240(1)	54(1)
O(2)	733(3)	2765(3)	2043(1)	65(1)

C(4)	1435(9)	1030(3)	-508(3)	76(1)
C(5)	1694(18)	180(4)	-1015(4)	115(3)
C(6)	3145(17)	118(5)	-1620(5)	126(3)
C(7)	4482(12)	898(8)	-1750(5)	136(3)
C(8)	4304(7)	1752(5)	-1265(3)	93(2)
C(9)	2749(5)	1799(3)	-623(2)	46(1)
C(10)	3687(8)	4458(3)	-611(2)	74(1)
C(11)	3214(15)	5280(4)	-1107(4)	103(2)
C(12)	1445(12)	5302(5)	-1629(3)	98(2)
C(13)	140(10)	4514(6)	-1657(4)	111(2)
C(14)	568(6)	3691(5)	-1168(3)	87(2)
C(15)	2342(5)	3660(3)	-639(2)	43(1)

Table 12 Bond lengths [Å] for diphyd-n.

Bond	Bond Distance
N(1)-C(2)	1.329(3)
N(1)-C(3)	1.455(3)
C(1)-O(1)	1.223(3)
C(1)-N(2)	1.342(3)
C(1)-C(3)	1.545(3)
C(2)-O(2)	1.209(3)
C(2)-N(2)	1.402(3)

C(3)-C(15)	1.525(5)
C(3)-C(9)	1.528(5)
C(4)-C(9)	1.337(6)
C(4)-C(5)	1.406(8)
C(5)-C(6)	1.306(13)
C(6)-C(7)	1.362(13)
C(7)-C(8)	1.386(9)
C(8)-C(9)	1.391(6)
C(10)-C(15)	1.370(6)
C(10)-C(11)	1.386(7)
C(11)-C(12)	1.369(11)
C(12)-C(13)	1.344(10)
C(13)-C(14)	1.375(8)
C(14)-C(15)	1.377(5)

Table 13 Bond angles [°] for diphyd-n.

Atoms	Bond Angle
C(2)-N(1)-C(3)	113.87(18)
O(1)-C(1)-N(2)	126.9(2)
O(1)-C(1)-C(3)	125.65(19)
N(2)-C(1)-C(3)	107.46(17)

O(2)-C(2)-N(1)	128.4(2)
O(2)-C(2)-N(2)	124.5(2)
N(1)-C(2)-N(2)	107.09(18)
C(1)-N(2)-C(2)	111.89(18)
N(1)-C(3)-C(15)	110.6(3)
N(1)-C(3)-C(9)	112.5(3)
C(15)-C(3)-C(9)	112.49(17)
N(1)-C(3)-C(1)	99.63(16)
C(15)-C(3)-C(1)	112.8(3)
C(9)-C(3)-C(1)	108.1(2)
C(9)-C(4)-C(5)	119.7(6)
C(6)-C(5)-C(4)	122.3(7)
C(5)-C(6)-C(7)	118.6(5)
C(6)-C(7)-C(8)	121.4(6)
C(7)-C(8)-C(9)	118.9(6)
C(4)-C(9)-C(8)	119.1(4)
C(4)-C(9)-C(3)	123.2(3)
C(8)-C(9)-C(3)	117.7(4)
C(15)-C(10)-C(11)	119.3(5)
C(12)-C(11)-C(10)	121.1(6)
C(13)-C(12)-C(11)	119.3(5)
C(12)-C(13)-C(14)	120.7(5)

C(13)-C(14)-C(15)	120.6(6)
C(10)-C(15)-C(14)	119.0(4)
C(10)-C(15)-C(3)	123.9(3)
C(14)-C(15)-C(3)	117.0(4)

Table 14 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for diphyd-n.

	X	Y	Z	U(eq)
H(1)	-440(60)	2670(40)	470(20)	61(9)
H(2)	4600(50)	2740(30)	1850(20)	50(7)
H(3)	660(70)	1000(50)	-60(40)	87(15)
H(4)	430(90)	-160(50)	-1000(40)	95(19)
H(5)	3290(110)	-340(70)	-2040(40)	140(20)
H(6)	5890(120)	770(60)	-2120(60)	160(30)
H(7)	5430(100)	2160(60)	-1310(40)	120(20)
H(8)	5250(100)	4420(50)	-180(40)	116(18)
H(9)	3560(130)	5870(70)	-960(60)	170(30)
H(10)	1310(80)	5930(50)	-1970(40)	99(16)
H(11)	-880(160)	4440(100)	-2120(60)	210(40)
H(12)	-550(100)	3070(50)	-1230(40)	130(20)

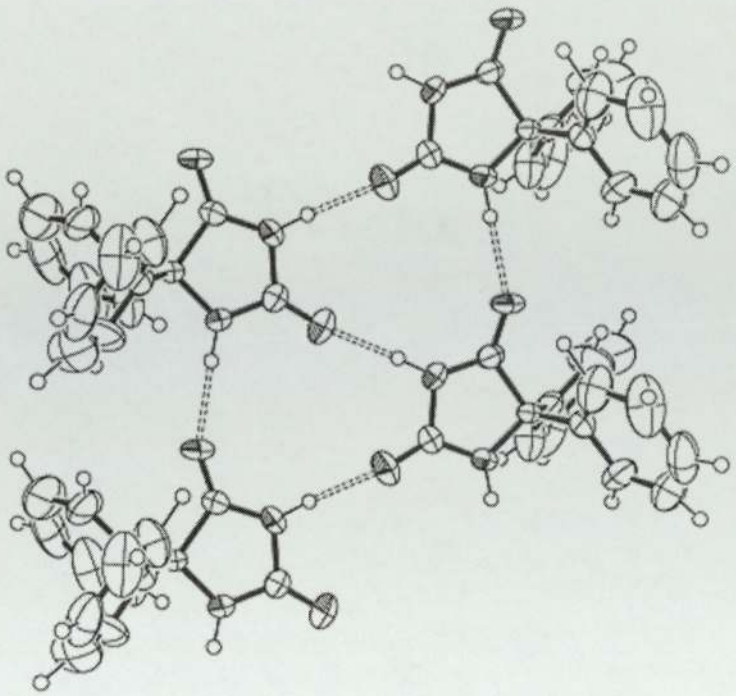


Figure 7 Crystal structure of 5,5-Diphenylhydantoin.

2.4 Prediction of crystal structure 5,5-dimethylhydantoin

Among the several crystalline drug substances examined by us, only the 5,5-dimethylhydantoin has a suitable space group ($P2_12_12_1$) that can be handled by FlexCryst. A crystal structure of high quality (R= 4.2%) and no disorder or errors has been reported by Cassady and Hawkinson. [53] FlexCryst was run with and without input of atomic charge to see if it could reproduce the observed structure and suggest plausible alternatives. The prediction result is listed below (Tables 15 and 16).

Table 15 The prediction data of 5,5-dimethylhydantoin without input of atomic charge.

		Unit cell dimension					
	Heat/KJ	a	b	c	α	β	γ
1	-104.6	6.261	6.667	13.715	90	90	90
2	-103.0	8.981	6.030	10.586	90	90	90
3	-102.4	9.621	10.198	6.499	90	90	90
4	-102.3	9.494	8.944	7.348	90	90	90
5	-101.5	9.798	6.633	10.340	90	90	90
6	-101.2	9.899	6.928	8.165	90	90	90
7	-101.1	7.589	5.965	12.768	90	90	90
8	-100.6	8.981	6.030	11.817	90	90	90
9	-99.1	8.981	6.208	10.733	90	90	90
10	-97.2	6.261	6.532	14.971	90	90	90

Table 16 The prediction data of 5,5–dimethylhydantoin with input of atomic charge calculated with Chem–X from electronegativity.

		Unit cell dimension					
	Heat/KJ	a	b	c	α	β	γ
1	-110.6	9.899	8.165	6.928	90	90	90
2	-107.3	8.981	8.485	6.928	90	90	90

3	-104.9	7.348	5.774	14.142	90	90	90
4	-103.6	8.981	10.733	5.842	90	90	90
5	-102.9	6.324	8.000	12.017	90	90	90
6	-101.4	9.621	6.928	9.285	90	90	90
7	-101.2	6.949	5.774	15.739	90	90	90
8	-100.1	7.333	5.821	15.037	90	90	90
9	-100.0	5.879	6.813	15.088	90	90	90
10	-99.9	7.348	8.552	9.602	90	90	90

The unit cell dimensions from CSD are a= 7.216, b= 7.203, c= 13.005 Å, β=90.00, refcode is BEPNIT.

Chapter 3 Conclusion and Discussion

3.1 Temozolomide

3.1.1 Definition of new hydrate

As we can see from Chapter two - Experimental Work and Results, the hydrate we got is a previously unreported pseudo-polymorphic form of the compound- temozolomide. However, with regard to the novelty of this form, there are still two possibilities existing. The first possibility is that the granular solid described in (iii) of Example 4 on page 8 of the U.S. patent could be the hydrate, since a solid was obtained from hot water. Its reported infrared spectrum shows differences from (i), where the product was confirmed to be anhydrous. The second one is that the granular solid could be the same anhydrous material that was prepared in (i), but with the surface of the crystals covered with water. We therefore attempted to prepare well-dried authentic anhydrous material and take its IR spectrum before and after allowing it to get wet.

To our surprise, we cannot obtain anhydrous material any more with procedure (i). The spectrum annotated "3rd May 2002" agrees well with a spectrum of the hydrate recorded in January. As this sample is allowed to get progressively wetter ("Wet 1, Wet 2, and Wet 3"), there is little change to the existing peaks but at last a broad new peak appears at 3660 cm^{-1}, presumably due to the water film. The identity of the initial sample is confirmed by the unit cell dimensions obtained with a crystal from this batch. This result is not altogether surprising since the solvent (acetone-water

3:1) still contains a lot of water. Perhaps it offers some support for the novelty of the hydrate, according to the following argument. We assume this hydrate is more stable than the anhydrous form, so that once seed crystals of the hydrate are available, in media containing water it will form in preference to anhydrous material. For anhydrous material to have been obtained in the patent under conditions (i), no hydrate could have existed in that laboratory at that time.

In order to prepare anhydrous temozolomide, we decided to use a completely non-aqueous solvent and we chose the dry acetonitrile as solvent; this method was described at the bottom of page 9 of the U.S. patent. The IR spectrum of this sample ("TEMO from acetonitrile") is clearly different from the hydrate. It is closer to the anhydrous material described in (i), but not exactly the same, and on page 9 it was described as a polymorph anyway. When this sample got wet, once again the existing IR peaks changed very little but a new broad peak appeared. However, this time the broad peak maximum was at 3564 cm^{-1}. So the position of water absorption appears highly changeable.

From the evidence above, we draw the following conclusion: (1) we still have not definitively established the identity of the material prepared in (iii), whether wet anhydrous material, our hydrate, or a completely different form. (2) Our two wet samples both show a broad peak in the IR at high but variable wave number.

3.1.2 The stability of the new hydrate and the old anhydrous form

The decomposition study of the Temozolomide **(2.1.5)** has yielded some information about the stability of the hydrate and the old anhydrous form. From the NMR spectrum, we can draw the conclusion below.

There are a total of six hydrogen atoms in the Temozolomide molecule, one connected to C6, another two connected to N82, and the remaining three connected to C31 (it is a methyl group). In our NMR ^{1}H spectrum, the six H atoms can be assigned well. The hydrogen connected to C6, which has a double bond with N7, appeared at lower field (8.8), and it is a singlet. The two active hydrogen atoms connected to N82, have coupling with each other, giving a dd peak. Because there are hydrogen bonds, their chemical shift appeared at higher field (7.6 & 7.8). The methyl group appeared as a normal singlet with a chemical shift at 3.8.

After two weeks, no disappearances of reactant peak took place, leading to the conclusion that no measurable decomposition affects the bonds connecting with these six hydrogen atoms and adjacent bonds. If there is some decomposition at other bonds, two peaks will appear correspondingly. However, because there are no such peaks, we can also conclude that the other bonds are stable. In a word, the hydrate and the anhydrous form are both relatively stable in light and the temperature of 37 °C.

Our limited original supply of Temozolomide prevented further testing to establish the

time when it begins to decompose. So this can be listed in our further work.

3.1.3 The DSC traces and their interpretation

Because of its ability to provide detailed information about both physical and energetic properties of a substance, which is difficult to obtain from other method, differential scanning calorimetry (DSC) is frequently used in the pharmaceutical thermal analysis. The same, in our experimental, in order to get more detail about the physical and energetic properties of our experimental substances, differential scanning calorimetry traces were obtained on a Perkin-Elmer DSC-4. The diagrams are listed in the Appendix I.

The new hydrate gave a different trace from the one of the anhydrous form: there is one peak that appears at 82° C and a valley at 210° C. We consider the peak means re-crystallization of hydrate, and it is exothermic. The valley means decomposition of the temozolomide, it is endothermic.

However, the anhydrous form that comes from method 3 only has one valley in its DSC trace, and it appears at 210° C, which is the decomposition point of this material. The above result agrees with the crystallographic result that the hydrate is not a wet anhydrous form but a new pseudo-polymorph.

3.1.4 Solubility study

There is insufficient original material for a comprehensive study of solubility and dissolution rate. Nevertheless, when we dissolved both the hydrate and the anhydrous form in DMSO, the hydrate dissolved much more quickly. We believe it may imply that the hydrate has better solubility in some kinds of solvent, which should be also listed in our further investigation. However, if water is the solvent, as we mentioned in the part of introduction (**1.1.7**), there is a rule: the anhydrous form of a substance is always more soluble in water than the corresponding hydrate which crystallized from water at the same temperature. We can get the result from the theoretical analysis. The solubility of an anhydrate form of a crystalline nondissociating organic compound A in water is proportional to the equilibrium constant Ks in the equilibrium

$$\text{A (solid)} \overset{Ks}{\rightleftharpoons} \text{A (aqueous)} \qquad (1)$$

$$Ks = a_{A(aqueous)} / a_{A(solid)} \qquad (2)$$

The solubility depends on temperature, pressure and the nature of the solid form (hydrate or anhydrate) and is approximately proportional to the thermodynamic activity of the latter. The equilibrium solubility of a hydrate of A, such as A· mH_2O in water is similarly proportional to the equilibrium constant $K_S^{'}$ in the equilibrium

$$\text{A}\cdot mH_2O\ \text{(solid)} \overset{K_S^{'}}{\rightleftharpoons} \text{A (aqueous)} + mH_2O \qquad (3)$$

$$K_S^{'} = [a_{A(aqueous)} \cdot a_{H2O}{}^{m}] / a_{[A\cdot mH2O\ (solid)]} \qquad (4)$$

The formation of hydrated crystals from anhydrous crystals is represented by the

equilibrium

$$A\,(solid) + mH_2O \overset{K_b}{\rightleftharpoons} A\cdot mH_2O\,(solid) \qquad (5)$$

Here $K_b = a_{[A\cdot mH2O\,(solid)]} / [a_{A\,(solid)} \cdot a_{H2O}{}^{m}] = Ks / K_S^{'}$ (6)

Where K_b is the equilibrium constant for the process show in (3), and $a_{A\cdot mH2O\,(solid)}$, $a_{A\,(solid)}$, a_{H2O} are the thermodynamic activities of the hydrate, the anhydrate and water, respectively. If we subtract (1) from (3), we can get the equilibrium (5). So we can know that $\Delta G_b^{\theta} = \Delta G_k^{\theta} - \Delta G_{k'}^{\theta}$, here, the ΔG_b^{θ}, ΔG_k^{θ} and $\Delta G_{k'}^{\theta}$ are standard free energy of equilibrium (5), equilibrium (1) and equilibrium (3), in which, equilibrium (5) represent the process of hydration. And $\Delta G_b^{\theta} = -R\,T\,\ln K_b$ (7)

The R is the gas constant and T is the absolute temperature.

Put (6) into (7), then we can get $\Delta G_b^{\theta} = -\,R\,T\,\ln Ks / K_S^{'}$ (8)

We can name $Ks / K_S^{'}$ solubility ratio. And because the hydrate has already interacted intimately with water, the free energy **released** on crystal dissolution and the further interaction with water is less for the hydrate than the anhydrate. [54] So we can know a negative value for standard Gibbs free energy of solution is less negative for the hydrate which is represented by equilibrium (3) than the anhydrate which is represented by equilibrium (3), i.e. $\Delta G_k^{\theta} < \Delta G_{k'}^{\theta}$, now we can calculate the standard Gibbs free energy of hydration $\Delta G_b^{\theta} = -\,R\,T\,\ln Ks / K_S^{'} = \Delta G_k^{\theta} - \Delta G_{k'}^{\theta} < 0$, and we also know the value of R and T is positive, so the value of $\ln Ks / K_S^{'}$ should also be positive to keep the value of ΔG_b^{θ} negative, then the value of $Ks / K_S^{'}$ should be more than one, that means the value of Ks is bigger than the value of $K_S^{'}$. Now, we can get

the conclusion that in water, the solubility of anhydrous form of a substance is always higher than the corresponding hydrate which crystallized from water at the same temperature.

To the dissolution rate, we can get the similar conclusion, under the same transport rate-controlled conditions, the dissolution rate of the anhydrate is greater than that of the corresponding hydrate. The calculation process is listed below:

$$J = (dm / dt)(1/A) = k\,(Cs\text{-}C) \quad (9)$$

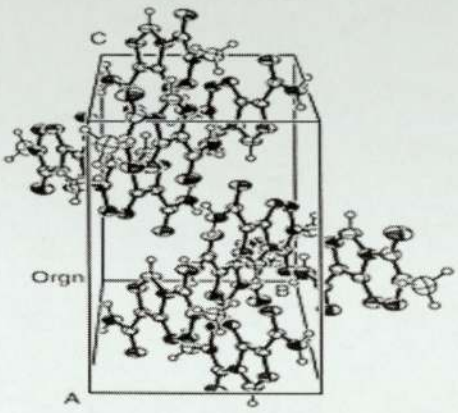
Where J is dissolution rate, A is the area of the solid exposed to the dissolution medium, k is the mass transfer coefficient, Cs is the molar solubility of the solid, C is the molar concentration dissolved. In sink conditions, $Cs >> C$. then (9) can be written as $J = KCs$ (10)

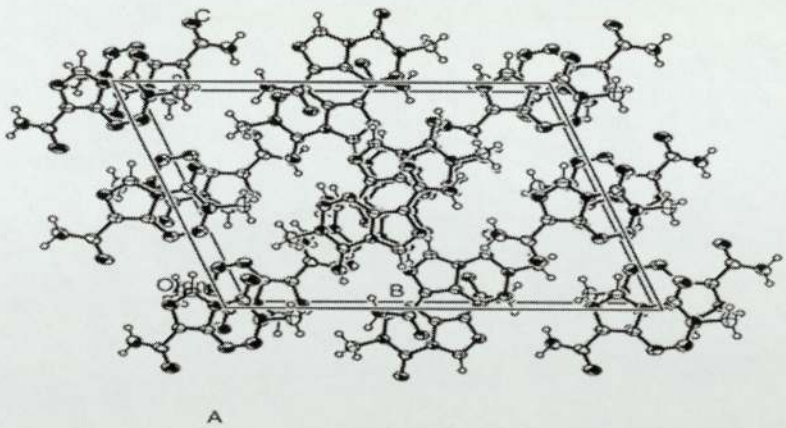
And as discussed above, the aqueous solubility Cs of the anhydrate is greater than that of its hydrate form at the same temperature, so we can get the conclusion about the dissolution which is mentioned above - the dissolution rate of the anhydrate is greater than that of the corresponding hydrate under the same transport rate-controlled conditions (i.e. with the same value of k).

3.1.5 The relationship between interaction and crystal shape

From the packing diagrams (**Figure 8**) we can see the theoretical growth rate is different in three dimensions because of the existence of the hydrogen bond. In the direction with hydrogen bonds, the molecules can interact easily; it means the crystal

can grow faster in this direction, so it is the maximum growth direction. On the contrary, in the direction where the molecule planes make side-to-side contact without hydrogen bonding, most intermolecular interactions are van der Waals interactions, which are much weaker than the hydrogen bond making it difficult for molecules to gather together, so it is the minimum growth direction.





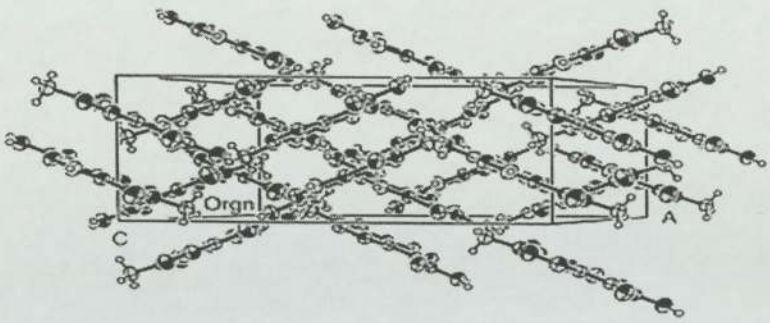


Figure 8 View of the boundary faces of the crystal of Temozolomide from three different directions.

3.2 5,5-Diphenylhydantoin

3.2.1 The effect of solvent on the crystal quality

In an attempt to obtain different polymorphs or solvates we used two methods to get the crystal of 5,5-dimethylhydantoin (**2.3.2** & **2.3.3**). In method 1 we formed the anion by using sodium hydroxide as the solvent, and in method 2, we relied on strong hydrogen bonding through the use of acetone: N-methylformamide = 1: 1 mixed solvent. Method 1 was used in the reported crystal structure determinations, [51,52] but these were impaired by significant phenyl ring disorder. Unfortunately we only got the same structure. Nevertheless, method 2 yielded a better-quality crystal and better X-ray data, in which after refinement only C5 and C6 had displacement parameters sufficiently anisotropic that SHELXL indicated that they may be split. From method 1, the data show that C5, C6, C8 and C12 may be split. So we can draw the conclusion that even the N-methylformamide cannot make 5,5-dimethylhydantoin form a new

crystal structure, but it can improve its crystal quality.

3.2.2 The DSC traces and their interpretation

Differential scanning calorimeter traces for 5,5-diphenylhydantoin were also obtained on the Perkin-Elmer DSC-4. The diagrams are listed in the Appendix I. There is a sharp peak at the position of 296° C, which must be the decomposition point of 5,5-diphenylhydantoin, and this decomposition is exothermic. Some sharp waves appear after 330° C, but they may simply be bursting of the pan seal after it was heated to an excessively high temperature, and this resulted in the recording of anomalous thermal events. Another possibility is, there occurred a great number of decompositions after the major decomposition due to the high temperature. [55]

3.3 Hydantoin

3.3.1 The studies of patterns of H-bonding in hydantoins with coordinates

As one of the results of experiment **2.2.4**, we get the patterns of hydrogen bonding in hydantoins with coordinates and their occurrence in the Cambridge Structural Database (CSD). Of 49 hydantoins with coordinates in the CSD bearing two ring N-H groups, seven form similar double dimers as our new crystal structure of hydantoin (two centrosymmetric N-H…O=C dimers). Their refcodes are BCOCHY, FINVON, GRNSHY, KESWOU, OCSHYD, SIKXEP and VARBAR, respectively. Three form double dimers which share one oxygen atom; two form one dimer and one chain which use both oxygen atoms; six form two chains which use both oxygen atoms. So

we can see this kind of hydrogen bonding (two centrosymmetric N-H…O=C dimers) is popular in the hydantoins with coordinates.

3.3.2 The molecular orbital calculations for hydantoin

As another result of experiment **2.2.4**, we get the optimized geometry of hydantoin, which is listed in the Table 17 and Table 18. There, we also compare it with the structural information that comes from our experiments.

Table 17 Bond lengths [Å] for hydantoin from CAChe and experiment

Bond	Bond distance (CAChe)	Bond distance
N(1)-C(2)	1.403	1.357(3)
N(1)-C(5)	1.447	1.444(4)
C(2)-O(2)	1.242	1.216(3)
C(2)-N(3)	1.427	1.379(4)
N(3)-C(4)	1.403	1.357(3)
C(4)-O(4)	1.231	1.219(3)
C(4)-C(5)	1.551	1.463(4)

Table 18 Bond angles (°) for hydantoin from CAChe and experiment

Atoms	Bond angle (CAChe)	Bond angle
C(2)-N(1)-C(5)	111.1	110.4(2)
O(2)-C(2)-N(1)	126.5	128.3(3)
O(2)-C(2)-N(3)	125.2	124.8(2)

N(1)-C(2)-N(3)	108.3	106.8(2)
C(4)-N(3)-C(2)	110.4	112.3(2)
O(4)-C(4)-N(3)	126.1	125.7(3)
O(4)-C(4)-C(5)	127.2	127.8(3)
N(3)-C(4)-C(5)	106.6	106.5(2)
N(1)-C(5)-C(4)	103.6	103.9(2)

We can see from the two tables above, the bond angles are almost coincident with the optimised geometry from molecular orbital calculations, but bond distances to sp^2 carbon atoms have lengthened upon optimisation.

3.3.3 The DSC traces and their interpretation

There is a peak at 220° C, which must be the decomposition point of hydantoin, and this decomposition is exothermic. There are also some sharp waves appearing after 250° C, in my opinion, resulting from the same cause as in section **3.2.2**

3.4 Prediction of crystal structure for 5,5-dimethylhydantoin

The predicted unit cell nearest to the observed unit cell is the first (lowest energy) one in Table 15. FlexCryst only uses the unit cell to convert fractional coordinates into orthogonal Ångstrom coordinates. From this point it is not further influenced by the input unit cell. Thus the ability to regenerate the observed unit cell is one measure of its success.

Hydrogen bonding is expected to have a strong influence on the crystal packing of hydantoin derivatives since each molecule has two N-H groups and two C=O groups. FlexCryst treats atoms that may form hydrogen bonds as "interaction sites" and tries to bring interaction sites together. This may be the reason why the closest match to the observed unit cell dimensions is found in Table 15, not using atomic charges. There is some consistency between the predictions with and without charges: the lowest-energy prediction in Table 16 is an alternative orientation of the sixth-lowest in Table 15, and axial lengths of 8.981 Å and 6.928 Å occur repeatedly.

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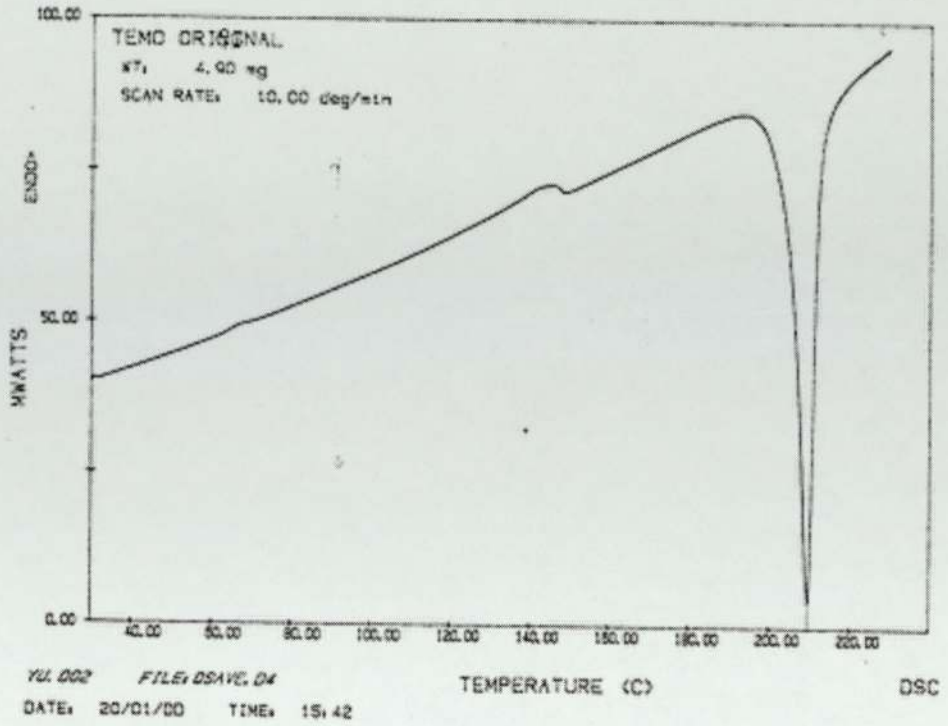
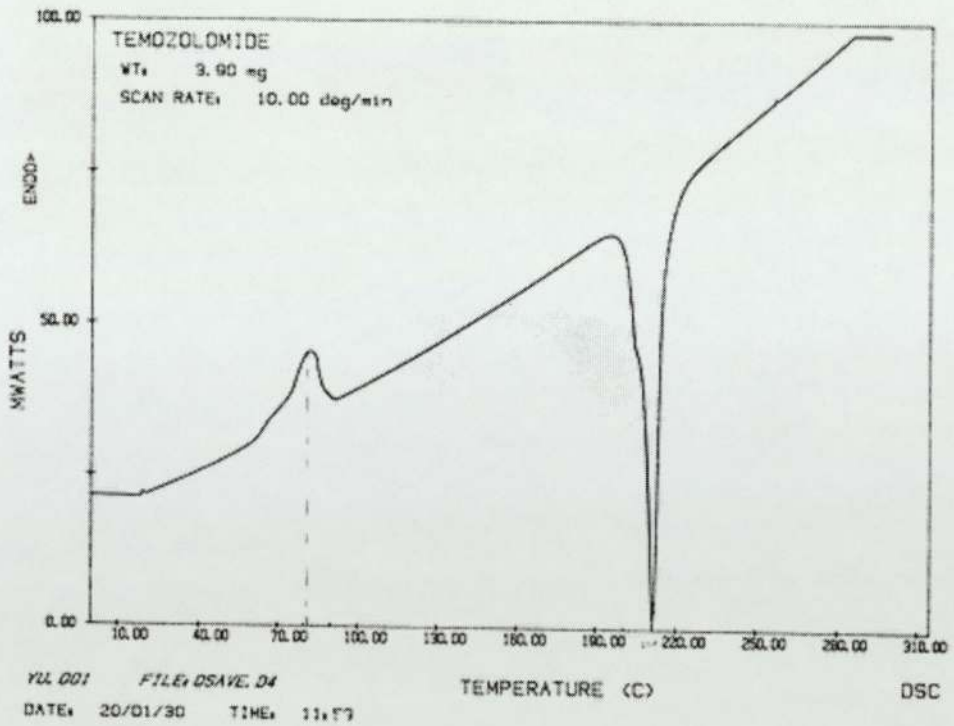
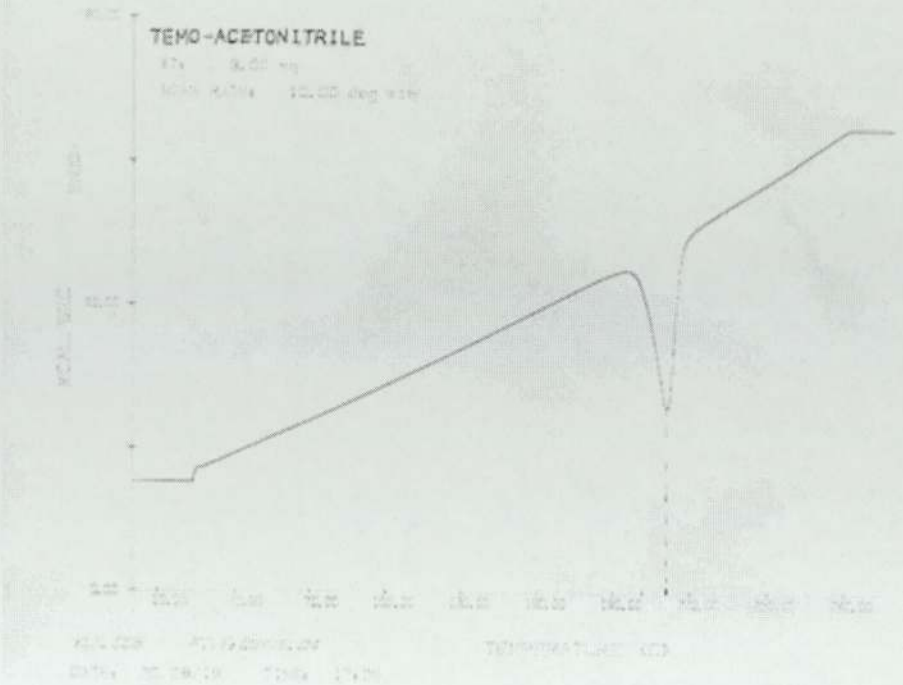
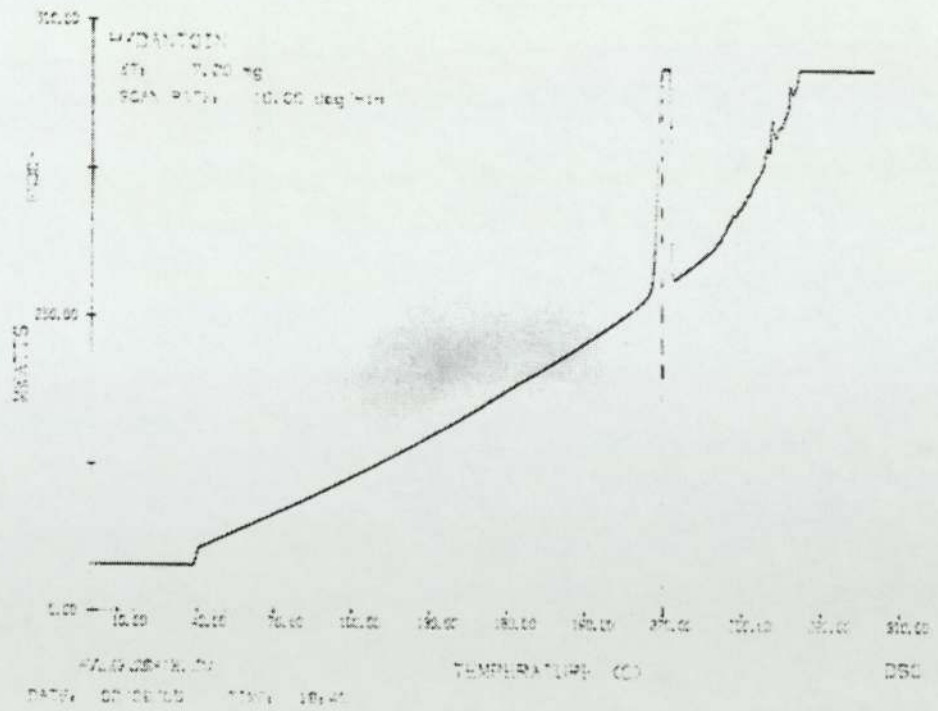
Appendices

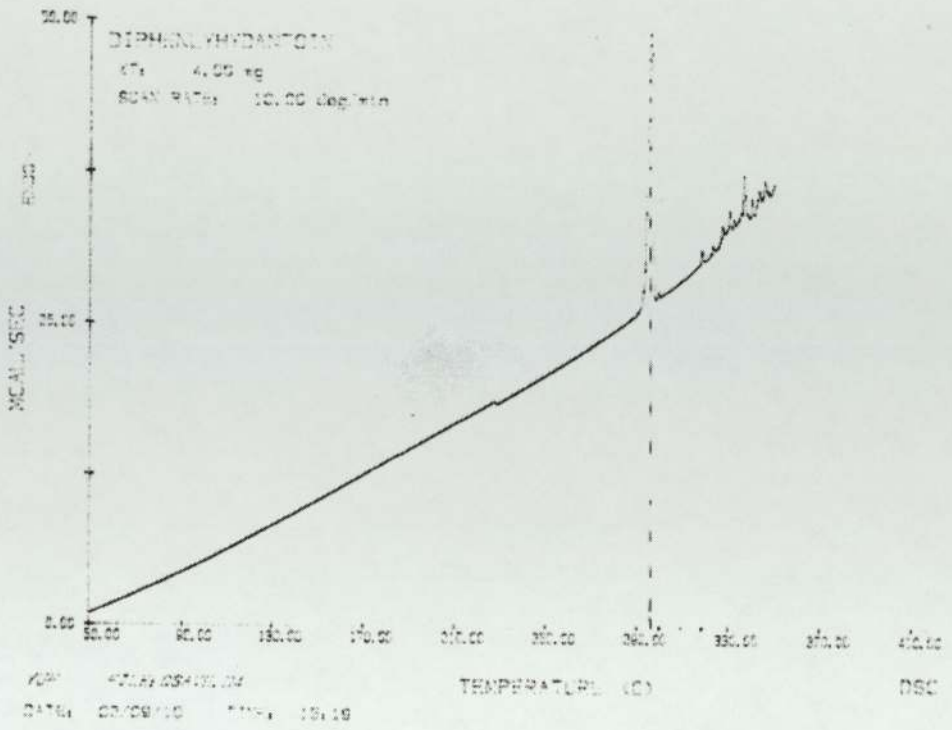
Appendix I The DSC Traces



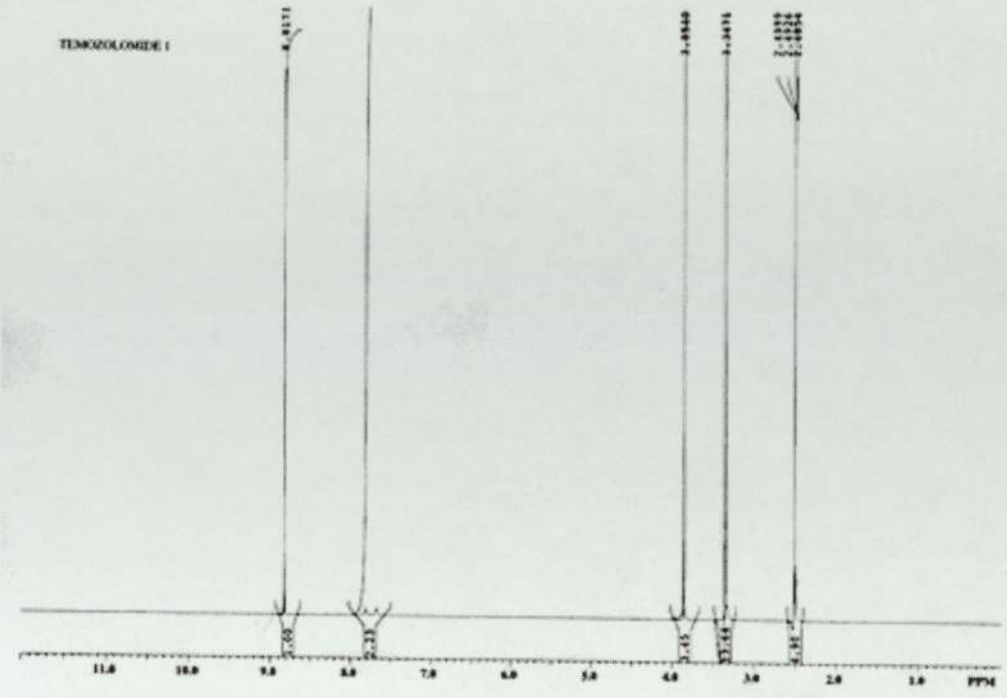


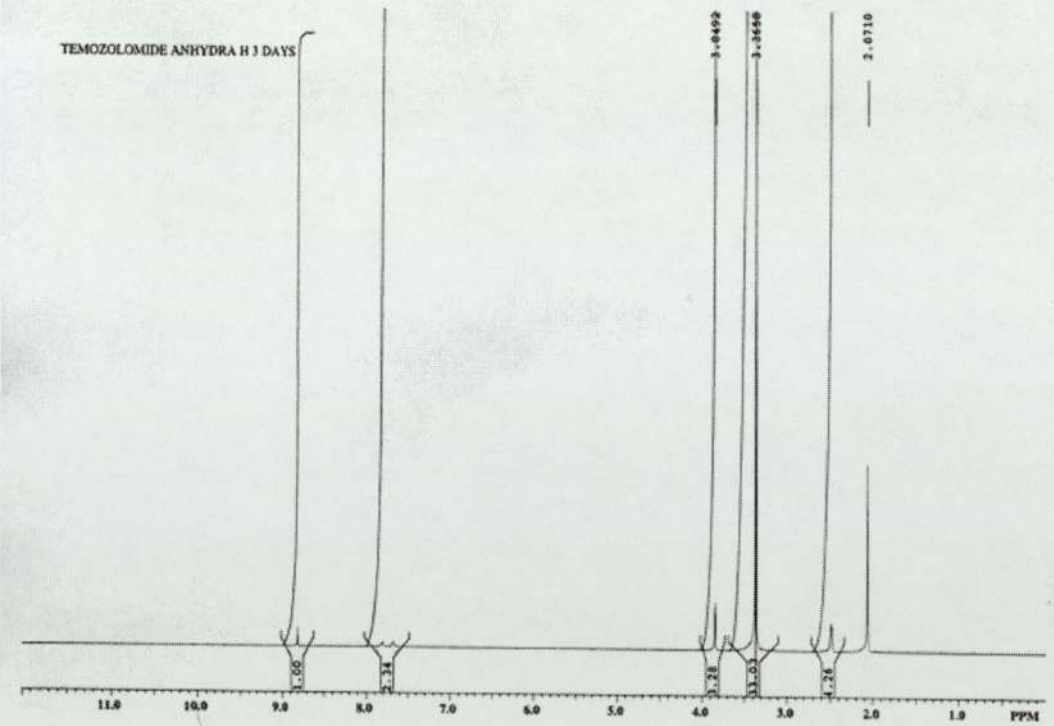

TEMO-ACETONITRILE

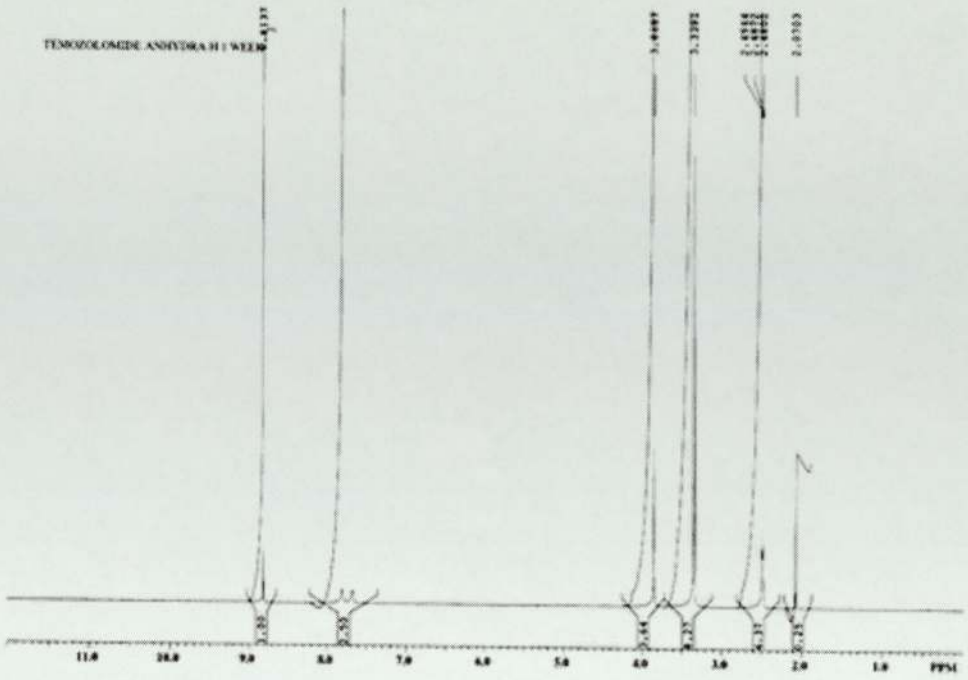


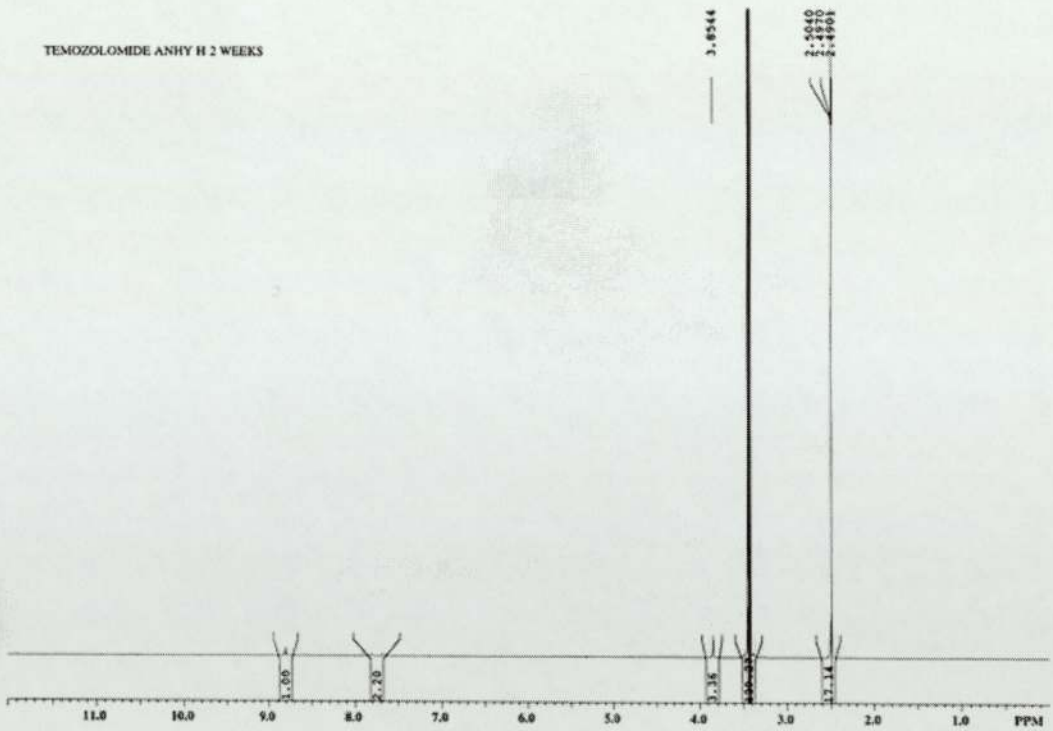

DIPHENYLHYDANTOIN
TEMPERATURE (C)
DSC

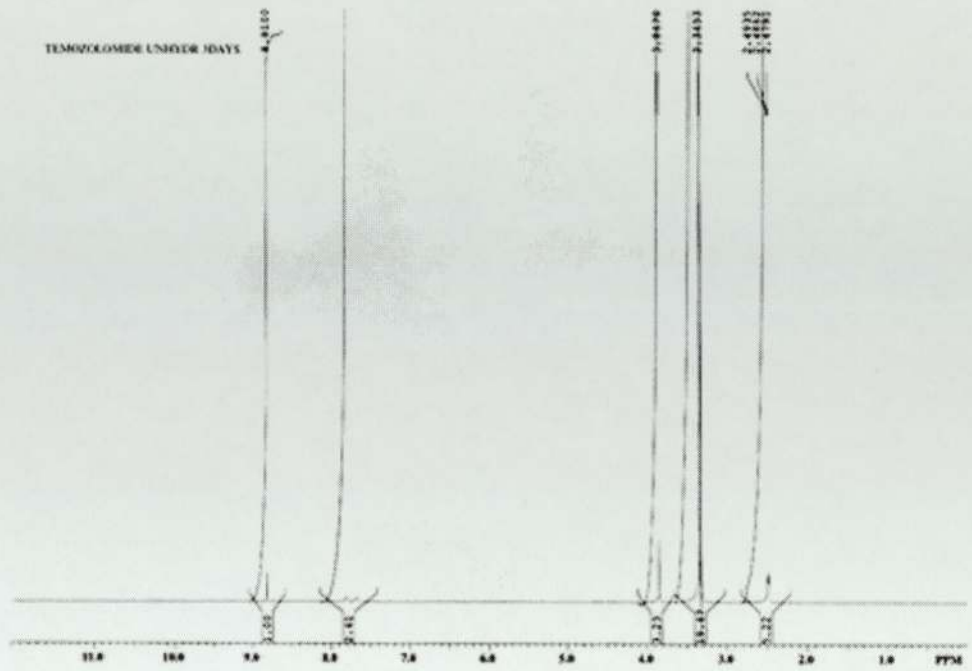
Appendix II The NMR Spectrum

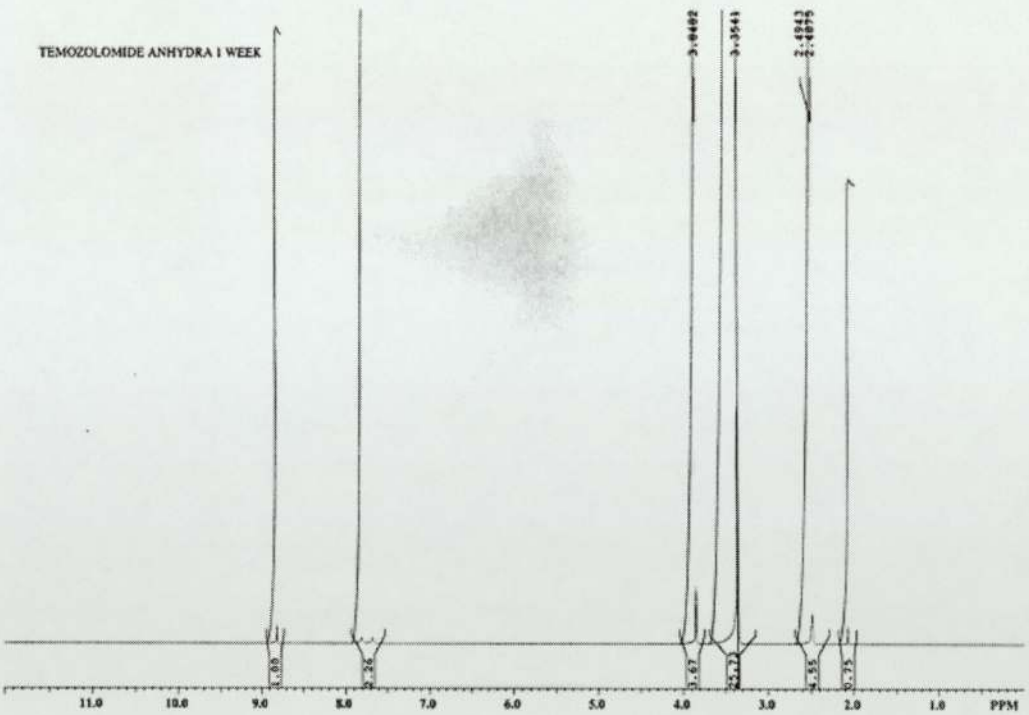


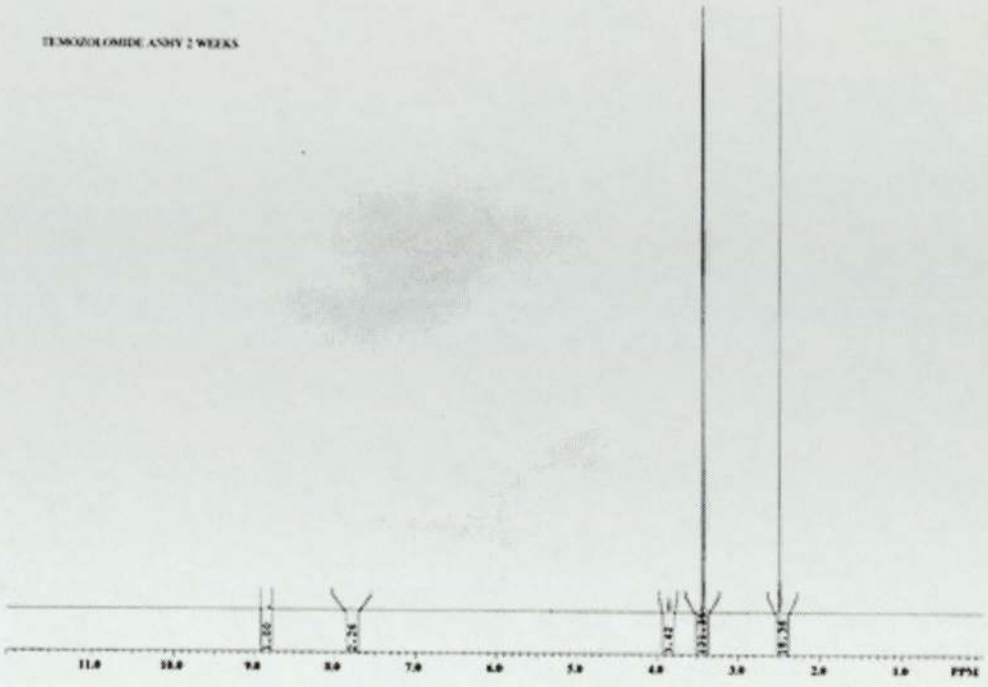


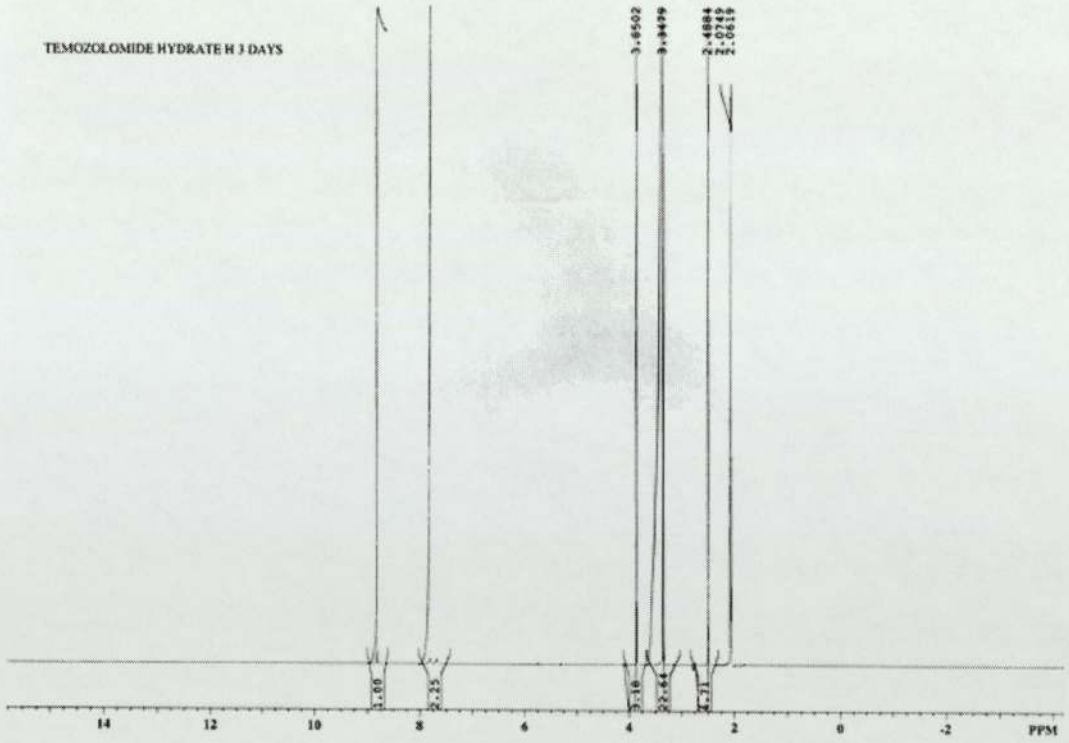

TEMOZOLOMIDE ANHYDRA H 1 WEEK
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

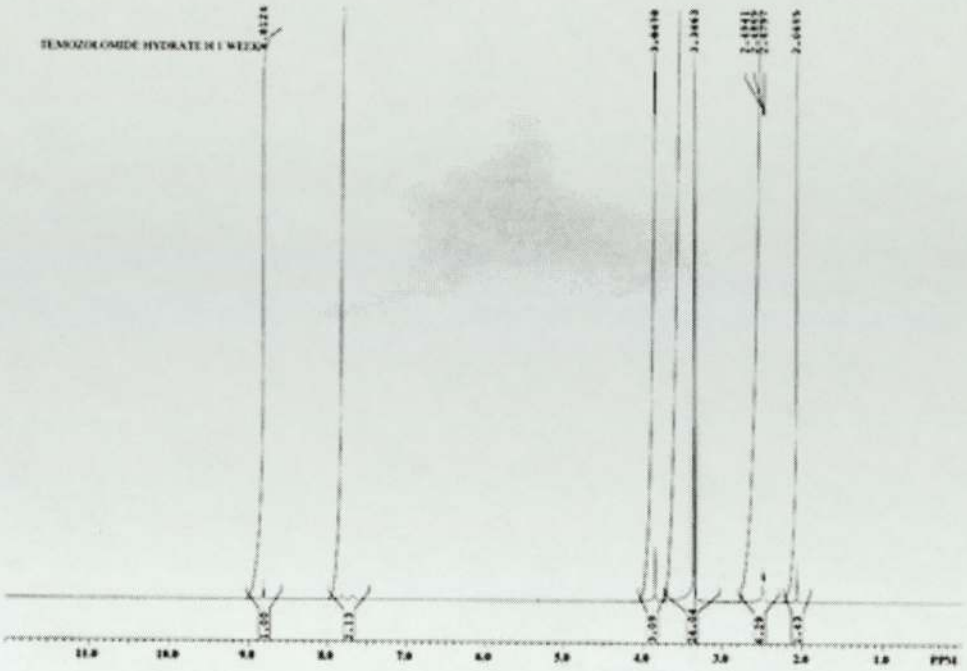

TEMOZOLOMIDE ANHY H 2 WEEKS
3.0544
2.5040
2.4880
2.4801
3.06
2.20
3.36
100.00
12.14
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

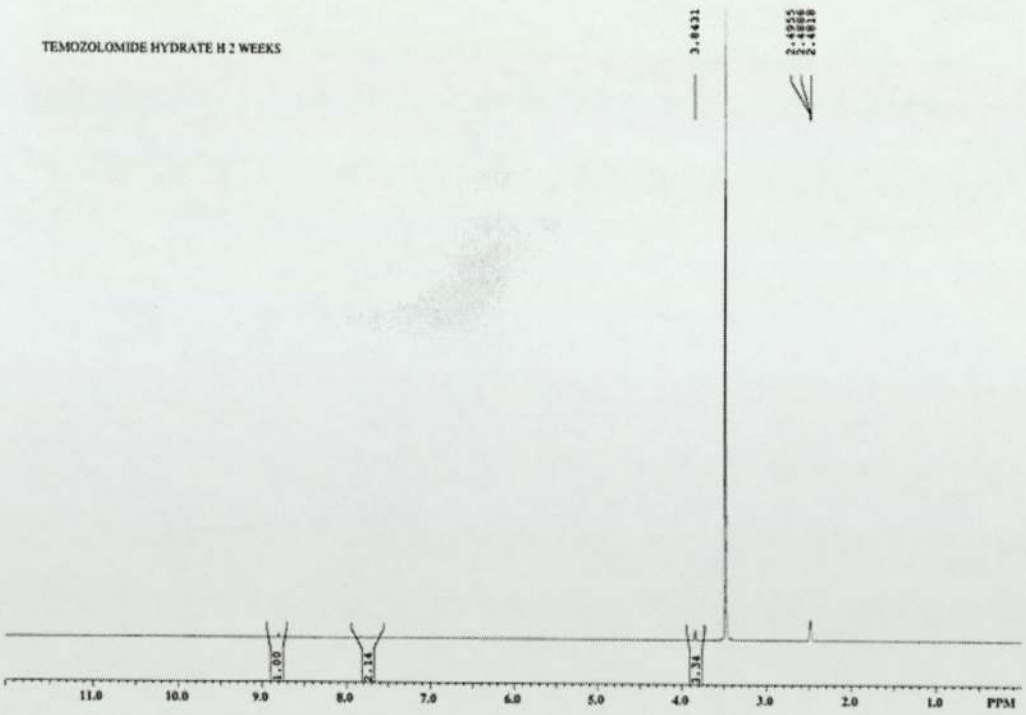

TEMOZOLOMIDE UNDER 3DAYS
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

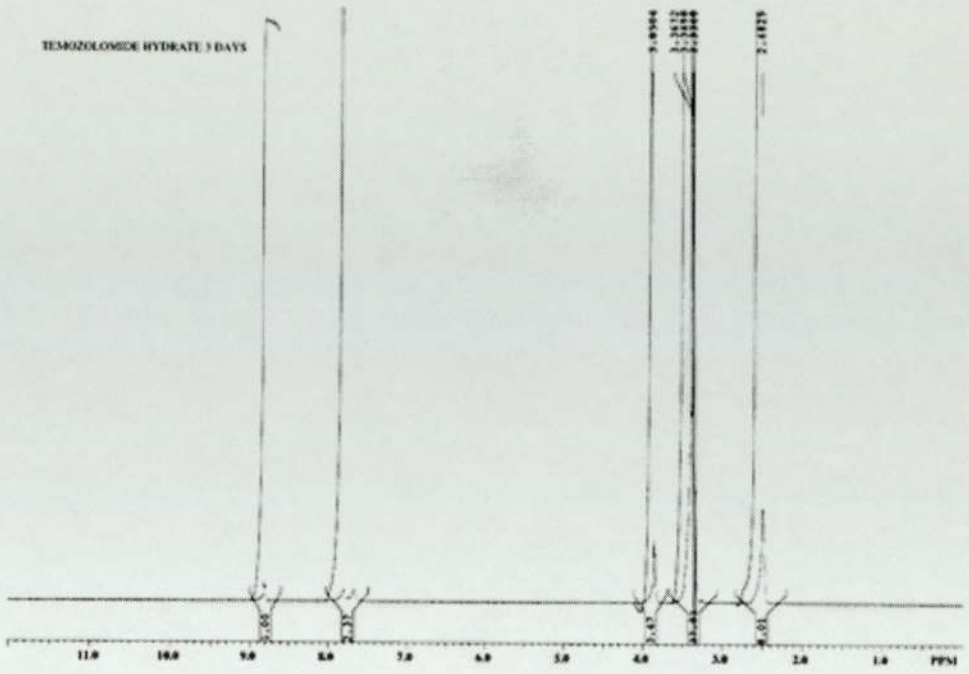

TEMOZOLOMIDE ANHYDRA 1 WEEK
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

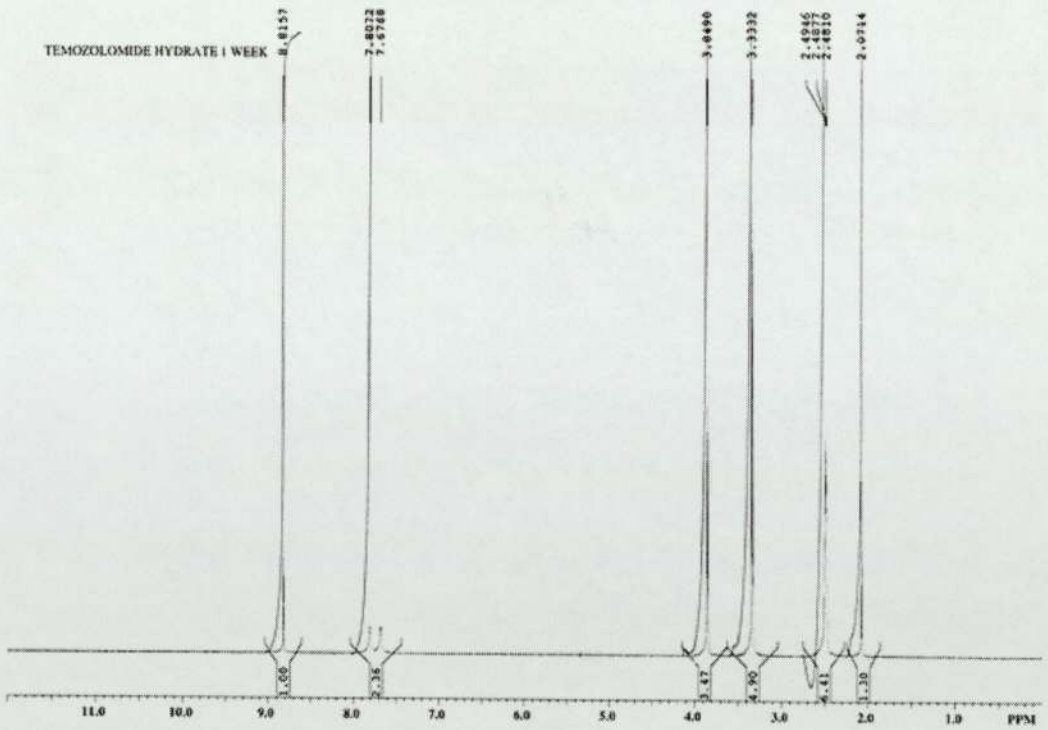

TEMOZOLOMIDE ANHY 2 WEEKS
PPM

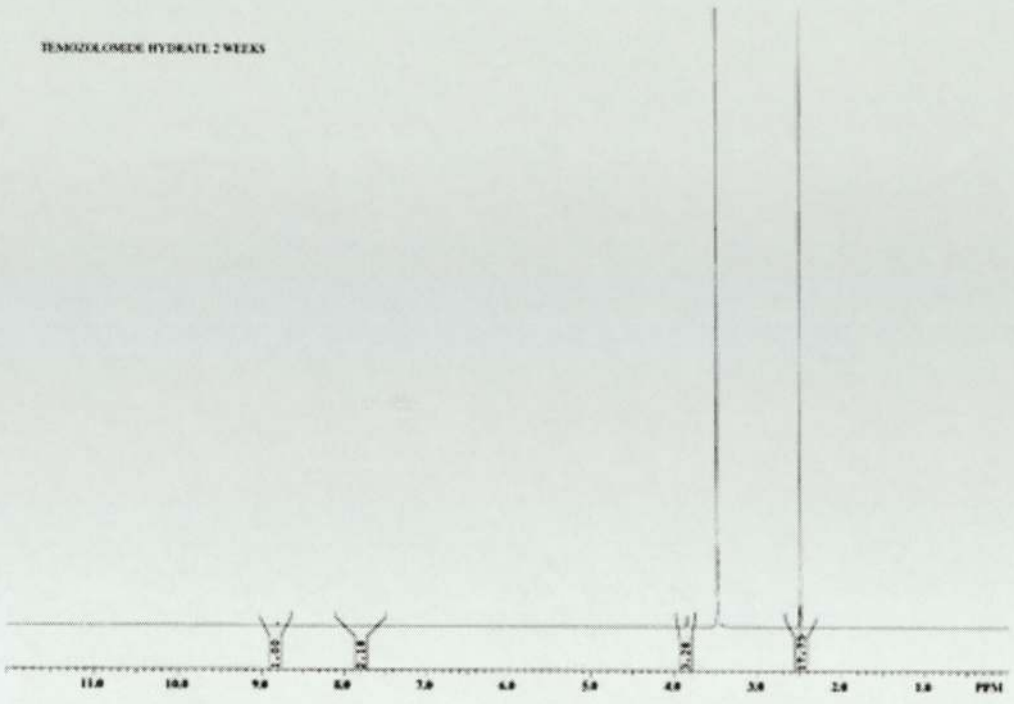

TEMOZOLOMIDE HYDRATE H 3 DAYS
3.6502
3.6499
2.4884
2.0749
2.0619
PPM




TEMOZOLOMIDE HYDRATE H 2 WEEKS
3.0431
2.4955
2.4888
2.4818
2.00
2.14
3.34
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


TEMOZOLOMIDE HYDRATE 3 DAYS
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


TEMOZOLOMIDE HYDRATE 1 WEEK
8.0157
7.8072
7.6768
3.6490
3.3332
2.4046
2.4877
2.4810
2.0714
1.00
2.36
3.47
4.90
6.41
1.30
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


TEMOZOLOMIDE HYDRATE 2 WEEKS
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

Appendix III Crystal structure details (Tables)

Temozolomide

Table 1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for Temozolomide from method 2. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
N(1)	90(3)	2500	4518(2)	45(1)
N(2)	-707(3)	2500	3307(2)	48(1)
N(3)	257(3)	2500	2118(2)	43(1)
C(4)	2075(3)	2500	2066(2)	41(1)
O(4)	2908(3)	2500	1028(2)	60(1)
N(5)	2882(2)	2500	3421(2)	37(1)
C(6)	4631(3)	2500	3836(2)	42(1)
N(7)	4844(3)	2500	5207(2)	40(1)
C(8)	3163(3)	2500	5714(2)	36(1)
C(8A)	1916(3)	2500	4614(2)	36(1)
C(31)	-872(4)	2500	811(3)	55(1)
C(81)	2838(3)	2500	7241(2)	41(1)
O(82)	1310(2)	2500	7633(2)	62(1)
N(82)	4239(3)	2500	8124(2)	58(1)

OW	7796(3)	2500	7230(2)	74(1)

Table 2 Bond lengths [A] for Temozolomide from method 2.

Bond	Bond Length
N(1)-N(2)	1.274(3)
N(1)-C(8A)	1.371(3)
N(2)-N(3)	1.376(3)
N(3)-C(4)	1.370(3)
N(3)-C(31)	1.471(3)
C(4)-O(4)	1.198(3)
C(4)-N(5)	1.398(3)
N(5)-C(6)	1.353(3)
N(5)-C(8A)	1.380(2)
C(6)-N(7)	1.308(3)
N(7)-C(8)	1.376(3)
C(8)-C(8A)	1.371(3)
C(8)-C(81)	1.488(3)
C(81)-O(82)	1.226(3)
C(81)-N(82)	1.314(3)

Table 3 Bond angles [°]for Temozolomide from method 2.

Atoms	Bond Angle

N(2)-N(1)-C(8A)	118.93(19)
N(1)-N(2)-N(3)	120.22(19)
C(4)-N(3)-N(2)	126.72(19)
C(4)-N(3)-C(31)	120.2(2)
N(2)-N(3)-C(31)	113.1(2)
O(4)-C(4)-N(3)	126.4(2)
O(4)-C(4)-N(5)	122.9(2)
N(3)-C(4)-N(5)	110.72(19)
C(6)-N(5)-C(8A)	107.62(17)
C(6)-N(5)-C(4)	129.77(19)
C(8A)-N(5)-C(4)	122.62(19)
N(7)-C(6)-N(5)	111.13(19)
C(6)-N(7)-C(8)	106.42(19)
C(8A)-C(8)-N(7)	109.61(18)
C(8A)-C(8)-C(81)	127.5(2)
N(7)-C(8)-C(81)	122.89(19)
C(8)-C(8A)-N(1)	134.0(2)
C(8)-C(8A)-N(5)	105.23(19)
N(1)-C(8A)-N(5)	120.80(19)
O(82)-C(81)-N(82)	122.5(2)
O(82)-C(81)-C(8)	120.1(2)
N(82)-C(81)-C(8)	117.4(2)

Table 4 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x !0^3) for Temozolomide from method 2.

	X	Y	Z	U(eq)
H(6)	5590(30)	2500	3230(30)	39(6)
H(31A)	-100(50)	2500	30(40)	74(9)
H(31B)	-1570(30)	1190(40)	760(30)	102(9)
H(82A)	5350(50)	2500	7890(40)	77(10)
H(82B)	4080(50)	2500	8990(40)	82(11)
HWA	8840(50)	2500	7250(40)	86(12)
HWB	7300(60)	2500	6420(50)	102(14)

Temozolomide

Table 1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for Temozolomide from method 3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
N(1)	9421(1)	2380(3)	3127(1)	45(1)
N(2)	10124(1)	3110(3)	3362(2)	50(1)
N(3)	10594(1)	3362(2)	4424(1)	43(1)
C(1)	11414(2)	4101(4)	4580(3)	58(1)
C(2)	10388(1)	2904(3)	5300(2)	40(1)
O(1)	10803(1)	3160(3)	6209(1)	62(1)
N(4)	9617(1)	2090(2)	4994(1)	36(1)
C(3)	9188(1)	1395(3)	5596(2)	45(1)
N(5)	8487(1)	736(2)	4995(1)	43(1)
C(4)	8439(1)	1008(3)	3954(2)	34(1)
C(5)	7722(1)	404(3)	3034(2)	37(1)
N(6)	7113(1)	-359(3)	3268(2)	47(1)
O(2)	7732(1)	635(2)	2122(1)	53(1)
C(6)	9141(1)	1843(3)	3928(1)	33(1)
N(7)	4154(1)	-3570(2)	-93(1)	33(1)
N(8)	3461(1)	-4349(2)	-465(1)	36(1)

N(9)	3107(1)	-4596(2)	-1558(1)	32(1)
C(7)	2315(1)	-5508(4)	-1883(2)	44(1)
C(8)	3424(1)	-4095(3)	-2330(2)	32(1)
O(3)	3081(1)	-4290(2)	-3281(1)	44(1)
N(10)	4185(1)	-3274(2)	-1887(1)	32(1)
C(9)	4716(1)	-2593(3)	-2354(2)	39(1)
N(11)	5370(1)	-1921(2)	-1632(1)	38(1)
C(10)	5270(1)	-2157(3)	-657(1)	30(1)
C(11)	5900(1)	-1527(3)	345(1)	32(1)
N(12)	6528(1)	-655(3)	200(1)	40(1)
O(4)	5838(1)	-1816(2)	1229(1)	43(1)
C(12)	4536(1)	-3005(2)	-790(1)	29(1)

Table 2 Bond lengths [Å] for Temozolomide from method 3.

Bond	Bond Length
N(1)-N(2)	1.271(2)
N(1)-C(6)	1.365(3)
N(2)-N(3)	1.382(3)
N(3)-C(2)	1.365(3)
N(3)-C(1)	1.469(3)

C(2)-O(1)	1.192(2)
C(2)-N(4)	1.395(2)
N(4)-C(3)	1.359(3)
N(4)-C(6)	1.387(2)
C(3)-N(5)	1.303(3)
N(5)-C(4)	1.368(3)
C(4)-C(6)	1.374(3)
C(4)-C(5)	1.487(3)
C(5)-O(2)	1.225(2)
C(5)-N(6)	1.319(3)
N(7)-N(8)	1.271(2)
N(7)-C(12)	1.367(2)
N(8)-N(9)	1.382(2)
N(9)-C(8)	1.363(2)
N(9)-C(7)	1.456(3)
C(8)-O(3)	1.208(2)
C(8)-N(10)	1.389(2)
N(10)-C(9)	1.364(3)
N(10)-C(12)	1.389(2)
C(9)-N(11)	1.310(2)
N(11)-C(10)	1.369(2)
C(10)-C(12)	1.374(3)

C(10)-C(11)	1.482(2)
C(11)-O(4)	1.230(2)
C(11)-N(12)	1.330(3)

Table 3 Bond angles [°] for Temozolomide from method 3.

Atoms	Bond Angle
N(2)-N(1)-C(6)	119.52(17)
N(1)-N(2)-N(3)	119.75(17)
C(2)-N(3)-N(2)	126.83(17)
C(2)-N(3)-C(1)	119.1(2)
N(2)-N(3)-C(1)	113.9(2)
O(1)-C(2)-N(3)	125.3(2)
O(1)-C(2)-N(4)	123.8(2)
N(3)-C(2)-N(4)	110.85(17)
C(3)-N(4)-C(6)	106.96(16)
C(3)-N(4)-C(2)	130.50(17)
C(6)-N(4)-C(2)	122.54(17)
N(5)-C(3)-N(4)	111.30(18)
C(3)-N(5)-C(4)	106.89(17)
N(5)-C(4)-C(6)	109.54(16)

N(5)-C(4)-C(5)	122.29(18)
C(6)-C(4)-C(5)	128.15(18)
O(2)-C(5)-N(6)	124.48(19)
O(2)-C(5)-C(4)	118.84(18)
N(6)-C(5)-C(4)	116.68(19)
N(1)-C(6)-C(4)	134.18(17)
N(1)-C(6)-N(4)	120.51(17)
C(4)-C(6)-N(4)	105.30(16)
N(8)-N(7)-C(12)	118.87(15)
N(7)-N(8)-N(9)	119.71(15)
C(8)-N(9)-N(8)	126.92(15)
C(8)-N(9)-C(7)	118.64(16)
N(8)-N(9)-C(7)	114.43(16)
O(3)-C(8)-N(9)	124.61(17)
O(3)-C(8)-N(10)	123.97(18)
N(9)-C(8)-N(10)	111.39(15)
C(9)-N(10)-C(12)	107.26(15)
C(9)-N(10)-C(8)	131.06(16)
C(12)-N(10)-C(8)	121.68(16)
N(11)-C(9)-N(10)	110.89(17)
C(9)-N(11)-C(10)	106.84(16)
N(11)-C(10)-C(12)	109.88(16)

N(11)-C(10)-C(11)	121.13(16)
C(12)-C(10)-C(11)	128.99(17)
O(4)-C(11)-N(12)	123.84(17)
O(4)-C(11)-C(10)	121.69(17)
N(12)-C(11)-C(10)	114.47(17)
N(7)-C(12)-C(10)	133.45(16)
N(7)-C(12)-N(10)	121.43(16)
C(10)-C(12)-N(10)	105.12(16)

Table 4 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for Temozolomide from method 3.

	X	Y	Z	U(eq)
H(1)	11767(16)	3120(40)	4820(20)	70(8)
H(2)	11393(18)	4530(40)	3860(20)	86(10)
H(3)	11534(17)	5030(40)	5150(20)	83(9)
H(4)	9418(14)	1370(30)	6380(20)	65(7)
H(5)	7127(12)	-400(30)	3912(18)	29(5)
H(6)	6662(17)	-820(40)	2720(20)	76(9)
H(7)	1880(20)	-4700(50)	-2270(30)	112(12)
H(8)	2330(20)	-6400(60)	-2310(30)	122(14)
H(9)	2160(19)	-5750(40)	-1280(30)	88(10)

H(10)	4586(12)	-2600(30)	-3093(18)	41(6)
H(11)	6537(13)	-420(30)	-453(19)	46(6)
H(12)	6940(14)	-160(30)	830(19)	50(6)

Hydantoin

Table 1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for hydantoin from method 2. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
N(1)	8503(3)	3918(2)	3655(4)	47(1)
C(2)	7973(3)	4948(2)	3201(4)	34(1)
O(2)	8518(2)	5817(2)	3852(3)	49(1)
N(3)	6641(3)	4842(2)	1855(4)	34(1)
C(4)	6328(3)	3783(2)	1353(4)	35(1)
O(4)	5238(2)	3459(2)	151(4)	50(1)
C(5)	7525(3)	3120(2)	2505(4)	39(1)

Table 2 Bond lengths [Å] for hydantoin from method 2.

Bond	Bond Length
N(1)-C(2)	1.359(4)
N(1)-C(5)	1.446(4)
C(2)-O(2)	1.218(4)
C(2)-N(3)	1.379(4)
N(3)-C(4)	1.353(4)
C(4)-O(4)	1.226(3)

C(4)-C(5)	1.458(4)

Table 3 Bond angles [°] for hydantoin from method 2.

Atoms	Bond Angle
C(2)-N(1)-C(5)	110.1(2)
O(2)-C(2)-N(1)	128.2(3)
O(2)-C(2)-N(3)	124.7(3)
N(1)-C(2)-N(3)	107.1(2)
C(4)-N(3)-C(2)	112.0(2)
O(4)-C(4)-N(3)	125.6(3)
O(4)-C(4)-C(5)	127.4(3)
N(3)-C(4)-C(5)	107.0(2)
N(1)-C(5)-C(4)	103.8(2)

Table 4 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for hydantoin from method 2.

	X	Y	Z	U(eq)
H(1)	9304	3764	4502	56
H(3)	6076	5385	1389	40
H(5A)	7153	2608	3290	47
H(5B)	8030	2713	1716	47

5,5-Diphenylhydantoin

Table 1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for diphenylhydantoin from method 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U(eq)
N(1)	977(10)	2697(12)	579(4)	47(2)
C(1)	4654(12)	2776(13)	487(5)	38(2)
C(2)	1744(11)	2756(15)	1373(5)	49(2)
N(2)	3970(10)	2798(11)	1315(4)	47(2)
C(3)	2645(10)	2758(18)	-89(4)	38(2)
O(1)	6489(7)	2794(9)	241(3)	60(2)
O(2)	738(9)	2739(11)	2039(3)	70(2)
C(4)	1390(30)	1028(12)	-511(9)	84(5)
C(5)	1580(80)	146(16)	-1015(17)	127(9)
C(6)	3220(60)	170(19)	-1649(17)	131(11)
C(7)	4440(40)	890(20)	-1763(16)	148(11)
C(8)	4310(20)	1698(18)	-1257(13)	105(7)
C(9)	2723(19)	1816(14)	-638(14)	51(5)
C(10)	3650(30)	4422(11)	-611(9)	73(4)
C(11)	3210(50)	5266(13)	-1082(14)	102(6)
C(12)	1480(50)	5327(15)	-1636(10)	101(8)
C(13)	140(30)	4495(19)	-1640(11)	108(6)

C(14)	610(20)	3663(17)	-1192(9)	91(5)
C(15)	2317(19)	3650(12)	-626(11)	46(5)

Table 2 Bond lengths [Å] for diphenylhydantoin from method 1.

Bond	Bond Length
N(1)-C(2)	1.323(10)
N(1)-C(3)	1.470(9)
C(1)-O(1)	1.205(8)
C(1)-N(2)	1.354(10)
C(1)-C(3)	1.538(9)
C(2)-O(2)	1.209(8)
C(2)-N(2)	1.390(9)
C(3)-C(15)	1.48(3)
C(3)-C(9)	1.54(3)
C(4)-C(9)	1.37(2)
C(4)-C(5)	1.44(3)
C(5)-C(6)	1.42(5)
C(6)-C(7)	1.26(4)
C(7)-C(8)	1.35(3)
C(8)-C(9)	1.39(2)
C(10)-C(15)	1.34(2)

C(10)-C(11)	1.39(2)
C(11)-C(12)	1.38(4)
C(12)-C(13)	1.40(3)
C(13)-C(14)	1.36(3)
C(14)-C(15)	1.380(19)

Table 3 Bond angles (°) for diphenylhydantoin from method 1

Atoms	Bond Angle
C(2)-N(1)-C(3)	113.4(6)
O(1)-C(1)-N(2)	126.8(7)
O(1)-C(1)-C(3)	126.0(6)
N(2)-C(1)-C(3)	107.2(6)
O(2)-C(2)-N(1)	127.4(7)
O(2)-C(2)-N(2)	125.0(8)
N(1)-C(2)-N(2)	107.6(7)
C(1)-N(2)-C(2)	112.0(7)
N(1)-C(3)-C(15)	110.2(14)
N(1)-C(3)-C(9)	111.5(17)
C(15)-C(3)-C(9)	111.8(6)
N(1)-C(3)-C(1)	99.6(5)
C(15)-C(3)-C(1)	115.2(15)

C(9)-C(3)-C(1)	108.0(13)
C(9)-C(4)-C(5)	122(2)
C(6)-C(5)-C(4)	115(3)
C(7)-C(6)-C(5)	124(2)
C(6)-C(7)-C(8)	121(2)
C(9)-C(8)-C(7)	123(2)
C(8)-C(9)-C(4)	116.2(19)
C(8)-C(9)-C(3)	120.2(17)
C(4)-C(9)-C(3)	123.4(16)
C(15)-C(10)-C(11)	121.0(17)
C(12)-C(11)-C(10)	122(2)
C(11)-C(12)-C(13)	114.8(15)
C(14)-C(13)-C(12)	122.6(17)
C(13)-C(14)-C(15)	120(2)
C(10)-C(15)-C(14)	118.7(16)
C(10)-C(15)-C(3)	122.9(13)
C(14)-C(15)-C(3)	118.3(16)

Table 4 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for diphenylhydantoin from method 1.

	X	Y	Z	U(eq)
H(1)	-450(190)	2410(90)	450(70)	100(50)

H(2)	4660(120)	2570(80)	1790(50)	50(30)
H(3)	740(120)	1100(70)	-10(60)	30(20)
H(4)	300(700)	0(500)	-900(200)	400(300)
H(5)	2420(160)	-680(90)	-1620(60)	60(30)
H(6)	5900(300)	750(110)	-2100(100)	130(60)
H(7)	5100(200)	2270(120)	-1430(100)	130(70)
H(8)	5430(120)	4310(50)	-160(50)	30(20)
H(9)	4300(400)	6000(200)	-1040(130)	210(100)
H(10)	1300(160)	5950(80)	-2150(60)	70(30)
H(11)	-1260(190)	4310(80)	-2170(70)	70(30)
H(12)	-330(110)	3250(50)	-1050(40)	0(18)