Chapter 1: Introduction

1.1 Introduction and Historical Background to Solid-State Organic Chemistry with Emphasis on Solid-State Photo-chemistry

The statement, *Corpura non agunt nisi fluida* ("Bodies do not act unless in the fluid state"), attributed to Aristotle, has been stated as one of the main reasons why reactions are more often than not carried out in the solution than in the solid-state [McLain, 1980], and why solid-state reactions have only relatively recently been actively studied. Many chemists still assume that reactions will not occur in the solid-state. According to McLain, the first conclusive proof that solids will react by themselves was the making of a ceramic pigment, Rinman's Green, by Hedvall (1912). He mixed and heated black Co_3O_4 and white ZnO and observed that small green crystals formed between 500 and 900 °C, temperatures at which neither liquid nor vapor phase could conceivably play a role. Solid-state chemistry literature is now abundant, though most of it has appeared after 1946, due to the discovery of solid-state electronics (semi-conductors) and advances in techniques useful in the study of the solid-state.

Organic photoreactions in the solid-state have been widely studied and have been reported since the last century [Ramamurthy & Venkatesan, 1987]. In fact eighteenth century chemists often carried out reactions in the solid-state because of the unavailability and expense of solvents. As time passed, chemists concentrated on reactions in solution media at the expense of the solid-state. A lot has been learned about the mechanisms and kinetics of reactions in solution with crystal chemistry being almost ignored. Today, though means are available to study crystals and solid state materials in general [X-ray crystallography, solid-state NMR, IR spectrostroscopy and other analytical tools; see Boldyreva (1999), Bernstein (2002) and Threlfall (1995) for a general discussion], and though a lot of work has been done on carrying out common organic synthesis reactions in the solid-state [Tanaka & Toda, 2000; Ohashi, 1993], most chemists still concentrate on the liquid state because it is better understood, more popular, easier to model and easier to manipulate. However, the move to 'green' chemistry is driving the study of reactions in the solid-state forward [Kaupp, 2003], as reactions in the solid-state often do not require a purification process or the removal and disposal of organic solvents. In pushing the idea to the extreme a paper titled '*Solvent-drop grinding: green polymorph control of cocrystallisation*', in which recrystallization was carried out using a molar ratio of organic solvent to crystalline material of 0.2 to 0.6, has recently been published [Trask *et al.*, 2004].

In the 1960's pioneering work in solid-state organic chemistry was carried out by Schmidt and his coworkers [Cohen & Schmidt, 1964; Cohen, Schmidt & Sonntag, 1964; Schmidt, 1964] in their study of the solid state photochemistry of cinnamic acids. It was in this work that they confirmed the topochemical postulate first enunciated by Kohlschutter in 1918 [Ramamurthy & Venkatesan, 1987]. The topochemical principle, states that reactions that occur in crystals proceed with minimal atomic and molecular motion, and are thus determined by the structures in the crystalline state of the starting materials. There are limitations to the postulate however. These are that the postulate only applies to reactions that truly occur in the crystal matrix and that the postulate does not lead to conclusions about the rate of reaction [Cohen & Green, 1973].

According to Ramamurthy & Venkatesan (1987) the important points to have emerged from Schmidt and his co-workers' work are as follows:

i. The intrinsic reactivity of the molecule is less important than the packing of the neighboring molecules around the reactant in the crystal.
ii. The separation distance, orientation and space symmetry of the reactant groups are crucial as these affect whether or not a product is obtained and what it will look like.

iii. In crystalline solids there are very few (usually one) conformations taken up by molecules, whereas in the liquid state molecules are quite flexible.
iv. Molecular crystals often display a diversity of polymorphic forms (crystal packing arrangements), in each of which a particular symmetry and separation of molecular groups will yield a similar diversity of reaction products.

Therefore chemistry in the solid-state differs from that done in solution in that it can allow reaction pathways to be controlled more precisely. This is due to lattice-control over reaction pathways and has two consequences. The first is that molecules, even flexible ones, crystallize in only a small number of conformations, although in most cases there is a unique conformation [see section 1.2 on the nature of Polymorphism]. The second is that geometries relating different molecules, and hence the types of intermolecular approaches, are limited in the crystal but not in other phases. These two consequences are closely interrelated with the result being that a compound may have a conformation in solid-state that is not found in solution [Cohen & Green, 1973]. For example, biphenyl molecules [Bastiansen, 1951; Almenningsen *et al.*, 1985; Fig. 1.1] and oxalate-ions [Dewar *et al.*, 1990; Naumov *et al.*, 1997] have planar conformations in the solid-state but staggered conformations in solution.

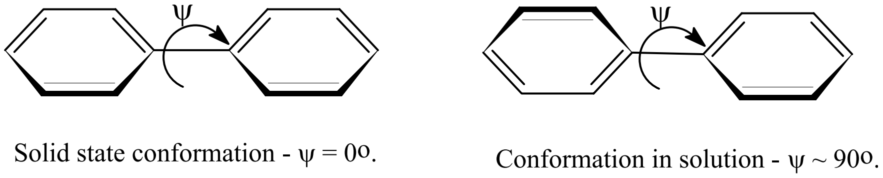
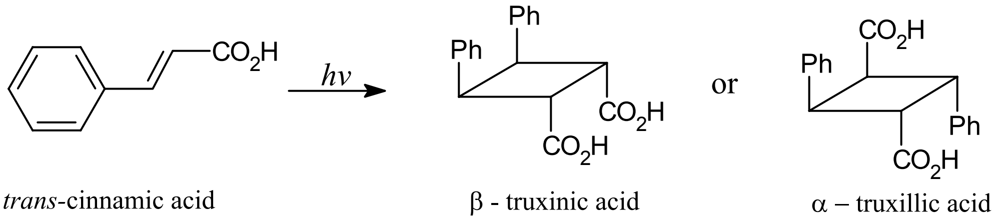


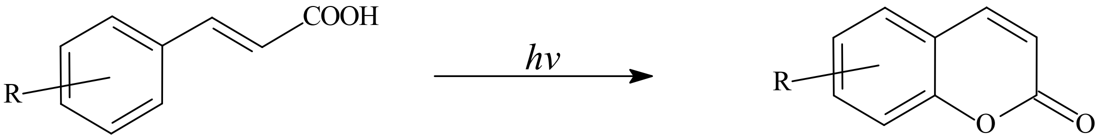
Figure 1.1: The conformation of the biphenyl molecule in the solid-state and in solution.

The reaction studied by Schmidt and his coworkers was the photodimerization of cinnamic acid with UV light to form a *β*-truxinic acid or *α*-truxillic acid (Scheme 1.1), a reaction observed as long ago as 1889 [Liebermann, 1889].



Scheme 1.1: The dimerization of cinnamic acid.

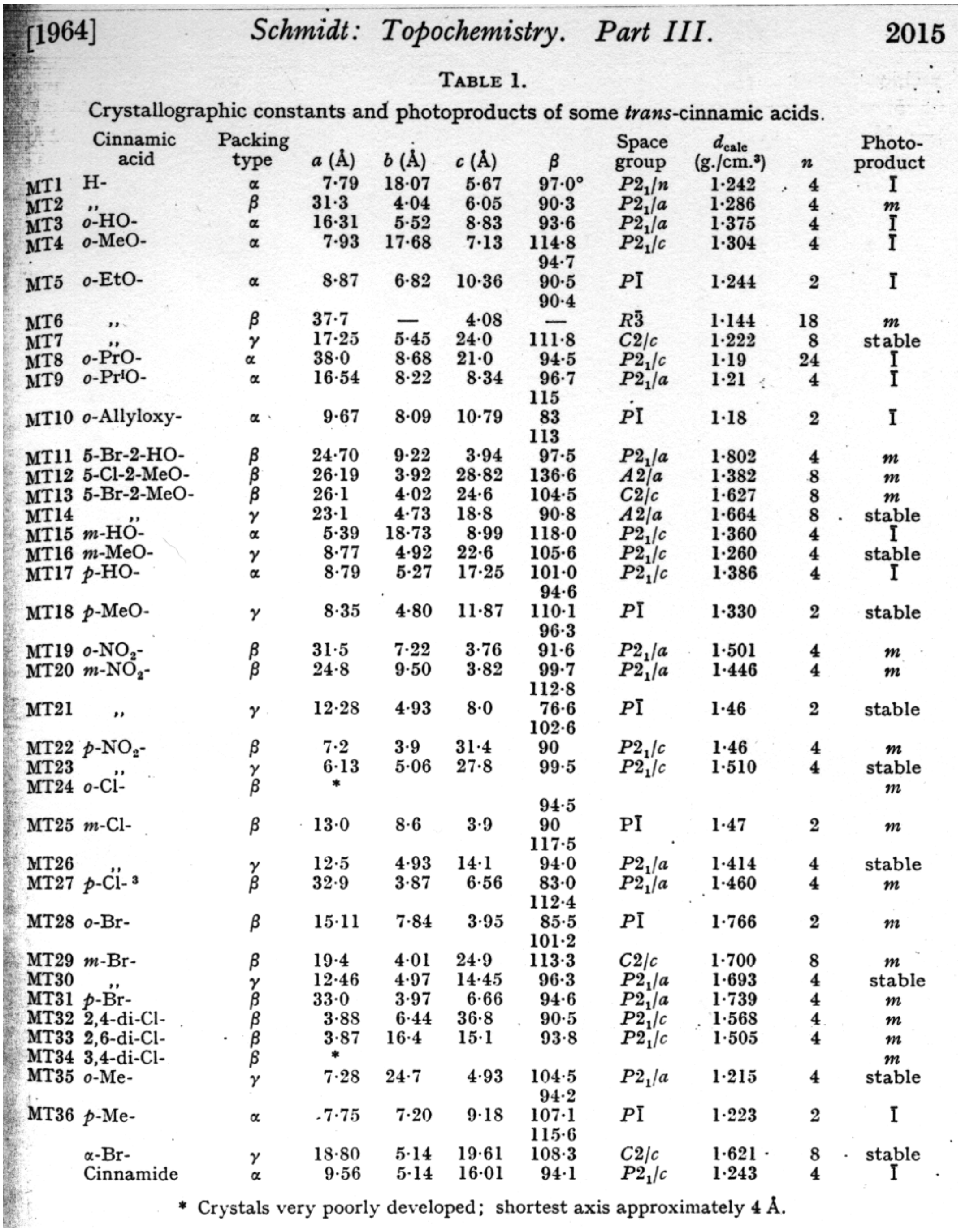
These products can only be obtained by reaction in the solid-state. Irradiating cinnamic acids in solution gives rise to a reversible *trans*-to-*cis* isomerization followed by photocyclization to a coumarin product (Scheme 1.2).



1: 2-chloro
2: 2-methoxy
3: 3-methoxy
4: 4-methoxy
5: 2,5-dimethoxy
6: 2,6-dichloro
7: 2,6-dimethoxy
8: 3,4-dimethoxy
9: 2,6-dimethoxy

Scheme 1.2: The reaction of cinnamic acids when irradiated in solution. For details, including reaction mechanisms, see Terrian *et al.* (1995), Pandey *et al.* (1986) and Weissbuch *et al.* (1991).

Some of the cinnamic compounds studied, by Schmidt and his co-workers, were cinnamic acid itself, hydroxy cinnamic acids, ethoxy cinnamic acids, nitro cinnamic acids and halocinnamic acids (Fig. 1.2).



[1964] *Schmidt: Topochemistry. Part III.* 2015

TABLE 1.

Crystallographic constants and photoproducts of some *trans*-cinnamic acids.

	Cinnamic acid	Packing type	*a* (Å)	*b* (Å)	*c* (Å)	β	Space group	d_{calc} (g./cm.^{3})	*n*	Photo-product
MT1	H-	α	7·79	18·07	5·67	97·0°	$P2_1/n$	1·242	4	$\bar{1}$
MT2	,,	β	31·3	4·04	6·05	90·3	$P2_1/a$	1·286	4	*m*
MT3	*o*-HO-	α	16·31	5·52	8·83	93·6	$P2_1/a$	1·375	4	$\bar{1}$
MT4	*o*-MeO-	α	7·93	17·68	7·13	114·8	$P2_1/c$	1·304	4	$\bar{1}$
MT5	*o*-EtO-	α	8·87	6·82	10·36	94·7 90·5 90·4	$P\bar{1}$	1·244	2	$\bar{1}$
MT6	,,	β	37·7	—	4·08	—	$R\bar{3}$	1·144	18	*m*
MT7	,,	γ	17·25	5·45	24·0	111·8	$C2/c$	1·222	8	stable
MT8	*o*-PrO-	α	38·0	8·68	21·0	94·5	$P2_1/c$	1·19	24	$\bar{1}$
MT9	*o*-Pr^{i}O-	α	16·54	8·22	8·34	96·7	$P2_1/a$	1·21	4	$\bar{1}$
MT10	*o*-Allyloxy-	α	9·67	8·09	10·79	115 83 113	$P\bar{1}$	1·18	2	$\bar{1}$
MT11	5-Br-2-HO-	β	24·70	9·22	3·94	97·5	$P2_1/a$	1·802	4	*m*
MT12	5-Cl-2-MeO-	β	26·19	3·92	28·82	136·6	$A2/a$	1·382	8	*m*
MT13	5-Br-2-MeO-	β	26·1	4·02	24·6	104·5	$C2/c$	1·627	8	*m*
MT14	,,	γ	23·1	4·73	18·8	90·8	$A2/a$	1·664	8	stable
MT15	*m*-HO-	α	5·39	18·73	8·99	118·0	$P2_1/c$	1·360	4	$\bar{1}$
MT16	*m*-MeO-	γ	8·77	4·92	22·6	105·6	$P2_1/c$	1·260	4	stable
MT17	*p*-HO-	α	8·79	5·27	17·25	101·0	$P2_1/c$	1·386	4	$\bar{1}$
MT18	*p*-MeO-	γ	8·35	4·80	11·87	94·6 110·1 96·3	$P\bar{1}$	1·330	2	stable
MT19	*o*-NO_2-	β	31·5	7·22	3·76	91·6	$P2_1/a$	1·501	4	*m*
MT20	*m*-NO_2-	β	24·8	9·50	3·82	99·7	$P2_1/a$	1·446	4	*m*
MT21	,,	γ	12·28	4·93	8·0	112·8 76·6 102·6	$P\bar{1}$	1·46	2	stable
MT22	*p*-NO_2-	β	7·2	3·9	31·4	90	$P2_1/c$	1·46	4	*m*
MT23	,,	γ	6·13	5·06	27·8	99·5	$P2_1/c$	1·510	4	stable
MT24	*o*-Cl-	β	*							*m*
MT25	*m*-Cl-	β	13·0	8·6	3·9	94·5 90 117·5	$P\bar{1}$	1·47	2	*m*
MT26	,,	γ	12·5	4·93	14·1	94·0	$P2_1/a$	1·414	4	stable
MT27	*p*-Cl-[3]	β	32·9	3·87	6·56	83·0	$P2_1/a$	1·460	4	*m*
MT28	*o*-Br-	β	15·11	7·84	3·95	112·4 85·5 101·2	$P\bar{1}$	1·766	2	*m*
MT29	*m*-Br-	β	19·4	4·01	24·9	113·3	$C2/c$	1·700	8	*m*
MT30	,,	γ	12·46	4·97	14·45	96·3	$P2_1/a$	1·693	4	stable
MT31	*p*-Br-	β	33·0	3·97	6·66	94·6	$P2_1/a$	1·739	4	*m*
MT32	2,4-di-Cl-	β	3·88	6·44	36·8	90·5	$P2_1/c$	1·568	4	*m*
MT33	2,6-di-Cl-	β	3·87	16·4	15·1	93·8	$P2_1/c$	1·505	4	*m*
MT34	3,4-di-Cl-	β	*							*m*
MT35	*o*-Me-	γ	7·28	24·7	4·93	104·5	$P2_1/a$	1·215	4	stable
MT36	*p*-Me-	α	7·75	7·20	9·18	94·2 107·1 115·6	$P\bar{1}$	1·223	2	$\bar{1}$
	α-Br-	γ	18·80	5·14	19·61	108·3	$C2/c$	1·621	8	stable
	Cinnamide	α	9·56	5·14	16·01	94·1	$P2_1/c$	1·243	4	$\bar{1}$

* Crystals very poorly developed; shortest axis approximately 4 Å.

Figure 1.2: Table entry from the original Schmidt paper [from Schmidt, G., 1964, with permission] listing some of the cinnamic acids studied by his group. In the photoproduct column, $\bar{1}$ represents the creation of an *α*-truxllic acid, while *m* represents a *β*-truxinic acid. Note that the reported d_{calc} is significantly lower for the *β*-polymorph of OETCA[1] when compared to the *α*- and *γ*-polymorphs.

---

[1] *ortho*-Ethoxy-*trans*-cinnamic acid

In the solid-state the close proximity between the two reactive alkenes in the two cinnamic acid molecules ensures that only the two products shown in Scheme 1.1 are obtained. For cinnamic acid, only two polymorphs are known: the *α*-phase obtainable from almost any organic solvent and on dimerization leading to the centrosymmetric (or inverted) product, *α*-truxillic acid; and the extremely difficult to grow and metastable *β*-phase obtained from a petroleum ether/diethyl ether solution and yielding the mirror product, *β*-truxinic acid (Fig. 1.2). Due to the constraints of the crystal environment each of these crystal forms leads to one product, unless some amorphous phase is present or is produced during the reaction leading to another product. However, it has been found that for cinnamic acid no products other than the above are formed.[2] It has been proposed that in order for a reaction to occur, the reacting double bonds have to be between 3.5 to 4.2 Å apart. This is referred to as Schmidt's criterion [Schmidt, 1964; Schmidt, 1971; Cohen & Green, 1973]. However, Schmidt did not seem to regard this range as a hard and fast limit and noted that reactions at slightly larger distances may still be possible. Though rare, an example of a photoreactive compound with inter double bond (C=C) distances greater than 4.2 Å in the solid-state is 7-chlorocoumarin [Gnanaguru *et al.*, 1985]. Here, the inter C=C distance is 4.45 Å and the reaction has been shown to be topochemical and to occur without the aid of lattice defects.

From the above experiments, Schmidt and his coworkers came to the following conclusions:

a) Each crystalline phase of the *trans*-acids is either light stable or gives its characteristic dimer.
b) No mixing of dimers occurs unless dimerization takes place under conditions permitting demonstrable transformation of the monomer to a new phase which then accounts for the second dimer species formed.

---

[2] It is possible that a solid-state reaction will yield more than one product. Though not found to occur in *trans*-cinnamic acids, this has been found to occur in the solid-state photodimerization of *cis*-cinnamic acids, anthracene, as well as many other compounds.

c) Even if a phase transition should occur then no dimers other than *α*-truxillic and *β*-truxinic acids are detectable.
d) No correlation could be found between ring substituent and photochemical behavior.

The above implies that by knowing the phase of the crystal, it is possible to work out what the product of the reaction should be. Conversely, the fact that a crystal phase will reliably give only one dimer, makes it possible to study the phase distributions in a material (*α*- or *β*-phases) by looking at the product distribution. This last property can act as a probe, allowing insight into the reaction mechanism and crystal environment without using more sophisticated analytical techniques. Schmidt and his co-workers came to their conclusions by studying the product distribution from the photodimerization of various cinnamic acids. This useful property has also been used to study the nucleation of crystals at the interface of a solution with air [Weissbuch *et al*., 1991 & 2003].

Because of the work done by Schmidt and his co-workers, cinnamic acid phases (or polymorphs) as well as those of other photoreactive materials, have been classified into *α*-, *β*- or *γ*-phases.[3] In cinnamic acids the *α*-phase always yields a centrosymmetric product, the *β*-phase always yields a mirror product, while the *γ*-phase is light stable (see Fig. 1.2 and Section 1.5).

Another way in which these phases can be classified is on the basis of the length of the shortest axis of the crystalline monomer. The shortest axis found in the *β*-type crystals are 3.9 ± 0.2 Å, in the *γ*-type crystals they are 4.9 ± 0.2 Å, and in the *α*-type crystals they are greater than 5.1 Å [Hung *et al.,* 1972].

---

[3] Other phases (or polymorphs) in other materials have been classified using a higher Greek letter based on whether another product is obtained or whether this is a new phase of the material, e.g. the fourth polymorph of a material could be labeled as the *δ*-polymorph (see section on the labeling of polymorphs).

In addition, Schmidt's work also lead to advances in the understanding of polymorphism and its use in the study of structure-property relationships. As reactions in the solid state are lattice controlled, an understanding of intermolecular interactions and their effect on the final solid state material is very important (Fig. 1.3).

Therefore, to understand and study solid-state reactions, a general understanding of crystallography, phase-transitions, weak intermolecular interactions, crystal engineering and various other concepts associated with solid-state reactions is required. Some of these concepts will be presented in the remainder of this chapter.

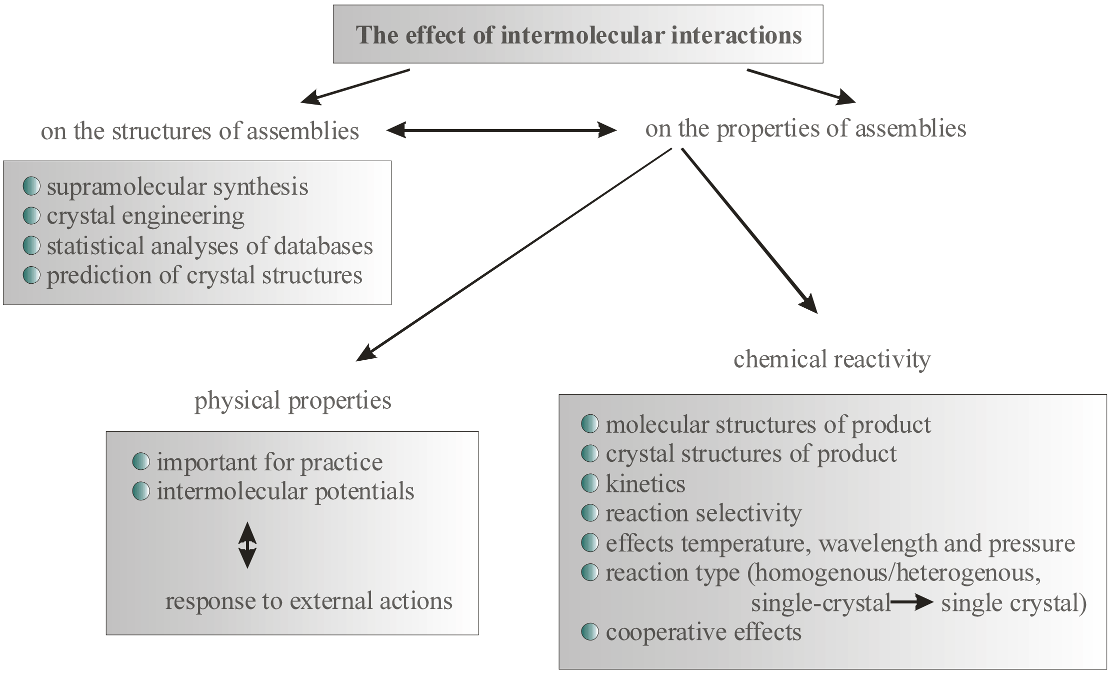


Figure 1.3: The problem of interplay between intra- and intermolecular interactions in supramolecular chemistry [after Boldyreva, E., 1999].

1.2 The Phenomenon of Polymorphism in Molecular Crystals

Possible reaction pathways in molecular crystals are determined by the arrangement of molecules in the solid-state. When only one arrangement is possible or is found in nature then no diversity in solid-state reactivity occurs. However, the phenomenon of polymorphism ensures that this is not the case.

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements in the solid state, i.e., same molecule but different crystal packing [McCrone, 1965] - this is actually only one of several slightly different definitions [see Bernstein, 2002]. There are also the complicating issues (complicating because these terms are often used to mean exactly the same thing) of pseudo-polymorphism, co-crystals, molecular complexes, solvates and hydrates in which another molecule, usually a solvent molecule, has co-crystallized with the molecule of interest [Bernstein, 2002; Desiraju, 2003]. Desiraju (2003) has suggested that the current use of co-crystal - meaning a crystal made up of two molecular components is incorrect. Instead he suggests that the term molecular complex be used in this case - as first defined by Kitaigorodskii (1984) - and that the term co-crystal instead be used when referring to a material in which two or more crystalline phases coexist.

In this thesis the word polymorph refers to the one-component crystal form of a given material (regardless of whether the molecule is present in more than one conformation, i.e. the emphasis being on chemical identity). The terms: solvate, pseudo-polymorph and molecular complex refer to the given molecule co-crystallized with a solvent molecule, i.e., more than one chemical component is present.

There are several types of polymorphism. For example, if a molecule adopts a different conformation in a set of polymorphs, then the polymorphs are termed conformational polymorphs [Dunitz, 1995]. Usually polymorphs differ because of the prevalence of different arrangements of weak interactions, e.g. different hydrogen bond patterns. However, at least one example of isotopomeric polymorphism exists - in the 1:1 complex of 4-methylpyridine and pentachlorophenol - in which the replacement of a proton involved in hydrogen bonding with a deuterium atom leads to the formation of another structure [Malarski *et al.*, 1996; Zhou *et al.*, 2004]. The change is quite significant as the structure changes from triclinic to monoclinic upon deuteration. Since polymorphs have different crystal structures they may differ in their physical properties such as density, hardness, solubility and optical and electrical properties. Polymorphs tend to be classified by different numbers such as *α*, *β*, *γ* or I, II, III, etc. Overall, fewer than 5% of the structures in the Cambridge Structural Database (CSD) are known to be polymorphic [Dunitz & Bernstein, 1995]; though it has been said that the number of known polymorphs is directly proportional to the time spent studying a given material [Dunitz & Bernstein, 1995].

A good example of a molecule with several polymorphs is 2-(2-methyl-3-chloroanilino)nicotinic acid (Fig. 1.4) which has four known polymorphic forms [Takasuka *et al.*, 1982]. Each polymorph is obtained through the use of a different solvent during crystal growth. These polymorphs crystallize in different space groups, have different unit cell dimensions (Table 1.1), different hydrogen bonding patterns, different crystal colors and different chemical properties. Basic unit cell diagrams for polymorphs I, III and IV are shown in Fig. 1.5.

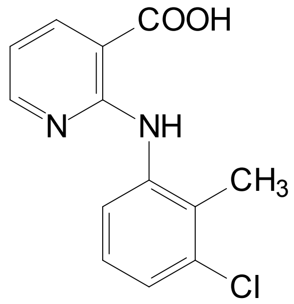


Figure 1.4: Molecular structure of 2-(2-methyl-3-chloroanilino)nicotinic acid

Table 1.1

Unit cell parameters and space groups for the various known polymorphs of 2-(2-methyl-3-chloroanilino)nicotinic acid

Polymorph	I	II	III	IV
Crystal System	Monoclinic	Orthorhombic	Triclinic	Triclinic
Space group	$P2_1/c$	$Pca2_1$	$P\bar{1}$	$P\bar{1}$
a/Å	7.625(1)	23.597(6)	13.810(1)	7.670(1)
b/Å	14.201(1)	4.4042(1)	3.858(1)	7.254(1)
c/Å	11.672(1)	12.127(3)	10.984(2)	10.882(1)
α/°	90	90	94.98(1)	100.66(1)
β/°	101.65(1)	90	94.42(1)	102.02(1)
γ/°	90	90	95.57(1)	86.97(1)
Crystal color	Colorless	Pale Yellow	Yellow	Yellow

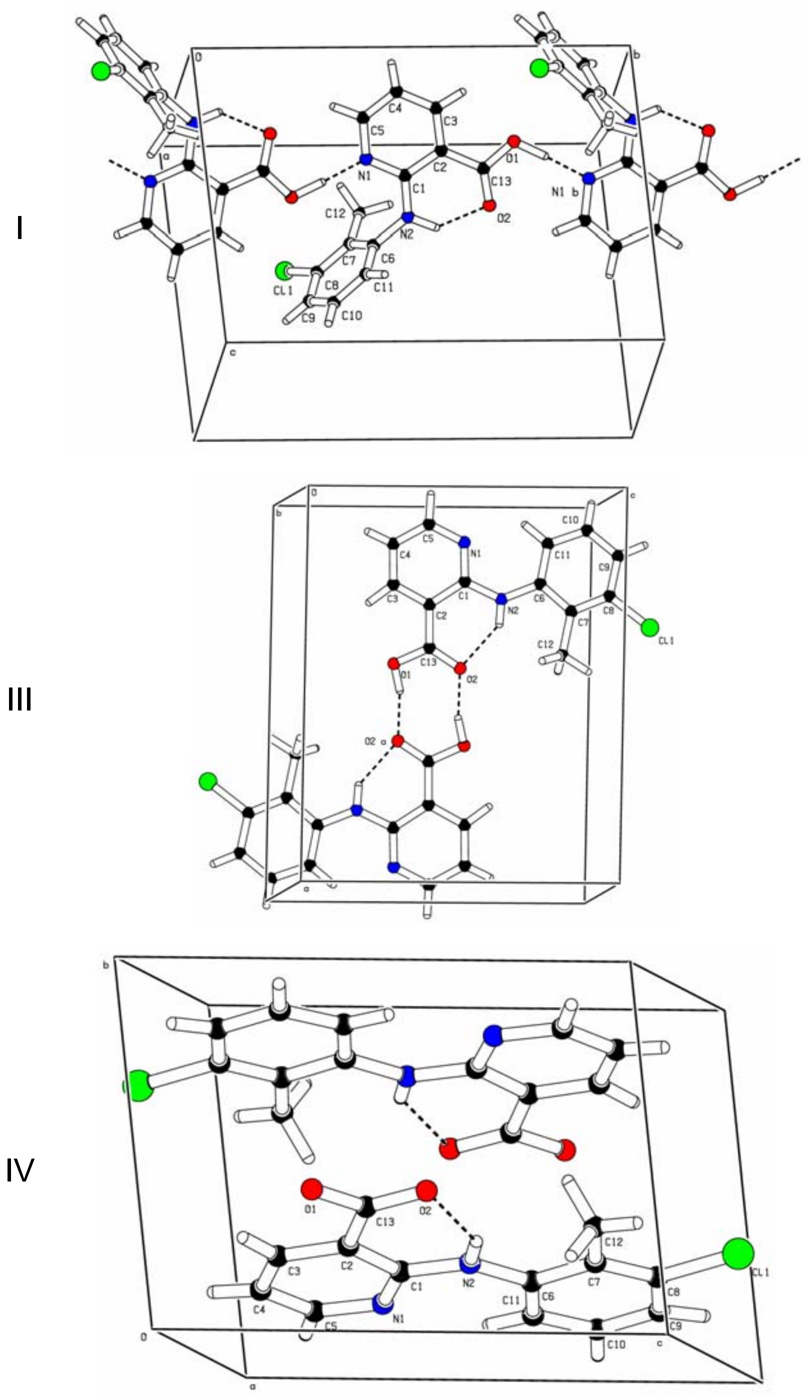


Figure 1.5: Unit cell diagrams for polymorphic forms I, III and IV of 2-(2-methyl-3-chloroanilino)nicotinic acid. For clarity some of the unit cell contents for form I have been omitted and emphasis has been placed on the hydrogen bond pattern instead. With the rotation around the C6-N2 bond, it is clearly visible that form I is the conformational polymorph of forms III and IV.

Several other compounds exhibit polymorphism depending on the growth conditions used, or undergo temperature dependent phase transitions from one polymorph to another, e.g. *p*-(trimethylammonio)benzenesulfonate [three known polymorphs whose existence is temperature dependent; Sarma & Dunitz, 1990] and the dimethyl ester of 2,5-dihydroxy-3,6-dichloroterephthalic acid [three polymorphs exhibiting different colors; Dunitz, 1991]. The last compound is also an example of concomitant polymorphism in that all three polymorphs are obtained under the same growth conditions in the same vessel. The phenomenon of concomitant polymorphism has been reviewed in detail with several examples given [Bernstein *et al.*, 1999].

Polymorphs of molecular crystals have much in common as shown by the results obtained from a CSD search done by Gavezzotti & Filippini (1995):

1. energy differences between crystal forms (polymorphs) are small (85% of the polymorphs researched were within 10% of each other);
2. density differences are within 5% of each other for 93% of the polymorphs studied;
3. lattice-vibrational entropies between polymorphs are very similar.

In addition, generalizations have been made about polymorphs:

- The polymorph with the higher density will tend to have the higher packing energy and the lower lattice vibrational entropy [Gavezzotti & Filippini, 1995; Dunitz, 1995]. This is now a commonly used rule of thumb, though there are some exceptions [see for example Thallapally *et al.*, 2004], and is based on the assumption that the stronger the interactions between the molecules, the tighter they will pack.
- The polymorph with the higher entropy will tend to become the thermodynamically more stable form as the temperature is raised [Dunitz & Bernstein, 1995].

Polymorphs are therefore very similar to each other in a number of ways. However, how they form has as yet not been conclusively determined since the crystallization process is currently not well understood. All that is known is that there are two stages to the crystallization process: the formation of a critical nucleus and its subsequent growth. The first stage is decisive since it can be associated with an activation energy and is therefore rate limiting. This allows supersaturated or supercooled solutions to exist (under special conditions) without crystallization taking place. In addition, it implies that when nucleation is rapid, many nuclei and crystals are formed. When the nucleation process is slow, a smaller number of nuclei are created leading to larger crystals being obtained [Dunitz & Bernstein, 1995].

It has been proposed that in crystallization experiments the appropriate nuclei for all the observed polymorphs are most probably present [Weissbuch *et al.*, 1995]. Indeed, some compounds have been found to yield three polymorphs from one solution [concomitant polymorphism; Dunitz, 1991 & 1995; Bernstein *et al.*, 1999].

In the crystallization process, each nucleus structure resembles that of the final crystal. This allows one to design inhibitors that would prevent the growth of unwanted crystals by binding to their nuclei. This process has the advantage of inhibiting thermodynamically favorable crystals in favor of kinetically favorable ones [Weissbuch *et al.*, 1995 & 2003] and is perhaps a way of selecting one polymorph out a set of various possible others.

In conclusion, there is general consensus that thermodynamic versus kinetic factors play a role in the crystallization process and formation of polymorphic forms. Knowledge about the crystallization process and the mechanisms involved are currently very limited.

1.3 Nature and Properties of Organic Crystals

1.3.1 Forces Keeping Organic Crystals Together

Molecular crystals can be thought of as being ordered supramolecules [Lehn, 1995], since their dimensions cover millions of molecules, and are held together in periodic arrangement by the same non-covalent bond interactions that are responsible for molecular recognition and complexation [Dunitz, 1995]. The fact that both strong intramolecular and relatively weak intermolecular forces affect the final crystal structure is unique to molecular crystals. Intramolecular forces determine the shape of the molecule and hence how close the molecules will get to each other affecting the packing density. Intermolecular forces on the other hand, if they are strong and directional, will modify the basic structure of the crystal by changing the orientations of the different molecules with respect to each other so that attractive intermolecular interactions are maximized while repulsive interactions are minimized. An understanding of the nature, strengths and dependence on molecular orientation and intermolecular separation of the different intermolecular forces is very important in order to understand the properties of molecular crystals. The short description of these forces given below is summarized from Wright (1987).

1.3.1.1 Interactions between Dipolar Molecules

The electric field produced by a dipole μ along its own direction at a distance r from its centre is $2\mu/r^3$. For two dipoles aligned head to tail at a distance r apart, the interaction energy U between them is given by:

$$U = -2\mu_1\mu_2/r^3 \quad (1)$$

However, in crystals the dipoles will not be necessarily be well aligned with each other. By considering the random orientation of the dipoles, defining their relative orientations using polar coordinates, and including attractive and repulsive interaction components, then Equation 2 may be obtained [derivation shown in Wright, 1987]:

$$U = -(\mu_1\mu/r^3)\{2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2\cos(\varphi_1 - \varphi_2)\} \quad (2)$$

From this equation it can be seen that the interaction energy between two dipoles in a crystal will be inversely proportional to r^3. This is quite different from solution where the force is inversely proportional to r^6 but usually equals zero due to the time averaged orientations of molecules in solution. Equation 2 has repulsive and attractive components so depending on the relative orientations of the dipoles this interaction can be attractive or repulsive.

1.3.1.2 Dipole-induced Dipole Interactions

The electric field of one dipole can induce a dipole on a second polarizable molecule. This interaction is dependent on the component μ_1 of the electric field of the dipole along the line joining it and the molecule centered at distance r. It is also dependent on the polarizability α_2 of the second molecule. The interaction between the dipole and induced dipole is given in Equation 3.

$$U = -4\alpha_2\mu_1^2/r^6 \quad (3)$$

In contrast to dipole-dipole interactions, this interaction is always attractive as only the magnitude of the interaction depends on the relative orientations of the two molecules. Since polar molecules can also be polarized, this interaction also contributes to the total interaction energy between the two dipolar molecules, i.e.

$$U_{\text{total}} = U_{\text{dipole-dipole}} + \Sigma U_{\text{dipole-induced dipole}} \quad (4)$$

1.3.1.3 Dispersion Forces or Induced Dipole-induced Dipole Interactions

Non-polar molecules can interact with each other even though they do not have permanent dipoles. A dipole in one molecule can be created from small instantaneous and transient changes in the positions of electrons (charge displacements = $r_1 = x_1y_1z_1$) in the molecule leading to a transient dipole. This transient dipole can then induce a dipole in the second molecule with the appropriate charge displacements. These two dipoles attract each other leading to a decrease in the potential energy of the system. The total potential energy is therefore made up from the energy needed to produce the dipoles (I) and the energy of interaction between the two resulting dipoles (II):

$$V = \underbrace{e^2r_1^2/2\alpha + e^2r_2^2/2\alpha}_{\mathrm{I}} + \underbrace{(e^2/r^3)(x_1x_2 + y_1y_2 - 2z_1z_2)}_{\mathrm{II}} \qquad (5)$$

With the exception of the different coordinate system, Term II is the same as Equation 2 and can be regarded as consisting of six oscillators. Equation 5 after some modification yields:

$$E_0 = 3hv_0 - (3/4)hv_0\alpha^2r^{-6} + \ldots\ldots. \qquad (6)$$

The term $3hv_0$ is the zero point energy of the two isolated species while the second term is the attractive dispersion energy. v_0 is the characteristic frequency of one of the species (how often it “flickers”). From Equation 6, it can be seen that the attraction between the molecules depends strongly on their polarizability. Since this interaction relies on close correlation between the two dipoles, the force between them will always be attractive or go to zero when the dipoles die out.

In practice, more complex charge displacements can occur between molecules leading to quadrupoles (as found in carbon dioxide) and higher multipoles. The true dispersion force experienced by a molecule is therefore better described by Equation 7:

$$U_{\text{dispersion}} = c_6 r^{-6} + c_8 r^{-8} + c_{10} r^{-10} + \dots\dots \qquad (7)$$

where c_6, c_8 etc. are constants.

Collectively, the above three interactions (dipole-dipole, dipole-induced dipole and dispersion forces) are referred to as van der Waals forces. The expressions above show that their magnitudes will be strongest between polar or very polarizable molecules. Important to note is that though the dispersion forces are not caused by permanent dipoles, they can have strengths comparable to what would be expected from dipole-dipole interactions. Also important to note about the three forces is that, since dipole-dipole interactions depend inversely on r^3 as opposed to the other interactions (which depend inversely on r^6), dipole-dipole forces are able to act over much further distances than the other two forces.

1.3.1.5 Repulsive forces

In addition to attractive forces, there are also repulsive forces in the crystal. The closest distance that molecules can get to each other in a crystal is determined by the point at which the repulsive forces exactly balance the attractive forces. Repulsive forces originate from two sources when the electron clouds of two molecules start interpenetrating significantly. The first arises from the Pauli Exclusion Principle in which electrons are not allowed to occupy regions of space where the orbitals of closed-shell species overlap [Atkins, 1990]. Secondly, since electrons are no longer allowed in these regions, they are not able to shield the nuclei they surround properly and as a result the columbic repulsion between nuclei on the two molecules increases. These repulsive forces are very difficult to calculate since they depend on the shapes and nature of the molecule of interest. Instead, empirical potentials are used and these tend to have the form ar^{-n} (n equal to 12 usually) or be^{-cr} with a, b, c and n being empirical constants. Since repulsion forces are inversely dependent on r^{12}, they are only important at very close range.

1.3.1.6 Atom-atom Potentials, Lattice Energy Calculations and Structure Prediction

In reality the above equations describing the interactions in crystals are very difficult to apply to real crystals. In addition, focusing on individual interactions is unrealistic. A more practical and quantitative approach is to sum the contributions of all the interactions of each atom in a molecule at some convenient origin relative to the atoms of the surrounding molecules. This calculation is not carried out very far since most of the intermolecular forces die off rapidly with increasing distance (because of the r^{-6} term). According to Wright (1987) a typical approach is to partition the interactions between atoms of types k and l at a distance r_{ij} into electrostatic, repulsive and van der Waals potential energies, giving an expression for the interaction energy $U^{kl}(r_{ij})$ of the form:

$$U^{kl}(r_{ij}) = (q_i q_j)/(D r_{ij}) + A^{kl}/r_{ij}^{12} - C^{kl}/r_{ij}^{6} \qquad (8)$$

Where q_i and q_j are the fractional charges on the atoms,
D is the effective dielectric constant,
A^{kl} is the repulsive coefficient,
and C^{kl} the attractive coefficient.

All these constants are empirically determined [see for example Williams & Hsu, 1985; Williams & Houpt, 1986]. This general method has been successfully used to estimate lattice energies, predict structures of molecular crystals, estimate the relative stability of proposed new structural modifications or defects and predict barriers to molecular motion in crystals. Examples of programs that are typically used in one or all of these roles is *ZIP-PROMET* [Gavezzotti, 1991], *MPA* [Williams, 1996], *DMAREL* [Beyer *et al.*, 2001] and *Polymorph Predictor* [Verwer & Leusen, 1998]. Quite a few other programs are available, and examples of their use in real world prediction of polymorphs can be found in Lommerse *et al.* (1999) and Motherwell *et al.* (2002).

In general the success rate of such programs is very low and the process of prediction very slow and arduous. Crystal structure prediction involves a process in which thousands of random cluster arrangements are generated for a given molecule. These arrangements are then energy minimized such that the lattice energy, as defined by Equation (8) or an equivalent equation, is at a minimum and ranked according to lattice energy. The real problem with structure prediction is that many of the potential structures have very similar lattice energies, with there being very little way of telling which are possible or 'real world' structures. In fact, it is often found that known 'real world' structures may not be ranked as the most stable structures. It has been shown that for acetic acid there are about 100 calculated structures within 5 kJ mol^{-1} of each other [Mooij *et al.*, 1998].

One source of the problem is that very high quality force-fields (good estimates of A and C in Equation 8 for a given atom type) are necessary but not available leading to the energy ranking technique not being as effective as one would like [Payne *et al.*, 1998]. To get round these problems, other sifting techniques such as ranking by crystal density and classification of the structures with the aid of graph sets [Cross *et al.*, 2003] are also used. In addition, crystal packing analysis and classification based on the probability of certain synthons[4] being present is also used [Sarma & Desiraju, 2002]. Alternatively, extra analysis of predicted crystal properties *via* computational techniques such as expected crystal morphology and mechanical properties have also been reported [Beyer *et*

---

[4] Structural building units such as carboxylic acid dimers being present as determined from similar molecules contained in the Cambridge Structural Database [CSD; Allen, 2002]

al., 2001]. One useful and successful application of crystal prediction is in solving the crystal structures of materials *via* their powder patterns. In this case calculated powder patterns of the predicted structures are compared with the measured powder pattern of the material until a match is found. The structure is then refined *via* Rietveld analysis [Rietveld, 1969] using the predicted structure as a starting point [Karfunkel *et al.*, 1996].

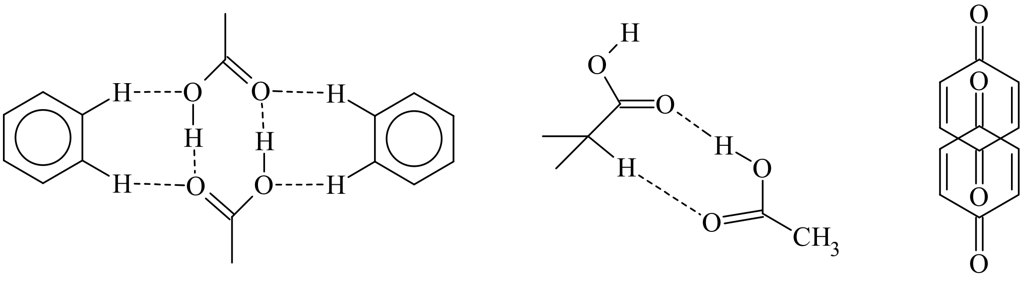
1.3.2 Examples of Important Intermolecular Interactions

Since molecular crystals are kept together by intermolecular interactions, it is of great interest to know what types of intermolecular interactions other than hydrogen bonding have been reported. In addition, knowledge and manipulation of these interactions will one day allow crystals to be predicted [a situation not yet achievable see Gavezzotti (1994) as well as Motherwell *et al*. (2002)].

Some interactions that have been reported are:

- Hydrogen bonding between carboxylic acids [Fig. 1.6a; Leiserowitz, 1976],
- C-H...O interactions (Fig. 1.6b) between benzene ring, alkyne, alkene or methyl group hydrogens and a carbonyl, carboxyl or -NO_2 oxygen [Desiraju, 1991 and 1996],
- π-π interactions between the polarizable benzene ring electrons in stacked structures [Sharma *et al.*,1993; Janiak, 2000; Gavezzotti, 1989],
- Cl...Cl interactions between two aromatic rings containing a chloro group [Ramamurthy & Venkatesan, 1987; Desiraju, 1987; Price *et al.*, 1994],
- carbonyl...carbonyl interactions [Allen *et al.*, 1998],
- interactions between carbon-bound halogens and oxygen or nitrogen atoms [Lommerse *et al.*, 1996; Kelly *et al.*, 2002; Garden *et al.*, 2002],

- carbonyl...aromatic ring interactions (Fig. 1.6c), where the carbonyl dipole induces a dipole in an aromatic ring above or below it in a crystal structure [Wright, 1987], and
- C-H...π interactions, between aromatic ring hydrogens and the electron cloud of another aromatic ring [Nishio, 2004; Bernstein, Etter & Leiserowitz, 1994; Janiak, 2000; Desiraju & Steiner, 1999].



a) b) c)

Figure 1.6: Some examples of reported weak interactions: a) the C-H...O interactions found in *p*-toluic acid [Bernstein *et al.*, 1994; Takwale & Paul, 1971], the C-H...O interaction found in the crystal structure of acetic acid [Weissbuch *et al.*, 1995] and the carbonyl - aromatic interaction found in benzoquinone [Wright, 1987].

Such interactions have been proposed in order to explain similarities between packing motifs (packing patterns) in structures of different compounds. For detailed reviews on the nature and energies of various hydrogen bonding and weak interactions that have been observed in crystal structures see Aakeröy & Seddon (1993), Desiraju (1995), Desiraju & Steiner (1999), Janiak (2000) and Steiner (2002). In addition, several systematic studies on interactions controlling crystal packing in hydrogen bonded molecular crystals are available, e.g., resonance-assisted hydrogen bonding in intermolecular chains of β-diketone enols [Gilli *et al.*, 1993; Bertolasi *et al.*, 1996]; RAHB and (-)CAHB (negative charge-assisted hydrogen bond) in squaric acid and squarate anion associations [Gilli *et al.*, 2001].

1.3.3 Favorable Symmetries Found in Crystals - Trends Followed by Molecules when Forming a Crystal

Unlike the packing of simple spheres (e.g. metals) or simple ionic substances, the packing of organic crystals is very complex. Whereas simple molecules rely mainly on maximizing packing density, organic molecules rely on a number of factors. These, such as irregular shape and varied arrangements, which can maximize intermolecular interactions and minimize electrostatic energy, make it very difficult to predict organic crystal structures. In this section the principal rules for packing in molecular crystals will be laid out, followed by symmetries that manipulate crystal packing so that they follow these rules. Some of these rules are already in use in current crystal structure prediction procedures.

1.3.3.1 Principles of Crystal Packing

Though the approach of predicting crystal structure involves generating thousands of random structures, the organization of molecules in crystals is not random. Also molecules pack in a very limited number of arrangements (usually only one) in crystals. These are consistently obtained no matter how many times the crystallization experiments are repeated. Crystal packing must therefore occur according to a set of rules. These are [adapted and summarized from Brock & Dunitz, 1994]:

- **Maximize density and minimize free volume.** This is the primary packing rule in all kinds of crystals and is referred to as Kitaigorodsky's principle of close packing [Kitaigorodsky, 1973]. It is especially important in polymorphic systems for crystals that are stable at $T = 0$ K where no energy is available to support more open structures. At higher temperatures, entropy (TS) plays a large role in allowing polymorphs with more molecular freedom to occur.
- **Satisfy hydrogen bond donors and acceptors and any other special kind of intermolecular interactions.** H-bonds are very strong in comparison with van der Waals forces. As a consequence their

presence is structure determining in molecular crystals. Also, in a structure, the strongest hydrogen bond donors always connect to the strongest hydrogen acceptors [Etter, 1990]. In addition to hydrogen bonds, it is also possible to have interactions between halogen atoms as electron acceptors and oxygen, nitrogen, sulfur, and selenium atoms as electron donors. Some of these can be as strong as hydrogen bonds and as directional as well, e.g. carbonyl-carbonyl interactions [Allen *et al.*, 1998].

- **Minimize electrostatic energy.** These types of interactions are more common in ionic crystals but are also found in molecular crystals - usually in organic salts and zwitterions. This means that like - like repulsive interactions must be minimized in favor of like - unlike attractive interactions. Dipoles in molecules as a whole are less important than local dipoles surrounding a bond.

1.3.3.2 Classification of Symmetries into Favorable and Unfavorable

The Cambridge Structural Database (hereafter, the CSD; Allen, 2002) is a database containing crystallographic data for molecular structures. It is made up of structures containing either organic or organometallic molecules that have been reported in literature. The database contains information from individual crystal analyses such as unit cell parameters, atom coordinates and crystal symmetry, from which molecular information such as bond lengths and angles can be derived. It has been used, amongst others, for studies of the frequencies of different space groups [Wilson, 1988 & 1990; Padmaja *et al.*, 1990; Brock & Dunitz, 1994], studies of typical bond lengths in molecules [Allen *et al.,* 1987], topochemical studies, studies of polymorphic forms of organic crystals [Gavezzotti & Filippini, 1995] and studies of weak interactions in crystals [Ramamurthy & Venkatesan, 1987; Allen *et al*., 1998].

Using the CSD, Brock & Dunitz (1994) have given a classification of the energetic and spatial attributes of different crystal symmetries, based on the frequencies (popularity) of different space groups in the database. Molecular crystal structures were studied with respect to what symmetry elements they contain and how these in one way or another followed the packing principles introduced above. Given below is a summary of their findings.

- **Inversion centers are favorable.** In the space groups $P2_1/c$ and $P\overline{1}$ (accounting for more than 50% of all molecular structures in the CSD), it is not uncommon to find unoccupied inversion centers implying that there is no energy penalty associated with this. Often centrosymmetric dimers are related to each other by a center of symmetry. These are often connected to each other by hydrogen bonding which is an energy lowering interaction. Inversion centers are also especially favorable for crystal packing since they diminish like-like interactions and are compatible with translation. They are unique in that they change the direction but not the orientation of intermolecular vectors.
- **Mirror planes are always occupied, usually by mirror-symmetric molecules.** Unoccupied mirror planes are especially unfavorable because they require like-like interactions between adjacent molecules. Also, if unoccupied, they produce a sheet of empty space in the crystal which has serious consequences in terms of packing density.
- **Groups with 3-, 4- and 6-fold rotation axes do not usually occur unless the axes are located within molecules of appropriate symmetry.** The reason for this is that it is difficult to fill the space around these rotation axes unless the molecules have the shape of the symmetry. For example 3-fold axes occur if the molecules occupying such axes are wedge shaped, i.e., have a 3-fold rotation symmetry themselves. This problem is especially acute for 4- and 6-fold axes. In addition, if they are unoccupied, they create an infinite rod of empty space with a diameter of 3-3.5 Å in the crystal, hence lowering the packing density of the structure. To compensate for this, areas where

these occur are usually filled with disordered solvent leading to the formation of a solvate. See for example the *β*-polymorph of *o*-ethoxy-*trans*-cinnamic acid (Chapter 3 and 5).

- **Twofold axes are sometimes occupied and sometimes not.** There thus seems to be no energy gain or loss associated with the use of this symmetry, though as mentioned for rotation axes above, if they are unoccupied they can lead to lower packing densities.

2_1 screw axes are more favorable than glide planes, which are comparable to pure translations. Translations are, however, still very favorable otherwise crystals would not exist. Translations tend to occur together with other symmetry elements.

These results essentially reinforce a similar result reported by Wilson (1988). Here it is shown that glide planes and screw axes are energetically favorable while mirror planes and rotation axes are energetically unfavorable. If mirror planes and rotation axes do occur, it is because their inhibiting effect is mitigated by the simultaneous presence of glide planes or screw axes or both. As a consequence, the ten most common space groups for organic compounds are $P2_1/c$, $P\bar{1}$, $P2_12_12_1$, $P2_1$, $C2/c$, $Pbca$, $Pnma$, $Pna2_1$, $Pbcn$ and $P1$. As a whole, these account for more than 75% of the structures in the CSD. The knowledge of this fact is exploited in crystal structure prediction to minimize calculation time by focusing on more probable space groups [Verwer and Leusen, 1998; Lommerse *et al.*, 2000].

Though not mentioned in detail here, the final crystal form obtained is strongly dependent of the crystal growth conditions used. In many papers there is mention of a thermodynamic or kinetic polymorph. These are strongly dependent on the presence of the appropriate crystal nuclei, formed by the molecule of interest in solution, which upon further aggregation lead to the observed crystal form. In the end, the final crystal form obtained may not be the most thermodynamically stable, as the crystal nuclei leading to its growth and existence may not be kinetically accessible in solution. Instead, the crystal form that does exist is derived from more abundant and easily formed nuclei. The final crystal form obtained may therefore not be the most stable for a given material but rather a kinetic form.

Nucleation has been reviewed in some detail [Weissbuch *et al.*, 2003]. In the end one should view nucleation as a supramolecular process, in which molecular recognition and weak interactions play a role, leading to the formation of stable clusters. These eventually grow in size (though they can also dissociate back into solution), potentially rearranging slightly, eventually reaching a critical size and arrangement of molecules that we recognize as the final crystal form. Nucleation is not unique to solution as the formation of new crystal phases in a phase transformation process is also nucleation dependent [see for example Oxtoby, 1998]. The final crystal form obtained is therefore not just dependent on energetically favorable symmetries being present (these being biased by shape and electronic properties of the molecule), but also on the crystal growth pathway taken to achieve it. In fact, the importance of nucleation in understanding the formation of crystals cannot be over emphasized. These issues act to further complicate the process of crystal structure prediction and are also important in solid-state reactions.

1.3.4 Crystal Habit and the Effects of the Crystallization Solvent

Crystal habit has not been focused on in this thesis but is important in the pharmaceutical industry as this can influence processing factors such as the uniformity of tablet weight, hinder the tabletting process and affect dissolution rates [Ristic *et al.,* 2001]. One crystal habit may even be more useful in a filtering process than another. Any extra steps needed to overcome these problems add to the final cost of the product. It is well known that crystallization solvent has a strong influence on the habit (shape) of crystals. This is due to the solvent interactions on the growing crystal surface. One explanation that is given to explain this phenomenon is that the solvent preferentially binds to particular faces of a growing crystal [Weissbuch *et al.*, 1995]. As these crystal faces now grow at a more depressed rate in comparison to non-inhibited faces, their influence on the final crystal shape will become more dominant with time. The fast growing crystal faces become less important (smaller), and eventually disappear since they are unable to grow further than the smaller faces will allow. The final crystal habit is therefore dominated by the slow growing faces.

1.3.5 Characterization of Hydrogen Bonds in Structures and Graph Set Notation.

Hydrogen bonds are the strongest and most directional intermolecular interaction in molecular crystals. It would be reasonable to expect that the more hydrogen bond donors and acceptors a molecule has the greater the variety of structures that it can form, since they might be expected to combine in a multitude of different ways [Bernstein, 2002]. However, it has been pointed out by Etter [1990 & 1991] that some donor-acceptor combinations are more favorable than others, with strong hydrogen donors preferentially hydrogen bonding with strong hydrogen acceptors. Hence, the preference for some hydrogen bond patterns to form will result in hydrogen bond patterns being retained in the various polymorphs of a specific compound rather than the creation of a variety of hydrogen bond patterns. The understanding and characterization of hydrogen bonds is therefore very important in order to understand their effect on crystal structure and graph set notation has been introduced in order to simplify this process [Etter, 1985, 1990 & 1991; Etter *et al.*, 1990a,b].

A useful feature of the graph set approach to the analysis of hydrogen bond patterns is that the most complicated networks can be reduced to four basic patterns [Bernstein *et al.*, 1995], each specified by a designator: chains (**C**), rings (**R**), intramolecular hydrogen bonded patterns (**S**), and other finite patterns (**D**).

In characterizing hydrogen bond patterns, graph set designators are given as $\mathbf{G}_{\mathbf{b}}^{\mathbf{a}}\mathbf{(n)}$**,** where **G** is one of the four possible designators (**C**, **S**, **D** and **R**), **a** gives the number of hydrogen bond acceptors and **b** gives the number of hydrogen bond donors in the pattern. In addition, the number of atoms in the pattern **n** is called the degree of the pattern and is given in parenthesis. Examples of graph set descriptors and their application to real examples is shown as Fig. 1.7.

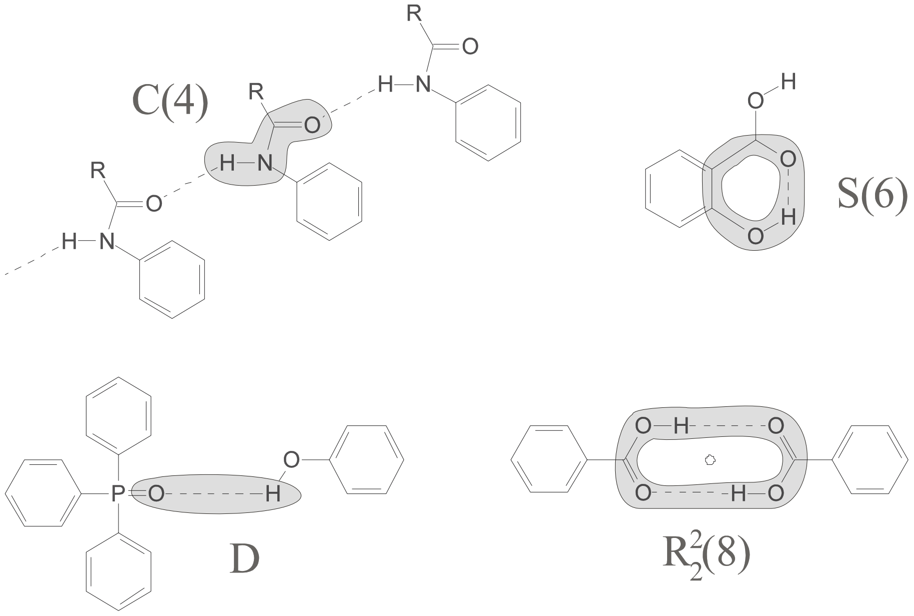
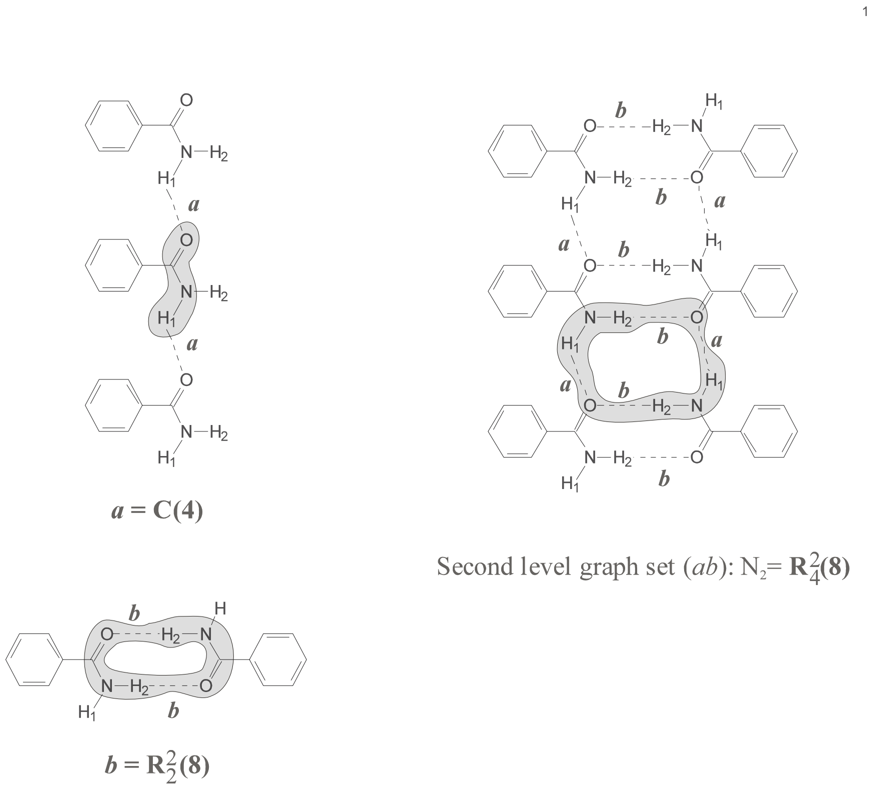


Figure 1.7: Some examples of the four basic descriptors used to define hydrogen bond patterns [adapted from Bernstein *et al.*, 1995]. The **C(4)** motif indicates a hydrogen bond pattern generated by a repeat unit of four atoms forming a chain of molecules. The **S(6)** motif indicates an intramolecular hydrogen bond involving six atoms. The **D** motif indicates a discrete hydrogen bond while the $\mathbf{R}_{\mathbf{2}}^{\mathbf{2}}\mathbf{(8)}$ motif indicates a pattern containing a total of eight atoms, two of them donors and two acceptors.

In order to understand complex hydrogen bond networks the network is broken down into its component patterns and given as a list of motifs. This list of component motifs is referred to as the unitary or first level graph set and is noted as $\mathbf{N_1}$. A pattern composed of only one type of hydrogen bond is referred to as a motif [Etter *et al.* 1990a,b] and is the basic unit of the unitary graph set. These unitary graph sets can then be combined to give higher level graph sets. A network formed by two different hydrogen bonds is referred to as a binary level graph set (noted as $\mathbf{N_2}$) while a network composed of three different hydrogen bonds is referred to as a tertiary level graph set (noted as $\mathbf{N_3}$), i.e. the more component hydrogen bonds in a specific pattern the higher the level of the graph set (Fig. 1.8).



a = $\mathbf{C(4)}$

Second level graph set (ab): N_2= $\mathbf{R^2_4(8)}$

b = $\mathbf{R^2_2(8)}$

First level graph set: N_1= $\mathbf{C(4)R^2_2(8)}$

Figure 1.8: Example of the use of graph set descriptors to define motifs and second level graph sets for schematic representations of hydrogen bond patterns in the crystal structure of benzamide [adapted from Bernstein *et al.*, 1995].

Though it may seem that graph sets are simply a way of describing a set of hydrogen bonds in a structure they are also a very useful method for systematically comparing crystal structures as they allow differences and similarities in structures to be highlighted. It is not unusual for structures with different hydrogen patterns at the unitary level graph set to be found to be equivalent once higher level graph sets have been examined [see Bernstein *et al.* (1995) for examples]. In such a way the characteristic hydrogen bond patterns can be discerned for a set of structures. In addition, apparently identical hydrogen patterns can be shown to have some differences through this method (Fig. 1.9).

While it is possible and useful to assign graph sets manually this method is often fraught with inconsistencies when very complex hydrogen networks are examined. In order to solve this problem the CCDC[5] now provides a software package (RPLUTO), which as part of the CSD allows for the automatic identification and visualization of complex networks.

1.4 Frontier Molecular Orbital (FMO) Theory and the Prediction of Photochemical Dimerization Reaction Products[6]

Molecules in solution are free to move wherever they can. Therefore, many molecular orientations are possible during a collision, which upon forming a transition state, can lead to a product. This also means that more than one product is possible for a given reaction (Scheme 1.3). However, in reality, for photochemical reactions in solution the situation is such that the HH (head-to-head) product is favored. This is due to favorable interactions between frontier molecular orbitals of the reactants causing them to prealign in the transition state leading to the HH product.

---

[5] Cambridge Crystallographic Database Centre, 12 Union Rd, Cambridge, CB2 1EZ, UK. http://www.ccdc.cam.ac.uk

[6] Adapted from Coxon & Halton ,1987 and Fleming, 1976.

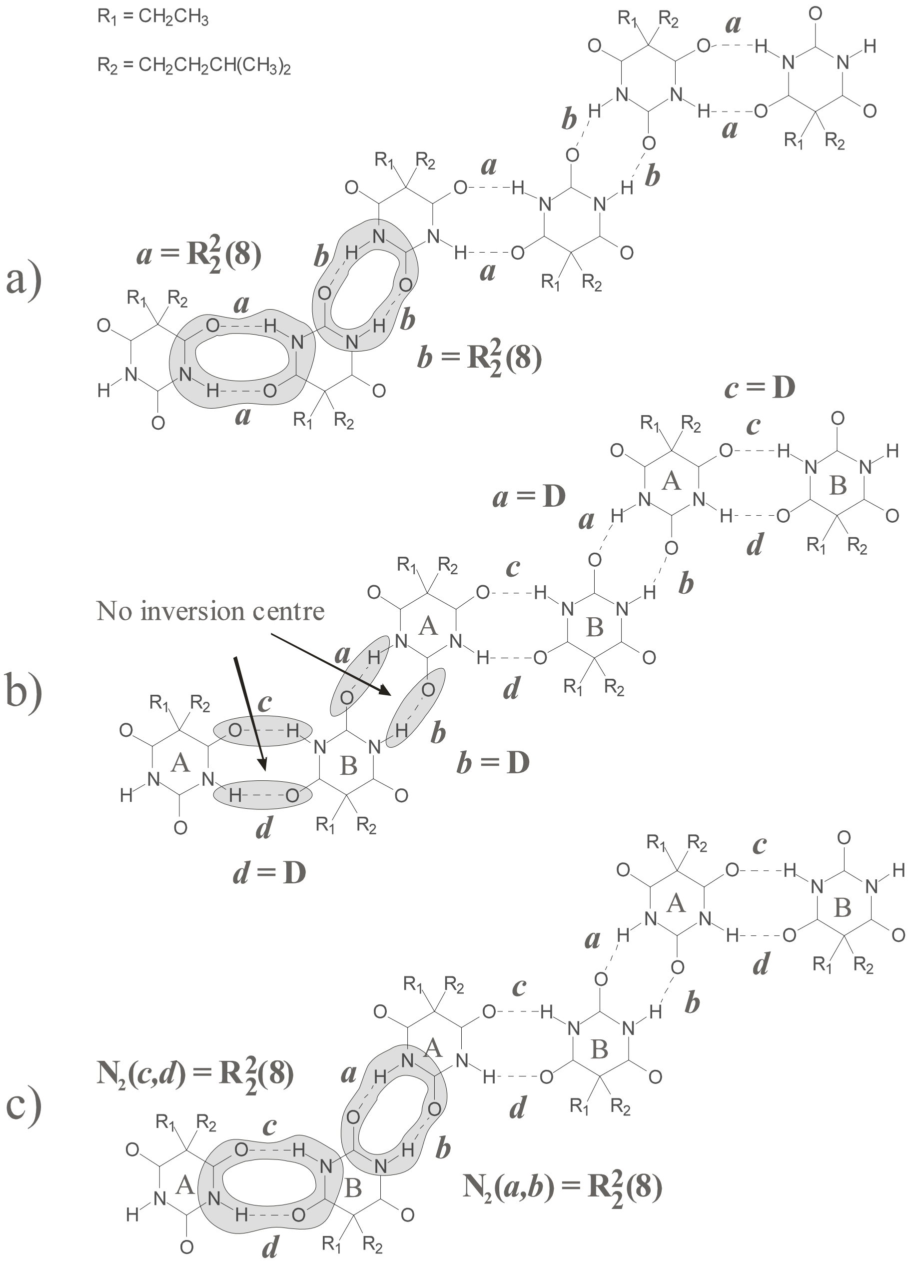
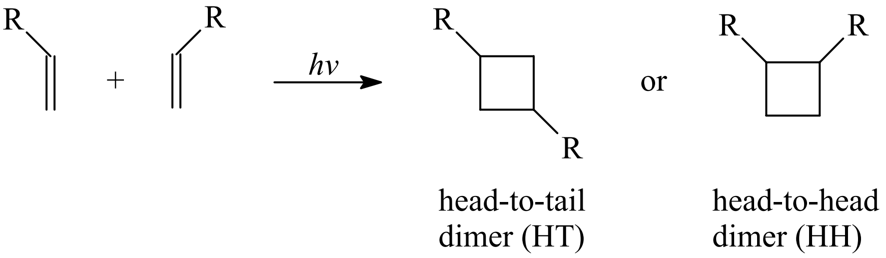


Figure 1.9: Schematic representation of hydrogen bond patterns in two polymorphs of amobarbital illustrating how graph set notation can be used to illustrate similarities and differences between crystal structures; a) Form I, first-level motifs; b) Form II, first-level motifs; A and B designate two different molecules in the asymmetric unit. The arrows indicate the loss of a center of inversion which means that hydrogen bonds *a* and *b*, and *c* and *d* are no longer equivalent. c) The characteristic hydrogen bond motif of Form I can be found in Form II at the binary graph set level [adapted from Bernstein *et al.*, 1995].



Scheme 1.3: The two geometrically different products possible from a photodimerization reaction (stereochemistry around the R-groups is ignored).

In general Frontier Molecular Orbital (FMO) theory is used to explain the product obtained by predicting what the transition state will look like. This theory relies on the application of the principle of conservation of orbital symmetry, first stated by Hoffmann and Woodward [1965 & 1968].

The cycloaddition of two alkene molecules to form cyclobutane (Scheme 1.3) is a well-known reaction. The reverse process is exothermic under thermal conditions releasing the strain energy of the four-membered ring. The energy required to form the strained cyclobutane ring is provided by the absorbed radiation, with the stability of the product resulting from the absence of an absorbing chromophore in the product. This is the driving force for the reaction since the product does not absorb light it also does not undergo carbon-carbon bond rupture under the conditions from which it was formed.

In order for a photochemical reaction to occur, an electron has to be excited from a lower energy state to a higher energy state. It is possible to do this for any kind of orbital but the process is easiest (and most practical - in terms of the energy needed) for π orbitals since they are low in energy relative to π^* orbitals. The excitation process for an alkene group is illustrated in Fig. 1.10, where π and π^* are the bonding and antibonding orbitals for the C=C bond, respectively.

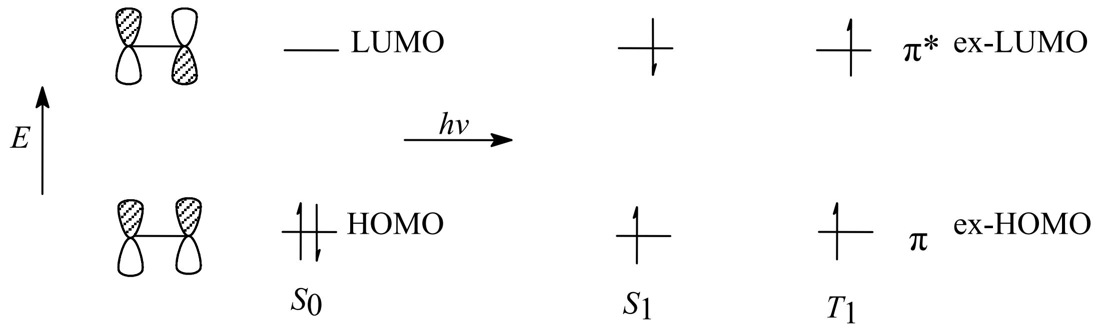


Figure 1.10: The π-π* excitation of ethene.

In the excitation process, an electron is excited from the π-bonding oribital to the π*-antibonding orbital resulting in two possible electron arrangements for the excited state. The ground state (S_0) leads to an arrangement with the electron spins paired, called the singlet state (S_1) or to an arrangement with the electron spins parallel called the triplet state (T_1). In general the triplet state is lower in energy than the singlet state and has a longer lifetime. Ethene, however, is an exception with the singlet state being lower in energy. As a result of the excitation process the LUMO (lowest unoccupied molecular orbital) becomes the HOMO (highest occupied molecular orbital) also designated as the ex-LUMO in the excited species.

In a bimolecular photochemical reaction, the HOMO and LUMO of one of the species in the ground state interacts with the ex-HOMO and ex-LUMO, respectively, of the excited species (Fig. 1.11).

This results in two energetically profitable frontier orbital interactions:

- the interaction between the singly occupied ex-LUMO orbital of the excited molecule with the LUMO of the molecule in the ground state, and
- the interaction of the singly occupied ex-HOMO orbital of the excited molecule and the HOMO of the molecule, which is in its ground state.

Both interactions are likely to be strong, because the interacting orbitals are very close in energy.

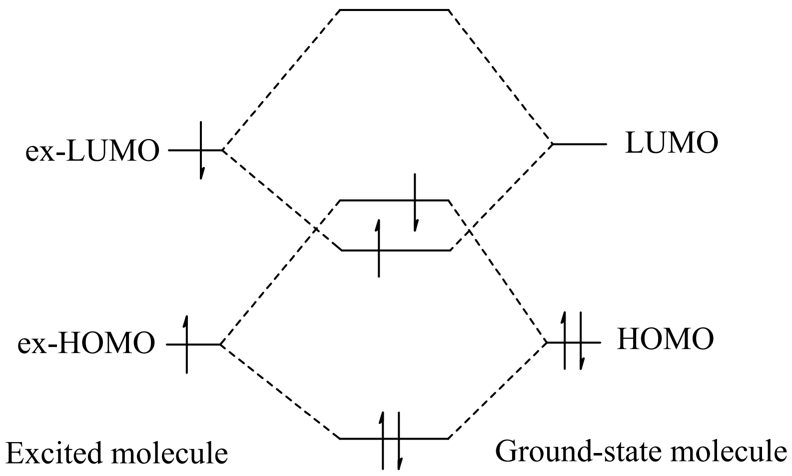


Figure 1.11: Frontier orbital interactions between the ground state and photochemically excited molecules.

In photochemical dimerization reactions, triplet-state reactions are more common than singlet-state reactions.

Another way of representing this interaction is shown in Fig. 1.12. The circles represent the π orbitals in a similar way to those in Fig. 1.10 except that the view is now from above. The relative size of the circle represents the contribution of that atomic orbital to the molecular orbital with the example in Fig. 1.12 being an alkene with an electron donating substituent. The relative sizes of the circles are dependent on the nature of the substituent, with the shading indicating lobes of opposite sign.

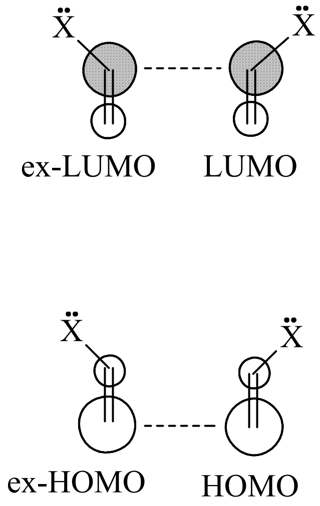


Figure 1.12: Regioselectivity in the photodimerization of alkenes.

As a rule when overlapping two lobes, the sign of the lobes must match (symmetry consideration) and of secondary importance the size of the orbitals should also match. Using these rules, it is clear from Fig. 1.12 that head to head dimers are favored for photochemical dimerization reactions.

In addition for singlet state type reactions more predictions can be made and these are that a mirror (endo-HH product) should be favored. This is because secondary interactions between other parts of the molecules will also be favorable (Fig. 1.13).

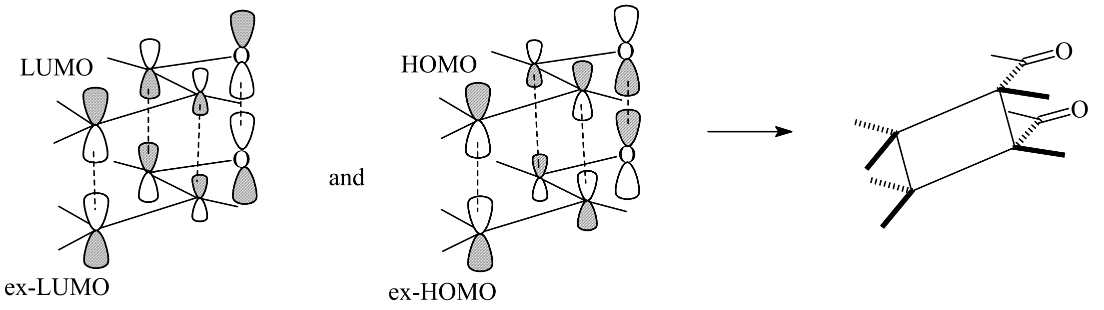
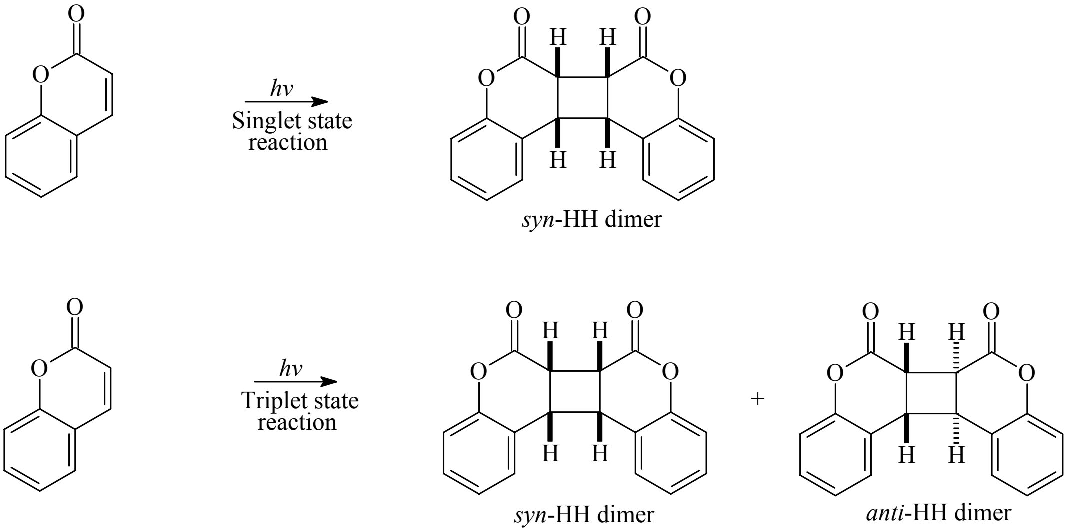


Figure 1.13: Secondary interactions (dotted lines) in photodimerization reactions stabilizing the endo transition state, which will eventually lead to an endo-HH product [Fleming, 1976].

Most photochemical reactions are of the triplet state type. This means that though HH products are favored, the formation of an endo-HH product will depend on whether a singlet or triplet state reaction is taking place. This is especially apparent in coumarin where if the reaction occurs *via* singlet state excitation, the endo-HH product is obtained. But, if the photodimerization reaction occurs via triplet state both the endo- and exo-HH products are obtained (Scheme 1.3).

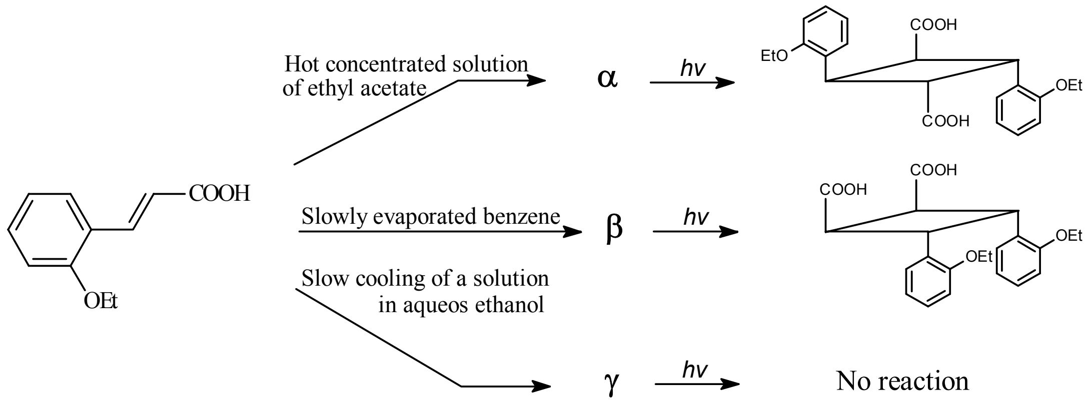


Scheme 1.3: Comparison of photochemical products obtained via singlet state or triplet state reaction in coumarin. The presence of secondary interactions ensures that only the *syn*-HH (or endo-HH) dimer is obtained for the singlet state reaction [Hoffman *et al.*, 1971].

The text above has shown that the stereo- and regioselectivity of a reaction in solution or gas is dependent on how the FMO interactions influence the geometry of the transition state, formed by the reactant molecules in a photodimerization reaction. This then leads to a few selected products, in spite of many other possible collision geometries and hence possible products in solution. In contrast, very little motion is possible in the solid-state, so stereo- and regioselectivity in solid-state photodimerizations is determined by the alignment of the monomers in the crystal lattice. The driving force for the reaction is the same as in the liquid state namely, that the loss of an absorbing chromophore in going from the reactant to the product ensures that the product is more stable than the reactant under irradiation conditions. Therefore, the stereo- and regioselectivity of photodimerization reactions in the solid-state does not depend on FMO interactions, but depends instead on lattice control; a greater variety of products are possible in the solid-state provided crystals containing the required symmetry and acceptable double bond distances are available.

1.5 Solid Photochemistry of *ortho*-Ethoxy-*trans*-cinnamic acid

ortho-Ethoxy-*trans*-cinnamic acid (hereafter OETCA) has been known to crystallize as three polymorphs for a very long time [Cohen & Schmidt, 1964; Cohen, Schmidt & Sonntag, 1964; Schmidt, 1964] but until recently had not been fully characterized [Fernandes *et al.*, 2001; Gopalan & Kulkarni, 2001]. These polymorphs, labeled as *α*, *β* and *γ*, were classified according to the products that they yielded upon exposure to UV light. As in the case of cinnamic acid, the *α*-phase of OETCA leads to the centrosymmetric product, 2,2'-diethoxy-*α*-truxillic acid, while the *β*-phase leads to the mirror product, 2,2'-diethoxy-*β*-truxinic acid. The *γ*-crystal phase of OETCA is however light stable (Scheme 1.4).



Scheme 1.4: The photodimerization of the various polymorphs of *o*-ethoxy-*trans*-cinnamic acid [adapted from Cohen & Green, 1973].

A schematic representation of the arrangements of cinnamic acids in the various forms of OETCA is shown in Fig. 1.14. This is the basis behind Schmidt's explanation, which follows, for the different photochemical behavior of each OETCA phase [Cohen & Green, 1973]. The molecules of OETCA form planar hydrogen bonded pairs across inversion centers in the crystal. As a consequence all three structures are layered with the OETCA acid pairs stacked parallel to each other. The difference between them is the angle that the stack axis makes with the normals to the molecular planes or layers, which results in the reacting double bonds being separated differently in the different crystals.

In Fig. 1.14 the stacking axis is shown as lines through the centres of symmetry of the hydrogen bonded dimers. In the *β*-type structure, the molecules are highly overlapped and are related by a short lattice repeat distance of 3.8-4.2 Å which is also the distance between the reacting double bonds. The reaction is therefore favored and a product with mirror symmetry obtained. In the *γ*-type crystal, the angle between the stack axis and the layer normal is slightly larger with the result being that the equivalent double bonds in two molecules across the layers is slightly offset leading to a separation distance of 4.8-5.2 Å and hence not allowing the reaction to occur. In the *α*-type structure, the angle between the stack axis and the layer normal is so large that the equivalent double bonds in two molecules across the layers are further than 5.5 Å apart, hence preventing the reaction from occurring between these bonds. However, this offset brings the centrosymmetrically related double bond of the adjacent layer to reacting distance, about 4 Å, allowing the centrosymmetric product to be obtained.

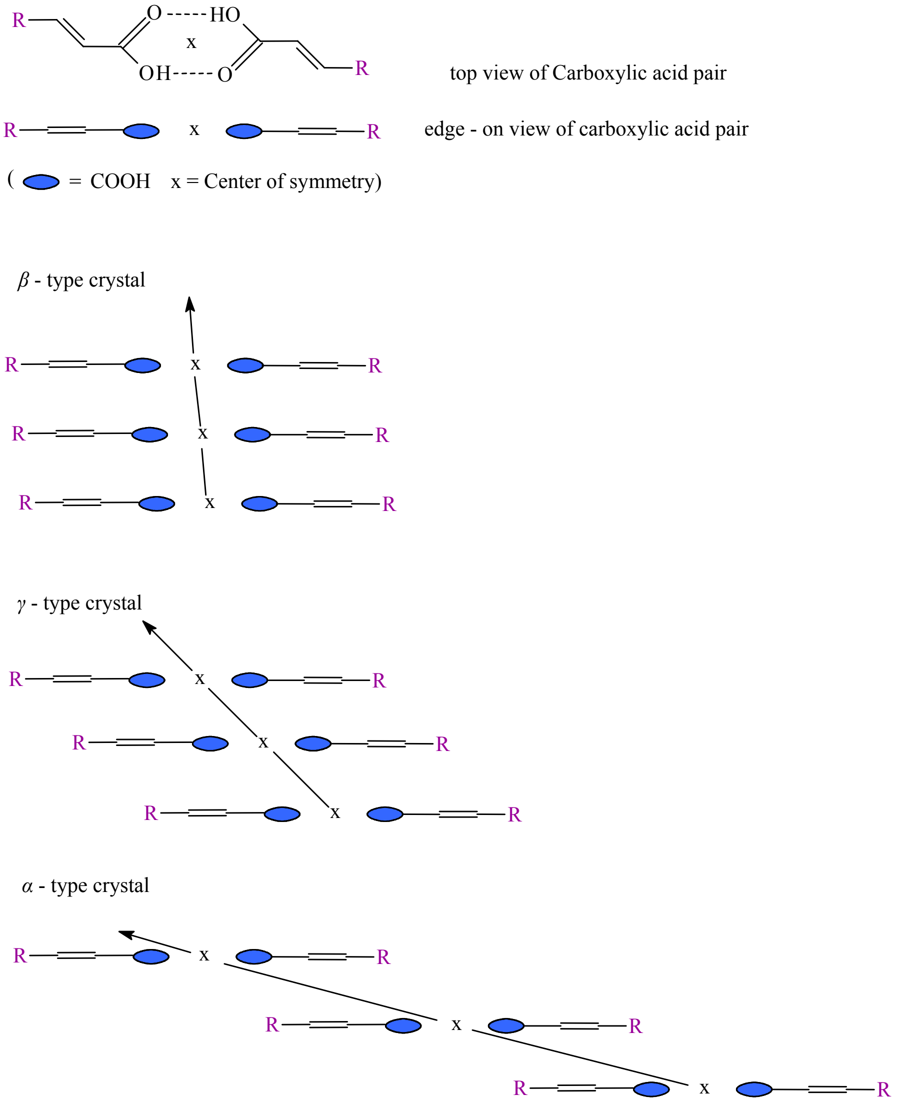


Figure 1.14: Plane separations in the different crystal forms of OETCA [adapted from Cohen & Green, 1973].

The above explanation of the photochemistry of OETCA gives the impression that the material was studied in detail and that little more can be said about the photochemistry of OETCA. However, although Schmidt and his coworkers came to these conclusions they did not obtain complete structures of the three polymorphs of OETCA. The only structural details that were reported were the unit cell parameters for each phase as well as the product obtained *via* photodimerization (Fig. 1.2). Nonetheless, the material has been cited in many textbooks as one of the classic examples of a material whose solid-state reactions follow the topochemical principle [Bernstein, 2002; Rao & Gopalakrishnan, 1997; West, 1984; Wright, 1987]. It is most likely that Schmidt's interpretations were based on structures of the other cinnamic acids studied and the passage of time from 1964 until now has also shown this interpretation to be essentially correct but not complete for OETCA.

The photodimerization of *o*-ethoxy-***cis***-cinnamic acid differs drastically from that of *o*-ethoxy-***trans***-cinnamic acid (OETCA) and illustrates an apparent lack of lattice control in the solid-state reaction (Fig. 1.15).

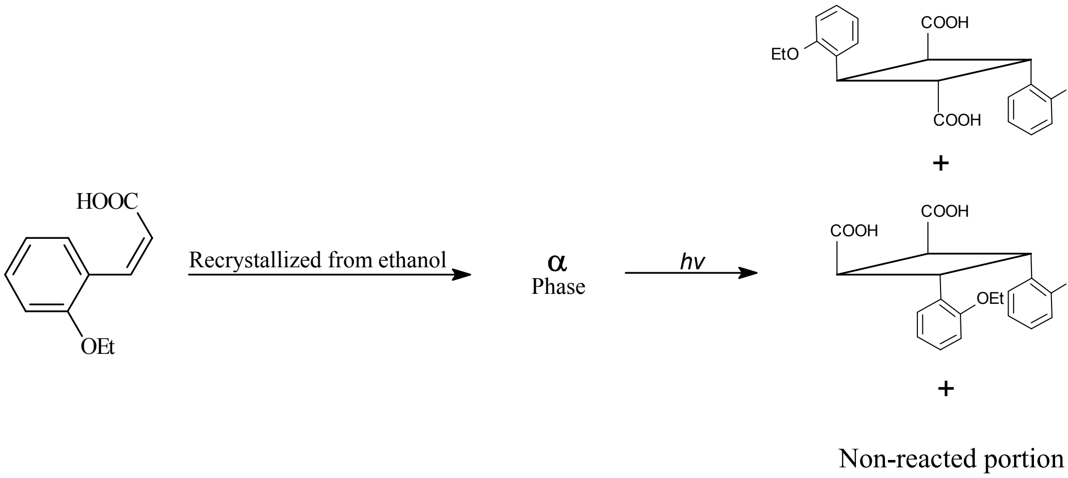


Figure 1.15: The solid-state photodimerization reaction of *o*-ethoxy-*cis*-cinnamic acid.

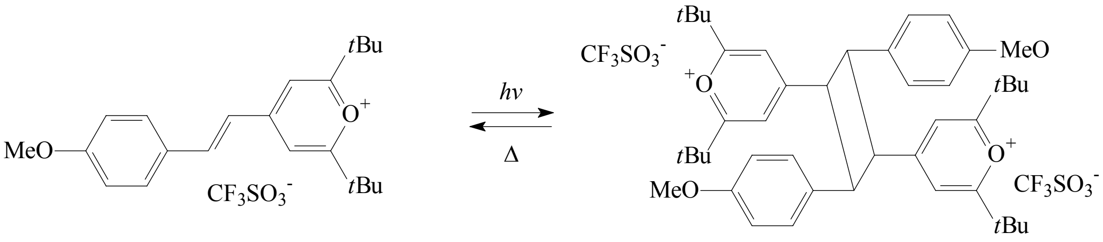
When exposed to UV irradiation *o*-ethoxy-***cis***-cinnamic first undergoes a *cis*-to-*trans* isomerization [Bregman *et al.*, 1964]. This process is usually reversible, as shown by the same isomerization in solution, but in the solid-state isomerization to the *trans* form is favored due to the formation of photodimer products, i.e. photodimerization of the *trans* isomer drives the *cis*-to-*trans* isomerization. The isomerization process also disrupts the crystal lattice leading to the production of a mixture of *α*-trullic and *β*-truxinic products. Some starting material is also obtained even after long exposure times. These results indicate that the crystal undergoes drastic changes during the *cis*-to-*trans* isomerization process, which upon phase rebuilding leads to the production of *α*-, *β*- and *γ*-type phases [Bregman *et al.*, 1964]. Once these three phases have been built up, lattice control in the photodimerization process is regained. The presence of the *γ*-polymorph was confirmed *via* powder diffraction, while the presence of the *α*- and *β*-polymorphs was inferred from the presence of their reaction products. The final product distribution (after 44 days of irradiation) was reported as 16% centrosymmetric (or *α*) dimer, 13% mirror (or *β*) dimer, 46% of *trans*-isomer (from the *γ*-polymorph), and 21% of recovered *cis*-monomer [Bregman *et al.*, 1964].

Bregman *et al.* (1964) also proposed that the *cis*-to-*trans* isomerization process occurs under lattice control, through interactions between C=C bonds in neighboring molecules which are in close contact (4.0-4.4 Å). This was later refuted on the basis of a crystal structure reported by Bryan & Hartley (1982). However, the work presented by Bregman *et al.* (1964) is rather convincing.

1.6 Latest Strategies in Studying Photodimerization Reactions

Since molecular movement is restricted in the solid state, it is the ideal environment in which to study chemical reactions. In particular, single-crystal-to-single-crystal (SCSC) reaction studies in which the reactant crystal reacts to form an intact product crystal are of great use in the study of solid-state reactions [Cohen, 1987]. This allows X-ray crystal structures at various reaction stages to be obtained. Information on the reactant's driving force, atomic movement, and direct information on the interaction between reactant molecules and interaction between product and reactant molecules can then be obtained.

In some compounds the reverse reaction from product back to reactant may also occur, e.g., 2,6-di-t-butyl-4-(2-(p-methoxyphenyl)ethenyl)pyrylium trifluoromethanesulfonate [Novak *et al.*, 1993; Scheme 1.6]. In this case dimerization takes place using UV radiation (λ > 570 nm) while the reverse reaction occurs if the product crystal is heated at temperatures above 100 °C. The forward and reverse reactions take place in a SCSC manner without crystal degradation - even allowing holograms to be stored using laser light which can later be erased thermally [Novak *et al.*, 1993].



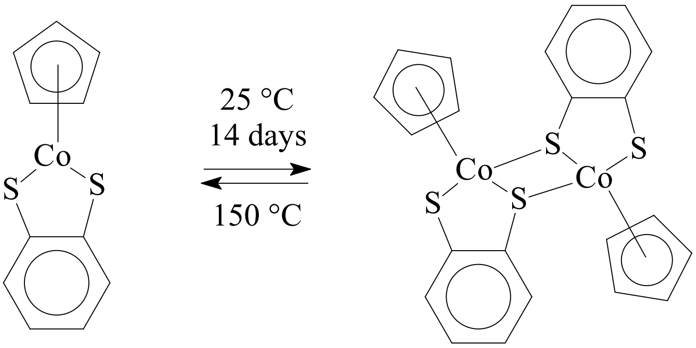
Scheme 1.6: Reversible [2+2] photodimerization in a crystal of 2,6-di-t-butyl-4-(2-(p-methoxyphenyl)ethenyl)pyrylium trifluoromethanesulfonate.

Compounds that undergo SCSC reactions are however rare and are not regarded as typical for solid-state reactions [Kaupp, 2003]. This is because most solid-state reactions take place with large amounts of stress being generated within the crystal as the reaction product fills the space originally filled by the reactant molecules. With the exception of a few compounds, the reaction usually leads to the crystal eventually shattering making a SCSC study impossible. A way of minimizing this problem is to react a crystal very slowly and uniformly allowing the crystal to slowly adjust to changes within it. This approach was first utilized by Enkelmann *et al.* [1993; see also Novak *et al.*, 1993] to study the photodimerization of the *α*-polymorph of unsubstituted *trans*-cinnamic acid. This was done by exposing crystals of the *α*-polymorph to weakly absorbed levels of UV radiation (the wavelength of the UV radiation corresponding to the chromophores absorption tail). As a result, most of the radiation goes through the crystal, allowing dimerization to occur very slowly and uniformly throughout the crystal and hence allowing the crystal to adapt to the slow changes occurring within it, maintaining crystal integrity through out the photodimerization process. Single crystal structures of the *α*-polymorph cinnamic acid crystal at 0, 28, 40, 67 and 100% conversion were obtained by Enkelmann in this way.

A related approach to maintaining crystal integrity is to react a crystal very slowly over a long period of time. An example of the use of this technique was carried out by Iwamoto & Kashino (1993), in which an α-(acetylamino)cinnamic acid dihydrate crystal was photodimerized in room daylight for three months. A structure solution for this crystal was obtained at 12% conversion. By comparing the structures of monomer and partly reacted crystal, information was obtained on volume changes during reaction, modes of hydrogen bonding between monomer-monomer, dimer-dimer and monomer-dimer (allowing some questions about the miscibility of the monomer phase in the dimer phase to be answered), and the atomic movements accompanying the photodimerization. Such long reaction times are however impractical, and often do not produce high reaction yields, so most forced SCSC tranformations tend to be carried out using Enkelmann's tail-end radiation method [Enkelmann *at al.*, 1993].

It should be said that some doubt as to the authenticity of the results that Enkelmann obtained with *α*-cinnamic acid has been expressed [Kaupp & Haak, 1998; Kaupp, 2002; Kaupp, 2003]. Kaupp found that irradiation of crystals of *α*-cinnamic acid using tail-end radiation with $\lambda > 350$ nm [Enkelmann used $\lambda > 360$ nm; Novak *et al.*, 1993], $\lambda > 405$ nm, or exposure to filtered daylight for half a year would lead to crystal disintegration at conversion levels of only 10-30%. However, Hosomi *et al.* (1998) seem to have been able to reproduce the result.

Though not the focus in this thesis, SCSC reactions are not limited to photochemical reactions but are in fact more common to thermally driven reactions. One very common group of solid-state thermal reactions are isomerizations, e.g. Bogadi *et al.* (2002). These are of interest as they share many features with phase changes and conformational polymorphism (a major focus of this thesis) especially if the transformation happens in an SCSC manner. An interesting example of a temperature dependent reversible SCSC reaction is shown in Scheme 1.7.



Scheme 1.7: Temperature dependent reversible chemical reaction in a single-crystal of cyclopentadienyl(*o*-di-thiobenzene)cobalt [adapted from Miller *et al.*, 1983].

1.7 Advanced Concepts in Solid-State Photodimerization Reactions

The topochemical principle (see section 1.1) states that reactions that occur in crystals proceed with minimal atomic and molecular motion, and are thus determined by the structures in the crystalline state of the starting materials. This is not always the case. Solid-state photodimerization reactions have been found to occur in crystals in which the distance between the reacting double bonds are greater than 4.2 Å, e.g. 7-chlorocoumarin [4.45 Å; Gnanaguru *et al.*, 1985] and *β*-polymorph of *p*-formylcinnamic acid [4.825 Å; Hasegawa *et al.*, 1985]. In addition, in order to react, molecules have to be orientated such that the reacting π-orbitals are suitably juxtaposed, i.e., the rotational angle of the C=C bond in one molecule with respect to that of the other has to be as close to 0° as possible. Examples of exceptions are 7-methoxycoumarin [67.5°; Ramasubbu *et al.*, 1982] and 1,4-dicinnamoyl benzene [28.5°; Hasegawa *et al.*, 1985].

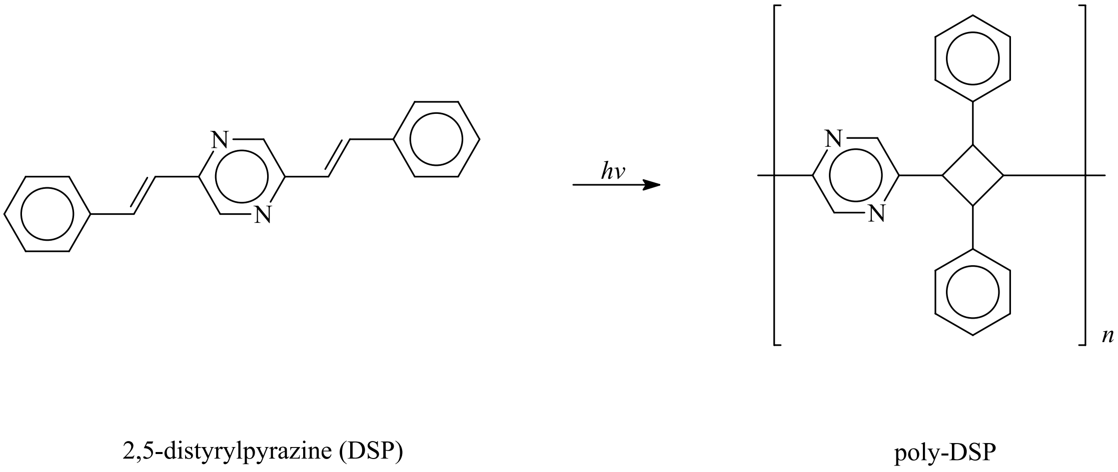
The source of this apparent anomaly can be found in the original definition of the topochemical principle [Schmidt, 1964], in that it defines the possibility of whether a reaction should or should not occur by a set of simple geometric criteria. These are based on the initial structure and on molecules whose ground state C=C π orbitals are suitably orientated. Upon excitation small movements take place leading to a photodimer of predetermined stereochemistry. This concept of preformation is deficient in at least two aspects [Murthy *et al.*, 1987]. Firstly, it does not take into account the presence of nearest neighbors both before and during the reaction. These can have a very serious impact on the reaction paths taken by a particular material, with the topochemically predicted reaction path inhibited by interactions between surrounding molecules, forcing an alternative pathway to be taken or the material to be photostable. 7-Chlorocoumarin mentioned above could be viewed as an example of this. Secondly, it does not take into account the effect of molecular excitation. In the same way that dipole-dipole interactions stabilize crystal structures, electronic excitation of molecules in the crystal can lead to significant movements in the crystal allowing reactions to occur in materials where the topochemical principle suggests that they should not.

Mechanisms such as crystal defects, the role of neighboring molecules (reaction cavity concept), and the electronic excitation of molecules in the solid-state (dynamical preformation), have been proposed to explain reactivity in crystals which apparently violate the topochemical principle. In addition, irradiating temperature and irradiating wavelength (in the photopolymerization of substituted diolefin crystals) have also been found to have an effect on such reactions [Hasegawa *et al.*, 1985].

It is also important to note that though the solid-state reactivity of some compounds violate the topochemical principle, most compounds do not. And the original definition of the topochemical principle is still a very useful and simple method of explaining the stereochemistry of the products obtained *via* a solid-state reaction. Its weakness lies in the fact that its static geometrical definition cannot explain why other products are formed, why products are formed when they are predicted not to, and why some crystals are photostable when they seem to be correctly aligned and within the Schmidt criterion distance. To get past these shortcomings an understanding of the dynamics in and between molecules in the solid-state is required.

1.7.1 The Effect of Irradiation Temperature on Solid-State Photodimerization Reactions

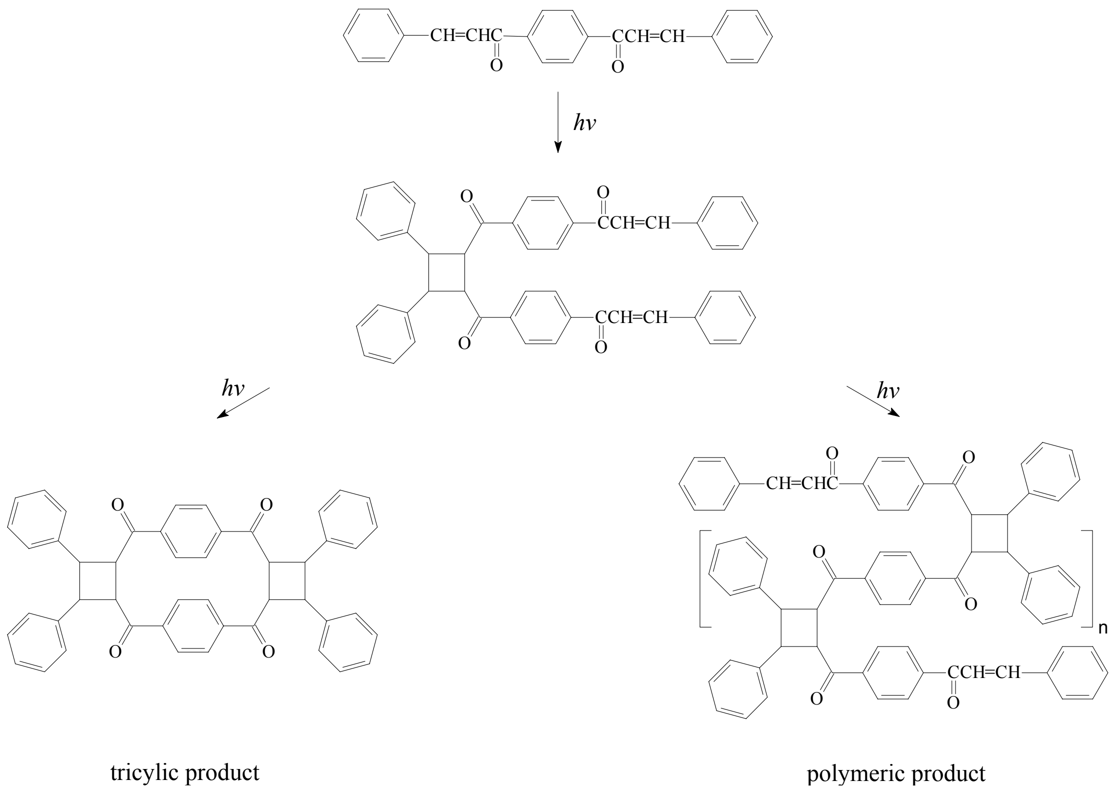
It has been found that lowering the irradiation temperature during the photopolymerization of α-type symmetrically substituted diolefin crystals (e.g. Scheme 1.8) leads to a higher degree of polymerization although the rate of reaction is depressed. In other examples of photopolymerization, lowering the irradiation temperature decreases the reactivity of the molecules.



Scheme 1.8: The polymerization of a symmetrical diolefin. This reaction has been carried out at temperatures as low as -60 °C [Wright, 1987].

Temperature, therefore, can either inhibit or promote reactions depending on the type of reactant. Reactions that are inhibited by large thermal motions in the crystal lattice can be promoted by decreasing irradiation temperature. Conversely, reactions that are being inhibited by the lack of molecular motion in their crystal lattices can be promoted by increases in temperature during irradiation. Therefore an irradiation temperature exists at which photoreaction rate is at a maximum [see for example Hasegawa *et al.* (1985) and Hasegawa & Saigo (1993)], and kinetic equations have been derived for some solid-state photochemical cyclo-addition reactions. These are dependent on the extent of thermal motion, which produce deviations from the average spatial position of photoreactive bonds. This leads to a more optimal orientation for a topochemical reaction to occur in the crystal. In the case of the photopolymerization of *α*-type unsymmetrically substituted diolefin crystals, it has been found that a certain amount of control in reaction products can be obtained by controlling irradiation temperature.

In addition, increasing the temperature used during irradiation can also lead to alternative products (perhaps due to a phase change or changing reaction dynamics in the solid state), or to changes in the relative ratios of a mixture of products being formed (if strict lattice control is lost). For example, 1,4-dicinnamoyl benzene yields two types of final products when irradiated [a tricyclic compound (or photodimer) and a range of polymeric compounds (or oligomers); Scheme 1.9], both of which can be reasonably interpreted from the molecular arrangement in the starting crystal [Hasegawa *et al.*, 1985]. The ratio of each product obtained shows a dependence on irradiation temperature, with the production of the tricylic compound being optimal at 25 °C (about 90% tricylic product with oligomers and starting material making up the remaining 10%) and less optimal at higher and lower temperatures, e.g. reaction at -17 °C yielded about 70% tricyclic product, 10% oligomers, and about 20% starting material. Reaction at 75 °C yielded about 80% tricyclic product, 10% oligomers, and about 10% starting material, respectively. This temperature dependence indicates that the reaction process is significantly affected by thermal vibration in the crystal lattice.



Scheme 1.9: Possible reaction pathways followed by the 1,4-dicinnamoyl benzene when irradiated with UV light at different temperatures [adapted from Hasegawa *et al.*, 1985].

1.7.2 The Concept of a Reaction Cavity and its Consequences in Predicting Products from Solid-State Photodimerization Reactions

Many solid-state photodimerization reactions give rise to unexpected products, e.g., a product where topochemical predictions would suggest that there should not be one - the reacting double bonds being too far apart. Alternatively, it could be a product that was not topochemically predicted, i.e. the reacting bonds involved are not necessarily the closest ones in the crystal. A good example is 7-chlorocoumarin [Gnanaguru *et al.*, 1985], where the closest inter C=C distance is 4.12 Å between a pair of centrosymmetrically related molecules, but instead the mirror product is obtained where the reacting molecules are separated by 4.45 Å (related by translation along the *a* axis).

In order to explain such reactions, the concept of “reaction cavity” has been introduced [Cohen, 1975; Cohen, 1979; Weiss *et al.*, 1993]. The reaction cavity is the space occupied by a molecule, surrounded by neighboring molecules, taking part in a solid-state reaction. During a reaction, any atomic movements by its neighboring molecules will exert 'pressure' on the reaction cavity. The distortions produced in such a process then produce repulsion forces between molecules as well as lowering the effect of attractive forces. Reactions that least distort the reaction cavity will be those that are most energetically favorable and hence likely to occur. The surrounding 'spectator' molecules therefore ultimately determine whether a reaction pathway will be taken or not.

The topochemical postulate can therefore be redefined as: reactions that proceed under lattice control do so with minimal distortion or change in the reaction cavity surface. Irradiation of crystals having more than one topochemically allowed product, would therefore lead to the product creating the least distortion to the reaction cavity surface. This idea has been used to show why the topochemically unfavorable product of 7-chlorocoumarin is obtained [Ramamurthy & Venkatesan, 1987]. The reaction cavity concept has also been useful in understanding why some crystals do not react even though the topochemical arrangement of the proposed reactant molecules is favorable.

In addition, free cavity space (voids in the crystal) in which the monomer can move and the product accommodated have also been used to explain why certain products are obtained in solid-state photochemical reactions [Hasegawa & Saigo, 1993]. For some reactions, especially molecular isomerizations or rearrangements, the cavity space around a moiety capable of undergoing isomerization has been quantified and linked to the kinetic behavior of the reaction - generally the larger the cavity the faster the reaction [Uchida *et al.*, 1984].

It has been known for a long time that the reaction environment can have an effect on the properties and reactions of a chemical species in a condensed state [see Boldyreva (1997) and references therein]. One of the first effects to be reported was that rates of reaction in solution can be affected by changing the solvent, e.g., it has been known since the 1890s that the rate of the reaction of trialkylamines with haloalkanes can change by up to 110000 times on going from one solvent to another. In 1934, it was noticed that the quantum yield for photodissociation in solution would often be lower when compared to the gas phase. In interpreting this phenomenon, Franck and Rabinowitsch (1934) described what is today known as the 'solvent cage effect': "Even though a molecule in solution may happen to dissociate after absorption, ... the radicals or atoms formed will be stopped by 'walls' of the solvent surrounding this 'cage' at a distance of one or few molecular diameters from one another" [Franck & Rabinowitsch, 1934; Boldyreva, 1997]. To give an idea of just how 'rigid' the solvent cage is, it has been found that in laser driven photodissociation of I_2 dissolved in CCl_4, only 14% of excited iodine molecules escape the solvent cage, while the rest recombine to reform I_2 [Plech *et al.*, 2004]. Similar effects have been seen in the solid state with an extreme example being nitroglycerine (a powerful explosive). When incorporated in *β*-cyclodextrin, nitroglycerine becomes so stable that it cannot be exploded even with an initiator [Stadler-Szoke & Szejtli, 1979; Boldyreva, 1997] - the reaction has a dependence on the presence of neighboring nitroglycerine molecules. Conceptually, there is a connection between the 'solvent cage effect' and the reaction cavity, and it has been suggested that the study of reactions in the solid-state can be useful for gaining a better understanding of reactions in solutions [Boldyreva, 1997]. The similarities and differences between the solvent and solid-state environment, and hence the 'solvent cage effect' and the reaction cavity, is shown in Table 1.2.

Table 1.2

Nature of environment in condensed states [after Boldyreva, 1997]

	Liquids	Solids	
		Glasses	Crystals
types of interactions	donor-acceptor (charge-transfer), hydrogen bonds, van der Waals		
life time	10^{-10}-10^{-11} s	long lived	
distribution	broad		usually: one type, rarely: a few types
methods of study	spectroscopy	(spectroscopy)	
	(diffraction)		diffraction

The concept of the reaction cavity as presented above serves as a starting point for determining reaction pathways and kinetics of reactions in the solid-state. Fully understanding and predicting phenomena in the solid-state requires a quantitative formulation of the reaction cavity. Such a treatment has been proposed and discussed in great detail by Luty & Eckhardt (1995), in which concepts such as quantitative descriptions of the reaction cavity, steric compression and reaction-induced stress are presented. In addition their work lead to further insights into phonon assistance, homogeneity of reactions, and the role of the product molecules, as perturbations, on the activation energy. Their theory has also been applied to temperature-induced polymerization reactions, photoinduced reactions, and shock-induced reactions (detonation of explosives).

Detonation is an interesting example of a thermal solid-state reaction as some models [Dlott & Fayer, 1990] assume that the mechanical energy of compression: "*is stored in a phonon bath and is subsequently transferred via 'doorway' modes*" [Dlott & Fayer, 1990; Tokmakoff *et al*., 1993] "*into the energetic molecules, this making them vibrationally hot*" [Luty & Eckhardt, 1995]. These vibrationally 'hot' molecules are assumed to be hot enough to be able to dissociate leading to the detonation process. However, the transfer of energy to the vibrationally 'hot' molecules is regarded as the initiation step in the detonation process, with crystal defects and impurities helping to localize or focus the energy transfer [the role of defects in solid state reactions is presented further on in the introduction].

In addition, theories presented by Luty & Fouret (1989) [see also Luty & Eckhardt (1995)] suggest that the deformation energy due to the formation of a product is a many-body phenomenon and thus non-additive. According to them: "*This implies that no matter how localized a perturbation may be in a chemical reaction, the cooperative nature of the crystal environment cannot be discounted and must of necessity have an influence on the reaction itself*". Work by Peachy and Eckhardt (1994) strongly support this.

Finally, though this general description of the reaction cavity gives one some understanding of forces driving reactions in the solid-state, it represents only a very small component of the implications derived from the reaction cavity concept. Three interesting papers (two based on DSP; Scheme 1.8), in which experiment and theory are combined to explain different features in the solid-state reactions can be found in Baughman (1978) and Peachey & Eckhardt (1993 & 1994).

1.7.3 Dynamical Preformation: The Concept of Photoinduced Lattice Instability

The solid-state photodimerization reaction of 7-methoxy-coumarin has been found to yield a centrosymmetric product in spite of the reacting double bonds in the monomers being rotated by 65° with respect to each other. This means that somewhere in the reaction process the molecules had to rotate into a favorable geometry (0°) with respect to each other in order for the reaction to be possible. A possible mechanism that has been proposed for the movement of the monomers before reaction is “dynamical preformation” or photoinduced lattice instability [Craig & Malett, 1982]. This means that a reaction that would not be expected under ground state conditions might occur under irradiated (excited) conditions.

In their review of solid-state photochemistry Ramamurthy & Venkatesan (1987) have described dynamical preformation as follows:

“Localized electronic excitation of a molecular crystal is expected to produce a particular type of instability of the lattice configuration leading to large molecular displacements. Localized excitation means the existence of an excited molecule which on account of its altered properties is seen by its neighbours as an impurity. The creation of this “impurity” molecule introduces local instability in the lattice configuration and leads to relaxation. This relaxation process could involve large displacements from the original lattice structure and in that sense far from the equilibrium configuration of the unexcited crystal”.

This photoinduced instability is quite feasible since the process would produce an electronically excited molecule. Such molecules are regarded to be generally more polarizable than ground state molecules. As such they will have bigger dispersion forces which attract them to their neighbors thus giving it a tendency to move off its average lattice site position [Wright, 1987] and increasing the overlap between the two molecules. Evidence for such an effect has been found in the photodimerization of *p*-formyl-*trans*-cinnamic acid [Busse *et al*., 2002]. It has also been shown *via* time-resolved X-ray diffraction on single-crystals and powders, that molecules in the excited state (due to excitation *via* laser light) can change shape, significantly affecting bond lengths [Kim *et al*., 2002] and angles [Techert *et al*., 2001]. In addition, at least one example exists of a reversible photoinduced phase transition - the direction of the phase transition being temperature dependent [Koshihara *et al*., 1992]. Kaupp (2003) has also suggested that the hypothesis of minimal atomic and molecular motion occurring in solid-state reactions, and embodied in the topochemical principle, cannot be correct. This conclusion is based on evidence of very large molecular movements, observed by using atomic force microscopy during a reaction. In the case of photochemical reactions these large molecular movements would have been, at least initially, photoinduced.

Dynamic preformation has been used to explain photoreactions in some anthracenes, 7-methoxy-coumarin and *m*-bromo-cinnamate and is useful to explain other reactions with unexpected photodimerization products [Ramamurthy & Venkatesan, 1987].

1.7.4 The Role of Defects in Producing Unexpected Products from Solid-State Photodimerization Reactions

In the same way as the concepts of dynamic preformation and reaction cavities, defects have been used to explain unexpected photodimerization products. It has been shown that the unexpected products obtained when irradiating anthracene can be explained by attributing the reaction sites to structural defects [Cohen *et al*., 1971; Craig *et al.*, 1976; Ramdas *et al*., 1978] or to zones (metastable phases in the crystal) having a more favorable inter olefin separation [Jones & Thomas, 1979].

Cohen (1987) presents two pieces of evidence in favor for the argument of structural defects as a reaction site:

(i) *"if an anthracene crystal is cleaved and one half irradiated, while the other half is etched, there is found to be a one-to-one correspondence between the positions of the product crystallites and of the etch pits. This shows that the dimer crystals separate from the parent crystal preferentially at emergent dislocations.*

(ii) *In a large number of anthracenes it was shown that certain defects (point, linear or planar) have structures which are suited to the formation of the observed products......."*

It has also been reported that the initial reaction rate in anthracene crystals varies from crystal to crystal. This would be in keeping with the varying concentrations of defects in these crystals (Cohen,1987). An induction effect is also often seen, in which no photodimerization occurs until defects are produced in the crystal. The rate of reaction then increases as more and more defects are created.

There are several reasons why reactions would happen at defects. One is that excitation can be mobile in the form of excitons, and these can move and become trapped on molecules at defect sites (whose energy is slightly different from those in normal sites). The longer residence time for the excitation at such sites makes reactions at such sites more probable. Another is that there is often more space at such sites allowing molecules to re-orientate themselves into favorable orientations for photodimerizations and accommodating the products of such reactions [Wright, 1987].

In the photodimerization of the *β*-polymorph of 9-cyanoanthracene, topochemical considerations predict the formation of a *cis* product, but instead a *trans* product is obtained. In explaining this result, Cohen *et al.* (1971) suggested that the reaction happens at defects, where molecules are more likely to have the correct orientation. In solution, it is known that the rate of the photodimerization reaction of anthracene to yield the *cis* dimer is much slower than that of the *trans* dimer. In view of this fact, Cohen *et al.* suggest that in the solid state, excitation energy captured by molecules in the undistorted lattice is transferred to surrounding molecules (because the formation of the *cis* product is relatively unfavorable), which is then retransferred molecule to molecule until a defect site is reached. At the defect site, where a pair of molecules potentially forming a *trans* product is likely to be found, the probability of the transfer of the excitation energy is lowered as the formation of the *trans* product is favored. Since the number of molecules at such sites is small, the reaction has to occur via the creation and spreading out of defects. It is also possible to inhibit the reaction with suitable dopants [Cohen & Green, 1973].

Orientational disorder, in which a molecule may be present in more than one orientation or conformation in a crystal, has also been found to have an effect on the photodimerization products obtained. Significant orientational disorder has been found to occur in the crystal structure of (*E*)-*β*-nitrostyrene due to a photochemically driven *trans*-to-*cis* isomerization. This disorder leads to the production of the expected inversion product as well as the production of an unexpected product in a 2:1 ratio [Pedireddi *et al.*, 1992].

Defects seem to play a very small role in the photodimerization of cinnamic acid type compounds. For these materials, reaction rate seems to be unaffected by the quality of crystal irradiated, implying that crystal defects are not involved. It is thought that these molecules are very efficient at radiationless deactivation and either take this path or react very quickly leading to de-excitation of the molecules before energy transfer can occur [Cohen, 1987].

1.8 The Importance of Solid-State Chemistry - Today

Solid state organic chemistry is a relatively new field and is of importance in materials design. Interest in crystal design has intensified over the past two decades with the design and synthesis of new materials exhibiting properties such as conductivity, superconductivity, ferromagnetism, and nonlinear optical effects. These characteristics are generally associated with non-molecular materials. Solid-state organic chemistry has also had a great impact in pharmaceutical chemistry where crystallization, morphology and polymorphism are very important [Ward & Hollingsworth, 1994; Threlfall, 1995; Ristic *et al*., 2001].

Some areas of growing interest in solid-state organic chemistry are the prediction of crystal packing, hydrogen bonding in the solid state, synthesis of co-crystals, crystal nucleation, crystal morphology, mechanical properties and growth phenomena, as well as topochemical synthesis studies [Ward & Hollingsworth, 1994; Beyer *et al.*, 2001; Papaefstathiou *et al*., 2004].

Currently, the most apparent influence of solid state organic chemistry is in the related field of solid state pharmaceutical chemistry. The field encompasses a wide range of studies involving the following [Byrn *et al.*, 1994; Bernstein, 2002; Knapman, 2000; Sharma, 2002; Ristic *et al.*, 2001; Beyer *et al.*, 2001]:

- Determination of physical and chemical properties of polymorphs and solvates. Drugs can crystallize in different crystal forms (polymorphs) each having a different melting point, density, solubility, chemical stability, moisture intake and other properties. In addition, solvates, desolvated solvates and amorphous forms of the drug can have properties that are different from each other. The rate of solution and the kinetics of reactions such as oxidation, dehydration, decarboxylation and other reactions involving the solid-state are also important so as to be able to predict the rate of drug uptake on administered drug, drug degradation and the shelf life of the drug, and what conditions it should be stored under and for how long. Complications such as amounts of an amorphous component in the crystals and crystal strain or disorder may also affect the performance of the drug. The most suitable form (polymorph / solvate / amorphous) of the drug must then be chosen. Being able to predict and control these properties would enable the development of a drug to occur at a more rapid rate and at lower cost.

- Physical transformations between polymorphs and solvates. A dictate of drug formulation is that once a drug is defined and verified, it should not change once the drug is manufactured. Therefore information about transformations between the different forms of the drug is of great importance. Solid to solid transformations are affected by one or more of the following variables: temperature, solubility in a given liquid phase and the vapor pressure of the solvent. Knowledge of the above is important so as to optimize the performance of the drug.
- Two main challenges to the analysis of pharmaceutical solids are dealing with mixtures of forms in the drug substance and identifying the solid form of the active ingredient in the formulated product, particularly when the drug is a minor component in the presence of numerous other materials (excipients).

There is also the issue of intellectual property rights in that once a patent has been taken on a particular drug it cannot be marketed by somebody else until the patent expires. This requires that the drug not only be precisely characterized, but also that any other polymorphs of the drug be search for, identified, characterized and possibly patented [Bernstein, 2002; Knapman, 2000; Cross *et al.*, 2003]. If this is not done properly and an alternative useful polymorph of the drug is discovered by another company, this company may patent the alternative drug and market it in competition with the original discoverer, without incurring the initial drug discovery costs.

1.9 The Aims of this Project

The existence of the three polymorphs of *ortho*-ethoxy-*trans*-cinnamic acid is often quoted as an example of the importance of intermolecular forces and crystal packing to solid-state reactions. However, searching the Cambridge Structural Database [CSD; Allen, 2002] it was discovered that the structure solution (including atom coordinates) had not been obtained for any of the crystal types. Details of these crystal structures (other than space groups and unit cell dimensions) had until recently [Fernandes *et al.*, 2001; Gopalan & Kulkarni, 2001] never been reported. Symmetries relating the different reacting molecules to each other seem to have been inferred from the symmetries of the resulting products.

The main aim of the project was therefore to establish the detailed crystallographic structures of all three polymorphs, to describe how each is prepared, and how the solid state structure affects the photochemical behavior of the different polymorphs. The thermal characteristics of each polymorph were also to be studied.

In addition, attempts were to be made to perhaps engineer new OETCA polymorphs using different crystal growth conditions such as different solvents and different temperatures. As the study progressed, other interesting phenomena and a new polymorph were discovered. As a consequence the project evolved to include the study of the mechanism of phase change to the new polymorph as well as to understanding its solid-state reactivity properties *via* single crystal analysis. This is in keeping with the current trend of studying phase changes, molecular conformation changes, molecular excitation states, and solid state reactions in situ [Shin *et al.*, 1997; Techert *et al.*, 2001; Moffat, 2001; Kim *et al.*, 2002; Busse *et al.*, 2002; Plech *et al.*, 2004]. Many of these are carried out in a time resolved manner allowing fine details on excitation or reaction processes to be obtained.