The Effect of Additives on the Growth of Benzophenone

A thesis presented for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

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List of Nomenclature

General

\( R \) – Universal Gas Constant (J K \text{ mol}^{-1})

\( x \) – concentration of component (mole fraction)

\( \mu^o_A \) – chemical potential of component A

\( \sigma \) – supersaturation (dimensionless)

\( k_b \) – Boltzmann Constant (J K^{-1} \text{ mol}^{-1})

\( \Delta H_{\text{sub}} \) – Sublimation Enthalpy (kJ/mol)

\( \Delta H_f \) – Enthalpy of Fusion (kJ/mol)

\( \Delta G_{\text{desolv}} \) – Free Energy of Desolvation (kJ/mol)

\( T_m \) – Temperature of Melting

\( \Delta G_{\text{ads}} \) – Free Energy of Adsorption (kJ/mol)

Lennard-Jones Potential

\( q \) – Atomistic charge

\( r \) – interatomic radius (m)

\( V_{ij} \) – Lennar-Jones potential (kJ/mol)

\( D \) – dielectric constant (C/m^2)

X-ray Diffraction

\( n \) – Miller Index

\( \lambda \) – Wavelength (Å)
\(d_{hkl}\) – Interplanar Spacing (Å)

**Nucleation/Induction Time**

A – pre exponential Kinetic Factor

\(J\) - Rate of Nucleation

\(\Delta G_{tot}\) – Gibbs free energy of nucleation (kJ/mol\(^{-1}\))

\(\Delta G_s\) – Gibb's free surface energy (kJ/mol\(^{-1}\))

\(\Delta G_v\) – Gibb's free volume energy (kJ/mol\(^{-1}\))

\(\tau_{ind}\) - Induction Time (mins)

\(\gamma\) – Interfacial Energy (J m\(^{-2}\))

\(v\) – Molecular Volume

\(r^*\) - Critical Three Dimensional Nucleus Radius

\(S\) – Supersaturation (dimensionless)

**Growth**

\(\alpha\) – Alpha Factor (dimensionless)

\(\xi\) – Crystallographic Factor (dimensionless)

\(V_\infty\) - Growth Rate at Monolayer Coverage

\(V\) – Growth Rate (μm/min\(^{-1}\))

\(v_{mono}\) – Growth Rate with Monolayer Coverage of Impurity (μm/min)

\(V_0\) – Pure Growth Rate (μm/min)
\( v_i \cdot \frac{v}{v_0} \) – Impure growth rate (dimensionless)

\( v_r = \frac{v_{\infty}}{v_0} \) – Relative Growth rate (dimensionless)

\( \gamma_e \) - Step Energy (kJ/mol\(^{-1}\))

\( \sigma_1 \) – BCF Parameter (dimensionless)

\( s \) – Strength of Dislocation (dimensionless)

\( v_i \) – Impure Growth Rate (\( \mu m/\text{min} \))

\( v_p \) – Pure Growth Rate (\( \mu m/\text{min} \))

\( p_c \) – Critical Sized Nucleus (Å\(^2\))

\( \bar{d}_{1}^{1} \) - Average separation of impurities

\( \gamma_{\text{surface}} \) – Surface Energy (kJ/mol\(^{-1}\))

\( q_{i}^{\text{ads}} \) – Concentration of adsorbed species (mole fraction)

\( q_{i}^{\text{mono}} \) – Concentration of adsorbed species at monolayer coverage (mole fraction)

\( K \) – Langmuir Constant (dimensionless)

\( \Theta \) – Fractional Coverage of Impurity (dimensionless)

\( \alpha \) – Impurity Effectiveness Factor (dimensionless)

\( L \) - Average separation between active sites (Å)

\( \alpha \) – Size of the growth unit (Å)

\( \lambda_s \) – mean surface diffusion distance

\( r_{2D}^* \) - Critical sized radius in the presence of impurity
$n_{max}$ – Number of sites available for an impurity to bind

$C$ – BCF parameter (μm/min)

$\sigma_c$ – Critical Supersaturation (dimensionless)

$h$ - Step Height (Å)

$\theta_{eq}$ - Equilibrium Surface Coverage (dimensionless)

**Computational**

$E_{cr}$ – Lattice Energy (kJ/mol$^{-1}$)

$E_{att}$ – Attachment Energy (kJ/mol$^{-1}$)

$E_{sl}$ – Slice Energy (kJ/mol$^{-1}$)

$E_b$ – Solute Binding Energy (kJ/mol$^{-1}$)

$E_{b}'$ - Additive Binding Energy (kJ/mol$^{-1}$)

$E_{sl}'$ - Slice Energy in the Presence of Additive (kJ/mol$^{-1}$)

$E_{att}'$ - Attachment Energy in the Presence of Additive (kJ/mol$^{-1}$)

$\Delta\Delta E$ – Relative Binding Energy (kJ/mol$^{-1}$)

$\Delta E_s$ – Solute Binding Energy (kJ/mol$^{-1}$)

$\Delta E_b^0$ – Solute Binding Energy (kJ/mol$^{-1}$)

$\Delta E_b'$ - Additive Binding Energy (kJ/mol$^{-1}$)

$\Delta\Delta E$ – Relative Binding Energy (kJ/mol$^{-1}$)

$E_{att,hkl}^0$ – Solute Attachment Energy (kJ/mol$^{-1}$)
\( E'_{\text{att},hkl} \) - Modified Attachment Energy (kJ/mol\(^{-1}\))

\( E_{\text{att},hkl}^{\text{vacuum}} \) - Attachment energy (kJ/mol\(^{-1}\))

\( \Delta E_a \) - Additive Binding Energy (kJ/mol\(^{-1}\))

\( E'_{hkl,i} \) - Energy of a slice containing bound additive (kJ/mol\(^{-1}\))

\( E_{hkl,i}^{\text{att}} \) - Attachment energy with impurity bound (kJ/mol\(^{-1}\))

\( \gamma_{hkl}^{\text{vacuum}} \) - Specific surface energy (kJ/mol\(^{-1}\))

\( Z \) - Number of molecules in the unit cell

\( V_{\text{cell}} \) - Molecular Volume

\( N_a \) - Avagadro’s number

\( U_{\text{probe}} \) - Specific interaction energy of probe molecule

\( S_R^{hkl} \) - \( \frac{V_{\text{cell}}}{a_{hkl}} \)

\( U_{\text{solution}} \) - Energy of solution - (kJ/mol\(^{-1}\))

\( S_{hkl}^R \) - the number of solvent molecules per reticular area

\( E'_{hkl} \) - Binding energy of additive molecule (kJ/mol\(^{-1}\))

\( K_i \) - relative lattice energy of pure and impure crystal (kJ/mol\(^{-1}\))

\( \gamma_{\text{kink}} \) - Surface Energy (kJ/mol\(^{-1}\))

\( \gamma_{\text{cryst}} \) - Crystal surface adhesion energy (kJ/mol\(^{-1}\))

\( \gamma_{\text{solv}} \) - Solvent adhesion energy (kJ/mol\(^{-1}\))

\( 2\sqrt{\gamma_{\text{cryst}} \gamma'_{\text{solv}}} \) - Surface adhesion energy (kJ/mol\(^{-1}\))
Complexation

\([A]_T\) – Total Solute Concentration (M)

\([A]_0\) – Solute Equilibrium Solubility (M)

\([AB]\) – AB Complex Concentration (M)

\([B]_0\) – Ligand Concentration in Complex (M)

\([B]_T\) – Total Ligand Concentration (M)

\(K_{11}\) – 1:1 Complex Equilibrium Constant (dm\(^3\) mol\(^{-1}\))
Abstract

The University of Manchester
Adrian Hutchinson
For the degree of Doctor of Philosophy

The Effect of Additives on the Growth of Benzophenone
May 2014

The effect of impurities on crystal morphology is a challenging problem, since even at low concentrations they can have drastic effects on the final habit. Industrially this causes problems with downstream processes such as filtration, processability and even storage. Conversely, structurally related additive molecules may be introduced to a system in order to mimic the effect of an impurity resulting in a beneficial effect on problematic crystal morphologies.

The work presented here considers the design and use of tailor made additives on a non-hydrogen bonded crystal, benzophenone. This compound is typical of many agrochemical materials in that the major intermolecular interactions are of the non-directional van der Waals type. Using crystal packing analysis a selection of additives has been chosen with the intent of specifically hindering certain directions of crystal growth.

From an initial group of nine molecules two additives, 4ABP and 4MBP were found to be particularly effective, both strongly hindering growth. Measured kinetic data suggests that these additives bind to steps in the growth spirals, drastically slowing growth of specific crystal faces altering the crystal morphology to a needle shape. Through nucleation experiments and product analysis the additives were shown to effect only crystal growth becoming incorporated into the crystal structure.

Computational modelling of the binding of additives to the crystal surfaces of benzophenone has been used in an attempt to rationalise the experimental effects. In many cases calculated binding energies were in agreement with experimental observation. However, modified attachment energies did not match well with experimental observations.
Declaration

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1. Introduction
Crystallisation from solution is a common method of chemical purification involving three dimensional organisation of randomly oriented molecules. Since individual crystal faces are highly discriminating towards molecules, growth of a crystal will involve high levels of product purity. The technique is often underestimated and is assumed to be simple and small variations in the method of crystallisation can have dramatic effects on the nature of the product. For instance, the purity, processability and bioavailability of a solid (in pharmaceuticals) can be very different depending on crystallisation conditions.

This process of crystallisation can be defined as the organisation of molecules or ions of solute, such that a new ‘ordered’ three dimensional solid phase is created. Crystallisation and the prediction of how the process occurs has been subject of much research and an understanding of the complex process of crystallisation is desirable. Attempts at predicting the rate of growth of specific crystal faces have been made using information from a previously grown crystal of the substance. However, solute molecules and crystals are very sensitive to changes in crystallising medium, temperature and the presence of impurities.

1.1 What is a Crystal?
A crystal can be defined as a three-dimensional solid phase exhibiting a periodic repeating pattern of atoms or molecules. Identification of single crystals can be performed easily using a light microscope, as a single crystal will polarize the plane of light and will appear clear and visible in an otherwise dark background. Crystals take many shapes and sizes such as needles, dendrites and rods to name a few.

1.2 Solubility
Solubility is an important parameter in crystallisation, especially since a common method of crystallisation exploits the change in solubility with temperature. When crystallising from solution, the saturation point for a compound corresponds to the equilibrium solubility at a given temperature, where the chemical potential of the solid and solute in the solution phase must be equal. This is the same as in a case of an ideal
solution where the interactions between the two components are the chemically equivalent to the interactions of the pure components.

\[ \mu^0_A(Solid) = \mu_A(Solution) = \mu^0_A(Liquid) + RT \ln x_2 \]

Equation 1

However, this cannot always be applicable since molecules and solvents will not always have the same capacity for interactions. Thus, the solution will not always be ideal except for in the case of dilute solutions. In this case the solvent experiences very little change in entropy as there is a very small amount of solute to disrupt the solvent arrangement, conversely, the entropy of the solute is now very different. The expression now becomes:

\[ \mu^0_A(Solid) = \mu_A(Solution) = \mu^\phi_A(Liquid) + RT \ln x_2 \]

Equation 2

\( \mu^\phi_A(Liquid) \) is an arbitrary constant due to the non-ideality of the solution.

1.2.1 Supersaturation

The solubility of a substance in a solvent is known to vary with temperature (Figure 1), and generally increases with temperature\(^\text{11}\). A solution containing more solute than its equilibrium solubility at a given temperature is said to be supersaturated. Generation of supersaturation is easy and cooling of a solution below the point of solubility (the saturation point) will create supersaturation, the thermodynamic driving force for crystallisation.
In Figure 1 the blue curve is the solubility curve and the red curve is the boundary between the metastable and labile zones. At point A (Figure 1), the solution is saturated and reducing the temperature further will cause the composition to move towards point B generating supersaturation. At point B the solution will be highly supersaturated and homogeneous nucleation and precipitation of crystals can occur. Point B represents the edge of the metastable region with the red curve the boundary of the metastable zone.

As the crystals are growing, the composition of the solution is changing and the solution concentration is reducing through crystal growth. As long as the temperature remains constant the composition of the solution will move towards point C in the diagram and crystallisation can continue until the composition reaches the saturation point.

The metastable zone of a compound lies between the solubility curve and the edge of the metastable boundary. A system can remain in the metastable region for a period of time without nucleating, hence the term metastable region. The edge of the metastable region signifies the point beyond which spontaneous nucleation will occur since the degree of supersaturation is high.

Supersaturation is generally expressed in dimensionless terms and is defined by comparing the equilibrium composition of a substance to the actual composition:
\[ \sigma = \frac{\mu_{ss} - \mu_{eq}}{k_b T} \]

Equation 3

\( \mu_{ss} \) and \( \mu_{eq} \) are the solute activities in supersaturated and saturated solutions respectively.

1.3 Nucleation

Nucleation is the physical process involving the formation of new clusters of molecules large enough to create a new solid phase (a crystal) from a supersaturated medium. There are two distinct types of nucleation; primary and secondary\(^{12}\) and the distinction arises from variables in the system. Homogeneous primary nucleation is said to occur when there is no influence from any other crystalline material\(^{13}\) and heterogeneous primary nucleation arises when dust particles or other solid surfaces (such as vessel walls) cause nucleation. Secondary nucleation arises from the influence of seed crystals in the system.

1.3.1 Homogeneous Nucleation

Classical nucleation is assumed to be a stepwise aggregation process\(^{14}\), since it is unlikely that a cluster of several molecules can be produced from concerted collisions. Stepwise addition of further molecules will continue to decrease the surface free energy of the crystal either until an equilibrium structure is reached or the crystallisation is stopped.

The overall energy (excess free energy) of a nucleus, \( \Delta G \), depends on the radius, \( r \), the surface free energy (\( \Delta G_s \)) and the free energy per unit volume (\( \Delta G_v \)). The free energy change associated with the assembly of a cluster is\(^{12}\):

\[ \Delta G_{tot} = \Delta G_s + \Delta G_v \]

Equation 4

The surface term is the excess surface free energy of the cluster, \( \Delta G_s \) corresponding to the excess free energy between the surface of the particle and the bulk of the solution.
The volume term is the volume excess free energy, $\Delta G_v$, and is the difference between the energy of a very large cluster ($r = \infty$) and the solute in solution.

$\Delta G_s$ is a positive term and $\Delta G_v$ is a negative term, hence the free energy for the growth of a nucleus will pass through a maximum energy (Figure 2).

![Figure 2. A diagram showing how the free energy of a cluster changes with the radius, r. Image taken from “Crystallization” 12.](image)

The above diagram shows how the energy of a nucleus varies with size. Before the nucleus reaches a critical size, shown on the diagram as $r^*$, the surface free energy term dominates the energy of the cluster. When the cluster reaches the critical size, $r^*$, the cluster is at the maximum energy possible and the cluster will seek to decrease its free energy. Before the nucleus has reached the critical size, the only way to reduce the free energy of the cluster is to dissolve$^{12}$. At the critical size growth or dissolution will reduce the free energy of the aggregated molecules and both outcomes are possible$^{15}$. However, as the solution will be supersaturated further growth is the more likely outcome.

Nucleation is an energetic barrier to crystallisation and is dependent on supersaturation. hence, increasing supersaturation decreases the energetic barrier increasing the probability that nucleation will occur.
1.3.2 Nucleation Rate

When supersaturated, a system will eventually nucleate and crystals will grow. The rate of nucleation can be expressed in simplified form as:

\[ J = A \exp \left( \frac{-B}{\ln^2 S} \right) \]

Equation 5

A is the kinetic parameter, S is the supersaturation of the solution and B is the thermodynamic parameter equal to:

\[ B = \frac{4}{27} \frac{C^2 v^2 \sigma_{\text{eff}}}{k_B T^3} \]

Equation 6

C is the shape factor and \( v \) is the molecular volume, Values for A and B can be determined from plots of \( \ln \left( \frac{J}{S} \right) \) vs \( 1/(\ln^2 S) \).

1.3.3 Heterogeneous Nucleation

It is very difficult to ensure complete sterility in any vessel or crystallizer; hence a concentration of impure material will inevitably be present. Heterogeneous nucleation involves the influence of a foreign substance which can induce nucleation and it is difficult to distinguish whether a nucleation process has occurred homogeneously or heterogeneously.

Due to the difficulty in full exclusion of impurities it can be said that true homogeneous nucleation is unlikely and most nucleation is heterogeneous in nature. Foreign bodies can cause nucleation to occur at lower levels of supersaturation than that required for spontaneous homogeneous nucleation. Thus, the free energy change involved can be lower than the energy change for creating a critical size nucleus by homogeneous nucleation. The main effect on \( \Delta G \) is from the interfacial energy between the growing cluster and the solvent as there are now three constituents, the solution, the impurity and the nucleus.
1.3.4 Secondary Nucleation

As seen in Equation 5 nucleation is supersaturation dependent, and at high supersaturation is more probable. However, it is possible to induce or encourage growth of new clusters at lower levels of supersaturation known as secondary nucleation. Secondary nucleation arises from the interaction of another crystal in the solution with molecules in the supersaturated system. This can arise by one of two (most common) mechanisms, either contact nucleation or by seeding.

1.3.5 Contact Nucleation

When ‘seed’ crystals are introduced to the mixture, this is known as contact nucleation. The nucleation rate has been known to increase by up to five times$^{12}$ when seed crystals have been added to a crystallising solution. Collisions occurring in the solution between crystal fragments or whole crystals can cause fractures or breaks in the crystal surfaces. These broken fragments may not be the product of a clean break and may be bound by high index faces containing high densities of kinks or steps at which new molecules easily bind.

As a result of this contact process, agitators or stirrers can also have a significant impact on nucleation. Collisions between crystal surfaces are much more common$^{13}$ due to the solution agitation, thus the faster or the harder the agitation of the system, the higher the probability of contact nucleation. Seed crystals don’t have to be the same species as the desired crystal and isomorphous substances have been known to cause crystallisation of other compounds$^{12}$.

1.3.6 Induction Time

The induction time is the time delay between the onset of supersaturation and the appearance of crystalline material. The occurrence of nucleation can be measured by monitoring solution characteristics over time, i.e. the temperature or volume, solution concentration and or optical transmittance. In an isothermal system the induction time ($\tau_{\text{ind}}$) can be estimated using some of the above techniques and is inversely proportional to the rate of nucleation ($J$)$^{13}$.
hence calculation of parameters such as the interfacial tension and also the critical radius is possible (see section 5)

1.4 Crystal Morphology or Habit

The morphology or habit of a crystal refers to the external, three dimensional shape. Two forms are usually defined, the growth habit and the equilibrium habit. The equilibrium habit of a crystal (corresponding to the lowest surface energy) is seldom achieved and in many cases the kinetically stable morphology of the crystal is produced\textsuperscript{13}. Many factors can affect the final morphology of a crystal, such as the solvent, agitation, temperature, supersaturation and also the presence of impurities\textsuperscript{19}. There has been much interest in prediction of crystal morphology\textsuperscript{7,20-22}, mainly due to the subsequent effects the habit can have on the downstream processes, notably filtration, handling, packing and storage\textsuperscript{13}.

Morphological importance is a way of describing the relative size of crystal faces in the final morphology. The concept was introduced by Bravais; the idea stems from the concept that smaller faces grow faster relative to larger faces. Hence the final morphology is dominated by these large slow growing faces. During dissolution the crystal will follow a similar pattern, i.e. the smallest face will dissolve faster relative to the larger faces of the crystal. Eventually faster growing faces can grow to extinction and Figure 3 shows this.

\[ J \propto \tau^{-1}_{\text{int}} \]

Figure 3. A picture showing how smaller faces can grow to extinction.
Faces labelled b are slower growing relative to faces labelled a and eventually the a faces grow to extinction leaving only faces labelled b in the final crystal habit.

1.4.1 Wulff Plot

The repeatable external symmetry of a crystal led to Gibbs theory that the shape of a crystal will seek to minimize the total surface free energy according to the area of the face. Wulff\textsuperscript{22} extended the idea stating that there is a relationship between surface energy and the distance of a face from a point within the crystal. Thus, faces with lower surface free energies will have higher surface areas. Figure 4 shows a typical Wulff plot, with several “cusp” minima corresponding to growth in directions of low surface energy. Tangents are then constructed to these growth vectors in order to construct a regular polyhedral shape for a crystal.

![Wulff plot](image)

Figure 4. A typical Wulff plot taken from “Application of Bravais-Friedel-Donnay-Harker, Attachment Energy and Ising Models to Predicting and Understanding the Morphology of Molecular Crystals”\textsuperscript{22}.

1.4.2 Bravais-Friedel-Donnay-Harker

Bravais recognised that there was a relationship between the internal properties of a substance and the relative rate of growth of its solid phase noting that certain faces of a crystal were almost always the most predominant. Surfaces with larger interplanar spacing were observed to grow slower than faces with smaller interplanar spacing. This is now referred to as the BFDH (Bravais-Friedel-Donnay-Harker) model and can be
used to predict the relative rates of growth of different crystal faces from a knowledge of the lattice geometry.\textsuperscript{13} The growth rate of the crystal faces, $v_{hkl}$ are proportional to the inverse of the interplanar spacing ($1/d_{hkl}$), meaning that crystal faces with molecules closer together have higher interaction energies resulting in faster growth. Thus, faces with the largest interplanar spacing ($d_{hkl}$) will correspond to the face with the greatest importance in the morphology.\textsuperscript{23}

### 1.4.3 Periodic Bond Chains (PBC’s)

Hartman and Perdok\textsuperscript{24} extended the idea of morphological dependence of crystal structure by Bravais by describing a crystal lattice as several repeating units of bonding interactions called periodic bond chains. The three dimensional crystal structure is held together by these periodic bond chains resulting from ionic or hydrogen bonds or van der Waals interactions.

![Diagram showing different bond chains](image_url)

**Figure 5. An image displaying different bond chains.**

Figure 5 shows two intermolecular bond types, a and b. Supposing that a shorter interaction results in a stronger interaction, bond a will be formed faster than bond b. The outcome would eventually be a crystal habit elongated this direction (a) of bonding.
Figure 6. An image of a theoretical crystal consisting of potential PBC's. Image taken from “On the Relations Between Structure and Morphology of Crystals. I”.

Figure 6 shows a hypothetical three dimensional crystal involving periodic bond chains denoted by vectors A, B and C. Faces consisting of two vectors parallel to the surface are flat faces, faces combining one vector parallel are stepped faces and faces consisting of zero vectors parallel are kinked faces. A flat face should have less binding potential at the surface compared to a stepped face having one PBC parallel. A kinked face will have no PBC’s in a layer since all of the binding potential is pointing out of the surface. Since a kinked site has more binding potential, sites such as this will grow faster compared to stepped or flat faces. Figure 7 shows the different crystal surface sites in more detail.

Figure 7. A diagram showing a specimen crystal face. The image is taken from “The growth of crystals and the equilibrium structure of their surfaces”.

It follows from the above PBC theory that the relative rates of growth of the faces will be:
R_k > R_s > R_f

R_k is the growth rate of a kinked surface, R_s is the growth rate of a stepped surface and R_f is the growth rate of a flat surface. When initial nucleation occurs, each face of the crystal grows at the same rate. However, as growth continues, and the individual facets develop, the faces of the crystal will begin to grow at different rates in accordance with the above principles. At this point no new faces will be created, only the faces which are present grow, and the mechanisms of binding described here contribute to the different relative growth rates of the crystal.

1.4.4 Attachment Energy Calculations

Periodic bond chains are a useful approximation. However, it is possible to accurately calculate precise energies for intermolecular interactions between molecules and layers. The attachment energy (E_{att}) of a crystal surface is the energy released when one slice of new molecules with thickness d_{hkl} (E_{sl}) are bound to the hkl face of a crystal. Faces with the potential to lose more energy are expected to grow faster relative to faces with lower potential, thus are expected to appear smaller in the final morphology. Using Equation 7, the interaction energies are described by independent van der Waals and coulombic terms. A and B are atom specific parameters. q_i and q_j are the charges from atoms i and j, D is the dielectric constant and r_{ij} is the interatomic distance. The strength of hydrogen bonds may also be included with more parameters.\[ V_{ij} = -\frac{A}{r_{ij}^6} + \frac{B}{r_{ij}^{12}} + \frac{q_i q_j}{Dr_{ij}} \]

Equation 7

For attachment energies of crystal surfaces the intermolecular interaction of a molecule with its nearest neighbours requires computational calculation. Summing the intermolecular interactions between a central molecule and all surrounding molecules yields \( E_{cr} \) the lattice energy (using Equations 8 and 9).
Equation 8

\[ E_{cr} = \frac{1}{2} \sum_{k=1}^{N} \sum_{i=1}^{n} \sum_{j=1}^{n} V_{kij} \]

\( V_{kij} \) is the interaction of atom \( i \) of the central molecule with atom \( j \) of the surrounding \( k \)th molecule.

Equation 9

\[ E_{cr} = E_{att} + E_{sl} \]

\( E_{sl} \) is the energy of formation of a slice of thickness \( d_{hkl} \) and \( E_{att} \) is the fraction of the total lattice energy released upon addition of a slice. The lattice energy must also satisfy the following\(^7,20\):

\[ E_{cr} = -\Delta H_{sub} - 2RT \]

Equation 10

where \( -\Delta H_{sub} \) is the sublimation enthalpy. From this, the morphology of a crystal can be predicted. Faces with large attachment energies will be faster growing than faces with low attachment energies since less energy will be released in comparison.

1.5 Crystal Growth

1.5.1 Crystal-Fluid Interfaces

Temkin proposed a ‘multilayer’ model\(^{13}\) to describe the interaction between the crystal surface and the fluid interface. The model is used to calculate the energetic change when a flat face is altered to contain a step or a kink site. If it is energetically favourable a step or a kink can be made on the surface by two-dimensional nucleation creating a source of growth for a new layer. The face can now grow at an appreciable rate as further molecules will add to this kink or step on the new layer.
From the above diagram it is easy to see that the net change in energy (ΔE) can now be calculated using a simple empirical relationship.

\[ \Delta E = 4\Phi_{sf} - 2\Phi_{ss} - 2\Phi_{ff} \]

Equation 11

\( \Phi_{ss} \) = the surface-surface interaction energy, \( \Phi_{sf} \) = the surface-fluid interaction energy, \( \Phi_{ff} \) = the fluid-fluid interaction energy. There is a net loss of two solid-solid interactions and two fluid-fluid interactions and a gain of four solid-fluid interactions. This can be redefined in dimensionless terms as:

\[ \alpha = \frac{\Delta E}{k_b T} \]

Equation 12

\( \Delta E \) is equal to the energy of removing a growth unit from the surface and replacing it such as to begin a new layer of growth (as shown in Figure 8). This \( \alpha \) factor forms the basis for some of the key models for crystal surface growth. If the value of \( \alpha \) is low, then the rate of growth of the crystal face will be large and high \( \alpha \) values correspond to low rates of crystal growth.

Kinked surfaces will have low \( \alpha \) values, typically less than 3 as the energy required to form a kink site is low. Stepped surfaces are expected to have an intermediate \( \alpha \) value as creation of step sites becomes less energetically favourable. A flat surface is expected to
have a large $\alpha$ value as the energy required to create a new step is high as the interfacial tension involved in forming a two dimensional nucleus on the surface is larger and energetically difficult to overcome.

$$\alpha_f > \alpha_s > \alpha_k$$

$\alpha_f$ is the alpha factor of a flat surface, $\alpha_s$ is the alpha factor of a stepped surface and $\alpha_k$ is the alpha factor of a kinked surface. The value of $\alpha$ can be evaluated from measurable quantities\textsuperscript{13,27}:

$$\alpha = \xi \left[ \frac{\Delta H_f}{RT} - \ln x_{eq} \right]$$

Equation 13

$\Delta H_f$ is the heat of fusion and $x_{eq}$ is the solubility in mole fraction and $\xi$ is a crystallographic factor describing intermolecular interactions in the crystal surface defined as\textsuperscript{13}:

$$\xi = \frac{E_{st}}{E_{ss}} \approx \frac{Z_s}{Z_t}$$

Equation 14

$E_{st}$ is the total interaction energy per molecule in the layer of the surface and $E_{ss}$ is the total crystallisation (lattice) energy. $Z_s$ is the number of neighbouring molecules in the surface and $Z_t$ is the total number of neighbouring molecules. The value of $\alpha$ has a wide range of values and is typically between 2 and 20.

1.5.2 Continuous Growth

Typical $\alpha$ values for kinked surfaces are less than 3 and the energy penalty for creating a kink site is very low. The surface can continually create further step and kink sites. These are expected to be quickly adopted by incoming growth units and almost every growth molecule approaching the surface will be incorporated since a vacant kink or stepped site will always be available. The growth rate of a kinked face will be linear over time and follows the form\textsuperscript{13}:
\[ v = k_{CG} \sigma \]

Equation 15

\( k_{cg} \) is the kinetic factor relating to continuous growth and \( \sigma \) is the supersaturation.

1.5.3 Surface Nucleation

Increasing values of \( \alpha \) imply that the surface is less able to form kinked or stepped sites and the resulting surface will have smooth areas known as ‘islands’ on the crystal surface. These islands consist of previously adsorbed molecules which have formed a two dimensional nucleus on the surface and the only source of step and kink sites will be at the edge of these islands. Not all approaching growth units can be incorporated into the surface and molecules which are not adsorbed are forced back into the solution.

Figure 9. An image of a crystal growing by the birth and spread model.

This growth mechanism is an example of two-dimensional nucleation, where a molecule is adsorbed onto the surface and new molecules cluster around this forming a two-dimensional nucleus on the crystal face as shown in Figure 9. Underneath these smaller clusters are larger islands which have step sites at the edge for growth to continue. As with three-dimensional nucleation a critical cluster size is required for growth of the cluster to be favourable.

The growth rate now follows the form\(^{13}\):
\[ u = K_{SN} \sigma \frac{5}{6} \exp \left\{ -\frac{\pi}{3\sigma} \left( \frac{\gamma_e}{kT} \right)^2 \right\} \]

Equation 16

\( K_{SN} \) is the kinetic factor relating to surface nucleation, \( \gamma_e \) is the interfacial edge tension from forming a two-dimensional nucleus of critical size and \( \sigma \) is the supersaturation.

1.5.3 Screw Dislocation

As the value of \( \alpha \) rises above 5, the surfaces of the crystal are expected to be smooth as the strongest intermolecular interactions are parallel with the surface. This in conjunction with a high interfacial energy nearly inhibiting two-dimensional surface nucleation removes the source of new step and kink sites for growth.

Frank\textsuperscript{28} suggested that growth of a crystal would be unlikely to proceed perfectly and most crystals contain dislocations or defects. Thus, Frank developed a model known as the screw dislocation model\textsuperscript{28}. Imperfections or defects develop naturally in a crystal as a result of unavoidable stresses during growth. The outcome is that the lattice is no longer perfect and becomes disrupted as shown in Figure 10. In the middle of the lattice an extra layer of atoms/molecules (highlighted in grey) has been incorporated causing the surrounding molecules to shift out of line with the other atoms/molecules below forming a structural defect. From this angle the effect on the surface is unclear. Figure 11 shows an alternate view of the dislocation and its resulting perturbation of the surface.
Figure 10. A dislocated crystal lattice.

Figure 11 shows a dislocated crystal surface with the dislocation becoming more severe towards the right. The cause of a dislocation can vary from supersaturation, mechanical stress and can naturally occur during nucleation. The effect of the dislocation on the surface is clear and kinked and stepped sites are available for crystal growth. Since the kinked sites are located in the centre of the surface these are expected to grow faster than the stepped sites leading to the spiral pattern of growth.

The surface growth rate is now dependent upon:
\[ v = k_{SG} \frac{\sigma^2}{\sigma_1} \tanh \left( \frac{\sigma_1}{\sigma} \right) \]

Equation 17

\[ k_{SG} \propto \exp \left( -\frac{\Delta G_{\text{desolv}}}{k_B T} \right) \]

Equation 18

\(-\Delta G_{\text{desolv}}\) is the free energy of desolvation and

\[ \sigma_1 \propto \frac{\gamma_s}{S} \]

Equation 19

\(k_{sg}\) is the kinetic factor for screw dislocation growth and \(S\) is the strength of the dislocation source (see Section 6).

Since the nature and creation of dislocations varies between crystals different growth rates will be observed for different crystals. As supersaturation increases the spiral winds tighter increasing the step density, thus more step and kink sites are available and growth will be similar to continuous growth, showing a linear trend.

Three potential models have been developed for crystal growth and distinguishing between each from growth rate measurements is possible. For continuous growth, the
rate will follow a linear trend with increasing supersaturation. For screw dislocation, the growth curve is different; and at low supersaturation (or when $\sigma < \sigma_1$) the growth rate follows the approximate relationship of $R \sim C \sigma^2$ and the curve will be parabolic. However when the supersaturation increases (or when $\sigma > \sigma_1$) the growth rate becomes linear following approximately the $R = C \sigma$ relationship. Growth by two-dimensional nucleation will exhibit a curve throughout the accessible supersaturation range.

![Figure 13. A diagram showing characteristic growth rate curves.](image)

Thus, measuring the growth rates of crystal faces as a function of supersaturation allows distinction of the growth mechanism by examining the curves such as those in Figure 13 and applying the growth models. Boistelle$^{29}$ measured the kinetics of octacosane crystals growing from solution concluding that the (110) face grew through screw dislocation rather than two-dimensional surface nucleation. Davey et al.$^{30}$ reported that the (011) face of $\alpha$-resorcinol grew by surface nucleation whilst the (011) face grew by a screw dislocation mechanism. Li and Rodriguez-Hornedo also applied both models to the {010} and {011} faces of $\alpha$ glycine, reporting that both faces followed a screw dislocation mechanism rather than two-dimensional surface nucleation$^{31}$. More recent developments in technology have allowed growth mechanisms to be explored using
atomic force microscopy proving that screw dislocations occur on the (010) face of α-lactose\textsuperscript{32}.

### 1.6 Impurity Effects

When impurities are encountered in systems they can cause drastic effects\textsuperscript{33} on nucleation and growth processes even at very low\textsuperscript{34} concentrations. Impurities can prevent nucleation or inhibit specific faces of a growing crystal, thus changing the relative growth rates altering the final morphology\textsuperscript{33}. Conversely it has been reported that the introduction of an impurity can accelerate the growth rate of specific faces of a crystal\textsuperscript{35, 36}. The modification of crystal growth processes has been the subject of much research\textsuperscript{37-39} for both organic\textsuperscript{40} and inorganic\textsuperscript{41} systems.

Since anything that is not the desired solute is an impurity, the solvent can be considered as an impurity and many compounds exhibit solvent dependent morphologies. A solvent can have different interactions with different surfaces due to surface composition. Thus, a surface with more attractive functionality to an impurity or a solvent may be hindered as binding is more likely to occur here.

#### 1.6.1 Tailor Made Additives

It was suggested that impurities or additives can be “tailored”\textsuperscript{42} to a system to selectively hinder the growth of a specific face or change the habit of the crystal in a predetermined way. Tailoring additives to a solute simply on a structural basis\textsuperscript{43} has been suggested. The procedure can be complex and may not always be possible.

When choosing an additive for a solute, it is said that the closer the impurity in molecular structure to the solute, the more efficient the impurity\textsuperscript{43}. Examination of crystal packing of the solute to obtain specific surface compositions and stereochemistry is normally performed. A suitable molecule with the same ability or affinity for the target surface can be chosen.
Figure 14. A schematic showing the effect of selectively adsorbed impurities on the resultant morphology. Image taken from “Tailormade Auxiliaries for Nucleation, Growth and Dissolution of Organic-Crystals”.

Figure 14 displays some of the rationale behind the use of tailor made additives. Figure 14a shows a normal morphology of a crystal, with large faces defined by growth rate $k_2$ and capping faces defined by growth rate $k_1$. The capping faces have a faster growth rate compared to the larger faces ($k_1 > k_2$). The rationale is that an additive is introduced to the system with the intent of binding to the faster growing faces only (Figure 14b). If successful the additive modifies the habit through reduction of the growth rate ($k_1$) of these capping faces compared to the larger faces. The resulting morphology is shown in Figure 14c where the relative growth rates have been reversed ($k_1 < k_2$) and the habit is now very different.

Morphological engineering has been the most widely studied area but the addition of impurities can also be employed to preferentially crystallise single enantiomers from racemic compositions. The introduction of additives is known to enable crystallisation of single enantiomers from racemic solutions as well as enable crystallisation of metastable polymorphs from otherwise unfavourable conditions.

1.6.2 Habit Modification

1.6.2.1 Weissbuch et al

Weissbuch postulated that all amino acids (except for proline) would selectively adsorb onto the growing faces of $\alpha$-glycine as the structures are chemically similar, albeit with
different chain lengths. It can be seen that adding single enantiomers of amino acids prevent growth on one face of the crystal causing pyramid shaped crystals, whereas, racemic amino acid additives caused platelets, hindering growth on both sides of the crystal (Figure 15). This is because the b axis of glycine is terminated by different hydrogens depending on whether it is the (010) or (0\bar{1}0) face. This is seen in Figure 15.

Figure 15. The morphology of glycine grown in the presence of a) no additives, b) (R,S)-α-amino acids, c) (S)–α-amino acids and d) (R)–α-amino acids. Image taken from “Tailormade Auxiliaries for Nucleation, Growth and Dissolution of Organic-Crystals”.

The effect of a single enantiomer on the habit disturbs the centrosymmetric dimers of glycine (Figure 16), with the R enantiomer affecting the (0\bar{1}0) face and the S the (010).
1.6.2.2 Adipic acid – Davey et al

Adipic acid is an example of a substance where additives have been shown to hinder the growth rates of specific faces of the crystal\textsuperscript{48}. There are three by-products produced in the synthesis of adipic acid which can be incorporated into the crystal and retard the growth of crystal faces. The three impurities all follow the same hydrogen bonding moiety as adipic acid, i.e. the hydrogen bonded chains from the acid groups have been shown to bind on different faces also forming co-crystals with adipic acid.

Davey et al\textsuperscript{48} introduced n-alkanoic acids to hinder the growth of specific faces of the acid. Figure 17 shows the crystal structure of adipic acid with the (100) and the (001) surfaces labelled. The morphology of the crystals was predicted by both the attachment energy and BFDH (Bravais-Friedel-Donnay-Harker) methods and the (100) face was found to be the dominant face in tabular shaped crystals, which fit with experimentally grown crystals. An additive binding at the (100) surface would cause significant distortion to the growth process as the CH—O bonds between molecules can no longer form.
Figure 17. The structure of adipic acid showing the binding methods between the molecules. Image taken from “Structural and Kinetic Features of Crystal Growth Inhibition – Adipic Acid Growing in the Presence of N-alkanoic Acids”.

Figure 18. The structures of a) adipic acid, b) caproic acid and c) octanoic acid.

Adding n-alkanoic acids of different chain lengths all exhibited similar effects on the morphology with increasing concentrations of the impurity producing elongation of the crystal creating more needle like habits. Davey et al\textsuperscript{48} reported the largest effect on growth to be from caproic and octanoic acid. The structures in Figure 18 are all similar in size and functionality with caproic acid consisting of a six-carbon chain, much like adipic acid and this similarity improves the efficacy of the additives. Octanoic acid is also a similar structure although has two more carbons in its chain and the steric hindrance of these two extra carbons would not be too major to prevent incorporation.
All three molecules can form the hydrogen bond to the adjacent molecule. However, as there is only one acid group on either caproic or octanoic acid the growth in the [100] direction is almost stopped.

1.6.2.3 Urea

![Figure 19. The structure of a) urea and b) biuret.](image)

Pure urea grows with a needle like morphology displaying aspect ratios of up to 50:1. When biuret is present in the crystallisation the length to breadth ratio is reduced greatly, creating cube like crystals. Biuret is a by-product of the urea synthesis and is the dimer of urea with an alternate conformation available (Figure 20).

![Figure 20. Alternate conformer of biuret.](image)

The crystals of pure urea form needles in the [100] direction and the presence of the above biuret conformation slows the growth of this face in particular and the crystals become much shorter. As shown in Figure 21, biuret mimics the way which urea binds to the (100) face and the binding of further molecules is not possible as the NH₂ group is involved in the intramolecular hydrogen bond. Therefore, no further intermolecular hydrogen bonds can be made in the [100] direction causing the observed change in morphology.
Figure 21. An example of biuret preventing further growth of the [100] face of urea. Image taken from “The Influence of Biuret on the Growth-Kinetics of Urea Crystals from Aqueous Solutions”\(^ {40}\).

Using molecular dynamics Salvalaglio et al confirmed this theory\(^ {49}\). The biuret molecules bind and interfere with the continuous growth mechanism of the (001) faces, whereas the biuret is unable to bind to the {110} surfaces affecting the birth and spread growth mechanism.

### 1.6.2.4 Other examples

Several examples of habit modification have been reported in both organic and inorganic systems\(^ {50}\). Rimer et al designed an additive to hinder the growth of L-cystine, known to form a common type of kidney stone\(^ {51}\). Using atomic force microscopy the screw dislocations on the (001) surface of L-cystine appeared roughened by the presence of L-cystine dimethylester, proving that the steps were pinned by the additive. Increasing the concentration of L-cystine dimethylester reduced the yield of pure L-cystine and at concentrations above 2mg/L approached complete inhibition. Thus, the additive could potentially be used as treatment of L-cystine kidney stones since low concentrations are effective in L-cystine growth hindrance.

Jarmer et al modified the acicular habit of griseofulvin with the addition of poly sebacic anhydride (PSA)\(^ {52}\). The PSA bound to the fastest growing face of the needle shaped crystal generating a bipyramidal habit at additive concentration ratios of 1:39 (PSA:griseofulvin). Ramalingom observed that urea concentrations of 0.01-0.04 mole fraction alters the crystal habit of epsomite (Figure 22)\(^ {53}\). The presence of urea increased the growth rate of the (110) face in comparison to the (100) and (010) faces causing the morphology to become square instead of octagonal at all concentrations.
Kwon and co-workers investigated the effect of auxiliaries on the morphology and polymorphism of organic polyene molecules. Figure 23 shows the effect of DAM1 on the growth of DAT2 crystals. The DAM1 alters the morphology and slows the growth of the {110} crystal surfaces which previously grew to extinction, changing the habit from a needle shape.
1.6.2.5 Non-hydrogen Bonded Crystals

Non-hydrogen bonded crystals consist of only van der Waals intermolecular interactions. Generally these are weaker than hydrogen bonds (typical hydrogen bond strength approx. 5-20 kJ/mol) and less directional. Non-hydrogen bonded crystals are common chemical products yet little research has been performed on the use of tailor made additives on the crystal growth. Some research has been performed on alkanes in the presence of additives due to the crystallisation of wax at low temperatures in diesel. During storage over winter paraffin crystallises out of the diesel causing problems when pumped to the engine, as the wax blocks the fuel filter until the surplus fuel has warmed enough to melt the crystals. Thus, co-polymers were introduced as additives to hinder the growth creating smaller crystals which do not block fuel filters.

Simon and Boistelle measured the growth of octacosane and hexatriacontane in pure and impure solutions. The common plate like crystals were observed for both alkanes with a large dead zone found for the growth of thicker hexatriacontane crystals in the presence of additive. Different solvents were found to have different effects on the growth rates, with lower molecular weight organic solvents showing a higher growth rate. The growth rates of these two alkanes were also observed to have a critical supersaturation when grown in the presence of copolymer additives. Similarly Hutter et al used poly(octadecyl acrylate) to inhibit the growth of tricosane and dodecane, drastically changing the habit to branched microcrystalline meshes.

Through cooling of a diesel fuel, Bennema et al obtained paraffin crystals consisting of different chain length polymers (n=10-30). These crystals again exhibited the large (001) face capped by (110) faces. Introducing an ethylene-vinlyacetate polymer at concentrations of 0.001wt% altered the habit of the paraffin crystal and further increasing the additive concentration to 0.005wt% changed the habit from a needle to a plate like morphology. Clydesdale et al performed computational analysis on docasane crystals in the presence of tailor made additives using both shorter and longer chain alkanes as additives. However, due to the structural similarity between solute and additive; modified attachment energy morphologies were similar to the pure solute morphologies. Several examples of research on the inhibition of paraffin crystals can be found, yet research on other types of van der Waals crystals is sparse.
1.6.3 Resolution of Enantiomers

Davey et al\textsuperscript{46} used a molecular modelling approach combined with crystal structure analysis to design an additive to selectively crystallise a pure enantiomer of 2-chloromandelic acid. The compound forms dimer structures between R and S enantiomers in the racemic crystal. Exploitation of this packing allowed the design of an additive to remove the potential for dimer formation encouraging pure enantiomer crystallisation through chains of the molecule rather than dimers. A carboxylic acid derivative was used to prevent this dimer forming and at levels of 10 w/w\% of the additive crystals of the pure enantiomer were formed.

Addadi et al reported the influence of (S\textsuperscript{'}\) amino acids on the morphology and kinetic resolution of (R) and (S) crystals of asparagine\textsuperscript{43}. Addition of the additives resulted in the crystallisation of pure enantiomer crystals from racemic mixtures. The (S\textsuperscript{'}\) additives were the pure (S) enantiomers of several other amino acids as the stereochemistry and molecular similarity can have a strong influence in additive efficiency. Supersaturated solutions of (racemic) asparagine were created, to which resolved impurity pure (R or S) enantiomers were added. Initially no morphological change was observed for asparagine crystals. However, over time (depending on impurity concentration and efficiency) the crystal habit began to alter.

The crystals of altered morphologies were found to have the same internal structure as the crystals of the unchanged morphology and now contained one enantiomer only. Mixtures of crystals were produced since the solution was supersaturated with respect to both enantiomers. The unchanged crystal habit consisting of one pure enantiomer and the altered crystals were the other pure enantiomer, depending on the stereochemistry of the additive\textsuperscript{43}.

1.6.4 Metastable Polymorph Resolution

Lee et al used the structurally related flufenamic acid to crystallise the metastable form of mefanamic acid\textsuperscript{47}. Previously the crystal structure of the metastable form (form II) was unsolved as quality crystals could not be grown.
Figure 24. The molecular structures of a) mefenamic acid and b) flufenamic acid. Image taken from “Additive-induced metastable single crystal of mefenamic acid”.

Figure 24 shows the molecular structures of mefenamic acid and also flufenamic acid. From ethanol solution form I of mefenamic acid is always crystallised without any presence of the metastable form. However, with the addition of flufenamic acid only the metastable form is achieved from ethanol solution. It is apparent that the molecular structures are quite similar, with derivitisation at carbons 10 and 11 allowing the molecule to prevent form I of mefenamic acid from growing in solution.

Dhanasekaran and Srinivasan introduced L-tyrosine to inhibit the growth of the β polymorph of L-glutamic acid in order to crystallise the less thermodynamically stable α form. From Figures 25 and 26 it is apparent that the tyrosine not only inhibits the growth of the β form the additive also modifies the habit of the α form and above concentrations of 0.07g/100mL inhibits the growth of both polymorphs.
Figure 25. Images of a) β-glutamic acid, b) α-glutamic acid grown in l-tyrosine (0.03g/100mL) and c) α-glutamic acid grown in the presence of l-tyrosine (0.07g/100mL). Image taken from “Nucleation Control and Growth of Metastable alpha-L-Glutamic Acid Single Crystals in the Presence of L-Tyrosine”\textsuperscript{52}.

Figure 26. Images of glutamic acid morphologies. Image taken from “Nucleation Control and Growth of Metastable alpha-L-Glutamic Acid Single Crystals in the Presence of L-Tyrosine”\textsuperscript{52}.

1.6.5 Solvent Effects

Crystal growth is a sequential addition of molecules to a crystal face, when performed from solution, there is a small layer between the solvent and crystal interfaces known as the adsorption layer. This is a thin layer of partially adsorbed molecules which can migrate in a two-dimensional fashion across a crystal surface. The process of complete integration of the growth unit involves desolvation followed by full adsorption of the molecule. Energetically it is dependent on the breaking of the bonds with the solvent and the creation of the bonds with the crystal surface.
The ability of the solute to desolvate can depend on some of the properties of the solvent such as polarity, molecular density as well as other mass transport characteristics.

Succinic acid is an example of solvent mediated crystal morphology\textsuperscript{63}, where crystals grown from aqueous and alcoholic solutions have different habits. When grown from vapour, the succinic acid crystal morphology is shown to agree with the theoretical prediction containing large (020) faces. However when grown from solution, the (020) faces grow much faster resulting in lower morphological importance in the final crystal habit.

![Figure 27. Succinic acid grown form a) water and b) isopropanol. Image taken from “Habit Modification of Succinic Acid Crystals”\textsuperscript{63}.

Succinic acid is structurally similar to adipic acid forming hydrogen bonded chains, in the [020] direction only. The (001) face has the carboxylic acid groups at the interface and these polar groups bond strongly to polar and alcoholic solvents. Growth in this direction therefore involves desolvation of large amounts of strongly bound solvent molecules, thus, the habit is dominated by large slow growing (001) faces.
Figure 28. Images of caprolactam morphologies. a) pure caprolactam grown from the melt, b) caprolactam in the presence of 5% ethanol, c) the theoretical pure caprolactam morphology and d) the predicted morphology grown in the presence of ethanol. Image taken from “Designing Crustal Morphology by a Simple Approach”.

Figure 28 shows images of caprolactam grown from the melt in the presence of ethanol and also the predicted morphology of these two instances. The effect of ethanol on the growth was predicted to be at the (111) surface, since the crystal packing of caprolactam has the oxygen atom of the carbonyl exposed at this surface. Thus it was envisaged that a hydrogen donator (ethanol) would exert an effect on the growth of these faces through hydrogen bonding. The growth rate of the (110) and (111) faces are similar when grown from the melt. However in the presence of ethanol the growth of the (111) surface is reduced to approximately half that of the (110) face, thus the (110) surface grows to extinction.

1.7 Growth in The presence of Impurities

Two different categories of impurity can be defined when concerned with crystallisation kinetics:

1) completely “immobile” impurities that adsorb to the crystal surface and remain fixed at the site where they first reach the crystal face

or

2) “mobile” impurities that enter an adsorption layer losing one degree of freedom and diffuse “two-dimensionally” across the crystal surface.
There are clear differences between the modes of action of mobile and immobile impurities. Strongly adsorbing (immobile) impurities are expected to have the largest effect on crystal growth. When the step is growing immobile impurities can bind to the surface and the step can continue to grow around the impurities. Conversely, mobile impurities are thought to be swept away as the surface continues to grow. However, mobile impurities are thought to have a more severe effect through adsorption at kink sites rather than at ledges as they are not swept away. The strength of the bonding between the impurity and the crystal surface is the defining factor for the above classification. “Immobile” impurities or strongly adsorbing molecules bind to the surface of a crystal in place of solute growth units. These impurities prevent or reduce the rate of growth of a crystal face potentially becoming incorporated into the crystal structure. “Mobile” impurities are incorporated into the adsorption layer and are free to diffuse across the crystal face in a two dimensional manner but may not irreversibly bind to the crystal face.

1.7.1 Cabrera-Vermilyea Model

The incorporation of impurities has been studied and mathematical models for growth in the presence of impurity derived. Cabrera and Vermilyea defined a model to describe the influence of immobile impurities upon the growth of a crystal face.  

\[ v_i = v_p \sqrt{1 - 2p_c d^2} \]  

Equation 20  

\( v_i \) is the step velocity in the presence of impurities, \( v_p \) is the step velocity in the absence of the impurity, \( p_c \) is the critical two dimensional nucleus and \( d^2 \) is the average surface density of impurities on the ledge ahead of the step. The movement of the step is expected to halt altogether when the distance between impurity sites is less than twice that of a critical two dimensional nucleus, \( 2p_c \). Spacing of impurities which are larger than \( 2p_c \) are expected to have less of an effect on the step velocity and growth is expected to continue around the impurities (as shown in Figure 29) at a reduced rate.
Since the size of a critical two-dimensional nucleus depends on supersaturation, so will the effect of the impurity. Thus a critical supersaturation is inferred, below which the crystal is not expected to grow.

Mathematically this is given by the relationship\(^6^5\):

\[
d^{rac{1}{2}} < 2p_c = \frac{2a\gamma_{surface}}{k_BT\sigma}
\]

Equation 21

\(a\) is the lattice constant, \(\gamma_{surface}\) is the interfacial tension. When supersaturation is high the impurity effect is small as the critical sized nucleus is also small. However, when the supersaturation is low, the size of the critical two dimensional nucleus is larger and the impurities can have a lower surface concentration to prevent growth.

**1.7.2 Isotherm Models**

Impurities bound to a crystal surface are expected to be in equilibrium with the impurity in solution, thus at a fixed temperature an adsorption isotherm can be applied if the concentration of impurity in solution is known. The general expression for the Langmuir isotherm is\(^6^5\):
Equation 22

\[ q_l^{ads} = q_l^{mono} \left( \frac{Kx_{l,liq}}{1 + Kx_{l,liq}} \right) \]

\( q_l^{mono} \) is the concentration of impurity adsorbed at the surface when there is monolayer coverage, \( x_{l,liq} \) is the mole fraction of impurity in the liquid phase and \( q_l^{ads} \) is the concentration of adsorbed impurities. \( K \) is the Langmuir constant. Manipulation of the Langmuir Isotherm has been employed by several workers to model the adsorption of the impurities into growth sites\(^6\), \(^{33}\), \(^{39}\), \(^{67}\), \(^{68}\). An expression for step, ledge or terrace adsorption was developed by Bliznakov\(^{69}\):

\[ v_l = v_p (v_p - v_{mono}) \Theta \]

Equation 23

\( \Theta \) is the fractional surface coverage of adsorbed impurity and is the degree of coverage from the Langmuir isotherm, \( v_p \) is the step velocity in pure solution and \( v_{mono} \) is the limiting step velocity at monolayer impurity adsorption. This equation can be re-expressed as\(^{39}\)

\[ \frac{v_{mono} - v_p}{v_l - v_p} = 1 + \frac{1}{Kx_{l,liq}} \]

Equation 24

A plot of \( \frac{v_{mono} - v_p}{v_l - v_p} \) against \( \frac{1}{x_{l,liq}} \) will yield the Langmuir constant \( K \). \( \Theta \) relates to the amount of substance adsorbed to the surface compared to the amount of potential adsorption sites.

1.7.3 Davey and Mullin\(^{70}\)

Assuming that monolayer coverage of the surface causes zero growth, Equation 24 can be reduced to:
Equation 25

\[
\frac{V_0 - V}{V_{\text{mono}} - V} = 1 + \frac{1}{Kx}
\]

and plotting \(\frac{V_0 - V}{V_{\text{mono}} - V}\) against \(\frac{1}{x}\) will yield the Langmuir constant directly. However, not all impure systems will be ideal and adsorption will not always occur at stepped and kinked sites. A surface may experience incomplete coverage in which case the growth of a face will be hindered but not completely stopped.

1.7.4 Kubota and Mullin Model

The Langmuir equation is further adapted by the addition of an effectiveness factor, \(\alpha\). 

\[
\frac{V}{V_0} = 1 - \alpha \theta
\]

Equation 26

If \(\alpha\) is less than 1, growth of the crystal face will not cease even if monolayer coverage of impurity on the crystal face is achieved. If \(\alpha\) is more than 1, the Kubota and Mullin model predicts that growth will cease before monolayer coverage is achieved and is \(\alpha\) is inversely dependent on supersaturation:

\[
\alpha = \frac{\gamma \alpha}{k_b T \sigma L}
\]

Equation 27

\(\alpha\) is the size of the growth unit, \(\gamma\) is the edge free energy and \(L\) is the separation of sites available for impurity adsorption. As supersaturation increases, the amount of growth units in solution available to bind to a kink site which at equilibrium would be occupied by an impurity is much higher; therefore at higher supersaturation the probability of impurity attachment is reduced. This results in an increase in the growth rate of the crystal to somewhere near that of pure growth.

If the impurity attachment time is small throughout the supersaturation range, no deviation from the impure growth rate will be observed. These cases are shown below;
the red line shows the time constant $\tau$ and its variation from 0 to $\infty$ after a certain supersaturation is achieved. This supersaturation level may be different to that required for impure growth to occur ($\tau = 0$), where the line would curve before the start of the impure growth line (not shown in Figure 30).

![Graph showing the variation of growth with supersaturation in the presence of impurities](image)

*Figure 30. A graph showing the variation of growth with supersaturation in the presence of impurities.*

As impurities are assumed to be indistinguishable from the solute, adsorption is expected to occur in the same active sites where solutes will bind. In a fast growing crystal face, there will be high amounts of kink sites. If the impurity acts upon this fastest growing face, the kink sites will be occupied preventing further growth.

### 1.7.5 Crystal Growth Rate Methods and Measurements

A lot of research into crystal growth rates from solution has been performed for both pure solutions and in the presence of additives. Various techniques were adopted such as monitoring the weight of a crystal, or using optical microscopy to allow time lapsed measurements. However, face specific measurements may be more insightful for kinetic measurements.

Glycine is a fairly well studied system with reports of growth hindrance yet also the increase of growth rate in the presence of additives. Dowling et al used a growth cell with stagnant solution in conjunction with an optical microscope to monitor the growing crystal. Malonic acid and racemic aspartic acid were reported to reduce the growth rate of the metastable $\alpha$ glycine. However, unexpectedly increased the growth
rate of the more stable polymorph $\gamma$ glycine. Li et al used a flow cell to measure the growth rate of glycine in the presence of leucine and other amino acids. A concentration dependence of $\alpha$ leucine on the growth rate of particular faces of $\alpha$ glycine was reported and below 8mg/ml leucine; the growth was hindered. However, above this concentration the growth of the (010), (011) and (01$\bar{1}$) faces of $\alpha$ glycine is promoted\(^{56}\). Yang et al measured the growth rate of L-alanine in pure solution and also in the presence of L-valine\(^{74}\). The growth rate of the (011) surface of L-alanine is initially found to be hindered by the presence of low concentrations of L-valine. However, increasing the additive concentration is found to promote the growth of the (011) surface.

Squaldino et al used mono-crystalline seeds to measure the growth rate of sucrose in pure solution and also in the presence of raffinose\(^{75}\). The seed crystals were mounted on framework in a preheated 500mL vessel before saturated solution was added. An optical microscope was used to monitor the growth. Beckmann and Boistelle\(^{76}\) used a similar flow cell method as Simon et al\(^{77}\) to measure the growth of butanone in the presence of an emulsifier (span 60). Seed crystals were mechanically attached to a holder in order to direct the solution flow perpendicular to the [001] direction of growth.

### 1.8 Molecular Modelling

Computational chemistry is widely employed within the crystallisation community and software is readily available for examining crystal surfaces (assuming a surface is a perfect termination of the bulk). The effects of additives or impurities on the growth of crystals is very difficult to predict. However, the use of molecular modelling or more specifically the comparison of the interaction of solute and additive molecules with specific surfaces can give valuable insight into the likely effect on the morphology of the crystals.

Molecular recognition at solid-fluid interfaces is the main advantage of crystallisation and this is exploited in molecular modelling. The technique has been used in several ways: to rationalise additive or impurity effects on a crystal morphology\(^{18, 78}\), to predict additive or solvent effects\(^{71, 79}\) and also to choose an additive in order to preferentially crystallise a single enantiomer\(^{46}\) from racemic solutions. The analysis is very versatile
and the methodology is easily varied to tailor the computation to more specific calculations. Different methodologies have been reported involving molecular dynamics\textsuperscript{49,80} and surface docking calculations\textsuperscript{78,81}. Molecular dynamics can provide much more insight into growth of a crystal. As molecules have motion, the technique is more sophisticated and calculations take longer compared to simple docking calculations\textsuperscript{82}.

Berkovitch-Yellin examined the binding of solute and additives to crystal surfaces\textsuperscript{20}. The energy of binding can be defined as the difference in energy when the solute or additive molecule is unbound compared to the energy once the solute or additive is bound to the crystal surface.

\[
E_b = E_{sl} - E_{att}
\]

Equation 28

\(E_b\) is the binding energy, \(E_{sl}\) is the slice energy and \(E_{att}\) is the attachment energy for a solute. Or:

\[
E_b' = E_{sl}' - E_{att}'
\]

\(E_b'\) is the binding energy for an impurity, \(E_{sl}'\) is the slice energy and \(E_{att}'\) is the attachment energy for a single impurity in a substrate crystal. Of more significance is the energy difference between the binding of the solute and the additive molecule defined as \(\Delta\Delta E\),

\[
\Delta\Delta E = \Delta E_s - \Delta E_a
\]

Equation 29

\(\Delta E_s\) is the binding energy of the solute molecule (\(E_b\)) and \(\Delta E_a\) is the binding energy of the additive (\(E_b'\)).

Positive values of \(\Delta\Delta E\) lead to the conclusion that the additive is more favourable to adsorb to the crystallising surface than the solute. Similar binding energies may lead to the possibility of the additive binding to the crystal surface. However, it is likely that the solute molecule will be incorporated. If the additive has a largely unfavourable energy it
can be concluded that the additive molecule is unlikely to bind and is unlikely to have an effect on the crystal morphology.

1.8.1 Surface Docking

Generally the morphology of the crystal is examined, either experimentally or using a morphology prediction to decipher the most morphologically important faces. Since BFDH and also $E_{\text{att}}$ energy predictions are readily available one need not know the experimental morphology in the first instance. However it is useful to know the morphology of the crystal grown from solvents or the melt to allow comparison. The surface compositions of the faces predicted as the most morphologically important are subjected to docking calculations.

Poornachary predicted the modified morphology of glycine and PMG crystals using an $E_{\text{att}}$ method\textsuperscript{78}. Initially the relative morphological importance of the crystal faces was analysed with the largest faces then cleaved and expanded to desired size in a vacuum. The energy of the crystal lattice was then calculated before (additive and solute) molecules were docked at the centre of the surface. The geometry of the docked molecules was optimised with the lattice constrained as rigid bodies before the energy was the recalculated. The energy values allow analysis of the interaction of solute and additive to specific surfaces explaining observed experimental effects from impurities.

Clydesdale et al\textsuperscript{22, 41} used probe (solute or solvent) molecules as rigid bodies in grid based searches to analyse the most energetically favourable binding site for surfaces of highest morphological importance. The technique differs in that the conformation of the additive used as the probe is treated as a rigid body from a solid state structure and remainns unchanged throughout.

Hammond derived an equation to calculate modified attachment energies of surfaces in the presence of additives\textsuperscript{79}. The technique is similar to that of Clydesdale in that additive molecules are treated as rigid bodies. However, a combination of water and ethanol were used as additives for the growth of aspirin crystals. The specific surface energy for the face (hkl) is related to the attachment energy by:
Equation 30

\[ \gamma_{hkl}^{\text{vacuum}} = \frac{Z E_{\text{att,hkl}}^{\text{vacuum}}}{2V_{\text{cell}}N_A} \]

Z is the number of molecules in the unit cell and \( E_{\text{att,hkl}}^{\text{vacuum}} \) is the energy released upon attachment of a growth slice. The lattice and slice energies are the pairwise summations of intermolecular interactions (on an atom-atom basis) between molecules in the crystal lattice and slice (of surface defined by h,k and l) respectively. Converting individual interaction energies for probe molecules (water, ethanol and aspirin) \( U_{\text{probe}} \) to specific interaction energies, \( \overline{U}_{\text{probe}} \) by:

\[ \overline{U}_{\text{probe}} = \frac{U_{\text{probe}}Z_{hkl}^{R}}{S_{hkl}^{R}N_A} \]

Equation 31

and

\[ S_{hkl}^{R} = \frac{V_{\text{cell}}}{d_{hkl}} \]

Equation 32

\( Z_{hkl}^{R} \) is the number of solvent molecules per reticular area, \( S_{hkl}^{R} \), \( V_{\text{cell}} \) is the unit cell volume, \( d_{hkl} \) is the perpendicular spacing between lattice planes (hkl) and \( N_A \) is Avogadro’s number. The attachment energy of a surface in the present of solution then becomes:

\[ E_{hkl}^{\text{solution}} = E_{hkl}^{\text{vacuum}} - \frac{2Z_{hkl}^{R}}{Z} U_{\text{solution}} \]

Equation 33

\( U_{\text{solution}} \) is the energy of the solution. The method is successful in that it predicts much more plate like morphologies of aspirin matching experimental data. However, mainly applies to growth in the presence of solvents and not in the presence of additives.
1.8.2 Molecular Dynamics (MD)

Lee et al docked a molecule (solvent) to the centre of a crystal surface and used molecular dynamics to move the molecule around the crystal surface whilst optimising the geometry and re-calculating the binding energy\(^83\). Using a previously derived equation by Hammond et al\(^79\) the modified attachment energy was used to calculate crystal habits in the presence of solvent with mixed results. Chen and Trout also used the same method of calculating modified attachment energies for form 2 of 2,6-dihydroxybenzoic acid, reporting needle shaped crystal habits in the presence of single solvent as well as mixed systems with limited accuracy\(^84\).

Kumar and Shastri used a BFDH morphology prediction in order to determine the most morphologically important crystal faces before molecular dynamics simulations were performed\(^80\). The method differs in that the crystal lattice is first constructed and then surrounded by solvent molecules. These layers consisted of pure solvent and also two component solvents (in order to simulate an anti-solvent), producing reasonable results. The interaction energy between the solvent layer and the surfaces were computed. Modified attachment energies were calculated a simplified equation\(^85\):

\[
E_{\text{interaction}} = E_{\text{total}} - (E_{\text{surface}} + E_{\text{additive}})
\]

Equation 34

\(E_{\text{interaction}}\) represents the modified attachment energy, \(E_{\text{total}}\) represents the total interaction energy of the system (i.e. the lattice as well as the docked additive), \(E_{\text{surface}}\) is the interaction energy of the atoms in the surface and \(E_{\text{additive}}\) is the interaction energy of the additive with the surface.

Duan et al used MD to examine the effect of acetone on the growth of HMX crystals\(^86\). The morphologically important faces were chosen from an attachment energy prediction. Each surface consisted of 72 HMX molecules with 200 acetone molecules at a temperature of 550K. The modified attachment energy was calculated matching well with experimentally grown crystals.
1.8.3.1 Ulrich Build in Method

Lu and Ulrich defined two different methods for analysing the effect of additives on the crystal morphology grown from the melt\(^\text{87}\). The build-in method involves introducing the additive into the unit cell after minimization, replacing one solute molecule. This unit cell is then expanded (with the symmetry reduced) resulting in host molecules becoming replaced with additives throughout the lattice. As the additive is not originally placed in the most energetically favourable lattice position, the additives geometry is minimised whilst the host molecules and unit cell dimensions are held constant followed by a molecular dynamics simulation to recalculate the charges. The incorporation energy of the host molecule is defined by:

\[
E_{hkl}^b = E_{hkl}^s + \frac{1}{2} E_{hkl}^{att}
\]

Equation 35

The incorporation energy of an additive is defined by:

\[
E_{hkl}^{b'} = K_i E_{hkl,i}^{st} + \frac{1}{2} E_{hkl,i}^{att}
\]

Equation 36

\[K_i = \frac{E_{cr}}{E_{cr,i}'},\]

\[E_{cr} \text{ is the lattice energy of a pure crystal, } E_{cr,i}' \text{ is the lattice energy of a crystal with an additive docked in position } i,\]

\[E_{hkl,i}^{st} \text{ is the slice energy of a surface (hkl) with an additive docked in position } i \text{ and } E_{hkl,i}^{att} \text{ is the attachment energy of a surface (hkl) with an additive in position } i.\]

The difference in incorporation of additive and solute is thus calculated by:

\[
\Delta E_{hkl,i}^b = E_{hkl}^b - E_{hkl}^{b'}
\]

Equation 37

and the modified attachment energy is given by:
\[ E_{\text{att}}^{\text{hkl}} = \frac{1}{n_s} \sum_{i=1}^{n_s} \left[ E_{\text{att}}^{\text{hkl}}(1 + f \times \Delta E_{hkl,i}) \right] \]

Equation 38

\[ f = -\frac{2}{E_M^{\text{att}}} \] and \( E_M^{\text{att}} \) is the attachment energy of the most important face of the crystal.

**1.8.3.2 Ulrich Surface Docking method**

Lu and Ulrich also reported a surface docking method in which the unit cell remains pure whilst the lattice is constructed. The additive molecule is then docked onto the crystal lattice (fixed in position) followed by molecular dynamics in conjunction with energy optimisation in order to calculate the most favourable binding position. The binding energy for a given face (hkl) is now:

\[ E_{b,hkl} = E_{s,hkl} - E_0 \]

Equation 39

\( E_{s,hkl} \) the minimum energy of the surface with the additive bound and \( E_0 \) is the energy of a single additive molecule when unbound. \( E_{b,hkl} \) is calculated for additive \( (E_{b,hkl}^0) \) and solute molecules \( (E_{b,hkl}^0) \). The binding energy difference between the two is:

\[ \Delta b_{hkl} = E_{b,hkl}^0 - E_{b,hkl}^0 \]

Equation 40

And the modified attachment energy is now:

\[ E_{\text{att}}^{\prime,hkl} = E_{\text{att},hkl}^0 - E_{\text{att},hkl}^0 \times \left( \frac{\Delta b_{hkl}}{E_{b,hkl}^0} \right) \]

Equation 41

\( E_{\text{att},hkl}^0 \) is the attachment energy of the pure crystal surface. The build in approach is reported to be limited as the approach does not predict accurate results for ethylparaben crystals whereas, the surface docking method is found to be more accurate. The surface docking approach is also applied to benzophenone with ethanol, benzoic acid
and diphenylmethane as additives producing reasonable morphology predictions. Lemmer and Reuther favoured the build in approach for succinic acid growing from water and acetonitrile. They reported that acetonitrile does not alter the habit whereas, water has a significant effect on the (100) crystal surface increasing the morphological importance as observed experimentally. Yang et al favoured the surface docking method for L-alanine crystals grown in the presence of L-valine predicting that the attachment energy of L-valine is more favourable than L-alanine.

1.8.4 Modelling Crystal Habits from Solution

Winn and Doherty developed a different method of predicting crystal habits grown from solution. The model uses calculated values for solvent interactions with kink sites in order to estimate the effects on crystal morphology. Initially the morphology is predicted using an attachment energy method. The surface composition of morphologically important faces is then analysed to determine important periodic bond chains within these faces. The effective interfacial free energy at a kink site is then calculated for each important bond chain using:

\[
\gamma^{kink} = \gamma^{\text{cryst}} \gamma^{\text{solv}} - 2 \sqrt{\gamma^{\text{cryst}} \gamma^{\text{solv}}}
\]

Equation 42

\(\gamma^{\text{cryst}}\) and \(\gamma^{\text{solv}}\) are the energy of cohesion for the crystal surface and solvent surface respectively, corresponding to the energy of forming a surface between a vacuum and either the crystal or solvent phases in this case. \(2\sqrt{\gamma^{\text{cryst}} \gamma^{\text{solv}}}\) is the adhesion energy between the two surfaces and is the geometric mean of the two cohesion energies. The value of \(\gamma^{kink}\) is then used to calculate \(\phi^{kink}\) from:

\[
\phi^{kink} = \gamma^{kink} A^{kink}
\]

\(A^{kink}\) is the kink area (cm²/mol). The energy of a step is then related to the energy of a kink and four possible equations can be used to calculate the step energy. If the largest \(\phi^{kink}\) value for a face is less than \(RT\) the face is expected to grow by two-dimensional nucleation. If the largest value of \(\phi^{kink}\) is larger than \(RT\) the screw dislocation model is applied. The relative growth rates are then calculated according to the relevant growth
model. Thus, habit prediction is possible using a Wulff plot. A limitation of the model is that it assumes that dispersive forces are the main interactions at steps and kinks. Thus, for inorganic systems the model does not predict accurate habits. However, in the cases of adipic acid grown from water, ibuprofen grown from hexane and ethanol and biphenyl from toluene predicted morphologies are in good agreement with experiment. One of the benefits of this system is that simple calculations using pure component properties allow simple evaluation of the effect of solvent on crystal morphology.

Various methods for modified attachment energies are available, all of which predict results matching with experiment in some cases. Molecular dynamics calculations can provide more accurate results and are more time consuming compared to rigid body docking calculations. However, the additive is of a fixed conformation which may not be the most potent growth site inhibitor.

1.9 Conclusions

This chapter has reviewed the theories of nucleation and crystal growth and the effects that impurities and additives can have on the growth process, including mechanisms of additive/impurity binding. The theory of crystal habit prediction has also been discussed including some examples of the effects of impurities (including ‘tailor made’ additives) on the resulting morphology of the crystals. Methodologies used to rationalise the effects of additives such as molecular mechanics and molecular dynamics have also been discussed.

1.9.1 Project Aims

The aim of this thesis is to observe the effects of tailor made additives on molecular crystals consisting of van der Waals intermolecular interactions. Previous tailor made additive work is mainly concerned with hydrogen bonded systems with strong directional intermolecular bonds with little research for molecular crystals containing weak non-directional van der Waals interactions. The principles of traditional ‘tailor made additive’ work will be applied to a van der Waals molecular crystal system. Crystal growth measurements from pure solution and in the presence of additives will be investigated to gain insight into the growth kinetics. In conjunction with this,
molecular modelling of additive incorporation into specific crystal faces is to be performed with the aim of predicting a modified morphology matching experimentally encountered effects. Products will be subjected to several analytical techniques such as powder and single crystal X-ray diffraction, microscopy as well as molecular modelling techniques to provide prediction and analysis of additive efficacy.
2. Experimental

This chapter describes the major experimental and analytical techniques used in this body of work.

2.1 Materials

Table 1 shows a table of the chemicals used in this study in conjunction with the supplier and purity information. All chemicals were used without further purification.

<table>
<thead>
<tr>
<th>Material</th>
<th>Chemical Formula</th>
<th>Purity</th>
<th>Molecular Weight</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzophenone</td>
<td>C_{12}H_{10}O</td>
<td>99%</td>
<td>182.217</td>
<td>Acros Organics</td>
</tr>
<tr>
<td>4-aminobenzophenone</td>
<td>C_{13}H_{12}NO</td>
<td>98%</td>
<td>197.23</td>
<td>Acros Organics</td>
</tr>
<tr>
<td>4-methylbenzophenone</td>
<td>C_{14}H_{12}O</td>
<td>99%</td>
<td>196.25</td>
<td>Sigma Aldrich</td>
</tr>
<tr>
<td>4-fluorobenzophenone</td>
<td>C_{13}H_{9}FO</td>
<td>98%</td>
<td>200.21</td>
<td>Alfa Aesar</td>
</tr>
<tr>
<td>Diphenylamine</td>
<td>(C_{6}H_{5})_{2}NH</td>
<td>99%</td>
<td>169.23</td>
<td>Sigma Aldrich</td>
</tr>
<tr>
<td>Diphenylethylene</td>
<td>(C_{6}H_{5})<em>{2}=CH</em>{2}</td>
<td>97%</td>
<td>180.25</td>
<td>Sigma Aldrich</td>
</tr>
<tr>
<td>Diphenylmethane</td>
<td>(C_{6}H_{5})<em>{2}CH</em>{2}</td>
<td>99%</td>
<td>168.24</td>
<td>Alfa Aesar</td>
</tr>
<tr>
<td>2-methylbenzophenone</td>
<td>C_{14}H_{12}O</td>
<td>98%</td>
<td>196.25</td>
<td>Alfa Aesar</td>
</tr>
<tr>
<td>3-chlorobenzophenone</td>
<td>C_{13}H_{9}ClO</td>
<td>99%</td>
<td>216.67</td>
<td>Acros Organics</td>
</tr>
<tr>
<td>4-nitrobenzophenone</td>
<td>C_{13}H_{8}NO_{3}</td>
<td>99%+</td>
<td>227.22</td>
<td>Acros Organics</td>
</tr>
<tr>
<td>Propan-2-ol</td>
<td>C_{3}H_{8}O</td>
<td>99%+</td>
<td>60.1</td>
<td>VWR</td>
</tr>
</tbody>
</table>

Table 1. A table of chemicals used in this study.

In this body of work the abbreviations in Table 2 will be used for chemicals other than benzophenone and propan-2-ol. The abbreviations are used throughout the remainder of the thesis.
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-aminobenzophenone</td>
<td>4ABP</td>
</tr>
<tr>
<td>4-methylbenzophenone</td>
<td>4MBP</td>
</tr>
<tr>
<td>4-fluorobenzophenone</td>
<td>4FBP</td>
</tr>
<tr>
<td>Diphenylamine</td>
<td>DPA</td>
</tr>
<tr>
<td>Diphenylethylene</td>
<td>DPE</td>
</tr>
<tr>
<td>Diphenylmethane</td>
<td>DPM</td>
</tr>
<tr>
<td>2-methylbenzophenone</td>
<td>2MBP</td>
</tr>
<tr>
<td>3-chlorobenzophenone</td>
<td>3ClBP</td>
</tr>
<tr>
<td>4-nitrobenzophenone</td>
<td>4NPB</td>
</tr>
</tbody>
</table>

Table 2. A summary of the chemical abbreviations used in this body of work.

### 2.2 Solubility

The solubility of benzophenone was measured using two techniques; the Crystal-16 and gravimetric analysis. Benzophenone is not very soluble in water and is very soluble in some polar solvents with toluene affecting the crystal habit. The solubility in alcoholic solvents is good, yet not too soluble so that large amounts are required to perform crystallisations at 15°C. Propan-2-ol was chosen as the solvent since the solubility of benzophenone in organic solvents is good (Section 4). However, the vapour pressure of propan-2-ol is slightly less than that of ethanol reducing the potential for evaporation in crystallisation experiments.

#### 2.2.1 Crystal-16

The Crystal-16 consists of 16 temperature controlled wells equipped with magnetic stirring and a light source. The wells are split into four independent blocks of four, allowing different experiments to run simultaneously. Placed into the well were standard HPLC vials containing various amounts of benzophenone in propan-2-ol (1mL) with a magnetic stirrer bar. As temperature is increased, the benzophenone dissolves and when 100% transmission of the light source is achieved (full dissolution of benzophenone), the clear point is recorded. This temperature is recorded as the saturation temperature. The vials are then cooled, when the light transmittance drops below 100% the sample has begun to crystallise. This is known as the cloud point and corresponds to the boundary of the metastable zone. By starting with different amounts of benzophenone in a fixed amount of propan-2-ol the saturation points of different compositions may be measured allowing construction of a solubility curve.
measured cloud points allow some assumptions about the minimum metastable zone width. Only pure solubility measurements were performed in the Crystal-16.

2.2.2 Slurry and Gravimetric Analysis

An isothermal excess solid method was used to measure the equilibrium solubility of benzophenone with the additives in propan-2-ol. Solution samples were analysed gravimetrically. Slurries of excess benzophenone in propan-2-ol were prepared and stirred at a constant temperature of 15°C using a jacketed vessel (sealed with a ground glass stopper) and connected to a Haake water bath. The solutions were allowed to equilibrate for 72 hours in pure solubility measurements and 24 hours for solubility measurements in the presence of additive. After equilibration the magnetic stirring was terminated and the solution was allowed to settle before a sample (approx. 1.5mL) was removed using a syringe and transferred (via a syringe filter) to a pre-weighed oven dried glass vial. The vial was then re-weighed with the solution and left for the solvent to evaporate. Once all solvent had evaporated (confirmed by no further weight loss of the sample over a 24 hour period) the weight of the vial is recorded. The solubility was then calculated from the mass of the pre-weighed vial \( m_v \), the mass of the vial containing a sample of solution \( m_{solvent} \) and also the mass of the vial after evaporation of the solvent \( m_{solid} \).

\[
\text{Solubility (g per g)} = \frac{m_{solid} - m_v}{m_{solvent} - m_v}
\]

For solubility measurements in the presence of additives, amounts of varying mole fraction of additive were added with respect to the solute. The additive was added to the solvent and fully dissolved before solute was added to the solution. Solubility measurements in the presence of additives assume a uniform distribution of additive in the solvent, so that the amount of final solid can be corrected to give the solubility of benzophenone.

2.3 Crystallisation Techniques

Crystallisation is possible using several techniques including slow solvent evaporation and slow cooling methods. For crystal growth kinetics measurements seed crystals were
generated using a cooling crystallisation method. As the seal on the growth cell is not perfect, the temperature is reduced in order to limit solvent evaporation. If measurements are performed at higher temperatures it is possible for mist to form in the cell limiting visibility, especially in the case of water. Hence for crystal growth experiments the temperature is fixed at 15°C.

### 2.3.1 Cooling Crystallisation

Using a jacketed vessel it is possible to accurately control the temperature of the crystallisation. Figure 31 shows the typical experimental set up used for cooling crystallisations.

![Figure 31. A diagram showing typical experimental set up for cooling crystallisation experiments.](image)

An amount of benzophenone (more than the equilibrium solubility at 15°C) was weighed and added to the jacketed vessel with 10g solvent. The solution was heated to dissolve the excess solid and then cooled to 15°C to generate supersaturation. The supersaturation of a solution was defined as:

\[
\sigma = \ln \left( \frac{x_{ss}}{x_{eq}} \right)
\]

\(x_{ss}\) is the solution concentration in mole fraction and \(x_{eq}\) is the equilibrium solubility of solute expressed in mole fraction.
2.3.2 Benzophenone Seed Preparation

Seed crystals of benzophenone were used in crystal growth rate measurements and were grown from pure propan-2-ol solutions using a slow cooling crystallisation. The seed crystals were isolated and dried using vacuum filtration. Seed crystals used in growth experiments were typically 100x100μm.

2.4 Growth Rate Measurements

A growth cell, as shown in Figure 32 was connected to a circulating water bath and placed under the objective of a Zeiss Axioplan 2 optical microscope in accordance with the apparatus shown in Figure 33.

Figure 32. Images of the jacketed growth cell.

A solution of benzophenone and propan-2-ol (typically 5g) of desired supersaturation was added to a jacketed vessel (Figure 31) and heated to dissolve any traces of solid. An amount of benzophenone solution (ca 3mL) was transferred to the growth cell (Figure 32) along with a benzophenone seed crystal. The growth cell was covered with cling film to prevent solvent evaporation. The solution was then heated slightly to partially
dissolve the seed crystal and completely dissolve any crystals which may have formed (during the agitation) from transportation of the solution. The temperature was then reduced to 15°C to generate supersaturation. Growth measurements were performed at 15°C to reduce the possibility of solvent evaporation in the growth cell since a ground glass stopper to cover the cell is unavailable.

Figure 33. A diagram of the experimental apparatus used for seeded crystal growth experiments.

Photographs (under magnification of 25x) of the crystal were continuously taken every 30 seconds for a period of time (up to approximately 48 hours) or until the crystal had grown too large to measure (see example in Figure 34). The images are of the crystal growing over time and the red lines on the individual images show the length and width measurements taken. The average growth rate of the crystal is calculated from these measurements of crystal dimensions over time. Experiments found to have more than one crystal in the cell were discarded since the calculated supersaturation is not accurate.
Figure 34. Images of a growing crystal of benzophenone.

Growth measurements in the presence of additives were performed in the same fashion, except the additive was added to the solution in the jacketed vessel. The amount of additive added to the solution was proportional to the benzophenone only. Hence a 10% additive concentration is calculated as 0.1 mole fraction of the total solid in solution.

2.5 Induction Times ($t_{\text{ind}}$)

Induction time measurements were performed on two different scales, 125 mL and 12.5 mL both at 15°C (since growth measurements were also performed at this temperature). The two experimental techniques have similarities differing in the method of detection and stirring. The induction time (Section 1.3.6) is recorded as the length of time taken for crystals to be detected after the solution reached 15°C. Times were measured using a stopwatch for small scale experiments and the time for an increase in solution turbidity to be detected for larger scale experiments.

2.5.1 12.5mL Scale (Jacketed Vessel)

A jacketed vessel (capacity 30 mL) was used in the same manner as solubility measurements (Figure 31). 12.5 mL (10g propan-2-ol) and an amount of solid
benzophenone depending on required supersaturation was added to the jacketed vessel. The solution was heated with stirring until all of the solute dissolved and then cooled to 15°C to generate supersaturation. The time taken for generation of detectable crystals to form is timed whilst the solution remains stirred at a constant rate.

The solution was then reheated and held at 30°C (for approx. 30 mins) until all trace of the solute dissolved and cooled to 15°C to repeat the experiment. This was then repeated at least four times for each supersaturation. Induction times in the presence of additives were performed in the same manner with the additive added to solution before initial heating was performed. The method of detection was by sight, thus generation of turbidity in the solution may occur before detection was humanly possible.

2.5.2 125mL Scale

A Syriss Atlas automated vessel (Figure 35) was used for induction times at 125mL scale. The jacketed vessel (250mL capacity) has integrated temperature and turbidity probes with a pitched blade overhead stirrer. The solvent and solute (125g propan-2-ol and 19.4752g benzophenone for \( \sigma = 0.12 \)) were added to the reactor at 15°C and held at this temperature before being heated to 35°C over the course of 30 minutes to dissolve any trace of solid benzophenone. After 30 minutes at 35°C the solution was then cooled to 15°C over the course of 30 minutes and then held at this temperature with stirring set to 200 rpm until a large change in turbidity of the solution was detected. The program was then repeated to obtain at least 4 measurements of \( \tau_{ind} \). Induction times in the presence of additives were performed with the same procedure with the additive added before temperature cycling began.
2.6 Molecular Modelling$^{82, 92}$

Computational analysis of molecules is now common practice and the theoretical prediction of molecular behaviour is now possible with advances in computer technology enabling rapid calculation. Many computational methods are available such as quantum mechanics and molecular mechanics differing in the method of calculation, accuracy and computer power required. In this work only molecular mechanics was used.

2.6.1 Molecular Mechanics and Force Fields

Molecular modelling, using a form of molecular mechanics was used to rationalise the experimental effects of additive molecules on the growth of benzophenone. Docking of additive molecules onto individual crystal surfaces is a useful technique in order to evaluate whether an additive molecule is likely to bind to a crystal surface. Force field methods were used in two ways, with Materials Studio using a Dreiding$^{93}$ force field with Gasteiger charges and secondly with a rigid body grid based docking search also using a Dreiding$^{93}$ force field with Gasteiger charges.
Not all computational problems in existence require complex calculations; hence, a rigorous and time consuming computer calculation method using quantum mechanics is not always desirable. In contrast to quantum mechanics, molecular mechanics requires much less computational power and thus is a much faster method of calculation. Force field methods use a different approach to the Born-Oppenheimer approximation, where molecules are represented as collections of spheres connected by springs. Thus, the motion of these atoms is then described by potential energy functions. Several force fields exist nowadays, all differing slightly in the functions used to describe the energy. Generally a force field describes the energy as a function of the bonded and non-bonded interactions between atoms. These two sets can again be split into several subcategories, in which the differences between force fields arise and the summation of these categories gives rise to the total energy (Equation 43).

\[ E_{FF} = E_{stretch} + E_{bend} + E_{torsion} + E_{vdw} + E_{el} + E_{cross} \]

**Equation 43**

\( E_{FF} \) is the total energy calculated by the force field, \( E_{stretch} \) is the stretching energy, \( E_{bend} \) is the energy from bending, \( E_{torsion} \) is the torsional energy, \( E_{vdw} \) is the energy from van der Waals forces, \( E_{el} \) is the electrostatic potential and \( E_{cross} \) is the energy from cross terms describing improper torsions of the molecule. Selecting a force field for a calculation can be time consuming since each force field defines different energies differently and several are now commercially available. Only Dreiding and Universal force fields are available in Materials Studio, hence the choice of a force field is not an issue.

### 2.6.2 Universal Force Field\(^{94}\)

The Universal force fields (UFF) have a reduced parameter set in order for quick calculations across a range of atoms in the periodic table. Reducing the parameter set limits the accuracy of the force field in comparison to a more parameterised force field such as Dreiding\(^{93}\) or Compass\(^{95}\).
2.6.3 Dreiding Force Field

The Dreiding force field is generally applicable to most molecules and uses a united atom approach. This approach treats a CH$_2$ group for example as one unit rather than a carbon and two hydrogens, thus simplifying calculations for larger molecules. The force field uses the full range of terms stated in Equation 43. For full methodological details see section 7.2.

2.6.2 Morphology Predictions

Using Materials Studio it is possible to predict crystal morphologies from a crystal structure using an attachment energy ($E_{\text{att}}$) method. The method calculates the release in energy of the lattice upon binding a ‘slice’ of thickness $d_{hkl}$ is added to the crystal face. The relative rates of growth for a crystal are dependent upon the magnitude of the $E_{\text{att}}$. Faces which result in a larger release in energy will grow faster in comparison to faces releasing less energy. Thus the morphological importance of a crystal face is inversely proportional to the $E_{\text{att}}$. The attachment energy method used in this body of work uses a Dreiding force field with Gasteiger charges.

2.6.2.1 Attachment Energy ($E_{\text{att}}$)

Materials Studio uses an attachment energy method to predict ‘growth morphologies’ of crystals. The relationship between the attachment energy of a surface (in a vacuum) to the relative growth rate is used in order to produce non-equilibrium morphology. The program analyses all possible surfaces and geometries producing morphologies based on the most stable faces which could limit the growth rate, thus, producing the most morphologically important faces. In conjunction with a three-dimensional crystal morphology, a table of relative facet areas and corresponding attachment energies are produced. It is then possible to alter these attachment energies and generate a new habit based on said values.

2.7 Analytical Techniques

This section covers the main analytical techniques used in this body of work.
2.7.1 X-ray Powder Diffraction (XRPD)\textsuperscript{9}

X-ray powder diffraction is a common analytical tool for testing crystalline samples. The spectra are easily comparable as each compound has its own ‘fingerprint’ type spectrum. Comparison of a sample with a reference is easy as the two spectra can be overlaid and the peaks checked for a match.

X-rays are scattered elastically and non-elastically by electrons of the atom they hit and are reemitted as spherical waves\textsuperscript{96}. If the atoms hit are arranged in a regular pattern, i.e. a crystalline lattice, the reemitted waves will experience constructive and destructive interference. This interference will cause X-rays of different intensities to be reemitted depending on the observing angle. The interference experienced is related to the symmetry of the crystal lattice and information from the pattern can be used to obtain the space group of the compound. The Bragg equation describes how the constructive interference is related to the angle of scatter, interplanar distance and also the wavelength of the radiation.

Figure 36. An image showing sample X-ray diffraction.

Figure 36 shows a sample diagram of the relationship of Bragg’s law and X-ray diffraction. When constructive interference (n = an integer) occurs between scattered waves, the path length between the two waves is equal to $2d_{hkl} \sin \theta$. \newpage
Different compounds will have different interplanar spacing, hence a different ‘fingerprint’ spectrum. A Rigaku Miniflex benchtop powder XRD machine was used for this project. This is set up in the Bragg-Brentano geometry, with the powder sample pressed flat onto the surface. The X-ray source and the detector are both at angle $\theta$ to the sample. The diffracted X-rays are sampled by the detector, a scintillation counter as the angle of the source and detector is varied in relation to the powder.

Samples were ground and placed in the silicon wafer sample holder, flattened with a microscope slide to reduce preferred orientation and typically scanned between angles of 3$^\circ$ and 40$^\circ$ 2-theta at a rate of 1.5$^\circ$ per minute with a step size of 0.03$^\circ$.

2.7.2 Single Crystal X-ray Diffraction (SCXRD)

Single crystal X-ray diffraction uses the same principles and PXRD, with larger single crystals used instead of a number of small crystals, and therefore, diffraction only occurs in one direction. The single crystal of a particular size (ideally 0.25mm by 0.25mm) is identified under a light microscope with crossed polarisers. The crystal is then mounted on a small glass fibre with a coating of immersion oil which freezes at low temperature holding the crystal in place. The goniometer is then placed in the X-ray beam and aligned such that upon rotation the crystal remains in the X-ray beam.

A quick set of diffraction patterns are taken to check that the crystal produces good diffraction spots, mainly to reduce exposure time and check good quality data can be obtained allowing structure solution. If the diffraction is poor, structure solution will be difficult and exposure time will need to be significantly increased. These initial images can be used to determine an initial unit cell and inherent crystal symmetry. A full set of data collection is then performed, rotating the crystal as time progresses to ensure diffraction at all angles is achieved (the crystal can be rotated in all three dimensions to enable this).

The data collected over the course of the diffraction is recorded and structure solution is then possible. The peaks provide information about the symmetry of the crystal and also the planes of symmetry with the intensities corresponding to the position of the atoms in the unit cell, as the intensity of the reflection is sensitive to changes in the position of

\[ n\lambda = 2d_{hkl} \sin \theta \]
atoms\textsuperscript{9}. This data is processed by a program such as SHELX\textsuperscript{97} to produce the crystal structure.

\textbf{2.7.2.1 Single Crystal Indexing}

When a crystal is mounted on a diffractometer as per the method above a unit cell measurement is taken by exposure to the X-ray beam. The unit cell was then compared to benzophenone for a match. The crystal is then rotated about one axis by \(1\)° increments taking an image at each point until an image at each rotation is achieved. These images are then used to assign crystal faces as the diffractometer knows the orientation of the crystal in the X-ray beam and also the unit cell symmetry. Hence faces can be assigned \(h,k\) and \(l\) values.

\textbf{2.7.3 Differential Scanning Calorimetry (DSC)}

DSC is a technique used to measure the energy required to heat a pan of a substance of interest compared to a pan containing a reference sample by the same amount. The temperature rise is valuable as melts, solvent evaporation and crystallizations concerning the substance require more energy for the same temperature rise and are represented as peaks in the thermogram of the substance.

The calorimeter is calibrated regularly using a reference material to ensure the measured heat flow is accurate. Once a new sample has been tested, the limits of the calorimeter are checked to ensure this accuracy; if the machine exceeds the limits recalibration is performed. Indium melts at 156.6\(^\circ\)C and shows a sharp endotherm peak (Figure 37).
DSC is a particularly useful technique to test whether a sample has retained or absorbed solvent or impurity\textsuperscript{98}. Other techniques may not show much difference in the spectrum if solvent has been absorbed although significant changes in a thermogram may be observed. The equipment used is a Mettler Toledo FP90 controller with a Mettler Toledo FP85 TA cell. Samples were weighed into a pan (typical weights of between 1 and 5mg) which was then sealed and pin holed allowing gases to evaporate. Heating rates of 10°C per minute were used.

**2.7.4 Optical Microscopy**

Since crystals exhibit a large range in size and morphology, an optical microscope can be used to examine crystal habit and the particle size distribution. Crystalline materials are generally anisotropic (inequivalent axes) exhibiting a property known as birefringence\textsuperscript{65}. Thus, elucidating a single crystal is possible using an optical microscope with crossed polarisers. The crystal will refract incident light into the plane of the polariser causing a crystal to appear illuminated in an otherwise dark background. Two microscopes were used for crystal analysis, a Reichert-Jung Polyvar and a Zeiss Axioplan 2. Both microscopes are equipped with cameras connected to a computer to allow photographs to be taken.
2.7.5 HPLC

High Performance Liquid Chromatography (HPLC) was used to analyse dissolved samples of benzophenone grown in the presence of additives. A Varian Star HPLC with an auto sampler and UV-detection at 254nm was used in this body of work. A 250 x 4.6 mm Phenomenex Hyperclone C8 BDS column with 5μm particle and 130Å pore sizes was used for all chromatography in conjunction with a mobile phase consisting of a 50:50 mixture of acetonitrile and water at a flow rate of 1mL/min. Two 20μL injections were performed for each sample tested. Samples of benzophenone were dissolved in propan-2-ol to desired concentrations (approx. 80-100μg/mL).

In ‘normal’ chromatography the stationary phase is polar; therefore, eluents which are more polar are retained in the stationary phase for longer. In ‘reverse’ phase chromatography a non-polar stationary phase is used resulting in the opposite. More polar analytes elute faster than non-polar as their solubility in the mobile phase is greater.

Calibration curves of 4MBP, 4ABP and DPM were all measured to allow calculation of concentrations of additive in samples of benzophenone. The area of the peak in the chromatogram of a pure additive sample was plotted against the concentration. A stock solution of sample was created and diluted allowing a range of concentrations to be tested. The relationship between peak area and concentration allows the concentration of additive in the sample to be determined. Sample concentrations of 1-20μg/mL were used to construct the calibration curves for 4MBP and 4ABP and concentrations of 2-40μg/ml for DPM.

2.7.6 Curve fitting

All curve fitting of equations is performed using OriginPro 9 where a custom non-linear fit function is created for each equation. The non-linear curve fits are performed using a Levenberg-Marquardt algorithm (a form of least squares curve fitting) to adjust parameter values in an iterative fashion until the fit converges on the data.
2.7.7 Confidence Intervals

In cases of linear trends, 90% confidence intervals are presented. These are obtained from the critical t value associated with the sample set multiplied by the error in the gradient of the line of best fit (calculated using the LINEST function in Excel).

2.8 Conclusion

This chapter has outlined the materials and methods used for crystal growth and induction time measurements of benzophenone have been presented. In conjunction with this the main analytical and computational methods have also been outlined.
3. Benzophenone

Benzophenone is an aromatic ketone with two known polymorphic forms, $\alpha^{100}$ and $\beta^{101}$. With the $\alpha$ form the more stable. The molecule (shown in Figure 38) is a non-linear optic material and also used as a photo inhibitor in perfumes, soaps and inks. Preparation of the $\beta^{102}$ form is difficult yet possible with the $\alpha$ the common product from solution or melt crystallisation. The $\alpha$ form crystallises in the orthorhombic $P2_12_12_1$ space group$^{100}$ whereas, $\beta$ has the monoclinic $C2/c$ space group$^{102}$.

![Molecular structure of benzophenone](image)

*Figure 38. The molecular structure of benzophenone.*

There is interest in this system as the only intermolecular interactions in the crystal structure are non-directional weak van der Waals forces, this is reflected in its low melting point ($49^\circ$C). Molecular van der Waals crystals are not uncommon in industrial produce (as discussed in Section 1) yet little research has been conducted on their growth in the presence of impurities or additives.

3.1 Benzophenone Morphology

The morphology of the $\alpha$ polymorph is well known and has been discussed in previous literature$^{103,104}$. The molecule crystallises both from the melt and from organic solvents with the same prominent crystal faces$^{90}$ and the reported experimental and predicted morphologies ($E_{att}$ method$^{21}$ in section 2.6.2.1) match as shown in Figure 39. The diagrams show a very similar morphology, the Miller indices of the faces differ because the two structure solutions use differently defined crystallographic axes. Thus Figure 39a uses the most recent structure solution (BPHENO12$^{105}$) for which $a = 7.7378$, $b = 10.2421$ and $c = 12.0395$. While Figure 39b, taken from the work of Groth$^{106}$ and reproduced by Strickland-Constable$^{104}$ was an earlier structure solution pre-dating X-ray
crystallography in which the a and c axes are interchanged. This is clarified in Figure 39b where the authors x, y and z have been re-labelled a, b and c. This means for example, that the \{011\} faces in Figure 39a are equivalent to \{110\} of Figure 39b. It is noted that Figure 39b shows the existence of \{111\} faces which are not reproduced with the same morphological importance in the E\textsubscript{att} prediction.

Figure 39. The morphology of benzophenone, a) predicted morphology (E\textsubscript{att}) and b) idealised experimental morphology taken from “The Rate of Crystal Growth From The Melt”\textsuperscript{104}.
Figure 40. Images of growing benzophenone crystals from pure propan-2-ol solution.

Figure 40 shows images of typical benzophenone crystals grown in this study from propan-2-ol solutions at different supersaturation. The overall morphology of the crystals is similar to those shown in Figure 39. They exhibit large {011} faces as well as smaller capping {101} and {110} facets. Examining the experimental and predicted crystal morphology, the aspect ratio is slightly more than 1, indicating that the crystal shows similar growth rates in both directions. This is reflected in the facet area of the crystals as the {011} faces account for approximately 50% and the faces bisecting the a axis ({101} and {110} faces) account for approximately 45%.

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<td>-278.69</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Predicted attachment energies and Facet areas of benzophenone.

3.1.1 Previous Benzophenone Research

Benzophenone has been studied previously\textsuperscript{100, 101, 107-110} as the molecule has an ability to form large crystals\textsuperscript{107} despite having weak intermolecular interactions and has previously been researched because the simple organic molecule is a common synthetic
precursor. The molecule forms a co-crystal with DPA\textsuperscript{111} and the solubility in various organic solvents\textsuperscript{112} is well known.

Groth\textsuperscript{9} originally reported the benzophenone morphology, and stated that \{111\} faces were not always present in the final morphology and the most morphologically prominent faces were the \{011\}. Roberts et al (using Groth’s axis notation) observed a change in the morphology when crystals were grown from toluene at temperatures close to the melting point where solubility is very high\textsuperscript{90}. Toluene was perceived to inhibit growth of the \{021\} faces, increasing the morphological importance and creating a more isotropic crystal habit with consisting of \{110\} and \{021\} faces as shown in Figure 41b.

![Diagram showing benzophenone habit](image)

**Figure 41.** A diagram to show the benzophenone habit when grown from a) most organic solvents and the melt and b) toluene. Image taken from “Understanding The Solvent Induced Habit Modification of Benzophenone in Terms of Molecular Recognition At The Crystal Solution Interface”\textsuperscript{90}.

### 3.1.2 Crystal Structure

The benzophenone molecule is non planar in the crystal structure as shown in Figure 42 and the aromatic rings have a torsion angle of 51° since the steric repulsion from the hydrogen atoms do not allow a planar arrangement\textsuperscript{18} (Figure 42b).
3.1.3 Space Group Symmetry

Benzophenone crystallises in the non-centrosymmetric $P_2_1_2_1_2_1$ space group. The crystal structure has one molecule in the asymmetric unit and four molecules in the unit cell. The three two fold screw axes lie along each of the $a$, $b$ and $c$ axes. Figure 43 shows the unit cell of benzophenone with each benzophenone molecule coloured differently, each of these molecules is related by symmetry to one another.

Figure 43. A diagram showing the symmetric relationship between two molecules along the $c$ axis with one molecule removed from the unit cell for clarity.
In Figure 44, the red molecule is related to the green molecule along a screw axis parallel to the a axis and is related to the blue and black molecules along screw axes parallel to the b and c axes respectively.

![Figure 44. Diagrams showing the operation of the two fold screw axes along the a b and c axes.](image)

**3.1.4 Inequivalence of Crystal Faces**

Since the P2₁2₁2₁ space group contains only two-fold screw symmetry along each of the crystallographic axes of the unit cell, certain crystal planes of the same type are inequivalent. This inequivalence is revealed in the surface of these faces. For example, there are 8 {111} planes which lead to two sets of four symmetrically related {111} faces, i.e. the (111), (111), (111) and (111) faces are all equivalent to each other. However these are inequivalent to the symmetrically related (111), (111), (111) and (111) faces.

A similar inequivalence is true for the {011} crystal faces as the lack of inversion symmetry results in a (011) surface inequivalent to the (011). Figure 45 shows the (011) and (011) with the surfaces highlighted in red with some molecules removed for clarity. It is apparent that the distances between carbonyl groups at the surfaces are the same. However the direction in which the carbonyl group points relative to the surface is different. At the (011) surface the carbonyl groups point out of the surface whereas the opposite is apparent for the (011).
Figure 45. A diagram showing the (011) and (0\bar{1}1) surfaces of benzophenone.

The (011) and (01\bar{1}) face are equivalent as are the (0\bar{1}1) and (0\bar{1}\bar{1}) shown in Figures 46 and 47. The carbonyl groups point out of the surface for the (011) and (01\bar{1}) faces and points into the surface for the (0\bar{1}1) and (0\bar{1}\bar{1}) surfaces.
Figure 46. Images of the (011) and (01̅1) crystal surfaces of benzophenone.

Figure 47. Images of the (0̅1̅1) and (0̅1̅1) crystal surfaces of benzophenone.
3.2 Crystal Packing

Figure 48 shows the crystal packing of benzophenone viewed along the a axis. The crystal consists of anti-parallel layers of benzophenone molecules labelled A and B.

![Crystal Packing Diagram](image)

**Figure 48.** An image of the benzophenone crystal packing viewed along the b axis.

### 3.2.1 The Intermolecular Interactions within Layer A

Upon closer examination of layer A (Figure 49), a common intermolecular interaction is apparent between the carbonyl group and a hydrogen of an aromatic ring from a neighbouring molecule. The carbonyl forms intermolecular interactions with two different hydrogen atoms, one situated at the three position and one at the four. The length of the interactions are similar at 2.682Å (3-position) and 2.617Å (4-position), one of which can be roughly traced along the c axis and along the b axis there are no intermolecular interactions.
Figure 49. An image of intermolecular interactions between benzophenone molecules in layer A viewed along the a axis.

3.2.2 The Intermolecular Interactions within Layer B

Figure 50 shows the intermolecular interactions between benzophenone molecules in layer B. The layer exhibits the same intermolecular interactions as that displayed in Figure 49 (layer A) and the distance between the carbonyl and hydrogen atoms are also the same.

Figure 50. An image of intermolecular interactions between benzophenone molecules in layer B viewed along the a axis.
3.2.3 The Interactions between Layers A and B

Figure 51 shows the intermolecular interactions between benzophenone molecules situated in layers A and B. There are two different length interactions between the molecules in different layers. One set of interactions are between the carbonyl group and the three position of the aromatic ring. This has the same length (2.617 Å) as observed in the individual layers between the hydrogen at the 3 position and the carbonyl. The second interaction is between the carbon of the carbonyl group and hydrogen at the two position of the ring of an adjacent molecule (2.867 Å).

![Image of intermolecular interactions between benzophenone molecules in layers A and B](image)

Figure 51. An image of the intermolecular interactions between benzophenone molecules in layers A and B viewed along the b axis.

Figure 52 shows a closer view of the interactions observed between one molecule in layer A and the molecules in layer B. The length of the two edge-face interactions is similar at 2.785 Å and 2.874 Å. The edge-face interactions are slightly longer than the interactions involving the carbonyl atom. However, not as long as the distance between the centres of the two rings measured in Figure 52.
3.2.4 Packing Summary - Strategy for Additive Selection

Benzophenone is a simple organic molecule, mainly forming intermolecular interactions from the carbonyl group, except for minor edge-face π interactions. The electronegative carbonyl group interacts with the slightly electropositive hydrogen atoms around the aromatic rings. There is slight variation in the length of the interactions observed depending on the ring position of the hydrogen.

Figure 53 shows the molecular structure of benzophenone and a summary of the intermolecular contacts formed. Each dotted red line from the molecule represents a different intermolecular interaction with a neighbouring benzophenone molecule. Applying the concepts of traditional ‘tailor made additives’ would involve manipulation of these interactions by altering the intermolecular potential or functionality a solute molecule will experience at the crystal surface when the additive molecule is bound. For example, if the intermolecular interactions at a crystal surface involves the weak C=O - - H-C bond, the introduction of a molecule without the potential to form this interaction may alter the growth of this particular surface.
Figure 53. A diagram of the molecular structure of benzophenone and the intermolecular interactions formed in BPHENO12.

Clearly the carbonyl is the most important group of benzophenone in terms of forming intermolecular interactions and derivitisation at this point would be expected to have an effect on the growth of the crystal. Since the carbonyl atom is involved in all three axes of growth, changing the functionality and the stereochemistry at this site could affect the crystal growth in all three directions, whereas derivitisation of one of the hydrogen atoms around the ring may have an effect on the b and c axes only.

3.2.5 Ideal Additive Situation

The ideal situation is that the additive molecule satisfies the intermolecular interactions in the crystal surface in order to be incorporated. However the altered functionality from the additive molecule ideally points out of the crystal surface. Figure 54 shows this case for the example 4ABP (see abbreviations in Section 2) at the benzophenone (011) surface, the bound additive molecule has satisfied the interactions from the crystal surface as the section of the additive bound is the same as the benzophenone molecule. The difference is that further incoming solute molecules experience a difference in the surface binding potential, i.e. the amino group instead of hydrogen. This can disturb the further growth of this crystal surface as an amino group often causes a steric barrier to further growth.
3.3 BFDH Morphology with Crystal Packing

Using the Mercury software it is possible to produce a BFDH morphology prediction packed with benzophenone molecules. This is shown in Figure 55 and it is clear that one of the benzophenone aromatic rings points directly out of the {011} faces. From this it can be concluded that additives with different substituents around this ring could potentially affect the growth of the {011} crystal faces, albeit to different extents depending on ring position. Logically the additive molecules with the altered functionality at the 4 position should have the strongest effects since the 4 position points directly out of the {011} faces and would be the group encountered by incoming molecules. This would be followed by the 3 and the 2 positions respectively.
3.4 Potential Morphologies

In order to explore potential morphological changes resulting from the presence of additives Materials Studio was used to create customised growth morphologies (based on E_{att} method), in which the relative growth rates of faces were altered. For example increasing the morphological importance of the \{011\} faces simulates the effect of an additive hindering the growth of these faces.

3.4.1 The \{011\} faces

The \{011\} faces intersect the b and c axes of growth and additives which bind here having an effect on the growth are expected to generate a morphology much like Figure 56. The \{011\} surface growth rate has been slowed in comparison to the \{101\} and \{110\} surfaces (which remain constant) and the resulting morphology is an elongated habit in comparison to the pure morphology (section 3.1).
3.4.2 The \{101\} and \{110\} surfaces

Figure 57 shows a potential morphology if the \{011\} face growth rate remains unchanged, while the \{101\} and \{110\} faces grow slower in comparison. It is clear that the \{011\} faces begin to decrease in morphological importance and the general shape of the crystal remains the same as for the pure morphology (Section 3.1). An effect on the morphology is apparent upon further suppression of the growth rate of these faces, resulting in a needle shaped crystal such as that shown in Figure 58. Hence for additives having a weak effect on the \{110\} and \{101\} faces no overall change in the morphology may be observed, whilst a strong effect will produce a needle shaped crystal as is the case for \{011\} surface hindrance.
3.5 Carbonyl Substitution – potential to disrupt all three axes of growth

3.5.1 Diphenylamine (DPA)

Replacement of the carbonyl with an amine group to give DPA changes the functionality and also the stereochemistry of the molecule (Figure 59). The hydrogen accepting carbonyl group is replaced by the hydrogen donating amine group. There is still potential for further growth of a surface if the additive is bound since the amine group is known to form intermolecular hydrogen bonds in the solid state with benzophenone. However, the options are limited since the only functional group that could potentially bind with the amine group in the crystallization is the carbonyl group of the benzophenone. The benzophenone-DPA co-crystal (BZPPAM01\textsuperscript{101}) is shown in Figure 60. The concentrations of DPA required to form the co-crystal is much higher than what would normally be found as an impurity or additive concentration i.e. ppm levels.
Since the molecules are known to interact the DPA molecule has a strong possibility of interfering with the growth of benzophenone. Since the carbonyl group is derivatised, DPA may affect growth in all directions.

### 3.5.2 Diphenylmethane (DPM)

In DPM (Figure 63) the carbonyl is replaced with the methyl group and the molecule consists of two aromatic rings joined by the same central carbon. However unlike benzophenone the carbon is saturated instead of the covalently bound oxygen, thus, removing all hydrogen acceptors from the molecule. The lack of functionality in the molecule may also prevent the molecule’s inclusion into the crystal structure as it may be unable to satisfy any required intermolecular interactions for surface incorporation.
Figure 62. A diagram of DPM taken from the crystal structure (ZZZMKS0179) solved without hydrogen atoms.

Figure 62 shows a diagram of the DPM molecule, it is apparent that the aromatic rings are far from planar in the crystal structure having a dihedral angle of 110° since the central carbon is sp³ hybridized compared to sp² in benzophenone. Figure 63 shows how the DPM molecules are arranged in the crystal lattice, there are some edge-face ring interactions (4.091 Å) which are longer than observed in benzophenone 3.721 Å (distance between C and centroid). There is no evidence of π-π stacking between the molecules, most likely due to the large angle between the ring planes preventing layer formation.

Figure 63. A crystal packing diagram of DPM.

As with DPA the functionality is altered at the carbonyl position, hence if the molecule is effective as a growth inhibitor it could possibly alter the growth of the a, b or c axes of growth. However, its lack of intermolecular bonding potential may limit the activity as a growth modifier for benzophenone.
3.5.3 Diphenylethylene (DPE)

Figure 64. A molecular structure diagram of DPE.

DPE (shown in Figure 64) has a low melting point (approximately 6°C) and its crystal structure has not been solved. The molecule contains a rigid double bond at the central carbon with the oxygen changed to a methylene, removing the hydrogen accepting ability of the molecule. If effective it is postulated that the molecule may hinder growth along all three of the crystallographic axes. As with DPM this molecules lack of hydrogen accepting groups may reduce the potential of the molecule to become incorporated into the crystal structure, hence, its effects may be limited on crystal growth of benzophenone.

3.6 Substitution of ring hydrogen at 4-position – potential disruption to b and c axes

3.6.1 4-aminobenzophenone (4ABP)

Figure 65. The molecular structure of 4ABP.

Substituting the hydrogen at the 4 position for a larger hydrogen donating amino group give 4ABP (Figure 65). The molecule has an amino group instead of a hydrogen providing a hydrogen donating source.
The additive molecule will most likely have an effect on the b and c axes of growth if successful. However, may not have a strong effect on the a axis. Much like the interactions observed in the crystal structure of the pure 4ABP, the amino group may allow the crystal surface to continue to grow since the group is observed to form intermolecular interactions with a carbonyl (Figure 66).

3.6.2 4-methylbenzophenone (4MBP)

Substitution of the hydrogen with a methyl group (Figure 67) maintains a similar functionality to benzophenone in terms of hydrogen donors and acceptors.
The intermolecular interactions in the 4MBP crystal structure are similar in nature and length to that formed in benzophenone. Only weak long range van der Waals interactions between the carbonyl group and hydrogen (at the 3 position) and the methyl group (at the 4 position) are observed (Figure 68). These interactions are of similar length and from the same ring positions observed in benzophenone. If incorporated the additive will potentially hinder the growth of the b and c axes of growth but it is not likely to have a strong effect on the a axis of growth.

### 3.6.3 4-nitrobenzophenone (4NBP)

The chemical structure of 4NBP is shown below.

Figure 69. A diagram of the chemical structure of 4NBP.
The crystal structure of 4NBP has not been solved and the compound consists of a substituted bulky nitro group in place of the hydrogen atom at the 4 position (Figure 69). Nitro groups can form intermolecular interactions since both oxygen and nitrogen can potentially be involved in hydrogen bonds. If effective it is suspected that the additive will have an effect on the growth of the b and c axes. However the bulky nitro group may limit the extent of incorporation into the crystal lattice and consequently the efficacy of the additive.

3.6.4 4-fluorobenzophenone (4FBP)

![Molecular structure of 4FBP](image)

**Figure 70. The molecular structure of 4FBP.**

Substitution of the slightly electropositive hydrogen with the electronegative fluorine (Figure 70) changes the nature of the intermolecular potential at the 4 position of the ring. However the size of the fluorine is similar in size to that of a hydrogen, thus, if incorporated into a crystal surface the disruption to the lattice would be minimal from a steric perspective. Fluorine is known to form interactions with hydrogen atoms from neighbouring molecules\(^\text{114}\), thus, from the 4 position of the ring there is still potential for a crystal surface to grow if the fluorine is situated at the crystal face. Altering functionality at the 4 position is expected to exert an effect on the b and c axes of growth. The molecule is small enough to incorporate into the crystal surface without too much disruption, hence may be successful in altering the morphology of benzophenone.
3.7 Other Substitutions

3.7.1 2-methylbenzophenone (2MBP)

![Molecular structure of 2MBP]

Figure 71. The molecular structure of 2MBP.

The crystal structure of 2MBP (Figure 71) has not been solved, possibly due to the low melting point of the compound which is liquid at room temperature. The two position of the ring is where the intermolecular edge-face ring interaction originates and substituting for a methyl group gives 2MBP. Increasing the size of substituent at this position from hydrogen to a methyl group could potentially disrupt the edge-face interactions. The edge-face interaction runs along the a axis of the crystal structure, hence it is expected that the additive molecule may hinder growth along this axis if successful.

3.7.2 3-chlorobenzophenone (3ClBP)

![Molecular structure of 3ClBP]

Figure 72. The molecular structure of 3ClBP.

The crystal structure of 3ClBP (Figure 72) is unsolved and the product is solid at room temperature. The three position of the benzophenone aromatic ring is involved in intermolecular interactions through the b and c axes with the carbonyl group changing
the hydrogen to chlorine may cause disruption to this interaction. The change in electronegativity and size of the substituent could have an effect on the growth of the benzophenone crystals. The 3 position of the ring is involved in intermolecular interactions along the b and c axes of growth and if successful the additive is expected to create a more needle shaped morphology, elongated along the a axis

3.8 Conclusions

The crystal packing of benzophenone has been analysed in crystallographic directions to identify key intermolecular interactions in the crystal structure. Using this information additive molecules have been designed and selected by altering the functionality with the intention of changing the morphology of benzophenone crystals as a basis for experimental studies and influencing growth rates. A selection of derivatised molecules has been chosen to alter growth in different directions.
4. Solubility and Crystal Morphology of Benzophenone

This chapter covers the solubility and crystal morphology of benzophenone grown from pure solution and in the presence of additives. The solubility of benzophenone has previously been measured in various solvents\textsuperscript{112} the data is summarised in Table 4 and Figure 73.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (g/100cm(^3) solvent), T(°C)</th>
<th>Solvent</th>
<th>Solubility (g/100cm(^3) solvent), T(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>13.5, T=17</td>
<td>Xylene</td>
<td>38.4, T=17.6</td>
</tr>
<tr>
<td>Ethanol</td>
<td>11, T=9.8</td>
<td>Nitro Benzene</td>
<td>58.8, T=15.8</td>
</tr>
<tr>
<td>Methanol</td>
<td>14.3, T=15</td>
<td>Chloroform</td>
<td>55.5, T=16.5</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>19.2, T=9.6</td>
<td>Bromoform</td>
<td>33.3, T=17.3</td>
</tr>
<tr>
<td>Carbon Disulphide</td>
<td>66.6, T=16.1</td>
<td>Toluene</td>
<td>55.5, T=17.2</td>
</tr>
<tr>
<td>Ethyl Ether</td>
<td>17.5, T=12.7</td>
<td>Ligroine</td>
<td>6.7, T=14.6</td>
</tr>
<tr>
<td>Benzene</td>
<td>76.9, T=17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. The solubility of benzophenone in a range of solvents\textsuperscript{112}.

![Graph showing solubility vs temperature for various solvents](image)

Figure 73. The solubility of benzophenone in a range of solvents\textsuperscript{112}.

Solvent choice is crucial when designing crystal growth measurements as many compounds (benzophenone included) can exhibit polymorphism as well as a solvent
dependent morphology\textsuperscript{90, 115}. Choosing a solvent which consistently generates the correct polymorph as well as a repeatable morphology provides a good basis for crystal growth measurements. The vapour pressure, boiling point, polarity of the solvent and also the temperature dependence of the solubility are all important parameters to consider.

4.1 Solvent Choice

The solubility of benzophenone in simple organic solvents such as methanol and ethanol is good (approx. 10-20 \%wt/wt) and from these solvents a well-defined repeatable morphology is formed. However, the main issue with the use of organic alcoholic solvents is adsorption of water from the atmosphere. Since, benzophenone is not very soluble in water and will float on the surface, using organic solvents with varying water content can offer differing solubility of benzophenone. Chadwick et al measured the solubility of benzophenone in methanol (0.76 g per g) and toluene (1.95 g per g) at 25°C\textsuperscript{101}. These values match the trend in Table 4 in that the non-alcohol based solvents offer much higher solubility of benzophenone even at relatively low temperature. Thus, crystallisation experiments in these solvents will require high amounts of benzophenone. In conjunction with this, toluene is found to alter the crystal habit of benzophenone\textsuperscript{90}. Propan-2-ol is similar to ethanol in terms of polarity with a slightly higher boiling point and a lower vapour pressure; hence evaporation of the solvent in experiments is less of an issue without compromising solubility. The solubility of benzophenone in propan-2-ol is expected to be similar to that in ethanol.
4.2 Propan-2-ol Solubility & Metastable Zone

![Graph showing solubility and nucleation points of benzophenone in propan-2-ol.](image)

Figure 74. A graph showing the solubility curve and nucleation points of benzophenone in propan-2-ol.

Figure 74 shows the solubility of benzophenone in propan-2-ol measured in this work using the Crystal-16, also shown are some nucleation points (green). The nucleation points of the solute indicate a metastable zone width of at least 5°C, providing a workable region for seeded growth experiments whilst limiting the possibility of uncontrolled spontaneous nucleation. As nucleation is a random event, there is scatter in the data.

Using gravimetric analysis and the Crystal-16 the equilibrium solubility of benzophenone in pure propan-2-ol solutions was measured as 0.171 ± 0.0025 g/g (solute/solvent) at 15°C. The two methods are effectively a different type of solubility experiment with the crystal-16 a more kinetic method and gravimetric analysis a thermodynamic measurement. However, in this case the two methods produce the same result.

4.3 The Effect of Additives on Solubility of Benzophenone

Additives or impurities are known to alter the solubility of solutes when introduced to a solution, either increasing or decreasing the solubility\(^8,^{12,116}\). In this study the solubility of benzophenone is observed to increase with the addition of the chosen additive.
molecules (concentrations up to 0.1 mole fraction). The extent of the increase differs between additives indicating different solution behaviour. Since introduction of the additive increases the solubility of the solute, intermolecular interactions between the solute and additive must occur in solution. However, the nature of these interactions are unknown.

<table>
<thead>
<tr>
<th>Additive (x = 0.1)</th>
<th>Solubility g per g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td>0.17</td>
</tr>
<tr>
<td>4ABP</td>
<td>0.23</td>
</tr>
<tr>
<td>4MBP</td>
<td>0.20</td>
</tr>
<tr>
<td>DPA</td>
<td>0.24</td>
</tr>
<tr>
<td>DPM</td>
<td>0.21</td>
</tr>
<tr>
<td>DPE</td>
<td>0.22</td>
</tr>
<tr>
<td>2MBP</td>
<td>0.22</td>
</tr>
<tr>
<td>3ClBP</td>
<td>0.23</td>
</tr>
<tr>
<td>4FBP</td>
<td>0.19</td>
</tr>
<tr>
<td>4NBP</td>
<td>Not Soluble</td>
</tr>
</tbody>
</table>

Table 5. A summary of the change in solubility with the addition of additive molecules.

The carbonyl group of benzophenone is known to form solid state intermolecular hydrogen bonds (with DPA for example, Section 3.5.1); this interaction with additive molecules in solution is potentially responsible for some of the increase in solubility. However, in some cases of the additive molecules (i.e. DPM and DPE) it is hard to envisage intermolecular hydrogen bonded interactions since the additives do not contain strong hydrogen bond donors or acceptors. All of the additives have aromatic rings and intermolecular interactions between the electron rich \( \pi \) systems are possibly contributing to the increase in solubility.

In all solubility measurements (method outlined in Section 2.2.2) in the presence of additive, slurry experiments were performed, followed by gravimetric analysis of the solution to determine the equilibrium solubility. After evaporation of the solvent from the sample, the solute product was a liquid which appeared to be more viscous than the original solution. The liquid was quite stable and remained in this state for long periods of time unless agitated. In some cases there were small crystals on the side of the vial away from the solution and upon contact of a crystal with the liquid, crystallisation of the remaining liquid occurred. Agitation caused the solution to crystallise and in some
cases severe shaking was required. This was not observed in pure samples after evaporation where the product was solid. Thus, the post evaporation product is thought to consist of a metastable undercooled melt (benzophenone m.p. 49°C) in which intermolecular interactions between additive and benzophenone stabilise the metastable melt. Overall this phenomenon contributed to inaccuracies in the gravimetric measurement of solubility.

The solubility of benzophenone in the presence of 0.1 mole fraction additive is summarised in Table 5. 4ABP, 3CLBP and DPA increase the solubility the most from 0.17 g per g to approximately 0.23/0.24 g per g solvent. Intermolecular hydrogen bonding interactions between the amino group of 4ABP and the carbonyl group of benzophenone are possible since the crystal structure of 4ABP shows a solid state intermolecular hydrogen bond this nature (Section 3.6.1). The 2MBP and DPE additives both increase the solubility by a similar amount. The functionality of these additives is different and they do not contain hydrogen acceptors. Thus, hydrogen bonding alone cannot be responsible for the increase in solubility of benzophenone when these additive molecules are present.

Figures 75, 76 and 77 show the increase in benzophenone solubility with increasing additive concentration (solubility data can be found in the appendix). These graphs are split into three groups in order to maintain clarity as there is some scatter in the data, notably for DPE. However, all cases appear to follow an almost linear increase in solubility with increasing additive concentration in solution. Table 6 (Section 4.3.3) shows the gradient of the lines and the quality of the linear fits.
Figure 75. A graph showing the solubility change with increasing concentration of additive with the carbonyl group substituted at 15°C.

Figure 76. A graph showing the solubility change with increasing concentration of additive with the hydrogen at the 4 position substituted at 15°C.
4.3.1 Solution Complexation\textsuperscript{116,117}

If increasing the concentration of a ligand (additive in this case) in solution increases the solubility of a solute, it is reasonable to assume that the formation of soluble complexes of solute and ligand are formed. One of two possible outcomes can occur; the solubility continues to increase with increasing ligand concentration or, the ligand increases the concentration of solute in solution to a point where the solubility of a complex ($S_mL_n$) is achieved and addition of further ligand causes formation of one or more solid complexes.

Three types of behaviour can occur when the addition of a ligand increases the solubility of the solute\textsuperscript{117}. Figure 78 shows the three cases schematically, $S_0$ is the molar solubility of the pure solute while $S_t$ is the solubility in the presence of ligand concentration $L_t$. The curves then correspond to the linear increase of $S_t$ with $L_t$ (AL), a nonlinear relationship with positive curvature (AP) and non-linear relationship with negative curvature (AN).
Some assumptions about the trends of the data can be made\textsuperscript{116, 117}. If the complexes formed are of the first order with respect to L, i.e. \( S_X L \) then a linear increase (type AL graph) should be observed. If the complexes are higher order in ligand i.e. \( SL_X \) then an AP type graph should be observed since the concentration of ligand in solution increases faster than the concentration of the solute. Graphs of type AN provide little conclusion about the complex and these graphs may arise either due to self-association of the ligand in solution, or it may be possible that the increased concentration of ligand affects the efficacy of the solvent in some other way.

4.3.2 Stoichiometric Analysis

Linear type AL curves which have a gradient higher than one must have one complex of at least \( S_2L \) possible in solution. It is impossible for one mole of ligand to incorporate more than one mole of solute in a 1:1 complex. It does not necessarily mean that a gradient of one or less corresponds to complexes of only \( SL \) in solution although usually assumed. In order to gain information about the solution complexation behaviour some equilibria can be defined. In the equations below, A corresponds to the solute and B corresponds to the ligand. \([A]_0\) is the equilibrium solubility of solute in the absence of B and \([A]_t\) is the total concentration of A in the presence of B.

\[
A_{\text{solid}} \rightleftharpoons S \rightarrow A_{\text{solute}}
\]

\[
S_{0,A} = [A]_{\text{solute}} = [A]_0
\]

Equation 45
\[ B_{\text{solid}} \xrightleftharpoons{S_0} B_{\text{solution}} \quad S_{0,B} = [B]_{\text{solution}} = [B]_0 \]

**Equation 46**

\[ A_{\text{solution}} + B_{\text{solution}} \xrightleftharpoons{K_{11}} AB_{\text{solution}} \quad K_{11} = \frac{[AB]}{[A][B]} = \frac{[AB]}{[A]_0[B]_0} \]

**Equation 47**

\( K_{11} \) is the complexation constant for the formation of a 1:1 complex of solute and ligand.

Mass balances for the equilibrium where 1:1 complexes are formed:

\[ [A]_T = [A]_0 + [AB] \]

**Equation 48**

\[ [B]_T = [B]_0 + [AB] \]

**Equation 49**

rearranging Equation 47 for the unknown \([AB]\):

\[ [AB] = K_{11}[A]_0[B]_0 \]

**Equation 50**

substituting Equation 50 into Equation 48 gives:

\[ [A]_T = [A]_0 + K_{11}[A]_0[B]_0 \]

**Equation 51**

Since \([B]_0\) is also unknown:

\[ [B]_T = [B]_0 + K_{11}[A]_0[B]_0 \]

**Equation 52**

\[ [B]_0 = \frac{[B]_T}{1 + K_{11}[A]_0} \]

**Equation 53**

Thus substituting Equation 53 into Equation 51 gives:
\[ [A]_t = [A]_0 + \frac{K_{11}[A]_0[B]_t}{1 + K_{11}[A]_0} \]

Equation 54

when \( m=1 \) in \( A_mB_n \), \( K_{1:1} \) can then be obtained from either of the following:\(^{116,118}\):

\[ K_{11} = \frac{\text{Slope}}{[A]_0(1 - \text{Slope})} \]

Equation 55

\[ K_{11} = \frac{[A]_t - [A]_0}{[A]_0([B]_t - [A]_t + [A]_0)} \]

Equation 56

Equation 56 assumes that the values of \( m \) and \( n \) in the complex \( A_mB_n \) are both equal to 1 which is not always the case. For complexes which are not \( A_1B_1 \), other equations can be used to evaluate complexation constants. Assuming that in an \( A_mB_n \) complex, \( n=1 \) the following equation can be used by assigning values to \( m \) to gain information about higher order complexes.

\[ A_t = \frac{mK[A]_0^mL_t + A_0}{1 + KA_0^m} \]

Equation 57

Since \( St \) is plotted against \( Lt \) the slope of the graph will be equal to:

\[ \text{Slope} = \frac{mK[A]_0^m}{1 + KA_0^m} \]

Equation 58

from which the estimated complexation constant can be evaluated. In order to determine the extent of complexation of benzophenone with additive molecules the molarity of benzophenone is plotted against the molarity of additive in Figure 79.
Figure 79. A graph comparing the extent of solubility increase of benzophenone with increasing additive concentration at 15°C.

Figure 79 shows the linear trend lines (from Figures 75 to 77) for the increase in solubility with increasing additive concentration (for all of the additives), all of the lines show a slightly different gradient. The nature of the linear data suggests complexes of stoichiometric ratios of more than one molecule of benzophenone are forming in solution as the gradient of the lines (shown in Table 6) are all higher than one. Note. The gradient is calculated using the LINEST function in Excel in order to estimate the error associated with the gradient and the validity of the model is expected to be reduced because of this. The 90% confidence interval shows that the data is expected to have a significant deviation from the line of best fit.
<table>
<thead>
<tr>
<th></th>
<th>Linest Gradient</th>
<th>Linest Error</th>
<th>Confidence Interval (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4FBP</td>
<td>1.14</td>
<td>0.29</td>
<td>1.52</td>
</tr>
<tr>
<td>DPM</td>
<td>1.75</td>
<td>0.31</td>
<td>0.39</td>
</tr>
<tr>
<td>4MBP</td>
<td>1.91</td>
<td>0.76</td>
<td>0.68</td>
</tr>
<tr>
<td>DPE</td>
<td>1.41</td>
<td>0.37</td>
<td>0.70</td>
</tr>
<tr>
<td>2MBP</td>
<td>1.79</td>
<td>0.36</td>
<td>1.47</td>
</tr>
<tr>
<td>DPA</td>
<td>2.52</td>
<td>0.28</td>
<td>0.66</td>
</tr>
<tr>
<td>3CIBP</td>
<td>2.33</td>
<td>0.19</td>
<td>0.51</td>
</tr>
<tr>
<td>4ABP</td>
<td>3.69</td>
<td>0.76</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Table 6. A table showing the gradients of the data plotted in Figure 79 above.

### 4.3.3 Stoichiometry Estimation

As the gradient is more than one in all cases, a stoichiometry of 1:1 is not possible. Assigning values of 2 and 3 to \( m \) in Equation 58 yields the following complexation constants (Table 7).

<table>
<thead>
<tr>
<th></th>
<th>( \text{Gradient} )</th>
<th>( K_{2:1}(\text{dm}^3\text{mol}^{-1}) )</th>
<th>( K_{3:1}(\text{dm}^3\text{mol}^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4FBP</td>
<td>1.30</td>
<td>2.12</td>
<td>0.75</td>
</tr>
<tr>
<td>DPM</td>
<td>1.65</td>
<td>5.38</td>
<td>1.71</td>
</tr>
<tr>
<td>4MBP</td>
<td>1.71</td>
<td>6.88</td>
<td>2.14</td>
</tr>
<tr>
<td>DPE</td>
<td>2.02</td>
<td>-96.07</td>
<td>1.08</td>
</tr>
<tr>
<td>2MBP</td>
<td>2.34</td>
<td>-7.85</td>
<td>4.34</td>
</tr>
<tr>
<td>DPA</td>
<td>2.37</td>
<td>-7.31</td>
<td>6.42</td>
</tr>
<tr>
<td>3CIBP</td>
<td>2.46</td>
<td>-6.09</td>
<td>4.25</td>
</tr>
<tr>
<td>4ABP</td>
<td>2.91</td>
<td>-3.66</td>
<td>39.56</td>
</tr>
</tbody>
</table>

Table 7. A table summarising the various stability constants of different stoichiometry complexes.

For \( S_2L_1 \) there are negative values for most of the additives, indicating that these complexes are not feasible in solution. As the gradient increases for the additives, the higher order complex \( (S_3L_1) \) shows larger values for stability constants, indicating that these complexes may be possible in solution. For the cases of 4FBP, DPM and 4MBP, \( K_{2:1} \) is higher than \( K_{3:1} \) indicating that a 2:1 complex might be more favourable than a 3:1. For all of the other additive molecules \( S_2L_1 \) yields the more favourable equilibrium constant since the \( S_2L_1 \) values are negative. The Gibbs free energy for complex formation is related to equilibrium constants by the following:
\[ \Delta G = -RT \ln K \]

**Equation 59**

<table>
<thead>
<tr>
<th></th>
<th>( K_{2:1} )</th>
<th>( \Delta G (K_{2:1}) ) kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>4FBP</td>
<td>1.52</td>
<td>-1.00</td>
</tr>
<tr>
<td>DPM</td>
<td>8.01</td>
<td>-4.98</td>
</tr>
<tr>
<td>4MBP</td>
<td>24.28</td>
<td>-7.64</td>
</tr>
<tr>
<td>DPE</td>
<td>2.73</td>
<td>-2.41</td>
</tr>
</tbody>
</table>

Table 8. A table summarising the Gibbs free energy of a 2:1 complex of benzophenone and selected additives.

It is only possible to calculate the free energy for a positive equilibrium constant, hence for most additives the free energy of a 2:1 complex is unfavourable. However for the four additives in Table 8 a reasonable energy change is associated with the complexation.

<table>
<thead>
<tr>
<th></th>
<th>( K_{3:1} )</th>
<th>( \Delta G (K_{3:1}) ) kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>4FBP</td>
<td>0.75</td>
<td>0.69</td>
</tr>
<tr>
<td>DPM</td>
<td>1.71</td>
<td>-1.29</td>
</tr>
<tr>
<td>4MBP</td>
<td>2.14</td>
<td>-1.83</td>
</tr>
<tr>
<td>DPE</td>
<td>1.08</td>
<td>-0.20</td>
</tr>
<tr>
<td>2MBP</td>
<td>4.34</td>
<td>-3.51</td>
</tr>
<tr>
<td>DPA</td>
<td>6.42</td>
<td>-4.45</td>
</tr>
<tr>
<td>3ClBP</td>
<td>4.25</td>
<td>-3.47</td>
</tr>
<tr>
<td>4ABP</td>
<td>39.56</td>
<td>-8.81</td>
</tr>
</tbody>
</table>

Table 9. A table summarising the Gibbs free energy of forming a 3:1 complex of benzophenone and selected additives.

Table 9 shows the free energy of complexation for 3:1 complexes of benzophenone:additive. For all of the additive molecules except for 4FBP a sensible Gibbs free energy change is calculated for a 3:1 complex. The equilibrium constants are an estimate only and do not prove that there is not more than one solute:ligand complex is formed or that self-association of solute occurs. The model relies on low solubility of solute as ideal solutions are assumed. As, benzophenone is quite soluble especially in comparison to salicylic acid\textsuperscript{116} (which has low solubility in aqueous solution), the model may not predict accurate complexation constants.
4.5 Additive Effects on Benzophenone Morphology

Seeded growth experiments were performed in the presence of the additive molecules at 15°C (in the jacketed growth cell) to determine whether or not growth inhibition occurred at concentrations of 10%. The crystals were subjected to optical microscopy (Figure 80) and single crystal X-ray diffraction to establish whether the additive was successful and to determine the specific faces where the additive has the strongest effect.

Figure 80. Images of benzophenone crystals grown in the presence of 10% additive.

Figure 80 shows the effect of additives on the growth of benzophenone with the a axis labelled (see Sections 4.5.1 to 4.5.9). It is clear that the 4ABP and 4MBP additives have a strong effect on the morphology with the other additive molecules having less of an
effect. To decipher the specific faces which are influenced single crystal X-ray crystallography was performed on crystals grown in the presence of the additives.

4.5.1 Pure Benzophenone Morphology

The morphology of benzophenone grown from pure propan-2-ol solutions was indexed to identify the three crystallographic axes. The crystal is mounted on the goniometer head and a unit cell is calculated for the crystal (Section 2.7.2.1). The unit cell of benzophenone was determined as $\alpha = 90.11$, $\beta = 90.20$, $\gamma = 90.05$, $a = 7.766$ Å, $b = 10.252$ Å and $c = 12.053$ Å which compares well with $\alpha = 90$, $\beta = 90$, $\gamma = 90$, $a = 7.7378$, $b = 10.2421$ Å and $c = 12.0395$ in BPHENO12.

![Figure 81. The morphology of pure benzophenone crystals.](image)

The diagram of the indexed crystal shown in Figure 82 is not a perfect representation of the crystal shape as can be seen from Figure 81 and it is possible to establish the crystallographic axes. The morphology drawn in Figure 82 is slightly larger than the crystal and does not show all of the previously determined faces of benzophenone (Section 3.1). However the morphology matches the crystal shape well.
The pure morphology of benzophenone indexed in Figure 82 shows that the solute grows with a very similar morphology to that previously described in the literature. The a axis of growth is marginally longer than the width of the crystal, indicating growth along this axis is faster relative to growth along the b and c axes.

**4.5.2 4-methylbenzophenone**

The unit cell parameters determined for the crystal grown in the presence of 4MBP are $a = 7.793$ Å, $b = 10.155$ Å, $c = 12.127$ Å, $\alpha = 90.0$, $\beta = 89.3$ and $\gamma = 90.0$, the same as benzophenone. Figure 83 shows the indexed benzophenone crystal and the crystal appears as a needle like morphology. This indicates that the additive molecule has hindered the growth of the $\{0 1 1\}$ faces relative to the a axis causing an elongation and a needle like morphology.
Figure 83. Images of the indexed benzophenone crystal grown in the presence of 4MBP.

4.5.3 4-aminobenzophenone

The unit cell of the crystal was determined as $a = 7.76\,\text{Å}$, $b = 10.23\,\text{Å}$, $c = 12.04\,\text{Å}$, $\alpha = 90.43\,^\circ$, $\beta = 90.3\,^\circ$, $\gamma = 90.2\,^\circ$ confirming that the crystal was pure benzophenone.
It is apparent from Figure 84 that the additive works in the same manner as 4MBP, slowing the growth of the \( \{011\} \) faces resulting in an elongation along the \( a \) axis as predicted.

### 4.5.4 4-fluorobenzophenone

The unit cell dimensions of the benzophenone crystal when grown in the presence of 4FBP are \( a = 7.757 \, \text{Å} \), \( b = 10.251 \, \text{Å} \), \( c = 12.055 \, \text{Å} \), \( \alpha = 90.16 \), \( \beta = 90.00 \) and \( \gamma = 90.08 \) confirming that the crystal was pure benzophenone.
The images of the indexed crystal in Figure 85 show a crystal morphology similar to that of benzophenone when grown from pure solution. Hence, it can be concluded that the 4FBP additive does not significantly hinder the crystal growth of benzophenone at this concentration.

4.5.5 Diphenylmethane

The unit cell of the crystal grown in the presence of DPM is $a = 7.788\,\text{Å}$, $b = 10.260\,\text{Å}$, $c = 12.037\,\text{Å}$, $\alpha = 90.08^\circ$, $\beta = 90.28^\circ$ and $\gamma = 90.01^\circ$ confirming that it is a benzophenone crystal.
Figure 86. Images of the indexed benzophenone crystal when grown in the presence of DPM.

Figure 86 shows the indexed benzophenone crystal and it is apparent that the crystal is slightly elongated along the a axis indicating that the b and c axes are only affected by the additive. This effect is not as distinct or strong as the effect of the 4ABP or 4MBP additives.

4.5.6 Diphenylamine

The unit cell dimensions of the crystal are $a = 7.75\, \text{Å}$, $b = 10.278\, \text{Å}$, $c = 12.057\, \text{Å}$, $\alpha = 89.98$, $\beta = 89.96$ and $\gamma = 90.00$ confirming that the crystal is benzophenone.
Figure 87. Images of the indexed benzophenone crystal grown in the presence of DPA.

Figure 87 shows the indexed benzophenone crystal is similar in shape to a crystal grown from pure solution, suggesting that DPA is not successful as a growth inhibitor at this concentration.

4.5.7 Diphenylethylene

The unit cell dimensions of the benzophenone crystal grown in the presence of DPE are $a = 7.821\,\text{Å}$, $b = 10.259\,\text{Å}$, $c = 12.042\,\text{Å}$, $\alpha = 89.98^\circ$, $\beta = 89.77^\circ$ and $\gamma = 89.92^\circ$ confirming that the crystal is pure benzophenone.
The indexed crystal in Figure 88 shows that the crystal has a very similar habit to pure benzophenone and none of the facets seem to have been hindered in the growth. Thus, DPE is not a successful inhibitor for the growth of benzophenone crystals at this concentration.

### 4.5.8 3-chlorobenzophenone

The unit cell of the crystal indexed is $a = 7.765\text{Å}$, $b = 12.010\text{Å}$, $c = 10.25\text{Å}$, $\alpha = 90.03^\circ$ $\beta = 90.02$ and $\gamma = 90.0$ confirming that the crystal is pure benzophenone.
Figure 89 shows a crystal with a slight elongation along the a axis of the crystal indicating that the \{011\} faces are slightly hindered by the additive.

4.5.9 2-methylbenzophenone

The unit cell of the crystal indexed is $a = 7.766$, $b = 10.22$, $c = 12.06\text{Å}$, $\alpha = 89.98$, $\beta = 89.96$ and $\gamma = 89.37$ confirming that the crystal is pure benzophenone.
Figure 90. Images of an indexed benzophenone crystal grown in the presence of 2MBP.

Figure 90 shows the crystal grown in the presence of 2MBP and the crystal has a very similar morphology to pure benzophenone. Thus, the 2MBP additive is not an effective growth modifier for benzophenone at this concentration.

4.6 Summary of Additive Effects

Table 10 summarises the predicted and experimental effects from the chosen additives.
<table>
<thead>
<tr>
<th>Additive</th>
<th>Predicted Effects</th>
<th>Axes Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>4MBP</td>
<td>b/c axes</td>
<td>b/c axes</td>
</tr>
<tr>
<td>4ABP</td>
<td>b/c axes</td>
<td>b/c axes</td>
</tr>
<tr>
<td>4FBP</td>
<td>b/c axes</td>
<td>Weak b/c axes</td>
</tr>
<tr>
<td>DPM</td>
<td>All three axes</td>
<td>Weak b/c axes</td>
</tr>
<tr>
<td>DPA</td>
<td>All three axes</td>
<td>No Effect</td>
</tr>
<tr>
<td>DPE</td>
<td>All three axes</td>
<td>No Effect</td>
</tr>
<tr>
<td>3CIBP</td>
<td>b/c axes</td>
<td>Weak b/c axes</td>
</tr>
<tr>
<td>2MBP</td>
<td>a axis</td>
<td>No Effect</td>
</tr>
</tbody>
</table>

Table 10. A table summarising the predicted and experimental effects of the chosen additives on benzophenone.

In all cases except 4ABP and 4MBP, little or no effect on the morphology is observed. Thus, only the effects 4ABP and 4MBP will be explored experimentally through nucleation and growth rate measurements. However, since DPM is found to have an effect on the growth of benzophenone from the melt\(^7\), the effect of this additive will also be explored.

4.7 Conclusions

The solubility of benzophenone in pure solutions and in the presence of the additive has been evaluated in propan-2-ol. The presence of additives in solution is found to significantly increase the solubility of benzophenone possibly as a result of 2:1 or 3:1 complexes. Not all of the additive molecules show an alteration to the final morphology of benzophenone. Only the 4MBP and 4ABP molecules show a significant change to the morphology of benzophenone with minor changes in the cases of DPM and 3CIBP. The 4ABP and 4MBP additive molecules strongly hinder growth of the \{011\} faces and cause the a axis to grow faster in comparison, resulting in a more needle like morphology. The next chapters cover the effects of additives on nucleation and crystal growth rates.
5. Induction Time Measurements and Impurity Uptake

This section covers the induction time of benzophenone from pure and impure solutions and additive incorporation.

The time delay between the generation of supersaturation and the onset of nucleation of the solute is known as the induction time\(^7\). Much research on nucleation and induction times of compounds has been performed\(^{17, 18, 119}\), including benzophenone\(^{101}\). From classical nucleation theory\(^{17}\) parameters such as the interfacial tension (\(\gamma\)) between the solute and solvent and the critical radius size (\(r^*\)) can be calculated. The interfacial tension has been seen to change between solvents\(^{101}\) and in the presence of additives. However only one solvent (propan-2-ol) is used in this study. Induction time measurements are only performed at one temperature, the same temperature which the growth measurements were performed, 15°C (Section 6).

These experiments are performed to gain insight into whether or not the additives hinder the nucleation of benzophenone as well as the growth. Since 4ABP and 4MBP affect the growth process of the \{011\} faces of benzophenone (Section 6), it is postulated that these additives may also affect the nucleation process. Since nucleation has a dependency on supersaturation; a successful additive is expected to have a stronger effect at lower supersaturation. Three additives were used, two of which strongly affect growth (4ABP and 4MBP) and one which weakly affects growth (DPM). Additionally characterisation was performed on the products to check for incorporation of additives.

5.1 Magnetic Stirring (12.5mL) Scale

On a 12.5mL scale (10g propan-2-ol) the induction times were measured following the experimental procedure (Section 2). The same jacketed vessel, magnetic stirrer bar, stirrer hot plate and water bath were used for each induction time experiment minimising experimental variables. As is to be expected with induction time measurements there is some scatter in the data. However, repeat measurements (minimum of 4) were performed.
5.1.2 Syriss Automated Vessel

The syriss automated jacketed reactor was used to determine the induction times on a 125mL scale. The experiment is essentially the same as the small scale experiment; magnetic stirring instead of an overhead pitched blade stirrer. This change to stirring mode limits the comparison to the smaller scale experiments as a different mechanism of stirring is known to have an effect nucleation\textsuperscript{12}. In addition to the mechanism of stirring the scale of induction time measurements is also known to have an effect. As the volume is increased the probability of nucleation is reduced. In a smaller vessel, there are less clusters, however, the probability of nucleation is greater from the limited amount. However, on a larger scale the amount of clusters is higher with a lower probability of nucleation.

5.2 β Polymorph of benzophenone

It has been reported that the β polymorph of benzophenone can be grown from a super cooled melt (m.p. 297-299K – close to room temperature\textsuperscript{102}). Thus, the β polymorph cannot be ignored when growing benzophenone, especially in the presence of additives designed to alter the crystallisation process. All of the products were analysed using XRD confirming that the α form crystallised in all experiments.
5.3 Induction Times

5.3.1 Pure Induction Time

Figure 91. A graph showing the induction time of benzophenone in pure propan-2-ol solution with increasing supersaturation.

Figure 91 shows the induction time measurements with increasing supersaturation. For each supersaturation measured, it is apparent that in larger scale experiments (Syriss in Figure 91), shows a longer average induction time for all measurements compared to smaller scale except for $\sigma = 0.12$. Table 11 shows the slope and error associated with the graph in Figure 92 calculated using the LINEST function in Excel. For the small scale experiments, the error in the graph is much smaller in comparison to the larger scale experiments, which is clear from the scatter in the observed data and a larger confidence interval is observed.

<table>
<thead>
<tr>
<th></th>
<th>Small Scale</th>
<th>Syriss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>-760.4</td>
<td>-259.4</td>
</tr>
<tr>
<td>Error</td>
<td>128.8</td>
<td>230.4</td>
</tr>
<tr>
<td>Confidence Interval (90%)</td>
<td>231.30</td>
<td>413.77</td>
</tr>
</tbody>
</table>

Table 11. A table showing the slope of the lines in Figure 92 with the error associated.

Table 12 shows the average induction times for benzophenone in pure propan-2-ol solution. At $\sigma = 0.12$ the average induction times between scales are comparable at
approximately 150-160 mins. However as supersaturation increases, the average induction time decreases faster for smaller scale measurements, with the average times of 27 and 105 mins for $\sigma = 0.3$ (small scale) and $\sigma = 0.29$ (large scale) respectively.

<table>
<thead>
<tr>
<th>Supersaturation</th>
<th>Average $\tau_{\text{ind}}$ (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>164</td>
</tr>
<tr>
<td>0.22</td>
<td>50</td>
</tr>
<tr>
<td>0.29</td>
<td>N/A</td>
</tr>
<tr>
<td>0.3</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 12. A table summarising the average induction time of benzophenone.

5.3.2 The Effect of 4-aminobenzophenone

Figure 92. A graph showing the induction time of benzophenone in the presence of 4ABP.

Figure 92 shows the induction time of benzophenone in the presence of 4ABP with increasing supersaturation. The induction time is observed to decrease with increasing supersaturation except for when $\sigma = 0.2$ in the Syriss experiments where there is an apparent increase in the average induction time. The smaller scale experiments exhibit faster induction times compared to larger scale. However at the higher supersaturation levels ($\sigma \approx 0.3$) the difference between the two sets is reduced. Table 13 shows the data obtained using the LINEST function in Excel and it is again clear that the larger scale
experiments show much more variation in the data and have a much larger confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>Small Scale</th>
<th>Syriss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slope</strong></td>
<td>-237.1</td>
<td>-336.2</td>
</tr>
<tr>
<td><strong>Error</strong></td>
<td>48.7</td>
<td>272.2</td>
</tr>
<tr>
<td><strong>Confidence Interval (90%)</strong></td>
<td>88.21</td>
<td>493.34</td>
</tr>
</tbody>
</table>

Table 13. A table showing the slope of the data in Figure 92 and also the error associated.

The average induction time (Table 14) in the presence of 4ABP are generally faster compared to the average pure induction time suggesting the presence of 4ABP speeds up nucleation.

<table>
<thead>
<tr>
<th>Supersaturation</th>
<th>Average $\tau_{ind}$ (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>Small</td>
</tr>
<tr>
<td>0.22</td>
<td>49</td>
</tr>
<tr>
<td>0.29</td>
<td>N/A</td>
</tr>
<tr>
<td>0.3</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 14. A table summarising the average induction times of benzophenone in the presence of 4ABP.

5.3.3 The Effect of 4-methylbenzophenone

![Figure 93](image-url) A graph showing the induction time of benzophenone in the presence of 4MBP.
Table 15. A table showing the slope of the best straight line fit to the data in Figure 94.

Figure 93 shows the induction time of benzophenone in the presence of 4MBP with supersaturation and Table 15 shows the slope of the line of best fit and the error associated (calculated using the LINEST function in Excel). The error in the slope due to the scatter in the data is much larger for the larger scale experiments and the confidence intervals are also large as a result.

It is clear that 4MBP has a large effect on the induction time of benzophenone on both scales and the average induction time is shown in Table 16. At $\sigma = 0.12$ for the large scale experiment (Syriss) nucleation does not occur even after 140 hours. A sample of this solution was transferred to the small scale vessel and the solution nucleated in approximately 24 hours. For small scale experiments at the same supersaturation, the induction time is approximately 53 hours and accurate measurement is difficult due to visual detection. At higher supersaturation benzophenone does nucleate and grow in the presence of 4MBP and increasing $\sigma$ continues to decrease the induction time. At $\sigma = 0.29$ the average induction time become similar to those in pure solution.

<table>
<thead>
<tr>
<th>Supersaturation</th>
<th>Average $\tau_{\text{ind}}$ (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>53 Hours</td>
</tr>
<tr>
<td>0.22</td>
<td>150</td>
</tr>
<tr>
<td>0.29</td>
<td>N/A</td>
</tr>
<tr>
<td>0.3</td>
<td>104</td>
</tr>
</tbody>
</table>

Table 16. A table summarising the average induction times for benzophenone in the presence of 4MBP.
5.3.4 The Effect of Diphenylmethane

Figure 94. A graph showing induction time in the presence of DPM with increasing supersaturation.

Figure 94 shows the measured induction times of benzophenone in the presence of DPM and shows the slope of the line of best fit and the error associated (calculated using the LINEST function in Excel). The values show that the larger scale experiments show much larger amounts of variation in the induction time data with the confidence interval almost the same value as the gradient itself.

<table>
<thead>
<tr>
<th></th>
<th>Small Scale</th>
<th>Syriss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slope</strong></td>
<td>-432.1</td>
<td>-499.3</td>
</tr>
<tr>
<td><strong>Error</strong></td>
<td>105.9</td>
<td>275.8</td>
</tr>
<tr>
<td><strong>Confidence Interval (90%)</strong></td>
<td>190.26</td>
<td>495.34</td>
</tr>
</tbody>
</table>

Table 17. The slope of the line of best fit and the error associated from the data in Figure 94.

The average induction time is shown in Table 18 and it is evident that with smaller scale experiments, increasing the supersaturation decreases the induction time. However, at larger scale this is not always the case due to an apparent increase in the average induction time at $\sigma = 0.3$ with respect to $\sigma = 0.2$ most likely to two longer measured induction times (experiments 3 and 4). The average induction times are faster in comparison to the pure experiments and show the same trend in that smaller scale experiments nucleate faster than larger scale.
Table 18. A table summarising the average induction times of benzophenone in the presence of DPM.

### Average \( \tau_{\text{ind}} \) (mins)

<table>
<thead>
<tr>
<th>Supersaturation</th>
<th>Small</th>
<th>Syriss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>91</td>
<td>156</td>
</tr>
<tr>
<td>0.22</td>
<td>17</td>
<td>58</td>
</tr>
<tr>
<td>0.29</td>
<td>N/A</td>
<td>79</td>
</tr>
<tr>
<td>0.3</td>
<td>16</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### 5.3.5 Compared Effects on Induction Time at Different Scales

Figure 95. A graph showing the effect of additives on the average induction time of benzophenone at small scale.

Figure 95 compares the average induction time of benzophenone in pure and impure solutions. The 4ABP and DPM additives appear to reduce the average induction time of benzophenone compared to pure solution whereas; 4MBP delays the average nucleation time.
Figure 96. A graph showing the effect of additives on the average induction time of benzophenone at larger scale.

Figure 96 shows the effect of additives on the average induction time of benzophenone in the Syriss experiments. 4ABP and DPM again both catalyse the nucleation throughout the supersaturation range. This indicates that these two additives only affect the growth process and not the nucleation. The 4MBP additive is again found to delay the nucleation except for at $\sigma = 0.29$, where the average induction time is slightly faster than for pure solution.

### 5.4 The Calculated Interfacial Tension

Induction time measurements allow estimation of interfacial tension ($\gamma$) and also critical cluster size ($r^*$). The nucleation rate is given by:

$$J = A \exp \left( \frac{-16\pi \gamma^3 v^2}{3k_B T^3 (\ln S)^2} \right)$$

Equation 60

$S$ is the supersaturation ratio $\left( \frac{X_{ss}}{X_{eq}} \right)$. 

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\[ J \propto \tau_{ind}^{-1} \]

Equation 61

Since nucleation rate is proportional to induction time a plot of \( \ln \tau_{ind} \) against \( \frac{1}{T^3(lnS)^2} \) yields a straight line in which it is possible to calculate \( \gamma \) from Equation 60.

5.4.1 Pure

![Figure 97](image-url)  

\[ y = 97657x + 4.6178 \]  
\[ y = 80014x + 2.8142 \]

Figure 97. A graph showing \( \ln \tau_{ind} \) (average) against \( 1/T^3(lnS)^2 \) for pure benzo phenone used to calculate the induction time.

Figure 97 shows the data points used to calculate the interfacial tension of benzo phenone from pure solutions. In this section the average induction time has been used in the plots and Table 19 contains information about the quality of the fit obtained using the LINEST function in excel.
5.4.2 4-aminobenzophenone

Figure 98. A graph showing $\ln \tau_{\text{ind}}$ (average) against $1/T^3(\ln S)^2$ used to calculate the induction time for benzophenone in the presence of 4ABP.

Figure 98 shows $\ln \tau_{\text{ind}}$ against $1/T^3(\ln S)^2$ for benzophenone in the presence of 4ABP.

5.4.3 4-methylbenzophenone

Figure 99. A graph showing $\ln \tau_{\text{ind}}$ (average) against $1/T^3(\ln S)^2$ used to calculate the induction time for benzophenone in the presence of 4MBP.
Figure 99 shows $\ln \tau_{\text{ind}}$ (average) against $1/T^3(\ln S)^2$ for benzophenone in the presence of 4MBP. Since induction times at $\sigma = 0.12$ are not measurable only two supersaturations can be used for this additive.

5.4.4 Diphenylmethane

Figure 100. A graph showing $\ln \tau_{\text{ind}}$ (average) against $1/T^3(\ln S)^2$ used to calculate the induction time for benzophenone in the presence of DPM.

Figure 100 shows $\ln \tau_{\text{ind}}$ (average) against $1/T^3(\ln S)^2$ for benzophenone in the presence of DPM and an almost linear trend is observed.

<table>
<thead>
<tr>
<th></th>
<th>Small Scale</th>
<th></th>
<th>Syriss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gradient</td>
<td>Error</td>
<td>Confidence Interval (90%)</td>
</tr>
<tr>
<td>Pure</td>
<td>800014</td>
<td>277368</td>
<td>809910.4</td>
</tr>
<tr>
<td>4ABP</td>
<td>837928</td>
<td>115930</td>
<td>338515.1</td>
</tr>
<tr>
<td>DPM</td>
<td>857663</td>
<td>205706</td>
<td>600659.9</td>
</tr>
</tbody>
</table>

Table 19. A table showing the fit of the LINEST function to the data used to calculate the interfacial tension values.

Table 19 shows the data calculated using the LINEST function in Excel for the average induction time graphs used to calculate the interfacial tension values in Section 5.4.5. The error associated with the fit of the straight line is fairly similar regardless of the scale of the experiment. However, the confidence intervals are significant in all cases. The error and confidence interval is zero in the case of 4MBP due to the limited data.
5.4.5 Calculated Interfacial Tension

<table>
<thead>
<tr>
<th></th>
<th>Small (mJ m$^{-2}$)</th>
<th>Syriss (mJ m$^{-2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td>1.20</td>
<td>0.57</td>
</tr>
<tr>
<td>4ABP</td>
<td>1.24</td>
<td>0.92</td>
</tr>
<tr>
<td>4MBP</td>
<td>1.25</td>
<td>2.19</td>
</tr>
<tr>
<td>DPM</td>
<td>1.21</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Table 20. A table summarising the interfacial tension values calculated for benzophenone in pure and impure solution.

The gradient of the lines in Figures 97 to 100 are used to estimate the values of $\gamma$ shown in Table 20. It is clear that the two methods of induction time measurements show different values for $\gamma$. However all values are of similar order to those calculated previously for benzophenone in chloroform ($\gamma = 1.218$ mJ m$^{-2}$ at 30°C) and carbon tetrachloride ($\gamma = 1.261$ mJ m$^{-2}$ at 30°C)\textsuperscript{119}.

There is a difference in the values calculated from the two methods, and the largest differences are in pure solution and in the presence of 4MBP. For small scale experiments the interfacial tension appears to be independent of the presence of the additive. However, on the larger scale the interfacial tension changes significantly with the addition of growth inhibitors. The change in stirring mechanism and heterogeneous surface of the vessel may be partly responsible for the difference.

5.4.5 Critical Cluster Size

Using the above interfacial tension values it is also possible to calculate the critical cluster size in order for nucleation to occur using Equation 62:

$$r^* = \frac{2\gamma v}{k_B T \ln S}$$

Equation 62

<table>
<thead>
<tr>
<th></th>
<th>ln(S)</th>
<th>r*Å (small)</th>
<th>r*Å (syriss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td>0.12</td>
<td>14.48</td>
<td>6.91</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>7.90</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>5.99</td>
<td>2.86</td>
</tr>
<tr>
<td>4ABP</td>
<td>0.12</td>
<td>14.93</td>
<td>11.14</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>8.14</td>
<td>6.08</td>
</tr>
</tbody>
</table>
Table 21 shows the calculated critical cluster sizes of benzophenone for pure and impure solutions at different $\sigma$. The trends are expected in that as supersaturation increases the critical cluster size decreases. For pure benzophenone using the interfacial tension value calculated from larger scale solutions the cluster size is less that the width of a benzophenone molecule which is not possible. The interfacial tension from the smaller scale measurements predicts cluster sizes of approximately 15Å at low supersaturation, indicating a very small cluster size of 2-3 benzophenone molecules which is also unlikely. Other reports of $r^*$ are 13.67Å, for benzophenone, which also seems very small. Jiang and ter Horst reported critical cluster sizes of between 10 and 35 molecules for both $m$-aninobenzoic acid and L-hystidine\textsuperscript{120}, a much larger figure. Teychene and Biscans estimated critical cluster sizes of eflucimibe polymorphs to be between 8 and 25Å\textsuperscript{121}. Thus reports of similar sized clusters are known and the size of the benzophenone cluster seems small, most likely due to the scatter in the data used to calculate $\gamma$, and the fact that this is an effective value for heterogeneous nucleation.

### 5.4.6. Summary

The only additive seen to significantly increase the induction time of benzophenone is 4MBP. Below $\sigma = 0.12$ the additive appears to completely prevent nucleation of benzophenone in the larger scale experiments whilst at smaller scale, increases the induction time to approximately 24 hours. The mechanism of the effect is unclear as two possible outcomes can occur. Since the 4MBP additive completely hinders the growth of benzophenone below $\sigma = 0.1$ (see Section 6) it is possible that the nucleation is unhindered yet the growth of the cluster to a detectable level is either prevented or is so slow that the crystals remain at an undetectable size.

<table>
<thead>
<tr>
<th></th>
<th>0.29</th>
<th>6.18</th>
<th>4.61</th>
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<tr>
<td>4MBP</td>
<td>0.12</td>
<td>15.08</td>
<td>26.37</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>8.23</td>
<td>14.38</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>6.24</td>
<td>10.91</td>
</tr>
<tr>
<td>DPM</td>
<td>0.12</td>
<td>14.59</td>
<td>12.53</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>7.96</td>
<td>6.83</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>6.04</td>
<td>5.18</td>
</tr>
</tbody>
</table>
5.5 Additive Incorporation

Crystalline products from induction time measurements were subjected to various solid state analytical techniques in order to determine whether additives were incorporated into the crystal lattice of benzophenone. The following section covers this product analysis.

5.5.1 Microscopy

Optical microscopy was used to check the morphology of the crystals to ensure that the pure samples produced a common repeatable morphology when grown in bulk from solution. This is then compared to the morphology of single crystals of benzophenone grown in the presence of additives.

5.5.2 Pure Benzophenone

![Image of benzophenone crystals grown at different supersaturations.](image)

Figure 101. Images of benzophenone crystals grown at different supersaturation, images on the left are from $\sigma = 0.1$ and images on the right from $\sigma = 0.3$ at magnification of 25x.

Figure 101 shows images of benzophenone grown from induction time measurements at different supersaturations. The images at the bottom are taken using crossed polarisers (background coloured purple using a filter) showing the samples consist of single crystals. The images are crystals grown from homogeneous nucleation experiments at $\sigma = 0.12$ (left) and $\sigma = 0.30$ (right). At $\sigma = 0.12$ the crystals are of a similar size (approx.
500 by 500µm) throughout the sample and all show a similar morphology. As supersaturation increases the expected result is more, smaller crystals and this is shown by the images on the right of Figure 101. The crystals grown from homogeneous nucleation at \( \sigma = 0.3 \) are slightly smaller (measured crystal on right hand side of image is 204 by 385µm) than those on the left. The morphology of the crystals grown at \( \sigma = 0.3 \) are also slightly less uniform compared to those on the left, suggesting the growth process may have been fast preventing well faceted crystals to form.

5.5.3 4-methylbenzophenone

![Images of benzophenone crystals](image)

Figure 102. Images of benzophenone crystals grown from induction time measurements in the presence of 4-aminobenzophenone at a supersaturation of 0.12 (left) and 0.3 (right) at magnification of 25x.

Figure 102 shows images of benzophenone crystals grown in the presence of 4MBP with (bottom) and without (top) crossed polarisers showing that the samples are crystalline. The images are from the products of the induction time measurements in the presence of 4MBP and the images on the left are from \( \sigma = 0.12 \) with the images on the right at \( \sigma = 0.3 \).

On first examination the opposite of the expected outcome appears, with several small crystals at low supersaturation and fewer larger crystals at higher supersaturation. For \( \sigma \)}
= 0.12 the result is a large amount of very small crystals, indicating that the nucleation process is unhindered as a large amount of clusters must have formed. However, the presence of the additive may strongly hinder the growth of these clusters; hence the result is a high number of small crystals. In induction time measurements at $\sigma = 0.12$ on large scale; the length of time between onset of supersaturation and detection of crystals may be extended so drastically because the growth of the clusters is so strongly hindered that they remain at an undetectable size. At $\sigma = 0.3$ the growth process appears less hindered as much larger crystals are formed. The morphology of these is still affected by the additive and a needle like crystal elongated along the a axis is the product (Section 5.5.6).

5.5.4 4-aminobenzophenone

Figure 103. Images of benzophenone crystals grown in the induction time measurements in the presence of 4ABP at a supersaturation of 0.1(left) and 0.3 (right).

Figure 103 shows images of benzophenone crystals grown in the presence of 4ABP at $\sigma = 0.12$ (left) and $\sigma = 0.3$ (right) with crossed (top) and uncrossed polarisers (bottom) showing that the sample is crystalline. The sample at $\sigma = 0.12$ shows fewer larger crystals whereas at $\sigma = 0.30$ the sample consists of more, smaller sized crystals as expected. The additive is observed to decrease induction time slightly and is seen to
alter the morphology of the crystals compared to pure (Figure 101). This is true regardless of supersaturation and the product is a needle like crystal elongated along the a axis.

5.5.5 Diphenylmethane

Figure 104. Images of benzophenone crystals grown in the presence of DPM.

Figure 104 shows images of benzophenone crystals grown in homogeneous nucleation experiments containing DPM at $\sigma = 0.12$ (left) and $\sigma = 0.3$ (right) with crossed (bottom) and uncrossed polarisers (top). The crystals produced are of similar size (approximately 800μm along longest axis) throughout the supersaturation range indicating that the additive is not strongly affecting the nucleation process and only has an effect on the growth of the crystals.
5.5.6 Summary

Figure 105. Powder X-ray diffraction patterns of benzophenone samples grown in the presence of additives. The calculated powder pattern of benzophenone is in red, the sample grown in the presence of 4ABP is in black, the sample grown in the presence of 4MBP is in blue and the sample grown in the presence of DPM is green.

Figure 105 shows powder diffraction patterns of samples grown in the presence of additives with zoomed in images in Figure 106. The samples are unground and it is clear that preferred orientation occurs in all three benzophenone samples. The \{011\} crystal planes of the predicted powder pattern of benzophenone are labelled on Figure 105 matching the preferred orientation peaks. Thus, the \{011\} surfaces are more prevalent in the sample confirming that the effects seen in bulk crystallisations are the same as seeded crystal growth experiments. From Figure 106 it is clear that the preferred orientation matches up for the (011), (022) and (033) planes. The peaks corresponding to the (022) planes are slightly shifted, compared to the pure benzophenone pattern, whilst the (011) and (033) peaks match quite well. The preferred orientation confirms that the samples contain larger (011) crystal faces as the relative peak intensity is larger for these crystal planes.
5.6 Analysis of Products

Since additive molecules are designed to become incorporated into the crystal lattice, a successful additive should be present in some concentration in the final product. Although this outcome is possible and likely, the characterisation and analysis of the product is often difficult due to sensitivity of analytical equipment. The induction time measurements were performed at concentrations of 0.1 mole fraction (with respect to solid). However the final solid composition is unlikely to be 90% benzophenone to 10% additive molecule and detecting levels of additive below these concentrations is potentially only possible using high pressure liquid chromatography. The use of powder X-ray diffraction and infrared spectroscopy may be useful although the difference between pure and impure samples may be subtle or even undetectable. Differential scanning calorimetry can indicate additive uptake as the melting point of samples can be very sensitive to the presence of impurity.

5.6.1 HPLC

High pressure liquid chromatography (HPLC) is perhaps the best technique available to analyse samples containing amounts of impurity or additive as the different molecules...
are separated completely and the technique can detect μg/ml levels. To quantify the levels of additive present in the samples, a calibration curve must first be created (Section 2.7.5). In an attempt to determine whether the additive molecule is bound only to the crystal surface or whether it is incorporated into the crystal, two samples were tested. Firstly a sample of the filtered product, secondly some of the filtered product was washed with cold solvent in an attempt to remove additive molecules bound to the surface. Hence, in the washed samples if additive was present in the chromatogram it can be assumed that the additive is incorporated into the lattice and not only bound to the surface. Standard elution times according to the method outlined in Section 2.7.5 are listed in Table 22.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Approximate Elution Time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzophenone</td>
<td>9</td>
</tr>
<tr>
<td>4MBP</td>
<td>12</td>
</tr>
<tr>
<td>4ABP</td>
<td>5</td>
</tr>
<tr>
<td>DPM</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 22. A summary table of elution times of benzophenone and the additive molecules.

From these it is evident that the presence of additives in samples of benzophenone should be detected since the elution times for all four molecules are all significantly different.
5.6.1.1 4-methylbenzophenone

Figure 107. Two chromatograms of 4MBP (blue) and benzophenone grown in the presence of 4MBP (red).

Figure 107 shows two chromatograms; one of dissolved benzophenone crystals grown in the presence of 4MBP (red) and one of dissolved 4MBP (blue). It is clear to see from the blue chromatogram (4MBP) that 4MBP elutes at 12 minutes and from the red chromatogram benzophenone elutes at 9 minutes. The red chromatogram has a large peak at 9 minutes due to benzophenone and a small peak at 12 minutes indicating a very low concentration of 4MBP present in the benzophenone crystal sample (see Table 23).

Table 23 shows the concentration of 4MBP found in samples of benzophenone grown from solutions containing the additive. At low supersaturation the only benzophenone samples which nucleated were of the small scale experiments, these remained unwashed due to the low yield hence conclusions about whether the 4MBP is situated in the crystal lattice or simply on the crystal surface are not possible at low $\sigma$. 
<table>
<thead>
<tr>
<th></th>
<th>$\sigma$</th>
<th>washed</th>
<th>Sample Concentration (µg/10mL)</th>
<th>Additive (µg/ml)</th>
<th>Benzophenone (µg/ml)</th>
<th>Mole frac add</th>
</tr>
</thead>
<tbody>
<tr>
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<td>70</td>
<td>0.21</td>
<td>69.79</td>
<td>0.003</td>
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<td>69.80</td>
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<td>120.60</td>
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<td></td>
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<td>99</td>
<td>1.52</td>
<td>97.48</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 23. A table showing the concentration of 4MBP found in the sample of benzophenone samples grown at different supersaturation.

There is a small concentration of 4MBP in the final product. At a supersaturation of 0.3 a washed sample was tested and it appears that the amount of 4MBP is reduced after washing with an amount of cold solvent. Thus, some of the additive must be present on the surface of the crystal and also some spread throughout the crystal lattice.

What is apparent is that at lower supersaturation the amount of additive in the solid is smaller compared to higher supersaturation. At low $\sigma$ the additive prevents growth of the crystal and the concentration of 4MBP in the crystal is low as the crystals are small. At higher $\sigma$ the concentration of 4MBP is higher and the growth of the crystals is less hindered, hence the additive is more likely to be included into the crystal.
5.6.1.2 4-aminobenzophenone

Figure 108. Selected chromatograms of 4ABP and benzophenone (green and orange) grown in the presence of 4ABP (blue and red).

Figure 108 shows chromatograms of benzophenone grown in the presence of 4ABP (blue and red) and also pure 4ABP (orange and green). It is clear that the samples of benzophenone grown in the presence of 4ABP show elution of 4ABP in the region expected. Thus, it can be determined that there is a concentration of 4ABP included into the benzophenone crystals (see Table 24).

Table 24 shows the concentration of 4ABP in the crystal samples from induction time experiments. From the HPLC it is clear to see that there is varying amounts of additive spread throughout the crystal lattice of benzophenone. There is no clear trend in the amount of additive in the sample and washed or unwashed the concentration remains similar. At higher supersaturation when the concentration of 4ABP in the product is similar even when washed indicating that the 4ABP is spread throughout the crystal lattice and not situated on the crystal surface only.
<table>
<thead>
<tr>
<th>4ABP</th>
<th>σ</th>
<th>washed</th>
<th>Sample Concentration (μg/10mL)</th>
<th>Additive (μg/ml)</th>
<th>Benzophenone (μg/ml)</th>
<th>Mole frac add</th>
</tr>
</thead>
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<td>81.48</td>
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<td>10.03</td>
<td>96.97</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

Table 24. A table showing the concentration of 4ABP found in the sample of benzophenone grown at different supersaturation.

5.6.1.3 Diphenylmethane

Figure 109 shows a chromatogram of DPM and it is clear that the molecule elutes at approximately 18 minutes. Figure 110 shows a chromatogram of a sample of benzophenone grown in the presence of DPM. The only peak present is due to benzophenone at approximately 9 minutes, and the absence of a peak around 18 minutes indicates that the additive is not incorporated into the crystal structure of benzophenone.
5.6.2 DSC

Analysis of the impure samples with differential scanning calorimetry is possible as impure samples will exhibit a difference in the melting point compared to pure benzophenone. Incorporation of the additive molecules can lower the melting point of the sample. Benzophenone itself produces a relatively broad peak even when the sample
is ground before analysis, potentially due to a small amount of impurity already present (99% purity). Figure 111 shows three pure benzophenone thermograms from DSC. There is some slight variation in the onset of melting with values of approximately 48.5°C in all three cases. The melting peak values show some variation with the melting peak ranging between 51 and 52°C. The normalized values show the largest range with a difference of approximately -15 Jg⁻¹ between the smallest and largest values. Hence there is some variation in the DSC thermograms of benzophenone potentially due to a small amount of impurity present in the batch (purity 99%).

Figure 111. An image showing three benzophenone thermograms from DSC experiments.
5.6.2.1 4-methylbenzophenone

Figure 112. The DSC spectra of benzophenone (black) and assorted samples grown in the presence of 4MBP, the black curve is pure benzophenone. The other curves are from benzophenone when grown in the presence of 4-methylbenzophenone at 0.1 unwashed (red) and washed (blue) and 0.3 when unwashed (green) and washed (purple).

The collection of spectra in Figure 112 indicate that the melting point of benzophenone generally decreases when grown in the presence of 4MBP from no effect (red) to a suppression of melting point (green). The heat of fusion is also different to that of pure benzophenone ranging between approximately -70 to -80 Jg⁻¹ whereas the heat of fusion of benzophenone is approximately -80 to -90 Jg⁻¹. This decrease in melting temperature indicates that an impurity may be present in the sample, since an impurity would disrupt the crystal packing, reducing the energy required to melt the sample. The range of different melting points shown also suggests that the samples may contain different amounts of additive.
5.6.2.2 4-aminobenzophenone

Figure 113. DSC spectra of pure benzophenone and benzophenone grown in the presence of 4MBP at different supersaturation, the black curve is pure benzophenone. The other curves are from benzophenone when grown in the presence of 4-aminobenzophenone at 0.1 unwashed (red) and washed (blue) and 0.3 when unwashed (green) and washed (purple).

Figure 113 shows the DSC spectra of benzophenone when grown in the presence of 4ABP from pure propan-2-ol. There is a clear trend in that when benzophenone is grown in the presence of 4ABP the melting point is decreased suggesting an impurity may be present in the sample regardless of supersaturation. All of the melting peaks are approximately 49°C whereas the pure benzophenone melting peak is approximately 51-52°C. The onset of the melting also occurs approximately 2°C lower than the pure sample and the heat of fusion is also lower on average.
5.6.2.3 Diphenylmethane

Contrary to Figures 112 and 113, Figure 114 does not appear to show a decrease in melting point of benzophenone when grown in the presence of the additive, regardless of supersaturation. The thermograms overlay quite well, suggesting that no DPM is incorporated into the crystal structure of benzophenone. The heat of fusion shows some difference between the samples with values ranging between \(-75\) and \(-85\) Jg\(^{-1}\), slightly lower than those observed for pure benzophenone. The onset of melting is slightly lower than the average value observed for pure benzophenone. However the peak is consistent with that of benzophenone, suggesting the samples are of the same composition.

5.6.2.4 Melting Point Suppression

If a liquid phase of a compound behaves in an ideal manner according to the Van’t Hoff relation, the Schröder van Laar equation can be used to predict the composition of the compound at known melting temperatures\(^{122, 123}\).
Figure 115 shows the Schroder van Laar prediction for benzophenone in conjunction with the melting points of samples of benzophenone grown in the presence of additives. The samples in Figure 115 are of known composition from HPLC analysis. In all samples tested the melting point is reduced compared to that of pure benzophenone. The samples containing 4MBP follow the ideal melting curve quite closely with increasing 4MBP composition. However the samples containing 4ABP seem to have the same melting temperature independent of composition. Thus, it can be assumed that the liquid phases of the two components do not behave in an ideal fashion\textsuperscript{123}.

### 5.6.3 Powder X-ray Diffraction

It is possible to identify solid solutions from powder X-ray diffraction patterns as the inclusion of additive or impurity molecules into the crystal can disrupt the lattice potentially altering the diffraction patterns. Different crystalline materials have different
powder patterns so it is possible to identify different samples using X-ray powder diffraction. If a large amount of the additive was incorporated into the crystal structure of benzophenone the X-ray powder pattern would be different.

Low levels of additive uptake may cause small amounts of peak shifting in the powder X-ray patterns and larger amounts of additive present in the sample, may cause larger shifts in the peaks. If the additive molecule was crystallising as its own entity in the presence of benzophenone crystals the expected result would be a mixture of all of the peaks from both molecules in the powder X-ray pattern. From experiments at these concentrations no evidence of co-crystal formation has been found.

5.6.3.1 4-methylbenzophenone

Figure 116 shows the powder X-ray diffraction patterns of benzophenone when grown from pure and impure solutions. The black pattern is from pure benzophenone, the red and blue patterns are from benzophenone samples grown in the presence of 4MBP at supersaturations of 0.1 and 0.3 respectively. The peaks in the red, blue and green spectra match quite well with some very minor peak shifting to lower 2θ values. Figure 117 shows a zoomed image of the cluster of peaks between 18 and 24 (2θ). The zoomed image shows that most of the observed peaks are shifted to slightly lower 2θ values when samples are grown in the presence of 4MBP. This indicates that the additive may be incorporated into the crystal lattice causing disruption to packing and subsequently the diffraction.
Figure 116. A stack of X-ray diffraction patterns of benzophenone samples. Pure experimental benzophenone (black), and benzophenone grown in the presence of 4MBP at supersaturations of 0.1 (red) and 0.3 (blue – unwashed, green - washed).

Figure 117. A zoomed in image of the stacked X-ray powder patterns of benzophenone samples grown in the presence of 4MBP. Pure experimental benzophenone (black), and benzophenone grown in the presence of 4MBP at supersaturations of 0.1 (red) and 0.3 (blue – unwashed, green - washed).

5.6.3.2 4-aminobenzophenone

Figure 118 shows powder X-ray diffraction patterns for benzophenone grown from pure and impure solutions. The presence of 4ABP appears to cause a minor shift in the peaks of the benzophenone diffraction pattern at 20 of 14, 16, 20 and 28, more noticeable at higher supersaturation. However not drastically and the sample is still benzophenone.
The cluster of peaks between 20 and 24 (2θ) are shown in more detail in Figure 119. The peaks appear slightly shifted throughout this range shown suggesting the additive may be incorporated.

Figure 118. A selection of X-ray diffraction patterns of benzophenone; pure experimental benzophenone pattern (black) and benzophenone grown in the presence of 4ABP at supersaturations of 0.1 (red – unwashed, blue -washed) and 0.3 (green – unwashed and pink -washed).

Figure 119. A zoomed in image of the stacked X-ray powder patterns of benzophenone samples grown in the presence of 4ABP. Pure experimental benzophenone pattern (black) and benzophenone grown in the presence of 4ABP at supersaturations of 0.1 (red – unwashed, blue -washed) and 0.3 (green – unwashed and pink -washed).
5.6.3.3 Diphenylmethane

Figure 120 shows the powder X-ray diffraction patterns of benzophenone from pure and impure solutions. The red and blue patterns are of benzophenone when grown in the presence of DPM and appear to match well throughout the 2θ range.

Figure 120. Selected powder X-ray diffraction patterns of benzophenone samples; pure experimental benzophenone (black) and benzophenone grown in the presence of DPM at different supersaturations of 0.2 (red – unwashed, blue - washed) and 0.3 (green – unwashed, pink - washed).

Figure 121. A zoomed in image of the stacked X-ray powder patterns of benzophenone samples grown in the presence of 4ABP, pure experimental benzophenone (black) and benzophenone grown in the presence of DPM.
at different supersaturations of 0.2 (red – unwashed, blue - washed) and 0.3 (green – unwashed, pink - washed).

Figure 121 shows the peaks at 2θ values between 20 and 24 in more detail. There is not much evidence of peak shifting to lower 2θ values throughout this range in this case. The X-ray diffraction patterns suggest that the additive may not be incorporated in this case.

5.7 Conclusions

The induction time for nucleation of benzophenone appears shortened by the presence of 4ABP and DPM. However, the 4MBP additive significantly extends the induction period and at low σ appears to prevent nucleation. This increase in induction time appears to be due to 4MBP strongly hindering the growth of the crystal to a detectable size, not the formation of clusters.

HPLC has been used to confirm the presence of the additives in the crystal lattice as indicated by the DSC and X-ray diffraction. 4MBP and 4ABP are both incorporated into the crystal structure whereas, DPM is not. However, DPM does not strongly hinder the growth or nucleation of benzophenone, hence incorporation of the additive is not expected to the same extent. The DSC indicates that the 4ABP and 4MBP additives are present in some concentration in the sample, as proven by the HPLC. This is not in the case for DPM. The powder X-ray diffraction patterns indicate that a small amount of impurity may be present in the samples since some peaks shift slightly in the cases of 4ABP and 4MBP. Thus the analytical techniques indicate that co-crystals and pure components do not crystallise, with some of the 4ABP and 4MBP incorporated into the crystal in the predicted fashion. One technique alone does not allow conclusions about the mechanism of incorporation. However, the three combined indicate that 4MBP and 4ABP are incorporated into the crystal lattice not just bound to the crystal surface.
6. Crystal Growth of Benzophenone

This chapter describes the growth rate kinetics of benzophenone crystals grown in pure and impure solutions.

6.1 Microscope Growth Experiments

Seeded crystal growth experiments were performed at various supersaturation levels in pure solution and in the presence of additives at different concentrations. Three additives, 4ABP, 4MBP and DPM were chosen for this study as a result of the morphological analysis (Section 4.5) showing that 4ABP and 4MBP have a strong effect on the growth of the \{011\} faces of benzophenone and DPM has a weak effect on the same faces. When grown from propan-2-ol solution, the observed crystal morphology is consistent with previous reports\textsuperscript{102,124,125} (Section 3.1).

![Figure 122. Images of growing benzophenone crystals at different supersaturation.](image)

Figure 122 shows pictures of growing benzophenone crystals at different supersaturation and the morphology is similar in all six images. Each crystal is slightly different as the nature of crystallisation causes minor differences in relative growth rates.
of the crystal faces. What is apparent from the crystals is that some grow with more
imperfections than others. Figure 122 shows six crystals grown in different experiments.
Image f shows a crystal with a high level of imperfections and defects, also apparent in
crystals e and c. However, crystals a, b and d appear slightly less defected in
comparison. Thus, the defect frequency in benzophenone does not follow an obvious
trend with supersaturation.

6.1.1 Relationship Between Microscope Images and Crystal Morphology

In a typical experiment a seed crystal (size approximately 100 by 100μm) is located in
the growth cell and its dimensions are followed over a period of time (typically up to 24
hours) whilst temperature and supersaturation are held constant (see Section 2.4 for full
method). Figure 122 shows a selection of typical seed crystals grown at various σ and
Figure 123 shows a time lapse sequence of one crystal growing at σ = 0.046. It is clear
that face specific measurements cannot be made, since the microscope can only provide
a two dimensional image of a three dimensional crystal.

![Image of crystals](image-url)

**Figure 123.** A time lapse sequence of images of a growing benzophenone crystal at σ = 0.046.

From Figure 122 it is clear to see that the ends of the crystal are inequivalent in some
cases, i.e. one end appears to be terminated by 5 faces while the other appears to consist
of 3 faces. However, in Figure 123 this is not the case and both ends appear to consist of
three faces at either end. In order to relate these 2-dimensional images to the 3-
dimensional shape of crystals, Materials Studio was used to create customised morphologies. The \{002\} faces were removed from the attachment energy morphology in order for clarity. Figure 124 shows an example of a customised morphology of benzophenone which is comparable to the crystals in Figure 123.

![Diagram](image)

(a) (b)

**Figure 124. Images of a customised morphology of benzophenone.**

The two images in Figure 124 are the same morphology, only coloured differently. Looking at the morphology prediction in (a), it appears as though there are 3 surfaces at either end of the crystal, though this is not the case. The flat part of the morphology (labelled A in Figure 125(b)) at either end of the crystal is due to the edge or intersection between two surfaces at the end of the crystal. The images in Figure 125 show the crystal rotated perpendicular to the a axis (in part) in image b and by 90° in image c. The extra edge (labelled A as in Figure 124) apparent at the end of the crystal in image a is in fact the edge between the (101) and (10\bar{1}) crystal faces.
Figure 125. Images of benzophenone crystals viewed at different angles.

Figure 126. Images of predicted benzophenone crystal morphologies with \{111\} faces with increased morphological importance.

Figure 126 shows a further modification of the morphology in which the \{111\} faces have been given increased morphological importance. Figure 126(a) shows a habit prediction where only one set of \{111\} are present while Figure 126(b) shows the case where both sets of \{111\} faces appear. When only one set of \{111\} faces are included the morphology has inequivalent ends along the a axis similar to that observed experimentally in Figure 122. However, when both sets of \{111\} faces grow the ends of the crystal are equivalent (unobserved experimentally). This analysis thus provides a link between the 3D morphology and the 2D microscope images. It is evident that the inequivalence of the two ends of the crystal arise from the point group, \(2_12_12_1\) in which
the \{111\} faces are non-equivalent. As a consequence of this, face specific measurements are not simple.

### 6.1.2 Crystal Growth Measurements

Given Section 6.1.1 it is evident that the microscope image is sufficient to allow identification of the a axis. This alone does not define the location of the b and c axes, hence, the index of the face normal to the axis of the microscope is unknown. The face may be the (011) or it may be the (01\bar{1}). To assign this face for each crystal is not possible since it would require removal of the crystal from the cell and application of XRD. The crystals are too small and fragile for this. Thus, Figure 127 shows a sample measurement for a modified morphology.

Looking down on the (0\bar{1}1) face, the measurements taken are the furthest distance between the two ends of the crystal for the a axis. For the width measurements the distance between two \{011\} faces is taken. In Figure 127 it is the distance between the (011) and (0\bar{1}1) surfaces. If the crystal was rotated 90° about the a axis, such that the top face was the (0\bar{1}1) surface, the width measurement would be between the (0\bar{1}1) and (01\bar{1}) surfaces. Regardless of the top crystal surface the resulting measurement is always between two inequivalent symmetry related \{011\} faces (Section 3.1.4). Thus, the average growth rate of one set of \{011\} faces cannot be measured, only the combination of \{011\} and \{01\bar{1}\}.

![Figure 127. A simulation of a typical crystal growth rate measurement.](image-url)
In order to calculate the growth rate of a crystal, a graph of size against time is plotted and a sample graph is shown in Figure 128 corresponding to the crystal growing in Figure 123. It is clear that the crystal dimensions follow a linear increase with time, indicating that the growth rate remains constant throughout the experiment. The average growth rate is then equivalent to the gradient of the line. The linearity of the plot indicates that the supersaturation is constant for long periods of time and that the measurements are a useful way of characterising the growth kinetics.

![Figure 128. A graph showing the change in crystal dimensions with time.](image)

In any crystallisation experiment the relative growth rates of crystal faces may fluctuate with some growing faster than others for a period of time. It is then possible that some faces may swap in relative growth rate to each other. Because the width of the crystal is the distance between two parallel faces, fluctuations in one of the \{011\} faces are accounted for as the average growth rate is calculated.

However the a axis is a different case as each measurement is between the point where the \{101\} and \{110\} faces meet. If throughout the experiment the (101) and (110) faces grow at the same relative rate yet the (10\bar{1}) and (1\bar{1}0) faces have different relative growth rates, the measurement is no longer parallel to the a axis since the intersection of the two faces will be skewed to one side of the crystal as in Figure 129b and Figure 130.
This leads to an error in the measurement of the growth, since the length of the crystal is not accurately measured.

Figure 129. Images of growing benzophenone crystals in the presence of additives; a) 4MBP and b) 4ABP.

Figure 129 shows two different benzophenone crystals growing in the presence of additives in the growth cell under the microscope. In both images the crystal is growing without apparent imperfections. However, the faces at the end of the crystal (a axis) are of slightly different morphological importance. When the crystal is below a certain width this does not make a difference in the measurement, since the measuring tool has a small tolerance. When the width of the crystal is larger it becomes more difficult to accurately measure the distance between the intersection of the \{101\} and \{110\} faces. Experiments where the distance between the furthest points of the a axis is highly skewed and not parallel to the a axis were rejected since the measurement is not truly of the a axis.
Figure 130. An image of a benzophenone crystal growing in the presence of 4ABP.

Figure 130 shows a crystal growing in solution in the presence of 4ABP and there is a clear difference to the crystals shown at either end of the a axis. Both ends of the crystal (the a axis) have faces which have grown at different rates relative to one another. At the lower end of the crystal one face is much larger than the other and near the end of this face the crystal appears to be very imperfect, and the imperfections appear to be parallel to one face. At the other end of the crystal this also appears to be true, and the faces are closer together in terms of morphological importance.

6.2 Growth Rate Measurements

Initially pure growth rate experiments at fixed temperature were performed before measuring the kinetics at fixed additive concentration (0.1 mole fraction additive with respect to the solute were performed). The supersaturation is defined as:

$$\sigma = \ln \frac{x_{ss}}{x_{eq}}$$

Equation 64

The equilibrium solubility of benzophenone in the presence of the additive is increased compared to pure solution, hence $x_{eq}$ is adjusted in each case (Section 4.3).

6.2.1 Pure Growth

The measurements of the width of the crystal and the a axis lead to similar growth rates as shown in Figure 131, with the a axis growing slightly faster than the width. The
growth rates increase with supersaturation as expected. Although there is some scatter in the data, it is possible to fit straight lines in Figure 131 to both sets of data. For growth by two-dimensional surface nucleation and spiral growth the line is expected to have a slight curve especially at low supersaturation. It is difficult to establish any such trend in the data in Figure 131 due to the scatter in the data points. Figure 131 differs from Figure 128 in that the growth rate of different crystals are plotted against supersaturation instead of the change in individual crystal dimensions over time. There is scatter in the data in Figure 131 as different crystals are expected to grow at different rates.

Figure 131. A graph of growth rate with supersaturation for pure benzophenone crystals.

### 6.2.2 Specific Impurity Effects – 0.1 molar fraction Additive concentration

Figure 132 and Figure 133 show the growth rates of the a axis and the width of benzophenone crystals when grown from pure and impure solution.
Figure 132. A graph to show the growth rate of the a axis of the crystal when grown from pure solution and also in the presence of additives.

From Figure 132 it appears as though the a-axis growth rate of crystals in the presence of DPM and 4ABP is not affected, with data points for both pure and impure lying on the same line. However, in the case of the 4MBP the growth rate of the a axis is significantly hindered with the rate of growth up to a $\sigma = 0.1$ effectively zero. As $\sigma$ increases, the growth rate of the a axis increases and returns to the growth rate of benzophenone in pure solution at approximately $\sigma = 0.3$. This suggests that the additive is strongly interfering with the growth process of the $\{101\}$ and $\{110\}$ faces at low $\sigma$. 
It is clear from Figure 133 that the DPM additive is not an effective growth modifier throughout the supersaturation range. Both 4MBP and 4ABP have a very strong effect on the width of the crystals, with the growth rates much lower in comparison to crystals grown from pure solution. 4MBP has a much stronger effect on the growth compared to 4ABP and at $\sigma$ up to 0.1, with a clear dead zone in the growth rate curve. The dead zone is the supersaturation range in which crystals do not grow at an appreciable rate due to the effect of the impurity. Above $\sigma = 0.1$ the growth rate does very slowly begin to increase. However for the width of the benzophenone crystal, this does not begin to reach the same as the rate of growth of a crystal in pure solution and the outcome is a needle like morphology.

Overall we can see that the process for additive selection based on the crystal structure of benzophenone has been successful. Two additives; 4ABP and 4MBP strongly hinder the growth of the \{011\} surfaces as expected with the 4MBP additive causing a dead zone in the growth at low supersaturation ($\sigma < 0.1$).
6.3 Mechanistic Interpretation

6.3.1 Screw Dislocation and Surface Nucleation

The calculated $\alpha$ factors suggest that the crystals could grow by either screw dislocation or surface-nucleation. Applying the following models to growth rate data at fixed additive concentration may allow interpretation of the growth mechanism of benzophenone. For surface nucleation the growth rate, $R$ is equal to:

$$ R = A\sigma^{5/6}\exp\left(-\frac{B}{\sigma}\right) $$

Equation 65

$A$ and $B$ are system related constants. Growth via a screw dislocation mechanism has a distinct trend with supersaturation with parabolic behaviour at low supersaturation shifting to a linear relationship at higher supersaturation. The rate of growth of a face growing by a spiral growth mechanism is $^{126}$:

$$ R = C \frac{\sigma^2}{\sigma_1} \tanh \frac{\sigma_1}{\sigma} $$

Equation 66

In which $\sigma$ is the supersaturation,

$$ C \propto (-\Delta G_{\text{desolv}}/kT) $$

Equation 67

$$ \sigma_1 = \frac{\gamma \cdot 9.5a}{k_BT \lambda_s} $$

Equation 68

$\Delta G_{\text{desolv}}$ is the free energy of desolavation, $\gamma$ is the step energy in J/molecule and $\lambda_s$ is equal to 0.5 $a$. When $\sigma_1 \gg \sigma$, $\tanh \frac{\sigma_1}{\sigma}$ tends to 1, and $R = \sigma^2$ contributing to the
parabolic part of the trend at low supersaturations. However, as $\sigma >> \sigma_1$, the expression is no longer parabolic and the linear Equation 69 is more useful

\[ R = C'\sigma. \]

Equation 69

6.3.2 Pure Growth

Figure 134. A graph comparing the screw dislocation and two dimensional surface nucleation growth models for the a axis of benzophenone crystals grown in pure solution.

Applying Equations 65, 66 and 69 to the pure growth rate data gives rise to the curves in Figures 134 and 135 and the values of C used for $R = C\sigma$ are shown in Table 25. It is clear in both Figures 134 and 135 that the two-dimensional surface nucleation curves do not fit the data, hence this model is rejected in favour of the screw dislocation model.
Figure 135. A graph comparing the screw dislocation and two dimensional surface nucleation models for the width of benzophenone crystals grown in pure solution.

Table 25. A table summarising parameters obtained from the screw dislocation data fit for benzophenone crystals grown from pure solution.

<table>
<thead>
<tr>
<th></th>
<th>BCF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (μm/sec)</td>
</tr>
<tr>
<td>a axis</td>
<td>1.0 ± 0.052</td>
</tr>
<tr>
<td>Width</td>
<td>0.8 ± 0.039</td>
</tr>
</tbody>
</table>

The parameters obtained from the fit suggest that the growth rates measured correspond to the linear portion of the BCF curve (i.e. Equation 69) not the parabolic curve (Equation 66), this is consistent with the BCF theory. As both of the fitted curves are close together, this indicates that σ >> σ₁ at all supersaturations measured. However, there is significant scatter in the data resulting in an amount of error in the parameters.

Since the data does not fit with the two-dimensional nucleation growth model for pure benzophenone, it is unlikely that this is the mechanism of growth. Thus, in the following analysis only the screw dislocation model is used and the fits of the two-dimensional nucleation model can be found in the appendix (Section A1).
6.3.3 Diphenylmethane

Figure 136. A graph comparing the screw dislocation growth equations for the a axis of benzophenone crystals grown in the presence of DPM.

Figure 137. A graph comparing the screw dislocation growth equations for the width of benzophenone crystals grown in the presence of DPM.

Figures 136 and 137 show the fitted curves and it is clear that both curves overlay each other suggesting that measurements taken are all above $\sigma_1$ as the trend in the data is linear. Estimating the parameters from the model is inaccurate since only the linear portion of the trend is observed.
6.3.4 4-aminobenzophenone

Figure 138. A graph comparing the screw dislocation growth equations for the a axis of benzophenone crystals grown in the presence of 4ABP.

For the a axis growth, Figure 138 shows the fitted BCF curve with values of \( C \) and \( \sigma_1 \) given in Table 26. Since the value of \( \sigma_1 \) is now significantly higher than in pure solution the fit of Equation 66 to the data estimates parameters with reasonable accuracy. For the width, the \( R = C\sigma \) curve grossly overestimates the growth rate of the crystals and the \( R = C\sigma \) curve is removed from Figure 139. Since the data measured is clearly in the parabolic region, accurate estimation of the parameters is not possible for the width data.
Figure 139. A graph comparing the screw dislocation growth fit for the width of benzophenone crystals grown in the presence of 4ABP disregarding the linear growth rate equation.

<table>
<thead>
<tr>
<th>BCF</th>
<th>C (μm/sec)</th>
<th>$\sigma_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a axis</td>
<td>1.33 ± 0.164</td>
<td>0.13 ± 0.059</td>
</tr>
</tbody>
</table>

Table 26. A table summarising the parameters obtained from the screw dislocation fit for benzophenone crystals grown in the presence of 4ABP.

In Table 26 value of C for the a axis is similar to that of pure solution while $\sigma_1$ is larger by a factor of approximately 5. This seems to be a reasonable outcome, suggesting that the additive is most effective at low step and kink site densities.

6.3.5 4-methylbenzophenone

For benzophenone grown in the presence of 4MBP, the linear fit of the screw dislocation dwarves the parabolic curve, hence is removed in Figure 140 and 141.
Since the trend in the growth rate data is parabolic throughout for both width and the a-axis, estimation of accurate BCF parameters is not possible. The growth data never reaches the linear part of the expected trend suggesting that measurements are always taken when $\sigma \ll \sigma_1$. 
6.3.6 Summary

In all cases the two dimensional surface nucleation model is rejected in favour of the screw dislocation model and calculated values for $\sigma_1$ (Equation 68) are seen to change significantly with the presence of additives. The linear and parabolic curves for the pure growth rate data both fit reasonably, with measurements always taken above $\sigma_1$. For growth in the presence of DPM the data fits the linear curve, with the parabolic curve overlaying very well suggesting that the value of $\sigma_1$ is very small and both data fits produce an almost linear fit. For 4ABP and 4MBP (the strong growth inhibitors) the curved line fits the data better than the linear suggesting that measurements are always taken at supersaturation values much lower than $\sigma_1$. As a consequence of this the linear portion of the model is never observed, hence significant error is associated with the estimation of the parameters. In addition there is significant scatter in the data points, which is difficult to eliminate since different crystal will naturally grow at different rates, thus, further contributing to the error.

For $\sigma_1$ to increase; either the interfacial energy must decrease or the strength of the dislocation source must increase or both. For $\sigma_1$ to decrease; either the interfacial energy must increase or the strength of the dislocation source must decrease or both. Since the presence of additives has been found to have little effect on the interfacial tension; (Section 5.4), and $\lambda s$ is equal to $0.5a^{127}$ the only way to affect $\sigma_1$ is for the strength of the dislocation source to change. This is explored in the next section.

6.4 Model Validation

6.4.1 Interfacial Tension

Values for interfacial tension calculated previously (Section 5.4) are similar for pure benzophenone and in the presence of the additive. These values are utilised here to estimate the step energies from the relationship:

$$\gamma' = \gamma \times area_{molecule}(J / Molecule)$$

Equation 70
The area of a benzophenone molecule is estimated using Mercury to create a step, this is then used to estimate the step energy of one benzophenone molecule.

### 6.4.2 Step Energies and Dislocation Sources

It is possible to estimate $S$ from $\sigma_1$ using Equation 68. An average of the eight values of $\gamma$ (Table 20, Section 5.4.5) is taken to yield $1.20$ (mJ m$^{-2}$) used for calculation of the strength of dislocation source. For (011) and the (011) surfaces the $\sigma_1$ values calculated for the width of the crystal are used and for the (101) and (110) faces the $\sigma_1$ value for the a axis is used.

### 6.4.3 Pure Benzophenone Growth

<table>
<thead>
<tr>
<th>Face</th>
<th>Surface Area m$^2$</th>
<th>$\gamma$ (J m$^{-2}$)</th>
<th>$\gamma'$ (J molecule)</th>
<th>$\sigma_1$</th>
<th>$S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(011)</td>
<td>2.78E-19</td>
<td>0.0012</td>
<td>3.34E-22</td>
<td>0.037</td>
<td>23</td>
</tr>
<tr>
<td>(011)</td>
<td>3.80E-19</td>
<td>0.0012</td>
<td>4.56E-22</td>
<td>0.037</td>
<td>31</td>
</tr>
<tr>
<td>(101)</td>
<td>4.44E-19</td>
<td>0.0012</td>
<td>5.33E-22</td>
<td>0.046</td>
<td>29</td>
</tr>
<tr>
<td>(110)</td>
<td>3.88E-19</td>
<td>0.0012</td>
<td>4.66E-22</td>
<td>0.046</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 27. A table summarising parameters extracted from the screw dislocation model for pure crystal growth of benzophenone.

From Table 27 the screw dislocation model predicts that between approximately 20 and 30 screw dislocations are co-operating on the crystal surfaces. It is unlikely that this number of growth spirals can operate successfully on one crystal surface without interfering with each other. For vapour growth of hexamethylene tetramine values of $S$ of between 1 and 3 were reported$^{128}$.

Since the value of interfacial tension is comparable to previous reports of approximately 1.218 to 1.272 mJ m$^{-2}$ for benzophenone$^{119}$ and less than 50 mJ m$^{-2}$ $^{129}$ for molecular compounds, the error is most likely from the calculated values of $\sigma_1$ as the data fit has a significant error associated. For growth of urea from pure ethanol solution values of $C = 509\mu$m/sec and $\sigma_1 = 0.012$ for the (001) crystal surface$^{40}$ were calculated which compare well with values of $C$ and $\sigma_1$ for pure benzophenone reported here. In the case of glucuronaric acid lactone the value of $\sigma_1$ is reported as 0.015 for the (100) face, 0.05 for the (101) and (110) faces and 0.03 for the (011) face$^{130}$. In the case of glycine $\sigma_1$ values of 0.08 and 0.03 are reported for the (011) and (010) faces respectively$^{131}$. For
pure stearic acid values of 0.48 and 0.079 were calculated\textsuperscript{132} with values between these two when grown in the presence of up to 2.0% Span. All of the calculated values of $\sigma_1$ in the literature are of similar order to those calculated for pure benzophenone. However for growth in the presence of additives the value of $\sigma_1$ is very different implying a different value for $S$. This is most likely due to the measurements in the presence of additives either being above or below $\sigma_1$. Thus, the measured data do not exhibit both regions of the trend producing inaccuracies. Since the value of $\sigma_1$ cannot always be estimated to a reasonable degree of certainty, values for the value of $S$ for benzophenone grown in the presence of additive are uncalculated.

6.5 Dead Zone

This section describes the experimental dead zone for benzophenone grown in the presence of 4MBP.

6.5.1 Experimental Dead Zone in Growth at $\sigma=0.04$

Below $\sigma = 0.1$ at fixed additive concentration of 10% 4MBP, zero growth rate of benzophenone is observed. Above $\sigma = 0.1$ the growth rate of the crystal increases indicating the effect of the additive is overcome by the supersaturation of the solution.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figures.png}
\caption{Images of a benzophenone crystal growing in the presence of 4MBP (10%) at $\sigma = 0.04$.}
\end{figure}
Figure 142 shows images of a growing benzophenone crystal in the presence of 4MBP. Image 1 is after the seed crystal is initially dissolved and the other images are from selected points throughout the experiment. It is clear that the seed crystal begins to grow developing facets before the growth almost halts due to the amount of time taken for the additive to bind to the surfaces. However the crystal is growing and the average growth rate is 0.012μm/min for the a axis and 0.013μm/min for the width, effectively a zero growth rate compared to pure growth rates of 1.99 μm/min and 1.35μm/min. Between images 7 and 8 the crystal has only grown by approximately 80 μm in length (a axis) and approximately 70 μm in width over the course of approximately 42 hours. In comparison for pure benzophenone growth at σ = 0.04, the crystal grows by 1516μ (a axis) and 1028μm (width) after approximately 13 hours.

### 6.5.3 Estimation of σc

Cabrera and Vermilyea\(^{47}\) and also Kubota and Mullin\(^{71}\) derived physical models for growth kinetic data defining a critical supersaturation, σ\(_c\) below which the growth rate is zero. Above σ\(_c\) the solute overcomes the effect of the additive and crystal growth continues. Using Kubota and Mullin’s model it is possible to predict a critical supersaturation from a fit of the screw dislocation model using\(^{133}\):\(^\text{133}\)

\[
G = A \sigma^2 \times \tanh\left(\frac{\sigma_1}{\sigma}\right) \times \left[1 - \left(\frac{\sigma}{\sigma_c}\right)^{-1}\right]
\]

**Equation 71**

Calculations were performed for both the width and axis growth in the presence of 4MBP since in this case a dead zone in the growth is observed. Calculations were also performed for the width growth in the presence of 4ABP in order to test the model as a dead zone is unobserved in the presence of this additive.

<table>
<thead>
<tr>
<th>Additive</th>
<th>Kubota Mullin Model</th>
<th>Measured Dead Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive</td>
<td>a axis</td>
<td>Width</td>
</tr>
<tr>
<td>4ABP</td>
<td>No Fit</td>
<td>0.15</td>
</tr>
<tr>
<td>4MBP</td>
<td>0.28</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Table 28. A table summarising the predicted dead zones in crystal growth for benzophenone when grown in the presence of additives
Using Equation 71 with parameters calculated previously (Section 6.3) yields the values of critical supersaturation, below which benzophenone crystals are not expected to grow (Table 28). For 4ABP, a dead zone is predicted for the width of the crystal up to a supersaturation of 0.15 which is unobserved in the growth rate data. For the 4MBP additive a dead zone in growth is predicted up to $\sigma = 0.28$ and $\sigma = 0.27$ for the a axis and width respectively. From the measured growth rate data in 4MBP the growth rate is approximately zero until the supersaturation reaches $\sigma = 0.1$ for both the a axis and the width. Hence an over estimation of approximately $\sigma = 0.17$ is calculated.

It is also possible to predict a critical supersaturation for Equation 71 using lattice parameters and the following relationship:

$$\sigma_c = \frac{\gamma_{step} \alpha Kc}{k_b TL(1 + Kc)}$$

Equation 72

When the concentration of impurity ($Kc$) is high, Equation 72 can be reduced to:

$$\sigma_c = \frac{\gamma_{step} \alpha}{k_b TL}$$

Equation 73

and

$$\gamma_{step} = \gamma h$$

Equation 74

$h$ is the step height, $\alpha$ is the size of the growth unit and $L$ is the average separation between active sites.

<table>
<thead>
<tr>
<th>Face</th>
<th>$a$ ($m^2$)</th>
<th>$h$ ($m$)</th>
<th>$L$ ($m$)</th>
<th>$T$ (K)</th>
<th>$\gamma_{step}$ ($J m^{-1}$)</th>
<th>$\sigma_c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(011)</td>
<td>4.46E-19</td>
<td>9.40E-10</td>
<td>8.10E-10</td>
<td>288</td>
<td>1.13E-12</td>
<td>0.16</td>
</tr>
<tr>
<td>(011)</td>
<td>4.46E-19</td>
<td>9.40E-10</td>
<td>8.10E-10</td>
<td>288</td>
<td>1.13E-12</td>
<td>0.16</td>
</tr>
<tr>
<td>(101)</td>
<td>3.73E-19</td>
<td>4.68E-10</td>
<td>6.22E-10</td>
<td>288</td>
<td>5.61E-13</td>
<td>0.08</td>
</tr>
<tr>
<td>(110)</td>
<td>3.94E-19</td>
<td>9.00E-10</td>
<td>7.11E-10</td>
<td>288</td>
<td>1.08E-12</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 29. A table summarising the values used for the predicted dead zone calculations.
Table 29 shows the values used to calculate the predicted dead zones in growth of different benzophenone crystal faces. Using the average calculated value for interfacial tension (Section 5.4.5) of 1.20 mJ m$^{-2}$ the model predicts a similar dead zone in growth for the (011) and (110) crystal faces. Experimentally the measured dead zone for growth in the presence of 4MBP is up to $\sigma = 0.1$ and the calculated values for the (011), (01 1) and (110) faces are slightly higher than this. However, the value calculated for the (101) surface is within this experimentally measured dead zone. This Kubota and Mullin prediction provides a better estimation compared to the calculated values from growth data (Equation 71) as less of an over estimation is observed.

### 6.6 Concentration Range

Having explored the impact of fixed additive concentration on R($\sigma$) curves we now look at the effect of fixing supersaturation and varying additive concentration. Impurities are known to have effects at very low concentrations, thus, concentrations of additive of 3, 5 and 7% with respect to the solid are used with supersaturation levels up to $\sigma = 0.1$, since this is the extent of the dead zone in growth found for 10% additive (for 4MBP). Since DPM is not an effective growth inhibitor at 10% it is very unlikely to have an effect on the crystal growth at concentrations lower than this, hence is eliminated from experiments. As only the width of the crystal is experimentally hindered by both additives, only width measurements are discussed in this section.

#### 6.6.1 4-aminobenzophenone

Figure 143 shows images of crystals at $\sigma = 0.03$ with varying additive concentration and Figure 144 the same for $\sigma = 0.1$. It is clear from these images that the additive causes an elongation of the crystal compared to pure benzophenone (Figure 122) regardless of the additive concentration. This confirms that the additive is in fact a strong growth inhibitor of the {011} crystal surfaces. Comparing the images between supersaturation of 0.03 and 0.1, the additive seems to have similar effects independent of supersaturation, with aspect ratios of approximately 2.5:1 (length:width) for concentrations up to 5%, approximately 3:1 for 7% and approximately 4:1 for 10%. Conversely, pure benzophenone crystals are much more isometric in shape (Figure 122) having aspect ratios of approximately 1.3:1.
Figure 143. Images of benzophenone crystals growing in the presence of different concentrations of 4ABP at fixed supersaturation of 0.03 for approx. 24-48 hours.

Figure 144. Images of benzophenone crystals grown in the presence of different concentrations of 4ABP at a fixed supersaturation of 0.1 for approx. 24-48 hours.
Figure 145 shows the change in growth rate of benzophenone crystals with increasing supersaturation at different additive concentrations. There is some scatter in the data with an indication that increasing the additive concentration decreases the growth rate compared to pure growth.

![Graph showing the change in growth rate](image_url)

Figure 145. A graph showing the change in the growth rate of the width of benzophenone crystals in solutions containing different concentrations of 4ABP.

### 6.6.2 4-methylbenzophenone

Figures 146 and 147 show benzophenone crystals grown in the presence of 3, 5, 7 and 10% 4MBP grown at $\sigma = 0.03$ and $\sigma = 0.1$ respectively. The aspect ratios of the crystals are approximately 3.5:1 (length:width) in all cases except for at 10% concentration and $\sigma = 0.03$; where it is noted that the crystal is within the dead zone (up to $\sigma = 0.1$). Since the rest of the imaged crystals have similar aspect ratios this also indicates that the additive is effective independent of supersaturation.
Figure 146. Images of benzophenone crystals grown in the presence of different concentrations of 4MBP at a fixed supersaturation of 0.03.
Figure 147. Images of benzophenone crystals grown in the presence of different concentrations of 4MBP at a fixed supersaturation of 0.1.

Figure 148. A graph showing the effect of additive concentration and supersaturation on the growth rate of benzophenone in the presence of 4MBP.
Figure 148 shows the related kinetic data. It is clear that increasing the concentration of the additive in the solution causes a decrease in the growth rate of the crystals compared to pure solution. In the next section various models are applied in order to estimate Langmuir constants for impurity adsorption.

6.7 Langmuir Isotherm

Impurities bind to key sites inhibiting growth and this adsorption can be related to solution concentration by assuming an isotherm. In general the surface coverage \( \theta_{eq} \) of impurity can be related to the solution concentration \( C \) by the Langmuir isotherm\(^{134} \):

\[
\theta_{eq} = \frac{KC}{1 + KC}
\]

Equation 75

\( K \) is the Langmuir constant and \( c \) is the concentration of impurity. The free energy of adsorption for an impurity is related to the Langmuir constant by the following relationship assuming steady state adsorption of impurity to the crystal surface\(^{70} \):

\[
K = \exp\left(\frac{-\Delta G_{ads}}{RT}\right)
\]

Equation 76

\( \Delta G_{ads} \) is the free energy of adsorption of the impurity, \( R \) is the gas constant and \( T \) is the absolute temperature.

6.7.1 Davey and Mullin

If the minimum growth rate in the presence of impurity \( (v_\infty) \) is zero as in the case of 4MBP, plotting \( \frac{v_0}{v_0 - v} \) against \( \frac{1}{x} \) directly yields the Langmuir constant using Equation \( 77^{39} \):
\[ \frac{V_0}{V_0 - v} = 1 + \frac{1}{x} \]

Equation 77

\( v_\infty \) is the growth rate when the surface is completely covered by impurity, \( v_0 \) is the pure growth rate, \( v \) is the growth rate in the presence of impurity, \( x \) is the impurity concentration and \( K \) is the Langmuir constant.

**6.7.1.1 4-aminobenzophenone**

Figure 149. A graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4ABP.

Figure 149 shows the fit of the equation to the growth data in the presence of 4ABP and the values obtained are shown in Table 30. The values of the Langmuir constant obtained are all reasonable and yield similar value for the free energy of adsorption of additive. As expected the value of \( \theta_{eq} \) increases with increasing additive concentration suggesting that the amount of additive adsorbed at equilibrium increases with increasing additive concentration.
Mole Fraction Additive | $K$  | $\theta_{eq}$ | $\Delta G_{ads}$ (Kj/mol) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>73.30</td>
<td>4.40</td>
<td>-10.28</td>
</tr>
<tr>
<td>0.05</td>
<td>175.02</td>
<td>17.50</td>
<td>-12.37</td>
</tr>
<tr>
<td>0.07</td>
<td>134.19</td>
<td>18.78</td>
<td>-11.73</td>
</tr>
<tr>
<td>0.1</td>
<td>110.87</td>
<td>22.17</td>
<td>-11.27</td>
</tr>
</tbody>
</table>

Table 30. A table summarising the Langmuir constant and the free energy of adsorption of the 4ABP additive into the benzophenone crystal surface.

<table>
<thead>
<tr>
<th>Mole fraction additive</th>
<th>Gradient</th>
<th>Error</th>
<th>Critical t Value</th>
<th>Confidence Interval (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>0.014</td>
<td>0.003</td>
<td>2.36</td>
<td>0.005</td>
</tr>
<tr>
<td>0.05</td>
<td>0.006</td>
<td>0.003</td>
<td>2.36</td>
<td>0.006</td>
</tr>
<tr>
<td>0.07</td>
<td>0.007</td>
<td>0.002</td>
<td>2.36</td>
<td>0.003</td>
</tr>
<tr>
<td>0.10</td>
<td>0.009</td>
<td>0.002</td>
<td>2.36</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Table 31. A table showing the gradient of the lines in Figure 149 along with the error and t value associated.

Table 32 shows the gradient of the line used to calculate the Langmuir constant along with the error associated, the calculated t value and the confidence interval calculated using the LINEST function in Excel. The critical t value is the same for each sample as the sample size is the same for each set. The 90% confidence interval is significant in each case suggesting that the fit of the line to the data contains some error.

6.7.1.2 4-methylbenzophenone

![Figure 150](image.png)

Figure 150. A graph showing the relative growth rate relationship with additive concentration for benzophenone grown in the presence of 4MBP.
Figure 150 shows the fit of Equation 77 to the data and Table 32 shows the values of $K$, $\theta_{eq}$ and $\Delta G_{ads}$. The Langmuir constants obtained are larger than those observed in the presence of 4ABP, as are the free energy of adsorption energies suggesting that it may be more energetically favourable to bind the 4MBP additive in comparison. The $\theta_{eq}$ values increase with increasing additive concentration except for at 0.1 mole fraction when a decrease is observed.

<table>
<thead>
<tr>
<th>Mole Fraction Additive</th>
<th>$K$</th>
<th>$\theta_{eq}$</th>
<th>$\Delta G_{ads}$(KJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>190.01</td>
<td>11.40</td>
<td>-12.56</td>
</tr>
<tr>
<td>0.05</td>
<td>313.86</td>
<td>31.39</td>
<td>-13.76</td>
</tr>
<tr>
<td>0.07</td>
<td>460.34</td>
<td>64.45</td>
<td>-14.68</td>
</tr>
<tr>
<td>0.1</td>
<td>255.19</td>
<td>51.04</td>
<td>-13.27</td>
</tr>
</tbody>
</table>

Table 32. A table summarising the Langmuir constant and the free energy of adsorption of the 4MBP additive into the benzophenone crystal surface.

<table>
<thead>
<tr>
<th>Mole fraction additive</th>
<th>Gradient</th>
<th>Error</th>
<th>Critical t Value</th>
<th>Confidence Interval (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>0.005</td>
<td>0.0032</td>
<td>2.36</td>
<td>0.008</td>
</tr>
<tr>
<td>0.05</td>
<td>0.003</td>
<td>0.0004</td>
<td>2.36</td>
<td>0.001</td>
</tr>
<tr>
<td>0.07</td>
<td>0.002</td>
<td>0.0004</td>
<td>2.57</td>
<td>0.001</td>
</tr>
<tr>
<td>0.10</td>
<td>0.004</td>
<td>0.0009</td>
<td>2.45</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 33. A table showing the gradient of the lines in Figure 150 along with the error and t value associated.

Table 33 shows the gradient of the line used to calculate the Langmuir constant above along with the error associated (calculated using the LINEST function in Excel) and the critical t value for the regression analysis. The confidence interval is significant in all three cases suggesting there is significant error in the data.
6.7.2 Cabrera-Vermilyea

The Cabrera-Vermilyea model describes step pinning by impurities bound at step sites. The distance between bound impurities describes the extent of the effect on the growing surface. If the distance between bound impurities is less than the size of the two-dimensional critical radius, the growth rate of the step is zero, since the step cannot advance past the bound impurities. If the distance between the bound impurities is greater than the size of the two dimensional critical radius, the step can continue to grow albeit at a reduced rate (Section 1.7.1). Applying the Langmuir isotherm to the growth model yields Equation 78:

\[
\left( \frac{1}{1 - \nu_r^2} \right)^2 = \frac{1}{4(r_{2D}^*)^2 n_{max}} + \frac{1}{4(r_{2D}^*)^2 n_{max} K} \cdot \frac{1}{C}
\]

Equation 78

\(r_{2D}^*\) is the size of the two dimensional nucleus, \(n_{max}\) is the number of available sites for an impurity to bind per unit area, \(\nu/\nu_0 = \nu_r\) and \(C\) is the impurity concentration. The value of \(n_{max}\) is set to 4 since there are four symmetrically related benzophenone molecules in the unit cell. In this case I presume that the Langmuir isotherm is used to describe additive adsorption at step sites.
6.7.2.1 4-aminobenzophenone

Figure 151. A graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4ABP.

The fit of Equation 78 to the data is shown in Figure 151 and the values of $K$, $\theta_{eq}$ and $\Delta G_{ads}$ are shown in Table 34. $\theta_{eq}$, the fractional coverage of the crystal surface when the rate of adsorption is equal to the rate of desorption. The fractional coverage is seen to increase with increasing solution concentration of additive. As the amount of adsorption sites available for the additive to bind to remains constant, increasing the concentration of additive in solution is expected to increase the fractional coverage as there are more molecules available to bind to the surface. The values suggest that the step sites are not completely occupied by the additive and at 10% a significant amount of the surface is covered by impurity.

<table>
<thead>
<tr>
<th>Mole Fraction Additive</th>
<th>$K$</th>
<th>$\theta_{eq}$</th>
<th>$\Delta G_{ads}$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>4.67</td>
<td>0.12</td>
<td>-3.69</td>
</tr>
<tr>
<td>0.05</td>
<td>11.91</td>
<td>0.37</td>
<td>-5.93</td>
</tr>
<tr>
<td>0.07</td>
<td>3.70</td>
<td>0.21</td>
<td>-3.13</td>
</tr>
<tr>
<td>0.1</td>
<td>12.08</td>
<td>0.55</td>
<td>-5.97</td>
</tr>
</tbody>
</table>

Table 34. A table summarising the Langmuir constant, the free energy of adsorption and the fractional coverage of the 4ABP additive on the benzophenone crystal surface.
### 6.7.2.2 4-methylbenzophenone

![Graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4MBP.](image)

Figure 152. A graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4MBP.

Figure 152 shows the fit of Equation 78 to the 4MBP data. The values of $K$, $\theta_{eq}$ and $\Delta G_{ads}$ shown in Table 35 are reasonable. However at supersaturation of 0.05 and 0.07 the isotherm reaches a zero growth rate which is not observed experimentally. The $\Delta G_{ads}$ values from the 4MBP are more negative compared to the 4ABP suggesting that it is more favourable to bind 4MBP in comparison. The fractional coverage of the surface again increases with increasing additive concentration and the values suggest that the step sites are almost completely covered throughout the concentration range, hence a dead zone or low relative growth rate is expected. The fractional coverage and $\Delta G_{ads}$ values between the 4ABP and 4MBP additives suggest that it may be slightly more energetically favourable to bind 4MBP compared to 4ABP, which is apparent from the difference in additive efficacy.

<table>
<thead>
<tr>
<th>Mole Fraction Additive</th>
<th>$K$</th>
<th>$\theta_{eq}$</th>
<th>$\Delta G_{ads}$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>329.51</td>
<td>0.91</td>
<td>-13.88</td>
</tr>
<tr>
<td>0.05</td>
<td>316.02</td>
<td>0.94</td>
<td>-13.78</td>
</tr>
<tr>
<td>0.07</td>
<td>216.42</td>
<td>0.94</td>
<td>-12.88</td>
</tr>
</tbody>
</table>
Table 35. A table summarising the Langmuir constant, the free energy of adsorption and the fractional coverage of the 4MBP additive on the benzophenone crystal surface.

6.7.3 Kubota-Mullin

The Kubota-Mullin\textsuperscript{6, 68} model expands on the Cabrera-Vermilyea model introducing an effectiveness factor for the impurity, $\alpha$. The model assumes that impurities are bound in ordered arrays across the crystal surface. Applying the Langmuir isotherm the equation takes the following form\textsuperscript{68}:

$$\left(\frac{1}{1 - \frac{v}{v_0}}\right) = \frac{1}{aK} \cdot \frac{1}{C} + \frac{1}{K}$$

Equation 79

and the growth rate in the presence of impurity is $v$, $v_0$ is the pure growth rate and $\alpha$ is the impurity effectiveness factor.

6.7.3.1 4-aminobenzophenone

![Graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4ABP.](image)

Figure 153. A graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4ABP.
Figure 153 shows the fit of the model to the 4ABP data and the values in Table 36 for K, $\theta_{eq}$ and $\Delta G_{ads}$ are reasonable. The free energy of adsorption is similar throughout the concentration range except for at 0.1 mole fraction, most likely due to the scatter in the data at this concentration. The fractional coverage of the surface is predicted to be higher compared to the values calculated by the Cabrera-Vermilyea model except for at supersaturation of 0.1, again this is potentially due to the scatter in the data.

<table>
<thead>
<tr>
<th>Mole Fraction Additive</th>
<th>K</th>
<th>$\Delta G_{ads}$ (kJ/mol)</th>
<th>$\theta_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>6.58</td>
<td>-4.51</td>
<td>0.16</td>
</tr>
<tr>
<td>0.05</td>
<td>13.22</td>
<td>-6.18</td>
<td>0.40</td>
</tr>
<tr>
<td>0.07</td>
<td>11.30</td>
<td>-5.81</td>
<td>0.44</td>
</tr>
<tr>
<td>0.1</td>
<td>1.94</td>
<td>-1.60</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 36. A table summarising the Langmuir constant, the free energy of adsorption and the fractional coverage of the 4ABP additive on the benzophenone crystal surface.

6.7.3.2 4-methylbenzophenone

Figure 154. A graph showing the relative growth rate relationship with additive concentration for benzophenone in the presence of 4MBP.

Figure 154 shows the fit of the model to the 4MBP growth data and the values for K, $\theta_{eq}$ and $\Delta G_{ads}$ are shown in Table 37. The fractional coverage of the surface is calculated to
increase with additive concentration. However is lower compared to the values calculated from the Cabrera-Vermilyea model. The model suggests that it is more energetically favourable to bind 4MBP compared to 4ABP to the crystal surfaces. This is reflected in the values calculated for the fractional coverage.

<table>
<thead>
<tr>
<th>Mole Fraction Additive</th>
<th>K</th>
<th>ΔG_{ads} (kJ/mol)</th>
<th>$\theta_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>109.68</td>
<td>-11.25</td>
<td>0.77</td>
</tr>
<tr>
<td>0.05</td>
<td>90.92</td>
<td>-10.80</td>
<td>0.82</td>
</tr>
<tr>
<td>0.07</td>
<td>84.05</td>
<td>-10.61</td>
<td>0.85</td>
</tr>
<tr>
<td>0.1</td>
<td>47.87</td>
<td>-9.26</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Table 37. A table summarising the Langmuir constant, the free energy of adsorption and the fractional coverage of the 4MBP additive on the benzophenone crystal surface.

6.7.4 Summary

The three models fit the data better well yielding sensible values for the free energy of adsorption to the crystal surface. The three models produce negative $\Delta G_{ads}$ values and indicate potentially high surface adsorption of the 4MBP additive to the crystal surface. All three models predict higher free energy of adsorption values for the 4MBP additive compared to the 4ABP additive suggesting that it may be more energetically favourable to bind the 4MBP additive to the crystal surface. This potentially explains the difference in additive efficacy. The Cabrera-Vermilyea model predicts higher values for K compared to the Kubota-Mullin model for the case of 4MBP. However, both models fit the data describing the binding of additives to step and kink sites well.

Kubota estimated the Langmuir constant to be 67 (mole fraction $^{-1}$)$^{33}$ for growth of sucrose in the presence of raffinose measured by Albon and Dunning$^{136}$. Squaldino et al again applied both models to the growth kinetics of sucrose in the presence of raffinose (at higher temperature) reporting Langmuir constants of between 885 and 1560 for a variety of sucrose crystal faces. Thus, the range of values seems reasonable.

6.8 Additive Mechanism

There is a clear difference in the effectiveness of the two growth modifying additives; at 10% concentration one inhibits growth of the crystal completely below a certain supersaturation, and the other additive only hinders growth of the {011} faces. This
must be due to the structure of the additive molecules; although similar in size and solid state conformation (in their relevant crystal structures) the effect on benzophenone is very different. This section seeks to gain insight into the structural differences in additives leading to the difference in effectiveness.

6.8.1 (011) Crystal surface

Figure 155 shows the (011) crystal surface with the 4 position of the benzophenone rings at the surface highlighted brown. It is clear to see that the 4 positions are all oriented to point out of the (011) crystal surface. Hence, if an additive derivatised at the 4 position bound to the surface instead of benzophenone, further growth is expected to be altered as is experimentally observed.

![Figure 155](image)

Figure 155. An image of the (011) crystal surface composition with the 4 position of the rings highlighted in brown.

It is easy to envisage kink sites in the (011) and (0̅11) surfaces and an example is shown in Figure 156. No matter whereabouts on the surface these kink sites are, the 4 position of the aromatic ring will be exposed to the incoming molecules, maximising the hindrance on further growth of the surface. The methyl and the amino groups are both larger than the hydrogen of benzophenone potentially causing steric hindrance.
Figure 156. An image of a kink site in the (011) crystal surface with an additive molecule approaching the surface.

Figure 157. An image of a molecule in a kink site of the (011) crystal surface of benzophenone interacting with a molecule in the next layer.

Figure 157 shows the same kink site as Figure 156. However also shows the molecule bound in the kink sites interaction with the benzophenone of the next growth layer. The distance between the hydrogen and the carbonyl is 2.617Å. Figures 158 and 159 show
images of the benzophenone molecule replaced with 4ABP and 4MBP molecules respectively. From the distances shown in the images it is clear to see that the C—O distance from 4MBP is shorter than the N—O distance from 4ABP, both of which are approximately 1 Å shorter than the interaction in benzophenone suggesting a steric clash would be the result of binding an additive in this site. The 4MBP has a bulkier methyl group which is closer to the carbonyl and it is expected that this group will cause more steric hindrance. This is potentially a reason for the difference in additive efficacy as the amino group causes less disruption to incoming growth units.

Figure 158. An image of the kink site of the (011) surface with 4ABP bound instead of benzophenone.
6.9 Conclusions

The growth rate of benzophenone in pure and impure solution at varying concentration has been evaluated. The alpha factors suggest that the growth mechanism of the crystal is by a screw-dislocation, this is proven with kinetic data and an applied screw-dislocation growth model. The two-dimensional surface nucleation growth model has been discounted as the mechanism of crystal growth due to poor fit of the data. Growth kinetics measurements have been performed in the presence of three additives with two found to hinder growth and one ineffective at all concentrations.

The additives show effects of different magnitude, both affecting the crystal in the same manner. 4MBP (x = 0.1) creates a dead zone in the crystal growth below a supersaturation of 0.1. At this concentration and below this supersaturation the crystal begins to grow, develops facets before growth ceases almost completely indicating a time delay in the additive adsorption to the crystal surface, a phenomenon known as growth hysteresis.

The screw dislocation model predicts that growth measurements in the presence of 4ABP and 4MBP are mostly taken at $\sigma \ll \sigma_1$ resulting in unreliable values for S and $\sigma_1$. 

Figure 159. An image of the kink site of the (011) surface with 4MBP bound instead of benzophenone.
This is most likely the case as the additive will have its strongest effect on growth by binding at step and kink sites found in a growth spiral. However, the model does not predict reasonable values for the growth source in all cases.

Using Kubota and Mullin’s model, dead zones have been calculated for the growth of the crystal. The model does show some validity for the 4MBP but overestimates the dead zone for 4ABP, assuming that a high concentration of impurity is bound to the surface which may not always be true.

Four models were applied to the growth rate data for different concentrations of additive and only two are considered to apply to the data. The Langmuir constants for impurity adsorption in two cases are very low (Bliznakov and Davey and Mullin) resulting in unfavourable free energy of adsorption values, which cannot be the case since the impurity is incorporated into the crystal as shown in (Section 6.7) However the Cabrera-Vermilyea and Kubota and Mullin models provide good fits to the data as well as reasonable free energy of adsorption values. The two models are also in reasonable agreement for the surface coverage from the additive molecules predicting that approximately half of the surface is polluted by the 4ABP and almost the entire surface is polluted by the 4MBP, as R is significantly reduced.

The effects of the additives are clear, two additives strongly affect the growth process of the {011} crystal surface causing needle like morphologies. Explanation of the potential mechanisms of binding to the surface is possible using the crystal structures of the additives and also the crystal structure of benzophenone. It is clear that the crystals grow by a step mechanism in which the steps are likely to be created by a screw dislocation. The adsorption of impurities to these step and kink sites on the surface is well described by the Cabrera-Vermilyea and Kubota-Mullin models.
7. Molecular Modelling

The next section describes the methodologies and calculations for additive docking.

7.1 Introduction

Two computational methods have been used to explore the energetics of binding additives to benzophenone crystal surfaces. Materials Studio was used to dock molecules into specific crystal surface sites, while a Stand-alone Systematic Search allowed the most favourable site in the surface for additive binding to be found. The former permits conformational change in the additive molecule during the binding process whilst the latter only allows fixed conformations to be docked.

7.2 Methodologies

7.2.1 Materials Studio

All Materials Studio calculations were performed with a Dreiding force field and Gasteiger charges. The crystal structure of benzophenone (BPHENO12) was first optimised with respect to energy and geometry of the lattice. A morphologically important crystal surface was then chosen from the attachment energy morphology prediction (Section 3). The structure was then cleaved to create this surface and the molecular ensemble placed in contact with a vacuum slab of 75 Å. The lattice energy was then calculated. A molecule was selected from the crystal surface and removed to a distance of 60 Å from the plane of the surface (see Figure 160) ensuring that it remains within the vacuum.
Figure 160. An image of a benzophenone crystal lattice with a molecule removed.

The energy of this arrangement is again calculated ($E_{unbound}$ in Equation 80) and the difference in the two energies is the binding energy of a benzophenone molecule, $\Delta E_b^0$ to the surface and site in question.

$$\Delta E_b^0 = E_{bound} - E_{unbound}$$

Equation 80

With the molecule removed from the lattice its molecular structure is altered to that of an additive molecule. The crystal lattice is fixed in position along with the central carbon of the additive molecule, whilst the geometry of the system is then optimised. Since the lattice is held in position it remains unaltered. However the geometry of the additive is altered to a more energetically favourable conformation. The energy of the system is then calculated to give $E'_{unbound}$ (Equation 81). With the benzophenone lattice fixed in position the additive molecule is then replaced into the vacant lattice site and the geometry of the additive is again optimised. The energy of the completed lattice is then recalculated to give $E'_{bound}$. Equation 81 then gives the binding energy of the additive molecule.

$$\Delta E_b' = E'_{bound} - E'_{unbound}$$

Equation 81
Figure 161 shows a schematic of the binding energy calculations performed using Materials Studio. The difference in energy between binding an additive and solute then allows interpretation of how the additive molecules interact with crystal surfaces. A negative ($\Delta \Delta E$) energy value indicates a more favourable binding of an additive molecule compared to the solute molecule. This is given in Equation 82 and is the same definition as Ulrich$^{87}$ (Section 1.8.3.2).

$$\Delta \Delta E = \Delta E_b' - \Delta E_b$$

Equation 82

**7.2.2 Stand-alone Systematic Search Code (Rigid Body)$^{137}$**

Using a Stand-alone Systematic Search Code$^{137}$ it is possible to automate a similar calculation to that performed using Materials Studio. The lattice parameters are customisable in x, y and z directions and each integer corresponds to one unit cell. The technique relies on detailed input information for the structure of the host crystal lattice, (benzophenone in this case) and also the probe molecule (benzophenone and additives).
The input files describe both the host and probe molecules using Dreiding notation for atoms and individual atomic charges (from Gasteiger). In conjunction with this description, structure files (CAR produced in Materials Studio) are also included with the input file. The input file itself also contains more detailed information about the host molecules crystal structure such as, the symmetry operations in order to build the lattice obtained from the CIF for each molecule. The associated ref codes are BPHENO12 for benzophenone, VOFVAN, VOFVAN21 and VOFVAN26 for 4ABP, FEVNAV01 and FEVNAV02 for 4MBP and ZZZMKS01 for DPA.

The program constructs the host crystal lattice as described by input file specifications and then calculates the energy of binding the probe molecule to the crystal surface. Once the calculation is performed the probe molecule is systematically shifted across the host crystal surface by rotation and translation followed by recalculating the energy. In all calculations for this body of work the degrees of rotation are fixed at 30° in the x, y and z direction with the translations fixed at step sizes of 1.0 Å, 0.2 Å and 0.2 Å (x, y and z directions (see Figure 162). Using $3 \times 3 \times 3$ crystal lattices yielded results which were almost identical to a $2 \times 2 \times 2$ crystal lattice. Hence $2 \times 2 \times 2$ lattices were used in order to reduce computation time.

One of the benefits of the program is that there is an energy cut off of zero, thus, any probe molecule position resulting in a positive binding energy is rejected leaving only binding positions which release energy from the crystal surface i.e. where binding a molecule is energetically favourable. The program creates an output file summarising
the energy of binding for various sites with values for the most favourable binding energy and also the average binding energies. These energy values also provide an image of the crystal lattice with the probe molecule bound to allow visual evaluation of whether the bound probe molecule is situated in a sensible position.

Since the 4MBP and 4ABP molecules have more than one ref code in the crystallographic database, analysis of all the structures prior to calculation was necessary in order to choose a conformation suitable for use in calculations.

### 7.3 Selection of Crystal Faces for Study

Faces were selected for additive docking on the basis of the crystal morphology of benzophenone. This has previously been discussed in Section 3 and additive molecules have been seen to alter the morphology of growing crystals by hindering the growth of the \{011\} crystal faces (Section 6). Using Materials Studio it is possible to determine the relative surface area of a specific face in a morphology prediction (Growth Morphology – attachment energy method) using a Dreiding force field with Gasteiger charges.

<table>
<thead>
<tr>
<th>hkl</th>
<th>Multiplicity</th>
<th>dhkl (Å)</th>
<th>Distance</th>
<th>% Total facet area</th>
</tr>
</thead>
<tbody>
<tr>
<td>{ 0 1 1}</td>
<td>4.00</td>
<td>7.80</td>
<td>45.24</td>
<td>51.38</td>
</tr>
<tr>
<td>{ 1 0 1}</td>
<td>4.00</td>
<td>6.51</td>
<td>53.04</td>
<td>29.51</td>
</tr>
<tr>
<td>{ 1 1 0}</td>
<td>4.00</td>
<td>6.17</td>
<td>56.98</td>
<td>15.76</td>
</tr>
<tr>
<td>{ 0 0 2}</td>
<td>2.00</td>
<td>6.02</td>
<td>61.03</td>
<td>3.27</td>
</tr>
<tr>
<td>{ 1 1 1}</td>
<td>4.00</td>
<td>5.49</td>
<td>63.06</td>
<td>0.04</td>
</tr>
<tr>
<td>{ 1 1 1}</td>
<td>4.00</td>
<td>5.49</td>
<td>63.06</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 38. A table summarising the morphological importance data for benzophenone.

Table 38 shows the values of the relative facet area of benzophenone crystal surfaces calculated in this way. The values are as expected from the morphology pictures with the most important faces the \{011\} followed by the \{101\} and the \{110\} faces. As these crystal faces are the most prevalent they will be the subject of the additive docking studies described here. Since the \{011\} face is slightly different in nature to the \{01\} due to the space group symmetry, both of these faces are cleaved and docked with additive molecules in this study. The \{111\} and \{002\} faces are not affected by the presence of the additive and hence calculations were not performed. The next section
compares the results between the two methods for all additives in the Materials Studio method and the 4ABP, 4MBP and DPM additives in the Stand Alone Systematic Search method.

### 7.4 Material Studio

Since each crystal surface is different in nature and contains more than one molecular environment (i.e. molecules in different arrangements) it is necessary to perform the calculation for each molecule in the surface as the additive could bind in any site. Since these sites are all different all of the additive molecules were situated in all possible lattice sites. Due to the different functional groups at different positions some additives may have the altered functionality pointing into the crystal lattice and some may have the altered functionality pointing out. Depending on the orientation, the effect of the additive towards growth can be different.

Some analysis is required in interpretation of the binding energies. Although these have been calculated for all of the sites only certain sites are applicable in terms of morphology modification i.e. the situation shown in Figure 163(b) where the additive binds with the derivatised position pointing out of the crystal lattice. However, the additive entering the surface in Figure 163(a) would not be expected to alter the crystal growth since the derivatised site points into the lattice. All possible bindings of additive molecules are calculated and interpreted in terms of whether the additive could potentially alter growth from the binding site.

![Figure 163. Images of 4MBP molecules approaching the crystal surface of benzophenone in two orientations.](image-url)
7.4.1 The (011) Face

In the (011) surface there are four symmetry related sites shown by the coloured molecules in Figure 164.

![Figure 164](image)

**Figure 164.** Images showing the (011) crystal surface of benzophenone highlighted in different colours. The red molecule is described as site 1, the green as site 2, blue as site 3 and the black molecule site 4.

Each of these molecules presents different functionality at the crystal surface. In the case of Sites 1 and 2 (red and green molecules in Figure 164) an additive molecule with altered functionality at the carbonyl position would be expected to affect the growth of benzophenone. For molecules with altered functionality at the 4-position of the ring, binding at sites 3 and 4 (blue and black) would be expected to have the strongest effect on growth of the crystal surface. Table 39 shows the values of ΔΔE in each of the four sites for all of the additives chosen in Section 3.

<table>
<thead>
<tr>
<th></th>
<th>ΔΔE (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site 1</td>
</tr>
<tr>
<td>Pure</td>
<td>0.00</td>
</tr>
<tr>
<td>DPM</td>
<td>27.45</td>
</tr>
<tr>
<td>DPA</td>
<td>-5.36*</td>
</tr>
<tr>
<td>DPE</td>
<td>41.00</td>
</tr>
<tr>
<td>4ABP</td>
<td>16.86</td>
</tr>
<tr>
<td>4MBP</td>
<td>41.42</td>
</tr>
<tr>
<td>4FBP</td>
<td>15.02</td>
</tr>
<tr>
<td>2MBP</td>
<td>1.97</td>
</tr>
<tr>
<td>3ClBP</td>
<td>69.45</td>
</tr>
</tbody>
</table>

Table 39. A table summarising the ΔΔE values for the (011) crystal surface. The red values indicate favourable binding of the additive compared to benzophenone and values marked with an asterisk indicate a favourable binding and also an expected effect on the crystal growth.
The negative values (highlighted in red) indicate those additive molecules which bind more favourably than benzophenone. From a crystal growth perspective the additives binding favourably are not always expected to have an effect on the growth. For sites 1 and 2 only four occurrences of favourable binding are apparent from DPA, 4ABP, 4FBP and 2MBP. Only DPA and 2MBP would be expected to have an effect on growth from these sites. For sites 3 and 4 there are 6 occurrences of favourable binding. Again not all of these are expected to affect growth and only 4ABP, 4MBP and 4FBP could hinder the growth from these binding positions.

7.4.2 The (011) Face

Figure 165 shows the (011) crystal surface and it is clear that the surface is similar to the (011) crystal surface in Figure 164. However the changes in molecular orientation lead to small differences in functionality at the surface.

![Image](Image)

**Figure 165.** Images of the (011) crystal surface of benzophenone. The red molecule is described as site 1, the green as site 2, blue as site 3 and the black molecule site 4.

For sites 1, 2 and 4 the additives which have the derivitisation at the 4 position of the rings would be expected to alter the growth of this face. For additives derivatised at the carbonyl position binding sites 1 and 3 would be expected to have an effect on the growth. Comparing the values in Table 40 to Table 39 there are fewer occurrences of a negative ΔΔE value for this face.
Table 40. A table summarising the ΔΔE values for the (011) crystal surface of benzophenone. The red values indicate favourable binding of the additive compared to benzophenone and values marked with an asterisk indicate a favourable binding and also an expected effect on the crystal growth.

For sites 1 and 2 only 4ABP and 3ClBp show a small favourable binding energy, both of which could have an effect on the growth. For sites 3 and 4 DPA and 3ClBP are the only additives showing favourable binding and both could hinder growth of these faces.

7.4.3 The (110) Face

![Figure 166](image)

**Figure 166.** Images of the (110) crystal surface of benzophenone with selected molecules used for calculations highlighted. The red molecule is described as site 1, the green as site 2, blue as site 3 and the black molecule site 4.

Figure 166 shows the selected molecules used for calculations performed on the (110) crystal surface of benzophenone. It is clear to see that the molecules in sites 2 and 3 are almost in the plane of the crystal surface, whereas, the molecules at sites 1 and 4 have the 4 position of the ring pointing out. Any of the additive molecules could exert an
effect on the growth from sites 1 and 4 as both the ring and the carbonyl group are situated at the surface.

<table>
<thead>
<tr>
<th></th>
<th>Site 1</th>
<th>Site 2</th>
<th>Site 3</th>
<th>Site 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>DPM</td>
<td>23.22</td>
<td>17.28</td>
<td>33.60</td>
<td>15.06</td>
</tr>
<tr>
<td>DPA</td>
<td>-2.26*</td>
<td>1.92</td>
<td>-4.73</td>
<td>1.67</td>
</tr>
<tr>
<td>DPE</td>
<td>35.44</td>
<td>5.19</td>
<td>33.60</td>
<td>2.47</td>
</tr>
<tr>
<td>4ABP</td>
<td>-5.90*</td>
<td>-1.59*</td>
<td>-4.02*</td>
<td>-3.47*</td>
</tr>
<tr>
<td>4MBP</td>
<td>-8.83*</td>
<td>6.07</td>
<td>1.30</td>
<td>-1.92*</td>
</tr>
<tr>
<td>4FBP</td>
<td>-5.27*</td>
<td>-4.69*</td>
<td>-7.57*</td>
<td>-3.72*</td>
</tr>
<tr>
<td>2MBP</td>
<td>23.81</td>
<td>-0.25</td>
<td>25.90</td>
<td>-5.65*</td>
</tr>
<tr>
<td>3ClBP</td>
<td>-3.26*</td>
<td>2.93</td>
<td>60.33</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Table 41. A table summarising the ΔΔE values for the (110) crystal surface of benzophenone. The red values indicate favourable binding of the additive compared to benzophenone and values marked with an asterisk indicate a favourable binding and also an expected effect on the crystal growth.

Table 41 shows a summary of the binding energies of the additive molecules for the (110) face of benzophenone. From site 1 all cases of favourable binding have potential to hinder crystal growth. For sites 2 and 3, only 4ABP and 4FBP have the potential to affect growth. For site 4 all occurrences of favourable binding could potentially bind to affect growth.

7.4.4 The (101) Face

Figure 167. Images of the (101) crystal surface of benzophenone with molecules used for calculations highlighted. The red molecule is described as site 1, the green molecule as site 2 and the blue molecule as site 3.
Figure 167 shows the (101) surface and it is clear that the aromatic rings are almost in the plane of the surface. Hence, binding at one of these sites from any of the additive molecules may alter the growth. Since the molecule in site 4 (black) would already be bound before the molecule in site 3 (blue) calculations were not performed as it would also require removing the molecule from site 3.

<table>
<thead>
<tr>
<th></th>
<th>Site 1</th>
<th>Site 2</th>
<th>Site 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>DPM</td>
<td>17.87</td>
<td>17.66</td>
<td>65.02</td>
</tr>
<tr>
<td>DPA</td>
<td>-4.27</td>
<td>-0.42*</td>
<td>22.72</td>
</tr>
<tr>
<td>DPE</td>
<td>4.23</td>
<td>14.69</td>
<td>65.31</td>
</tr>
<tr>
<td>4ABP</td>
<td>11.72</td>
<td>0.79</td>
<td>36.44</td>
</tr>
<tr>
<td>4MBP</td>
<td>27.03</td>
<td>6.82</td>
<td>38.28</td>
</tr>
<tr>
<td>4FBP</td>
<td>10.17</td>
<td>-4.94</td>
<td>36.48</td>
</tr>
<tr>
<td>2MBP</td>
<td>15.77</td>
<td>9.25</td>
<td>35.52</td>
</tr>
<tr>
<td>3CIBP</td>
<td>1.17</td>
<td>2.13</td>
<td>44.22</td>
</tr>
</tbody>
</table>

Table 42. A table summarising the ΔΔE values for the (101) crystal surface of benzophenone. The red values indicate favourable binding of the additive compared to benzophenone and values marked with an asterisk indicate a favourable binding and also an expected effect on the crystal growth.

Only DPA and 4FBP show favourable binding in sites across the (110) surface and only DPA could potentially have an effect on growth.

7.4.5 Summary

Faces for which docking calculations were performed show examples of favourable binding of an additive which could affect the growth of the crystal. However, the calculations also show favourable binding for additives which are not expected to have an effect. For the (011) crystal surface 4MBP and 4ABP show favourable binding in sites expected to affect the growth. Conversely there are occasions where the calculations suggest favourable binding of an additive but no effect is seen experimentally. This is true for the DPA, 4FBP and the 2MBP additives.

For the (011) face there are fewer cases of favourable binding compared to the (011) surface with cases of binding where an effect on the growth is expected for both. The only favourable binding which correlates with experimental data is for the 4ABP
additive showing a very small $\Delta\Delta E$ value. DPA and 3CIBP show favourable binding in sites which are expected to hinder growth and experimentally this is not the case.

For the (110) crystal surface, there are multiple occasions of favourable binding where an additive is expected to have an effect of the growth and only DPM and DPE show unfavourable binding. This disagrees with the experimental data since the faces along the a axis are not hindered by any of the additives (except for the 4MBP additive at 10% concentration and below $\sigma = 0.1$). 4MBP shows favourable binding in two out of four sites and could potentially hinder the growth of the surface from both. While 4ABP shows favourable binding in all four sites with the potential to affect growth, experimentally the additive does not have an effect. The (101) crystal surface has few cases of favourable binding and DPA is expected to have an effect on the crystal growth which experimentally is not the case.

The method does not account for all observed experimental effects, since favourable binding is found in cases which do not show any experimental effects. The geometry of the additive is optimised each time it is added to the crystal surface, hence the energy associated with the molecule may not always be the most favourable. The method is a good approximation. However, the global minimum energy for the additive may not be calculated as steric clashes can prevent this. Experimentally for an additive to bind there needs to be minimal steric clash with the lattice already in place. For additives with larger substituents than hydrogen such as the amino and methyl groups this may not always be possible, potentially the reason that these additives do not favourable binding on all of the {011} surfaces. Conversely, favourable binding may not be found for additives because the correct surface sites and geometries are not found in these calculations. Moreover, if a molecule does show favourable binding, this does not necessarily result in an effect on growth, even if the derivatised position points out of the surface.

### 7.5 Stand-Alone Systematic Grid Based Searching Method

As described previously in Section 7.2.2 a grid based search method was used to determine the binding energy of rigid additive molecules onto a host lattice. The results described here are for the most favourable binding energy for a particular probe on a
particular surface. Since only 4ABP, 4MBP and DPM are experimentally found to hinder growth, these three additives only are used in calculations here.

7.5.1 4-methylbenzophenone

There are three crystal structure determinations for 4MBP\textsuperscript{138, 139} with two different possible conformations. $Z'$ is equal to one in all three crystal structures hence only one conformation of the molecule is present in the crystal structure. Table 43 summarises key information corresponding to the crystal structure of 4MBP. The torsion angle listed is the angle between the planes of the aromatic rings. Figure 168 shows the different conformation of 4MBP in each crystal structure.

<table>
<thead>
<tr>
<th></th>
<th>Torsion</th>
<th>R Factor</th>
<th>Space Group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FEVNAV\textsuperscript{138}</td>
<td>-60.96</td>
<td>8.2</td>
<td>P2\textsubscript{1}/a</td>
<td>Figure 168a</td>
</tr>
<tr>
<td>FEVNAV01\textsuperscript{139}</td>
<td>-60</td>
<td>3.3</td>
<td>P2\textsubscript{1}/c</td>
<td>Figure 168b</td>
</tr>
<tr>
<td>FEVNAV02\textsuperscript{139}</td>
<td>54.92</td>
<td>2.1</td>
<td>P3\textsubscript{1}</td>
<td>Figure 168c</td>
</tr>
</tbody>
</table>

Table 43. A table summarising crystal structure data of FEVNAV.

![Figure 168. Images showing the difference in conformation of FEVNAV in the crystal structure database.](image)

FEVNAV and FEVNAV01 have essentially the same torsion angle and a similar space group, thus these two structures are repeats of one another, FEVNAV01 having a lower R factor. FEVNAV02 has a different space group and also a different torsion angle ($\Delta \tau = 114^\circ$) indicating a different conformation of the molecule. Figure 169 shows that FEVNAV and FEVNAV01 contain the same conformation of 4MBP as the red and green molecules overlay well. The green and blue molecules are clearly different as expected and FEVNAV02\textsuperscript{139} is the metastable form grown from a supercooled melt. However, this conformation may be present in solution. In order to provide more rigorous analysis both FEVNAV01 and FEVNAV02 conformations are used as probe molecules.
Figure 169. Images of overlaid 4MBP molecular structures from the REF codes FEVNAV (red), FEVNAV01 (green) and FEVNAV02 (blue). a) contains FEVNAV and FEVNAV02 and b) contains FEVNAV01 and FEVNAV02.

7.5.2 4-aminobenzophenone (VOFVAN)

There are nine crystal structure solutions in the database for 4ABP, all crystallising in the P2₁ space group with the details summarised in Table 44. The torsion angles appear to suggest the existence of two solid state conformations of this molecule, one having \( \tau \approx 55^\circ \) (VOFVAN, VOFVAN21, VOFVAN22) and a second having \( \tau \approx 37^\circ \) (VOFVAN23, VOFVAN24, VOFVAN25 and VOFVAN26).

<table>
<thead>
<tr>
<th>Ref Code</th>
<th>Torsion</th>
<th>R Factor</th>
<th>Space Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOFVAN</td>
<td>54.84</td>
<td>8.3</td>
<td>P2₁</td>
</tr>
<tr>
<td>VOFVAN21</td>
<td>57.5</td>
<td>10.21</td>
<td>P2₁</td>
</tr>
<tr>
<td>VOFVAN22</td>
<td>54.99</td>
<td>11.85</td>
<td>P2₁</td>
</tr>
<tr>
<td>VOFVAN23</td>
<td>40.52</td>
<td>7.45</td>
<td>P2₁</td>
</tr>
<tr>
<td>VOFVAN24</td>
<td>37.18</td>
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<tr>
<td>VOFVAN25</td>
<td>35.38</td>
<td>6.18</td>
<td>P2₁</td>
</tr>
<tr>
<td>VOFVAN26</td>
<td>32.98</td>
<td>4.94</td>
<td>P2₁</td>
</tr>
</tbody>
</table>

Table 44. A table summarising the crystal structures of 4ABP crystals.

Figure 170. Images of overlaid VOFVAN molecular conformations. VOFVAN (Coloured by atom), VOFVAN21 (purple), VOFVAN22 (light blue), VOFVAN23 (red), VOFVAN24 (green), VOFVAN25 (pink), and VOFVAN26 (grey).
Figure 170 shows images of overlaid molecular conformations of 4ABP molecules from all crystal structures. In Figure 170a all of the available molecular conformations are overlaid and it is evident that there are indeed two distinct groups as reported\textsuperscript{141}. Figure 170b shows a difference in the hydrogen positions on the amino groups of VOFVAN, VOFVAN21 and VOFVAN22 shown in more detail in Figure 171.

Figure 171. A zoomed in image of the hydrogen positions of VOFVAN (coloured by atom), and VOFVAN21 (purple) and VOFVAN22(blue).

For calculations here three structures have been used. VOFVAN, VOFVAN21 and VOFVAN26. Since VOFVAN and VOFVAN21 are the same conformation ($\tau \approx 55^\circ$) with different hydrogen positions while VOFVAN26 has the second conformation ($\tau \approx 37^\circ$).

7.5.3 \{011\} Faces

Table 8 summarises the lowest binding energy of the additives to the \{011\} crystal surfaces.

<table>
<thead>
<tr>
<th>Probe</th>
<th>{011}</th>
<th>$\Delta\Delta E$</th>
<th>{011}</th>
<th>$\Delta\Delta E$</th>
<th>{011}</th>
<th>$\Delta\Delta E$</th>
<th>{011}</th>
<th>$\Delta\Delta E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZP</td>
<td>-36.50</td>
<td>0.00</td>
<td>-31.17</td>
<td>0.00</td>
<td>-29.61</td>
<td>0.00</td>
<td>-30.58</td>
<td>0.00</td>
</tr>
<tr>
<td>DPM – ZZMK01</td>
<td>-30.61</td>
<td>5.89</td>
<td>-27.95</td>
<td>3.22</td>
<td>-28.84</td>
<td>0.78</td>
<td>-31.64</td>
<td>-1.06</td>
</tr>
<tr>
<td>4ABP-VOFVAN21</td>
<td>-30.07</td>
<td>6.43</td>
<td>-32.48</td>
<td>-1.31</td>
<td>-30.87</td>
<td>-1.26</td>
<td>-32.16</td>
<td>-1.59</td>
</tr>
<tr>
<td>4ABP-VOFVAN26</td>
<td>-28.33</td>
<td>8.18</td>
<td>-29.00</td>
<td>2.17</td>
<td>-29.10</td>
<td>0.51</td>
<td>-31.59</td>
<td>-1.01</td>
</tr>
<tr>
<td>4ABP-VOFVAN27</td>
<td>-28.40</td>
<td>8.11</td>
<td>-31.83</td>
<td>-0.66</td>
<td>-30.26</td>
<td>-0.65</td>
<td>-27.76</td>
<td>2.82</td>
</tr>
<tr>
<td>4MBP-FEVNAV01</td>
<td>-31.60</td>
<td>4.90</td>
<td>-31.91</td>
<td>-0.74</td>
<td>-30.51</td>
<td>-0.90</td>
<td>-32.90</td>
<td>-2.33</td>
</tr>
<tr>
<td>4MBP-FEVNAV01</td>
<td>-28.79</td>
<td>7.72</td>
<td>-32.85</td>
<td>-1.68</td>
<td>-32.54</td>
<td>-2.92</td>
<td>-29.06</td>
<td>1.52</td>
</tr>
</tbody>
</table>

239
Table 45. A table summarising the most energetically favourable binding energies for probe molecules on the {011} crystal surfaces.

For the (011) crystal surface none of the additives bind with a more favourable energy than benzophenone. However, for the other three surfaces the search finds a site which additive binding is slightly more favourable than binding benzophenone. In the case of DPM this occurs for the (0\overline{1}1) face while for 4ABP it can occur on the (0\overline{1}1), (01\overline{1}) and (01\overline{1}) faces depending on the conformation chosen. For 4MBP this is only true for the (0\overline{1}1) face with the others showing favourable binding for both conformations.
Table 46. A table summarising the most and least favourable binding of additive molecules to the \{011\} crystal surfaces.
Table 46 shows a summary of the most favourable and least favourable binding of additives to the \{011\} crystal surfaces. For the \{011\} surface the binding energy is unfavourable, hence the additive is unlikely to bind and have an effect. For the \{0\overline{1}1\}, \{01\overline{1}\} and \{0\overline{1}1\} faces the 4MBP additives are all likely to bind favourably compared to benzophenone. In conjunction with this the derivatised part of the molecule points out of the surface, suggesting an effect on the growth may be observed.

7.5.4 \{101\} Faces

<table>
<thead>
<tr>
<th>Probe</th>
<th>Lowest attachment energy (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(101)</td>
</tr>
<tr>
<td>BZP</td>
<td>-34.54</td>
</tr>
<tr>
<td>DPM – ZZZMKS01</td>
<td>-29.72</td>
</tr>
<tr>
<td>4ABP-VOFVAN</td>
<td>-34.33</td>
</tr>
<tr>
<td>4ABP-VOFVAN21</td>
<td>-31.99</td>
</tr>
<tr>
<td>4ABP-VOFVAN26</td>
<td>-31.67</td>
</tr>
<tr>
<td>4MBP-FEVNAV02</td>
<td>-35.65</td>
</tr>
<tr>
<td>4MBP-FEVNAV01</td>
<td>-34.85</td>
</tr>
</tbody>
</table>

Table 47. A table summarising the most energetically favourable binding energies for probe molecules on the \{101\} crystal surfaces.

Table 47 shows the lowest possible binding energies for additive molecules to the \{101\} crystal surfaces. There are some cases of more favourable binding of the additives and generally the difference between binding the solute and binding an additive is small. Again DPM shows unfavourable energies across all of the surfaces.
<table>
<thead>
<tr>
<th>Face</th>
<th>Most Favoured</th>
<th>Least Favoured</th>
</tr>
</thead>
<tbody>
<tr>
<td>(101)</td>
<td>4MBP, $\Delta \Delta E = -1.11$ kJ/mol</td>
<td>DPM, $\Delta \Delta E = 4.82$ kJ/mol</td>
</tr>
<tr>
<td>(10\bar{1})</td>
<td>4ABP, $\Delta \Delta E = -2.08$ kJ/mol</td>
<td>DPM, $\Delta \Delta E = 2.99$ kJ/mol</td>
</tr>
<tr>
<td>(\bar{1}01)</td>
<td>4ABP, $\Delta \Delta E = -4.51$ kJ/mol</td>
<td>DPM, $\Delta \Delta E = 1.99$ kJ/mol</td>
</tr>
<tr>
<td>(\bar{1}0\bar{1})</td>
<td>4ABP, $\Delta \Delta E = -3.96$ kJ/mol</td>
<td>DPM, $\Delta \Delta E = 0.26$ kJ/mol</td>
</tr>
</tbody>
</table>
Table 48. A table summarising the most favourable and least favourable binding of additive molecules to the \{101\} crystal surfaces.

For the \{101\} faces, the most favourable bindings shown in Table 48 all show favourable binding compared to benzophenone. In all four, the derivatised position of the additive is roughly in the plane of the crystal surface, thus, could potentially have an effect on growth since the surface potential will be altered.

### 7.5.5 \{110\} Faces

<table>
<thead>
<tr>
<th>Probe</th>
<th>Lowest attachment energy (kJ/mol)</th>
<th>((110))</th>
<th>(\Delta\Delta E)</th>
<th>((110))</th>
<th>(\Delta\Delta E)</th>
<th>((110))</th>
<th>(\Delta\Delta E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZP</td>
<td>-30.44</td>
<td>0.00</td>
<td>-37.41</td>
<td>0.00</td>
<td>-31.83</td>
<td>0.00</td>
<td>-30.21</td>
</tr>
<tr>
<td>DPM – ZZMKS01</td>
<td>-30.16</td>
<td>0.27</td>
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<td>-30.88</td>
<td>0.95</td>
<td>-40.34</td>
</tr>
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<td>7.72</td>
<td>-29.67</td>
<td>2.16</td>
<td>-32.27</td>
</tr>
<tr>
<td>4ABP-VOFVAN21</td>
<td>-30.77</td>
<td>-0.33</td>
<td>-31.46</td>
<td>5.94</td>
<td>-29.74</td>
<td>2.08</td>
<td>-33.19</td>
</tr>
<tr>
<td>4ABP-VOFVAN26</td>
<td>-30.52</td>
<td>-0.09</td>
<td>-34.64</td>
<td>2.77</td>
<td>-30.27</td>
<td>1.56</td>
<td>-28.60</td>
</tr>
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<td>-31.84</td>
<td>-1.40</td>
<td>-37.84</td>
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<td>-31.46</td>
<td>0.37</td>
<td>-30.78</td>
</tr>
<tr>
<td>4MBP-FEVNAV01</td>
<td>-30.87</td>
<td>-0.44</td>
<td>-32.17</td>
<td>5.24</td>
<td>-28.60</td>
<td>3.23</td>
<td>-29.72</td>
</tr>
</tbody>
</table>

Table 49. A table summarising the most energetically favourable binding energies for probe molecules on the \{110\} crystal surfaces.

Table 49 shows a summary of the calculations for the \{110\} crystal face. For the \{110\} crystal surface all of the VOFVAN and FEVNAV molecules show very small energetic gains from binding to this face. The only other crystal surface showing favourable energetics is the \(\overline{1}10\) face, even for DPM which does not show favourable binding energies for many other surfaces.
Table 50. A table summarising the most favourable and least favourable binding of additive molecules to the \{110\} crystal surfaces.

Table 50 shows the most and least favourable binding of additives to the \{110\} crystal faces. For the most favourable bindings only three out of the four sites show a
favourable binding energy. In the case of the (110) and (11̅0) surfaces the derivatised methyl group points into the crystal lattice, hence the growth of these surfaces are not expected to be hindered. However the (11̅0) surface has the derivatised position approximately in the plane of the surface, suggesting an effect on growth may be observed if the additive bound here.

7.6 Modified Attachment Energies and Morphology Predictions

Previous work has sought to predict morphologies of crystals influenced by the presence of an additive/impurity or a solvent\textsuperscript{23, 41, 88, 142}. The binding energy of the additive or solvent is used to calculate a modified attachment energy for the surface. This attachment energy ($E'_{\text{att}}$) is the used instead of the attachment energy of solute to predict a modified morphology\textsuperscript{79}. Equation 83 gives the relationship between the pure attachment energy, $E_{\text{att,hkl}}^0$ and the modified attachment energy in the presence of additive:

$$E'_{\text{att,hkl}} = E_{\text{att,hkl}}^0 - \left( E_{\text{att,hkl}}^0 \times \frac{\Delta\Delta E_{hkl}}{\Delta E_{b,hkl}^0} \right)$$

Equation 83

$\Delta\Delta E_{hkl}$ is the binding energy of the additive molecule and $\Delta E_{b,hkl}^0$ is the binding energy of the solute molecule\textsuperscript{87}. Note in this equation $\Delta\Delta E_{hkl}$ is defined as:

$$\Delta\Delta E_{hkl} = E_{\text{additive}} - E_{\text{solute}}$$

hence, a favourable binding energy will remain negative.

If $\Delta\Delta E_{hkl} > 0$, the modified attachment energy will be reduced, hence will become less morphologically important. If $\Delta\Delta E_{hkl} < 0$, the modified attachment energy will be larger and the face will become more morphologically important. Since the additive molecules have marginally different binding energies compared to benzophenone, modified attachment energies for the {011}, {110} and {101} surfaces were calculated using Equation 83. The {111} and {002} surfaces were not considered.
The calculations using Materials Studio gives a value for different sites, more than one attachment energy value is possible leading to more than one $E'_{att,hkl}$. In the following calculations the average attachment energy for the surfaces were used. However, it was observed that using the most favourable binding energy for each surface resulted in similar morphologies due to the minor differences in binding energy between additive and solute. When using the systematic search, the most favoured binding for each additive is used as the $\Delta\Delta E$ value for the modified attachment energy.

### 7.6.1 Materials Studio

<table>
<thead>
<tr>
<th></th>
<th>$E'_{att}$ (kJ/mol)</th>
<th>Facet Area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(011)</td>
<td>(101)</td>
</tr>
<tr>
<td>Pure</td>
<td>-197.9</td>
<td>-230.6</td>
</tr>
<tr>
<td>4ABP</td>
<td>-228.8</td>
<td>-258.9</td>
</tr>
<tr>
<td>4MBP</td>
<td>-202.9</td>
<td>-225.9</td>
</tr>
<tr>
<td>DPM</td>
<td>-216.5</td>
<td>-229.5</td>
</tr>
</tbody>
</table>

Table 51. A table showing the calculated modified attachment energies and the corresponding facet areas for the Materials Studio calculations.

Figure 172. Morphology predictions of benzophenone crystal using modified attachment energies from Materials Studio calculations. In all morphologies, the (011) crystal surface is the front most face, i.e. in the plane of the paper.
Table 51 shows the modified attachment energies for the additive molecules and also the relative facet area from the morphology predictions using the modified attachment energies. The energies for the \{011\} and \{110\} faces are much the same as for pure benzophenone except for in the case of 4ABP. Conversely, the \{101\} faces show different attachment energies in the presence of additives (Table 51) and the morphological importance of these faces is decreased in the associated morphology prediction. Figure 172 shows the morphology predictions using the energies from Table 51 and the images show the (011) surface as the front most face (roughly in the plane of the paper). Some subtle differences are clear, and in all cases it is apparent that the morphology is slightly wider along the b/c axes with larger \{101\} surfaces. However, experimentally (Figure 174) the morphologies are much different to this prediction, indicating that the binding calculations do not validate experimental results.

### 7.6.2 Stand-Alone Systematic Search (Rigid Body) Calculations

<table>
<thead>
<tr>
<th>Eatt (kJ/mol)</th>
<th>Facet Area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>{011}</td>
</tr>
<tr>
<td>Pure</td>
<td>-197.9</td>
</tr>
<tr>
<td>DPM</td>
<td>-211.6</td>
</tr>
<tr>
<td>VOFVAN</td>
<td>-201.5</td>
</tr>
<tr>
<td>VOFVAN21</td>
<td>-213.1</td>
</tr>
<tr>
<td>VOFVAN26</td>
<td>-212.8</td>
</tr>
<tr>
<td>FEVNAV02</td>
<td>-199.3</td>
</tr>
<tr>
<td>FEVNAV01</td>
<td>-205.0</td>
</tr>
</tbody>
</table>

Table 52. The attachment energy of pure benzophenone and modified attachment energies along with the changes in facet area of the important faces.
Table 52 shows the modified attachment energies for benzophenone in the presence of the additives from rigid body calculations. The facet areas of the three main sets of faces do not change by much throughout the calculations. The binding energies are different to pure benzophenone, and in most cases all of the calculated values change by a similar amount for each face producing a similar morphology to pure benzophenone. Increasing the attachment energy of each face by a similar amount will not have a drastic result on the predicted morphology, since the relative rate of growth will still be similar. Figure 173 shows images of the morphology predictions of benzophenone using modified attachment energies, the front most face is the (011) crystal face. The facet areas remain similar throughout, except for the case of DPM where the {110} faces become slightly more morphologically important at the expense of the {101}.

7.7 Computation vs Experimental

Some experimentally grown crystals are shown in Figure 174 and it is clear that we observe much more drastic results on the crystal morphology than is predicted.
computationally in Figures 172 and 173. Experimentally for DPM, the morphology is almost the same as when grown from pure solution. However, for 4ABP and 4MBP the additives cause an elongation of the crystal along the a axis. From the calculations there are occurrences of favourable binding across the various surfaces. However, this does not serve to predict drastic changes in the morphology as the difference between binding a solute and additive is small. Thus, the changes are small resulting in modified morphologies similar to pure benzophenone. Computationally there are also occurrences of favourable binding to surfaces which do not show any experimental effect. A favourable binding energy does not necessarily mean that the additive will bind in this site. Moreover, it does not guarantee that the additive will be effective on this surface when bound.

![Images of experimentally grown crystal of benzophenone grown in pure and impure solution.](image)

**Figure 174. Images of experimentally grown crystal of benzophenone grown in pure and impure solution.**

The calculations assume that growth occurs by addition of slices (hkl) to a face (hkl) assuming that the energy released is the rate determining process. However, the calculations do not provide any analysis of the effects of solvent which may be important in the growth of the surfaces. The growth models discussed (section 6) suggest that the additives bind at step sites reducing the growth rate of the spirals, whereas the calculations are performed on complete surfaces or vacant surface site instead of step sites. Thus the energy calculated may not be the most relevant binding energy since strictly speaking it is not the energy of binding an additive to a step. A
more relevant calculation such as binding solute molecules to a surface containing additives may be more useful since the effect of an additive in a complete surface may result in further attachment of benzophenone being unfavourable. Experimentally this would correspond to slower growth or even complete hindrance since the benzophenone molecules may be forced back into solution.

7.8 Conclusions

The computational analysis suggests that additives bind favourably in sites which could affect growth. The Materials Studio calculations suggest that the \{011\} faces should be hindered to an extent by the 4MBP, 4ABP, DPA, 2MBP and 4FBP additives. The computation is successful in prediction of the 4ABP and 4MBP additives. However the three other additives do not have a measurable effect on the crystal growth of benzophenone despite the favourable \(\Delta\Delta E\). The calculations for the \{110\} faces are perhaps the least reliable since none of the additives (bar 4MBP) are found to have an effect on the growth. However, DPA, 4MBP, 4ABP, 3ClBP and 4FBP are all found to have energetically favourable binding in sites with the potential to affect growth. The calculations for the \{101\} crystal surface shows favourable binding of an additive into a position where it is expected to have an effect for one additive. Thus, suggesting that additives may bind to surfaces without affecting the growth of the surface. All of the calculations are performed in the absence of solvent which could potentially be a reason that the calculations do not support the experimental observations. The interaction between solvent and solute and or solvent and additive may influence the growth rate of the crystals which is computationally difficult to simulate.
8. Project Conclusions

Through crystal packing analysis of a molecular van der Waals crystal, additives have successfully been tailored to benzophenone, hindering specific directions of crystal growth. Two additives in particular have a very strong effect of the {011} crystal faces causing a needle like morphology. One of which, causes a dead zone in the crystal growth and below a certain supersaturation the crystals do not grow. These two additives have been found to be incorporated into the crystal lattice using HPLC. This proves that the two additives must satisfy certain surface interactions with benzophenone in order to bind.

Attempts to estimate solution complexation constants have been made in order to identify the cause of the observed increase in benzophenone solubility when additives are introduced. From this the free energy of complexation has been estimated, suggesting 3:1 complexes of benzophenone:additive is possible. The induction time of benzophenone has been measured in pure and impure solutions. One additive in particular – 4MBP – has been found to significantly increase the apparent induction time.

The growth kinetics of benzophenone crystals have been measured in pure and impure solutions. The growth mechanism has been identified as screw dislocation through application of the BCF growth model to fixed temperature growth rate data. The model has been found to be applicable to growth from pure propan-2-ol solution and also in the presence of additives. Different concentrations of additives have shown that the Kubota-Mullin and Cabrera-Vermilyea models for impure growth both apply. In both cases Langmuir constants for additive adsorption to key growth sites have been evaluated in conjunction with free energy of impurity adsorption values.

Molecular mechanics has been used in order to quantify the additive adsorption to specific crystal surfaces. Both methods used have positives and negatives in the method of calculation. Materials Studio allows the user to alter the conformation of the additive, since in solution there will likely be a range of different conformations of the additive present. The rigid body systematic search method is much faster and easier to perform calculations for several surfaces and binding sites. However, previous information about
the crystal structure of the additive is preferential to ensure a sensible conformation is used. The method has provided limited success showing that additive molecules can bind with a similar relative energy to benzophenone, somewhat limiting the applicability of a modified attachment energy model to predict habit changes of crystals. Thus, validation of the experimental effects of additives is not possible using computation.

Overall, the aim of the project has been fulfilled in that traditional tailor made additive rationale has been applied to a molecular van der Waals crystal. The morphology of benzophenone has been significantly altered with concentrations of additive as low as 0.03 mole fraction.

8.1 Further Work

The next section outlines potential further work.

8.2 Crystal Growth

Growth of benzophenone from the melt in the presence of additives should be explored as DPM is seen to have a stronger effect on the growth from the melt. Since the β form of benzophenone is observed to grow from the melt, perhaps it is possible that an additive may induce the crystallisation of the metastable polymorph. This may not be possible hence the crystal packing of the β form should be analysed with the intent of introducing an additive to preferentially crystallise this metastable form. Crystal growth kinetics in agitated solution should also be explored.

8.3 Computational

As with all molecular modelling experiments there are several options for further work. Both methods have similarities and subtle difference and further work in both cases is possible. Altering the size of the lattices in both cases should be performed, although, changing the depth of the lattice in the rigid body calculations was observed to have minimal effect on the energy values. Modelling calculations should be repeated using Molecular Dynamics in order to estimate the effect of the solvent.
8.3.1 Material Studio

Using a larger crystal lattice and also more than one additive molecule should be calculated. Since the crystal lattice is user defined it is possible to create step and kink sites in the crystal surface by deleting specific molecules. Since kink sites are occupied the fastest, binding molecules the most strongly, the energy of binding at these sites should be calculated.

8.3.2 Stand-Alone Systematic Search (Rigid Body)

The limitation of this method lies in the rigid body input files, using Materials Studio it is possible to generate several different input files corresponding to different conformations for the additive molecules. Using several different input structures would provide a more in depth analysis and potentially provide more insight into the binding of additives.

8.3.3 General Computational

The binding energy of benzophenone onto surfaces containing the additive would give more insight into how the additive affects the growth of the crystal. The energy of binding an additive is a good approximation of whether an additive can bind to a surface. What this calculation lacks is the energetics of binding benzophenone molecules once the surface is polluted with additive. This could be an important aspect in determining why some faces show favourable binding of additive molecules and would also provide more insight into the difference in effectiveness for 4MBP and 4ABP.
References

Appendix

A1. Two Dimensional Nucleation Curve Fits

The two-dimensional nucleation curve fits for benzophenone in the presence of additives are shown below.

A1.1 4-aminobenzophenone

Figure 175. The plot for the data for the a axis of benzophenone grown in the presence of 4ABP.
Figure 176. The plot for the data for the width of benzophenone grown in the presence of 4ABP.
A1.2 4-methylbenzophenone

Figure 177. The plot for the data for the a axis of benzophenone grown in the presence of 4MBP.

Figure 178. The plot for the data for the width of benzophenone grown in the presence of 4MBP.
A1.3 Diphenylmethane

Figure 179. The plot for the data for the a axis of benzophenone grown in the presence of DPM.

Figure 180. The plot for the data for the width of benzophenone grown in the presence of DPM.
### A2. Solubility Data in the presence of Additives

#### DPA

<table>
<thead>
<tr>
<th>Mole fraction Additive</th>
<th>BZP conc (M)</th>
<th>Additive Conc (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.94</td>
<td>0.00</td>
</tr>
<tr>
<td>0.01</td>
<td>0.94</td>
<td>0.01</td>
</tr>
<tr>
<td>0.02</td>
<td>0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>0.03</td>
<td>0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>0.04</td>
<td>1.02</td>
<td>0.04</td>
</tr>
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<td>0.07</td>
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<td>0.09</td>
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<td>0.10</td>
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#### DPE

<table>
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<th>BZP conc (M)</th>
<th>Additive Conc (M)</th>
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<td>1.047</td>
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</tr>
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<td>0.0012</td>
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<td>1.228</td>
<td>0.0012</td>
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</table>

#### DPM

<table>
<thead>
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<th>Additive Conc (M)</th>
</tr>
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<tbody>
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</tr>
<tr>
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</tr>
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<td>0.1</td>
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</tbody>
</table>
### 4ABP

<table>
<thead>
<tr>
<th>Mole fraction Additive</th>
<th>BZP conc (M)</th>
<th>Additive Conc (M)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
</tr>
<tr>
<td>0.03</td>
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</table>

### 4FBP

<table>
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<th>BZP conc (M)</th>
<th>Additive Conc (M)</th>
</tr>
</thead>
<tbody>
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### 4MBP

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2MBP

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3CiBP

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<th>Additive Conc (M)</th>
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A3. Systematic Search Binding Energies

A3.1 {002} Faces

Table 53 shows the lowest attachment energies of additives to the {002} faces of benzophenone from the rigid body systematic search method.

<table>
<thead>
<tr>
<th>Probe</th>
<th>Lowest attachment energy (kJ/mol)</th>
<th>[002]</th>
<th>ΔΔE</th>
<th>[00-2]</th>
<th>ΔΔE</th>
</tr>
</thead>
<tbody>
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<td>-36.87</td>
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</tr>
<tr>
<td>DPM – ZZZMKS01</td>
<td>-34.18</td>
<td>-0.66</td>
<td>-34.66</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>4ABP-VOFVAN</td>
<td>-27.78</td>
<td>5.74</td>
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<tr>
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<td>6.03</td>
<td>-26.73</td>
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<tr>
<td>4ABP-VOFVAN26</td>
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<tr>
<td>4MBP-FEVNAV02</td>
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<td>-37.90</td>
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<td>-33.73</td>
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</table>
Table 53. A table summarising the binding energy for additive molecules into the \{002\} crystal surfaces of benzophenone.

**A3.2 \{111\} Faces**

Tables 54 and 55 show the lowest attachment energies of additives to the \{111\} faces of benzophenone from the rigid body systematic search method.

<table>
<thead>
<tr>
<th>Probe</th>
<th>[11-1]</th>
<th>(\Delta \Delta E)</th>
<th>[-1-1-1]</th>
<th>(\Delta \Delta E)</th>
<th>[-111]</th>
<th>(\Delta \Delta E)</th>
<th>[1-1]</th>
<th>(\Delta \Delta E)</th>
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</thead>
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<td>-32.07</td>
<td>0.00</td>
<td>-29.78</td>
<td>0.00</td>
<td>-32.07</td>
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</tr>
<tr>
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<td>-31.82</td>
<td>-3.47</td>
<td>-33.47</td>
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<td>-32.29</td>
<td>2.52</td>
<td>-33.47</td>
<td>1.40</td>
</tr>
<tr>
<td>4ABP–VOFVAN</td>
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<td>-36.21</td>
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<td>4.15</td>
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<tr>
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<td>-6.82</td>
<td>-34.30</td>
<td>2.24</td>
<td>-30.71</td>
<td>0.93</td>
<td>-34.30</td>
<td>2.24</td>
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<tr>
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<td>-32.55</td>
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<td>-30.66</td>
<td>0.88</td>
<td>-34.30</td>
<td>2.23</td>
</tr>
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<td>-33.86</td>
<td>1.80</td>
<td>-31.22</td>
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</table>

Table 54. A table summarising the binding energies of additive molecules to the \{111\} crystal surfaces of benzophenone.

<table>
<thead>
<tr>
<th>Probe</th>
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<th>[-1-1-1]</th>
<th>(\Delta \Delta E)</th>
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<th>(\Delta \Delta E)</th>
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<td>-32.07</td>
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<td>DPM – ZZZMKS01</td>
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<td>-33.47</td>
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<td>-32.29</td>
<td>-2.52</td>
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</tr>
<tr>
<td>4ABP–VOFVAN</td>
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<td>4.27</td>
<td>-36.21</td>
<td>-4.15</td>
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<td>4ABP–VOFVAN21</td>
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<td>-31.69</td>
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<td>-30.16</td>
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Table 55. A table summarising the binding energies of additive molecules to the \{111\} crystal surfaces of benzophenone.