Understanding the Solvent-Induced Habit Modification of Benzophenone in Terms of Molecular Recognition at the Crystal/Solution Interface[†]

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Crystallization is an important, energy efficient, process for the purification and separation of bulk and fine chemicals as well as being a particularly important unit operation in the preparation of speciality particulates such as agrochemicals, pharmaceuticals, dyestuffs, and monomer units for high-performance polymers. Crystallization is a key stage during manufacture and can affect the production and final physical form characteristics of a material including ease of separation, rheology, caking, packing density, and dissolution rate. With increasing focus on the manufacture of speciality products within the chemical industry and the increased requirements for process control and product differentiation, it is clear that the expectations of the crystallization process are likely to be greater.[1] As a result of this increased expectation, there is in turn a need for an improved understanding of the underlying molecular processes taking place during the crystallization event. In recent years significant effort has been devoted toward understanding/predicting the external crystal shape in terms of the internal solid-state structure using a combination of classical crystallography and calculations of intermolecular interactions.[2-5] These morphological investigations are now not only possible for systems of academic interest but can be applied to real industrial problems.[6] Problems remain in modelling the effects of the external environment (solvent/impurities) on crystal shape. A much greater understanding has been achieved thanks to the elegant work of Lahav and co-workers at the Weizmann Institute.[7,8] Work continues to examine the effects of tailor-made additives on crystal shape[9] in order to allow the design/control of the system during crystallization which will in turn give the desired product differentiation.

Table 1. Comparison between the Relative Growth Rates for Benzophenone Crystals Grown from the Melt (after Ref 17) and from Toluene Solution (This Work)[a]

(hkl)	melt	toluene solvent
{110}	1.00 (58.3%)	1.00 (23.9)
{101}	1.56 (9.3%)	1.48 (*)
{011}	1.47 (13.9)	0.70 (*)
{020}	1.43 (2.64)	0.64 (*)
{111}	1.47 (8.0%)	1.30 (*)
{021}	1.50 (5.7%)	0.50 (76.1)
{002}	1.66 (2.2%)	0.83 (*)

[a] The data are normalized with respect to the {110} form with values for the toluene case representing the maximum values for the nonobserved faces (asterisks), i.e., such that they do not appear in the external crystal morphology. Surface areas are given in parentheses.
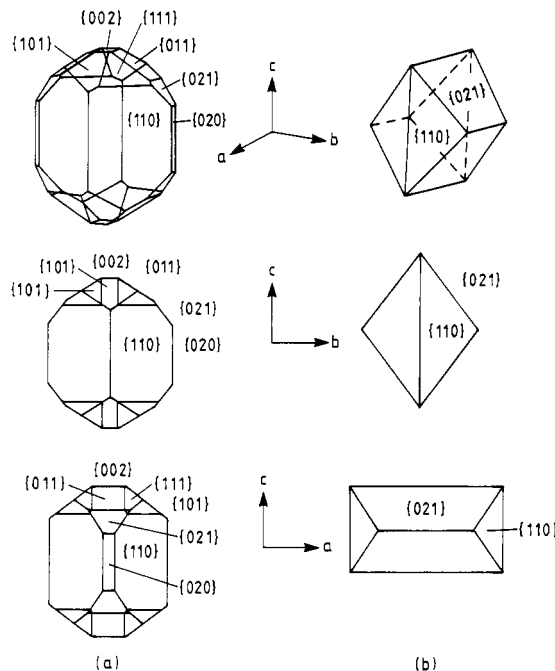

Figure 1. Morphological drawings of benzophenone crystals: (a) as-grown from the melt and most solvents, aspect ratio with respect to *c* axis 1.72; (b) as-grown from toluene solutions, aspect ratio 0.32.

The crystallization process essentially involves the gathering together of a vast number of molecules into a unique ordered arrangement. This gathering is repeatable given the same crystallization conditions. The solid-state arrangements adopted by organic molecules are the result of an "intermolecular synthesis"[10] which is due to a subtle balance of interactions between the atoms which constitute the molecular framework. Solid-state structures are essentially the consequence of molecular recognition on a grand scale.[10-13] The adoption of different arrangements (polymorphism) is due to the recognition of a different balance of the subtle interactions. Partitioning the lattice energy into the important intermolecular interactions between molecules not only is crucial in the prediction of crystal shape but also provides the key link between molecular structure and solid-state arrangement. An

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[†] Dedicated to the memory of Peggy Etter.
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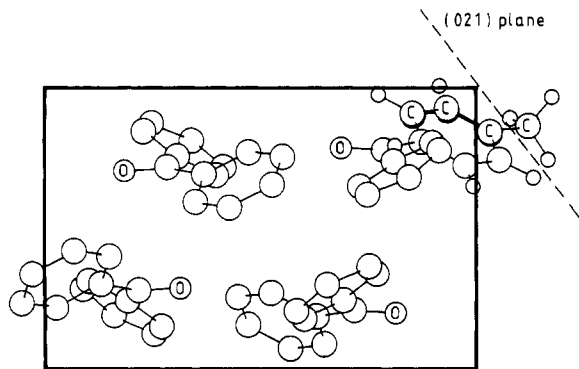
Figure 2. Overlay showing the fitting of the toluene solvent molecule onto one of the phenyl groups. The position of the (021) crystal plane is indicated. Only the hydrogen atoms on the solvent molecule are shown for clarity.

understanding of the relative strengths of these interactions is fundamental to the study of polymorphism, crystal structure prediction, host–guest complexes,[12,13] crystal shape calculation and habit modification studies. The process of altering the crystal shape by tailor-made additives or some solvents is essentially a case of "molecular trickery". The solvent or additive "fools" the crystal surface into accepting it as a pure host molecule. Once in the surface the additive/solvent prevents further molecules getting to their rightful sites on the surface. In this paper we consider the habit modifying effect of toluene solvent molecules on the morphology of benzophenone in an examination of the role played by molecular recognition at the crystal/solution interface. In this we have adopted a similar approach to that used for tailor-made additives[9] in which we have applied energy calculations to determine the surface sites that can accept these solvent additive molecules.

Benzophenone [$(C_6H_5)_2C{=}O$] is an aromatic ketone which crystallizes in an orthorhombic noncentrosymmetric crystal structure, with space group $P2_12_12_1$, with four molecules in a unit cell of dimensions $a = 10.26$ Å, $b = 12.09$ Å, and $c = 7.88$ Å.[14] The crystal morphological data for benzophenone is summarized in Table 1 and Figure 1. From the undercooled melt and from most solvents benzophenone crystallizes with a well-defined morphology[15–18] dominated by large {110} faces with smaller {200}, {011}, {101}, {111}, {002}, and {200} forms in a habit elongated along the c crystallographic axis is shown in Figure 1a. Figure 1b shows the morphology of benzophenone as grown from toluene solutions at solution temperatures close to the melting point, i.e., where the solubility is very high. This morphology differs considerably from that of the melt exhibiting a morphology dominated by {021} and {110} forms; sometimes small {111} forms are also observed.

The growth morphology of the un-doped crystal can be predicted through a calculation of the surface attachment energy (E_{att})[19,20] which is defined as the energy released on the addition of a growth slice to the surface of a growing

crystal[21] and is related to the crystallization energy or lattice energy (E_{cr}) by

$$E_{cr} = E_{sl} + E_{att} \qquad (1)$$

where E_{sl} is the intermolecular bonding energy contained within the surface growth slice. The growth rate of a give crystal face (hkl) can be taken to be proportional to E_{att}.[21] The latter, providing we assume that the relative intermolecular bond strengths as a function of (hkl), do not change significantly upon crystallization, can be calculated from the bulk crystal structure.[22] The procedures for such calculations have been described elsewhere.[24–26]

To assess how easily heterogeneous "impurity" molecules will adsorb on a given crystal surface (hkl) Lahav and co-workers[27] defined a relative "binding or incorporation energy" (Δb) as

$$\Delta b = E_{sl'} + E_{att'} - E_{cr} \qquad (2)$$

where $E_{sl'}$ and $E_{att'}$ are, respectively, slice and attachment energy terms for the impurity-modified surface. Thus crystal faces where there is minimum change in the incorporation energy are where the additives are likely to incorporate. If Δb is strongly dependent upon crystal orientation then the incorporation will be specific to one crystal face and vice versa. Additionally we can define[9,24] a further parameter $E_{aH''}$, which reflects the energy released on the addition of a pure growth slice onto a surface on which solvent has been adsorbed. This additional parameter can be used as a direct measure of the effect on growth of a crystal face "poisoned" with solvent.

Calculations of the intermolecular bond strengths were made using the atomic parameters based on the crystal structure using the computer program HABIT[23] which calculates the intermolecular bonds by considering each interaction to be the sum of the constituent atom–atom interactions.[28] For benzophenone we used a combined Lennard-Jones/Coulombic potential force field function (parameters provided by Carruthers and co-workers[29]) together with fractional coordinates for C and O[30] and H.[25] The partial electronic charges were calculated by semiempirical quantum chemistry calculations using MO-PAC.[31] The overall summation, which involved calculating the interaction of the origin molecule with 454 neighboring molecules, yielded a lattice energy −24.5 kcal/mol. The electrostatic contribution to the overall lattice energy was very low contributing only −0.7 kcal/mol, thus showing that dipolar effects do not significantly contribute to the cohesive energy of benzophenone in the solid state. Allowing for the vibrational contribution to the crystal

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Communications

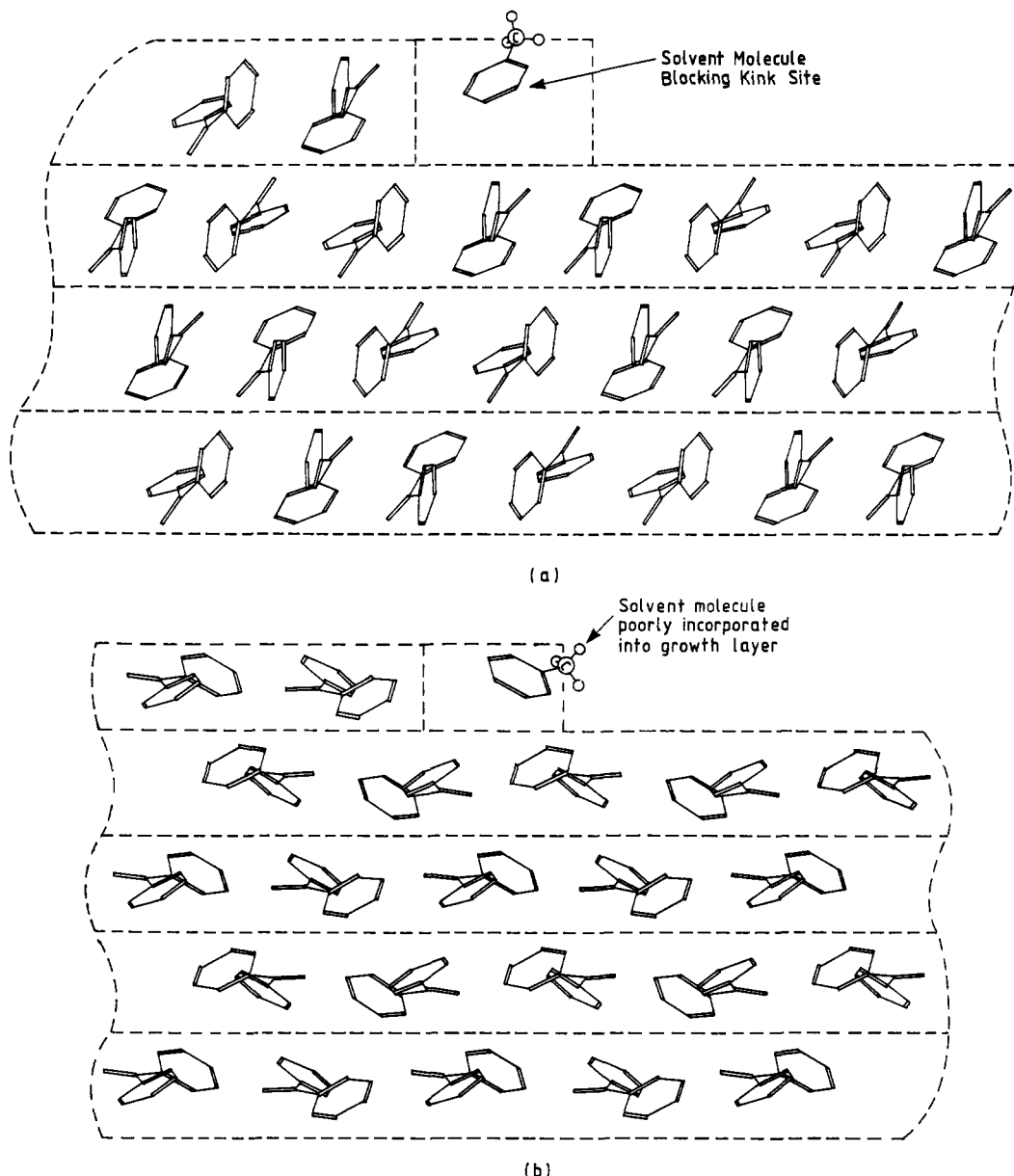Chem. Mater., Vol. 6, No. 8, 1994 1101

(a)

(b)

Figure 3. Molecular packing diagrams as projected onto the crystallographic a axis showing the structural implications for solvent binding at surface growth steps: (a) the solvent-modified (021) surface; (b) the unaffected (002) surface.

enthalpy,[32] we estimate an experimental lattice energy of −23.9 kcal/mol based on a sublimation enthalpy of 22.73 kcal/mol.[33] The excellent agreement between experimental and calculated lattice energies demonstrates the applicability of the force field used.

Values of Δb and $E_{att''}$ for the case of toluene molecules as a surface blocking additive were calculated using an early version of the computer program HABIT94 (see, e.g., ref 24). In this we constructed the solvent molecule using the molecular graphics package INTERCHEM[34] and fitted it to one of the phenyl groups of the host benzophenone molecule. Figure 2 shows an overlapy of the two structures revealing the closely matching structures of the host and solvent molecules.

The increased prominence of the {021} form observed in material crystallized from saturated toluene solutions reflects a decreased growth rate for this surface. Figure 3a shows a molecular packing projection down the crystallographic a axis showing the molecular arrangement on the {021} habit-modified surface; a toluene molecule as fitted onto the crystal lattice of benzophenone is also shown. The molecular origin associated with toluene interactions are immediately clear in that this surface provides a molecular surface arrangement such that the phenyl rings of the host benzophenone molecules mostly lie along the growth normal. From this we can see that while the toluene molecules can easily adsorb by mimicking the host system, subsequent growth following adsorption becomes blocked due to the pinning of surface steps by the methyl group of the solvent which provides a steric hinderance to further surface growth. Figure 3b shows the same projection as Figure 3a but this time highlighting the surface chemistry of a form which is unaffected by solvent, in this case {002}. Here it can be seen that the

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Table 2. Changes in Incorporation Energy Δb and the Attachment Energy ($E_{att''}$) for the Adsorption of Pure Material onto a Toluene Solvent-Mediated Surface for the Seven Faces of Benzophenone

face	molecule	Δb	$E_{att''}$
(101)	1	7.07	−0.42
	2	14.21	+1.87
	3	14.24	−0.62
	4	7.10	+8.70
(011)	1	15.63	+2.57
	2	13.54	−1.98
	3	15.60	−2.24
	4	13.50	+4.90
(021)	1	13.50	+2.42
	2	5.50	−1.97
	3	13.50	−2.91
	4	5.60	+10.07
(002)	1	11.76	−3.76
	2	11.76	−3.76
	3	11.77	+3.02
	4	11.77	+3.02
(111)	1	20.87	−3.82
	2	12.59	−2.12
	3	12.83	−0.80
	4	5.62	+9.14
(110)	1	12.93	−1.46
	2	16.82	−3.93
	3	13.85	−0.71
	4	14.14	+5.25
(020)	1	6.51	+7.89
	2	6.49	−0.90
	3	6.49	−0.90
	4	6.51	+7.89

adsorption of a solvent molecule is unfavorable in terms of stereochemistry as the projection of the solvent methyl group is inclined with respect to the growth layer, thus preventing easy surface adsorption. Examination of surface molecular models for all the crystal faces, with the exception of the {021}, reveal similar tendencies.

The validity of this model is borne out through the calculation of Δb and $E_{att''}$, as calculated with toluene as an additive: the results, summarized in Table 2, show the change in incorporation energy and the subsequent interaction of the toluene molecule with the oncoming molecules to the surface. From the calculated values of Δb it can be seen that toluene molecules appear to be able to get into (021) at sites 2 and 4 with the least loss in energy. Site 4 on the (111) face also seems to be another candidate as a site for toluene incorporation and the four sites for (020). When in these sites the interaction with the oncoming molecules is preventing further growth. This indicates that (021) and (111) and possibly (020) should become more important. The positive values for $E_{att''}$ indicate that toluene is acting like a blocker additive preventing molecules getting to the surface and affecting growth rate. These results are in agreement with what is found experimentally except that the minor (020) form is not observed. A possible explanation is that (021) and (020) are developing in the same zone (see Figure 1) and if (021) is dominating then (020) would not be observed.