Application of the Periodic Bond Chain (PBC) Theory and Attachment Energy Consideration to Derive the Crystal Morphology of Hexamethylmelamine

Piet Hartman[1] and Hak-Kim Chan[2,3]

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The habit (external morphology) of a crystal is controlled by both the external (environmental) conditions of crystallization and the internal (structural) factors of the crystal. In order to separate the effects of the crystal structure and of the solvent and other external factors on the experimentally observed growth habit, the theoretical habit can be derived from the crystal structure using the periodic bond chain (PBC) theory and attachment energy considerations. According to the PBC theory the crystal habit is governed by a set of uninterrupted chains of strong bonds formed in the crystal lattice. In addition, the attachment energy (E_{att}) is defined as the energy released per mole when a new layer is deposited on a crystal face. Since the habit of a crystal is determined by the relative growth rate (R) of the various faces, by taking R proportional to E_{att}, the theoretical habit can thus be derived from E_{att}. Using this approach, we obtained the theoretical crystal habit of an antitumor drug, hexamethylmelamine (HMM). The possible effect of solvents on the habit modification of HMM is discussed. This technique, based purely on the knowledge of the crystal structure, is directly applicable to other pharmaceuticals in deriving their theoretical crystal habit.

KEY WORDS: crystal habit; structural morphology; hexamethylmelamine (HMM); periodic bond chain (PBC); attachment energy (E_{att}).

INTRODUCTION

The size, shape, surface morphology, and density of solid particles are the properties which affect the suitability of materials in the pharmaceutical industry. Most pharmaceutical solids are prepared by crystallization. This primary process, which determines to a large extent the ultimate properties of the solid material, has been studied by a number of pharmaceutical investigators (1–3).

The external appearance of solid particles, i.e., the crystal habit, will vary, depending on the unit cell structure. In other words, polymorphism and pseudopolymorphism (solvates) give rise to different crystal habits. Change from one polymorph to another tends to modify their physical and chemical stability and processing characteristics. Therefore, "engineering" the crystal habit of pharmaceutical solids (i.e., habit modification) without polymorphic transformation is of particular interest, as it is unlikely to cause changes in chemical stability. We have carried out successfully such a modification of the crystal habit of an antiasthmatic agent, cromoglycic acid (4), and an antitumor agent, hexamethylmelamine (5–8), leading to crystals with advantageous aerodynamic properties for drug delivery by aerosols into the lungs. Another example was found in the widely used chemotherapeutic drug methotrexate, in which we obtained spherical particles by controlled crystallization (9,10). Crystal habit modifications are indeed very common in drugs and pharmaceuticals (11). In practice, habits affect numerous physical properties of solids, e.g., flowability, compressibility, crystal face wettability, and dissolution rate anisotropy (12–14).

Predictive crystal habit theory has been widely used in other areas of industrial crystal growth (15–19), but not much in pharmaceutical research as yet. Such theoretical approach, however, could enable habit modification to be carried out in a more systematic and logical way. For example, knowing the theoretical habit, any external effects due to crystallization conditions on the growth morphology could then be separated and studied in more detail. The results can in turn be used to control the crystallization.

Hartman (18) summarized the various factors affecting the growth habit of a crystal into two main categories. First, the internal or structural factors include the crystal packing, defects, and dislocations. Second, the external factors are all the physicochemical parameters of the crystallization conditions such as supersaturation, temperature, impurities, and solvents (9,18,19). Generally, slow growth is expected to favor formation of crystal habits less likely affected by external factors. Under special growth conditions, such as rapid crystallization at high supersaturations (20,21), the external factors could lead to a habit change. In this report, we focus in particular on the solvent effects.

It has been long recognized that the external form of a crystal is the expression not only of its internal structure but also of the interaction between solute and solvent (20,21). The generally accepted hypothesis for solvent effects is due to solute–solvent interactions which can occur both in the solution and at the crystal–solution interface. The basic steps of the process of crystal growth from solution include (19): (i) volume diffusion of solvated solute molecules toward the crystal surface, (ii) desolvation of both the solute molecules and the growth sites on the crystal surfaces, and (iii) incorporation of solute molecules into the crystal lattice, which includes surface kinetics processes such as adsorption, surface diffusion, and incorporation at kinks. It is apparent that the activation energies associated with i and ii are dependent on the strength of intermolecular interactions between the solute and the solvent molecules.

A knowledge of the theoretical growth habits is essential in differentiating the effects of solvents on the observed crystal growth habits. Therefore, knowing the theoretical crystal shape, any deviation observed can be attributed more precisely to those crystal faces on which solvent effects are involved. The theoretical growth habit of a crystal can be

[1] Section Crystallography, Department of Geochemistry, Institute of Earth Sciences, State University of Utrecht, Postbus 80021, 3508 TA Utrecht, The Netherlands.

[2] Department of Pharmaceutical Research and Development, Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, California 94080.

[3] To whom correspondence should be addressed.

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predicted from structural and energetic considerations. The periodic strong bond chain (PBC) and attachment energy approach of Hartman (22,23) has been widely applied to various classes of inorganic and organic crystals (15,16,22, 23,25).

Hexamethylmelamine [(HMM; 2,4,6-tris(dimethylamino)-1,3,5-triazine)] is a chemotherapeutic agent effective against human small-cell lung carcinoma. Different crystal forms of HMM have been prepared with suitable aerodynamic properties aimed at reducing its adverse effects by direct administration into the respiratory tract (5,6). The crystal habit of HMM is controlled by the solvent used in crystallisation: solvents such as methanol, acetone, and dichloromethane yielded predominantly acicular crystals, while in nonpolar solvents (cyclohexane, benzene) hexagonal compact crystals were formed (Fig. 1 and, schematically, Fig. 2). The mechanism responsible for the solvent effect on the crystal habit of HMM was previously investigated in a series of mechanistic and crystal growth kinetics studies (7,8). In order to separate the effects of the crystal structure and of the solvent, we presently derived the theoretical habit from the crystal structure using the periodic bond chain (PBC) theory and attachment energy consideration (24).

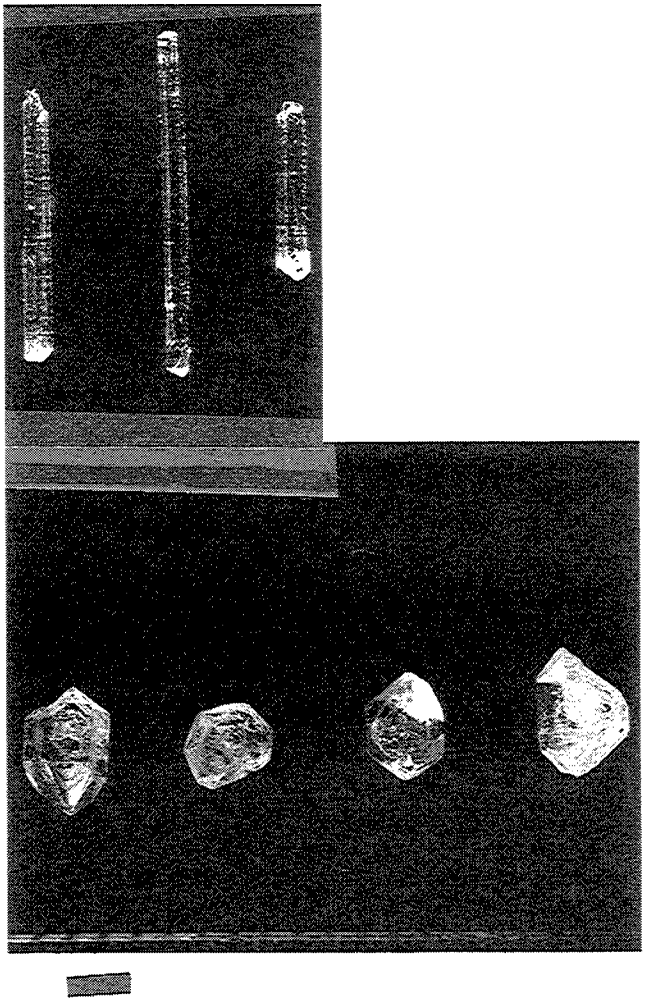

Fig. 1. The crystal habits of hexamethylmelamine. Scale bar, 2 mm for compacts and 1.5 mm for needles.

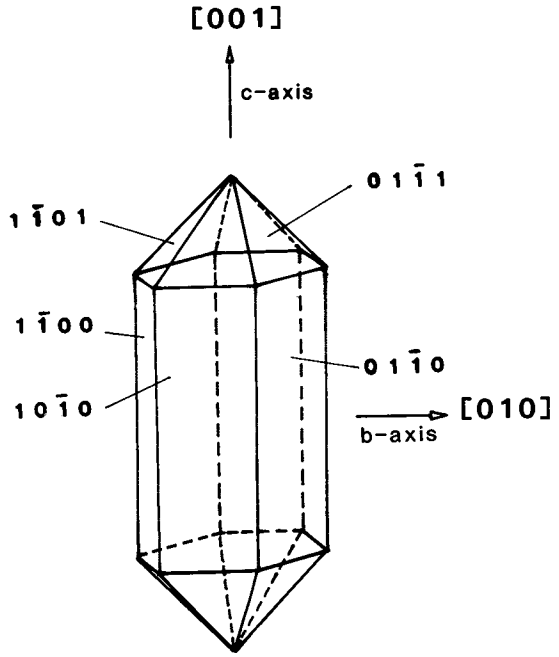

Fig. 2. Schematic representation of the HMM crystal.

MATERIALS AND METHODS

PBC Theory and the Attachment Energy

The habit of a crystal is bound by the dominant crystallographic faces, which are the ones with the slowest growth rate. The external shape of a crystal is therefore determined by the relative development of the various crystallographic faces governed by their growth kinetics.

The PBC theory (22,23) is based on the assumption that crystal growth can be considered as the formation of bonds between crystallizing particles such as atoms, ions or molecules. Because these particles have to come close together in order to form the crystal, only *strong bonds* are considered, defined as *bonds in the first coordination sphere*. In molecular structures the bonds are the hydrogen bonding, dipolar force, or Van der Waals contacts between atoms of neighboring molecules. In other words, a crystal is bound by the straight edges that are parallel to directions in which the growth units are bonded by an uninterrupted chain(s) of strong bonds or periodic bond chains(s) (PBC). Using this concept, three categories of faces can be identified.

F faces or flat faces: A slice (layer) d_{hkl}[4] contains two or more PBCs.

S faces or stepped faces: A slice d_{hkl} contains only one PBC.

K faces or kinked faces: A slice d_{hkl} contains no PBC at all.

[4] Notations: (hkl), crystal face or lattice plane; $\{hkl\}$, crystal form, comprising all faces equivalent by symmetry to (hkl); $[uvw]$, crystal edge or lattice row or zone axis; $[x,y,z]$, fractional coordinates of a molecule in the unit cell; d_{hkl}, spacing between two consecutive lattice planes; Mi,uvw, a molecule Mi that underwent a lattice translation $[uvw] = [ua + vb + wc]$, where a, b, and c are the unit cell dimensions.

The slice thickness d_{hkl} is the interplanar distance of the crystallographic face (hkl). The three categories have accordingly three different growth mechanisms (22). The F faces are able to grow according to the layer mechanism, so that their growth rate is the slowest. Therefore they determine the theoretical habit. The growth of K faces can occur everywhere on the surface without nucleation, so the growth rate is the highest and the faces do not occur on the crystal. The S faces are intermediate between F and K. They would need one-dimensional nucleation, but because in practice at all temperatures there are sufficient kinks present, they also grow fast and normally do not occur on the crystal. It should be noted that a planar face is not automatically an F face and a straight step of a growth layer is not of necessity parallel to a PBC. This is because of the possible effects of the growth condition such as solvent–solute interactions on the crystal faces. Hence, F faces and PBCs cannot be determined by observation or by experiment, but have to be deduced from the crystal structure.

The attachment energy (E_{att}) is defined as the energy released per mole when a new layer is deposited on a crystal face (22–24). Since the habit of a crystal is determined by the growth rates R of the various faces, a theoretical habit can be obtained by taking the growth rate of the various F faces proportional to their respective attachment energy (22–24). Theoretically, E_{att} should be calculated by taking into account the interaction energies between all molecules. However, for molecular structures the broken bond approximation can be used, in which E_{att} refers to only the bonds in the first coordination sphere of the crystallizing particles.

Methods of Determination of PBCs, F Faces, and E_{att}

There are two methods to find PBCs and F faces (22,23). We focus on the earlier method, which uses projections of crystal structure because of its explicit physical character.

(i) The method starts with the determination or assumption of the crystallizing particles. In the present case, they are the individual HMM molecules. (ii) Then the decision on the first coordination spheres is made. For HMM, it is illustrated in Fig. 3 (also see Results and Discussion). (iii) From ii, all bonds in a primitive unit cell are listed (as shown in Table I). (iv) Projections of the crystal structure along various lattice translations (or possible PBC directions) onto a

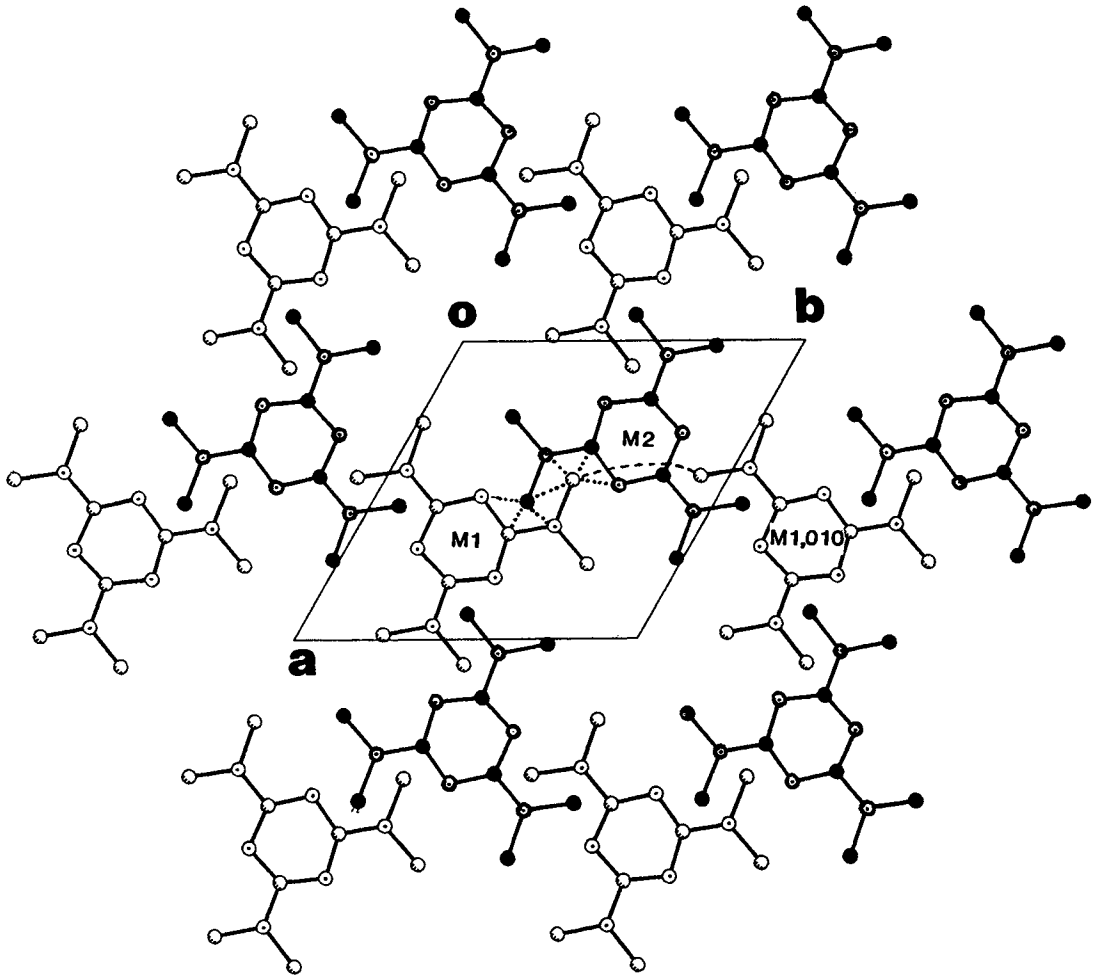

Fig. 3. Projection of the hexamethylmelamine crystal structure along the crystallographic c axis. Open circles with central dot, N; other circles, C; open circles, atoms at z = ¼; filled circles and dotted circle with enhanced outline, atoms at z = ¾. Interatomic distance between molecules smaller than 0.4 nm are indicated by the dotted lines (bond p) and the dashed curve (bond q) (see Results and Discussion).

Table I. A Complete List of Bonds

Bond p	Bond q
M1—M2	M1—M1,010
M1—M2,100	M1—M1,100
M1—M2,0$\bar{1}$0	M1—M1,110
M1—M2,00$\bar{1}$	M2—M2,010
M1—M2,10$\bar{1}$	M2—M2,100
M1—M2,0$\bar{1}\bar{1}$	M2—M2,110

plane perpendicular to the lattice row are made. In this report, these were produced using a graphic program (SHELXTL-PC, Siemens Analytical X-ray Instruments Inc., Madison, WI). (v) With the aid of the list of bonds, PBCs are sought in the projection directions, the symmetrically equivalent PBCs are sketched in the figure, and these are combined to complete PBCs. Then possible bonds between complete PBCs are sought so as to construct F slices d_{hkl}. This procedure is repeated until a self-consistent set of PBCs and F faces is obtained. Computer methods to determine PBCs and F faces have also been developed (see Ref. 22, 23).

For the determination of the attachment energy, the simplest way is the so-called broken bond approximation, in which only the interactions of the first coordination spheres (i.e., the nearest neighbors) are considered (22,23). "Broken bonds" are those bonds that need to be broken when the corresponding slice boundary is cut through. The total number of broken bonds across a crystal slice boundary is counted per unit cell and then divided by the number of molecules per unit cell. The attachment energy can be calculated when the interaction or bond energies between the molecules are known. If the latter is unknown, E_{att} can be expressed simply in terms of the number of broken bonds involved.

Recently a FORTRAN program, HABIT (27), has been developed that allows calculation of attachment energies for organic crystals. These calculations are based on nonbonded atom–atom potentials. The program does not include a search for PBCs. Applications have been presented by Docherty *et al.* (28).

RESULTS AND DISCUSSION

The crystal structure of HMM has been determined by Bullen et al (26). The crystals are hexagonal, space group $P6_3/m$, with two molecules in the unit cell of dimensions a = 0.999 nm and c = 0.711 nm. The centers of the molecules are at (⅔, ⅓, ¼) for M1 and at (⅓, ⅔, ¾) for M2, where M1 and M2 refer to an individual HMM molecule in a layer inside the crystal with coordinates given in the parentheses. Figure 3 shows a projection of the crystal structure along the c axis with the molecules M1, M1,010, and M2 (Mi,uvw means molecule Mi translated by the lattice vector $[uvw] = [ua + vb + wc]$) involving two bonds p. A molecule M1 is surrounded by six other equivalent (M1) molecules lying in the same plane (0001), by three molecules M2 in the plane located at the vertical distance z = ¾ (along the c axis), and another three M2 molecules in the plane located at $z = -¼$. Thus the packing is a hexagonal close packing compressed along the c axis because of the planarity of the molecules. The bond between M1 and M2 is called p and is secured by seven contacts smaller than 0.4 nm (indicated by the dotted lines in Fig. 3), as pointed out by Bullen *et al.* (26) (Fig. 3). The bond between M1 and M1,010 is called q and consists of only one contact between methyl groups smaller than 0.4 nm (indicated by the dashed curve in Fig. 3). It is therefore likely that bond p is much stronger than bond q.

According to the PBC theory, the crystal habit is governed by a set of uninterrupted chains of strong bonds formed in the crystallization process. In the present case the strong bonds are the p and q bonds. The repeat period of a PBC encompasses one or two molecules. Figure 4 shows also a projection along the c axis, but here for illustration, only the centers of the molecules are given. There is a PBC [001] consisting of two bonds p. PBC [001] is composed of the following molecules: M1—M2—M1,001; with M1 at (⅔, ⅓, ¼) and M2 at (⅓, ⅔, ¾). Because of the symmetry there are three such PBCs. The other two are: M1—M2,100—M1,001 and M1—M2,0$\bar{1}$0—M1,001. Such PBCs [001] are also bonded laterally in slices of the faces of the hexagonal prism {10$\bar{1}$0}, which is therefore classified as an F form, which is defined by the conditions that there are PBCs in two or more directions within a slice of thickness d_{hkl}. For the face (10$\bar{1}$0), there are other types of PBCs, denoted [010]A and [010]B, defined by one bond q and two bonds p, respectively, and [011] and [0$\bar{1}$1], both defined by two bonds p, as listed in Tables II and III.

Figure 5 is a projection along [010] or the b axis. Because the HMM molecule is basically planar, all atoms are on one line and some almost overlap. In the upper left part of

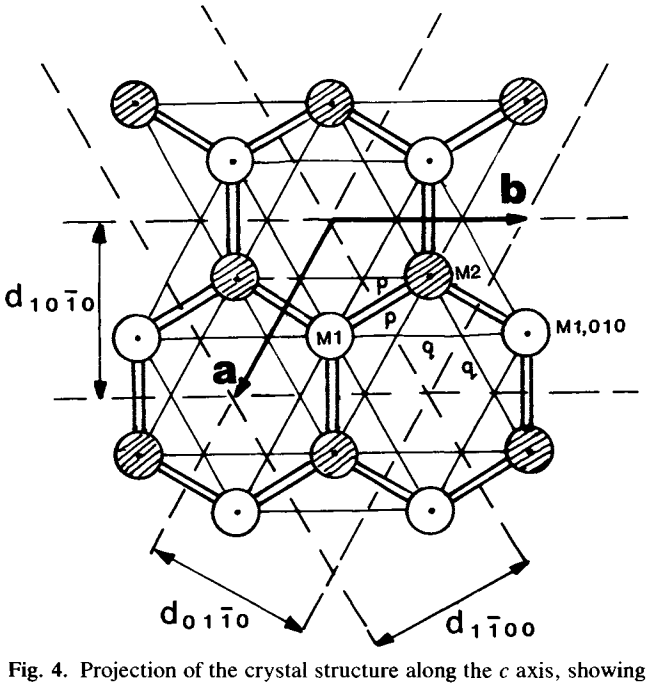

Fig. 4. Projection of the crystal structure along the c axis, showing only the centers of the molecules. p bonds (thick lines) and q bonds (thin lines) are indicated and slices (10$\bar{1}$0), (01$\bar{1}$0), and (1$\bar{1}$00) are drawn. Open and shaded circles refer to the molecules M1 at z = ¼ and M2 at z = ¾ as in Fig. 3.

Table II. A Complete List of PBCs

[001]	M1—M2—M1,001	
	M1—M2,100—M1,001	
	M1—M2,0$\bar{1}$0—M1,001	
[010]A[a]	M1—M1,010 M2—M2,010	
[100]A	M1—M1,100 M2—M2,100	
[110]A	M1—M1,110 M2—M2,110	
[010]B[a]	M1—M2—M1,010	M1—M2,00$\bar{1}$—M1,010
[100]B	M1—M2,100—M1,100	M1—M2,10$\bar{1}$—M1,100
[110]B	M1—M2,100—M1,110	M1—M2,10$\bar{1}$—M1,110
[011]	M1—M2—M1,011	
[$\bar{1}$01]	M1—M2—M1,$\bar{1}$01	
[$\bar{1}\bar{1}$1]	M1—M2,0$\bar{1}$0—M1,$\bar{1}\bar{1}$1	
[0$\bar{1}$1]	M1—M2,0$\bar{1}$0—M1,0$\bar{1}$1	
[101]	M1—M2,100—M1,101	
[111]	M1—M2,100—M1,111	

[a] A and B refer to the two subtypes of PBC (involving HMM molecules in different coordinates) in the same crystallographic direction.

the unit cell are drawn all interatomic contacts smaller than 0.4 nm that make out bond p as mentioned above. In the lower part is drawn the bond q, from M1 to M1,$\bar{1}$00 or from M1 to M1,$\bar{1}\bar{1}$0. In this way the rugged surface of (10$\bar{1}$0) becomes apparent, in contrast to the more smooth surface of (10$\bar{1}$1). Such ruggedness could result in a difference of solvent adsorption to the prismatic and pyramidal faces of the crystal. Figure 6 is a different version of Fig. 5 in which the molecules are represented as boxes seen on edge. These molecules (and PBCs) are bonded laterally in slices of (10$\bar{1}$1) and (0002), so the hexagonal dipyramid {10$\bar{1}$1} and the pinacoid {0002} are also F forms. A projection along the PBC [011] does not reveal other F forms. To sum up, the F faces (or forms) are found to be the prismatic (10$\bar{1}$0), pyramidal (10$\bar{1}$1), and pinacoid (0002) (Table III).

The habit of a crystal is determined by the growth rates R of the various F faces. An estimate of the HMM habit is obtained by taking the growth rate proportional to the attachment energies (F_{att}), which refer to only the bonds in the first coordination sphere: M1 at z = ¼ makes 6 bonds p (three above, three below) and 6 bonds q (in the same plane at z = ¼). With two molecules in the unit cell, the crystal energy (or lattice energy), E_{cr}, which is defined as the energy per molecule released when the crystal is formed from the crystallizing particles, equals (3p + 3q) bonds. To obtain the attachment energy of a face, the number of bonds that cut the corresponding slice boundary is counted. In Fig. 4, consider the slice with thickness $d_{10\bar{1}0}$: Molecule M1 makes 4 bonds p within the slice, while 2 bonds p stick outward on the (10$\bar{1}$0) side. Furthermore, it makes 2 bonds q within the slice, 2 bonds q point outward on the (10$\bar{1}$0) side, and 2 bonds q point outward on the ($\bar{1}$010) side. Molecule M2 makes 4p + 2q bonds within the slice. The bonds pointing out of the slice are 2 bonds q on the (10$\bar{1}$0) side and (2p + 2q) bonds on the ($\bar{1}$010) side. So altogether, the bonds pointing out on the (10$\bar{1}$0) side are (2p + 2q) for M1 and 2q for M2; average, (p + 2q) per molecule.

Table III. A List of the F Forms

{10$\bar{1}$0}	Slice (10$\bar{1}$0) determined by [001], [010]A, [010]B, [011], [0$\bar{1}$1]
{10$\bar{1}$1}	Slice (10$\bar{1}$1) determined by [010]A, [010]B, [$\bar{1}$01], [$\bar{1}\bar{1}$1]
{0002}[a]	Slice (0002) determined by [010]A, [100]A, [110]A

[a] It is interesting to consider that the bonds p and q do not have the same energy. If the Coulomb interaction is important (due to local dipoles in the molecule), this would lead to an increase in the difference between p and q. When q is not considered (but it should be, because it is part of the first coordination sphere), the slice (0002) is no longer an F face. The [010] PBC then consists of two bonds p, occurring in the slices of (10$\bar{1}$0) and (10$\bar{1}$1).

For slice $d_{10\bar{1}1}$ in Fig. 6 we find that M1 makes 3p and 2q bonds within the slice (note that these q's are perpendicular to one directly above and one directly below the plane of drawing and therefore cannot be drawn but can be inferred from Fig. 4). Further, this M1 molecule has (p + 2q) bonds pointing out on the (10$\bar{1}$1) side and (2p + 2q) bonds on the ($\bar{1}$01$\bar{1}$) side. M2 makes (3p + 2q) bonds within the slice, (2p + 2q) bonds pointing out on the (10$\bar{1}$1) side, and (p + 2q) bonds on the ($\bar{1}$01$\bar{1}$) side. So the attachment energy is ½ of [(p + 2q) + (2p + 2q)] bonds = (3p/2 + 2q) bonds per mole on the (10$\bar{1}$1) side.

For slice d_{0002} both molecule M1 and molecule M2 make 6 bonds q within the slice, 3 bonds p pointing out on the (0002) side and 3 bonds p on the (000$\bar{2}$) side. So the attachment energy on the (0002) side is 3 bonds p.

The attachment energies in terms of broken bonds are therefore (p + 2q) for (10$\bar{1}$0), (3p/2 + 2q) for (10$\bar{1}$1), and 3p for (0002). As argued before, bond p will be much stronger than bond q, so {10$\bar{1}$0} has the slower growth rate, followed by {10$\bar{1}$1}, while {0002} has a rather high growth rate and may not occur on the growth form. The predicted habit is thus the compact form. Actually, when the bond strength ratio p/q is lower than 2.44, the form {0002} should appear. The length/breadth ratio β_m (8) becomes 1.59 when p/q = 10 and 1.68 when q is entirely neglected. It should be noted that "crystal breadth" in Refs. 7 and 8 is the distance between two opposite edges of the hexagonal prism and therefore corresponds to $(2/\sqrt{3})E_{att}(10\bar{1}0)$. These values should be compared with the experimental results from Ref. 7. For growth from methanol, β_m at t = 25 min is 1.69 on the average; from cyclohexane at t = 65 min, it is 1.61. The agreement with the theoretical values is very good. The experiments in Ref. 7 have been performed at relatively low supersaturation. Those in Ref. 8 have been conducted at various, sometimes much higher supersaturations, because a slightly undersaturated solution during evaporation can easily acquire a rather high supersaturation before nucleation occurs. Habit elongation in Ref. 8 occurs only with polar solvents or amphiphilic solvents having a large dipole moment. It was suggested that in these solvents, the equilibrium crystal habit of HMM may be also compact; the elongation being affected by the growth rate and supersaturation (8). This may be interpreted in terms of an interplay between high supersaturation (rapid growth) and stronger interactions of these solvent molecules with the more rugged prismatic faces: When crystal growth occurs from a solution, the surface of the crystal as well as the solute molecules will be solvated. For a growth

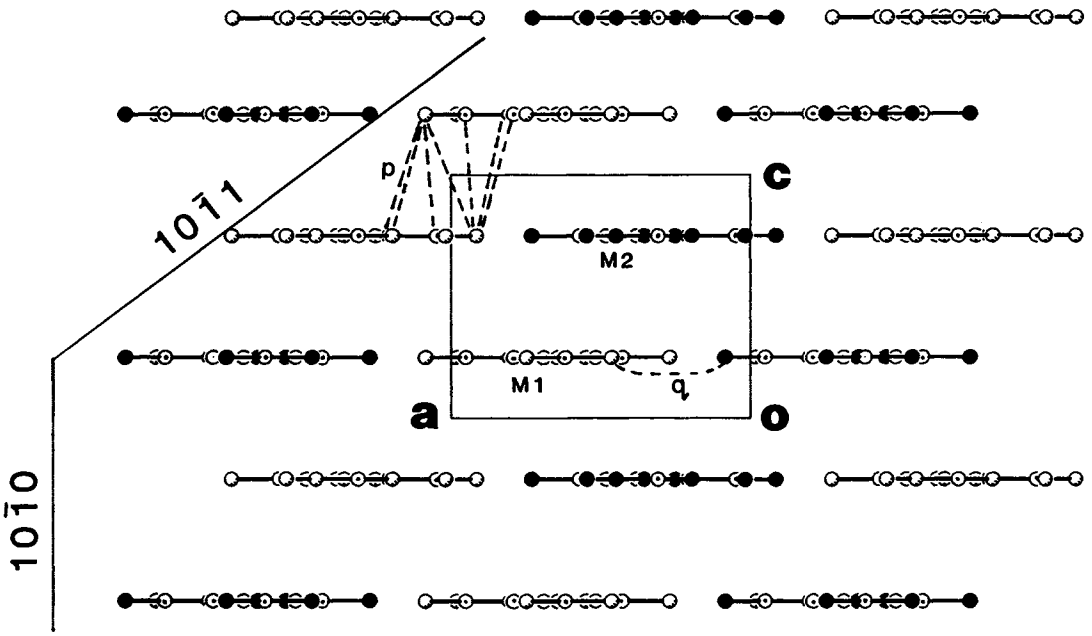

Fig. 5. Projection of the crystal structure along the *b* axis, showing the planarity of the molecules. In the upper left part of the unit cell are drawn all interatomic contacts smaller than 0.4 nm that make out bond p as explained in the text. In the lower part is drawn the bond q, from M1 to M1,$\bar{1}00$ or from M1 to M1,$\bar{1}\bar{1}0$. In this way the rugged surface of ($10\bar{1}0$) becomes apparent, in contrast to the more smooth surface of ($10\bar{1}1$). Open circles with central dot, N; other circles, C. Note that in this projection the centers of the molecules occur at two levels: one (open) at height 0 and the other (darkened or outline enhanced) at high $d_{\bar{1}2\bar{1}0}$.

layer the spreading rate is determined by the incorporation rate of the solute molecules into the growth step and by the desolvation rate at the crystal–solution interface. This desolvation occurs differently at different crystal faces. A higher supersaturation leads to a higher spreading rate of growth layers on the face, that is, the incorporation rate of solute molecules into the step increases. When this rate becomes comparable to the desorption rate of the solvent molecules adsorbed on the surface, the growth rate of the face will slow down and a habit change can occur. An alternative possible explanation is that the habit elongation is due to solvent-mediated dislocations arising at the ends of the needle crystal (7).

A compact habit of HMM in nonpolar solvents could have resulted either from a lack of anisotropic solvent–crystal interactions or, alternatively, from the inhibition of elongation due to solvent interactions on the bipyramidal faces. The PBC theory supports the former rather than the latter explanation.

The PBC and energy approach have been used considerably in crystal growth in general. Recently, an extensive application of PBC method to 30 organic compounds including adipic acid and naphthalene was reported (25). It is our hope to see its potential use in pharmaceutical crystals.

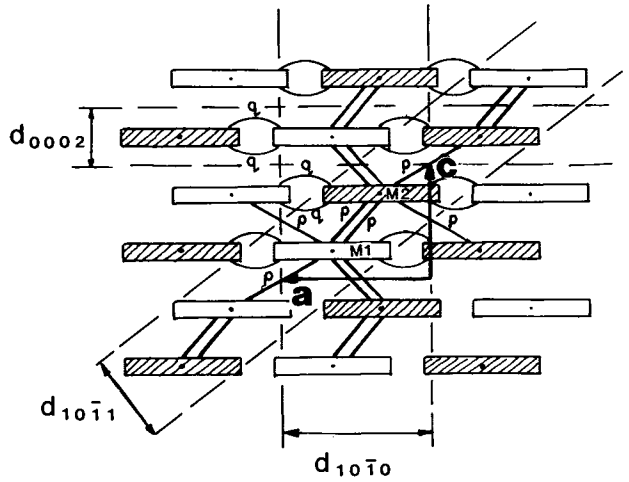

Fig. 6. A different version of Fig. 5 in which the molecules are represented as boxes seen on edge. P bonds (thick lines) and q bonds (bend curves) are shown. Slices of ($10\bar{1}0$), ($10\bar{1}1$), and (0002) are indicated. As in Fig. 5, the centers of the molecules occur at two different levels, one (open) at height 0 and the other (shaded) at height $d_{\bar{1}2\bar{1}0}$.

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