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Specific Surface Energies and Dissolution Behavior of Aspirin Crystal

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The displacement velocity of each crystalline face of aspirin on dissolution in distilled water was determined by using large single crystals grown from ethanolic solution. It was found that each crystalline face of aspirin has its own displacement velocity. The specific surface energies for those crystalline surfaces in water and *in vacuo* were calculated from a set of atom–atom pairwise potential functions. The relative rate of diminution of surface area on dissolution of the crystal can be correlated to the sensitivity of the surface energy to the polarity of the solvent.

Keywords——aspirin; crystalline face; crystal habit; dissolution velocity constant; specific surface energy

Introduction

It is well known that the dissolution velocity of aspirin crystals depends upon what type of solvent they are recrystallized from.[1-6] Tawashi reported that recrystallization of aspirin from ethanol and *n*-hexane led to different polymorphic forms, that from *n*-hexane being dissolved in water 50 percent faster than the other.[1] Attempts to obtain these polymorphs for further studies have been unsuccessful so far and the existence of the polymorphs has been questioned.[2-4] Alternatively, Watanabe *et al.*[7] have correlated the effect of recrystallizing solvent on the dissolution velocity of aspirin with the difference in crystal habit resulting from the change of the solvent. This interpretation is reasonable, since the crystal habit should affect the surface excess energy of microcrystals.

Hartman and Perdox[8] considered the specific surface energy from the viewpoint of the attachment energy. According to these authors, the attachment energy is defined as the bond energy released when one building unit is attached to the surface of a crystal face. Their basic assumption is that the time taken for the formation of a bond decreases with increasing bond energy, and consequently the displacement velocity of a crystal face during growth increases with increasing attachment energy. They divided the crystalline faces into three classes; *F*-faces ((*h*00), (0*k*0) and (00*l*)) which are the most important faces, *S*-faces ((*hk*0), (*h*0*l*) and (0*kl*)) which are of medium importance and *K*-faces ((*hkl*), $hkl \neq 0$) which are very rare or do not occur at all. Applying the argument of Hartman and Perdox to the reverse process of crystal growth, we may expect that the displacement velocity of a crystal face on dissolution

decreases with increasing attachment energy.

In order to obtain experimental as well as theoretical evidence of such a correlation between crystal habit and dissolution behavior, we recrystallized aspirin from ethanol as large single crystals. The displacement velocities of their *F*-faces on dissolution were measured in distilled water, and the specific surface energies of the *F*- and *S*-faces were calculated from a set of atom–atom pairwise potential functions which had been proved to be consistent with the crystal structure and the elastic constants.[9]

Experimental

Materials and Equipment——Aspirin crystals of JP grade were used. Single crystals of aspirin were prepared as monoclinic plates by slow evaporation of the solvent from an ethanolic solution at room temperature. The formation of single crystals was confirmed by observing that each crystal showed a parallel extinction through a polarizing microscope.[10] Crystal habits were measured by using a micrometer. Apparatus 2 for the dissolution test in USP XX (Toyama Sangyo Co., Osaka, Japan) was used in combination with a Shimadzu UVD-2 spectrophotometer. The dissolution medium was 900 ml of distilled water.

Measurement of Displacement Velocity on Dissolution——The aspirin single crystals used were considered to be parallelepipeds and their average size was $(8.5 \pm 2.0) \times (10.0 \pm 6.0) \times (2.0 \pm 1.5)$ mm^3. There was a tendency for them to sink during the dissolution experiment. Because the crystalline edges along the *a* axis are mostly shorter than one-fifth of the other two, the face-(001) inevitably becomes parallel with the bottom surface of the container and cannot be dissolved as smoothly as the other two *F*-faces. Special care was thus necessary in order to measure the displacement velocity of each crystal face under the same conditions of contact with the solvent. The central small area of one *F*-face was fixed on a small glass plate, then the crystal was put on the bottom of the dissolution equipment mentioned above and the solution was stirred at 150 rpm while being maintained at a constant temperature. At suitable time intervals, the sample was removed from contact with the solvent, and the two crystal habits parallel to the fixed face were measured with the micrometer. The constancy of the dissolution rate was monitored by circulating the solution through a flow cell of the ultraviolet (UV) spectrophotometer and recording the dissolution curve at 254 nm. The same procedure was carried out after fixation of different *F*-faces.

Calculation

The fracture of a crystal along crystalline planes results in the formation of new surfaces. The specific surface energy is defined as half the energy per unit area required to separate the crystal along a plane parallel to the surface.[11]

In order to estimate this energy, we first imagine an infinite set of equidistant parallel planes given in the crystal coordinate system as

$$F_{hkl}(X^c) \equiv (hx^c + ky^c + lz^c - 1)/P = N \qquad N = \cdots, -2, -1, 0, 1, 2, \cdots \tag{1}$$

where h, k and l are Miller indices and P is their greatest common divisor. The number of such planes lying between two points X_p^c and X_q^c is given by the absolute value of the difference between the integer parts of $F_{hkl}(X_p^c)$ and $F_{hkl}(X_q^c)$, each being corrected by subtracting unity if negative.

The specific surface energy of the face-(hkl) of a crystal is then calculated as

$$E(hkl) = 1/2 S_{hkl}^{-1} \sum_i \sum_{j \neq i} f(r_{ij}) N_{ij}(hkl) \tag{2}$$

where S_{hkl} is the surface area per unit cell, $f(r_{ij})$ is the pairwise atom–atom interaction potential function, and r_{ij} is the distance between the atoms i and j. The area S_{hkl} is calculated as the unit cell volume divided by the period in the direction perpendicular to the face-(hkl).

In Eq. 2 the atomic index i runs over all the molecules in one unit cell on one side of the specified plane, and j over all the molecules that are outside the plane at one half of the crystal.

$N_{ij}(hkl)$ is the number of planes (hkl) existing between the centers of the two molecules of which one includes the atom i and the other the atom j, and is calculated from the function $F_{hkl}(X^c)$ in Eq. 1. This factor is necessary because the plane (hkl) per area S_{hkl} separates N_{ij}

equivalent pairs of atoms which interact through the term $f(r_{ij})$. The molecular center is placed at the aromatic carbon atom at which the acetoxy group is substituted.

Kitaigorodsky[11] and Kim *et al.*[12] calculated the specific surface energies of anthracene and polyethylene crystals, respectively. Since each unit cell of these crystals contains only two centrosymmetric molecules, one can specify a given crystal surface uniquely by using three Miller indices which have no common divisor other than unity. On the other hand, a unit cell of aspirin crystal contains four asymmetrical molecules, and this may lead to several ways of choosing parallel but non-equivalent planes for a given macroscopic crystal face. The use of Miller indices which are composite (*F*-faces) or not prime to each other (*S*-faces) in this work is necessary for distinguishing between these planes. In order to select the intermolecular potential functions $f(r_{ij})$ and to check the reliability of the potential parameters, we calculated the energy-minimized structure of aspirin crystal and its elastic constants, and confirmed that they agreed well with the experimental data.[9] Based on this result, we adopted the sum of the pairwise potential terms of three types: the exp-6 type non-bonded potential (V_1), the Lippincott type hydrogen bond stretching potential (V_2)[13] and the Coulomb potential including the complementary error function as a convergence factor (V_3).[14] The summation limit for V_1 was taken to be 8 Å. By taking the convergence constant K as 0.20, the summation limit of 10 Å for V_3 was found to be sufficient.[14] The lattice spacing and the atomic coordinates used in this work were determined in our previous work.[9]

The numerical calculations were carried out on a FACOM M382 computer at the Data Processing Center of Kyoto University.

Results and Discussion

A typical form of aspirin crystal obtained from ethanolic solution is shown in Fig. 1, where the habit parameters *a*, *b* and *c* defined by Watanabe *et al.*[7] are also shown. Ethanol is the most suitable recrystallizing solvent for aspirin to provide crystals of considerable size and sufficient stability against shock. It is well known that the face-(100) of aspirin crystal is a cleavage plane. Umeyama *et al.* studied the cleavage of aspirin crystals by the CNDO MO method. They reported that the cleavage occurs along the plane through which the intermolecular interaction energy per unit area is the smallest.[15]

The estimated displacement velocities of surface planes of aspirin crystals are listed in Table I. The initial crystal habits parallel to the fixed face were measured with a micrometer prior to the dissolution experiment. The crystal habits of samples 5 and 6 were adjusted by cutting along the cleavage plane. Through the adjustment of crystal habits, we attempted to detect any possible influence of the characteristic shape of the crystal on the dissolution rate of each surface plane. In order to confirm the validity of the experiment, discs with a diameter of

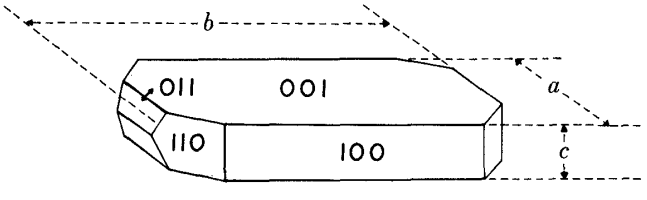

Fig. 1. Aspirin Single Crystal Obtained from Ethanolic Solution and Its Habit Parameters

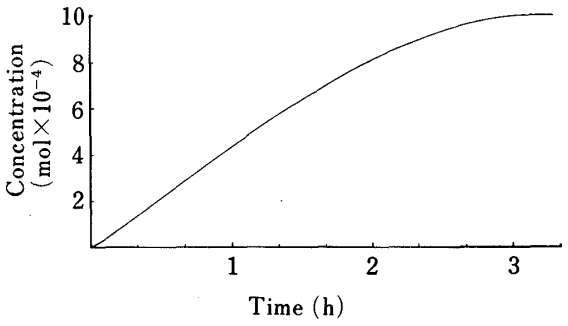

Fig. 2. Dissolution Curve of an Aspirin Single Crystal (183.8 mg) in 900 ml of Distilled Water at 36 °C and 150 rpm

TABLE I. Diminution Rate of Each Crystal Habit for Dissolution of Aspirin Single Crystal in Distilled Water at Various Temperatures

Sample No.	Initial cryst. hab. (mm)			Temp. (°C)	Displacement velocity (mm/h)			Fixed face	Dissol. time (min)
	a_0	b_0	c_0		Face-*bc* a/t	Face-*ca* b/t	Face-*ab* c/t		
1	9.220	9.904		36	1.192	1.644		*ab*	60
2	8.430	9.798		36	1.194	1.695		*ab*	60
3		16.643	3.618	36		1.610	0.863	*bc*	60
4		8.287	1.406	36		1.746	0.676	*bc*	30
5	7.505		2.307	36	1.233		0.837	*ca*	40
6	3.509		3.239	36	1.206		0.794	*ca*	40
7	6.501		1.350	36	1.196		0.604	*ca*	30
8	9.892	9.788		26	0.664	0.925		*ab*	60
9		7.570	1.836	26		0.908	0.412	*bc*	30
10	6.994		1.320	26	0.684		0.460	*ca*	60
11	9.007	9.142		46	2.702	3.598		*ab*	20
12		9.080	1.552	46		3.608	1.236	*bc*	20
13	8.820		1.402	46	2.600		1.268	*ca*	15

The height of the paddle was 2.5 cm from the bottom of the container.

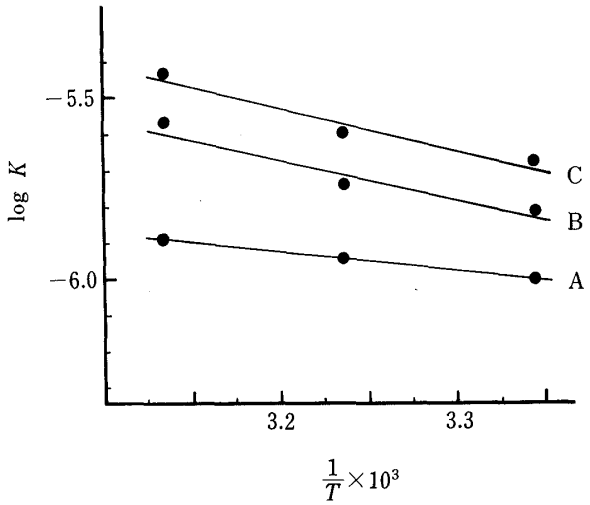

Fig. 3. Dependence of $\log K$ of Each Crystalline Face on Temperature

A, face-*ab*; B, face-*bc*; C, face-*ca*.

1 cm were prepared by compression of finely ground aspirin crystals at about 3000 kg/cm^2 in a punch-die assembly for infrared (IR) spectroscopy. Each disc was cut and polished into a rectangular parallelepiped similar to the shape of a typical aspirin single crystal. The dissolution experiment was carried out for these parallelepipeds in exactly the same way as done for the single crystal. The displacement velocity of the face parallel to the basal plane was less than those of the other two faces because the discs were pressed in the direction of their axes. With various adjustments of the lengths corresponding to the crystal habits, the displacement velocities of the two faces vertical to the base were confirmed to agree with each other within the experimental accuracy of 0.01 mm h^{-1}. We were able to confirm that the crystal habit in which *c* is short as compared with *a* and *b* has no influence on the displacement velocity of each face. The dissolution curve of one aspirin single crystal is shown in Fig. 2. The dissolution times in Table I are between the initial one-third and half of the linear part of the dissolution curve. As shown in Table I, each surface plane has a specific displacement velocity

of its own at each temperature. The average values are listed in Table II together with the velocity constants of dissolution, K, of each face at 26, 36 and 46 °C. The latter constants are defined by the Noyes Whitney equation,

$$\frac{dC}{dt}=KS(C_s-C) \quad (C_s \gg C) \tag{3}$$

where C_s is the solubility. The surface area, S (cm^2), is related to the displacement velocity by

$$\frac{dC}{dt}=\frac{d_a S}{V_0}\frac{dl}{dt} \tag{4}$$

where V_0 is the volume of solution, and d_a is the density (mol/cm^3). From Eqs. 3 and 4, we obtain

$$K=\frac{d_a\frac{dl}{dt}}{V_0 C_s}$$

The C_s data were taken from refs. 3 and 16. Plots of $\log K$ against $1/T$ for the faces *ab*, *bc* and *ca* are shown in Fig. 3. They are approximately linear, as expected under experimental conditions such that the concentration of dissolved solute is negligible compared with C_s and the transport process is controlled.[3)]

According to Watanabe *et al.*[7)] the velocity constant of dissolution per unit area of aspirin crystals can be correlated well with the relative surface area, which may be characrerized by a parameter, the habit coefficient, and this parameter can be regulated by changing the polarity of the recrystallizing solvent. They remarked that thicker crystal in which face-(001) is less predominant has a larger habit coefficient and velocity constant, and the velocity constant is approximately proportional to the habit coefficient $=(S_{ca}+S_{bc})/S_{ab}$, where the surface area of face-(001) is comparable to the sum of the other two. Face-(001) is just face-*ab*, which has the smallest displacement velocity according to our experiment, as shown in Tables I and II.

The results of Watanabe *et al.*[7)] are given in Table III along with the habit coefficients calculated from a new definition, $S_{ca}/(S_{bc}+S_{ab})$, in which the face with the largest displacement velocity is taken as the standard. The newly defined habit coefficients not only follow the same order as those defined by Watanabe *et al.* but also show a good proportionality with the velocity constant K. These results indicate that the experimental data of Watanabe *et al.* are consistent with ours even though the dissolution medium used in our work is different from

TABLE II. Average Displacement Velocity and Dissolution Velocity Constant of Each Face

Temp. (°C)	Face	Displacement velocity (mm/h)	Dissolution velocity constant ($cm^{-2}\,h^{-1}$)
26	Face-*ca*	0.917	2.11×10^{-6}
26	Face-*bc*	0.674	1.55×10^{-6}
26	Face-*ab*	0.436	1.00×10^{-6}
36	Face-*ca*	1.674	2.54×10^{-6}
36	Face-*bc*	1.204	1.82×10^{-6}
36	Face-*ab*	0.755	1.14×10^{-6}
46	Face-*ca*	3.603	3.70×10^{-6}
46	Face-*bc*	2.651	2.72×10^{-6}
46	Face-*ab*	1.252	1.29×10^{-6}

TABLE III. Dissolution Constants and Habit Coefficients of Aspirin Crystals Recrystallized from Various Solvents

Crystal	Velocity const.[a] ($mm^{-2}\,min^{-1}$)	Habit coefficient	
		$(S_{ca}+S_{bc})/S_{ab}$[b]	$S_{ca}/(S_{ab}+S_{bc})$[c]
From water	1.07	0.0209	0.0070
From water+EG[d]	2.67	0.0424	0.0139
From dioxane	3.88	0.6900	0.0227
Market product	8.42	0.8810	0.1595

a) The data in ref. 7 were multiplied by 1000 to convert the unit from $mg\,mm^{-2}\,min^{-1}$ to $mm^{-2}\,min^{-1}$. *b*) From ref. 7. *c*) Each surface area was calculated from the habit parameters in ref. 7. *d*) Ethylene glycol.

TABLE IV. Specific Surface Energy (E_{hkl}) of Aspirin Crystal

Surface	$(hkl)/P$	P	E_{hkl} (mJm^{-2})	
			In vacuo ($D=1.0$)	In water ($D=78.56$)[a]
ab	(001)	4	163.64	157.46
bc	(100)	2	131.48	127.24
ca	(011)	1	236.92	182.46
ca	(110)	1	237.82	208.01
ca	(010)	2	394.92	296.29

a) D means dielectric constant.

theirs.

The velocity constant of face-*ab* is the smallest and that of face-*ca* is the largest. We can consider this experimental result from another viewpoint, the rate of diminution of surface area. The rate of diminution of surface area is the smallest with face-*ca* and the largest with face-*ab*. This point of view will be utilized in later discussion.

The calculated specific surface energies are given in Table IV. The surface energy of face-(010), which is the least developed or does not appear, is the largest of the three *F*-faces, as expected. Since face-(100) of aspirin crystal is a cleavage plane as mentioned above, the fact that its energy is the least in Table IV seems to be reasonable, being in agreement with the CNDO calculation of Umeyama *et al.*[15] This result, however, suggests that the most developed surface would be face-(100), which is not in agreement with the finding for real aspirin single crystals grown from ethanol. Some solvent–surface interaction may be responsible for this discrepancy between the order of the surface areas developed in a certain solvent and the calculated surface energies *in vacuo*. In addition, the container walls in contact with crystallite seeds may impede the growth of a particular crystalline face.[17]

When the wall effect is negligible, a crystal recrystallized from a given solvent should show a characteristic shape which is the most stable energetically in that solvent. Different crystal habits may be caused by differences in the solvent–crystalline surface interactions (which of the van der Waals and the Coulomb interactions and the hydrogen bonding is predominant). The calculated surface energy for each plane in Table IV can be divided into three parts arising from V_1, V_2 and V_3. The relative amounts of the Coulombic part may be related to the sensitivity of the surface stability to change in the polarity of the solvent with which the surface is in contact. To check this point we calculated the surface energies of all the planes by using the dielectric constant of water in V_3.

As the dielectric property of non-polar solvents is approximated by that of a vacuum, the decrease of surface energy on changing the dielectric constant in V_3 from 1 to 78.56 may be taken to represent the stabilization energy of the surface on transferring the crystal from a non-polar solvent to water. As shown in Table IV, the surface energies of the three faces which constitute face-*ca* are much more sensitive to the dielectric constant in V_3 than are those of faces-*ab* and -*bc*. This result suggests that face-*ca* which showed the largest displacement velocity is relatively strongly influenced by the Coulomb force. If a single crystal recrystallized from a non-polar solvent is immersed in pure water, dissolution of the crystal as a whole takes place in parallel with readjustment of the relative areas of the developed faces in such a way as to minimize the total surface energy under the new solvent–crystal interactions. In this case, as the surface energy of face-*ca* diminishes appreciably with increase of the dielectric constant, it is expected that face-*ca* in contact with water resists diminution of its area more strongly than the other faces. For this reason, it can be understood that, when a single crystal of aspirin is dissolved by contact with unsaturated water, the rate of diminution of surface area is the smallest with face-*ca*. The experimental and theoretical procedures developed above should be useful for understanding the dissolution process of crystals at the molecular level.

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