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Structure Redetermination and Packing Analysis of Aspirin Crystal

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The crystal structure of aspirin has been redetermined by X-ray diffraction analysis at room temperature. The lattice energy, the eleastic constants and the structure parameters corresponding to the equilibrium of a model potential of aspirin crystal have been calculated by taking account of the non-rigidity of the molecule and applying the condition of vanishing stress. The model potential consists of the exp-6 type dispersion and exchange repulsion terms, the Lippincott type hydrogen bond stretching terms and the electrostatic interaction terms between fixed atomic charges. The atomic coordinates of the calculated structure agree well with those determined crystallographically.

Keywords——aspirin; crystal structure; intermolecular potential; elastic constant

Introduction

There have been many reports concerning the differences in the dissolution behavior and the rate of intestinal absorption among aspirin crystals grown into different crystal habits.[1-6]

Aiming at understanding the effect of crystal habits on the dissolution behavior of aspirin at the molecular level, we have recently determined the displacement velocities of the surface planes with different Miller indices (F- and S-face)[7] on dissolution in water, and have calculated their surface energies by using a suitable potential model for the intermolecular interaction.[8] Since there is no direct method to measure the surface energy of a given crystal plane, the reliability of the potential parameters used in the calculation should be checked in terms of their ability to predict as many other crystal properties deducible from the intermolecular potential as possible.

The crystal structure of aspirin was analyzed earlier by Wheatley.[9] At the beginning, we made an attempt to calculate the elastic constants and normal frequencies using his structure. Despite various trials to adjust parameters, however, those calculations proved to be disappointing, as the matrix of elastic constants could not be made positive-definite, and the calculated normal frequencies did not fit with the measured vibrational spectra, especially for some methyl group modes.

Thus, we decided to redetermine the crystal structure of aspirin. The revised structure was found to give reasonable values of elastic constants compared with those obtained from the Brillouin scattering measurement[10] and also of lattice frequencies compared with the observed Raman spectra.[11]

In a previous paper, we reported a general method of crystal packing optimization, in which the molecules were assumed to be non-rigid and the stability condition was checked in terms of the number of positive eigenvalues of the matrix of the elastic constants.[12] In the present work, taking account of the internal force of non-rigid molecules, we have calculated the crystal structure of aspirin corresponding to the energy minimum with adjustment of the cell constants and the structure parameters in the asymmetric unit.

Crystal Structure

Aspirin ($C_9H_8O_4$, M.W. = 180.16) crystallizes in monoclinic space group $P2_1/c$. The unit cell contains four molecules. The structure consists of centrosymmetric dimers, in which two molecules are linked by a pair of hydrogen bonds between their carboxyl groups.

The single crystal used for the present refinement was obtained by slow evaporation of the solvent from a saturated ethanolic solution. The crystal, with dimensions $0.1 \times 0.2 \times 0.2$ mm, was mounted on a Rigaku AFC-5 diffractometer operating with a RU200 X-ray generator (40 kV, 15 mA) delivering CuK_α radiation ($\lambda = 1.54178$ Å). The unit cell parameters were determined by the least-squares method using 24 2θ values larger than 40°. $a = 11.430$ (1), $b = 6.591$ (1), $c = 11.395$ (2) Å. $\beta = 95.68$ (1)°, $V = 854.2$ (4) Å^3, $D_x = 1.401$ g/cm^3, $D_m = 1.400$ g/cm^3. The crystal data are not significantly different from Wheatley's data. Intensities of 1352 reflections with $2\theta < 120$, h −12—12, k 0—7, l 1—12, were measured in the 2θ—ω scan mode with a scan speed of 2° (ω)/min. No significant intensity variation for three standard reflections was observed during the measurement. No absorption correction was applied. Full-matrix least-squares refinement minimizing $\sum w||F_o|-|F_c||^2$ [$w = 1/\{\sigma^2(F_o) + (0.0023F_o)^2\}$] yielded $R = 0.046$ and $R_w = 0.070$ for 1192 unique reflections with $|F_o| > 3\sigma(F_o)$. The hydrogen atoms were located from the difference Fourier synthesis and included in the least-squares refinement with the isotropic thermal parameters. The atomic scattering factors were obtained from International Tables for X-Ray Crystallography.[13] The final fractional coordinates for all atoms are listed in Table I. Bond lengths and valence angles are given in Table II.

Packing Analysis

There have been numerous reports proposing various methods of crystal packing analysis and advocating many types of model potential functions and their parameters. Unfortunately, however, most of them make no mention of the elastic constants in spite of the fact that they are the most fundamental quantities in lattice dynamics. Even when no

TABLE I. Fractional Coordinates of Aspirin Crystal

Atom	X	Y	Z	B_{iso}
C(1)	0.1534 (1)	0.5640 (2)	0.0674 (1)	3.12 (1)
C(2)	0.2462 (1)	0.4877 (2)	0.0095 (1)	3.20 (1)
C(3)	0.2983 (2)	0.3047 (3)	0.0416 (2)	4.00 (1)
C(4)	0.2604 (2)	0.1961 (3)	0.1338 (2)	4.32 (1)
C(5)	0.1696 (2)	0.2676 (3)	0.1931 (2)	4.06 (1)
C(6)	0.1165 (2)	0.4496 (3)	0.1598 (1)	3.58 (1)
C(7)	0.0903 (1)	0.7573 (2)	0.0376 (1)	3.17 (1)
C(8)	0.3659 (2)	0.7384 (3)	−0.0637 (1)	3.52 (1)
C(9)	0.3974 (2)	0.8378 (4)	−0.1728 (2)	5.01 (1)
O(1)	0.1203 (1)	0.8603 (2)	−0.0508 (1)	4.25 (1)
O(2)	0.0104 (1)	0.8118 (2)	0.0965 (1)	4.41 (1)
O(3)	0.2857 (1)	0.5878 (2)	−0.0880 (1)	3.47 (1)
O(4)	0.4036 (1)	0.7801 (2)	0.0345 (1)	4.98 (1)
HC3	0.3616 (19)	0.2559 (29)	−0.0009 (17)	4.16 (42)
HC4	0.2926 (19)	0.0651 (33)	0.1552 (17)	4.65 (42)
HC5	0.1400 (18)	0.1883 (35)	0.2554 (18)	4.82 (45)
HC6	0.0528 (18)	0.4995 (29)	0.1990 (15)	3.46 (36)
HC9A	0.4560 (23)	0.9410 (38)	−0.1600 (19)	5.99 (51)
HC9B	0.3265 (26)	0.8883 (41)	−0.2139 (22)	7.00 (57)
HC9C	0.4220 (27)	0.7389 (41)	−0.2266 (23)	7.05 (61)
HO1	0.0737 (23)	0.9863 (42)	−0.0626 (19)	6.24 (52)

TABLE II. Bond Lengths (Å) and Valence Angles (Deg.)

Bonds		Angles	
C(1)–C(2)	1.397 (2)	C(2)–C(1)–C(6)	117.6 (1)
C(2)–C(3)	1.378 (2)	C(6)–C(1)–C(7)	117.4 (1)
C(3)–C(4)	1.376 (3)	C(2)–C(1)–C(7)	125.1 (1)
C(4)–C(5)	1.376 (3)	C(1)–C(2)–O(3)	121.5 (1)
C(5)–C(6)	1.380 (3)	C(3)–C(2)–O(3)	117.2 (1)
C(6)–C(1)	1.394 (2)	C(1)–C(2)–C(3)	121.2 (1)
		C(2)–C(3)–C(4)	119.8 (2)
		C(3)–C(4)–C(5)	120.4 (2)
		C(4)–C(5)–C(6)	119.7 (2)
		C(1)–C(6)–C(5)	121.3 (2)
C(3)–HC3	0.965 (22)	C(4)–C(3)–HC3	121.2 (12)
C(4)–HC4	0.961 (22)	C(2)–C(3)–HC3	119.0 (12)
C(5)–HC5	0.969 (22)	C(5)–C(4)–HC4	118.1 (13)
C(6)–HC6	0.950 (20)	C(3)–C(4)–HC4	121.3 (13)
		C(6)–C(5)–HC5	119.6 (13)
		C(4)–C(5)–HC5	120.7 (13)
		C(5)–C(6)–HC6	120.5 (11)
		C(1)–C(6)–HC6	118.1 (11)
C(1)–C(7)	1.487 (2)	C(1)–C(7)–O(1)	118.0 (1)
C(7)–O(2)	1.239 (2)	O(1)–C(7)–O(2)	122.5 (1)
C(7)–O(1)	1.289 (2)	C(7)–O(1)–HO1	111.5 (14)
O(1)–HO1	0.989 (27)	C(1)–C(7)–O(2)	119.5 (1)
C(2)–O(3)	1.405 (2)	C(2)–O(3)–C(8)	116.4 (1)
O(3)–C(8)	1.361 (2)	O(3)–C(8)–O(4)	122.2 (2)
C(8)–O(4)	1.191 (2)	C(9)–C(8)–O(3)	111.5 (1)
C(8)–C(9)	1.481 (3)	C(8)–C(9)–HC9A	114.3 (13)
C(9)–HC9A	0.956 (26)	C(8)–C(9)–HC9B	107.5 (17)
C(9)–HC9B	0.955 (27)	C(8)–C(9)–HC9C	110.6 (17)
C(9)–HC9C	0.952 (28)	C(9)–C(8)–O(4)	126.3 (2)
		HC9A–C(9)–HC9C	109.5 (23)
		HC9A–C(9)–HC9B	112.0 (22)
		HC9B–C(9)–HC9C	102.2 (23)
O(1)···O(2′)[a]	2.649 (2)	O(1)–HO1···O(2′)	173.8 (23)
HO1···O(2′)	1.665 (27)		

a) Atom of the neighboring molecule.

experimental data on the elastic constants are available, the calculated constants must be useful to check whether the adopted model potential is consistent with the observed structure. In a series of studies on the vibrational spectra and crystal structure of several amino acids,[14] we have shown that the elastic constants can be successfully applied to discussion of the lattice stability.

The atomic coordinates at the minimum of a model potential of aspirin crystal were calculated by the method of crystal packing optimization described previously.[12] The lattice energy was calculated as the sum of three types of atom–atom pairwise potential energy functions. Two sorts of combinations of model potential functions were tested. The first combination (calculation I) consists of the exp-6 type non-bonded potential (V_1), the Lippincott type hydrogen bond stretching potential (V_2),[15] and the Coulomb potential including the complementary error function as a convergence factor.[16] The potential parameters for V_1 and V_2 are listed in Table III. The second combination (calculation II) was taken from the work of Momany *et al.*[17] It consists of the Lennard–Jones 6—12 potential, the general hydrogen bond 10—12 potential and the Coulomb interaction including the

TABLE III. Potential Parameters for Non-bonded Atom–Atom Interaction (V_1) and Hydrogen-Bond Stretching (V_2)

Potential	Atom pair	Parameters		
		A (10^{-6} aJnm^6)	B (aJ)	C (nm^{-1})
V_1	H---H[a]	0.25	27.79	37.4
	C---H[a]	0.9657	65.38	36.7
	C---C[a]	3.717	517.30	36.0
	O---H(C)	0.7841	136.5	40.35
	O---C	3.0234	588.9	39.65
	O---O[b]	2.4593	588.9	39.65
		k_H (Ncm^{-1})	D (kJmol^{-1})	r^e (nm)
V_2	O---H(O)	0.10	20.92	0.165[c]

a) Taken from ref. 19. *b*) Taken from ref. 20. *c*) Newly estimated.

reciprocal of the effective dielectric constant. In both calculations I and II, the atomic charges were obtained by the INDO method.[18]

Iterative minimization of the potential energy was carried out by the Newton–Raphson method in which the first and the second derivatives of the potential with respect to the atomic displacements were calculated according to the usual lattice dynamics for crystal vibrations.[12] The corrections to the lattice constants and those to the molecular translation and rotation at each step of iteration were calculated in the form of vectors $\Delta \boldsymbol{a}^*$ and $\boldsymbol{T}^*_{ex}$, respectively, according to the previously derived expressions.[12]

The potential energy per unit cell of a uniformly deformed molecular crystal under a small strain was expanded as the Taylor series of the deformation parameters.[12] The matrix of the elastic constants was constructed from the quadratic coefficients of this expansion according to the method of Shiro and Miyazawa.[21]

On starting the energy minimization, the positions of the hydrogen atoms were adjusted by scaling the C–H bond lengths of the methyl group and benzene ring to 1.038 Å and 1.028 Å, respectively, since the adopted potential parameters were fitted to the crystal structures derived from neutron diffraction in the case of amino acids.[14] The C–O and the C=O bond lengths were also adjusted to be 1.320 and 1.230 Å, respectively, by referring to the work of Umemura and Hayashi on the crystal energy of benzoic acid. This correction is justified by the recent evidence that the carboxylic hydrogen atoms of a wide variety of carboxylic acids in the crystalline state are statistically distributed at room temperature between two positions along the lines of hydrogen bonds.[22,23]

The maximum intermolecular interatomic distance for which the Coulomb interactions were taken into account was 10 Å, and in calculation I, the convergence constant was taken to be 0.20.[16] The summation limit for the van der Waals interaction was taken to be 8 Å.

Results and Discussion

The structure projected down the vertical of the plane of the benzene ring is given in Fig. 1, which shows that the skeleton of the acetoxy group lies approximately on a plane perpendicular to the benzene ring. The labelling of the atoms is given in Fig. 2.

We have found that many of the bond lengths and valence angles calculated from the atomic coordinates reported by Wheatley differ from the newly determined structure significantly. For instance, the C1–C2, C4–C5 and O2–C7 bond lengths deduced from his coordinates are about 0.04 Å shorter than ours. For the C2–O3–C8, O3–C8–O4, O3–C8–C9

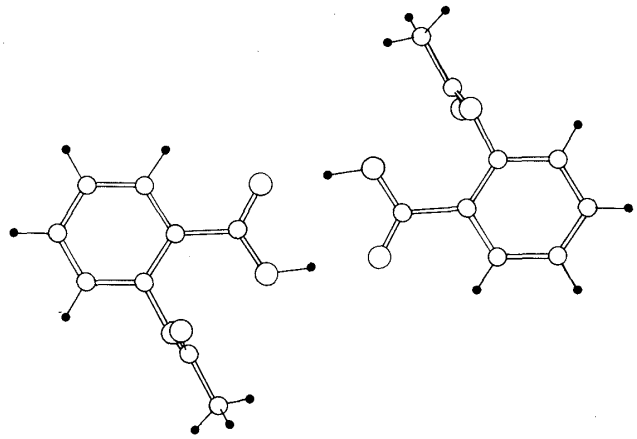

Fig. 1. The Structure of the Hydrogen-Bonded Dimer of Aspirin in the Crystalline State

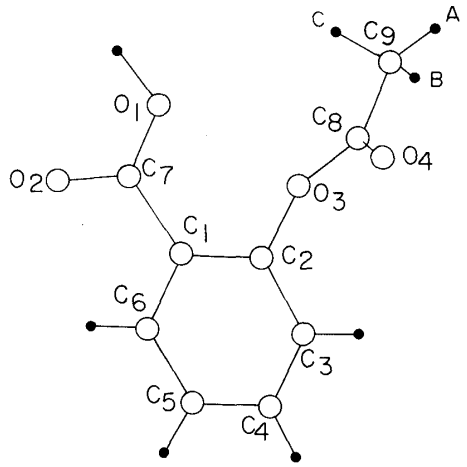

Fig. 2. The Labelling of Atoms of the Aspirin Molecule

TABLE IV. Lattice Energy and Components of $\Delta \boldsymbol{a}^*$ and $\boldsymbol{T}^*_{ex}$ of Aspirin Crystal

	Calculation I	Calculation II
V (kJmol^{-1})	−116.3	−98.3
Δa^* (Å)	−0.372	0.173
Δb^* (Å)	0.472	0.154
Δc^* (Å)	0.617	0.465
$\Delta \beta^*$ (rad)	−0.083	−0.142
T_1^* (Å)	−0.150	−0.479
T_2^* (Å)	0.056	0.124
T_3^* (Å)	0.077	−0.089
R_1^* (rad)	−0.047	0.025
R_2^* (rad)	0.012	−0.001
R_3^* (rad)	0.043	−0.239

and C5–C4–C3 angles, the differences between his structure and ours are larger than 3.2°. Almost the same situation is seen for the valence angles centered on C1, C7 and C9 too. There seem to be some mistakes in Wheatley's table of atomic coordinates since the structure parameters given in his report agree well with ours except for those related to the hydrogen atoms.

The calculated values of the lattice energy and the components of the correction vector $\boldsymbol{T}^*_{ex}$ and $\Delta \boldsymbol{a}^*$ for the initial structure are listed in Table IV, and the elastic constants in Table V. No experimental data on the lattice energy are available at present, but the calculated value seems to be reasonable in comparison with those of salicylic and benzoic acids.[24]

As to the components of $\boldsymbol{T}^*_{ex}$ and $\Delta \boldsymbol{a}^*$, which indicate the direction of the pathway toward a minimum on the potential supersurface, it is difficult to determine which of the calculations I or II gives the better result. Calculation II seems to give smaller deviations from the equilibrium for Δa^*, Δb^* and Δc^*, while calculation I is preferred with respect to $\Delta \beta^*$, T_1^* T_2^* and R_3^*.

As the aspirin crystal is monoclinic, the number of independent elastic constants is thirteen. In the calculation with the structure determined by Wheatly and the same potential parameters as in calculation I (calc. I'' in Table IV), the elastic constants C_{55} and C_{66} were

TABLE V. Elastic Constants of Aspirin Crystal (GNm^{-2})

	Calc. I	Calc. II	Calc. I′	Calc. I″	Obsd.
C_{11}	10.18	8.06	8.44	6.08	10.76
C_{22}	8.14	7.20	6.35	7.96	12.30
C_{33}	9.24	9.86	7.15	5.70	—
C_{44}	3.25	2.70	2.17	2.50	4.57
C_{55}	2.13	2.12	1.26	−0.02	2.72
C_{66}	3.86	4.50	2.87	−1.71	3.77
C_{12}	5.49	6.28	4.50	4.61	5.88
C_{13}	4.50	5.19	3.55	3.31	—
C_{23}	4.56	3.89	3.60	4.66	—
C_{15}	−1.73	−1.95	−1.05	−0.49	−0.03
C_{25}	0.19	−0.15	0.20	0.04	0.64
C_{35}	−0.64	−0.90	−0.25	0.41	—
C_{46}	−0.22	−0.39	−0.15	−0.03	−0.06

TABLE VI. Experimental and Calculated Structure Parameters and Average and Maximum Deviation of Atomic Positions of Aspirin Crystal

		Obsd.		Calc.
Lattice constants	a (Å)	11.430		11.434
	b (Å)	6.591		6.390
	c (Å)	11.395		11.169
	β (°)	95.68		97.70
Volume	(Å^3)	854.23		808.69
Coordinates of centers of masses	x_g (Å)	2.538		2.557
	y_g (Å)	2.623		2.602
	z_g (Å)	0.296		0.223
Eulerian angles	ϕ (°)	−44.886		−44.643
	θ (°)	57.374		54.467
	χ (°)	61.098		60.925
Dev. of atomic pos.	Δr (Å)		Average	0.148
			Max.	0.220

negative, implying that the model is not stable to shearing stress along the *ca* and *ab* planes. The situation was improved by applying the same model potential to the newly determined crystal structure with no adjustment of the bond lengths (calc. I′), and further improvement was achieved by adjusting the C–H, C–O and C=O lengths (calc. I). From a comparison among calculations I″, I′ and I, the calculated values of elastic constants seem to be very sensitive to the assumed molecular geometry. For the structure with the adjusted bond lengths, calculations I and II were both found to give all positive eigenvalues of elastic constants to keep the crystal stable against hydrostatic and shearing stresses. Although all thirteen elastic constants have not yet been measured experimentally, calculation I coincides better with the experimental data obtained from the Brillouin scattering[11] than calculation II. The elastic constant along the *b* axis, C_{22}, is calculated to be smaller than the experimental data, but the other diagonal constants show excellent agreements with the observed values.

The iterative search for the minimum of the model potential by the Newton–Raphson method was repeated until the elements of the correction vectors became less than 0.01 (Å or rad). In this procedure, calculation II failed to converge to any minimum points. The

calculated equilibrium structure after convergence of calculation I ($V = -122.8\,\mathrm{kJmol^{-1}}$) is described in Table VI in terms of the lattice constants, the unit cell volume, the coordinates of the center of mass and the Eulerian angles of the principal axes of inertia of the molecule.

For the sake of comparison, the maximum and the average distances between the calculated and the observed atomic positions are given too. The deviations of the calculated lattice constants from the observed values do not coincide well with the components of $\Delta \boldsymbol{a}^*$ in Table IV because of the presence of the terms higher than quadratic in the potential expansion at the starting point. The difference between the calculated and the observed cell volumes reflects the effect of the thermal expansion correctly. The Eulerian angles in Table VI indicate that the calculated and the experimental orientations of aspirin molecule are very similar to each other. The coordinates of the center of masses show rather good coincidence between the two structures. The average deviation of the atomic positions is not large in comparison with the thermal motions of atoms in usual crystals. Analysis of the infrared and Raman spectra of aspirin crystal based on the same model potential as used in this work are in progress.

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