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Physicochemical Studies of Medicinal Drug Polymorphism. I. Structural Studies of Bromodiethylacetylurea by Thermal and X-Ray Crystal Analyses

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Three crystalline forms of bromodiethylacetylurea (named α, β and γ) were characrerized by thermal analyses. The α→β→γ structural conversion was accompanied with endothermic change: the transition temperature and enthalpy change were 70.7—83.0 °C, $\Delta H = 0.71(5)$ kcal/mol for the α→β transition and 83.0—96.5 °C, $\Delta H = 0.65(4)$ kcal/mol for the β→γ transition, respectively. The γ-type crystal emerged only between 90 and 110 °C. X-Ray analyses were performed for α- and β-type crystals. They have two molecules in the asymmetric unit (molecules A and B for α-type, molecules C and D for β-type). Conformational differences among these molecules were not significant, although the hydrogen bond networks characteristic of the two crystal types may be significant in relation to the bioavailabilities of this drug.

Keywords——X-ray structure determination; thermal analysis; polymorphism; bromodiethylacetylurea; structural conversion

Introduction

Many medicinal drugs such as barbital,[1] bromovalerylurea[2] and cimetidine[3] are well known to have several crystalline forms (polymorphism). Since the crystalline form of a medicinal drug significantly affects its bioavailability,[4,5] information concerning the stereostructural differences among polymorphs should be very helpful in relation to clinical application.[6]

It has been shown by infrared (IR) spectral and X-ray powder diffraction measurements[7,8] that bromodiethylacetylurea has three kinds of crystalline forms (α, β and γ), but the structural differences among these forms are not yet fully clarified. This paper deals with the physicochemical properties of bromodiethylacetylurea polymorphs as characterized by thermal and X-ray structural analyses.

Experimental

Preparation of α- and β-Type Crystals of Bromodiethylacetylurea——α-Type crystals of bromodiethylacetylurea were obtained from methanol or acetone solution by slow evaporation at 20 °C as platelets. Needle crystals of β-type appeared from saturated methanol solution, when the solution was heated to boiling point and then slowly cooled to room temperature (23 °C). These crystals showed a distinct IR spectrum.[7,8]

Crystal densities were measured by the flotation method in the aqueous potassium iodide solution.

Thermal Analysis——The calorimetric changes accompanying structural conversion were measured by using differential scanning calorimetry (DSC) instruments (Rigaku Denki Co.). The DSC profiles were obtained using *ca.* 20 mg of powdered sample, and potassium nitrate was used as a standard for the calibration of enthalpy changes (ΔH). The heating rate was 5 °C/min. The resulting of three measurements were averaged. The values of ΔH were calculated from the weight of the peak area cut out from the chart.

X-Ray Structure Determination and Refinement——The intensities of 3326 (α-type) and 3471 (β-type) independent reflections were obtained by using the θ—2θ scanning technique ($\sin\theta/\lambda < 0.588\,\text{Å}^{-1}$) with graphite-monochromated Cu-K_α radiation. The scanning speed was 4°/min (in θ) and the intensities of three standard reflections for every 100 reflections remained constant, suggesting that no structural deterioration occurred due to X-ray irradiation.

The structures of both types were solved by the direct method using the program MULTAN78.[9] Nonhydrogen atoms were located on the weighted Fourier and the difference Fourier maps. The refinement was carried out by the block-diagonal least-squares method. The weighting scheme in the final least-squares refinement was: for α-type $w = 0.9314$ for $F_O = 0.0$, $w = 1.0$ for $0.0 < F_O < 30.0$, $w = 0.7149$ for $30.0 < F_O < 50.0$ and $w = 0.0887$ for $50.0 < F_O$; for β-type, $w = 0.3513$ for $F_O = 0.0$ and $w = 1.0$ for $0.0 < F_O$.

These calculations were carried out at the Computing Center of Osaka University (ACOS-700 computer) using the UNICS programs.[10]

Results and Discussion

Thermal Behavior of Bromodiethylacetylurea Polymorphs

Figure 1 shows the DSC profiles of α- and β-crystalline forms. In these curves, the endothermic peaks near 118 °C correspond to the respective melting points. The calorimetric changes of α- and β-types were 7.2 (4) and 6.53 (7) kcal/mol, respectively. Because this drug begins to sublime near the melting point, precise measurement of ΔH was difficult.

The peak of β-type at 83.0—96.5 °C represents the enthalpy change accompanying the structural conversion from β- to γ-type ($\Delta H = 0.69$ (2) kcal/mol). In the case of α-crystals, two endothermic peaks appeared at 70.7—83.0 °C and 83.0—96.5 °C and they correspond to the $\alpha \rightarrow \beta$ ($\Delta H = 0.75$ (5) kcal/mol) and $\beta \rightarrow \gamma$ ($\Delta H = 0.68$ (4) kcal/mol) structural changes, respectively.

γ-Type crystals existed only between near 90 and 110 °C, and could not be obtained by cooling from 105 °C to room temperature. This is consistent with the reports of Inoue and Sato[7] and Watanabe.[8] Therefore, the γ-type appears to be a metastable phase which can only exist at higher temperature than 90 °C.

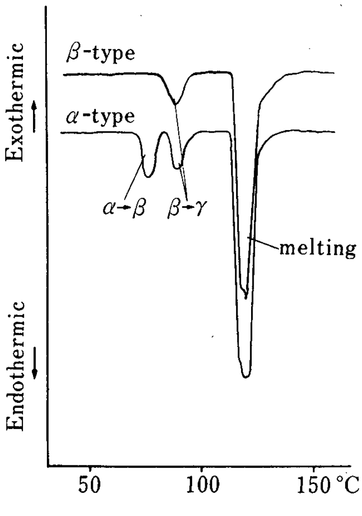


Fig. 1. The DSC Profiles

Upper; β-type, showing two peaks at 90 and 120 °C. Lower; α-type, three peaks at 77, 90 and 120 °C. Peaks at near 120 °C are the melting peaks and the others are phase conversion peaks (indicated in the figure).

Table I. Crystal Data

	α-Type	β-Type
Chemical formula	$C_7H_{13}BrN_2O_2$	$C_7H_{13}BrN_2O_2$
Molecular weight	236.99	236.99
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1/c$
Cell constant		
a (Å)	13.565 (5)	14.910 (4)
b (Å)	20.503 (6)	14.182 (3)
c (Å)	14.100 (3)	10.585 (2)
β (°)	90.0	114.89 (2)
Volume (Å^3)	3921.5 (2)	2030.3 (9)
Z	16	8
D_m (Mg/m^3)	1.596 (1)	1.540 (2)
D_x (Mg/m^3)	1.606	1.561
μ (cm^{-1}) (Cu-K_α)	24.45	24.73
$F(000)$	928	464
Number of reflections ($2° < 2\theta < 128°$)	3326	3471
R-Value	0.067	0.080

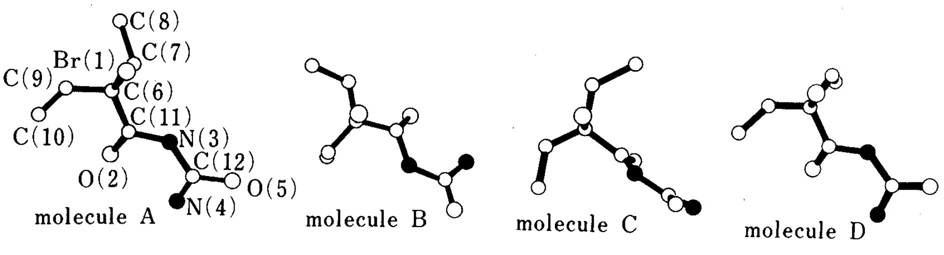


Fig. 2. Molecular Conformations and Nomenclature

All four molecules were numbered in the same manner as illustrated for molecule A.

Crystal Structures of Bromodiethylacetylurea

Crystal data for α- and β-type crystals are listed in Table I. Both types of crystals contain two crystallographically independent molecules in an asymmetric unit (molecules A and B for α-type crystal, molecules C and D for β-type). Nonhydrogen atomic parameters are given in Table II. Molecular conformations and the atomic numbering are shown in Fig. 2. No significant difference among the molecules could be found in the bond lengths and bond angles, but the torsion angles differed, as shown in Table III. For example, the torsion angle around C(6)–C(11) affects the spatial orientation between the ureide group and the diethyl side groups, and the angles of Br(1)–C(6)–C(11)–O(2) are 142.3, −123.2, 164.5 and 133.4° for the molecules A, B, C and D, respectively. These torsion angles reflect the main differences between the conformations of the four molecules, and are related to the rotation of the ureide group. However, it is more important in relation to the properties of the α- and β-crystals to consider the intermolecular interactions in the crystal packing. Figure 3 represents the hydrogen bonding networks observed in crystals, and these parameters and short contacts are summarized in Table IV. Four hydrogen bonds for α-type (N(4)A···O(5)B, N(4)B···O(5)A, N(3)B···O(2)A and N(4)B···O(5)A) and four for β-type (N(4)C···O(5)C, N(4)D···O(5)D, N(4)C···O(5)D and N(4)D···O(5)C) were found, and these networks stabilize the crystal packing. The most significant difference between the two crystals is that in the crystal packing of the β-type there is no hydrogen bond corresponding to the N(3)B···O(2)A

TABLE II. Atomic Coordinates and Thermal Parameters with Their Standard Deviations

Atom	x	y	z	B[a)]
Molecule A				
Br(1)A	0.31000 (4)	0.11857 (2)	0.81330 (3)	2.6 (2)
O(2)A	0.1880 (2)	0.2547 (1)	0.6553 (2)	1.7 (1)
N(3)A	0.1851 (2)	0.1455 (2)	0.6348 (3)	1.2 (1)
N(4)A	0.0568 (3)	0.1902 (2)	0.5467 (3)	2.0 (1)
O(5)A	0.0748 (2)	0.0811 (2)	0.5608 (2)	2.3 (1)
C(6)A	0.3192 (3)	0.1954 (2)	0.7288 (3)	1.4 (2)
C(7)A	0.3373 (3)	0.2559 (2)	0.7890 (3)	2.2 (2)
C(8)A	0.2633 (4)	0.2692 (3)	0.8674 (4)	3.3 (2)
C(9)A	0.4005 (3)	0.1835 (2)	0.6559 (3)	2.0 (2)
C(10)A	0.5048 (3)	0.1790 (4)	0.6958 (4)	3.9 (3)
C(11)A	0.2235 (3)	0.2011 (2)	0.6723 (3)	2.0 (1)
C(12)A	0.1009 (3)	0.1366 (2)	0.5777 (3)	1.3 (1)
Molecule B				
Br(1)B	0.02466 (4)	0.12701 (3)	0.05691 (4)	3.3 (2)
O(2)B	0.2182 (2)	−0.0011 (2)	0.1036 (3)	2.8 (1)
N(3)B	0.2483 (2)	0.1075 (2)	0.1080 (3)	1.6 (1)
N(4)B	0.3872 (3)	0.0571 (2)	0.0425 (3)	2.3 (2)
O(5)B	0.3797 (2)	0.1661 (2)	0.0623 (2)	2.5 (1)
C(6)B	0.0835 (3)	0.0672 (2)	0.1527 (3)	1.5 (1)
C(7)B	0.0842 (3)	0.1025 (2)	0.2468 (3)	2.1 (2)
C(8)B	0.1324 (4)	0.0645 (3)	0.3245 (2)	3.6 (2)
C(9)B	0.0251 (3)	0.0041 (2)	0.1514 (4)	2.3 (2)
C(10)B	−0.0826 (4)	0.0103 (3)	0.1804 (6)	4.9 (3)
C(11)B	0.1903 (3)	0.0539 (2)	0.1177 (3)	1.5 (2)
C(12)B	0.3439 (3)	0.1113 (2)	0.0688 (3)	1.5 (2)
Molecule C				
Br(1)C	0.9085 (1)	0.3104 (1)	0.8666 (1)	6.0 (1)
O(2)C	0.7411 (5)	0.3332 (6)	0.4535 (6)	4.7 (3)
N(3)C	0.7084 (5)	0.3622 (5)	0.6413 (7)	3.4 (3)
N(4)C	0.5839 (5)	0.4348 (5)	0.4472 (6)	3.1 (3)
O(5)C	0.5844 (4)	0.4410 (5)	0.6613 (5)	3.4 (2)
C(6)C	0.8618 (8)	0.2800 (10)	0.6663 (9)	5.7 (5)
C(7)C	0.8578 (10)	0.1876 (10)	0.6407 (11)	7.0 (6)
C(8)C	0.7708 (14)	0.1261 (12)	0.6582 (17)	9.5 (9)
C(9)C	0.9513 (8)	0.3279 (12)	0.6288 (11)	7.0 (6)
C(10)C	0.9580 (12)	0.4378 (16)	0.6391 (21)	11.5 (11)
C(11)C	0.7658 (6)	0.3298 (7)	0.5775 (9)	3.7 (4)
C(12)C	0.6213 (5)	0.4152 (6)	0.5841 (8)	2.8 (3)
Molecule D				
Br(1)D	0.1815 (1)	0.3923 (1)	0.2323 (1)	5.8 (1)
O(2)D	0.1829 (4)	0.2324 (4)	−0.0637 (6)	3.5 (2)
N(3)D	0.1585 (5)	0.1817 (5)	0.1254 (7)	3.0 (3)
N(4)D	0.0704 (5)	0.0820 (5)	−0.0558 (6)	2.4 (2)
O(5)D	0.0649 (5)	0.0708 (4)	0.1544 (6)	3.7 (2)
C(6)D	0.2585 (6)	0.3274 (6)	0.1424 (8)	3.1 (3)
C(7)D	0.2837 (7)	0.3990 (7)	0.0547 (10)	4.4 (14)
C(8)D	0.1955 (10)	0.4552 (8)	−0.0520 (12)	5.9 (5)
C(9)D	0.3518 (7)	0.2901 (8)	0.2635 (9)	4.3 (4)
C(10)D	0.4181 (8)	0.2332 (10)	0.2161 (10)	5.6 (5)
C(11)D	0.1942 (6)	0.2466 (6)	0.0555 (8)	2.8 (3)
C(12)D	0.0946 (5)	0.1104 (5)	0.0742 (8)	2.4 (3)

a) B-Values were calculated with anisotropic temperature factors by using the following equation: $B=4/3(B_{11}\cdot \boldsymbol{a}^2+B_{22}\cdot \boldsymbol{b}^2+B_{33}\cdot \boldsymbol{c}^2+\boldsymbol{a}\cdot \boldsymbol{b}\cdot B_{12}\cdot \cos\gamma+\boldsymbol{a}\cdot \boldsymbol{c}\cdot B_{13}\cdot \cos\beta+\boldsymbol{b}\cdot \boldsymbol{c}\cdot B_{23}\cdot \cos\alpha)$.

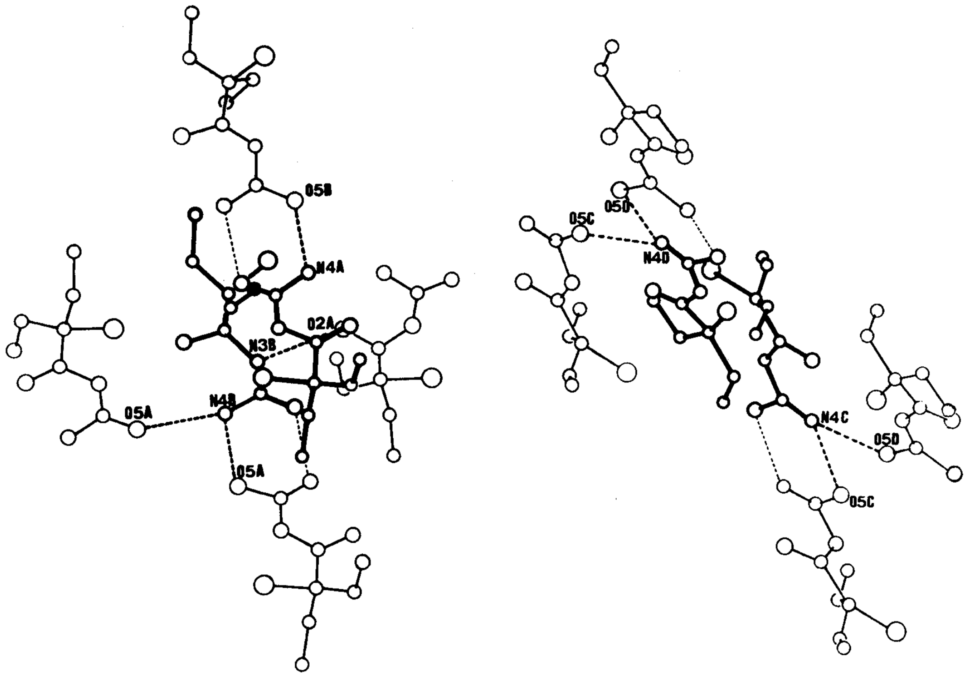
TABLE III. List of Bond Lengths, Bond Angles and Torsion Angles with Their Standard Deviations

	A	B	C	D
Bond lengths (Å)				
Br(1)–C(6)	1.979 (4)	1.992 (4)	1.981 (14)	1.997 (9)
O(2)–C(11)	1.224 (5)	1.206 (6)	1.206 (13)	1.217 (11)
N(3)–C(11)	1.361 (6)	1.360 (5)	1.373 (13)	1.370 (11)
N(3)–C(12)	1.408 (6)	1.412 (6)	1.399 (11)	1.396 (11)
N(4)–C(12)	1.325 (6)	1.311 (6)	1.344 (11)	1.330 (10)
O(5)–C(12)	1.216 (5)	1.226 (5)	1.218 (11)	1.245 (10)
C(6)–C(7)	1.522 (6)	1.511 (6)	1.459 (21)	1.525 (14)
C(6)–C(9)	1.532 (6)	1.518 (6)	1.687 (22)	1.535 (14)
C(6)–C(11)	1.529 (6)	1.554 (6)	1.516 (17)	1.529 (13)
C(7)–C(8)	1.517 (7)	1.495 (8)	1.573 (26)	1.546 (18)
C(9)–C(10)	1.528 (9)	1.523 (10)	1.563 (28)	1.515 (18)
Bond angles (°)				
C(11)–N(3)–C(12)	129.8 (4)	128.0 (4)	128.6 (8)	128.8 (8)
Br(1)–C(6)–C(7)	108.8 (3)	107.6 (3)	112.5 (10)	108.7 (6)
Br(1)–C(6)–C(9)	109.0 (3)	107.9 (3)	102.0 (9)	105.2 (6)
Br(1)–C(6)–C(11)	108.7 (3)	105.4 (3)	112.2 (9)	107.0 (6)
C(7)–C(6)–C(9)	113.0 (4)	115.0 (4)	109.1 (12)	111.7 (8)
C(6)–C(7)–C(8)	116.5 (4)	113.3 (4)	114.5 (14)	115.9 (9)
C(6)–C(9)–C(10)	115.1 (4)	115.2 (5)	114.8 (14)	113.3 (9)
O(2)–C(11)–N(3)	121.8 (4)	123.9 (4)	123.6 (9)	122.9 (8)
O(2)–C(11)–C(6)	120.3 (4)	120.6 (4)	118.0 (10)	121.8 (8)
N(3)–C(12)–N(4)	116.6 (4)	118.4 (4)	117.8 (8)	118.8 (7)
N(3)–C(12)–O(5)	118.0 (4)	116.3 (4)	118.0 (4)	117.9 (7)
N(4)–C(12)–O(5)	125.3 (4)	125.3 (4)	124.1 (8)	123.3 (8)
Torsion angles (°)				
C(12)–N(3)–C(11)–C(6)	−177.6 (4)	−173.0 (4)	175.2 (9)	176.6 (8)
C(12)–N(3)–C(11)–O(2)	−3.7 (7)	9.3 (7)	−9.8 (16)	−9.1 (14)
C(11)–N(3)–C(12)–O(5)	−172.2 (4)	175.7 (4)	−176.3 (9)	−174.0 (8)
C(11)–N(3)–C(12)–N(4)	8.0 (7)	−4.2 (7)	3.5 (14)	7.5 (13)
Br(1)–C(6)–C(7)–C(8)	−55.5 (5)	−176.5 (4)	73.0 (15)	−53.1 (11)
C(9)–C(6)–C(7)–C(8)	−176.7 (4)	63.3 (5)	−174.6 (13)	−168.6 (9)
C(11)–C(6)–C(7)–C(8)	64.4 (5)	−61.6 (5)	−55.2 (17)	65.3 (12)
Br(1)–C(6)–C(9)–C(10)	−65.7 (5)	−63.4 (5)	−65.9 (15)	176.8 (8)
C(7)–C(6)–C(9)–C(10)	55.4 (6)	56.7 (6)	174.9 (15)	−65.5 (12)
C(11)–C(6)–C(9)–C(10)	177.6 (4)	−177.7 (5)	52.2 (17)	61.4 (11)
Br(1)–C(6)–C(11)–O(2)	142.3 (3)	−123.2 (4)	164.5 (8)	133.4 (8)
Br(1)–C(6)–C(11)–N(3)	−43.7 (4)	59.0 (4)	−20.3 (13)	−52.3 (9)
C(7)–C(6)–C(11)–O(2)	22.3 (5)	120.6 (5)	−67.1 (15)	14.1 (12)
C(7)–C(6)–C(11)–N(3)	−163.7 (4)	−57.3 (5)	108.1 (13)	−171.6 (8)
C(9)–C(6)–C(11)–N(3)	73.2 (4)	174.8 (4)	−131.5 (11)	62.1 (10)
C(9)–C(6)–C(11)–O(2)	−100.8 (4)	−7.4 (6)	53.2 (14)	−112.2 (10)

hydrogen bond found in the α-crystal. The intramolecular hydrogen bond (O(2)···N(4): 2.696 (5), 2.724 (6), 2.728 (11) and 2.736 (9) Å for molecule A, B, C and D, respectively) does not affect individual crystal packing or stability.

The Stability of Bromodiethylacetylurea Polymorphs Based on the Thermal and X-Ray Analyses

The molecules A and B in the α-crystals are bound by three N(4)···O(5) type and one N(3)B···O(2)A type hydrogen bonds as shown in Table IV, where the hydrogen bond



(a) (b)

Fig. 3. Intermolecular Hydrogen Bonding System

(a), α-type, (b), β-type. The thick lines and broken lines represent the molecules of the asymmetry unit and hydrogen bonds, respectively. The thin lines represent adjacent molecules.

Table IV. The Intermolecular Hydrogen Bonds and Short Contacts (Less than 3.5 Å) with Their Standard Deviations

Hydrogen bonds Donor	Hydrogen bonds Acceptor	Distance (Å)	Equivalent position of acceptor		
N(4)A	O(5)B	2.984 (5)	$-1/2+x$,	y,	$1/2-z$
N(4)B	O(5)A	2.972 (5)	$1/2+x$,	y,	$1/2-z$
N(3)B	O(2)A	3.014 (5)	x,	$1/2-y$,	$-1/2+z$
N(4)B	O(5)A	2.893 (5)	$1/2-x$,	$-y$,	$-1/2+z$
N(4)C	O(5)C	2.879 (10)	$1-x$,	$1-y$,	$1-z$
N(4)D	O(5)D	2.843 (10)	$-x$,	$-y$,	$-z$
N(4)C	O(5)D	2.992 (10)	$1/2+x$,	$1/2-y$,	z
N(4)D	O(5)C	3.105 (9)	$-1/2+x$,	$1/2-y$,	$1-z$
Short contact (less than 3.5 Å)					
N(3)A	O(2)B	3.267 (6)	$1/2-x$,	$-y$,	$-1/2+z$
O(5)A	O(2)B	3.307 (5)	$1/2-x$,	$-y$,	$-1/2+z$
C(9)A	O(5)B	3.364 (6)	x,	$1/2-y$,	$1/2-z$
C(10)A	N(3)A	3.487 (8)	$1/2+x$,	y,	$3/2-z$
O(2)A	C(7)B	3.496 (6)	x,	$1/2-y$,	$1/2-z$
O(2)A	O(5)B	3.333 (5)	x,	$1/2-y$,	$1/2-z$
C(7)D	N(4)D	3.172 (11)	$1/2-x$,	$1/2+y$,	$-z$
N(3)D	O(2)C	3.172 (11)	$-1/2-x$,	$1/2-y$,	z
N(4)D	C(7)D	3.382 (13)	$1/2-x$,	$-1/2+y$,	$-z$
O(2)C	O(4)C	3.172 (11)	$1/2+x$,	$1/2-y$,	z
O(2)C	O(2)D	3.432 (10)	$1/2+x$,	$1/2-y$,	z
O(5)D	O(2)C	3.432 (10)	$-1/2+x$,	$1/2-y$,	$1-z$

distance of N(3)B···O(2)A (3.014 Å) is longer than the others. On the other hand, the C and D molecules in the β-crystals, are bound to each other by four N(4)···O(5) hydrogen bonds, and consequently the crystal packing is more stable to the thermal atomic motions caused by increasing temperature.

The results of thermal analysis showed that the phase transition temperature of the β-crystals is higher than that the α-crystals, that is, the β-type crystal structure is thermodynamically more stable than that of α-type. At 77 °C, α-type crystals are converted to β-type due to the breakage of the N(3)B···O(2)A hydrogen bond and the formation of the N(4)A···O(5)B hydrogen bond, and similar changes presumable occur in the $\beta \rightarrow \gamma$ structural conversion. Therefore, the endothermic energies accompanying the structural conversions of $\alpha \rightarrow \beta$ or $\beta \rightarrow \gamma$ may reflect the energy of reconstruction of the crystal packing.

References

1) J. Clements and D. Stanski, *Can. J. Sci.*, **6**, 9 (1971).
2) A. Watanabe, *Yakugaku Zasshi*, **58**, 145 (1938).
3) M. Schibata, H. Kokubo, K. Morimoto, K. Morisaka, T. Ishida, and M. Inoue, *J. Pharm. Sci.*, **72**, 1436 (1983).
4) J. Haleblian and W. McCorne, *J. Pharm. Sci.*, **58**, 911 (1969).
5) J. Haleblian, *J. Pharm. Sci.*, **60**, 1269 (1975).
6) F. Sjoquist, *Biochem. Soc. Trans.*, **12**, 101 (1984).
7) M. Inoue and K. Sato, *Yakugaku Zasshi*, **81**, 615 (1961).
8) A. Watanabe, *Yakugaku Zasshi*, **60**, 416 (1940).
9) P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Decleq, and M. M. Woolfson, "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data, MULTAN 78," University of York, England, 1978.
10) "The Universal Crystallographic Computing System," Library of Programs, Computing Center of Osaka University, Osaka, 1979.