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The Crystal Structure of Tegafur (β-Form): Comparison with α-Form

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The crystal structure of the second polymorphic form of the title compound (α-form: *Chem. Pharm. Bull.*, **30**, 2629 (1982)) has been determined by X-ray diffraction analysis of a single crystal. The crystal of the β-form, $C_8H_9FN_2O_3$, is monoclinic, space group $P2_1/n$, with $a=11.891$ (5), $b=14.556$ (2), $c=5.062$ (1) Å, $\beta=99.05$ (2)°, $U=865.3$ (4) Å^3, $M_r=200.17$, $Z=4$; $D_c=1.54$, $D_m=1.54\,\mathrm{gcm}^{-3}$, $F(000)=416$, λ(Mo $K\alpha$)$=0.7107$ Å, $\mu=1.433\,\mathrm{cm}^{-1}$. The structure was solved by the direct method using the MULTAN 78 program. Refinement by the full-matrix least-squares method gave a final R factor of 0.055 (1669 independent reflections). Bond lengths and angles agree well with those of both molecules in the α-form. The molecular conformation is very similar to one of those in the α-form. The cyclic dimer structure of the β-form is different from that of the α-form.

Keywords——tegafur; polymorphism; X-ray analysis; molecular structure; hydrogen bond; crystal structure

5-Fluoro-1-(tetrahydro-2-furyl)uracil, known as ftorafur or tegafur, is a masked compound of 5-fluorouracil and is widely used in the treatment of various cancers. Nakajima and co-workers suggested the existence of polymorphic forms.[1] We have been studying the polymorphism of tegafur, and have so far found four polymorphic forms (α, β, γ- and δ-forms)[2] and reported the crystal structure of the α-form.[3] The α- and β-forms were obtained by crystallization of commercial tegafur from acetone and methanol, respectively. This paper deals with the crystal structure determination of the β-form of tegafur in comparison with the α-form.

Experimental

Materials——Colorless prismatic single crystals of tegafur (β-form) were obtained by seeding a saturated methanol solution with microcrystals obtained from methanol solution at room temperature. A crystal of approximate size $0.75\times0.50\times1.375$ mm was employed for diffraction data collection.

Diffraction Data Collection——Approximate cell dimensions and space group information were obtained from oscillation and Weissenberg photographs. Accurate cell dimensions were subsequently refined from measurement of the 2θ values of 22 high-angle reflections on a Rigaku four-circle diffractometer.

The crystal data are summarized in Table I. Space group $P2_1/n$ was confirmed by the structure analysis. Intensity data were collected on a Rigaku automated four-circle diffractometer with a graphite-monochromated Mo $K\alpha$ radiation at 20 °C. The intensities obtained were corrected for Lorentz and polarization factors but not for absorption. A periodic check on the intensities of three standard reflections [(200), (020), (011)] showed that there was no crystal decomposition during data collection. A total of 2174 reflections were measured by the ω–2θ scan technique in the range of $3°<2\theta<55°$, using a scan speed of 2 °/min, and among them, 1669 independent reflections with $F>3\sigma(F)$ were used in the calculations.

Structure Determination and Refinement——The structure was solved by the direct method with the MULTAN 78[4] program. The E-maps with the highest combined figure of merit (CFOM) calculated from 300 reflections with

TABLE I. Crystal Data of Tegafur (β-Form)

Monoclinic	$C_8H_9FN_2O_3$
Space group $P2_1/n$	$M_r=200.17$
$a=11.891$ (5) Å	$F(000)=416$
$b=14.556$ (2)	$Z=4$
$c=5.062$ (1)	μ(Mo $K\alpha$) $=1.433\,cm^{-1}$
$\beta=99.05$ (2)°	λ(Mo $K\alpha$) $=0.7107$ Å
$V=865.3$ (4) Å^3	$D_c=1.54\,gcm^{-3}$
	$D_m=1.54$

TABLE II. Positional Parameters ($\times 10^4$ for Non-hydrogen Atoms, $\times 10^3$ for H Atoms) and Equivalent Isotropic (Non-hydrogen Atoms) and Isotropic (H Atoms) Thermal Parameters (Å^2) with e.s.d.'s in Parentheses (β-Form)

	x	y	z	B_{eq}[a] or B_{iso}		x	y	z	B_{eq}[a] or B_{iso}
N(1)	4779 (2)	1968 (2)	3809 (4)	2.92	C(8)	3961 (3)	3742 (2)	−62 (5)	3.74
C(1)	5515 (2)	1588 (2)	5909 (5)	3.04	O(3)	4492 (2)	2850 (1)	−137 (3)	3.67
O(1)	6501 (2)	1831 (2)	6465 (4)	4.19	H(N2)	549 (3)	59 (2)	845 (7)	2.92
N(2)	5060 (2)	904 (2)	7285 (4)	3.19	H(C4)	319 (2)	212 (2)	212 (5)	1.32
C(2)	3943 (2)	622 (2)	6973 (5)	3.25	H(C5)	600 (2)	248 (2)	190 (5)	0.63
O(2)	3619 (2)	18 (2)	8346 (4)	4.58	H(C61)	556 (3)	351 (2)	567 (7)	2.70
C(3)	3247 (2)	1103 (2)	4840 (5)	3.39	H(C62)	591 (2)	399 (2)	314 (6)	1.78
F	2132 (1)	876 (1)	4405 (4)	5.31	H(C71)	356 (2)	376 (2)	372 (5)	1.36
C(4)	3649 (2)	1733 (2)	3360 (5)	3.13	H(C72)	421 (2)	476 (2)	301 (5)	1.32
C(5)	5255 (2)	2707 (2)	2257 (5)	3.17	H(C81)	314 (3)	368 (2)	−82 (6)	2.23
C(6)	5345 (2)	3604 (2)	3765 (5)	3.51	H(C82)	436 (3)	422 (2)	−110 (6)	2.42
C(7)	4192 (3)	4037 (2)	2847 (5)	3.73					

a) B_{eq} defined according to Hamilton (1959).[7]

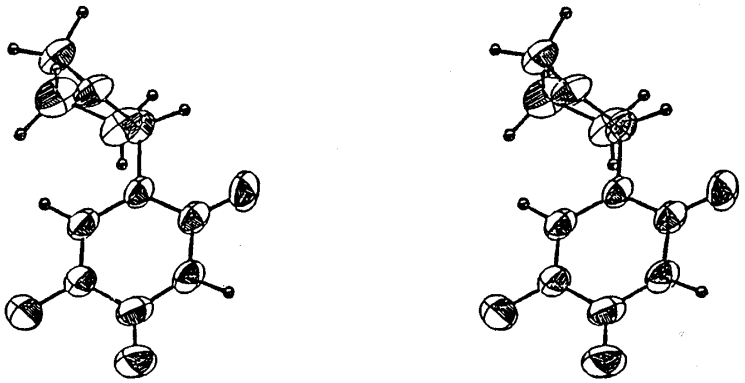
$E>1.00$ revealed the positions of the non-hydrogen atoms other than C(8), C(3), which were determined on the subsequent difference map. In the initial stages, a block-diagonal least-squares method, computed on a PANAFACOM U-1300 mini computer, was used with isotropic temperature factors of 3.5 Å^2 for all non-hydrogen atoms. The R factor converged to 0.154. Further refinement with anisotropic temperature factors for all non-hydrogen atoms reduced R to 0.093. The published atomic scattering factors were used.[5] The H atoms were calculated and then geometrically confirmed in a difference Fourier synthesis. Refining the non-hydrogen atoms anisotropically and the H atoms isotropically gave an R value of 0.059. In the final stages, full-matrix least-squares refinement,[6] performed on HITAC M-200H computers at the Computer Centre of the University of Tokyo, led to a final R value of 0.055 and $R_w=(\sum w[|F_o|-|F_c|]^2/\sum w|F_o|^2)^{1/2}=0.051$. A final difference map showed no peak larger than 0.1 eÅ^{-3}. The final atomic positional parameters and thermal parameters for all the atoms are listed in Table II.

Results and Discussion

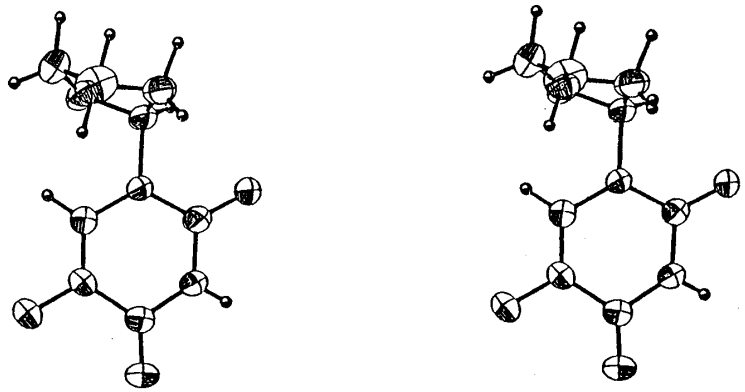
With regard to the crystal shapes, the crystals of the β-form differ entirely from those of the α-form. Crystals of the α-form were colorless pillar-shaped crystals and those of the β-form were prismatic crystals.

The crystal of the α-form consists of two conformationally different molecules, A and B. Figure 1 shows stereoscopic views of the molecules (α- and β-forms).

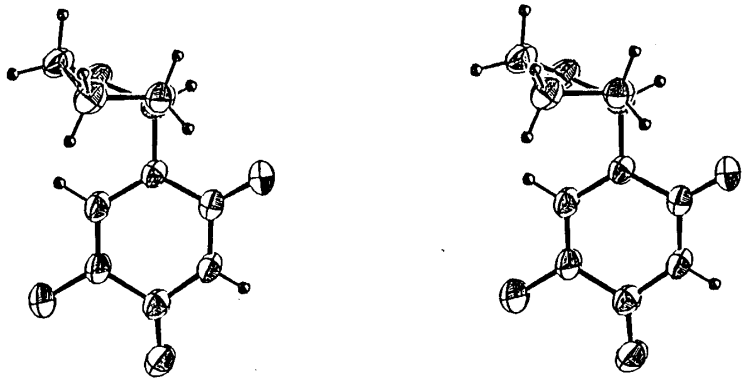
The bond lengths and bond angles of the β-form involving the non-hydrogen atoms, together with the atomic numbering, are indicated in Fig. 2. These values are reasonable. The C–H and N–H bond lengths were from 0.85 (3) to 1.06 (3) Å. With regard to bond lengths and bond angles, there is little difference in these values among molecule A, molecule B (α-form) and the β-form molecule. Selected torsion angles of the molecules (α- and β-forms) are listed



(1) molecule A in α-form



(2) molecule B in α-form



(3) β-form

Fig. 1. ORTEP (Johnson, 1965)[8] Drawings of the Tegafur Molecules in the α- and β-Forms

Ellipsoids represent 50% probability distribution. (1) molecule A in α-form; (2) molecule B in α-form; (3) β-form.

in Table III. In the α-form, torsion angles, C(4)–N(1)–C(5)–O(3), are significantly different in the two molecules (52.6 (6) °; in molecule A, −17.3 (7) °; in molecule B). The corresponding torsion angle in the β-form is very similar to that in molecule B (α-form). Therefore, the conformation of the β-form is consistent with that of molecule B of the α-form. The six-membered (pyrimidine) ring systems in molecule A and molecule B (α-form) are planar, but that in the β-form is not, as shown in Table IV.

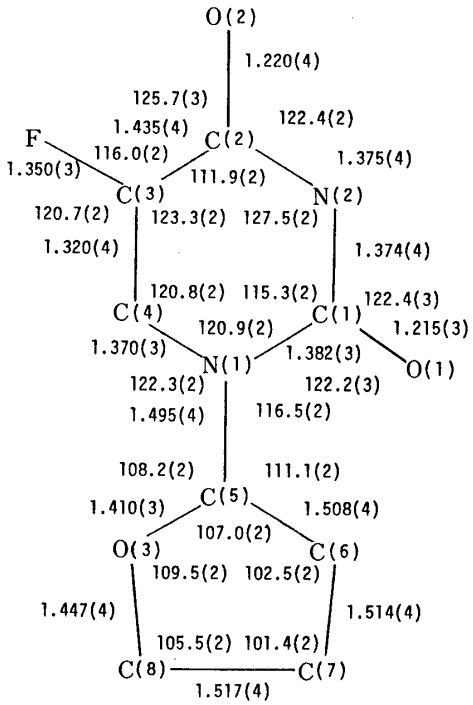


Fig. 2. Bond Lengths (Å) and Bond Angles (°) of Tegafur (β-Form)

TABLE III. Torsion Angles (°)[9]

	α-Form		β-Form
	(A)	(B)	
C(4)–N(1)–C(5)–C(6)	−63.7 (7)	99.4 (6)	97.1 (3)
C(4)–N(1)–C(5)–O(3)	52.6 (6)	−17.3 (7)	−20.0 (3)
N(1)–C(5)–O(3)–C(8)	−135.5 (5)	107.9 (5)	111.3 (2)
N(1)–C(5)–C(6)–C(7)	108.1 (5)	−86.2 (5)	−89.0 (3)
C(6)–C(5)–O(3)–C(8)	−14.1 (6)	−12.2 (6)	−8.5 (3)
O(3)–C(5)–C(6)–C(7)	−8.8 (6)	31.3 (6)	28.9 (3)
C(5)–C(6)–C(7)–C(8)	26.5 (6)	−36.9 (5)	−36.8 (3)
C(6)–C(7)–C(8)–O(3)	−35.6 (6)	30.6 (6)	32.6 (3)
C(7)–C(8)–O(3)–C(5)	31.8 (6)	−12.0 (6)	−15.6 (3)

TABLE IV. Least-Squares Planes and Deviations (Å) of Atoms from Them and Dihedral Angles (°) for the α- and β-Forms

α-Form

Molecule A

Plane (1): $0.810(1)x+0.410\ (1)y-0.550\ (1)z=-1.442\ (8)$

N(1) 0.012 (2), C(1) −0.009 (3), N(2) −0.007 (2), C(2) 0.020 (3), C(3) −0.009 (3), C(4) −0.012 (3), O[a](1) −0.022 (5), O[a](2) 0.059 (5), F[a] −0.031 (5), C[a](5) 0.054 (5)

Plane (2): $0.514\ (2)x-0.468\ (2)y+0.565\ (1)z=0.999\ (14)$

C(5) −0.049 (2), C(6) −0.094 (3), C(7) 0.233 (3), C(8) −0.217 (2), O(3) 0.076 (1), N[a](1) 1.125 (5)

Molecule B

Plane (3): $0.795\ (1)x+0.077\ (1)y+0.540\ (1)z=7.499\ (12)$

N(1) −0.006 (1), C(1) 0.003 (3), N(2) 0.006 (2), C(2) −0.012 (2), C(3) 0.005 (3), C(4) 0.007 (2), O[a](1) 0.023 (5), O[a](2) −0.047 (5), F[a] 0.009 (5), C[a](5) −0.084 (5)

Plane (4): $-0.137\ (2)x+0.829\ (1)y+0.557\ (2)z=11.747\ (17)$

C(5) −0.108 (2), C(6) 0.238 (3), C(7) −0.237 (3), C(8) 0.109 (2), O(3) −0.001 (1), N[a](1) −1.522 (4)

β-Form

Plane (5): $-0.313\ (1)x+0.703\ (1)y+0.680\ (1)z=1.573\ (7)$

N(1) −0.025 (2), C(1) 0.035 (2), N(2) −0.022 (2), C(2) −0.003 (2), C(3) 0.014 (2), C(4) 0.000 (2), O[a](1) 0.108 (4), O[a](2) −0.028 (5), F[a] 0.047 (4), C[a](5) 0.020 (5)

Plane (6): $0.740\ (1)x+0.494\ (1)y-0.567\ (1)z=6.036\ (6)$

C(5) −0.115 (2), C(6) 0.177 (2), C(7) −0.262 (2), C(8) 0.158 (3), O(3) 0.005 (1), N[a](1) −1.511 (4)

Dihedral angles

(1) ∧ (2): 94.3 (1) (1) ∧ (3): 71.6 (1) (1) ∧ (4): 97.0 (1)
(2) ∧ (3): 33.7 (1) (2) ∧ (4): 104.0 (1) (3) ∧ (4): 82.3 (1)
(5) ∧ (6): 100.1 (1)

The planes are expressed by $Lx+My+Nz=D$ in Å. *a*) Atoms not included the plane calculations.

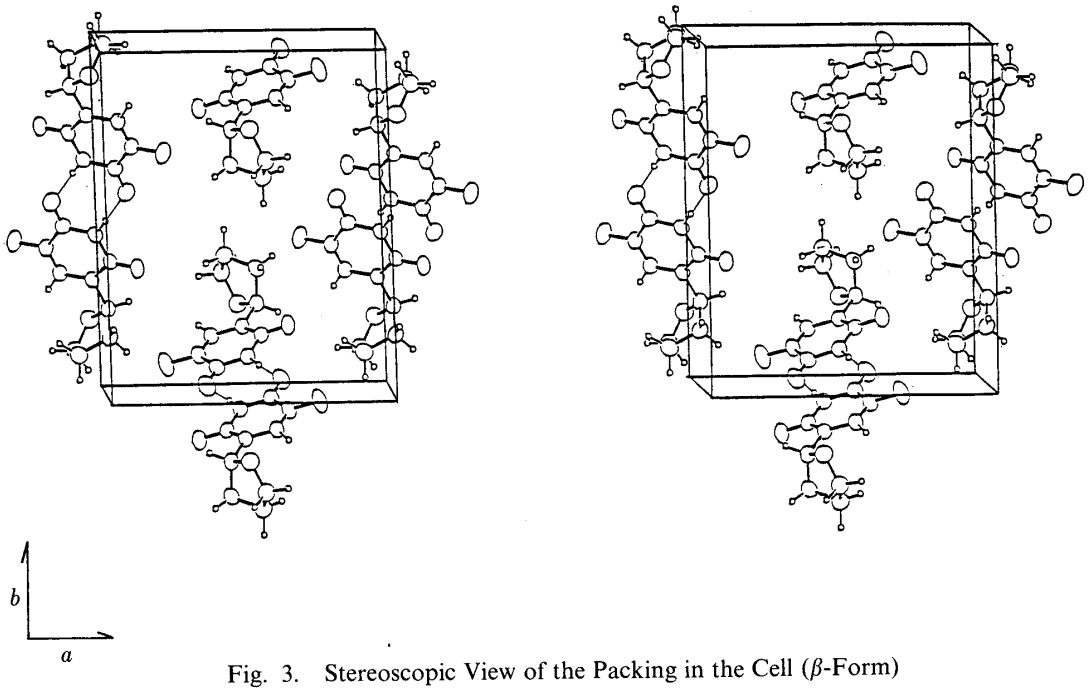


Fig. 3. Stereoscopic View of the Packing in the Cell (β-Form)

Intermolecular lines indicate hydrogen bonds.

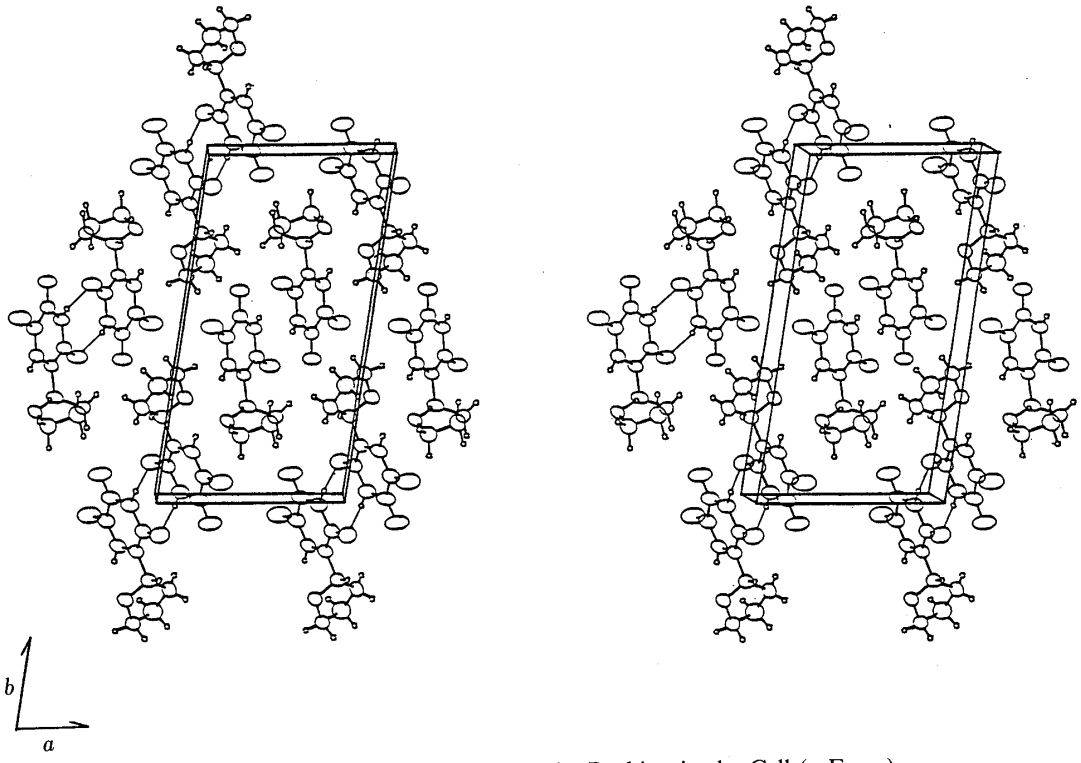


Fig. 4. Stereoscopic View of the Packing in the Cell (α-Form)

Intermolecular lines indicate hydrogen bonds.

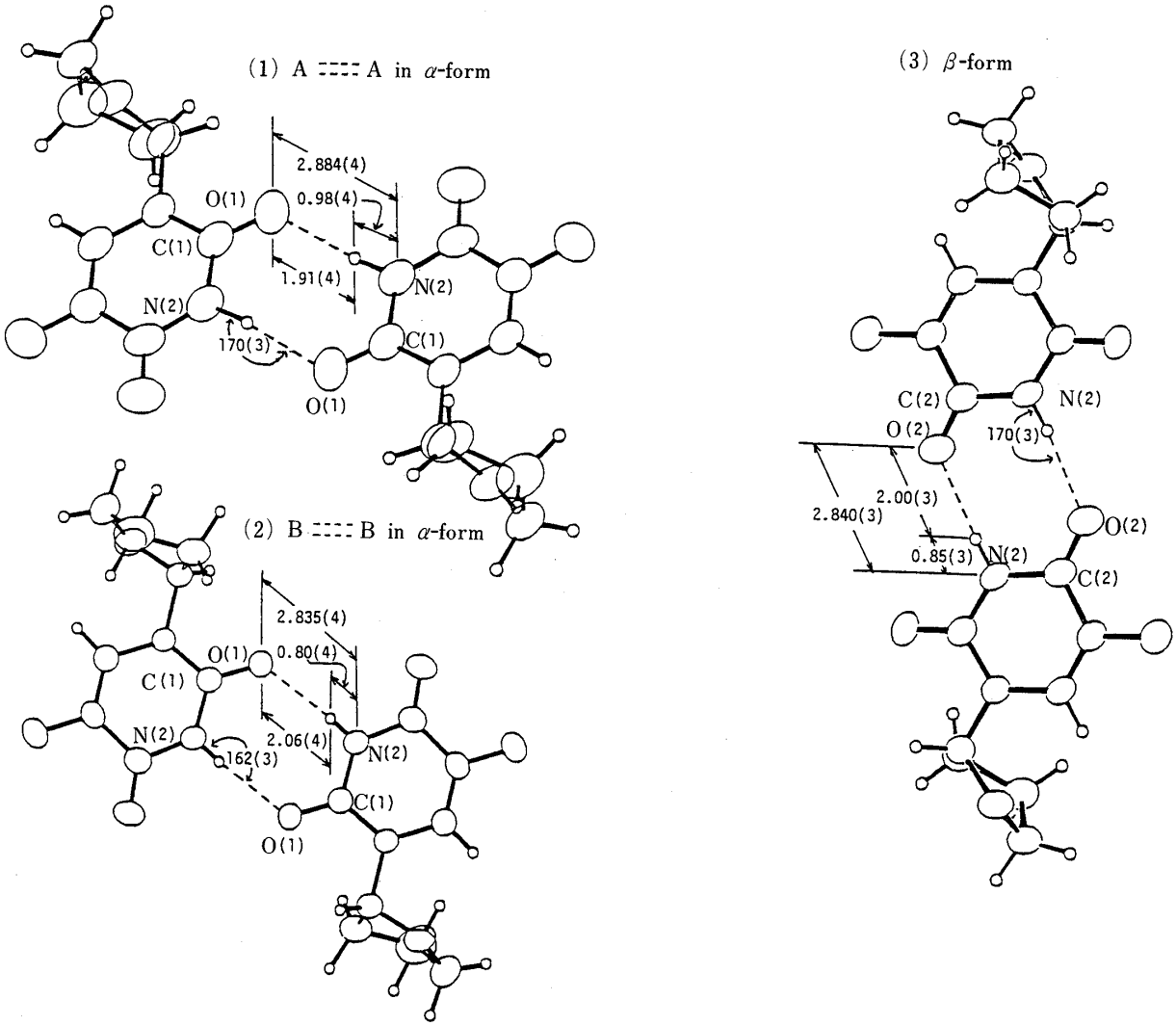


Fig. 5. Intermolecular Hydrogen Bond Systems for α- and β-Forms
(1) molecule A to A in the α-form; (2) molecule B to B in the α-form; (3) β-form.

The packing of the β-form is shown in Fig. 3; it differs significantly from the packing of the α-form (Fig. 4). The distances and angles of intermolecular hydrogen bonds are shown in Fig. 5. Cyclic dimer structures are formed by intermolecular hydrogen bonding for both the α-form (molecule A to A and B to B) and the β-form. However, the hydrogen bond systems are entirely different between the α- and β-forms. In the α-form, N(2) is hydrogen-bonded to O(1) of the adjacent enantiomeric molecule: for example, N(2)–H in molecule A and molecule B of *S*-configuration of tegafur are hydrogen-bonded to O(1) in molecule A and molecule B of *R*-configuration, respectively. In the β-form, on the other hand, N(2) is hydrogen-bonded to O(2) of the adjacent enantiomeric molecule: N(2)–H in the molecule of *S*-configuration is hydrogen-bonded to O(2) in the molecule of *R*-configuration, and *vice versa*. As mentioned above, it is clear that the difference of hydrogen bond systems between α- and β-forms has a great influence on the packing of these two forms. Intermolecular contacts (except for hydrogen bonds) are normal.

References and Notes

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