Intermolecular Interactions of Fluorine Atoms in the Crystal of 1,3-Dimethyl-5-fluorouracil and Its Mixed Crystal with 1,3-Dimethyluracil

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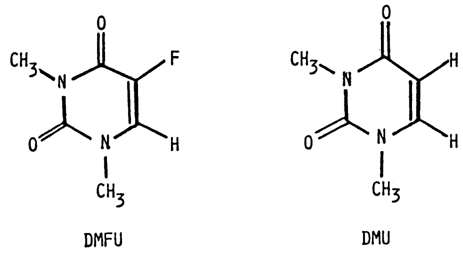
(Received June 20, 1988)

A crystal of 1,3-dimethyl-5-fluorouracil can be used to solve large amounts of 1,3-dimethyluracil as a solid-solution crystal. The crystal structure has been determined by an X-ray method. The planar molecules are arranged in a parallel sheet, and the molecules within the same sheet interact with each other through short CH···O and CH···F contacts. The short intermolecular C···F distance is 2.999(6) Å. The stability of a mixed crystal could be explained in terms of intermolecular interactions around the fluorine atom.

A mixed crystal of organic compounds is generally formed in the case that two component molecules have similar sizes and shapes.[1] On the other hand, the similarity of the atomic sizes between a fluorine atom and a hydrogen atom is one of the important characteristics for fluorine-substitution effects.[2] Thus, a rigid organic compound and its fluorine substituent have a high possibility to form a mixed crystal. We therefore tried to form a mixed crystal between 1,3-dimethyluracil (DMU) and 1,3-dimethyl-5-fluorouracil (DNFU), and obtained fairly stable mixed crystals over a wide range of their mixing ratios. The DMU and DMFU compounds were obtained by methylations of uracil and 5-fluorouracil. The 5-fluorouracil is a well-known antitumor-active agent, and its fluorine-substitution effects have received special attention.[2] The crystal structure of DMU had already been reported by Banerjee et al.[3] However, the crystal structure of DMFU was unknown, and the mixed crystal was isomorphic to the DMFU crystal. Thus, the present X-ray analyses of the DMFU and mixed crystals were performed in order to study the fluorine-substitution effects in the mixed crystals.



Scheme 1.

Experimental

Structure Determination of DMFU. The colorless single crystals of DMFU were obtained from an ethanol solution and a crystal (0.1×0.3×0.3 mm) was mounted on a Rigaku AFC-5RU diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ=1.54178 Å). The crystal data were $C_6H_7N_2O_2F$, M_r=158.13, orthorhombic, $P2_12_12_1$, a=6.605(2), b=8.455(2), c=12.621(2) Å, V=704.8 Å^3, Z=4, D_x=1.490 Mg m^{-3}. Intensity data of 638 reflections were collected within $2\theta<120°$ (h 0—6, k 0—8, l 0—14) in a 2θ-ω scan mode with a scan width of $0.8°+0.5°\tan\theta$ and scan speed 2° ω/min. The intensity fluctuation during data collection was less than 2% for three standard reflections measured at every 56 reflections. Intensities were corrected for Lorentz and polarization factors, but no absorption correction was applied (μ=11.54 cm^{-1}). The structure was solved by MULTAN78[4] and refined by a full-matrix least-squares method using a modified version of the program ORFLS.[5] The minimized quantity was $\sum w(|F_o|-k|F_c|)^2$, where k is a scale factor and w is a weight equal to $[\sigma(F_o)+(0.023\ F_o)^2]^{-1}$. All hydrogen atoms were located on a difference Fourier map. The refinement of C, N, O and F atoms with anisotropic temperature factors and of H atoms with isotropic temperature factors converged an R value to 0.047 (wR=0.057) for 541 unique reflections with $F_o>2\sigma(F_o)$, in which (200) reflection was omitted due to a large extinction effect.

Mixed Crystal Formed between DMFU and DMU. Condensed ethanol solutions of DMFU-DMU mixtures with 1 : 1, 2 : 3, 1 : 2, and 1 : 5 molar ratios for DMFU : DMU were prepared at room temperature (27 °C). Transparent columner crystals were obtained by cooling the solution in a refringerator (5 °C) for a few days. The HPLC analyses using a Shimadzu LC-3A apparatus equipped with an SPD-2A UV detector showed that the molar content of DMU in the obtained crystals were 0.36, 0.50, 0.61, and 0.77, corresponding to the above-mentioned solutions. Preliminary microscopic and X-ray photographic studies indicated that the mixed crystals were isomorphic to the DMFU crystal. The mixed crystal obtained from a 1 : 1 DMFU : DMU solution was subjected to a single-crystal X-ray analysis. The crystal size was 0.3×0.3×0.3 mm, and the unit cell dimensions were a=6.634(1), b=8.439(1), and c=12.530(1) Å, V=703.6 Å^3. The calculated crystal density was 1.425 Mg m^{-3} for Z=4. Data collections and structure refinements were performed in the same way as in the case of the DMFU crystal. Intensity data of 652 reflections (h 0—6, k 0—8, l 0—14) were collected. Disorders of the F(5) and H(5) atoms were assumed in the structure, and an occupancy of 0.6 was assigned for the F(5) atom. The disordered structre was refined to R=0.075 (wR=0.125) for 540 reflections with $F_o>3\sigma(F_o)$.

The atomic scattering factors used for all atoms were obtained from the International Table for X-ray Crystallography.[6] All computations were undertaken on a FACOM M382 in the Data Processing Center of Kyoto University, using the program KPPXRAY.[7]

Results and Discussion

Molecular Structure of DMFU. The atomic coordinates and thermal parameters for nonhydrogen atoms are listed in Tables 1 and 2.[8] A perspective view of the DMFU molecule with the atomic numbering is given in Fig. 1. The molecule is planar within 0.04 Å, except for the hydrogen atoms of the methyl groups. Bond distances and bond angles, except for the C(4)-C(5)-C(6) angle (Table 3), agree well with those of the usual uracil derivatives.[9] The C(5)-F(5) bond distance of 1.348(3) Å is close to the usual values, but the C(4)-C(5)-C(6) bond angle of 123.4(3)° is significantly larger than the average value of 120.7° for those of other uracil derivatives. A similar trend regarding such a large bond angle has been observed in several compounds which have a conjugated ring substituted with a fluorine atom, e.g. fluorobenzens[10] and *m*-, *o*-, *p*-fluorobenzoates.[11–13]

Table 1. Atomic Coordinates and Temperature Factors of DMFU (Estimated Standard Deviations in Parentheses)

Atom	x	y	z	B_{eq}/Å^{2} a)
F(5)	0.2536(11)	0.2097(3)	0.3405(1)	6.62
C(1)	0.2545(21)	0.6354(5)	0.5865(5)	6.36
C(2)	0.2488(15)	0.3629(4)	0.6489(2)	4.08
C(3)	0.2545(21)	0.0876(6)	0.7109(4)	6.29
C(4)	0.2476(13)	0.1412(4)	0.5214(3)	4.22
C(5)	0.2494(15)	0.2600(4)	0.4418(2)	4.40
C(6)	0.2504(16)	0.4126(4)	0.4628(2)	4.13
N(1)	0.2518(15)	0.4652(3)	0.5655(2)	4.19
N(3)	0.2464(11)	0.2036(3)	0.6238(2)	4.08
O(2)	0.2467(14)	0.4090(3)	0.7401(2)	6.07
O(4)	0.2490(16)	−0.0007(3)	0.5049(2)	6.30

a) $B_{eq}=(4/3)(\beta_{11}a^2+\beta_{22}b^2+\beta_{33}c^2)$.

Table 2. Atomic Coordinates and Temperature Factors of DMFU-DMU Meixed Crystal (Estimated Standard Deviations in Parentheses)

Atom	x	y	z	B_{eq}/Å^{2} a)
F(5)	0.2547(18)	0.2069(7)	0.3383(4)	7.21
C(1)	0.2525(18)	0.6319(8)	0.5830(7)	7.66
C(2)	0.2459(14)	0.3609(6)	0.6450(3)	4.42
C(3)	0.2504(20)	0.0854(8)	0.7080(6)	6.89
C(4)	0.2483(14)	0.1390(7)	0.5166(5)	5.08
C(5)	0.2523(12)	0.2556(7)	0.4364(4)	5.08
C(6)	0.2477(12)	0.4079(8)	0.4582(4)	4.90
N(1)	0.2453(11)	0.4614(5)	0.5607(3)	4.71
N(3)	0.2498(11)	0.2005(6)	0.6195(4)	4.66
O(2)	0.2510(13)	0.4056(6)	0.7367(3)	7.29
O(4)	0.2558(15)	−0.0043(5)	0.5010(4)	7.20

a) $B_{eq}=(4/3)(\beta_{11}a^2+\beta_{22}b^2+\beta_{33}c^2)$.

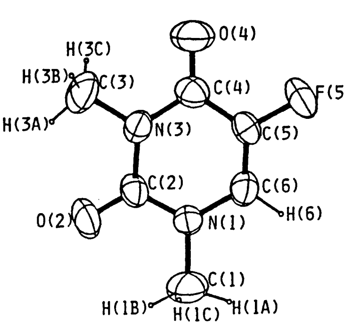


Fig. 1. The molecular structure of DMFU with the numbering scheme.

Table 3. Bond Distances and Bond Angles of DMFU and DMFU-DMU Mixed Crystals (Estimated Standard Deviations in Parentheses)

Bond distance (l/Å)	DMFU	Mixed
F(5)-C(5)	1.348(3)	1.296(7)
C(1)-N(1)	1.463(5)	1.467(8)
C(2)-N(1)	1.363(4)	1.355(6)
C(2)-N(3)	1.384(4)	1.391(7)
C(2)-O(2)	1.215(4)	1.210(6)
C(3)-N(3)	1.474(6)	1.474(9)
C(4)-C(5)	1.421(5)	1.407(8)
C(4)-N(3)	1.396(5)	1.390(8)
C(4)-O(4)	1.218(4)	1.226(7)
C(5)-C(6)	1.317(5)	1.314(9)
C(6)-N(1)	1.370(4)	1.361(6)
Bond angle (ϕ/°)	**DMFU**	**Mixed**
N(1)-C(2)-N(3)	116.2(2)	115.5(4)
N(1)-C(2)-O(2)	121.9(3)	123.1(5)
N(3)-C(2)-O(2)	121.9(3)	121.4(5)
C(5)-C(4)-N(3)	112.8(3)	113.7(5)
C(5)-C(4)-O(4)	125.1(3)	125.1(6)
N(3)-C(4)-O(4)	122.1(3)	121.1(6)
F(5)-C(5)-C(4)	116.6(3)	117.1(6)
F(5)-C(5)-C(6)	120.0(3)	120.5(5)
C(4)-C(5)-C(6)	123.4(3)	122.4(5)
C(5)-C(6)-N(1)	120.5(3)	121.4(5)
C(1)-N(1)-C(2)	119.0(3)	117.7(5)
C(1)-N(1)-C(6)	119.4(3)	120.3(5)
C(2)-N(1)-C(6)	121.6(3)	121.9(5)
C(2)-N(3)-C(3)	118.5(3)	117.9(5)
C(2)-N(3)-C(4)	125.4(3)	125.2(5)
C(3)-N(3)-C(4)	116.0(3)	116.9(5)

Molecular Packing of DMFU. The planar DMFU molecules form a sheet parallel to the *bc* plane. Such sheets cross the *a*-axis at $a=1/4$ and 3/4 with the interplaner distance of 3.3 Å. The projection of the molecular stacking along the *a*-axis is shown in Fig. 2. The molecules related by the 2_1-axis along the *a*-axis are close to each other, the short van der Waals distances being 3.32(1) Å between C(4) and C(6), 3.33(1) Å between C(2) and F(5), 3.37(1) Å between N(3) and F(5), and 3.40(1) Å between N(3) and C(5). The molecular stacking pattern is different from those of other uracil crystals. However, the molecular overlapping, such as the fluorine atom which lies near the adjacent uracil ring, resembles those observed in purine and haloganated pyrimidine complexes.[14] This type of molecular stacking may be favorable for dipole-induced dipole interactions between the fluorine atom and the conjugated ring.

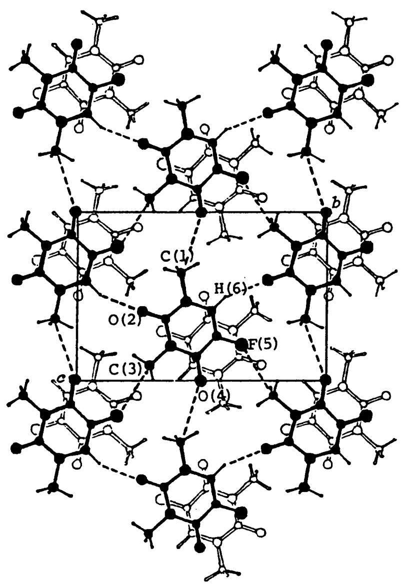


Fig. 2. Projection of the crystal structure viewed along the *a*-axis.

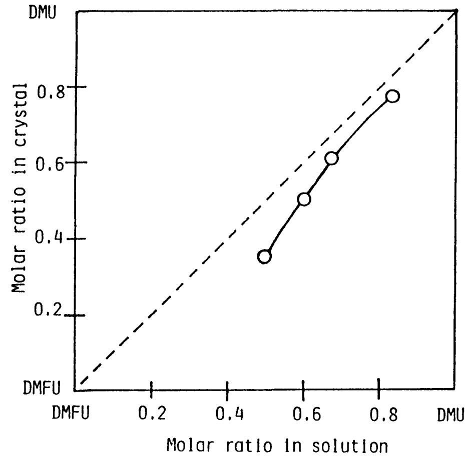


Fig. 3. Plots of the molar ratios in the prepared solutions and in the crystals.

CH ··· O Hydrogen Bonds. As shown in Fig. 2, one DMFU molecule is surrounded by six neighbor molecules within the same sheet; very short intermolecular contacts, C(6)H ··· O(2) (C ··· O 3.190(4) Å and H ··· O 2.28(3) Å) and C(1)H_3 ··· O(4) (C ··· O 3.245(5) Å and H ··· O 2.63(4) Å) were observed within the sheet. The C ··· O and H ··· O distances are significantly shorter than the sum of the van der Waals radii, 1.75, 2.0, 1.50, and 1.20 Å for C, CH_3, O, and H, respectively.[15] Similar short NCH_3 ··· O contacts have been observed in the DMU crystal,[3] and similar short C(aromatic)-H ··· O contacts have been also observed in the benzoquinone crystal.[16] The short CH ··· O interactions may be classified into the CH ··· O hydrogen-bonds[17–19] which strongly bind to the planar molecules in the sheet.

Mixed Crystal Formation between DMFU and DMU. The crystal structure of DMFU is quite different from that of DMU, and the mixed crystal has an isomorphic form to the DMFU crystal. A comparison of the molar ratios in the prepared solutions and in the obtained mixed crystals are given in Fig 3. The observed line is located below the dotted diagonal line, and the DMU amounts in the mixed crystal are smaller than those in the solution. However, very large amounts of DMU can be mixed into a DMFU crystal. Even if the DMU molar ratio is 77%, the mixed crystal has the same DMFU form. In this mixed crystal, the larger the amounts of DMU molecules are solved, the more the unit cell volume of the mixed crystal decreases, though the decrement of the unit cell volume is smaller than the expected value for the DMU amounts; for instance, a volume decrement of 1.2 $Å^3$ for a mixed crystal with a 0.4 DMU/DMFU molar ratio corresponds to about half of the volume change estimated from the van der Waals volumes.

Thus, the small volume change is one of the unique properties of this mixed crystal. Usually a mixed crystal formed without any volume change is classified into a block solution in which impurity molecules occupy defect sites of the crystal or are located at the boundaries of mosaic blocks. However, in the present case it must be a true substitutional solid solution in which the host molecules are replaced with guest molecules at random. The structure of such a solid solution model was successfully refined by a least-squares method for the 0.4 molar ratio DMU mixed crystal. The refined structure was essentially the same as that of the DMFU crystal, although the C–F bond in the mixed crystal seems to be slightly shortened.

Intermolecular NCH_3 ··· F Interaction. The fluorine atom in the DMFU crystal has a short intermolecular contact to the methyl group of the neighbouring molecule with an F(5) ··· C(3) distance of 2.999(6) Å. According to Nyburg and Faerman,[20] the van der Waals radius for a fluorine atom varies from 1.30 to 1.38 Å, depending on the directions of the intermolecular contacts. The present F ··· C distance is shorter than the van der Waals sum of the smallest F radius (1.30 Å) and the C radius (1.75 Å), and it is the shortest in the resemble F ··· CH_3 contacts observed so far.[21,22] The Coulomb interaction between the approached F and CH_3 is attractive; the interaction energy is about -11 kJ mol^{-1} for a simple point charge model with net charges of -0.195 a.u. on F and 0.124 a.u. on CH_3. Thus, the replacement of F by H in a mixed crystal will cause a loss of Coulomb energy. On the other hand, the van der Waals interaction between the F and CH_3 is repulsive in the DMFU crystal because of the very short F ··· CH_3 distance. Thus, the replacement of F by H will decrease the van der Waals energy; the estimated energy gain is about 2.7 kJ mol^{-1} for the coefficients by Williams and Houpt.[23] The entropy effect, owing to a mixing of two components, also decreases the free energy of the mixed crystal, though this contribution (maximum $-3\ \mathrm{kJ\ mol^{-1}}$ for an ideal case) is small if the mixing ratio is different from 1 : 1.

In conclution, the DMFU crystal consists of very stable sheets of planar DMFU molecules which are bonded by $\mathrm{CH\cdots O}$ hydrogen bonds. Repulsive van der Waals interactions at short $\mathrm{F\cdots CH_3}$ contacts cause the DMFU crystal to become a stable solid solution for DMU over a wide range of mixing ratios. Such easy replacement of fluorine substituents must be one of the important properties of a fluorine atom in considering the fluorine-substitution effects.

The authors wish to thank Professor Kenji Osaki for his motivation of this work. They also thank Dr. Takashi Harayama and Dr. Reiko Yanada for their kind supply of 1,3-dimethyl-5-fluorouracil.

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