

# X-ray powder diffraction analysis of tegafur

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An experimental X-ray powder diffraction pattern was produced and analyzed for alpha-polymorphic tegafur, also called Ftorafur (an antineoplastic agent). The indexed data matched the powder patterns in the ICDD PDF-4/Organics database calculated from the reported single-crystal X-ray diffraction data in the Cambridge Structural Database. Alpha tegafur has a triclinic crystal system, with reduced cell parameters of  $a=16.720(6)$  Å,  $b=9.021(5)$  Å,  $c=5.995(3)$  Å,  $\alpha=93.66(4)^\circ$ ,  $\beta=93.15(8)^\circ$ ,  $\gamma=100.14(4)^\circ$ . There are four formula units contained in one unit cell. The cell volume and space group were determined to be  $886.27$  Å<sup>3</sup> and  $P-1$ , respectively. © 2006 International Centre for Diffraction Data. [DOI: 10.1154/1.2210952]

Key words: tegafur, C<sub>8</sub>H<sub>9</sub>FN<sub>2</sub>O<sub>3</sub>, X-ray powder diffraction, polymorphs, hydrogen bonding

## I. INTRODUCTION

Tegafur, C<sub>8</sub>H<sub>9</sub>FN<sub>2</sub>O<sub>3</sub> [5-fluoro-1-(tetrahydro-2-furyl)uracil] (Figure 1), has been used in conjunction with uracil as a chemotherapeutic agent for the treatment of various forms of cancer, especially colorectal cancer, for over 20 years. Most recently, it was studied for certain types of lung cancer with promising results. There have been a number of detailed studies of its single-crystal polymorphic forms (Yamamoto *et al.*, 1993; Nakai *et al.*, 1982; Guo *et al.*, 1983). However, its powder data has not been well explored. The ICDD PDF-4/Organics database contains three powder patterns, two  $\alpha$  and one  $\beta$  polymorph, calculated from single-crystal data. Here, we would like to report the results of our experimental X-ray powder diffraction study of  $\alpha$ -tegafur.

## II. EXPERIMENTAL

Tegafur (99% pure), purchased from Aldrich Chemicals, was dissolved in 99.5% warm acetone. The supersaturated solution was filtered through Whatman #4 filter paper. The filtrate was cooled to room temperature. The needlelike colorless crystals were formed through the slow evaporation of acetone at room temperature and were filtered and dried. A 110 mg KBr pressed pellet containing 1 mg tegafur was prepared for the infrared spectrum (IR). IR data were collected on a Nicolet Nexus 470 FT-IR spectrometer. A 7 mg sample was heated from 30 °C to 180 °C at a rate of 5 °C per min under nitrogen flow on a Perkin-Elmer DSC 7 differential scanning calorimeter (DSC).

The X-ray powder diffraction data were collected from a Rigaku Ultima+ D/M-2200T and a PANalytical Alpha One with an X'Celerator detector for the preliminary study and a Bruker D4 diffractometer for the final analysis. The use of different diffractometers was based purely on their availability at the time of the experiments and is not indicative of their qualities. Tegafur crystals were gently ground with an agate mortar and pestle. The powder was front-loaded to a flat plate for both Ultima+ and D4 diffractometer experi-

ments. A capillary was used for the Alpha One diffractometer. The preliminary study used 0.02 deg  $2\theta$  step size and 2 h scan time from 5–60 deg  $2\theta$ . The powder diffraction experimental conditions using Bruker D4, with smaller step size and longer scan time, are listed in Table I. The powder pattern is presented in Figure 2.

## III. RESULTS AND DISCUSSION

IR data showed three, instead of two, C=O absorption bands as a result of hydrogen bonding of the alpha-polymorphic form. This finding is consistent with the IR data reported by Yamamoto *et al.* (1993). A DSC scan showed an endothermic melting point peak at 172 °C, preceded by a polymorphic phase transition thermal change at about 161 °C. Crystallization from acetone produced only the polymorphic alpha form. This observation was supported by the X-ray powder diffraction data. A separate experiment showed the presence of a minor amount of polymorphic beta form when the more polar solvent methanol was used for crystallization. In the absence of special kinetic crystallization conditions, thermodynamically more stable alpha form is the predominant product. All data for both the preliminary and final study were processed using the PANALYTICAL X'PERT HIGH SCORE PLUS software and the ICDD PDF-4/Organics database (ICDD, 2004–2005). Background subtraction for the data was performed followed by peak searches. The data were then smoothed with a six-point smoothing fast Fourier algorithm. Alpha-2 peaks, when present, were stripped using the Rachinger method. The data were indexed

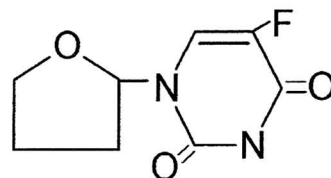


Figure 1. Tegafur.

TABLE I. X-ray powder diffraction data collection conditions for tegafur.

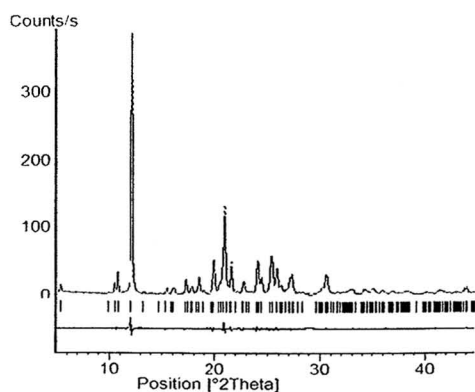
Diffractometer	Broker D4
Slits	DIV 0.6 mm
Radiation	X-ray, Cu K $\alpha$ 1/K $\alpha$ 2
Power	40 kV, 40 mA
Detector	Vantec <sup>TM</sup>
Scan	0.0091° steps, 5 s/step
Rotation	30 rpm

and refined with AIDS (ICDD/JCPDS powder pattern evaluation program), DICVOL 91, and Rietveld methods respectively. The result from AIDS is shown in Table II.

The best-matched pattern from the ICDD reference database is that of  $\alpha$ -tegafur [PDF 02-060-4959:  $a = 6.004(2)$  Å,  $b = 9.022(8)$  Å,  $c = 16.702(11)$  Å,  $\alpha = 99.78(6)^\circ$ ,  $\beta = 93.43(3)^\circ$ ,  $\gamma = 94.18(6)^\circ$ ] (ICDD, 2005) calculated, with POWD 12++ software, from the Cambridge Structural Database. The indexing programs AIDS and DICVOL 91 yielded figure of merits  $F(30) = 52.74(.012, 30)$  and  $F(20) = 64.7$ , respectively, with zero unindexed lines. The triclinic structure is shown in Figure 3. The long  $a$ -axis coincides with the axes formed by a dimer of a pair of enantiomers. The asymmetric carbon on the five-member ring is the source of each chiral molecule. These two enantiomeric molecules are bonded by two intermolecular hydrogen bondings between hydrogen atoms of N-H and oxygen atoms of C=O.

#### IV. CONCLUSION

Tegafur has been reported to have at least four polymorphs. It was shown here that, with appropriate solvent polarity, the pure polymorph can be isolated and characterized by IR and DSC. However, most powerful of all is the ability to



$a = 16.720(6)$  Å,  $b = 9.021(5)$  Å,  $c = 5.995(3)$  Å,  
 $\alpha = 93.66(4)^\circ$ ,  $\beta = 93.15(8)^\circ$ ,  $\gamma = 100.14(4)^\circ$   
 $R_p = 7.66\%$ ,  $R_{wp} = 9.20\%$

Figure 2. X-ray powder diffraction pattern for tegafur.

TABLE II. X-ray powder diffraction data for tegafur.

$h$	$k$	$l$	2Th. (o)	2Th. (c)	$d$ -sp. (Å)	2Th. (d)	$I/I_{\max}$
1	0	0	5.3850	5.3770	16.3995	-0.008	23
0	1	0	9.9490	9.9810	8.8837	0.032	2
1	-1	0	10.453	10.453	8.4568	0.000	41
2	0	0	10.769	10.767	8.2093	-0.002	83
1	1	0	12.166	12.171	7.2692	0.005	999
2	-1	0	13.289	13.309	6.6573	0.020	12
1	0	-1	15.429	15.437	5.7384	0.008	20
2	1	0	15.985	15.976	5.5401	-0.009	18
1	0	1	16.122	16.125	5.4934	0.003	26
0	1	-1	17.263	17.270	5.1329	0.007	56
2	0	-1	17.754	17.758	4.9919	0.004	23
1	-1	1	17.847	17.857	4.9661	0.010	28
1	-1	-1	18.496	18.492	4.7934	-0.004	62
2	0	1	18.936	18.946	4.6829	0.010	17
2	-1	1	19.977	19.960	4.4411	-0.017	113
3	1	0	20.535	20.539	4.3218	0.004	40
2	1	-1	20.783	20.822	4.2707	0.039	100
2	-2	0	20.996	20.993	4.2278	-0.003	305
3	0	-1	21.217	21.255	4.1843	0.038	47
4	0	0	21.629	21.630	4.1056	0.001	104
4	-1	0	22.127	22.148	4.0142	0.021	14
3	-1	-1	22.784	22.734	3.9000	-0.050	40
2	1	1	22.868	22.861	3.8858	-0.007	42
3	-1	1	23.193	23.185	3.8321	-0.008	11
3	-2	0	23.433	23.437	3.7934	0.004	15
0	2	-1	24.110	24.095	3.6884	-0.015	122
2	2	0	24.480	24.482	3.6335	0.002	60
2	-2	1	25.363	25.342	3.5090	-0.021	128
1	-2	-1	25.515	25.505	3.4884	-0.010	120
0	2	1	25.907	25.916	3.4365	0.009	90
-2	2	1	26.288	26.252	3.3875	-0.036	29
4	-2	0	26.790	26.801	3.3252	0.011	22
5	-1	0	27.177	27.184	3.2787	0.007	66
1	2	1	27.425	27.437	3.2496	0.012	65
3	2	0	28.056	28.091	3.1780	0.035	10
4	1	-1	28.381	28.447	3.1423	0.066	13
0	3	0	30.257	30.256	2.9516	-0.001	28
3	2	-1	30.645	30.627	2.9151	-0.018	71
3	-3	0	31.720	31.718	2.8187	-0.002	11
4	2	0	32.287	32.273	2.7706	-0.014	11
0	-3	1	32.789	32.801	2.7292	0.012	17
3	2	1	33.159	33.146	2.6997	-0.013	22
5	-2	-1	34.232	34.210	2.6174	-0.022	16
5	-2	1	34.506	34.503	2.5972	-0.003	17
1	-2	2	35.176	35.127	2.5493	-0.049	24
4	0	-2	35.971	35.962	2.4948	-0.009	17
1	3	1	36.333	36.337	2.4708	0.004	11
4	-1	-2	36.965	36.935	2.4299	-0.030	13
6	0	1	37.031	37.016	2.4258	-0.015	14
6	-2	-1	38.200	38.179	2.3542	-0.021	14
4	0	2	38.420	38.436	2.3412	0.016	12
-5	3	1	40.277	40.301	2.2374	0.024	8
3	-4	0	41.123	41.103	2.1933	-0.020	7
7	-1	1	41.543	41.545	2.1721	0.002	17
5	0	2	42.252	42.232	2.1373	-0.020	7
4	-4	0	42.813	42.736	2.1106	-0.077	7
-2	3	2	44.149	44.195	2.0498	0.046	21
5	3	0	44.779	44.794	2.0224	0.015	8
-4	4	1	46.028	46.031	1.9704	0.003	2

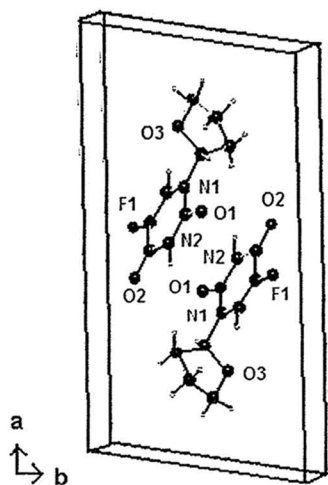


Figure 3. Tegafur crystal structure.

apply X-ray powder diffraction total pattern analysis technique to characterize the pure polymorph by comparing the experimental powder data with the data calculated from single-crystal data in the PDF-4/Organics database (Needham and Faber, 2003).

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