Crystal structure of capecitabine from X-ray powder synchrotron data

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Abstract The crystal structure of capecitabine was determined from high-resolution X-ray synchrotron powder diffraction data using parallel tempering method. Data were collected on synchrotron ESRF in Grenoble on beam line ID31. Capecitabine crystallizes in P212121 space group, Z=4, with unit cell parameters a=5.205(3) Å, b=9.522(5) Å, c=34.78(5) Å, V=1724 Å3. The initial model was generated by AM1 semi-empirical QM computing method as implemented in program MOPAC. The structure was solved in program FOX. The initial model was restrained with bonds and angles restrains. The structure was refined in the GSAS program. During the final refinement the capecitabnine molecule was treated as relaxed one with bonds and angles restrain. The final agreement factors are Rp=0.096 and Rwp=0.158. Molecules in the crystal structure of capecitabine are connected together by hydrogen bonds. It creates infinite layers in the a-b direction.

Keywords: Crystal structure, capecitabine, powder diffraction

1. Introduction

Capecitabine is the first FDA-approved oral chemotherapy for the treatment for some types of cancer, including advanced bowel cancer or breast cancer [1,2]. Capecitabine is 5´-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine, Figure 1, and *in vivo* is enzymatically converted to the active drug 5-fluorouracil. Crystal structure determination of capecitabine was not apparently reported yet. In this paper we report crystal structure determination of capecitabine from the powder diffraction data using synchrotron radiation

2. Experimental and structure solution

The samples of crystalline capecitabine were prepared by these two methods.

a. Capecitabine (10g) was dissolved in EtOH (80g). The solution was concentrated under reduced pressure to a residual volume of 25mL and kept under stirring overnight. The solid was filtered off and dried at room temperature furnishing capecitabine (6g).

b. Capecitabine (18g) was dissolved in DCM (200g) and the solution was evaporated to dryness under reduced pressure. The residue was taken up with toluene (400g) and about 150g of solvent were distilled off. The solution was heated up to 50°C and then allowed to 3 spontaneously cool to 25°C. After cooling to 0°C, the solid was filtered off, washed with toluene and dried at 60°C under vacuum to constant weight furnishing capecitabine (16.5g).

2.1. Data Collection

Both procedures lead to one crystalline form of capecitabine. It was confirmed by measuring on X-Ray powder diffractometer PANalytical X'pert Pro, CuKα radiation, λ = 1.541874 Å. X'Celerator detector active length (2 Θ) = 2.122 mm, laboratory temperature 22-25°C. Zero background sample-holders. Precision of peak positions is ± 0.2 deg. 2Θ. Attempts to determine the structure from these data were unsuccessful probably due to flexible molecule of capecitabine and low resolution of these data.

The powder obtained by the first procedures was used for structure determination. X-Ray diffraction data were collected on the high resolution diffractometer ID31 of the European Synchrotron Radiation Facility. The monochromatic wavelength was fixed at 0.79483(4) Å. Ge (111) crystal multi-analyser combined with Si (111) monochromator was used (beam offset angle α = 2°). A rotating 1-mm-diameter borosilicate glass capillary with capecitabine powder was used for the experiment. Data were measured from 1.002°2θ to 34.998°2θ at the room temperature, steps scans was set to 0.003°2θ.

2.2. Structure solution and refinements

The first 20 peaks were used by CRYSFIRE 2004 package [3] to get a list of possible lattice parameters. All included auto-indexing programs were used for indexing. The most probable result, which was found by TAUPv3.3a [4], DICVOL91 [5] and KOHLv7.01b [6] programs, was selected (a = 5.21 Å, b = 9.52 Å, c = 34.79 Å, V = 1724 Å3, FOM (20) = 330). If 15 Å3 are used as an atomic volume for C, N, O and F and 5 Å3 as a volume for hydrogen atom, the approximately molecular volume should be 485 Å3. The found volume of 1724 Å3 suggests that there are four molecules in one cell (Z = 4). P212121 space group was selected on the basic of peaks extinction and on the basic of agreement of the Le-bail fit. Le-bail fit was performed by HighScore software [7]. A precious agreement Rexp=0.024, Rp=0.085, Rw=0.124 was achieved.

The structure was solved in program FOX [8] using parallel tempering algorithm. The initial model was generated by AM1 computing method implemented in program MOPAC [9]. For the solution process the hydrogen atoms were removed. This model was restrained with bonds and angles restrains, automatically generated by program FOX [8]. 20 results were produced and arranged in order to cost function [10]. 18 result were the same, two results with highest const function differed. The result with lowest cost function was selected for the refinement (GoF 15.6, CHI 176670 [10]).

At first all necessary parameters were initialized. Background was refined using a shifted Chebyschev function type with 20 terms. The Pseudo-Voigt profile function with Finger-Cox-Jephcoat asymmetry parameters was selected and profile parameters were refined (U, V, W, LX, LY, S/L and H/L). After it 68 bonds and 86 angles restrains were generated using perl script plab.pl [11]. Uiso thermal parameters were constrained in the following way – one parameter for non-hydrogen atoms and one for hydrogen atoms. Atomic coordinates and two Uiso parameters were refined to the final agreement factors: Rp=0.096 and Rwp=0.158. At the final stage the hydrogen atoms were added in positions based on geometry. The summary of crystallographic and refinement information are given in the Table 1. Fig. 2 shows measured and calculated data and its difference curve. Atomic coordinates and thermal isotropic parameters are given in the Table 2.

In the measured pattern the first peak was very asymmetric. This peak made problems during parallel tempering computing nevertheless the computing went fast to a minimum. During the refinement bonds and atoms restrains were added as “soft constraint data” in the “last squares refinement set up”. At the beginning the overall restraints weigh factor for both bonds and angles F = 10000 were set. This factor was step by step set lower and lower to the final value F = 10 for angles and F = 1000 for bonds.

3. Results and discussion

The Crystal structure of capecitabine is illustrated in Figure 3. Capecitabine molecule is found considerably elongated. Intra and intermolecular hydrogen bonding system is showed in Figure 4. Based on the distances evaluation it is possible that there are two types of hydrogen bonds in this structure. The first is between O8 and N17 atoms and the second is between O8 and N14 atoms. Molecules of capecitabine connected by hydrogen bonds are forming in parallel infinite a-b layers Fig. 5. Data about hydrogen bonds are given in the Table 3.

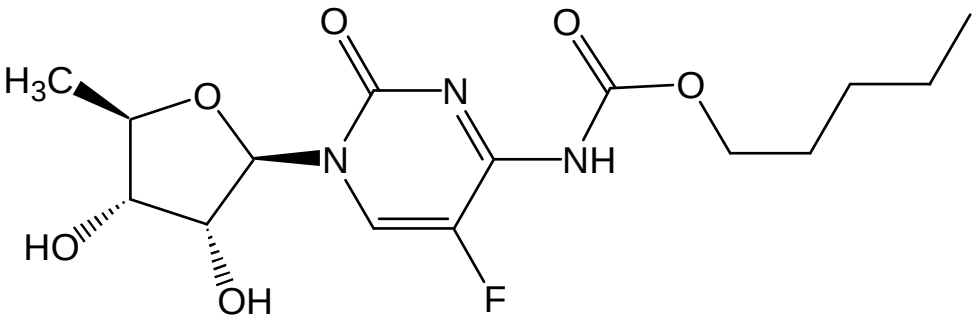

Figure 1 The structure of capecitabine

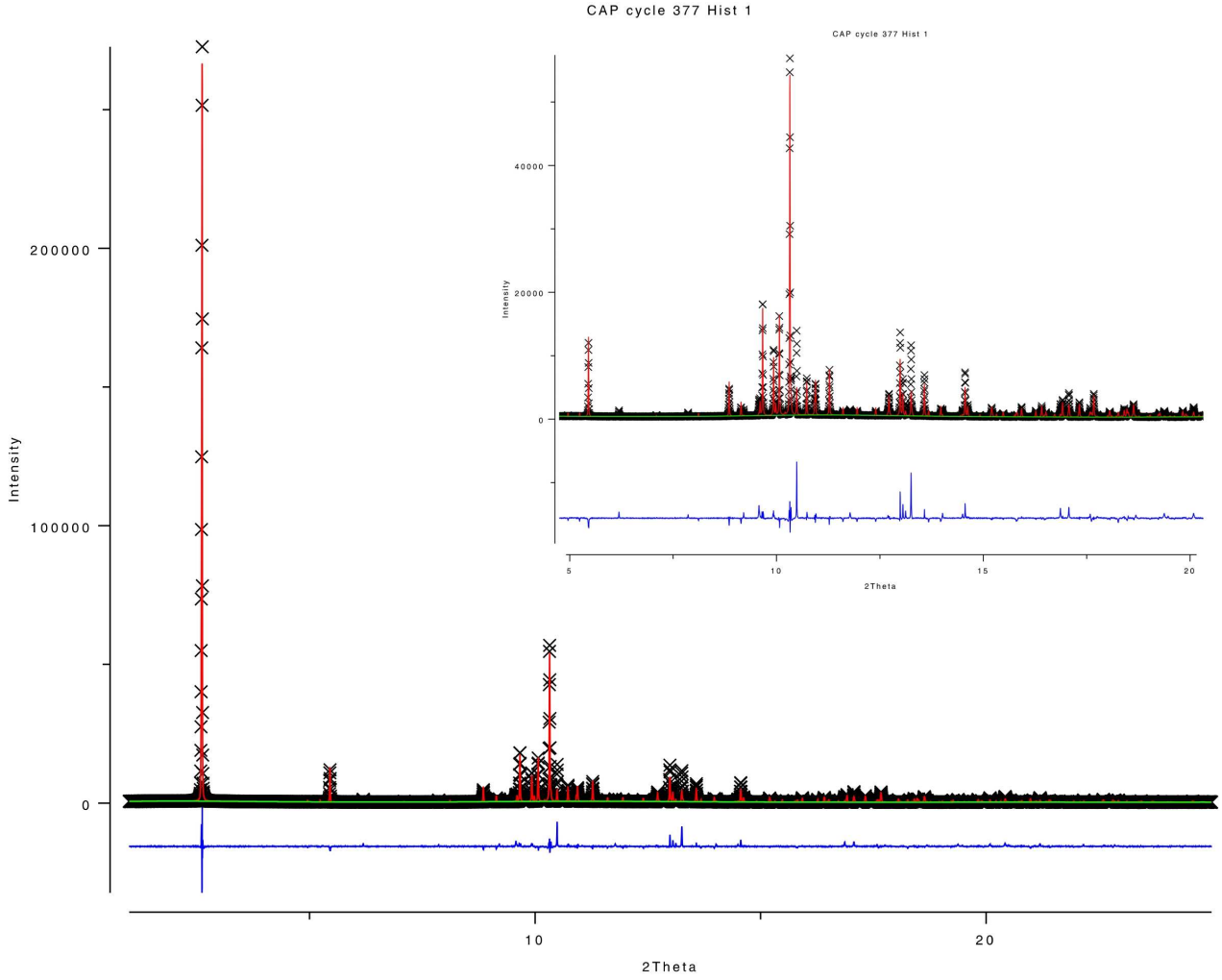

Figure 2 Final rietveld plot. Calculated data – red line, measured data – black crosses, difference curve – blue line

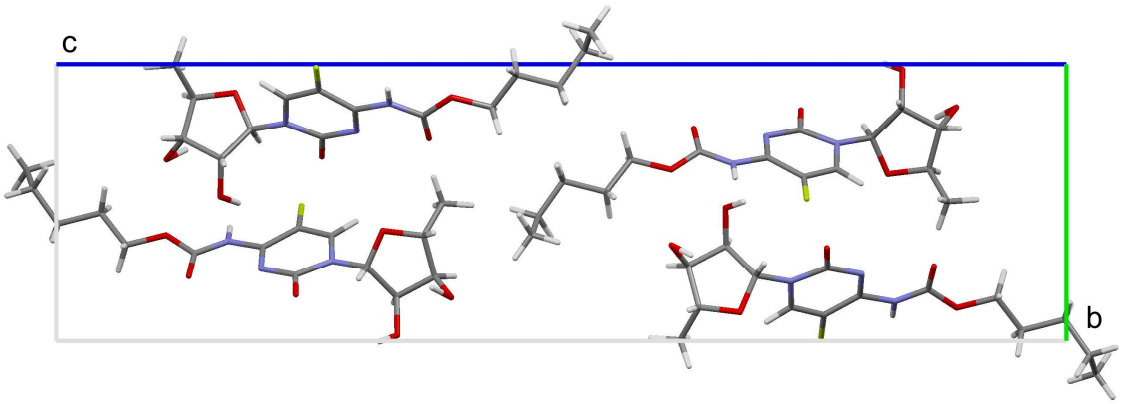

Figure 3 Projection of the structure along a-axis

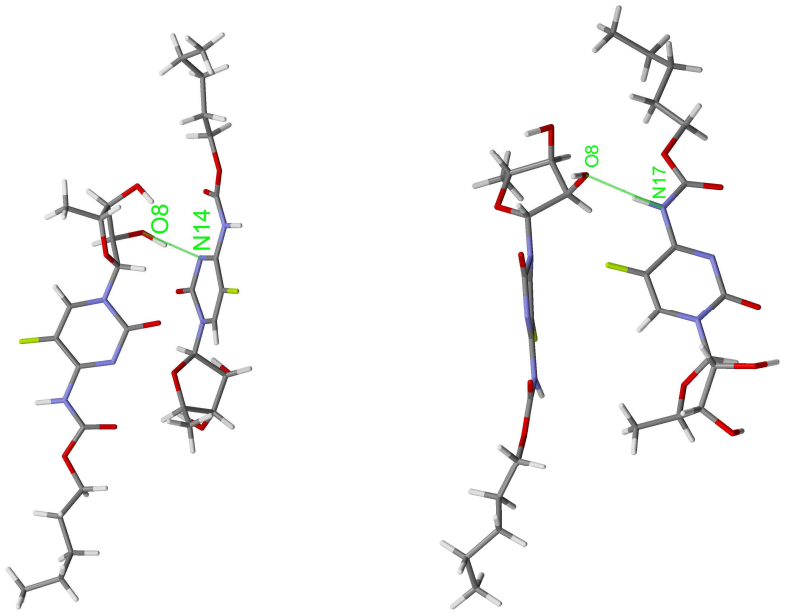

Figure 4 a) Detail of N14 - O8 hydrogen bond. b) Detail of N17 - O8 hydrogen bond

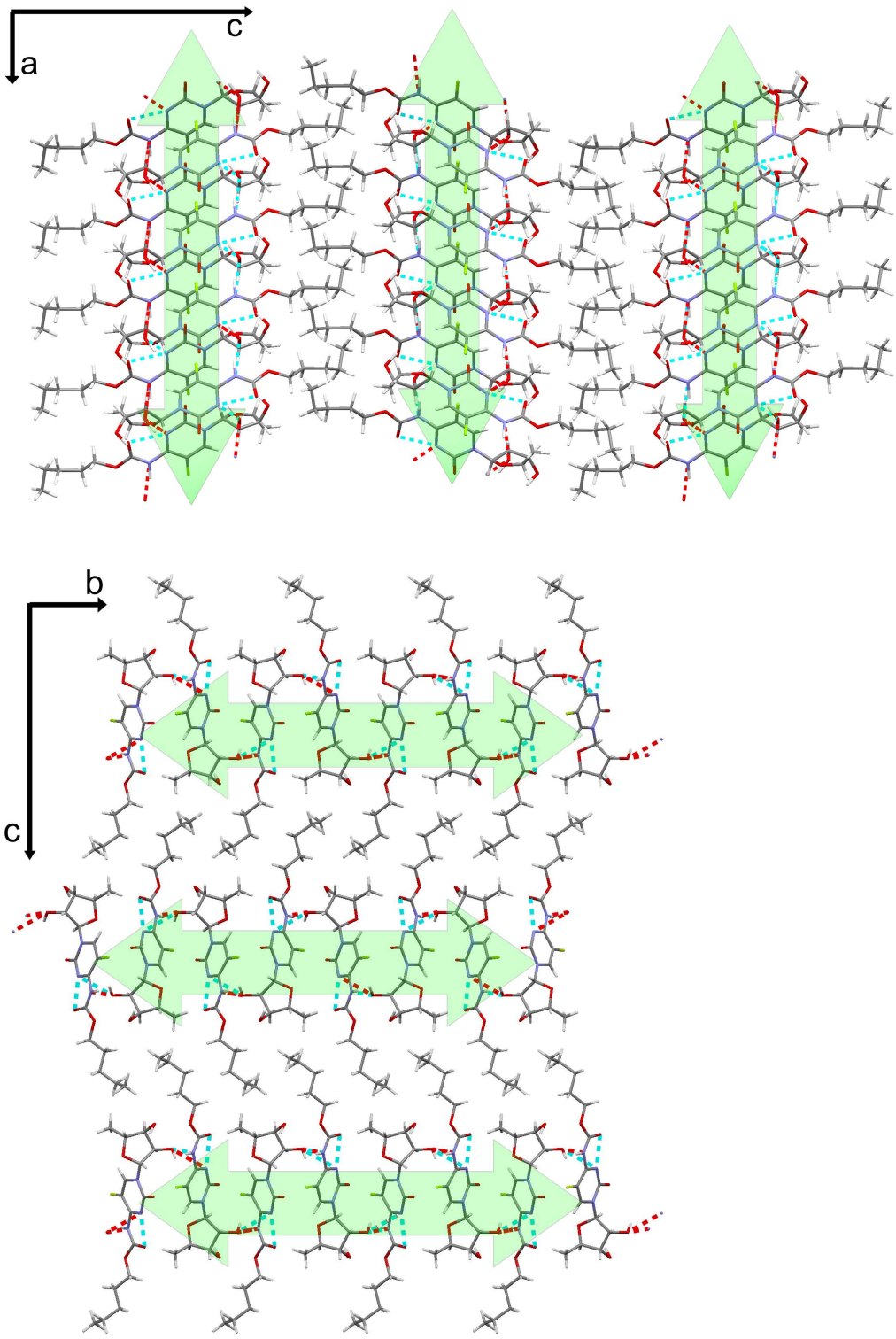

Figure 5 Hydrogen bonding system in the crystal structure of capecitabine. Connected molecules by hydrogen bonds create infinite layers in a-b directions

Table 1 Summary crystallographic and refinement data

Formula	$C_{15}H_{22}FN_3O_6$
Temperature (K)	293

M_r	359.35
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	5.20463(4)
b (Å)	9.52134(8)
c (Å)	34.7771(6)
V (Å^3)	1723.38(4)
Z	4
2Theta range (°)	1.002 - 34.998
Step size (°)	0.003
Wavelenght (Å)	0.79483(4)
No. of profile data steps	11333
Rp	0.096
Rwp	0.158
chi^2	24.79

Table 2 Atomic coordinates

C1	0.44590(10)	0.62041(5)	0.636359(16)	Uiso	0.0930(20)
C2	0.52961(9)	0.76959(6)	0.625446(20)	Uiso	0.0930(20)
C3	0.61448(12)	0.84098(7)	0.662963(22)	Uiso	0.0930(20)
C4	0.48936(13)	0.73453(8)	0.692630(20)	Uiso	0.0930(20)
O5	0.43231(23)	0.60275(8)	0.676856(19)	Uiso	0.0930(20)
C6	0.59854(9)	0.50302(5)	0.617566(15)	Uiso	0.0930(20)
O7	0.32967(15)	0.84485(16)	0.60896(4)	Uiso	0.0930(20)
O8	0.49866(13)	0.98017(9)	0.66244(6)	Uiso	0.0930(20)
N9	0.63433(23)	0.71318(17)	0.727076(29)	Uiso	0.0930(20)
C10	0.5319(11)	0.7624(10)	0.76341(6)	Uiso	0.0930(20)
C11	0.8341(13)	0.6212(8)	0.72758(8)	Uiso	0.0930(20)
C12	0.9736(16)	0.5935(11)	0.75988(10)	Uiso	0.0930(20)
C13	0.8908(14)	0.6620(11)	0.79564(9)	Uiso	0.0930(20)
N14	0.6762(19)	0.7400(16)	0.79736(11)	Uiso	0.0930(20)
O15	0.3346(19)	0.8339(16)	0.76289(10)	Uiso	0.0930(20)
F16	1.1828(20)	0.5126(15)	0.75717(12)	Uiso	0.0930(20)
N17	1.0379(7)	0.6409(7)	0.830043(32)	Uiso	0.0930(20)
C18	0.9615(10)	0.6847(8)	0.863183(31)	Uiso	0.0930(20)
O19	0.7890(27)	0.7690(16)	0.86895(7)	Uiso	0.0930(20)
O20	1.09643(22)	0.61860(14)	0.891384(27)	Uiso	0.0930(20)
C21	1.02703(10)	0.65436(5)	0.931093(17)	Uiso	0.0930(20)
C22	1.13514(9)	0.53793(5)	0.955890(13)	Uiso	0.0930(20)
C23	1.13175(10)	0.57723(5)	0.998151(12)	Uiso	0.0930(20)
C24	1.12018(8)	0.44904(4)	1.023064(15)	Uiso	0.0930(20)
C25	1.37766(8)	0.38413(5)	1.029060(14)	Uiso	0.0930(20)

Table 3 Possible hydrogen bonds

atoms	symmetry operation	distance [Å]
O8 - N14	N14: 1-x, 1/2+y, 3/2-z	3
O8 - N17	N17: 2-x, 1/2+y, 3/2-z	2.86

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