Crystal Structure of a Fluoroquinolone Antibiotic, Enoxacin

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Crystals of Enoxacin, one of commercial fluoroquinolone antibiotics, were grown from acetonitrile/methanol and the crystal structure was determined. Results show that the unit cell contains two crystallographically independent molecules (A and B), three water and one methanol molecules. The carboxylic group is ionized and the N4 atom from the piperazine ring is protonated, resulting a zwitter ionic structure. The interlayer π - π interactions and the intermolecular hydrogen bonds stabilize the crystal packing.

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Fluoroquinolones are very useful antibiotics, which are increasingly being used for the treatment of many infections.¹ Enoxacin (1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid) (Fig. 1) is one of these agents, and used to treat certain infections caused by bacteria, such as gonorrhea and urinary tract infections.^{2,3} In spite of a large amount of data on the activity of enoxacin in biology and chemotherapy, its crystal structure has not been available. Herein, we describe the structure of this molecule based on an X-ray crystal analysis.

Enoxacin was purchased from Sigma Co. and used without further purification. Colorless crystals suitable for X-ray crystallography were grown by slow evaporation from acetonitrile/methanol (9:1) at room temperature. The crystal and experimental data are given in Table 1. The structure was solved by a direct method. H atoms bonded to the N atom of the piperazine ring were found from difference Fourier maps and then refined freely. H atoms of the water molecules were not included. Other H atoms were included in the calculated positions with isotropic thermal parameters 1.2-times those of the attached atoms. The atomic coordinates and selected geometric parameters are presented in Tables 2 and 3, respectively. The molecular structure and the atomic numbering are given in Fig. 2.

The unit cell contains two crystallographically independent

molecules, A and B, together with three water and one methanol molecules. Molecules A and B show no significance difference in bond lengths and angles. The carboxylic group is in the ionized form, showing the typical bond distances of carboxylic anion in the range of 1.248(4) – 1.263(4) Å, and the N4 atom of the piperazine ring is protonated, resulting a zwitter ionic structure in both molecules. There was no residual density near carboxylic O atoms, which can be assigned by H atoms. The

Table 1 Crystal and experimental data

Formula: C ₃₁ H ₄₄ F ₂ N ₅ O ₁₀
Formula weight = 726.74
Temperature: 100 K
Crystal size: 0.40 × 0.20 × 0.20 mm
Crystal color: colorless
Crystal description: plate
Crystal system: monoclinic
Space group: <i>P</i> 2 ₁ / <i>c</i> <i>Z</i> = 4
<i>a</i> = 8.4053(6) Å
<i>b</i> = 22.1236(16) Å
<i>c</i> = 17.1548(12) Å
β = 100.903(1)°
<i>V</i> = 3132.4(4) Å ³
<i>D_x</i> = 1.541 g/cm ³
Radiation: 0.71073 (Mo K α)
2 θ _{max} = 56.56°
<i>R</i> = 0.0683
<i>wR</i> ₂ = 0.2242
Goodness-of-fit = 1.059
($\Delta\rho$) _{max} final cycle: 0.000
($\Delta\rho$) _{max} = 0.952 e Å ⁻³
($\Delta\rho$) _{min} = -0.930 e Å ⁻³
No. of reflections used = 7395 [$>2\sigma(I)$]
No. of parameters = 461
Diffractometer: Bruker SMART CCD system
Monochromator: graphite
Structure determination: SHELXTL
Refinement: full-matrix least-squares

Fig. 1 Chemical structure.

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Table 2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$)

Atom	x	y	z	U(eq)
F(1A)	2144(2)	7410(1)	6097(1)	16(1)
O(1A)	4005(3)	9103(1)	4559(1)	20(1)
O(2A)	5291(3)	9661(1)	3337(1)	24(1)
O(3A)	6991(3)	9088(1)	2819(1)	25(1)
N(1A)	5439(3)	7515(1)	3661(1)	13(1)
N(2A)	4350(3)	6952(1)	4579(1)	12(1)
N(3A)	3256(3)	6348(1)	5450(1)	14(1)
N(4A)	2705(3)	5148(1)	5968(2)	18(1)
C(1A)	5931(3)	9164(1)	3239(2)	15(1)
C(2A)	5798(3)	8057(1)	3370(2)	14(1)
C(3A)	5394(3)	8609(1)	3636(2)	14(1)
C(4A)	4499(3)	8635(1)	4280(2)	15(1)
C(5A)	3367(3)	8009(1)	5253(2)	13(1)
C(6A)	3055(3)	7453(1)	5524(2)	12(1)
C(7A)	3586(3)	6915(1)	5193(2)	13(1)
C(8A)	4629(3)	7502(1)	4297(2)	12(1)
C(9A)	4201(3)	8045(1)	4612(2)	13(1)
C(10A)	5836(3)	6953(1)	3267(2)	15(1)
C(11A)	4594(4)	6824(2)	2526(2)	24(1)
C(12A)	3434(4)	6211(1)	6304(2)	16(1)
C(13A)	2330(4)	5690(1)	6420(2)	19(1)
C(14A)	2617(4)	5291(1)	5113(2)	16(1)
C(15A)	3700(4)	5824(1)	5009(2)	16(1)
F(1B)	2795(2)	2569(1)	8614(1)	23(1)
O(1B)	1149(3)	891(1)	10277(1)	21(1)
O(2B)	306(3)	394(1)	11671(1)	27(1)
O(3B)	-1673(3)	930(1)	12043(1)	19(1)
N(1B)	-68(3)	2509(1)	11207(1)	14(1)
N(2B)	864(3)	3048(1)	10229(1)	14(1)
N(3B)	1840(3)	3661(1)	9342(1)	16(1)
N(4B)	2592(3)	4865(1)	8912(2)	19(1)
C(1B)	-518(4)	871(1)	11680(2)	16(1)
C(2B)	-417(3)	1972(1)	11514(2)	14(1)
C(3B)	-68(3)	1415(1)	11239(2)	15(1)
C(4B)	726(3)	1372(1)	10560(2)	14(1)
C(5B)	1719(3)	1993(1)	9529(2)	15(1)
C(6B)	2001(3)	2545(1)	9239(2)	16(1)
C(7B)	1548(3)	3093(1)	9589(2)	15(1)
C(8B)	619(3)	2504(1)	10527(2)	13(1)
C(9B)	989(3)	1955(1)	10201(2)	14(1)
C(10B)	-319(3)	3105(1)	11565(2)	15(1)
C(11B)	-1022(4)	3064(1)	12309(2)	21(1)
C(12B)	1881(4)	3815(1)	8514(2)	18(1)
C(13B)	3085(4)	4325(1)	8491(2)	20(1)
C(14B)	2437(4)	4716(1)	9745(2)	19(1)
C(15B)	1302(4)	4183(1)	9765(2)	18(1)
O(1W)	-68(3)	4611(1)	2126(1)	25(1)
O(2W)	2479(3)	5677(1)	1404(1)	28(1)
O(3W)	2388(10)	4281(4)	3667(4)	155(3)
O(7)	3920(5)	5004(2)	3380(2)	62(1)
C(31)	4774(6)	5357(2)	3073(3)	55(1)

$$U_{\text{eq}} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* (a_i \cdot a_j).$$

largest difference Fourier peak ($0.95 \text{ e\AA}^{-3}$) is located at a short distance ($0.06 \text{ \AA}$) from O3W of the non-hydrated water molecule. The naphthyridone rings are almost planar with average deviations of $0.015(2) \text{ \AA}$ for molecule A and $0.017(2) \text{ \AA}$ for molecule B, respectively, from the least-squares planes defined by all non-hydrogen atoms. The molecules are stacked by π - π interactions (average distance of two planes, $3.40(1) \text{ \AA}$). The intermolecular hydrogen bonds including solvent molecules also stabilize the molecular packing (figure not shown). The hydrogen-bonding parameters are summarized in Table 4.

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Table 3 Selected bond lengths ($\text{\AA}$) and angles ($^\circ$)

Molecule A		Molecule B	
F(1A)-C(6A)	1.359(3)	F(1B)-C(6B)	1.366(3)
O(1A)-C(4A)	1.243(3)	O(1B)-C(4B)	1.248(3)
O(2A)-C(1A)	1.248(4)	O(2B)-C(1B)	1.263(4)
O(3A)-C(1A)	1.259(4)	O(3B)-C(1B)	1.255(4)
N(1A)-C(2A)	1.354(3)	N(1B)-C(2B)	1.354(4)
N(1A)-C(8A)	1.393(3)	N(1B)-C(8B)	1.396(4)
N(1A)-C(10A)	1.484(3)	N(1B)-C(10B)	1.486(3)
N(2A)-C(7A)	1.336(4)	N(2B)-C(7B)	1.337(4)
N(2A)-C(8A)	1.346(3)	N(2B)-C(8B)	1.338(3)
N(3A)-C(7A)	1.375(3)	N(3B)-C(7B)	1.364(4)
N(3A)-C(12A)	1.476(3)	N(3B)-C(12B)	1.468(4)
N(3A)-C(15A)	1.471(3)	N(3B)-C(15B)	1.478(4)
N(4A)-C(13A)	1.494(4)	N(4B)-C(13B)	1.495(4)
N(4A)-C(14A)	1.489(4)	N(4B)-C(14B)	1.497(4)
C(2A)-N(1A)-C(8A)	118.9(2)	C(2B)-N(1B)-C(8B)	118.2(2)
C(7A)-N(2A)-C(8A)	118.6(2)	C(7B)-N(2B)-C(8B)	120.1(2)
C(15A)-N(3A)-C(12A)	111.2(2)	C(15B)-N(3B)-C(12B)	111.0(2)
C(14A)-N(4A)-C(13A)	111.3(2)	C(14B)-N(4B)-C(13B)	111.5(2)
O(2A)-C(1A)-O(3A)	124.3(3)	O(2B)-C(1B)-O(3B)	124.8(3)

Fig. 2 ORTEP drawing of the title compound, representing heavy atoms as 30% probability ellipsoids and H atoms as spheres of arbitrary radius.

Table 4 Hydrogen-bonding geometry ($\text{\AA}$, $^\circ$)

D-HA	D-H ($\text{\AA}$)	HA ($\text{\AA}$)	DA ($\text{\AA}$)	D-HA ($^\circ$)
N(4A)-H(4A)O(7) ⁱ	0.900	1.998	2.870(5)	161.6
N(4A)-H(4B)O(1B) ⁱⁱ	0.900	2.112	2.794(3)	131.9
N(4A)-H(4B)O(2B) ⁱⁱ	0.900	2.046	2.806(3)	141.5
N(4B)-H(4D)O(1A) ⁱⁱⁱ	0.900	1.989	2.714(3)	136.5
N(4B)-H(4D)O(2A) ⁱⁱⁱ	0.900	2.118	2.840(3)	136.7
N(4B) ^{iv} -H(4C)O(1W)	0.900	1.885	2.755(4)	161.8
O(7)-H(7)O(3W)	0.960	1.844	2.731(3)	96.1
O(7)-H(7)O(3A) ^v	0.960	1.935	2.817(3)	170.0
O(7)O(3B) ^{vi}			2.907(3)	
O(3A) ^v O(1W)			2.168(9)	
O(3A) ^v O(3W)			2.730(8)	
O(2A) ^v O(2W)			2.791(4)	
O(2B) ^v O(1W)			2.876(4)	

Symmetry code: (i) $1-x, 1-y, 1-z$ (ii) $x, 1/2-y, -1/2+z$ (iii) $x, 3/2-y, 1/2+z$ (iv) $-x, 1-y, 1-z$ (v) $1-x, -1/2+y, 1/2-z$ (vi) $-x, 1/2+y, 3/2-z$

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