Anionic Favipiravir in Salt-type Cocrystals with Monoethanolamine and Ethylenediamine

Odil CHORIEV,* Jamshid ASHUROV,** Aziz IBRAGIMOV,* Shukhrat TURABOEV,** and Vahobjon SABIROV**,*†

*Institute of General and Inorganic Chemistry, Uzbekistan Academy of Sciences, 100170, Kh. Abdullaev Str., 77a, Tashkent, Uzbekistan

**Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, 100125, Kh. Abdullaev Str., 83, Tashkent, Uzbekistan

***Tashkent State Technical University, Almalyk Branch, Ulug'bek Str., 45, 110100, Almalyk, Uzbekistan

Salt-like cocrystals of favipiravir (FVR) with monoethanolamine (MEA) (I) and ethylenediamine (*en*) (II) have been determined by X-ray crystallography. The crystallographic data are (I), monoclinic $P2_1/c$, $Z = 4$, $a = 12.2433(3)$, $b = 22.5400(5)$, $c = 7.3223(3)$ Å, $\beta = 106.287(3)^\circ$, $V = 1939.6(1)$ Å³, $R_1 = 0.0499$; (II), triclinic $P\bar{1}$, $Z = 2$, $a = 8.5903(12)$, $b = 9.4980(10)$, $c = 10.0337(13)$, $\alpha = 83.464(10)$, $\beta = 79.338(11)$, $\gamma = 80.665(10)$ Å, $V = 790.90(18)$ Å³, $R = 0.0709$. In both of compounds, FVR is a single charged anion with a deprotonated 2-hydroxyl group. The asymmetric unit of the lattice consists: (1) of two FVR anion and two MEA cations; (2) of two FVR anions and one a double charged *en* cation.

(Received September 30, 2021; Accepted October 28, 2021; Published on web January 10, 2022)

Favipiravir (FVR) is an antiviral medication used to treat influenza in Japan (Fig. 1). It is also being studied to treat a number of other viral infections. Like experimental antiviral drugs T-1105 and T-1106, it is a pyrazinecarboxamide derivative.¹ It is, however, only indicated for novel influenza (strains that cause more severe disease), rather than seasonal influenza. The mechanism of its actions is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase.²

The possible tautomerism of FVR has been investigated computationally.³ It was found that the *enol*-like form was substantially more stable in aqueous solution than the *keto*-like form, meaning that FVR likely exists almost exclusively in the *enol*-like form in aqueous solution (Fig. 2).

An *enol* form of FVR was found in the crystal structure of FVR.⁴ The crystal structure of FVR has been analyzed *in silico* research for structural analysis of FVR and its activity against COVID-19.^{5,6} It was found that four tautomeric structures could be considered to be ligands obtained by density functional theory

(DFT) calculations. The crystal structures of the cocrystals of many organic compounds with neutral FVR are already known,^{6,7} but an anionic form of FVR similar to that studied in this work has not yet been known.

This is for the first time obtained and crystallographic studied as an anionic form of FVR, which has been obtained using a basic co-former as monoethanolamine (MEA) and ethylenediamine (*en*). The given results can be used to describe the interaction of FVR with the amino acids of a protein molecule.

The purpose of this paper is to study the effects of the salt formation of FVR with the basic molecules MEA and *en* on its geometric parameters and its conformation. Salts of FVR with MEA (1) and *en* (2) were prepared by a similar procedure: (1): the reaction of FVR (0.1 mM, 0.157 mg) and MEA (0.1 mM, 6.11 mg), and (2): the reaction of FVR (0.1 mM, 6.11 mg) and *en* (0.1 mM, 6.01 mg), which were dissolved in ethanol (10 mL). The reaction mixtures were stirred for 15 min at a temperature of ~60°C. Both crystals were obtained by slow evaporation of the reaction solutions at the room temperature. The hydrogen atoms of the amino groups in both structures were located on a difference-Fourier map, but other hydrogen

Fig. 1 Chemical formula of FVR.

Fig. 2 Tautomeric (a) *enol* and (b) *keto* forms of FVR.

† To whom correspondence should be addressed.
E-mail: v_sabirov@mail.ru

atoms were positioned geometrically ($\text{OH} = 0.82 \text{ \AA}$ and $\text{CH} = 0.93 \text{ \AA}$) and refined using a riding model, with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ and $1.5 U_{\text{eq}}(\text{O})$. Crystal data and details of the

Table 1 Crystal and experimental data for (1) and (2)

Chemical formula:	$\text{C}_7\text{H}_{11}\text{N}_4\text{O}_3\text{F}$	$\text{C}_{11}\text{H}_{10}\text{NOF}$
Formula weight =	218.20	178.53
$T =$		293(2)K
Crystal system:	monoclinic	triclinic
Space group:	$P2_1/c$	$P\bar{1}$
$a =$	12.2433(3) Å	8.5903(12) Å
$b =$	22.5400(5) Å	9.4980(10) Å
$c =$	7.3223(3) Å	10.0337(13) Å
$\alpha =$	90°	83.464(10)°
$\beta =$	106.287(3)°	79.338(11)°
$\gamma =$	90°	80.665(10)°
$V =$	1939.60(10) Å ³	790.90(18) Å ³
$Z =$	4	2
$D_x =$	1.494 g cm ⁻³	1.125 g cm ⁻³
$\mu(\text{Cu } K\alpha) =$	1.130 mm ⁻¹	0.621 mm ⁻¹
$F(0\ 0\ 0) =$	912.0	282.0
Crystal size =	0.35 × 0.35 × 0.45 mm ³	0.30 × 0.35 × 0.40 mm ³
Radiation:	Cu $K\alpha$ ($\lambda = 1.54184 \text{ \AA}$)	
2 θ range for data collection:	7.844 to 152.342°	9.002 to 152.38°
Index ranges:	$-14 \leq h \leq 15, -26 \leq k \leq 28, -6 \leq l \leq 9$	$-10 \leq h \leq 10, -6 \leq k \leq 11, -12 \leq l \leq 12$
Reflections collected =	13436	5590
Independent reflections =	3991 [$R_{\text{int}} = 0.0468, R_{\text{sigma}} = 0.0362$]	3191 [$R_{\text{int}} = 0.0661, R_{\text{sigma}} = 0.0965$]
Data/restraints/parameters =	3991/0/315	3191/0/238
Goodness-of-fit on $F^2 =$	1.068	0.985
Final R indexes [$I > 2\sigma(I)$]:	$R1 = 0.0499, wR2 = 0.1314$	$R1 = 0.0568, wR2 = 0.1191$
Final R indexes [all data]:	$R1 = 0.0709, wR2 = 0.1562$	$R1 = 0.1085, wR2 = 0.1515$
Largest diff. peak/hole =	0.27/−0.31 e Å ⁻³	0.27/−0.31 e Å ⁻³
Data collection:	"XtaLAB Synergy, Single source at home/near, HyPix3000"	
CCDC deposition number:	21087698	2108797

structure refinement are presented in Table 1.

The crystalline structure of (1) composed of two FVR^- anions and two MEA^+ cations is shown in Fig. 3a. Both MEA^+ cations are linked with two different FVR^- anions through the $\text{N7-H}\cdots\text{O}$ and the $\text{N1-H}\cdots\text{O}$ hydrogen bonds. Both MEA^+ are in a *gauche* form: the torsion angles O10-C9-C8-N7 equal to $-64.0(3)^\circ$ and $-55.2(2)^\circ$. Crystal (2) is built from two FVR^- anions linked to each other by an H_2en^{2+} cation through $\text{N-H}\cdots\text{O2}$ hydrogen bonds (Fig. 3b). The N2 and N3 atoms participate in the hydrogen bonds $\text{N8-H8B}\cdots\text{N2B}$ and $\text{N8-H8C}\cdots\text{N3B}$, and also in the weak intermolecular bond $\text{C4B-H4B}\cdots\text{N3A}$.

In both compounds, FVR is in an anionic state with a deprotonated 2-OH-group (Fig. 4). The differential electron density peak does not appear in the vicinity of OH, but appears at NH_2 -groups. The C3-O2 bond distance is shortened compared with that in crystalline FVR ,⁴ 1.328(2) Å, and equal to: 1.287(2) and 1.292(2) Å in (1), and 1.282(4) and 1.276(4) Å in (2). The C3-N3 bond distance is equal to 1.355(3) in (1) and 1.378(3) Å in (2), while it is 1.340(2) Å in FVR .⁴ A comparison of these values of the interatomic distances shows that the C3-N3 bond is elongated compared with 1.306(3) Å in crystalline FVR . Thus, these values of the interatomic distances show that an anionic FVR is in the following tautomeric form shown in Fig. 2.

A negative charge of the FVR anion should be located at the N3 atom. Instead of intramolecular $\text{O2-H}\cdots\text{O1}$ hydrogen bond, a new intramolecular $\text{N1-H}\cdots\text{O2}$ hydrogen bond is formed. The carboxamide group is rotated one-half revolution around the C1-C2 bond in that case. The torsion angle N1-C1-C2-N2 is equal to $-117.3(2)$ and $-179.9(2)$ in (1), and, $-172.4(3)$ and $-177.9(3)$ in (2).

Fig. 4 Anionic FVR with deprotonated 2-OH-group.

Fig. 3 Molecular structure of (I) (a) and (II) (b) showing with displacement ellipsoids at the 35% probability level.

In the given salt-type cocrystals, an anionic form of FVR with the deprotonated 2-OH group has been found. Instead of an intramolecular O2-H...O1 hydrogen bond, a new intramolecular N1-H...O2 hydrogen bond is formed. The carboxamide group in both structures is rotated one-half revolution around the C1-C2 bond.

Acknowledgements

The authors to thank the Ministry of the Science and Innovation of the Republic of Uzbekistan for financial supporting by performing given work.

Supporting Information

All geometrical parameters of the molecule and all hydrogen bonds are presented in Tables S1 – S4, Figs. S1 and S2 in

Supporting Information.

References

1. Y. X. Du and X. P. Chen, *Clin. Pharm. Therap.*, **2020**, *108*, 242.
2. K. Shiraki and T. Daikoku, *Pharm. Therapeutics.*, **2020**, *209*, 107512.
3. L. Antonov, *Theor. Chem. Acc.*, **2020**, *139*, 145.
4. F. Shi, Z. Li, L. Kong, Yu. Xie, T. Zhang, and W. Xu, *Drug. Discov. Ther.*, **2014**, *8*, 117.
5. K. Harismah and M. Mirzaei, *Adv. J. Chem. B*, **2020**, *2*, 55.
6. P. Deka, D. Gogoi, Kh. Althubeiti, D. R. Rao, and R. Thakuria, *Cryst. Growth Des.*, **2021**, *21*, 4417.
7. A. S. Goloveshkin, A. A. Korlyukov, and A. V. Vologzhanina, *Pharmaceutics*, **2021**, *13*, 139.
8. X. Wang, L. Wang, Ch. Yao, G. Xie, Sh. Song, H. Li, Y. Qu, and X. Tao, *Cryst. Growth Des.*, **2021**, *21*, 3807.