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 (1), monoclinic P21/c, Z = 4, a = 12.2433(3), b = 22.5400(5), c = 7.3223(3) Å, β = 106.287(3)°, V = 1939.6(1) Å³, R1 = 0.0499; (II), triclinic P1, Z = 2, a = 8.5903(12), b = 9.4980(10), c = 10.0337(13), α = 83.464(10), β = 79.338(11), γ = 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.

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

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 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 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) 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 atoms were added using the riding model.

Fig. 1 Chemical formula of FVR.

Fig. 2 Tautomeric (a) enol and (b) keto forms of FVR.
atoms were positioned geometrically (OH = 0.82 Å and CH = 0.93 Å) and refined using a riding model, with $U_{iso}(H) = 1.2 U_{eq}(C)$ and 1.5 $U_{eq}(O)$. Crystal data and details of the 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 N7–H···O and the N1–H···O hydrogen bonds. Both MEA+ are in a gauche form: the torsion angles O10–C9–C8–N7 equal to –64.0(3)(A) and –55.2(2)(B). Crystal (2) is built from two FVR− anions linked to each together by an H2en2+ cation through N–H···O2 hydrogen bonds (Fig. 3b). The N2 and N3 atoms participate in the hydrogen bonds N8–H8B···N2B and N8–H8C···N3B, and also in the weak intermolecular bond C4B–H4B···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 NH2-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. 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 O2–H···O1 hydrogen bond, a new intramolecular N1–H···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).

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

| Chemical formula: | C7H11N4O3F | C11H10NOF |
|-------------------|------------|------------|
| Formula weight    | 218.20     | 178.53     |
| $T$ =             | 293(2)K    |            |
| Space group       | P21/c      | P1         |
| $a$ =             | 12.2433(3)Å| 8.5903(12)Å|
| $b$ =             | 22.5400(5)Å| 9.4980(10)Å|
| $c$ =             | 7.3233(3)Å | 10.0337(13)Å|
| $\alpha$ =        | 90°        | 83.464(10)°|
| $\beta$ =         | 106.287(3)°| 80.665(10)°|
| $\gamma$ =        | 1939.60(10)Å | 790.90(18)Å|
| $Z$ =             | 4          | 2          |
| $D_1$ (g cm$^{-3}$)| 1.494     | 1.25 g cm$^{-3}$ |
| $\mu$ (Cu Kα) =  | 1.130 mm$^{-1}$ | 0.621 mm$^{-1}$ |
| $F(0 0 0)$ =      | 912.0      | 282.0      |
| Crystal size =    | 0.35 x 0.35 x 0.45 mm$^3$ | 0.30 x 0.35 x 0.40 mm$^3$ |
| 2θ range for data | 7.844 to 152.342° | 9.002 to 152.38° |
| Reflections       | 13436      | 5590       |
| Independent reflections | 3991 [R_m = 0.0468, R_{free} = 0.0965] | 3991/0.315 [191/0.238] |
| Data/restraints/parameters | 3991/0.0/315 | 3191/0/238 |
| Goodness-of-fit on $F^2$ | 1.068 | 0.985 |
| Final $R$ indexes | $R_1 = 0.0499, wR_2 = 0.1314$ | $R_1 = 0.0568, wR_2 = 0.1191$ |
| [f > 2σ(f)]:      | $R_1 = 0.0709, wR_2 = 0.1562$ | $R_1 = 0.1085, wR_2 = 0.1515$ |
| Largest diff. peak/hole | 0.27/–0.31 eÅ$^{-1}$ | 0.27/–0.31 eÅ$^{-1}$ |
| Data collection:  | “XtaLAB Synergy, Single source at home/near, HyPix3000” | |
| CCDC deposition number: | 21087698 | 2108797 |

![Fig. 3](image3.png) **Molecular structure of (I) (a) and (II) (b) showing with displacement ellipsoids at the 35% probability level.**

![Fig. 4](image4.png) **Anionic FVR with deprotonated 2-OH-group.**
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.

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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.

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