



# Favipiravir tautomerism: a theoretical insight

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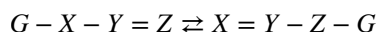
## Abstract

There is no experimental information about the tautomerism of Favipiravir (**T-705**). Therefore, its tautomeric state was predicted by using density functional theory in gas phase and in solution (toluene, acetonitrile and water). The results have shown that, in neutral state, the enol form is strongly dominating in both gas phase and solution. The carboxamide group is easily protonated in the presence of acid, which leads to shift of the tautomeric equilibrium toward the keto tautomer. In order to validate the theoretical predictions, 2-hydroxy pyridine and 2-hydroxy pyrazine were also included in the set of studied compounds. The available experimental data about their tautomerism are in very good agreement with the theoretical predictions, which validate the conclusions made for **T-705**.

**Keywords** T-705 · Avigan · Favilavir · Favipiravir · COVID-19 · Tautomerism · Density functional calculations

## 1 Introduction

According to the IUPAC definition [1], tautomerism is “Isomerism of the general form:



where the isomers (called *tautomers*) are readily interconvertible; the atoms connecting the groups *X*, *Y*, and *Z* are typically any of C, N, O, or S, and *G* is a group that becomes an electrofuge or nucleofuge during isomerization. The commonest case, when the electrofuge is  $H^+$ , is also known as *prototropy*.”

Although the prototropic tautomerism can occur (really or potentially) in relatively limited number of molecules, it is one of the important phenomena in organic chemistry in respect of the property and reactivity [2]. The interconvertivity is the major difference with the other types of isomers: enantiomers, or *cis* and *trans* isomers, for instance, also possess a formulaic identity just as tautomers do, but are difficult to interconvert, which allows physically to be isolated. Tautomers have chameleonic nature in most of the cases. They are able to switch from one, well-known,

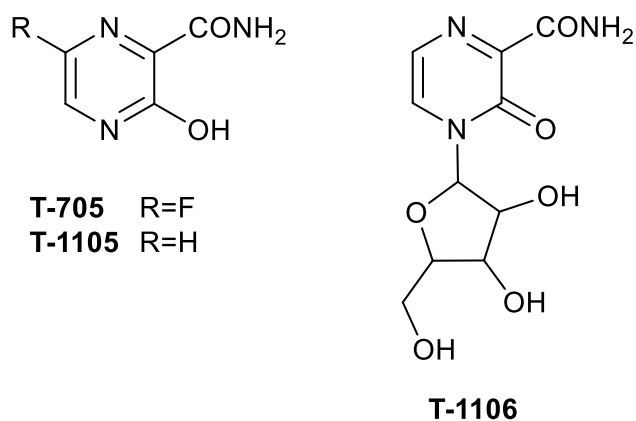
structure to another following the changes in the local environment, and then to return back, when original conditions are restored. The transfer of the proton from one place of the molecule to another dramatically changes the electronic structure and, hence, variety of properties. As a result, the tautomeric forms differ in shape, functional groups, surface, and hydrogen bonding pattern.

Biological activity is one of the properties that are heavily affected by the proton transfer. The vital importance of knowing the tautomeric state in various aspects of the drug design has been underlined by many authors [3–7]. Martin [4] wrote recently that about 21% of molecules in various drug discovery databases are potentially tautomeric [8–10], and it is crucially important to know the exact tautomeric state in the different stages of the drug design.

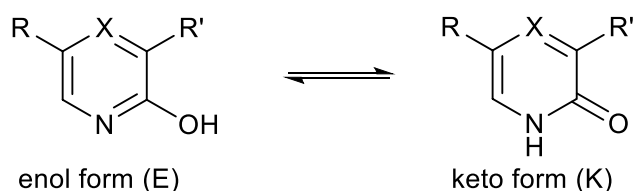
Favipiravir (also known as **T-705**, Avigan, Favilavir, Scheme 1) is an antiviral drug [11–14], developed by FUJIFILM Toyama Chemical Co (<http://fftc.fujifilm.co.jp/en/di/pipeline/index.html>) [15]. Along with other experimental antiviral drugs (**T-1105** and **T-1106**) [11], it belongs to the pyrazine carboxamide family. According to the results of clinical studies, **T-705** revealed activity against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus, as well as other flaviviruses, arenaviruses, bunyaviruses, and alphaviruses [11, 12]. Recently, the same drug has shown promising results in the treatment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China [16–20].

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**Scheme 1** Compounds in the current study



**Scheme 2** Tautomerism of the studied compounds

As seen from Scheme 1, **T-705**, as well as its analogues (**T-1105** and **T-1106**), belong to the potentially tautomeric 2-hydroxy pyrazine family. The studies of the mechanism of action of **T-705** revealed its activity as a nucleobase analogue [21]. It is converted into the ribonucleoside triphosphate intracellularly and ultimately acts on the viral RNA-dependent RNA polymerase [22–24]. The **T-705** and **T-1105** ribonucleosides [25] are nothing else than fixed keto tautomeric forms as **T-1106** actually is.

At this moment of urgent need for COVID-19 treatment solutions, any additional information, including tautomeric one, about this family of compounds, could be useful. The experimental investigations of the tautomerism of **T-705** will be performed in future for sure, but in the current communication, the potential of theoretical chemistry will be used to predict the tautomeric state of favipiravir and the effects of substitution in the pyrazine ring. Such study is not unrelated to reality, because there is sufficient number of experimental and theoretical data for the tautomerism of structurally similar compounds, which can be used to validate the theoretical predictions.

## 2 Results and discussion

The tautomeric equilibrium in the studied compounds is sketched in Scheme 2. Strictly speaking, this is lactim–lactam tautomerism, but for simplicity in the discussion below,

enol and keto tautomers will be used. The corresponding stabilities of the tautomers are collected in Table 1 in gas phase and in three solvents with different polarity. Taking into account that implicit solvation is used to describe the solvent effect, the results in the table has to be considered only in the light of the relative stabilization of the more polar tautomer, i.e., the expected specific solute–solvent interactions are not accounted in water. Logically, the increased dielectric constant of the solvents, from toluene to water, leads to relative stabilization of the more polar keto form in each of the listed compounds.

Having in mind that the relative stability of the tautomers strongly depends on the used level of theory, selected basis set and the solvent description, reference compounds, for which reliable experimental data are available, are needed to validate the overall approach. The tautomerism of both, **T-705** and **T-1105**, has never been studied experimentally before. Therefore, **1** and **2**, having the same tautomeric backbone, are included in the set in order to clarify the reliability of the theoretical predictions.

As seen, in the case of 2-hydroxy pyridine (**1**), the enol form is more stable in gas phase (~90%), while going to a condensed phase its fraction is reduced from ~20% in toluene to a negligible amount in the rest of the solvents. The replacement of the carbon atom with nitrogen in **2** leads to destabilization of the keto tautomer. The results suggest that the equilibrium is almost fully shifted toward **2E** in gas phase, and following the same trend as in **1**, the increased solvent polarity stabilizes **2K**. Fluorine substitution in **3** and a carboxamide group in **T-1105** leads to a further stabilization of the enol tautomers. Both effects are accumulated in **T-705** suggesting that the keto tautomer is not likely to be experimentally observed. This conclusion agrees with the recent calculations of da Silva [26], performed at a different level of theory. There is a detail in **T-1105** and **T-705**, which should be taken into account. The tautomeric proton in the enol form is a part of a strong intramolecular hydrogen bonding, while the NH proton in the keto form is available for interaction with proton acceptor solvents like water. Additional stabilization of the keto tautomer, where two neighbor carbonyl groups are present, can be achieved also by a complexation with metal ions. This could change the tautomeric state, but only further experiments can prove or not such expectations. It should be noted that some recent cases of tautomerism of drugs (curcumin [27] and piroxicam [28]) show that theoretically unfavored tautomers can be stabilized in water as a result of specific interactions.

The keto–enol tautomerism of 2-hydroxy pyridine (**1**) is one of the most studied tautomeric cases, both theoretically and experimentally. Very detailed description of the effects of the used level of theory can be found in [7, 29, 30]. For gas phase, most of the density functionals overestimate (some of them very strongly) the keto form stability, while

**Table 1** Relative energies\* at M06-2X/def2TZVP level of theory (TautLYP/6-31 ++Gdp in the brackets) of the tautomers of the studied compounds (see Scheme 2)

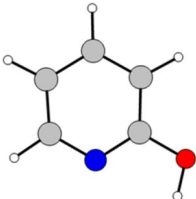
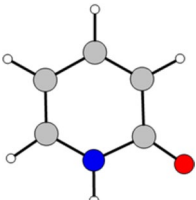
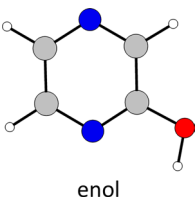
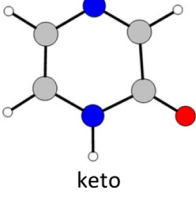
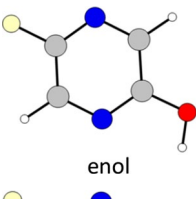
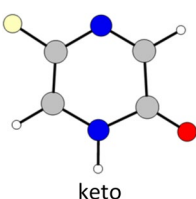
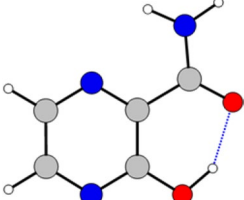
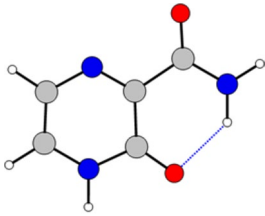
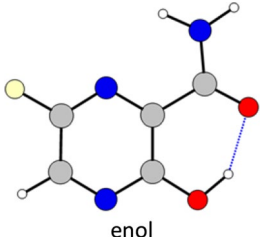
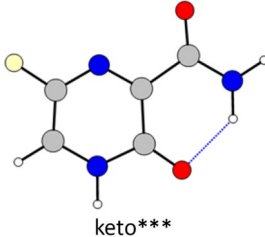
Comp.	Tautomer**	$\mu$ [D]	$\Delta E$ [kcal/mol]			
			Gas phase	Toluene	Acetonitrile	Water
<b>1</b> X=CH R=H R'=H	 enol	1.3	-1.26 (-1.41)	0.76 (0.84)	3.07 (3.44)	3.18 (3.57)
	 keto	4.3				
<b>2</b> X=N R=H R'=H	 enol	1.4	-2.33 (-2.47)	-0.41 (-0.34)	1.84 (2.19)	1.96 (2.32)
	 keto	4.1				
<b>3</b> X=N R=F R'=H	 enol	2.2	-5.82 (-5.66)	-3.82 (-3.47)	-1.49 (-0.87)	-1.37 (-0.74)
	 keto	3.2				
<b>T-1105</b> X=N R=H R'=CONH <sub>2</sub>	 enol	4.5	-10.2 (-10.9)	-7.25 (-7.63)	-3.73 (-3.73)	-3.55 (-3.52)

Table 1 (continued)

Comp.	Tautomer**	$\mu$ [D]	$\Delta E$ [kcal/mol]			
			Gas phase	Toluene	Acetonitrile	Water
	 keto	6.0				
<b>T-705</b> X=N R=F R'=CONH <sub>2</sub>	 enol	3.3	-13.3 (-13.7)	-10.2 (-10.4)	-6.53 (-6.27)	-6.33 (-6.05)
	 keto***	6.0				

\*Difference between the total energies of the enol and keto forms ( $\Delta E = E_E - E_K$ ), negative value indicates more stable enol form and vice versa

\*\*Presented as the most stable isomer

\*\*\*Orientation of the CONH<sub>2</sub> group corresponds exactly to the crystal structure of **T-705**-ribonucleoside as reported in [25]

HF and post-HF methods predict more, but not dramatically, stable **1E**. Fortunately, there are experimental data to compare. The  $\Delta G^\circ$  value has been estimated, in kcal/mol units, by variety of techniques and at different temperatures as follows:  $-0.8$  (573 K, IR spectroscopy [31]; 412 K, UV spectroscopy [32]),  $-0.57$  (403 K, X-ray photoelectron spectroscopy [33]),  $-0.88$  (323 K, photoelectron spectroscopy [34]),  $-0.87$  (360 K, IR matrix-isolated technique) [35] and  $-0.77$  (356 K, microwave spectroscopy) [36]. The decrease in the temperature leads to elevation of the enol form content from 68% [37] at 473 K to 80% at 323 K [34]. In this respect, the prediction of 90% for **1K** at room temperature, as shown in Table 1, is very reasonable. Even at CCSD(T)/def2TZVP level of theory, the stability of the enol form is slightly overestimated in respect of the experiment, predicting  $\Delta E$  values of  $-1.2$  kcal/mol [38]. It is worth to underline that the estimation of the relative stability of the tautomers in gas phase is based, in some of the cases, on assumption that both tautomers have equal individual responses (UV/IR individual intensity, ionization cross section, etc.). This is a

common problem in spectroscopy when tautomeric equilibria are investigated, because the individual tautomers cannot be isolated, and hence, their individual responses are unknown. Details about possible assumptions and deviations of the results can be found in [39, 40]. Returning back to the classical work of Beak and Fry [32], the tautomeric ratio was determined in the range 393–412 K by means of gas-phase UV spectroscopy. In this particular case, the tautomeric fractions were estimated using the intensities of the O and N methylated compounds (so-called fixed tautomers) as individual responses of the pure tautomers, which makes the approach physically reliable [2, 40]. The estimated enol fractions are in the range 50–80% ( $2.5 \pm 1.5/1$  ratio of **1E/1K**), which leads a  $\Delta G^\circ$  value varying from 0 to  $-1.1$  kcal/mol.

The data for the tautomerism of **1** in solution are also helpful in validating the approach. Such information is available for cyclohexane [41, 42], carbon tetrachloride [43] and acetonitrile [42], determined by UV spectroscopy and methylated compounds as references. The corresponding  $\Delta G^\circ$  values are 0.3, 1.3 and 2.7 kcal/mol respectively, which

indicates predominance of the keto tautomer as predicted by the calculations. The results for water are approximate (based on the pKa approximation [42, 44, 45]) and indicate a ratio  $1E/1K < 1/900$ , i.e., the equilibrium is practically switched toward the keto tautomer.

Comparing to **1**, in the case of **2**, less experimental data are available. By using IR matrix-isolated technique,  $\Delta G^\circ$  values were estimated as follows:  $-1.55 \pm 0.11$  (360 K) [35] and  $-1.85 \pm 0.24$  (360 K) [46] kcal/mol, confirming that the enol form strongly dominates in gas phase. The stabilization of the enol in **2** is larger comparing to **1**, as the calculations suggest. It was shown in DMSO by NMR that the **2K** form is dominating [47].

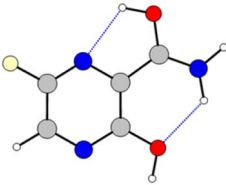
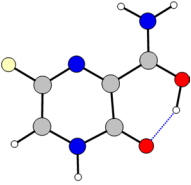
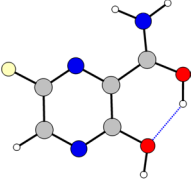
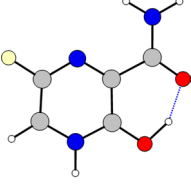
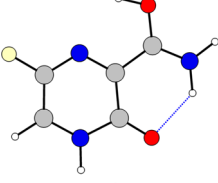
The experimental data for **1** and **2** confirm the predicted effects of the solvent environment and the structural changes on the tautomerism in the studied heterocycles. Therefore, we can assume that the theoretical predictions should be correct in the case of the other compounds for which there are no experimental data available. It should be expected that the neutral **T-1105** and **T-705** with high probability exist as enol tautomers in most of the organic solvents and water.

**T-705** is an orally administered drug and some aspects of the drug-delivery process should be taken into account when the tautomerism is discussed. The dissolution takes place in the stomach at pH ~ 1, which leads to protonation. In Table 2 the relative stabilities of the most stable protonated forms are collected. The data clearly indicate that the CO group from carboxamide is a preferred protonation site (**KE** is the only exception, which will be discussed below), which change leads to the change in the tautomeric state. The other protonation scenarios lead to structures with relative stability of 10 and more kcal/mol in gas phase. As seen from the Table, in gas phase a mixture of structures with similar stabilities is possible, while with increasing solvent polarity it becomes evident that the protonated keto tautomer **K1** becomes the most stable one. From structural point of view, the structures **K1** and **KE** could be considered as a protonated keto form, where the coming acidic proton is delocalized and chelated between two neighbor carbonyl groups. It could be concluded that the protonation of **T-705** leads to shift of the equilibrium from the enol to the keto tautomer.

### 3 Conclusions

Due to the lack of experimental data for the tautomerism of favipiravir, its tautomeric state was predicted by means of DFT calculations. The results have been validated by including 2-hydroxy pyridine and 2-hydroxy pyrazine, where experimentally determined tautomeric constants are available at variety of conditions, in the set of investigated compounds. According to the calculations, the enol tautomer is substantially more stable in the neutral **T-705** and its analogue **T-1105**. Upon

**Table 2** Relative energies\* (M06-2X/def2TZVP) of the most stable protonated forms of **T-705**

Structure	$\Delta E$ [kcal/mol]			
	Gas phase	Toluene	Acetonitrile	Water
 E1	0.0	1.37	2.88	2.95
 K1	0.20	0.0	0.0	0.0
 E2	0.73	2.13	3.69	3.76
 KE	1.28	0.69	0.06	0.02
 K2	1.53	1.45	1.58	1.59

\*Difference between total energies of the protonated compounds

acid addition, the equilibrium should be shifted to the keto tautomer. Of course the exact answer about the tautomerism of favipiravir and related compounds could be given by experimental studied. The corresponding investigations are in progress and will be reported.

## 4 Methodology

Quantum chemical calculations were performed by using the Gaussian 09 D.01 program suite [48]. The M06-2X functional [49, 50] was used with def2TZVP [51] basis set. This fitted hybrid meta-GGA functional with 54% HF exchange is specially developed to describe main-group thermochemistry and non-covalent interactions, showing very good results in prediction of the position of tautomeric equilibria [27–29, 52–54]. In addition, TautLYP [55], a specially optimized to predict the tautomerism in azodyes and Schiff bases, B3LYP-based functional, was used with 6–31 ++Gdp basis set. All structures were optimized in ground state without restrictions, using tight optimization criteria and ultrafine grid in the computation of two-electron integrals and their derivatives. Solvent effects are described using the Polarizable Continuum Model (PCM, the integral equation formalism variant, IEFPCM, as implemented in Gaussian 09) [56]. The true minima were verified by performing frequency calculations in the corresponding environment.

The relative stability of the tautomers was presented as difference between the total energies of the enol and keto forms ( $\Delta E = E_E - E_K$ ) in the corresponding solvent. A negative value indicates more stable enol form and vice versa.

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