

Structural flexibility of favipiravir and its structural analogues in solutions: experimental and computational insight

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Supporting information

Contents:

Figure S1. Cluster of composition 3:50 H ₂ O optimized with the use of B3LYP-3c	S2
Figure S2. Cluster of composition 3:50 H ₂ O optimized with the use of PBE/def2-SVP	S2
Analysis of the tautomeric composition of solid 2 by IR spectroscopy and quantum chemical computations	S3
List of references	S6

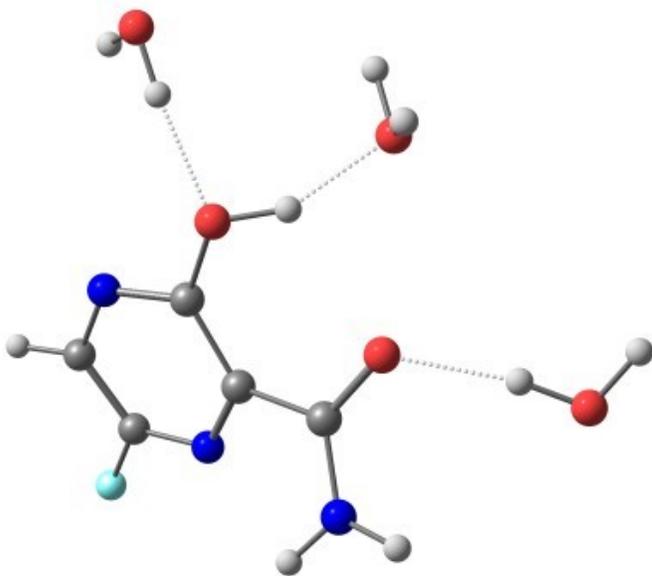


Figure S1. Fragment of structure of cluster of composition **3:50** H₂O optimized with the use of B3LYP-3c. 47 H₂O molecules are omitted for clarity.

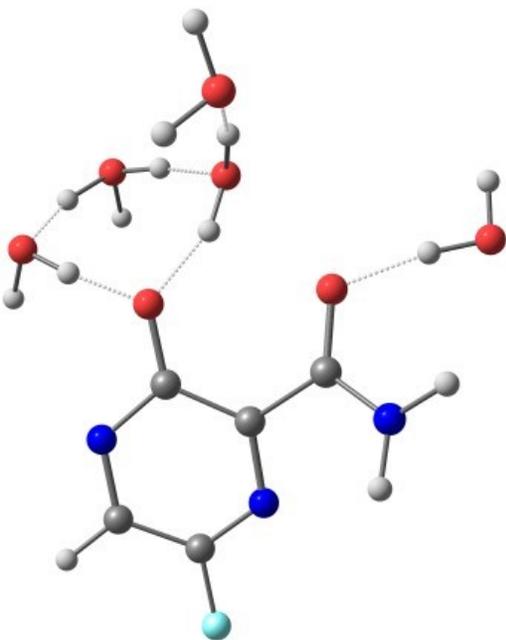


Figure S2. Fragment of structure of cluster of composition **3:50** H₂O optimized with the use of PBE-D3/def2-SVP. 45 H₂O molecules are omitted for clarity.

Analysis of the tautomeric composition of solid **2** by IR spectroscopy and quantum chemical computations

IR spectra of solid **2** and **5** are very close to each other (Fig. S3) in the spectral region of 1000-1800 cm^{-1} (taking into account the presence of an ethyl fragment in **5**), which strongly suggests that in the solid state **2** exists in keto form.

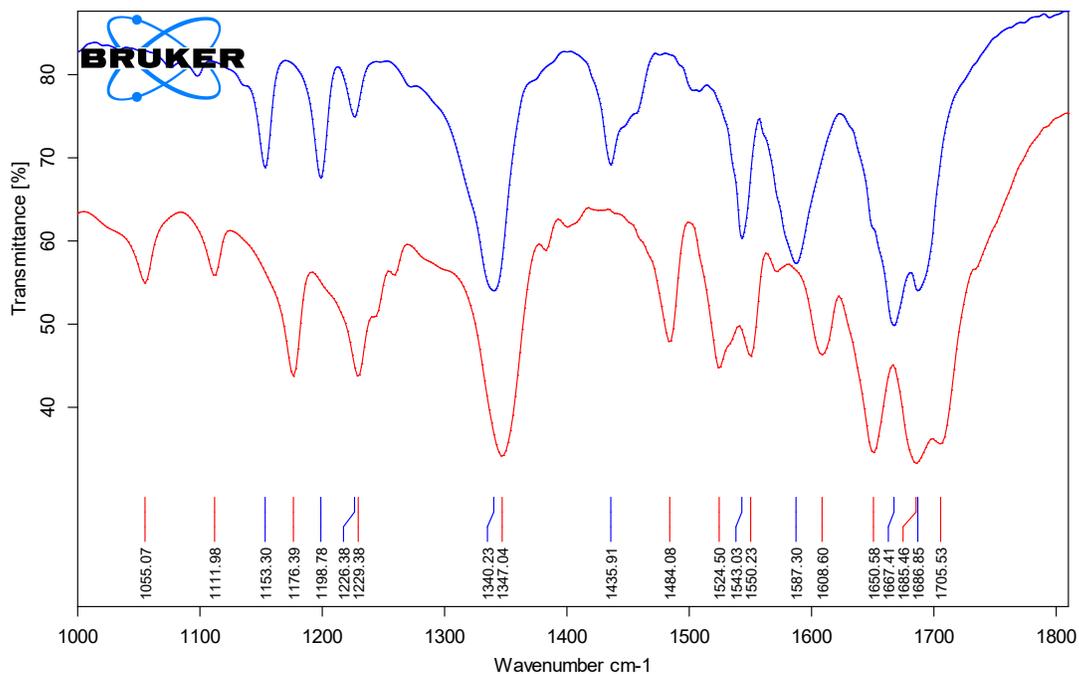
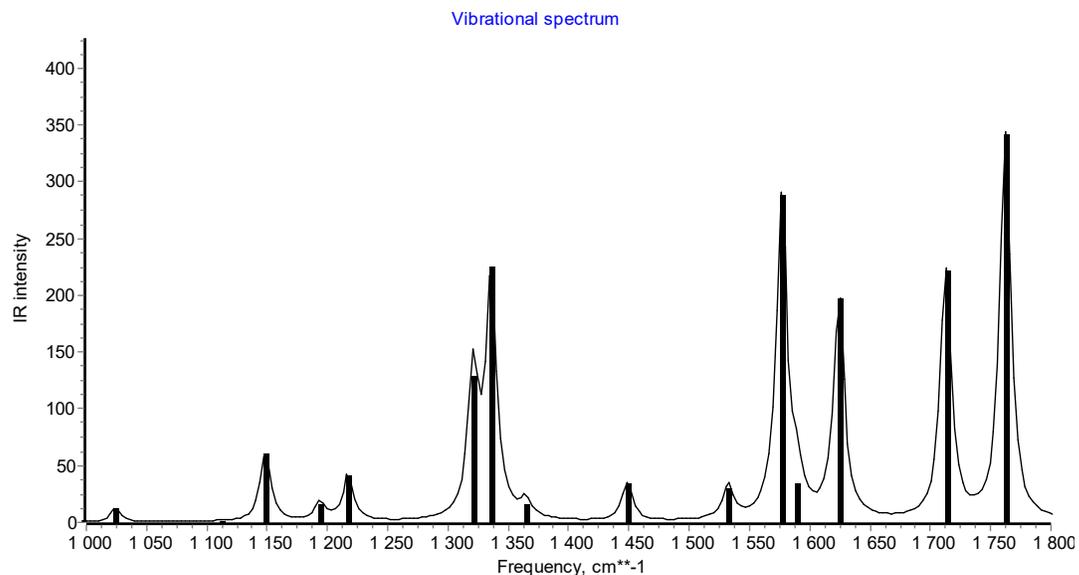


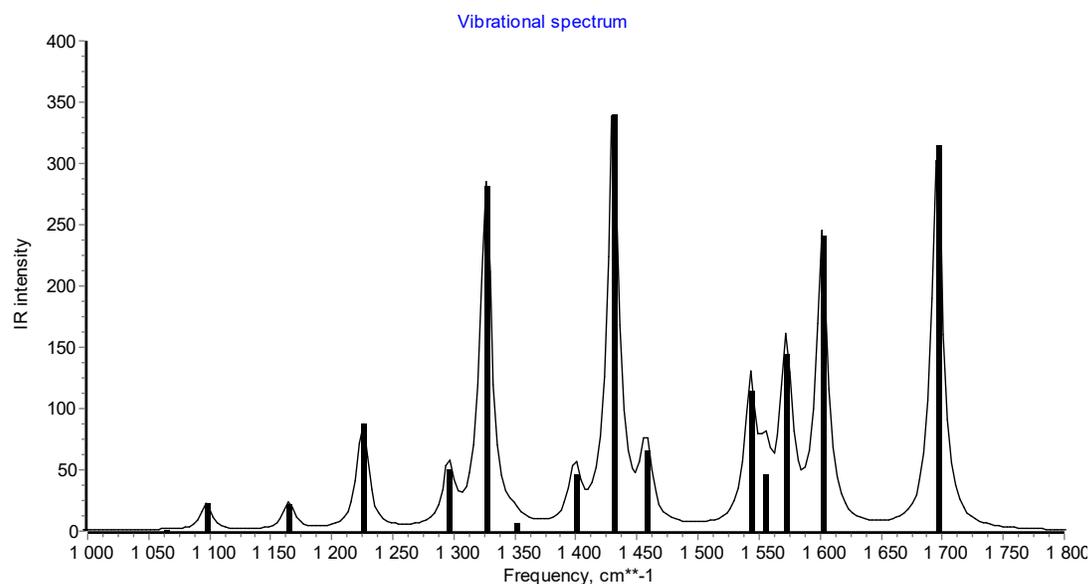
Figure S3. FTIR spectra of solid **2** (red) and **5** (blue) in KBr pellets.

Indeed, a comparison of spectra of keto and enol tautomers of **2** simulated with the use of B3LYP-3c method¹ (Fig. S4) demonstrates that experimental spectrum (Fig. S3) matches theoretical spectrum of keto tautomer much better than the computed spectrum of enol form.



NO2keto

and



NO2enol

Figure S4. Simulated IR spectra of keto and enol tautomers of isolated molecule **2**

The main feature of the theoretical spectrum of enol form, allowing to reject this tautomer on the basis of a simple comparison of Figs. S3 and S4, is a very strong band of bending vibrations of the hydroxyl group, δOH , at 1430 cm^{-1} , which is absent both in the experimental spectrum and in the simulated spectrum of keto tautomer. Naturally, the spectra of molecule **2**, containing several moieties capable of forming intermolecular hydrogen bonds (HBs), are expected to change at transition from the gas state to the condensed state. Thus, to make a more reliable comparison of the experimental solid-state spectrum with the simulated spectra of the tautomers, the simulations were repeated for the clusters

keto:20DMF and enol:20DMF generated with the use of QCG program² (for details, see Experimental). In these clusters, the NH, OH and NH₂ groups of molecules **2** form HBs with the carbonyl groups of DMF molecules (Fig. S5), which approximates a possible H-bonding in the crystal. The simulated spectrum of the cluster enol:20DMF (Fig. S6) still contains very strong bands at 1406 and 1420 cm⁻¹ produced by complex vibrations with strong participation of δOH. The absence of any intense bands between 1360 and 1470 cm⁻¹ in the experimental spectrum (Fig. S1) allows to exclude the significant presence of enol tautomer in solid **2**.

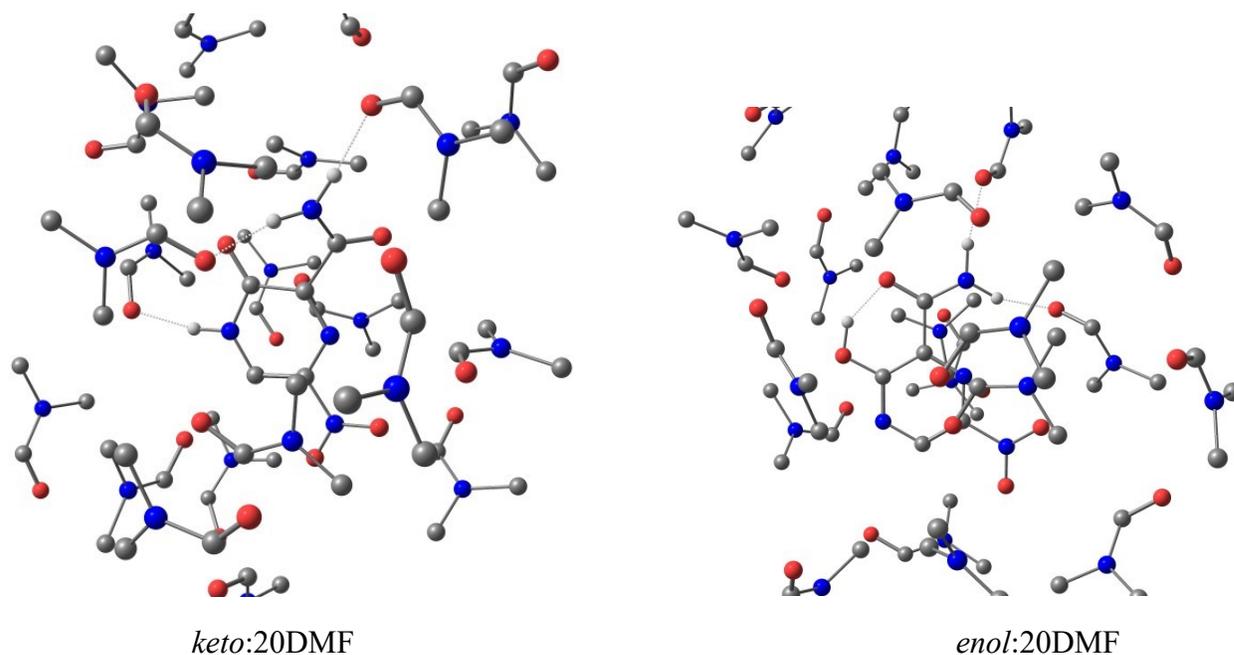


Figure S5. Central fragments of clusters *keto:20DMF* and *enol:20DMF*. Hydrogen atoms at carbon atoms are omitted for clarity. Hydrogen bonds are shown with dotted lines.

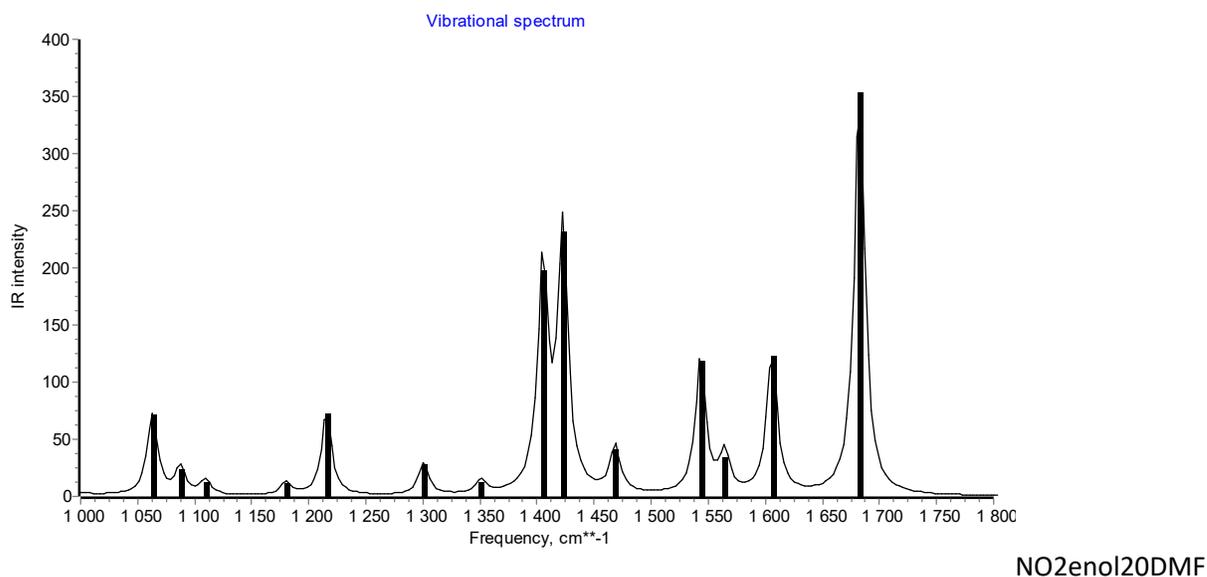


Figure S6. Simulated IR spectrum of cluster *enol:20DMF*, shown in Fig. S5

List of references

¹ Pracht P., Grant D., Grimme S. Comprehensive Assessment of GFN Tight-Binding and Composite Density Functional Theory Methods for Calculating Gas-Phase Infrared Spectra, *J. Chem. Theory Comput.* **2020**, *16*, 7044-7060.

² Spicher, S., Plett, C.; Pracht, P.; Hansen, A.; Grimme, S., Automated Molecular Cluster Growing for Explicit Solvation by Efficient Force Field and Tight Binding Methods. *J. Chem. Theory Comput.* **2022**, *18*, 5, 3174–3189.