DFT study of tegafur complexes with MoS_2: structure, interaction energies and vibrational spectra

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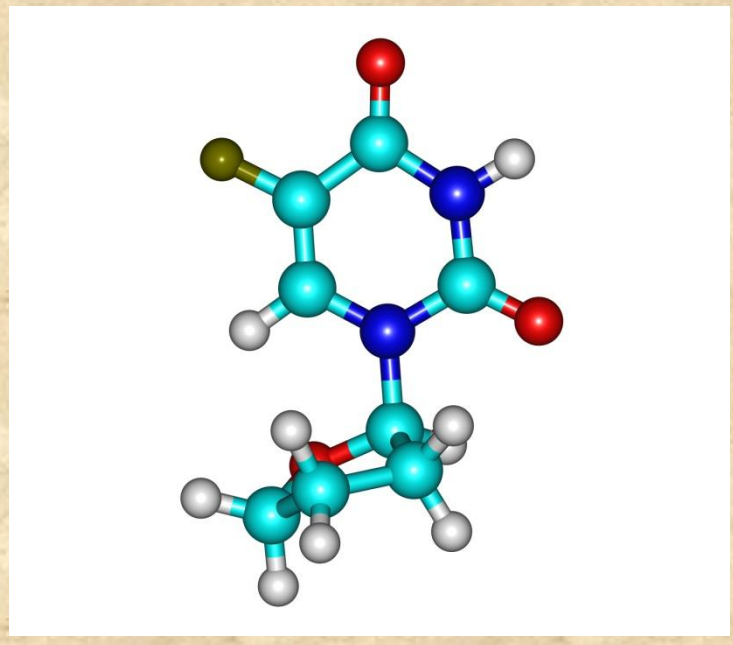
aim

The aim of this study is to determine the structure, stability and spectral characteristics of molybdenum disulfide (MoS_2) complexes with the tegafur molecule using the quantum mechanical DFT/M06-2X method.

MoS_2 is considered as a potential platform for drug delivery.

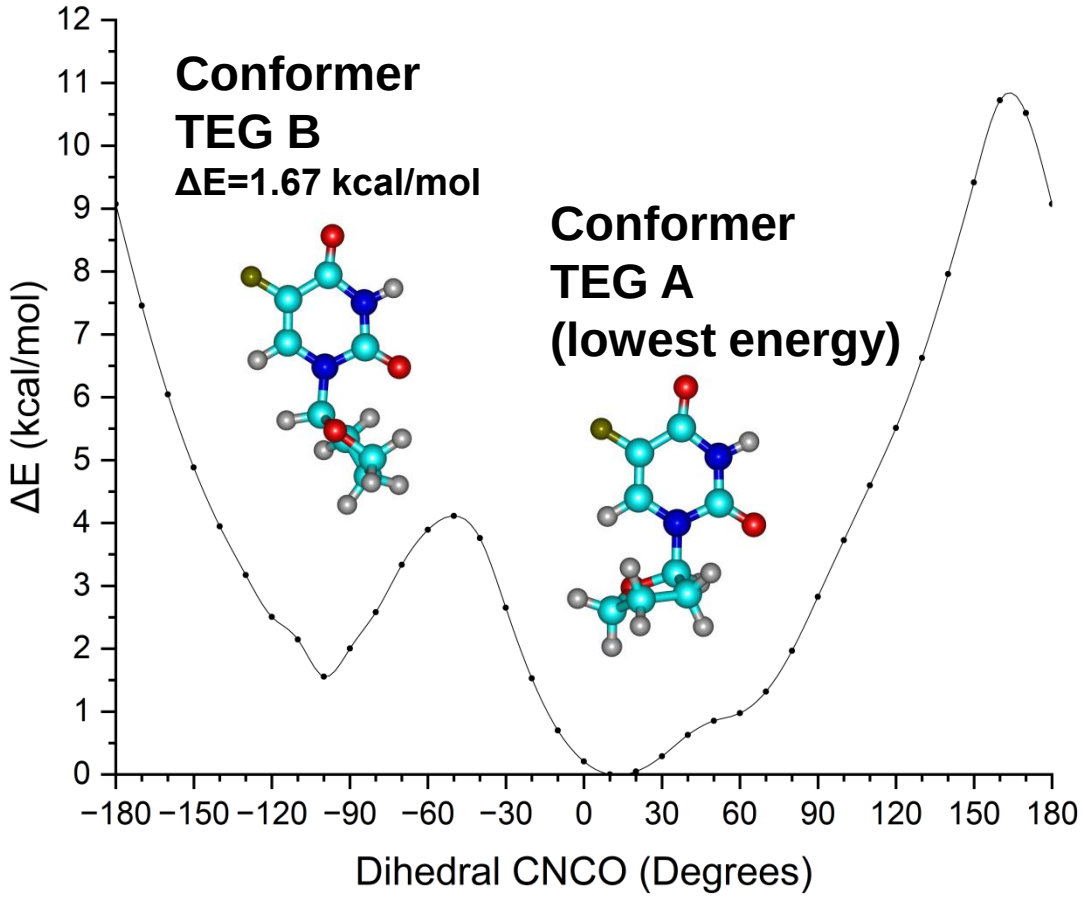


Structure of tegafur

Tegafur *(5-fluoro-1-(oxolan-2-yl)-pyrimidine-2,4-dione or 1-(oxolan-2-yl)-5-fluorouracil)* is a chemotherapeutic prodrug of 5-fluorouracil.

Tegafur is metabolized to 5-fluorouracil by the CYP2A6 enzyme.

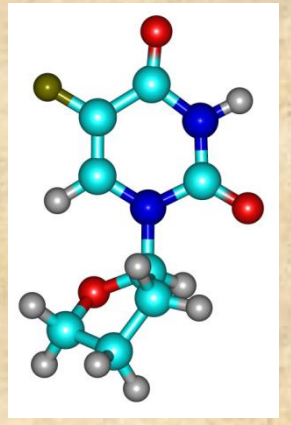
tegafur conformers



Dependency of energy of tegafur molecule on the rotation of oxolane fragment around the N1-C bond calculated at the B3LYP/aug-cc-pVDZ level of theory.

Conformers **TEG A** and **TEG B** differ in rotation of the oxolane fragment around the N1-C bond. Conformer **TEG C** differ in conformation of the 5-membered oxolane ring.

Conformer
TEG C
ΔE=0.45 kcal/mol



mos2-tegafur complexes / methods

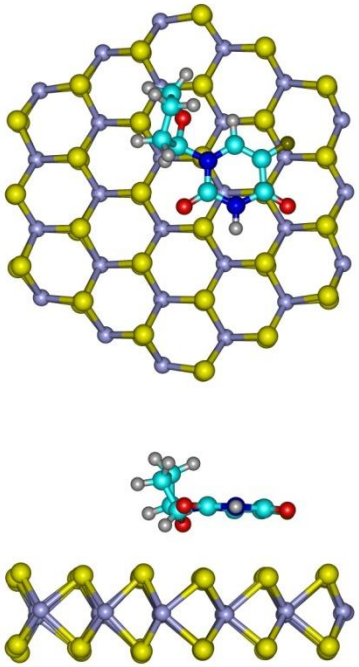
DFT/M06-2X: geometry optimization and frequency calculations

Basis sets:
Mo : LANL2DZ Effective Core Potential (ECP)
S: LANL2DZdp ECP + Diffuse + Polarization
tegafur: 6-31++G(d,p)

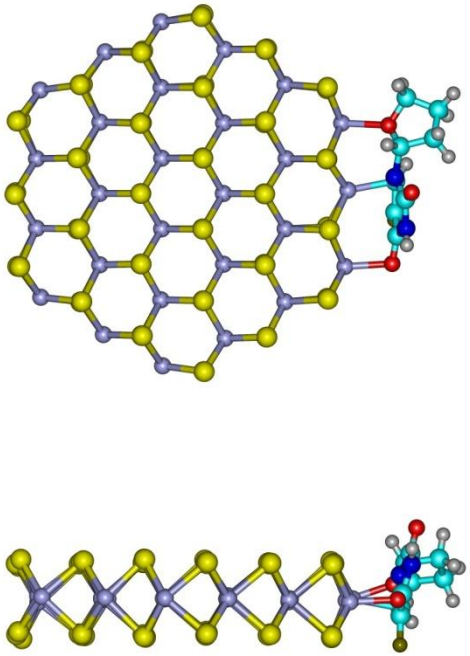
Structure of possible complexes formed by the most stable conformer of tegafur (TEG A) and the MoS_2 fragment (27 molybdenum atoms and 54 sulfur atoms) was calculated.

Five complexes with the pristine MoS_2 fragment were found in which the tegafur molecule interacts with the MoS_2 surface formed by sulfur atoms (stacked complexes).
Four other complexes were also found in which the tegafur molecule is located at the edge of the MoS_2 fragment (covalently bonded complexes).

mos2-tegafur complexes / structure



MoS_2-TEG Stacked
IE= -12.2 kcal/mol

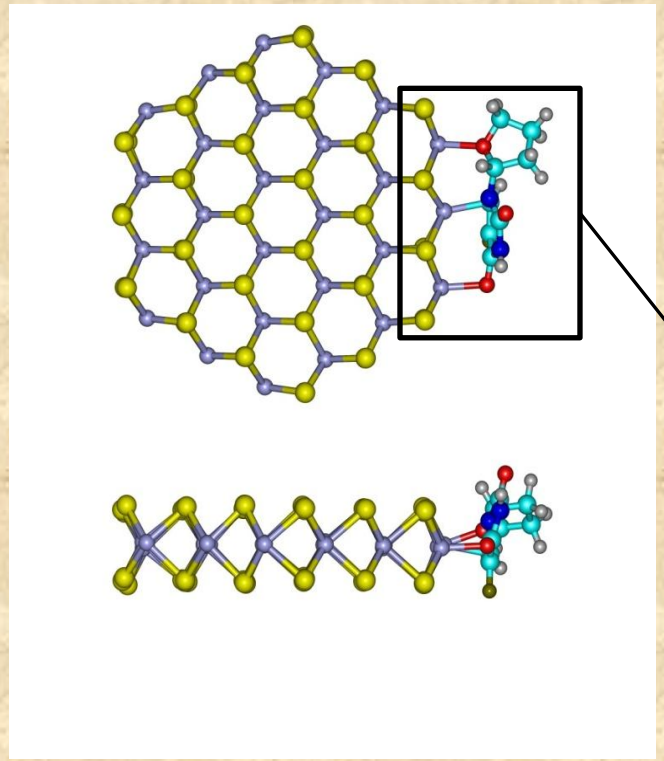


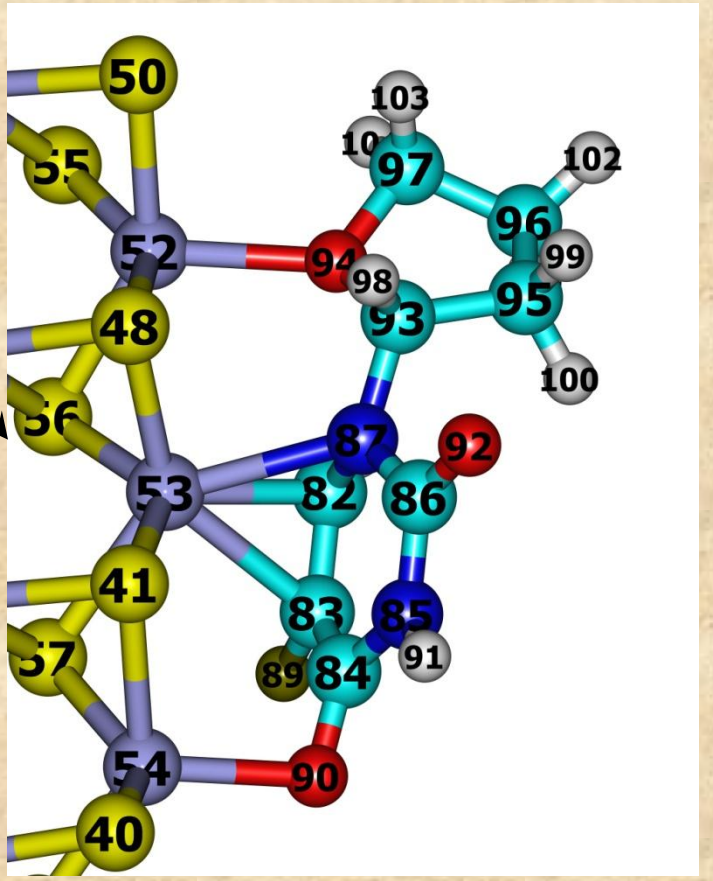
MoS_2-TEG Bonded
IE= -72.3 kcal/mol

Calculated structure of the most stable stacked and covalently bonded MoS_2-tegafur complexes

Calculations showed significant differences in the interaction energies between stacked and bonded complexes. In the stacked complexes, the interaction energy is approximately in the range from -10 to -12 kcal/mol, while in the bonded complexes it reaches -72 kcal/mol. This difference is explained by relatively weak van der Waals interactions in the stacked complexes and significantly stronger interactions in the complexes with covalent bonds. Taking into account the aqueous environment (PCM approach) leads to a significant weakening of the interaction in all complexes. The interaction energy in stacked complexes decreases to approximately -3 kcal/mol, and in the bonded complexes to -20 kcal/mol.

mos2-tegafur complexes / Wiberg bond indexes



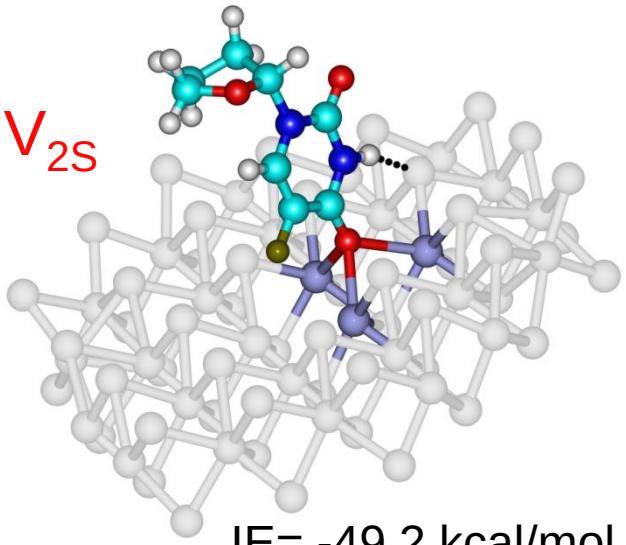


Calculated Wiberg bond indexes:

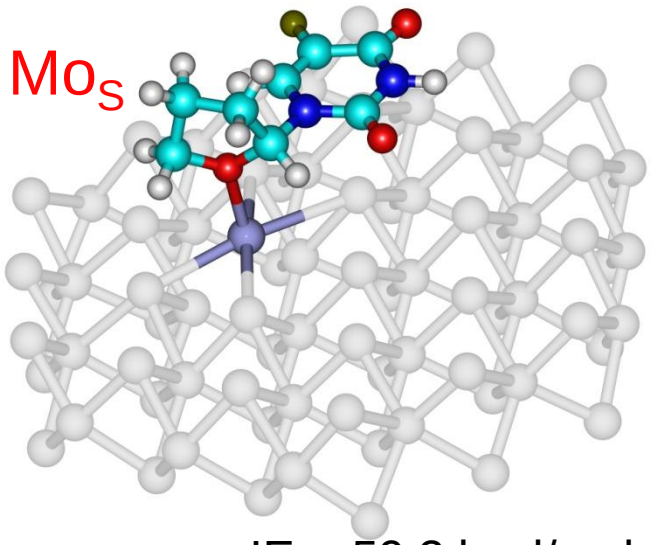
Bond	WBI
52-94	0.39
53-82	0.59
53-83	0.30
53-87	0.31
54-90	0.55

NBO (Natural Bond Orbital) analysis demonstrated the formation of **coordination covalent bonds** between the tegafur atoms and the edge molybdenum atoms in the most stable MoS_2-tegafur bonded complexes.

mos2-tegafur complexes / mos2 point defects



IE= -49.2 kcal/mol



IE= -59.2 kcal/mol

We also studied tegafur complexes with the MoS_2 surface that have point defects of two types:

substitution of a surface sulfur atom by a molybdenum atom (denoted as Mo_S),

vacancy of two adjacent surface sulfur atom (denoted as V_{2S}).

Six complexes for MoS_2 with Mo_S defect and four complexes for MoS_2 with the V_{2S} defect were found. The presence of the mentioned defects leads to the formation of covalent bonds with the tegafur molecule located on the surface of the fragment.

As a result, the interaction with the surface increases to
-60 kcal/mol.

mos2-tegafur complexes / spectra

We also analyzed calculated vibrational spectra of all studied complexes and located spectral (IR and Raman) markers of tegafur interaction with MoS_2.

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conclusions

- Five stacked and four covalently bonded MoS_2-tegafur complexes were located. Calculations showed significant differences in the interaction energies between stacked and bonded complexes. In the stacked complexes, the interaction energy is approximately in the range from -10 to -12 kcal/mol, while in the bonded complexes it reaches -72 kcal/mol.
- Natural Bond Orbital analysis demonstrated the formation of coordination covalent bonds between the tegafur atoms and the edge molybdenum atoms in the bonded complexes.
- Taking into account the aqueous environment (PCM approach) leads to a significant weakening of the interaction in all complexes. The interaction energy in the stacked complexes decreases to approximately -3 kcal/mol, and in the bonded complexes to -20 kcal/mol.
- Structure of tegafur complexes with the MoS_2 surface that have point defects of two types (substitution of a surface sulfur atom by a molybdenum atom and vacancy of two adjacent surface sulfur atom) were determined. The presence of the defects leads to the formation of covalent bonds with the tegafur molecule located on the surface of the fragment. As a result, the interaction with the surface increases to -60 kcal/mol.
- Analysis of calculated vibrational spectra of all studied complexes allowed us to determine spectral (IR and Raman) markers of tegafur interaction with MoS_2.