



# Peculiarities of interaction of the sulfur-containing antiviral drug lamivudine with molybdenum disulfide

T. Piddubnyi<sup>1</sup>, S. Stepanian<sup>1</sup>, L. Adamowicz<sup>2</sup>

<sup>1</sup>B. Verkin Institute for Low Temperature Physics and Engineering of NAS of Ukraine, 47 Nauky Ave., Kharkiv, 61103, Ukraine

<sup>2</sup>Department of Chemistry and Biochemistry, University of Arizona, 85721 Tucson AZ, USA  
e-mail: [piddubnyi@ilt.kharkov.ua](mailto:piddubnyi@ilt.kharkov.ua)

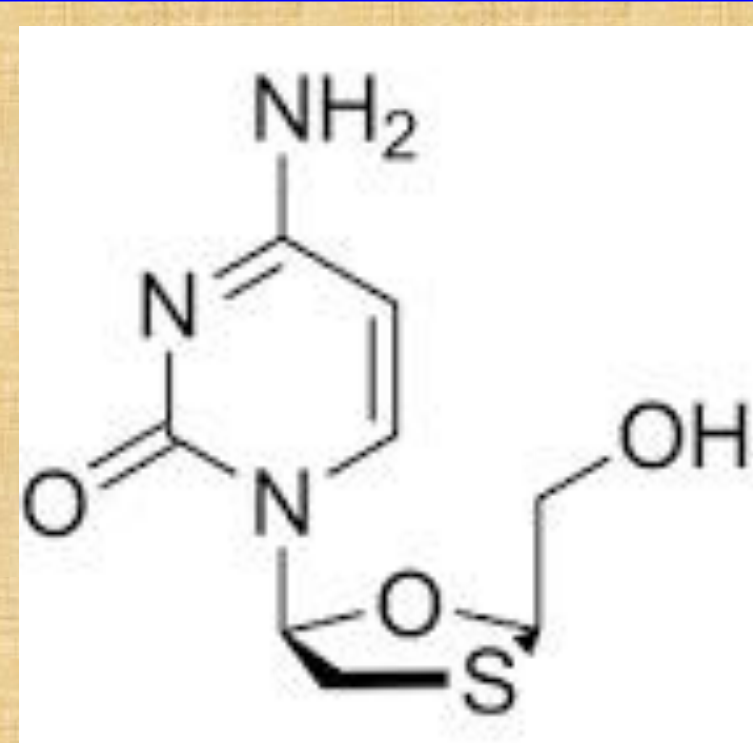


Fig. 1. Lamivudine.

The aim of this work is to determine the structure, stability and spectral characteristics of molybdenum disulfide ( $\text{MoS}_2$ ) complexes with lamivudine using the quantum mechanical DFT method.  $\text{MoS}_2$  is considered as a potential platform for drug delivery. Lamivudine (2',3'-dideoxy-3'-thiacytidine) is an antiretroviral drug used to treat HIV/AIDS and hepatitis B. Lamivudine (Fig. 1) is a derivative of the nucleic acid base cytosine with added a 1,3-oxathiolane saturated heterocycle.

## Lamivudine conformers

The presence of the oxathiolane heterocycle ensures high conformational lability of the lamivudine molecule. In total, we located 16 conformers of lamivudine using the DFT and MP2 quantum-mechanical methods. The two most stable conformers (Fig. 2, denoted as **Lam 1** and **Lam 2**) are stabilized by  $\text{OH}\cdots\text{S}$  and  $\text{OH}\cdots\text{O}$  intramolecular hydrogen bonds, respectively. Conformer **Lam 1** is the most stable structure of lamivudine while ZPVE corrected relative energy of the conformer **Lam 2** calculated at the MP2/aug-cc-pVDZ level of theory is 0.85 kcal/mol higher.

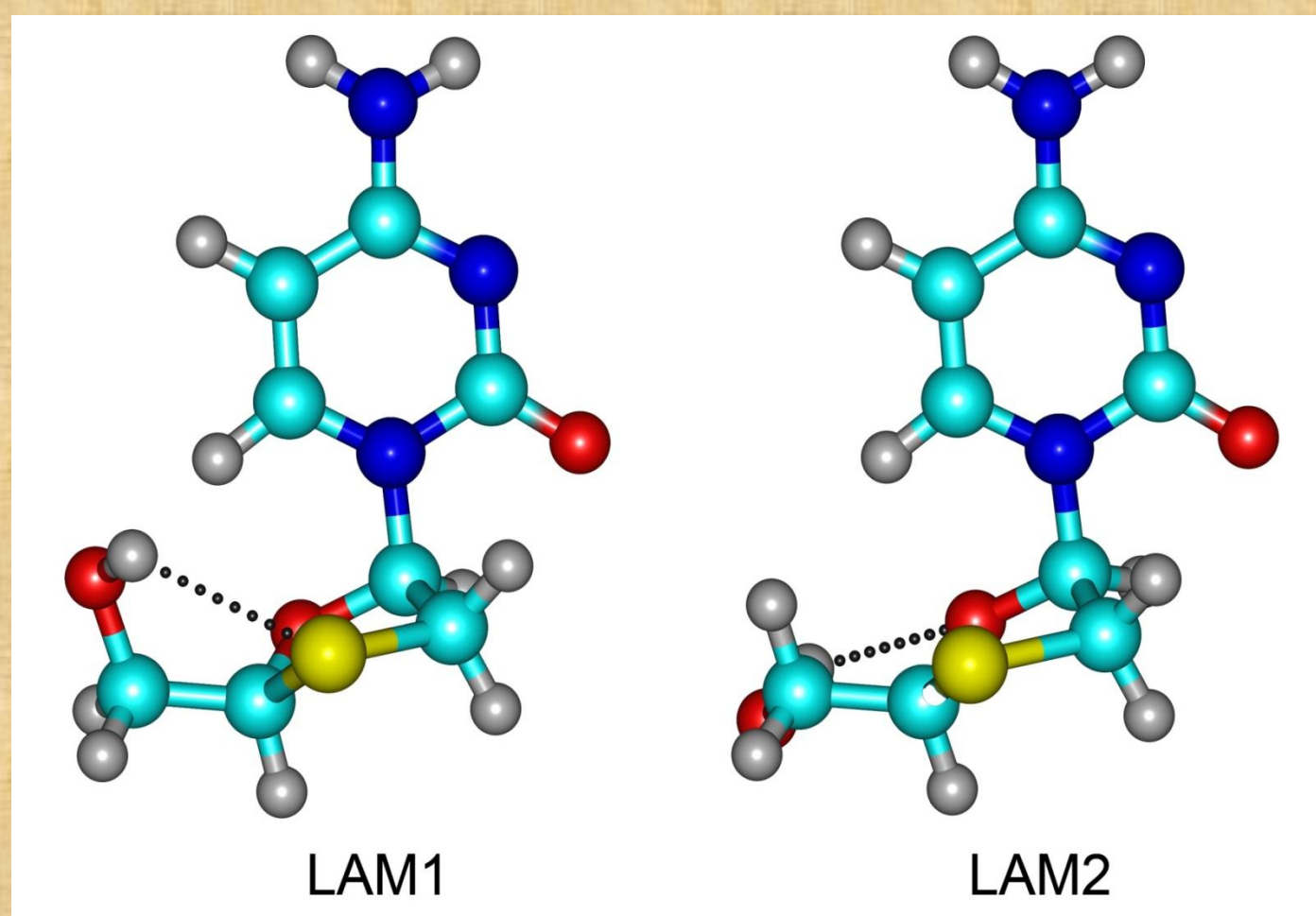


Fig. 2. Structure of the most stable lamivudine conformers.

## $\text{MoS}_2$ - lamivudine complexes

For these two most stable conformers of lamivudine, calculations of the structure, interaction energies, and vibrational spectra of complexes with the pristine  $\text{MoS}_2$  fragment were performed in vacuum approach and with accounting for the aqueous environment using the PCM method. This fragment included 27 molybdenum atoms and 54 sulfur atoms. The calculations were performed using the DFT/M06-2X method. Calculations were also carried out for complexes of lamivudine with the  $\text{MoS}_2$  fragment having point structural defects (substitutions and vacancies). The results obtained for the lamivudine complexes were compared with ones obtained for cytosine and other nucleic acid bases. A total of 12 stable complexes of lamivudine with pristine  $\text{MoS}_2$  and 16 complexes with  $\text{MoS}_2$  having point defects were found.

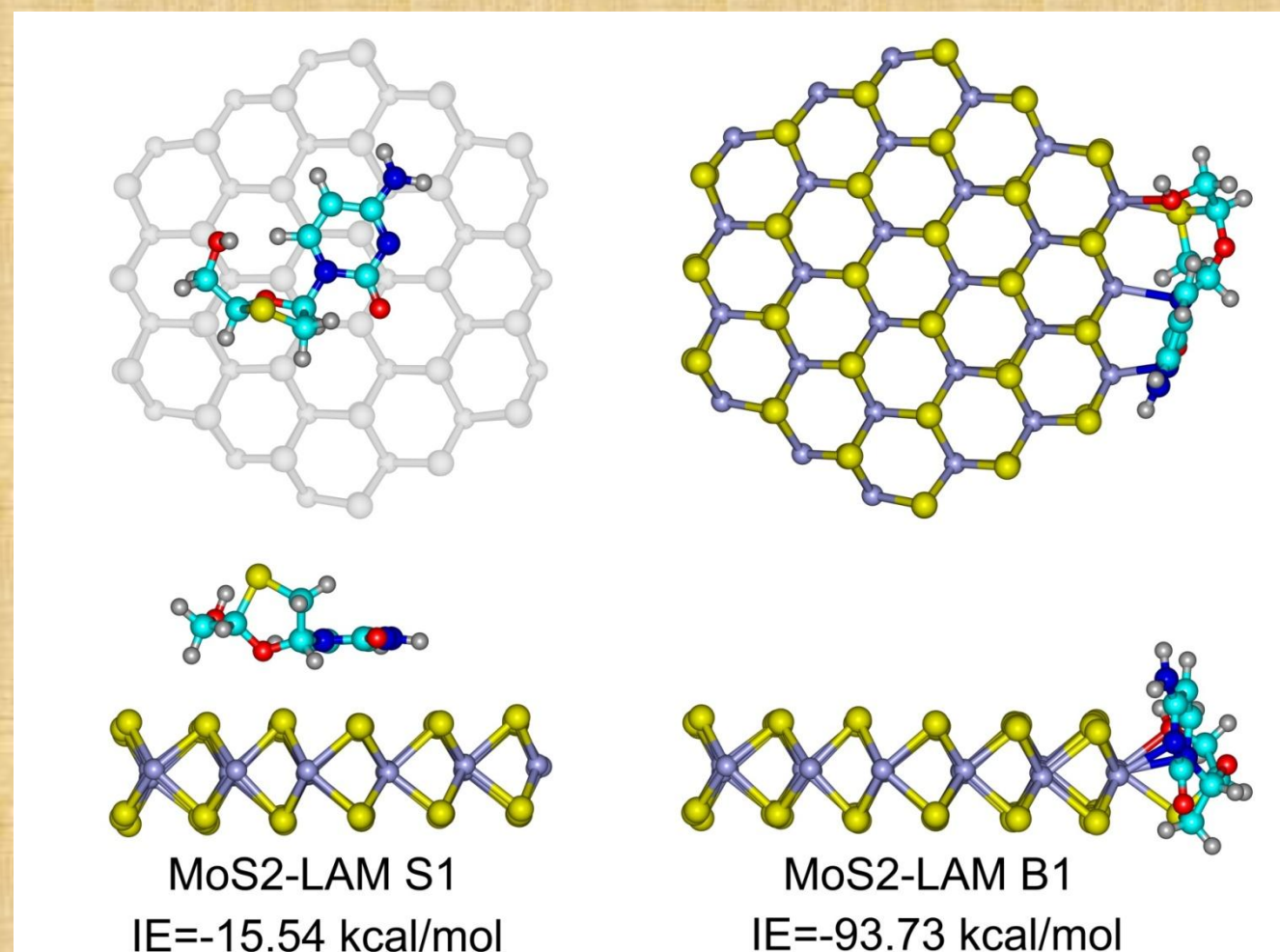


Fig. 3. Structure and interaction energies of the most stable  $\text{MoS}_2$  - lamivudine complexes.

It is shown that lamivudine molecules in the complexes interact either with the surface formed by  $\text{MoS}_2$  sulfur atoms or with molybdenum atoms at the terminal sections of the  $\text{MoS}_2$  fragment. In the first case, stacked complexes stabilized by dispersion and Coulomb interactions are formed. In the second case, covalently bonded complexes with coordination chemical bonds between molybdenum atoms and lamivudine atoms having electron lone pairs are formed. The structure of the most stable stacked and bonded complexes is shown in Fig. 3.

It should be noted that there is a significant difference in the interaction energies in the stacked and bonded complexes. Accounting for aqueous environment results in significant decrease of the interaction energies (in absolute values) for both complexes, which are -5.09 and -18.76 kcal/mol for the  $\text{MoS}_2$ -LAM S1 and  $\text{MoS}_2$ -LAM B1 complexes, respectively.

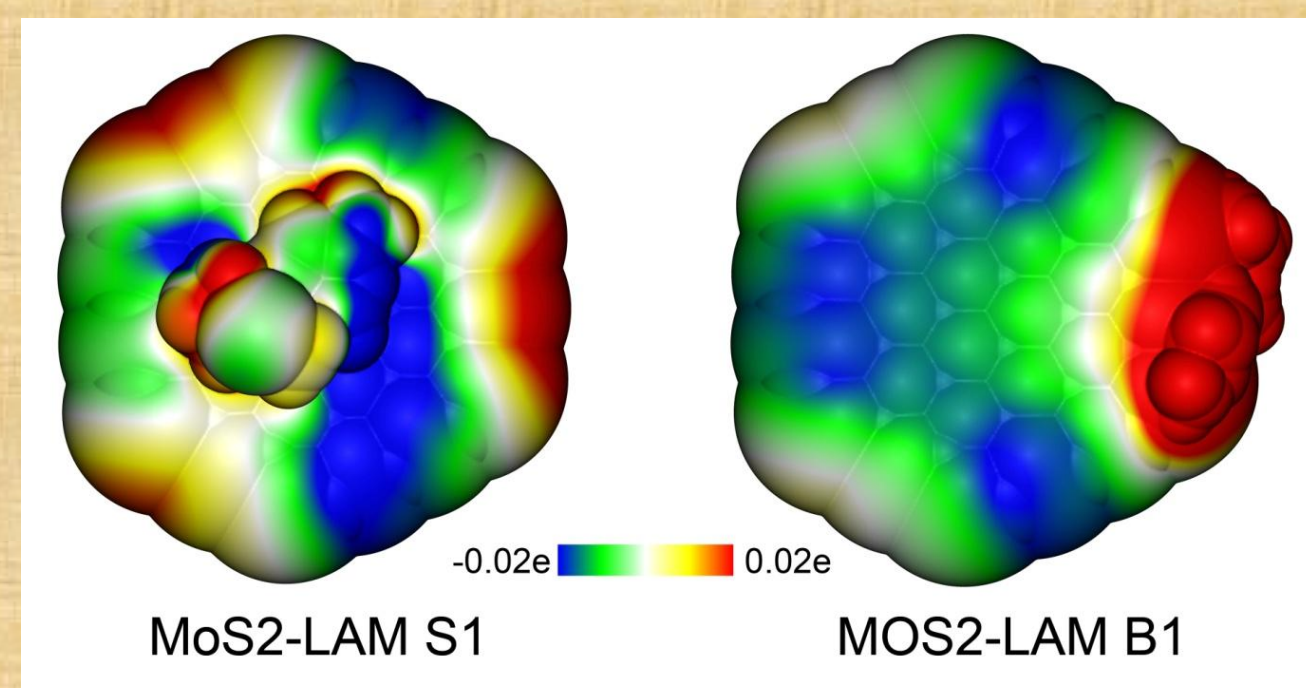


Fig. 4. Calculated distribution of electrostatic potential of the  $\text{MoS}_2$ -lamivudine complexes.

The intermolecular interaction of  $\text{MoS}_2$  with lamivudine significantly affects the electronic structure and spectra of both components of the complexes. For both types of complexes, a charge transfer from lamivudine to  $\text{MoS}_2$  is observed, which is -0.52e for the stacked complex and -0.76e for the bonded complex (atomic charges were calculated according to the Merz-Singh-Kollman scheme). As a result, negatively charged areas appear on the surface of  $\text{MoS}_2$  (Fig. 4).

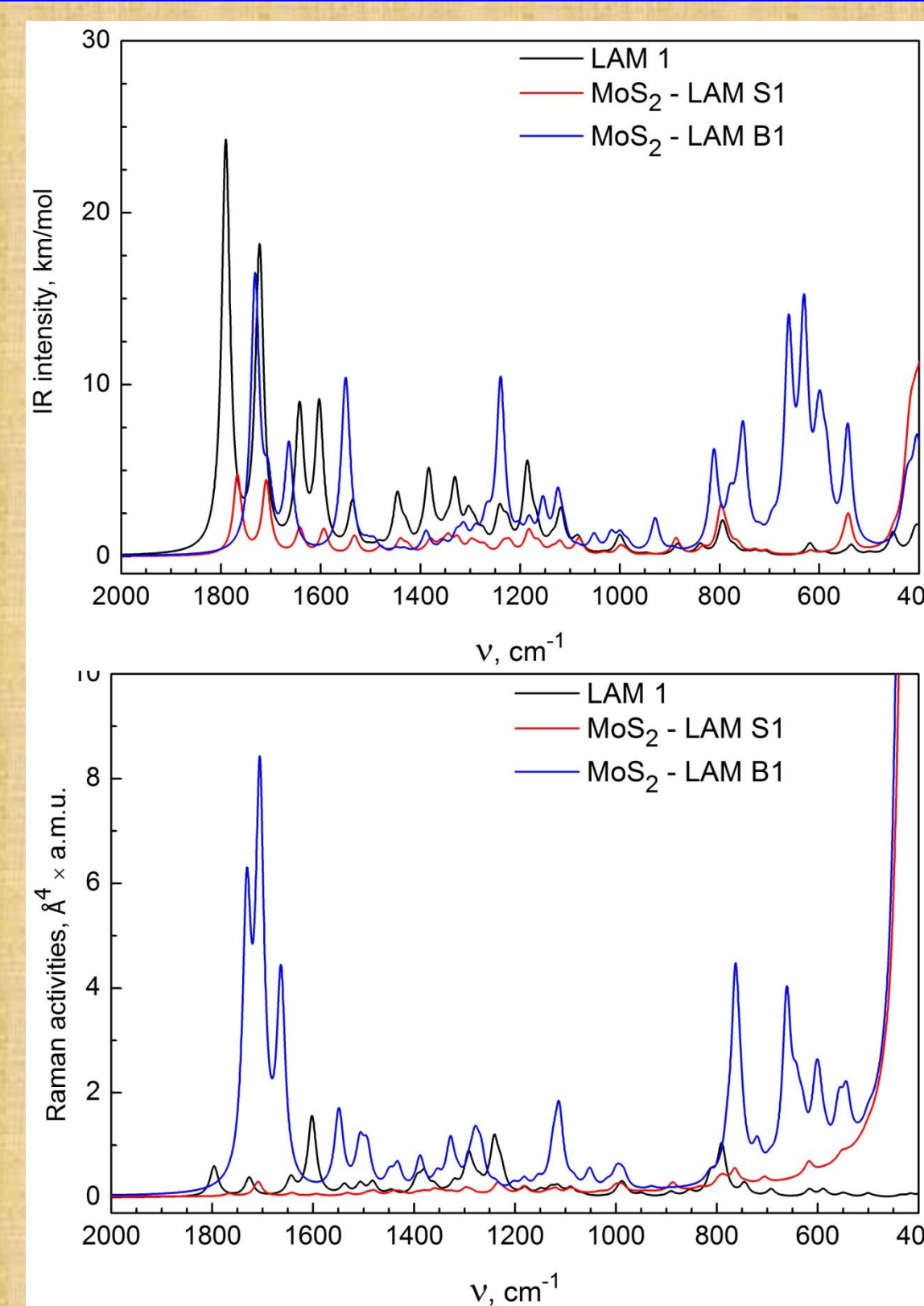


Fig. 5. Calculated IR and Raman spectra of the  $\text{MoS}_2$ -lamivudine complexes.

Fig. 5 shows the calculated IR and Raman spectra of the complexes. Only lamivudine vibrations are observed in the 2000-400  $\text{cm}^{-1}$  region, since all vibrations of the  $\text{MoS}_2$  fragment are located below 400  $\text{cm}^{-1}$ . As can be seen, the interaction with  $\text{MoS}_2$  leads to significant changes in the frequencies and intensities of lamivudine vibrations. Thus, a decrease in the intensities of the vibration bands is observed in the IR spectra of the stacked complex. An increase in the IR intensities in the region below 800  $\text{cm}^{-1}$  is observed for the bonded complex. A very strong increase in the intensities of almost all bands is observed in the Raman spectrum of the bonded complex. This can be used as a spectral marker for the formation of bonded complexes of lamivudine with  $\text{MoS}_2$ .

This work was supported by the NAS of Ukraine (Grant 0123U100628)