

# SPECTROSCOPIC SIGNATURES AND STRUCTURAL MOTIFS IN ISOLATED AND HYDRATED XANTHINE : A COMPUTATIONAL STUDY

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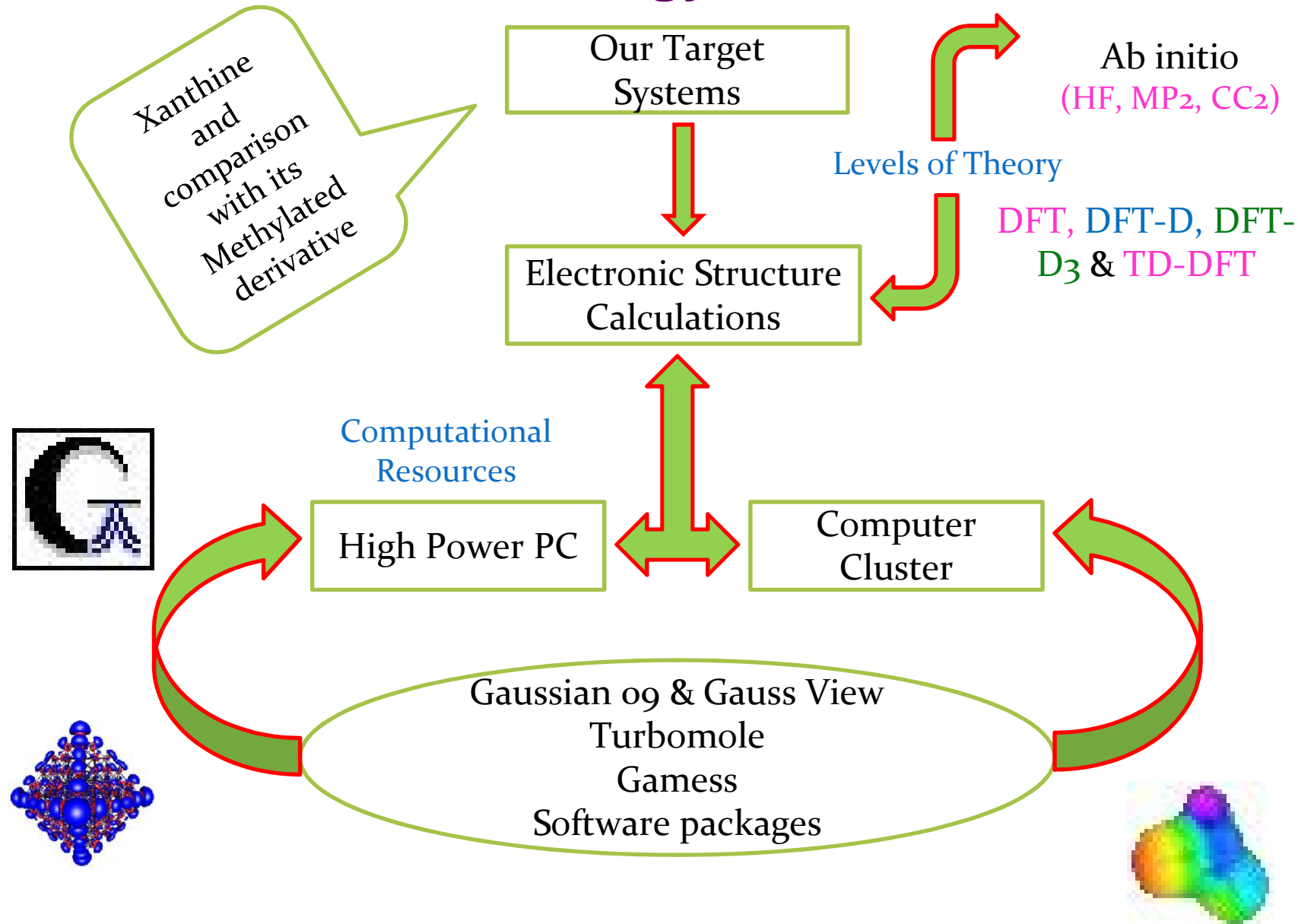
# OUTLINE

- ◉ **Motivation**
- ◉ **Introduction**
- ◉ **Computations**
- ◉ **GS Optimized geometries and harmonic wave-numbers of Xanthine monomer and dimer.**
- ◉ **GS Optimized geometries of mono-hydrated clusters of Xanthine; Blue and Red-shifts in Vertical Excitation Energy of S1-excited state due to mono-hydration.**
- ◉ **Computed carbonyl stretching mode of Xanthine, Theophylline and Caffeine.**
- ◉ **Conclusion**
- ◉ **Acknowledgment**

# MOTIVATION

- ◉ The understanding of the photo physical and photochemical properties of nucleic acid bases, the most fundamental building blocks of life, is essential for the rationalization of the photo stability as well as photodamage mechanism of DNA and RNA.<sup>1</sup> In this regard photo dynamics of nucleic acid analogue, xanthine (3,7-dihydro-purine-2,6-dione), plays an important role with the goal of transferring the experience obtained in these simpler systems to more complex situation found in DNA. Understanding the stability of the tautomeric forms of xanthine as well as their electronic structure can provide important information towards their biological activity and possibly their involvement in early prebiotic scenarios.<sup>2</sup> The lowlying excited states of xanthine are important in understanding photophysics and photochemistry of DNA complexes
- ◉ Spectroscopic signatures of isolated bio-molecules and their hydrated clusters may provide insight on their preferred conformations, dynamical flexibility, and inter- and intra- molecular interactions determining their skeletal structures.
- ◉ In the isolated xanthine, the lowest excited state  $S_1$  exhibits  $\pi^*$  character and primary photo-excitation involves this optically bright state  $S_1$  ( $1 \pi^*$ ). It is common knowledge that hydration can shift electronic states and hence, it can modify the excited state dynamics. Microsolvation can open new relaxation channels and hydrogen bond formation can affect the  $\pi$ -electron structure of particular isomers of a biomolecular complex.
- ◉ Second order Moller-Plesset perturbation theory method (MP2) offers a better approach for describing non-covalent interactions, since it can be extended to much larger systems. To the best of our knowledge none of the computational paper including the stabilization of xanthine dimer takes into account employing a high degree of electron correlation.
- ◉ In continuation of our earlier work on spectroscopic signatures of caffeine and theophylline, similar electronic structure calculations were performed on xanthine to compare the results.
- ◉ 1. Yamazaki, S., Sobolewski, A. L. & Domcke, W.. *Phys. Chem. Chem. Phys.* **2009**, *11*, 10165.
- ◉ 2. Chen, J.; Kohler, *Phys. Chem. Chem. Phys.* **2012**, *14*, 10677-10682.
- ◉ 3. V. B. Singh, RSC Adv., 2014, 4, 58116-58126.
- ◉ 4. V. B. Singh, RSC Adv., 2015, 5, 11433-11444.

# Methodology



## OPTIMIZED GEOMETRIES OF TWO LOWEST ENERGY TAUTOMERS OF XANTHINE MONOMER

The optimized structures of the two lowest energy tautomers, N7H and N9H, of xanthine, at the MP2/aug-cc-pVDZ level of theory are shown in the Figure. Xanthine has two carbonyl groups, C<sub>2</sub>-O<sub>11</sub> and C<sub>6</sub>-O<sub>13</sub>, joined to N<sub>1</sub> atom. At the MP2/ aug-cc-pVDZ level of theory the bond distance of C<sub>6</sub>-O<sub>11</sub> carbonyl of N7H tautomer, 1.233 Å, is found slightly greater than that of C<sub>2</sub>-O<sub>10</sub> carbonyl, 1.229 Å, while in N9H tautomer the C<sub>6</sub>-O<sub>11</sub> bond distance, 1.225, is found slightly lower than that of C<sub>2</sub>-O<sub>10</sub> bond distance, 1.229. Overall the difference in the bond lengths of the optimized geometries in two tautomers of bare xanthine were found to be less than 0.06 Å. However significant changes were found in the selected bond angles. The total electron density of xanthine indicates a build-up of charge density on the nitrogen and oxygen atoms and nodes at the other atoms. We found that there is an electronic charge displacement from O<sub>11</sub> and N<sub>7</sub> atoms and accumulations of charges on the N<sub>1</sub> and N<sub>9</sub> atoms due to the tautomerisation of N7H into N9H form. Furthermore the computed dipole moment of the ground state N9H tautomer of 8.09 Debye is much larger than the dipole moment, 5.06 D, of N7H at the MP2 aug-cc-pVDZ level of theory. Therefore it seems that the electronic charge displacement in the N9H tautomer causes a large separation between the effective charges forming the dipole.

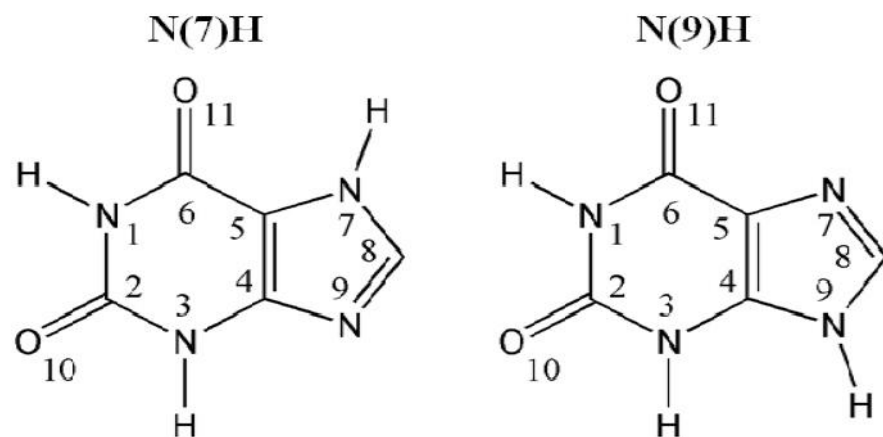
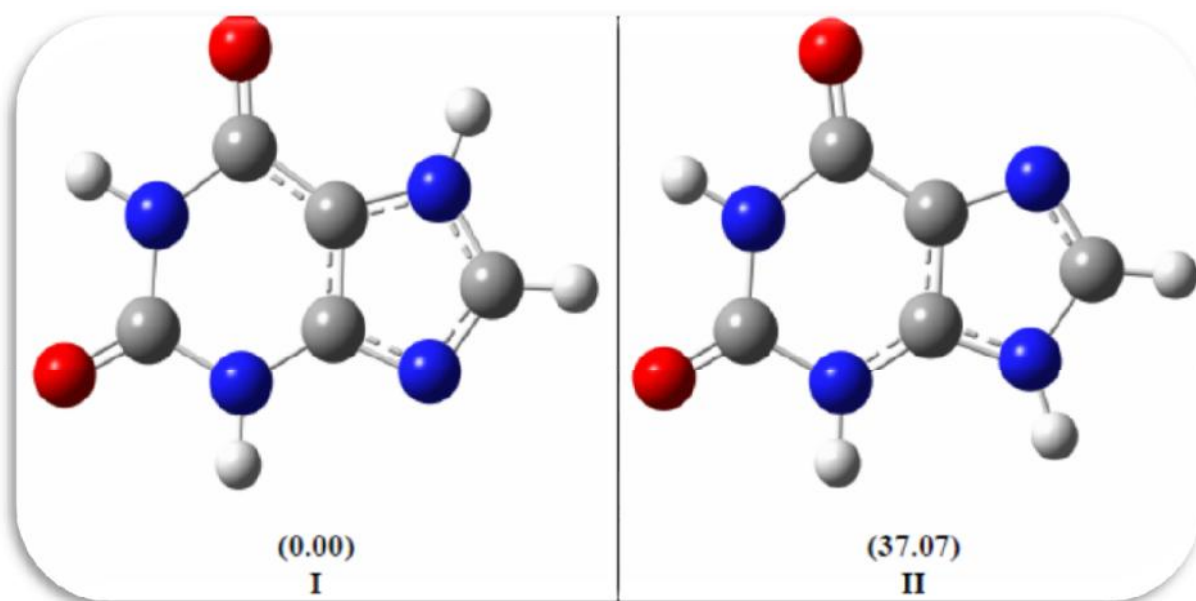


Fig. 1(a) Chemical structures of xanthine tautomers.

Optimized structures and relative energies (kJ mol<sup>-1</sup>) of the two most stable tautomers of neutral xanthine at MP2/aug-cc-pVDZ level



## NBO ELECTRONIC CHARGES FOR THE TWO TAUTOMERS OF XANTHINE AT MP2 AND CC2 LEVEL

	7H		9H	
	MP2/aug-cc-pVDZ	CC2/aug-cc-pVDZ	MP2/aug-cc-pVDZ	CC2/aug-cc-pVDZ
N1	0.797	0.702	0.804	0.710
N3	0.747	0.657	0.755	0.671
N7	0.628	0.544	0.506	0.454
N9	0.635	0.529	0.683	0.598
O10	0.759	0.609	0.758	0.609
O11	0.738	0.585	0.702	0.551

## THE RELATIVE ENERGIES AND THE DIPOLE MOMENTS OF THE TWO LOWEST ENERGY TAUTOMERS OF XANTHINE USING MP2, CC2 AND DFT(B3LYP) –D3 METHODS

Level Of Theory	Xanthine (N7H)		Xanthine (N9H)	
	Relative Energy (in KJ/Mol)	Dipole Moment (debey)	Relative Energy (in KJ/Mol)	Dipole Moment (debey)
CC2/aug-cc-pVDZ	0.0	4.21	39.35	7.30
MP2/aug-cc-pVDZ	0.0	5.06	37.07	8.09
B3LYP-D3/aug-cc-pVDZ	0.0	4.36	38.31	7.39

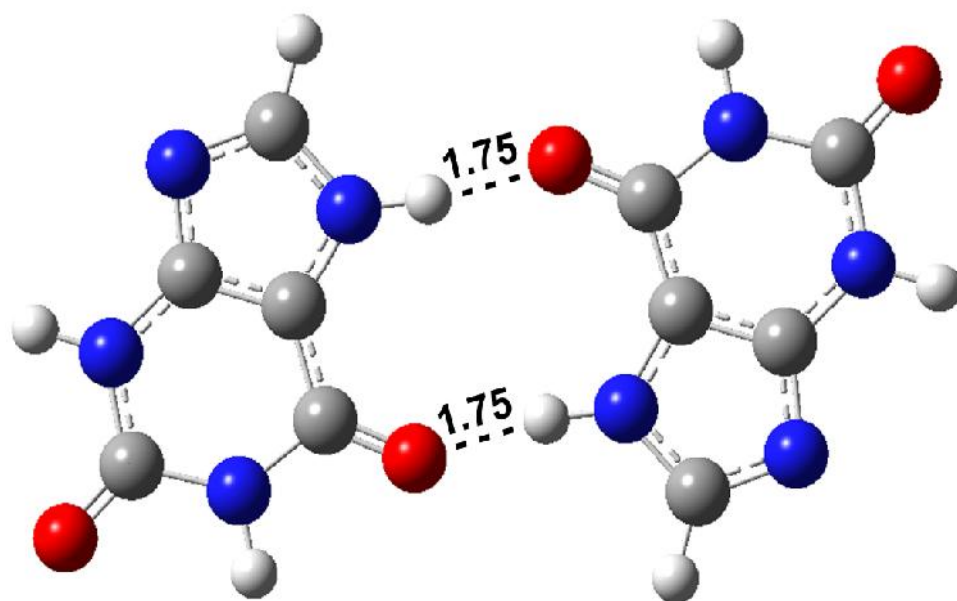


## SELECTED STRETCHING MODES FREQUENCIES OF THE TWO TAUTOMERS OF XANTHINE

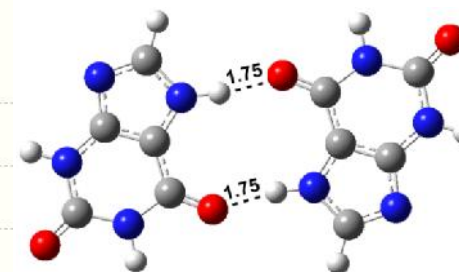
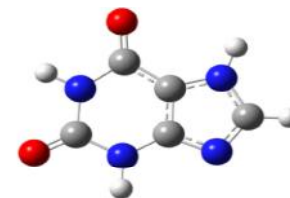
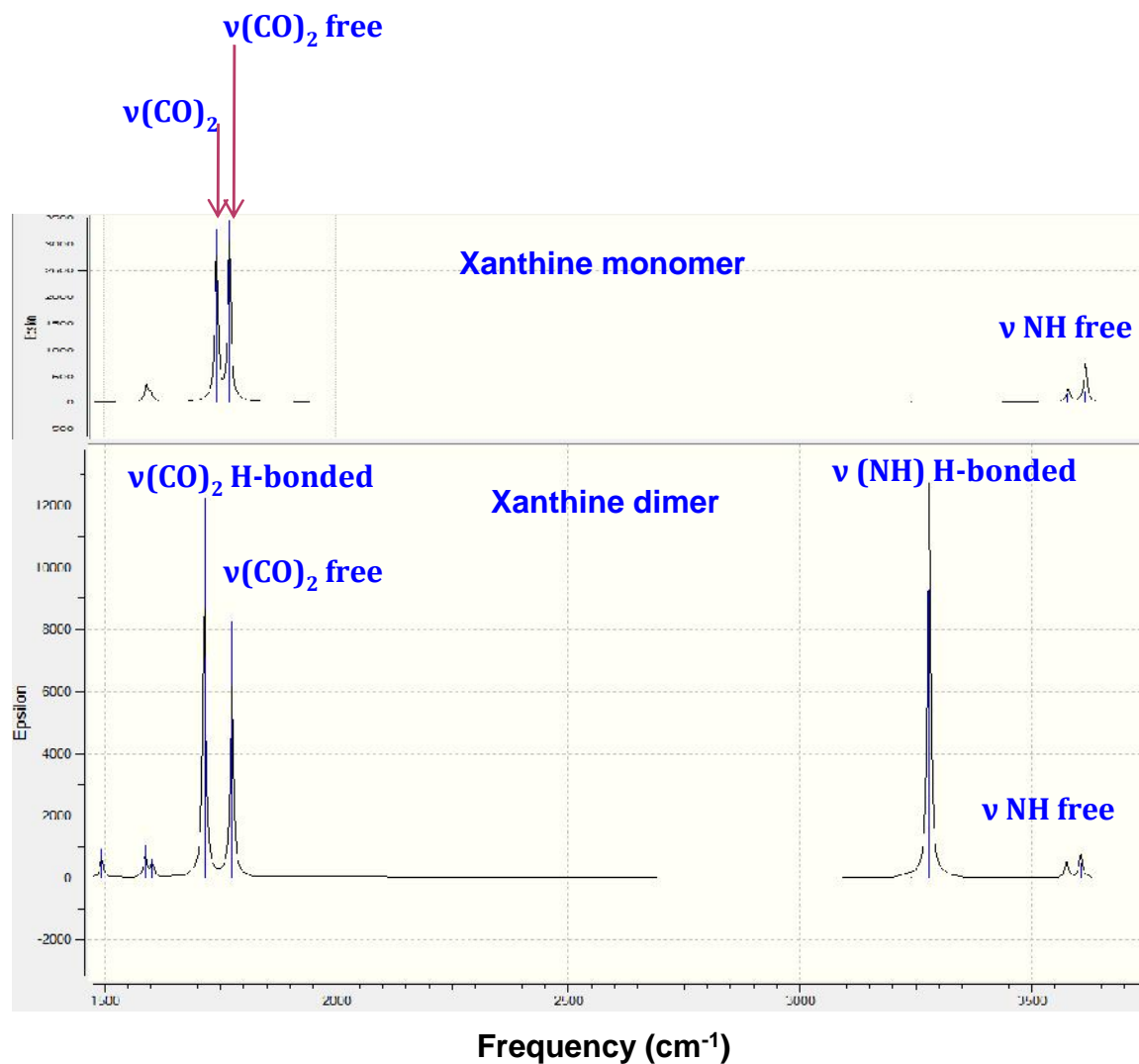
Description of Vibrations	Harmonic wavenumber s (cm <sup>-1</sup> ) and IR intensity (in parenthesis) of xanthine monomer at B3LYP/aug-cc-pVDZ		**Experimental wavenumber s (cm <sup>-1</sup> )
	7H	9H	
<b>N7H - Stretching</b>	*3500(111)	3495(102)	<b>3501</b>
<b>N3H- Stretching</b>	*3486(105)	3491(64)	<b>3485</b>
<b>N1H- Stretching</b>	*3446(84)	3445(77)	<b>3444</b>
<b>(C2=O)- Stretching</b>	1700(889)	1700(944)	<i>1693</i>
<b>(C6=O)- Stretching</b>	1688(755)	1696(575)	<i>1672</i>
<b>(C=C)- Stretching/ Aromatic</b>	1586(36)	1611(62)	<i>1572</i>

- \* Scaled by a factor 0.975
- \*\*Callahan M.P., Crews B., Abo-Riziq A., Grace L., de Varies M. S., Gengeliczki Z., *Phys. Chem. Chem. Phys.* **2007**, 9, 4587-4591.
- Italic Values;Arivazhagn M., Jeyavijayan, S. *Spectrochimica Acta A* **2011**,79, 161-168.

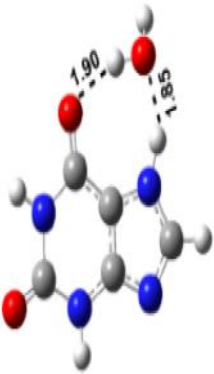
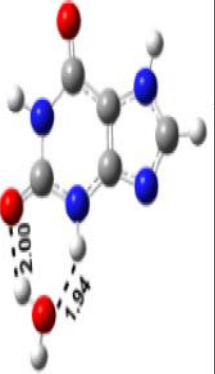
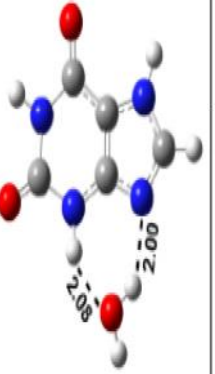
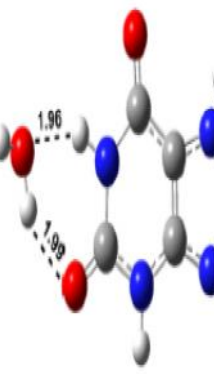
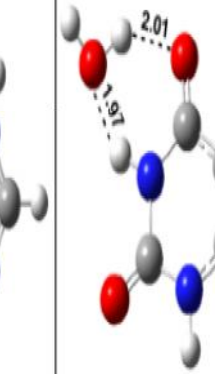
**COMPUTED OPTIMIZED GEOMETRIES OF XANTHENE DIMER AT MP2/6-311++G(D,P) LEVEL.**



## Computed IR Spectra of Xanthine monomer and dimer at B3LYP/6-311++G(d,p) level



## Computed optimized geometries and relative energies of xanthine monohydrates {Xan<sub>1</sub>-(H<sub>2</sub>O)<sub>1</sub>} at MP2/6-311++G(d,p) level

Conformer	Xan <sub>1</sub> -(H <sub>2</sub> O) <sub>1</sub> (I)	Xan <sub>1</sub> -(H <sub>2</sub> O) <sub>1</sub> (II)	Xan <sub>1</sub> -(H <sub>2</sub> O) <sub>1</sub> (III)	Xan <sub>1</sub> -(H <sub>2</sub> O) <sub>1</sub> (IV)	Xan <sub>1</sub> -(H <sub>2</sub> O) <sub>1</sub> (V)
Relative energy (kJ/mol)	0.00	15.15	15.67	18.34	20.11
Structure	 (I)	 (II)	 (III)	 (IV)	 (V)

## MONOHYDRATED CLUSTERS OF XANTHINE AND RELATIVE SHIFT IN VERTICAL EXCITATION ENERGY OF THE $S_1$ ( $^1\pi\pi^*$ ) EXCITED STATE

Similar to caffeine and theophylline, xanthine possesses three main sites for hydration, into which a water molecule can bind strongly: (1) the C(6) carbonyl group (2) the C(2) carbonyl and (3) the N9 atom. Figure shows the optimized ground state structures of five lowest energy conformers of xanth1-(H<sub>2</sub>O)<sub>1</sub> clusters, two O11-bonded (involving C6=O carbonyl), two O10-bonded (involving C2=O carbonyl) and one N-bonded cluster. In each complex, the input geometry of the N7H tautomer of bare xanthine was used for the complexation with a water. As shown in Figure these complexes are assigned as (I), (II), (III), (IV) and (V) isomers according to the order of their relative energies and stability.

The lowest excited  $^1\pi\pi^*$  state is dominated by single configuration corresponding to HOMO  $\rightarrow$  LUMO (0.68) excitation. We have carried out calculations for the lowest lying excited state  $S_1$  for all the five isomers of monohydrated xanthine by TDDFT method in order to estimate the spectral shift caused by micro-hydration. We found that the VEE to the lowest  $S_1$  ( $^1\pi\pi^*$ ) excited state of xanthine clusters involving C6=O carbonyl was red shifted by 640 and 379 cm<sup>-1</sup> for I and V isomers respectively. The VEE to the same state for N-bonded Isomer III is significantly red shifted by 1197 cm<sup>-1</sup> whereas for caffeine and theophylline only slight red shift was reported. The VEE to the  $S_1$  ( $^1\pi\pi^*$ ) state of xanthine clusters involving C2=O was blue shifted by 444 and 31 cm<sup>-1</sup> for IVth and IIth isomers respectively.

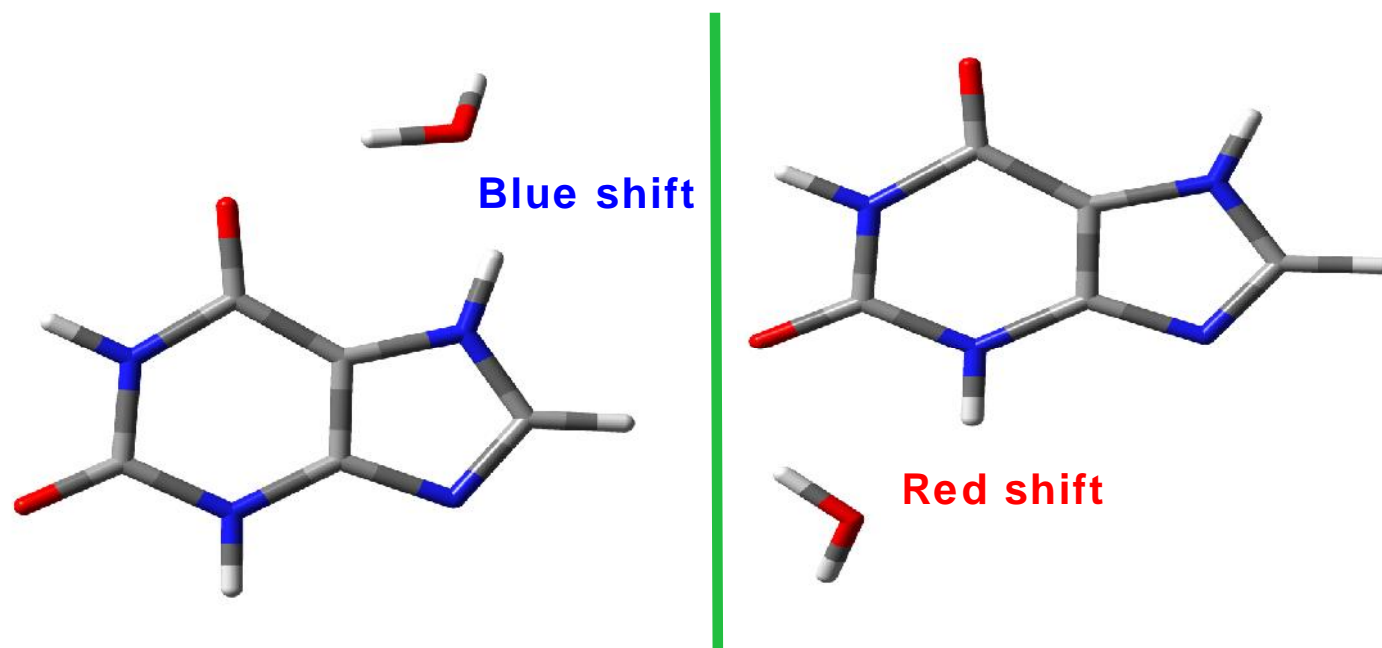
Infact, hydration of a carbonyl containing heterocyclic organic molecule tends to cause a little red-shift for a  $\pi\pi^*$  transition and an appreciable blue shift for  $n\pi^*$  transition. This anomalous blue shift for a  $\pi\pi^*$  transition can be explained, as reported earlier for caffeine and theophylline. For heterocyclic compounds the conjugation generally results in bathochromic (red) and hypsochromic (blue) shifts in electronic absorption for a  $\pi\pi^*$  and  $n\pi^*$  transition respectively. A comparison of the  $\pi\pi^*$  energy gap in a series of compounds shows that longer the conjugated system, longer is the wavelength of the absorption maximum which is in consonance to the predicted red shift of  $\pi\pi^*$  transition for xanthine monohydrates involving C6=O carbonyl. However in the case of smaller (or non) conjugated system,  $\pi\pi^*$  transition may exhibit opposite behavior, as reported recently by Boni et al.<sup>5</sup> Therefore, a blue shift for a  $\pi\pi^*$  transition is attributed to the reduction in the  $\pi$ -electron conjugation length of the O10-bonded xanthine monohydrates (involving isolated carbonyl) in contrast to the O1-bonded monohydrates.

3 V. B. Singh, RSC Adv., 2014, 4, 58116–58126.

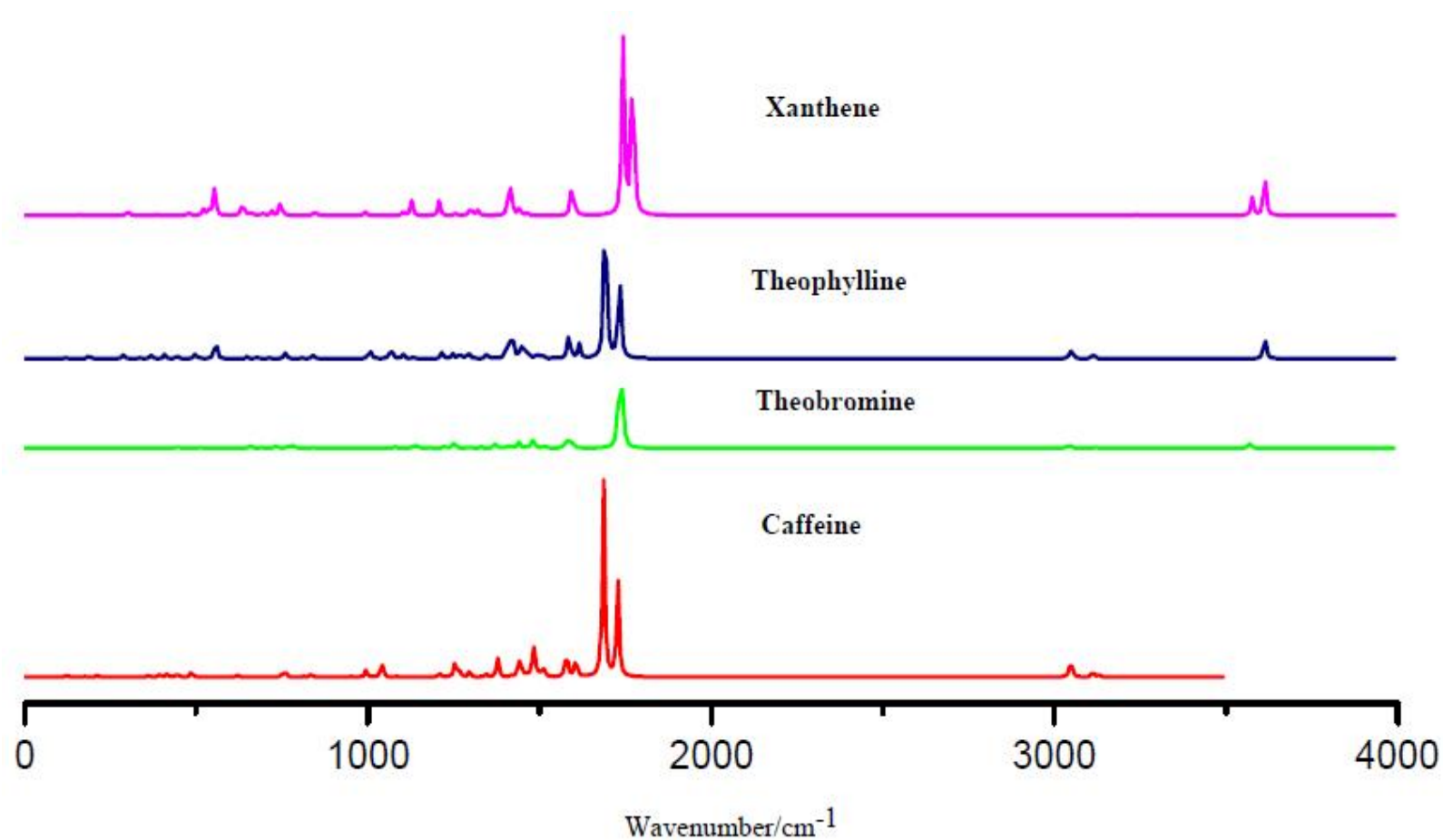
4V. B. Singh, RSC Adv., 2015, 5, 11433–11444.

5 De Boni L.; Taro C.; Zillo, S.C.; Mendonca, C.R.; Hernandez, F.E. *Chem. Phys. Lett.* **2010**, 487, 153-324.

**BLUE AND RED SHIFTS OF THE VEE OF THE  $S_1$  ( $1\pi\pi^*$ ) STATE OF XANTHINE AFTER FORMING COMPLEX WITH WATER AT C2=O AND C6=O CARBONYL SITES.**



# CARBONYL STRETCHING VIBRATIONAL MODES OF XANTHINE AND ITS METHYLATED DERIVATIVES



# CONCLUSIONS

The optimized structures and harmonic wavenumbers of the two lowest energy tautomers, N7H and N9H, of xanthine monomer at the MP2/aug-cc-pVDZ and CC2/aug-cc-pVDZ levels of theory are reported, which are found in agreement with experiment.

Present work reported five lowest energy isomers of Xanthine<sub>1</sub>-(H<sub>2</sub>O)<sub>1</sub> cluster at the MP2/6-311++G(d,p) and DFT-B3LYP/M06-2X/6-311++G(d,p) of levels of theory. The isomer –I, involving hydrogen bond between (in which both Xanthine and water act as accepters as well as donors) was found the most stable isomer. Due to formation of a relatively strong hydrogen bond between C6=O and N7H with water, the NH stretching mode of this (lowest energy) monohydrated complex is red shifted significantly by 379 cm<sup>-1</sup>.

The binding energy of Xanthine Dimer, connected by double N-H...O6=C hydrogen bond, was found to be 87.265 and 80 KJ/Mol at MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) levels respectively. Dimerization induced changes in vibrational frequencies and intensities have been determined. The N7H-Stretching band of this dimer shifted by 310 cm<sup>-1</sup> which is less than the large red shift 411 cm<sup>-1</sup> found in the similar theophylline dimer Form IV, indicating more strong hydrogen bonding structure in theophylline inspite of methylation. Further stability is being conferred to the N-H...O=C hydrogen bonding of the Xanthine Dimer with interaction of water molecule at N<sub>9</sub> sites, similar to theophylline Dimer IV.

The lowest excited <sup>1</sup>\* state is dominated by single configuration corresponding to HOMO → LUMO (0.68) excitation. One striking feature is the coexistence of the blue and red shift of the vertical excitation energy of the optically bright state S1 (<sup>1</sup>\* ) of xanthine upon forming a complex with water at C2=O and C6=O carbonyl sites, respectively.



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- ◉ **2. University Grants commission**  
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