

Electronic Supplementary Information (ESI) to the  
manuscript entitled

# Absorption Spectra of Xanthines in Aqueous Solution: a Computational Study

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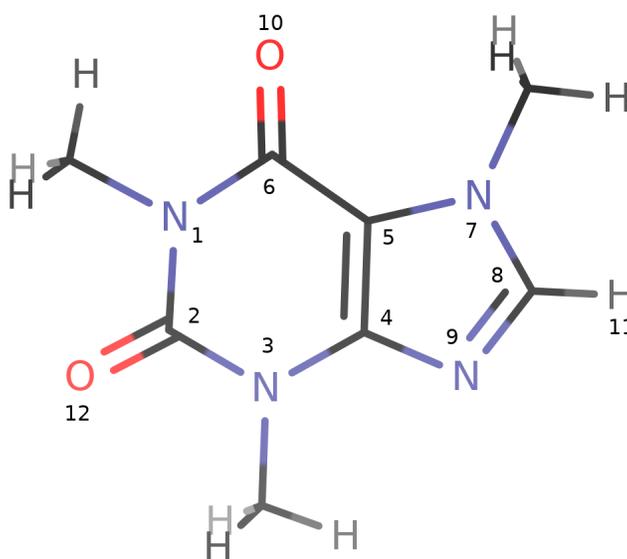
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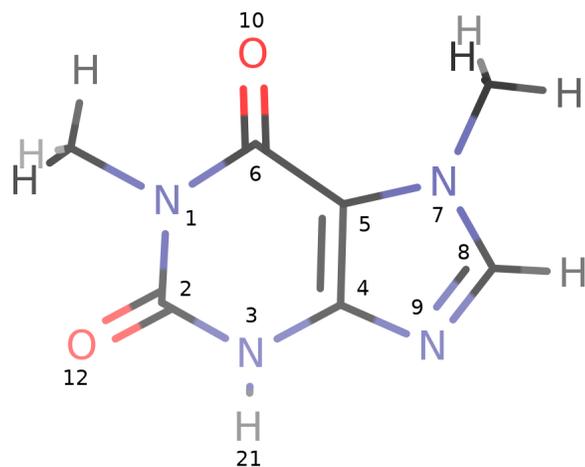
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## 1 Structures and Atom Numbering

### CAFFEINE



# PARAXANTHINE



# THEOPHYLLINE

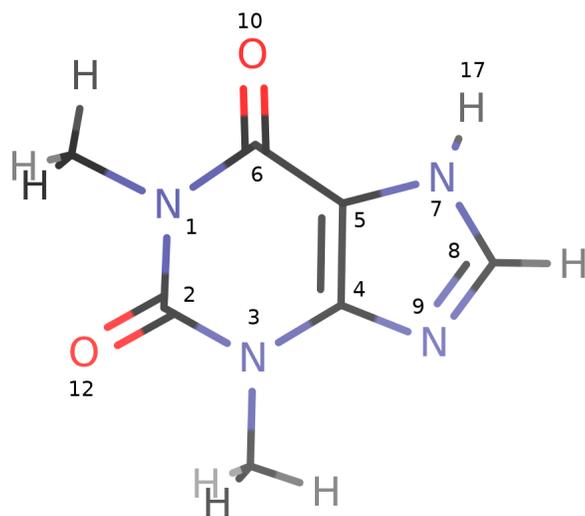


Figure S1: Xanthines structures and atom numbering adopted in this work.

## 2 Additional information for Caffeine

### 2.1 Time evolution and dihedral distribution function for the methyl rotation

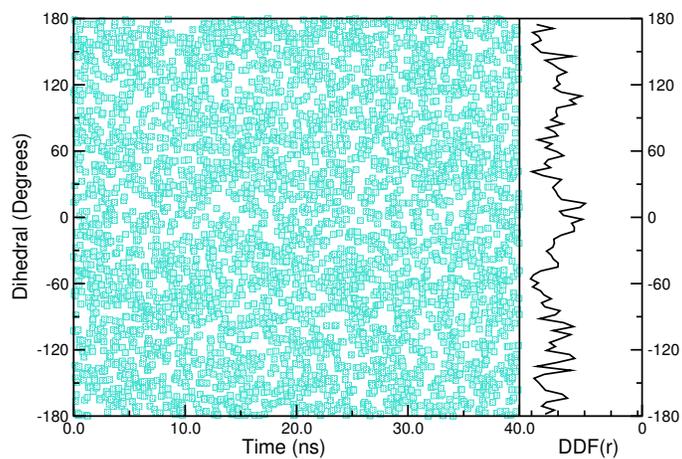


Figure S2: Time evolution of one of the dihedral angles associated to a methyl rotation during the MD simulation for caffeine. Dihedral distribution function (DDF) is also depicted.

## 2.2 Assessing the convergence of computed UV spectra with respect to the number of extracted snapshots

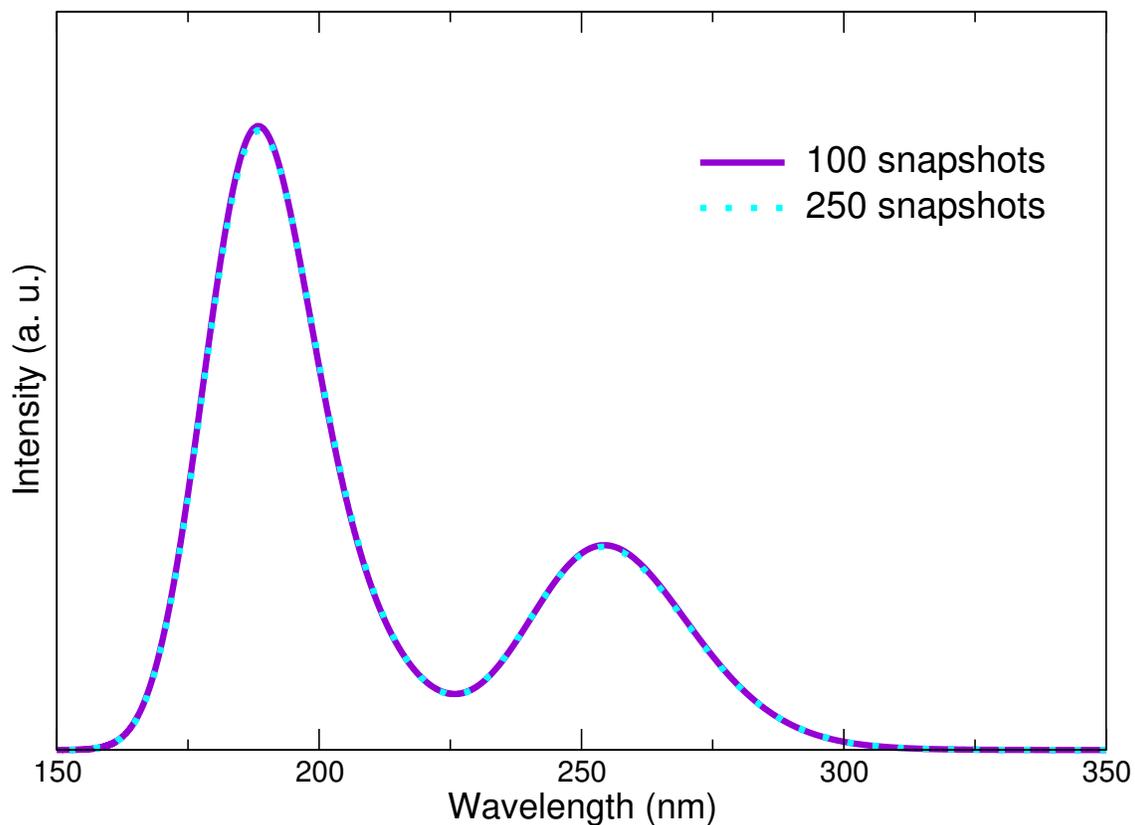
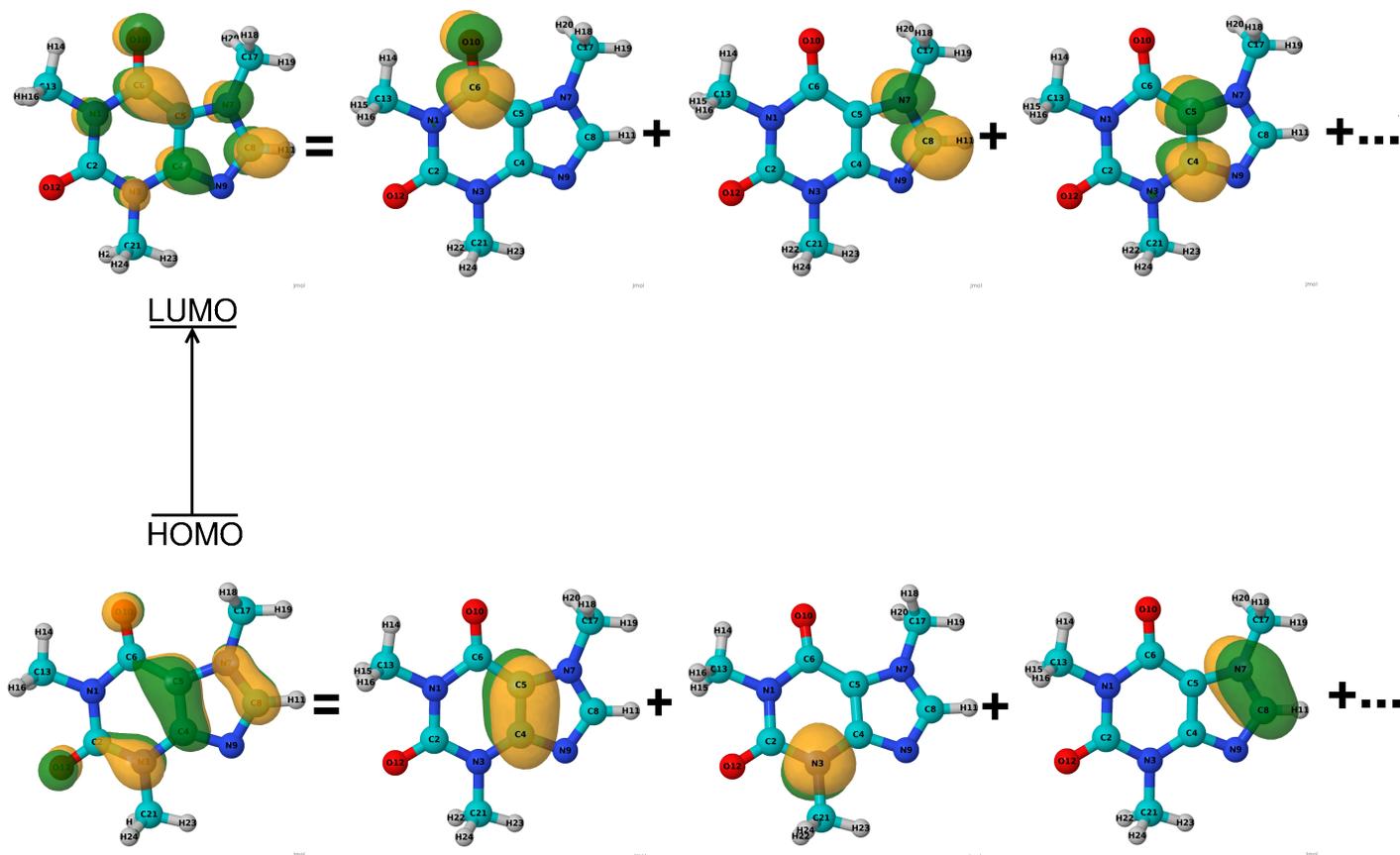


Figure S3: Simulated electronic absorption spectra for caffeine in aqueous solution. Fluctuating charges model was used in the MM portion, that is, QM/FQ[1] with parameters taken from Ref. [2]. Both 100 and 250 snapshots extracted from Molecular Dynamics runs produce similar results. All calculations were performed at the CAM-B3LYP/6-311++G(d,p) level of theory.

## 2.3 HOMO and LUMO expressed as linear combinations on the NBO basis

$$LUMO_{CAF\text{ solvated}} = 0.594\pi_{C6-O10}^* + 0.561\pi_{N7-C8}^* - 0.395\pi_{C4-C5}^* +$$

...



$$HOMO_{CAF\text{ solvated}} = -0.585\pi_{C4-C5} + 0.439n_{N3} - 0.411\pi_{N7-C8} + \dots$$

Figure S4: Decomposition of the delocalized canonical orbitals HOMO and LUMO into the localized NBOs of which they are comprised. As the first electronic transition involves a HOMO  $\rightarrow$  LUMO charge transfer, it can be easily assigned to the  $\pi - \pi^*$  type because the bonding orbital  $\pi_{C4-C5}$  and the antibonding  $\pi_{C6-O10}^*$ ,  $\pi_{N7-C8}^*$  orbitals have the dominant contributions in the respective linear combinations.

## 2.4 Effect of the choice of DFT functional on vertical excitation energies and spectra

Table S1: Comparison between the excitation energies obtained with different functionals. The experimental wavelength for the first electronic transition is 273 nm (4.54 eV), whereas the second peak is located around 205 nm (6.05 eV). All calculations using 6-311++G(d,p) basis set and PCM model.  $D_{CT}$  index, which evaluates the charge transfer extent is also listed.

Functional	Peak	Wavelength (nm)	VEE (eV)	%error	$D_{CT}$ (Å)
M062X	1	249.13	4.98	10	1.457
	2	192.05	6.46	7	—
CAM-B3LYP	1	252.02	4.92	8	1.466
	2	192.86	6.43	6	—
B3LYP	1	268.24	4.62	2	1.941
	2	206.23	6.01	1	—

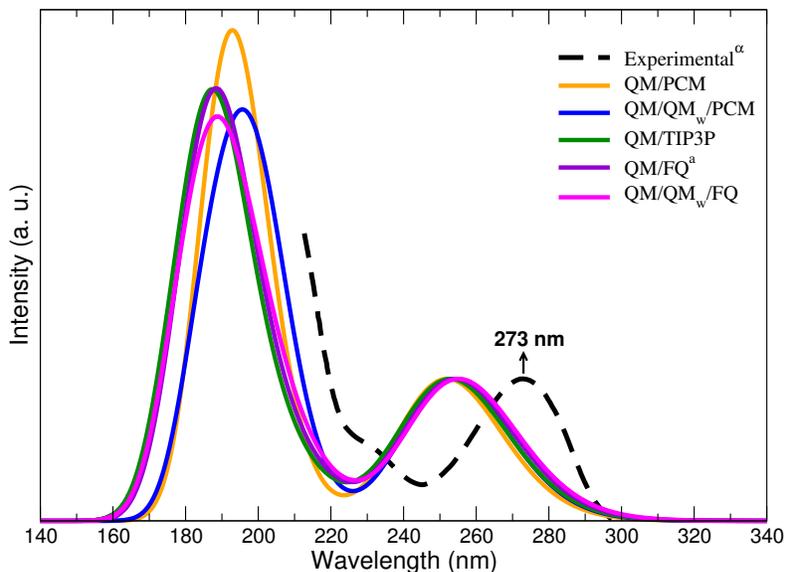


Figure S5: Simulated (CAM-B3LYP/6-311++G(d,p)) electronic absorption spectrum of caffeine in aqueous solution by using QM/PCM, QM/QM<sub>w</sub>/PCM (an average of 4 water molecules per frame at the DFT level), QM/TIP3P and QM/FQ, QM/QM<sub>w</sub>/FQ as model solvation. Experimental[3] UV-Vis spectrum is also depicted. 250 snapshots used in the QM/MM calculations were extracted from 50 ns Molecular Dynamics runs. The spectrum is clearly sensitive to the functional used in the TD-DFT calculations, because a great improvement in the results is found by changing the functional to B3LYP.

### 3 Charge transfer index, $D_{CT}$

Table S2: Length of the charge transfer,  $D_{CT}$ , in Å, associated to the first excitation for all solvated xanthenes studied in this work. In the QM/QM<sub>w</sub>/PCM approach, caffeine presents  $D_{CT}$  values of 1.777 and 1.345 Å at B3LYP and CAM-B3LYP, respectively. All calculations using 6-311++G(d,p) basis set.

Xanthine	QM/PCM		QM/TIP3P		QM/FQ <sup>a</sup>		QM/FQ <sup>b</sup>		QM/QM <sub>w</sub> /FQ	
	B3LYP	CAM-B3LYP	B3LYP	CAM-B3LYP	B3LYP	CAM-B3LYP	B3LYP	CAM-B3LYP	B3LYP	CAM-B3LYP
<b>Caffeine</b>	1.941	1.466	1.873	1.535	1.891	1.526	1.683	1.479	1.83	1.505
<b>Paraxanthine</b>	1.756	1.334	1.749	1.442	1.774	1.441	1.631	1.415	1.717	1.427
<b>Theophylline</b>	1.979	1.466	1.949	1.515	1.970	1.517	1.805	1.462	1.935	1.508

## 4 Study of tautomeric forms for Paraxanthine and Theophylline

### 4.1 Paraxanthine tautomers

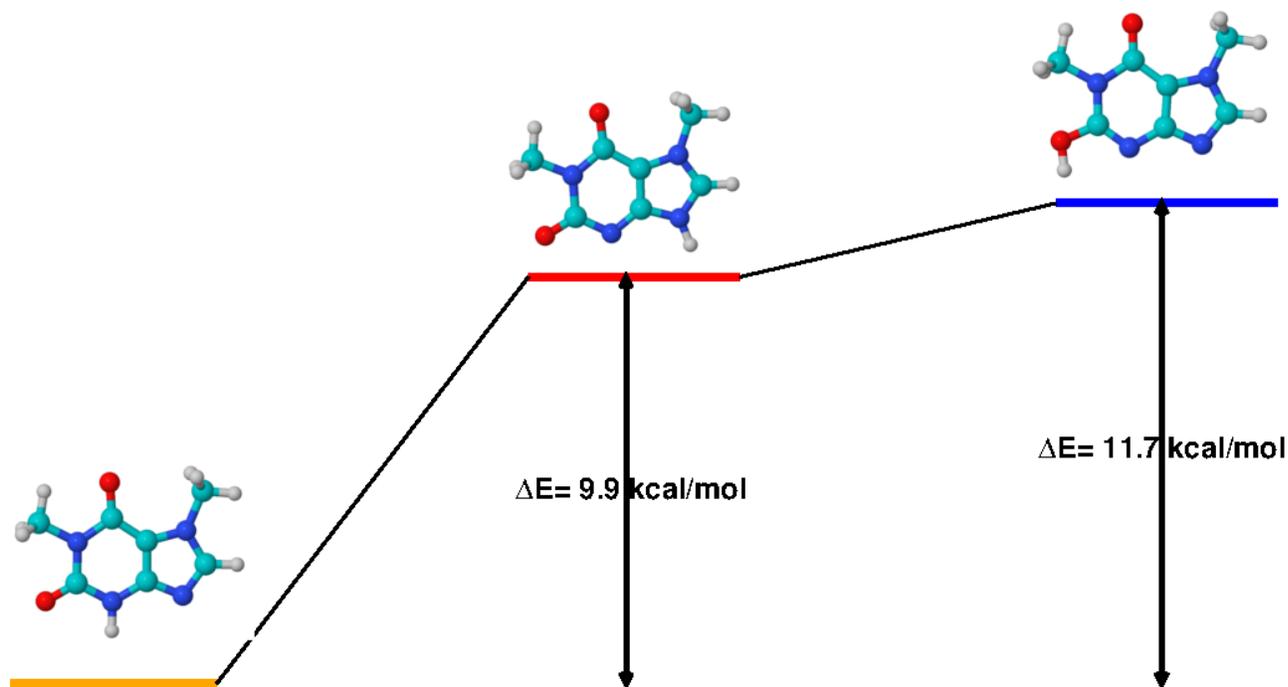


Figure S6: Relative energies (kcal/mol) for paraxanthine tautomers. All calculations using the B3LYP/6-311++(d,p) level of theory and the polarizable continuum model (PCM).

## 4.2 Theophylline tautomers

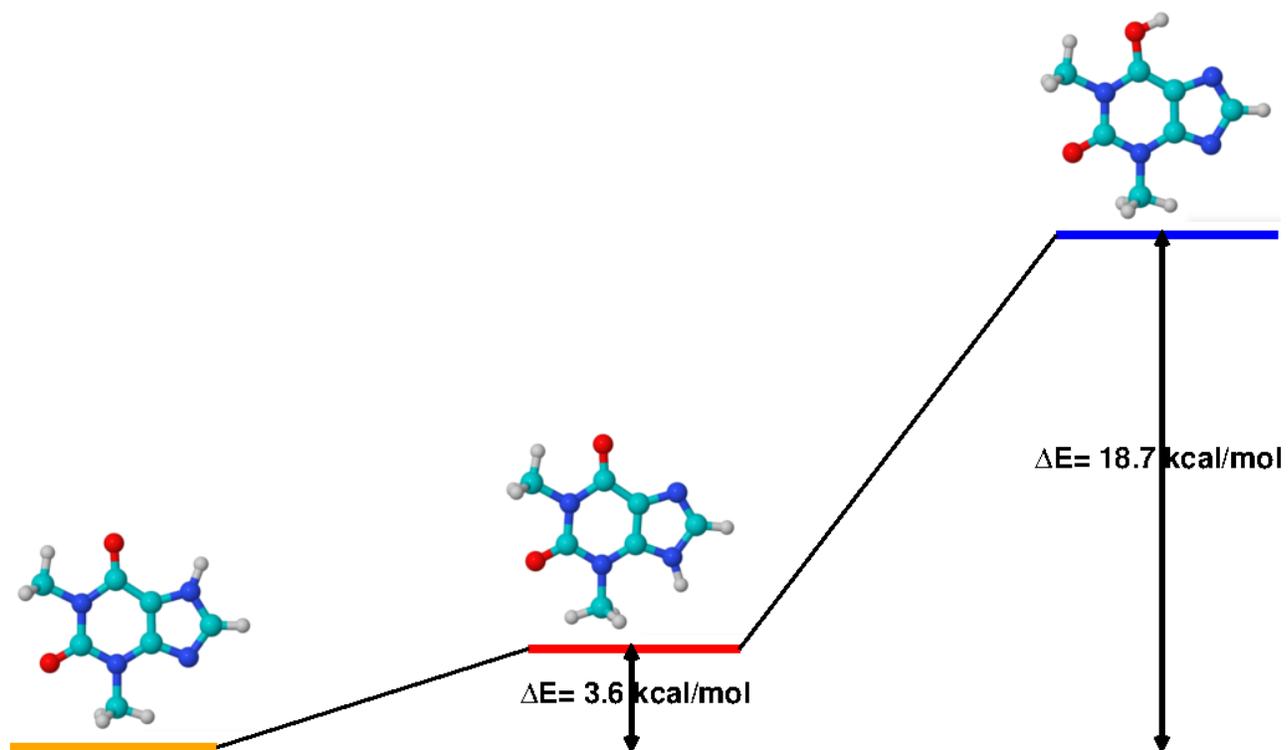


Figure S7: Relative energies (kcal/mol) for theophylline tautomers. All calculations using the B3LYP/6-311++(d,p) level of theory and the polarizable continuum model (PCM).

## 5 Stick spectra obtained by using the QM/FQ<sup>b</sup> solvation model

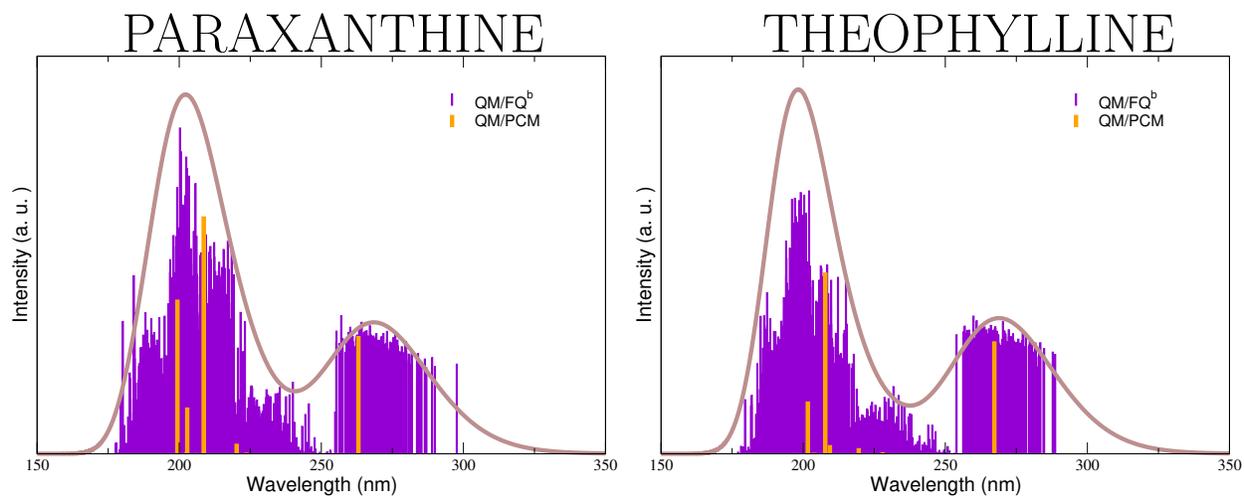


Figure S8: QM/FQ<sup>b</sup> B3LYP/6-311++G(d,p) raw data and convoluted excitation spectra. FWHM = 0.66 eV.

6 Plot of the orbitals involved in the first transitions of paraxanthine (left) and theophylline (right).

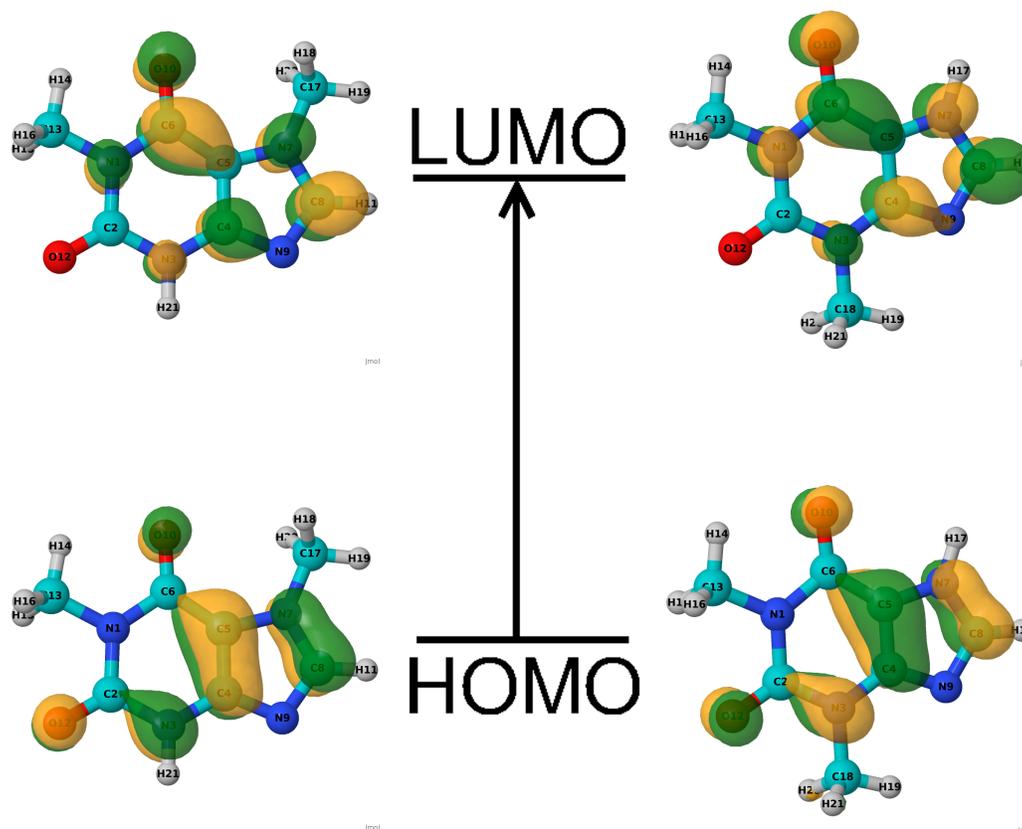


Figure S9: Molecular orbitals involved in paraxanthine and theophylline transitions giving rise to the main band in the absorption spectra.

## References

- [1] T. Giovannini, M. Macchiagodena, M. Ambrosetti, A. Puglisi, P. Lafiosca, G. Lo Gerfo, F. Egidi, and C. Cappelli, “Simulating vertical excitation energies of solvated dyes: From continuum to polarizable discrete modeling,” *Int. J. Quant. Chem.*, vol. 119, no. 1, p. e25684, 2019.
- [2] S. W. Rick, S. J. Stuart, and B. J. Berne, “Dynamical fluctuating charge force fields: Application to liquid water,” *J. Chem. Phys.*, vol. 101, no. 7, pp. 6141–6156, 1994.
- [3] J. Chen and B. Kohler, “Ultrafast nonradiative decay by hypoxanthine and several methylxanthines in aqueous and acetonitrile solution,” *Phys. Chem. Chem. Phys.*, vol. 14, pp. 10677–10682, 2012.