Investigation of the Tacrine-Saccharin Complex: A Combined Computational and Experimental Study

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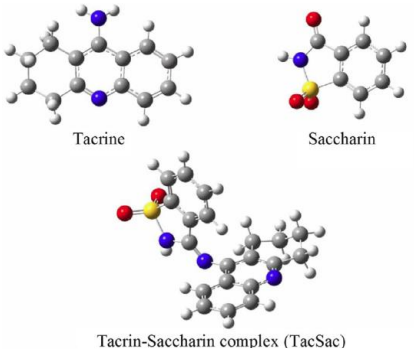
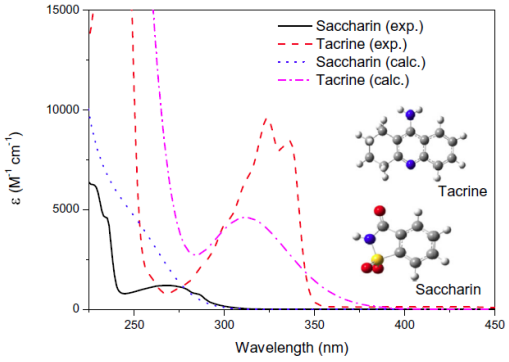
Tacrine is a drug used in the treatment of different diseases including Alzheimer's disease. It is also of great interest to researchers due to its unusual interaction properties. Saccharin is a sweetener used as a sugar substitute in commercial products. There are many studies reported on tacrine and saccharin; but neither experimental nor computational studies are reported on the tacrine-saccharin complex formed by the reaction of tacrine and saccharin to form an amidine (TacSac) except our recent studies [1,2]. We investigated the spectroscopic properties of TacSac using computational and experimental tools.





Geometry optimizations, and frequency calculations were performed with Gaussian 09 Revision-C.01 [3]. Optimization were carried out with B3LYP, M06-2X, M06L, and ωB97XD functionals in addition to MP2. Pople type 6-311++G(d,p) basis set was used in all calculations. Frequency calculations followed geometry optimizations and all calculated frequencies were positive. The most stable conformer for each system was used in further calculations. Excited state calculations were carried out with CIS and TD-DFT (B3LYP, CAM-B3LYP) methods to obtain UV-Vis spectra. The polarizable continuum model (PCM) was used with default options in Gaussian 09 to evaluate the solvent effect. Calculations were repeated with the SMD (solvation model based on density) approximation to observe the contributions of nonelectrostatic solute–solvent interactions. Atomic Polar Tensor (APT) approach was used for charge analysis.

Similar geometries for TacSac was obtained in gas phase and in H_2O both with PCM and SMD models using MP2 in contrast to DFT results. Since the discrepancy was observed in PCM calculations in DFT, it may be concluded that the electrostatic interactions were overestimated in DFT-PCM calculations causing significant deviations in the geometry. The MP2 results also revealed that the formed amidine is stable. This conclusion is also significantly different than DFT results which showed that the formation reaction of TacSac between tacrine and saccharin has highly positive complexation energy values and free energy differences. The MP2 results indicate that the TacSac system can be easily synthesized with a condensation reaction, and the amidine product is a potential candidate for photochemical charge-transfer systems.

Some of the calculations were performed on TUBITAK-ULAKBIM TRUBA resources.

[1] N. Acar, C. Selçuki, E. Coşkun, *J. Mol. Model*, **2017**, *23*, 17.
[2] N. Acar Selçuki, *Turkish Comp. Theo. Chem.*, **2019**, *3*, 25-37.
[3] M. J. Frisch *et al.*, Gaussian 09 Revision C01, Gaussian Inc., Wallingford CT, **2009**.