

## Electronic Structure and Absorption Spectra of Fluorescent Nucleoside Analogues

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Due to the emissive nature of some modified nucleobases, new fluorescent nucleosides, nucleotides, and oligonucleotides have been used to investigate fundamental biochemical transformations observed in DNA and RNA, facilitating the understanding of structural changes taking place due to environmental changes or interaction with light [1]. Recently, a second generation of a new emissive RNA alphabet, based on the isothiazolo[3,4-d]-pyrimidine structure, was synthetized [2] (Figure 1). These new molecules present not only isomorphism with the canonical ones, but also exhibit an isofunctional character making them prone for the above mentioned applications. The experimental absorption spectra were obtained in 1,4-dioxane and water. However, the molecular nature of the absorption and emission bands were not fully analyzed. To better understand these physical chemical properties we carried out a systematic investigation employing quantum chemical and molecular mechanics tools.

Solvent effects were taken into account combining the Sequential QM/MM methodology [3] with an average electrostatic embedding (ASEC) [4] and the Free Energy Gradient method (FEG) [5], called the ASEC-FEG method [6]. Furthermore, the absorption spectra were computed with the state of the art CASPT2 model. The molecular nature of the ground and excited states, charge distribution, geometries and hydrogen bonding in gas phase, dioxane and water were also studied. With these computational methods, we are able to carry out an atomistic treatment the solvent as well as a statistical treatment for the geometries and hydrogen bonding configurations.



*Figure 1: New fluorescent nucleobases obtained from isothiazolo*[4,3-d]*pyrimidine (sugar was substituted by hydrogen atoms).* 

Analysis of the atomic charges showed that no significant difference was noticed between the gas and dioxane media. In water, the charge redistribution is larger, leading to a significant increase in the dipole moment for all cases, ranging from 1.9 D for  $^{tz}I$  to 5.0 D for  $^{tz}G$ . The computed absorption spectra are in good agreement with those observed

experimentally; however special attention was needed to reproduce the results obtained in 1,4-dioxane, probably because of its lower dielectric constant in comparison to water. In addition, the changes in geometry when changing from the gas to the condensed media are especially noticeable in the pyramidalization of the -NH<sub>2</sub> group for <sup>tz</sup>A and <sup>tz</sup>C, on which the amino group is placed in position 6 of the ring. The pyramidalization of the -NH<sub>2</sub> group, is not observed in <sup>tz</sup>G, in which the group is in position 2. All molecules are hydrogen bond donors and acceptors, but only water exhibits the same characteristic, with dioxane acting as an acceptor only. In respect to the number of hydrogen bonds obtained, the following trend was obtained: <sup>tz</sup>I < <sup>tz</sup>A < <sup>tz</sup>U < <sup>tz</sup>C < <sup>tz</sup>G.

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