

Theoretical Investigation of the Emission Spectra and Stokes Shift of Modified Nucleobases in Gas Phase, 1,4-dioxane and Water

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Very interesting compounds, obtained from simple chemical modifications on the natural canonical nucleobases, have received considerable attention from theoretical and experimental chemists. Fluorescent nucleosides are among these new compounds, deserving special attention due to potential applications in biophysical analyses and for fabricating effective discovery assays [1]. Recently a second generation of a new class of fluorescent ribonucleoside alphabet was synthesized, employing isothiazole[4,3-d]pyrimidine as a template [2]. These emissive species are isomorphic nucleoside surrogates, with strong resemblance to their native counterparts (isomorphism). Due to these properties, they can replace their canonical counterparts on the genetic code, imposing a minimal change in the native structural and functional properties. That is, they are very good fluorescent probes.

The emission spectra of the emissive nucleobases presented above were investigated in gas phase and solution, employing the Sequential QM/MM methodology [3] and multiconfigurational methods. Solvent effects were included by combining the Sequential QM/MM methodology [3] with an average electrostatic embedding (ASEC) [4] and the Free Energy Gradient method (FEG) [5], called ASEC-FEG method [6]. This methodology has been applied successfully for describing the electronic (ground and excited states) properties of several molecules in solution [7]. For the sake of comparison, the conventional PCM model was employed.

Emission spectra, from the lowest-lying $^1(\pi\pi)^*$ state (bright state) were investigated in two solvents: 1,4-dioxane and water. In gas phase, the geometry of first bright state were optimized at the Multi-State CASPT2 level. However, in solution the geometries were optimized at the CASSCF level to reduce computational costs. The active space comprises the full set of π , π^* orbitals. For consistency with previous work concerning the absorption spectra, emission energies were computed with the single-state CASPT2 method, enlarging the full set of π , π^* orbitals with three n-orbitals (CAS(18,13)). The n-orbital associated to the sulfur atom was kept inactive because its occupation number was always close to two. All CASPT2 calculations were done with no IPEA shift correction and applying an imaginary level shift of 0.2 Hartree.

The main differences between the optimized geometries of the ground and low-lying $^1(\pi\pi^*)$ states are related to the bond lengths and the pyramidalization of the amino group. Emission spectra and Stokes shift were better described when the MS-CASPT2



XIX SBQT

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optimized geometry was adopted, in contrast to the results obtained with the optimized CASSCF structures.

Two approaches were used to describe qualitative the $^1(\pi\pi^*)$ states lifetimes in solution. First, lifetimes were supposed to be long, which allows the achievement of an electrostatic equilibrium between solute and solvent (equilibrium approach). In the second approach (non-equilibrium approach), the lifetimes are considered to be short and the electrostatic equilibrium is not reached. Our results indicate that ^3C does not reach electrostatic equilibrium with the two solvent. The ^3G in water is also better described using the non-equilibrium solvation. Following these assumptions, a better understanding of the photophysics in solution were obtained, with theoretical emission spectra and Stokes shifts in agreement with experimental results. On the other hand, the PCM model does not describe well the emission spectra and the Stokes shift.

Deactivation pathways from the FC to the minimum in the low-lying $^1(\pi\pi^*)$ states were computed with the MEP (minimum energy path) method in gas phase. Furthermore, conical intersections between the ground and the bright states were computed, and linear interpolations in internal coordinates were employed to connect the relevant structures. The computed pathways for the ^3A , ^3G and ^3I molecules are similar to the 2-aminopurine [8], exhibiting a high barrier between the minimum and the conical intersection, which explain the fluorescent property. As to the ^3C molecule, the conical intersection is inaccessible because it is located in a high energetic region. Solvent effects were considered solvating each point on the pathways.

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