



Research paper

Theoretical modeling of the absorption spectrum of aqueous riboflavin

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ABSTRACT

In this study we report the modeling of the absorption spectrum of riboflavin in water using a hybrid quantum/classical mechanical approach, the MD-PMM methodology. By means of MD-PMM calculations, with which the effect of riboflavin internal motions and of solvent interactions on the spectroscopic properties can be explicitly taken into account, we obtain an absorption spectrum in very good agreement with the experimental spectrum. In particular, the calculated peak maxima show a consistent improvement with respect to previous computational approaches. Moreover, the calculations show that the interaction with the environment may cause a relevant recombination of the gas-phase electronic states.

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1. Introduction

Riboflavin (RBF), also known as vitamin B2, is a biologically relevant flavin-based chromophore (see Fig. 1). The widespread of flavins and their significant contribution to biological processes has induced intensive studies of the physical and chemical properties of these compounds. The photochemical, spectroscopical, and photophysical properties of flavins have been widely studied [1–4] as well as their role in photosensitized reactions involving a wide range of substrates [5–7]. The electron transfer activity of flavins and RBF has been also investigated [8–10]. In addition, different flavin-related compounds and different substituted or chemically modified derivatives display differences in absorption wavelengths, providing a mean to modulate the spectroscopy of the compounds [11].

A reliable method to predict the absorption spectrum for RBF may thus help in determining suitable modifications to the structure in order to tailor photochemical properties in, e.g., drug design. For instance, flavin analogues may be designed to provide a particular excitation energy for a specific photochemical reaction.

Computing accurate absorption spectra of riboflavin and some of its derivatives has proven a difficult task for computational chemistry. Quantum chemical calculations of RBF and its derivatives at different levels of theory have been performed showing a high variability in the results [12–20]. Time-dependent density functional theory (TD-DFT) calculations have been employed using

a variety of recent range-separated and hybrid meta functionals to investigate ultraviolet and visible spectra of RBF [12–15,18,20]. Most of the methods tested provided absorption peaks considerably deviating from experimental results and inaccurate reproductions of the spectral line shape. An improvement was obtained when the effect of the solvent was included explicitly in TD-DFT calculations by using a few structures, obtained from molecular dynamics (MD) simulations, of the molecule embedded in the first water layer [20]. Nevertheless, the resulting spectra from the MD-simulated clusters showed a high variability of the spectral line shapes often miss-reproducing the relative intensities of the peaks and leading to an average wavelength of the peaks still blue-shifted by ≈ 20 nm compared to the experimental data (corresponding to a disagreement of ≈ 0.15 eV for the main peak and ≈ 0.2 eV for the secondary peak: the calculated absorption maxima are at 424 nm and 356 nm and the corresponding experimental maxima at 444 nm and 375). Moreover, because of this noise in the spectra, which is probably due to insufficient sampling and solvation effects included in the quantum chemical calculations, a reliable average spectrum cannot be obtained.

In complex systems, like a chromophore in solution, it is necessary to accurately take into account the interaction of the substrate with the environment that perturbs and affects the electronic degrees of freedom, modifying the molecular properties with respect to those measurable in vacuo. Nevertheless, the inclusion of electronic degrees of freedom (necessary for studying an electronic excitation) into a simulation of a large number of molecules (necessary for a reliable modeling of a condensed phase) is still challenging from a computational point of view. A number of approaches have been proposed to address the inclusion of

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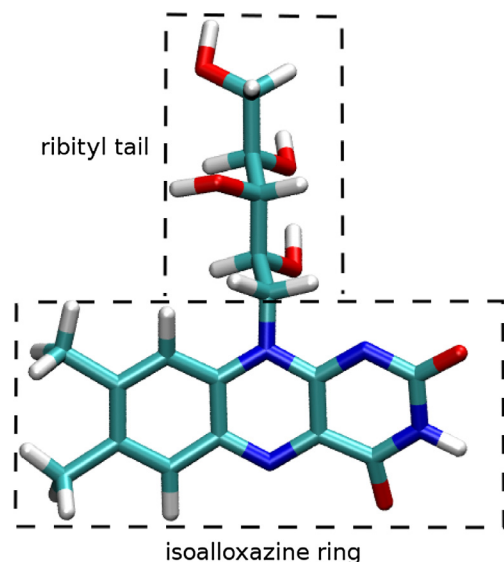


Fig. 1. Representative structure of riboflavin (RBF). The two moieties, the isoalloxazine ring and the ribityl tail, are highlighted.

environmental effects into the calculation of spectral properties in complex systems, mostly based on hybrid quantum/classical models [21–23], also including the determination of the vibronic structure [24] besides the inhomogeneous broadening due to the solvent. In this context, we proposed a theoretical computational approach, the perturbed matrix method (PMM) [25,26], whose main computational feature is the possibility of calculating the electronic properties of a chemical system embedded into a complex atomic-molecular environment along a classical MD simulation trajectory. With respect to other methodologies that use a limited number of snapshots extracted from an MD simulation to perform electronic calculations on a solute embedded in its first solvent hydration shell, the PMM allows, with a relatively low computational cost, both an extensive sampling of the whole system configurations and the inclusion of the effect of the whole environment. On the other hand, as the PMM approach does not make use of any adjustable parameter, it might be in some cases less accurate than other methodologies in reproducing the observables under investigation. In a number of recent applications, which were carried out both on large biomolecular systems [27–29] and on typical small solutes [30–32], the MD-PMM procedure actually revealed to be a rather reliable and accurate computational tool for evaluating the spectroscopic properties in the condensed phase.

Herein we address the modeling of the absorption spectroscopy of RBF in water via the MD-PMM approach. The results are critically compared with the experimental data showing a good agreement with the experimental absorption spectrum and reasonably well reproducing the spectral line shape. In addition, the good quantitative reproduction of the experimental spectral signals allows us to characterize the nature of the excited electronic states showing the recombination effects of the environment interaction.

2. Theory and methods

2.1. Perturbed matrix method calculations

The basic features of MD-PMM [25,26] and the strategies utilized for calculating absorption spectra have been explained in details in previous papers [31,32] and, hence, only a part of the related essential aspects are herein mentioned. In general, in line

with the most popular quantum mechanics/molecular mechanics (QM/MM) computational procedures [33–35], MD-PMM is based on the approximation of dividing the whole atomic-molecular system into a quantum center (QC) (to be treated at the electronic level) where the quantum processes of interest occur, and its environment which is modeled as an atomic-molecular semi-classical subsystem interacting with the QC. In the present case, the QC is lumiflavin (the isoalloxazine moiety saturated with a methyl group) while the ribityl tail is included in the perturbing environment. When the perturbation can be properly described as an external field (i.e., the molecules and/or chemical groups of the environment can be considered as electronically uncoupled from the QC), the level of approximation of PMM is given by the order of the multipolar expansion of the perturbation operator and the operative dimension of the unperturbed eigenstates space used to construct the perturbed Hamiltonian matrix. The accuracy of the former depends on the amount of variation of the perturbing field within the QC rather than on its intensity, the latter can provide an accurate evaluation of a set of perturbed eigenstates only when the intensity of the perturbation provides interaction energies significantly lower than the energy difference between the unperturbed ground and highest energy excited states.

The computational strategy of MD-PMM strategy can be briefly outlined as follows. At first, MD simulations are carried out for the system of interest, in this case RBF and water molecules, describing the QC-environment semi-classical dynamics. Secondly, the QC quantum properties are recalculated *a posteriori* as explained below. A set of unperturbed electronic eigenstates ϕ_j^0 , eigenfunctions of the QC unperturbed (gas-phase) electronic Hamiltonian matrix (\tilde{H}^0), are evaluated providing the basis set for constructing the QC perturbed electronic Hamiltonian matrix (\tilde{H}):

$$\tilde{H} \simeq \tilde{H}^0 + \tilde{I}q_T\mathcal{V} + \tilde{Z}_1 + \Delta V\tilde{I} \quad (1)$$

$$[\tilde{Z}_1]_{j,j'} = -\mathbf{E} \cdot \langle \phi_j^0 | \hat{\boldsymbol{\mu}} | \phi_{j'}^0 \rangle \quad (2)$$

where q_T and $\hat{\boldsymbol{\mu}}$ are the QC total charge and the dipole operator, \mathcal{V} and \mathbf{E} are the electrostatic potential and field, respectively, exerted by the environment (in this case the solvent and the ribityl tail) on the QC center of mass at each frame of the simulation and ϕ_j^0 are parametrical functions of the QC nuclear coordinates which can be expressed within the QC internal reference of frame (within the used Born-Oppenheimer approximation, the electronic eigenfunctions are considered independent of the nuclei motions). This implies that each ϕ_j^0 is invariant for the QC roto-translations being possibly dependent only on the QC internal nuclear coordinates or, more specifically, considering the chromophore vibrationally relaxed in its initial state each ϕ_j^0 to be used in PMM calculations fully defined by only the QC conformational coordinates (i.e., the semi-classical internal coordinates providing relevant structural changes) with all the other internal coordinates (i.e., the vibrational coordinates corresponding to small harmonic or quasi-harmonic fluctuations) energy minimized at each position of the conformational ones [31,32]. Finally, ΔV includes all the other terms treated as a simple short range potential and \tilde{I} is the identity matrix.

At each frame of the simulation the electronic Hamiltonian matrix is first constructed, according to the instantaneous values of the perturbing electric field, and then diagonalized producing a continuous trajectory of perturbed eigenvalues and eigenvectors to be used for evaluating whatever QC instantaneous perturbed quantum observable.

To calculate the absorption spectrum, once the perturbed frequencies (ν) and transition dipoles ($\boldsymbol{\mu}_{j,i}$) are obtained at each of the N frames of the trajectory, we can evaluate their distribution

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