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Solvent Effect on the Fluorescence Spectra of Coumarin 120 in Water: A Combined Quantum Mechanical and Molecular Mechanical Study

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The solvent effect on the steady-state and time-resolved fluorescence spectra of coumarin 120 in water was studied utilizing a molecular dynamics simulation with combined quantum mechanical/molecular mechanical method. The constructed steady-state fluorescence spectra reproduced the Stokes shift of the experimental data. The solvent effects on the spectra were examined by constructing three different spectra: spectra using the entire system, spectra including water molecules only in the first solvent shell, and spectra excluding all water molecules. We found that the variation in C-C bond length makes the largest contribution to the solvent shift in the fluorescence spectrum, which indicates the importance of the electronic structure variation.

KEYWORDS: Combined Quantum Mechanical/Molecular Mechanical Method, QM/MM, Molecular Dynamics Simulation, Solvation Dynamics, Electronic Structure Calculation

1. Introduction

Solvation dynamics has been studied intensively both experimentally [1–11] and theoretically [12–32] because it plays an important role in the kinetics of chemical reactions in solution. Observation of the dynamic Stokes shift, which is suitable for detecting ultrafast solvation dynamics, is a powerful tool in studying solvation dynamics. Rosenthal *et al.* [1] connected the relaxation of the dynamic Stokes shift with the dynamics of the solvent molecules. They observed a two-part character in the solvation response. Their observation indicates that an initial fast inertial motion of the solvent occurs after the excitation of the solute, and then the solvent reorganizes slowly through rotational diffusion. While most works have focused on the relaxation of the peak shift to study solvation dynamics, Murakami and co-workers [3] and Nishiyama and co-workers [7, 8, 11] have made efforts to investigate solvation dynamics observing the relaxation of the spectral bandwidth as well. Nishiyama *et al.* examined the relaxation of the peak shift and the spectral bandwidth in polar solvents at room or lower temperature [7, 8], and in binary solvent mixtures by transient hole-burning spectroscopy and time-resolved fluorescence spectra [11]. They found that at room temperature, the bandwidth relaxation is slower than the peak shift relaxation by an order of magnitude. They suggested that the two relaxation processes of the spectra have their origins in different solvation dynamics: the peak shift relaxation arises from the solvent rotational diffusion, and the bandwidth relaxation originates from the solvent translational diffusion.

A large variety of theoretical studies have contributed to understand the solvation dynamics observed in dynamic Stokes shift experiments. Among various methods, molecular dynamics (MD) simulations based on an all-atom model succeeded in providing detailed microscopic features of sol-

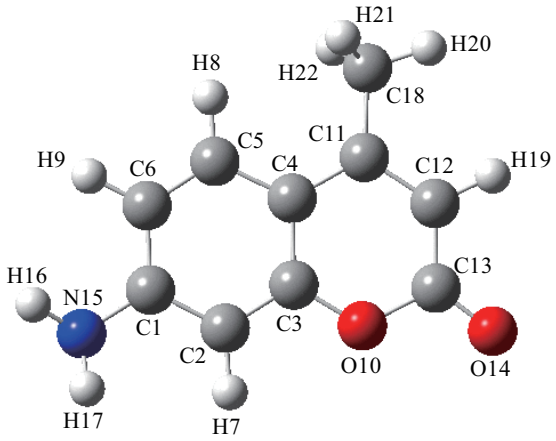


Fig. 1. Structure of C120. [Color Online]

vation dynamics. Belhadj *et al.* studied the solvation dynamics of formaldehyde in water and found an interaction between the formaldehyde and water molecules that occurs in the first solvent shell [17]. Jimenez *et al.* simulated the dynamical Stokes observation of coumarin 343 (C343) in water and compared their results with experimental data [20]. They found a significant difference in the simulation of solvation dynamics using an realistic all-atom model and an atomistic solute model. Kumar *et al.* [21] investigated the effect of the solute molecule on solvation dynamics using an all-atom model and found that the solute attribute of foremost interest is the charge distribution difference in the solute between the electronic ground and excited states, which emphasizes the importance of describing the solute molecule accurately. However, these simulations above used fixed charges and rigid body models. The molecular and electronic structures fluctuate during the relaxation process, which can affect the solvation dynamics. The variation in electronic structures accompanied with molecular distortion has not been taken into account in studying solvation dynamics so far.

In this article, we introduce our ongoing research, which aims to elucidate the relations between the relaxation of the time-resolved fluorescence spectra and solvation dynamics of coumarin 120 (C120, 7-amino-4-methyl-1,2-benzopyrone, Fig. 1) in water solution. The constructed fluorescence spectra, which consider variation in electronic structures accompanied with molecular distortion, can be compared with the solvent effect of absorption spectra we have studied previously [33].

2. Computational Details

We applied combined quantum mechanical/molecular mechanical (QM/MM) calculations [34] to C120 in water, where the solute, C120, was treated quantum mechanically, and the solvent water molecules were treated molecular mechanically. First, we executed 10 QM/MM MD simulations of the ground state of C120 with 417 water molecules, in a spherical boundary of 15 Å radius. Each simulation consisted of 30,000 steps with a 0.5 fs time step. A Nosè-Hoover thermostat [35, 36] was used to obtain the NVT ensemble. Time-dependent density functional theory [37,38] with the B3LYP functional [39–41] was used for the quantum mechanical calculation of the electronic excited state. The 6-31G basis set [42] was used for all the quantum mechanical calculations. The initial structures were chosen randomly from the ground state simulation executed using B3LYP with 6-31G basis set. The CHARMM27 force field parameters [43] and TIP3P water parameters [44] were used for the MM calculations. The solute C120 molecule moves freely, while rigid body model for water molecules is used. CHARMM [45] and Gaussian09 [46] package programs were employed for the QM/MM MD simulation.

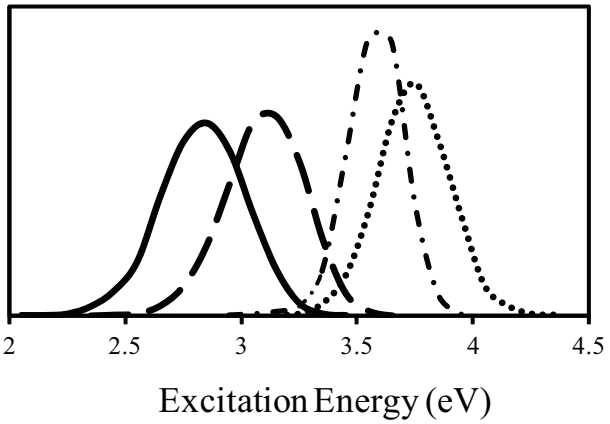


Fig. 2. The constructed absorption (dotted curve) and steady-state fluorescence spectra of Models I (solid curve), II (dashed curve), and III (alternate long and short dash curve).

3. Results and Discussion

3.1 The steady-state fluorescence spectra and solvent effect

We constructed steady-state fluorescence spectra by averaging all ten runs to understand the equilibrium solvent effect on the fluorescence spectra. Fluorescence spectra originate from the first excited state of C120, which has a $\pi \rightarrow \pi^*$ character. We constructed three spectra: the fluorescence spectrum of C120 in water obtained from the simulation (denoted as Model I), spectrum of C120 excluding water molecules out of the first solvation shell from Model I (Model II), and spectrum excluding all water molecules from Model I (Model III). This allows us to extract the effect of the polarization of waters in the first shell and other waters from the fluorescence spectra. The first-shell solvents were the water molecules within σ = 3.15 Å of the heavy atoms in the solute molecule. The spectra are illustrated in Fig. 2 with the constructed absorption spectrum. The standard deviations of the spectra are good indices for the bandwidth of the spectra. The peak of the fluorescence spectrum of Model I and the constructed absorption spectra agrees well with the experimental spectra observed by Arbeloa *et al.* [47]. This shows the accuracy of our calculation scheme. The comparison between Models I and III shows the solvent effect from all of the solvent molecules on the fluorescence spectrum of C120 in water, and the comparison between Models II and III shows the solvent effect from the solvent molecules in the first solvent shell. Table I lists the peak values and the standard deviations of the calculated excitation energies. The constructed fluorescence spectra from our calculations showed large red shifts in water solution. Hereafter, we focus on this red shift of the fluorescence spectra in water to discuss the solvent effect. Comparing the peak values of Models I and III, we find a large red shift of 0.71 eV because of the solvent. We next find that 0.47 eV is the red shift value of the peak because of the first-shell solvent by comparing Models II and III. This shows that the contribution of the water molecules in the first solvent shell to the red shift of the fluorescence spectra is 66.2% of the entire shift. It means that the contribution of the red shift is mostly localized in the first solvent shell. The contribution of the first solvent shell is quite large. The standard deviations of Models III and I I were 66.9% and 96.1% of Model I, respectively. The difference in the standard deviation between Models I and II is small compared with the peak shift difference. The water molecules in the first solvent shell play a dominant role in the spectra, broadening the steady-state fluorescence spectra of C120 in water.

The relation between the steady-state fluorescence spectra and solvation of C120 can be investigated by calculating correlation coefficient, the covarience of two variables divided by the product

Table I. The peak value and standard deviation of the absorption and steady-state fluorescence spectra for the three different models. The solvation shift values (eV) of the peak value from Model Ⅲ are in parentheses.

	Peak Value (eV)	Standard Deviation (eV)
Absorption Spectra	3.74	0.11
Fluorescence Spectra		
Model Ⅰ	2.86 (0.71)	0.18
Model Ⅱ	3.10 (0.47)	0.17
Model Ⅲ	3.57 (0.00)	0.12

of their standard deviations, between the calculated excitation energies for the three models and various parameters of C120 in water. We selected 19 parameters of geometry of C120 and water: the open-close conversion of the amino group, the rotation of the amino group around the C1-N15 bond, the bending motion of the C13=O14 bond against the coumarin ring, the out-of-plane bending of C3-O10-C13, the rotation of the methyl group around the C11-C18 bond, the end-to-end distance between the hydrogen atoms of the amino group and the hydrogen atoms of the methyl group, which is the coupling between motions of the methyl group and the amino group, the bond alternation of the benzene ring, the bond alternation of the pyrone ring (in bonds C4-C11-C12-C13), bond length of C13=O14, bond length of C1-N15, bond length of C11-C18, the number of hydrogen bonds between water and N15 via H16 or H17, number of hydrogen bonds between water and O14, number of water molecules in the first solvent shell (within σ = 3.15 Å) from the solute molecule, number of water molecules in the second solvent shell (in between σ and 2σ = 6.3 Å) from the solute molecule, number of water molecules in the first solvent shell from N15, number of water molecules in the second solvent shell, number of water molecules in the first solvent shell from O14 , and number of water molecules in the second solvent shell from O14.

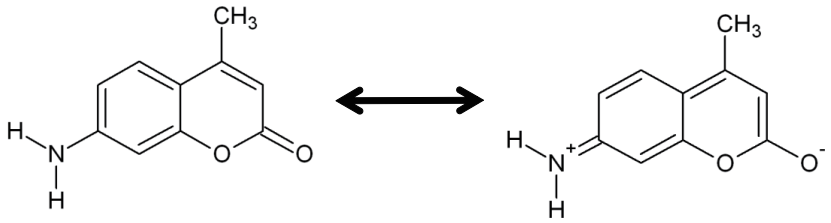
The correlation coefficients of Models Ⅰ and Ⅱ show the relation between the calculated excitation energies and the solvent shift of the steady-state fluorescence spectra. The dominant contribution to these models is the bond alternation of the C-C bonds in the pyrone ring, with the coefficient of 0.48. The positive sign of the correlation coefficients for bond alternation shows that as the bond alternation increases, the excitation energy increases. In other words, the excitation energy increases as the aromaticity of the pyrone ring becomes larger. This can be explained by the two structures in Fig. 3. The stable structure in the excited state leads to an increase in the dipole moment of the solute molecule, which causes the red shift, and enhances the polarization of the solute molecule. Hence, the interaction between the solute and solvent molecules increases. This was also found in the simulation of C120 in water for the ground state [33]. The bond alternation influences the π orbitals, which plays an important role in the $\pi \rightarrow \pi^*$ excitation. This indicates that the introduction of the oscillation of the electronic structure is essential to simulate the solvation dynamics observed in time-resolved fluorescence spectra. The absolute value of the correlation coefficents related to the solvent structure were all below 0.2, which showed small contribution compared to the bond alternation of the pyrone ring.

3.2 The time-resolved fluorescence spectra and solvent effect

We next calculated the time-resolved fluorescence spectra. As in previous studies, we define the response function for the relaxation process as follows:

$$S_e(t) = \frac{\tilde{\nu}(t) - \tilde{\nu}(0)}{\tilde{\nu}(\infty) - \tilde{\nu}(0)}$$

where $\tilde{\nu}(t)$ stands for the average of the excitation energies (the peak of the fluorescence spectra in experiments) calculated at time t. We constructed five response functions, which are described in Fig.



Stable Structure in the Ground State

Stable Structure in the Excited State

Fig. 3. The stable structures in the electronic ground and excited state.

4. Fig. 4(a) shows the response function of the excitation energy of Model I, and (b) shows that of Model Ⅱ. The dotted lines of these two figures are the response function of Model Ⅲ. The response functions are obtained by averaging all ten runs. After the electronic excitation, the solute molecule immediately responds. The large change of the π conjugate network leads to a quick response of the solvent molecules as well, which is seen in the time region of 0-0.4 ps. About 80% of the solvation response of the fluorescence spectra is achieved in this stage. Compared with response functions with atomic or atomistic single charges as a solute, our response functions show that the response of the solvent is less collective to the solute response. This is due to the rapid spatial variation of the electronic structure of the solute compared with atomic solutes, in which the solvent molecules respond. A similar tendency is seen in the response function of C343 in water constructed by Jimenez *et al.* [20]. The fast initial response is followed by slow relaxation with oscillation. The response functions of Models I and Ⅱ show similar oscillations to those found in Model Ⅲ, which suggests that the oscillation arises from the fluctuation of the solute structure and the π conjugate network of the C120. In the response functions constructed by Jimenez *et al.* [20], the oscillation of the response functions attenuates. However, the oscillation of the response functions of Models I and Ⅱ increases at 0.4-0.7 ps. The dotted curves in Figs. 4(a) and (b) show that the fluctuation of the excitation energy contribution from the solute molecule is enhanced as well. To investigate the effect from the solvents, we constructed two more response functions. Fig. 4(c) shows the response function of the solvent shift of the excitation energy of Model I, and (d) shows that of Model Ⅱ, which allows us to focus on the solvent contribution to the excitation energies. The response functions of the solvent shift of Models I and Ⅱ show similar oscillations. However, the oscillations at 0.4-0.7 ps in Model Ⅱ are seen around the average, while the oscillations in Model I increase. This shows us that not only the solvent molecules in the first solvation shell, but also solvent molecules in the outer region contribute to the large oscillations.

The relation between the time-resolved fluorescence spectra and solvation of C120 can be investigated by calculating correlation coefficients between the calculated excitation energies for the three models and various parameters of C120 in water. The correlation coefficients of Models I and Ⅱ show the relation between the calculated excitation energies and the solvent shift of the time-resolved fluorescence spectra. The dominant contribution to these models stems from the bond alternation of the C-C bonds in the pyrone ring with the coefficient of 0.43, as seen in the equilibrium case. A large difference from the equilibrium case was mostly found in the parameters of the solvation structure. There are positive correlations in the number of hydrogen bonds from water to N15 (coefficient of 0.33), and the number of waters found in the first solvation shell from N15 (coefficient of 0.13) , while a negative correlation is found for the number of waters in the second solvation shell from N15 (coefficient of -0.25). In the initial stage of the dynamics, solvent molecules rotate to construct hydrogen bonds with the solute. The water motion toward the solute and construction of the hydrogen

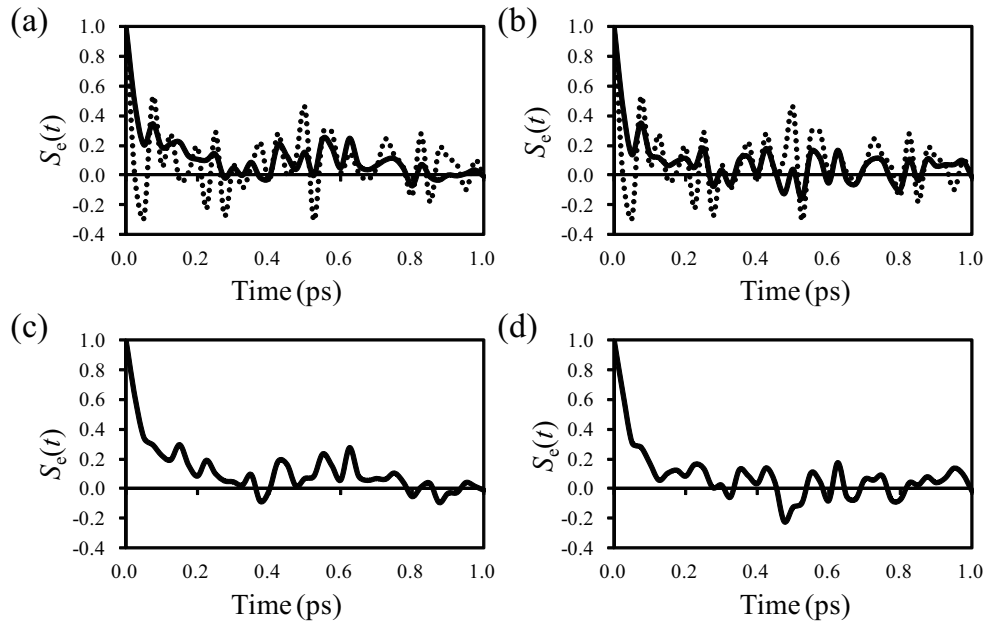


Fig. 4. Response functions of the relaxation of calculated time-resolved fluorescence spectra: (a) response function of the excitation energies calculated for Model I (solid line) with response function of Model Ⅲ (dotted line), (b) response function of the excitation energies calculated for Model Ⅱ (solid line) with response function of Model Ⅲ (dotted line), (c) response function of the solvent shift of the excitation energies calculated for Model I, (d) response function of the solvent shift of the excitation energies calculated for Model Ⅱ.

bonds leads to an increase in the solvation shift of the fluorescence spectra. The increase of the water molecules in the second solvent shell, which in most cases leads to a decrease in the first solvent shell, leads to a decrease in the fluorescence spectra. Aside from these, a large negative correlation is found in the end-to-end distance between the CH3 and NH2 groups with the coefficient of −0.41. This is related to the open-and-close motion of a book, where C5-C4-C3-O10 works as the spine. This motion had the largest contribution in C120 in water for the ground state [33]. This large motion affects the solvation around C120, which leads to a decrease in the fluorescence spectra at the initial stage in the solvation dynamics. This indicates that the introduction of molecular distortion may affect solvation dynamics, which can lead to slower solvation dynamics compared with other simulations, where the solute structure is fixed.

Our research is still in progress. We have introduced electronic structure fluctuation in our solvation dynamics simulation. The model became more realistic; however, the analysis of the fluorescence spectra became more complex because the electronic structure fluctuation of the solute molecule plays an important role in the solvent effect on the spectra. Thus, we need further analysis of the solvent effect on the time-resolved fluorescence spectra to determine its relation with solvation dynamics. QM/MM calculations require large computation resource so the number of the MD runs are limited, but we plan to increase the number of MD runs to obtain more reliable average feature. In this work, we carried out the MD simulation at constant temperature. We next plan to execute the simulation at constant energy.

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