

Research Article

A Coupled Potential QM/MM Simulation of 2-(2-fury)-3-hydroxychromone: Insights into the ESIPT Process

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Abstract

Hybrid quantum mechanics/molecular mechanics (QM/MM) simulations are a powerful method for studying chemical reactions in condensed phases. This approach combines two levels of modeling: regions involved in chemical processes are treated using quantum mechanics, while the remaining parts of the system are modeled with molecular mechanics. This method allows for the analysis of chemical reactivity, such as the Excited-State Intramolecular Proton Transfer (ESIPT) process. In this study, two simulations were performed to examine the behavior of 2-(2-fury)-3-hydroxychromone (FHC) in a periodic box with a polar protic solvent. The first simulation uses classical molecular dynamics (MD), while the second applies the semi-empirical PM3 Hamiltonian to the FHC molecules. The goal was to compare the results of both simulations to better understand the system's dynamics. A key feature of this approach is the abrupt change in the description of the molecule when it crosses a given cutoff, leading to sudden changes in the energy and forces involved. This study provides new insights into the use of QM/MM hybrid simulations to analyze proton transfer processes like ESIPT and their application in complex molecular systems where interactions between molecules play a crucial role. In summary, the study highlights the potential of hybrid simulations to understand the dynamics of chemical processes at the molecular scale, particularly for complex phenomena like ESIPT.

Keywords

Quantum Mechanics, Molecular Mechanics, QM/MM, Molecular Dynamics, FHC, ESIPT

1. Introduction

2-(2-furyl)-3-hydroxychromone (FHC) ([Figure 1](#)) is a dual-emitter fluorescent probe that induces excited-state intramolecular proton transfer (ESIPT) reactions in solution and is incorporated into biological-macromolecules. Its two fluorescent bands are designated the short-wavelength normal form (N*) and the long-wavelength band is the tautomeric form (T*), the product of the ESIPT reaction [\[1\]](#). To understand the mechanism responsible for the occurrence of the

ESIPT reaction, the compound was monitored in water. Among ESIPT dyes, the photophysics of FHC in solution has been intensively studied using steady-state fluorescence measurements and time-resolved fluorescence decay analysis [\[4, 7\]](#) to determine the response of such molecules. Many biochemical systems like proteins are simply too large to be described at any level of ab initio theory. In addition, the current molecular mechanics force fields are not adaptable for

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modeling processes where there is a formation or cleavage of a chemical bond. In order to go beyond a full quantum mechanical description on one side and a full molecular mechanics treatment on the other side, methods have been available that provide quantum chemistry (QM) treatment for a small part of the system while keeping the faster force field (MM) level of theory for the larger part. The original hybrid QM/MM strategy was proposed by Warshel and Levitt [3].

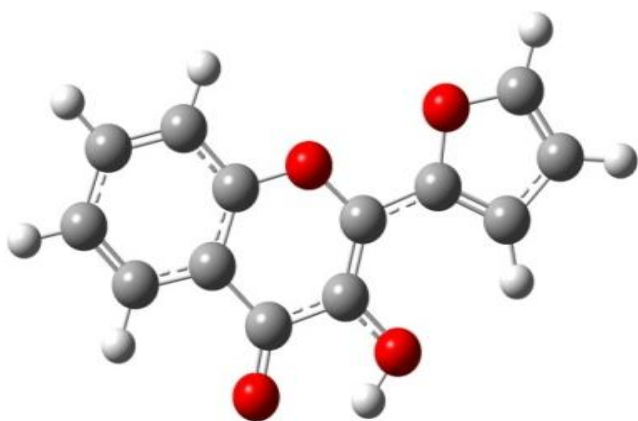


Figure 1. FHC in the normal form (reactant).

2. Methodology

The size and complexity of the system require the use of classical molecular dynamics for the nuclear degrees of freedom and quantum mechanics to model the electronic rearrangements during a chemical reaction. In molecular dynamics (MD) simulations, Newton's equations of motion are solved numerically to obtain the trajectory of the dynamics of a molecule over a period of time [2]. The QM/MM method provides potential energies and forces. Molecular dynamics simulations can be performed using these forces. However, the timescales that can be achieved in QM/MM simulations are rather limited due to the computational effort required to perform *ab initio* calculations.

The first step is to create topology and coordinate files for the FHC in TIP3P water.

1) Classical MD

We have performed QM/MM excited-state dynamics simulations of FHC chromophore in water to examine the effect of an aqueous environment. The water molecules were modeled using the TIP3P model, and the chromophore was described at the PBE0/TZVP level of theory. The FHC geometry was first optimized in its S_0 (FC) excited state with the TDDFT method, in both the N^* and T^* forms, the FHC geometry was first optimized in its S_0 (FC) with the DFT method, in normal form.

To study the photoexcitation process of FHC, we conducted equilibration in the S_0 (FC) ground state.

After that, we calculated the molecular electrostatic potential over a grid of points on the S_0 (FC)-optimized geometries

at the PBE0/TZVP level of theory. We then fit the electrostatic potential to an atom-centered point charge model according to the RESP procedure for the normal form [8-10]. This yields the so-called RESP charges that were assigned to each atom. The FHC was then solvated with a 20 Å cubic box of 1265 water molecules [1].

We can now perform classical molecular dynamics since we have our coordinate files and topology.

For this system, we perform energy minimization, slowly heat the system, and then perform production MD with temperature control with a Langevin thermostat and a Berendsen barostat for constant pressure simulation.

First, we need to minimize our ability to remove any bad contacts created by solvation and to allow our artificially created FHC structure to relax. For this purpose, we will run 1000 steps of minimization. We use periodic boundaries with PME for both classical and QM/MM MD (NTB=1). AMBER also supports shaking for QM atoms, and since we are not interested in any kind of reaction involving hydrogen in the QM/MM simulation, we will use shaking (NTC=2, NTF=2) for this simulation to allow us to use a 2 fs time step. Since this is a periodic simulation with PME, we can safely use a cutoff of 12 angstroms.

After minimization of the system, we will run 1,000 fs of molecular dynamics at a constant temperature of 300 K. Normally, we will slowly heat our system to 300 K, but since this is just a small FHC molecule in solution, it should be fairly stable and should survive beginning at 300 K. During the MD, we will write to both our output file and the mdcrd file every step.

2) QM/MM MD

We used a coupled QM/MM potential and ran for the simulation. While we model water classically, we use the semiempirical PM3 Hamiltonian to model the FHC molecule. There are no bonds that cross the QM/MM boundary in this scenario. Three classes of interactions are present in the hybrid QM/MM potential energy: interactions between atoms in the QM region, interactions between atoms in the MM region, and interactions between atoms in QM and MM.

The interactions within the QM and MM regions are relatively straightforward to describe, that is, at the QM and MM levels, respectively. The interactions between two subsystems are more difficult to describe, and several approaches have been proposed. These approaches can be roughly divided into two categories: subtractive and additive coupling schemes. In the subtractive scheme, the QM/MM energy of the system is obtained in three steps. First, the energy of the total system, consisting of both the QM and MM regions, is evaluated at the MM level. The QM energy of the isolated QM subsystem is added in the second step. Third, the MM energy of the QM subsystem is computed and subtracted. The last step corrects for including the interactions within the QM subsystem twice:

$$V_{\text{QM/MM}} = V_{\text{MM}}(\text{MM+QM}) + V_{\text{QM}}(\text{QM}) - V_{\text{MM}}(\text{QM})$$

For QM/MM MD, the input files look very similar. However, there are a few notable differences related to the specification of the atoms to be modeled quantum mechanically.

3. Results and Discussion

We should discover that the temperatures are fairly stable and comparable if we compare the output files in more detail. These parameters will not be exactly the same since we are tracking different trajectories.

Notably, the dynamics of the OH groups are different in the

QM/MM calculations. The QM/MM behavior here is believed to be more accurate. OH backbone dynamics are known to be troublesome to model accurately with classical force fields.

The comparison of the energies for the system in Figure 2 is provided by the results. The temperature, potential energies, and total energies in this work all fluctuate around a constant mean value according to the other simulations, however, the QM/MM methods (red curve) appear to be more stable than does the MD (black curve).

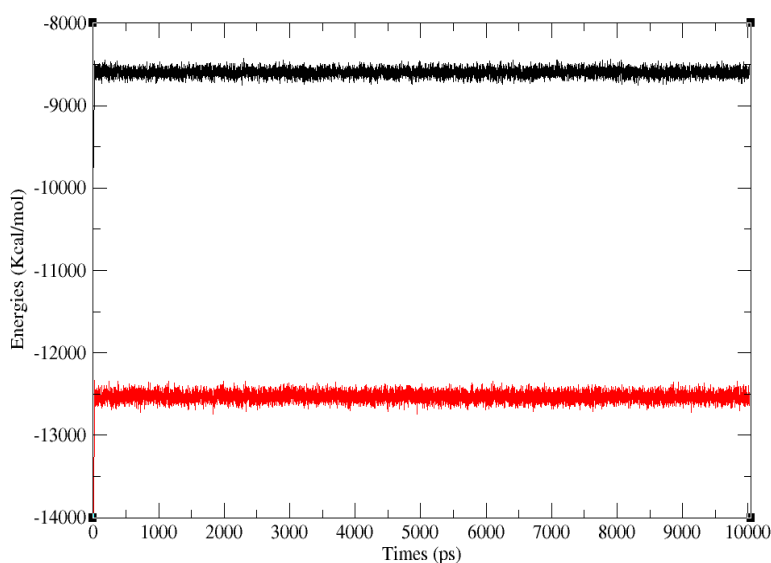


Figure 2. FHC potential energies; black (MD), red (QM/MM).

The root mean squared deviation (RMSD) (Figure 3) is a measurement of how similar a structure's internal atomic coordinates are relative to some reference molecule coordinates. The root mean square deviation in the particle number is on the order of two to three for most calculations [11]. We measured how the internal atomic coordinates change relative to the minimized structures. Specifically, we analyzed the furyl atoms. The RMSD values for the MD and QM/MM comparisons were 0.5 Angstrom and 0.25 Angstrom, respectively.

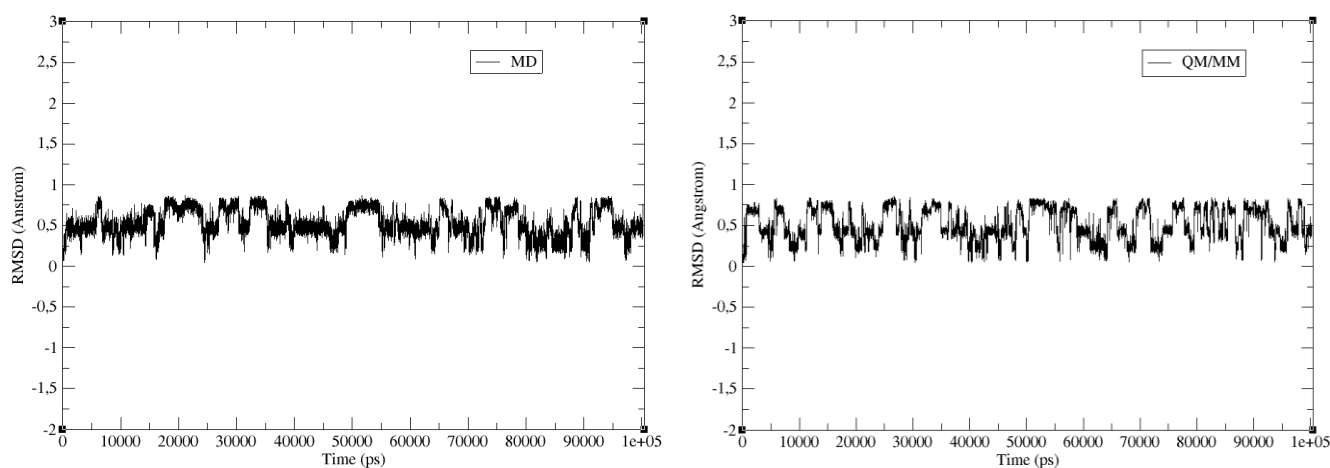


Figure 3. FHC MD and QM/MM.

There was no significant conformational change in the positions of the FHC atoms relative to the starting structures according to the two methods.

The pair distribution function $g(R)$ between the solvent H-bond donor groups in the N^* form and the acceptor oxygen

Oa or donor oxygen Od was computed in Figure 4 in order to elucidate the role of the H-bond in the ESIPT mechanism. The $g(R)$ measures the probability of finding the solvent H-bond donor atom at a distance R from Oa (resp. Od), relative to that for an ideal gas.

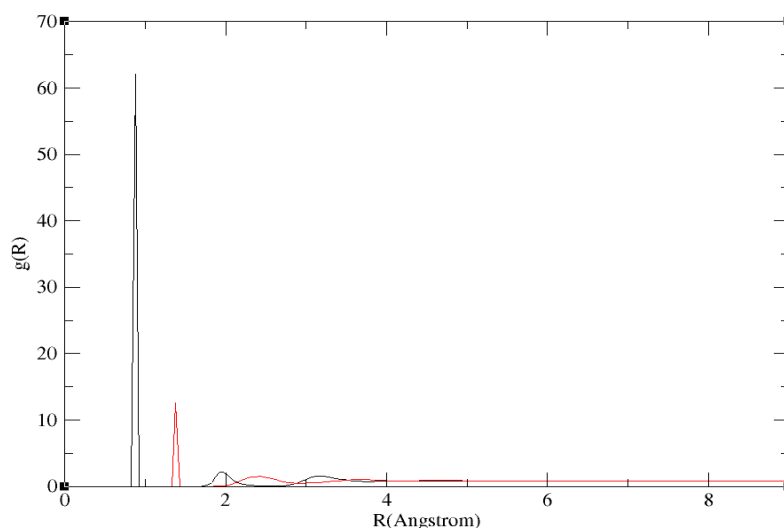


Figure 4. Radial distribution functions of the QM/MM (black) and MD (red) methods.

The radial distribution functions (RDFs) computed with the QM/MD method are compared with the corresponding MD results of Abdallah Brahim et al. [1], as shown in Figure 4, by comparing both the height and the position of the peaks. The radial distribution function curve presented a profile with two strong peaks at approximately 0.95 Å in the QM/MD group and at approximately 1.45 Å in the MD group for the first solvent shell. This represents the short distance between the solvent molecules and the FHC, and its value of approximately 2 Å in the considered solvents is characteristic of H-bonding interactions [1]. This indicates that at least one solvent molecule forms a H-bond contact with Oa (Od) in the first solvent shell. According to previous work, only the H-bond at the Oa site has a spectroscopic impact, as the N^* and T^* emission wavelength positions were accurately predicted when considering a solvated complex of FHC with a single explicit solvent molecule positioned at this site [12]. The second peaks are obtained at 1.98 and 2.5 Å, respectively. These differences in the positions of the peaks obtained by the two methods reveal the solidity of the H-bond networks present in the polar solvent.

4. Conclusion

In this work, we have discussed QM/MM methods and their applications to the FHC of ESIPT processes. This balancing act between computational efficiency and accuracy for the system of interest renders semiempirical QM/MM models

especially attractive, with parallelisation and limiting upper boundaries on electronic structure accuracy being crucial areas on which to focus, in addition to calibration and direct comparison against higher-level QM/MM approaches. Going forward, a number of aspects may allow for more quantitative and versatile QM/MM analyses of progressively complex problems.

The simplest application of this approach assumes an abrupt change in the description of a molecule when it crosses a given cutoff, leading to sudden changes in the energy and forces involved.

We believe that such approaches have broad applications in biomolecular simulations and that the strategies outlined in this perspective will help overcome the quantitative limitations of existing semiempirical QM/MM calculations without massive increases in computational cost.

The perspectives of this study focus on the importance of understanding excited-state reactions, such as photoisomerization, to better grasp the dynamics of proton transfer processes and their role in various chemical reactions. As demonstrated by Bellucci and Coke [5], and Vandrell et al. [6], the excited-state intramolecular proton transfer (ESIPT) process can be significantly influenced by the vibrational modes in the system. This knowledge paves the way for designing innovative materials and a deeper understanding of processes involving excited states and proton transfer, which are crucial in fields such as photochemistry, material science, and molecular electronics.

Abbreviations

QM/MM	Quantum Mechanics/Molecular Mechanics
FHC	2-(2-furyl)-3-hydroxychromone
ESIPT	Excited State Intramolecular Proton Transfer

Author Contributions

Abdallah Brahim Elhadj Ali: Conceptualization, Supervision, Writing – original draft

Pale Wang-yang: Conceptualization, Supervision, Writing – original draft

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Conflicts of Interest

The authors declare no conflicts of interest.

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