Theoretical Study of the ESIPT Process for a New Natural Product Quercetin

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The investigation of excited-state intramolecular proton transfer (ESIPT) has been carried out via the density functional theory (DFT) and the time-dependent density functional theory (TDDFT) method for natural product quercetin in dichloromethane (DCM) solvent. For distinguishing different types of intramolecular interaction, the reduced density gradient (RDG) function also has been used. In this study, we have clearly clarified the viewpoint that two kinds of tautomeric forms (K1, K2) originated from ESIPT process consist in the first electronic excited state (S1). The phenomenon of hydrogen bonding interaction strengthening has been proved by comparing the changes of infrared (IR) vibrational spectra and bond parameters of the hydrogen bonding groups in the ground state with that in the first excited state. The frontier molecular orbitals (MOs) provided visual electron density redistribution have further verified the hydrogen bond strengthening mechanism. It should be noted that the ESIPT process of the K2 form is easier to occur than that of the K1 form via observing the potential energy profiles. Furthermore, the RDG isosurfaces has indicated that hydrogen bonding interaction of the K2 form is stronger than that of the K1 form in the S1 state, which is also the reason why the ESIPT process of the K2 form is easier to occur.

The ESIPT process resulted from photo-protolytic phenomena is one of the most important processes in photo-chemistry, photobiology and so forth1–3. The hydrogen bonding interaction exists in numbers of organic compounds, which possess hydrogen donor group and hydrogen acceptor group. Upon the photo-induced process, the hydrogen bonding interaction could be fast impacted, the primary properties of the compounds could be changed concomitantly. The intermolecular hydrogen bond between solvent and solute molecules can be strengthened dramatically in the excited states, which has been proposed by Han and co-workers4–11. The ESIPT process has been investigated extensively by various theoretical and experimental measures since the phenomenon was experimentally first observed by Weller et al. in 195512. In fact, the ESIPT reaction is an ultrafast process occurred in the femtosecond to picosecond time scale, where the protontransfer pathway is linked by a hydrogen bond, and the proton donor group and acceptor group in close proximity13.

The hydrogen bonding interaction could offer the driving force for the ESIPT process14,15. To date, numbers of scientists have widely studied some compounds that can form one or more intramolecular hydrogen bonds. In most cases, the hydrogen bond group is composed of a proton donor and acceptor. For example, Pi-Tai Chou et al. has reported that the ESIPT processes of the 3-hydroxyflavone (3HF) monomer and the 5-hydroxyflavone (5HF) monomer, respectively16. In a similar way, Jin-Feng Zhao et al. reported that two ESIPT processes exist in D3HF molecule, the conclusion has been demonstrated that the excited-state double proton transfer (ESDPT) process cannot occur simultaneously along with corresponding hydrogen bonding pathway17. However, we have paid great attention to the peculiar construction of new natural product quercetin. It is noteworthy that there are two intramolecular hydrogen bonds shared in common proton acceptor in the quercetin. It is puzzling that the two ESIPT processes exist in the quercetin molecule which one should take place first? However, the novel phenomenon is hardly illustrated experimentally. Therefore, we will give people visualized insight into the particular ESIPT processes by means of the detailed theoretical calculation in this study. As shown in the Fig. 1, the configuration of quercetin molecule is stable in the ground state (S0) that the ESIPT processes cannot spontaneously occur. Upon the photo-induced process, the new tautomer forms (K31, K32) can be generated by means of the fast ESIPT processes in the S1 state. The compounds K31 and K32 will play an important role in the most application.

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fields and will have wide application prospects, for example, the filters materials, the fluorescence sensors, the laser dyes and LEDs, etc.18–27.

The natural product quercetin, a good molecular construction system, is one of the most extensively subsistent flavonoids. It possesses the extensively biological activities, in especial the natural product has been used as food supplement such as it has been reported in some documents that the quercetin has many therapeutic functions in food supplement. For example, the anticancer, the antiviral, anti-inflammatory and anti-neoplastic function28–31.

The two hydrogen bond groups existed in the quercetin structure consist of a common proton acceptor and two-proton donors in close proximity. The both proton donors are the hydroxyl group while the common proton acceptor is the carbonyl oxygen atom in the hydrogen bond group moiety32. In addition, two hydrogen bond groups form the five-membered and six-membered ring structure, respectively. Two ESIPT processes can occur along with the orientation of corresponding hydrogen bond group in the ring structure33,34. Therefore, the interactions of hydrogen bond have been defined as the important driving force in the ESIPT process35,36. Simkovitch et al. have investigated the time-resolved fluorescence of the quercetin experimentally through the steady-state absorption spectroscopy and fluorescent up-conversion techniques32. However, the above measures cannot primarily account for the two ESIPT processes that the proton jumps from the corresponding proton donor to the common proton acceptor. Herein, to comprehend the two ESIPT processes occurred on the corresponding hydrogen bond group, we have theoretically investigated the ESIPT processes in terms of the quantum chemical calculation methods.

**Results and Discussion**

The quercetin has the normal configuration in the S0 state. On the contrary, upon the photo-induced process there are two tautomeric forms K1 and K2 resulted from ESIPT processes in the S1 state. These structures have been fully optimized by DFT method in the S0 state and TDDFT method in the S1 state. Herein, the normal structure as well as the K1 and K2 forms located in the S1 state have been shown in Fig. 2(a–c), respectively. It should be noted that the intramolecular hydrogen bonds have existed initially in the S0 state, in which the constructions of the five-membered and the six-membered ring are linked by the each intramolecular hydrogen bond group. In order to illustrate preferably the all above phenomena, we will come up with a few accessible evidences that cannot be provided experimentally.

**The optimization of configurations.** The natural product quercetin has been optimized by means of the DFT/TDDFT methods throughout based on B1B95 function as well as 6–31+G (d, p) basis set in the DCM solvent. The three structures have been optimized and presented on Fig. 2. It is evident that the four intramolecular hydrogen bond groups (O1-H2⋯O5), (O3-H4⋯O5), (O5-H2⋯O1) and (O5-H4⋯O3) can be observed from the
three planar geometric structures. The primary bond lengths (Å) and bond angles (°) relevant to the hydrogen bond groups have been listed in Table 1. The bond lengths O₁-H₂ and O₃-H₄ of normal form are optimized to be 0.986 Å and 0.976 Å in S₀ state, but they drastically increase to be 1.001 Å and 0.983 Å in the S₁ state, respectively. Meanwhile, we have observed that the bond lengths O₅-H₂ and O₅-H₄ obviously convert from 1.746 Å and 2.022 Å in the S₀ state to 1.663 Å and 1.984 Å in the S₁ state, respectively. The hydrogen bond angles O₁-H₂···O₅ and O₃-H₄···O₅ are enlarged respectively from 148.2° and 117.9° to 152.6° and 120.1° upon photo-excitation process. Therefore, we can make a conclusion that the intramolecular hydrogen bonds O₁-H₂···O₅ and O₃-H₄···O₅ are strengthened in the S₁ state.

The fast ESIPT processes occurred in the S₁ state have resulted in the distinct changes of the molecular structure, in which the new hydrogen bonds O₅-H₄···O₃, (O₅-H₂···O₁) have been constituted in tautomeric forms K₁ and K₂, respectively. It is very interesting that the O₃-H₄ bond length obviously reduced from 2.013 Å in the S₁ state to 1.809 Å in S₀ state, while the bond length of O₅-H₄ increased from 0.979 Å in the S₁ state to 1.000 Å in the S₀ state for the hydrogen bond O₅-H₄···O₃ of K₁ form. The above analysis results have indicated that hydrogen bond O₅-H₄···O₃ is stronger in the S₀ state than that in the S₁ state. In addition, the phenomenon of the intramolecular hydrogen bond strengthening has also been verified by the change of O₅-H₄···O₃ bond angle, which changes from 116.9° in the S₁ state to 124.0° in the S₀ state.

**Calculated spectrum of absorption and emission.** The UV-vis spectra of quercetin have been investigated experimentally via steady-state measuring method by the researchers Simkovitch *et al.*, and the information

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**Table 1.** The primary optimized bond lengths (Å) and bond angles (°) of the hydrogen bond groups for the normal form and tautomeric forms (K₁, K₂) of the quercetin in the S₀ and S₁ state.

| Bond Length or Angle | Normal form | S₀ | S₁ | K₁ form | S₀ | S₁ | K₂ form | S₀ | S₁ |
|----------------------|-------------|----|----|---------|----|----|---------|----|----|
| O₁-H₂                | 0.986       | 1.001 | 0.969 | 0.971   | 1.770 |
| O₃-H₄                | 0.976       | 0.983 | 1.809 | 2.013   | 0.969 |
| O₅-H₂                | 1.746       | 1.663 | 1.934 | 1.888   | 0.987 |
| O₅-H₄                | 2.022       | 1.984 | 1.000 | 0.979   | 2.155 |
| δ(O₁-H₂-O₅)          | 148.2°      | 152.6° | 140.5° | 142.0°   | 146.5° |
| δ(O₃-H₄-O₅)          | 117.9°      | 120.1° | 124.0° | 116.9°   | 113.1° |
of absorption and emission spectra have been revealed in their paper. However, the mechanism of the ESIPT processes is very elusive in the quercetin molecule. Therefore, for further gaining the fluorescent emission and absorption spectrum, we have carried out the theoretical calculation based on the quantum chemistry methods. For comparison to experiment, the spectrum has been displayed in Fig. 3. As shown in the Fig. 3, the top-right legend has clearly illustrated the significance of each spectral line. In addition, the violet vertical lines stand for corresponding peak values obtained in the experiment. It has been found that the absorption peak assigned to the $S_0 \rightarrow S_1$ transition process locates in 372 nm, which has an amazing coincidence that the absorption wavelength is about 380 nm in the experiment. Following the photo-excitation process, quercetin molecule will go through a fast radiative decay process from the $S_1$ state to the $S_0$ state, the fluorescence emission peak of normal construction at 434 nm is extremely close to the experimental value of 430 nm. Besides, the emission peaks of K1 and K2 forms are located at 566 nm and 593 nm, which are also coincident with the experimental peak value of 585 nm. It should be noted that the large Stokes shift values are 194 nm and 221 nm between the absorption peak and the emission peaks of tautomeric forms (K1, K2), respectively, which have been observed in the spectral graph. The large Stokes shifts have suggested that the tautomeric structures have drastic changes, which compare with the normal structure. The unusual changes of photophysical property are frequently accompanied by the enormously changes of molecular structure, such as the ESIPT processes. Therefore, we draw a conclusion that the ESIPT processes can take place along with the orientation of intramolecular hydrogen bonds in the five-membered ring and the six-membered ring, since both hydrogen bonding interactions are strengthened following the photo-excitation.

**Infrared (IR) vibrational spectra analysis.** The infrared (IR) vibrational spectrum is one of the most prime tools for investigating the hydrogen bond strengthening. Therefore, the effect of the hydrogen bond strengthening can be further illustrated by comparing the IR vibrational spectra of fluorophore in the $S_0$ with that in the $S_1$ state. The quantum chemical calculation has been carried out for obtaining the IR vibrational spectra of different electronic states. In Fig. 4(a), the IR vibrational spectra of hydroxyl groups $O_1H_2$ and $O_3H_4$ stretching absorption band in the $S_0$ and $S_1$ state. The IR vibrational spectra of the normal form (a) The IR vibrational spectra of the tautomeric K1 form (b) The legend can give reader the detail explanations.
to 3086 cm\(^{-1}\) in the S\(_0\) → S\(_1\) state. Analogously, the O\(_3\)–H\(_4\) stretching vibrational frequency has a relatively minor red-shifted 258 cm\(^{-1}\) from 3803 cm\(^{-1}\) to 3545 cm\(^{-1}\). Therefore, these analyses have shed light on the viewpoint that two hydrogen bonds (O\(_1\)–H\(_2\)···O\(_5\)), (O\(_3\)–H\(_4\)···O\(_5\)) have been obviously enhanced in the S\(_1\) state. Moreover, IR vibrational spectra of hydrogen bond groups on K\(_1\) form have been shown in Fig. 4(b). It should be noted that hydroxyl group O\(_1\)–H\(_2\) stretching vibrational frequency has a slight red-shifted 33 cm\(^{-1}\) from 3765 cm\(^{-1}\) to 3732 cm\(^{-1}\) in the S\(_0\) → S\(_1\) state. However, hydroxyl group O\(_5\)–H\(_4\) stretching vibrational frequency exists a distinct blue-shifted 363 cm\(^{-1}\) from 3254 cm\(^{-1}\) to 3617 cm\(^{-1}\) in the S\(_0\) → S\(_1\) state. The results can indicate that the hydrogen bond O\(_5\)–H\(_4\)···O\(_3\) has been obviously strengthened in the S\(_0\) state. In Fig. 4(b), the IR vibrational spectra of the K\(_2\) form haven’t been shown, since the K\(_2\) form is nonexistent in the S\(_0\) state. This is also the reason why we cannot compare the IR vibrational spectra of the hydrogen bond group in the S\(_1\) state with that in the S\(_0\) state for the K\(_2\) form.

Frontier molecular orbitals (MOs) analysis. To the best of our knowledge, upon photo-induced processes the electron population in the quercetin molecule will be significantly changed. Herein, the frontier MOs theory has been applied to comprehend the properties of the electronic excitation. The electron cloud around the molecule is subdivided into different molecular orbitals possessed of different energy levels, where the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) tremendously affect the reaction in this study. The HOMO with \(\pi\) character and the LUMO with \(\pi^*\) character have been shown in Fig. 5. The typical \(\pi\pi^*\) character has been primarily assigned to the transition from the HOMO to LUMO, and the transition composition of the HOMO → LUMO and oscillator strength of the first excited state have been shown in Table 2. It is evident that the electron density of hydroxyl oxygen O\(_1\) and O\(_3\) has decreased in the LUMO, which induces the dissociation of hydrogen protons. Meanwhile, the electron density of ketonic oxygen O\(_5\) has increased distinctly, which contributes to attracting the hydrogen protons dissociated from hydroxyl group. In addition, we have described the change of atomic charge for the hydrogen bond groups via Mulliken charge population analysis. Herein, we found that the negative charge of atom O\(_1\) and O\(_3\) has decreased from \(-0.562\) and \(-0.582\) in the S\(_0\)

| Transition | \(\lambda\) (nm) | \(f\) | Composition | CI (%) |
|------------|-----------------|------|-------------|--------|
| S\(_0\) → S\(_1\) | 371.69 | 0.6723 | H→L | 96.47% |
| S\(_0\) → S\(_2\) | 320.13 | 0.0535 | H−1→L | 94.58% |

Table 2. The excitation wavelength (nm), the major composition of orbital transition with its ratio (%), and corresponding oscillator strength.
state to $-0.557$ and $-0.571$ in the $S_1$ state, respectively. On the contrary, the negative charge of atom $O_5$ increases from $-0.698$ to $-0.706$. In conclusion, the redistribution of electron population can strengthen the intramolecular hydrogen bond ($O_1$-$H_2$···$O_5$) and ($O_3$-$H_4$···$O_5$) upon photo-induced process, which further contributes to the proceeding of ESIPT processes.

The potential energy profiles analysis. To further explain the ESIPT processes of the quercetin, we have plotted the potential energy curves of the reaction pathways that the protons migrate from the hydroxyl groups to the carbonyl group. The potential energy curves are the function of corresponding energy versus O-H bond lengths, as shown in Fig. 6. The energy of corresponding molecular structurein $S_0$ state or $S_1$ state have been calculated with the hydroxyl group (O-H) bond lengths increased by the fixed step sizes. Although the TDDFT method is unlikely to accurately acquire the correct order of closely spaced excited states, a number of foregoing research work have manifested that the method was relatively reliable with respect to analyzing qualitatively the reaction pathways and the potential barrier of ESIPT processes. The potential energy curves of six-membered ring proton transfer process shown in Fig. 6(a) have revealed that the energy of structure is gradually increase with augment of bond length $O_1$-$H_2$, where the energy has not shown a sign of slowing in the $S_0$ state. Therefore, in this case, the proton transfer process cannot occur in the $S_0$ state. This phenomenon has definitely illustrated that the $K_2$ form was nonexistent in the $S_0$ state. On the contrary, upon photo-induced process, it is clearly observed from the figure that the potential barrier $1.88$ kcal/mol of ESIPT process is almost negligible, the ESIPT process is comparatively easy to occur in the $S_1$ state. However, as shown in Fig. 6(b), for the five-membered ring segment of the quercetin molecule, the potential barrier $6.28$ kcal/mol of ESIPT process in the $S_1$ state has indicated that ESIPT process is more difficult to occur than the six-membered ring proton transfer process. It should be noted that a large potential barrier ($15.11$ kcal/mol) in the $S_0$ state has been exhibited in the Fig. 6(b), which indicates the proton transfer process cannot occur spontaneously in the $S_0$ state. In addition, the potential barrier of reversed proton transfer is $8.80$ kcal/mol in the $S_1$ state and is $1.14$ kcal/mol in the $S_0$ state. Further, we could make a conclusion that the reversed proton transfer process of $K_1$ form is easier to occur in the ground state than that in the first excited state. Herein, we have known that the hydrogen bond $O_5$-$H_4$···$O_3$ of the $K_1$ form is stronger in the ground state. So the reversed proton transfer process can be enhanced by the hydrogen bonding interaction.

Discriminating weak interaction types by filling color to RDG isosurfaces. For distinguishing different types of interaction, herein the RDG function has been used. The equation can be expressed as

$$RDG(r) = \frac{1}{2(3\pi)^{1/3} \rho(r)^{4/3}} \left[ \frac{\nabla \rho(r)}{\rho(r)^{2/3}} \right]$$

where $\rho(r)$ is the total electron density, the RDG ($r$) is the reduced density gradient of the exchange contribution. According to Bader's Atoms in Molecules (AIM) theory, the relative to the second largest eigenvalue $\lambda_2$ of Hessian matrix of electron density and the total electron density $\rho(r)$ may be written in the form

$$\Omega(r) = \text{Sign}(\lambda_2(r)) \rho(r)$$

where the weak interaction depends not only on the electron density $\rho$, but also is concerned with the eigenvalue $\lambda_2$. Herein, we have utilized $\lambda_2$ to distinguish the types of the bonding ($\lambda_2 > 0$) and antibonding ($\lambda_2 < 0$) interaction. Therefore, the sign $\lambda_2$ has been further analyzed via plotting the scatter diagram of the function 1 (RDG) value versus the function 2($\Omega(r)$) value. As shown in Fig. 7(a), in order to clearly describe the different types of the interactions, we have used the color gradient to stand for $\rho(r)$ and $\lambda_2$ value, and filled in the RDG isosurfaces. As shown in Fig. 7(b), the visual graph can be obtained via the visual software Chemcraft. The contour value is set as 0.5, the values range of RDG isosurfaces is set as $-0.04$ to $0.02$. From the Fig. 7(b), it could be greatly noted that

Figure 6. The function curves of the corresponding energy versus the O1-H2 bond length (a) The corresponding energy versus the O3-O4 bond length (b) The numerical values in the graphs stand for the potential barriers of the proton transfer process.
the hydrogen bonding interaction of the six-membered ring is stronger than that of the five-membered ring in the S₁ state. Further, the ESIPT process in six-membered ring segment is easier to occur than that in five-membered ring segment.

Conclusion
In summary, on the basis of DFT/TDDFT methods, the viewpoint that tautomeric forms (K₁, K₂) originate from the ESIPT processes has been successfully proved by analyzing the fluorescent spectroscopy and potential energy curves. We have made an important conclusion that the intramolecular hydrogen bonding interaction can be enhanced in the S₁ state via comparing the changes of bond parameters of hydrogen bond groups in the S₀ state with that in the S₁ state. In addition, the frontier MOs analysis has also confirmed the hydrogen bonding interaction strengthening upon the process of photo-excitation. However, it’s worth noting that the hydrogen bond O₅-H₄…O₃ of K₁ form has become stronger in the S₀ state than that in the S₁ state. Therefore, the reversed proton transfer process can be greatly facilitated by the stronger hydrogen bonding interaction in the S₀ state. On the Fig. 6(b), we have found that the potential barrier of the reversed proton transfer process is 8.80 kcal/mol in the S₁ state and is 1.14 kcal/mol in the S₀ state. We have made a conclusion that the reversed proton transfer process of the K₁ form is easier to occur in the ground state than that in the first excited state. However, for the ESIPT process, the potential barrier 1.88 kcal/mol of K₂ form is almost nonexistent. On the contrary, the potential barrier of K₁ form is 6.28 kcal/mol, so the ESIPT process of K₂ form is easier to occur than the process of K₁ form. Besides, on the Fig. 7, the RDG isosurfaces have clearly indicated that the interaction of hydrogen bond (O₁-H₂…O₅) is stronger than the interaction of hydrogen bond (O₃-H₄…O₅). In brief, the stronger hydrogen bonding interaction is, the more prone ESIPT process is to occur.

Computational details. With regard to our work, we have accomplished the theoretical calculation for all parameters based on the DFT and TDDFT methods by the Gaussian 09 program suite. The TDDFT method has been extensively applied to investigate the hydrogen bond dynamics in the S₁ state. Herein, the Becke One Parameter Hybrid Functionals (B1B95) has been used. Moreover, the Pople’s 6-31++G (d, p) triple-ζ quality basis set with diffused and polarization functions has been carried out throughout. The vibrational frequencies...
of the different configurations have been calculated to confirm the local minimum of each optimized structure in $S_0$ and $S_1$ state. To simulate the solvent effect of quercetin in dichloromethane (DCM), we have selected the self-consistent field (SCF) method with the conductor-like screening model (COSMO) as the solvent model in our all calculations. In this study, we have scanned the potential energy curves in the $S_0$ and $S_1$ state by means of increasing $\text{O}_2\text{-H}_2$ and $\text{O}_1\text{-H}_1$ bond length at a fixed step size. Therefore, the thermodynamic corrections of corresponding electronic states have been obtained via analyzing the constrained optimization and vibrational frequency. Because we have employed the diffused functions, the calculation of vertical excitation energy would be unreliable. Therefore, the self-consistent field (SCF) convergence threshold has been set to be 10$^{-10}$ (default settings are 10$^{-8}$). In addition, we apply the RDG function to investigate the weak interaction types via the Multiwfn software.

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AUTHOR CONTRIBUTIONS

Y.L. supervised the project, Y.Y. and Y.L. performed calculations. Y.Y., J.Z. and Y.L. analyzed data and wrote the paper.

ADDITIONAL INFORMATION

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