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Proton-Transfer and Photo-deamination Reactive Mechanisms Studies of Amines Compounds

Yunfan Yang [1], Yu zhao [1,2], Wei Shi [1,2] , Qiang Guo [1,2,*] and Yong-Qing Li [1,2,*]

[1]*Department of Physics, Liaoning University, Shenyang 110036, China*
[2]*Lvyuan Institute of Energy & Environmental Science and Technology, Liaoning University, Shenyang 110036, China*
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Abstract: The reference [J. Org. Chem. 2015, 80, 10817.10828] has reported that the Quinone Methides (QMs) that are of significant medicinal benefits in biological field can be generated *via* photo-deamination reaction. In this study, the density functional theory (DFT) and time-dependent DFT (TDDFT) methods have been carried out to investigate the reactive mechanisms of free amines compounds **1** and **3**. The excited state hydrogen bonding strengthening mechanism has been demonstrated by analyses of frontier molecular orbitals (MOs). Potential energy surfaces (PESs) calculations have been performed for illustrating excited state intramolecular proton transfer (ESIPT) and photo-deamination reactions of forms 1 and 3. The reactive sites of QM1 and QM3 molecules can be accurately predicted via analyses of ESP.

AMS subject classifications:65D18, 78M50, 74E40

Keywords: Photo-deamination reaction; Excited state intramolecular proton transfer; Potential energy surfaces; Hydrogen bond

The Quinone methides (QMs) acted as reactive intermediates have great valuable bioactivities in biochemistry and photochemical fields, *etc* [1, 2]. Moreover, the QMs have played a pivotal role in antineoplastic antibiotics efficacy, when they react with biomacromolecules such as DNA, proteins, basic groups and so on [3]. In addition, the QMs

* Corresponding author. *E-mail*: gq.ly@126.com
yqli@lnu.edu.cn

can show antiproliferative activity by reacting with proteins [4]. The QMs can be produced within two reactions: thermochemical reaction and photochemical reaction [5, 6]. However, the photo-deamination reaction, serving as common photochemical method, is extremely advantageous to be performed [7]. Photo-deamination reactions are widely applied to researches of bioactivity and production modes of QMs, but the mechanisms and processes of photo-deamination reactions are rarely studied. Skalamera *et al.* have investigated qualitatively the reactive mechanism of photo-deamination reaction for amines compounds [8]. In this study, the free amines compounds **1** and **3** have been paid intriguing attentions, since the hydrogen bond interactions are crucial moieties in two compounds. The nonnegligible effects of ESIPT reactions along with corresponding orientations of hydrogen bonds should be taken into consideration on photo-deamination reaction. Upon photoexcitation process the compounds **1** and **3** can undergo the ESIPT reactions, and then the photo-deamination reactions will occur because of nitrogen protonation. For quantificationally and qualitatively accounting for the mechanisms of photo-deamination reactions, the theoretical computational methods have been performed in this study. The information of wave function has been calculated and analyzed for compounds **1** and **3** in different electronic states *via* DFT and TDDFT methods, respectively. Most of contemporary

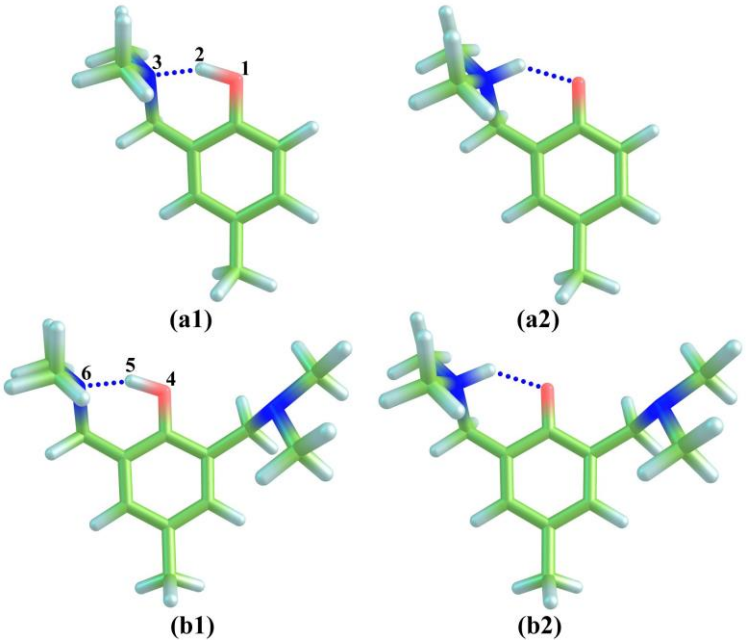

Figure 1: The optimized geometrical configurations of (a1) **1**, (a2) **1-T**, (b1) **3**, (b2) **3-T** in the S_1 state. Labeled symbol of elements and newly named serial number 1-8 of crucial atoms. The green sticks: C atoms. Red sticks: O atoms. Blue sticks: N atoms. Cyan sticks: H atoms.

researchers have extensively adopted these theoretical methods to investigate photophysical and photochemical reaction mechanisms of organic molecules in the past [9-22]. The whole computational processes are based on the Gaussian 09 program [23]. The environment of solvent is simulated as acetonitrile (ACN, dielectric constant ε=38.8) where the solvent model is set as Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEFPCM)[24]. The structures of normal and derivative forms have been fully optimized based on hybrid functional *ω*B97XD [25] method in which the corresponding vibrational frequencies also have been calculated without any imaginary frequencies. The calculated level basis set 6-31+G(d) is used for form **1** and **3** throughout. The optimized structures have been shown in **Figure 1**. The graphs can be depicted by Chemcraft program suites [26]. In addition, the frontier molecular orbitals (MOs) of compounds **1** and **3** calculated by CAM-B3LYP [27] have been shown in **Figure 2**. The transition of electronic states can be regarded as the transition of MOs. The electron population of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) predominantly exhibits the ππ* character for **1** and **3** forms in **Figure 2**, which belongs to localized excitation (LE) type. The electron population of hydroxyl oxygen atom has obviously reduced in transition process from the ground state (S_0) to the first excited state (S_1) for form **1**. However, it should be noted that the transition mode of form **3** mainly exhibits

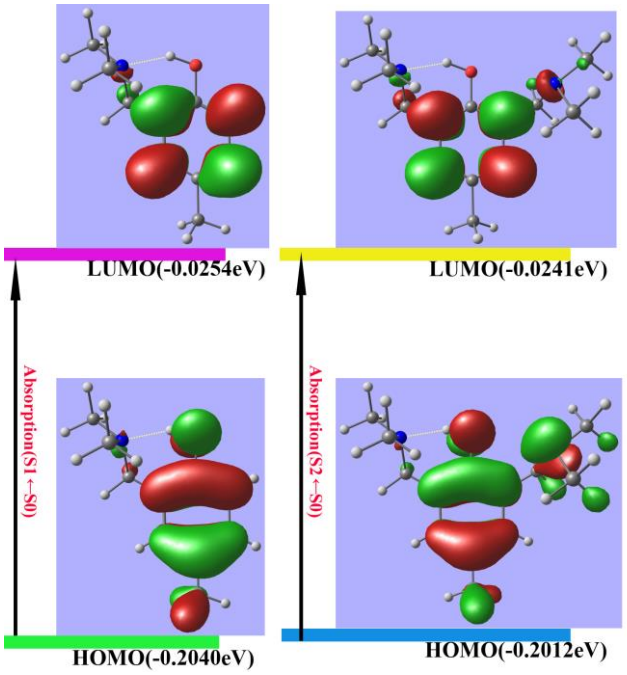

Figure 2: Frontier molecular orbitals of forms **1** and **3** playing dominated contribution on the transition processes.

the jumping from the S_0 state to the second excited state (S_2). The electron population of hydroxyl oxygen atom of form **3** also has been reduced. It is indicated that acidity of hydroxyl oxygen atoms of forms **1** and **3** is increasing in excited state. Therefore, the transfer processes of hydrogen protons are easier to occur between the hydroxyl oxygen atoms and dimethyl nitrogen atoms in the excited state, since the intramolecular hydrogen bonds O1-H2···N3 and O4-H5···N6 are enhanced with acidity of proton donor groups increasing. The excited state hydrogen bonding strengthening mechanism has been excellent demonstrated via analysis of MOs.

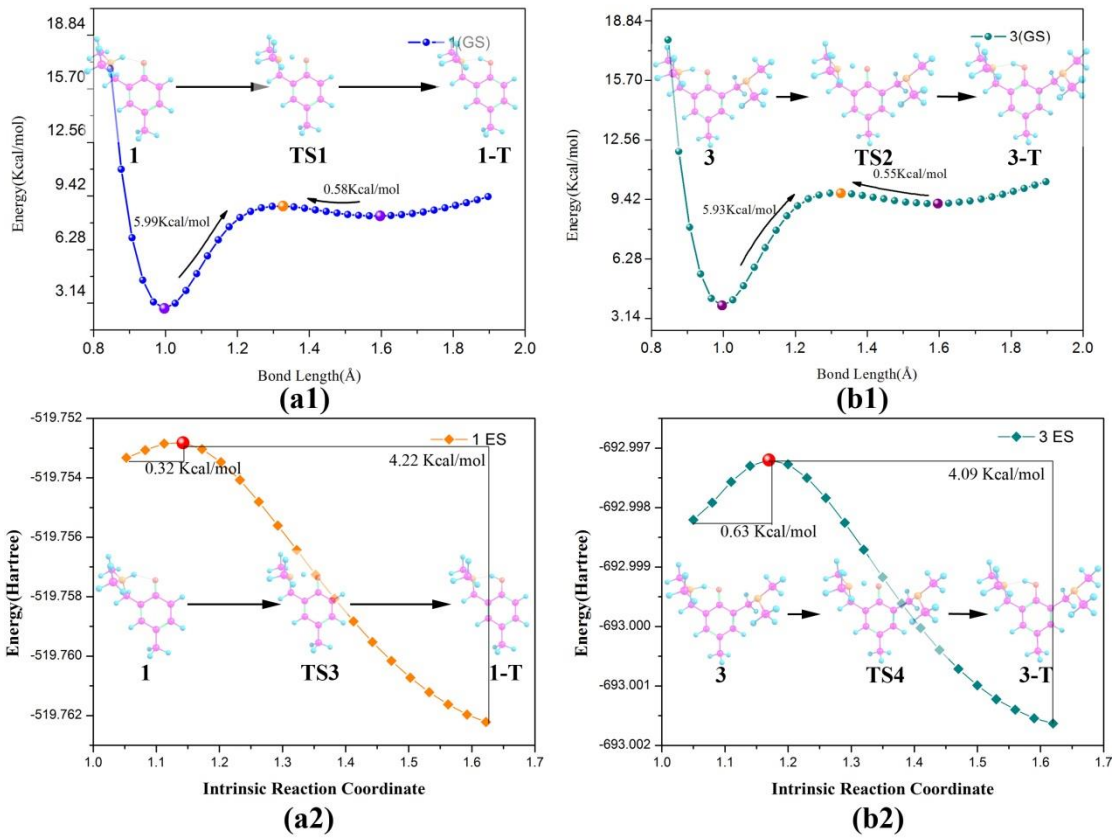

Figure 3: The optimized potential energy surfaces for proton transfer reaction of (a) form **1** and (b) form **3** in the S_0 and S_1 state. The labeled corresponding barrier energies and structures in the diagram. (a1, b1) form **1** and **3** in the S_0 state, respectively. (a2, b2) form **1** and **3** in the S_1 state, respectively .The corresponding details can be shown in legend.

The 0-0 and vertical transition energies have been calculated by using O3LYP/6-311+G(2d, p). The vertical excitation energies of forms **1** and **3** are 268 nm and 271 nm, respectively, which is well agreement with absorption spectra values 283 nm in

experiment. The 0-0 transition energies that has corrected by zero-point energy (ΔZPE) are 274.4 nm and 276.5 nm for forms **1** and **3,** respectively, which coincides with values in experiment. The fluorescence spectra values we have calculated are 305 nm and 307 nm for normal **1** and **3** structures, respectively. The emission values of isomers **1-T** and **3-T** are 358 nm and 361 nm, respectively. The observed spectra values of normal and isomer structures are 308 nm and 370 nm in experiment, respectively. We have calculated all spectra values within the error range. It concludes that the computing methods we have selected are reliable to investigate the photophysical and photochemical reactions and properties of compounds **1** and **3**.

For quantificationally researching the mechanisms of ESIPT and photo-deamination reactions, the corresponding reactive energy barriers have been calculated by PESs scanning. As discussed by Cui *et al*.[28], the reactive pathways can be illustrated by scanning potential energy curves. The reactive pathways of forms **1** and **3** have been shown in **Figure 3**. As shown in **Figure 3 (a1)**, **TS1** is transition state of proton transfer reaction for form **1**. The energy barrier of proton transfer reaction is 5.99 kcal/mol In the **Figure 3 (b1)**, **TS2** is transition state of proton transfer reaction for form **3.** The energy barrier of proton transfer reaction is 5.93 Kcal/mol. As shown in **Figure 3 (a2, b2)**, the energy barriers of transition state **TS3** and **TS4** of ESIPT reactions are 0.32 kcal/mol and 0.63 Kcal/mol for form **1** and **3** in the S_1 state, respectively.. Therefore, it concludes that the proton transfer reactions can only occur in S_1 state. Finally, we have quantitatively investigated the potential energy curves of deamination reactions *via* changing N-C bond length as shown in the **Figure 4**. In the **Figure 4 (a)**, the deamination reactions of **1** and **3** forms need to cross about 61.9 kcal/mol and 61.5 kcal/mol in the S_0 state, respectively.

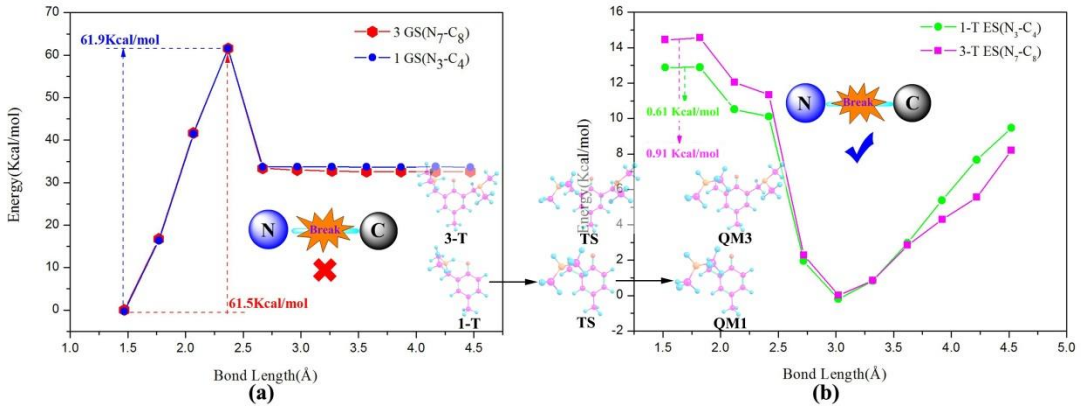

Figure 4: The optimized potential energy surfaces for deamination reactions in the S_0 and S_1 states. The labeled corresponding barrier energies and structures in the diagram. (a) form **1** and **3** in the S_0 state, (b) form **1-T** and **3-T** in the S_1 state.

However, the photo-deamination reactions of **1-T** and **3-T** forms need to get over about 0.61 kcal/mol and 0.91 kcal/mol in the S_1 state, respectively. Therefore, we can conclude that the deamination reactions of **1** and **3** forms are unable to take place in the S_0 state and the photo-deamination reactions of **1-T** and **3-T** forms can spontaneously occur in the S_1 state.

The reactive sites of QMs can be predicted by the analyses of ESP. The ESP isosurfaces of **QM1** and **QM3** have been portrayed in **Figure 5** *via* VMD[29]. ESP maxima and minima of **QM1** and **QM3** have been exhibited in the isosurfaces *via* Multiwfn program[30], respectively. As shown in **Figure 5** four regions have been labeled in ESP isosurfaces of **QM1** (**Figure 5 (a)**) and **QM3** (**Figure 5 (b)**), respectively, which is extremely favorable sites for chemical reactions. It indicates that region 1 is the site of ESP maxima, which is the most probable to occur nucleophilic attack reactions, similarly, region 4 of ESP minima is most feasible site for electrophilic attack reactions in isosurfaces of **QM1** and **QM3**, respectively. Therefore, the reactive sites of **QM1** and **QM3** molecules can be accurately predicted via analyses of ESP.

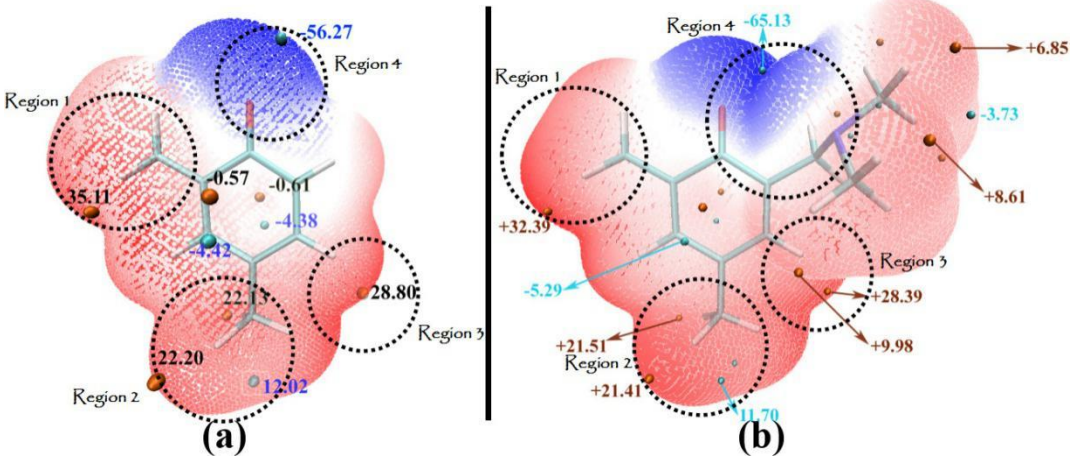

Figure 5: The ESP isosurfaces of **QM1** (a) and **QM3** (b) molecules. The corresponding maxima and minima have been labeled in the isosurfaces.

In short, we primarily investigate the photochemical and photophysical reaction mechanisms of free amines compounds **1** and **3**. The corresponding ESIPT and photo-deamination reactions have been studied quantitatively and qualitatively *via* theoretical analyses of MOs and PESs. The corresponding calculations and analyses can reveal that ESIPT and photo-deamination reactions are spontaneous processes. It concludes that the reactions of proton transfer can only occur in S_1 state, since redistribution of electron population upon photoexcitation process induces strengthening of intramolecular hydrogen bond. The feasible photo-deamination reactions depend on protonation of N atoms in S_1

state. QMs can be generated by photo-deamination reactions. What's more important, the reactive sites can be accurately predicted by ESP analyses. Therefore, our work can guide experiments and application of QMs for antiproliferative activity, *etc*.

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Reference

[1] M. Lukeman, H. Simon, P. Wan, Y.-H. Wang, Photocyclization and Photoaddition Reactions of Arylphenols via Intermediate Quinone Methides, J. Org. Chem., 80 (2015) 11281-11293.

[2] N. Basaric, N. Doslic, J. Ivkovic, Y.-H. Wang, J. Veljkovic, K. Mlinaric-Majerski, P. Wan, Excited State Intramolecular Proton Transfer (ESIPT) from Phenol to Carbon in Selected Phenylnaphthols and Naphthylphenols, J. Org. Chem., 78 (2013) 1811-1823.

[3] S. Arumugam, J. Guo, N.E. Mbua, F. Friscourt, N.N. Lin, E. Nekongo, G.J. Boons, V.V. Popik, Selective and reversible photochemical derivatization of cysteine residues in peptides and proteins, Chem. Sci., 5 (2014) 1591-1598.

[4] M. Kralj, L. Uzelac, Y.H. Wang, P. Wan, M. Tireli, K. Mlinaric-Majerski, I. Piantanida, N. Basaric, Enhancement of antiproliferative activity by phototautomerization of anthrylphenols, Photoch. Photobio. Sci., 14 (2015) 1082-1092.

[5] N. Basaric, K. Mlinaric-Majerski, M. Kralj, Quinone Methides: Photochemical Generation and its Application in Biomedicine, Curr. Org. Chem., 18 (2014) 3-18.

[6] M. Yato, T. Ohwada, K. Shudo, 4H-1,2-benzoxazines as novel precursors of ortho-benzoquinone methide, J. Am. Chem. Soc., 112 (1990) 5341-5342.

[7] S. Colloredo-Mels, F. Doria, D. Verga, M. Freccero, Photogenerated quinone methides as useful intermediates in the synthesis of chiral BINOL ligands, J. Org. Chem., 71 (2006) 3889-3895.

[8] D. Skalamera, C. Bohne, S. Landgraf, N. Basaric, Photodeamination Reaction Mechanism in Aminomethyl p-Cresol Derivatives: Different Reactivity of Amines and Ammonium Salts, J. Org. Chem., 80 (2015) 10817-10828.

[9] Y.-J. Zhang, J.-F. Zhao, Y.-Q. Li, The investigation of excited state proton transfer mechanism in water-bridged 7-azaindole, Spectrochim. Acta A, 153 (2016) 147-151.

[10] Y. Zhang, M. Sun, Y. Li, How was the proton transfer process in bis-3, 6-(2-benzoxazolyl)-pyrocatechol, single or double proton transfer?, Sci. Rep., 6 (2016).

[11] T.S. Chu, B.T. Liu, Establishing new mechanisms with triplet and singlet excited-state hydrogen bonding roles in photoinduced liquid dynamics, Int. Rev. Phys. Chem., 35 (2016) 187-208.

[12] J. Zhao, J. Chen, J. Liu, M.R. Hoffmann, Competitive excited-state single or double proton transfer mechanisms for bis-2,5-(2-benzoxazolyl)-hydroquinone and its derivatives, Phys. Chem. Chem. Phys., 17 (2015) 11990-11999.

[13] J. Zhao, J. Chen, Y. Cui, J. Wang, L. Xia, Y. Dai, P. Song, F. Ma, A questionable excited-state double-proton transfer mechanism for 3-hydroxyisoquinoline, Phys. Chem. Chem. Phys., 17 (2015) 1142-1150.

[14] F. Yu, P. Li, B. Wang, K. Han, Reversible Near-Infrared Fluorescent Probe Introducing Tellurium to Mimetic Glutathione Peroxidase for Monitoring the Redox Cycles between Peroxynitrite and Glutathione in Vivo, J. Am. Chem. Soc., 135 (2013) 7674-7680.

[15] J.-S. Chen, G.-J. Zhao, T.R. Cook, K.-L. Han, P.J. Stang, Photophysical Properties of Self-Assembled Multinuclear Platinum Metallacycles with Different Conformational Geometries, J. Am. Chem. Soc., 135 (2013) 6694-6702.

[16] D. Li, X. Huang, K. Han, C.-G. Zhan, Catalytic Mechanism of Cytochrome P450 for 5 '-Hydroxylation of Nicotine: Fundamental Reaction Pathways and Stereoselectivity, J. Am. Chem. Soc., 133 (2011) 7416-7427.

[17] G.-J. Zhao, K.-L. Han, Time-dependent density functional theory study on hydrogen-bonded intramolecular charge-transfer excited state of 4-dimethylamino-benzonitrile in methanol, J. Comput. Chem., 29 (2008) 2010-2017.

[18] G.-J. Zhao, R.-K. Chen, M.-T. Sun, J.-Y. Liu, G.-Y. Li, Y.-L. Gao, K.-L. Han, X.-C. Yang, L. Sun, Photoinduced intramolecular charge transfer and S-2 fluorescence in thiophene-pi-conjugated donor-acceptor systems: Experimental and TDDFT studies, Chem. Eur. J., 14 (2008) 6935-6947.

[19] D. Jacquemin, E.A. Perpete, G.E. Scuseria, I. Ciofini, C. Adamo, TD-DFT performance for the visible absorption spectra of organic dyes: Conventional versus long-range hybrids, J. Chem. Theor. Comput., 4 (2008) 123-135.

[20] M. Cossi, V. Barone, Time-dependent density functional theory for molecules in liquid solutions, J. Chem. Phys., 115 (2001) 4708-4717.

[21] P.T. Chou, C.Y. Wei, C.R.C. Wang, F.T. Hung, C.P. Chang, Proton-transfer tautomerism of 7-hydroxyquinolines mediated by hydrogen-bonded complexes, J. Phys. Chem. A, 103 (1999) 1939-1949.

[22] Y. Yang, J. Zhao, Y. Li, Theoretical Study of the ESIPT Process for a New Natural Product Quercetin, Sci. Rep., 6 (2016).

[23] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S.

Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

[24] E. Cances, B. Mennucci, J. Tomasi, A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics, J. Chem. Phys., 107 (1997) 3032-3041.

[25] B.J. Siwick, M.J. Cox, H.J. Bakker, Long-range proton transfer in aqueous acid-base reactions, J. Phys. Chem. B, 112 (2008) 378-389.

[26] Andrienko, G. A. *Chemcraft* 1.8. website: http://www.chemcraftprog.com. (2016) (Date of access: 08/10/2016).

[27] T. Yanai, D.P. Tew, N.C. Handy, A new hybrid exchange-correlation functional using the Coulomb-attenuating method (CAM-B3LYP), Chem. Phys. Lett., 393 (2004) 51-57.

[28] Y.-L. Cui, P.-Y. Li, J. Wang, P. Song, L.-X. Xia, An investigation of excited-state intramolecular proton transfer mechanism of new chromophore, Commun. Comput. Chem., 6 (2015) 23-33.

[29] W. Humphrey, A. Dalke, K. Schulten, VMD: visual molecular dynamics, J. Molec. Graphics., 14.1 (1996) 33-38.

[30] T. Lu, F.-W. Chen, Multiwfn: a multifunctional wavefunction analyzer, J. Comput. Chem., 33 (2012) 580-592.