



Theoretical study on the double proton transfer in a hetero-hydrogen-bonded dimer of 11-propyl-6*H*-indolo-[2,3-*b*]quinoline (6HIQ) and 7-azaindole (7AI)

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ABSTRACT

A theoretical study on the double proton transfer dynamics of the 11-propyl-6*H*-indolo-[2,3-*b*]quinoline (6HIQ)/7-azaindole (7AI) hydrogen-bonded hetero-dimer in both the ground and electronically lowest lying excited state was presented. In the ground state, the double proton transfer was concluded to undergo a *concerted-asynchronous* pathway. In the electronically excited state, both CIS and TD-M06-2X theory predicted that the reaction favored a stepwise process; however it could not be unambiguously determined which proton triggered the reaction. Higher-level theory (EOM-CCSD) suggested a highly asynchronous pathway without intermediates and the proton from the 6HIQ triggered the double proton transfer reaction.

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1. Introduction

In an aim to mimic the photo-induced mutation of A–T and G–C hydrogen-bonded base pairs, 7-azaindole (7AI) hydrogen-bonded dimer has long served as a paradigm to study on excited-state double proton transfer (ESDPT) [1–9]. A recent ESDPT issue being revitalized is relevant to concerted (synchronous or asynchronous cases) versus stepwise reactions on the 7AI dimer; several elegant works [10–19] are worthy to note for readership regarding the fundamental of ESDPT.

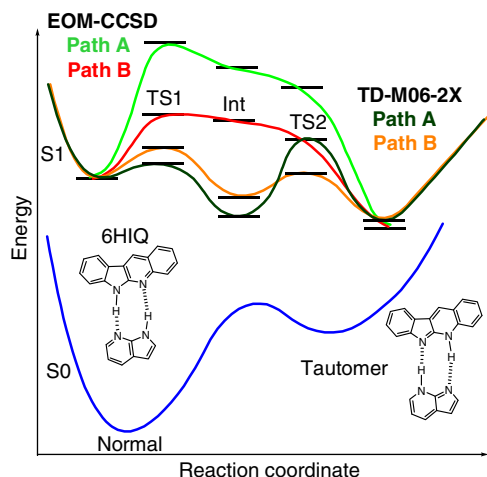
Realizing that the key for photo-induced mutation to be mimicked, from the viewpoint of A–T and G–C base pairs, lies in a hetero-dimeric structure per se, we recently strategically designed a 7AI derivative, 11-propyl-6*H*-indolo-[2,3-*b*]quinoline (6HIQ). 6HIQ possesses a fused four-ring aromatic system, while the 7AI core chromophore credited for ESDPT remains intact. In nonpolar solvent such as cyclohexane, the concentration dependent absorption and emission spectra of 6HIQ indicate that the dimerization occurs via dual hydrogen-bonding formation. Upon excitation of the 6HIQ dimer, ESDPT takes place, resulting in a tautomer dimer emission maximized at ~560 nm. Fluorescence up-conversion dynamics monitored at the tautomer dimer emission revealed system response limited ESDPT rate constant ($>10^{12} \text{ s}^{-1}$) in the nonpolar cyclohexane [20]. This led to the conclusion that ESDPT in the 6HIQ dimer may have a rather small barrier, although whether ESDPT dynamics is concerted or stepwise, limited by the system response time, is pending resolution. What is more, an asymmetric

ESDPT system, i.e., 6HIQ/7AI hetero-dimer, also has been investigated [20]. The results unveiled a possibly stepwise ESDPT process in the 6HIQ/7AI hetero-dimer, in which 6HIQ (deuterated 6HIQ), upon electronic excitation, delivers the pyrrolyl proton (deuteron) to 7AI (deuterated 7AI) in less than 150 fs (system response limit), forming an intermediate with a charge-transfer-like ion pair, followed by the transfer of pyrrolyl proton (deuteron) from cation-like 7AI (deuterated 7AI) to the pyridinyl nitrogen of anion-like 6HIQ (deuterated 6HIQ) in $\sim 1.5 \pm 0.3 \text{ ps}$ ($3.5 \pm 0.3 \text{ ps}$). The barrier of the second proton transfer has been estimated to be 2.86 kcal/mol for the 6HIQ/7AI hetero-dimer. The results led to a proposal incorporating an ion-pair intermediate during ESDPT, in which the greater photoacidic moiety (6HIQ) was assumed to form an anionic-like species, while the counterpart 7AI acted as a photobasic moiety, forming a cationic-like species, providing perhaps indirect support for recent reports that proton transfer in A–T (or G–C) pair may undergo a charge-transfer state [21–25]. To continue our effort in ESDPT dynamics, herein, we present a timely theoretical approach on modeling the proton transfer dynamics of the 6HIQ/7AI hydrogen-bonded hetero-dimer in both ground and excited states. As a result, the pros and cons between theoretical and experimental approaches can be fairly compared and discussed.

It should be noted that the *n*-propyl substituent at C₁₁ (see Scheme 1) of 6HIQ was replaced by a hydrogen to simplify the calculation. Therefore, hereafter 6HIQ symbolizes 6*H*-indolo-[2,3-*b*]quinoline throughout the text. Since the *n*-propyl group is neither involved in the proton transfer transition nor contributing to the lower lying electronic transition, its neglect would not affect the comparison between experimental and computational results.

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Scheme 1. The ground and excited-state pathways of the double proton transfer reaction in 6HIQ/7AI hetero-dimer. For the ground state, the reaction energetics calculated by B3LYP, M06-2X, and MP2 theories were very similar, revealing a *concerted-asynchronous* pathway. For the lowest electronically excited state, reaction paths calculated via TD-M06-2X and EOM-CCSD theories are adopted. Note that independent of various theories, the normal form on S1 has been normalized at the same energy level for clarity.

2. Method

The ground-state geometry of 6HIQ, 7AI, 7AI homo-dimer, 6HIQ/7AI hetero-dimer, and the proton transfer tautomers and transition states of the dimers was calculated using the hybrid density functional theory B3LYP with the 6-31+G(d,p) basis set. Single-point energy calculation was also performed using the MP2 theory and the M06-2X density functional [26]. The vertical excitation energies of the dimers at ground-state geometry were calculated using the time-dependent B3LYP (TD-B3LYP) and M06-2X (TD-M06-2X) density functional theory, and the equation-of-motion CCSD (EOM-CCSD) theory.

The excited-state geometry of the dimers was calculated using the CI-singles (CIS) theory with the 6-31+G(d,p) basis set. Single-point excited state energies were also calculated using the TD-B3LYP, TD-M06-2X and CIS(D) (CI-singles with doubles correction included perturbatively) theory with the same basis set, and using the EOM-CCSD theory with the 6-31G(d,p) basis set. We cautioned that the geometry calculated using the CIS theory might not be very accurate since the theory does not include higher-level electron correlation. However, it is unfortunate that no other currently available excited-state methods can perform excited-state geometry optimization accurately and efficiently enough to model large systems as in the current study. Ideally, for excited-state energy calculation, one would expect the CASSCF, CASPT2, or the MRCI theory to give more accurate results. However, due to the large size of the current system: 42 atoms with 574 basis functions using the 6-31+G(d,p) basis set for the 6HIQ/7AI dimer, currently those high-level theories are not computationally feasible. On the other hands, the TD-B3LYP and CIS theory have been used to model similar systems with qualitative and sometimes even quantitative success [14,27,28]. In current Letter we also used the relatively new EOM-CCSD theory which includes higher-level electron correlation both on the ground- and the excited-states, and it should give a more balanced treatment across the relevant regions of the potential energy surface. The EOM-CCSD calculation was performed using the MOLPRO 2009.1 program [29], and all other electronic structure calculation was performed using the GAUSSIAN 03 program [30].

3. Results and discussion

3.1. Ground-state properties

The calculated normal and tautomer forms of ground-state 6HIQ/7AI dimer and the corresponding double proton-transfer TS are shown in Fig. 1. The association energy was calculated to be 13.2 kcal/mol at the B3LYP/6-31+G(d,p) level. This was very similar to the calculated association energy of 14.0 kcal/mol for the ground-state 7AI homo-dimer at the same level. If the counterpoise corrections (CP) for basis set superposition errors (BSSE) were included, the calculated association energies were 12.5 and 13.3 kcal/mol for 6HIQ/7AI and 7AI/7AI, respectively. As expected, CP corrections were not very significant for the B3LYP method. The 6HIQ/7AI tautomer and TS were calculated to be 12.3 and 16.2 kcal/mol higher in energies, respectively, than the normal

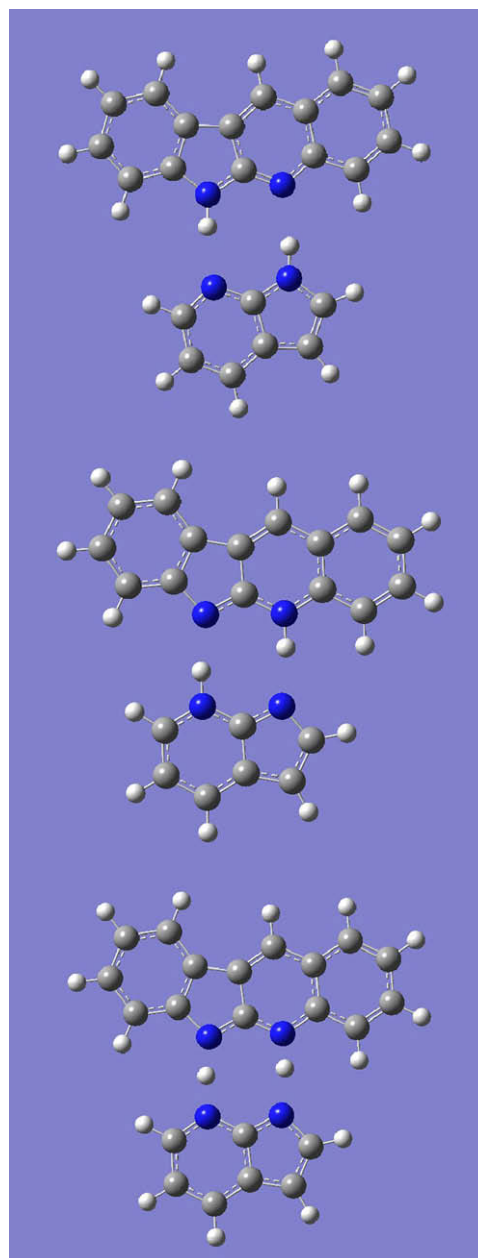


Fig. 1. Calculated structures of the ground-state 6HIQ-7AI dimers, from top: the normal form, the tautomer form, and the transition state.

form. In comparison, the corresponding energies for the 7AI homo-dimer are 14.5 and 17.0 kcal/mol, respectively. The calculated ground-state energetics was summarized in Table 1. The CP corrections were even smaller for the relative energies of the dimers using DFT methods due to error cancellation. The MP2 theory as expected had a larger CP correction of 2.8 kcal/mol at the TS. Although the tautomer form was found to be an energy minimum, the reverse proton-transfer reaction was barrierless if the zero-point energies were taken into account. As shown in Table 1, the relative energies calculated by B3LYP, M06-2X, and MP2 theory were similar, which suggested the calculated ground-state energetics should be reasonably accurate. Only one proton-transfer TS and no intermediates were found at the B3LYP/6-31+G(d,p) level. As shown in Fig. 1, the TS corresponds to a *concerted-asynchronous* pathway where the pyrrolyl hydrogen (or proton) of the 7AI had essentially moved to the pyridinyl site of the 6HIQ while the pyrrolyl hydrogen of 6HIQ was just on its way to the pyridinyl site of the 7AI. Due to the high energy barrier and the barrierless reverse reaction, the double proton transfer reaction would not thermally occur on the ground state (S_0 , Scheme 1). The essential calculated features of the ground-state surface of the current system were very similar to those of the 7AI homo-dimer system calculated in the current and a previous study [28].

3.2. Excited-state properties

The calculated vertical excitation energy of the 6HIQ/7AI normal dimer at the ground-state geometry to the S_1 state is 3.27 eV or 380 nm in wavelength using the TD-B3LYP theory. This is in very good agreement with the experimental measurement ($\lambda_{\max} \sim 380$ nm). The calculated geometry of the dimers of the normal and tautomeric forms on the first excited state (S_1) was qualitatively similar to that of the ground-state and was included in the Supplementary material. The vertical excitation energy between S_0 and S_1 calculated at the optimized tautomer dimer structure on S_1 surface was predicted to be 2.10 eV or 590 nm in wavelength using the TD-B3LYP theory. This is also in good agreement with the observed tautomer emission band which was broad and centered at 560 nm.

However, the reaction path of the double proton transfer on the S_1 potential energy surface was found to be much more complex than on the ground state. Firstly, the reaction was found to be step-wise at the CIS/6-31+G(d,p) level. That is, two TS and one intermediate were located on the reaction path. Secondly, two different paths were predicted by theory. On one path (path A), the pyrrolyl proton of the 7AI was transferred first to 6HIQ, followed by the transfer of the pyrrolyl proton of the 6HIQ to 7AI. On the other path (path B), the order of the transfer was reversed. We thus labeled the corresponding TS and intermediates on paths A and B as TS (A1), TS (A2), Int (A), and TS (B1), TS (B2), Int (B), respectively (see Table 2). The calculated geometry of these stationary points was shown in Figs. 2 and 3. The predicted energetics of the double proton transfer reaction on S_1 is listed in Table 2, and the calculated vertical excitation energies and some critical bond lengths of the stationary points are shown in the Supplementary material.

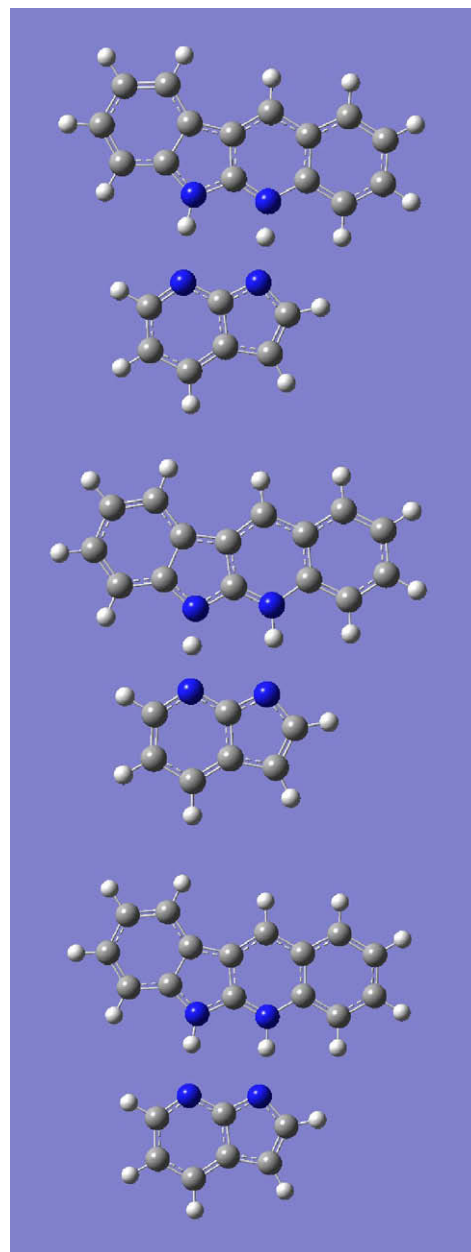


Fig. 2. Calculated structures of the 6HIQ–7AI excited-state double proton transfer on path A. From top: TS (A1), TS (A2), and Int (A).

Considering the size of the current system, it is much more difficult to calculate the reaction energetics on the excited state than on the ground state. Thus, it is not surprising that in Table 2 different theory sometimes gave very different results. It is generally accepted that the CIS theory gives reasonable geometry but relatively poor energetics, especially on barrier heights. Thus, in Table 2 the CIS barrier heights were very likely to be significantly overestimated and the relative energies of the intermediates would also be too high. The CIS(D) theory makes huge second-order corrections to the CIS energies. While the estimated barrier on path A was more reasonable, the predicted vertical excitation energy of the normal dimer (~ 300 nm) was too high and thus the predicted energy of the reaction was possibly too low. This also caused path A to have only one TS and path B to be barrierless, which might just be an artifact of the theory. Since the TD-B3LYP theory gave good results on both the excitation energy of the normal form and the emission

Table 1
Calculated ground-state energetics (kcal/mol) of the 6HIQ–7AI system.

	B3LYP	M06-2X	MP2
Normal form	0.0 ^a (208.0) ^b	0.0	0.0
Transition state	16.2 [16.5] ^c (203.6)	15.3 [15.7]	16.1 [18.9]
Tautomeric form	12.3 [12.4] (207.7)	13.3 [13.4]	13.6 [14.3]

^a Born–Oppenheimer energy, not including vibrational zero-point energy (ZPE).

^b Calculated ZPE in kcal/mol.

^c Relative energies including counterpoise corrections for BSSE.

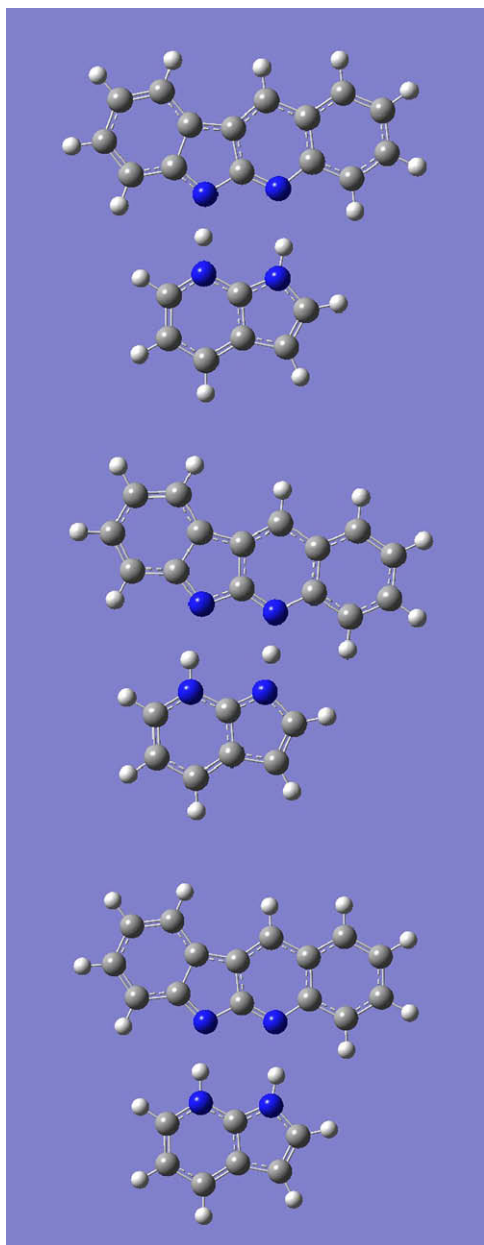


Fig. 3. Calculated structures of the 6HIQ–7AI excited-state double proton transfer on path B. From top: TS (B1), TS (B2), and Int (B).

Table 2
Calculated excited-state (S_1) energetics (kcal/mol) of the 6HIQ–7AI system.

	CIS	CIS(D)	TD-B3LYP	TD-M06-2X	EOM-CCSD
Normal form	0.0 ^a (220.0) ^b	0.0	0.0	0.0	0.0
TS (A1)	22.5 (216.9)	8.7	−15.2	2.2	12.5
Int (A)	22.3 (218.9)	8.2	−21.7	−3.7	10.8
TS (A2)	23.5 (217.0)	1.4	−12.4	4.7	9.8
TS (B1)	17.3 (217.2)	−3.3	−5.3	3.3	6.1
Int (B)	15.9 (220.0)	−2.4	−18.6	−1.3	5.9
TS (B2)	19.4 (217.5)	−8.7	−4.0	2.0	4.7
Tautomer	4.7 (221.1)	−13.1	−4.2	−3.5	−4.4

^a Born–Oppenheimer energy, not including vibrational zero-point energy (ZPE).

^b Calculated ZPE in kcal/mol.

energy of the tautomer form, it was very likely that it gave reasonably accurate reaction energy of -4.2 kcal/mol. However, the past

experience showed that the TD-B3LYP theory is not able to handle the zwitterionic structure properly and tends to underestimate the double proton transfer barriers [27]. Since the kinetic isotope effect experiment by Chou and co-workers [20] showed that the reaction was very likely to have small energy barriers, the barrierless reaction path predicted by TD-B3LYP was probably not qualitatively correct in the proton-transfer regions. Alternatively, the recently developed M06-2X functional [26] was famous for its high accuracy on the ground electronic state. In very limited tests on excited states, the performance of the TD-M06-2X theory was also reasonably accurate [26]. The reaction energy predicted by the TD-M06-2X theory was very similar (within 1 kcal/mol) to that predicted by the TD-B3LYP theory. In comparison to the experimental results, the energetics predicted by TD-M06-2X in the proton transfer regions looked more reasonable in Table 2. Accordingly, the reaction energetics for both paths A and B is depicted in Scheme 1. On path A, a small barrier TS (A1) could cause a very fast transfer of the first proton followed by a significantly slower transfer of the second proton which had to cross the second TS (A2) that was 2.5 kcal/mol higher in energy than TS (A1). This picture seems energetically consistent with the experimental study by Chou and coworkers [20]. On path B, TD-M06-2X predicted a first barrier of 3.3 kcal/mol, which is 1 kcal/mol higher than the first barrier on path A, and a smaller second barrier of 2.0 kcal/mol. Thus path B might also contribute to the total reaction. However, Chou and coworkers [20], based on the higher photo-acidity of the 6HIQ, proposed that the reaction would start from the transfer of the pyrrolyl proton of the 6HIQ to the pyridinyl site of the 7AI (path B in the current study). This viewpoint is not totally consistent with the current TD-M06-2X result. Furthermore, TD-M06-2X predicted that the energy of Int (A) was slightly lower than the tautomer, which is also not entirely consistent with the experiment where the tautomer emission was clearly observed. Thus the TD-M06-2X method seemed to predict the correct sign and order of the magnitude for the barrier heights but unable to obtain very accurate relative energies in the proton-transfer region on S_1 .

The electronic $S_0 \rightarrow S_1$ excitation of the normal dimer is primarily a HOMO to LUMO process. The calculated HOMO and LUMO of the normal dimer are plotted in Fig. 4. Since both orbitals are localized on the 6HIQ unit, it is indeed reasonable to assume that the photo-induced double proton transfer would start from the proton on 6HIQ. We then pushed our computational capability to current limit by performing a more reliable EOM-CCSD calculation. Table 2 shows that for both paths A and B, EOM-CCSD theory predicted the energies monotonically decrease after the first TS. That is, along the approximate paths calculated by the CIS theory, the EOM-CCSD theory does not predict potential energy wells for the zwitterionic intermediates or a stepwise mechanism (see Scheme 1). Furthermore, the EOM-CCSD theory predicted that path B is favored by more than 6 kcal/mol in barrier height, which is consistent with the pictures based on the photo-acidity and HOMO-LUMO shapes. The barrier of path B after zero-point correction (3.3 kcal/mol) is also more consistent with the experimentally derived value (2.9 kcal/mol).

Due to the charge separation in Int (A) and Int (B), they would have stronger stabilization energy with respect to the normal and the tautomeric form in polar non-protic solvents. However, it is unfortunate that for the current 6HIQ–7AI system experiment could only be carried in the nonpolar solvent such as cyclohexane used in our previous study [20]. The main reason lies in the fact that the association constant of hetero-dimer and/or dimer formation drops dramatically in polar solvents. For example, the association constant dropped by a factor of more than 10 in benzene ($<10^3 \text{ M}^{-1}$) and could not be measured in e.g. ether, CH_2Cl_2 and CH_3CN , etc. Thus, experimentally, it was not possible to prepare sufficient concentration (absorbance) of 6HIQ/7AI hetero-dimer

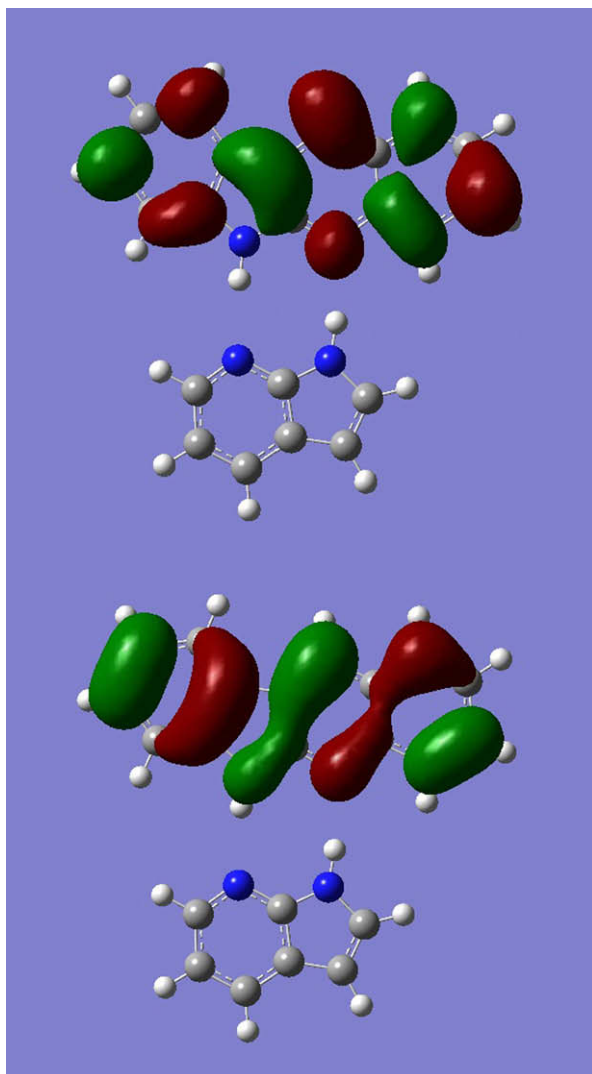


Fig. 4. Calculated HOMO (bottom) and LUMO (top) of the normal 6HIQ–7AI dimer.

in solvents other than cyclohexane for the fluorescence up-conversion experiments (optical path ~ 1 mm).

Last but not least, we also would like to mention that we found on S1 surface two low-energy ‘neutral’ complexes structurally similar to the zwitterionic intermediates Int (A) and Int (B) but without charge separation. The energies of the these two complexes were calculated to be 9.9 and 18.6 kcal/mol at CIS/6-31+G(d,p) level and -5.7 and 0.8 kcal/mol at EOM–CCSD level relative to the normal dimer. The neutral complexes have been characterized in previous study on the 7AI dimer system [15,28]. Since these complexes are probably not located on the reaction paths, their role in the ESPDT process is still unclear.

4. Conclusion

To sum up, the theoretical modeling presented in this study rendered a timely approach on double proton transfer reaction of the 6HIQ/7AI hetero-dimer in both ground and lowest lying electronic excited states (singlet manifold). In the electronic ground state, the double proton transfer more plausibly corresponded to a *concerted-asynchronous* pathway, in which the structure of TS can be described as the pyrrolyl proton (or hydrogen) of 7AI moved to the pyridinyl site of the 6HIQ, while the pyrrolyl proton (hydro-

gen) of 6HIQ was just on its way to the pyridinyl site of 7AI. Conversely, despite the system complication such that the predicted energetics/dynamics of ESDPT varied with respect to the modeling levels, it was more likely, based on the highest-level of theory, that on the excited state the reaction also favored a concerted but highly *asynchronous* process (see Scheme 1), and the order of proton transfer is reversed relative to that of the ground state. The high-level theory (EOM–CCSD) also predicted that the transfer of the proton on 6HIQ triggered the ESDPT reaction, which is consistent with the viewpoint based on photo-acidity and HOMO–LUMO shapes. We thus believe that this approach provides timely support and comparison to the experimental results regarding the ESDPT for 6HIQ/7AI hetero-dimer [20] and also paves a road for future challenges using more sophisticated theoretical models and experimental techniques.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.cplett.2009.12.005.

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