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Theoretical Investigation on the Absence of Spore Photoproduct Analogue at Cytosine-Thymine Site[†]

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As a well known DNA photolesion product, the special UV induced pyrimidine dimmer called spore photoproduct (SP), has aroused strong research interests. The SP formation was reported solely between two adjacent thymidine residues. It remains unclear in pervious experimental observations why there is an absence of the cytosine-derived SP-like photoproduct formation at the cytosine containing DNA strand, although the cytosine residue holds great similarity to thymine in terms of molecular structure. From a theoretical perspective, we have explored this issue in this work by means of density functional theory at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level for the DNA dinucleotide fragment, cytosine phosphate thymine (CpT). Key factors blocking the formation of the SP-like product between two adjacent cytosine and thymidine residues are revealed. Instead of undergoing photochemical SP reaction, a photophysical deactivation pathway back to the ground state turns out to be favorable for the CpT dinucleotide fragment.

Key words: DNA photolesion, Cytosine phosphate thymine (CpT), SP photoproduct analogue, Density functional theory

I. INTRODUCTION

UV radiation is a known deleterious and ubiquitous risk factor, which mainly induces damage to the chromosome of cell in most of the organisms [1]. Three types of UV induced DNA photoproduct were well studied and confirmed: *cis-syn* cyclobutane pyrimidine dimers (CPDs), pyrimidine (6-4) pyrimidone photoproducts (6-4PPs), and related Dewar valence isomers (DewPPs) [2, 3]. Additionally, a totally different photoproduct produced exclusively in bacterial spores, the so called spore photoproduct (SP), has been intensively studied during the past nearly half century since its first isolation and characterization [4, 5], and has become a research hot spot in recent years [6]. The SP refers to the special UV induced pyrimidine dimmer, 5-thyminyl-5,6-dihydrothymine, which is formed by linking the allylic carbon to the C5 of the adjacent thymidine (Scheme 1). In our previous work about the SP formation, a consecutive DNA photochemical mechanism which involves both the lowest-lying triplet and ground singlet has been elucidated [7], supporting further prior experimental studies [8].

Although the SP formation was solely reported between two adjacent thymidine residues (TpT), considering the similarities between cytosine and thymine, the possibility of photo-induced reaction which follows the SP formation mechanism at the cytosine containing site in DNA strand (denoted with the dinucleotide CpT) should also be taken into account. Could the photochemical reaction occur to form the SP-like product at the site of dinucleotide cytosine-thymine (CpT) or thymine-cytosine (TpC) sequence, which involves one hydrogen atom transfer from methyl of thymine (denoted as T) moiety to C6 position of C5=C6 bond in cytosine (denoted as C) moiety and followed by linking the allylic carbon (C7′) to C5 position of cytosine (Scheme 1)? In order to answer this question, the SP-like product had been searched in previous experiments. Setlow *et al.* reported that no detectable formation of SP derivative can be generated between adjacent C and T residues after UV irradiation [11]. Clivio found that no cytosine-derived SP-like photoproduct could be isolated either *in vivo* or *in vitro* [12]. Even under the condition of dry DNA and CpT rich strand, which should be favorable for the formation of SP, Douki and Cadet declared no detectable amount of CT or TC SP-like product formation, while products CPDs and 6-4PPs were obvious in the measurements of HPLC-mass spectrometry [9]. So far, no SP-like product has been isolated and detected [10]. It is presumed that the lack of C containing SP analogous adduct could be related to the decreased susceptibility of the C5 position of cytosine compared with that of thymine when attacked by

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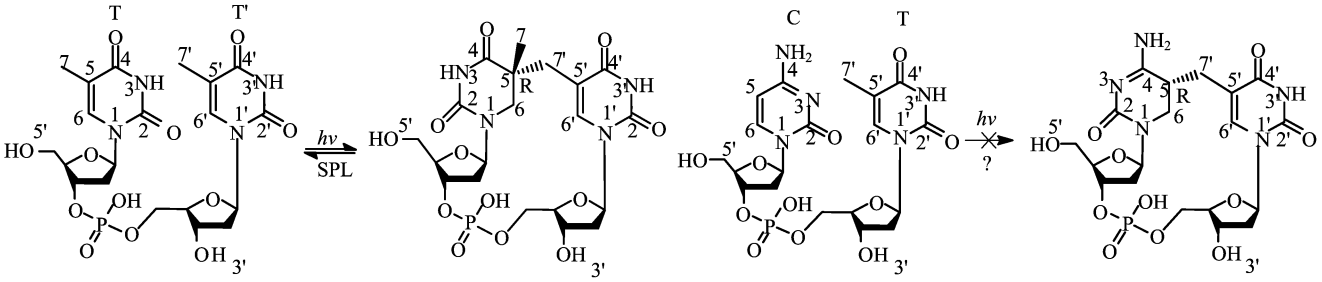

Scheme 1 SP reaction in TpT and the possible SP-like reaction in CpT sequence upon UV irradiation of DNA.

the methyl group of neighboring thymine [11]. Another postulation implied that the influence of C4 position substituent of cytosine residue may have specific but unclear chemical properties [12]. However, no explanation for the deficiency of SP like derivative at CpT or TpC site in DNA strand has been given definitely, neither experimentally nor theoretically. Obviously, further studies are required to explore this issue.

It is interesting that SP-like photochemical reactions have high stereo specificity, just like the reported photo induced DNA dimer formation in natural environment [13]. For instance, the most popular UV photoproducts in cellular or isolated DNA, intrastrand CPDs, exclusively adopt a *cis-syn* conformation [2], as a result of right handed double helix and the *anti* conformation of *N*-glycosidic bond in DNA. The twist direction of DNA helix also leads to preference of the thymine methyl group at 3′-end attacking the thymine C5 carbon located in the 5′-end in SP formation, as has been mentioned in previous NMR study [14]. Therefore, for the cases of SP-like photochemical reaction in CpT or TpC sequence, the initial step of hydrogen transfer is favored for CpT when T resides in the 3′-end. Hence, only the CpT sequence is investigated as a model system demonstrating the cytosine-derived SP-like photoproduct formation and discussed hereafter.

In the present work, we mainly focuses on exploring the key factors which block the formation of the SP-like product between two adjacent cytosine and thymidine residues by theoretical means. We choose to calculate the photoreaction of cytosine phosphate thymine (CpT) dinucleotide, as it is the smallest DNA fragment to accommodate a SP like product and sustains the constraints of the DNA backbone. The potential energy profiles for the photoproduct formation in the lowest-lying triplet and singlet ground state as well as the interaction between these two states are explored at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory. The reason why a SP like product cannot be obtained at CpT site has been investigated by the Fukui function and atomic charge distribution analysis. It is found that lower atomic reactivity of C5 and C7′ atoms is exhibited with CpT compared with TpT, and electrostatic repulsion between allylic carbon atom of T residue and C5 carbon of C moiety blocks the cross-link to form the SP like product. These results provide a rationale for the mystery of absence of the cytosine-derived SP-like photoproduct formation.

II. COMPUTATIONAL METHODS

In the present work, we choose the smallest DNA fragment, the dinucleotide cytosine dinucleoside monophosphate (CpT), as the reaction system. Although it is favorable to use a simple model of two free bases taking account of computational efficiency, as reported previously when dealing with CPDs and the (6-4) reaction [15, 16], the influence of DNA backbone has been neglected in that case. Actually, the glycoside and the phosphoester have definite effect on the motion and transformation of the pyrimidine residues, in spite that the absorption of UV light by DNA commonly leads to localization of energy mainly at the sites of bases. Therefore, CpT is chosen to be our current model system, which is similar to that used in previous work of SP formation mechanism [7], and it is close to the natural situation of DNA strand, in which the SP-like reaction may take place between the adjacent cytosine and thymine residues.

The SP-like reaction is invoked by an initial excitation of the base at 5′-end to a singlet excited state. Besides the returning to the ground state by internal conversion, intersystem crossing (ISC) results in a long-lived triplet state. Although the quantum yield is low, the long-lived triplet state is believed to be a possible reactive intermediate which leads to the photoproduct.

We calculated the potential energy profiles along the T_1 and S_0 states for the possible reaction pathway toward the SP-like derivative with the Gaussian 03 program package [17]. The geometries of reactants, products, intermediates, and transition states along the T_1 and S_0 state were optimized using hybrid density functional theory (B3LYP) with the standard basis sets of 6-31G(d,p) [18], which is an appropriate quantum chemical approach for the current large reaction system of CpT. The single-point energies were calculated at the B3LYP/6-311++G(d,p) level while the B3LYP/6-31G(d,p) basis were used for geometrical optimiza-

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TABLE I Relative energies without ZPE correction (in kcal/mol) of the stationary structures along the T_1 and S_0 reaction pathways.

		RS	RT	TS1	TI	TS2	TP	STS1	SI	P	STSC	(5-6) product
B3LYP/6-31G(d,p)	Vaccum	0.0	71.1	84.7	62.1	91.5	75.8	66.3	62.1	9.0	69.2	26.3
	ε=4.3	0.0	72.7	86.0	62.3	92.2	77.3	66.0	62.3	9.7	69.5	26.8
B3LYP/6311++G(d,p)	Vaccum	0.0	71.8	85.1	61.8	92.2	77.2	65.5	61.8	9.7	71.2	29.5
	ε=4.3	0.0	73.2	86.0	61.6	92.7	78.5	64.6	61.6	10.3	71.8	29.8

tion. The harmonic frequency analysis was performed to identify the stationary point as either local minima (reactants, intermediates, and products) or first-order saddle points (transition states). The intrinsic reaction coordinate (IRC) calculations have been performed to check the connections of the transition states between two local minima [19]. Bulk solvation effects were considered by using the integral electron formalism of the polarized continuum model (IEF-PCM) [20]. A concerted mechanism for the CpT photoreaction has also been explored on the ground singlet state and the S_1 excited state. The vertical excitation energies have been calculated by using TD-DFT method. According to the framework of the van der Lugt and Oosterhoff model [21], the geometrical structures of the excited-state species are similar to those of the ground-state species, thus, an approximate excited-state potential energy surface can be calculated using ground-state geometries.

Additionally, we calculated the condensed Fukui function of C5 atom and C7′ atom in the intermediate species of both CpT and TpT systems using previously optimized geometries and performed single point calculation at B3LYP/6-311++G(d,p) level in both gas phase and solution. Due to the requirement of a constant external potential [22], the systems with one electron plus and one electron loss are all calculated with the geometry of the neutral species.

III. RESULTS AND DISCUSSION

As shown in Scheme 1, the ideal SP-like photoproduct could be formed by cross-link between the methyl group of the 3′-end thymine and the C5 carbon of 5′-end cytosine (5′→3′). The possibility of the SP-like product formation between two adjacent cytosine and thymidine residues in the triplet and singlet state has been searched. The nonadiabatic pathway from triplet to singlet state and the concerted reaction pathways in the ground state and singlet excited state are also discussed.

A. Potential energy profile along T_1 and S_0 states

The potential energy profiles along T_1 and S_0 states were calculated with DFT method. The optimized steric structures of reactants, intermediates, transition states, and products are shown in Fig.1. The computed single-point energies are listed in Table I. The zero-point energy (ZPE) corrections affect the reaction barriers slightly and thus are not taken into account in the following calculation. Bulk solvation with the dielectric constant ε=4.3 is used to simulate the apolar surroundings in DNA [23].

TABLE II Mulliken spin densities (e^-, B3LYP/6-311++G(d,p) level) of selected atoms in each species along the triplet and singlet pathway.

	RT	TS1	TI	RS	STS1	SI
C5	0.68	0.75	0.80	−0.00	−0.23	−0.80
C6	0.69	0.38	−0.07	0.00	0.10	0.07
C4	−0.01	−0.10	−0.12	0.00	0.03	0.12
C5′	−0.00	−0.08	−0.21	0.00	−0.04	−0.21
C6′	0.01	0.20	0.46	−0.00	0.08	0.46
C7′	0.00	0.38	0.73	0.00	0.16	0.72

For the triplet reaction, initiated from the C=C $\pi\rightarrow\pi^*$ excitation, the main structural character of the lowest-lying triplet state of the dinucleotide CpT (denoted as RT) is the transformation of the C5=C6 bond (1.361 Å) of cytosine residue into a σ-bond (1.470 Å) at 5′-end, while the thymine moiety at 3′-end remains intact (see the structure in Fig.1). Consequently, the triplet CpT can be imagined as a biradical species with spin densities mainly localized on the C5 and C6 atoms. The biradical character can also be revealed from the Mulliken spin density analysis (Table II). Thus, the C5 and C6 atoms become reactive and can induce the cross-link of cytosine residue and thymine residue.

The consecutive reaction pathway in the triplet state is shown in Fig.2. The first step is the H8′ migration from the methyl C7′ of T to C6 of C via TS1, which proceeds facilely with a low barrier of 13.3 kcal/mol. In the transition state TS1 (see Fig.1), C6−H8′ distance is 1.442 Å and C7′−C8′ distance is 1.336 Å. Taking into account the bulk solvation effect, this barrier is reduced to 12.8 kcal/mol. The intermediate TI lies 10 kcal/mol below the triplet reactant RT, indicating that the hydrogen migration is an exothermic process. In the intermediate TI, a p-π conjugation occurs for the T base among the allylic C7′ carbon and the ethylenic C5′ and C6′ carbons as indicated from the shortened C5′−C7′ bond (1.394 Å) and elongated C5′−C6′ bond

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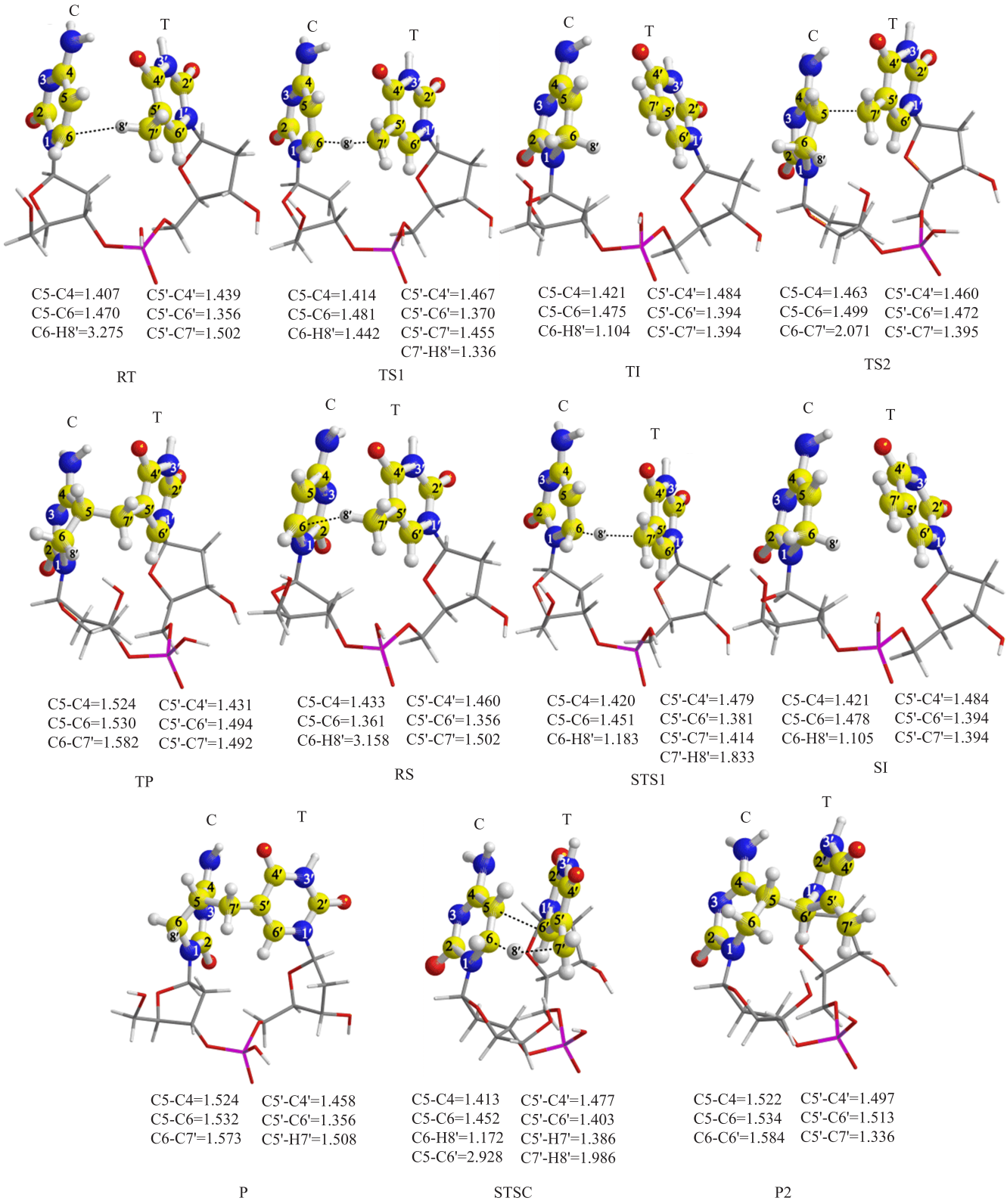

FIG. 1 Optimized geometries of reactants, intermediates, transition states, and products in the S_0 and T_1 states at the B3LYP/6-31G(d,p) level. Bond lengths are in Å.

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(1.394 Å) compared to those in RT, that is, C5′−C7′ bond (1.502 Å) and C5′−C6′ bond (1.356 Å). Thus, the triplet intermediate TI is more stable compared with the reactant RT. Bulk solvation affects the exothermicity (11.6 kcal/mol) slightly. Considering the exothermicity and low barrier involved, the hydrogen atom transfer from the T residue at 3′-end to C residue at 5′-end is expected to take place favorably on the triplet surface. However, the consecutive step from TI to TS2, which is the cross-link of the allylic C7′ carbon to the C5 atom of the adjacent cytosine base, requires to overcome a high energy barrier of 30.4 kcal/mol. Furthermore, the resulting triplet product (denoted as TP) is 77.2 kcal/mol above the initial reactant RS, which is quite unstable energetically. Thus, there is little possibility that the SP-like photoproduct can be produced solely on the triplet surface for the dinucleotide CpT.

The potential energy profile along the S_0 state is also shown in Fig.2. For the ground-state CpT, the cytosine residue (C) and the thymine residue (T) adopt face-to-face configuration, as shown in RS of Fig.1. In the reactant RS, C5−C6 bond of C moiety (1.361 Å) and C5′−C6′ bond of T moiety (1.356 Å) possess the ethylenic double-bond character. Hydrogen atom H8′ migrates from the methyl C7′ of T base to C6 of C base via STS1, leading to the formation of the intermediate SI. This step requires to overcome a barrier of 65.5 kcal/mol (64.6 kcal/mol with bulk solvation effect). In the intermediate SI, the bond length of C5−C6 has been elongated from 1.361 Å to 1.475 Å, indicating its conversion to the single bond character due to the hydrogen addition. The formed intermediate SI lies 61.8 kcal/mol above the reactant (61.6 kcal/mol with bulk solvation effect). Such an unstable species corresponds to a biradical character, because the unpaired electrons are anticipated to be localized on C5 and C7′ atoms after hydrogen atom transfer, as has been shown from the Mulliken spin density analysis (Table II). Starting from intermediate SI, the cross-link transition state to form the SP-like product cannot be located in the ground-state singlet surface. In addition, SP-like product formation is energetically infeasible along the triplet surface. These results suggest that the SP-like photoproduct is unlikely to be formed from the CpT dinucleotide fragment of DNA, which is consistent with prior experimental observations that no detectable formation of SP derivative can be generated between adjacent C and T residues after UV irradiation.

According to our previous studies [7], SP photoproduct formation for the dinucleotide TpT occurs easily involving both T_1 and S_0 states. The initial hydrogen atom transfer occurs along the T_1 state with a barrier of 14.2 kcal/mol (11.9 kcal/mol in bulk solution) forming the triplet intermediate TI, from which the T_1/S_0 surface crossing occurs. After intersystem crossing from the triplet intermediate TI to the singlet intermediate SI, the subsequent C5−C7′ bond formation towards the final SP formation proceeds facilely in S_0 state with a barrier of only 5.9 kcal/mol (3.8 kcal/mol in bulk solution). In contrast, for the dinucleotide CpT, the reaction pathway is simply stagnated in the singlet intermediate SI, without undergoing the cross-link to form the SP dimmer. What is the reason causing such an absence of SP reaction in CpT dinucleotide fragment?

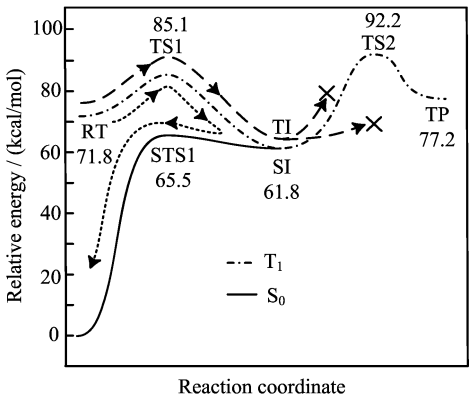

FIG. 2 Potential energy profiles of the reaction pathways along the S_0 and T_1 surfaces for the dinucleotide CpT. The dotted line highlights the photophysical deactivation pathway.

The reactivity of C5 and C7′ atoms in CpT or TpT are the crucial factors determining SP reaction, which may be different for the two dinucleotides due to the substituent effect. It is well known that the prediction and interpretation of intra- and intermolecular reactivity has been an important area in modern theoretical organic chemistry [24], several reactivity descriptors for both molecules and atoms are available through large numbers of calculation approaches [25]. Among those descriptors, the condensed Fukui function f_X^0 is one of the most popular and reliable atomic reactivity indices [26]. For the reaction involving radical attacks, the condensed Fukui function is defined by the following equation,

$$f_X^0 = \frac{1}{2}\left[Q_X\left(N+1\right) - Q_X\left(N-1\right)\right] \tag{1}$$

where $Q_X(N+1)$ and $Q_X(N-1)$ are the electronic charge of atom X in the $N+1$ and $N-1$ electron systems respectively. For a system of N electrons, independent calculations are to be made for corresponding $N+1$, N, and $N-1$ electron systems with the same molecular geometry. The condensed Fukui function is introduced as a measure for describing the reactivity of a site in a molecule. Here, a comparison between CpT and TpT employing condensed Fukui function has been performed and the results are listed in Table III.

For the dinucleotide TpT, the step of the hydrogen atom transfer proceeds in the T_1 state and forms the intermediate TI. Then TI tends to cross over to the singlet intermediate SI. The singlet intermediates SI of both CpT and TpT are biradical species, and the unpaired electrons are localized at C5 and C7′ respectively.

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TABLE III Condensed Fukui functions f_X^0 of the singlet intermediate SI of CpT and TpT calculated at B3LYP/6-311++G(d,p) level.

		f_X^0	
		CpT	TpT
Gas phase	C5	0.156	0.179
	C7′	0.174	0.197
Solvation	C5	0.193	0.204
	C7′	0.157	0.178

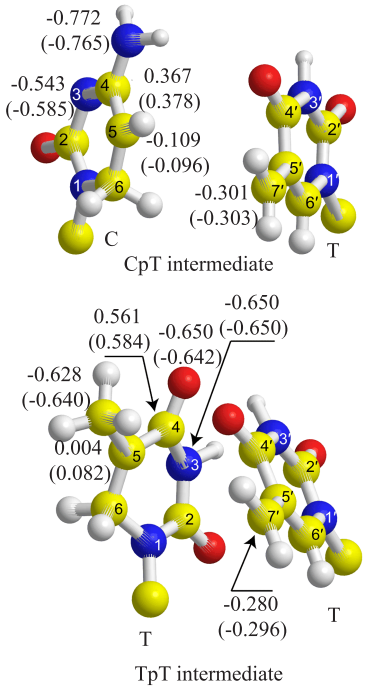

FIG. 3 NPA charge distributions of the ground-state singlet intermediates of CpT, TpT in both gas phase and solution (in parentheses).

Starting from SI, the cross-link of C7′ to C5 leads to the final SP product in the ground state. Therefore, the singlet intermediate SI plays a key role in the formation of SP product. Whether or not the cross-link can occur dependent mainly on the reactivity of C5 and C7′ atoms in the singlet intermediate SI, which can be described by their f_X^0. As shown in Table III, both C5 and C7′ atoms in TpT system have higher f_X^0 values than those in CpT system. As the higher f_X^0 value means greater reactivity, the results indicate that the C5 and C7′ atoms are more likely to react with each other in TpT than in the case of CpT. The atomic reactivity difference explains the deficiency of SP product formation for CpT compared with TpT.

To explore further the different reactivity of CpT and TpT towards SP reaction, charge distributions for the key radical intermediate SI are analyzed, by the method of natural population analysis (NPA) that has been proven to give reliable atomic charges [27]. As shown in Fig.3, in the intermediate SI for both CpT and TpT, the C7′ atoms are carrying negative charge, due to the hydrogen abstraction and the p-π conjugation among C7′, C5′, and C6′. However, the charge distributions at C5 atom of 5′-end moiety are varied, which has negative charge of −0.109 e (−0.095 e in solution) for CpT, but with positive charge of 0.004 e (0.082 e in solution) for TpT. Such a charge difference may be caused by the different substituents around C5 atom. For CpT, the C4 amino group NH_2 conjugating with C5 atom is of a electron-donating character, leading to the negative charge of C5 atom. While for TpT, the C4 carbonyl group is electron-withdrawing and thus makes the C5 atom positively charged through hyper conjugation. Considering the charge distributions on C5 and C7′ atoms, it is found that an electrostatic attraction exists for TpT, while CpT is exhibited with charge repulsion. Since the crucial final step leading to SP product is through the C5−C7′ bond formation, it is reasonable that the SP reaction is stagnated in the singlet intermediate SI, without undergoing the cross-link to form the SP dimmer for the CpT dinucleotide, but proceeds to form SP dimmer for the TpT dinucleotide. It shows here that the deficiency of SP reaction in CpT should be correlated with the charge distribution properties influenced by the C4 position substituent of cytosine residue.

B. Nonadiabatic deactivation pathway from triplet to singlet state

Without undergoing photochemical reaction to form SP product, the fate of the photoexcited dinucleotide CpT should be just photophysical deactivation to ground state. Interestingly, we found that the located the singlet biradical SI was equal to the triplet biradical TI in energy, as shown in Fig.2 and Table I. This indicates a T_1/S_0 surface intersection and a facile intersystem crossing from T_1 to S_0. To obtain the singlet-triplet interaction profile, the PES scanning was performed from TS1 to TI and from STS1 to SI respectively, by varying the C7′−H8′ distance from a configuration which is close to TS1 (the initial optimized value is 1.38 Å) and STS1 (1.83 Å) with a step length of 0.15 Å and optimizing the remaining coordinates. The energy scans for the singlet and triplet (both in vacuum and in solution) are displayed in Fig.4. It is noticed that the energy curve goes closer and closer when approaching TI and finally equalizes with each other, both in vacuum or in bulk solution, convincing further the triplet-singlet surface crossing. Through T_1/S_0 surface intersection, the photoexcited dinucleotide CpT easily crosses over to S_0 state. Once in S_0 state, the intermediate SI tends to recover to the ground state reactant through STS1 via a low barrier of 3.7 kcal/mol. This constitutes a favorable deactivation relaxation pathway for the photoexcited dinucleotide CpT, which is labeled

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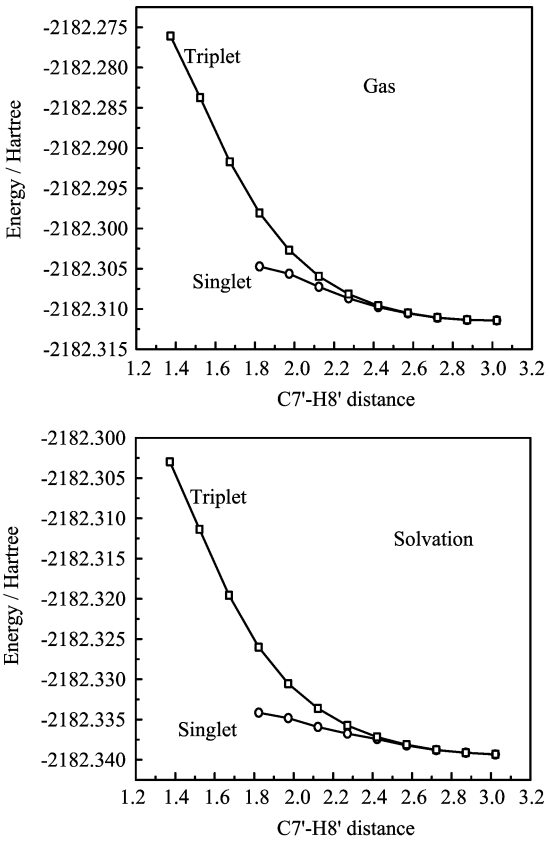

FIG. 4 Relaxed potential energy curves for ground singlet and the lowest lying triplet states, obtained at the level of B3LYP/6-31G(d,p).

by dotted arrow lines in Fig.2.

C. A concerted mechanism leading to (5-6) cross-link product

Additionally, the possibility of a concerted mechanism which should involve a simultaneous hydrogen atom transfer and a cross-link of the two residues in CpT has also been explored. To one's surprise, along the concerted pathway, the concerted transition state does not lead to a SP-like product but a (5-6) cross-link product (see STSC and P2 in Fig.1). This (5-6) cross-link product has never been reported before. In the singlet ground state, it needs to surmount a barrier of 71.2 kcal/mol to reach the concerted transition state. As shown in Fig.1, the concerted reaction product P2 is obviously different from the SP-like product. In the concerted transition structure STSC, the C5$\cdots$C6′ distance (2.93 Å) is 0.37 Å shorter than the C5$\cdots$C7′, which probably be one of the reasons why C5−C6′ cross-link product is formed, but not the SP-like product. For the singlet reaction pathway along S1 state, the approximate potential energy profile is obtained by TD-DFT calculations and shown in Fig.5. Obviously, the

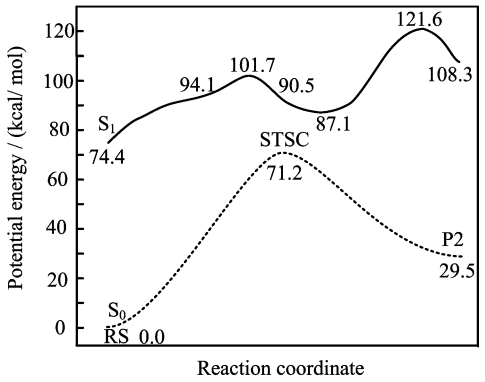

FIG. 5 Potential energy profiles of concerted mechanism toward the C5−C6′ cross-link product P2 on the S_0 and S_1 surfaces.

concerted path towards the C5−C6′ cross-link product is unlikely to occur due to the inaccessible high barriers involved and large endothermicity.

IV. CONCLUSION

In the present work, we have studied the possibility of formation of cytosine-derived SP-like photoproduct for the CpT. The potential energy profiles for the photoproduct formation in the possible lowest-lying triplet and singlet ground state as well as the interaction between those two states have been calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level. The possible concerted mechanism for CpT was also explored on the S_0 and S_1 potential energy surface combined with the method of TD-DFT.

Our calculations demonstrate that the SP-like reaction along the T_1 triplet state is energetically infeasible, which involves the initial hydrogen migration from the C7′ atom of 3′-end thymine residue to the C6 atom of 5′-end cytosine residue and a subsequent C5−C7′ cross-link. There is not a pathway leading to the SP like product in the ground state. The reason of the absence of the cytosine-derived SP-like photoproduct has been uncovered by the Fukui function and atomic charge distribution analysis. It is found that lower atomic reactivity is exhibited with CpT compared with TpT, and the charge repulsion blocks the cross-link of C5 and C7′ atoms to form the SP like product. Such charge distribution properties are induced by the C4 position substituent of cytosine residue. These results provide a rationale for the deficiency of SP reaction in CpT and solve the mystery of absence of the cytosine-derived SP-like photoproduct formation in previous experimental observations. Meanwhile, without undergoing photochemical reaction to form SP product, the fate of the photoexcited dinucleotide CpT is shown to be a favorable photophysical deactivation pathway via the T_1/S_0 surface intersection, leading to the ground state reactant CpT. Such a recovery mechanism may play pho-

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toprotective roles in UV irradiation for the DNA sequences containing CpT dinucleotide fragment.

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