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REGULAR ARTICLE

Sequence Dependent Photochemistry of Adenine-Thymine and Thymine-Adenine Dinucleotides

Jian Luo[†,‡], Yan Liu[†,‡], Songqiu Yang[†*]

[†]*State Key Laboratory of Molecular Reaction Dynamics, Dalian Institute of Chemical Physics (DICP), Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, China.*

[‡]*University of Chinese Academy of Sciences, Beijing 10049, China.*

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ABSTRACT. Under ultraviolet irradiation, DNA thymine-adenine dinucleotide (TpdA) might undergo a cycloaddition while its isomer adenine-thymine deoxy-dinucleotide (dApT) is of high photostability. By using time-dependent density functional theory and molecular dynamics simulations, we found that the cycloaddition of TpdA is a barrierless process via a charge-transfer state. In contrast, the cycloaddition of dApT was found to be energy consuming. We also revealed that in aqueous solution, the average interbase distance of dApT is larger than that of TpdA, further contributing to the high photostability of dApT.

AMS subject classifications: 92C40, 81V19, 00A72, 70H12

Keywords: M052X, DNA damage, TDDFT, photoreaction.

Introduction

The photochemical processes in DNA have attracted much attention owing to their relation with carcinogenic mutations [1,2]. Under UV irradiation, DNA thymine-adenine dinucleotide (5′-3′ side, TpdA, **Fig. 1**) can undergo a [2+2] cycloaddition, where thymine (T) and adenine (A) form a T<>A intermediate. This photoreaction breaks the highly conserved TATA

* Corresponding author. *E-mail address:* sqyang@dicp.ac.cn

sequence in DNA promoter and impedes normal gene expression [3,4]. Unexpectedly, adenine-thymine dinucleotide (5′-3′ side, dApT, **Fig. 1**), an isomer of TpdA with the contrary base sequence, is of high photostability [3]. This sequence dependent photochemistry has been explained by the larger interbase distance of dApT than TpdA in aqueous solution [5]. In that study, the interbase distance of dApT was calculated to be 7~6.2 Å, too far to form charge-transfer (CT) states that can be formed only in well-stacked conformations [6]. However, CT states in dApT have been determined in time-resolved experiments [7]. Thus, a more accurate description about the interbase distance distribution is necessary. On the other hand, although the T<>A formation has been suggested to be induced by the CT state, the reaction path remains unconstructed. An excited-state reaction path can give a deep insight into the contrary photostability of the two dinucleotides.

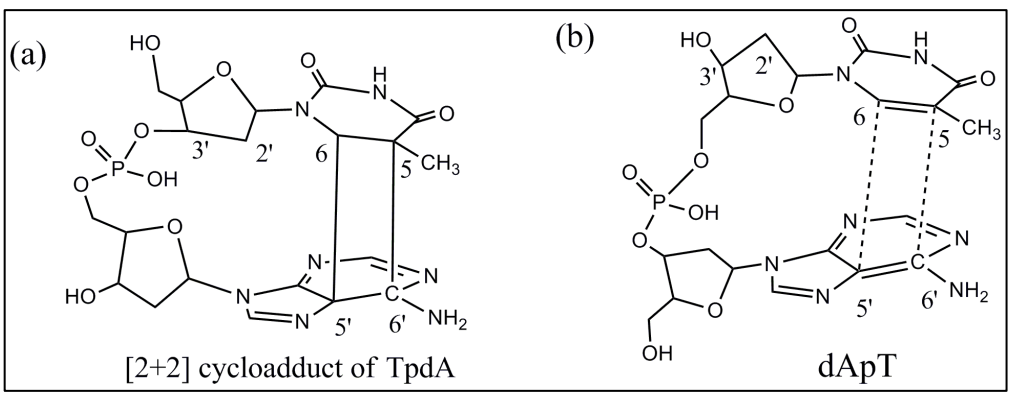

Fig. 1: Structures of the photoproducts of (a) TpdA and (b) dApT.

In this work, by combining time-dependent density functional theory (TD-DFT) calculations and molecular dynamics (MD) simulations, we attempted to explain the sequence dependent photochemistry. The cycloaddition paths of both TpdA and dApT were calculated by TD-DFT calculations and turned out to be different. MD simulations were used to analyze the interbase distances of the two dinucleotides in aqueous solution.

Computational Methods

DFT and TD-DFT Calculations All calculations were carried out using the Gaussian 09 programs [8]. Default parameters were used in all calculations unless otherwise indicated. The M052X functional [9] was the primary functional in this work, which was determined to be efficient to deal with the CT states of π-stacked systems [10]. The defaulted solvation polarizable continuum model (PCM) [11,12] and linear-response PCM (LR-PCM) [13] were

used to simulate bulk water environment. Initial structures of dApT and TpdA were derived from a B-DNA structure (pdb: 3BSE) [14]. Linear interpolation between the ground-state (S_0) reactant and product followed by optimizing the lowest excited state (S_1) geometry by fixing the C5-C6′ and C6-C5′ bond distances constructs the cycloaddition path of TpdA and dApT. The reaction coordinate <*d*> is defined as the average C5-C6′ and C6-C5′ bond distances.

MD Simulations MD simulations were performed on the GROMACS program [15]. The starting geometries were also derived from 3BSE B-DNA [14]. Each solute molecule was solvated with 5034 SPCE [16] water molecules in a dodecahedron box with a size of 6.0 nm. The CHARMM27 force field [17] was employed, which had been used in simulations of nucleosides and DNA [18-21]. A Nosé-Hoover thermostat [22,23] and a Parrinello Rahman barostat [24] were used to keep the system at 298 K and 1 bar. The total simulation time was 100 ns with a step size of 1 fs. Conformations were saved every 5 ps. The root-mean-square deviation was converged in the first 1 ns. Snapshots of the last 95 ns were used for analysis. The number of the total snapshots was 1.9×10^4.

Results and Discussions

1. Ground-state geometries

As shown in **Fig. 2a** and **2c**, the S_0 geometries between TpdA and dApT differ largely. In TpdA, the reactive bond distance *d*(C5-C6′) is 3.70 Å and *d*(C6-C5′) is 3.97 Å, while in dApT, the respective values are 4.21 and 3.91 Å. The orientation of the C5-C6 and C5′-C6′ bonds of the two dinucleotides are also different. The dihedral angle η (C5-C6-C6′-C5′) of TpdA is -12° and that of dApT -84°, indicating that the reactive C5-C6 and C6′-C5′ bonds are approximately parallel in TpdA while perpendicular in dApT. Besides the base arrangements, the sugar conformations of the two dinucleotides also differ. In TpdA, the two sugar are both C2′-endo puckering. In dApT, the sugar of adenosine is C2′-endo while the sugar of thymidine is O′-endo. Although the S_0 geometries of dApT and TpdA are quite different, their Gibbs free energies are within only 3.5 kcal/mol difference.

The equilibrium S_0 geometries of the T<>A and A<>T photoproducts are shown in **Fig. 2b** and **2d**. The cis-syn structure of the T<>A photoproduct is in line with the NMR results [4]. In the two photoproducts, the sugar of thymidine is O′-endo and the sugar of adenosine is C2′-endo. Thus, upon assumed photoreaction of dApT the two sugar conformations do not have a change. However, in the case of TpdA, the sugar of thymidine is changed from C2′-endo to O′-endo puckering upon photoreaction.

2. Excited-state reaction path

In order to explore the role of excited states in the photoreactions of dApT and TpdA, the optimized excited-state reaction paths are constructed, as shown in **Fig. 3**. The S_1 state of both dApT and TpdA is always a CT state before the potential energy profile approaches the conical intersection. It is clear that the cycloaddition of TpdA is a coincident process through a conical intersection connecting the CT and ground states. The CT state can either decay back to the reactant or form the T<>A photoproduct through the conical intersection. Both the two processes are barrierless. In contrast, the formation of dApT through the CT state is an energy consuming process. After the interbase distance of dApT decreases to approximate 3.1 Å, the CT state energy starts to increase, making the photoreaction impossible. Therefore, the CT state profiles of TpdA and dApT can perfectly explain the photochemistry of TpdA and photostability of dApT.

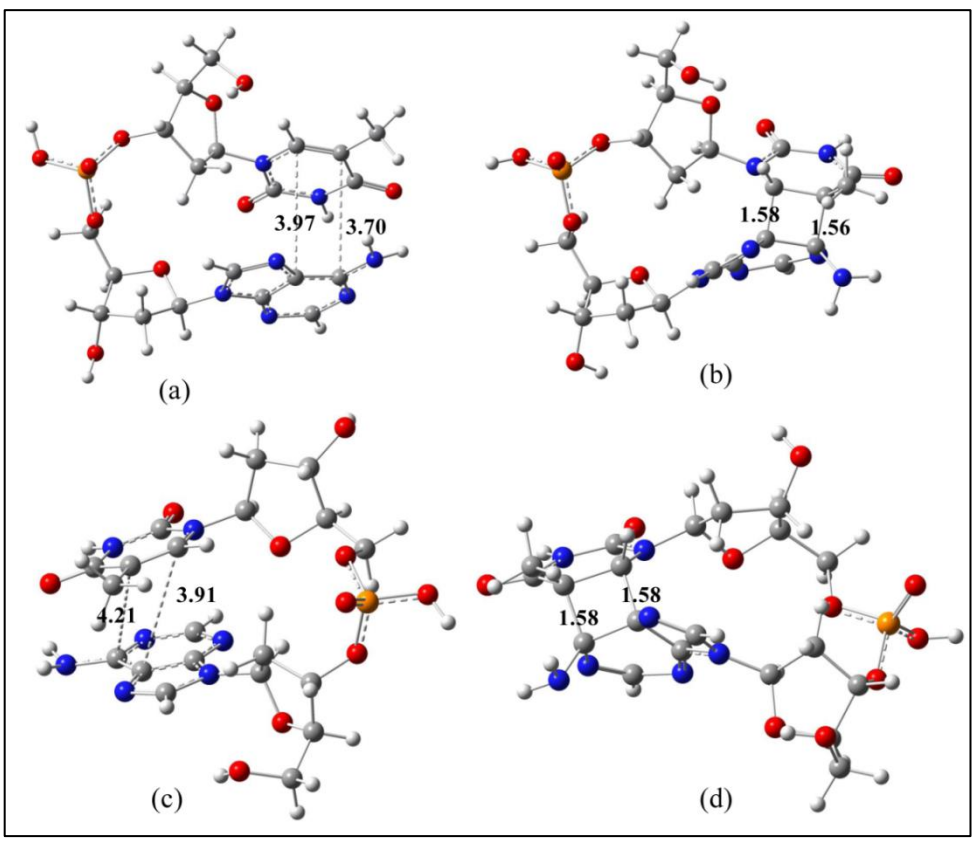

Fig. 2: Equilibrium ground-state geometries under the PCM/M052X/6-31g(d) level: (a) TpdA; (b) the photoproduct of TpdA; (c) dApT; (d) the photoproduct of dApT. The reactive C5-C6′ and C6-C5′ bond distances are shown in unit Å.

3. MD simulations

In order to investigate the favored conformations for TpdA cycloaddition, MD simulations are performed. A previous study has suggested that it is the larger interbase distance of dApT than TpdA that contributes to the higher photostability of dApT [5], thus the conformation distribution of dApT is also explored. As shown in **Fig. 4a**, the probability densities for the *d*(C5-C6′) and *d*(C6-C5′) of TpdA have significantly narrower distributions in comparison to dApT. And the peaks in the probability densities for *d*(C5-C6′) and *d*(C6-C5′) of TpdA lie at shorter distances (ca. 3.9 and 4.0 Å) than dApT (ca. 4.2 and 4.5 Å). Thus, dApT has larger reactive bond distances than TpdA, in agreement with previous studies [5]. This conclusion is also in line with the DFT calculations, as shown in **Fig. 2**.

Inspired by the S_0 conformation controlled T<>T formation [20,21], the cycloaddition of TpdA is also assumed to be controlled by S_0 conformations. Using the dimerization quantum yield for $(dT)_{20}$ as a benchmark, the reactive bond distance less than 3.52 Å is determined to be the single criterion for the dimerization [20]. Similarly, the distribution of conformers satisfying *d*(C5-C6′) < 3.52 Å and *d*(C6-C5′) < 3.52 Å is shown in **Fig. 4b**. It is clear to see that the number of TpdA conformers is much larger than the number of dApT conformers. Given that the quantum yield of TpdA photoproduct is 7×10^{-4} and the total snapshots for statistics is 1.9×10^{4} [3], there should be only 14 snapshots that can form the product. Thus, the average reactive bond distance <*d*> should be less than 3.3 Å. There is no dApT snapshot satisfying this criterion. Therefore, the zero quantum yield of the A<>T dimer is elucidated.

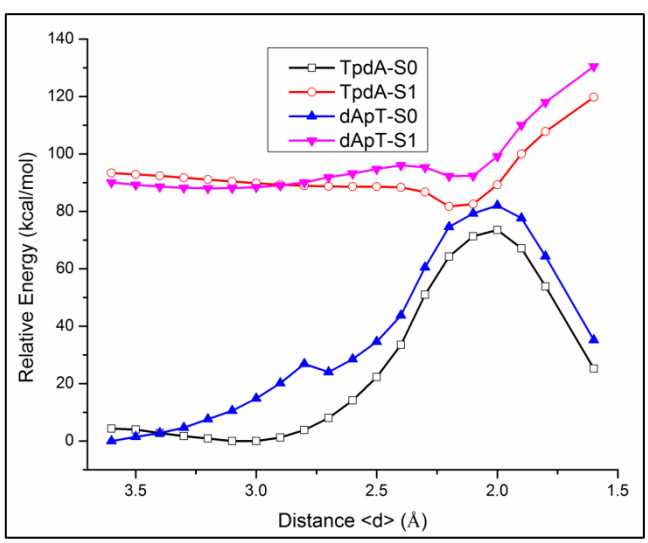

Fig. 3: The optimized excited-state cycloaddition paths by using the LR-PCM/TD-M052X/6-31g(d) method for TpdA and dApT. Reactive coordinate <*d*> is the average distance of the C5-C6′ and C6-C5′ bonds.

Although the MD simulation results can explain the different photostabilities of dApT and TpdA, this conclusion should be drawn on the basis of the ultrafast barrierless cycloaddition of TpdA, which has been determined by the aforementioned TD-DFT results. This is the prerequisite that the cycloaddition of TpdA is controlled by S_0 conformations, as same as the TT dimerization.[34,35] The criterion $\langle d \rangle < 3.3$ Å is not an accurate value because MD simulations likely overestimate the stacking interactions of DNA [25]. However, the conclusion that dApT has a larger interbase distance than TpdA is still believable. Even though there are some dApT conformers satisfy the criterion, the energy barrier in the reaction path can also lead to the cycloaddition impossible. As a result, the knowledge of the excited-state reaction path can give a deep insight into the understanding of the MD results.

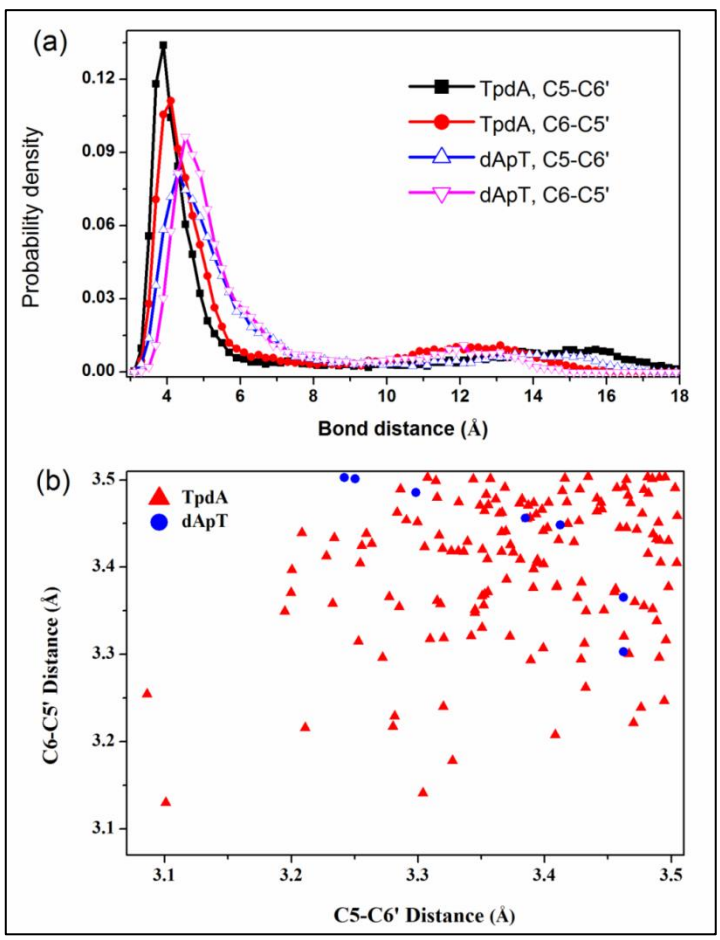

Fig. 4: (**a**) Probability densities as a function of the C5-C6′ and C6-C5′ bond distances of TpdA and dApT. The integral of the probability density is 1.0. (**b**) The distributions of dApT and TpdA conformers with both the C5-C6′ and C6-C5′ bond distances less than 3.52 Å.

Conclusions

In summary, we have explored the mechanism underlying the different photostabilities of TpdA and dApT by TD-DFT calculations and MD simulations. The CT state is responsible for the cycloaddition of TpdA. This photochemical reaction is a barrierless process via the CT state. In contrast, there is an energy barrier in the cycloaddition of dApT, lowering its reaction probability. Furthermore, MD simulations suggest that the reactive bond distances of dApT are larger than that of TpdA. As a result, we suggest that both the ground-state conformations and excited-state reaction profiles lead to the sequence-dependent photochemistry of TpdA and dApT.

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