

REGULAR ARTICLE

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

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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.

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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 \rightleftharpoons A intermediate. This photoreaction breaks the highly conserved TATA

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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.

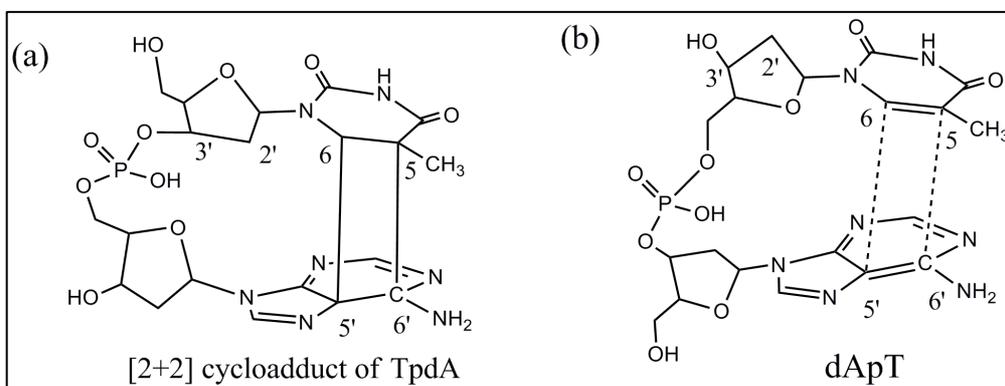


Fig. 1: Structures of the photoproducts of (a) TpdA and (b) dApT.

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