



A Polymerase – Tautomeric Model for Targeted Frameshift Mutations: Deletions Formation during Error-prone or SOS Replication of Double-stranded DNA Containing *cis-syn* Cyclobutane Thymine Dimers

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Abstract: Now it is still unclear how frameshift mutations arise at cyclobutane pyrimidine dimers. The author develops polymerase – tautomeric model of ultraviolet mutagenesis. The model is described that is based on the formation of rare tautomeric bases in *cis-syn* cyclobutane thymine dimers. A mechanism was proposed for targeted deletions caused by *cis-syn* cyclobutane thymine dimers. Targeted deletions are frameshift mutations when one or several nucleotides are dropped out in a DNA site opposite to a lesion capable of stopping DNA synthesis. Ultraviolet irradiation may result in changes of tautomer states of DNA bases. Thymine molecule may form 5 rare tautomer forms. They are stable if these bases are part of cyclobutane dimers. Structural analysis indicates that opposite one type of *cis-syn* cyclobutane thymine dimers containing a single tautomeric base (TT_2^* , with the ‘*’ indicating a rare tautomeric base and the subscript referring to the particular conformation) it is impossible to insert any canonical DNA bases with the template bases with hydrogen bonds formation. Therefore it is proposed that under synthesis DNA containing *cis-syn* cyclobutane thymine dimers TT_2^* specialize or modified DNA polymerases will leave one nucleotide gaps opposite these *cis-syn* cyclobutane thymine dimers. Daughter DNA strand opposite *cis-syn* cyclobutane thymine dimers TT_2^* may fall out. If in opposite DNA strand the loop is formed, daughter strand becomes shorter. Some DNA nucleotides are lost. Targeted deletion is formed. According to the polymerase-tautomeric model of ultraviolet mutagenesis *cis-syn* cyclobutane thymine dimers wherein a thymine is in the canonical tautomeric forms do not result in mutations. *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric forms T_1^* , T_4^* , or T_5^* were shown to cause only targeted base substitution mutations. *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric form T_2^* may result in targeted frameshift mutations (targeted insertions and targeted deletions).

Keywords: UV-mutagenesis, Rare Tautomeric Forms, Targeted Frameshift Mutations, Targeted Deletion, *cis-syn* Thymine Cyclobutane Dimers, Error-prone Replication, SOS-replication

1. Introduction

UV radiation produces photoproducts in DNA. As indicated above, both cyclobutane pyrimidine dimers and (6-4) adducts are formed [1-6]. The most common lesions are *cis-syn* cyclobutane pyrimidine dimers [4], in which the bases preserve their original orientation relative to the sugar-phosphate backbone [7]. Cyclobutane pyrimidine dimers and (6-4) adducts cause substitution mutations [8-19], frameshifts [11, 20, 21], and complex mutations [22]. Only a few photodimers result in mutations, while more than 90% of these lesions do not [9]. Frameshift mutations are the

structural DNA changes wherein one DNA strand becomes shorter or longer than the other as a result of a deletion or insertion of a number of nucleotides that is not divisible by three [23]. The point mutation rate of phage $\Phi X174$ was determined [24]. One nucleotide deletions appear most often [25]. Frameshift mutations may be targeted and untargeted types [26]. Mononucleotide runs are hot spots for frameshift mutations in mismatch repair (MMR)-deficient cells. Frequencies of frameshift mutations increase as a function of the number of reiterated base pairs at DNA sites [27]. Both the length of a mononucleotide microsatellite and its sequence context influence mutation rate in defective DNA in

mismatch repair (MMR)-deficient cells [28]. Ultraviolet radiation C (UVC) or reactive oxygen species-induced CC to TT tandem mutations is markedly enhanced in MMR-deficient cells. CC to TT tandem mutations in MMR-deficient cells form more readily in a homocytosine run than in a sequence limited to two cytosines [29]. The deletion frequency increases with repeat length, decreases with the distance between repeats [30]. The Y-family DNA polymerase Dpo4 make single-base deletion errors at high frequencies in repetitive sequences, especially those that contain two or more identical pyrimidines with a 5' flanking guanosine [31].

The postreplicative mismatch repair (MMR) system is important for removing mutational intermediates that are generated during DNA replication, especially those that arise as a result of DNA polymerase slippage in simple repeats [32]. Both replication fidelity and MMR are affected by the microsatellite's nucleotide composition [33]. PCNA and RPA suppress large deletion errors by preventing the primer terminus at a repeat from fraying and/or from relocating and annealing to a downstream repeat [34]. DNA polymerase IV uses a template slippage mechanism to create single base deletions on homopolymeric runs [35]. DNA polymerase IV, which creates single-base deletions, prefers to extend slipped DNA substrates with the skipped base at the -4 position [36]. Overexpression of enzymes of the base excision repair pathway is known to increase the frequency of frameshift mutations [37]. Human polymerase kappa uses a classical Streisinger template-slippage mechanism to generate -1 deletions in repetitive sequences, as do the bacterial and archaeal homologues [38, 39]. Frameshift-inducing mutagens can selectively induce mutations in mismatch repair-deficient cells versus mismatch repair-proficient cells. Environmental exposures may, therefore, favor development of cancers with microsatellite instability in tissues like the gut [40]. Cancer-associated mutations in cancer genes constitute a diverse set of mutations associated with the disease.

The Streisinger model [41] is now the best-grounded model of frameshift mutations [42-44] suggesting gaps and DNA strand slippage during synthesis as the causes of mutations. It is shown that deletions formation due to the appearance of template bases looped-out as a bulge [44]. The second model [45, 46] states that certain (-1)-frameshifts are initiated by a nucleotide misincorporation. The model [46] has been confirmed [38, 48, 49]. Functional studies and information on the structures of DNA polymerases allow refinement of Streisinger's original hypothesis and offer possible explanations for why misalignment error rates during DNA synthesis can vary by 10,000-fold, depending on the DNA polymerase and the nucleotide composition, symmetry, and location of the synthesis error [47]. Two distinct mechanisms contribute to slipped misalignments: simple replication misalignment events are sensitive to DNA polymerase III exonuclease, whereas SCE-associated events are sensitive to exonuclease I [43]. It is proposed two mechanisms for palindrome-stimulated spontaneous deletion [50]. It is presented evidence for three mechanisms of RecA-

independent sequence rearrangements: simple replication slippage, sister-chromosome exchange-associated slippage, and single-strand annealing [50]. However, the models [27, 41, 45, 46] fails to explain how *cis-syn* cyclobutane pyrimidine dimers result in frameshift mutations and why these lesions cause nucleotide substitutions in some cases and frameshifts in other ones.

I have attempted to construct a polymerase-tautomeric model for UV-induced mutagenesis [52-73], based on idea by Watson and Crick [74] that changes in tautomeric state are possible for DNA bases. The results of studies on the structure of the active centers polymerases show that the bases in rare tautomeric forms may exist in the active sites of polymerases [75-80]. A mechanism for changes in the tautomeric state of base pairs has been proposed [52, 54, 55, 57, 61, 63-65]. It was assumed that the tautomeric state of the constituent bases may change during the formation of cyclobutane pyrimidine dimers [57, 61, 63, 65]. A mechanism for changes in the tautomeric state of base pairs has been proposed for the case when DNA is UV-irradiated and cyclobutane pyrimidine dimers are formed [61, 63]. Five new rare tautomeric conformations of A:T [61, 63] and G:T [56, 62] base pairs are proposed that are capable of influencing the character of base pairing. The rare tautomeric forms of bases are stable at *cis-syn* cyclobutane pyrimidine dimers formation and in DNA synthesis [63, 65]. The part of *cis-syn* cyclobutane pyrimidine dimers with bases in certain rare tautomeric forms may result in targeted substitution mutations [58, 64, 66]. Three mechanisms for untargeted substitution mutations formation also have been developed [60, 62, 67, 69]. A model was developed for the formation of hot and cold spots of UV-induced mutagenesis [68]. A mechanisms was proposed for targeted insertions [70, 71], targeted complex insertions [73] and targeted deletions (provisional article [72]) caused by *cis-syn* cyclobutane thymine dimers. *Cis-syn* cyclobutane thymine dimers with bases in certain rare tautomeric forms may result in targeted frameshift mutations. A structural analysis showed that none of the canonical nucleotides can be incorporated opposite to these *cis-syn* cyclobutane thymine dimers [70-72]. In this paper a mechanism was proposed for targeted deletions caused by *cis-syn* cyclobutane thymine dimers.

2. Error-prone or SOS DNA Synthesis on a Template Containing *cis-syn* Thymine Dimers

If not removed by the repair mechanisms, cyclobutane pyrimidine dimers may allow targeted mutations to arise during error-prone or SOS synthesis. Incorrect bases can be inserted when DNA containing cyclobutane pyrimidine dimers acts as the template for error-prone or SOS-replication, repair, or transcription [81-84]. The mutations that result from these incorrect bases are often targeted; that is, they occur at the same position as the cyclobutane pyrimidine dimers [9, 10, 13]. Mutations arise when

modified [85] or specialized [86-97] DNA polymerases are involved in DNA synthesis.

Modified or specialized DNA polymerases incorporate canonical bases capable of forming hydrogen bonds with dimerized bases in template DNA [64]. Error-prone DNA synthesis proceeds the same way as error-free synthesis. When a canonical nucleotide cannot be added opposite to a cyclobutane pyrimidine dimer so that the opposite bases are hydrogen bonded, specialized or modified DNA polymerases leave a one-nucleotide gap. For instance, this is the case when an abasic site occurs in the template, leading to one-nucleotide deletion [25].

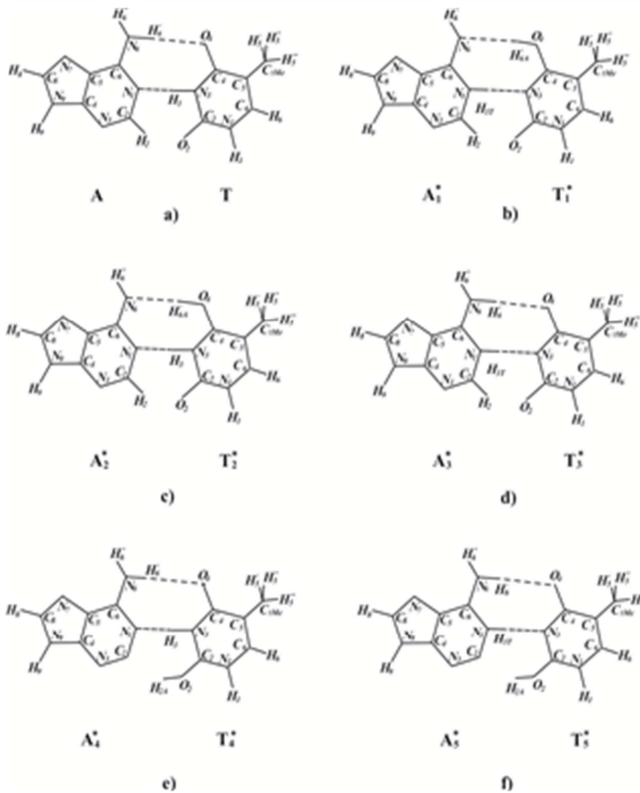


Fig. 1. Rare tautomeric states of thymine and adenine. (a) Watson-Crick pair A-T and (b-h) rare tautomeric states possible for thymine and adenine upon UV irradiation of DNA.

Frameshift mutations most commonly arise in DNA sites with a homogenous nucleotide composition, such as monotonous runs of G-C or A-T pairs. Five rare tautomeric forms are possible for thymine (Fig. 1) [63]. The forms are stable when the respective bases are involved in cyclobutane thymine dimers [63, 64]. This is because the DNA strand bends once pyrimidine dimers arise, and the hydrogen bonds between the bases are broken between the bases that neighbor the cyclobutane pyrimidine dimers [4, 98-101]. Consider a DNA site with a homogenous nucleotide composition wherein one strand contains *cis-syn* cyclobutane dimers TT₂* (Fig. 1). One base of the dimer is a canonical thymine (T), and the other is the rare tautomeric form T₂* (Fig. 2a). The question is how deletions of one or more nucleotides can form in this case. Let us the site is replicated by error-free DNA polymerases. In result a post replicate gap may appear

opposite cyclobutane dimers (Fig. 2b). Let us the post replicate gap is replicated by specialized or modified DNA polymerases in result error-prone or SOS synthesis.

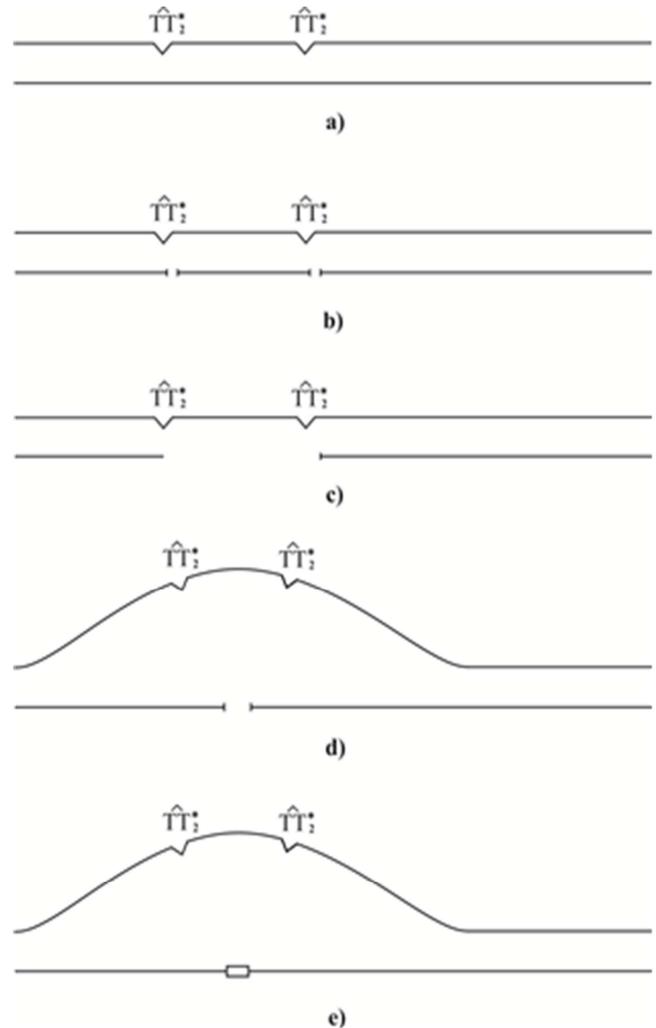


Fig. 2. Generation of a targeted deletion of several nucleotides. a) A DNA site contains the *cis-syn* cyclobutane thymine dimers TT₂*; b) a post replicative gap arises opposite to *cis-syn* cyclobutane dimers TT₂*; c) post replicative gap is filled using modified or specialized DNA polymerases. One-nucleotide gaps arise opposite to the *cis-syn* cyclobutane thymine dimers TT₂*; d) site of the DNA strand is lost; e) a loop forms; f) the gap is filled. An insertion of several nucleotides formed, but smaller than the fallen DNA site. A targeted deletion of several nucleotides is formed.

A structural analysis is performed for the incorporation of DNA nucleotides opposite to T₂* (Fig. 3b) to identify the canonical nucleotides that can be inserted opposite to T₂* to allow hydrogen bonding of the two bases. Canonical thymine cannot be inserted opposite to T₂* by DNA polymerase because of repulsion between the hydrogen H₃ of the canonical thymine and H₃ of T₂* (Fig. 3c). Adenine cannot be inserted because of repulsion between H'₆ of adenine and H'_{6A} of T₂* (Fig. 3d). Cytosine incorporation is prevented by repulsion between H'₄ of cytosine and H'_{6A} of T₂* (Fig. 3e), and guanine incorporation is prevented by repulsion between H'₁ of guanine and H₃ of T₂* (Fig. 3f). That is, none of the canonical bases can be incorporated opposite to T₂*.

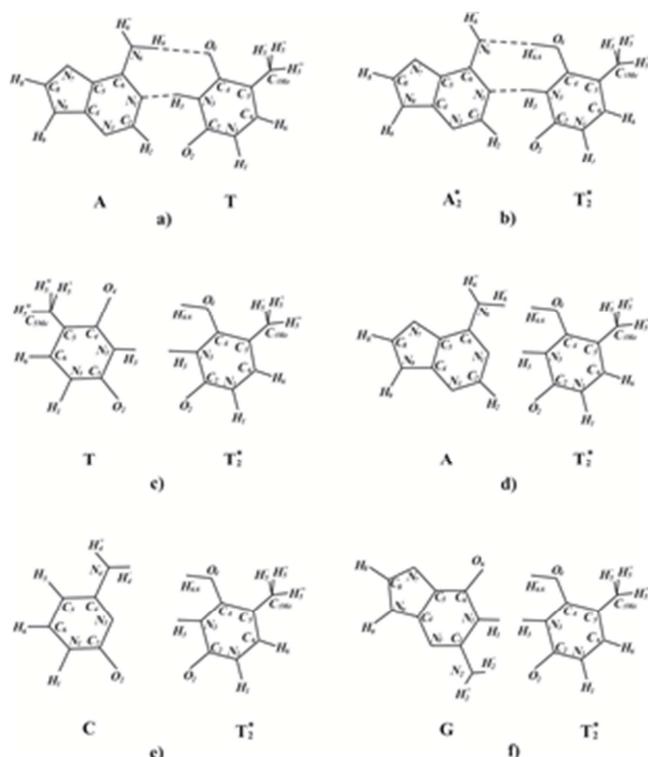


Fig. 3. Possible base pairs formed between thymine in rare tautomeric conformations T_2^* and bases in canonical tautomeric conformations. (a) A:T canonical pair; (b) $A_2^*:T_2^*$ pair, wherein the bases are in the rare tautomeric state; (c) T_2^* and thymine; (d) T_2^* and adenine; (e) T_2^* and cytosine; (f) T_2^* and guanine.

A one-nucleotide gap arises opposite to a *cis-syn* cyclobutane dimer TT_2^* (Fig. 2b) as a result of translesion synthesis driven by modified *E. coli* DNA polymerase III or mammalian DNA polymerase δ or ϵ or specialized (mammalian Pol η or Pol ζ or *E. coli* DNA polymerase IV or V) DNA polymerases. As was demonstrated experimentally, such a gap arises during DNA synthesis when the template contains an abasic site, leading to a one-nucleotide deletion [25]. The site in nascent DNA strand may be lost (Fig. 2c) because a bend forms in the site containing cyclobutane pyrimidine dimers and the hydrogen bonds between the bases are broken [4, 98-101]. A DNA site containing the *cis-syn* cyclobutane dimers TT_2^* , may form a loop as shown in Figure 2e. The resulting smaller gap is usually filled in by constitutive DNA polymerases (Fig. 2f), leading to the precipitation of several bases (deletion formation).

One nucleotide deletions appear most often. In this case, one nucleotide falls. This deletion may cause a one *cis-syn* cyclobutane dimer TT_2^* (Fig. 4). A one-nucleotide gap arises opposite to a *cis-syn* cyclobutane dimer TT_2^* (Fig. 4b) as a result of translesion synthesis. DNA strand containing *cis-syn* cyclobutane dimer TT_2^* may form a small loop (Fig. 4c). In this case, the DNA site containing the gap is shifted by one nucleotide and DNA strand is connected to a new place (Fig. 4c). This is possible because the frameshift mutations are formed on homogeneous site of the DNA, in this case, consisting only of thymine molecules.

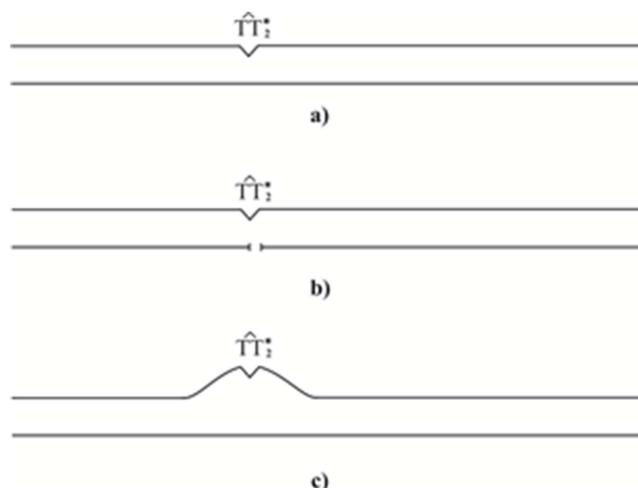


Fig. 4. Generation of a one-nucleotide targeted deletion. (a) A DNA site contains the *cis-syn* cyclobutane thymine dimer TT_2^* ; (b) one-nucleotide gaps arise opposite to the *cis-syn* cyclobutane thymine dimer TT_2^* ; (c) DNA strand containing *cis-syn* cyclobutane dimer TT_2^* forms a small loop. The DNA site containing the gap is shifted by one nucleotide. A one-nucleotide targeted deletion is formed.

Thus, *cis-syn* cyclobutane thymine dimers wherein one or both of the bases occur in the rare tautomeric states that prevent their hydrogen bonding with canonical DNA bases are a possible source of frameshift mutations and, in particular, deletions. The above mechanisms of deletions formation agree with the models [27, 41, 45, 46].

3. Conclusion

To further develop the polymerase-tautomeric model of UV-induced mutagenesis, a mechanism was proposed for targeted deletions (frameshift mutations) caused by *cis-syn* cyclobutane thymine dimers. A structural analysis showed that none of the canonical nucleotides can be incorporated opposite to a *cis-syn* cyclobutane thymine dimer TT_2^* with formation of hydrogen bonds between the T_2^* bases of the template DNA and the inserted canonical bases. The analysis is based on the fact that the canonical bases capable of hydrogen bonding with template DNA bases are incorporated opposite to cyclobutane dimers by specialized or modified DNA polymerases during DNA synthesis [63]. Double-stranded DNA synthesis was considered for the case where one of the strands contains *cis-syn* cyclobutane thymine dimers wherein one or both of the bases occur in the rare tautomeric state T_2^* . When modified or specialized DNA polymerases drive the synthesis, a one-nucleotide gap can arise opposite to a *cis-syn* cyclobutane thymine dimer containing T_2^* . The DNA strand is bent and H-bonds between the bases are broken [4, 98-101]. Therefore, the DNA site opposite of the *cis-syn* cyclobutane dimers TT_2^* be lost. The DNA site containing the *cis-syn* cyclobutane dimers TT_2^* , may form a loop. A daughter strand becomes shorter. As a result, several DNA nucleotides fall and a deletion is formed. One *cis-syn* cyclobutane dimer TT_2^* may result in one-nucleotide deletion. A one-nucleotide gap can arise opposite to a *cis-syn* cyclobutane thymine dimer TT_2^* . The DNA site

containing one *cis-syn* cyclobutane dimer TT₂*, may form a small loop. A daughter strand shift on one nucleotide and one-nucleotide deletion is formed.

According to the polymerase-tautomeric model of ultraviolet mutagenesis *cis-syn* cyclobutane thymine dimers wherein a thymine is in the canonical tautomeric forms do not result in mutations [63]. *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric form T₂* may result in targeted frameshift mutations (targeted insertions and targeted deletions) [69-71]. *Cis-syn* cyclobutane thymine dimers wherein a thymine is in the rare tautomeric forms T₁*, T₄*, or T₅* were shown to cause only targeted base substitution mutations [63]. I propose the mechanisms of targeted insertions formation during error-prone or SOS synthesis of DNA containing *cis-syn* cyclobutane thymine [69] and cytosine [70] dimers. Therefore, the *cis-syn* cyclobutane thymine dimers that contain the rare tautomeric form T₂* were demonstrated to cause targeted frameshift mutations. Thus, different targeted mutations, including both nucleotide substitutions and frameshifts, can be explained in the context of the polymerase-tautomeric model of UV-induced mutagenesis. In addition, the model is able to explain nature and mechanisms formation of targeted complex ultraviolet mutations [72], mechanisms of hot and cold spots formation [67] and mechanisms of untargeted base substitution mutations formation [68].

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