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Journal

Journal of the American Chemical Society, 147(24)

ISSN

0002-7863

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Publication Date

2025-06-18

DOI

10.1021/jacs.5c02209

Peer reviewed

Topochemical Synthesis, *micro*-Electron Diffraction (3D ED), and Electron Beam-Initiated Topotactic Dimer Splitting of *cis,syn*-Thymine Dimer Crystals

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KEYWORDS *Thymine-dimer, Nanocrystalline suspension, Photodimerization, Crystal, Micro-electron diffraction.*

ABSTRACT: A solid-state photochemical reaction of crystalline thymine hydrate (**TH**) resulted in a clean topochemical transformation into the *cis,syn*-dimer (**TD**), matching the structure as the one responsible for most UV-lesions in DNA. Microcrystals of **TD** grown by drop casting piperidine solutions in a TEM grid made it possible to determine their structure by micro-electron diffraction (3D ED) and to confirm expectations that an *in-situ* electron-beam ionization reaction could result in a topotactic dimer splitting that, in this case, retains single crystal-to-single crystal character up to ca. 30% conversion. The packing structure of dimer **TD** and the as formed monomer **T** display a novel trimeric hydrogen bonding motif, and the latter represents a new crystal phase. Beyond interesting analogies between single crystals of **T** and **TD**, and DNA, such as templated dimer formation and electron-transfer induced repair, this work is a rare example of an electron beam-induced chemical reaction in the crystalline solid state.

Introduction

The exposure of living tissue to ultraviolet (UV) radiation from the sun results in DNA lesions that inhibit replication and may cause to mutations leading to skin cancer.^{1,2,3} As illustrated in Figures 1a/1b, the most common lesions occur via the [2+2] photocycloaddition of neighboring thymines (**T**), which are templated by the double helix to form cyclobutane *cis,syn*-thymine dimers (**TD**). Dimerization leads to structural changes that stall RNA polymerase, and cause misreading of the genetic code.^{4,5,6} Fortunately, most **TD** formed *in vivo* are repaired within minutes through a visible light, electron transfer-mediated reaction carried out by the enzyme photolyase that splits the dimer back to the monomer.^{7,8} Substantial interest in this reaction has led to studies documenting light-initiated, and high energy radiation,⁸ reductive and oxidative electron transfer **TD** splitting (shown by an “e⁻” in Figures 1b/c), both in model systems and in DNA.^{6,9}

Our recent discovery of an efficient electron-transfer chain reaction in crystals of a Dewar benzene exposed to the high energy electrons of an electron microscope¹⁰ motivated us to explore the beam splitting of thymine dimer crystals. We set out to accomplish three goals: (1) to investigate a large scale topochemical synthesis of *cis,syn* **TD**, (2) to determine its elusive crystal structure, and (3) to explore the potential of *in situ* dimer splitting via a radical-ion reaction in **TD** crystals using the beam of an electron microscope¹¹ (Figure 1c).

Results and Discussion

As it pertains to the topochemical synthesis of **TD**, out of three

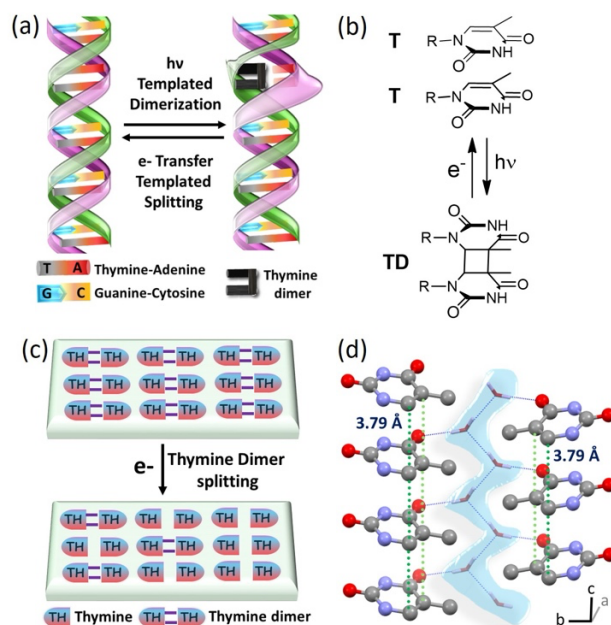


Figure 1. (a) Representation of DNA damage and repair process. (b) Chemical structures of thymine **T** and the *cis,syn*-thymine dimer **TD** and their interconversion by UV-irradiation and e-transfer reactions. (c) Hypothetical single crystal of dimer **TD** reacting back to monomer upon exposure to the electron beam of an electron microscope. (d) Packing arrangement of thymine hydrate (**TH**) crystals illustrating a topochemically favorable T...T alignment.

known crystal structures (SI section 1.1) only thymine hydrate **TH**,¹² in the space group $P2_1/c$, seemed promising.^{13,14,15} Crystals of **TH** have been widely studied in the context of crystal hydration and dehydration properties and dynamics.^{13,14} The hydrate displays a molecular packing with adjacent **T** molecules held together by $C=O \cdots H-O$ hydrogen bonding (H-bonding) interactions between carbonyl groups in **T** and H_2O (Figure 1d). The stoichiometry departs from $T:H_2O = 1:1$ to $1:0.8$. The thymine $-C=C-$ bonds are parallel to each other with a center-to-center distance of 3.79 Å, favorably disposed for a topochemical reaction to the DNA-relevant *cis-syn-TD* isomer (Figure 1b). Interestingly, previous synthesis of *cis-syn-TD* reported involve photoirradiation of frozen aqueous solutions, suggesting their formation in **TH** nanocrystals.^{16,17,18,19}

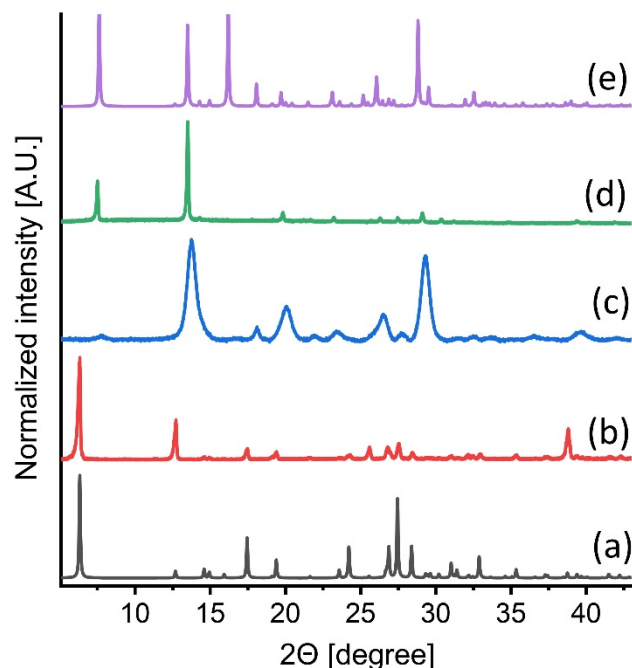


Figure 2. (a) Simulated PXRD pattern from the crystal structure of **TH** at 298K. (b) Experimental PXRD of **TH** prepared in this work. (c) Experimental PXRD of **TD** prepared by irradiation of **TH**. (d) Experimental PXRD of **TD** recrystallized from piperidine, and (e) simulated PXRD pattern from the 3D ED structure of **TD**.

To complete our first goal, we scaled up the crystallization of **TH** in a reproducible manner by flash cooling in an ice bath for 15 min a hot supersaturated solution of **T** (SI section 1.2). This resulted in precipitation of very fine plates with the PXRD of the desired **TH** phase, albeit displaying preferential alignment (Figure 2a,b). While dry **TH** samples were stable when kept at ambient temperature, the wet **TH** phase had a tendency to transform into the anhydrous **T** phase when allowed to reach ambient temperature. To avoid that, samples were dried at low temperature under high vacuum after most of the cold water had been removed.²⁰ A water content of ca. 6.7% w/w obtained by TGA (Figure S5) is lower than the expected value of 10.2% for the known 0.8 hydrate, suggesting that the flash cooling method leads to the formation of the same phase, but with a lower water content of ca. 0.5. Small scale photochemical experiments (~10 mg) with dry polycrystalline **TH** between two borosilicate glass slides led to 82% conversion to the desired dimer **TD** after ~34

h (SI section 1.5). Scale up and optimization of the topochemical synthesis of **TD** was accomplished by taking advantage of nanocrystalline suspensions^{21,22} using a top-down approach, by suspending finely ground **TH** crystals in hexane, which was selected as a non-solvent (SI.6.1 and 1.6.2). A photoreaction conducted with 80 mg of **TH** in 80 ml hexane yielded 89% of the pure dimer after 18.5 h of irradiation, a substantial improvement when compared to results obtained with dry powders (SI section 1.6.3 and 1.6.4). A yield lower than 100% is determined by statistical factors resulting from dimerization occurring along either direction of the 1D chain, such that some isolated monomers are randomly left between newly formed dimers.²³ Nanocrystals allow for uniform irradiation of suspended crystallites as compared to the one-sided illumination and light blockage that occurs when crystallites are piled together in static powder bed. A control experiment with the anhydrous $P2_1/c$ polymorph showed no photoreaction after prolonged irradiation.

Pure **TD** samples obtained by washing the filtered solid with MeOH (SI section 1.7) showed no weight loss below 300 °C by TGA, indicating water loss during the reaction (SI section 1.8). PXRD analysis of “as synthesized” **TD** showed broad signals (Figure 2c) consistent with crystals calculated with the Scherrer equation to have a very small domain size (~10-12 nm). Recrystallization *via* slow evaporation in various organic solvents was not effective due to the poor solubility of the dimer. Small and low-quality irregular **TD** crystals of few μm in size precluded the use of single crystal X-ray diffraction (SC-XRD) for structure determination. As we turned our attention to the use of 3D micro-electron diffraction (3D ED), we obtained no useful data from the “as formed” and recrystallized **TD** microcrystalline specimens. Eventually, we were able to obtain regular, needle-shaped crystals (Figure 3a, b) by drop casting a diluted piperidine solution of **TD** directly onto the TEM grid. Analysis of these **TD** microcrystals by PXRD (Figure 2d) suggested that the same crystalline phase as the “as-formed” ones (Figure 2c). Also shown in Figure 2e is a PXRD simulated from the 3D ED structure of **TD** described below. Differences between Figures 2d and 2e are in part related to preferential alignment in the macroscopic sample, and to the predicted presence of monomer formed in a topotactic reaction that occurs upon e-beam exposure.

The 3D ED data were collected on a TF Spectra 300C TEM and reduced in CrysAlisPro/PETS2 software suit.^{24,25} The final structure was determined using ShelX software package in Olex2 for kinematical refinement^{26,27} and in Jana2020 for dynamical refinement.²⁸ The detailed procedure is described in the SI. Our initial data collection revealed a dynamic diffraction pattern that evolve as a function of exposure to the electron beam. At early times we observed a diffraction pattern transformation with a four-fold reduction of the unit cell along the *a* cell constant followed by the appearance of diffuse scattering. This can be seen in supplementary video SVID1 recorded at ambient temperature with supercell reflections along *a** gradually disappearing after few seconds of electron beam exposure. These changes are related to the ionization-induced dissociation of **TD**, as supported by chemical analysis of polycrystalline samples exposed to the electron beam that react to completion (see below) and a structure determination with ca. 30% of monomer **T** obtained from the topotactic splitting of **TD**. Data collection was performed as fast as possible to reduce the total number of electrons deposited onto the crystal and the ensuing reaction, while retaining useful diffraction peaks intensities.

Moreover, the beam position was scanned along the long axis of the needle-shaped crystals, which is also the axis of rotation for 3D ED data collection. This allowed to collect from non-reacted parts of the same crystal and further limit the extent of **TD** splitting. To increase the intensities of reflections and slow down the reaction, measurements were performed at 100 K. This strategy was successful, and meaningful data were obtained for a supercell determination, as shown in the *h*01 section reconstruction in Figure 3c. Reflections such as the one shown in cyan, corresponding to the original supercell, decreased in intensity relative to those corresponding to the reduced product cell, which are illustrated in magenta.

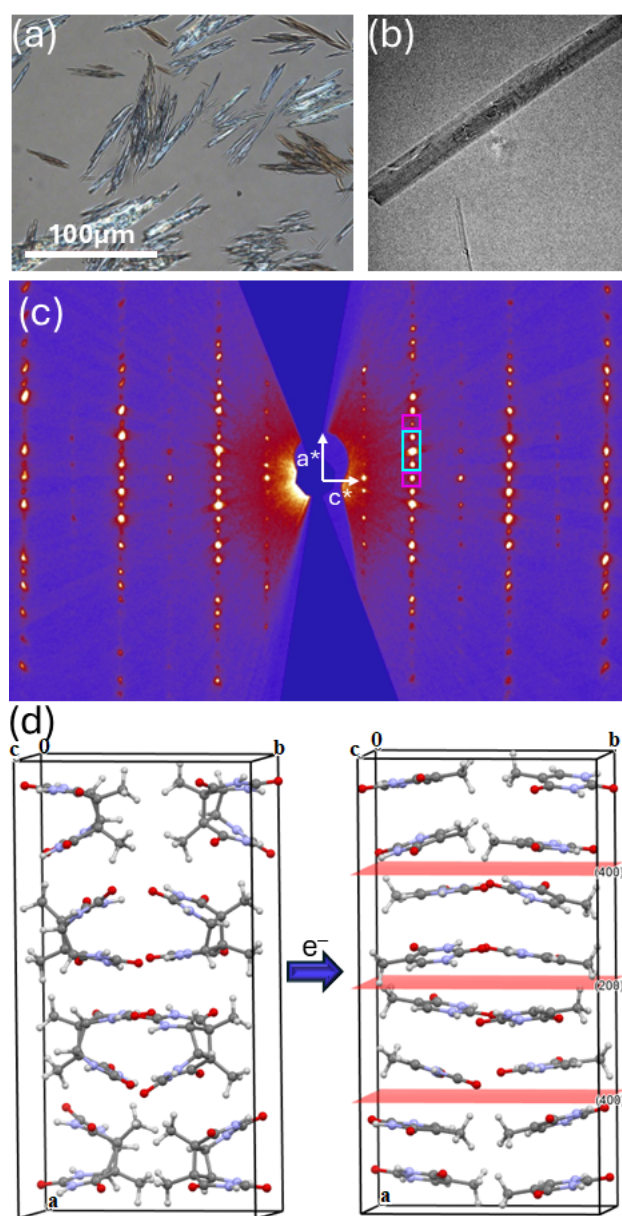


Fig. 3. (a) Optical and (b) TEM images of **TD** crystals obtained from piperidine, (c) The *h*01 section reconstruction of **TD** diffraction pattern from 3D ED with supercell (cyan) and reduced cell (magenta) reflections indicated, and (d) visualization of the real space transformation corresponding to the diffraction pattern transformation induced by electrons. The unit cell on the left correspond

to the ideal pure dimer and the one on the right to the ideal pure monomer.

The crystal structure of **TD** was determined in the space group *Pccn* with ca. 30% of the dimer randomly substituted by two thymine monomers, presumably formed by the effects of the e-beam. A representation of the dimer and monomer structures in the lattice is illustrated in Figure 4a. While extended e-beam exposure resulted in a relatively rapid evolution and subsequent deterioration of the diffraction pattern prevented characterization of the product to conversions beyond ca. 30%, ¹H NMR analysis of polycrystalline samples exposed to the electron beam confirmed a very clean chemical reaction with 100% monomer formation.

We conclude that thymine dimers undergo a topotactic, ionization-induced splitting reaction with a single crystal-to-single crystal transformation limited to ca. 30% with a reconstructive phase transition likely to occur at higher monomer accumulation values.

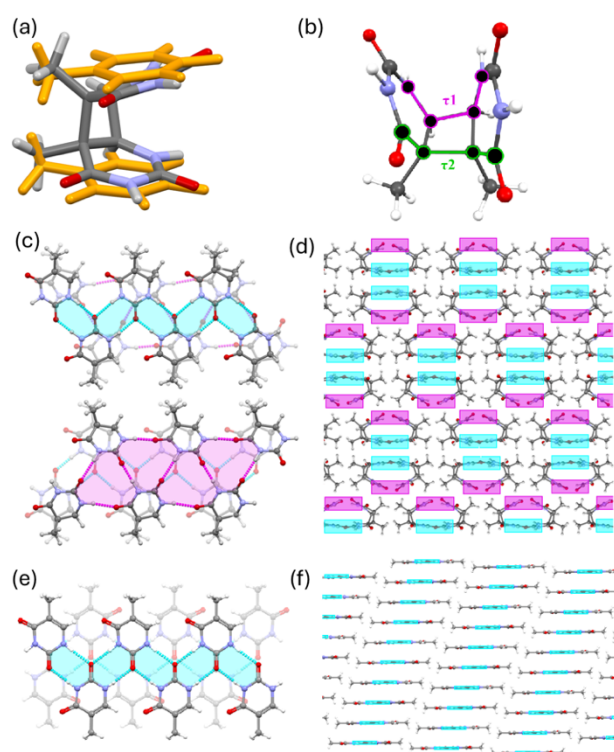


Figure 4. (a) Asymmetric unit of **TD** with ca. 30% of dimers split into monomers (orange). (b) Structure of **TD** with torsion angles τ_1 and τ_2 highlighting a deviation from internal mirror symmetry. (c) H-bond network in **TD** (cis, syn) forming dimeric zigzag (cyan) and trimeric (magenta) supramolecular units formed by N-H...O H-bonds; (d) H-bonding layer arrangement as viewed along the (001) plane, and (e, f) analogous representations for a crystal structure of thymine.¹³

In order to facilitate a description of the crystal structure and the electron beam-induced splitting one can visualize hypothetical structures of the pure dimer and monomer, as illustrated by unit cells represented, respectively, on the left side and right side of Figure 3d. The cis,syn-**TD** molecular structure lacks internal mirror symmetry (Figure 4b) as the steric repulsion between the two thymine rings leads to cyclobutane ring puckering. Torsion

angles τ_1 and τ_2 between the two thymine rings (Figure 4b) deviate from ideal parallel alignment values, $\tau_1 = \tau_2 = 0^\circ$, to of $\tau_1 = 16.09^\circ$ and $\tau_2 = 19.68^\circ$, indicating significant twisting. The deviation of atoms in the three rings from the best-fit for each plane gives rmsd value $s_1 = 0.117 \text{ \AA}$ for the puckered cyclobutene and $s_{2A} = 0.092 \text{ \AA}$ and $s_{2B} = 0.071 \text{ \AA}$ for each of the two thymines. By comparison, $s_1 = 0 \text{ \AA}$ and $s_{2A} = s_{2B} = 0.038 \text{ \AA}$ for the strain-free trans,anti-**TD** crystal structure (Table S4). The molecular geometry of cis,syn-**TD** and of those determined for several substituted **TD** derivatives are discussed in page S18.

At the supramolecular level, the two halves of the two dimers are engaged in self-complementary H-bonding interactions to form a supramolecular capsule. The half shown in cyan color in Figure 4c engages one of its two carbonyls in a bifurcated H-bonding to form edge-sharing 8-membered rings with amide N-H donors from two molecules on the opposite chain. This arrangement results in co-planar zig-zag ribbons on the *bc*-plane with the free carbonyls adopting a polar orientation, all pointing to the left for the layer in Figure 4c. The other half of the dimers, shown in magenta color, use both carbonyl acceptors and assemble into trimeric 12-membered rings forming supramolecular ribbons that deviate substantially from planarity (not shown). Each thymine is engaged in two N-H $\cdots$ O=C H-bond with molecules in the opposite chain, and the third one with a neighbor in the same chain. Figure 4d shows H-bonding layers on the *bc* plane stacked along the *a* direction with two the dimeric zig-zag cyan ribbons enclosed between two trimeric magenta ribbons.

Structural 3D ED data reveal that the e-beam splitting reaction occurs in a topotactic manner, such that thymine monomers retain their original position in the H-bonding ribbons as they occur in the dimer. Diffraction changes as a function of reaction include a decrease in the unit cell *a*-constant by a factor of four, as suggested by the horizontal lines going from cyan to magenta in Figure 3d. The thymine packing formed in this reaction suggest the potential formation of new metastable phases characterized by an unprecedented hydrogen bonding structures with two different types of H-bonding ribbons, either zigzag (cyan) or trimeric (magenta). In fact, recent computational and experimental studies highlight the potential formation of various polytypic and disordered **T** phases based on zig-zag H-bonding ribbons that differ by the relative orientation of the free carbonyls along the ribbon axis and in ribbons occupying different layers. These features occur in the two known thymine crystals, which have the free carbonyls on the two chains pointing in same¹³ or opposite directions²⁹ along the ribbon axis. Notably, while the H-bonding ribbons that occur in the ideal “as-formed” thymine are polar, and analogous to one of the known **T** polymorphs, the new structure cannot be transformed to the known crystal phase by in-plane rotation of the trimeric magenta ribbons to the more common zig-zag cyan ribbons. In fact, the **T** polymorphs pack in layers of ribbon with alternating polarity while the ideal, as formed **T** has a repeat pattern that alternates polarity every two layers.

Conclusions

Topotactic photochemical reaction of the crystalline thymine hydrate **TH** greatly facilitated the formation of the cis-syn-dimer **TD**, and the use of 3D ED enabled the acquisition of its crystal structure to confirm an expected and remarkably clean e-beam ionization reaction. Studies in progress are aimed at a

detailed analysis of the reaction mechanism, including the possibility of a radical-ion chain reaction.¹⁰

Materials and Methods

TH was prepared with commercially purchased **T** without further purification using deionized water. Nanocrystalline suspensions of **TH** were prepared *via* top-down approach by suspending hand-ground **TH** crystals into hexane. Photoirradiation of **TH** to form **TD** was carried out using 450 W medium pressure mercury lamp. Borosilicate glassware ($\lambda > 290\text{nm}$) were used for photoirradiation studies. All the structural characterizations of **TH** and **TD** were carried out at room temperature using Bruker Avance (400 MHz) NMR spectrometer, Perkin Elmer® infrared spectrometer equipped with universal ATR sampling accessory. Solid samples were analyzed using a Cu-K α 1 radiation (1.5406 Å) powder X-ray diffractometer and a Perkin Elmer TGA8000 thermogravimetric analyzer (heating rate 5 °C/min, nitrogen flow 20.0 mL/min). The 3D ED data were collected on a TF Spectra 300C TEM with Ceta-D camera.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <http://pubs.acs.org>.

Experimental and computational details; characterization data; spectroscopic data (NMR and IR); PXRD and 3D ED refinement details (PDF).

Supplementary video SVID1 (MP4) illustrating the time evolution of the diffraction pattern.

Accession Codes

CCDC 2417033 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

ACKNOWLEDGMENT

We thank the National Science Foundation for support of this work through grants CHE-2154210 and BioPACIFIC Materials Innovation Platform Award No. DMR-1933487 for instrumentation support.

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Table of contents graphic:

