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Conformationally Gated Charge Transfer in DNA Three-Way Junctions

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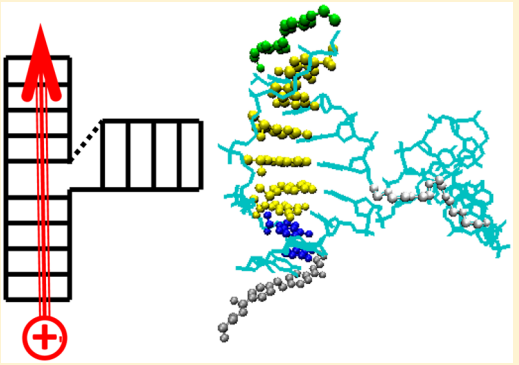
Supporting Information

ABSTRACT: Molecular structures that direct charge transport in two or three dimensions possess some of the essential functionality of electrical switches and gates. We use theory, modeling, and simulation to explore the conformational dynamics of DNA three-way junctions (TWJs) that may control the flow of charge through these structures. Molecular dynamics simulations and quantum calculations indicate that DNA TWJs undergo dynamic interconversion among "well stacked" conformations on the time scale of nanoseconds, a feature that makes the junctions very different from linear DNA duplexes. The studies further indicate that this conformational gating would control charge flow through these TWJs, distinguishing them from conventional (larger size scale) gated devices. Simulations also find that structures with polyethylene glycol linking groups ("extenders") lock conformations that favor CT for 25 ns or more. The simulations explain the kinetics observed experimentally in TWJs and rationalize their transport properties compared with double-stranded DNA.



DNA is a target for studying charge transport in self-assembled organic structures.[1−3] To explore DNA constructs that are evocative of the kinds of functionality present in conventional electronics,[4−6] the examination of junction structures is essential. DNA three-way junctions (TWJs),[5,7−15] G4 junctions,[4,16−18] and double-crossover assemblies[14,18] are thus promising candidates. Long-distance radical cation migration[9] and Förster resonance energy transfer[8] in DNA TWJs have been examined previously; however, little is known regarding the nature of charge transport in structures with the kinds of large-amplitude structural fluctuations present in these TWJs.

Lewis, Wasielewski, and coworkers recently found that charge migrates through the DNA TWJs shown in Figure 1.[19] For distances of ∼10 bases, hopping among purines is believed to dominate the charge transfer (CT).[12,15,20−25] Thus, purine networks are appealing frameworks for splitter/combiner designs. Charge separation dynamics and quantum yields were measured using transient absorption spectroscopy for structures **1a**, **1b**, **1c**, and **1d** shown in Figure 1 (see ref 19 and Supporting Information (SI)). The quantum yields for these DNA TWJs are relatively low compared with the yields in double-stranded DNA with similar sequences and donor−acceptor distances, while the charge-transfer times are of the same order of magnitude for both systems. Importantly, CT is not complete in the 7 ns measurement window for TWJ **1c** and **1d**, and the hole-trapping kinetics are well-fit using a zero-order kinetic scheme, suggesting that CT may be gated by conformational changes.[19]

Assuming a hopping mechanism,[20,22,24,25] the CT rate is proportional to the square of the electronic coupling between hopping sites. In the DNA TWJs, the nearest-neighbor electronic couplings within the same branch are found in

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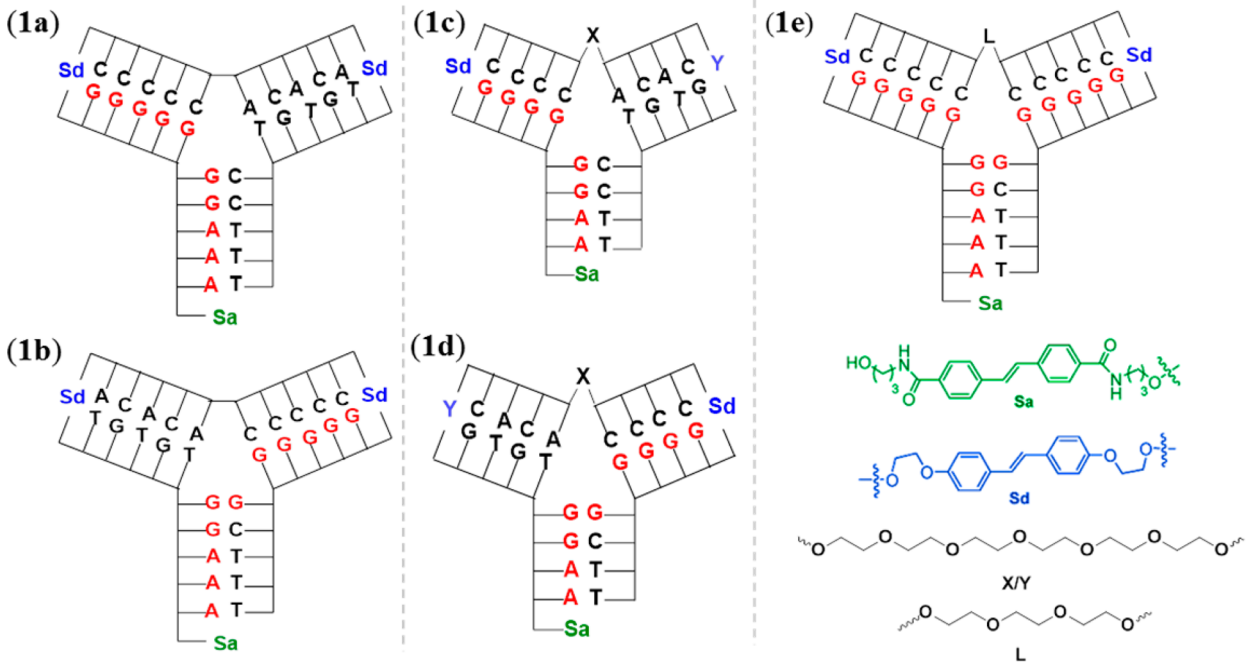

Figure 1. Structures of DNA TWJs. (**1a**,**1b**) DNA TWJs with one extended guanine pathway and no polyethylene glycol (PEG) linking group. (**1c**,**1d**) DNA TWJs with one extended guanine pathway with one PEG linking group. (**1e**) A proposed DNA TWJ with guanine pathways on all three arms that may serve as a charge splitter/combiner. Structures **1a**, **1b**, **1c**, and **1d** adapted from ref 19 were studied experimentally.

simulations to be as strong as ∼0.08 eV, similar to values in B-DNA;[26,27] however, these couplings between bases in different branches ("cross-junction" couplings) depend on the structure of the junction. Thus, the bottleneck for CT in DNA TWJs may involve charge hopping through the junction gated by conformational changes. The aim of our study is to explore this hypothesis.

We used molecular dynamics (MD) simulations to model the structural fluctuations of DNA TWJs. The junctions are found in simulations to undergo large-scale conformational changes on the nanosecond time scale. The simulations indicate that two of the three DNA strands can form a B-DNA like stack, while the third branch can adopt a position nearly perpendicular to the stack, thus forming a "T" shaped structure; see Figure 2. Conformational switching among "T" structures

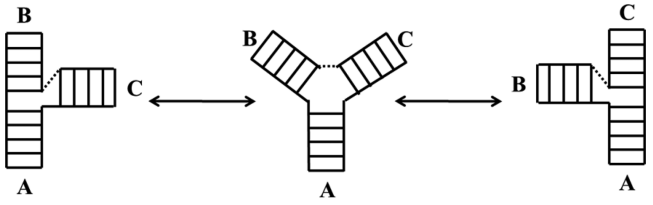

Figure 2. Illustration of conformational switching between "T" and "Y" forms. The dotted lines represent PEG linkers.

may thus gate charge flow through the junctions. Structures with polyethylene glycol (PEG) linkers are found to remain in the "T" shape geometries as long as 25 ns. We examined the electronic properties of the different conformations and found that B-DNA-like stacks have interbranch couplings that are enhanced by several orders of magnitude compared with the disrupted stacks. These findings indicate that charge flow through the DNA TWJ will likely be gated by conformational changes.

Methods. The DNA three-way junction structures (Figure 1) were constructed by combining 3 B-DNA segments generated from x3DNA,[25] and the PEG linker was added to structures **1c**, **1d**, and **1e**. The conformational ensembles were generated with extended MD simulations (up to 25 ns) using the NAMD program[28] with the CHARMM[13] force field. Electronic structure calculations were performed on the MD snapshots using a semiempirical INDO/s method.[6] The electronic couplings between sites were computed with a block-diagonalization method.[10,24] Further details appear in the SI.

Results and Discussion. The experiments of Lewis, Wasielewski, and coworkers find that the CT kinetics across the TWJ are very different for junctions with and without PEG linkers. Without PEG, the CT experiment is challenging to reproduce. With PEG linkers present, the CT kinetics is very similar to that found in duplex DNA with similar sequences (shown in Figure S3 in the SI). Our simulations indicate that the difference in the CT behavior in the two classes of structures arises from the distinctive conformational fluctuations displayed in TWJs with and without the PEG linkers. Moreover, TWJs with PEG are able to stay in a CT-active "T" form for tens of nanoseconds, making the CT in these stacked structures during the lifetimes of the stacked geometry very similar to CT in duplex DNA.

DNA TWJ without a Linking Group: Rapid Switching between Conformations. In structure **1a** (no PEG), the purine pathway was designed to direct charge into the upper-left branch. In contrast, structure **1b** uses a G-G mismatch at the junction that was intended to direct charge onto the upper-right branch. In the MD simulations of **1a** and **1b**, significant conformational changes were observed on the nanosecond time scale, as indicated in Figure 3 and Movie 1. In some trajectories, three arms of the TWJ fluctuate out of the plane and later return to the plane.[9]

In structure **1a**, the computed coupling between the two guanines at the junction is enhanced by one order of magnitude when a T conformation forms. The steric repulsion at the

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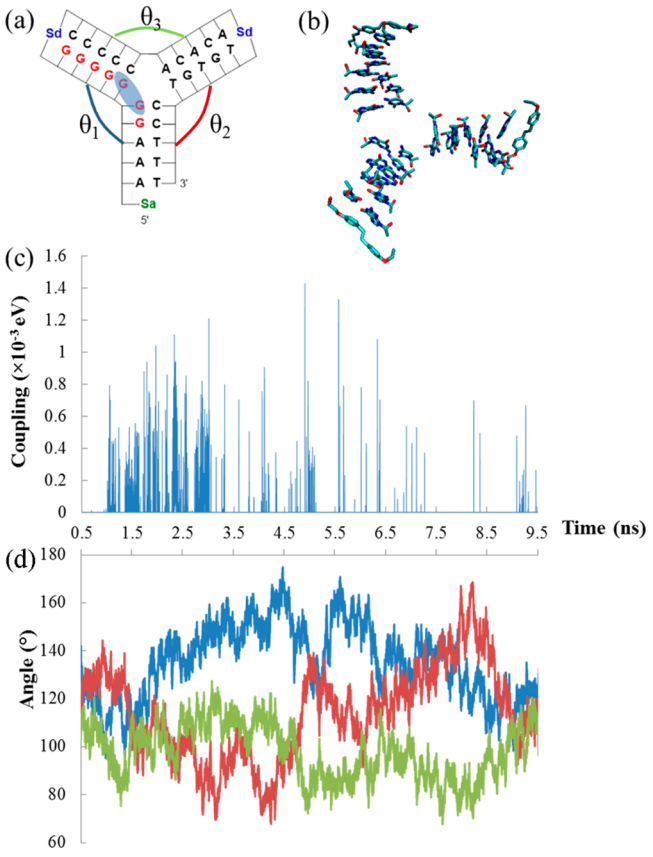

Figure 3. (a) Structure of a DNA TWJ (**1a**). (b) Typical snapshot of a T-shape conformation. Backbones, linking group, and hydrogens are removed for clarity. (c) Coupling between Gs at the junctions (shown in blue oval in panel a). Once the π-stacked geometries form, the cross-junction coupling is enhanced. (d) Time evolution of the angles between the three DNA branches is shown with colors as in panel a.

junction prohibits the angle between arms from reaching 180°; however, in the T conformation, the "cross-junction" coupling is three orders of magnitude weaker than nearest-neighbor couplings in well-stacked B-DNA.

In structure **1b**, we found conformational changes around T-like structures, similar to those found in structure **1a**. The G−G mismatch base pair is found to disconnect and reform on the nanosecond time scale in some of the simulations. When the guanines are not hydrogen-bonded, they sometimes form a zipper-like[23] G−G stacking pattern that enhances interactions between the two branches to create a CT pathway (Figures S1 and S2 in the SI).

The DNA TWJs simulated here reveal the dynamical nature of their base stacking. Indeed, the experimental kinetic measurements find that CT rates in **1a** and **1b** do not follow simple kinetics (in contrast with B-DNA linked species) and are difficult to reproduce (see Figure S3 in the SI). To stabilize base stacking and to increase electronic coupling, a PEG linker was embedded in the second generation of TWJ structures. The kinetics of charge transfer in these PEG-linked structures is reported in ref 19, and the simulations of these structures are reported later.

DNA TWJ with a Linker: Stabilizing "T" Conformations. Simulations of DNA TWJ structures with a PEG linking group (Figure 1c,d) indicate that both dynamics and CT characteristics of these strain-relieved systems are quite different from those revealed for systems without PEG. MD simulations of structures **1c** and **1d** show that distances between terminal oxygen atoms of the PEG groups vary from ∼3 to 17 Å. The PEG linkers accommodate strain induced at the DNA TWJ, thus slowing conformational interconversions between "T" structures and making π-stacked geometries more stable.

In one MD trajectory of TWJ **1c**, the structure stacks in a "T"-shaped conformation 0.6 ns after starting in a nearly "Y"-shaped geometry. The RMS "cross junction" coupling between the two guanines at the junction is 5.4×10^{-3} eV during the first 0.6 ns and then increases to 9.0×10^{-2} eV (Figure S4 in the SI). Once the π stack forms, CT is expected to proceed with almost the same rate as for transport in canonical B-DNA with the same sequence.

In the first ∼1.7 ns of MD simulations for structure **1d**, the RMS averaged "cross-junction" G1−G2 coupling is 5.4×10^{-3} eV, similar to that in structure **1c**. After ∼1.7 ns, the structure is locked into a "T" conformation (Figure 4b and Movie 2), and the G1−G2 coupling increases to an average of ∼0.12 eV, close to the coupling between nearest bases in B-DNA.[26,27] Thus, when the stable "T" conformation forms, the electronic coupling across the TWJ becomes very similar to that in B-DNA. Once π-stacked geometries are formed, the bottleneck in

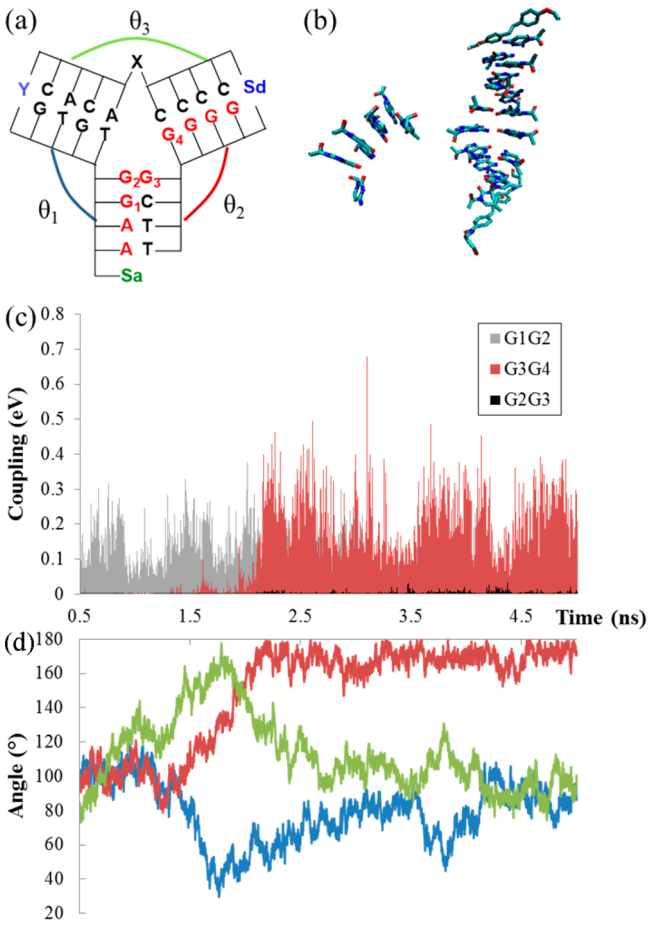

Figure 4. (a) Structure of a DNA TWJ (**1d**) with a PEG linker (**X**) (adapted from ref 19). (b) Typical snapshot of a T-shape conformation. Backbones, linking group, and hydrogens are removed for clarity. (c) Coupling between Gs at the junctions (labeling as in panel a). Once the π-stacked geometries form, the cross-junction coupling is strongly enhanced. (d) Time evolution of the angles between the three DNA branches is shown with colors as in panel a. This structure is locked in the T-shaped geometry after ∼2 ns.

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the CT pathway is likely to be the hopping step between the two mismatched Gs, characterized by RMS coupling of ~2.6 × 10^{-3} eV.

We extended the MD simulations of **1c** and **1d** to times as long as 25 ns, and the "T" conformation persisted. In some MD trajectories, the formation of a stable "T" configuration was not observed.

Our simulations replicate the key experimental findings. That is, the PEG-modified structures transfer charge with kinetics similar to that found in duplex DNA with similar sequences (see Figure S3 in the SI). The quantum yields for CT in the PEG-modified structures are found experimentally to be lower than is found in duplex DNA (Table S1 in the SI).[19] This observation is probably explained by the simulation result that indicates only a portion of TWJs remain in CT-active well-stacked conformations during the measurement time window of the experiment. The stochastic, conformationally gated CT mechanism is expected to produce zero-order CT kinetics, as is found experimentally in these systems.[19]

A Proposed DNA TWJ Charge Splitter/Combiner. In the TWJ structures considered above, charge is directed toward one of two branches because of the asymmetric nature of the purine pathways. A next step in the design of TWJs is the splitter/combiner motifs with equivalent branches (Figure 1e).

The DNA TWJ has a G−G base pair on the lower branch near the junction, providing hopping routes into both upper branches. Both upper branches are designed with energy-favored purine hole pathways. In the MD simulations, a stable "T"-shaped conformation appeared after several nanoseconds (similar to structures **1c** and **1d**). These conformations were found to have two orientations (Figure 5), which allow charge to penetrate into both upper arms. In our simulations, the structure is locked in the "T" geometry for 25 ns.

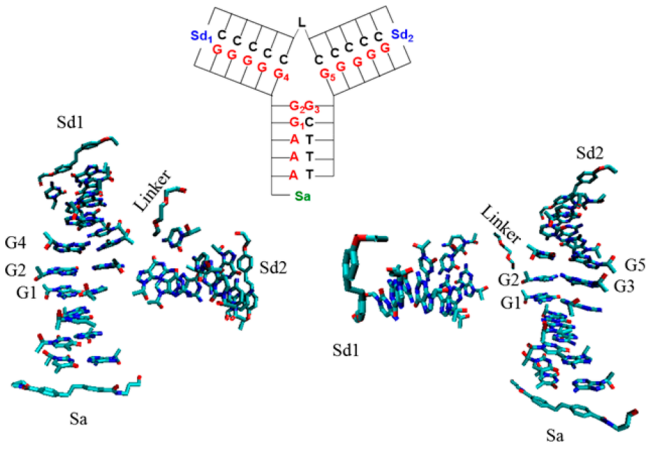

Figure 5. Typical MD snapshots representing two different "T" shaped conformations. These two snapshots are taken from different trajectories. (left) "T" shaped conformation facilitates transport along the upper-left pathway. (right) "T" shape conformation facilitates transport along the upper-right pathway.

In one trajectory leading to a T-like conformation, as shown on the left side of Figure 5, the lower- and the upper-left branches form a B-DNA-like stacked geometry after ~0.3 ns. Once formed, the cross-junction coupling between G2 and G4 is 0.097 eV and the G1−G2 coupling is 0.12 eV, similar to the nearest-neighbor couplings in B-DNA. Consequently, one expects that charge will flow through the junction to the acceptor on the upper-left branch with a rate similar to that in well-stacked B-DNA. An alternative MD trajectory was also obtained that was locked in a "T" conformation (right side of Figure 5) that aligns two other strands (Figure S5 in the SI).

These simulations illustrate the key dynamical aspects of a charge splitter/combiners on the single-molecule scale. Note that we were not able to observe switching between the two kinds of stable "T" conformations in the designed splitter (Figure 5), probably because the switching time scale is beyond the reach of the MD simulations implemented here.

Simulated DNA TWJs are found to fluctuate among multiple "T" structures. The coupling across the junctions is enhanced when a "T" structure establishes B-DNA-like π-stacking. This is found in the simulations only when PEG linkers are embedded in DNA. Indeed, the more poorly stacked structures have nearest-neighbor couplings that are several orders of magnitude weaker than in B-DNA. These simulations are consistent with measured CT rate and yield data. Structures **1a** and **1b** are found to undergo rapid switching among different "T" conformations. Even while in "T" conformations, the "cross-junction" couplings are several orders of magnitude smaller than the nearest-neighbor couplings in B-DNA. Structures with PEG linkers (**1c** and **1d**) are locked into well-stacked "T" conformations, where the "cross-junction" couplings are similar to the nearest-neighbor couplings in B-DNA. As a result, the PEG-linked structures should have CT kinetics similar to that found in B-DNA with a corresponding purine pathway. We also explored the CT pathways in a possible DNA TWJ charge splitter/combiner, **1e**. The simulations indicate that charge can indeed proceed to both of the upper arms of the TWJ, thus suggesting that DNA-based splitter/combiners should be within reach.

■ ASSOCIATED CONTENT

Supporting Information

Computational details, additional simulation results, links to movies showing molecular dynamics trajectories, and a summary of experimental data are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpclett.5b00863.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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