Energy Transfer in DNA

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Triplet–Triplet Energy Transfer in DNA: A Process that Occurs on the Nanosecond Timescale**

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In the last decade, much progress has been made in the understanding of DNA excited-state dynamics.[1] In this context, theoretical studies focused both on the photophysical properties of individual nucleobases as well as on the relevant interactions in assemblies of two or more bases have been a valuable tool for exploring decay mechanisms of excited states in DNA. In contrast to singlet excited states, our knowledge on the energetics and dynamics of triplet excited states is still largely limited to the properties of individual bases.[2] Thus, despite the fact that triplet–triplet electronic energy transfer (TET) can initiate phototoxic reactions in DNA,[3,4] such as the formation of thymine cyclobutane dimers,[5] little is known about the strength of the electronic interactions and the timescales for TET in nucleobase π stacks: the factors that determine the fate of triplet states in native DNA. Therefore, the assignment of decay components measured through ultrafast spectroscopy experiments remains a difficult task owing to the fundamental uncertainty regarding the degree of delocalization of triplet excited states and the approximate timescales for their migration.[1]

Herein, we present a study of TET between stacked adenine–adenine (A–A) and tymine–thymine (T–T) in polyA–polyT DNA sequences. We applied the semiempirical ZINDO method to investigate how DNA structural dynamics modulate the couplings for TET along a 15 ns classical molecular-dynamics (MD) trajectory. The suitability of the ZINDO method for describing the energetics and TET couplings of low-lying $\pi \rightarrow \pi^*$ triplet states was validated by comparison with equation-of-motion coupled-cluster models with single and double substitutions (EOM-CCSD) and calculations of configuration interaction with single excitations (CIS). The couplings were calculated by using the method fragment excitation difference (FED) recently developed by Hsu and et al.[6] This method extends the fragment-charge-difference scheme[7] to couplings of excited states and enabled us to estimate the electronic couplings for nonsymmetrical arrangements of the bases, while accurately accounting for the short-range interactions between stacked bases that promote TET. Finally, we applied Marcus theory to predict TET rates between the base pairs.[8] We found that in both A–A and T–T stacks, triplet excitons are localized on single bases and can migrate along the DNA on the nanosecond timescale.

We explored the ability of the semiempirical ZINDO method to accurately estimate electronic couplings by comparison with correlated EOM-CCSD calculations with the 6-31G basis set for symmetrical A–A and T–T dimers. As TET couplings depend on wavefunction overlap, we explored the effect of polarization and diffuse functions on the results at the CIS level by using the 6-31G, 6-31G(d), and 6-311++G(d,p) basis sets. This effect was also considered at the EOM-CCSD level for several model systems. Our results indicate that ZINDO underestimates the couplings by approximately 20–40% (see the Supporting Information for a detailed discussion). Thus, given that the TET rate is proportional to V^2, the predicted efficiency of TET is expected to be about 2–3 times too low. To check the performance of ZINDO, we also estimated electronic couplings for 500 configurations of the π stack at the CIS/6-31G(d) level (see below).

In Figure 1, we show the distribution of squared electronic couplings obtained for 15000 structures extracted from the MD simulation, whereas in Table 1, we report the MD averages as well as the results obtained for A- and B-DNA reference structures.[9] The TET rate can be estimated by

Table 1: Delocalization length of the lowest triplet excited state (L_1), squared electronic coupling (V^2), reorganization energy (λ), and TET time (τ_{TET}) computed for the A_7–A_8 and T_{23}–T_{24} stacked base pairs along the 15 ns molecular-dynamics trajectory. For comparison, values obtained for reference DNA structures[9] are also listed.

	L_1	V^2 [eV]	λ [eV]	τ_{TET} [ns]
	A_7–A_8			
MD average	1.03	2.12×10^{-5}	0.607	0.80
A-DNA[9]	1.03	6.39×10^{-6}	–	2.66
B-DNA[9]	1.03	1.19×10^{-5}	–	1.43
	T_{23}–T_{24}			
MD average	1.01	1.59×10^{-6}	0.557	6.35
A-DNA[9]	1.08	4.83×10^{-5}	–	0.21
B-DNA[9]	1.02	2.91×10^{-6}	–	3.46

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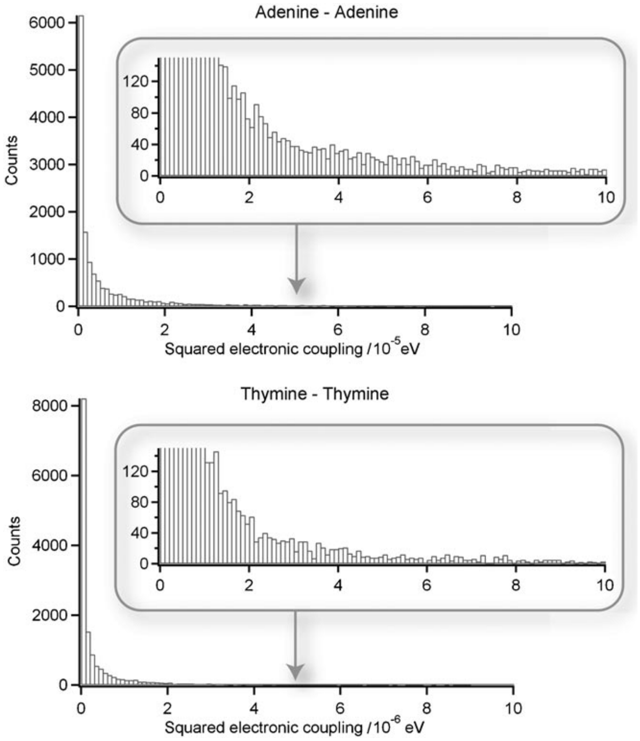

Figure 1. Distribution of squared electronic couplings obtained for A_7–A_8 and T_{23}–T_{24} stacked base pairs (15 000 structures were extracted from a 15 ns MD trajectory of 5′-GG(AAAA)$_3$G-3′). Insets show a detailed view of the long tail.

using the Marcus equation.[8] The reorganization energy λ is derived from the variance of the energy gap along the MD trajectory, $\lambda = \sigma(\Delta E)^2/(2k_B T)$,[10] in which k_B is the Boltzmann constant and $T = 298$ K. The obtained λ values (Table 1) are in good agreement with previous data derived from QM calculations of the nucleobases in the ground-state and triplet-excited-state geometries.[2b,d,e]

Our results indicate that the squared coupling for A–A stacks, $\langle V^2\rangle = 2.12\times10^{-5}$ eV, is one order of magnitude stronger than the value $\langle V^2\rangle = 1.59\times10^{-6}$ eV found for the T–T pair. Accordingly, we predict TET times to be 0.80 and 6.35 ns for A–A and T–T, respectively. Calculations on a reduced 500-snapshot subset at the CIS/6-31G(d) level led to similar results, with squared couplings of $\langle V^2\rangle = 9.18\times10^{-6}$ and 1.57×10^{-6} eV predicted for A–A and T–T, respectively. These latter values correspond to TET times of 1.85 and 6.42 ns and thus support our conclusion that triplet migration occurs on the nanosecond timescale.

Interestingly, the distribution of V^2 in Figure 1 includes long tails toward large coupling values. The corresponding conformations have a strong impact on the overall transfer rate, as illustrated in Figure 2. Thus, neglecting 10 % of the most favorable conformations leads to a significant decrease (by a factor of about 5–8) in the migration rate. When only 1 % of the structures with the largest coupling values are excluded, the TET rate becomes about 2–3 times smaller. Thus, the process is boosted remarkably by a limited number of conformations with the strongest electronic interaction. Furthermore, the triplet excitation energies and their splitting were found to also be sensitive to structural disorder (see the Supporting Information).

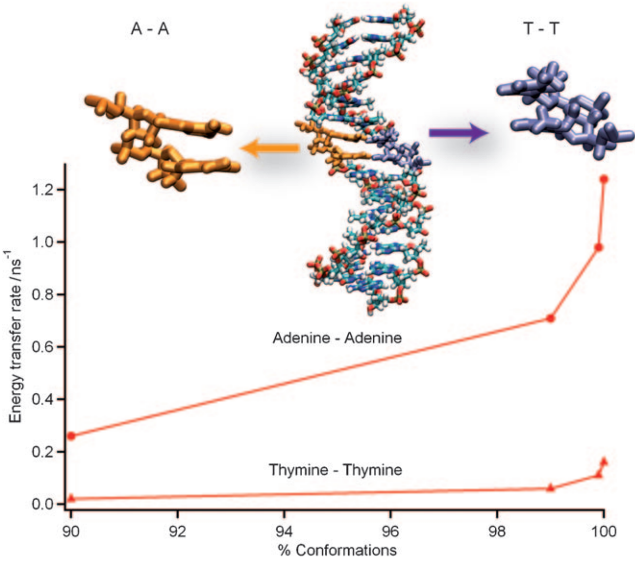

Figure 2. Rate of triplet–triplet energy transfer obtained by excluding conformations with the largest electronic-coupling values. The curves show that a small number of structures induce a remarkable boost in the process.

The remarkable conformational boosting of the TET process described above arises from the exquisite sensitivity of the coupling values to structural fluctuations of the DNA π stack. Analysis of the correlation between base-pair-step parameters and electronic couplings (see the Supporting Information) revealed that A–A interactions are particularly sensitive to changes in the twist structural parameter, possibly owing to the degree of overlap between adenine five-membered rings, whereas significant distortions in shift and slide parameters are mainly involved in large T–T interactions. The rates derived from static A- and B-DNA structures deviate essentially from the MD average values (Table 1).

An important question regards the degree of delocalization of triplet excited states in DNA. The delocalization lengths (see the Supporting Information) obtained for the A–A and T–T stacks were 1.03 and 1.01 bases, respectively. These values indicate that triplet excitons in DNA are confined to single bases. Moreover, the delocalization length was found to be less than 1.1 bases in reference A- and B-DNA dimers, in which both sites have identical internal geometries. Delocalization of the excited states depends on the electronic coupling and the gap between the states (no assumption regarding the localized character of triplet excitons was used in our model). Recently, by using the same method, we showed that singlet excited states in the DNA π stacks are almost completely delocalized over stacked nucleobases.[11] Thus, there is a significant difference in the character of triplet (localized) and singlet (delocalized) excitons in DNA.

We thus conclude that triplet excited states in DNA are localized on single bases and are expected to migrate along the double strand on the nanosecond timescale. Further studies will have to address the impact of the environment (including counterion dynamics) on the process, through potential modulation of electronic couplings[12] or reorganization energies. Nevertheless, these effects for TET are expected to be relatively small as compared with those found for electron transfer in DNA.[13,14]

The predicted timescale is in agreement with the experimental data of Holmlin et al.[4] Because the estimated time for triplet-exciton hopping is longer than the approximately 140 ps required for the formation of cyclobutane thymine dimers,[5b] we suggest that this lesion should arise on the base pairs where the triplet state is initially formed.

Experimental Section

Electronic energy transfer is the process by which excitation energy is nonradiatively transferred from a sensitized donor molecule (D) to a proximate acceptor (A). TET is overall a spin-allowed process, which can be viewed as a simultaneous transfer of two electrons with different spins. It is mediated by wavefunction overlap and decays exponentially with the D–A separation.[15] When the donor and acceptor states are degenerate, the electronic coupling V between these diabatic states is simply given by the energy splitting of related adiabatic states, $V = 1/2(\Delta E_{+} - \Delta E_{-})$.[15b] The FED method, however, enables estimation of the electronic coupling also in situations in which the diabatic states are not degenerate.[6] The FED results are in excellent agreement with directly computed interaction matrix elements.[16] We used the half-splitting scheme to evaluate the electronic couplings for symmetrical dimers, whereas the FED approach enabled us to accurately calculate the couplings in nonsymmetrical π stacks sampled along the MD. We employed the 15 ns benchmark MD trajectory for the double-stranded DNA sequence 5′-GG(AAAA)$_3$G-3′ obtained within the ABC project.[17] To avoid potential artifacts from end effects, we estimated the TET parameters for midstack bases. All ab initio calculations were performed with Gaussian09;[18] ZINDO couplings along the MD trajectory were computed by the program SECA.[19]

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