Triplet-triplet energy transfer in DNA

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Triplet-triplet energy transfer in DNA occurs on the nanosecond time scale

Carles Curutchet, and Alexander A. Voityuk**

In the last decade much progress has been achieved 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 to explore 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 time scales for TET in nucleobase π stacks that determines the fate of triplet states in native DNA. Thus, assignment of decay components measured through ultrafast spectroscopy experiments remains a difficult task due to the fundamental uncertainty regarding the degree of delocalization of triplet excited states and the approximate time scales for their migration.[1]

Here, we present a study of TET between stacked adenine-adenine (A-A) and tymine-thymine (T-T) in polyA-polyT DNA sequences. We apply 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 performance of the ZINDO method in describing the energetics and TET couplings of low-lying π→π* triplet states has been validated by comparison to equation-of-motion coupled-cluster with singles and doubles (EOM-CCSD) and configuration interaction with singles (CIS) calculations. The calculation of the couplings is performed by using the method FED (fragment excitation difference) recently developed by Hsu and co-workers,[6] which extends the fragment charge difference scheme[7] to couplings of excited states. This methodology allows us to estimate the electronic couplings for the non-symmetric arrangements of the bases, while accurately accounting of short-range interactions between the stacked bases that promote TET. Finally, we apply Marcus theory to predict TET rates between the base pairs.[8] We find 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 time scale.

The ability of the semiempirical ZINDO method to accurately estimate electronic couplings was explored by comparison to correlated EOM-CCSD calculations using the 6-31G basis set for symmetric 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 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 ~20-40 % (see *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 ~2-3 times too low. Further, to check the performance of ZINDO, we estimated electronic couplings for 500 configurations of the π stack at the CIS/6-31G(d) level (*vide infra*).

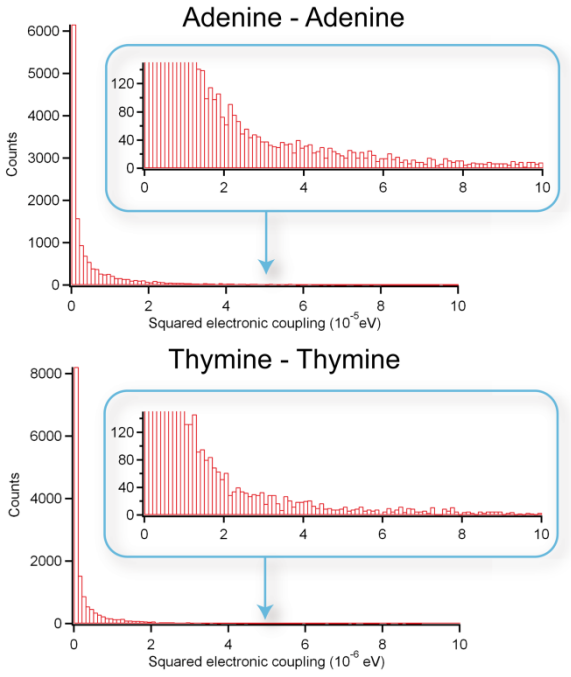

Figure 1. Distribution of squared electronic couplings obtained for A_7-A_8 and T_{23}-T_{24} stacked base pairs (15000 structures were extracted from a 15 ns MD trajectory of 5'-GG(AAAA)$_3$G-3'). A detailed view of the long tail is provided by the insets.

In Fig. 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]

[*] Dr. C. Curutchet
Institut de Química Computacional and Departament de Química, Universitat de Girona
Campus Montilivi, 17071 Girona, Spain
Fax: (+34)972183241
E-mail: carles.curutchet@udg.edu

Prof. Dr. A. Voityuk
Institució Catalana de Recerca i Estudis Avançats
08010 Barcelona, Spain
Institut de Química Computacional, Universitat de Girona
Campus Montilivi, 17071 Girona, Spain
Fax: (+34)972418356
E-mail: alexander.voityuk@icrea.es

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The TET rate can be estimated using Marcus equation.[8] The reorganization energy λ is derived from the variance of the energy gap along the MD-trajectory, $\lambda = \sigma(\Delta E)^2/(2k_BT)$,[10] where 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 at the ground and triplet excited state geometries.[2b][2d][2e]

Our results indicate that the squared coupling for A-A stacks, $\langle V^2\rangle = 2.12\cdot10^{-5}$ eV, is one order of magnitude stronger than the value $\langle V^2\rangle = 1.59\cdot10^{-6}$ 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 lead to similar results, predicting squared couplings $\langle V^2\rangle = 9.18\cdot10^{-6}$ eV and $\langle V^2\rangle = 1.57\cdot10^{-6}$ eV for A-A and T-T, respectively. These latter values predict 1.85 and 6.42 ns TET times, thus supporting our conclusion that triplet migration occurs on the nanosecond time scale. Interestingly, the distribution of V^2 in Fig. 1 includes long tails toward large couplings values. These corresponding conformations have a strong impact on the overall transfer rate, as illustrated in Fig. 2. Thus, neglecting 10 % of the most favorable conformations leads to a significant decrease (by a factor ~5-8) of the migration rate. When only 1 % of the structures with largest coupling values are excluded, the TET rate becomes ~2-3 times smaller. Thus, a remarkable boost of the process is mediated by a limited number of conformations with the strongest electronic interaction. Furthermore, the triplet excitation energies and their splitting are found to be also sensitive to structural disorder (see *Supporting Information*).

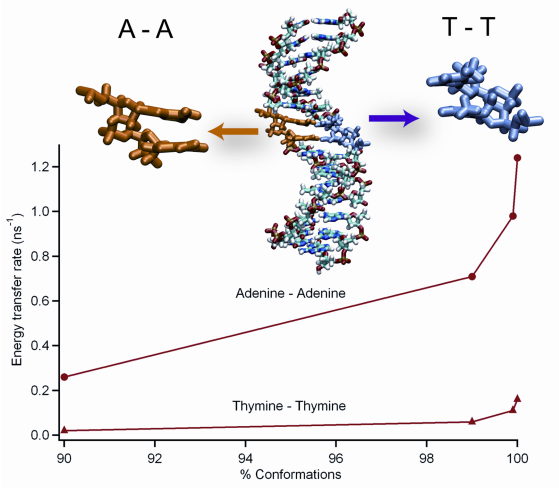

Figure 2. Triplet-triplet energy transfer rate obtained by excluding conformations with largest electronic coupling values. The curves show that a remarkable boost of the process is induced by a small number of structures.

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 *Supporting Information*) reveals that A-A interactions are particularly sensitive to changes in the twist structural parameter, possibly due to an improved overlap between adenine 5-membered rings, whereas significant distortions in shift and slide parameters are mainly involved in large T-T interactions. We note that the rates derived using static A- and B-DNA structures deviate essentially from the MD-average values (Table 1).

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	$2.12\cdot10^{-5}$	0.607	0.80
Ref. A-DNA	1.03	$6.39\cdot10^{-6}$	-	2.66
Ref. B-DNA	1.03	$1.19\cdot10^{-5}$	-	1.43
	T_{23}-T_{24}			
MD-average	1.01	$1.59\cdot10^{-6}$	0.557	6.35
Ref. A-DNA	1.08	$4.83\cdot10^{-5}$	-	0.21
Ref. B-DNA	1.02	$2.91\cdot10^{-6}$	-	3.46

An important question regards the degree of delocalization of triplet excited states in DNA. The delocalization length (see *Supporting Information*) obtained for the A-A and T-T stacks is 1.03 and 1.01. It means that triplet excitons in DNA are confined to single bases. Moreover, the delocalization length is found to be <1.1 in reference A- and B-DNA dimers, where both sites have identical internal geometries. Delocalization of the excited states depends on the electronic coupling and the gap between the states (no assumption on the localized character of triplet excitons was used in our model). Recently, 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.

In summary, we conclude that triplet excited states in DNA are localized on single bases and are expected to migrate along the double strand on the nanosecond time scale. Further work will have to address the impact of the environment (including counterion dynamics) on the process, either 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 through DNA.[13][14]

The predicted time scale is in agreement with the experimental data of Holmlin et al.[3] Because the estimated time for triplet exciton hopping is longer than ~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.

Methods

Electronic energy transfer is the process where the excitation energy is non-radiatively 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 spin. 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, allows estimation of the electronic coupling also in situations where 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 symmetric dimers, whereas the FED approach allowed us to accurately calculate the couplings in non-symmetric π stacks sampled along the MD. We employed the 15 ns

benchmark MD trajectory for double-stranded DNA sequence 5'-GG(AAAA)$_3$G-3' obtained within the ABC project.[17] To avoid potential artefacts from end effects, we estimate the TET parameters for mid-stack bases. All *ab initio* calculations were performed using Gaussian09,[18] ZINDO couplings along the MD trajectory were computed by the program SECA.[19]

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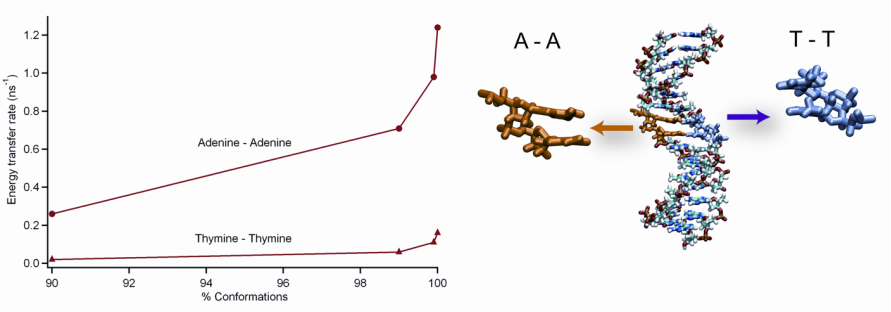

Triplet-triplet electronic energy transfer in polyA-polyT DNA sequences is studied using semiempirical quantum chemical methods coupled to classical molecular dynamics simulations. Triplet excited states in DNA are found to be almost completely localized on single nucleobases; the characteristic time for their migration along the A-A and T-T stacks are 0.8 and 6.4 ns.