

Environment effects on triplet-triplet energy transfer in DNA

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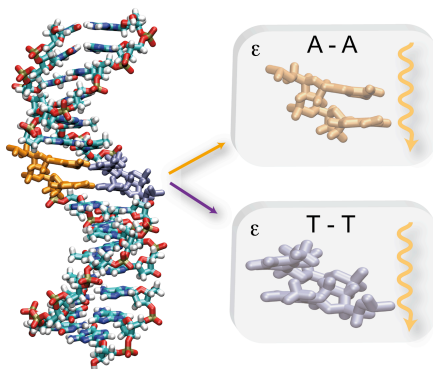
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ABSTRACT

We present a quantum-chemical study of the impact of the environment on triplet exciton migration in polyA–polyT DNA sequences. Electronic couplings are estimated by combining the fragment excitation difference scheme with the polarizable continuum model. Conformational fluctuations are taken into account by considering 500 structures extracted from a classical molecular dynamics trajectory. In contrast to singlet transfer, we find that the environment effect is not strongly correlated with the coupling magnitude in vacuum, and can significantly enhance or reduce its value in individual conformations. Conformational averaging, however, leads to a net cancellation of medium effects on the overall transfer rate.



Highlights: > Environment effects on triplet-triplet energy transfer in DNA are studied theoretically. > Electronic couplings are significantly enhanced or reduced in individual conformations. > Conformational averaging leads to an overall cancellation of polarization effects. > Rate of triplet exciton transfer is expected to be rather insensitive to medium effects.

1. Introduction

Environment effects play a central role in electronic energy transfer, a ubiquitous non-radiative process where the excitation energy is transferred from a sensitized donor molecule to a proximate acceptor.[1] This is because of two main reasons: 1) environment may determine the arrangement of donor and acceptor, as found e.g. in photosynthetic light-harvesting pigment-protein complexes,[2] 2) the short- and long-range interactions of the medium with the corresponding electronic transitions modulate the resonance conditions for the energy transfer.[3] In addition, the environment induces strong screening effects in the electronic couplings that promote singlet-singlet energy transfer. Recently, significant advances in quantum-chemical methods coupled to continuum or discrete descriptions of the environment have allowed a critical assessment of Förster screening factor ($1/n^2$, where n is the refractive index of the medium), widely used to describe screening effects. This has unveiled, for example, significant deviations from Förster approximation at close donor–acceptor separations (below 20 Å),[4] and due to the dielectric heterogeneous nature of a protein environment.[5]

Recently, we estimated the absolute rate and delocalization of triplet excitons in DNA.[6] These characteristics remain largely unknown, despite the fact that triplet energy transfer (TET) can initiate phototoxic reactions,[7,8] such as the dimerization of thymine.[9,10] We found that triplet excitons are localized on single bases and can migrate along DNA on the nanosecond timescale.[6] However, we did

not consider the role of the environment on the TET process. Because TET couplings are not mediated by Coulomb interactions, but depend on orbital overlap, the environment does not induce screening effects as in singlet exciton transfer (SET), but can otherwise modulate the donor–acceptor interaction through a superexchange mechanism. The superexchange effects have been explored for TET in linked bichromophoric systems.[11] However, because in DNA there are no intervening molecules between the stacked base pairs, these interactions are expected to be small. The screening and superexchange effects refer to the explicit participation of the surrounding medium in the donor-acceptor interaction. The environment can also indirectly modulate the interaction by changing the properties of donor and acceptor with respect to vacuum. Typically, in SET solvation induces a significant increase in transition dipole moments and consequently in electronic couplings, which can be easily rationalized within the point-dipole approximation adopted in Förster theory[12] The question of how the polar environment affects the TET coupling is, however, less straightforward, because there is no general rule to predict how overlap of the donor and acceptor diabatic states is modulated by the surrounding medium.

Here, we use the polarizable continuum model (PCM)[13] to explore the role of solvation on the TET couplings between stacked adenine–adenine (A–A) and thymine–thymine (T–T) bases in polyA-polyT DNA sequences. We use the CIS (configuration interaction of single excitations) method along with the 6-31G(d) basis set to estimate electronic couplings between the lowest $\pi \rightarrow \pi^*$ triplet states of A–A and T–T using the fragment excitation difference (FDE) scheme.[14] This approach was shown to provide electronic coupling values within $\sim 20\%$ agreement with EOM-CCSD (equation-of-motion coupled cluster with single and double substitutions) estimations.[6] In addition, it avoids problems related to the artificial stabilization of charge-transfer states in dimeric systems typically found in TD-DFT (time-dependent density functional theory).[15]

We computed the TET parameters for 500 nonsymmetrical conformations of A–A and T–T stacks sampled from a 15 ns classical molecular dynamics (MD) trajectory of the duplex 5'-GG(AAAA)₃G-3'). Our results show that the polar environment can indeed significantly modify the shape of the donor/acceptor excited state wave functions, leading to important differences between

electronic couplings obtained for individual conformations in vacuum and in solvent. The averaging over a large number of DNA structures suggests, however, that the *effective* TET coupling remains rather unchanged. This is because the environment can increase or decrease the electronic interaction between the triplet excitons, leading in average only to very small effects. The changes induced by solvation are found to be relatively small as compared with the largest coupling values.

2. Computational methods

Electronic couplings for triplet-triplet transfer reactions in A–A and T–T stacks were computed in vacuum and in the presence of the dielectric environment using the fragment excitation difference (FED) method developed by Hsu et al.,[14] which extends the fragment charge difference scheme[16] to couplings between excited states. The FED method provides results in excellent agreement with directly computed interaction matrix elements[17] and allows to accurately account for short-range contributions mediated by orbital overlap promoting TET. All calculations were performed at the configuration interaction with single substitutions (CIS) level of theory, using the 6-31G(d) basis set, which was found to agree well with correlated EOM-CCSD/6-311++G(d,p) calculations.[6] Environment effects were accounted for in CIS calculations using the Polarizable Continuum Model (PCM).[13] PCM cavities were constructed from atomic radii obtained applying the United Atom Topological Model to the radii of the UFF force field, and using the SES (solvent excluding surface) algorithm to define the chromophore-environment boundary, as implemented in Gaussian09. The DNA polar environment surrounding A–A and T–T base pairs was modeled with the static and the optical dielectric constants $\epsilon=10$ and $\epsilon_{\text{opt}}=2$, respectively. In order to check the sensitivity of the results to the static dielectric constant, we also computed electronic couplings for symmetric A–A and T–T stacks[6] using $\epsilon = 5, 20$ and 80. The computed δ values ($\delta=V_{\text{sol}}-V_{\text{vac}}$) do not deviate from the reference data obtained with $\epsilon=10$ by more than 20%.

Using this methodology we have computed TET couplings for 500 A-A and T-T π -stacks sampled along an MD trajectory to account for a high sensitivity of TET properties to structural fluctuations. In particular, we extracted the structures from the 15 ns benchmark trajectory for the double-stranded DNA sequence 5'-GG(AAAA)₃G-3' obtained within the ABC project[18] (see ref. [6] for additional details). In order to avoid potential artifacts from end effects, we estimated the TET parameters for the mid-stack bases. All ab initio calculations were performed with Gaussian09.[19] To derive the coupling the Gaussian outputs were processed by using the program FCM.[20] Note that absolute values of the TET coupling are considered throughout this study. Although the sign of TET couplings can in principle be determined by analyzing the shape of wave functions as described in detail for ET matrix element,[21] we have not succeeded in elaborating a robust numerical procedure to determine the sign of TET matrix elements, because of the complex structure of excited state wave functions.

3. Results and discussion

Figure 1 shows the time evolution of the ratio V_{sol}/V_{vac} between electronic couplings computed in vacuum and in the polar environment. As seen, the medium significantly affects the electronic interaction between the bases. In $\sim 17\%$ of the conformations, there is a two-fold increase or decrease in the coupling, and for $\sim 6\%$ of them, the electronic matrix element changes by a factor of 4. Figure 2 represents the V_{sol}/V_{vac} values with respect to V_{vac} . There is a clear trend in V_{sol}/V_{vac} , the larger the coupling values the smaller its relative change upon solvation. This trend essentially differs from that observed in singlet energy transfer, where both polarization and screening effects are directly determined by the magnitude of V_{vac} . In particular, since the SET coupling is proportional to the transition dipoles of the donor and the acceptor (the dipole approximation), $V \propto \mu_D \times \mu_A$, [22] V_{sol} should be proportional to the magnitude of V_{vac} . [4] In contrast with SET, TET is mediated by orbital overlap, rather than by the long-range Coulomb interaction. If the triplet excited state of each fragment contains a significant contribution of the HOMO \rightarrow LUMO excitation (i.e. between the highest occupied and lowest unoccupied molecular orbitals, respectively), as in the considered A-A and T-T pairs, the TET

coupling approximately depends on the overlap between the HOMOs, as well as that between the LUMOs, localized on each fragment.[23] Because of that, the effect of the environment δ on the TET coupling ($V_{sol}=V_{vac}+\delta$) is not straightforward, as illustrated in Figure 3. Depending on the sign of V_{vac} and δ , V_{sol}^2 can be larger or smaller than V_{vac}^2 . This can be explained as follows. In some cases, both the overlap between donor-acceptor HOMOs and LUMOs are reduced upon solvation, leading to a decreased coupling in the presence of the environment. In the opposite case, both overlaps are increased, leading to a net interaction enhanced compared to that in vacuum. Finally, in cases where the overlap between HOMOs increases, whereas that between LUMOs decreases (or vice versa), the net coupling could eventually either increase or decrease. In Figure 4 we illustrate how solvation modifies the HOMO and LUMO orbitals corresponding to the donor and acceptor for an individual A–A pair. These orbital changes are rather similar in different conformations, but depending on the mutual arrangement between donor and acceptor units, the changes induced on the electronic coupling vary considerably.

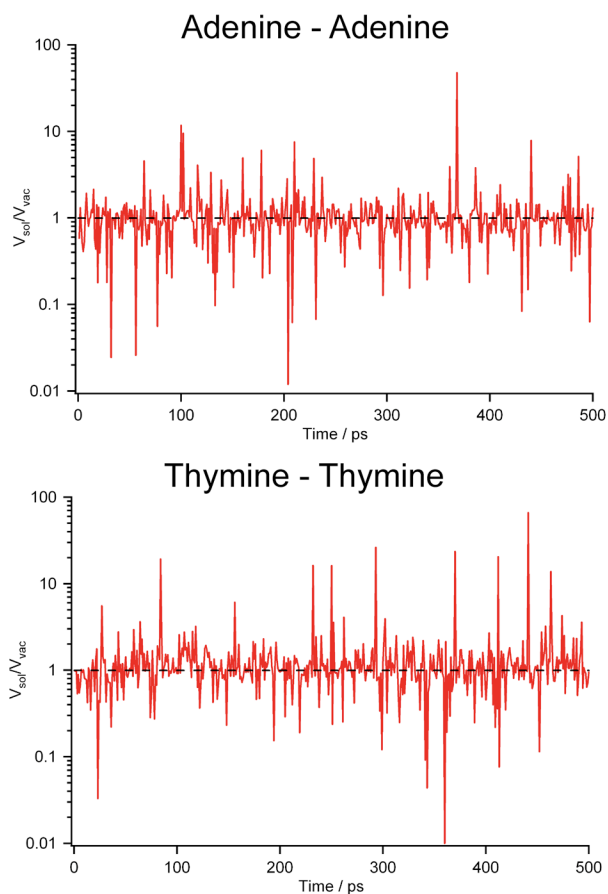


Figure 1. Time-evolution of the ratio of electronic couplings in the polar environment and in vacuum derived for A₇-A₈ and T₂₃-T₂₄ stacks.

Overall, we find that the average absolute value of the environment effect, $|\delta|$, for A-A and T-T stacks is $0.43 \cdot 10^{-3}$ eV and $0.20 \cdot 10^{-3}$ eV, respectively. As already noted, the magnitude of this effect does not depend on the magnitude of the overall coupling, as illustrated in Figure 3. This seems to indicate that the changes in HOMO and LUMO orbitals upon solvation, and the corresponding effects induced on the TET coupling, are somewhat similar across the range of structures sampled. Thus, when the V_{vac} coupling is much larger than the typical δ values induced by the medium ($< 2 \cdot 10^{-3}$ eV), the overall coupling values remain rather unaffected.

Interestingly, the effective coupling obtained by averaging the matrix elements squared over the MD trajectory remain largely unaffected upon the polar environment (see below). This arises from the fact that environment effects are small for structures that show a strong electronic interaction, and thus contribute more to the average coupling value,[6] as illustrated in Figure 2, but also because averaging over many conformation leads to an overall cancellation of the polarization effects. Our results clearly demonstrate the need to account for a sufficiently large number of conformations in order to explore the effect of the environment. Focusing on single conformations can lead to opposite conclusions about the effects of the polar medium on the TET coupling, as shown by Figure 2.

At this point, let us clarify how the dielectric properties used to mimic the environment (static and optical dielectric constants) modify the triplet excitation energies and electronic couplings derived from our CIS calculations. If one assumes a frozen environment response, excitation energies are obtained in the presence of the environment kept in equilibrium with the ground state charge distribution. This effect is described in the CIS-PCM methodology through the static dielectric constant, which describes the complete nuclear and electronic response of the medium. Because this frozen environment polarization modifies the properties of the chromophores (molecular orbitals, transition densities, etc) compared to those in vacuum, the static dielectric constant induces an *implicit* solvent effect on the

electronic coupling in both singlet-singlet and triplet-triplet energy transfer, and is the origin of the environment effect we discuss in this study.

The optical dielectric constant ϵ_{opt} (i.e. the square of the refractive index), in turn, is introduced to describe the effects arising from the fast response of the environment electronic polarization to the excited state. In the linear response CIS-PCM scheme, such an effect is approximately proportional to the square of the transition dipole moment between the ground state and the excited state of interest (see Ref. [24] for a detailed discussion on the difference between linear response and state-specific methods in the context of continuum solvation models). Thus, such an effect (and the ϵ_{opt} value adopted in the model) does not affect triplet excited states having a null transition dipole, whereas it plays a role in singlet transitions. Thus, in contrast to singlet-singlet energy transfer, the refractive index properties of the environment, represented by the $\epsilon_{\text{opt}} \approx n^2$ value, do not contribute to a screening of triplet-triplet electronic couplings. This effect can be understood from the fact that triplet-triplet couplings are mediated by orbital overlap, not Coulomb interactions, therefore superexchange interactions mediated by the solvent can not be accounted for using a continuum solvation model.[25] Because there are no solvent molecules between the stacked bases we study, superexchange effects are however expected to be small, so in this study we have focused on the polarization effects induced by changes on the nucleobase properties upon solvation.

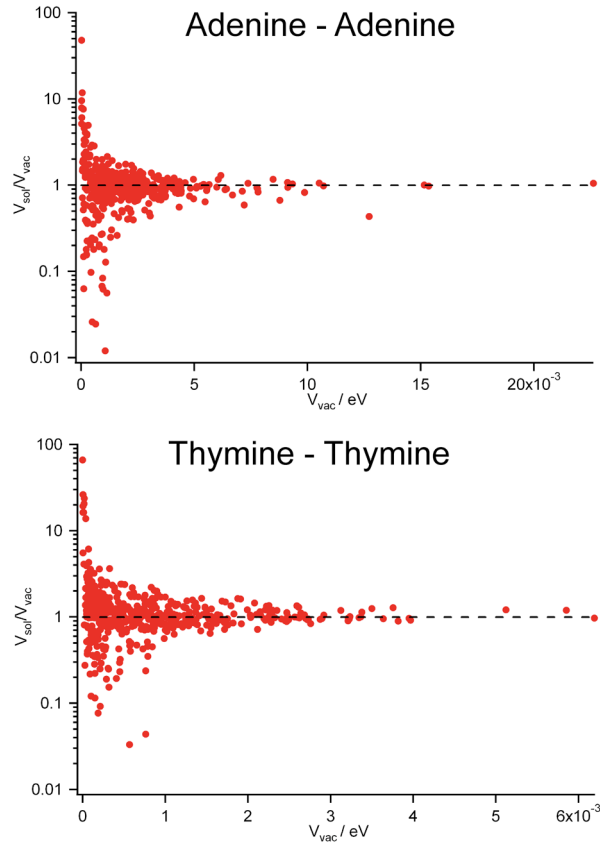


Figure 2. Ratio of electronic couplings in the polar medium and in vacuum computed for A_7-A_8 and $T_{23}-T_{24}$ stacks (500 structures for each type were considered).

At this point, we note that according to Marcus equation,[26] the TET rates scale as the square of the electronic couplings. In Table 1, we report the effective squared couplings derived by averaging V^2 values in vacuum and in the presence of the environment. For the A–A stack, V^2 is reduced by 7 % (9.16×10^{-6} to 8.53×10^{-6} eV²) when the polar medium is accounted for, whereas for T–T, we find an enhancement of the coupling by 16 % (1.57×10^{-6} to 1.83×10^{-6} eV²). Therefore, the absolute rates obtained in our previous study for TET within a homogeneous DNA stack[6] do not change significantly when the polar environment is accounted for. Finally, we note that the highly localized character of the triplet excitons in DNA stacks found in that study remains unchanged by their embedding in the polar medium.

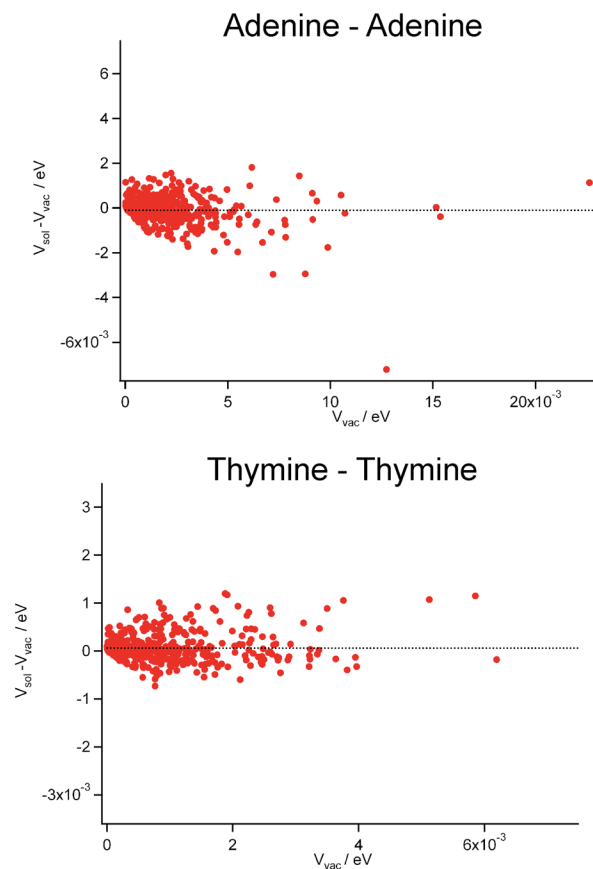


Figure 3. Effect of the polar environment ($\delta = V_{sol} - V_{vac}$) on the TET coupling computed for A_7-A_8 and $T_{23}-T_{24}$ stacks (500 structures for each type were considered). The dashed line corresponds to the average value.

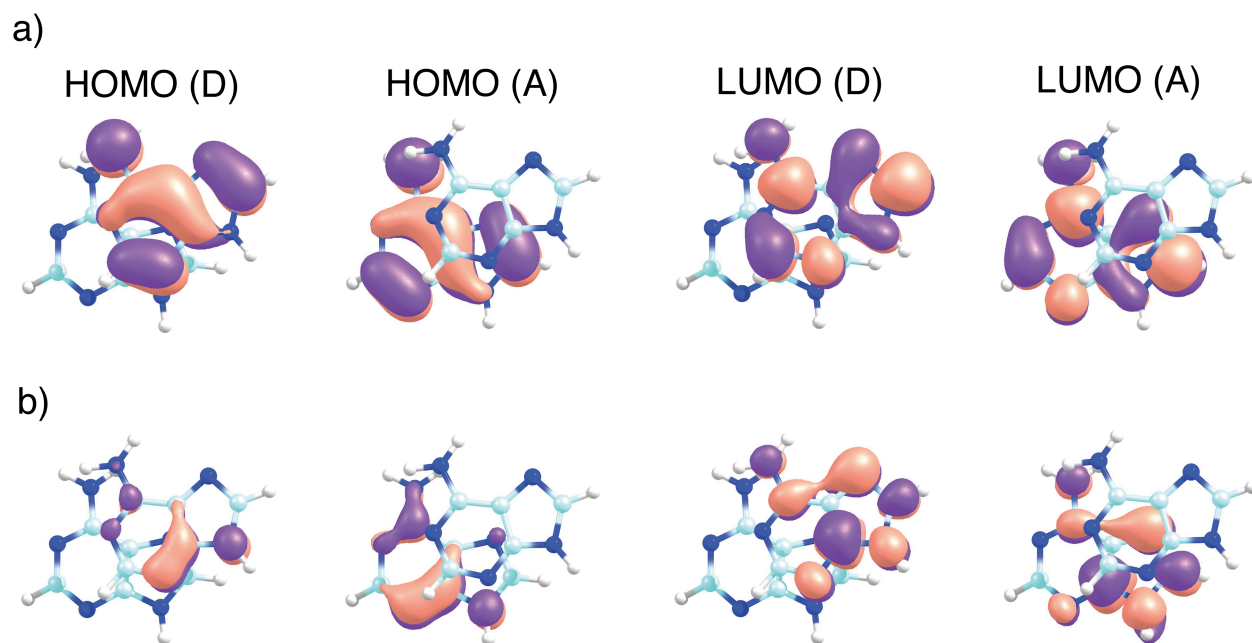


Figure 4. a) HOMO and LUMO orbitals corresponding to the donor and acceptor units for an individual A₇-A₈ pair (surface isovalue 0.03 a.u.). b) Changes of the HOMO and LUMO orbitals when passing from vacuum to the polar environment (surface isovalue 0.003 a.u.).

Table 1. Effective electronic couplings squared V^2 , calculated for the A₇-A₈ and T₂₃-T₂₄ stacks in vacuum and embedded in the dielectric environment. Results are averaged over 500 conformations sampled from a 15 ns molecular dynamics trajectory. Values are in eV².

	A ₇ -A ₈	T ₂₃ -T ₂₄
Vacuum	9.16×10^{-6}	1.57×10^{-6}
Environment	8.53×10^{-6}	1.83×10^{-6}

4. Conclusions

This is a first computational study on the effects of the polar environment on the TET coupling. Conformational flexibility of the donor and acceptor sites was accounted for by performing CIS-PCM calculations on 500 snapshots of A-A and T-T π stacks. The polarization (reaction field) contribution to the coupling (its average absolute value for A-A and T-T is $0.43 \cdot 10^{-3}$ eV and $0.20 \cdot 10^{-3}$ eV, respectively), can considerably modulate its values in individual conformations. This effect can be traced to the perturbation of molecular orbitals of each fragment and thus to a change of their overlap upon solvation, which translates into a new electronic coupling value. The effective coupling is not, however, essentially affected (its value for A-A and T-T changes only by a factor 0.93 and 1.16, respectively), because averaging over many conformations leads to an overall cancellation of the polarization effects. We note that absolute changes of the TET coupling in the π stacks due to the solute-solvent interaction are calculated to be significantly smaller than the coupling values in conformations with strong electronic interaction between donor and acceptor.

Despite the fact that A and T nucleobases (and their stacks) are very polar species (e. g. our estimated dipole moments are ~ 2.5 and ~ 5.0 D, respectively) only moderate effects of the polar medium on the TET effective coupling are found. Thus, one can expect that also in other TET systems, the triplet exciton mobility should not be very sensitive to the polarization effects of the environment.

Acknowledgement. C.C. acknowledges support from the Departament d'Innovació, Universitat i Empresa of the Generalitat de Catalunya (grant no. 2008BPB00108). A.A.V. is grateful to the Spanish Ministry of Education and Science for financial support (project CTQ2008- 06696BQU).

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