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Can Charge Recombination in DNA Hairpins Be Controlled by Counterions?[†]

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To decide whether counterions can affect the rate of charge recombination in DNA hairpins, the influence of the salt concentration on the free energy of this process was studied computationally using molecular dynamics simulations. The calculations were performed using the implicit treatment of the surroundings (the MM-PBSA and MM-GBSA techniques) and the explicit description of counterions and water molecules (thermodynamic integration). The data obtained with these distinct approaches were found to be in good agreement. The effect of counterions on the free energy of the charge recombination process was found to be small. For the hairpins with six A/T base pairs between the donor and acceptor chromophores, the difference in the value of the free energy does not exceed 0.5 kcal/mol when the environment changes from pure water to the 0.1 M NaCl solution typical for kinetic measurements of charge recombination in DNA hairpins. Even a smaller salt effect has numerically been obtained for a shorter hairpin containing three A/T pairs. These results suggest that under typical experimental conditions, the counterions cannot control the rate of charge recombination. For a highly concentrated salt solution (1 M NaCl), the influence of counterions on the energetics of the process becomes stronger. Since in this case the free energy for charge recombination exhibits a more substantial but still kinetically insignificant increase, the calculated rate of the process only slightly decreases with the salt concentration.

Introduction

Long-range migration of radical cations (electronic holes) along the stack of base pairs (the so-called π stack) inside of the DNA double helix has received much attention during past two decades and still remains an area of intense experimental and theoretical investigations.¹ The ability of DNA to serve as a medium for long-range charge transfer is essential for a variety of DNA applications in molecular electronics, molecular computing, and electrochemical biosensoric devices. The same property is shown to be also important for developing new techniques to detect structural changes due to protein binding and mismatches in base pairing. For these and some other potential applications, the elucidation of key mechanisms responsible for charge-transport phenomena in DNA turns out to be crucial. The solution of this challenging problem is also vital for current research on oxidative damage of DNA, which may cause apoptosis, mutations, and cancer.

The investigations of electronic properties of DNA reveal several mechanisms of charge transport along the pathways provided by this “molecule of life”. In particular, it has been shown that a hole can be transferred between the initial and final distant sites either via a coherent single-step tunneling or due to an incoherent multistep hopping of a positive charge between guanine (G) “resting sites” through bridges of adenine

(A)/thymine (T) pairs (the so-called G-hopping). Although the latter mechanism was successfully applied to the interpretation of many experimental results (see, for example, refs 2–7), G-hopping failed to rationalize several recent experimental findings.^{8–11} For example, this mechanism does not allow one to understand why the actual position of the G base strongly affects the hole transfer rate in DNA hairpins.¹¹ It was also established^{1m} that G-hopping alone cannot explain both the steep decrease in the efficiency of hole transfer, ϕ , (and the hole transfer rate, k) as the positive charge carriers traverse the initial three adenines and the slower decrease as they further traverse A nucleobases.² Conwell considered such dependencies as evidence in favor of the long-range polaron hopping mechanism of charge transport.¹² This mechanism suggests that a hole is able to form a polaron due to the self-trapping of the excess charge by a distortion of the base pair stack¹² or because of the polarization of the surrounding water molecules.¹³ As a consequence, the excess positive charge can be extended over several bases, and the hole motion is expected to proceed via sequential phonon-assisted polaron transitions.⁷ However, recent calculations¹⁴ indicate that polar surroundings essentially suppress charge delocalization in DNA, and hole states are localized on individual G bases. This result does not support the earlier conclusion of Basko and Conwell¹⁵ that a positive charge can be spread over five or more G/C sites, leading to the polaron formation in DNA oligomers² and hairpins.⁸ In addition, the computational data obtained by Olofsson and Larsson show¹⁶ that spatially well-localized hole states can be energetically stabilized due to the internal reorganization of nucleobases, thus reinforcing the hole localization on a single base pair.

Thus, although the long-range polaron hopping is consistent with the measured dependencies of ϕ and k on the number of

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the A/T pairs between donor and acceptor, n , this mechanism contradicts the results following from quantum chemical studies of localization/delocalization phenomena of excess positive charge in DNA.^{14,16} On the other hand, the mechanism of G-hopping based on the hole confinement to a single G base is supported by the quantum chemical investigations^{14,16} of localization/delocalization phenomena but does not account for the dependence of ϕ (and k) versus n .

To overcome the difficulties mentioned above, the additional mechanism of charge migration through DNA known as A-hopping has been proposed.^{2,17,18} This mechanism involves temporal localization of holes on A sites and subsequent transitions of a positive charge to the neighboring A. Note, however, that the possibility of A-hopping is hard to justify within the framework of physical models treating the DNA structure as static. Usually, such models rely on the estimates of redox potentials for individual nucleosides in solution¹⁹ and disregard the influence of the DNA structure and structural dynamics on the energetics of hole transport. According to the results obtained using this static approximation,^{19b} the radical cationic state G^+ is more stable than the state A^+ by $\Delta = 0.4$ eV. This leads to the very small Boltzmann factor, $\exp[-\Delta/(k_B T)]$, for the thermal population of the A bridge at room temperature $T = 298$ K. Therefore, thermally induced transfer of a hole from G^+ to A and subsequent hopping to a neighboring adenine base is energetically implausible for static DNA.²⁰

The failure of the earlier attempts to justify the mechanism of A-hopping from an energetic point of view can be attributed to the breakdown of the main assumption inherent in the most of the previous treatments of energetics for the hole migration in DNA. Namely, it was presumed that π stacks in DNA duplexes represent a rigid system without dynamic changes along various possible conformational degrees of freedom.²¹ Meanwhile, even in the absence of charge carriers, the DNA structure and its surroundings exhibit extremely complex time behavior. Dynamic processes responsible for such behavior range from vibrations with periods as short as tens of femtoseconds to a broad spectrum of diffusion motions (of nucleobases, counterions, and water molecules) that evolve on time scales between tens to hundreds of picoseconds.²² Taking into account that both site energies and electron coupling depend on the arrangement of adjacent base pairs in the stack,^{21,23–26} one can expect that energetics of the hole transport in dynamic and static DNA will be different.

To discuss processes associated with the hole transport in dynamic DNA, it is convenient to distinguish effects arising due to the fluctuations of DNA structure, dynamic variations of the water environment, and the effects caused by counterions. Several models have been proposed in order to describe the effect of structural fluctuations and electron–phonon coupling approximately. These models attempt to simulate the influence of relative motions of neighboring bases^{21a,23,27,28} as well as the impact of internal vibrational modes of nucleobases on site energies and electron coupling,^{29,30} that is, on two main parameters, which determine the efficiency and the rate of hole transfer in DNA. In particular, Grozema et al.^{24,31} performed an extensive study of the effects of structural fluctuations and electrostatic interactions on the rates of photoinduced charge transfer from donor to acceptor through bridges containing only A/T base pairs. Molecular dynamic simulations of the DNA structural dynamics combined with density functional theory calculations of charge-transfer integrals and orbital energies show that for short DNA hairpins (<4 base pairs), the hole motion occurs via the single-step superexchange mechanism

with a relatively strong dependence of k on the number of A/T pairs. For longer hairpins, a crossover to a fluctuation-assisted incoherent charge transport was theoretically predicted. Analysis of the charge distribution during the charge-transfer process indicates that for longer bridges, substantial charge density builds up on the bridge, but this charge density is mostly confined to the adenine next to the hole donor. This is caused by the electrostatic interaction between the hole on the A/T bridge and the negative charge on the hole donor. The results obtained allow the conclusion that the relatively strong (exponential) dependence of k versus n for short bridges is mostly due to this electrostatic interaction, while structural fluctuations play a critical role in hole migration, especially across longer bridges.^{24,30} A similar approach enables one to explain the strong dependence of the charge-transfer rate in DNA hairpins on the position of a single GC base pair inserted in the sequence containing A/T pairs. Thus, fluctuations of DNA structure allow the justification of A hopping, the explanation of the observed dependences of the charge-transfer rate on the number of A/T base pairs in the stack of nucleobases, and consistent interpretation of other experimental findings which can be hardly understood within the models based on the concept of static DNA.

It should be noted, however, that nearly all theoretical studies of charge transfer in dynamic DNA ignore the influence of solvent modes and counterions on the kinetics of the process. This is also true for the approaches that describe the solvent polarization effects using implicit solvent models,^{12,32} which can render merely the overall polarization of nucleobases by the solvent but no specific interaction.³² The first step toward quantitative study of the effect of solvent fluctuations on charge migration along the stack of nucleobases was made in ref 27 by using the INDO/S method coupled to classical MD simulations of DNA in a solvent environment. It has been shown that the coupling of hole transfer parameters to the solvent degrees of freedom can result in fluctuations in site energies as large as 0.4 eV, which are able to serve as a driving force for transport of positive charges in DNA.²⁷ Similar estimates were obtained later by Elstner and co-workers using a tight-binding DFT approach.³³

Counterions in the vicinity of nucleobases also strongly affect the energetics of radical cation states and are able to facilitate hole transfer from G to A in DNA π stacks.²⁶ Due to this circumstance, hole transport in DNA hairpins can proceed via to the so-called “ion-gating” mechanism.²² The dynamics of water molecules and counterions considerably modulates the relative redox potentials of the nucleobases. As a result, fluctuations of the DNA environment can render hole transfer processes from the G/C to A/T pair energetically feasible.²⁷ Another consequence which is actively discussed in the literature (see, for example, refs 34 and 35) is the possibility to control the charge recombination (CR) rate in DNA hairpins by counterions. This effect relies on the assumption that for systems analogous to the stilbene-linked DNA hairpin shown in Figure 1 as an example, two distinguishable charge-separated states $Sa^--(AT)_n-Sd^+$ exist. One of these states with the energy E_I arises if a Cl^- counterion is bound to a Sd^+ cation, while the other with the higher hole energy $E_{II} > E_I$ is associated with Sd^+ , which only has water molecules nearby. Therefore, the potential barrier for CR is expected to be larger in the presence of Cl^- bound to Sd^+ than that in the absence of a counterion. This implies that for the tunneling mechanism of recombination, the process will be slower in the presence of counterions than that in their absence.

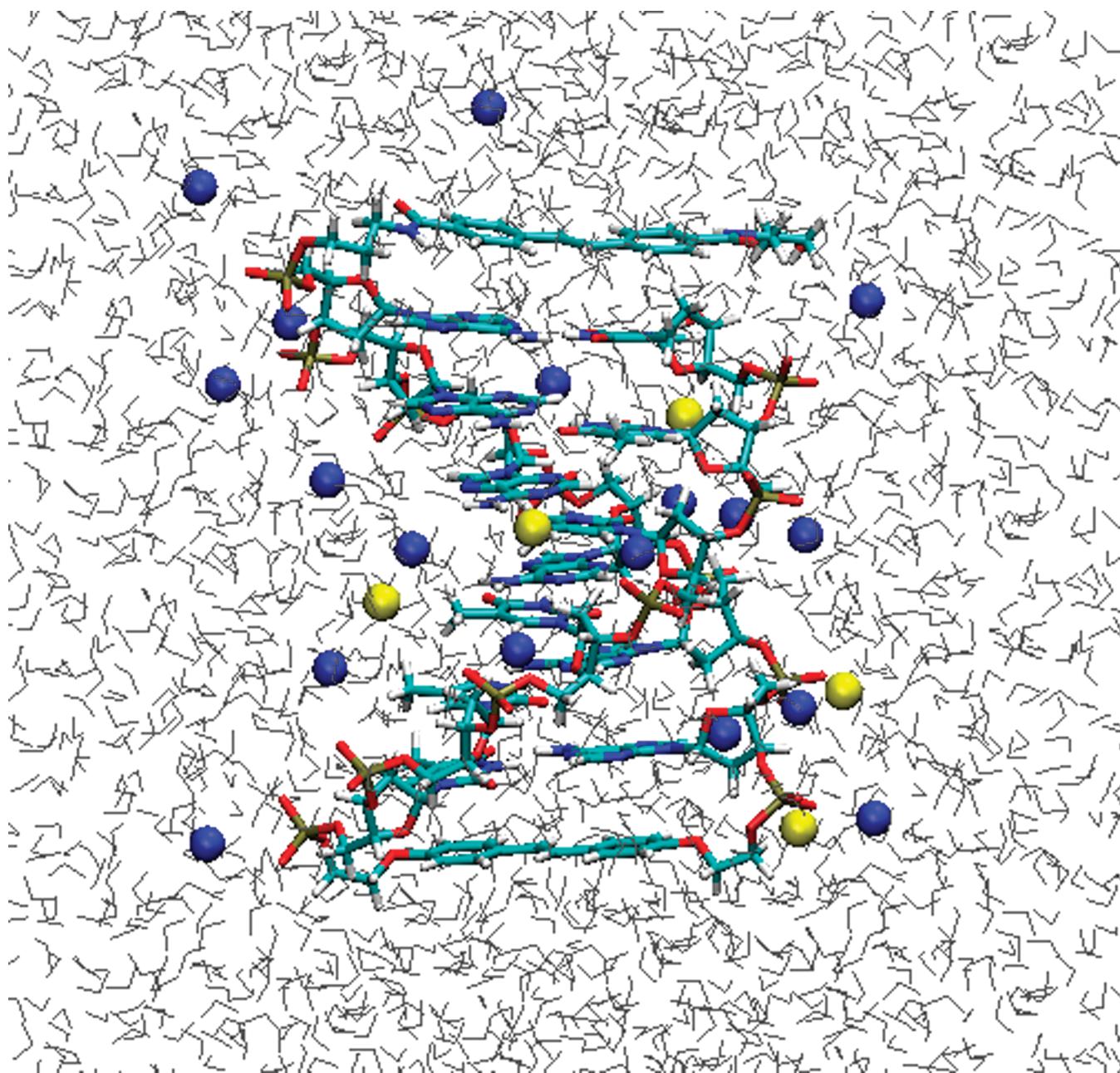


Figure 1. DNA hairpin A6 in 0.1 M NaCl water solution. The system includes 2935 water molecules, 5 Cl^- depicted in yellow, and 18 Na^+ shown in blue. Thirteen Na^+ positive ions compensate the negative charge of hairpin phosphate groups, and the rest arise due to the dissociation of NaCl.

In the present work, we use molecular dynamics simulation techniques to address the question of whether the CR kinetics in DNA hairpins can be controlled by counterions. The answer to this question is important for gaining deeper insight into the mechanism of hole motion in DNA and for a variety of applications that exploit the charge-separation phenomenon such as fabrication of photovoltaic diodes and solar cells.³⁶ A straightforward way to decide to what extent counterions are able to change the rate of tunneling recombination is to estimate the free energy for the CR in the presence and in the absence of counterions in the surroundings of the Sd^+ cation. The required calculations were performed here within the framework of approaches that allow implicit [molecular mechanics Poisson–Boltzmann surface area (MM-PBSA) and molecular mechanics generalized Born surface area (MM-GBSA) schemes] and explicit (thermodynamic integration technique) treatments of the solvent and counterions; see also refs 37 and 38. Using

this computational methodology, we show that counterions cannot have a large influence on the kinetics of charge recombination.

2. Computational Details

2.1. Model Systems and MD Simulations. Hairpins. Eight nanosecond MD trajectories were generated for several systems including DNA hairpins, $\text{Sa}-\text{d}(\text{A}_n)-\text{Sd}-\text{d}(\text{T}_n)$, with a short ($n = 3$) and a long ($n = 6$) A/T sequence shown in Chart 1 as representative examples. In what follows, these hairpins will be designated as A3 and A6, respectively.

Two distinct states of each hairpin are considered, namely, the charge-separated (CS) state, Sa^--Sd^+ , and the $\text{Sa}-\text{Sd}$ state formed after CR. MD simulations of these states were performed for A3 and A6 hairpins in aqueous solutions. To investigate the influence of salt on the structure of the hairpins and on the rate of the CR reaction, the systems were embedded in pure water as well

CHART 1



TABLE 1: Number of Ions and Water Molecules in Simulated Systems

system	number of Na^+	number of Cl^-	number of water molecules
A3 in water	7	0	2113
A3 in 0.1 M NaCl water solution	11	4	2105
A3 in 1 M NaCl water solution	43	36	2041
A6 in water	13	0	2945
A6 in 0.1 M NaCl water solution	18	5	2935
A6 in 1 M NaCl water solution	65	52	2841

as in the 0.1 and 1.0 M solutions of NaCl. An example of the stilbene-linked DNA hairpins studied experimentally^{8,11} and theoretically^{24,25b,31,35} is shown in Figure 1. This and other systems simulated in the present work are listed in Table 1. Thus, MD trajectories for 12 systems were computed. In addition, MD simulations of several intermediate states were performed for thermodynamic integration.

MD Simulations. Molecular dynamics simulations of hairpins were carried out using the AMBER 9 program.³⁹ The starting structures of hairpins were generated by incorporating the optimized chromophore structures into the B-DNA stacks consisting of 3 and 6 A/T pairs. The force field parameters of Sa and Sd were generated within the established procedure (for details, see Supporting Information). The parm99 force field⁴⁰ and TIP3P⁴¹ parameters for water were employed.

The unrestrained MD simulations were performed at constant temperature (300 K) and pressure (1 atm) using a time step of 2 fs. The SHAKE algorithm was applied to all hydrogen atoms.⁴² Periodic boundary conditions, the 8 Å cutoff for nonbonded interactions, and the smooth particle mesh Ewald method⁴³ for the treatment of electrostatic interactions were applied. After the equilibration step (for more details, see Supporting Information), the production run was initiated for 8 ns. The coordinates were stored every 1 ps.

2.2. Estimations of Free Energy: MM-PBSA and MM-GBSA. The common approach to estimate the free energy of the system from MD trajectories is based on the MM-PBSA and the MM-GBSA schemes. These schemes combine MM for the solute in the gas phase with a continuum model for solvation free energy.^{44–47} The free energy G is computed using the expression

$$G = H_{\text{gas}} + H_{\text{trans/rot}} + G_{\text{solv}} - TS \quad (1)$$

averaged over a MD trajectory. In eq 1, H_{gas} is the gas-phase energy calculated by MM, $H_{\text{trans/rot}}$ is the contribution to the G

values coming from translational and rotational degrees of freedom (at 300 K, this contribution is equal to ~ 1.8 kcal/mol), and G_{solv} is the solvation free energy. The latter quantity was estimated using the generalized Born (GBSA) and the Poisson–Boltzmann (PBSA) methods. Both methods have been successfully applied to predict free energies for various biological molecules, including proteins and nucleic acids. In this study, we employed both the PBSA and GBSA approaches⁴⁸ implemented in the AMBER 9 package. The entropy term TS was estimated by normal-mode analysis (NMODE) with a distance-dependent dielectric constant ($\epsilon = 4R_{ij}$).⁴⁹

2.3. Thermodynamic Integration. The salt effect for the free energy of the CR reaction was also calculated using thermodynamic integration (TI). To use this approach, MD trajectories were obtained for intermediate states between CR and CS states. As discussed in the literature, even the simplest numerical TI technique provides quite reliable estimates of the reaction free energy for systems, which can be smoothly transformed from the initial to the final state by varying atomic charges.^{50,51}

Since excess negative and positive charges on the hole donor and on the hole acceptor are delocalized over several atoms, the TI approach should give quite reliable estimates. In intermediate states, atomic charges \tilde{Q}_i are calculated as

$$\tilde{Q}_i = Q_i^0(1 - \lambda) + \lambda Q_i^1$$

where Q_i^0 and Q_i^1 are the charges in the chromophores in initial ($\lambda = 0$) and final ($\lambda = 1$) states and λ is the mixing parameter.

The ΔG value is evaluated within the TI scheme as the ensemble average of the derivative of the potential energy with respect to λ

$$\Delta G = \sum_{i=1}^n w_i \left\langle \left(\frac{\partial V}{\partial \lambda} \right)_{\lambda_i} \right\rangle \quad (2)$$

where V is the potential energy of the system and $\langle \rangle$ denotes averaging over an MD trajectory generated for intermediate state i . The salt effects on CR are clearly dominated by the electrostatic energies, and the free energy of CR can be well estimated at the midpoint ($\lambda = 1/2$)

$$\Delta G = \left\langle \left(\frac{\partial V}{\partial \lambda} \right)_{\lambda=1/2} \right\rangle \quad (3)$$

In addition, we also employ three-point interpolation with the values of parameters as follows: $\lambda_1 = 0.1127$, 0.5, and 0.883; $w_1 = w_3 = 5/18$; $w_2 = 4/9$.

TABLE 2: Free Energy, G , and Its Components Obtained from MM-PBSA and MM-GBSA Analysis of the MD Trajectory for CR and CS States of the A6 Hairpin (in kcal/mol)

energy terms in eq 1	ground CR state			CS state		
	water	0.1 M NaCl water solution	1 M NaCl water solution	water	0.1 M NaCl water solution	1 M NaCl water solution
H_{gas}	877.7	881.8	852.5	878.1	878.0	882.3
$-TS$	-403.5	-402.7	-403.0	-403.6	-403.9	-402.8
G_{solv}	-2821.8	-2826.3	-2793.1	-2848.3	-2850.4	-2854.2
G	-2345.7	-2345.4	-2341.8	-2372.0	-2374.5	-2372.9
G_{solv}	-2750.1	-2770.0	-2746.3	-2777.6	-2795.0	-2809.0
G	-2274.0	-2289.1	-2295.0	-2301.4	-2319.1	-2327.7

3. Results and Discussion

3.1. MM-PBSA and MM-GBSA Analysis. The values of the energy terms in eq 1 calculated for the A6 hairpin are presented in Table 2. More details as well as the corresponding data for the A3 hairpin are provided in Supporting Information. The gas-phase energy, H_{gas} , which involves the internal, van der Waals, and electrostatic interactions within the hairpin was found to be positive. This suggests that in the gas phase, the electrostatic repulsion interaction of the negatively charged sugar-phosphate backbone makes the main contribution in the H_{gas} values of the hairpins.^{46,47} The H_{gas} values calculated for CR and CS states in water and in the 0.1 M NaCl water solution are computationally found to be similar. As follows from our data, CR is much more stabilized in the 1 M NaCl water solution than in pure water and in the 0.1 M NaCl water solution, while the stability of the CS state in these three cases remains almost the same (cf. the values of H_{gas} in the first row of Table 2). This can be explained by structural changes of the A6 hairpin in the CR state caused by the decrease of the electrostatic repulsion of phosphate groups. Note that the smaller number of these groups in the A3 system significantly reduces H_{gas} in comparison with the value obtained for the A6 hairpin. As can be seen from the Supporting Information, the calculations give approximately the same value of $H_{\text{gas}} \approx 115$ kcal/mol for CS states of the A3 hairpin in pure water and in water solutions of NaCl. This is much smaller than the value of $H_{\text{gas}} \approx 880$ kcal/mol obtained for the A6 hairpin in the similar water surroundings (see Table 2).

The solvation free energy, G_{solv} , was calculated using the PBSA and GBSA methods. Although the absolute values of G_{solv} derived with these two methods differ substantially (the Poisson-Boltzmann equation yields larger negative values of G_{solv} than estimates based on the GBSA scheme), the free energies calculated for the CR reaction, Δ_{CR} , turn out to be very similar. For instance, the Δ_{CR} values found for the A6 hairpin in pure water with the PBSA and GBSA methods are 26.3 and 27.3 kcal/mol, respectively. These values are slightly smaller than those obtained for the 0.1 M NaCl water solution ($\Delta_{\text{CR}} = 29.1$ and 30.0 kcal/mol, respectively). A further increase of the ion concentration by adding 1 M NaCl to water leads to $\Delta_{\text{CR}} = 31.1$ and 32.7 kcal/mol. Thus, on the basis of the computational results obtained, one can assume that in the presence of counterions, the CR reaction slows down. However, the reduction of the CR rate with the increase of the NaCl concentration turns out to be much smaller than the tendency predicted in refs 34 and 35. Although the salt effect calculated with PBSA and GBSA (see, for example, ref 52) is larger than the effect obtained by a more accurate thermodynamic integration method, these estimates of Δ_{CR} appear to be reasonable. Note, however, that to obtain the absolute values of free energy for the CR

reaction, the relative energies deduced here should be corrected by a negative term Δ_0 , with the value determined by changes of electronic energy when the system undergoes the transition from the higher-lying CS state $\text{Sa}^- - \text{A}_n - \text{Sd}^+$ of the isolated hairpin to the lower-lying state $\text{Sa} - \text{A}_n - \text{Sd}$ of the same hairpin with neutral chromophores Sa and Sd. To estimate Δ_0 , accurate quantum mechanical methods should be invoked (see, for example, ref 53). By definition, the Δ_0 value is not affected by the environment and does not influence the salt effects considered here.

3.2. Thermodynamic Integration. This approach enables us to obtain more reliable estimates for the effect of the salt concentration on Δ_{CR} . To perform such estimations, it is convenient to divide the free energy of the CR reaction into two parts denoted by Δ_0 and Δ_{solv} . The first term Δ_0 has already been discussed in Section 3.1. Here we are mainly interested in the second term Δ_{solv} since this term is entirely responsible for the effects of the environment on the CR reaction.

Theoretically, the value of Δ_{solv} is determined by the difference in the interaction of the CS and CR states of the DNA hairpin with the surroundings. The CR process leads to a significant decrease of the dipole moment of the hairpin, thus considerably reducing the interaction of the hairpin with the polar environment ($\Delta_{\text{solv}} > 0$). Because changes in the electrostatic interaction, Δ_{EL} , make the main contribution into the Δ_{solv} value, the corresponding calculation of Δ_{EL} was also performed. The data obtained using the middle-point TI scheme and three-point interpolation (see section 2.3) are found to be in good agreement (see Table 3), suggesting that the TI procedure is robust and can provide reliable values for Δ_{solv} and Δ_{EL} . Computational results for A3 and A6 hairpins in water and NaCl solutions are summarized in Table 3. The obtained data suggest the following:

(1) Since the values of Δ_{solv} and Δ_{EL} evaluated for the CR process in A3 and A6 hairpins are very similar, both quantities are not very sensitive to the length of the A/T bridge.

(2) The influence of counterions on the energetics of the CR process is small. In the case of the A3 hairpin, the changes in the Δ_{solv} and Δ_{EL} values due to the adding of 0.1 M NaCl to water do not exceed 0.05 kcal/mol and may be neglected. Although, in the longer A6 hairpin, the effect is more significant (about 0.5 kcal/mol), the counterions cannot strongly affect the rate of the CR process in this case as well. A stronger effect for the A6 hairpin as compared to the shorter hairpin with three A/T base pairs can be explained by a larger charge separation (dipole moment) in $\text{Sa}^- - \text{A}_6 - \text{Sd}^+$ as compared to that in $\text{Sa}^- - \text{A}_3 - \text{Sd}^+$.

(3) For the 1 M NaCl water solution in which the concentration of the salt exceeds the value used in experiment by a factor of 10, the influence of counterions on the energetics of the CR

TABLE 3: Δ_{solv} Values and Changes in the Electrostatic Interaction Δ_{EL} Computed for the CR Reaction in the A3 and A6 Hairpins by Using Thermodynamic Integration^a

scheme	water		0.1 M NaCl water solution		1 M NaCl water solution	
	Δ_{solv}	Δ_{EL}	Δ_{solv}	Δ_{EL}	Δ_{solv}	Δ_{EL}
CR Process in the A3 Hairpin: $\text{Sa}^- - \text{A}_3 - \text{Sd}^+ \rightarrow \text{Sa} - \text{A}_3 - \text{Sd}$						
middle-point TI scheme	26.51	17.74	26.56	17.77	29.20	18.43
three-point interpolation TI scheme	26.52	17.78	26.52	17.76	29.27	18.46
CR Process in the A6 Hairpin: $\text{Sa}^- - \text{A}_6 - \text{Sd}^+ \rightarrow \text{Sa} - \text{A}_6 - \text{Sd}$						
middle-point TI scheme	26.48	17.85	26.83	18.53	27.43	18.94
three-point interpolation TI scheme	26.27	17.77	26.74	18.44	27.42	19.12

^a All data are in kcal/mol.

process becomes more remarkable. For instance, the comparison of the data obtained for the A3 hairpin in pure water and in the 1 M NaCl solution show that the Δ_{solv} value becomes higher by ~ 3 kcal/mol (while Δ_{EL} increases by 0.7 kcal/mol). For the A6 hairpin, the analogous change in Δ_{solv} is about 1 kcal/mol. Thus, the rate of the CR process indeed becomes smaller as the salt concentration increases, in accord with the estimations presented in section 3.1. The significant decrease is predicted, however, only for a relatively high concentration of NaCl. In the 0.1 M NaCl/water solution used in the experiment, the free energy of the CR process is very similar to that found for hairpins in pure water.

Previously, it was assumed that the free energy of CR depends on the nature of the negatively charged counterions and that replacing of NaCl by NaBr will remarkably affect the ET rate.^{34,35} For $\text{Sa}^- - \text{A}_6 - \text{Sd}^+$ in 0.1 M NaCl, we found, however, that the average shortest distance between Cl^- and Sd^+ , 13.6 Å, is considerably longer than the distance between Na^+ and Sd^+ , 6.4 Å. Because the hairpin has a large negative charge equal to -13 (13 phosphate groups with charge -1 each), it attracts cations but repulses anions. Thus, one may expect that the nature of cations rather than anions will mainly affect the CR process in solution with a high salt concentration. It means that the replacement of NaCl with KCl should produce more significant effects than the replacement of NaBr with NaCl. These effects will be discussed in more detail in a separate publication.

It should also be noted that the residence time of counterions around DNA varies from tens to hundreds of picoseconds,⁵⁴ and therefore, it is unlikely that MD trajectories longer than ~ 10 ns can yield any additional theoretical findings.

4. Conclusion

In summary, we have employed molecular dynamics simulations to address the question of whether the salt concentration can strongly affect the rate of the charge recombination process in DNA hairpins. To solve the problem, the difference in the energies of the charge-separated and the charge recombination states in water and NaCl solutions was estimated using the implicit description of the surroundings (the MM-PBSA and MM-GBSA techniques) and the explicit treatment of counterions and water molecules (thermodynamic integration). The estimates obtained within these two frameworks provide very similar results.

The influence of counterions on the free energy of the charge recombination process was found to be small. When the surroundings changed from pure water to the 0.1 M NaCl solution, the difference in the value of this energy did not exceed 0.5 and 0.05 kcal/mol for the DNA hairpins with six and three A/T base pairs, respectively. This suggests that under typical experimental conditions, the counterions cannot significantly

affect the rate of charge recombination. A stronger effect found for longer hairpins is explained by larger charge separation in $\text{Sa}^- - \text{A}_6 - \text{Sd}^+$ than that in $\text{Sa}^- - \text{A}_3 - \text{Sd}^+$.

For a highly concentrated salt solution (1 M NaCl), the influence of counterions on the energetics of the CR process becomes more significant. Because the free energy for charge recombination exhibits a more substantial increase in this case, the calculated rate of the process should decrease with the salt concentration.

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Supporting Information Available: Computational details of MD simulations; generation of the force field parameters for chromophores Sa and Sd; and the data on the MM-PBSA and MM-GBSA analysis of the MD trajectory for A3 and A6 hairpins. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) For a review, see, for example: (a) Diederichsen, U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2317–2319. (b) Beratan, D. N.; Priyadarshy, S.; Risser, S. M. *Chem. Biol.* **1997**, *4*, 3–8. (c) Kelley, S. O.; Barton, J. K. *Chem. Biol.* **1998**, *5*, 413–425. (d) Turro, N. J.; Barton, J. K. *J. Biol. Inorg. Chem.* **1998**, *3*, 201–209. (e) Jortner, J.; Bixon, M.; Langenbacher, T.; Michel-Beyerle, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12759–12765. (f) Grinstaff, M. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 3629–3635. (g) Schuster, G. B. *Acc. Chem. Res.* **2000**, *33*, 253–260. (h) Giese, B. *Acc. Chem. Res.* **2000**, *33*, 631–636. (i) Berlin, Y. A.; Burin, A. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 260–268. (j) Lewis, F. D.; Letsinger, R. L.; Wasieleski, M. R. *Acc. Chem. Res.* **2001**, *34*, 159–170. (k) Dekker, C.; Ratner, M. A. Electronic properties of DNA. *Phys. World* **2001**, *14*, 29–33. (l) Lewis, F. D.; Liu, J. Q.; Weigel, W.; Rettig, W.; Kurnikov, I. V.; Beratan, D. N. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 12536–12541. (m) Bixon, M.; Jortner, J. *Chem. Phys.* **2002**, *281*, 393–408. (n) Schuster, G. B., Ed. *Long-range charge transfer in DNA*; Springer-Verlag: Berlin, Germany, 2004. (o) Wagenknecht, H.-A., Ed. *Charge transfer in DNA*; Wiley-VCH: Weinheim, Germany, 2005. (p) Voityuk, A. A. In *Computational studies of RNA and DNA*; Sponer, J., Lankas, F., Eds.; Springer: Dordrecht, The Netherlands, 2006; pp 485–512. (q) Chakraborty, T., Ed. *Charge migration in DNA*; Springer: Berlin, Germany, 2007. (r) Genereux, J. C.; Boal, A. K.; Barton, J. K. *J. Am. Chem. Soc.* **2010**, *132*, 891–905.
- (2) Giese, B.; Amaudrut, J.; Köhler, A.-K.; Spermann, M.; Wessely, S. *Nature* **2001**, *412*, 318–320.
- (3) Meggers, E.; Michel-Beyerle, M. E.; Giese, B. *J. Am. Chem. Soc.* **1998**, *120*, 12950–12915.
- (4) Giese, B.; Wessely, S.; Spormann, M.; Lindemann, U.; Meggers, E.; Michel-Beyerle, M. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 996–998.

- (5) Nakatani, K.; Dohno, C.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 10854–10855.
- (6) Ly, D.; Sanii, L.; Schuster, G. B. *J. Am. Chem. Soc.* **1999**, *121*, 9400–9410.
- (7) Henderson, P. T.; Jones, D.; Hampikian, G.; Kan, Y.; Schuster, G. B. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 8353–8358.
- (8) (a) Lewis, F. D.; Zhu, H.; Daublain, P.; Cohen, B.; Wasielewski, M. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7982–7985. (b) Lewis, F. D.; Zhu, H.; Daublain, P.; Fiebig, T.; Raytchev, M.; Wang, Q.; Shafirovich, V. *J. Am. Chem. Soc.* **2006**, *128*, 791–800.
- (9) Kawai, K.; Takada, T.; Tojo, S.; Majima, T. *J. Am. Chem. Soc.* **2003**, *125*, 6842–6843.
- (10) Takada, T.; Kawai, K.; Cai, X.; Sugimoto, A.; Fujitsuka, M.; Majima, T. *J. Am. Chem. Soc.* **2004**, *126*, 1125–1129.
- (11) Lewis, F. D.; Daublain, P.; Cohen, B.; Vura-Weis, J.; Wasielewski, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 3798–3800.
- (12) Conwell, E. M. *Top. Curr. Chem.* **2004**, *237*, 73–101.
- (13) Conwell, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8795–8799.
- (14) (a) Voityuk, A. A. *J. Chem. Phys.* **2005**, *122*, 204904. (b) Blancafort, L.; Voityuk, A. A. *J. Phys. Chem. A* **2006**, *110*, 6426–6432.
- (15) Basko, D. M.; Conwell, E. M. *Phys. Rev. Lett.* **2002**, *88*, 098102.
- (16) Olofsson, J.; Larsson, S. *J. Phys. Chem. B* **2001**, *105*, 10398–10406.
- (17) Giese, B.; Biland, A. *Chem. Commun.* **2002**, *7*, 667–672.
- (18) Berlin, Y. A.; Burin, A. L.; Ratner, M. A. *Chem. Phys.* **2002**, *275*, 61–74.
- (19) (a) Seidel, C. A. M.; Schultz, A.; Sauer, M. H. M. *J. Phys. Chem.* **1996**, *100*, 5541–5553. (b) Steenken, S.; Jovanovic, S. V. *J. Am. Chem. Soc.* **1997**, *119*, 617–618.
- (20) Radical cation states of cytosine, C⁺, and T⁺ are considerably higher in energy than G⁺ with the energy gap of about 1 eV^{14b} and hence are very unlikely to accept an electronic hole in DNA.
- (21) See, for example: (a) Voityuk, A. A.; Siriwong, K.; Rösch, N. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5421–5425. (b) Starikov, E. B.; Cuniberti, G.; Tanaka, S. *J. Phys. Chem. B* **2009**, *113*, 10428–10435.
- (22) Barnett, R. N.; Cleveland, C. L.; Joy, A.; Landman, U.; Schuster, G. B. *Science* **2001**, *294*, 567–571.
- (23) Senthilkumar, K.; Grozema, F. C.; Guerra, C. F.; Bickelhaupt, F. M.; Lewis, F. D.; Berlin, Y. A.; Ratner, M. A.; Siebbeles, L. D. A. *J. Am. Chem. Soc.* **2005**, *127*, 14894–14903.
- (24) Grozema, F. C.; Tonzani, S.; Berlin, Y. A.; Schatz, G. C.; Siebbeles, L. D. A.; Ratner, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 5157–5166.
- (25) (a) Voityuk, A. A. *J. Chem. Phys.* **2008**, *128*, 115101. (b) Siriwong, K.; Voityuk, A. A. *J. Phys. Chem. B* **2008**, *112*, 8181–8187. (c) Voityuk, A. A. *J. Phys. Chem. B* **2009**, *113*, 14365–1468.
- (26) Kubaø, T.; Elstner, M. *J. Phys. Chem. B* **2008**, *112*, 7937–7947.
- (27) Voityuk, A. A.; Siriwong, K.; Rösch, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 624–627.
- (28) Grozema, F. C.; Siebbeles, L. D. C.; Berlin, Y. A.; Ratner, M. A. *ChemPhysChem* **2002**, *3*, 536–539.
- (29) Volobuyev, M.; Saint-Martin, H.; Adamowicz, L. *J. Phys. Chem. B* **2007**, *111*, 11083–11089.
- (30) Starikov, E. B. *Philos. Mag.* **2005**, *85*, 3435–3462.
- (31) Grozema, F. C.; Tonzani, S.; Berlin, Y. A.; Schatz, G. C.; Siebbeles, L. D. A.; Ratner, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 14204–14205.
- (32) Cramer, T.; Steinbrecher, T.; Labahn, A.; Koslowski, T. *Phys. Chem. Chem. Phys.* **2005**, *7*, 4039–4050.
- (33) Kubaø, T.; Kleinekathofer, U.; Elstner, M. *J. Phys. Chem. B* **2009**, *113*, 13107–13117.
- (34) Blaustein, G. S.; Demas, B.; Lewis, F. D.; Burin, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 400–401.
- (35) Blaustein, G. S.; Lewis, F. D.; Burin, A. L.; Shrestha, R. In *Lecture Notes in Computer Science*, Part II; Allen, G., Seidel, E., Dongarra, J., Nabrzyski, J., VanAlbada, G. D., Sloot, P. M. A., Eds.; Springer-Verlag: Berlin, Germany, 2009; Vol. 5545, pp 189–196.
- (36) See, for example: Granstrom, M.; Petritsch, K.; Arias, A. C.; Lux, A.; Anderson, M. R.; Friend, R. H. *Nature* **1998**, *395*, 257–260.
- (37) (a) Popovic, D. M.; Zaric, S. D.; Rabenstein, B.; Knapp, E. W. *J. Am. Chem. Soc.* **2001**, *123*, 6040–6053. (b) Mao, J.; Hauser, K.; Gunner, M. R. *Biochemistry* **2003**, *42*, 9829–9840. (c) Stephens, P. J.; Jollie, D. R.; Warshel, A. *Chem. Rev.* **1996**, *96*, 2491–2513. (d) Simonson, T. *Curr. Opin. Struct. Biol.* **2001**, *11*, 243–252.
- (38) Shurki, A.; Strajbl, M.; Schutz, C. N.; Warshel, A. *Methods Enzymol.* **2004**, *380*, 52–84.
- (39) Case, D. A.; Darden, T. A.; Cheatham, T. E., III; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Merz, K. M.; Pearlman, D. A.; Crowley, M.; Walker, R. C.; Zhang, W.; Wang, B.; Hayik, S.; Roitberg, A.; Seabra, G.; Wong, K. F.; Paesani, F.; Wu, X.; Brozell, S.; Tsui, V.; Gohlke, H.; Yang, L.; Tan, C.; Mongan, J.; Hornak, V.; Cui, G.; Beroza, P.; Mathews, D. H.; Schafmeister, C.; Ross, W. S.; Kollman, P. A. *AMBER 9*; University of California: San Francisco, CA, 2006.
- (40) Wang, J.; Cieplak, P.; Kollman, P. A. *J. Comput. Chem.* **2000**, *21*, 1049–1074.
- (41) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926–935.
- (42) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327–341.
- (43) Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H.; Pedersen, L. G. *J. Chem. Phys.* **1995**, *103*, 8577–8593.
- (44) Gohlke, H.; Case, D. A. *J. Comput. Chem.* **2004**, *25*, 238–250.
- (45) Srinivasan, J.; Cheatham, T. E., III; Cieplak, P.; Kollman, P. A.; Case, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 9401–9409.
- (46) Kollman, P. A.; Massova, I.; Reyes, C.; Kuhn, B.; Huo, S.; Chong, L.; Lee, M.; Lee, T.; Duan, Y.; Wang, W.; Donini, O.; Cieplak, P.; Srinivasan, J.; Case, D. A.; Cheatham, T. E., III. *Acc. Chem. Res.* **2000**, *33*, 889–897.
- (47) Siriwong, K.; Chuichay, P.; Saen-oon, S.; Suparpprom, C.; Vilaivan, T.; Hannongbua, S. *Biochem. Biophys. Res. Commun.* **2008**, *372*, 765–771.
- (48) Onufriev, A.; Bashford, D.; Case, D. A. *J. Phys. Chem. B* **2000**, *104*, 3712–3720.
- (49) Kottalam, J.; Case, D. A. *Biopolymers* **1990**, *29*, 1409–1421.
- (50) Frenkel, D.; Smit, B. *Understanding Molecular Simulation: From Algorithms to Applications*, 2nd ed.; Academic Press: San Diego, CA, 2002.
- (51) Kollman, P. *Chem. Rev.* **1993**, *93*, 2395–2417.
- (52) Srinivasan, J.; Trevathan, M. W.; Beroza, P.; Case, D. A. *Theor. Chem. Acc.* **1999**, *101*, 426–434.
- (53) Cauet, E.; Valiev, M.; Wear, J. H. *J. Phys. Chem. B* **2010**, *114*, 5886–5894.
- (54) Feig, M.; Pettitt, B. M. *Biophys. J.* **1999**, *77*, 1769–1775.