Estimate of the Reorganization Energy for Charge Transfer in DNA

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The solvent reorganization energy λ_s can have a significant effect on the activation energy for charge transfer in DNA and its dependence on donor (D)–acceptor (A) distance R_{DA}. To estimate λ_s and the resulting effective contribution β_s to the falloff parameter β for the overall transfer rate constant, the Poisson equation was solved numerically for several systems representing DNA duplexes, 5′-GGGT$_n$GGG-3′, in a realistically structured heterogeneous dielectric, as determined by molecular dynamics (MD) simulations. The charge transfer was modeled primarily for holes localized on single guanine bases. Effects of thermal fluctuations on λ_s were taken into account via structures for a given duplex sampled from MD trajectories. Calculated values of λ_s were found to be rather insensitive to thermal fluctuations of the DNA fragments but depended in crucial fashion on details of the dielectric model (shape and dielectric constants of various zones) that was used to describe the polarization response of the DNA and its environment to the charge transfer. λ_s was calculated to increase rapidly at small R_{DA} values (<15 Å), and accordingly the falloff parameter β_s (defined as a local function of R_{DA}) decreases appreciably with increasing R_{DA} (from 1.0 Å^{-1} with only one intermediate base pair between D and A to 0.15 Å^{-1} for systems with five intervening pairs). Calculated λ_s values were accurately fitted (standard deviation of ~0.5 kcal/mol) to a linear function of $1/R_{DA}$, including all cases except contact ($R_{DA} = 3.4$ Å), where some overlap of D and A sites may occur. A linear fit to an exponential (of form $\exp(-\beta_s R_{DA})$) gave comparable accuracy for the entire R_{DA} range. λ_s based on D and A holes delocalized over two adjacent guanine bases was uniformly ~12 kcal/mol smaller than the corresponding results for holes localized on single guanines, almost independent of R_{DA}. The internal reorganization energy for hole transfer between GC pairs was calculated at 16.6 kcal/mol at the B3LYP/6-31G* level.

Introduction

Charge transfer in DNA has attracted great interest from both experimentalists[1–4] and theoreticians[5–12] for a number of reasons, including in particular: (1) understanding the mechanisms of the oxidative damage and the photorepair of DNA[13,14] and (2) the potential role of DNA in the design of nanoelectronic devices.[15–17] The efficiency of DNA-mediated charge transfer depends on both the structure of DNA (sequence and mutual conformation of base pairs) and its environment. At temperature T, the nonadiabatic rate constant k_{DA} for charge transfer between donor (D) and acceptor (A) can be expressed as[18,19]

$$k_{DA} = \frac{2\pi}{\hbar} |H_{DA}|^2 (4\pi\lambda RT)^{-1/2} \exp[-(\Delta G° + \lambda)^2 / 4\lambda RT] \quad (1)$$

where H_{DA} is the electronic coupling matrix element, $\Delta G°$ is the reaction free energy, and λ is the reorganization energy; eq 1 represents the classical limit in which nuclear quantum effects are neglected. Quantum chemical calculations of H_{DA} and its distance and conformational dependence were considered in several recent papers.[8,20,21] We assume that hole transfer occurs as a charge shift between equivalent D and A sites, and therefore $\Delta G°$ is zero and will not be considered in the present work. If D and A sites differ, the corresponding determination of $\Delta G°$ can be performed at the quantum chemical level.[10,22] The reorganization energy is usually divided into two parts, $\lambda = \lambda_s$

$+ \lambda_i$, including the solvent and internal (molecular) terms, respectively. Often, the term λ_s is treated classically,[18,23–25] whereas the internal component is calculated with a quantum-chemical approach.[26,27] In the following we will focus mainly on the calculation of λ_s for hole transfer in a number of DNA duplexes. Evaluation of λ_s for electron transfer was considered in detail previously,[23,24] and particular applications to DNA have been reported recently.[11,28]

A very recent experimental investigation of the apparently anomalous distance dependence of charge transfer rates in DNA duplexes containing a covalently appended acridinium chromophore revealed that, in addition to the electronic coupling, the solvent reorganization energy can influence the distance dependence of the charge-transfer rate in an essential fashion.[24] On the basis of measured activation energies, the reorganization energy for different donor–acceptor distances was estimated.[25]

Tavernier and Fayer[29] studied the effects of dielectric heterogeneity (in both DNA and its environment) on λ_s for charge transfer in DNA, employing model calculations based on a total of four different zones (three distinct dielectric zones surrounding the D and A sites), and with the electric displacement field approximated by the vacuum field. Subject to this approximation, λ_s may be formulated additively in terms of contributions obtained for individual dielectric zones. The authors compared their results with experimental data of Lewis et al.[30] and concluded that the distance dependence of λ_s must be taken into account when interpreting the experimental data on DNA-mediated charge transfer in the range $R_{DA} < 15$ Å. These calculations[29] may be expected to overestimate the

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reorganization energy somewhat because a rather large value of the static dielectric constant, $\epsilon = 12.4$, was assigned to the base stack zone, in contrast to other estimates in the range of 2 to 4.[31] Furthermore, the geometry of the DNA fragment and its environment were kept fixed,[29] and the possible role of structural fluctuations was not considered. Such fluctuations may be significant for the interaction of DNA with surrounding counterions and water molecules.[31] Thus for understanding the charge-transfer kinetics, it is of interest to estimate the size of these effects.

The physical framework for a quantitative treatment of charge transfer in DNA has also been considered recently by Beratan and co-workers.[10,11] They evaluated λ_s for several DNA-based systems, using a model composed of two dielectric zones: a DNA zone with $\epsilon = 4$ ($\epsilon = 2$ was also considered) and a solvent zone with $\epsilon = 81$.[11] Once again, a significant increase of λ_s with R_{DA} was obtained, roughly linear for the case of one to three AT base pairs between holes localized on single guanine D and A sites (1.1–1.5 eV).[11] Solvation energetics was shown to favor localization of the hole, although delocalization over two or three guanines may be energetically feasible, depending on the details of the DNA and its environment.[10]

In the vicinity of DNA, namely, in the "bound water" zone, the local dielectric constant deviates from the bulk value as a consequence of the much lower mobility of water molecules that interact with charged and polar groups of DNA. Beveridge et al.[28,32] studied the dielectric behavior of solvent water and found in particular that the average dielectric constant in the zone within 3 Å from DNA is considerably lower than that of the bulk water. The structure of the "bound water" zone was also recently explored in terms of X-ray diffraction data,[33] yielding a picture in which the chain of phosphates is surrounded by two solvation shells of regular geometry. The first layer is partially occupied by counterions, and because of site-specific binding of cations, the structure of this "spine" depends on the DNA sequence.[33]

In the present study, we report calculations of λ_s for hole transport in DNA duplexes, using a heterogeneous dielectric model that exploits recent estimates of zone-specific dielectric constants (both within the DNA itself and within its aqueous environment) obtained from the analysis of molecular dynamics (MD) simulations.[28,32,34] Our calculations employ the new Delphi Poisson equation solver[35,36] and do not involve the vacuum field approximation for the displacement field. The relevant structures for DNA and aqueous solvent are obtained from MD simulations, which also permit evaluation of the effect of structural fluctuations on λ_s. The particular DNA systems studied here are duplex fragments of the type 5′-GGGT$_n$GGG-3′ ($n = 0$–6).

Details of Calculations

Molecular Dynamics Simulations. Molecular dynamics (MD) simulations were carried out on the seven DNA duplexes, 5′-GGGT$_n$GGG-3′, $n = 0$–6. Ideal structures of these DNA fragments were created using the program 3DNA.[37] As in a previous study,[21] we employed geometries of bases optimized with the B3LYP method. Then the LEaP module of AMBER6[38] was used to embed a DNA fragment into a rectangular box of TIP3P[39] water molecules. The water box was extended by approximately 9 Å in each direction from the DNA fragment. This yielded 1983, 2218, 2347, 2508, 2676, 2825, and 2945 water molecules for the duplexes with $n = 0, 1, ..., 6$, respectively. Na$^+$ ions were included to keep each system neutral. Because the terminal ribose moieties did not have

external phosphates (being terminated with O5′ or O3′ groups), a given n corresponds to $2(n + 5)$ Na$^+$ ions.

MD simulations were run using the SANDER module of AMBER6 with an integration step of 1 fs. The AMBER95 force field of Cornell et al.[40] was employed. The particle mesh Ewald method (PME)[41] was applied to account for long-range effects. A cutoff of 8 Å was used for the Lennard-Jones interactions. Two types of MD simulation were carried out: (1) constrained MD ($n = 0$–6), where the ideal structure of the duplexes was fixed and (2) unconstrained ($n = 0, 2, 4,$ and 6). The internal geometry of the water molecules was kept fixed in all cases. Equilibration was achieved as described previously,[42] followed by 1 ns production runs.

Solvent Reorganization Energy. The calculation of λ_s for hole transfer between donor and acceptor was based on a scheme described previously in which the dielectric function (generally a spatially varying quantity, $\epsilon(r)$) is treated in a piecewise fashion as constant within each of k zones: ϵ_j ($j = 1-k$). λ_s for a charge-transfer process is the difference of solvation energies E_{solv} calculated using static and optical dielectric constants, ϵ_k^{st} and ϵ_k^{op}

$$\lambda_s = E_{solv}(\epsilon_1^{op}, \epsilon_2^{op}, ..., \epsilon_k^{op}, \Delta\mathbf{q}_{if}) - E_{solv}(\epsilon_1^{st}, \epsilon_2^{st}, ..., \epsilon_k^{st}, \Delta\mathbf{q}_{if}) \quad (2)$$

where $\Delta\mathbf{q}_{if} = \mathbf{q}_f - \mathbf{q}_i$ represents the difference of the charge distributions for the initial and final states of the D and A sites.[43,44] The quantities $\mathbf{q}_i$ and $\mathbf{q}_f$ are vectors corresponding to a point charge representation of the charge distributions (one atom-centered charge for each heavy atom, to which the charge of any bonded H atoms has been added). For each hole state, the set of $\mathbf{q}$'s ($\mathbf{q}_i$ or $\mathbf{q}_f$) sums to $+1e$, where e is the magnitude of the electronic charge. In the results reported below, the $\mathbf{q}$'s were based on a Mulliken population analysis (alternative charges, such as those based on electrostatic potentials, yielded very similar results for λ_s). In most cases, the D and A hole states were confined to single guanine (G) sites, and in general, the G's constituting the D and A sites (including some cases where the hole is delocalized over 2 G's) are given in italics, e.g., 5′-G*G*$^+$GT$_n$G*GG*-3′ and 5′-GG*G*T$_n$G*G*$^+$G-3′.

The solvation energies were calculated using the program Delphi II,[35,36] which employs a finite difference solver of the Poisson equation for systems composed of multiple zones with different dielectric constants. The sodium counterions were included explicitly in the Delphi II calculations, with no background ionic strength.[45,46]

Each system under consideration was divided into five dielectric zones as shown in Figure 1. For the D and A zones, the static and optical dielectric constants were taken as $\epsilon_1^{st} = \epsilon_1^{op} = 1$. The next two zones corresponded to bases and sugar–phosphate backbone, respectively. On the basis of previous results,[34] the static dielectric constants of these zones were assigned the values 3.4 and 20.6, respectively. A value of 2 was used for the corresponding optical dielectric constants, $\epsilon_2^{op} = \epsilon_3^{op} = 2$. Two types of water zone were considered, to take into account the fact that water molecules near DNA exhibit a reduced mobility compared to bulk water. A zone of "bound water" was constructed as a shell of thickness 3 Å, adjacent to the surface of the DNA fragment (corresponding roughly to the first hydration shell).[32,33] Because the static dielectric constant of such bound water is not precisely determined, we carried out calculations using five different values of ϵ_4^{st}: 2, 4, 8, 32, and 80. For the bulk water zone, the value $\epsilon_5^{st} = 80$ was used. The optical dielectric constant of water was taken as $\epsilon_4^{op} = \epsilon_5^{op} = 1.8$.

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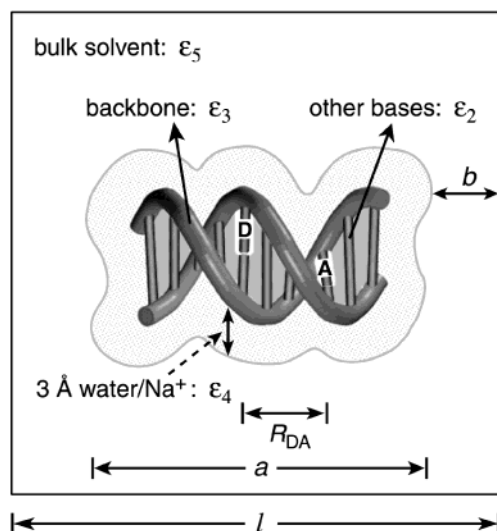*J. Phys. Chem. B, Vol. 107, No. 11, 2003* **2597**

Figure 1. Sketch of five dielectric zones: (1) donor (D) and acceptor (A), (2) other nucleobases of the DNA π stack, (3) sugar–phosphate backbone, (4) "bound water" within 3 Å from the surface of DNA, (5) bulk water. The following parameters of the dielectric model are shown: box size l, length a of the system (DNA oligomer and bound water), minimum distance b between the system and the edge of the box, and distance R_{DA} between donor and acceptor.

In all production calculations with Delphi II, we used a cubic lattice with a grid size of 201 in each dimension and a scale parameter of 2 grid points/Å (distance $d = 0.5$ Å between grid points), yielding a box size of 100 Å. This box size is large enough to accommodate all DNA fragments considered here. The dielectric boundary between DNA and the solvent was taken as the molecular surface defined by a 1.4 Å probe sphere rolling on atomic spheres with radii $R_H = 1.0$, $R_C = 1.7$, $R_N = 1.5$, $R_O = 1.4$, $R_{Na^+} = 1.8$, and $R_P = 2.0$ Å.[47] The calculated λ_s results were based on snapshot structures extracted from MD trajectories, from which averaged λ_s values were then obtained.

Internal Reorganization Energy. The internal reorganization energy λ_i was calculated at the B3LYP/6-31G(d) level.[48] For radical cation states, the unrestricted Kohn–Sham method was applied. To estimate λ_i for the charge-transfer process,[26,27] the following terms were computed for donor and acceptor: (1) energies of neutral species at optimized geometries, $E_0(D)$ and $E_0(A)$, (2) energies of the corresponding radical cations at optimized geometries, $E_+(D^+)$ and $E_+(A^+)$, (3) energies of neutral D and A, calculated at the geometries of the corresponding cation radicals, $E_+(D)$ and $E_+(A)$, and (4) the energies $E_0(D^+)$ and $E_0(A^+)$ of the oxidized states D^+ and A^+ at the geometries of corresponding neutral molecules. Then λ_i for the charge-transfer reaction $D^+ + A \rightarrow D + A^+$ is a sum of the reorganization energies of donor and acceptor, $\lambda_i = \lambda_i(D) + \lambda_i(A)$, where D and A were taken as single GC pairs in vacuo. The energies $\lambda_i(X)$, where $X = D, A$, are

$$\lambda_i(X) = \frac{1}{2}[E_+(X) - E_+(X^+) + E_0(X^+) - E_0(X)] \quad (3)$$

Results and Discussion

Sensitivity to Parameters of the Dielectric Model. We performed several tests to check the sensitivity of the λ_s values to parameters of the dielectric model used in the Delphi II calculations: the box length l, related to the shortest distance, b, between the edge of the system and the box boundary (Figure 1), and the distance d between grid points. Three B-DNA

TABLE 1: Solvent Reorganization Energy λ_s (kcal/mol) Calculated for Hole Transfer between Guanine Units (G) within the Rigid Duplexes 5′-GGGT$_n$GGG-3′ ($n = 0-6$), for Different Values of the Dielectric Constant ϵ_4^{st} of the "Bound Water" Zone

		λ_s				
n	R_{DA} (Å)	$\epsilon_4^{st} = 2$	$\epsilon_4^{st} = 4$	$\epsilon_4^{st} = 8$	$\epsilon_4^{st} = 32$	$\epsilon_4^{st} = 80$
0	3.4[a]	17.4 ± 0.8	21.4 ± 0.4	24.3 ± 0.9	27.9 ± 1.3	29.0 ± 1.5
0	6.8[a]	27.9 ± 0.7	32.4 ± 0.5	35.8 ± 1.0	40.3 ± 1.4	41.8 ± 1.6
0	10.1[a]	33.6 ± 0.8	37.8 ± 0.5	41.2 ± 1.0	45.6 ± 1.4	47.1 ± 1.6
1	13.5	36.2 ± 0.7	40.6 ± 0.4	44.0 ± 0.6	48.2 ± 0.7	50.1 ± 0.8
2	16.9	38.4 ± 0.6	42.9 ± 0.3	46.5 ± 0.5	51.1 ± 0.8	52.7 ± 0.8
3	20.3	39.7 ± 0.7	44.3 ± 0.4	48.0 ± 0.6	52.7 ± 0.9	54.4 ± 1.0
4	23.7	40.8 ± 0.7	45.4 ± 0.4	48.9 ± 0.5	53.5 ± 0.7	55.2 ± 0.7
5	27.0	42.1 ± 0.8	46.7 ± 0.5	50.2 ± 0.7	54.7 ± 1.0	56.3 ± 1.1
6	30.4	42.9 ± 0.6	47.5 ± 0.3	51.0 ± 0.5	55.4 ± 0.9	57.2 ± 1.0

[a] Different donor–acceptor separations were considered for the 6-mer 5′-G$_1$G$_2$G$_3$G$_4$G$_5$G$_6$-3′ duplex: 3.4 Å (G$_3$G$_4$), 6.8 Å (G$_2$G$_4$) and 10.1 Å (G$_2$G$_5$).

duplexes of differing overall length a and D–A distance R_{DA} were considered: (i) 5′-GGGTGGG-3′, with $R_{DA} = 13.5$ Å and $a = 35$ Å; (ii) 5′-GGGTTTTTTGGG-3′, with $R_{DA} = 30.4$ Å and $a = 53$ Å; and (iii) 5′-AGTGTGGGTTGTTGGGTTATT-3,′ with $R_{DA} = 27.0$ Å and $a = 83$ Å. Each system was placed at the middle of a cube of length $l = 2b + a$, where b ranged from 3 to 25 Å. Calculations were performed with the grid parameter d ranging from 0.2 to 1.6 Å.

Calculated data for the duplex 5′-GGGTGGG-3′ are given in the Supporting Information (Table SM1). When the parameters used in the Delphi II program[35,36] to specify the model were varied, we found the results to be very robust, with λ_s remaining almost unchanged when the grid parameter d increased from 0.2 to 1.0. As expected, the magnitudes obtained were also insensitive to the distance b over the range studied. Furthermore, the calculations on larger duplexes, namely 5′-GGGTTTTTTGGG-3′ and 5′-AGTGTGGGTTGTTGGGTTATT-3′ (see the Supporting Information), also support the conclusion that the calculated values of λ_s are practically independent of the parameters of the model. However, we do not recommend the use a grid parameter $d > 1.0$ Å.

Solvent Reorganization Energy. *Rigid Duplexes.* Let us first consider the λ_s results obtained for duplexes of ideal structure (Table 1). These include the 6-mer duplex 5′-G$_1$G$_2$G$_3$G$_4$G$_5$G$_6$-3′ with several assumed D and A sites and associated R_{DA} values: 3.4 Å (G$_3$G$_4$), 6.8 Å (G$_2$G$_4$), and 10.1 Å (G$_2$G$_5$). A broad range of assumed values for the dielectric constant of the bound water zone was also considered ($\epsilon_4^{st} = 2, 4, 8, 32$, and 80). The quantitative influence of this parameter is displayed in Table 1. For example, in the 6-mer, λ_s for hole transfer between D and A sites separated by two base pairs ($R_{DA} = 10.1$ Å) was calculated at 33.6, 37.8, 41.2, 45.6, and 47.1 kcal/mol when ϵ_4^{st} was 2, 4, 8, 32, and 80, respectively, thus increasing by roughly a factor of 1.4 over this interval of ϵ_4^{st}. The dependence of λ_s on R_{DA} calculated with different ϵ_4^{st} is shown in Figure 2. As expected, a sharp dependence of λ_s on R_{DA} is found, most pronounced at short separations ($R_{DA} < 15$ Å), and leveling off beyond 20 Å; e.g., for $\epsilon_4^{st} = 32$, λ_s was calculated at 27.9 and 48.2 kcal/mol when R_{DA} was 3.4 and 13.5 Å, respectively. In the following discussion we will focus on the results computed with $\epsilon_4^{st} = 32$, a value comparable to the mean of the range of values within the first hydration shell obtained by Beveridge et al.[28] In all cases, the first hydration shell (zone 4) generated by the MD simulations was found to contain about ~10% of the Na$^+$ counterions.
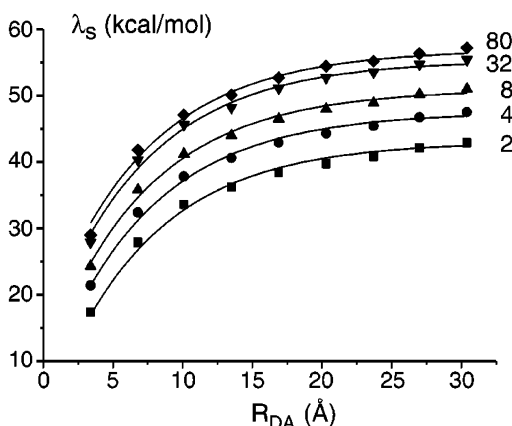
Figure 2. Dependence of the solvent reorganization energy λ_s on the distance R_{DA} between donor and acceptor sites. Calculated results for different values of ϵ_4^{st}. The data were fitted with the function $A(\epsilon_4^{st}) - B \exp(-CR_{DA})$, with $B = 42$ kcal/mol, and $C = 0.14$ Å^{-1}; for values of A, see text. For an alternative fit linear in R_{DA}^{-1}, see text and Figure 4.

TABLE 2: Effect of Hole Delocalization on the Solvent Reorganization Energy λ_s (kcal/mol), Calculated with $\epsilon_4^{st} = 32$ for the Rigid Duplexes 5′GGG(T)$_n$$GGG$-3′, $n = 0$−6^a

n	$R_{DA}{}^b$ (Å)	λ_s
0	6.8^c	27.1 ± 0.8
0	10.1^c	33.5 ± 0.8
1	13.5	37.0 ± 0.5
2	16.9	39.6 ± 0.5
3	20.3	41.1 ± 0.5
4	23.7	42.0 ± 0.5
5	27.0	42.8 ± 0.6
6	30.4	43.8 ± 0.6

^{a} The hole is distributed equally over adjacent guanines in the GG donor and acceptor sites. ^{b} R_{DA} is the mean distance between the GG donor and acceptor sites. ^{c} In the 6-mer 5′-$G_1G_2G_3G_4G_5G_6$-3′ duplex, two donor−acceptor separations were considered: $R_{DA} = 6.8$ Å between (G_2G_3) and (G_4G_5) and $R_{DA} = 10.1$ Å between (G_1G_2) and (G_4G_5).

We now consider the degree of localization expected for guanine-based hole states, particularly with respect to the guanine triads dealt with in the present study. There is, of course, a close relationship between localization, solvation, and reorganization effects. Because the redox potentials of the guanine moieties in the GGG triads are similar,[22] the charge can delocalize over more than one guanine. On the other hand, because the polar environment tends to localize the hole,[10] an increase in medium polarity will increase λ_s due to both the larger solvent dielectric constant and the greater degree of localization of the hole. This tendency has been observed in recent theoretical studies that found hole states over one to three adjacent guanines to be energetically accessible at room temperature in the presence of a polar medium.[10] We have estimated the effect of charge delocalization on λ_s for several systems, as illustrated in Table 2. In both initial and final states of the D and A sites, the hole is assumed to be equally distributed over the first two guanines of the triad (the 5′ and the central guanines). An example of results supporting this assignment of charge is given by in vacuo HF/6-31G* calculations within the Koopmans' approximation, which yield a hole distribution in the duplex T$G_1G_2G_3$T localized on G_1 (39%) and G_2 (59%). For the case of such delocalized holes, the effective donor−acceptor distance can be estimated as the mean value: $R_{DA} = (R_{D'A'} + R_{D''A'} + R_{D'A''} + R_{D''A''})/4$, where D′ and D″ are two neighboring guanines of the donor site and A′ and A″ are neighboring G units of the acceptor site. Comparing λ_s values obtained for localized (Table 1) and delocalized (Table 2) hole

states with common R_{DA} values and with $\epsilon_4^{st} = 32$, one notes that charge delocalization leads to a consistent decrease of the reorganization energy by ∼12 kcal/mol, almost independent of the donor−acceptor separation. For instance, for $R_{DA} = 16.9$ Å we calculated λ_s at 51.1 and 39.6 kcal/mol for localized and delocalized holes, respectively.

In other calculations (not presented) we have examined the sensitivity of λ_s for a given R_{DA} value to the chemical nature of the D and A bases, finding that for adenine bases, λ_s is consistently larger, by ∼1−2 kcal/mol, than the λ_s values obtained for guanines (some relevant data are given in the Supplementary Information, Tables SM2 and SM3); e.g., at $R_{DA} = 10.1$ and $\epsilon_4^{st} = 32$, the results are 46.9 kcal/mol for adenine (Table SM 3) and 45.6 kcal/mol for guanine (Table 1). However, hole states localized on adenine may be appreciably higher in energy than those localized on guanine, and in such a case the nature of their role in thermal hole transport would require a detailed kinetic analysis.[49]

The calculations discussed so far have involved fixed structures for the DNA fragments, and the small fluctuations in λ_s magnitudes (Table 1) are due to fluctuations of the DNA environment. More specifically, the number of water molecules found within the cutoff distance of 3 Å (the "bound water" zone) were 170 ± 5, 195 ± 5, 223 ± 5, 251 ± 7, 278 ± 7, 302 ± 8, and 328 ± 6 for duplexes 5′-GGGT$_n$$GGG$-3′, $n = 0, 1, ..., 6$, respectively. These fluctuations lead to small changes of the zone boundaries of our model (Figure 1) and thus to variations of λ_s.

Flexible Duplexes. Unconstrained MD simulations, in which structural fluctuations of the DNA fragments were allowed, yielded λ_s values within ∼1 kcal/mol (Table SM4) of the corresponding values based on rigid ideal DNA structures. Taking into account structural changes of the duplexes and further averaging of results allows one to minimize any numerical inaccuracy of the Delphi solver because of different placement of the DNA duplex relative to the grid.[46] Furthermore, the standard deviations due to fluctuations in the unconstrained cases are quite similar in magnitude (≤1 kcal/mol) to those for the rigid systems (Table 1), where only the solvent fluctuations contribute. The following discussion, therefore, deals only with the results obtained for rigid duplexes.

Contribution of Different Dielectric Zones. The λ_s calculations reported here, based on a multi-zone[50] dielectric model implemented with Delphi II,[35,36] do not permit a rigorous additive partitioning into contributions from the individual zones, in contrast to previous models in which the displacement field was approximated by the vacuum field[29] (see also ref 51). In the present work, contributions for isolated zones are not well-defined, because the displacement field in one zone depends on the details of the full multi-zone dielectric system.[52]

Bearing in mind the above considerations, we have nevertheless explored approximate additivity schemes that might be useful in the present context. Consider the following expression

$$\lambda_s = \sum_{j=1}^{4} \lambda_s(j) \qquad (4)$$

where

$$\lambda_s(j) = E_{solv}(\epsilon_j^{op}, \epsilon_{j+1}^{op}, \Delta \mathbf{q}_{if}) - E_{solv}(\epsilon_j^{st}, \epsilon_{j+1}^{st}, \Delta \mathbf{q}_{if}) \qquad (5)$$

and where the parameters in eq 5 are the same as defined for eq 2. In the simple case of a set of nested spherical dielectric zones, in which the scalar Δq_{if} represents the shift in magnitude of a single point charge at the center, eqs 4 and 5 give an exact

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partitioning of the total λ_s into contributions from each $j/j + 1$ zone interface ($j = 1-4$). Applied, for example, to the rigid duplex 5′-G*G*GTTG*G*G-3′ included in the present study (with $\epsilon_4^{st} = 32$), we obtain $\lambda_s(j)$ values 22.1, 18.5, 3.6, and 0.4 kcal/mol, respectively, for $j = 1-4$. The sum of these contributions (44.6 kcal/mol) is within 15% of the value (51.3 kcal/mol given by the full calculation, eq 3).[53] It warrants further study to explore how useful eqs 4 and 5 or other partitioning schemes may be in the present context.

Decay Parameter. Experimental studies of the distance dependence of hole transfer through DNA indicate[2-4] that the corresponding rate constants in several cases exhibit an overall exponential decay with donor−acceptor distance, R_{DA}:

$$k(R_{DA}) = k_0 \exp(-\beta R_{DA}) \qquad (6)$$

where the decay parameter β depends on the nature of the D and A sites and the intervening bridge. Because the electronic coupling and the reorganization energy participate in separate factors in eq 1, the parameter β in eq 6 can be expressed approximately as a sum of two terms $\beta = \beta_{el} + \beta_s$.[54] It is of interest to know the extent to which the β parameters may be viewed as global constants over a broad range of R_{DA}, an issue that may be addressed on the basis of theoretical calculations. The parameter β_{el} can be estimated on the basis of quantum-chemical calculations of the electronic coupling matrix elements.[9,21] Here we consider the second parameter, β_s, which reflects the distance-dependence of λ_s. For the purpose of numerical fitting, this dependence on R_{DA} is accurately expressed as (see Figure 2 and Table SM5) $\lambda_s(\text{kcal/mol}) \approx A_i - B \exp(-CR_{DA})$, where R_{DA} is in Å. The parameters A_i ($i = 1-5$ for $\epsilon_4^{st} = 2, 4, 8, 32,$ and 80), B, and C were obtained simultaneously using a nonlinear least-squares fitting procedure. The resulting values are $A_i = 43.0, 47.5, 51.0, 55.3,$ and 57.0 kcal/mol for $\epsilon_4^{st} = 2, 4, 8, 32,$ and 80, respectively, $B = 42$ kcal/mol, and $C = 0.14$ Å^{-1}. We may now express β_s as $\beta_s = -d \ln k'_{DA}/dR_{DA}$, where k'_{DA} denotes the Boltzmann factor on the right-hand side of eq 1. Because $\Delta G° = 0$ and λ_i is taken as independent of R_{DA} (see below), the resulting expression for β_s is $\beta_s(\text{Å}^{-1}) \approx 2.5 \exp(-0.14R_{DA})$. For systems with one intervening base pair between D and A sites ($R_{DA} \sim 6.8$ Å), β_s is quite large (~ 1.0 Å^{-1}), but it is nearly an order of magnitude smaller (0.15 Å^{-1}) for systems containing five intervening pairs between D and A sites ($R_{DA} \sim 20$ Å).

Internal Reorganization Energy. The internal reorganization energy was calculated at the B3LYP/6-31G* level for AT and GC units. For hole transfer between two GC base pairs, we obtained $\lambda_i = 16.6$ kcal/mol; hole transfer between two AT pairs yields a notably smaller value, $\lambda_i = 10.2$ kcal/mol.

Because $\Delta G° = 0$, the activation barrier for the charge shift process can be taken as $(\lambda_s + \lambda_i)/4$ (see eq 1). Combining $\lambda_i = 16.6$ kcal/mol with the λ_s values from Table 1 (for $\epsilon_4^{st} = 32$) yields activation energies for charge transfer in the duplex 5′-G*G*GT$_n$G*G*G-3′ ranging from 16.2 kcal/mol for $n = 1$ to 18.0 kcal/mol for $n = 6$.

Comparison with Other λ_s Estimates. Figure 3 compares λ_s values for hole transfer between GGG moieties in DNA, calculated with different dielectric models, all with hole states confined to single guanine moieties. The estimated values vary considerably among the different schemes. For systems with a D−A separation of ~ 10 Å (two intervening nucleobase pairs), λ_s ranges from ~ 31 kcal/mol, calculated by Tong et al.,[11] to ~ 69 kcal/mol, as calculated by Tavernier and Fayer,[29] whereas the present calculations yield the value 45.6 kcal/mol (with ϵ_4^{st}
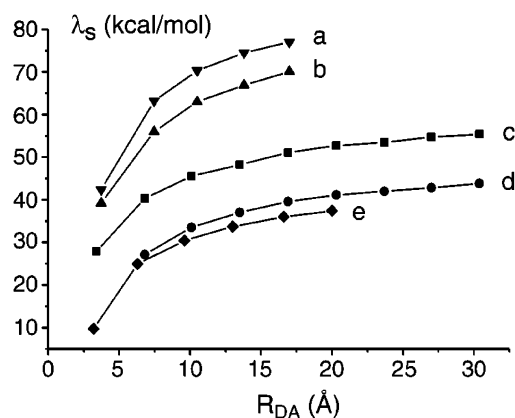

Figure 3. Solvent reorganization energies calculated with different dielectric models for charge transfer between nucleobases in DNA: (a) and (b) results of Tavernier and Fayer[29] calculated with $\epsilon_2^{st} = 12$ and 4 for the nucleobase zone, respectively; (c) and (d) data obtained in the present study with $\epsilon_4^{st} = 32$ for localized and delocalized holes, respectively; (e) data obtained by Tong et al.[11] using the $\epsilon^{st} = 4$ for all DNA zones.

$= 32$). As already discussed, delocalization of the hole over two bases can decrease the reorganization parameter by ~ 12 kcal/mol, yielding results that happen to be rather close to those of Tong et al. (see Figure 3), which involved a notably different (two-zone) model with holes localized on single guanine bases.[11] For systems with at least one intervening nucleobase pair between D and A sites, and with hole states localized on single guanines ($R_{DA} \geq 7$ Å), the λ_s values calculated in the present work on the basis of the estimates of dielectric constants obtained from analysis of MD simulations[28,34] are systematically larger by ~ 15 kcal/mol than the corresponding values obtained by Tong et al.[11] while at the same time being systematically smaller by ~ 25 kcal/mol than the results of Tavernier and Fayer.[29] These differences may be attributed to differing definitions of the dielectric zones (both the structure and the dielectric constants) used to describe the response of the DNA and its environment to the charge-transfer process.

We have emphasized the sensitivity of the calculated values of λ_s to the choice of the dielectric constants, in particular for the "bound water" zone (see Figure 2). Although computational studies of DNA provide estimates of dielectric constants for different zones of solvated DNA,[28,34] significant uncertainties remain concerning the construction of a multi-zone dielectric model, including the degree to which distinct zones may be meaningfully distinguished. In the present five-zone model, the sugar and phosphate fragments in DNA are treated as one zone with mean dielectric constant set to 20.6, whereas distinct zones (with dielectric constants of 2 and 33, respectively) were identified in ref 34. Tavernier and Fayer[29] employed a four-zone model in which all water was treated as bulk, and Tong et al.[11] assigned a mean dielectric constant to the entire DNA duplex. Of course, ultimately one desires a molecular-level treatment beyond the dielectric continuum framework.

Another issue concerns the spatial extent of the different dielectric zones, especially the D and A sites. It is thus of interest to consider simple models that help to gauge the effective size of these latter sites. We first attempt to model the λ_s data in terms of the simple two-sphere model of Marcus, where λ_s is given as[55]

$$\lambda_s = \frac{\Delta q^2}{2}\left(\frac{1}{a_D} + \frac{1}{a_A} - \frac{2}{R_{DA}}\right)\left(\frac{1}{\epsilon^{op}} - \frac{1}{\epsilon^{st}}\right) \qquad (7)$$
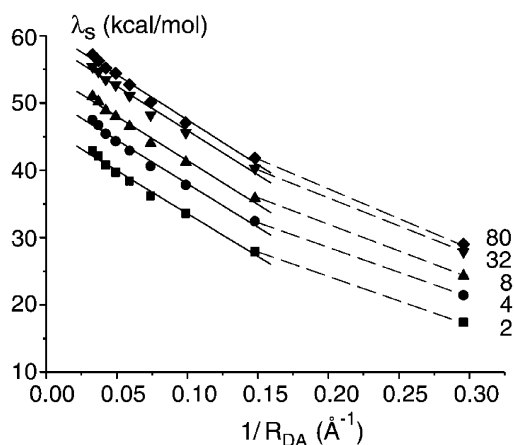
Figure 4. Calculated solvent reorganization energy λ_s as a function of R_{DA}^{-1} and the corresponding linear fit (based on data for $n > 0$).

Here a_D and a_A are the effective radii of donor and acceptor and Δq is the magnitude (unity) of the point charge that is transferred from the center of one sphere to the other. The formula is applicable to nonintersecting spheres, $R_{DA} > a_D + a_A$.[56] According to eq 7, λ_s should decrease linearly with $1/R_{DA}$. Previous computational studies involving D−A systems departing strongly from a simple two-sphere geometry[43,44,57] reveal, nevertheless, that the form of eq 7 may account quite well for the R_{DA} dependence of λ_s while at the same time providing definitions of effective D and A radii. Figure 4 shows that, indeed, the λ_s data calculated with the present five-zone dielectric model is linear in $1/R_{DA}$ for $R_{DA} \geq 6.8$ Å (see also Table SM6). Moreover, the Marcus two-sphere model can be employed to rationalize why delocalization of the hole over two guanine units reduces λ_s in a manner almost independent of the R_{DA}, because delocalization of the transferring charge over neighboring bases would imply increased effective radii of D and A sites (a_D and a_A, respectively).

Returning to the case of localized guanine holes, we find that the fits displayed in Figure 4 in conjunction with eq 7 yield (to within 10%) $a_D = a_A = \sim 3$ Å, where the dielectric factor (the last factor in eq 7) has been assigned a value of 0.5 (an approximate effective value representing the heterogeneous environment of the D and A groups). Similar estimates are obtained from model two-zone Delphi calculations of either the solvation energy for a single guanine cation or λ_s for hole transfer between a pair of guanines. In each of these model calculations, the guanines were given the same molecular structure as employed in the five-zone calculations described above, and were immersed in a homogeneous aqueous solvent ($\epsilon^{st} = 80$ and $\epsilon^{op} = 1.8$). Fitting the Delphi results for solvation energy and λ_s, respectively, to one-sphere (Born) or two-sphere (eq 7) models yields once again an effective guanine radius of ~ 3 Å. A value of this magnitude is appreciably larger than the radii (1.87 Å) assigned by Tavernier and Fayer to the spheres that constituted the D and A sites in their calculations,[29] thus helping to explain why their λ_s values are appreciably larger than the present values.

Finally, we note a previous analysis[57] of effective radii for atoms in solvated species, in which the idea of defining distinct radii for high-frequency and low-frequency medium response for use in reaction field calculations was implemented on the basis of empirical solvation energy and λ_s data. The resulting effective radii for low-frequency response, which controls the magnitude of λ_s, were appreciably greater than the scaled van der Waals radii used for the high-frequency part of the reaction field. These larger radii yielded a corresponding reduction in λ_s values.

Conclusions

We have carried out a computational study of the solvent reorganization energy, λ_s, for hole transfer through DNA. For several DNA fragments with different donor−acceptor distances, we estimated λ_s as the difference of the solvation free energies, calculated with static and optical dielectric constants, by solving the Poisson equation for models composed of five different dielectric zones. We showed λ_s to be rather sensitive to the parameters of the model, noting in particular, the influence of the dielectric constant (ϵ_4^{st}) used for the "bound water" zone in the immediate vicinity of the DNA. We found λ_s for hole transfer between guanine units to increase rapidly at short donor−acceptor distances ($R_{DA} < 15$ Å). The R_{DA} dependence of λ_s (for $\epsilon_4^{st} = 32$ and with hole states confined to single guanines) can be accurately fitted using the expression λ_s (kcal/mol) $\approx 55 - 42 \exp(-0.14 R_{DA})$, with R_{DA} in Å. The corresponding falloff parameter then becomes $\beta_s(\text{Å}^{-1}) \approx 2.5 \exp(-0.14 R_{DA})$, varying from ~ 1.0 Å^{-1} for a system with one intermediate base pair between D and A sites, to 0.15 Å^{-1} for systems with five intervening pairs. Delocalization of the hole states over two neighboring guanines causes λ_s to decrease by ~ 12 kcal/mol, almost independent of the D−A separation. The internal reorganization energy (λ_i) for hole transfer between GC pairs was calculated at 16.6 kcal/mol. The calculated activation barrier for charge transfer, $(\lambda_s + \lambda_i)/4$, increases only slightly with R_{DA}, from 16.2 kcal/mol with one base pair between D and A to 18.0 kcal/mol for six intervening base pairs.

The distance dependence of λ_s found in the present and recent theoretical studies[11,29] is qualitatively consistent with the Arrhenius analysis of experimental kinetic data for hole transfer between an intercalated acridine derivative (hole donor) and 7-deazaguanine (hole acceptor) separated by one or two (AT) base pairs.[25] On the other hand, significant distance dependence of λ_s was not indicated in the analysis of isothermal hole transfer in the hairpin duplexes studied by Lewis et al.[4] Furthermore, the present calculated magnitudes of λ_s are appreciably larger (30−50 kcal/mol for $n = 0−3$ intervening base pairs and $\epsilon_4^{st} = 32$) than the estimates inferred from experiment ($\sim 10−40$ kcal/mol for $n = 0−3$).[4,25] Our data were calculated for thermoneutral charge transfer in unperturbed DNA duplexes and therefore cannot be compared in a fully quantitative fashion with kinetic data gained for systems with hairpin or intercalated chromophores. Clearly, more detailed and comprehensive analysis of charge delocalization, polarity of the environment in the vicinity of the chromophore, and structural features of DNA−intercalator complexes is called for in the future.

Supporting Information Available: Solvent reorganization energies and results of the nonlinear fit of λ_s as a function of R_{DA} and R_{DA}^{-1}. This material is available free of charge via the Internet at http://pubs.acs.org.

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(50) As used here, "zone" refers to a zone of fixed dielectric constant, which in general may involve spatially disjoint components (e.g., as in the case of zone 1, displayed in Figure 1).

(51) Sharp, K. A. *Biophys. J.* **1998**, *73*, 1241; this work treated a multi-zone case additively by combining results obtained from two-zone calculations based on the original Delphi code.

(52) These "image effects" are implicitly included in calculations carried out with the Delphi II code, which uses a scalar charge density/electrostatic potential formulation, equivalent to one based on displacement fields.

(53) The result of 51.3 kcal/mol, based on a single "snapshot" structure, is very close to the mean value given in Table 1.

(54) The Boltzmann factor in eq 1 contains only a reorganization contribution, because $\Delta G° = 0$ for the thermoneutral charge shift processes dealt with here.

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(56) Aside from the structural simplification entailed in the two-sphere model for present purposes, we note that even when appropriate, corrections of the form $C_4/R_{DA}^4 + C_6/R_{DA}^6 + ...$ should be added to eq 7 when the spheres come into contact or begin to overlap. See: Levine, S.; Wringley, H. E. *Discus. Faraday Soc.* **1957**, *24*, 43. Inclusion of the first correction term allows all of the present λ_s data (including the contact case at $R_{DA} = 3.4$ Å) to be fitted accurately (Table SM7). It has also been noted above that a simple exponential form for describing the calculated dependence of λ_s on R_{DA} is quite accurate (Table SM5) and convenient from a practical point of view, although no physical justification can be given.

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