Conformations of poly{G}–poly{C} π stacks with high hole mobility

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Charge transfer properties of DNA depend strongly on the π stack conformation. In the present paper, we identify conformations of homogeneous poly-{G}–poly-{C} stacks that should exhibit high charge mobility. Two different computational approaches were applied. First, we calculated the electronic coupling squared, V^2, between adjacent base pairs for all 1 ps snapshots extracted from 15 ns molecular dynamics trajectory of the duplex G_{15}. The average value of the coupling squared $\langle V^2 \rangle$ is found to be 0.0065 eV^2. Then we analyze the base-pair and step parameters of the configurations in which V^2 is at least an order of magnitude larger than $\langle V^2 \rangle$. To obtain more consistent data, $\sim$65 000 configurations of the $(G:C)_2$ stack were built using systematic screening of the step parameters *shift*, *slide*, and *twist*. We show that undertwisted structures (twist $< 20°$) are of special interest, because the π stack conformations with strong electronic couplings are found for a wide range of slide and shift. Although effective hole transfer can also occur in configurations with twist $= 30°$ and $35°$, large mutual displacements of neighboring base pairs are required for that. Overtwisted conformation (twist $\geq 38°$) seems to be of limited interest in the context of effective hole transfer. The results may be helpful in the search for DNA based elements for nanoelectronics. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2823015]

INTRODUCTION

Charge transfer in DNA (Refs. [1] and [2]) has attracted great interest for a number of reasons, including, in particular, (1) understanding the mechanisms of the oxidative damage and the photorepair of DNA (Refs. [3] and [4]) and (2) the potential role of DNA in the design of nanoelectronic devices.[5] Also, DNA molecules comprise an excellent model system for charge transport in one-dimensional polymers.

An electron hole generated in DNA is expected to quickly localize at the nearest guanine residue to form a guanine radical cation (G$^{·+}$) since guanine is the site of lowest oxidation potential in DNA. Then, the hole can become mobile in DNA via electron transport from a distant G residue to a G$^{·+}$.[6–8] This leads to charge migration, which will continue until the competing irreversible trapping reactions occur. *In vitro*, charge transport in DNA occurs over distances > 200 Å.[9] High-level calculations (CAS-PT2) show that an excess charge in π stacks is quite localized on single nucleobases,[10] and therefore, hopping mechanism for hole transfer (HT) can be applied.[11,12]

It has been shown that the electrical conduction of single molecules is closely related to the electron transfer rate[13–15] being determined by electronic coupling and nuclear Franck-Condon factors.[16,17] The efficiency of hole transport depends both on the structure of DNA sequence and mutual orientation of base pairs (BPs), and its environment.[1,2] Moreover, thermal fluctuations in π stack conformation[18–20] as well as the motion of surrounding water molecules and counterions[21,22] play an important role in determining hole mobility within DNA.

It has become clear that natural DNA is a rather poor electrical conductor and the DNA conductivity must be essentially improved to be sufficient for various applications in nanoelectronics. Since DNA enables an endless number of structural manipulations, it appears to be quite feasible to get π stacks with improved electric conductivity.

Homogeneous DNA sequences are of special interest as molecular wires.[5] Porath *et al.* observed semiconducting behavior with a well-defined poly-{G}–poly-{C} sequence.[23] Electron transfer in poly-{G}–poly-{C} sequences has also been considered in several theoretical and experimental studies.[5,24–26] In particular, it has been found that (1) oligo-dG sequences have a higher conductance than comparable oligo-N sequences ($N=A$, C, and T) and (2) the conductance of the double-stranded DNA is an order of magnitude higher than that for single-stranded sequences with similar numbers of bases.[26]

In this work, we try to identify structural parameters of poly-{G}–poly-{C} π stacks with a high charge transfer efficiency. Because electronic couplings between nucleobases in DNA are very sensitive to conformational changes,[18] different conformations must exhibit quite different conduction properties. It should be noted that changes in mutual position and orientation of BPs in a stack primarily affect the electronic coupling between nucleobases, while a rather weak conformational dependence is predicted for the HT free energy and the reorganization energy.[27,28] Therefore, analysis of electronic couplings in many different conformations should provide valuable information about π stack configuration with high hole mobility.

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COMPUTATIONAL DETAILS

We used a molecular dynamics (MD) trajectory for a homogeneous sequence consisting of 15 G:C base pairs (hereafter called simply G_{15}) obtained within the ABC project;[29] the 15 ns MD trajectory, as well as the parameter file for this oligomer, was downloaded from the web site of the Beveridge group.[30] The MD simulations[29] were performed within well established protocol (the following parameters and options were used: $T=300$ K, $P=1$ atm, 2 fs integration step, parm94 force field,[31] TIP3P water molecules,[32] periodic boundary conditions, cutoff of 9 Å for nonbonded interactionos, particle-mesh Ewald algorithm[33] for treatment of electrostatic interactions). Detailed description of the methodology is given elsewhere.[29]

Quantum chemical calculations

Recently it has been demonstrated that the INDO/S method provides surprisingly good estimates for the HT energetics and electronic couplings in DNA π stacks compared to the CASPT2 and CASSCF results.[34] Because the INDO/S method is computationally very efficient, we use it for treatment of all 1 ps snapshots of the 15 ns MD trajectory for the G_{15} stack as well as for $\sim$60 000 configurations of the $(G:C)_2$ stack generated by systematic variation of base-step parameters.

The adiabatic energies and dipole moment matrix for each snapshot were computed with the INDO/S approach.[35] The electronic couplings were estimated using the generalized Mulliken-Hush method introduced by Cave and Newton.[36,37]

Conformational screening

The structural parameters which characterize individual DNA base pairs (translations *shear*, *stretch*, and *stagger* and rotations *buckle*, *propeller-twist*, and *opening*) and BP steps (translations *slide*, *shift*, and *rise* and rotations *tilt*, *roll*, and *twist*) are illustrated in Fig. 1. Intra-base-pair parameters shear, stretch, and opening do not disturb the planar arrangement of nucleobases in a base pair; however, it becomes nonplanar when at least one of the parameters stagger, buckle, or propeller-twist is not zero [Fig. 1(a)]. In a stack, BP planes are parallel to each other when roll and tilt are equal to zero, while variation of shift, slide, rise, and twist cannot disturb the parallel arrangement of BPs [Fig. 1(b)]. Detailed discussion of the base pair and step parameters is given elsewhere.[38,39] Here we note that the step parameters depend on the choice of base-pair reference frame and can be significantly perturbed by distortions of the BP geometry; extreme values of step parameters in a stack may simply reflect a distorted BP geometry.[38]

To analyze and rebuild the structure of π stacks, we used the program 3DNA;[40] atomic coordinates of the nucleobases were taken from Ref. 41.

RESULTS AND DISCUSSION

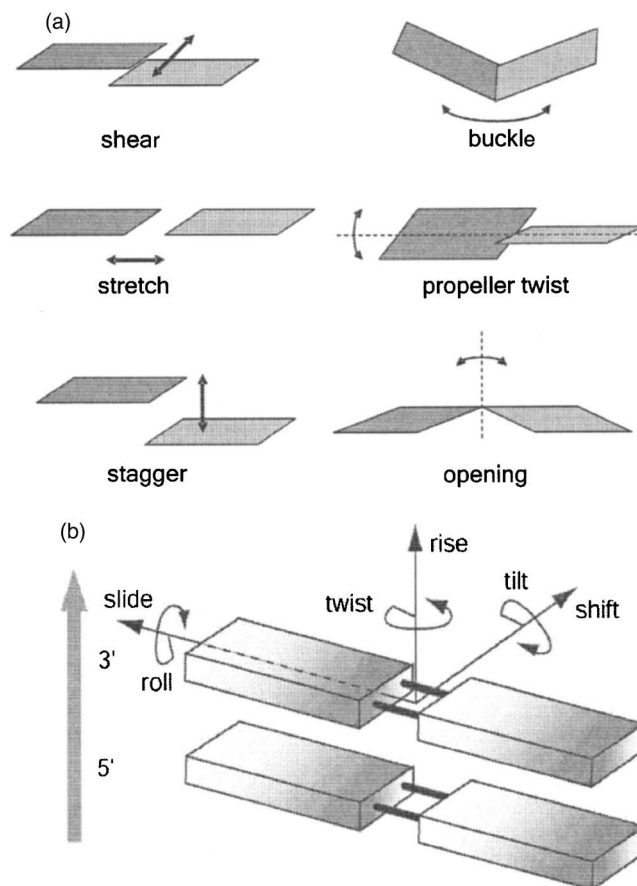Because conformational changes of a DNA stack affect primarily the electronic coupling while the free energy and

FIG. 1. Illustration of parameters used to define π stack geometries: (a) the base-pair parameters and (b) the step parameters.

reorganization energy of HT do not change significantly, we will assume that the conformational dependence of the charge mobility is determined by the coupling squared (V^2).

Reference π stack structures

First we should define a reference for the HT efficiency through G_n stacks. Two conformations of the $(G:C)_2$ stack are of interest: (1) a *symmetrical* structure [Fig. 2(a)] where all step parameters, except rise, are equal to zero and (2) B-DNA regular geometry [Fig. 2(b)] which arises from the symmetrical conformation by mutual rotation of BPs through 36° along the main DNA axes (in the regular stack, twist $=36°$, rise$=3.4$ Å, while other step parameters are equal to zero). Both stacks are constructed using G:C pairs of the standard geometry (all base-pair parameters are assumed to be zero).

Let us consider a π stack consisting of two identical molecules with a fixed distance between their planes. Among all possible configurations of the stack, the eclipsed configuration (twist$=0°$, the system has Cs symmetry) exhibits the stronger electronic couplings for charge transfer between the subunits. According to our calculation, in a $(G:C)_2$ stack with the eclipsed arrangement of BPs, the electronic coupling is found to be 1.020, 0.372 and 0.127 eV when the intermolecular separation, rise, is 2.9, 3.4, and 3.9 Å, respectively. Thus, the coupling depends strongly on the distance between base pairs. This relationship can be approximately
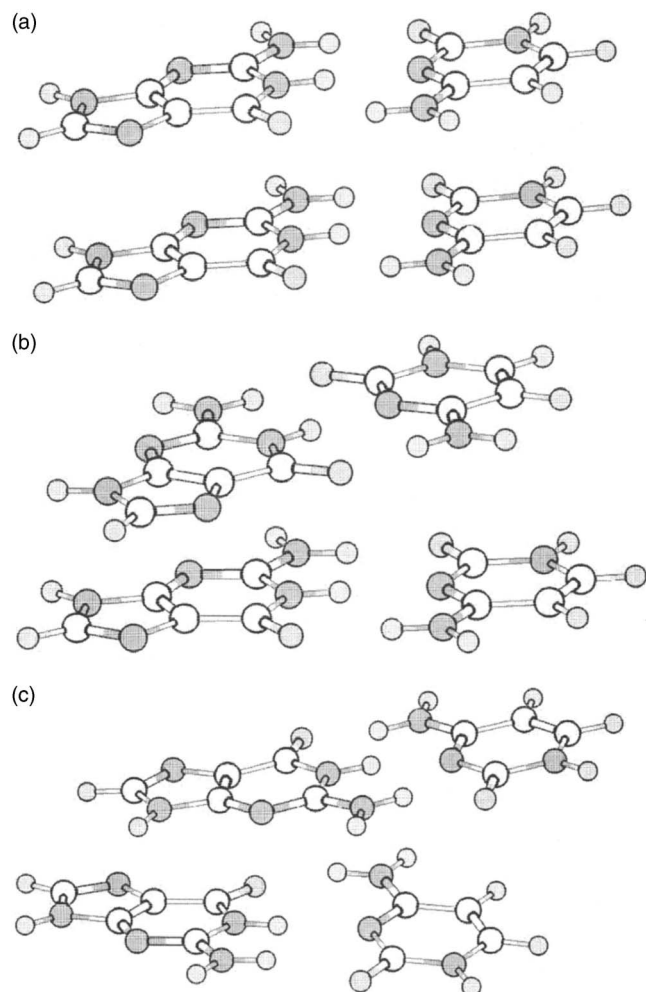
FIG. 2. Geometries of the $(G:C)_2$ stack: (a) symmetric structure and (b) B-form structure. (c) A snapshot from the MD trajectory with the largest electronic coupling value.

FIG. 3. G_7-G_8 electronic coupling squared (in eV^2) calculated for a 15 ns MD trajectory of the duplex G_{15}.

described by the exponential function $\exp(-\alpha \text{rise})$ with $\alpha = 2.1$ Å^{-1}. Obviously, decrease of the parameter rise will be accompanied by a considerable increase in the hole mobility within the π stack. However, it is hardly possible to obtain a π stack with the rise parameter to be substantially smaller than 3.4 Å. Because of that, we may consider $V_{max}^2 = 0.138$ eV^2 as a measure of the highest hole mobility which can be achieved in poly-{G}–poly-{C} wires ($V_{max} = 0.372$ eV is a coupling value calculated in the $(G:C)_2$ dimer with rise$=3.4$ Å).

For comparison, in a (G:C) stack of the canonical B-DNA structure, the calculated coupling squared V^2 is only 0.0022 eV^2, i.e., by a factor of 63 smaller than V_{max}^2. This example clearly demonstrates that the hole mobility should be very sensitive to conformational changes in π stacks. More detailed information about the variation of the coupling can be derived from quantum mechanics (QM)/MD calculations.

Electronic couplings computed for MD trajectory of G_{15}

Let us consider fluctuations of V^2 between the G_7 and G_8 base pairs computed for the 15 ns MD trajectory of the du-
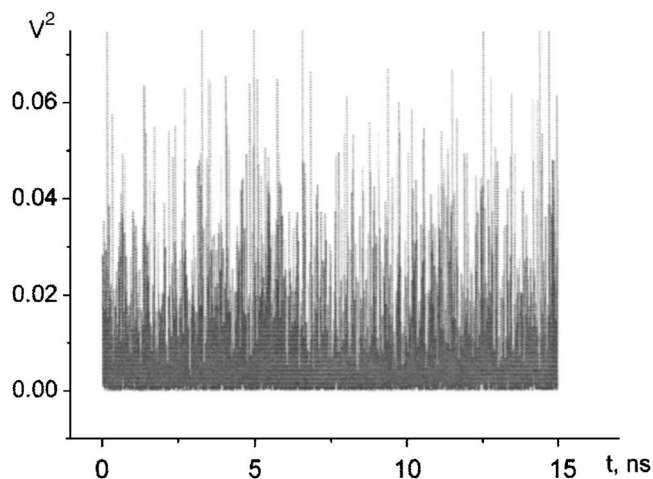
plex G_{15}. To exclude end effects, we consider the coupling of hole states localized on the middle BPs of the oligonucleotide. Figure 3 shows the fluctuation of V^2 due to thermal motion of the stack. The average value of the coupling squared, $\langle V^2 \rangle$, is found to be 0.0060 eV^2, which is three times as large as $V^2 = 0.0022$ eV^2 calculated for the canonical B-DNA structure (see above). A quite large dispersion of V^2 ($\sigma = 0.0076$ eV^2) compared to the average value suggests considerable fluctuations of the hopping rate between neighboring guanines. The largest V^2 value found for the trajectory of 0.106 eV^2 is comparable with V_{max}^2. Actually there are 12 snapshots where V^2 is at least an order of magnitude larger than $\langle V^2 \rangle$. One of these structures is shown in Fig. 3(c).

Using the 3DNA program,[40] we estimated the structural parameters of the G_7-G_8 π stack along the MD trajectory. 15 000 snapshots were taken into account. Average values of the BP and step parameters are listed in Table I. The mean values of buckle and propeller-twist and their relatively large dispersions ($\sim 9°$ and $7°$, respectively) suggest that the G:C pairs may substantially deviate from a planar structure. The effects of the base-pair parameters on electronic couplings in DNA have been recently considered.[42] As to the step parameters, lower twist ($\sim 30°$) and large negative slide (-1.75 Å) indicate that the G_{15} structure is situated between the A and B forms of DNA. It is known that simulations of DNA with the parm94 force field lead to undertwisted structures with remarkable negative slide values.[29]

Analysis of π stack conformations that exhibit very strong electronic couplings shows that (1) in several snapshots, the arrangement of the nucleobases is quite similar to that in the canonical G:C pair, while in some cases, the base pairs are remarkably distorted. Overall, we have not found any clear requirements for BP parameters. As to the step parameters, the QM/MD results indicate that a necessary condition for strong coupling is a combination of large negative slide (-1.5 to 2.3 Å) with positive shift (0.6–1.0 Å) and smaller twist angle (twist$< 30°$).

Figure 4 compares the 12 strongest electronic coupling values, $V(\text{QM}/\text{MD})$, directly calculated for snapshots of the MD trajectory with corresponding values calculated for

TABLE I. Average structural parameters of G_7–G_8 stack and their dispersion calculated for 15 ns MD trajectory of the G_{15} oligomer.

Base-pair parameters					
BP	Shear (Å)	Stretch (Å)	Stagger (Å)	Buckle (deg)	Propeller (deg)	Opening (deg)
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$(G:C)_7$	-0.17 ± 0.31	-0.07 ± 0.11	-0.27 ± 0.36	-3.46 ± 9.15	-1.51 ± 7.32	-0.57 ± 3.10
$(G:C)_8$	-0.17 ± 0.31	-0.07 ± 0.11	-0.23 ± 0.36	-2.72 ± 8.63	-1.83 ± 7.57	-0.59 ± 3.08

Step parameters					
BP	Shift (Å)	Slide (Å)	Rise (Å)	Tilt (deg)	Roll (deg)	Twist (deg)
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G_7/G_8	0.23 ± 0.51	-1.75 ± 0.45	3.38 ± 0.33	-0.14 ± 4.34	4.02 ± 5.36	28.62 ± 3.90

structures which were rebuilt using BP and step parameters. As can be seen, V(QM/MD) of selected snapshots ranges from 0.25 to 0.33 eV. Note that the structure of nucleobases extracted from a MD usually deviates from reference geometries determined by averaging x-ray data.[41] In particular, in many MD snapshots, the planar structure of guanines and cytosine is to some extent distorted. When rebuilding an oligomer structure using the BP and step parameters extracted from a snapshot of interest, the geometries of "real" nucleobases are replaced by the corresponding standard data (in particular, planar geometries of bases are used). This modification of the system structure affects the electronic coupling. However, as illustrated in Fig. 4 by closed squares, V values computed for the rebuilt stacks do not deviate significantly from V(QM/MD). They lie in the range from 0.2 to 0.35 eV. However, when the base pairs are assumed to be planar (parameters stagger, buckle, and propeller-twist are set to be zero while other parameters remain unchanged), considerable changes in the calculated couplings (see data labeled by a closed circle in Fig. 4) are found. The V values in the artificial dimers (except for two systems) are essentially smaller than V(QM/MD). Stronger couplings found in the two stacks can be explained as follows. As discussed by Olson *et al.*,[38] the effects of BP deformations on step parameters are most pronounced when perturbations of the same

type but of the opposite sense occur in successive base pairs; in particular, the negative difference of the buckle parameters in the two stacks leads to apparently smaller values of rise (2.85 and 3.04 Å). Then, these artificially small rise values are applied to construct stacks of planar BPs. As a result, one gets systems with inappropriate short distances between intrastrand nucleobases, which in turn leads to overestimated couplings. On the contrary, a positive difference of the buckle parameters in neighboring pairs of MD stacks will end up with too weak couplings in the rebuilt structures with coplanar nucleobases.

A further "idealization" of the stack structures (in order to get π stacks with parallel BP planes, tilt and roll are set to be zero) has relatively small influence on the coupling (see data labeled by closed triangles in Fig. 4).

Overall, the analysis of MD snapshots does not provide a clear notion on the stack structures (in terms of the step parameters) which show high hole mobility. Then, not all potentially important structures of π stacks can be present in the MD trajectory generated at the standard conditions. Moreover, modification of the backbone (as, for instance, in protein nuclear acids[43]), incorporation of transition metal ions, variation of the environment, etc., may considerably affect the arrangement of base pairs in the stack. Therefore, to get more consistent information on stack configurations, which facilitate the hole transport, another approach must be applied.

FIG. 4. Comparison of electronic couplings V(QM/MD) calculated for G_7–C_8 π stacks from the MD trajectory with the corresponding values (in eV) computed for rebuilt structures: (■) the standard geometries of nucleobases are used, (●) planar base pairs are assumed, and (▲) planar base pairs are assumed to be parallel (roll=0°, tilt=0°).

Screening of π stack conformation

To cover a wide range of possible configurations of $(G:C)_2$, we carried out extensive screening of the step parameters shift slide, and twist, which do not affect parallel arrangement of BPs in the π stack. Note that recently, Hobza and Sponer estimated the stacking interaction between nucleobases to be stronger than 10 kcal/mol,[44] which suggests an essentially planar structure of BPs in π stacks with or without the backbone.

We generated π stacks consisting of parallel G:C pairs of ideal geometries. It means that in all considered systems, the following parameters remain constant: (1) six BP parameters for each G:C pair are set to be zero, (2) rise=3.4 Å, and (3) tilt=0° and roll=0°. The translations shift and slide were independently varied in the range from -2.0 to 2.0 Å with a
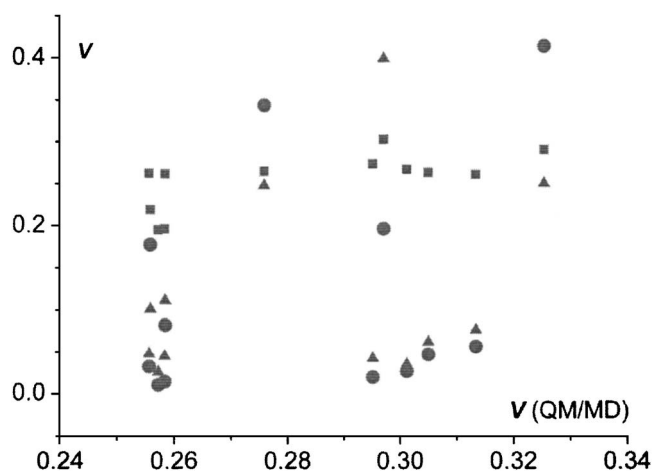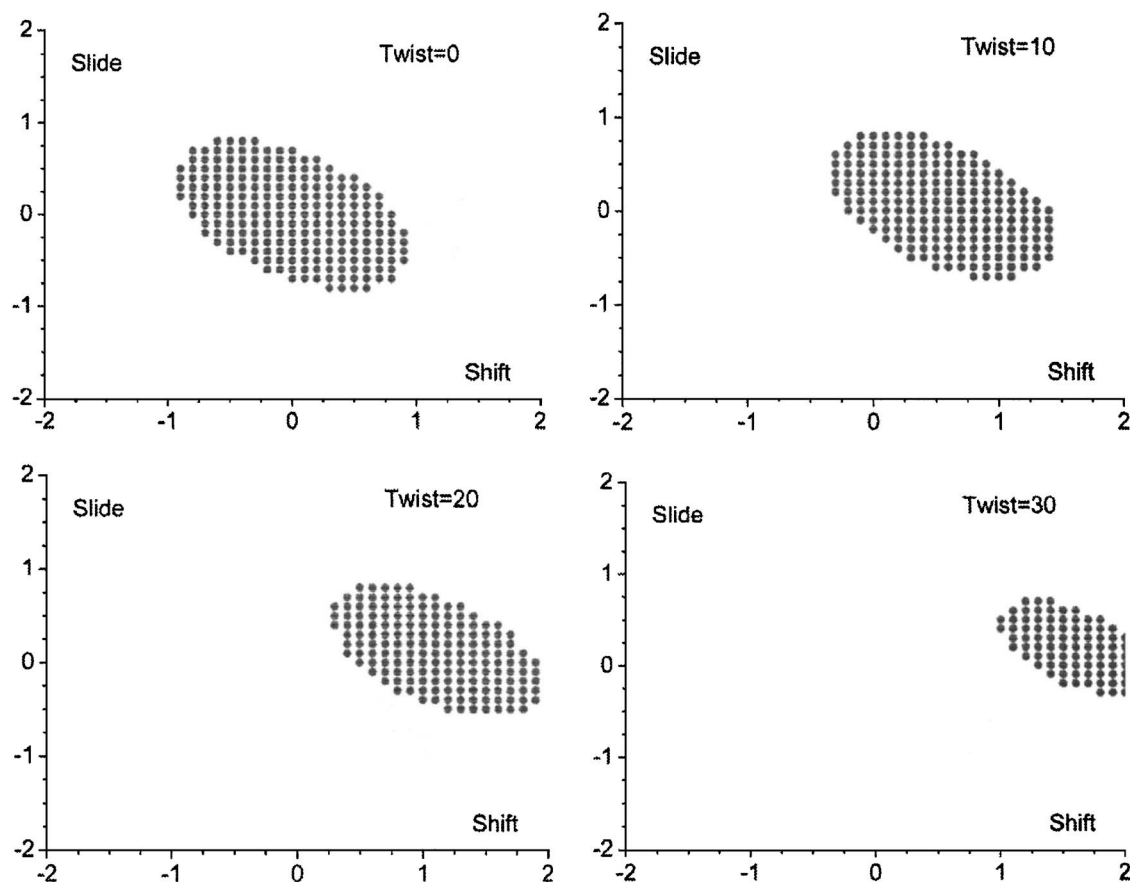
FIG. 5. Step parameters (shift, slide, and twist) of π stacks which exhibit high hole mobility [in the stacks, V^2 between neighboring (G:C) pairs is at least an order of magnitude larger than $\langle V^2 \rangle$ estimated for the 15 ns MD trajectory].

step of 0.1 Å, while twist was changed from 0° to 40° with steps of 1°. In addition, a number of configurations with shift > 2 Å were generated.

Figure 5 presents the parameter values of stack configurations where the electronic coupling squared for HT between G:C pairs is at least an order of magnitude larger than the average value $\langle V^2 \rangle = 0.0065$ eV^2 found for the 15 ns trajectory of G$_{15}$. As expected, there are many configurations with small twist angles (see diagrams twist=0° and twist =10° in Fig. 5). When twist=0°, slide and shift are in the range from −1 to +1 Å. As twist increases, the parameter shift becomes more positive; its average values are found to be ~0.5 and 1 Å in configurations with twist=10° and twist=20°, respectively. At twist=30°, the corresponding shift values range from 1 to 2.6 Å while slide ranges from −0.4 to 0.8 Å. When twist=35°, base pairs in the stack must be significantly shifted (shift ≥ 1.5 Å). No configuration with high hole mobility (i.e., with $V^2 > 0.065$ eV^2) cannot be found for twist > 38°.

Thus, to obtain π stacks of G:C pairs with significantly enhanced hole transfer properties, the following structural requirements must be accounted for: (1) the twist angle between neighboring BPs should be as small as possible; (2) when twist ≥ 20°, a quite large relative displacement of adjacent pairs (shift ~ 1 Å) is required; (3) overtwisted configurations, with twist > 40°, do not show strong electronic coupling.

Estimation of electrical conductance of the G$_{15}$ duplex

Using the approach suggested by Berlin and Ratner,[15] we can estimate the electrical conduction of G$_{15}$ stacks of different conformations. The following model has been used: (1) all site energies and intersite couplings are assumed to be identical; (2) the reorganization energy is taken to be 0.7 eV, in line with experimental estimates;[45] (3) the gap between the bridge energy and the Fermi level of the electrode is set to 0.1 eV. Within this model, the calculated electrical conductance for G$_{15}$ of the canonical B-DNA structure is 0.47 nS. The highest conductivity of 28.1 nS is found for the unwound stack configuration (twist=0°, rise=3.4 Å). This value may be considered as the upper limit for the G$_{15}$ conductance. Note that using $\langle V^2 \rangle = 0.0060$ eV^2 found for the MD trajectory gives the conductance of 1.3 nS, which agrees well with the experiment value of ~1 nS.[26]

CONCLUSIONS

Charge transfer properties of DNA depend strongly on the π stack conformation. In the present paper, we identify conformations of homogeneous (G:C)$_n$ stacks that should exhibit very high charge mobility. First, we calculated the electronic coupling squared, V^2, between adjacent base pairs for all 1 ps snapshots extracted from 15 ns molecular dynamics trajectory of the duplex G$_{15}$. The average value of the

coupling squared $\langle V^2 \rangle$ is found to be 0.0065 eV^2. Then we analyze the base-pair and step parameters of the configuration in which V^2 is at least an order of magnitude larger than $\langle V^2 \rangle$. To obtain more consistent data, ~65 000 configurations of the stack were additionally built using systematic screening of the step parameters shift, slide, and twist. We have identified the stack conformations that should exhibit high charge mobility. According to the calculations, undertwisted structures (twist < 20°) are of special interest because in the π stacks, strong couplings are found over a wide range of the slide and shift parameters. Although large values of the couplings are also found for configurations with twist = 30° and 35°, in the stacks, a large mutual displacement of neighboring BPs is required. Overtwisted conformations (twist ≥ 38°) seem to be of limited value in the context of effective hole transfer.

It should be noted that for heterogeneous DNA sequences, the effect of conformation motion is important also for the coherent mechanism of charge transfer along the stack. Therefore the obtained results are not restricted to the hopping regime of charge propagation and important also for other transport mechanisms.

ACKNOWLEDGMENTS

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