Can Charge Transfer in DNA Significantly Be Modulated by Varying the π Stack Conformation?

Alexander A. Voityuk*

Institució Catalana de Recerca i Estudis Avançats, Barcelona 08010, Spain, and Institut de Química Computational, Universitat de Girona, 17071 Girona, Spain

Received: September 6, 2009; Revised Manuscript Received: September 16, 2009

DNA is an ideal target for single-molecule manipulations. The conformation of stacked basepairs in DNA depends sensitively on various factors such as temperature, the kind of solvent and counterions, changes in the backbone, applied forces, etc. This raises the question of whether the rate of charge transfer (CT) through the stack can be considerably enhanced by tuning of *"observed"* DNA conformations. Using a stochastic approach to account for the effects of thermal fluctuations, we study how the efficiency of CT in poly(dA)−poly(dT) and poly(dG)−poly(dC) sequences will change by variation of the π stack structure. The CT process is shown to be not very sensitive to the torsional angle (twist) while affected more strongly by altering translation modes (shift and slide). We conclude that the design of basepair stacks with significantly improved electrical conductivity, as compared to poly(dG)−poly(dC), appears to be quite elusive. Specific changes of the π stack structure can increase the efficiency of CT by a factor of ~3 (e.g., in systems with negative shift); much stronger effects can hardly be expected. This result, formally derived for molecular ensembles, should also be applicable for single-molecule systems because of the strong effects of dynamical disordering.

Introduction

During the two last decades, charge transfer in DNA has been intensively studied both experimentally and theoretically.[1−4] Nevertheless, several important points remain to be explored. One of the most interesting issues is whether the hole transfer (HT) through DNA can be significantly enhanced by changing the π stack conformation. DNA reveals a large structural flexibility and adopts different conformations depending on the counterions, solvent, and other factors.[5] The arrangement of stacked basepairs is affected by external forces,[6] and can vary essentially when the backbone is changed (e.g., by replacing the DNA sugar−phosphate backbone by a peptide backbone in PNA[7]). On the other hand, electronic coupling V, a key parameter that determines the rate of the nonadiabatic CT,[8,9]

$$k = \frac{2}{\hbar} V^2 \rho_{FC} \qquad (1)$$

is shown to depend strongly on the arrangement of basepairs in the stack.[10−12] Therefore, one might suggest that the CT rate can be modulated significantly by variation of the π stack structure. The situation, however, is more complicated because of thermal fluctuations.

Equation 1 was derived by assuming the Condon approximation (i.e., the coupling V does not depend on the nuclear coordinates). In many cases, this approximation does not hold and several extensions of eq 1 have been considered.[13−15] In particular, it has been shown that eq 1 can be applied also for structurally flexible donor−acceptor systems when the electronic coupling changes are much faster than the charge transfer process. In this case, the CT rate can be expressed by eq 1, providing that V is replaced by the root-mean-square (rms) coupling $V_{rms} = [(1/n)\sum_{i=1}^{n} V_i^2]^{1/2}$ averaged over thermally accessible configurations.[13−16]

As noted above, the electronic couplings for HT through DNA are dramatically affected by the arrangement of adjacent basepairs in the stack.[10] Combining quantum mechanical (QM) calculations with molecular dynamics (MD), Troisi and Orlandi showed that fast structural fluctuations of nucleobases strongly modulate the electronic coupling and V_{rms} is much larger than the average coupling $\bar{V}$. Moreover, V_{rms} can substantially differ from the coupling derived for idealized or X-ray structures. QM/MD simulations have been applied to explore different aspects of CT in DNA.[17−26] The effects of conformational dynamics on the efficiency of HT have also been considered for DNA hairpins[27,28] and PNA.[29] The spectroscopic time-resolved measurements[30,31] and computational studies[11,21−29] revealed that nuclear motion on the picosecond time scale are responsible for the coupling variation. On the other hand, the HT process in DNA is much slower (by a factor of 10^3−10^5).[1−3] In particular, the hole hopping between adjacent AT pairs proceeds on the nanosecond time scale.[32,33] Thus, the fast coupling fluctuation limit can be applied to HT in DNA, and the HT rate can be estimated as the average over an ensemble of thermally accessible conformations.

Nowadays, molecular dynamics (MD) simulations have reached a level at which accurate dynamical models of DNA structure in solution have been obtained.[34] MD simulation may be considered as a single-molecule computational experiment and its combination with quantum mechanical (QM) calculations provides a reliable approach to model CT in natural and modified DNA. The QM/MD approach is a valuable complement to single-molecule measurements of electron transfer through DNA sequences, and interesting results obtained within this scheme have been reported for several systems[11,17−29] Still, the question of how the CT process depends on the "observed" π stack conformation has not been considered. While the

* E-mail: alexander.voityuk@icrea.es.

10.1021/jp908603w CCC: $40.75
Published on Web 10/01/2009

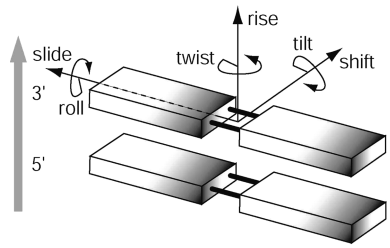

Figure 1. Step parameters that define the arrangement of adjacent basepairs in a π stack.

arrangement of basepairs strongly affects the electronic coupling, the charge transfer process is expected to be less sensitive to structural changes because of the dynamic disorder and self-averaging. Quantitative estimation of the dependence of the HT rate on the π stack conformation is important for better understanding of the electron transport through DNA and of significant interest for researchers who design new DNA-based materials for nanoelectronics.

If we want to consider the CT probability as a function of the "observed" stack structure, the QM/MD approach becomes of limited use. Actually, one can gradually change the torsional angle in the stack by applying external forces;[6] however, to get an average structure with a specified value of shift (or slide) from MD simulation is much more difficult. In this study, we use an alternative approach, which combines a stochastic scheme to generate an ensemble of stack conformations (instead of a series of MD trajectory snapshots) and QM calculations. As described below, this approach allows one to take into account the effects of thermal fluctuations (dynamic disordering) and obtain the average structure with predetermined parameters. We apply the scheme to two homogeneous sequences poly(dA)−poly(dT) and poly(dG)−poly(dC). As shown in the paper, HT through these DNA stacks cannot be enhanced significantly by changing their average conformation. Because the electrical conduction of single molecules is closely related to electron transfer rate,[35,36] the design of molecular wires on the basis of stacked nucleobases appears to be quite elusive. Formally, this result is obtained for molecular ensembles. Because the stochastic model can well reproduce QM/MD data (see below), we believe that this scheme provides a reasonably good description of single-molecule systems.

Computational Details

Structural features of poly(dA)−poly(dT) and poly(dG)−poly(dC) can be described in terms of six step parameters that define the arrangement of adjacent basepairs in the stack. Usually one considers three translation modes—shift, slide, and rise—and three rotation angles—tilt, roll, and twist (see Figure 1). Assuming for each parameter P_i the normal distribution with the mean $\bar{P}_i$ and dispersion $\sigma(P_i)$, we generated random six-component vectors $\mathbf{P} = \{P_1, P_2, ..., P_6\}$ that describe different conformations of the π stack. Reference (average) configurations are defined by vector $\bar{\mathbf{P}} = \{\bar{P}_1, ..., \bar{P}_6\}$. For each $\mathbf{P}$, six independent random numbers were used.[37] The parameter dispersions characterize the structural flexibility of the π stack. The following $\sigma(P_i)$ values were used to generate stack conformations: 0.5 Å for shift and slide, 0.3 Å for rise, and 5° for tilt, roll, and twist. These values are close to the standard deviations of the step parameters extracted from the analysis of A- and B-DNA crystal structures[38] and MD simulations.[39] Atomic coordinates of the stacks were calculated using the program X3DNA.[40]

To exclude high-energy configurations, which are thermally inaccessible, we compute the electrostatic and van der Waals interactions of basepairs in the complex

$$E = \sum_{\substack{a\in A\\ b\in B}} \frac{q_a q_b}{R_{ab}} + \sum_{\substack{a\in A\\ b\in B}} \left(\frac{\varepsilon_{ab}(r_a + r_b)^{12}}{R_{ab}^{12}} - \frac{2\varepsilon_{ab}(r_a + r_b)^{6}}{R_{ab}^{6}} \right)$$

where R_{ab} is the distance between atoms a and b of basepairs A and B. Atomic charges q_a and q_b, parameters ε_{ab}, and van der Waals radii r_a and r_b are adopted from the parm94 force field.[41] All conformations with the energy $E > \bar{E} + 5RT$ ($\bar{E}$ is the energy of the reference structure, $5RT \approx 3$ kcal/mol at room temperature) were eliminated. To calculate V_{rms} for each reference configuration, 1000 energetically allowed structures were treated.

QM calculations were carried out using the INDO/S method,[42] which provides accurate values of electronic coupling.[43] The FCD scheme[44] has been employed to derive the electronic coupling from the QM calculations.

Results and Discussion

Equation 1 is usually applied in the high-temperature limit

$$k = \frac{2\pi}{\hbar} \frac{{V_{rms}}^2}{\sqrt{4\pi\lambda k_B T}} \exp\left[-\frac{(\Delta G + \lambda)^2}{4\lambda k_B T} \right] \qquad (2)$$

where ΔG is the driving force and λ is the reorganization energy. In homogeneous stacks, $\Delta G = 0$. The reorganization energy remains almost unchanged by structural fluctuation of π stacks.[45] Therefore, the conformational dependence of the HT rate is determined by ${V_{rms}}^2$. In the following discussion, we consider the conformational dependence of ${V_{rms}}^2$ (instead of V_{rms}) which describes directly the behavior of the rate.

Formally, the stochastic approach provides the results for molecular ensembles. On the other hand, QM/MD simulation can be considered as a single-molecule computational experiment. To corroborate that the stochastic scheme properly describes self-averaging of the coupling in a single DNA stack, let us compare the QM/MD data derived for G_{15} and $GA_{13}G$[25] with the results obtained using the stochastic model. For G_7-G_8, the stochastic V_{rms} value (0.0711 eV) is somewhat larger than 0.0627 eV obtained within QM/MD;[25] the corresponding values for A_7-A_8 are 0.0439 and 0.0576 eV. As seen in both cases, the stochastic scheme provides reasonable estimates of V_{rms}. On the basis of this comparison, we believe that the stochastic approach provides a reasonably good description of the effects of dynamical disorder in single-molecule systems.

Poly(dA)−Poly(dT). Usually the angles tilt and roll in DNA stacks (Figure 1) are close to zero, indicating that the basepairs are parallel. Relatively small changes of interbase distance (rise) are found.[38,39] Thus, we focus on the step parameters shift, slide, and twist, variations of which leave the related basepairs parallel. We recall that, in the ideal B-DNA, rise = 3.38 Å, twist = 36°, and other parameters are equal to zero. The left panel of Figure 2 demonstrates the dependence of the electronic couplings squared computed for single structures (1S) and for related ensembles. A total of 1000 thermally distorted conformations were generated for each ensemble. As seen, V^2(1S) is very sensitive to the torsional angle (twist). At twist = 34°, it has a very small value, 1.94×10^{-5} eV^2. As seen, relatively

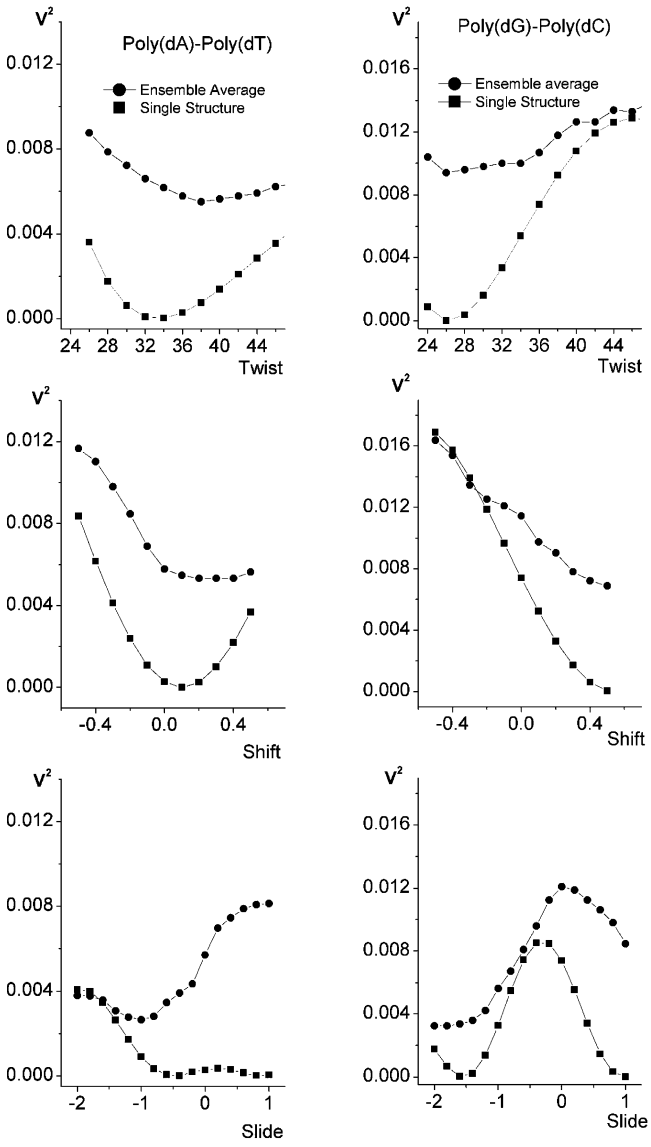

Figure 2. Electronic coupling squared (in eV^2) computed for single structures of the π stacks (■) and by averaging over the ensemble of thermally accessible configurations (●).

small changes in the torsional angle lead to a large increase of the coupling. In particular, in the stacks with twist = 28 and 40°, the V^2 values ($\sim 2 \times 10^{-3}$ eV^2) are 2 orders of magnitude larger than in the configuration with twist = 34°. Relying on these data, one might infer that the CT in unwound and overtwisted stacks should be much more efficient than that in the stack of regular structure. However, self-averaging of the coupling due to thermal distortions results in much larger values: in conformations with twists of 28, 34, and 40°, V_{rms}^2 is calculated to be 7.8×10^{-3}, 6.2×10^{-3}, and 5.6×10^{-3} eV^2, respectively. Thus, in fact, twisting of the π stack has no significant impact on the CT rate through poly(dA)−poly(dT). The strong conformational dependence derived from 1S calculations is washed out by self-averaging of the coupling. Note that the V^2(1S) and V_{rms}^2 minima are found at different twist values, ~34 and 36°, respectively (see Figure 2). According to our estimation, the calculated CT rate will increase only by a factor of 2 when passing from the ideal configuration (twist = ~36°), which has the smallest V_{rms}^2 value, to the unwound stack (twist = 26°). In the structure with twist = 46°, $V_{rms}^2 = 6.2 \times 10^{-3}$ eV^2 is just higher (by 10%) than in the ideal stack. The translation modes shift and slide have a stronger impact on V_{rms}^2 than twist. The data plotted in Figure 2 suggest that an improvement of CT may be expected for stacks with negative shift and positive slide. For instance, V_{rms}^2 doubly increases in the stack with shift = −0.5 Å. A similar effect is found for conformations with slide = ~1 Å. We recall that, in the standard A-DNA, twist = 31°, shift = 0, and slide = −1.5 Å. 1S calculations of the coupling predict the HT in A-DNA to be 4 times faster than that in B-DNA (V^2 is 1.3×10^{-3} and 0.3×10^{-3} eV^2, correspondingly). In contrast, self-averaging of the coupling (V_{rms}^2 is 1.9×10^{-3} and 5.7×10^{-3} eV^2) suggests that HT in A-DNA should be 3 times less efficient than that in B-DNA. This example shows that even qualitative results on conformational dependence of CT through π stacks derived from single-structure calculations can be misleading.

Poly(dG)−Poly(dC). To explore the effects of conformational fluctuations on the G−G coupling, let us consider the right panel of Figure 2. Here, we compare V^2(1S) and V_{rms}^2 calculated in different conformations of the stack. As seen, in spite of the strong dependence of V^2(1S) on the twist, the V_{rms}^2 values are not very sensitive to this parameter; it ranges from 9.4×10^{-3} and 13.2×10^{-3} eV^2. HT in overtwisted stacks is predicted to be faster than that in unwound and regular structures. Single structure calculations provide acceptable estimates of the coupling in stacks with twist ≥36. They fail, however, to provide acceptable coupling values in unwound stacks; e.g., in the stack with twist = 26°, V^2(1S) is by a factor of 600 smaller than V_{rms}^2. The strong coupling is found in G−G stacks with negative shift. In contrast, HT becomes remarkably slower in the structures with positive shift. The slide dependence of the G−G coupling squared shows a maximum in the vicinity of slide = 0 (regular B-DNA geometry). Both 1S and stochastic calculations predict the HT in B-DNA to be faster than that in A-DNA (the rate ratio derived from V_{rms}^2 is 2.6).

We note that for many conformations of A−A and G−G stacks, the HT probabilities calculated within the 1S approach deviate significantly from the corresponding data obtained using the stochastic scheme (see Figure 2); i.e., the effect of stochastic averaging depends on the reference conformation. In some structures, V(1S) is similar to V_{rms} (e.g., in the GG stack of regular B-DNA geometry), which might lead to the assumption that estimates based on the QM treatment of single configurations are quite acceptable. Our results show that the 1S approach overestimates dramatically the conformational effects on the hole transfer. Self-averaging of the coupling scales down these effects; in the limiting case, when thermal distortions are very strong, the ET rate does not depend at all on the stack conformation. The V_{rms}^2 values computed for distinct stack geometries clearly show that the changes of the π stack conformation should have a rather small impact on the HT through poly(dA)−poly(dT) and poly(dG)−poly(dC). Specific changes of π stack structure (e.g., the design of stacks with negative shift) can increase the efficiency of the electron transfer process by a factor of 2 or 3, as compared with regular B-DNA stacks. Comparison of V_{rms}^2 plotted in the left and right panels of Figure 2 indicates that HT through poly (dA)−poly(dT) should be remarkably lower than that through poly(dG)−poly(dC). This result is in agreement with experimental observations.[46]

Conclusions

Recent computational studies of HT in DNA have shown that the electronic coupling is very sensitive to conformational changes of the π stack and the root-mean-square coupling V_{rms} should be used to estimate the HT rate through DNA. Because "observed" π stack structures can be varied by changing

different factors, the question of how strong the HT process depends on the π stack conformation is quite interesting. To explore this issue, we have systematically studied the dependence of V_{rms} on the *average* conformation of stacked basepairs. To take into account self-averaging of the coupling due to thermal structural distortions, a stochastic approach was applied to generate thermally accessible configurations of poly(dA)−poly(dT) and poly(dG)−poly(dC) stacks. Because the stochastic scheme reproduces reasonably well the QM/MD results, it can be applied to simulate the effects of dynamic disorder in single-molecule systems.

The following results have been obtained. In spite of the electronic coupling between stacked nucleobases dramatically depending on their arrangement, averaging over thermally distorted structures of the stack considerably decreases the extent to which the HT rate is affected by the stack conformation. Thus, the design of basepair stacks with significantly enhanced electrical conductivity, as compared to poly(dG)−poly(dC), appears to be quite elusive. Specific changes of the π stack structure can increase the efficiency of the electron transfer process by a factor of 3; much stronger effects, however, can hardly be expected.

The introduced computational scheme, which combines QM calculations with stochastic generation of thermally distorted structures, can be very helpful in the situations when more consequent approaches, e.g., QM/MD, are of limited use.

References and Notes

(1) *Long-range Electron Transfer in DNA*; Schuster, G. B., Ed.; Topics in Current Chemistry 236 and 237; Springer: Berlin, 2004.

(2) *Charge Transfer in DNA*; Wagenknecht, H.-A., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

(3) Berlin, Y. A.; Kurnikov, I. V.; Bertran, D. N.; Ratner, M. A.; Burin, A. L. *Top. Curr. Chem.* **2004**, *237*, 1.

(4) Voityuk A. A. In *Computational studies of RNA and DNA*; Šponer, J., Lankas, F., Eds.; Springer: Dordrecht, The Netherlands, 2006.

(5) Bloomfield, V. A.; Crothers D. M.; Tinoco I. *Nucleic Acids: Structures, Properties, and Functions*; University Science Books: Sausalito, CA, 1999.

(6) Prevost, C.; Takahashi, M.; Lavery, R. *ChemPhysChem* **2009**, *10*, 1399.

(7) Nielsen, P. E. *Acc. Chem. Res.* **1999**, *32*, 624.

(8) Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265.

(9) Newton, M. D. *Chem. Rev.* **1991**, *91*, 767.

(10) Voityuk, A. A.; Siriwong, K.; Rösch, N. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5421.

(11) Troisi, A.; Orlandi, G. *J. Phys. Chem. B* **2002**, *106*, 2093.

(12) Rösch, N.; Voityuk, A. A. *Top. Curr. Chem.* **2004**, *237*, 37.

(13) Troisi, A.; Nitzan, A.; Ratner, M. A. *J. Chem. Phys.* **2003**, *119*, 5782.

(14) Berlin, Y. A.; Grozema, F. C.; Siebbeles, L. D. A.; Ratner, M. A. *J. Phys. Chem. C* **2008**, *112*, 10988–11000.

(15) Skourtis, S. S.; Beratan, D. N. *J. Phys. Chem. B* **1997**, *101*, 1215.

(16) Balabin, I. A.; Beratan, D. N.; Skourtis, S. S. *Phys. Rev. Lett.* **2008**, *101*, 158102.

(17) Lewis, J. P.; Cheatham, T. E.; Starikov, E. B.; Wang, H.; Sankey, O. F. *J. Phys. Chem. B* **2003**, *107*, 2581.

(18) Voityuk, A. A.; Siriwong, K.; Rösch, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 624.

(19) Gervasio, F. L.; Laio, A.; Parrinello, M. *Phys. Rev. Lett.* **2005**, *94*, 158103.

(20) Volobuyev, M.; Saint-Martin, H.; Adamowicz, L. *J. Phys. Chem. B* **2007**, *111*, 11083.

(21) Voityuk, A. A. *Chem. Phys. Lett.* **2007**, *439*, 162.

(22) Steinbrecher, T.; Koslowski, T.; Case, D. A. *J. Phys. Chem. B* **2008**, *112*, 16935.

(23) Reha, D.; Barford, W.; Harris, S. *Phys. Chem. Chem. Phys.* **2008**, *10*, 5436.

(24) Kubar, T.; Elstner, M. *J. Phys. Chem. B* **2008**, *112*, 8788.

(25) Voityuk, A. A. *J. Chem. Phys.* **2008**, *128*, 115101.

(26) Gutierrez, R.; Caetano, R. A.; Woiczikowski, B. P.; Kubar, T.; Elstner, M.; Cuniberti, G. *Phys. Rev. Lett.* **2009**, *102*, 208102.

(27) 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.

(28) Siriwong, K.; Voityuk, A. A. *J. Phys. Chem. B* **2008**, *112*, 8181.

(29) He, W.; Hatcher, E.; Balaeff, A.; Beratan, D. N.; Gil, R. R.; Madrid, M.; Achim, C. *J. Am. Chem. Soc.* **2008**, *130*, 13264.

(30) Wan, C. Z.; Fiebig, T.; Kelley, S. O.; Treadway, C. R.; Barton, J. K.; Zewail, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 6014.

(31) Wan, C. Z.; Fiebig, T.; Schiemann, O.; Barton, J. K.; Zewail, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 14052.

(32) Takada, T.; Kawai, K.; Fujitsuka, M.; Majima, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 14002.

(33) Lewis, F. D.; Daublain, P.; Cohen, B.; Vura-Weis, J.; Shafirovich, V.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 15130.

(34) Orozco, M.; Perez, A.; Noy, A.; Luque, F. J. *Chem. Soc. Rev.* **2003**, *32*, 350.

(35) Nitzan, A.; Ratner, M. A. *Science* **2003**, *300*, 1384.

(36) Berlin, Y. A.; Ratner, M. A. *Radiat. Phys. Chem.* **2005**, *74*, 124.

(37) The random number generation routines written by R. Chandler and P. Northrop are available from http://www.homepages.ucl.ac.uk/~ucakarc/work/randgen.html.

(38) Olson, W. K.; Bansal, M.; Burley, S. K.; Dickerson, R. E.; Gerstein, M.; Harvey, S. C.; Heinemann, U.; Lu, X. J.; Neidle, S.; Shakked, Z.; Sklenar, H.; Suzuki, M.; Tung, C. S.; Westhof, E.; Wolberger, C.; Berman, H. M. *J. Mol. Biol.* **2001**, *313*, 229.

(39) Beveridge, D. L.; Barreiro, G.; Byun, K. S.; Case, D. A.; Cheatham, T. E.; Giudice, S. B.; Lankas, F.; Lavery, R.; Maddocks, J. H.; Osman, R.; Seibert, E.; Sklenar, H.; Stoll, G.; Thayer, K. M.; Varnai, P.; Young, M. A. *Biophys. J.* **2004**, *87*, 3799.

(40) Lu, X.-J.; Olson, W. K. *Nucleic Acids Res.* **2003**, *31*, 5108.

(41) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.

(42) Ridley, J. E.; Zerner, M. C. *Theor. Chim. Acta* **1973**, *15*, 134. The U_p parameter for nitrogen was set to−51.2 eV.

(43) Voityuk, A. A. *Chem. Phys. Lett.* **2006**, *427*, 177.

(44) Voityuk, A. A.; Rösch, N. *J. Chem. Phys.* **2002**, *117*, 5607.

(45) Siriwong, K.; Voityuk, A. A.; Newton, M. D.; Rösch, N. *J. Phys. Chem. B* **2003**, *107*, 2595.

(46) van Zalinge, H.; Schiffrin, D. J.; Bates, A. D.; Haiss, W.; Ulstrup, J.; Nichols, R. J. *ChemPhysChem* **2006**, *7*, 94.

JP908603W