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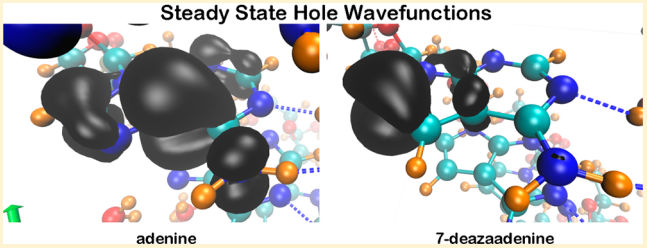
Hole Wave Functions and Transport with Deazaadenines Replacing Adenines in DNA

Alexander J. Breindel,[†] Rachel E. Stuart,[†] William J. Bock,[†] David N. Stelter,[‡] Shane M. Kravec,[†] and Esther M. Conwell*,[†,‡]

[†]Department of Physics and [‡]Department of Chemistry, University of Rochester, Rochester, New York 14627, United States

ABSTRACT: Transport of a hole along the base stack of DNA is relatively facile for a series of adenines (As) paired with thymines (Ts) or for a series of guanines (Gs) paired with cytosines (Cs). However, the speed at which a hole was found to travel was much too small to make useful semiconductor-type devices. Quite recently it was found that replacing one of the electronegative nitrogens (N3 or N7) with a carbon and a hydrogen, thus turning A into deazaadenine, increased the hole speed in what was A/T by a factor 30. To study the effect of the substitution we have carried out simulations for the wave function of a hole on an A/T oligomer with As modified by replacing N3 or N7, or both, with C−H's. The simulations were carried out using QM/MM and the code CP2K. We find, for either N, or both, replaced, the wave function of the hole behaves similarly to that of a hole on A/T in being delocalized immediately after hole insertion for up to ∼20 fs, and then becoming localized on one of the modified As. The time for localization could be decreased by placing additional water within ∼1.8 Å of N3 or N7, encouraging the formation of hydrogen bonds with these nitrogens. Because of their positive charge the hydrogen bonds tend to repel holes. However, these bonds were found to decay on a femtosecond time scale, thus unlikely to affect the hole hopping, which occurs on approximately a nanosecond scale in A/T. Replacement with a C−H of one or both of the electronegative Ns, along with the structural changes that result, is expected to decrease the activation energy and thus account for the larger hole hopping rate in the deaza-modified DNA.



1. INTRODUCTION

Following what one of the authors characterized as "our first provocative publication on long-range charge transfer in a DNA assembly"[1,2] there have been many investigations of hole and extra electron transfer in DNA.[3] The majority of these have been on DNA in solution, which can be more clearly characterized than DNA in air or in vacuum, and we will confine our investigations to the case of holes in DNA in solution. There are two reasons for interest in charge propagation in DNA: First, the traveling charge can interact with the bases it encounters, doing chemistry, and second, holes and electrons traveling freely in DNA might, as in conventional semiconductors, be used to make devices. Measurements have made it clear that the highest speeds have been attained for holes traveling in a series of adenines (As) paired with thymines (Ts) or guanines (Gs) paired with cytosines (Cs). However, the speeds are so small that the devices would operate only at such low frequencies as to be of little interest.

Recently, however, it was demonstrated that hole speeds in an A/T sequence can be increased by a factor of 30 by replacing adenine with deazaadenine.[4] Speed increase can similarly be obtained in G/C by replacing guanine with deazaguanine.[4] Shown in Figure 1 is deazaadenine, to be denoted 7-zA, obtained by replacing N7 in adenine by a carbon and a hydrogen. Similarly, 3-zA is obtained by replacing N3 with a carbon and a hydrogen. In principle, it is also possible to have adenines in which both nitrogens (Ns), N3 and N7, have been replaced. These will be denoted by 3,7-zA. The formal name for the latter material is 1*H*-pyrrolo[3,2-*c*]pyridine-4-amine. The set of guanines with electronegative Ns replaced has similar subspecies.

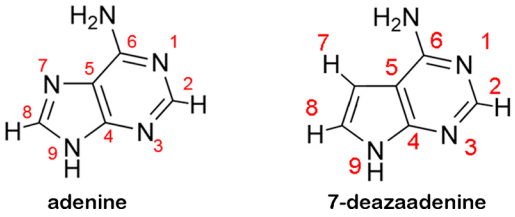


Figure 1. Structures of adenine and deazaadenine.

Parallel to the experimental observations there have been theoretical calculations, in particular of the wave function of a hole on a series of As or of Gs. Most early calculations were for Gs and led to wave functions delocalized over several Gs.[5] An early calculation for a series of As led to the conclusion that the hole wave function is spread over 4 As.[6] Later calculations found that in the steady state, for sequences of Gs, the wave

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function is localized on a single site.[7] The simulations of ref 8, and the discussion of ref 9, made it quite clear that the different results of early and later calculations were due to the neglect of water in the early calculations.[10] Although it had been suggested earlier,[7] the simulations showed clearly that the localization of the hole wave function is due to the polarization of the surrounding water by the hole.[9] Perhaps there is also some contribution due to nuclear relaxation on cation radical formation from the neutral parent. It is of interest that a DFT (density functional theory) calculation of Kumar and Sevilla for a hole on a set of stacked As led to the hole wave function delocalized over 2 or 3 adenines in the absence of water.[11] However, in a calculation for a base-stacked adenine dimer cation radical surrounded by 18 water molecules the hole wave function was ∼3 times as concentrated on one of the adenines as on the other.[12]

The effect of water on hole transport in a series of A/Ts has been investigated more generally in simulations by Mantz et al. using the code CP2K.[13] They showed that a strong hydrogen bond can be formed between a water hydrogen and an electronegative nitrogen atom, N7 or N3, of a neutral adenine. When such a bond is formed the positive charge on the H tends to repel a hole, thus in principle, affecting the transport of holes in a series of A/Ts. On the other hand, however, if a hydrogen bond is not formed, the attractive force of the higher electron density around an electronegative nitrogen contributes to the binding of a hole. This, and the various other forces that contribute to binding, result in the requirement of an activation energy for hole hopping. This activation energy has been measured as 2.8 kcal/mol, or 0.12 eV, for hole hopping in G/C.[14] It has been calculated as 0.26 eV for hole hopping in A/T.[15]

In what follows we will present the results of further simulations with CP2K (which we earlier used to obtain the hole wave function on a series of A/Ts[8]) to find hole wave functions with the adenine in A/T replaced by 7-zA, 3-zA, or 3,7-zA. We will study particularly the effect of the formation of hydrogen bonds due to close-by water molecules on the hole wave functions in these cases. It is found that, as in A/T, at short times (fs) after the introduction of the hole the wave function is delocalized, but localizes on a single deazaadenine or a 3,7-zA, within ∼20 fs. The time for localization and the distribution of the hole wave function on the chain depend on the amount and location of water molecules nearby. Replacing A with one of the As missing one or two of the electronegative nitrogens will decrease the number of hydrogen bonds formed with water, and thereby decrease the hydration of the chain. Lewis et al. attribute the increased speed of the hole in deazaadenine to "increased conformational mobility and decreased major groove hydration."[4] The former is expected because an A/T oligomer is particularly stiff.[16] The contribution of the latter is not so clear; it will be discussed after presentation of the results of the simulations.

2. COMPUTER MODELS FOR DEAZAADENINES AND 3,7-ZA

Before calculating the hole wave functions it is necessary to set up computer models of the molecules in terms of bond lengths and point charges on each of the atoms. For this we used a publicly available specification of the coordinates for the different atoms from PubChem[17a,b,c] and attached a phosphate backbone to the bases using the backbone coordinates of deoxyadenosine. With RESP appropriate fragments were built to use the RED service[18] to derive charges for the atoms. The RED service provides a free-to-use computer cluster setup to allow users to automatically generate the ESP (Electrostatic Potential) for their molecules and molecular fragments. The structure is first minimized and a molecular electrostatic potential (MEP) is calculated on a three-dimensional grid. Then, with the use of the RESP method, atom-centered charges are fit to the MEP. This procedure was used also for 3,7-zA.

To assign the parameters used for describing the bonding, Antechamber from the *Amber* suite of programs[19] was used. From the structure of the molecule, Antechamber determines atom types for the atoms in the molecule. These atom types describe the bonds that make up the molecule. To use Antechamber for a given nucleotide it is necessary to cap the nucleotide. The generated atom types and existing atom types from deoxyadenosine are then assigned by analogy to the uncapped fragments.

3. SIMULATIONS

We have carried out QM/MM simulations on a 10-mer duplex of A′/T where A′ stands for 3-zA, 7-zA, or 3,7-zA. The 10-mer was generated using the *Amber 9* software suite for A/T,[19] replacing A with A′. Eighteen Na^+ counterions, matching the number of phosphates, were placed along the backbone, and the initial structure was equilibrated. Following this minimization a truncated octahedron of ∼3000 TIP3P waters was added. After further minimizations, 5 contiguous A′ base pairs and their sugar plus backbone atoms were chosen as the quantum system. Water was introduced into the QM region by adding to it the waters contained within a given radius, 5−8 Å, of some of the principal atoms: N3 or C3, N7 or C7 on A′, and N1 and a pair of carbons on the thymine. One electron was removed to introduce a hole.

In describing the quantum system, as in refs 8 and 13, we used the Kohn−Sham energy functional expression at the restricted open shell DFT-Becke−Lee−Yang−Parr level, ROBLYP,[20,21] with an empirical self-interaction correction[22] added. As noted earlier, the simulations were carried out using CP2K, with a time interval of 0.5 fs. They were done with an initial temperature of 300 K, which was allowed to rise with time. The simulations were carried out to at least 40−50 fs for all these cases, 70 fs for some, well beyond the time for which localization was seen.

4. HOLE WAVE FUNCTIONS

In our early calculations,[8] as well as in the calculations of Mantz et al,[13] immediately after the introduction of the hole, its wave function was spread over the 5 As of the QM region, with minimum amplitude on the end adenines.[8,9,13] In our current calculations for all cases of A′ we again found the hole wave function immediately after the hole introduction to be delocalized. In some cases we added more water by inserting individual water molecules within a distance of ∼1.8 Å from an N3 or N7 on the individual zAs to study the effect of additional H-bonds. With the additional water in the QM region, upon introduction of a hole it was again found to be delocalized over the zAs of the QM region. However, in contrast to the case of the As, in the case of the zAs the hole was usually found to be spread over two to four sites rather than the five sites in the QM region available to it.. In some cases it was localized on two zA sites separated by a site that did not support any of the hole wave function. Specific investigation into some of these cases

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showed that there was a water molecule on the site without any hole wave function. It was expected that this would be generally true, according to the finding of ref 13, that a hole did not form on an adenine when its N7 or N3 was within ∼1.8 Å of a water molecule. Interestingly, however, we and Mantz et al. as well did find cases of As being home to both a hydrogen bond and a part of a delocalized hole wave function. The hydrogen bond might have been a relatively weak one, with a nonoptimum bond length or angle, and of course there is less repulsion for a part of the hole on an A or zA than for the entire hole. After times of about several femtoseconds the hydrogen bonds tended to disappear, and new ones appeared.[23]

Just as had been seen for A/T in ref 8, with increasing time the hole wave function on one of the zAs grew at the expense of the others until finally the hole was localized on a single zA. Localization took up to 20 fs, the time depending somewhat on the amount of excess water. With additional water around N3 or N7 the time required for localization was found to decrease. This is to be expected because the presence of additional water close to a zA tends to repel the hole. Not surprisingly, the presence of additional water affected the distribution of the wave function over an adenine or deazaadenine molecule, limiting the coverage, as had been found earlier for a series of A/Ts.

Plots of the localized wave functions are shown in Figures 2−5. The hole wave function is in black, oxygens red, hydrogens orange, nitrogens blue, carbons aqua. In contrast to the localized wave function for adenine, shown in the TOC figure, which is spread over the adenine molecule, the wave functions for the modified adenines are essentially confined to a part of the molecule. The localized wave function for 7-zA is seen to be mainly on the 5-sided ring, while that for 3-zA is mainly on the 6-sided ring. In both cases the hole is avoiding the ring that has the remaining nitrogen. The hole wave function for 3,7-zA, which was localized at 11.5 fs, was less stable than those of the others. It continued to evolve with considerable changes in shape until 36.5 fs, after which it did not change for the duration of the calculations, 41.5 fs. Starting at 11.5 fs, where it was spread out on both 5- and 6-sided rings, it ended up at 36.5 fs mostly on the 6-sided ring, concentrated on C3 which had replaced N3. In general, although those other than 3,7-zA did not change much with time in the range we investigated, the hole wave functions tended to contract slightly with time.

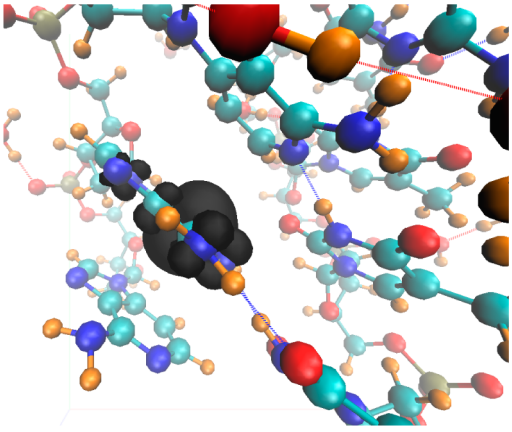

Figure 2. Localized hole wave function in 3-zA/T.

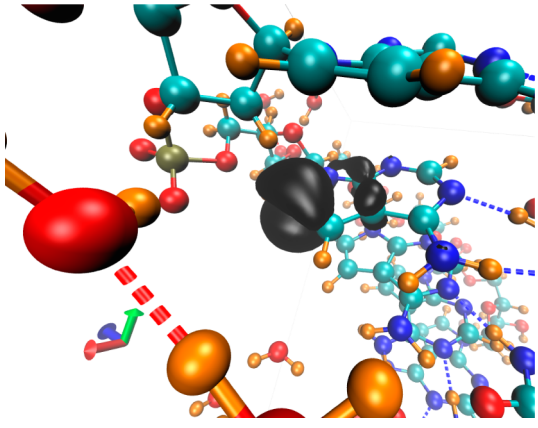

Figure 3. Localized hole wave function in 7-zA/T.

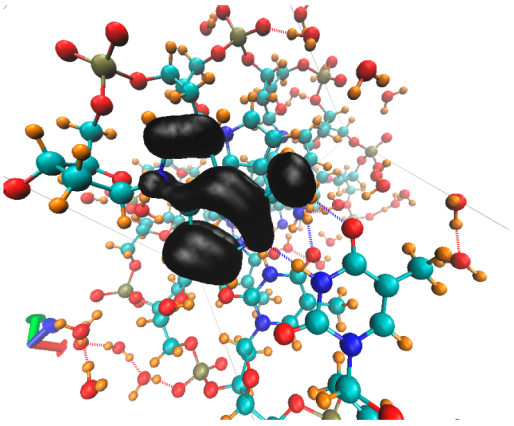

Figure 4. Localized hole wave function for (3,7)-zA/T at 11.5 fs.

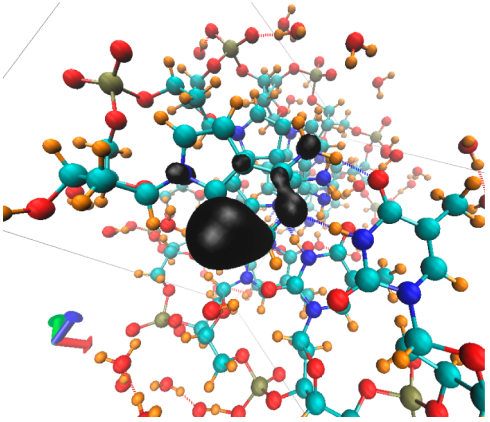

Figure 5. Localized hole wave function for (3,7)-zA/Tat 26.5 fs.

5. SUMMARY AND CONCLUSIONS

The modified adenines we have considered behave very similarly to adenine on introduction of a hole. Up to ∼20 fs after introduction of the hole its wave function is delocalized over some of the modified adenines in the QM region (5 bases in our simulations). It is reasonable to expect that the pattern of the delocalized hole wave function is partly determined by the presence of water molecules. One of the modified adenines still retaining an electronegative N could form a hydrogen bond with a close enough water molecule, tending to repel the hole from that modified adenine.

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Localization of the hole to a single modified A occurs in a time varying from ∼4 to 20 fs, in principle depending somewhat on the number of water molecules close by. Again, the pattern of the wave function will be determined partly by the proximity of water. In general the localized wave function is less spread out over the modified adenine than it would be over an adenine. It is even less spread out for the case where both N3 and N7 are missing, in that most of it is concentrated on C3. One may speculate that hopping is more difficult for a hole whose wave function consists of several relatively widely separated parts.

Over the times used in our simulations, a bond between a water's H and an electronegative N forms and disintegrates on a femtosecond time scale. If that were the only effect due to hydration, it would not be expected to affect the hole hopping time, which is ∼0.1 ns. However, other studies show that there are more extensive interactions of DNA with water than the single-site interaction we have been discussing. These suggest that formation of hydrogen bonds may act to nucleate an agglomeration of water and counterions. As pointed out by Ganguly et al., such agglomeration has been seen in high-resolution X-ray structures of DNA, where there are ordered waters, with some counterions included, associated with the floor of the minor groove and extending outward in several layers.[24] Agglomeration of water and counterions has also been seen on the floor of the major groove. Such ordered structures have not been seen in A/T, but Ganguly et al. have made it clear that agglomerates of water and counterions exist in A/T and G/C and in the compounds where A has been replaced by deazaadenine and G by deazaguanine. Comparison of different types of measurements on A/Ts with the same measurements on 7-zA/Ts have led to the conclusion that replacement of N7s with C−H's results in a decrease of water and counterions in the major groove. Replacing N3s by C−H's has been shown to lead to a decrease of water and counterions in the minor groove.[24,25] It is concluded that conversion of adenine to deazaadenine in A/T or conversion of guanine to deazaguanine in G/C results in less hydration. It appears likely that C−H substitution for both the electronegative Ns would result in a further decrease in hydration.

In summary, the large increase in hole mobility found by substituting C−H for one of the electronegative Ns in A/T is due partly to the greater flexibility of the substituted DNA, as pointed out in ref 4. It is also a result of the decrease in the activation energy for hole hopping due to removal of the attractive force of the high electron density around the electronegative N on the hole. There may be a further decrease due to the reorganization with the agglomeration of water and counterions that results from removal of a nitrogen. To account for an increase in hole velocity of a factor of 30 at room temperature the activation energy must decrease by 0.09 eV.

AUTHOR INFORMATION

Corresponding Author

*E-mail: conwell@chem.rochester.edu. Telephone: (585) 275-5841.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Murphy, C. J.; Arkin, M. R.; Jenkins, Y.; Ghatlia, N. D.; Bossmann, S. H.; Turro, N. J.; Barton, J. K. Long Range Photoinduced Electron Transfer through DNA Helix. *Science* **1993**, *262*, 1025−1029.

(2) Murphy, C. J.; Arkin, M. R.; Ghatlia, N. D.; Bossmann, S. H.; Turro, N. J.; Barton, J. K. Fast Photoinduced Electron Transfer through DNA. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 5315−5319.

(3) For extensive discussion see Genereux, J. C.; Barton, J. K. Mechanisms for DNA Charge Transport. *Chem. Rev.* **2010**, *110*, 1642−1662.

(4) Thazhathveetil, A. K.; Trifonov, A.; Wasielewski, M. R.; Lewis, F. D. Increasing the Speed Limit for Hole Transport in DNA. *J. Am. Chem. Soc.* **2011**, *133*, 11485−11487.

(5) See, for example, Sugiyama, H.; Saito, I. Theoretical Studies of GG-Specific Photocleavage of DNA via Electron Transfer: Significant Lowering of Ionization Potential and 5′-Localization of HOMO of Stacked GG Bases in B-Form DNA. *J. Am. Chem. Soc.* **1996**, *118*, 7063−7068.

(6) Basko, D. M.; Conwell, E. M. Effect of Solvation on Hole Motion in DNA. *Phys. Rev. Lett.* **2002**, *88*, 098102.

(7) Voityuk, A. A. Charge Transfer in DNA: Hole Charge Is Confined to a Single Base Pair Due to Solvation Effects. *J. Chem. Phys.* **2005**, *122*, 204904.

(8) Kinz-Thompson, C.; Conwell, E. Proton Transfer in Adenine-Thymine Radical Cation Embedded in B-Form DNA. *J. Phys. Chem. Lett.* **2010**, *1*, 1403−1407.

(9) Kravec, S. M.; Kinz-Thompson, C. D.; Conwell, E. M. Localization of a Hole on an Adenine-Thymine Radical Cation in B-Form DNA in Water. *J. Phys. Chem. B* **2011**, *115*, 6166−6171.

(10) (a) An apparent exception to this is the much-cited paper of Basko and Conwell, ref 6, which, although it did include water, led to the conclusion that the wavefunction is spread over ∼4 As. Actually, the calculation led correctly to the extent of the wavefunction being proportional to the transfer integral, but erred in its conclusion because of an incorrect guess for the value of the transfer integral, which had not yet been properly calculated at that time. With its correct value, 0.03 eV, (obtained from refs 10b−d) the Basko and Conwell calculation leads to a wavefunction localized on a single site. (b) Voityuk, A. A.; Rosch, N.; Bixon, M.; Jortner, J. Electronic Coupling for Charge Transfer and Transport in DNA. *J. Phys. Chem. B* **2000**, *104*, 9740−9745. (c) Grozema, F. C.; Siebbeles, L. D. A.; Berlin, Yu.A.; Ratner, M. A. Hole Mobility in DNA: Effects of Static and Dynamic Structural Fluctuations. *ChemPhysChem* **2002**, *2*, 536−539. (d) Senthilkumar, K.; Grozema, F. C.; Fonseca Guerra, C..; Bickelhaupt, F. M.; Matthias, F.; Lewis, F. D.; Berlin, Y. A.; Ratner, M. A.; Siebbeles, L. D. A. Absolute Rates of Hole Transfer in DNA. *J. Am. Chem. Soc.* **2005**, *127*, 14891−14903.

(11) Kumar, A.; Sevilla, M. D. Density Functional Theory Studies of the Extent of Hole Delocalization in One-Electron Oxidized Adenine and Guanine Base Stacks. *J. Phys. Chem. B* **2011**, *115*, 4990−5000.

(12) Adhikary, A.; Kumar, A.; Khanduri, D.; Sevilla, M. D. Effect of Base Stacking on the Acid−Base Properties of the Adenine Cation Radical [A^+] in Solution: ESR and DFT Studies. *J. Am. Chem. Soc.* **2008**, *130*, 10282−10292.

(13) Mantz, Y. A.; Gervasio, F. L.; Laino, T.; Parrinello, M. Solvent Effects on Charge Spatial Extent in DNA and Implications for Transfer. *Phys. Rev. Lett.* **2007**, *99*, 058104.

(14) Conron, S. M. M.; Thazhathveetil, A. K.; Wasielewski, M. R.; Burin, A. L.; Lewis, F. D. Direct Measurement of the Dynamics of Hole Hopping in Extended DNA G-Tracts. An Unbiased Random Walk. *J. Am. Chem. Soc.* **2010**, *132*, 14388−14390.

(15) Tesar, S. L.; Leveritt, J. M., III; Kurnosov, A. A.; Burin, A. L. Temperature Dependence for the Rate of Hole Transfer in DNA: Nonadabatic Regime. *Chem. Phys.* **2012**, *393*, 13−18.

(16) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984.

(17) *PubChem Compound Database*; National Center for Biotechnology Information, U.S. National Library of Medicine: Bethesda, MD; http://www.ncbi.nlm.nih.gov/pccompound. Identifying numbers are: (a) 5359620 for 7-zA, (b) 23190 for 3-zA, and (c) 324312 for 3,7-zA.
(18) Dupradeau, F.-Y.; Pigache, A.; Zaffran, T.; Savineau, C.; Lelong, R.; Grivel, N.; Lelong, D.; Rosanski, W.; Cieplak, P. The R.E.D. Tools: Advances in RESP and ESP Charge Derivation and Force Field Library Building. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7821−7839.
(19) Case, D. A.; Darden, T. A.; Cheatham, T. E., III; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Merz, K. M.; Wang, B.; Pearlman, D. A.; et al. *Computer Code Amber 9*; University of California: San Francisco, 2006.
(20) Becke, A. D. Density-Functional Exchange-Energy Approximation with Correct Asymptotic Behavior. *Phys. Rev. A* **1988**, *38*, 3090−3100.
(21) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37*, 785−789.
(22) Mantz, Y. A.; Gervasio, F. L.; Laino, T.; Parrinello, M. Charge Localization in Stacked Radical Cation DNA Base Pairs and the Benzene Dimer Studied by Self-Interaction Corrected Density-Functional theory. *J. Phys. Chem. A* **2007**, *111*, 105−112.
(23) Mantz; et al. In ref 13 found a time of approximately a picosecond for creation or destruction of a hydrogen bond, but this was for the special case where the QM region consisted of a single A with a hole localized on it.
(24) Ganguly, M.; Wang, R.-W.; Marky, L. A.; Gold, B. Thermodynamic Characterization of DNA with 3-Deazaadenine and 3-Methyl-3-Deazaadenine Substitutions:The Effect of Placing a Hydrophobic Group in the Minor Groove of DNA. *J. Phys. Chem. B* **2010**, *114*, 7656−7661.
(25) Ganguly, M.; Wang, F.; Kaushik, M.; Stone, M. P.; Marky, L. A.; Gold, B. A Study of 7-Deaza-2′-deoxyguanosine-2′-deoxycytidine Base Pairing in DNA. *Nucleic Acids Res.* **2007**, *35*, 6181−6195.