Published in final edited form as:

Chem Phys Lett. 2007 September 26; 446(1): 151–158. doi:10.1016/j.cplett.2007.07.095.

Effect of base mismatch on the electronic properties of DNA-DNA and LNA-DNA double strands: Density-functional theoretical calculations

Takayuki Natsume^a, Yasuyuki Ishikawa^b, Kenichi Dedachi^a, Takayuki Tsukamoto^a, and Noriyuki Kurita^{a,*}

^a Department of Knowledge-based Information Engineering, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441-8580, Japan

^b Department of Chemistry, University of Puerto Rico, P. O. Box 23346, UPR Station, San Juan, PR 00931-3346, USA

Abstract

The electronic properties of double-stranded octameric DNA-DNA and LNA-DNA with a single-base mismatch were compared with those having fully complementary base pairs to quantify the effect of the base mismatch on hybridization energies (HE). A single T-G mismatch in the LNA-DNA gives rise to a significant reduction in HE, which is consistent with a significant lowering of the melting temperature for mismatched LNA-DNA. By contrast, the hybridization strength of the mismatched DNA-DNA depends strongly on local hydrogen-bonding arrangements in the mispaired T-G. The difference in HE is explained in terms of variation in charge distributions around the hydrogen-bonded base pairs.

1. Introduction

Recently significant progress has been made in DNA array technology toward rapid and accurate detection of specific DNA sequences. In order to develop highly sensitive DNA sensors, it is essential to produce an oligomer having stronger hybridization with a complementary single-stranded DNA. To this end, a multitude of modifications to native nucleic acids have been introduced to develop new nucleic acids such as peptide nucleic acid and locked nucleic acid (LNA) [1]. LNA is a nucleic acid analogue of RNA in which the furanose ring of the ribose sugar is chemically locked by the linkage of O2 and C5-methylene (Fig. 1).

LNA single strands display high affinity toward both DNA and RNA single strands having a complementary base sequence, forming double-stranded LNA-DNA and LNA-RNA through the Watson-Crick hydrogen bonds between the bases [1]. The melting temperatures (T_m) of LNA-RNA and LNA-DNA hybrids are, respectively, 2 – 10 °C and 1 – 8 °C higher than those of DNA-RNA and DNA-DNA. In addition, the introduction of a mispaired T-G into octameric

*Corresponding author Noriyuki Kurita, Associate professor, Toyohashi University of Technology, Department of Knowledge-based Information Engineering, Tempaku-cho, Toyohashi, 441-8580, Japan, Tel.& Fax: +81-532-44-6875, E-mail: kurita@cochem2.tut.ac.jp.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DNA-DNA and LNA-DNA double strands has been shown to significantly reduce their T_m by 26 °C [2]. The 26 °C T_m reduction for the mismatched LNA-DNA is much greater than the 10 °C reduction for the mismatched DNA-DNA, indicating that the base mismatch weakens the hybridization in LNA-DNA to a much greater degree than it does in DNA-DNA. Thus the single-stranded LNA would be more sensitive in detecting the base mismatch than its DNA counterpart.

In our recent study [3], the electronic properties of trimeric PNA-DNA and LNA-DNA double strands were investigated in density-functional theory (DFT) calculations. The computed hybridization energy of the trimeric LNA-DNA was greater than that of the DNA-DNA counterpart, indicating higher affinity of the single-stranded LNA to a complementary DNA. This greater hybridization strength in LNA-DNA could be accounted for by the charge distribution around the hydrogen bonds between the LNA and DNA bases.

In the present DFT study, we determine the hybridization energies and electronic properties of octameric DNA-DNA and LNA-DNA [2] with and without a single T-G mismatch to elucidate the effect of the base mismatch on hybridization energies. Drawing on the theoretical and earlier experimental [2] results, we assess the potential use of LNA for a highly sensitive DNA sensor.

2. Details of calculations

A standard B-form of the octameric DNA double strand was modeled by using the software HyperChem [4]. The base sequence of the double strand 5'-d(TGCTGGTG)₂-3' is identical to that employed in the experimental study [2]. The 3' and 5' ends of the double strand were both terminated by hydrogen atoms. To neutralize the negative charges on the sugar phosphate groups in the backbone, counter ions (Na⁺) were added. The structure of the backbone, including the terminal hydrogen atoms and Na⁺ ions, was partially optimized by the classical molecular mechanics (MM) method based on an AMBER force field [5]. Some sections of the base pairs are held fixed during the optimization because classical MM often causes a distorted structure for stacked base pairs in a double-stranded DNA.

In the optimized structure of the double strand, a T-A base pair was replaced by a mispaired T-G, and subsequently the structure of the mismatched double strand was re-optimized by the MM method as above. It should be noted that two possible hydrogen-bonded (H-bonded) structures for the mismatched T-G base pair were considered in the present study.

The individual nitrogenous bases in the 5'-d(TGCTGGTG)₂-3' are labeled below, in which the mismatched T-G base pair is underlined.

- a. The double strand with fully complementary base pairs;

5' – T1 – G2 – C3 – T4 – G5 – G6 – T7 – G8 – 3'

3' – A16 – C15 – G14 – A13 – C12 – C11 – A10 – C9 – 5'

- b. The double strand with a mispaired T-G;

5' – T1 – G2 – C3 – T4 – G5 – G6 – T7 – G8 – 3'

3' – A16 – C15 – G14 – G13 – C12 – C11 – A10 – C9 – 5'

The LNA-DNA hybrid was constructed by modifying the ribose sugar unit of the nucleic acid in the same manner as described in our previous study [3]. The structure of the modified ribose sugar section of LNA (Fig. 1) was optimized by the MM method. Whereas the A-form is generally the preferred conformation for the LNA-LNA double strand, we here employed the B-form LNA-DNA hybrid, since our previous DFT study [3] on the A- and B-form trimeric

LNA-DNA hybrids indicated that the hybridization energy of the B-form is greater by as much as 62.8 kcal/mol than that of the A-form. The complementary T4-A13 base pair in the LNA-DNA was replaced with the mispaired T4-G13, and subsequently, the structure of the mismatched hybrid was optimized in the same manner as for the mismatched DNA-DNA.

In the present study, the electronic properties of the octameric DNA-DNA and LNA-DNA with and without the T-G base mismatch were computed with the DFT algorithm of the Dmol³ program package [6]. The Dmol³ employs numerical basis functions that are capable of describing long-range interactions. The DFT calculations employed the RPBE functional [7] for the exchange-correlation energies and basis sets of double-numerical plus *d*- and *p*-polarization functions (DNP), respectively, for heavy atoms and hydrogen.

3. Results and discussion

3.1. Structures of DNA-DNA and LNA-DNA hybrids

To assess the reliability of MM-optimized structures of the octameric LNA-DNA hybrids, we compare our calculations for structural parameters of the ribose sugar group (Fig. 1) of the LNA-DNA hybrid with experimental results from Egli et al. [8]. The calculated values in Table 1 are the average over the 8 ribose-sugar units in the LNA strand in the complementary and base-mismatched LNA-DNA hybrids. The atom labels in Table 1 are given in Fig. 1. The calculated structural parameters are comparable to the experimental data, indicating the reliability of the model ribose-sugar structure of the constructed LNA in the present study.

As for the structure of the mismatched T-G and complementary T-A base pairs in DNA-DNA (Fig. 2), the calculated bond lengths and bond angles for the H-bonded atoms are compared in Table 2 with experimental results from Allawi and SantaLucia [9] (PDB ID is 1BJD). Although Allawi and SantaLucia [9] only reported a strongly H-bonded T-G structure (Fig. 2(a)), the present study also predicted another weak H-bond arrangement for the mispaired bases (Fig. 2(b)).

3.2. Effect of base mismatch on the electronic properties of DNA-DNA and LNA-DNA hybrids

Computed total energies and hybridization energies of the octameric DNA-DNA and LNA-DNA, with and without the T-G base mismatch, are compared in Table 3. The unique design of the LNA backbone has a significant effect on its hybridization with DNA. The hybridization energy of the LNA-DNA hybrid with fully complementary base pairs is 15.8 kcal/mol greater than that of its DNA-DNA counterpart. The result is consistent with the experiment [1] as well as with our previous DFT results [3], which showed that the hybridization energy of trimeric LNA-DNA was 6.5 kcal/mol greater than that of DNA-DNA counterpart. In Table 4, the charge distributions on the H-bonded atoms in the complementary DNA-DNA are compared with those in the complementary LNA-DNA. The partial charges were determined using the Dmol³ program package to reproduce the electrostatic potential (ESP). The LNA backbone causes significant increases in the negative charges on the N atoms in G2-C15, T4-A13, and G5-C12 in LNA-DNA. It also increases the positive charges on the adjacent hydrogen atoms involved in the H-bonding, thereby increasing the hybridization energy.

The computed structural parameters in Table 2 indicate that the backbone of LNA has a significant effect on the conformation of the strongly H-bonded T-G mismatch (Fig. 3(a)). Compared with the sugar-phosphate backbone in DNA, the unique design of LNA backbone causes alterations in bond lengths by as much as 0.1 Å. The two alternative H-bonding arrangements in the mispaired T-G (Figs. 3(a) and 3(b)) reduce the hybridization energy of the mismatched LNA-DNA hybrid by 2.9 and 18.9 kcal/mol, respectively, as shown in Table 3. The results are consistent with those of Mouritzen et al. [2], which showed the T-G mismatch

in the octameric LNA-DNA hybrid causes a 26 °C reduction in T_m . In particular, the weakly H-bonded form of T-G base mismatch (b) (Fig. 3(b)) significantly weakens the hybridization of LNA-DNA.

The LNA backbone significantly alters the charge distribution around the mismatched T-G base pair (a) (Fig. 3(a)), leading to some strengthening of the H-bonding between the mismatched bases. Consequently, the introduction of mismatched T-G weakens the hybridization of LNA-DNA only slightly, by 2.9 kcal/mol. As for the T-G base pair (b) shown in Fig. 3(b), the effect of the backbones is so minuscule that the T-G structures are nearly the same in both DNA-DNA and LNA-DNA. In contrast to the stable structure (a) (Fig. 3(a)), the O4-H4 hydrogen bond in structure (b) (Fig. 3(b)) is significantly longer at 2.385 Å, indicating a weakly H-bonded base pair. These differences in the H-bonding network in the mismatched base pairs give rise to significant differences in hybridization energies.

By contrast, the two forms of mispaired T-G in Figs. 2(a) and 2(b) affect the DNA-DNA hybridization differently. Compared with the fully complementary DNA-DNA, the strongly H-bonded T-G base pair (a) (Fig. 2(a)) increases the hybridization energy of the mismatched DNA-DNA slightly by 2.4 kcal/mol, whereas the weakly hydrogen-bonded T-G base pair (b) (Fig. 2(b)) reduces the hybridization energy by as much as 15.3 kcal/mol. Therefore, the strongly H-bonded T-G base pair alone in the mismatched DNA-DNA would raise its T_m . However, Mauritzen et al. [2] found the T_m of the mismatched DNA-DNA to be 10 °C lower than that of the fully complementary DNA-DNA in a pH=7 buffer solution. The discrepancy between theory and experiment may come from the absence of hydrating water molecules around the base pairs in our model calculations on dry DNA duplexes. The water molecules H-bonded to the base pairs in the minor groove of DNA-DNA double strand were previously found to have significant effect on the electronic properties of DNA-DNA in a combined molecular dynamics/DFT study [10,11]. To address the effect of hydrating water molecules on the hybridization energy, DFT study is underway on the complementary and mismatched DNA-DNA and LNA-DNA by explicitly including the hydrating water molecules.

The charge distribution around the H-bonds is also examined to elucidate the effect of the T-G mismatch on the DNA-DNA hybridization energy. The partial charges on the H-bonded atoms in the complementary and mismatched DNA bases are listed in Table 5. The results in Table 5 indicate that the atomic charges on the strongly H-bonded T4-G13 base pair (a) differ significantly from those on the complementary T4-A13 base pair. The partial charges on the H and N atoms in the mispaired T4-G13 are as much as 0.28 – 0.37 greater in magnitude than those for T4-A13. Due to the increased electrostatic interaction within the hydrogen bonds, the hybridization energy of DNA-DNA having the strongly H-bonded T-G (a) is 2.4 kcal/mol greater than that of the normal Watson-Crick base-paired DNA-DNA (Table 3). The introduction of the strongly H-bonded T4-G13 mismatch in DNA-DNA also induces significant change in atomic charges on the neighboring G5-C12 and C3-G14 base pairs; the partial charges on the N and H atoms increase in magnitude by as much as 0.18 and 0.09, respectively. The effect is also evident in the H-bond lengths: The O6-H6 bond length in T-A is longer by as much as 0.114 Å than O2-H2 in the T-G pair, implying weaker hydrogen bonding of T-A. Therefore, the introduction of the strongly H-bonded form of T-G mismatch into DNA-DNA entails enhancement of the hybridization.

Table 5 also displays the atomic charges on the DNA-DNA involving the weakly H-bonded T-G (b). The atomic charges on the weakly H-bonded T4-G13 are up to 0.15 lower than those on the complementary T4-A13 base pair, resulting in reduced hybridization energy for the mismatched DNA-DNA. This result is radically different from the mismatched DNA-DNA with the strongly H-bonded T-G (a). The structural difference in the mispaired T-Gs in Figs. 2(a) and 2(b) gives rise to a significant difference in the charge distribution on the atoms

involved in the H-bonding, leading to a significant difference in the hybridization energies between the two mismatched DNA-DNA duplexes.

The atomic charges on the octamer LNA-DNA with and without a mispaired T-G are compared in Table 6. The values in Table 6 represent the LNA-DNA hybrid with the strongly H-bonded T-G mismatch (Fig. 3(a)) and with the weakly H-bonded T-G mismatch (Fig. 3(b)). The charge distribution on the strongly H-bonded T4-G13 (a) is significantly altered by the mismatch. The atomic charges on the H-bonded O(T4)...H-N(G13) unit in the mispaired T-G are greater in magnitude than those on the O(T4)...H-N(A13) in the complementary T-A base pair, whereas the partial charges on the N-H(T4)...O(G13) are comparable or even smaller than those on the N-H(T4)...N(A13). The smaller atomic charges on the N-H(T4)...O(G13) in the mismatched LNA-DNA indicate reduction in the hybridization energy of LNA-DNA. The partial charges on the atoms involved in the weakly H-bonded T4-G13 pair (Fig. 3(b)) in the mismatched LNA-DNA are up to 0.13 less than those on the complementary T4-A13 pair. The marked difference leads to the reduced strength of hybridization between the LNA and DNA single strands. The effect of the mismatched base pair on the atomic charge distributions is quite different between DNA-DNA and LNA-DNA.

To compare the chemical reactivity of these double strands, the energy levels and spatial distributions of the highest occupied molecular orbital (HOMO), the next highest occupied molecular orbital (HOMO-1), and the lowest unoccupied MO (LUMO) were examined. Table 7 lists the energy levels and spatial distributions of these MOs. The HOMO-LUMO energy gap in DNA-DNA is not affected by the introduction of the two forms of T-G mismatches shown in Figs. 2(a) and 2(b). By contrast, the energy gap in LNA-DNA is significantly altered by the presence of T-G mismatch; the T-G mismatch (a) in Fig. 3 enlarges the gap by 0.12 eV, while the T-G mismatch (b) in Fig. 3(b) reduces the gap by 0.08 eV. Therefore, the chemical reactivity of mismatched LNA-DNA would be lower than that of mismatched DNA-DNA.

Since the HOMO and LUMO mediate, respectively, the hole and electron transfer through DNA, the spatial distributions of HOMO and LUMO are of crucial importance in understanding the charge-transfer pathways. While the HOMOs are all localized on guanine bases (Table 7), the T-G mismatch shifts the HOMO distribution on LNA-DNA from the G5/G6 bases to other guanine bases (G2, G14 and G13). These MOs localized on the G5/G6 bases exist as HOMO-1 in the mismatched LNA-DNA. On the other hand, the LUMOs are all localized on the counter ions, indicating a strong possibility that the electron transfers through the counter ions. The results displayed in Table 7 indicate that the spatial distributions of HOMO and LUMO are altered by the mispaired T-G in the mismatched DNA-DNA and LNA-DNA.

4. Conclusions

The unique design of the LNA backbone has a significant effect on its hybridization with DNA. The hybridization energy of the LNA-DNA hybrid with fully complementary base pairs is 15.8 kcal/mol greater than that of its DNA-DNA counterpart. To quantify the effect of the base mismatch on hybridization energies, the electronic properties of octameric DNA-DNA and LNA-DNA with a single T-G base mismatch were compared with those having fully complementary base sequence. Two alternative H-bonding arrangements in the mismatched T-G base pair were accounted for in the present study. The strength of DNA-DNA hybridization depends strongly on the types of H-bonding framework in the mispaired T-G, while that of LNA-DNA decreases uniformly for both forms of T-G mismatch. The computed results on LNA-DNA are consistent with the experimental finding [2] that the presence of the T-G mismatch lowers the T_m of LNA-DNA by as much as 26 °C.

The increase in the computed DNA-DNA hybridization energy caused by the strongly H-bonded T-G mismatch (a) (Fig. 2(a)) contradicts the experimental finding [2] that the presence of a T-G mismatch lowers T_m . In contrast, the marked reduction in the computed hybridization energy of the DNA-DNA involving the weakly H-bonded T-G mismatch (b) (Fig. 2(b)) is consistent with experiment. Thus, we posit that at high temperature the weakly H-bonded T-G (b) becomes the dominant form in the mismatched DNA-DNA. The significant change in the computed hybridization energies caused by the single T-G mismatch is apparent in the marked changes in charge distribution in the vicinity of the hydrogen bonds. Comparison of the computed hybridization energies between the mismatched DNA-DNA and LNA-DNA indicates that the single-stranded LNA would detect the base mismatch in DNA more readily than its DNA counterpart.

Acknowledgments

This work was supported in part by the grants from the CASIO Science Promotion Foundation, the Kayamori Foundation of Informational Science Advancement, the Inamori Foundation and the Japan Society for the Promotion of Science (No. 15310088). T. N. gratefully acknowledges the support from the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for JSPS Fellows (No. 18.282). Y. I. gratefully acknowledges the support of National Institute of Health SCoRE Program-Grant No. S06GM08102.

References

1. Petersen M, Wengel J. Trends Biotechnol 2003;21:74. [PubMed: 12573856]
2. Mouritzen PA, Nielsen AT, Pfundheller HM, Choleva Y, Kongsbak L, Møller S. Expert Rev Mol Diagn 2003;3:27. [PubMed: 12528362]
3. Natsume T, Ishikawa Y, Dedachi K, Tsukamoto T, Kurita N. Chem Phys Lett 2007;434:133. [PubMed: 18548123]
4. HyperChem 6.03. Hypercube; Gainesville, FL, USA: 2000.
5. Cornell WD, Cieplak P, Bayly CI, Gould IR, Merz KM, Ferguson DM, Spellmeyer DC, Fox T, Caldwell JW, Kollman PA. J Am Chem Soc 1995;117:5179.
6. Delley B. J Chem Phys 2000;113:7756.
7. Hammer B, Hansen LB, Norskov JK. Phys Rev B 1999;59:7413.
8. Egli M, Minasov G, Teplova M, Kumar R, Wengel J. Chem Commun 2001:651.
9. Allawi HT, SantaLucia J Jr. Nucleic Acids Res 1998;26:4925. [PubMed: 9776755]
10. Tsukamoto T, Ishikawa Y, Vilkas MJ, Natsume T, Dedachi K, Kurita N. Chem Phys Lett 2006;429:563.
11. Tsukamoto T, Ishikawa Y, Natsume T, Dedachi K, Kurita N. Chem Phys Lett 2007;441:136. [PubMed: 19587836]

Figure 1.
Optimized structure of the ribose sugar group in the LNA-DNA hybrid.

(a)

(b)

Figure 2.

Optimized structures of (a) strongly H-bonded T-G base pair; (b) weakly H-bonded T-G base pair in the mismatched DNA-DNA hybrids; (c) T-A base pair in the DNA-DNA having fully complementary base pairs. The H-bond lengths are shown for comparison.

(a)

(b)

Figure 3.

Optimized structures of two alternative H-bonded forms of T-G base pairs in the mismatched LNA-DNA hybrids; (a) the strongly H-bonded base pair; (b) the weakly H-bonded base pair. The H-bond lengths are shown for comparison.

(a)

(b)

Figure 4.
Optimized structures of (a) mismatched octamer DNA-DNA; (b) mismatched octamer LNA-DNA. Counter ions (Na^+) are shown by large balls.

Table 1

Comparison with experiment [8] of the computed bond lengths and torsion angle for the ribose sugar units of the LNA-DNA hybrid. The computed structural parameters are the average over the eight sugar units in the LNA strands in the fully complementary and mismatched LNA-DNA hybrids. The labeling of each atom is given in Fig. 1.

Experiment Calculated			
Bond length (Å)			
C4'-C5	1.528		1.540
C5-O2	1.462		1.449
O2-C2'	1.465		1.451
Torsion angle (degree)			
C4'-C5-O2-C2'	5.8		1.5

Table 2

Bond lengths and bond angles for the two H-bonded structures of the mismatched T-G base pair in the DNA-DNA and LNA-DNA hybrids. The calculated structural parameters for the mismatched DNA-DNA and LNA-DNA are compared with the experimental data [9] for the mismatched DNA-DNA. The labeling of each atom is given in Fig. 2.

	Experiment	Calculated (a)			Calculated (b)		
		DNA-DNA	DNA-DNA	LNA-DNA	DNA-DNA	LNA-DNA	LNA-DNA
O1-H1	1.649	1.896	1.799	O3-H3	1.937	1.947	
H1-N1	1.008	1.020	1.020	H3-N3	1.020	1.019	
N2-H2	1.009	1.020	1.019	O4-H4	2.385	2.383	
H2-O2	1.686	1.742	1.707	H4-N4	1.009	1.010	
O1-H1-N1	161.9	171.3	171.0	O3-H3-N3	160.7	159.8	
N2-H2-O2	162.9	171.1	169.2	O4-H4-N4	160.6	160.7	

Table 3

The computed total energies (Hartree) and hybridization energies^a (kcal/mol) for the DNA-DNA and LNA-DNA hybrids with and without the T-G mismatches given in Figs. 2(a) and 2(b) (DNA-DNA) and Figs. 3(a) and 3(b) (LNA-DNA).

	Total energy			Hybridization energy
	DNA-DNA	DNA-*	*-DNA	DNA-DNA
No mismatch	-23186.438	-11794.849	-11391.372	135.7
T-G mismatch (a)	-23261.747	-11794.869	-11466.658	138.1
T-G mismatch (b)	-23261.674	-11794.849	-11466.633	120.4
	LNA-DNA	LNA-*	*-DNA	LNA-DNA
No mismatch	-24093.187	-12701.576	-11391.370	151.5
T-G mismatch (a)	-24168.520	-12701.620	-11466.663	148.6
T-G mismatch (b)	-24168.417	-12701.576	-11466.630	132.6

$$^a E_{\text{hyb}} = E_{\text{DNA-*/LNA-*}} + E_{\text{*DNA}} - E_{\text{DNA/LNA-DNA}}$$

Table 4

ESP-fitted atomic charges on the H-bonded atoms in the fully complementary DNA-DNA and LNA-DNA. The values are those averaged over all oxygen, nitrogen, or hydrogen atoms involved in the hydrogen bonds.

Base-pair	Atoms	DNA-DNA		LNA-DNA	
T1-A16	N-H...N	-0.69	0.44	-0.70	0.44
	O...H-N	-0.53	0.47	-0.53	0.47
G2-C15	N-H...O	-0.77	0.43	-0.89	0.46
	N-H...N	-0.81	0.39	-0.86	0.43
	O...H-N	-0.60	0.56	-0.61	0.57
C3-G14	O...H-N	-0.70	0.48	-0.90	0.46
	N...H-N	-0.81	0.45	-0.73	0.45
	N-H...O	-1.11	0.60	-0.62	0.57
T4-A13	N-H...N	-0.52	0.35	-0.63	0.39
	O...H-N	-0.54	0.42	-0.53	0.41
G5-C12	N-H...O	-0.60	0.35	-0.73	0.39
	N-H...N	-0.89	0.41	-0.85	0.41
	O...H-N	-0.61	0.55	-0.62	0.55
G6-C11	N-H...O	-0.94	0.49	-1.00	0.51
	N-H...N	-0.67	0.49	-0.66	0.49
	O...H-N	-0.55	0.55	-0.55	0.53
T7-A10	N-H...N	-0.93	0.52	-1.01	0.53
	O...H-N	-0.60	0.50	-0.58	0.48
G8-C9	N-H...O	-1.02	0.51	-1.02	0.51
	N-H...N	-0.78	0.47	-0.81	0.47
	O...H-N	-0.58	0.57	-0.60	0.56

Base-pair	Atoms	DNA-DNA	DNA-DNA	LNA-DNA
	average	-0.73	0.48	-0.80

Base sequences: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'
3' - A16 - C15 - G14 - A13 - C12 - C11 - A10 - C9 - 5'

Table 5

ESP-fitted atomic charges on the H-bonded atoms in the fully complementary and mismatched DNA-DNA. The values are those averaged over all oxygen, nitrogen, or hydrogen atoms involved in the hydrogen bonds. The values in parentheses are the differences in partial charges between the fully complementary and mismatched DNA-DNA.

Base-pair	Atoms	No mismatch		T-G mismatch (a)			T-G mismatch (b)			
T1-A16	N-H...N	-0.69	0.44	-0.68	-0.73 (-0.04)	0.45 (0.01)	-0.66 (0.02)	-0.72 (-0.03)	0.46 (0.02)	-0.69 (-0.01)
	O...H-N	-0.53	0.47	-0.97	-0.53 (0.00)	0.47 (0.00)	-0.95 (0.02)	-0.54 (-0.01)	0.47 (0.00)	-0.97 (0.00)
G2-C15	N-H...O	-0.77	0.43	-0.64	-0.77 (0.00)	0.42 (-0.01)	-0.64 (0.00)	-0.76 (0.01)	0.42 (-0.01)	-0.64 (0.00)
	N-H...N	-0.81	0.39	-0.68	-0.89 (-0.08)	0.42 (0.03)	-0.70 (-0.02)	-0.73 (0.08)	0.36 (-0.03)	-0.66 (0.02)
	O...H-N	-0.60	0.56	-1.01	-0.61 (-0.01)	0.57 (0.01)	-1.03 (-0.02)	-0.59 (0.01)	0.56 (0.00)	-0.99 (0.02)
C3-G14	O...H-N	-0.70	0.48	-0.90	-0.75 (-0.05)	0.50 (0.02)	-0.98 (-0.08)	-0.72 (-0.02)	0.50 (0.02)	-0.98 (-0.08)
	N...H-N	-0.81	0.45	-0.73	-0.93 (-0.12)	0.54 (0.09)	-0.84 (-0.11)	-0.82 (-0.01)	0.40 (-0.05)	-0.67 (0.06)
	N-H...O	-1.11	0.60	-0.62	-1.09 (0.02)	0.58 (-0.02)	-0.58 (0.04)	-1.05 (0.06)	0.60 (0.00)	-0.57 (0.05)
T4-A13 or T4-G13	N-H...N	-0.52	0.35	-0.74	-	-	-	-	-	-
	O...H-N	-0.54	0.42	-0.83	-	-	-	-	-	-
	O...H-N	-	-	-	-0.74	0.63	-1.11	-0.57	0.39	-0.68
	N-H...O	-	-	-	-0.78	0.53	-0.66	-0.49	0.39	-0.57
G5-C12	N-H...O	-0.60	0.35	-0.60	-0.78 (-0.18)	0.43 (0.08)	-0.65 (-0.05)	-0.72 (-0.12)	0.42 (0.07)	-0.61 (-0.01)
	N-H...N	-0.89	0.41	-0.67	-1.02 (-0.13)	0.50 (0.09)	-0.68 (-0.01)	-0.79 (0.10)	0.40 (-0.01)	-0.77 (-0.10)
	O...H-N	-0.61	0.55	-0.98	-0.63 (-0.02)	0.58 (0.03)	-0.95 (0.03)	-0.59 (0.02)	0.53 (-0.02)	-0.94 (0.04)
G6-C11	N-H...O	-0.94	0.49	-0.63	-0.91 (0.03)	0.48 (-0.01)	-0.65 (-0.02)	-0.94 (0.00)	0.50 (0.01)	-0.64 (-0.01)
	N-H...N	-0.67	0.49	-0.83	-0.73 (-0.06)	0.52 (0.03)	-0.81 (0.02)	-0.67 (0.00)	0.51 (0.02)	-0.84 (-0.01)
	O...H-N	-0.55	0.55	-1.04	-0.56 (-0.01)	0.56 (0.01)	-1.04 (0.00)	-0.55 (0.00)	0.55 (0.00)	-1.04 (0.00)
T7-A10	N-H...N	-0.93	0.52	-0.88	-0.94 (-0.01)	0.55 (0.03)	-0.91 (-0.03)	-0.94 (-0.01)	0.54 (0.02)	-0.90 (-0.02)
	O...H-N	-0.60	0.50	-0.92	-0.59 (0.01)	0.49 (-0.01)	-0.92 (0.00)	-0.60 (0.00)	0.50 (0.00)	-0.92 (0.00)
G8-C9	N-H...O	-1.02	0.51	-0.68	-0.97 (0.05)	0.47 (-0.04)	-0.58 (0.10)	-1.02 (0.00)	0.50 (-0.01)	-0.68 (0.00)

Base-pair	Atoms	No mismatch	T-G mismatch (a)		T-G mismatch (b)	
	N-H...N	-0.78 0.47	-0.72 (0.06)	0.43 (-0.04)	-0.78 (0.00)	-0.77 (0.00)
	O...H-N	-0.58 0.57	-0.58 (0.00)	0.56 (-0.01)	-0.58 (0.00)	-1.03 (0.00)
	average	-0.73 0.48	-0.77 (-0.04)	0.51 (0.03)	-0.72 (0.00)	-0.79 (0.00)

Base sequences:

Complementary: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'
 3' - A16 - C15 - G14 - A13 - C12 - C11 - A10 - C9 - 5'
 T-G mismatched: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'
 3' - A16 - C15 - G14 - G13 - C12 - C11 - A10 - C9 - 5'

Table 6

ESP-fitted atomic charges on the H-bonded atoms in the fully complementary and mismatched LNA-DNA. The values are those averaged over all oxygen, nitrogen, or hydrogen atoms involved in the hydrogen bonds. The values in parentheses are the differences in partial charges between the fully complementary and mismatched LNA-DNA.

Base-pair	Atoms	No mismatch	T-G mismatch (a)			T-G mismatch (b)		
T1-A16	N-H...N	-0.70	0.44	-0.67	-0.72 (-0.02)	0.46 (0.02)	-0.68 (-0.04)	-0.68 (-0.01)
	O...H-N	-0.53	0.47	-0.96	-0.53 (0.00)	0.47 (0.00)	-0.53 (0.00)	-0.95 (0.01)
G2-C15	N-H...O	-0.89	0.46	-0.66	-0.82 (0.07)	0.44 (-0.02)	-0.64 (0.02)	-0.88 (0.01)
	N-H...N	-0.86	0.43	-0.77	-0.85 (0.01)	0.40 (-0.03)	-0.72 (0.05)	-0.78 (0.08)
	O...H-N	-0.61	0.57	-1.00	-0.61 (0.00)	0.55 (-0.02)	-1.00 (0.00)	-0.60 (0.01)
C3-G14	O...H-N	-0.65	0.46	-0.92	-0.67 (-0.02)	0.48 (0.02)	-1.04 (-0.12)	-0.67 (-0.02)
	N...H-N	-0.80	0.45	-0.71	-0.86 (-0.06)	0.52 (0.07)	-0.80 (-0.09)	-0.82 (-0.02)
	N-H...O	-1.02	0.57	-0.60	-0.99 (0.03)	0.55 (-0.02)	-0.58 (0.02)	-0.97 (0.05)
T4-A13 or T4-G13	N-H...N	-0.63	0.39	-0.78	-	-	-	-
	O...H-N	-0.53	0.41	-0.82	-	-	-	-
	O...H-N	-	-	-	-0.73	0.68	-1.21	-0.55
	N-H...O	-	-	-	-0.59	0.45	-0.68	-0.48
G5-C12	N-H...O	-0.73	0.39	-0.60	-0.90 (-0.17)	0.48 (0.09)	-0.68 (-0.08)	-0.83 (-0.10)
	N-H...N	-0.85	0.41	-0.68	-0.90 (-0.05)	0.48 (0.07)	-0.69 (-0.01)	-0.68 (0.17)
	O...H-N	-0.62	0.55	-0.97	-0.60 (0.02)	0.50 (-0.05)	-0.80 (0.17)	-0.59 (0.03)
G6-C11	N-H...O	-1.00	0.51	-0.65	-0.97 (0.03)	0.49 (-0.02)	-0.65 (0.00)	-1.00 (0.00)
	N-H...N	-0.66	0.49	-0.84	-0.77 (-0.11)	0.53 (0.04)	-0.79 (0.05)	-0.67 (-0.01)
	O...H-N	-0.55	0.53	-1.02	-0.59 (-0.04)	0.56 (0.03)	-1.02 (0.00)	-0.55 (0.00)
T7-A10	N-H...N	-1.01	0.53	-0.84	-0.95 (0.06)	0.54 (0.01)	-0.87 (-0.03)	-1.01 (0.00)
	O...H-N	-0.58	0.48	-0.91	-0.58 (0.00)	0.48 (0.00)	-0.90 (0.01)	-0.58 (0.00)
G8-C9	N-H...O	-1.02	0.51	-0.68	-0.97 (0.05)	0.47 (-0.04)	-0.59 (0.09)	-1.02 (0.00)

Base-pair	Atoms	No mismatch	T-G mismatch (a)		T-G mismatch (b)	
	N-H...N	-0.81 0.47	-0.77 (0.04)	0.43 (-0.04)	-0.66 (0.11)	-0.80 (0.01)
	O...H-N	-0.60 0.56	-0.59 (0.01)	0.55 (-0.01)	-1.02 (0.01)	-0.60 (0.00)
average		-0.75 0.48	-0.76 (-0.01)	0.50 (0.02)	-0.81 (-0.01)	-0.73 (0.01)

Base sequences:

Complementary: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'

3' - A16 - C15 - G14 - A13 - C12 - C11 - A10 - C9 - 5'

T-G mismatched: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'

3' - A16 - C15 - G14 - G13 - C12 - C11 - A10 - C9 - 5'

Table 7

HOMO-1, HOMO, and LUMO level energies (eV) and their spatial distributions for the fully complementary and mismatched DNA-DNA and LNA-DNA.

	HOMO-1		HOMO		LUMO	H-L gap
	Level	Distribution	Level	Distribution		
DNA-DNA						
No mismatch	-3.30	G2, G14	-3.19	G5, G6	Na-G14	0.53
T-G mismatch (a)	-3.49	G2, G14, G13	-3.37	G5, G6	Na-C15, Na-A16	0.53
T-G mismatch (b)	-3.27	G6, G13	-3.18	G5, G6, G13	Na-G14	0.52
LNA-DNA						
No mismatch	-3.66	G2, G14	-3.64	G5, G6	Na-G14	0.67
T-G mismatch (a)	-4.00	G5, G6, G13	-3.92	G2, G14	Na-G14, Na-C15	0.79
T-G mismatch (b)	-3.70	G2, G5, G6	-3.54	G13	Na-G14	0.59

Base sequences:

Complementary: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'

3' - A16 - C15 - G14 - A13 - C12 - C11 - A10 - C9 - 5'

T-G mismatched: 5' - T1 - G2 - C3 - T4 - G5 - G6 - T7 - G8 - 3'

3' - A16 - C15 - G14 - G13 - C12 - C11 - A10 - C9 - 5'