Size-Expanded DNA Bases: An Ab Initio Study of Their Structural and Electronic Properties

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The size-expanded DNA bases, xA, xC, xG, and xT, are benzo-homologue forms of the natural DNA bases; i.e., their structure can be seen as the fusion of a natural base and a benzene ring. Recently, a variety of DNAs, known as xDNAs, have been synthesized in which size-expanded and natural bases are paired. In this paper we use second-order Møller−Plesset perturbation theory and density functional theory to investigate the structural and electronic properties of xA, xC, xG, and xT and their natural counterparts. We find that whereas natural and size-expanded bases have both nonplanar amino groups the latter have also nonplanar aromatic rings. When density functional theory is used to investigate the electronic properties of size-expanded and natural bases, it is found that the HOMO−LUMO gap of the size-expanded bases is smaller than that of the natural bases. Also, xG should be easier to oxidize than G.

I. Introduction

The synthesis of modified versions of DNA is an area that is receiving much attention. The reasons for this are varied, and they span from the investigation of whether alternative genetic systems could exist to therapeutic and biotechnological applications. Until now, the backbone of DNA has been the subject of chemical modifications, and modified DNAs such as peptide nucleic acids (PNAs),[1] locked nucleic acids (LNAs),[2] and threose nucleic acids (TNAs)[3] have been synthesized. But in a series of recent papers, Kool and co-workers have developed modified bases and demonstrated that it is possible to use them to construct a new class of size-expanded DNA, known as xDNA.[4]

Figure 1 shows benzo-homologue forms of the DNA bases, xA, xC, xG, and xT, that Kool's group has synthesized. Here we refer to these bases as the x-bases. Figure 2 shows the natural bases adenine (A), cytosine (C), guanine (G), and thymine (T). An x-base is larger than its natural counterpart due to the lateral extension introduced by the benzene ring.

By means of a DNA synthesizer, the x- and natural bases have been combined to form different xDNAs. For example, an xDNA has been made that contains all eight bases, i.e., A, C, G, T, xA, xC, xG, and xT.[4h] In this xDNA, the x-bases either are placed on one strand alone or alternate from one strand to the other, but regardless of their position they always pair with a natural base (xA only pairs with T, xT with A, xC with G, and xG with C). Neither nonnatural enzymes that can incorporate the x-bases nor xDNAs that contains paired x-bases, as in xA−xT and xC−xG, have yet been made.

The x-bases have several interesting properties. First, thanks to the extra benzene ring, the x-bases are inherently fluorescent, and this could be useful in probing size and steric effects in protein−DNA recognition. Second, the extra π-electrons introduced by the benzene ring make, in some cases, xDNA more stable than biological DNA, B-DNA. This has been demonstrated in a series of thermodynamics studies where the melting temperature of xDNAs was compared to that of B-DNAs. It is argued that the higher stability of xDNAs is due to the stronger $\pi-\pi$ coupling between stacked bases. And third, the fact that all x- and natural bases can be combined to form artificial DNA with eight bases could have implications in information storage technology,[5] since a system with eight bases has a higher storage density than a system with four bases.

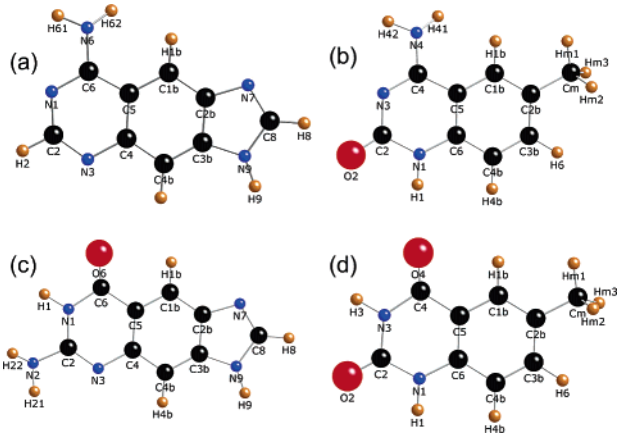

Figure 1. Size-expanded DNA bases (x-bases): (a) xA; (b) xC; (c) xG; (d) xT. Color code: oxygen, red; carbon, black; nitrogen, blue; hydrogen, maroon.

We are interested in the possibility that xDNA could be used as a nanowire. We ask ourselves if the benzene ring of the x-bases could introduce extra π_z electrons that would facilitate charge migration in xDNA. For example, these extra electrons could introduce large $\pi-\pi$ coupling interactions between stacked bases that in turn would facilitate band transport. This could be elucidated by investigating the electronic properties of xDNA with ab initio techniques. Unfortunately, currently there is limited experimental information regarding the structure of xDNA, and only one sequence has been investigated with NMR.[4e] However, molecular dynamics simulations could be used to determine the structure of xDNA. The structure

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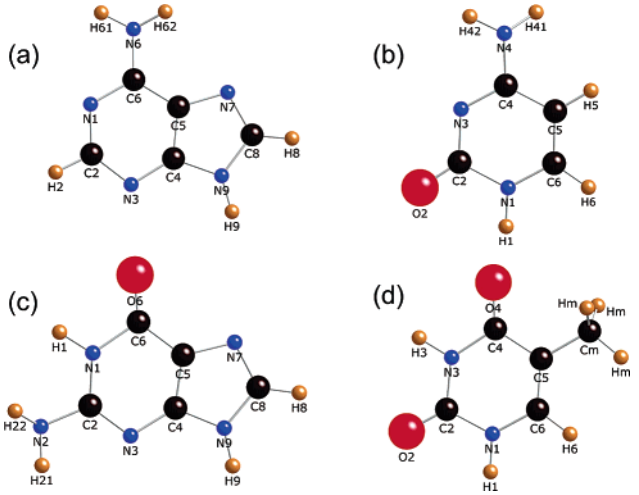

Figure 2. Natural DNA bases: (a) adenine, A; (b) cytosine, C; (c) guanine, G; (d) thymine, T. Color code: oxygen, red; carbon, black; nitrogen, blue; hydrogen, maroon.

determined by molecular dynamics could then be used to perform electronic structure calculations. But the precision of molecular dynamics simulations is extremely sensitive on the force field that one uses, and it is generally necessary to first test whether a particular force field can reproduce data on isolated bases. Unfortunately, there are no data on the structure of isolated x-bases. In this paper we use quantum chemistry methods to investigate the structural properties of isolated x-bases. Additionally, we have investigated their electronic properties. Both results pave the road for future studies and to determine whether xDNA could be used in nanotechnological applications that require good conductivity.

II. Methods

The NWCHEM suite of programs was used for all the calculations,[6] and optimized geometries were obtained at the MP2/6-31G** level. For the benzo-purine bases, planar and nonplanar structures were optimized. The planar structures were relaxed using both symmetry and nonsymmetry restrictions; in either case, the relaxed structures were also planar. The nonplanar structures are characterized by having the two hydrogen atoms of the amino group in a plane different to that occupied by the rest of the atoms; these structures were relaxed without symmetry restrictions. For the benzo-pyrimidine bases, only nonplanar structures were optimized. (For these bases planar structures cannot be considered due to the nonplanarity of the methyl groups.)

For comparison purposes, the natural bases A, C, G, and T were also optimized at the MP2/6-31G** level. For A, C, and G, nonplanar and planar structures were optimized, whereas for T only a nonplanar structure was optimized.

The electronic properties of the ground state of each base was obtained using Hartree−Fock and density functional theory. To asses the reliability of our results, different functionals were used for the exchange−correlation potential. These functionals are the local-density and generalized-gradient approximation, LDA[7] and GGA,[8] respectively, and the hybrid form B3LYP.[9]

III. Results

A. Structural Properties. Figure 1 shows the x-bases xA, xC, xG, and xT, and Figure 2 shows the natural bases A, C, G, and T. Since this is the first study of the structure of the x-bases, comparison with previous studies is not possible. For this reason,

TABLE 1: Size Expansion (Å) for the Benzo-purine and Benzo-pyrimidines Bases

xA		xG	
bond	length	bond	length
C4C3b	2.375	C4C3b	2.376
C5C2b	2.389	C5C2b	2.383
xC		**xT**	
bond	length	bond	length
C6C3b	2.409	C6C3b	2.409
C5C2b	2.434	C5C2b	2.426

TABLE 2: Nonplanarity of the Amino Groups as Calculated by the Torsion Bond Angles (deg) for the Optimized Structures of the Natural and Size-Expanded DNA Bases[a]

bond	angle	bond	angle
		A	
H61−N6−C6−N1	17.75 (16.5)	H62−N6−C6−C5	−19.77 (−15.3)
		xA	
H61−N6−C6−N1	−13.75	H62−N6−C6−C5	34.98
		C	
H42−N4−C4−N3	−13.80 (12.6)	H41−N4−C4−C5	25.47 (−21.4)
		xC	
H42−N4−C4−N3	−12.09	H41−N4−C4−C5	34.18
		G	
H22−N2−C2−N1	−42.23 (39.2)	H21−N2−C2−N3	12.09 (−13.3)
		xG	
H22−N2−C2−N1	−45.49	H21−N2−C2−N3	10.46

[a] For the natural bases, results from previous theoretical studies at the MP2/6-311G(2df,p) level are shown in brackets.[11]

information regarding bond lengths and bond angles of the x-bases is presented in the Supporting Information of this paper. (To support the reliability of our results, in the Supporting Information we have also included our results regarding bond lengths and angles of the natural bases, and the comparisons with previous studies are good.) Some of the bond lengths of the x-bases refer to the magnitude of the size expansion that results from adding a benzene ring to the natural bases; these bond lengths can be compared to existing estimations.

The size expansion is given by a set of two bond lengths. For the benzo-purine bases this set is C4C3b and C5C2b, and for the benzo-pyrimidine this set is C6C3b and C5C2b. We have collected these bond lengths in Table 1. It is seen that for the benzo-purine bases the size expansion is between 2.375 and 2.389 Å, and between 2.409 and 2.434 Å for the benzo-pyrimidine bases. These values are very close to the estimated 2.4 Å;[4a] however, for each base the extension is not uniform. For example, for the xA base C4C3b is 2.375 Å and C5C2b is 2.389 Å. This nonuniformity is caused by the nonplanarity of the aromatic rings of the bases. We refer to this next.

When the planar and nonplanar bases are compared, it is useful to characterize the latter bases by the nonplanarity of the amino groups and the aromatic rings. Indications that the amino groups are nonplanar but acquired a pyramidal configuration were first found by Leszczynski.[10] This study was later followed by others confirming the pyramidalization of the amino groups.[11] In this configuration, both hydrogen atoms are pointing out of the plane in one direction, while the nitrogen is also out of the plane, but in the opposite direction. The importance of this finding resides in the possibility that in DNA the amino group atoms could participate in out-of-plane bonds.[12] However, other theoretical methods[13] have found a much weaker nonplanarity of the amino groups, and this plus the lack of direct

TABLE 3: Torsion Bond Angles (deg) for the Benzo-purines and Benzo-pyrimidines Bases

xA (A)		xG (G)	
bond	angle	bond	angle
C2−N1−C6−C5	−1.96 (−0.22)	C2−N1−C6−C5	−0.38 (0.41)
N1−C6−C5−C4	4.92 (−0.09)	N1−C6−C5−C4	2.13 (0.66)
C6−C5−C4−N3	−4.64 (0.50)	C6−C5−C4−N3	−3.72 (−2.06)
C5−C4−N3−C2	1.46 (−0.50)	C5−C4−N3−C2	3.24 (2.01)
C4−N3−C2−N1	2.08 (0.13)	C4−N3−C2−N1	−1.36 (−0.73)
N3−C2−N1−C6	−1.86 (0.22)	N3−C2−N1−C6	0.0 (−0.38)
C4−C5−C1b−C2b	−0.48	C4−C5−C1b−C2b	−1.56
C5−C1b−C2b−C3b	1.32	C5−C1b−C2b−C3b	1.40
C1b−C2b−C3b−C4b	−2.36	C1b−C2b−C3b−C4b	−1.55
C2b−C3b−C4b−C4	2.34	C2b−C3b−C4b−C4	1.69
C3b−C4b−C4−C5	−1.43	C3b−C4b−C4−C5	−1.76
C4b−C4−C5−C1b	0.55	C4b−C4−C5−C1b	1.79
C3b−C2b−N7−C8	−0.32 (0.34)	C3b−C2b−N7−C8	−0.33 (−0.24)
C2b−N7−C8−N9	0.05 (−0.13)	C2b−N7−C8−N9	0.05 (0.04)
N7−C8−N9−C3b	0.25 (−0.13)	N7−C8−N9−C3b	0.25 (0.17)
C8−N9−C3b−C2b	−0.42 (0.31)	C8−N9−C3b−C2b	−0.42 (−0.30)
N9−C3b−C2b−N7	0.47 (−0.41)	N9−C3b−C2b−N7	0.47 (0.35)
N3−C4−C5−C1b	177.84	N3−C4−C5−C1b	179.26
C4b−C3b−C2b−N7	178.27	C4b−C3b−C2b−N7	179.32
C4b−C4−C5−C6	178.08	C4b−C4−C5−C6	178.81
N9−C3b−C2b−C1b	179.84	N9−C3b−C2b−C1b	179.60
N6−C6−C5−C4	−178.99 (−177.18)	C2−N1−C6−O6	179.13 (179.86)
H2−C2−N1−C6	179.32 (−179.96)	N2−C2−N1−C6	−176.88 (−176.88)
H8−C8−N7−C2b	179.96 (179.88)	H1−N1−C6−C5	−173.63 (−174.74)
H9−N9−C8−N7	−179.99 (−179.94)	H8−C8−N7−C2b	−179.97 (−179.94)
		H9−N9−C8−N7	179.62 (179.78)

xC (C)		xT (T)	
bond	angle	bond	angle
C2−N3−C4−C5	−1.22 (0.38)	C2−N3−C4−C5	0.02 (−0.02)
N3−C4−C5−C6	5.52 (0.11)	N3−C4−C5−C6	−0.04 (0.02)
C4−C5−C6−N1	−3.93 (−0.29)	C4−C5−C6−N1	0.10 (0.0)
C5−C6−N1−C2	−1.54 (0.0)	C5−C6−N1−C2	−0.11 (0.04)
C6−N1−C2−N3	5.89 (0.46)	C6−N1−C2−N3	0.06 (0.00)
N1−C2−N3−C4	−4.33 (−0.63)	N1−C2−N3−C4	−0.0 (0.00)
C6−C5−C1b−C2b	−0.17	C6−C5−C1b−C2b	0.13
C5−C1b−C2b−C3b	1.04	C5−C1b−C2b−C3b	−0.10
C1b−C2b−C3b−C4b	−1.77	C1b−C2b−C3b−C4b	0.08
C2b−C3b−C4b−C6	1.60	C2b−C3b−C4b−C6	−0.10
C3b−C4b−C6−C5	−0.68	C3b−C4b−C6−C5	0.12
C4b−C6−C5−C1b	−0.03	C4b−C6−C5−C1b	−0.14
N1−C6−C5−C1b	178.05	N1−C6−C5−C1b	−179.98
C4b−C6−C5−C4	177.99	C4b−C6−C5−C4	179.96
O2−C2−N1−C6	−175.76 (−179.96)	O2−C2−N1−C6	−179.96(180.0)
N4−C4−N3−C2	−177.91 (−176.82)	H1−N1−C6−C5	180.0 (180.0)
H1−N1−C6−C5	−177.24 (−179.90)		

[a] The angles for the corresponding natural bases, as obtained in this work, are presented in brackets. (See text for an explanation regarding how comparisons were made.)

experimental evidence makes the nonplanarity of the amino groups somewhat controversial. The nonplanarity of the aromatic rings is much less relevant.[14] Here we have found that the x-bases have nonplanar amino groups but also that the nonplanarity of their aromatic rings is larger than that in natural bases.

The nonplanarity of the amino groups for the x- and natural bases is compared in Table 2. In some cases, the torsion angles in the natural and x-bases have different signs. For example the torsion angle defined by H61−N6−C6−N1 is positive in A and negative in xA. This difference in sign is caused by the direction in which the hydrogen atoms were bent away from the plane of the aromatic rings in the initial configurations. In the example above, we initially bent the hydrogen atoms of A and xA in opposite directions, and the optimization of the structures did not change this fact. Despite this, comparisons can still be made. We observe that the pyramidalization of the amino group in xG is very similar to that in G. The reason for this is that the local structure around the amino group of xG is not very different from that in G. In particular, in both bases the H1 atom introduces a repulsion that creates an asymmetric pyramidalization. However, the asymmetric pyramidalization is more pronounced in xA and xC than those in A and C, respectively. The stronger asymmetry in xA and xC is due to the H1b atom, which is not present in A and C.

The nonplanarity of the aromatic rings for the x- and natural bases is compared in Table 3. In making comparisons we have divided the atoms of the x-bases into three groups and introduced several assumptions. The first group is composed of atoms that belong to the benzene ring alone. The second group comprises atoms that belong to the natural bases alone. And the third group contains atoms that belong to both the natural bases and the benzene ring. For example, in the xA base, the first group comprises the atoms C1b, H1b, C4b, and H4b; the second group is made up of H61, N6, H62, C6, N1, C2, H2, N3, N7, C8, H8, N9, and H9; the third group contains the atoms C5, C4, C2b, and C3b. Now, in comparing the torsion angles in the x- and natural bases, we have assumed the following. (i) Torsion angles that involve either atoms of the first group or a combination of

TABLE 4: Differences in Energy (kcal/mol), ΔE, between Nonplanar and Planar Structures, for the Size-Expanded and Natural DNA Bases[a]

base	ΔE
A	−0.2296 (−0.13)
C	−0.2871 (−0.15)
G	−1.4162 (−1.12)
xA	−0.8803
xG	−1.7989

[a] For the natural bases, results from previous theoretical studies at the MP2/6-311G(2df,p) level are shown in brackets.[11]

atoms from the first and third group exist only for the x-bases, and so comparisons with corresponding torsion angles in the natural bases cannot be made. For example, the torsion angles C4−C5−C1b−C2b and C1b−C2b−C3b−C4b exist only for the xA base. (ii) Torsion angles that involve atoms of the second group can be compared easily to corresponding angles in the natural bases. The angles N3−C2−N1−C6 and H9−N9−C8−N7 exist in both the xA and the A bases. (iii) And only in some cases, torsion angles that involve atoms from the third group can be compared to corresponding angles in the natural bases. For example, for the xA base, the angles N3−C4−C5−C1b, C4b−C3b−C2b−N7, C4b−C4−C5−C6, and N9−C3b−C2b−C1b cannot be compared to similar angles in the A base. However, the angles C3b−C2b−N7−C8 in the xA base can be compared to the angle C4−C5−N7−C8 in the A base; to do so, one just has to assume that the carbon atoms C3b and C2b of xA are equivalent to the atoms C4 and C5 of A, respectively. We have collected the torsion angles for the x- and natural bases in Table 3, and after making comparisons one reaches the conclusion that the natural bases are more planar than the x-bases. In Table 4, we have compared the difference in energy between nonplanar and planar structures for x- and natural bases. This difference is given by the term ΔE, which can only be computed for the bases xA, xG, A, C, and G, since for xC, xT, and T, only nonplanar structures were considered. ΔE is larger for xA than for A, and the same is true for xG and G; this suggests that the x-bases have a higher preference for a nonplanar state.

For many years, force fields were not able to reproduce the nonplanarity of the natural bases. Only recently, Ryjáček et al.[15] have fitted the Cornell force field as to account for nonplanarity. Ryjáček et al. expect that for DNA duplexes with planar hydrogen-bonded Watson−Crick base pairs molecular dynamics simulations performed with the old and new Cornell force field may not differ significantly. Whether xDNA duplexes have or do not have planar hydrogen-bonded Watson−Crick base pairs remains to be seen. In the meantime, our finding that the x-bases prefer a nonplanar configuration, even so more than the natural bases, suggests exercising caution when investigating xDNA duplexes with force fields that do not account for nonplanarity.

B. Electronic Properties. The possibility that B-DNA could be used as a nanowire has driven much of the efforts toward understanding its electronic properties.[16] However, the issue of whether B-DNA conducts or not is rather controversial, as can be appreciated in the review by Endres et al.[17] Despite this, we think that it is worthwhile to ask whether xDNA could be a conductor. The reasons are that the extra benzene ring of the x-bases could induce the following two factors: (i) The HOMO−LUMO gap of x-bases could be smaller than that of the natural bases, making the band gap of xDNA smaller than that of B-DNA, and (ii) stacked bases in xDNA could have stronger $\pi-\pi$ interactions than those of stacked bases in B-DNA. Both factors could facilitate charge migration in xDNA.

TABLE 5: HOMO and LUMO Orbital Energies and HOMO−LUMO Gap for the Size-Expanded and Natural Bases as Calculated with LDA[a]

base	HOMO	LUMO	gap
A	0.4612	4.345	3.88 (3.84)
C	0.4022	4.0364	3.63 (3.64)
G	0.710	4.708	4.00 (3.85)
T	0.000	3.866	3.87 (3.76)
xA	0.616	3.518	2.90
xC	0.478	3.518	3.04
xG	0.790	3.949	3.16
xT	0.119	3.523	3.40

[a] The energies are given as relative to T's HOMO. All of the energies are in electronvolts. For the natural bases, the intrabase transition calculated with plane waves, ultrasoft pseudopotentials, and GGA are also shown in brackets.[13]

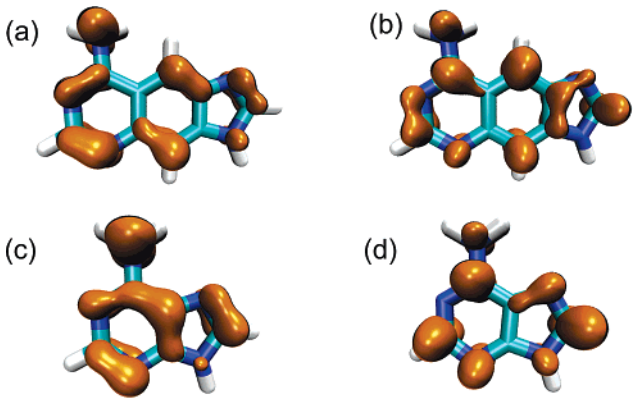

Figure 3. Charge density for the HOMO and LUMO states of xA and A as calculated with LDA: (a) HOMO of xA; (b) LUMO of xA; (c) HOMO of A; (d) LUMO of A. The charge densities for the HOMO and LUMO states of xC, xG, and xT contain similar contributions from the atoms of the benzene ring.

In this section we study the electronic properties of isolated x-bases using density functional theory. Our purpose is to compare their HOMO−LUMO gap to that of the natural bases. To explore the sensitivity of the results to the choice of approximation used for the exchange−correlation potential, we have investigated the electronic properties with Hartree−Fock, LDA, GGA, and B3LYP.

In Table 5 we have collected the HOMO and LUMO orbital energies of the x- and natural bases, as computed with LDA; the energies are given as relative to T's HOMO. Table 5 shows that all of the x-bases have HOMO energies higher than their natural counterparts, although the difference is not too large. However, the LUMO of the x-bases all have lower energies than the LUMO of the natural bases, and the differences are large. For example, the LUMO of A and xA differ by about 0.8 eV. The LUMO energies of xA, xC, and xG are practically the same; this is not the case for their natural counterparts. It is worth noticing that according to these results xG should be easier to oxidize than G; the HOMO of xG is about 0.08 eV higher than the HOMO of G. This result may be relevant in the context of the charge transport mechanism in xDNA duplexes. In B-DNA, it has been argued that charge migration is hole-mediated thanks to the fact that G is easy to oxidize. Due to the lack of conductivity measurements, it is not known at this time whether the oxidation of xG bases could as well induce hole-mediated charge migration in xDNA duplexes. In Table 5 we have also compared the HOMO−LUMO gaps of the x- and natural bases; in all the cases, the x-bases have smaller HOMO−LUMO gaps. These trends hold when we compute the electronic properties using Hartree−Fock, GGA, and B3LYP as well

(Supporting Information). In Table 5 and for the natural bases, we have compared our LDA results with GGA results performed with plane waves and ultrasoft pseudopotentials.[13] Although the methodologies are different, the results are very similar. Finally, in Figure 3 we show the charge densities for the HOMO and LUMO states of the bases xA and A. Both the HOMO and the LUMO states of xA contain π_z electrons contributed by the atoms of the benzene ring. The same observations hold when one compares the charge densities of the HOMO and LUMO states of xC and C, xG and G, and xT and T.

IV. Conclusions

In this paper we present the first ab initio study of the size-expanded bases xA, xC, xG, and xT. These bases have already been used experimentally to synthesize a new type of DNA known as xDNA. The size-expanded bases, unlike the natural ones, contain an extra benzene ring that provides them with a lateral extension. We were drawn to investigate the size-expanded bases because we are interested in the possibility that xDNA could function as a nanowire. We reasoned that the π_z electrons contributed by the atoms of the benzene ring could introduce the following two factors: (i) The HOMO−LUMO gap of size-expanded bases could be smaller than that of natural bases, making the band gap of xDNA smaller than that of B-DNA, and (ii) Stacked bases in xDNA could have stronger $\pi-\pi$ interactions than those of stacked bases in B-DNA. Both factors could facilitate charge migration in xDNA. Unfortunately, there is not enough structural information on xDNA duplexes, and so it is wiser to start by investigating isolated size-expanded bases. Concerning the structural properties, we have found that the size-expanded bases, as the natural ones, contain nonplanar amino groups; however, unlike the natural bases, the size-expanded bases also possess nonplanarity in the aromatic rings. This information suggests exercising caution when investigating xDNA duplexes with force fields that do not account for nonplanarity. Concerning the electronic properties, we have found encouraging results; for the size-expanded bases all have smaller HOMO−LUMO gaps than the natural bases. We have not investigated the $\pi-\pi$ interactions between stacked bases, but we have found that the HOMO and LUMO states of the size-expanded bases do contain charge density contributions from the atoms of the benzene ring. Finally, we predict that xG is more readily oxidized than the G. Because there are not experimental measurements available, it is not known whether the oxidation of xG could as well induce hole-mediated charge migration in xDNA duplexes. We hope that the results presented here will encourage experimental measurements of the conductivity of xDNA.

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Supporting Information Available: Atomic coordinates for all the structures investigated and their absolute energies in hartrees, bond lengths, bond angles and dipole moments, and HOMO and LUMO energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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