Local Aromaticity in Natural Nucleobases and Their Size-Expanded Benzo-Fused Derivatives

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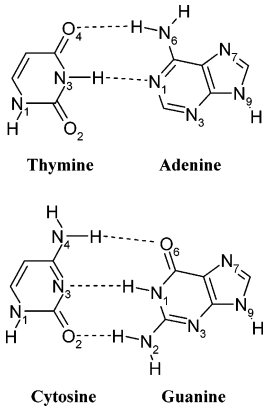
The influence of the insertion/addition of a benzene ring to the natural nucleic acid bases on the local aromaticity of the so-called size-expanded (xN, with N being adenine, guanine, cytosine, and thymine) bases is examined. To this end, the local aromaticity of the six- and five-membered rings in both the natural bases and their benzoderivatives is determined using HOMA, NICS, aromatic fluctuation index (FLU), and para-delocalization index (PDI) descriptors. In general, there is a good correspondence between the different indices, so that ring moieties with more negative NICS values also have larger HOMA and PDI measures and lower FLU indices. The results also point out notable differences in the aromatic character of the natural and size-expanded bases, which generally are hardly affected upon hydrogen bonding. The differences in the highest occupied molecular orbital−lowest unoccupied molecular orbital (HOMO−LUMO) gap determined for the size-expanded nucleobases show an inverse correlation with the aromaticity of the fused benzene ring, so that the larger the HOMO−LUMO gap is, the lower the destabilization experienced by the benzene upon insertion/addition to the natural bases. This finding suggests that the introduction of suitable chemical modifications in the benzene ring might be useful to modulate the HOMO−LUMO gap while enabling the design of modified DNA duplexes that are able to act as molecular wires.

Introduction

The model of the DNA duplex proposed by Watson and Crick[1] provides a direct link between the chemical structure of the four natural nucleic acid bases and the maintenance of the genetic information. Such a link is based on the specific recognition (see Scheme 1) between adenine (A) and thymine (T) through formation of the hydrogen bonds $N_1(A) \leftarrow N_3(T)$ and $N_6(A) \rightarrow O_4(T)$ and between guanine (G) and cytosine (C) through the hydrogen bonds $N_1(G) \rightarrow N_3(C)$, $N_2(G) \rightarrow O_2(C)$, and $O_6(G) \leftarrow N_4(C)$. In principle, the recognition pattern of physiological DNA could be enlarged by using unnatural nucleobase derivatives possibly expanding the genetic alphabet and leading to new DNA duplexes with improved biotechnological properties. Different strategies have been considered to accomplish this goal, such as, the development of modified bases that interact through nonnatural hydrogen-bonding patterns, hydrophobic analogues without hydrogen-bonding functionalities, and metal-mediated base pairs.[2]

SCHEME 1



Kool and co-workers recently reported a new strategy to enlarge the genetic alphabet that consists of using expanded analogues of the natural bases obtained by inclusion of a benzene moiety, which permits combining the hydrogen-bond properties of the bases with the increased hydrophobicity of the benzene ring.[3] A first set of benzo-fused expanded bases was designed based on the linear extension of the natural bases by insertion (in purines) and addition (in pyrimidines) of a benzene ring, leading to the so-called x-bases (see Figure 1). The first studies

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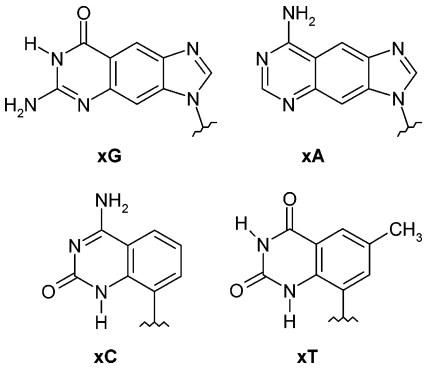


Figure 1. Schematic representation of x-bases in the widened nucleoside analogues.

performed with the expanded nucleobases (xN, with N being A, G, C, T) have shown that they can effectively replace the natural base in a single step of the DNA duplex, but the resulting duplex is less stable than the natural one,[3b,4] as expected from the loss of base-pair isomorphism introduced by the presence of the size-expanded nucleobase. However, experiments performed for fully expanded DNAs composed of mixed pairs of natural bases and benzo-fused derivatives have shown a substantial stabilization of the helix with regard to the natural duplex.[3a,5]

Theoretical studies have shown that in an aqueous solution, the x-bases mainly populate the corresponding canonical-like tautomers of the natural bases. This indicates that the N_9-substituted nucleosides can pair selectively through the formation of Watson−Crick hydrogen bonds, thus mimicking the behavior of the natural bases.[6] In fact, the pairing energies determined for the formation of hydrogen-bonded complexes xA−xT and xG−xC are very close to those obtained for the canonical pairs A−T and G−C, respectively. Indeed, the results also showed that the stacking of benzobases is accompanied by an enhanced stabilization relative to the stacking of natural bases.[6] In conjunction with the larger hydrophobicity of the benzobases, these findings suggest that the size-expanded bases might be valuable building blocks to design nonnatural DNA duplexes.

The preceding experimental and theoretical findings support the use of benzo-fused derivatives of the nucleic acid bases as elements not only to expand the genetic alphabet but also to develop DNA-like molecular devices with potential nanotechnological applications.[7] In fact, a challenging area that has attracted much interest in the past few years is the ability of DNA to mediate charge transport.[8] This interest also is sustained by the self-assembly, replication properties and structural integrity of DNA, which are desirable features for the development of nanoelectronic technology. In this context, since the x-bases have smaller highest occupied molecular orbital−lowest unoccupied molecular orbital (HOMO−LUMO) gaps than the natural bases,[9] it can been conjectured that DNA material modified through the inclusion of xDNA bases could be more appropriate than the natural DNA duplex for molecular wire applications.

Because the electronic properties of nucleobases are of fundamental importance for the unique character of these molecular systems,[10−12] this study investigates how the presence of the benzene ring affects the electron delocalization in the size-expanded benzobases. Several studies have analyzed the local aromaticities of the natural bases isolated and in the Watson−Crick hydrogen-bonded dimer,[13−16] as well as the aromaticity changes due to interaction of some of the base pairs with metal cations[16] and protonation.[13] However, the changes in local aromaticities in going from natural to benzo-fused bases and base pairs have not been addressed yet. In particular, our aim is to determine the differences in the local aromatic character of five- and six-membered rings (5- and 6-MRs) present in the natural and the size-expanded bases. The information gathered will be examined for the energy difference of the frontier orbitals, which provides a measure of the global aromaticity.[17]

Methods

Indexes of Aromaticity. On the basis of the multidimensional character of aromaticity,[18,19] it is usually recommended to employ more than one aromaticity index for aromaticity comparisons.[20,21] For our purposes, we have chosen different indexes of aromaticity based on structural, magnetic, and electron delocalization properties.

As a structure-based measure, we have made use of the HOMA index, defined by Kruszewski and Krygowski[22−24] as

$$\mathrm{HOMA} = 1 - \frac{\alpha}{n}\sum_{i=1}^{n}(R_{\mathrm{opt}} - R_i)^2 \qquad (1)$$

where n is the number of bonds considered, and α is an empirical constant (for C−C and C−N bonds $\alpha = 257.7$ and 93.52, respectively) fixed to have HOMA = 0 for a model nonaromatic system, and HOMA = 1 for a system with all bonds equal to an optimal value R_{opt} (1.388 and 1.334 Å for C−C and C−N bonds, respectively), which is assumed to be achieved for a fully aromatic system. Finally, R_i stands for a running bond length. Despite its simplicity, this index was found to be one of the most effective structural indicators of aromaticity.[25]

Magnetic indices of aromaticity are based on the π-electron ring current that is induced when the system is exposed to external magnetic fields. In this work, we have used the NICS index, proposed by Schleyer and co-workers,[21,26,27] which is one of the most widely employed indicators of aromaticity. It is defined as the negative value of the absolute shielding computed at a ring center or at some other interesting point of the system. Rings with large negative NICS values are considered aromatic.

As an aromaticity criterion based on electron delocalization, we have used the recently reported para-delocalization index (PDI),[28,29] which is obtained by employing the delocalization index (DI)[30−32] as defined in the framework of atoms-in-molecules theory.[33,34] The PDI is an average of all DI of para-related carbon atoms in a given 6-MR. The DI value between atoms A and B, δ(A,B), is obtained by double integration of the exchange-correlation density ($\Gamma_{\mathrm{XC}}(\vec{r}_1,\vec{r}_2)$) over the basins of atoms A and B, which are defined from the condition of zero-flux gradient in the one-electron density.

$$\delta(\mathrm{A,B}) = -\int_{\mathrm{A}}\int_{\mathrm{B}}(\Gamma_{\mathrm{XC}}(\vec{r}_1,\vec{r}_2))\mathrm{d}\vec{r}_1\mathrm{d}\vec{r}_2 - \int_{\mathrm{B}}\int_{\mathrm{A}}(\Gamma_{\mathrm{XC}}(\vec{r}_1,\vec{r}_2))\mathrm{d}\vec{r}_1\mathrm{d}\vec{r}_2 = -2\int_{\mathrm{A}}\int_{\mathrm{B}}(\Gamma_{\mathrm{XC}}(\vec{r}_1,\vec{r}_2))\mathrm{d}\vec{r}_1\mathrm{d}\vec{r}_2 \qquad (2)$$

For closed-shell molecules and for single determinant wave functions, eq 2 is simplified to

$$\delta(\mathrm{A,B}) = 4\sum_{i,j}^{N/2} S_{ij}(\mathrm{A})S_{ij}(\mathrm{B}) \qquad (3)$$

where the summations in eq 3 are run over all the N/2 occupied molecular orbitals. S_{ij}(A) is the overlap of the molecular orbitals

TABLE 1: Aromaticity Indices for the Constituent Six- and Five-Membered Rings of Isolated Natural and Benzo-Fused Bases[a]

base	ring[b]	HOMA	NICS(0)[c]	NICS(1)[c]	NICS(−1)[c]	NICS(1)$_{zz}$[c]	FLU	PDI
A	6	0.986	−6.588	−8.360	−8.288	−22.447	0.012	0.060
	5	0.893	−11.366	−9.480	−9.459	−27.174	0.028	
xA	6	0.824	−4.302	−7.529	−7.419	−19.711	0.019	0.050
	B	0.889	−11.747	−12.020	−12.153	−32.004	0.013	0.068
	5	0.834	−10.021	−9.008	−9.144	−25.563	0.030	
G	6	0.777	−2.517	−3.060	−3.083	−6.333	0.045	0.032
	5	0.890	−11.491	−9.136	−9.085	−26.014	0.025	
xG	6	0.641	−0.099	−2.025	−2.070	−3.247	0.053	0.023
	B	0.941	−10.631	−10.971	−10.960	−28.656	0.010	0.070
	5	0.848	−10.397	−9.322	−9.293	−26.390	0.029	
T	6	0.359	−0.938	−1.471	−1.471	−2.087	0.079	0.026
xT	6	0.329	0.139	−0.874	−0.874	0.584	0.082	0.016
	B	0.980	−8.706	−9.786	−9.786	−25.635	0.004	0.086
C	6	0.714	−2.326	−3.261	−3.235	−6.657	0.044	0.042
xC	6	0.706	0.047	−2.287	−2.295	−3.356	0.053	0.026
	B	0.971	−8.433	−9.571	−9.664	−25.681	0.005	0.085

[a]NICS is in ppm, and PDI is in electrons. [b]The 6 and 5 denote the six- and five-membered rings of nucleobases. B stands for the benzene moiety in the benzo-fused derivatives. [c]NICS(0) values computed at the ring centers were determined by the nonweighted mean of the heavy atoms coordinates; NICS(1) and NICS(−1) computed at 1 Å above and below the molecular plane.

i and *j* within the basin of atom A. δ(A,B) provides a quantitative idea of the number of electron pairs delocalized or shared between atoms A and B. Therefore, the PDI is clearly related to the idea of electron delocalization that is often found in textbook definitions of aromaticity. For a given compound, a decrease in the PDI with regard to the value determined for a typical aromatic molecule (i.e., benzene) reflects a loss in the degree of aromaticity. The main inconvenience of PDI is that it cannot account for the aromaticity of rings having a number of members different from six. Moreover, it can only be used to analyze the local aromaticity of a given ring and not to describe the global aromatic character of a molecule having several fused rings.

Owing to the preceding shortcomings, we also have used the aromatic fluctuation index (FLU),[35] which is a new aromaticity index also based on electron delocalization measures. FLU describes the fluctuation of electronic charge between adjacent atoms in a given ring, taking into account not only the amount of electron sharing between contiguous atoms but also the similarity of electron sharing between adjacent atoms. Thus, FLU is determined from the following expression:

$$\mathrm{FLU} = \frac{1}{n}\sum_{\mathrm{A-B}}^{\mathrm{RING}}\left[\left(\frac{V(\mathrm{B})}{V(\mathrm{A})}\right)^{\alpha}\left(\frac{\delta(\mathrm{A,B}) - \delta_{\mathrm{ref}}(\mathrm{A,B})}{\delta_{\mathrm{ref}}(\mathrm{A,B})}\right)\right]^2 \qquad (4)$$

where the summation runs over all adjacent pairs of atoms around the ring, *n* is equal to the number of atoms of the ring, *V*(A) is the global delocalization of atom A given in eq 6, δ(A,B) and δ_{ref}(A,B) are the DI values for the atomic pairs A and B and its reference value (the δ_{ref}(A,B) values of 1.4 and 1.2 e for C−C and C−N bonds are taken from benzene and pyridine,[35] respectively), and

$$\alpha = \begin{cases} 1 & V(\mathrm{B}) > V(\mathrm{A}) \\ -1 & V(\mathrm{B}) \le V(\mathrm{A}) \end{cases} \qquad (5)$$

$$V(\mathrm{A}) = \sum_{\mathrm{B}\neq\mathrm{A}} \delta(\mathrm{A,B}) \qquad (6)$$

For the indexes used, we note that the more negative the NICS values, the lower the FLU index, and the higher the HOMA and PDI results, the more aromatic the rings are.

Computational Details. Calculations have been performed at the density functional theory (DFT) level using the BHandHLYP functional[36] (as implemented in Gaussian-03)[37] and the cc-pVTZ basis set. Choice of this computational strategy was dictated by the results obtained in previous computational studies,[6,38] which showed that increasing the fraction of Hartree−Fock (HF) exchange significantly improved the relative stabilities predicted for DNA base tautomers, leading to relative stabilities between tautomers very close to the values determined at high level of ab initio theory. The indexes of aromaticity were determined using the molecular geometries obtained from a full geometry optimization at the BHandHLYP/cc-pVTZ level. Integrations of DIs were performed by use of the AIMPAC collection of programs.[39] Calculation of these DIs at the DFT level of theory cannot be performed exactly,[40] because the electron-pair density is not available at this level of theory. As an approximation, we have used the Kohn−Sham orbitals obtained from DFT to calculate HF-like DIs using eq 3.[40] Finally, the statistical analysis was performed using the SPSS 14.0 program.

Results and Discussion

This section is organized as follows. First, we analyze the performance of the different aromaticity indexes to assess the electron delocalization in the different ring units of nucleobases and their size-expanded derivatives. Second, we examine the differences in the local aromaticity of the rings promoted upon insertion/addition of the benzene ring to the natural nucleobases, as well as to the influence exerted by hydrogen-bonded pairing between bases. Finally, we discuss the relationship between the local aromaticity indices in the natural and benzo-fused bases, and the global aromaticity measured from the energy gap between HOMO and LUMO.

Comparison of the Local Aromaticity Indices. For the whole set of natural and modified bases, Table 1 reports the HOMA index, the NICS(0), NICS(1), NICS(−1), and NICS(1)$_{zz}$ values, and the PDI and FLU indicators of local aromaticity for the 6- and 5-MR units. In general, there is a good correspondence between the different indices, so that ring moieties with more negative NICS values also have larger HOMA and PDI measures and lower FLU indices.

Quantitative comparison of the local aromaticity measures can be gained from inspection of Figure 2. Structural HOMA and electronic FLU indices give almost the same order of aromaticity for the different rings in natural and benzo-fused bases, as noted in the Pearson correlation coefficient (*r*) of 0.96.

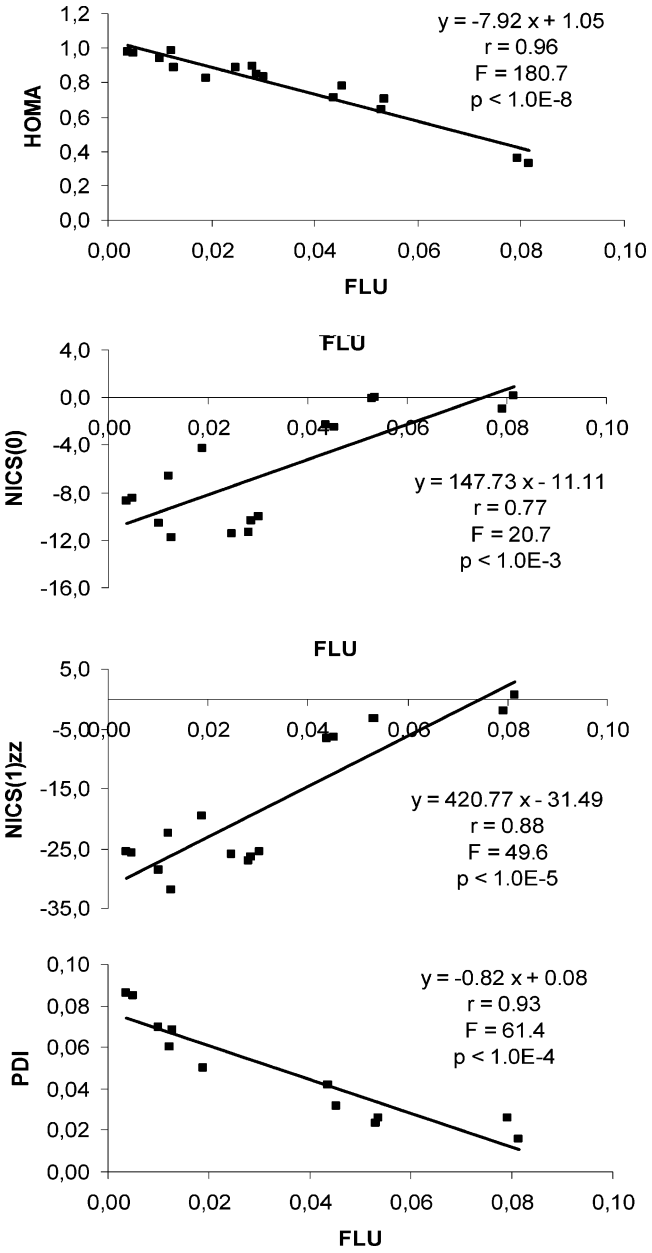
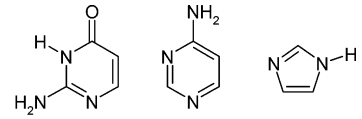


Figure 2. Representation of the local aromaticity indices determined from HOMA, NICS(0), NICS(1)$_{zz}$, FLU, and PDI descriptors for the six- and five-membered rings of natural and size-expanded nucleobases.

The close correspondence found between HOMA and FLU can be attributed partly to the fact that FLU is constructed following, to some extent, the HOMA philosophy, that is, with the purpose of measuring the aromaticity by comparison with the values of a specific aromatic manifestation in indisputable aromatic systems such as benzene. Moreover, both indices concentrate on differences between contiguous atoms around the ring, though FLU measures cyclic electron fluctuation differences, while HOMA compares bond lengths.

Analysis of NICS aromaticity values shows that there is an excellent correlation between NICS(0), NICS(1), NICS(−1) and NICS(−1)$_{zz}$ ($r > 0.96$ in all cases; see Supporting Information) that demonstrates that the spurious contributions from the in-plane components of the magnetic shielding tensors that are not related to aromaticity[41] have a relatively constant influence on the NICS measured in the molecular plane for all 6-MRs. Moreover, it also indicates that the effect due to pyramidalization

SCHEME 2



of the amino groups is negligible as can be deduced from the similarity between the NICS(1) and NICS(−1) values.

Comparison of NICS(0) and FLU indices reveals, however, only a moderate correlation ($r = 0.77$; see Figure 2), which mostly originates from the different treatment of the aromaticity of the 5-MRs by FLU and NICS. Whereas the FLU values determined for the 5-MRs in adenine, guanine, and their benzoderivatives ($0.025 < \text{FLU} < 0.030$) are within the range of FLU measures found for the 6-MRs in both natural and benzo-fused bases ($0.012 < \text{FLU} < 0.082$), there is a clear separation between the NICS(0) values determined for 5-MRs ($-11.491 < \text{NICS}(0) < -10.021$) and 6-MRs ($-6.588 < \text{NICS}(0) < 0.139$). This finding, nevertheless, is not unexpected, as several studies have shown that the magnitude of NICS depends to some extent on the size of the ring,[27,42−44] thus, contributing to the lack of a good correlation with the FLU index. Comparison with the *zz* component of NICS(1) (i.e., NICS(1)$_{zz}$), which has been claimed to be a better descriptor of the aromaticity than the NICS(0) index,[45] improves the correlation with the FLU values (see Figure 2). The correlation coefficient obtained in the NICS(1)$_{zz}$ vs FLU comparison ($r = 0.88$) is, however, still lower than that found between HOMA vs FLU. Indeed, comparison of the NICS, HOMA, and FLU values for the 5-MRs with those of both the 6-MRs and the benzene ring in adenine, guanine, and their corresponding benzo-fused bases suggests that the aromaticity of the 5-MRs is overestimated by the NICS index, especially by NICS(0). At this point, it is worth noting that other studies also have reported discrepancies between the local aromaticity of inner rings in polyacenes determined from NICS measurements compared to other aromaticity indices.[42,46−48]

Finally, the PDI descriptor displays a good correlation with FLU measures ($r = 0.93$; see Figure 2). This finding can be realized taking into account that both PDI and FLU describe the aromaticity of rings from measurements of the electron delocalization. Overall, there is a good correspondence between the different indices, which is particularly relevant for the HOMA, FLU, and PDI predictors.

Local Aromaticity in Natural and Benzo-Fused Bases. Inspection of the local aromaticity indices given in Table 1 points out notable differences between the different rings present in the natural bases.

The FLU index of the 6-MR in adenine and guanine amounts to 0.012 and 0.045, respectively, which are only slightly larger than those obtained for the corresponding unfused 6-MRs (0.004 and 0.041 for the isolated 6-MR present in adenine and guanine, respectively; see Scheme 2). A larger change in the FLU index is observed for the 5-MR, whose aromaticity varies from 0.011 for the isolated imidazole (see Scheme 2) to 0.028 in adenine and 0.025 in guanine. The FLU index obtained for cytosine (0.044) is very similar to that determined for the 6-MR of guanine and notably smaller than the value obtained for thymine (0.079). Therefore, it can be stated that the degree of aromaticity of the 6-MR of natural nucleobases varies in the order A > G ∼ C > T (see Figure 3). Similar trends are also deduced from the comparison of the HOMA, NICS(0), and PDI measures (see Table 1). For instance, the HOMA index varies from 0.986 in

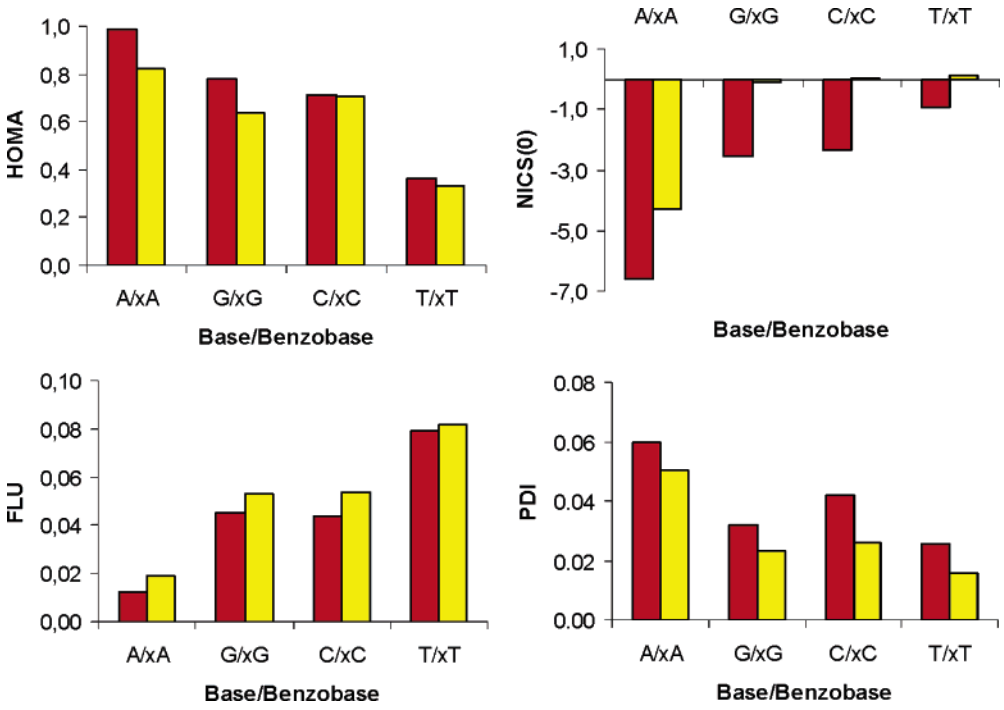


Figure 3. Representation of the local aromaticity descriptors for the six-membered ring of both natural (red) and benzo-fused (yellow) bases.

adenine to 0.359 in thymine, while intermediate values are obtained for guanine (0.777) and cytosine (0.714) (see Figure 3). Similarly, the NICS(0) values become less negative in the order adenine (−6.588), guanine (−2.517), cytosine (−2.326), and thymine (−0.938), and also the PDI index decreases from adenine (0.060) to thymine (0.026). The ordering of local aromaticity found is in line with previous studies showing that adenine is the most aromatic of the heterocyclic bases while thymine (and uracil) is the least aromatic.[13−15] Moreover, these results support the conclusion made by Cyrañski et al. that the variability in the aromatic character of the 6-MR can be interpreted in terms of the dearomatizing effect played by the exocyclic substituents that are of a double-bond character.[15]

The same ordering of local aromaticity discussed above for the 6-MR is found for the size-expanded nucleobases (see Figure 3), because the FLU values vary from 0.019 in benzoadenine, to 0.053 in benzoguanine and benzocytosine, and to 0.082 in benzothymine. Likewise, the HOMA values decrease from 0.824 in benzoadenine, to 0.706 in benzocytosine and 0.641 in benzoguanine, and finally to 0.329 in benzothymine (see Figure 3). A similar ordering of aromaticity is obtained when the NICS-(0) and PDI values determined for the 6-MR are examined (see Figure 3), as noted in the values obtained for the two descriptors, which vary from −4.302 (NICS(0)) and 0.050 (PDI) for benzoadenine to 0.139 and 0.016 (NICS(0) and PDI, respectively) for benzothymine. Comparison of the local aromaticity descriptors determined in the natural bases and their benzo-fused derivatives, however, indicates that insertion/addition of the benzene ring reduces the local aromaticity of the 6-MRs in natural bases, an effect also observed in the local aromaticity of the 5-MRs. The fact that benzofusion reduces the aromaticity of the attached ring is a trend already observed in acenes, according to HOMA and PDI indicators of aromaticity.[47]

For the purine bases (A and G), insertion of the benzene ring causes the FLU index of the 6-MR to be increased by around 0.008. A similar behavior is observed from the changes in the values of the HOMA, NICS(0), and PDI indices. Thus, the HOMA values decrease by ∼0.15, whereas the NICS(0) index values increase by ∼2.4 and the PDI decreases by ∼0.009. With regard to the 5-MR present in A and G, the insertion of the benzene ring gives rise to changes in the aromaticity descriptors smaller than those found for the 6-MR. Thus, the changes in HOMA, NICS(0), and FLU measures, which are similar for both adenine and guanine, on average are −0.051, 1.220, and 0.003, indicating in all cases that insertion of the benzene ring promotes a small decrease in the aromaticity of the 5-MR.

For the pyridimidine bases (T and C), the FLU index also predicts a decrease in the aromaticity of the 6-MR in the x-bases compared to the natural base. Such a reduction in the aromaticity of the pyrimidine ring is larger in cytosine than in thymine, as noted in changes in the FLU index that are 0.009 and 0.003, respectively. Again, these trends also are observed in the results determined from HOMA, NICS(0), and PDI measurements.

Compared to the isolated benzene (HOMA = 0.988, NICS-(0) = −8.793 ppm, FLU = 0.000, and PDI = 0.102 e), the insertion/addition of a benzene ring to the nucleobases promotes a small decrease in its local aromaticity.[49] Thus, addition of benzene to either cytosine or thymine increases the FLU index determined for the benzene ring by around 0.004. In contrast, insertion of benzene in adenine and guanine promotes changes in the aromaticity of the benzene ring that amounts to 0.013 for adenine and 0.010 for guanine, as expected from the larger degree of electron sharing between the benzene ring and the adjacent 6- and 5-MRs.

Effect of Hydrogen-Bonding Pairing on the Local Aromaticity. Because the basic structural units in the DNA duplex are the Watson−Crick hydrogen-bonded pairs A−T and G−C, it is worth examining the influence of hydrogen bonding on the aromaticity indices determined for the constituent 6- and 5-MRs of the natural and size-expanded bases.

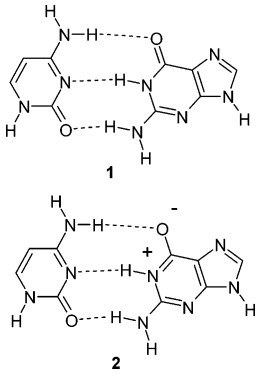
Comparison of the aromaticity indices for the hydrogen-bonded pairs (see Table 2) with those reported for the separated bases (see Table 1) reveals that, in general, hydrogen bonding does not have a large effect on the local aromaticity of the bases, and that the only noticeable changes in general are restricted to the 6-MRs that participate directly in the hydrogen-bond interaction. Thus, in agreement with previous studies,[14−16] the formation of the hydrogen-bonded pairs tends to enlarge the

TABLE 2: Aromaticity Indices for the Constituent Six- and Five-Membered Rings of Watson−Crick Hydrogen-Bonded Pairings in Natural and Benzo-fused Bases[a]

base	ring[b]	HOMA	NICS(0)[c]	NICS(1)[c]	NICS(−1)[c]	$NICS(1)_{zz}$[c]	FLU	PDI
A	6	0.982	−5.922	−7.586	−7.593	−19.745	0.013	0.056
	5	0.893	−11.350	−9.397	−9.413	−26.880	0.027	
xA	6	0.808	−4.512	−6.900	−6.939	−17.255	0.020	0.046
	B	0.897	−11.521	−11.875	−11.875	−31.431	0.012	0.069
	5	0.838	−10.065	−9.079	−9.106	−25.653	0.030	
G	6	0.888	−2.942	−3.385	−3.364	−6.702	0.038	0.034
	5	0.882	−10.943	−8.604	−8.722	−24.563	0.028	
xG	6	0.734	−0.584	−2.457	−2.457	−4.002	0.045	0.026
	B	0.926	−10.126	−10.559	−10.559	−27.272	0.011	0.069
	5	0.837	−10.053	−8.957	−8.954	−25.326	0.030	
T	6	0.381	−0.939	−1.525	−1.530	−1.850	0.073	0.028
xT	6	0.331	0.419	−1.094	−1.111	0.848	0.076	0.017
	B	0.978	−8.900	−9.858	−9.873	−25.431	0.004	0.085
C	6	0.744	−0.943	−2.487	−2.564	−4.567	0.043	0.039
xC	6	0.738	−0.088	−2.003	−2.002	−2.097	0.051	0.024
	B	0.971	−8.478	−9.675	−9.676	−25.905	0.005	0.095

[a] NICS is in ppm and PDI is in electrons. [b] The 6 and 5 denote the six- and five-membered rings of nucleobases. B stands for the benzene moiety in the benzo-fused derivatives. [c] NICS(0) values computed at the ring centers were determined by the nonweighted mean of the heavy atoms coordinates; NICS(1) and NICS(−1) computed at 1 Å above and below the molecular plane.

SCHEME 3



1

2

aromaticity of the 6-MR, though this tendency varies considerably for the different bases (see Tables 1 and 2). The local aromaticity is kept almost constant for adenine and benzoadenine, in which the change in the FLU index induced upon base pairing is ∼0.001, whereas it is ∼0.008 for guanine and benzoguanine. On the other hand, the FLU index varies by ∼0.001 for cytosine and benzocytosine upon hydrogen-bond pairing, though such a change is ∼0.006 for thymine and benzothymine. Hydrogen-bond interactions in the G−C (and analogously in xG−xC) pair stabilize the charge separation resonance structure **2** in Scheme 3 as compared to **1**, thus increasing the aromaticity of the guanine (and benzoguanine) 6-MR and keeping the aromaticity of cytosine (and benzocytosine) unchanged.[13b,16] The same situation (not shown in Scheme 3) that justifies the increase of aromaticity for the 6-MR of thymine and benzothymine and not for that of adenine and benzoadenine is found in the A−T and xA−xT base pairs. These findings, therefore, suggest that the different sensitivity of the aromaticity index is related to the presence of the −C(O)NH amide fragment in the base (T in A−T, and G in G−C) involved in hydrogen bonding.

Compared to the FLU values, there are differences in the fine details of the changes in local aromaticity of the 6-MR predicted by HOMA and NICS upon hydrogen-bond pairing. Inspection of the HOMA results reveals an increase (by ∼0.102) of the aromaticity of the 6-MR in guanine and benzoguanine. Such an increase, nevertheless, is sensibly larger than that experienced for the 6-MR in thymine, where the HOMA increases by 0.022, and for benzothymine, where the HOMA remains nearly unaffected upon base pairing. In fact, a larger change is observed for cytosine and benzocytosine, where the HOMA index increases by ∼0.031. Likewise, whereas the pairing of adenine slightly decreases the NICS(0) value (by ∼0.67) of the 6-MR, there is a small increase in the aromaticity of the corresponding ring in benzoadenine (by ∼0.21), which is similar to that found in the 6-MR of both guanine and benzoguanine (by ∼0.45) upon hydrogen-bond pairing. Finally, all the measures agree in predicting that the local aromaticity of the benzene ring remains nearly unaltered upon hydrogen bonding.

TABLE 3: HOMO and LUMO Energies (eV) for the Natural and Size-Expanded Nucleobases,[a] and the Global Measures of Aromaticity Determined by Using HOMA and FLU Descriptors

base	ϵ_{HOMO}	ϵ_{LUMO}	$\Delta\epsilon$	global HOMA	global FLU
A	−7.25	0.63	7.88	0.936	0.018
xA	−6.87	−0.48	6.39	0.860	0.017
G	−6.97	0.97	7.94	0.802	0.041
xG	−6.72	−0.02	6.70	0.789	0.033
T	−8.07	0.04	8.11	0.359	0.079
xT	−7.64	−0.53	7.11	0.773	0.050
C	−7.73	0.25	7.98	0.714	0.044
xC	−7.48	−0.57	6.91	0.807	0.032

[a] Determined at the BHandHLYP/cc-pVTZ level.

Overall, even though there is a consensus in predicting that base pairing has a small influence on the local aromaticity of both natural and size-expanded bases, almost all of the indices predict in general that such an effect is slightly larger for guanine, thymine, and their benzoderivatives, which can be realized from the electronic changes induced upon hydrogen-bond pair formation.

Global Measures of Aromaticity. On the basis of the maximum hardness principle (MHP),[50] the degree of aromaticity of a molecule can be measured from the global hardness,[17] which is an indicator of the molecular stability. In turn, the global hardness of the system can be estimated in an approximate way from the energy gap between HOMO and LUMO frontier orbitals.[17]

Table 3 reports the HOMO and LUMO energies for the natural and size-expanded nucleobases determined at the BHandLYP/cc-pVTZ level. The HOMO energies of natural and benzo-fused bases show the same ordering with thymine having the lowest HOMO followed by cytosine, adenine, and guanine.

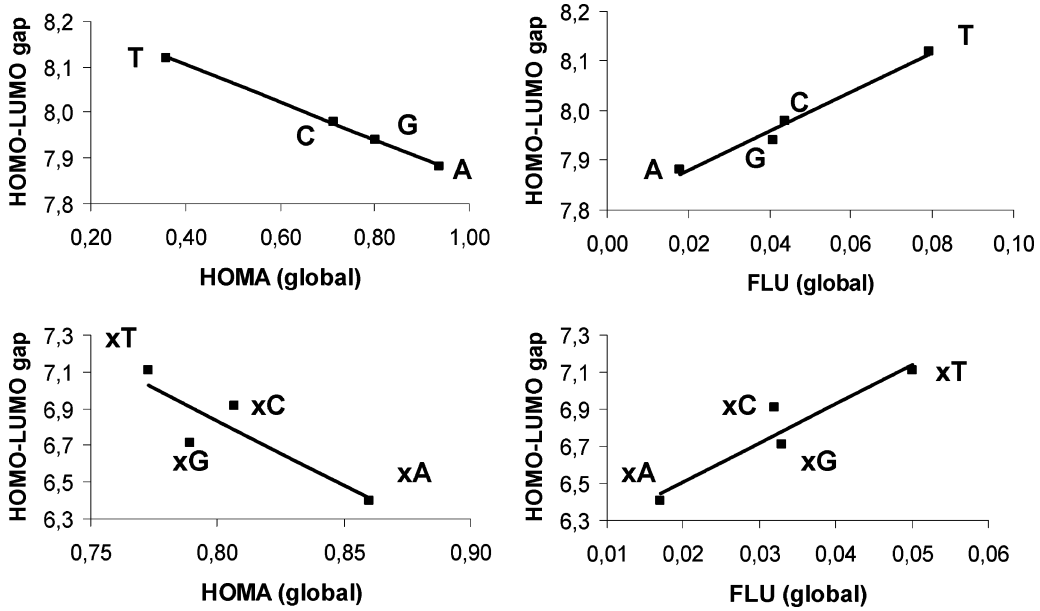


Figure 4. Representation of the HOMO−LUMO gap (eV) for the natural (top) and size-expanded (bottom) nucleobases vs the global aromaticity determined from HOMA and FLU indexes.

With regard to the LUMO, in the natural bases thymine has the lowest LUMO followed by cytosine, adenine, and guanine. In the benzobases, however, both benzothymine and benzocytosine have similar LUMO energies followed by benzoadenine and benzoguanine. It can be stated that insertion/addition of the benzene unit reduces the HOMO−LUMO energy gap by 1.48 and 1.23 eV in adenine and guanine, respectively, and by 1.07 and 1.01 eV in cytosine and thymine, respectively. This is not unexpected in cyclic π-systems, as they usually experience a reduction of the HOMO−LUMO gap when the number of conjugated π-bonds is increased.[51] This effect arises from a destabilization of the HOMO by 0.25−0.43 eV and a larger stabilization (by 0.57−1.11 eV) of the LUMO. These findings are also reflected in the HOMO and LUMO energies determined at the HF level as well as from DFT computations performed by using LSDA and hybrid B3LYP functionals (data not shown; see Supporting Information).

Figure 4 shows the dependence of the HOMO−LUMO gap on the global aromaticity of natural and benzo-fused bases determined by using HOMA and FLU indexes for the set of bonds that define the whole perimeter of the compounds (see Table 3). For the two sets of nucleobases, there is an inverse correlation between the HOMO−LUMO gap and the global aromaticity, so that the larger the HOMO−LUMO gap, the lower the global aromaticity. On the other hand, inspection of the data shown in Table 3 shows that the reduction in the HOMO−LUMO gap induced upon insertion/addition of benzene to the natural bases (see above) is not accompanied by a reduction in the global aromaticity as expected from the MHP. In particular, we found a significant increase of aromaticity for thymine and cytosine when going from the natural bases to the benzo-fused ones. This change is indicated both by HOMA, which increases by 0.414 and 0.093 units, and by FLU, which decreases by 0.029 and 0.012 units, respectively. For adenine and guanine the changes in the global aromaticity upon insertion of the benzene ring to the natural bases are less remarkable. In these cases, the two indices predict different behaviors. According to HOMA, there is a small decrease in the aromaticity of adenine and guanine (the global HOMA is reduced by 0.076 and 0.013 units, respectively), while FLU indicates a minor increase in global aromaticity (by 0.001 and 0.008 units, respectively). Not surprisingly, the effect in the global aromaticity of adding a new benzene ring to bases with two rings already (adenine and guanine) is less important than for the bases initially having a single ring (thymine and cytosine).

According to the MHP,[50] molecular systems at a given temperature evolve to a state of maximum hardness. Following this principle, one may suggest that a larger hardness, or as an approximation to the hardness a larger HOMO−LUMO gap, should go with an increased aromaticity. However, when going from the natural bases to the benzo-fused derivatives, we found the opposite behavior. At this point, it is worth noting that a formal proof of the MHP based on statistical mechanics and the fluctuation−dissipation theorem was given by Parr and Chattaraj[52] under the constraints that the chemical potential and the external potential ($v(\vec{r})$) must remain constant. These are two severe constraints that are usually not fulfilled and, in particular, neither the external nor the chemical potentials are kept constant when going from the natural to the benzo-fused bases. For this reason, the breakdown of the MHP in our systems is not completely unexpected, and, in fact, there are many examples of failures of the MHP in chemical reactions.[53] More importantly, the MHP fails to detect a reduction of aromaticity in the benzene ring (and many other aromatic species) because of the distortion along the bond length alternation mode of b_{2u} symmetry.[54]

Local vs Global Measures of Aromaticity. For the natural bases, the HOMO−LUMO gap exhibits an inverse correlation with the local aromaticity of the 6-MR as measured from the local HOMA and FLU indexes (see Figure 5), thus mimicking the trends observed in the comparison of the HOMO−LUMO gap with the global aromaticity indices (see above and Figure 4). A similar finding is found in the comparison of the corresponding properties determined for the size-expanded nucleobases, where the increase in the HOMO−LUMO gap is accompanied by a reduction in the aromaticity of the 6-MRs (see Figure 5). However, the opposite behavior is found between the HOMO−LUMO gap and the aromaticity of the fused benzene ring, so that the larger the HOMO−LUMO gap, the lower the destabilization in the aromaticity of the benzene ring that originated upon insertion/addition to the natural bases. This finding, which agrees with the intuitive correspondence between

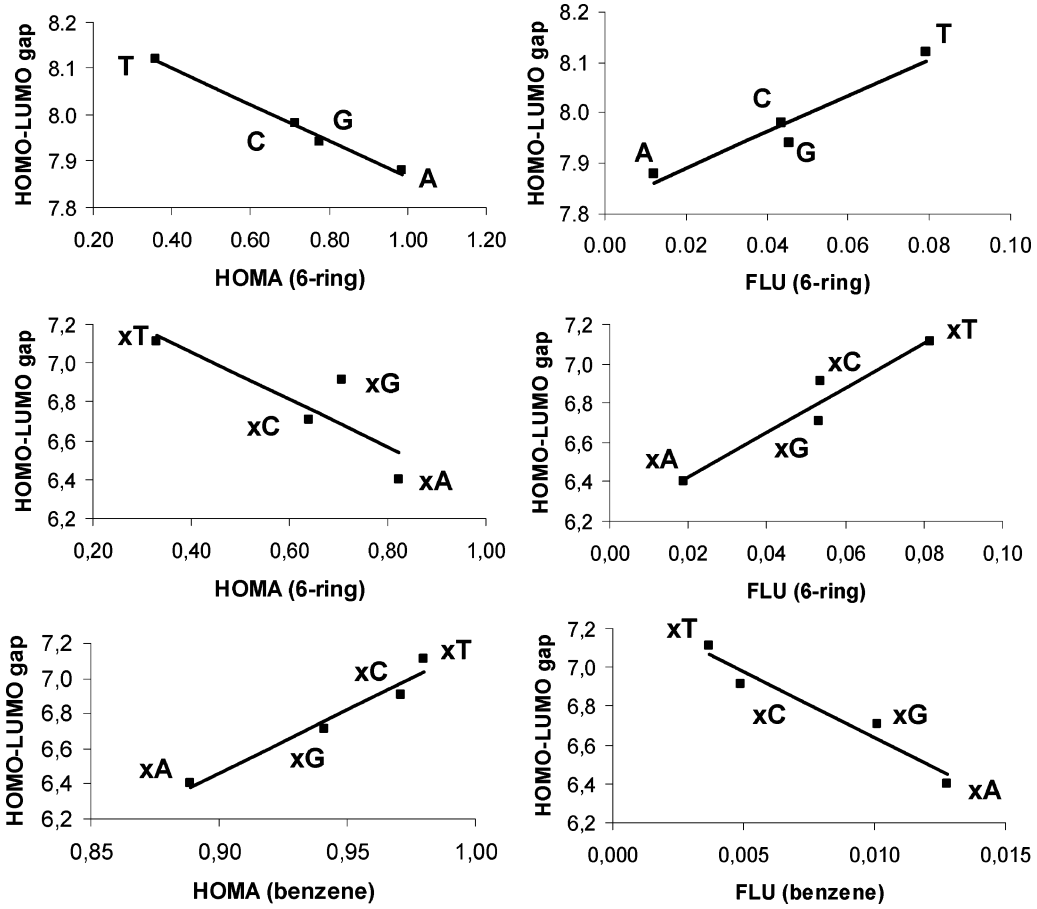


Figure 5. Representation of HOMO−LUMO gap (eV) for the natural and size-expanded nucleobases vs the local aromaticity determined from HOMA and FLU indexes for the six-membered and benzene rings.

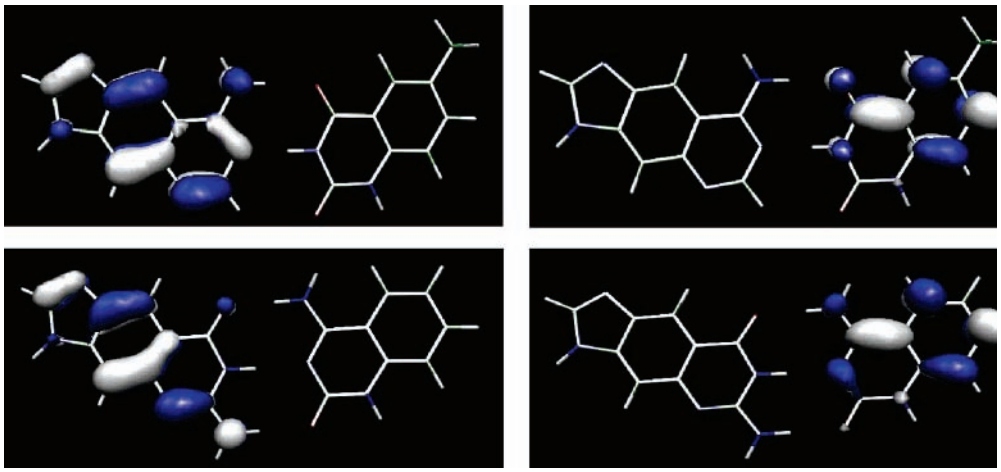


Figure 6. Representation[58] of the HOMO and LUMO orbitals (isodensity contours of ±0.05 au) in the Watson−Crick hydrogen-bonded pairs between size-expanded bases. Benzoadenine−benzothymine (top) and benzoguanine−benzocytosine (bottom). The HOMO and LUMO orbitals are shown in the left and right sides, respectively.

the aromaticity of a compound and the energy gap between HOMO and LUMO orbitals, reflects the large contribution played by the benzene fragment to the HOMO and LUMO orbitals not only for the isolated bases,[9a] but also in the hydrogen-bonded pairs (see Figure 6).

The preceding results suggest that the HOMO−LUMO gap in benzo-fused bases can be modulated to some extent by controlling the degree of local aromaticity of the benzene ring. Thus, by introducing suitable chemical modifications in the benzene ring, one might modulate the HOMO−LUMO gap without affecting the hydrogen-bonding recognition properties of the size-expanded nucleobases that would enable the formation of modified DNA duplexes with altered properties. In turn, because the electrical conductivity properties of DNA can be related in a first approximation to the distribution of the HOMO and LUMO band in a DNA duplex,[55] the presence of certain chemical groups in the benzene unit of xDNA bases should allow the modulation of the charge transfer properties, while the structural integrity of the duplex should be largely preserved. Alternative approaches might also include changing the chemical nature of the ring used to expand the size of the natural bases, the use of different size-expansion schemes, as has been

conceived in the so-called y-bases,[56] or even the design of size-expanded bases with a higher degree of aromatic conjugation. In these cases, however, the modified bases should be able to retain the recognition properties that ensure a proper Watson−Crick pairing between complementary bases, as it is critical to build up stable duplexes that might act as molecular wires.

Conclusion

The analysis of the local aromaticity performed by using HOMA, NICS, FLU, and PDI descriptors has revealed relevant differences in the aromatic character of the size-expanded benzobases. The degree of aromaticity of the 6-MR of xDNA bases varies in the order xA > xG ∼ xC > xT, which reflects the dearomatizing effect played by the exocyclic substituents that are of a double-bond character already suggested for the natural bases.[15] Insertion/addition of the benzene ring, nevertheless, reduces the local aromaticity of the 6-MRs in natural bases, an effect also observed in the local aromaticity of the 5-MRs. These features are generally hardly affected upon hydrogen-bonding base pairing, and the main changes are limited to the 6-MR. Interestingly, the differences in the HOMO−LUMO gap of the xDNA bases show an inverse correlation with the aromaticity of the fused benzene ring. Therefore, by introducing suitable chemical changes in the benzene ring, one might modulate the HOMO−LUMO gap thus enabling the design of modified nucleobases that might be used to mediate charge transport mechanisms in DNA duplexes.[57]

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Supporting Information Available: Complete ref 37. HOMO and LUMO energies for the natural and size-expanded nucleobases determined at the HF, LSDA, and B3LYP levels using the cc-pVTZ basis set. Representation of the variation in NICS(0), NICS(1), NICS(−1), and NICS(1) values for isolated bases and of the HOMO and LUMO orbitals in the Watson−Crick hydrogen-bonded pairs between natural bases. This material is available free of charge via the Internet at http://pubs.acs.org.

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