A Post-SCF Quantum Chemistry Study On Local Minima of 8-oxo-Guanine Stacked With All Four Nucleic Acid Bases in B-DNA Conformations

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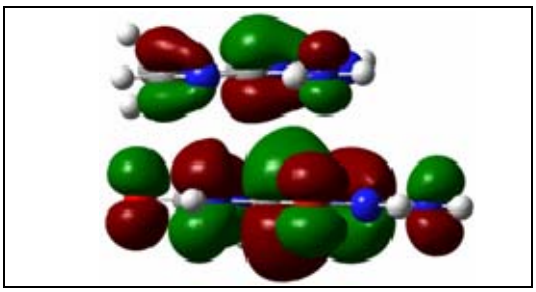

The post SCF MP2/6-31G*(d=0.25) method was applied to obtain potential energy surface of 8-oxo-guanine stacked with all four canonical DNA bases. The spatial neighbourhood was scanned of stacked complexes found in the native B-DNA. The presented results suggest that the hydroxyl radical modification of guanine at C_8 position has significant impact on structural, energetic, orbital and electrostatic properties of stacked complexes with canonical DNA bases. The pair stabilization energy, including electron correlation terms, suggests that the 5'-A/GA-3' pair is the most stable among all of the studied complexes. The 8-oxo-guanine has been found as a source of significant changes in electro-accepting properties compared to stacked pairs formed by canonical guanine since both electron affinities and localization of HOMO orbital were altered. However, electro-donation abilities are not modified after replacement of guanine with 8-oxo-guanine irrespectively on the context of B-DNA bases.

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INTRODUCTION

The 8-oxo-guanine is one of the most abundant derivatives among many possible products of hydroxyl radical DNA degradation [1]. All aerobic organisms suffer persistent oxidation of guanine (G) to 8-oxo-guanine (GA) [2]. Highly promutagenic character of this genotoxic product was demonstrated in variety of *in vivo* [3] and *in vitro* experiments [4]. Replicative DNA polymerases misread 8-oxo-guanine residues and insert not only cytosine but also adenine opposite the oxidized base. This is responsible for GC=>TA transition often observed in tumour cells [3-7]. Besides, context-dependent effects are observed. When 8-oxo-guanine is positioned between T and C it may cause the insertion of all four bases with the same frequency [3]. However, if 8-oxo-guanine is present between A and T there are observed mainly insertions of C and T [7]. One of the reasons of such context-dependence of 8-oxo-guanine coding abilities might be the intermolecular interactions with neighbouring bases within the same strand. Thus, the detailed knowledge of stacking interactions of this modified guanine seems to be valuable for deeper insight into the 8-oxo-guanine role in cellular processes. It has been shown that 8-oxo-guanine exists predominantly as amino-diketo tautomer [8,9]. Since modification of guanine at C_8 position leads to significant alteration of coding properties it is worth knowing the impact of such guanine modification on other intermolecular interactions with canonical bases. However, the stacking properties of 8-oxo-guanine in B-DNA context were not the subject of detailed studies up to date. Although in previous paper [10] the global minima of 8-oxo-guanine stacked with canonical bases were presented, no direct comparison to B-DNA conformations were provided till now. Recently, the method for PES scan [11] has been successfully applied for the regions corresponding to the mean B-DNA [12] conformations. In this paper we intend to describe the local minima of stacked pairs of 8-oxo-guanine with all four nucleic acid bases in conformations potentially present in B-DNA. The DNA base stacking is a complex phenomenon, which is characterized by several competitive contributions. The interaction of bases with environment formed by DNA backbone, the phosphate groups and ribose, are also important both for canonical and oxidized bases. Besides, the impact of aqueous solution containing counter ions may significantly influence both the interaction energy and the thermodynamic properties of stacked complexes. The estimation of the influence of the environment on each of

these contributions is a non-trivial task and as it was demonstrated by Hobza *et al*. [13-16], the reliable prediction of the stacking energy can be accomplished only by the use of the advanced quantum chemical methods. The empirical, semiempirical and density functional theory are known [17] to be inadequate tools for description of stacked complexes. In particular, the proper description of the dispersion component of the interaction energies requires the application of the methods that accounts for the electron correlation (*i.e*. MP2, CCSD(T)) [18,19]. Since the computational cost grows rapidly with the system size (*i.e*. the number of so-called basis functions), the model system that mimics the influence of the modifications of the nucleotides on the stability of the DNA should be as simple as possible. In particular, one may concentrate on relative stacking properties of modified DNA bases with respect to canonical ones. Although the effect of base stacking on nucleic acid stability is a result of a complex interplay of the intrinsic base-base interactions and additional environmental contributions in the first approximation, one can consider additive nature of the intrinsic and external contributions to stacking. If this is correct the external contributions do not affect the intrinsic interactions. The former, however, may reverse the stability order as given by the latter. The external contributions primarily corresponding to the electrostatic component of base stacking are substantially dependent on the DNA or RNA three-dimensional architecture. It is known that the base-pairs in isolation are not sufficient to predict univocally the conformational properties of different DNA sequences and experimentally observed step geometries do not always correspond to minima in the stacking potential energy surface. The principle reason for this discrepancy is that the backbone plays an important role in defining the conformational properties of double-helical DNA and the chosen conformation of a dinucleotide base step involves a compromise between the preferred stacking interactions and the preferred backbone conformation. Although a choice of the model system comprising stacked bases is not capable of prediction of the stability of the nucleic acids, it may provide better understanding of the underlying physical phenomena. Despite all of these content-related and methodological limitations the information obtained for simple model, in which one takes into account only stacking of two subsystems (nucleic bases) can be very useful for the characterization and prediction of the influence of oxidation of nucleotides on the intermolecular interaction energy. The aim of the present study is to investigate the influence of the guanine oxidation at C_8 centre on the properties of the stacked complex of two model nucleotides.

Methods. Details about the method of calculations were presented elsewhere [11] and only brief description will be given here. Figure 1a presents local parameters describing mutual orientation of stacked pairs used in model studies of stacked complexes [15-17,20]. Unfortunately, commonly used parameters describing conformations of B-DNA are not directly related to such arbitrary definition of stacking pairs (Figure 1b). Thus, we have used 3DNA program [21] for preparation of meaningful complexes geometries. However, the default structures implemented in this program were replaced with those optimized at the MP2/6-31G*(d=025) level of theory [11,13-17] imposing C_s symmetry. To mimic N-glycosidic bond the N_1- or N_9-methyl substituted purines and pyrimidines analogs were used. The structure of 8-oxo-guanine denoted further as GA correspond to the 6,8-diketo tautomer, which is the most stable tautomer of this guanine analog [9]. The systematic PES scan was performed by modification of the twist angle and rise values around geometry defined by mean structure of B-DNA [12]. Values of the remaining parameters (tilt, roll,

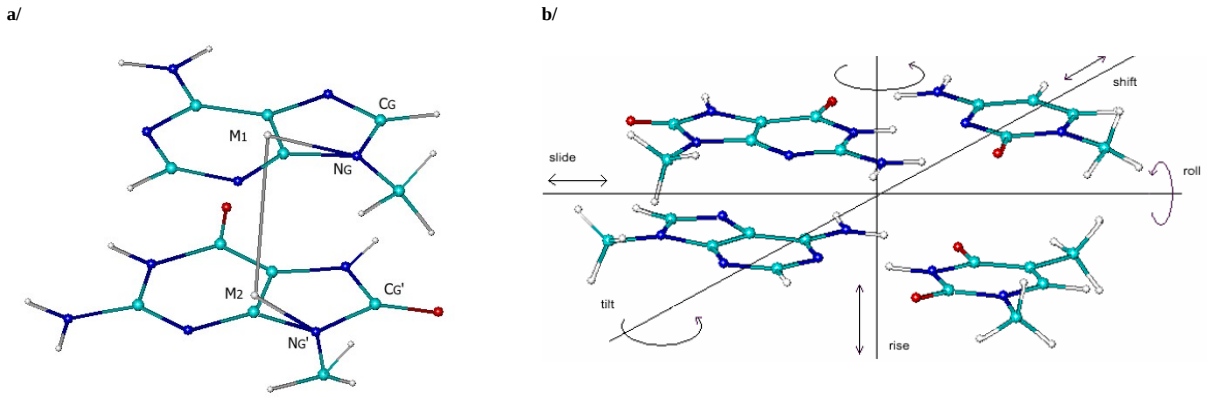
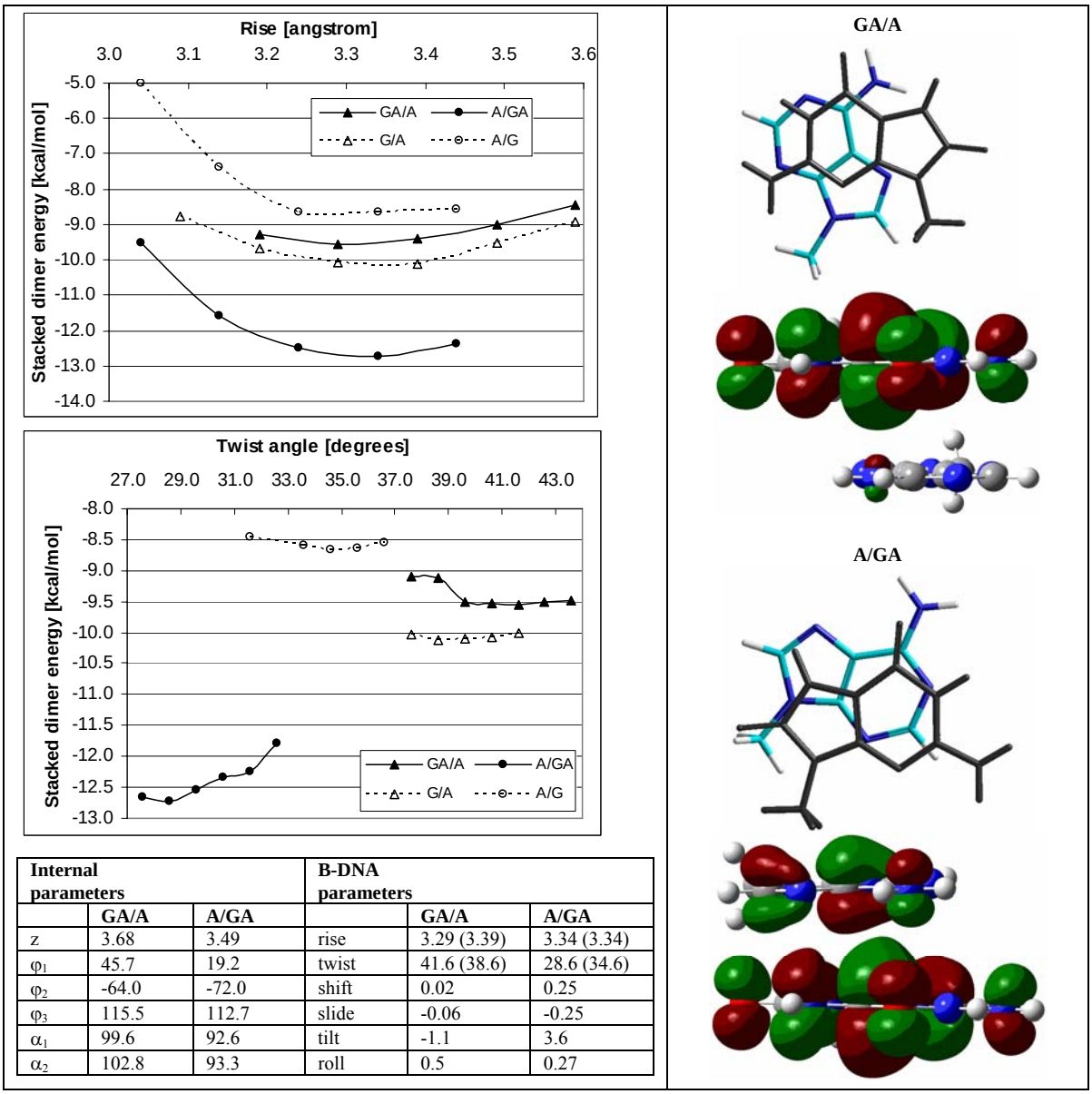


Figure 1. Definition of stacked pairs geometries: a/ arbitrary parameters defining orientation of monomers in stacked complex: z – M_1-M_2 separation, α_1 – N_G–M_1-M_2 valence angle, α_2 – N_G–M_1-M_2 valence angle, φ_1 – N_G–M_1-M_2–N_G' torsion angle, φ_2 –C_G-N_G–M_1-M_2 torsion angle, φ_3 – M_1-M_2–N_G'-C_G' torsion angle, where M_i denotes mass center of i-th monomer, N_G stands for N-glycosidic nitrogen atom (N_1 for pyrimidines and N_9 for purines) and C_G means C_8 carbon atom for purines and C_2 one for pyrimidines; b/ commonly used parameters defining geometry of DNA double helix (rise, twist, shift, slide, tilt, roll)



Internal parameters			B-DNA parameters		
	GA/A	**A/GA**		**GA/A**	**A/GA**
z	3.68	3.49	rise	3.29 (3.39)	3.34 (3.34)
φ_1	45.7	19.2	twist	41.6 (38.6)	28.6 (34.6)
φ_2	-64.0	-72.0	shift	0.02	0.25
φ_3	115.5	112.7	slide	-0.06	-0.25
α_1	99.6	92.6	tilt	-1.1	3.6
α_2	102.8	93.3	roll	0.5	0.27

Figure 2. Structural properties of 8-oxo-guanine stacked with adenine in conformation corresponding to local minimum closest to mean B-DNA structure [17]. Notation X/Y stands for 5'-X/Y-3' sequence, where X and Y denote nucleic acid bases or 8-oxo-guanine. The values of parameters corresponding to the local minima formed by native guanine [11] are presented in parenthesis. On structure schemes the 8-oxo-guanine is marked by thick lines. The localization of HOMO orbital on stacked complexes is plotted.

Table I Energetic and electrostatic properties of 8-oxo-gunanie complexes stacked with four DNA bases. Energies characterize the most stable stacked guanine complexes corresponding to local minima estimated by energy scan on *ab-initio* MP2/6-31G*(d=025) level. Symbols ΔE^{SCF}, ΔE^{correl}, ΔE^{total} denote HF energy, correlation energy contribution and stacking pair energy corrected for BSSE [19], respectively. EA stands for adiabatic electron affinity, IP represents the gap between HOMO and LUMO orbital.

pair	ΔE^{SCF}	ΔE^{correl}	$\Delta E^{stacking}$	EA	HOMO	LUMO	IP
	kcal/mol			eV			
GA/A	6.27	-15.81	-9.54	0.37	-0.280	0.136	0.41
A/GA	4.29	-17.01	-12.72	1.95	-0.279	0.131	0.41
GA/G	8.07	-14.35	-6.29	2.63	-0.270	0.129	0.40
G/GA	6.22	-14.11	-7.89	3.02	-0.280	0.123	0.40
GA/T	6.55	-15.04	-8.49	0.99	-0.286	0.095	0.38
T/GA	1.28	-7.77	-6.49	1.41	-0.285	0.108	0.39
GA/C	2.11	-12.40	-10.29	1.31	-0.284	0.099	0.38
C/GA	1.36	-10.22	-8.86	1.64	-0.275	0.114	0.39

shift, slide) were kept unchanged since they have minor impact on pair stabilization energy [22]. Resulting values of energies and molecular properties are presented in Figures 2-5. Final energies, provided in Table I, were corrected for basis set superposition error [23]. All calculations were performed in Gaussian 03 software package [24].

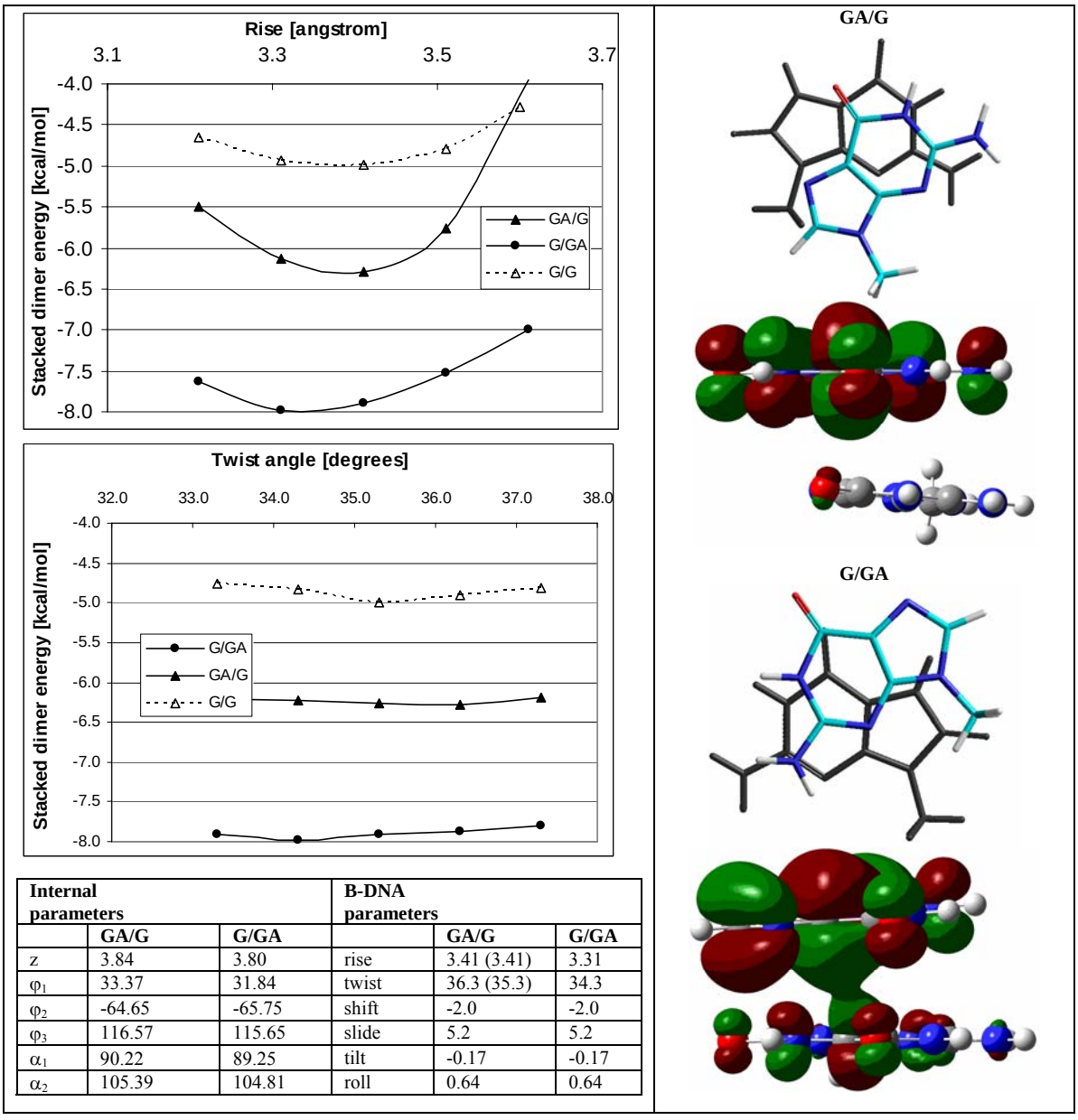
RESULTS AND DISCUSSION

Stacked Complexes of 8-oxo-Guanine with Adenine. The influence of the mutual orientation of 8-oxo-guanine and adenine on stacking energy is presented in Figure 2. The energy plots indicate that there are local minima for both GA/A and A/GA pairs. Interestingly, rise parameter is almost identical for all these complexes and local minima formed by canonical guanine [11]. Thus, modification of guanine at C_8 position has negligible effect on optimal separation of guanine or 8-oxo-guanine with adenine and for the four complexes investigated here is equal to 3.3 Å. On the contrary, significant variations are observed in values of twist angle corresponding to local minimum structures. The values of this parameter are equal to 41.6° and 28.6° for the GA/A and A/GA complexes, respectively. Such a difference was also observed for guanine stacked with adenine, but in case of 8-oxo-guanine more significant discrepancy in twist angle is found. Also the stabilisation energy of the stacked 8-oxo-guanine with adenine differs significantly from ones characterising the guanine and adenine system. Both GA/A and A/GA are more stable compared to pairs formed by unoxidized guanine. However, the latter pair is about 25% more stable (~2.5kcal/mol) than A/G and its stabilization energy is the highest among all complexes studied here. The corresponding data are presented in Table I. Both stacked pairs formed by 8-oxo-guanine and adenine have also modified electrostatic features with respect of complexes formed by canonical guanine. The localization of HOMO orbital in case of the GA/A pair is mostly on 8-oxo-guanine, while significant dislocation towards adenine molecule is observed for the A/GA complex as it is presented in Figure 2. About 92.8% of HOMO is located on 8-oxo-guanine in case of the GA/A complex, while only 82.9% for the A/GA pair. This is also resembled in changes of adiabatic electron affinities (EA). The GA/A has about six times smaller values of EA than the A/GA complex, which suggests much higher electrophilic character of the A/GA pair. Interestingly, the electron affinities of the G/A and A/G complexes are much higher and equal to 2.24 and 2.94, respectively [11]. Thus, significant increase of electron accepting properties with respect of standard guanine stacked to be expected for 8-oxo-guanine complexes with adenine. However, the energies of HOMO and LUMO are almost the same for both stacked complexes of 8-oxo-guanine and guanine. In conclusion, one may emphasize that despite energetic and structural similarities, particularly pronounced in case of the GA/A and G/A pairs, the replacement of guanine by its oxidized analogue, 8-oxo-guanine, leads to significant context-dependent changes in stacking abilities, the intra-strand intermolecular interactions and electrostatic properties.

Stacked Complexes of 8-oxo-Guanine with Guanine. There are two distinct stacked pairs of 8-oxo-guanine formed with guanine, which is the first remarkable result of guanine modification by hydroxyl radical. As it is demonstrated in Figure 3 both pairs, GA/G and G/GA, are significantly more stable than the G/G pair [11]. For the former case the stacking energy is increased by about 30% and for the latter pair even more than 60% higher compared to standard guanine. Interestingly, the mutual orientation of guanine and 8-oxo-guanine in stacked complexes is almost the same. The differences in rise parameter are of order of 0.1 Å and alteration of twist angle is within 2 degrees. All conformations are very close to mean B-DNA structure [11,12]. Thus, the modification of guanine does not have any major impact on the structural properties of stacked complexes still increasing the stabilization energy. Stacked pairs formed by 8-oxo-guanine and guanine are characterized by the highest values of adiabatic electron affinity among all studied pairs. The electron affinity for G/G pair is equal to 2.88eV [11], while in the case of G/GA complex the modified guanine possess slightly weaker electro-accepting character than guanine. Interestingly, the GA/G pair is characterized by slightly lower values of EA than G/G stacked complex. Thus, introduction of 8-oxo-guanine into B-DNA will result in context-dependent alteration of electron trapping properties. The G/GA pair seems to be the most effective source of high resistance towards electron trapping among all studied stacked complexes. One of the expected consequences might be the termination of electron flow along DNA chain since changes in values of electron affinities increases noticeably if modified guanine is present in the poly–nucleo–tide chain. There is another interesting feature noticed in case of the G/GA pair. As it is demonstrated in Figure 3, the localization of HOMO orbital is significantly different compared both to other pairs formed by 8-oxo-guanine as well as to dimers formed by guanine with all four DNA bases. Usually the highest occupied orbital is predominantly located on 8-oxo-guanine but it is not the case for the G/GA pair. Here, only 16.5% of HOMO is present on modified guanine and standard guanine comprises the remaining 84.5% of this frontal orbital. Such a characteristic is observed only for this particular stacking complex. Interestingly, the GA/G pair is characterized by the HOMO located in 94.6% on 8-oxo-guanine. Thus, despite great structural similarities of

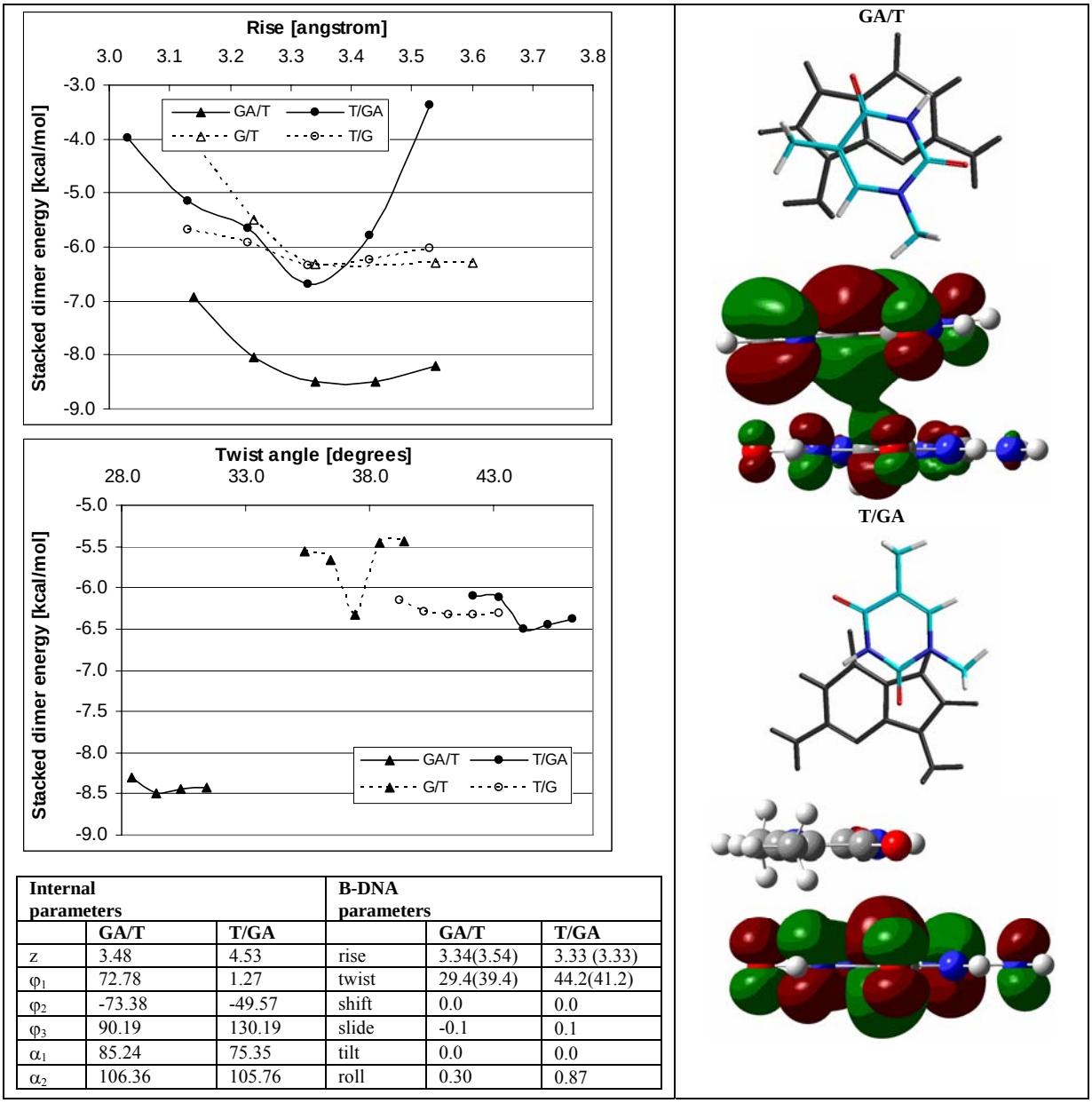
guanine and 8-oxo-guanine stacked with guanine, significant modification in stabilization energies and electrostatic properties are caused by the presence of the oxidized guanine.

Stacked Complexes of 8-oxo-Guanine with Thymine. The standard guanine stacked with thymine is characterized by almost the same energy for both G/T and T/G pairs [11]. This is not the case if 8-oxo-guanine is involved in stacking with this pyrimidine base. Although the T/GA pair is only slightly more stable than the T/G complex, the GA/T dimer has about 35% higher stacking energy compared to canonical T/G pair. However, all the local minima found on the energy plots (Figure 4) correspond to structures of very similar monomers separations. The variations in rise value are within 0.2 Å. On the contrary, mutual orientation of the monomers in the optimal stacked complex is context-dependent. The twist angle for the GA/T pair equals 29°, while for T/GA is about 15° higher. It is noteworthy that canonical guanine has much smaller difference in twist angle values for pairs related to the G/T and T/G sequences [11]. Such geometry alterations lead also to differences in electrostatic properties. First of all, about 25% reduction of adiabatic electron affinities is noticed compared to standard guanine if paired with thymine. Since, LUMO are mostly localized on thymine (61.4% and 61.9% for



Internal parameters			B-DNA parameters		
	GA/G	G/GA		GA/G	G/GA
z	3.84	3.80	rise	3.41 (3.41)	3.31
φ_1	33.37	31.84	twist	36.3 (35.3)	34.3
φ_2	-64.65	-65.75	shift	-2.0	-2.0
φ_3	116.57	115.65	slide	5.2	5.2
α_1	90.22	89.25	tilt	-0.17	-0.17
α_2	105.39	104.81	roll	0.64	0.64

Figuer 3. Structural properties of 8-oxo-guanine stacked with guanine in conformations corresponding to local minimum closest to mean B-DNA structure. Notation was explained in Figure 2.



Internal parameters			B-DNA parameters		
	GA/T	**T/GA**		**GA/T**	**T/GA**
z	3.48	4.53	rise	3.34(3.54)	3.33 (3.33)
φ_1	72.78	1.27	twist	29.4(39.4)	44.2(41.2)
φ_2	-73.38	-49.57	shift	0.0	0.0
φ_3	90.19	130.19	slide	-0.1	0.1
α_1	85.24	75.35	tilt	0.0	0.0
α_2	106.36	105.76	roll	0.30	0.87

Figure 4. Structural properties of 8-oxo-guanine stacked with thymine in conformations corresponding to local minimum closest to mean B-DNA structure. Notation was explained in Figure 2.

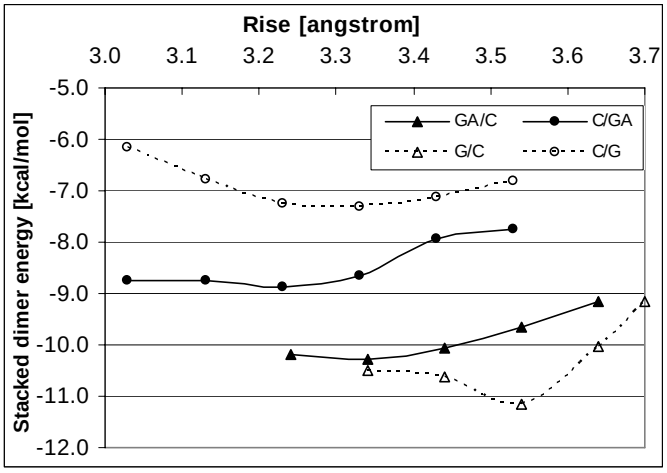
GA/T and T/GA pairs, respectively) the observed decrease of electrophilic properties has it source in the 8-oxo-guanine presence in B-DNA. Besides, energy levels of frontal orbitals and resulting ionization potential are equal to 0.4 eV for all pairs formed with thymine both for standard and modified guanine.

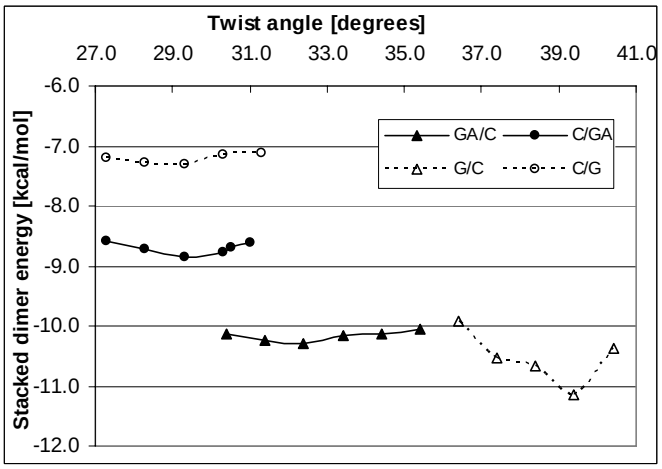
Stacked Complexes of 8-oxo-Guanine With Cytosine. Last set of stacked pairs includes 8-oxo-guanine and cytosine complexes. Figure 5 demonstrates existence of very shallow minima on energy plots. The C/GA pair is about 21% more stable compared to the C/G pair. However, the only situation in which the modified guanine forms a less stable pair than the unoxidized guanine is the case of the GA/C complex. The rise values are, however, very close to each other for all four stacked complexes of cytosine with canonical and modified guanine. The values of the twist angle are very similar for 5'-3' and 3'-5' sequences in case of 8-oxo-guanine and separate local minima by only 3 degrees. The HOMO are mostly located on purine bases as it is presented in Figure 5 and in Table II. The stacked pairs consisting of 8-oxo-guanine and cytosine are characterized by lower values of

electron affinity than the canonical guanine stacked with cytosine. On the other hand, the pairs formed by modified guanine have higher percentage of LUMO localized on purine base. Thus, twofold effect is observed as a result of guanine oxidation for complexes with cytosine. The decrease of pair electron accepting abilities is followed by increase of the 8-oxo-guanine as an electron acceptor centre. However, the energy levels of HOMO and LUMO are insensitive both to changes in bases orientation and guanine modification at C_8 position. Thus, electro-donating abilities are insensitive to guanine modification.

Table II Percentage of frontal orbitals located on 8-oxo-guanine in 5'-GA/X-3' and 5'-X/GA-3' or guanine in 5'-G/X-3' and 5'-X/G-3' sequences, where X stands for each of four canonical nucleic acid bases.

	HOMO	LUMO		HOMO	LUMO
GA/A	92.8%	45.9%	**G/A**	75.1%	69.2%
A/GA	82.9%	82.9%	**A/G**	89.5%	29.8%
GA/G	94.6%	51.4%	**G/G**	93.8%	31.6%
G/GA	16.5%	87.7%	-	-	-
GA/T	97.1%	38.6%	**G/T**	93.8%	33.5%
T/GA	93.5%	38.1%	**T/G**	92.2%	49.0%
GA/C	93.6%	60.5%	**G/C**	96.2%	53.0%
C/GA	96.0%	41.0%	**C/G**	96.5%	29.2%





Internal parameters			B-DNA parameters		
	GA/C	**C/GA**		**GA/C**	**C/GA**
z	3.56	3.82	rise	3.44 (3.34)	3.23 (3.33)
φ_1	59.56	1.26	twist	32.4 (39.4)	29.3 (29.3)
φ_2	-68.16	-62.51	shift	0.0	0.0
φ_3	101.17	122.99	slide	-6.0	6.2
α_1	90.20	86.46	tilt	0.0	0.0
α_2	109.15	97.34	roll	0.38	0.82

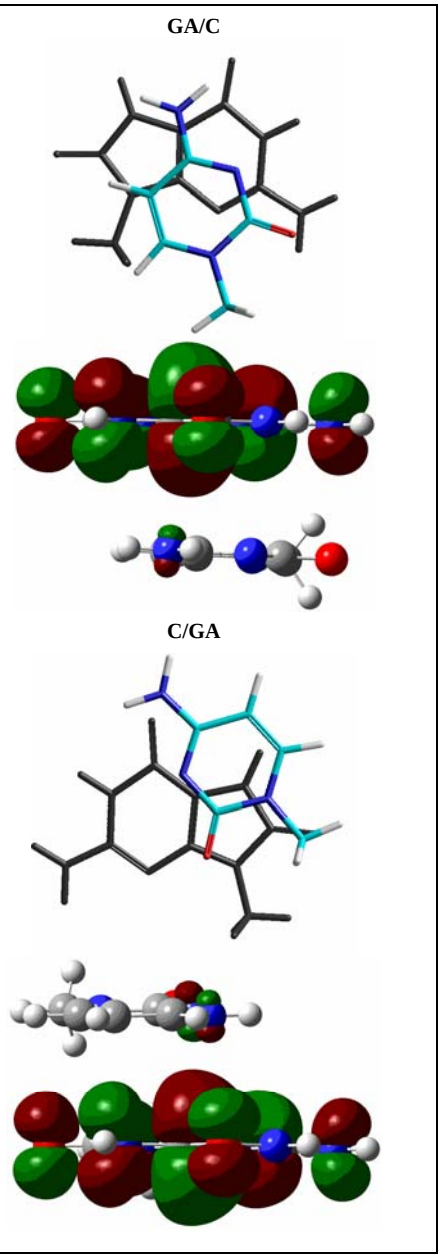


Figure 5. Structural properties of 8-oxo-guanine stacked with cytosine in conformations corresponding to local minimum closest to mean B-DNA structure. Notation was explained in Figure 2.

CONCLUSIONS

Modified guanine, if present in B-DNA, adopts conformations, which correspond to local minima on energy plots. However, conformation of optimal stacking complex is not the same as formed by standard guanine. Usually, more significant changes upon guanine oxidation are observed for twist angles than for rise parameter. The separation distance in local minima of stacked complexes seems to be insensitive to guanine modification and to the changes in mutual orientation of monomers. This conclusion relies on the fact that for all eight pairs of 8-oxo-guanine and seven pairs of canonical guanine [11] the separation distance is almost the same within 0.3 Å. The significant alteration of twist angle is observed for structures corresponding to local minima. The mean value of twist angle equals to 34.5° or 36.8° for pairs comprising 8-oxo-guanine and canonical guanine, respectively. The difference between highest and lowest values of this geometric parameter is about 15.6° for pairs containing modified and about 11.9° for those containing canonical guanine. This is not surprising difference since oxygen atom bonded to C_8 centre significantly alters the electrostatic properties of imidazole part of guanine, what is mainly manifested in twisting of monomers. Besides, significant influence of guanine oxidation is observed on stabilization energies. Usually stacked complexes formed by 8-oxo-guanine with canonical DNA bases are more stable than the pairs formed by unoxidized guanine. The only exception takes place in case of the GA/C pair. The data presented in Table I suggest that stabilization effect comes from electron correlation energy for all pairs formed by 8-oxo-guanine. On the contrary, the SCF energy of pairs formation is positive for all studied complexes which additionally justify the necessity of using a post-SCF methodology in studying of stacking complexes. The most stable pair among those studied here is the A/GA pair and at the same time this complex is characterized by highest electron correlation contribution to dimer energy. The least stable stacked complex is formed by 8-oxo-guanine and guanine (GA/G). Additionally, 8-oxo-guanine if present in stacked pairs is a source of significant changes in electro-accepting properties, since great changes in electron affinities are observed. The G/GA complex has the highest value of EA among all pairs studied here. On the contrary the GA/A complex is characterized by more then eight times smaller value of electron affinity compared to G/GA pair. This feature was not observed for stacked complexes formed by native guanine. This suggests significant differences in electron trapping properties. If all stacked pairs had similar electron affinities, the electrons might flow perpendicularly throughout the B-DNA chain [25,26]. However, significant alteration of electron affinities causes disturbance in such spontaneous electron movement. This is actually the case for some pairs containing 8-oxo-guanine. The electron affinities of standard guanine in stacked complexes corresponding to B-DNA conformation are between 1.3 eV and 2.94 eV [11]. From Table I it is apparent that the GA/A, GA/T and G/GA complexes have EA values outside of this region, which indicates context-dependent alteration of electro-accepting properties of modified guanine. Besides, significant alterations of LUMO localization are also observed. Table II shows that usually this frontal orbital is located in higher percentage on 8-oxo-guanine in oxidized stacked complexes than on guanine in non-oxidized ones. The only exception is the T/GA pair. Finally one can conclude that the electro-donating abilities are not affected by replacement of guanine with 8-oxo-guanine irrespective of the context of B-DNA bases. The values of ionization potential are almost the same for all pairs formed by 8-oxo-guanine and guanine with all four canonical bases. The mean value of IP is equal to 0.4eV. However, the localization of HOMO is significantly affected by guanine oxidation. As is demonstrated in Figures 2-5 and in Table II, very high HOMO contribution is observed on 8-oxo-guanine. The only intriguing exception is the G/GA pair for which HOMO is mostly placed on guanine instead of 8-oxo-guanine. However, in most cases the percentage of HOMO is close or slightly higher for stacked 8-oxo-guanine than for stacked native guanine. Thus, the hydroxyl radical modification of guanine at C_8 position leading to 8-oxo-guanine has significant influence on structural, energetic, orbital and electrical properties of stacked complexes with all four canonical DNA bases. It is worth mentioning that stacking energies itself do not determine directly and unambiguously the stability of nucleic acids. This observation indicates the fact that there is no straight-forward way to correlate the stacking interactions with the thermodynamic data [14]. For example the stacking energy of A/T and G/C pairs estimated on RI-MP2/aug-cc-pVQZ level are equal to -15.08 kcal/mol and -20.85 kcal/mol [13], respectively. On the other hand the experimental values of Gibbs free energy of coaxial stacking obtained for TA dinucleotide is equal to -0.85 kcal/mol, while for GC stack equals stack to -2.76 kcal/mol at room temperature [27,28]. Thus, thermodynamic data cannot be unambiguously derived from stacking energies and vice versa. However, a proper description of the intrinsic interactions nevertheless is helpful in understanding the basic principles governing interactions of subsequent bases. Since thermodynamic analysis even for such restricted model of stacking as two bases in gas phase is not feasible to date on level including the electron correlation, the energy calculations is the only contribution which may be estimated at present.

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