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Structure and properties of hydroxyl radical modified nucleic acid components
II. 8-Oxo-adenine and 8-oxo-2′-deoxy-adenosine

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Abstract

The tautomerism of the 8-oxo-adenine (8-oxo-A) and 8-oxo-2′-deoxy-adenosine (8-oxo-dA) was analysed on the basis of semiempirical, SCF ab initio and DFT density functional quantum chemistry calculations. The results of full gradient geometry optimisation of all possible 8-oxo-A and 8-oxo-dA structures lead to the conclusion that the most stable form is 8-keto-6-amino-tautomer. The second stable tautomer corresponds to 8-hydroxy-isomer. Such an order was unchanged after solvating process. In all studied solvents: water, methanol, acetone, cyclohexane the keto-tautomer proceeds the enol one. The preferred N-glycoside torsion angle corresponds to syn rotamer of 8-oxo-dA in all studied cases. However, the PM3 method predicted reversed order of syn and anti conformers for 8-oxo-dA tautomer.

Both tautomers have miscoding properties resulting in the formation of stable base pairs with cytosine and guanine instead of thymine (as it is in the case of canonical adenine). Despite less stability of enol tautomer the pair formed with cytosine is as much stable as pair comprising 8-oxo-tautomer. The most stabile pairs are those, where O_8 oxygen or H_{O8} hydrogen atoms are involved in the hydrogen bond formation. The Watson–Crick like pairs of cytosine and guanine with one of two most stable 8-oxo-A tautomer are more stable than standard A–T pairs. This may be the reason of experimentally observed AT ⇒ CG transversion or AT ⇒ GC transition. © 1997 Elsevier Science B.V.

Keywords: Tautomerism; 8-Oxo-adenine; 8-Oxo-2′-deoxyadenosine; Base pairs; Hydrogen bonds; Ab initio

1. Introduction

The hydroxyl radical may lead to different modifications of adenine molecule. Among variety of potential products three of them were found as the most important from the biological point of view: 2-hydroxy-adenine (known also as iso-guanine), 8-oxo-adenine and 2,6-diamino-4-hydroxy-5-formamidopirimidine (often abbreviated as fapy-adenine) [1–15]. All of these products are formed when DNA is treated with an oxygen radical-forming systems [1–6]. Such derivatives exist in cellular DNA and may cause both energetical and structural deformations [7]. It has been also observed that the incorporation of the modified adenine into the DNA molecule may lead to mispairing and consequently to errors

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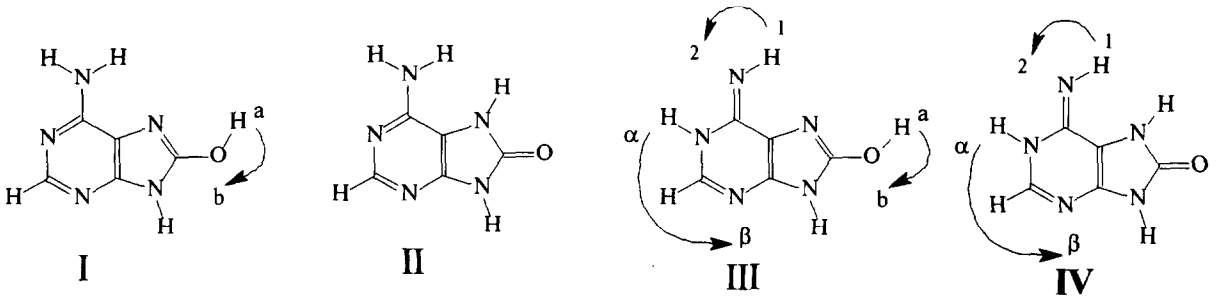

Fig. 1. All possible H_9 tautomers of 8-oxo-adenine. The arrows describe the potential direction of hydrogen migration leading to distinct tautomeric isomers.

during replication and transcription processes [8–10].

Due to its promutagenic potential, the 8-oxo-A is an interesting subject for theoretical studies. Although there has been a great interest concerning standard nucleic acid bases [11–15] the hydroxyl radical modified DNA components were of minor interest for theoretical studies. Aida and Nishimura [16] used the ab initio method with medium basis set expansion to characterise some chosen tautomers of 8-oxoguanine. Miaskiewicz et al. [17,18] studied the thymine glycol and 5,6-dihydro-thymine conformations by means of ab initio calculations. Recently, Cysewski et al. have studied tautomerism of three adenine derivatives [19,20] and fapy-guanine on ab initio Hartree–Fock level [21].

This paper deals with hydroxyl radical modified adenine at C_8-position. The aim of this work is to characterise the tautomeric properties of 8-oxo-adenine (8-oxo-A) and 8-oxo-2′-deoxyadenine (8-oxo-dA) in non-polar and polar environments and its ability of pairs formation with standard DNA bases. To the authors best knowledge, this is the first theoretical study of C_8 hydroxyl radical modified adenine and 2′-deoxyadenosine.

2. Calculations

In this study the semiempirical PM3 quantum chemistry calculations were performed as the initial step for finding optimal geometry of 8-oxo-A, 8-oxo-dA and pairs of two most stable tautomers of 8-oxo-A with canonical DNA bases. The MOPAC 6.0 [22] program was used across all optimisations. The modified adenine and adenosine were additionally studied on more sophisticated quantum chemistry levels. The full gradient geometry optimisations were performed by means of 3-21G, 6-31G and 6-31G** SCF ab initio method. No geometry restrictions were imposed during the minimisation process. Additionally, the post Hartree–Fock procedure was applied for finding the electron correlation contribution to the total energy of most stable tautomers. The resulting 6-31G** geometry of studied species were then used for single point energy calculation via post-SCF MP2 technique. All SCF calculations were performed on the basis of Hondo package [23]. The same tautomers were also studied by a relatively new method, which based on the density functional theory (DFT) approach [24]. For the density calculations the Dmol program supported by BioSym molecular modelling package was applied. The simplest Janak–Moruzzi–Williams [23] algorithm of local correlation function was used. The molecular orbital basis function expansion was controlled by keyword mesh = fine for the numerical integration process. The gradient criterion was set to 0.0005. The resulting basis set has the quality comparable to 6-31G* basis set in the traditional SCF approach.

Besides, the solvent effect was estimated on the basis of self-consistent reaction field facility. The full geometry optimisation of studied tautomer were performed in the presence of the solvent field. Four distinct solvent were chosen: water, methanol, acetone and cyclohexane. They are characterised by the following values of the dielectric constant: 78.54, 32.63, 20.70, 2.02, respectively. Thus the broad range of solution polarities were considered. This step was performed on the basis of the Dmol program [25].

Table 1
The results of gradient geometry optimisation of all possible H_9 tautomers of 8-oxo-adenine. The relative heat of formation (PM3 method), total and binding energies (DFT method) were presented as the difference between actual value and one corresponding to the most stable tautomer (A3). The reference level is characterised by the following values: heat of formation $H^f = 0.5033$ kcal mol^{-1}, total energy $E^{DFT} = -538.3676$ Ha and binding energy $E^{bind} = -3.413$ Ha

Code	Symbol	H^f (kcal mol^{-1})	E^{DFT} (kcal mol^{-1})	E^{bind} (kcal mol^{-1})
A1	Ia	10.6	9.2	9.4
A2	Ib	16.2	15.4	15.7
A3	II	0.0	0.0	0.0
A4	IIIa1α	21.5	20.7	20.7
A5	IIIb1α	27.5	26.4	26.4
A6	IIIa2α	27.5	26.4	26.4
A7	IIIb2α	34.2	33.7	33.9
A8	IIIa1β	30.9	40.3	40.8
A9	IIIb1β	37.2	47.6	47.7
A10	IIIa2β	30.6	40.0	40.2
A11	IIIb2β	37.41	48.1	48.3
A12	IV1α	13.8	11.4	11.9
A13	IV2α	16.2	12.0	12.6
A14	IV1β2	1.9	28.8	28.9
A15	IV2β	17.6	22.8	23.2

3. Results and discussions

3.1. The tautomerism of 8-oxo-adenine

All possible H_9 tautomers of 8-oxo-A are schematically presented in the Fig. 1. The four groups of structures correspond to different classes of tautomers: I—enol-amino; II—keto-amino; III—enol-imino; and IV—keto-imino. Additionally, the rotation of side groups was taken into account. Thus, there are 15 potential tautomeric forms of 8-oxo-A to be considered. All of them were optimised by PM3 semiempirical quantum chemistry approximation and DFT method. The resulting energies are presented in the Table 1. Additionally, the geometry of three most stable tautomers was the subject of SCF ab initio quantum chemistry calculations. The results of the full geometry optimisation in 6-31G and 6-31G** basis sets and single point electron correlation calculations in the MP2 (6-31G**) formalism are collected in the Table 2. The presented data allow to conclude that the most stable tautomer is keto-amino form of 8-oxo-A. Such an observation is common both for all ab initio and semiempirical calculations. However there are slight differences in the stabilisation energies estimated by DFT and SCT methods. The HF energy differences between the tautomers are larger then those obtained by DFT and PM3 methods. The source of this discrepancy is mainly due to the differences in the basis set expansion used during the SCF procedure. The next tautomer A1 (8-hydroxy-6-amino-adenine) is destabilised by about 10 kcal mol^{-1}. The overall succession of the studied groups of tautomers is the following: I (keto-amino) $>$ II (enol-amino) $>$ IV (keto-imino) $\gg$ III (enol-imino).

Table 2
The ab initio SCF results of gradient geometry optimisation of three most stable 8-oxo-adenine tautomers. The energies are expressed in atomic units

Code	$E^{6\text{-}31G}$ (Ha)	$E^{6\text{-}31G**}$ (Ha)	E^{correl} (Ha)	E^{total} (Ha)
A1	−539.1134	−539.3973	−1.6342	−541.0315
A3	−539.1501	−539.4230	−1.6330	−541.0560
A12	−539.0717	−539.3583	−1.6375	−540.9958

Table 3
The results of gradient geometry optimisation in the presence of the solvent by the DFT method. (ε stands for the solvent dielectric constant)

Solvent	Code	E^{DFT} (Ha)	E^{bind} (Ha)
Water (ε = 78.54)	A1	−538.3881	−3.4332
	A3	−538.4081	−3.4532
	A12	−538.3933	−3.4384
Methanol (ε = 32.63)	A1	−538.3870	−3.4321
	A3	−538.4068	−3.4518
	A12	−538.3919	−3.4369
Acetone (ε = 20.7)	A1	−538.3859	−3.4310
	A3	−538.4054	−3.4505
	A12	−538.3904	−3.4355
Cyclohexane (ε = 2.02)	A1	−538.3661	−3.4112
	A3	−538.3821	−3.4271
	A12	−538.3651	−3.4102

The solvent effect may play an important role in the reactions and chemical equilibria. Especially the tautomerisation process may be sensitive to the polarity of the environment [26]. In order to estimate such an effect on the tautomeric properties of 8-oxo-A, the geometry optimisation of three most favourable tautomers was performed in the presence of different solvents. The results which were collected in the Table 3 and additionally in the Fig. 2 lead to the conclusion that the polarity of the solvent has not very

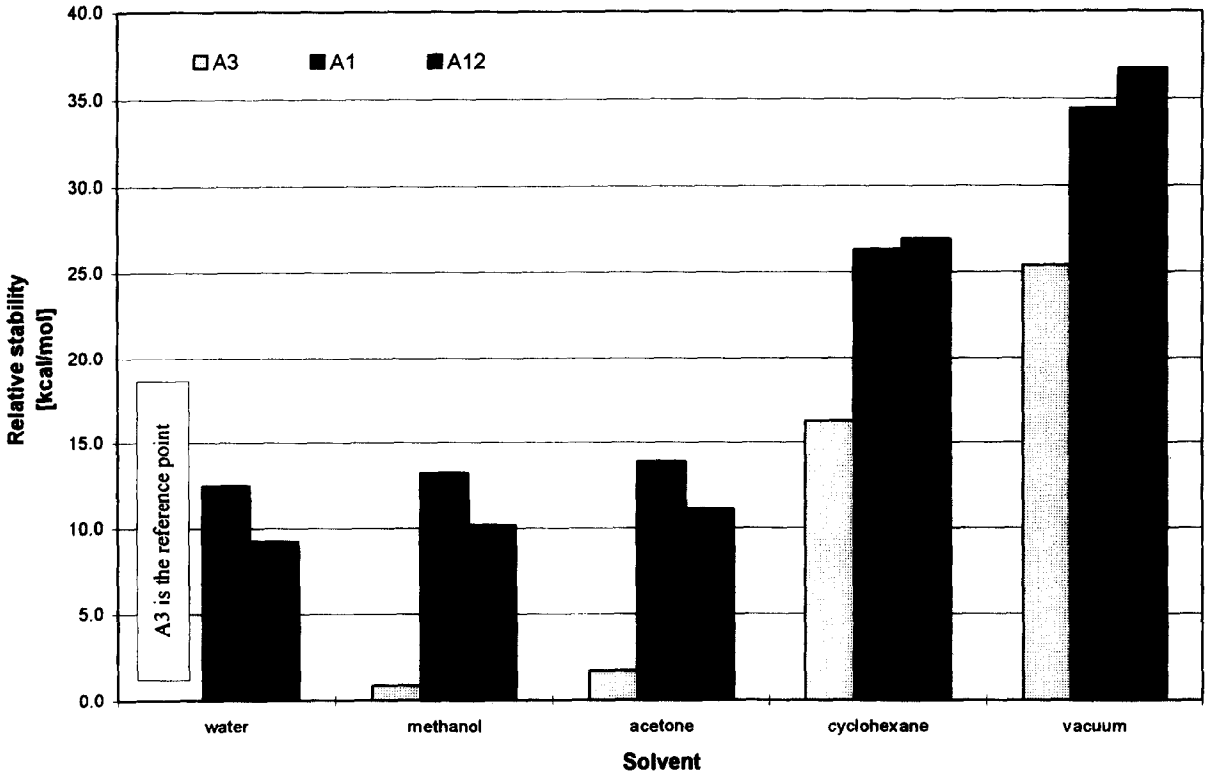

Fig. 2. The relative stability of 8-oxo-adenine tautomers estimated on the basis of DFT calculations. The bars correspond to the difference in the total energy of each of three most stable tautomers and energy of most stable isomer (A3) in water.

Table 4
The tautomerism of 8-oxo-2′-deoxyadenosine in syn and anti conformations estimated by PM3 semiempirical method. The values of the relative heat of formation were calculated with respect of the heat of formation of most stable tautomer dA3 declared as the reference point (H^f = (dA3) = − 129.742 kcal mol^{-1})

Code	Symbol	Anti conformers	Syn conformers
		H^f (kcal mol^{-1})	H^f (kcal mol^{-1})
dA1	Ia	12.4	10.9
dA2	Ib	15.7	15.0
dA3	II	0.0	1.4
dA4	IIIa1α	23.4	22.5
dA5	IIIb1α	27.7	26.9
dA6	IIIa2α	29.3	28.8
db7	IIIb2α	34.2	33.8
dA8	IIIa1β	32.6	33.9
dA9	IIIb1β	36.7	39.1
dA10	IIIa2β	32.3	33.6
dA11	IIIb2β	36.8	38.1
dA12	IV1α	13.4	14.0
dA13	IV2α	15.6	16.8
dA14	IV1β	22.0	24.9
dA15	IV2β	17.5	20.1

high influence on the tautomers stability. The most stable tautomer is 8-keto-one in all studied solutions. The Fig. 2 presents the relative energy for studied systems. The reference point was defined by the energy of tautomer A3 in water. The increase of the polarity of the solvent generally increases the relative stability of tautomers. However, in the case of structures A1 and A12 the relative stability depends on the polarity of the solvent. In the polar environment tautomer A1 proceeds the A12 one. In the non-polar solvent the reverse of stability is observed.

Thus, the 8-oxo-A is best represented as the 8-keto-6-amino tautomer in vaccum and solutions, what is in agreement with similar observations made in the solid state [27] and in solutions [28].

Table 5
The results of DFT gradient geometry optimisation of three most stable tautomers of 8-oxo-adenosine in syn and anti conformations in gas and water states

8-Oxo-dA	Anti conformer's			Syn conformers		
	dA01	dA03	dA12	dA01	dA03	dA12
Vacuum						
E^{DFT} (Ha)	−956.1523	−956.1864	−956.1698	−956.1760	−956.1899	−956.1706
H-bond[a]		1.73	1.67	1.69	1.69	1.74
H-angle[b]		165.54	170.33	175.06	175.31	172.11
N-glyc[c]	−52.11	−52.26	−58.32	125.72	118.13	125.40
Water						
E^{DFT} (Ha)	−956.2059	−956.2406	−956.2263	−956.2229	−956.2437	−956.2283
H-bond[a]		1.62	1.61	1.64	1.64	1.66
H-angle[b]		166.93	167.96	174.07	174.10	173.53
N-glyc[c]	−50.25	−55.83	−58.61	127.96	121.39	123.30

[a] Internal hydrogen bond length (in angstroms): for anti conformation: O_8–H_5', for syn conformation N_3–H_5'.
[b] Internal hydrogen bond angle (in degrees):for anti conformation: O_8–H_5'–O_5' for syn conformation N_3–H_5'–O_5'.
[c] N-Glycosidic torsion angle (in degrees): C_8–N_9–C_1'–C_2'.

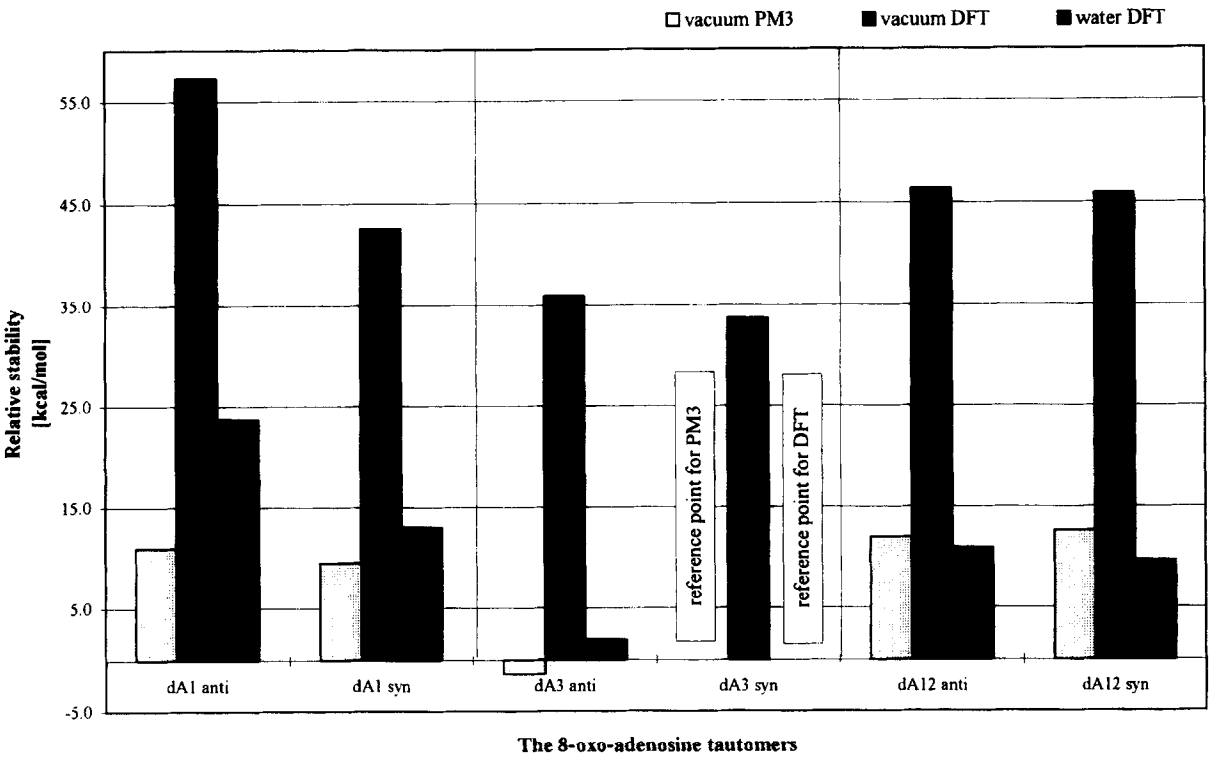

Fig. 3. The relative stability of 8-oxo-2′-deoxyadenosine in syn and anti conformations. The syn conformation of keto-tautomer dA3 in water was chosen as the reference point for DFT calculations. The PM3 result were presented with respect of the same tautomer but in the vacuum state.

3.2. The tautomerism of 8-oxo-2′-deoxyadenosine

The influence of the sugar backbone on the tautomerism of 8-oxo-A was the next subject of our interest. All tautomers of 8-oxo-dA were optimised by means of the PM3 approximation both in syn and anti conformations and additionally three most stable structures were minimised by DFT method. The resulting energies and some chosen geometric parameters were collected in the Table 4 and Table 5.

Additionally, the relative stability of three most favourable 8-oxo-dA tautomers were presented in the Fig. 3. The introduction of the sugar moiety into the 8-oxo-A molecule does not change the relative stability of the tautomers which is the same as for isolated 8-oxo-A. The preferred N-glycoside torsion angle corresponds to syn rotamer in all studied cases. However, the PM3 method predicted reversed order of syn and anti rotamers for dA3 tautomer. In the light of the available detailed NMR studies [28,29] one should consider the DFT results as more realistic. It is interesting to mention that both syn and anti rotamers are potentially able to form the internal hydrogen bond. The enol tautomers may be stabilised by only N_3–H_5' bond in syn conformation while keto tautomers can form additionally O_8–H_5 bond in anti conformation. The more detailed hydrogen bond characteristics are presented in the Table 5. The vales of all internal hydrogen bond lengths are about 1.7 for structures optimised in the vacuum. However, in water solutions they are significantly shortened. The N-glycoside bond dihedral angle is also solvent dependent but the correlation is not univocal.

3.3. The mispairing properties of 8-oxo-adenine

It is well known that standard adenine and thymine may form pair stabilised by two hydrogen bonds. On the other hand it one may expect that any modification introduced to the one of the component may reflect in the stability of the dimer. Thus, the hydroxyl radical modified nucleic acid bases may have promutagenic

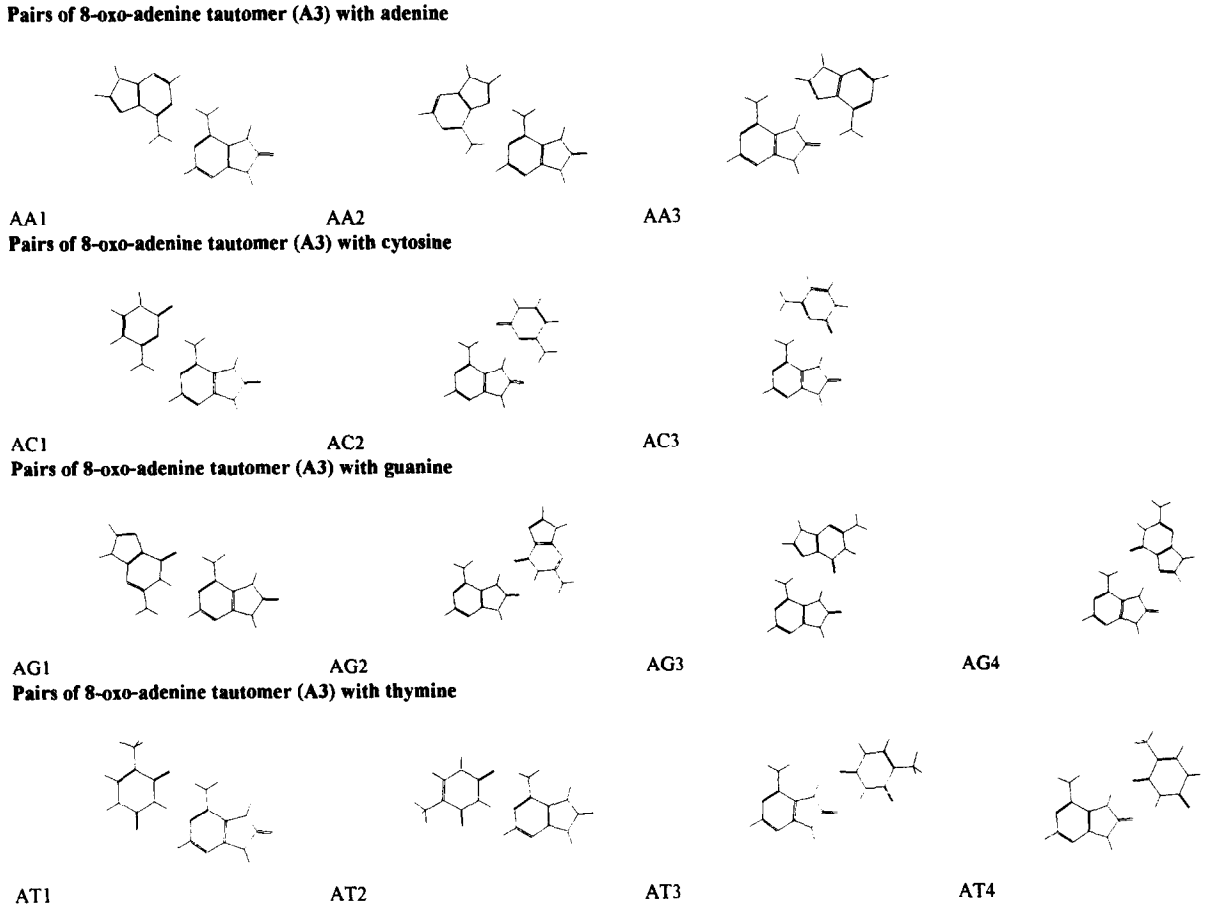

Fig. 4. The schematic representation of possible pairs of most stable tautomer (A3) of 8-oxo-A with standard nucleic acid bases. Pairs were prepared by the docking of the 8-oxo-A to adenine, cytosine, thymine or guanine and optimised by means of PM3 method. The dimers were stabilised by Watson–Crick-like or Hogsteen-like bonds.

properties. The 8-oxo-adenine was found to possess some miscoding properties [30–32]. If formed in vivo this derivative may be responsible for A → G transition. It is interesting that such a substitution was observed by Ohtsuka group [30] in c-Ha-ras genes containing 8-oxo-adenine. They have also detected A → C transversion. Shibutani et al. [31] reported that dTMP and dGMP is incorporated opposite 8-oxo-dA when they are provided as the substrate for DNA polymerase. Wood et al. [32] found that oxidising of adenine at C8 position results in the G → T transversion. However, 8-oxo-A is an order less mutagenic than 8-oxo-guanine.

The following section aimed to characterise the pairing potential of 8-oxo-A. The dimers formed by one of two most stable tautomers of 8-oxo-A and standard DNA base were then constructed and optimised on the basis of PM3 method. The studied structures are presented in Fig. 4 and Fig. 5. All pairs may be stabilised by only two intermolecular hydrogen bonds. The structures were prepared by the docking of 8-oxo-A to each of standard DNA bases and PM3 geometry optimisation. The pairs of interests were stabilised by Watson–Crick-like or Hogsteen-like hydrogen bonds. The mispairing potential of two most stable tautoerms of 8-oxo-A were considered. The results of the geometry optimisations are summarised in Table 6 and Table 7 for 8-oxo-A and 8-hydroxy-A dimers, respectively. Besides, the relative stability are presented in Fig. 6 and Fig. 7. The

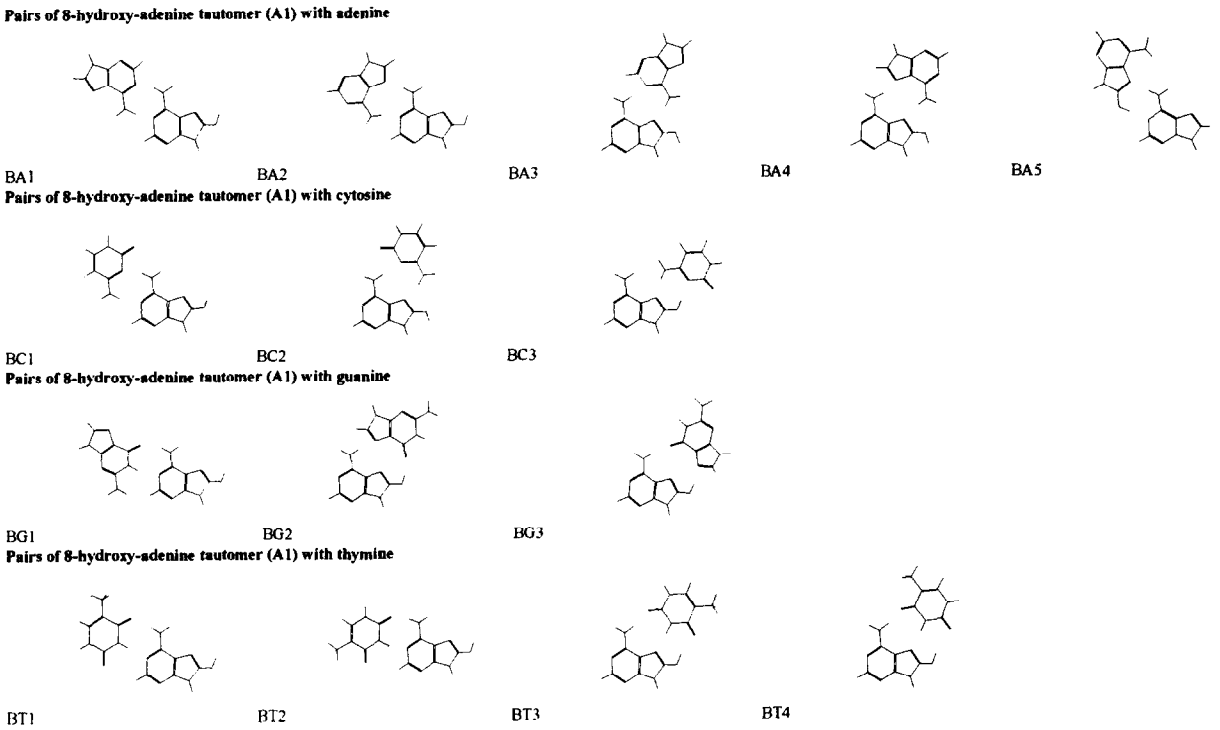

Fig. 5. The possible pairs of second stable tautomer of 8-oxo-A (A1) with standard nucleic acid bases.

8-oxo-A in both tautomeric isomers may form pairs which are more stable than standard AT pair. It is interesting to see that the destabilisation of tautomer A1 is compensated by the intermolecular interaction and final pairs may be as stable as those containing tautomer A3. The general pairing potential of C8-modified adenine is as follows: the most stable pairs are formed with cytosine, than thymine and guanine. The most stabile dimers are those having hydrogen bond with O_8 oxygen or H_{O8} hydrogen atom. This is true not only for pairs with cytosine (pairs AC2 and BC3, which are the most stable over all studied here), but also for all other nucleic acid bases. However, in the DNA strand such pairs will be probably forbidden due to the steric interaction. Thus, the Watson–Crick like pairs should be analysed despite their weaker stability. The most favourable pairs of this type is BC1, which has almost the same value of the stabilisation energy as AC1 pair. They are followed by BG1 dimer, which is more stable than AG1 one. The pairs with thymine are slightly less stable than standard AT pairs. Finally, adenine does not form the pairs with modified adenine. The presented results allow to

Table 6
Results of the semiempirical PM3 optimisation of pairs formed by the most stable tautomer of 8-oxo-adenine (A3) with standard nucleic acid bases. The heat of formation of adenine–thymine Watson–Crick pair is equal to −5.70 kcal mol^{-1}. The dimers more stable than A–T one are marked with bold text

Pair	H_f (kcal mol^{-1})	ΔH_f (kcal mol^{-1})
AA1	52.0	−3.5[a]
AA2	52.5	−3.0
AA3	50.3	−5.1
AC1	−20.2	**−7.4**[a]
AC2	−23.8	**−11.0**
AC3	−19.4	**−6.7**
AG1	0.8	**−6.1**[a]
AG2	0.8	**−8.6**
AG3	2.6	−4.2
AG4	0.2	**−6.7**
AT1	−82.3	−5.3[a]
AT2	−82.4	−5.4
AT3	−82.2	−5.2
AT4	−82.1	−5.1

[a]Watson–Crick dimer analogues.

Table 7
Results of the semiempirical PM3 optimisation of pairs formed by the second stable tautomer of 8-hydroxy-adenine (A1) with standard nucleic acid bases. The notation as for Table 6

Pair	H_f (kcal mol^{-1})	H_f (kcal mol^{-1})
BA1	62.1	−3.8
BA2	62.6	−3.5
BA3	66.6	0.5
BA4	63.6	−2.5
BA5	57.3	**−8.8**
BC1	−9.7	**−7.6**[a]
BC2	−8.4	**−6.2**
BC3	−13.9	**−11.8**
BG1	10.15	**−6.9**[a]
BG2	7.6	**−9.9**
BG3	10.0	**−7.5**
BT1	−71.9	−5.5[a]
BT2	−72.0	−5.7
BT3	−76.9	**−10.6**
BT4	−77.1	**−10.7**

conclude that the occurrence of the 8-oxo-adenine both in the enol and keto tautomeric form may lead to miscoding properties mainly due to the pair formation with cytosine and guanine. This in turn may be lead to AT ⇒ CG transversions or AT ⇒ GC transitions. These results are in interesting agreement with experimental observations [30–32].

4. Conclusion

The results of the geometry optimisation of different tautomers of 8-oxo-A in vacuum lead to the conclusion that the best representation of this adenine derivative is 8-keto-6-amino tautomer. This is in accord to NMR observations in the solid and solution states [28,29].

The question about the stability of tautomeric form is crucial when the mispairing properties of non-standard

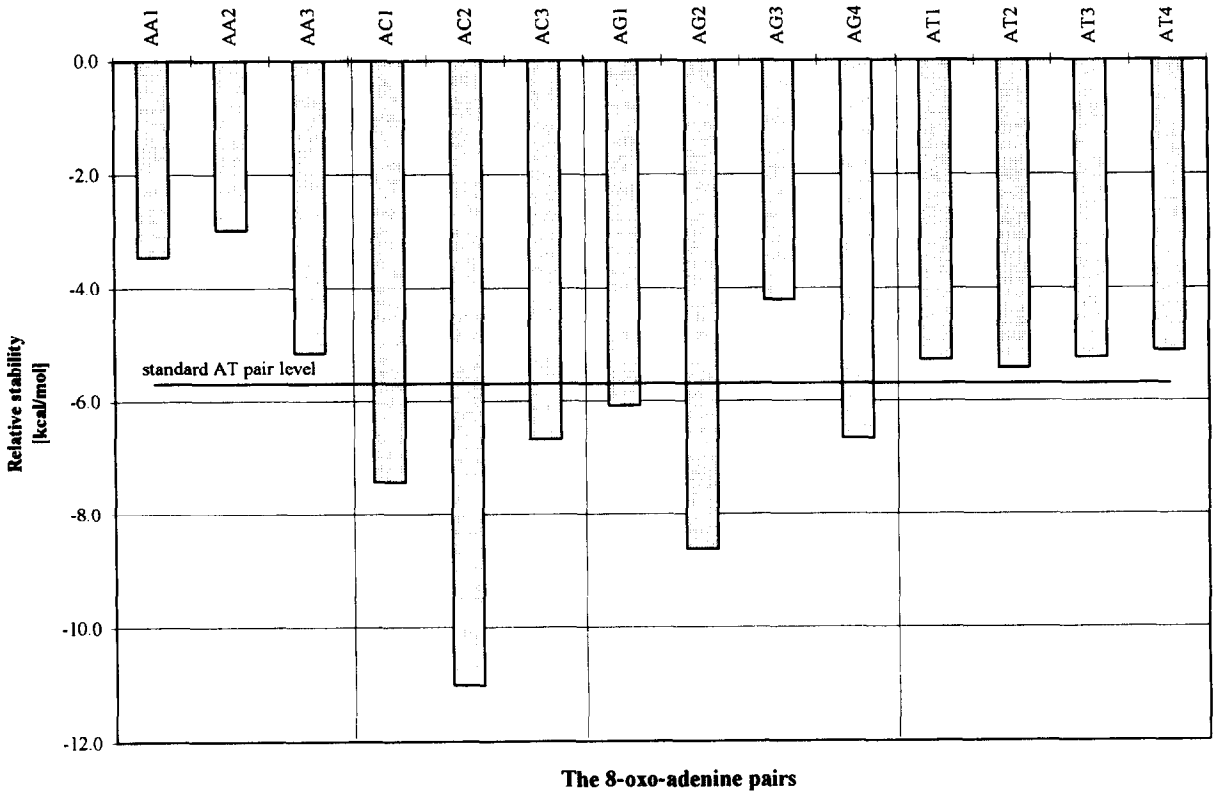

Fig. 6. The stability of studied pairs of A3 tautomer with standard DNA bases. The bars correspond to the difference in heat of formation between pair and isolated components.

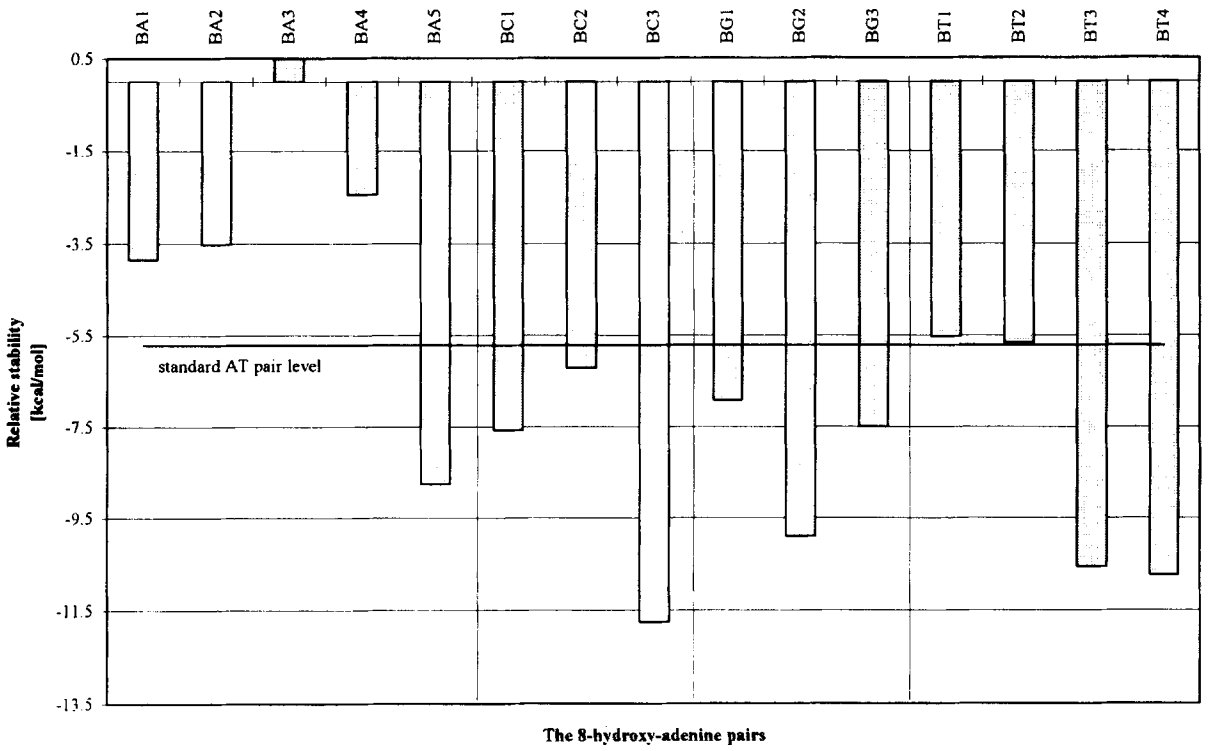

Fig. 7. The stability of studied pairs of A1 tautomer with standard DNA bases. The bars correspond to the difference in heat of formation between pair and isolated components.

nucleic acid bases are considered. The formation of the stable dimers between canonical and odd nucleic acid bases is strongly related to the hydrogen bonds formations. This in turn pertain significantly on the tautomer form. The problem is complicated by the fact that the polarity of the environmental may exchange the tautomers relative stability. However, as it was presented above, this is not the case for C8 hydroxyl radical modified adenine due to the stability of only one form both in polar and non-polar environment. The C_8 modified adenosine has the same tautomeric properties as 8-oxo-A. Our study suggests that the syn conformation is preferred one what is in good accord to NMR studies in water [29].

The 8-oxo-A is able to form stable pairs both in keto and enol forms. The appearance of the O_8 oxygen atom modifies significantly the electrostatic properties and intermolecular interaction potential. It results in formation of the most stable pairs with cytosine and guanine. The most interesting however, are pairs which may potentially exist within the DNA double helix. This must involve Watson–Crick side of the 8-oxo-A. Although there is not direct modification at this side the 8-oxo-A exhibits significant changes in the pairing with standard nucleic acid bases. The keto and enol tautomer form more stable pairs with cytosine and guanine than with the standard thymine. This may be the reason of the observed T ⇒ C transition and T ⇒ G transversion [30–32].

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References

[1] H. Kasai and S. Nishimura, Nucleic Acid Res., 12 (1984) 2137.

[2] R. Oliński, T. Zastawny, J. Budzbon, J. Skokowski, W. Zegarski and M. Dizdaroglu, FEBS Lett., 309 (1992) 193.

[3] H. Kamiya, T. Ueda, T. Ohgi, A. Matsukage and H. Kasai, Nucleic Acid Res., 5 (1995) 761.

[4] A. Bonicel, N. Mariaggi, E. Hughes and R. Teoule, Radiat. Res., 83 (1980) 19.

[5] E. Gajewski, G. Rao, Z. Nackerdien and M. Dizdaroglu, Biochemistry, 29 (1990) 7876.

[6] O.I. Arouma, B. Halliwell and M. Dizdaroglu, J. Biol. Chem., 264 (1989) 13024.

[7] H. Kamiya, T. Ueda, T. Ohgi, A. Matsukage and H. Kasai, Nucleic Acid Res., 5 (1995) 761.

[8] H. Kamiya, T. Sakaguchi, N. Murata, M. Fujimoro, H. Miura, H. Ishikawa, M. Shimizu, H. Inue, S. Nishimura, A. Matsukage, C. Masutani, F. Hanaoka and E. Ohtsuka, Chem. Pharm. Bull., 40 (1992) 2792.

[9] M.L. Wood, M. Dizdaroglu, E. Gajewski and J.M. Essigmann, Biochemistry, 29 (1990) 7024.

[10] S. Shibutani, V. Bodepudi, F. Johnson and A.P. Groliman, Biochemistry, 32 (1993) 4615.

[11] S. Shibutani, M. Takeshita and A.P. Grollman, Nature, 349 (1991) 431.

[12] M. Moriya, Proc. Natl. Acad. Sci. USA, 90 (1993) 1122.

[13] J.S. Kwiatkowski, R.J. Barlett and W.B. Person, J. Am. Chem. Soc., 110 (1988) 2353.

[14] J. Leszczynski, J. Phys. Chem., 96 (1992) 1649.

[15] A. Les and L. Adamowicz, J. Phys. Chem., 93 (1989) 7078; ibid., 94 (1990) 7021.

[16] M. Aida and S. Nishimura, Mutat. Res., 192 (1987) 83.

[17] K. Miaskiewicz, J. Miller and R. Osman, Int. J. Radiat. Biol., 63 (1993) 677.

[18] K. Miaskiewicz, J. Miller, R. Orstein and R. Osman, Biopolymers, 36 (1994) 113.

[19] P. Cysewski, C. Vidal-Madjar, V. Noinville and R. Oliński, Bull. Soc. Chim. Fr., 132 (1995) 453.

[20] P. Cysewski, D. Jeziorek, R. Oliński and W. Woznicki, J. Phys. Chem., 99 (1995) 9702.

[21] P. Cysewski, D. Jeziorek and R. Oliński, J. Mol. Struct. Theochem, (1996) in press.

[22] J.J.P. Stewart, MOPAC 6.0, QCPE program 455.

[23] D.A. Erstrin, G. Corongiu and E. Clementi, in E. Clementi (Ed.), MOTECC 94, Methods and Techniques in Computational Chemistry, Vol. B, Sted, Caliari, 1993.

[24] R.G. Parr and W. Yang, Density-Functional Theory of Atoms and Molecules, Oxford University Press, Oxford, 1965.

[25] Discover User Guide, version 2.3.0., San Diego, Biosym Technologies, San Diego, 1992.

[26] J. Sepiol, Z. Kazimierczuk and D.Z. Shugar, Naturforsch., 31c (1976) 361.

[27] H. Guy, Helv. Chim. Acta, 71 (1988) 1566.

[28] B.P. Cho and F.E. Evans, Nucleic Acid Res., 19 (1991) 1041.

[29] I.I. Uesugi and A. Okehara, J. Am. Chem. Soc., 99 (1977) 3250.

[30] H. Kamiya, H. Miura, N. Murata-Kamiya, H. Ishikawa, T. Sakaguchi, H. Inue, T. Sasaki, C. Masutani, F. Hanaoka, S. Nishimura and E. Ohtsuka, Nucleic Acid Res., 23 (1995) 2893.

[31] S. Shibutani, V. Bodepudi, F. Jahnson and A.P. Grollman, Biochemistry, 17 (1993) 4615.

[32] M.L. Wood, A. Esteve, M.L. Morningstar, G.M. Kuziemko and J.M. Essigmann, Nucleic Acid Res., 20 (1992) 6023.