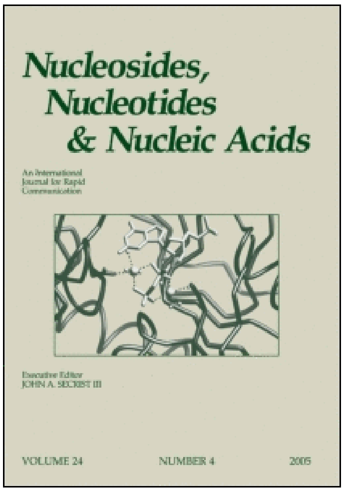

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Investigations of Some Nucleic Acid Component Analogs

Yuri Rubin[a]; Jerzy Leszczynski[b]
[a] Institute for Low Temperature Physics & Engineering, Kharkov, Ukraine [b] Jackson State University, Jackson, MS, USA

To cite this Article Rubin, Yuri and Leszczynski, Jerzy(1999) 'Investigations of Some Nucleic Acid Component Analogs', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 1119 — 1122
To link to this Article: DOI: 10.1080/15257779908041664
URL: http://dx.doi.org/10.1080/15257779908041664

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 1119–1122 (1999)

INVESTIGATIONS OF SOME NUCLEIC ACID COMPONENT ANALOGS.

Yuri Rubin *,
Institute for Low Temperature Physics & Engineering, Kharkov, 310164, Ukraine,
Jerzy Leszczynski
Jackson State University, P.O. Box 17910, Jackson, MS 39217, USA

ABSTRACT. *Ab initio* calculations of some nucleic acid bases analogs - 6 thioguanine, 4-thiouracil, 5- and 6-azacytosines, 6-azauracil, 5- and 6-fluorouraciles and 5azaC+Gua dimer had performed. 6-Thioguanine and 4-thiouracil were studied by experimental methods also. Total energies, geometries, charge distributions, entropies, heat capacities, vibrational spectra and solvent effects using high level *ab initio* methods were calculated.

It is known that many of nucleic asid component analogs have antitumour, antiviral and immunosuppressive properties[1] . 5-Fluorouracil and 6-thioguanine and their derivatives are parts of well known antitumour drugs , 5-azacytosine is part of new antitumour drug - Fazarabine [2] and so one.

For investigation of molecular action mechanism we performed *ab initio* calculations of some nucleic acid bases analogs - 6 thioguanine (6TU), 4-thiouracil(4TU) , 5- and 6-azacytosines (5azaC and 6azaC), 6-azauracil (6azaU), 5- and 6-fluorouraciles (5FU, 6FU). 6-Thioguanine and 4-thiouracil and their substituted, which modeled it tautomers were studied by experimental (UV absorption, luminescence and Circular Dichroism) methods also.

We performed calculations of such physico-chemical properties: total energies, geometries, charge distributions, entropies, heat capacities, vibrational spectra and solvent effects using high level *ab initio* at the second and fourth order (MP2 and MP4 (SDQ) levels of correlated Moller-Plesset theory). We used basis sets from 6-31G* to 6-311**G++. These calculations were performed on supercomputes with 4 Gb memory and 40 Gb disk space using Gaussian 92 and Gaussian 94 softwares [3] . We also performed the calculation of 5azaC+Gua dimer .The energies of excited states, dipole moments, charge distributions and bond orders in ground states and their changes in excited states were calculated using CNDO/S methods. *Ab initio* opimised geometries of investigated molecules were used for these calculations.

The investigation of different 6TG tautomer forms showed that, although in gas phase the N9H-SH(trans) tautomer is more stable[4], in water solution and DNA 6TG exists as the N9H thion tautomer. Decrease of solvent polarity shifts tautomeric equilibria to N7H tautomer.Ethanol 6TU solution consists approximately 40% of N7H tautomer and 60% of N9H tautomer In gas phase a row stability of 6TG has a view: N9H-SH> N7H> N9H>N7H-SH [5] .

Investigations of total energies and electronic spectra of 4TU tautomer and ionic forms showed existense of two 4TU tautomers in polar solvents. Row stability of 4TU in polar solvent has a view: 4TU keto-thion> 4TU enol-1 > 4TU thiol-1 > 4TU thiol-enol > 4TU enol-2 >4TU thiol-2 [6] . Probably second 4TU tautomer is formed in excited state[7] . *Ab initio* calculations by MP2 method with 6-311 ++ G** basis sets confirmed the existence of two 4TU tautomers in alkaline media. The calculations of total energies of three 4TU anion tautomers showed that N1H tautomer is more stable by 4kcal/mol in comparison with N3H tautomer in polar solvent. Decrease of polarity of alcaline solvent increases the stability of N1H tautomer.

Computed total energies, dipole moments, entropies and heat capacities of various nucleic acid bases analogs and cytosine and uracil are shown at Tab 1. The comparison of total energies on 5azaC and 6azaC with cytosine (C) shows increase ones due by more amount of electrons in nitrogen to compare with carbon. Increase of basis sets in MP2* method give a bigger value of total energies. The including of nitrogen in pyrimidine ring leads to decrease of 5azaC and 6azaC dipole moments.5azaC and 6azaC have bigger values of entropies and heat capacities to compare with C. The analysis of charge distribution on molecules of 5azaC shows an increase of charges at 4, 5 and 6 atoms of 5azaC on 25%, 100% and 80% recpectively. Charge at the first atom on 6azaC decrease at 30%, charges at 5 and 6 atoms on 6azaC even change signs [8,9] .

The total energies of 6azaU, 5FU and 6FU are larger to compare with U (Tab.1) The substitution of the sixth carbon by nitrogen leads to decrease of 6azaU dipole moment.

TABLE 1. Ab initio computed Total Energies (E, hartree), Dipole Moments (D, Debye), Entropies (S, cal/mol K), Heat Capacities (C, cal/mol K) of various analogs on nucleic acid bases in gas phase, calculated by diverse methods: Hartree-Fock (HF) and Moller-Pleset theory (MP) with basis sets: 6-31G** - (MP2) and 6-311++G(2d,2p) - (MP2*)

	C	5azaC	6azaC	6TG (N9H)	Method
E	-393.79273	-409.82654	-409.78310	-863.62807	MP2
		-410.11309	- 410.06944	-863.84097	MP2*
D	7.12	5.26	6.36	8.64	HF
	6.40	4.60	5.83	7.42	MP2
S	77.42	78.36	80.15		
C	21.80	22.19	23.0		

	U	6azaU	5FU	6 FU	Method
E	-413.65023	-429.63768	-512.64484	-512.65791	MP2
		-429.94282		-513.04364	MP2*
D	4.72	1.82	4.19	3.29	HF
	3.92	1.65	3.64	2.85	MP2
S	77.52	77.50	81.94	81.74	
C	21.47	20.80	24.50	24.37	

Dipole moments or 5FU and 6FU are smoller than U dipole moment too. Analysis of charge distribution on 6azaU molecules shows a significant alter of charges on 1, 5 and 6 atoms. Charge at sixth atom even changes a sign [10] .Our calculations confirm the existence a large negative charge on fluorine atoms of 5FU and 6FU.

Energy interaction of H-bonded pair Gua+5azaC is decreased approximately on 4 kcal/mol in comparison with one of pair Gua+C[11]. Geometry, charges and frequencies alter on fragments N1-C2-N3-C4-N8-H9 and C2=O7 of 5azaC, when it forms H-bonds with Gua.

REFERENCES

1. Harmon R.E.; Robins R. K.; Townsend L.B. (eds.) Chemistry and Biology of Nucleosides and Nucleotides, Academic Press, New York, 1978

2. Wallace R.E.; Lindh D.; Durr F.E. *Proc. Amer. Assoc.Cancer Res.* 1987,**28**,307-315

3. Gaussian 94, Revision E.1, Frisch M.J.; Trucks G.W.; Schlegel H.B.; Gill P.M.W.; Johnson B.G.; Robb M.A.; Cheeseman J.R.; Keith T.; Petersson G.A.; Montgomery J.A.; Raghavachari K.; Al-Laham M.A.; Zakrewski V.G.; Ortiz J.V.; Foresman J.B.; Cioslowski J.; Stefanov B.B.; Nanayakkara A.; Challacombe M.; Peng C.Y.; Ayala P.Y.; ChenW.; Wong M.W.; Andres J.L.; Replogle E.S.; Gomperts R.; Martin R.L.; Fox D.J.; Binkley J.S.; Defrees D.J.; Baker J.; Stewart J.P.; Heard-Gordon M.; Gonzalez C.; and Pople J.A.; Gaussian, Inc., Pittsburgh PA, 1995.

4. Szczepaniak K.; Person W.B.; Leszczynski J.; Kwiatkowski J. *Adv. Biochem.* 1995,**41**,1995-2003

5. Stewart M.; Leszczynski J.; Rubin Yu. V.; Blagoi Yu.P.; *J. Phys.Chem* 1997, **101**, .4753-4760

6. Rubin Yu. V.; Morozov Yu V.; Venkateswarlu D.; Leszczynski J. *J. Phys Chem* 1998, **102**, 2194-2201

7. Rubin Yu.V.; Savin F.A.; Blagoi Yu.P. *Studia biophys.* 1988, **123** ,205-215

8. Rubin Yu. V. *Vestnik problem biologi i medicini,* 1998, **4**, 151-156 (in Russian)

9. Rubin Yu. V. *Vestnik problem biologi i medicini,* 1998, **16** (in press)

10. Rubin Yu.V . *Vestnik problem biologi i medicini,* 1998, **16** (in press)

11. Sponer J.; Leszczynski J.; Hobza P. *J. Phys. Chem.* 1996, **100**, 1965-1974