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Theoretical Survey on Tautomerism of Thioguanine Tautomers by Polarisable Continuum Method (PCM)

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ABSTRACT

Computational calculations at B3LYP/CC-PVDZ level were employed in the study of tautomers of Thioguanine (TG) in the gas phase and selected solvents such as benzene , tetrahydrofuran (THF), methanol, Dimethyl sulfoxide (*DMSO*) and water using PCM model. All tautomers are optimized at this level. In addition, stability of the tautomers in different solvents shows interesting results. In the gas phase, benzene and THF, TG1 form is more stable than the other forms but in polarisable solvents (methanol, DMSO and water) TG5 is the most stabilized form. Variation of dipole moments and NBO charges on atoms in the solvents were studied.

Key words: NBO charge, PCM model, Thioguanine, Tautomerism.

INTRODUCTION

6-Thioguanine (SG) is a known anti-cancer agent that is readily incorporated in place of guanine during DNA replication. The incorporation of SG nucleotides into DNA and RNA by polymerases can lead to cell death. The replacement of oxygen by sulfur at the O6 position of guanine has been proposed to hinder hydrogen bonding necessary for normal G-tetrad formation and could lead to changes in telomere stability. Adenine-based purines, such as adenosine and ATP, are ubiquitous molecules that exert several biological roles. In particular, they may act as neurotransmitter/regulatory agents acting via interaction with membrane receptors, belonging to the superfamily of P1 and P2 purinoreceptors with high affinity for adenosine and ATP, respectively. However, guanine-based purines can also be considered part of the purinergic system and they are released from neurons and/or glia both under basal conditions and after various types of stimulation, including stress conditions[1-3]. Thus, although traditionally guaninebased purines have been studied as modulators of intracellular processes, they can exert extracellular effects not related to their direct modulation of G proteins, including modulation of the glutamatergic activity[4-13], behavioural effects[14,15], and trophic effects on neural cells[16]. Some of the actions of the guanosine may be mediated intracellularly after its uptake, even if many trophic effects of guanine-

based purines are not substantially affected by the nucleoside uptake inhibitors indicating that they are independent of intracellular mechanisms[17]. Guanosine also stimulates the release of adeninebased purines from astrocytes, which, in turn, may be responsible for some other effects of guanosine[18]. However, many of the effects of guanine-based purines persist in the presence of P1 and/or P2 purinoreceptor antagonists[17]. In addition, several of the effects of guanosine may be mediated through G protein-dependent signalling pathways involving cyclic nucleotides or MAP kinase pathway[19], and a specific binding site for guanosine has been detected on membrane preparations from rat brain[20,21]. Thus, the possibility of the existence of distinct receptors for guaninebased purines has been raised.

Computational methods

All these calculations were carried out on a core i7 personal computer by means of GAUSSIAN09 program package. First, all the compounds structures were drawn using Gauss View 03 and optimized in GAUSSIAN09. The tautomers were also optimized in solvents according to the polarisable continuum method of Tomasi and co-workers, which exploits the generating polyhedra procedure[22-26] to build the cavity in the polarisable continuum medium, where the solute is accommodated. Atomic charges in all the structures were obtained using the Natural Population Analysis (NPA) method within the Natural Bond Orbital (NBO) approach[27].

RESULTS AND DISCUSSION

Gas phase

Structures and numbering of Thioguanine are depicted in Figure 1 and the results of energy comparisons of five tautomers in the gas phase and different solvents are given in Table 1. In the gas phase TG1 form is more stable than the other forms. The most and the least differences between TG1 and the other forms in gas phase are found for OP3 amd OP1 with 7.706 kcal mol^{-1} and 2.017 kcal mol^{-1} respectively(Table 2). The order of stability of all the tautomers in the gas phase is TG1 > TG3 > TG5> TG4> TG2. The calculated dipole moments for all forms are presented in Table 3. TG1 tautomer has the smallest dipole moments than the other forms

Table 1: Total energies[a] at B3LYP/CC-PVDZ in the gas phase and solvents

Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol(33)	DMSO(46.7)	Water(78.4)
TG1	-865.5701762	-865.5812024	-865.5881465	-865.5906873	-865.5909194	-865.5911345
TG2	-865.5578956	-865.5665682	-865.5720349	-865.5740419	-865.5742255	-865.5744396
TG3	-865.5669607	-865.5737931	-865.5779902	-865.5795129	-865.5796515	-865.5797799
TG4	-865.5656759	-865.5728722	-865.577321	-865.5789366	-865.579084	-865.5792205
TG5	-865.5659248	-865.5788965	-865.5875863	-865.5908908	-865.5919651	-865.5914803

[a]Hartree.

Table 2: Energy[a] difirrence between the tautomers of Thioguanine

Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol(33)	DMSO(46.7)	Water(78.4)
TG1	0.0000000	0.0000000	0.0000000	0.0002035	0.0010457	0.0003458
TG2	0.0122806	0.0146342	0.0161116	0.0168489	0.0177396	0.0170407
TG3	0.0032155	0.0074093	0.0101563	0.0113779	0.0123136	0.0117004
TG4	0.0045003	0.0083302	0.0108255	0.0119542	0.0128811	0.0122598
TG5	0.0042514	0.0023059	0.0005602	0.0000000	0.0000000	0.0000000

[a]Hartree.

Table 3: Calculated dipole moments of optimized tautomers of Thioguanine (Deby)

Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol(33)	DMSO(46.7)	Water(78.4)
TG1	1.8761	2.1679	2.3776	2.4603	2.468	2.4751
TG2	3.2401	3.891	4.3657	4.5573	4.5714	4.587
TG3	3.7901	4.293	4.7081	4.8709	4.8862	4.9002
TG4	3.4403	3.9404	4.2954	4.4342	4.4471	4.4592
TG5	7.4765	8.9092	9.9701	10.3946	10.4345	10.4716

Table 4: Calculated NBO charge for Thioguanine tautomers

	Atom	Gas	Benzene	THF	Methanol	DMSO	Water
TG1	C1	0.6983	0.7021	0.7057	0.7071	0.7072	0.7073
	N2	-0.5582	-0.6151	-0.6115	-0.6101	-0.6100	-0.6099
	C3	0.0206	0.0585	0.0650	0.0674	0.0676	0.0678
	C4	0.3668	0.4057	0.4063	0.4065	0.4065	0.4065
	N5	-0.5315	-0.5930	-0.6013	-0.6043	-0.6046	-0.6049
	N6	-0.4563	-0.5600	-0.5746	-0.5799	-0.5804	-0.5809
	C7	0.1824	0.2929	0.2992	0.3015	0.3017	0.3019
	N8	-0.5077	-0.5731	-0.5709	-0.5701	-0.5700	-0.5700
	C9	0.0487	0.0367	0.0359	0.0357	0.0357	0.0357
	N10	-0.8353	-0.8339	-0.8330	-0.8325	-0.8324	-0.8324
TG2	C1	0.6687	0.6654	0.6652	0.6651	0.6651	0.6651
	N2	-0.5047	-0.6056	-0.6094	-0.6108	-0.6109	-0.6110
	C3	0.0383	0.1269	0.1273	0.1274	0.1274	0.1275
	C4	0.3638	0.4218	0.4193	0.4182	0.4181	0.4180
	N5	-0.5253	-0.5897	-0.6021	-0.6069	-0.6073	-0.6077
	N6	-0.4345	-0.5640	-0.5811	-0.5874	-0.5880	-0.5886
	C7	0.1777	0.2963	0.3019	0.3039	0.3041	0.3043
	N8	-0.5153	-0.5948	-0.5901	-0.5882	-0.5881	-0.5879
	C9	0.0857	0.0172	0.0183	0.0188	0.0189	0.0189
	N10	-0.8403	-0.8239	-0.8262	-0.8271	-0.8272	-0.8272
TG3	C1	0.6772	0.6744	0.6735	0.6732	0.6731	0.6731
	N2	-0.5442	-0.6086	-0.6151	-0.6176	-0.6178	-0.6181
	C3	0.0781	0.1421	0.1399	0.1389	0.1388	0.1388
	C4	0.4079	0.4357	0.4366	0.4370	0.4370	0.4371
	N5	-0.5714	-0.6166	-0.6187	-0.6193	-0.6193	-0.6194
	N6	-0.6098	-0.6117	-0.6087	-0.6075	-0.6074	-0.6073
	C7	0.1558	0.2719	0.2780	0.2805	0.2807	0.2809
	N8	-0.3123	-0.5469	-0.5574	-0.5612	-0.5616	-0.5619
	C9	-0.0599	0.0010	-0.0003	-0.0008	-0.0008	-0.0008
	N10	-0.8405	-0.8182	-0.8199	-0.8205	-0.8205	-0.8206
TG4	C1	0.6791	0.6747	0.6742	0.6739	0.6739	0.6739
	N2	-0.5500	-0.6174	-0.6210	-0.6222	-0.6224	-0.6225
	C3	0.0649	0.1442	0.1420	0.1411	0.1410	0.1409
	C4	0.4085	0.4360	0.4369	0.4373	0.4373	0.4374
	N5	-0.5701	-0.6155	-0.6178	-0.6184	-0.6184	-0.6185
	N6	-0.6107	-0.6129	-0.6097	-0.6084	-0.6083	-0.6082
	C7	0.1521	0.2698	0.2757	0.2780	0.2782	0.2784
	N8	-0.2976	-0.5362	-0.5501	-0.5553	-0.5557	-0.5562
	C9	-0.0434	0.0037	0.0016	0.0008	0.0007	0.0006
	N10	-0.8399	-0.8192	-0.8206	-0.8211	-0.8211	-0.8212
TG5	C1	0.7022	0.7129	0.7157	0.7167	0.7168	0.7169
	N2	-0.5515	-0.6227	-0.6188	-0.6172	-0.6171	-0.6169
	C3	0.0368	0.0642	0.0713	0.0739	0.0741	0.0743
	C4	0.4025	0.4164	0.4221	0.4244	0.4247	0.4249
	N5	-0.5693	-0.6199	-0.6180	-0.6167	-0.6166	-0.6165
	N6	-0.6144	-0.6011	-0.5976	-0.5961	-0.5960	-0.5959
	C7	0.1832	0.2611	0.2690	0.2721	0.2724	0.2727
	N8	-0.2768	-0.5146	-0.5337	-0.5411	-0.5418	-0.5424
	C9	-0.0225	0.0197	0.0157	0.0143	0.0141	0.0140
	N10	-0.8364	-0.8270	-0.8251	-0.8241	-0.8241	-0.8240

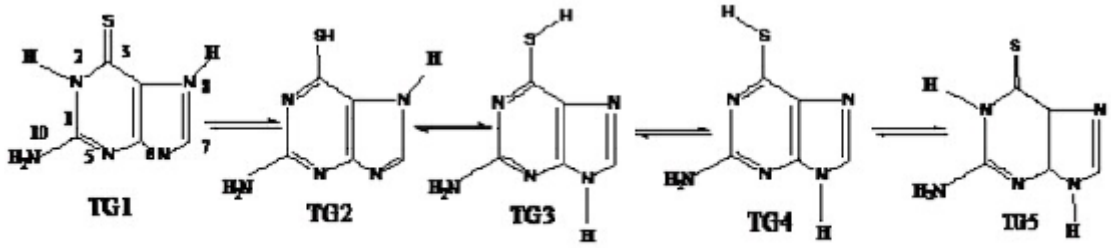

Fig. 1: Tautomeric forms of Thioguanine

with 1.8761 D. TG5 tautomer has the largest dipole moments with 10.4716 D in water. The major diûerence of dipole moment belongs to TG5 form with 2.9951 D in gas and water phase. The calculated values NBO charges using the natural population analysis (NPA) of optimized structures of Thioguanine tautomers in the gas phase and solvents are listed in Table 4. In all phases, N10 atom of TG5 form carries the largest negative charge, in TG5 and TG2 nitrogen atoms at position 2,6 and 9 carry the largest negative charge, all carbons atoms except C9 (in the gas phase) carry the positive charge and will most effectively interact with nucleophiles. And because of its negative charge, C9 (in the gas phase) will interact with electrophiles

Solvent effects

Solvent effects are relevant in tautomers stability phenomena, since polarity differences among tautomers can induce significant changes in their relative energies in solution. PCM/b3lyp calculations were used to analyze the solvent effects on tautomerism of Thioguanine. It is important to stress that the PCM model does not consider the presence of explicit solvent molecules; hence specific solute–solvent interactions are not described and the calculated solutions effects arise only from mutual solute–solvent electrostatic polarization. The data presented in Table 1 show that polar solvents increase the stability of all Thioguanine tautomers in compare to gas phase. The difference between the total energies of Thioguanine and the other forms shows a regular trend when changing from gas phase to more polar solvents (water). In gas phases and benzene and THF solvents, TG1 is more stable than other forms, but in polarisable solvents like methanol, DMSO and water TG5 form is more stable than other forms. The order of stability of all the tautomers in gas phase is TG1 > TG3 > TG5> TG4> TG2, and for benzene (non-polarisable solvent) and THF the order of stability is TG1 > TG3 > TG5> TG4> TG2, and for polarisable solvents methanol, DMSO and water the order of stability is TG5 > TG1 > TG3> TG4> TG2. Total energy shows a regular trend by changing the gas phase to the solution, polarisable solvents increase tautomeric stability compared with gas phase. Based on Table 3 The dipole moments are increase by changing the gas phase to the solution as well as by increasing the solvent polarity. The highest dipole moment belongs to TG4 in water solvent by 10.4716 D and the biggest difference of dipole moment is for water anad gas phases by 2.9951 D. The least dipole moment amount for all the forms in all phases belongs to TG1 by 1.8761 D. We have examined the charge distribution of tautomers in the solvent as well as gas phase by using calculated NBO charges. The charge distribution in solvents with increase of polarity differently varies for any atoms.

CONCLUSION

1. In the gas phase, benzene (non-polarisable solvent) and THF, TG1 form is more stable than the other forms but in methanol DMSO and water (polarisable solvents) TG5 is the most stabilized form.
2. The dipole moments of all compounds are affected by solvent. With increase of the polarity of solvents the dipole moments of all tautomers were increased. With increase of polarity total energy of all compounds were more negative.
3. The charges on all seven positions were affected by solvents. In addition with increase of dielectric constant a variation was found.

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