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Structural Properties of some Purine Derivative Drugs

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I. Introduction

The genomic DNA of all living species consists of four DNA bases. These are adenine (A), thymine (T), guanine (G) and cytosine (C). The entire genetic information is consisted in specific order of these bases which varies among living bodies. The integrity of genome and its transfer from parents to offspring depends upon the ability of DNA replication machinery. A mis-matched selection of base by replication machinery can lead to mutation in the genome and thereby may result in unwanted health complications.

Various modified DNA bases have been in practice as potential drugs for treatment of several diseases. For example, 6-mercaptopurine and azathiopurine, the thio-derivatives of purine bases, have been used in the treatment of inflammatory bowel disease [1 – 4]. Similarly, thiouracils have been shown to be effective drugs. Particularly, 2-thiouracil has been shown to act as carcinogen, neoplastigen and teratogen agent (5). The anti-thyroid activity of 2-thiouracil has also been demonstrated [6, 7]. Furthermore, Le Page and coworkers [8– 12] showed that 6-thioguanine inhibits the synthesis of nucleotides and is incorporated readily into nucleic acid during replication of genome. The mercaptopurines generally exhibit high activity against certain types of tumours [13]. Despite the reports of toxicity associated with 6-mercaptopurine [14], it is widely used as a drug in acute human leukemia treatment [15].

The clinically relevant and extremely important nucleic acid base derivative is ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-carboxamide). It is a guanine derivative, acts as mutagen and inhibits the growth of almost all RNA viruses [16]. It must be emphasized here that ribavirin is a synthetic compound and does not exist in nature either as a metabolite or the product of a biological reaction. The viral RNA polymerases incorporate ribavirin in place of guanine leading to uncapped transcripts which cannot be translated efficiently [17]. These examples highlight the importance of the nucleic acid base derivatives irrespective of their natural existence or synthetic development. In addition, these examples also emphasize that simple modification at one or more groups lead to creation of extremely important biological entity.

In order to understand the biological functions of above mentioned modified nucleic acid bases, Semiempirical quantum chemical calculations using AM1 approximation were carried out. The geometry of all the molecules was fully optimized and compared with the crystal structures (where available). The molecular properties were then computed to understand the effect of substitution on the electronic properties of individual compounds. The results suggest that the computed geometry (bond lengths and bond angles) of guanine and 6-thioguanine are in excellent agreement with the crystal structure with a root mean square deviation of 0.012 Å in the bond lengths and 1.13° for the bond angles. The computed geometries of 6-mercaptopurine and, 6-azathio-purine and ribavirin are presented. In addition, the effect of the presence of ribose moiety in ribavirin has been compared with that of guanine.

II. Results

AM1 geometries of guanine and 6-thioguanine:

Guanine is one of the four bases of DNA and RNA. According the Watson-Crick base-pairing scheme this base forms three hydrogen bonds with cytosine. The keto tautomer of guanine present in the minor groove of DNA, the N3 atom of guanine serves as the H-bonding acceptor for and serves the purpose for the non-specific recognition by most of the proteins. The crystal structure of guanine was solved long ago by Bugg and Thewalt [18-19].

The energies and heats of formation of these molecules are collected in Table 1. The gas phase ionization potential and dipole moments are also included in this table. The heats of formation and energies of these guanine and 6-thioguanine have been estimated previously by Norinder [20] and Civicir [21], respectively using AM1 quantum chemical calculations. Since, we used same methodology for the optimization of the geometries of these molecules, no difference in the computed values was obtained.

AM1 studies of 6-mercaptopurine

The crystal structure together with the solution structure of 6-mercaptopurine has been solved by Pazderski et al. [22]. They also used *ab initio* quantum chemical calculations to calculate the gas phase optimized geometry of this molecule. Thus, the geometry of 6-mercaptopurine has been determined in all three

(solid, aqueous and gas) phases [22]. The tautomersim of 6-mercaptopurine was evaluated in terms of the presence of proton at N7 or N9 position. It has been shown that 6-mercaptopurine favours the N7H tautomer over N9H [22]. Both the tautomers contained thiol group and no thione was observed. We have computed the optimized geometry of 6-mercaptopurine using AM1 semiempirical approximation. The optimized bond lengths and bond angles are compared with experimental values Table 2. A perusal of the bond length and bond angle values shows that the both computed bond lengths and bond angles are in very good agreement with experimental values. In general, the most difference in bond lengths is in C=S bond length. This observation is consistent with AM1 studies carried by Civicir [21] for his studies of tautomersim of 6-thioguanine.

The *ab initio* quantum chemical calculations have been carried out for two tautomers of 6-mercaptopurine [22]. However, the calculations were used only for NMR peak assignments and no details about the electronic parameters were presented. For this reason, we are unable to compare the electronic parameters of this compound. The AM1 determined parameters are listed in Table 1. The comparison with 6-thioguanine shows that 6-mercaptopurine is somewhat less stable than 6-thioguanine. The substitution of amino group at 2nd position of purine ring does not alter the ionization potential significantly suggesting comparable stability of the two molecules. In contrast, the dipole moment of the two molecules (6-merceptoguanine and 6-mercaptopurine) is significantly different (1.506 versus 5.581 eV). This difference is the result of the charge distribution of on ring atoms. The net atomic charges on various atoms of 6-mercaptopurine and 6-thioguanine are given in Table 3. The only difference between 6-thioguanine and 6-mercaptopurine is the presence of amino group at 2nd position of the purine ring. This difference appears to impact significantly on the charge distribution on heavy atoms. Most significantly, the charge on sulphur atom in 6-mercaptopurine is higher than the one in 6-thioguanine. To get the more precise estimate of charge distribution on two molecules, the total partial charge on two molecules (including hydrogens) was computed. The charge on 6-thioguanine is close to zero (-0.0001) compared to -0.3831 on 6-mercaptopurine suggesting higher reactivity of 6-mercaptopurine than that of 6-thioguanine.

6-thioazapurine

The azathiopurine molecule consists of two moieties: 6-mercaptopurine and an imidazole derivative moiety (see Table 2). The structure of 6-thioazapurine has been also extensively studied at both theoretical and experimental avenues [23, 24, 25]. The crystal structure in the form of dinuclear compound has been solved [24], whereas PM3 method has been used to determine salvation parameters of this molecule. The crystal structure was solved in presence of copper ions. Four copper ions chelated two molecules of azathiopurine to form dinuclear association [24]. The other crystal structure of 6-azathiopurine has been solved by Cook and Bugg [25]. This structure has been solved in the form of dehydrate. Compared to the dinuclear form chelated by copper ions [24], this structure was reported by Cook and Bugg [25]. The bond lengths and bond angles reported in crystal structure determination and obtained from AM1 quantum chemical calculation together with reported by Cook and Bugg [25] are provided in Table 3. The bond lengths and bond angles are compared only for heavy atoms. It is clear from the comparison of bond lengths determined by crystal structure and computed by AM1 semiempirical method shows that they are in good agreement. However, the resemblance between crystal structure and quantum chemical calculations is not as good as noted for 6-mercaptopurine. There may be two reasons for this discrepancy. First, the crystal structure was solved in dehydrated form. This could lead to the reduction in the bond lengths. Second, the crystal packing forces could reduce the bond lengths. Thus, the apparent discrepancy may not be the result of AM1 approximation.

The ionization potential of 6-azathiopurine is not significantly different than that of 6-mercaptopurine. However, there is substantial difference in the dipole moment values of the two compounds (Table 1). The total net atomic charge on both molecules is nearly zero suggesting the difference in charge delocalization due to the presence of imidazole-derivative ring in 6-azathiopurine. The impact of charge delocalization is also evident from the amount of partial charge on S-atom in 6-azathiopurine. The charge on S-atom in this molecule is 0.3779 compared which is significantly more than the charge on S-tom in 6-thioguanine and 6-mercaptopurine (-0.2187 and -0.1176, respectively) (Table 4). The positive charge on S-atom in 6-thioguanine also suggests that this atom is prone to nucleophilic attack, which is required for the metabolism of this molecule to be used as drug.

Ribavirin

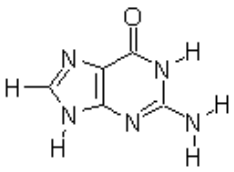
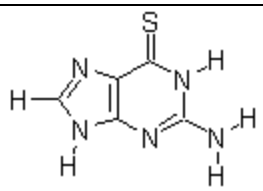
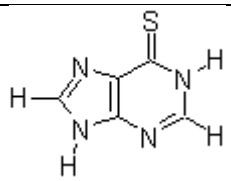
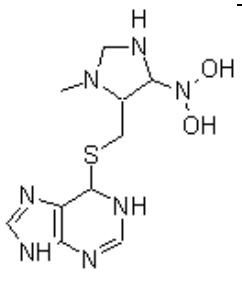
Ribavirin is a guanine derivative and inhibits almost all viral RNA dependent RNA polymerases [26]. The nucleoside form of ribavirin is metabolized in the cell to the triphosphate form, which then is incorporated by RNA polymerases during viral genome replication. This drug works as mutagen as the resultant RNA strand contains mutation at the site of incorporation. Since it is a guanine derivative and no crystal structure in available for this molecule in isolation, AM1 quantum chemical calculations were carried to determine (i) the

optimal geometry and (ii) the electronic properties. These properties were then compared with guanine in order to understand the effect of ribavirin in place of in RNA.

The bond lengths and bond angles for ribavirin base are compiled in Table 5. The atomic nomenclature corresponds to the standard one and used for guanine. The comparison of bond lengths of ribavirin-base and guanine base shows that there exist subtle differences in the bond lengths between two compounds. However, the overall geometry of the two compounds does not seem to be affected by the modification of guanine to ribavirin base. The same tends to be true for bond angles as well.

The electronic properties such as dipole moment and ionization potentials of the two molecules are listed in Table 1. The comparison suggests that the dipole-moment of ribavirin base is significantly higher than the dipole moment of guanine. This result suggests a greater flexibility of this base when present in the double helical nucleic acid (RNA), which may lead to altered selection of nucleotide by RNA polymerase and therefore causing the mutation in virus gene. To get better insight and to explore if there exist such a mechanism, the net atomic charges on the ring atoms of guanine and ribavirin were compared. The results are presented in Table 6. It must be pointed out here that the H-bonding between the two bases of nucleic acids involves O6, N1 and NH2 atoms. In ribavirin, the NH2 group is placed at N1 position, therefore it can only form two hydrogen bonds compared to three formed by the guanine. Two hydrogen bonds are formed in the case of A-U base pair as well as in G-U and C-U mispairs. These two kind of mispairs lead to mutation in the genomic architecture of viral RNA. In addition, the difference in the charge distribution may also alter the H-bond strength formed by ribavirin. The atoms in Table 6 shown are only those in the ribavirin base and the nomenclature corresponds to guanine standard base. The comparison of charges on the hydrogen-bonding moieties shows significant differences in the partial charge on N1 (NH2) atom. The ribavirin has more negative charge on this atom compared to guanine suggesting a weaker H-proton donating tendency compared to guanine. The O6 atom in either case contains comparable partial charges. Taken together, the H-bonding capacity of ribavirin base appears to be weaker than guanine and that may be one of the reasons for accepting mismatches by the RNA polymerase.

Table 1: Electronic properties of various purine derived drugs

Molecule	Structure	Energy (eV)	ΔH_f (kCal/mol)	Ionization Potential (eV)	Dipole moment (Debye)
Guanine		-2062.44	50.33	8.84	1.684
6-Thioguanine		-1935.98	105.49	8.57	1.506
6-mercaptopurine		-1715.22	100.69	8.61	5.581
6-azathio-purine		-3567.53	142.86	7.48	8.312

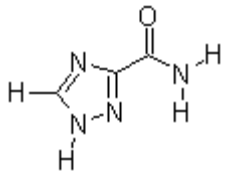
Ribavirin – base only		-1585.42	41.30	10.52	5.732

Table 2: Comparison of experimental bond lengths and bond angles of 6-mercaptopurine with computed values

Bond lengths (Å)			Bond Angles (°A)		
Bond	Experimental*	Computed by AM1	Bond Angle	Experimental*	Computed by AM1
N1-C2	1.352	1.386	C6-N1-C2	125.1	123.7
C2-N3	1.308	1.325	N1-C2-N3	123.3	126.6
N3-C4	1.364	1.361	C2-N3-C4	113.1	113.3
C4-C5	1.396	1.391	N3-C4-C5	124.0	124.1
C5-C6	1.402	1.440	C4-C5-C6	122.0	120.2
C6-N1	1.380	1.410	C5-C6-N1	110.5	112.1
C6-S6	1.674	1.574	N1-C6-S6	122.4	120.8
C5-N7	1.370	1.397	C5-C6-S6	127.1	127.0
N7-C8	1.352	1.347	C5-N7-C8	106.2	105.1
C8-N9	1.362	1.411	N7-C8-N9	113.6	113.4
N9-C4	1.367	1.392	C8-N9-C4	104.3	105.9
			N9-C4-C5	110.2	106.1
			C4-C5-N7	105.7	109.7

*Taken from Ref [20].

Table 3: Comparison of experimental bond lengths and bond angles of 6-thioazapurine with computed values

Bond lengths (Å)			Bond Angles (°A)		
Bond¶	Experimental*	Computed by AM1	Bond Angle	Experimental*	Computed by AM1
N1-C2	1.335	1.385	C6-N1-C2	117.6	123.7
C2-N3	1.334	1.324	N1-C2-N3	128.2	126.6
N3-C4	1.336	1.391	C2-N3-C4	112.0	113.3
C4-C5	1.394	1.449	N3-C4-N9	128.8	124.1
C5-C6	1.378	1.447	C4-C5-C6	115.8	120.2
C6-N1	1.323	1.400	C5-C6-N1	120.9	112.1
C6-S11	1.768	1.609	N1-C6-S11	102.1	120.8
C5-N7	1.367	1.395	C5-C5-N7	127.1	127.0
N7-C8	1.312	1.348	C5-N7-C8	103.0	105.1
C8-N9	1.363	1.410	N7-C8-N9	114.9	113.4
N9-C4	1.368	1.392	C8-N9-C4	104.3	105.9
C4-C5	1.382	1.405	N9-C4-C5	105.2	106.1
C15-N7	1.403	1.328	C4-C15-N7	110.8	109.7
S11-C15	1.737	1.686	C6-S11-C15	102.1	101.8
C15-C16	1.371	1.423	C16-C15-N19	103.5	102.7
C16-N17	1.353	1.410	N19-C15-S11	124.2	123.6
N17-C18	1.305	1.345	C15-C16-N17	103.5	102.8
C18-N19	1.360	1.404	C15-C16-N22	120.3	120.9
C16-N22	1.435	1.462	C16-N17-C18	103.4	102.9
N22-O26	1.236	1.333	N17-C18-N19	112.8	113.2
N22-O27	1.217	1.351	C18-N19-C15	107.2	106.7
N19-C21	1.475	1.425	C18-N19-C21	125.1	124.8

……..Contd.

Bond lengths (Å)			Bond Angles (°A)		
Bond¶	Experimental*	Computed by AM1	Bond Angle	Experimental*	Computed by AM1
			C15-N19-C21	117.6	123.7
			C16-N22-O27	119.2	126.6
			C16-N22-O26	117.0	113.3
			O26-N22-O27	123.8	124.1

¶For numbering scheme see Fig. 1.
*Taken from Ref [25].

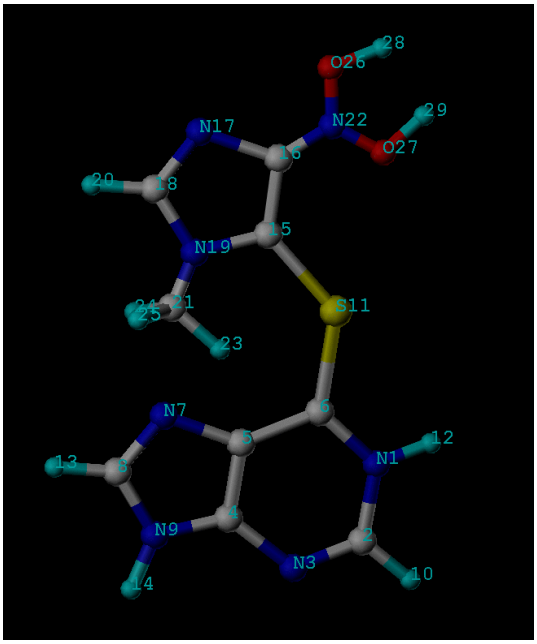


Fig. 1: Chemical structure of 6-azathiopurine and numbering scheme used in Table 3.

Table 4: Net atomic charges on purine ring atoms of various drugs/bases

Atom	Molecules				
	Guanine	6-thioguanine	6-mercaptopurine	6-azathio-purine	Ribavirin (base only)
N1	-0.3318	-0.2643	-0.2745	-0.2315	-0.4299
C2	0.1997	0.1865	0.0571	0.0452	---
N3	-0.1864	-0.1716	-0.1657	-0.1670	-0.0764
C4	0.0410	0.0440	0.0124	0.0138	-0.1487
C5	-0.2404	-0.2005	-0.1770	-0.1742	---
C6	0.3843	0.0854	0.0641	-0.0916	0.3899
N7	-0.1670	-0.1676	-0.0598	-0.0949	-0.0914
C8	-0.0471	-0.0332	-0.0808	-0.0756	-0.0917
N9	-0.1193	-0.1213	-0.1918	-0.1910	-0.1850
N (NH2)	-0.3193	-0.3180	---	---	---
O6/S6	-0.3611	-0.2187	-0.1176	0.3779	-0.3340

Table 5: Bond lengths and bond angles of ribavirin-base and guanine

Ribavirin-base				Guanine			
Bond	Bond Length (Å)	Bond Angle	Angle (°A)	Bond	Bond Length (Å)	Bond Angle	Angle (°A)
N1 – C6	1.373	N1 - C6 - O6	121.0	N1 – C6	1.409	N1 - C6 - O6	117.5
C6 – O6	1.244	O6 - C6 - C5	121.8	C6 – O6	1.245	O6 - C6 - C5	128.2
C5 – C6	1.498	C6 – C5 – N7	122.1	C5 – C6	1.445	N4 – C5 – N7	130.7
N4 – C5	1.377	C5 – N7 – C8	103.7	C4 – C5	1.442	C5 – N7 – C8	104.9
N4 – N9	1.327	N7 – C8 – N9	109.1	C4 – N9	1.408	N7 – C8 – N9	113.2
N9 – C8	1.409	N9 – N4 – C5	104.9	N9 – C8	1.357	N9 – N4 – C5	105.7
N7 – C8	1.347	N1 – C6 – C5	117.2	N7 – C8	1.396	N1 – C6 – C5	113.9
C5 – N7	1.415			C5 – N7	1.391		

Table 6: Net atomic charges on ribavirin base, guanine, ribavirin and guanosine

Atom	Ribavirin base	Ribavirin	Guanine	Guanosine
O6	-0.3340	-0.3470	-0.3611	-0.3260
C6	0.3899	-0.0147	0.3843	0.3965
N1 (NH2)	-0.4299	-0.4211	-0.3193	-0.3293
C5	-0.1487	-0.1437	-0.2404	-0.2437
N4	-0.0764	0.0151	0.0410	0.0776
N7	-0.0914	-0.1542	-0.1670	-0.0645
C8	-0.0917	-0.0892	-0.0471	-0.0900
N9	-0.1850	-0.1772	-0.1193	-0.1666

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