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Theoretical Study of Anticancer Drug Mercaptopurine Structure by Using Quantum Calculations

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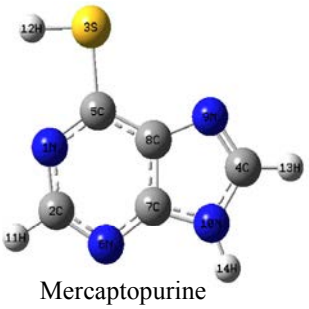
Abstract: Mercaptopurine is a medicine used to prevent the formation and spread of cancer cells. Mercaptopurine, known chemically as 1,7-dihydro-6H-purine-6-thione, is an analogue of the purine bases adenine and hypoxanthine. This work reports an investigation of anticancer drug Mercaptopurine with the combined density functional theory and Its structure were optimized at B3LYP/6-31G*, level and The molecular structure in the different solvents (SCRF calculation), NMR parameters were calculated by the DFT using B3LYP/6-31G* basis set. and finally we calculated Natural Bond Orbital (NBO) parameters for this structure and then we compared this results with adenine structure.

Key words: molecular orbital (MO) · Natural Bond Orbital (NBO) · Density functional theory (DFT)

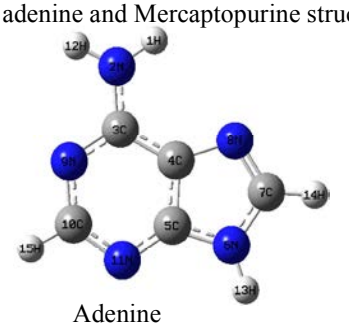
INTRODUCTION

Mercaptopurine is a medicine used to prevent the formation and spread of cancer cells. Mercaptopurine is also called 6-Mercaptopurine or 6-MP and is available under the brand name Purinethol. Mercaptopurine is an analog of purine, a component of DNA/RNA and belongs to antimetabolites that prevent the biosynthesis, or utilization, of normal cellular metabolites. It has been used for several decades in combination with other chemotherapy drugs for the treatment of different types of acute adult and childhood leukemias (ALL and AML). It has also been shown to be effective for the treatment of inflammatory bowel disease (IBD) (which includes Crohn's disease and ulcerative colitis), certain types of arthritis and polycythemia vera (above normal increase in red cells in the blood). Mercaptopurine (Fig 1) helps to decrease the dose of steroids in patients with IBD and to reduce their dependence on steroids to control symptoms of their disease. The medicine is taken up by red cells in the blood and works by decreasing the formation of certain genetic material (DNA and RNA) in patients with cancer and by altering the activity of the immune system in patients with IBD. Adenine is one of the most important organic molecules for life as we know it today. Adenine (Fig 2) is a purine. Purines are six-member rings attached to five member rings. When Adenine is attached to DNA, it forms a bond with another molecule called Thymine, a pyrimidine, on the other side of the DNA strand. It is these bonds which give DNA its double-helix structure. The sequence of DNA, or the order in which nucleotides are placed, allows for the diversity among all living organisms. The importance of Adenine to RNA is similar to that of DNA.



Mercaptopurine

Fig. 1: The adenine and Mercaptopurine structures



Adenine

Fig. 2: Adenine Mercaptopurine

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DNA is one of the most important biological molecules targeted bymany small molecules (proteins represent extremely important targets as well). Also, during the past decades, molecules binding with DNA have been seriously taken into concern [1-7]. A lot of investigations on the interaction of drug molecules with DNA have been studied [8-13].

Computational Details: In our current study, extensive quantum mechanical calculations [14-18] of structure of adenine and Mercaptopurine (Fig. 1) and solvent effects on structure of adenine and Mercaptopurine and calculations of NMR parameters have been Performed on a Pentium-4 based system using GAUSSIAN 03 program. At first, we have modeled the structure of adenine and Mercaptopurine with Chem office package and then optimized at the DFT level of theory with 6-31G* basis set. After fully optimization of those structures, we have calculated NMR parameters at the levels of B3LYP/6-31G* theory and theoretically explored the solvent effects (water, methanol, ethanol) on structure of adenine and Mercaptopurine. All the relative energy values and NMR shielding parameters were calculated supposing gauge-included atomic orbital (GIAO) method.

RESULTS AND DISCUSSION

In this paper DFT method with 6-31G* basis set were Employed for investigating the structures optimization and energy minimization of adenine and Mercaptopurine, (Fig1) have been summarized in Table 1.

The Gauge Including Atomic Orbital (GIAO) approach was used. The abinitio GIAO calculations of NMR chemical shielding tensors were performed using the DFT method. The chemical shielding tensors were calculated with the GAUSSIAN 03 program. The isotropic chemical shielding (σ_{iso}) and anisotropy shielding ($\Delta\sigma$) for C5-S3 bonding of Mercaptopurine and C3-N2 bonding of adenine (Fig 1) have been summarized in Table 2. because that tow structures has different only in that bonds (C5-S3 and C3-N2).

In the NBO analysis, in order to compute the span of the valence space, each valence bonding NBO (σ_{AB}), must in turn, be paired with a corresponding valence antibonding NBO (σ^*_{AB}): Namely, the Lewis σ-type (donor) NBO are complemented by the non-Lewis σ^*-type (acceptor) NBO that are formally empty in an idealized Lewis structure picture. Readily, the general transformation to NBO leads to orbitals that are unoccupied in the formal Lewis structure. As a result,

Table 1: Calculated energy values (kcal/mol)adenine and Mercaptopurine at the level of DFT/6-31G*

Mercaptopurine/ B3LYP/6-31G*(gas)	-508370.695752426
Mercaptopurine/ B3LYP/6-31G*(water)	-508372.131683559
Mercaptopurine/ B3LYP/6-31G*(methanol)	-508372.081671012
Mercaptopurine/ B3LYP/6-31G*(ethanol)	-508372.054186074
Adenine/ B3LYP/6-31G*(gas)	-298894.368358209
Adenine/ B3LYP/6-31G*(water)	-293247.430090095
Adenine/ B3LYP/6-31G*(methanol)	-293247.410009775
Adenine/ B3LYP/6-31G*(ethanol)	-293247.398902848

Table 2: NMR parameters value (ppm) of (C5-S3 bond and C3-N2 bond) Mercaptopurine and Adenine in gas phase and different solvent at the level of B3LYP/ 6-31G* basis set at the DFT theory

B3LYP/6-31G*	Isotropic (σiso)	Anisotropy (Δσ)
Mercaptopurine/S3(gas)	474.8215	445.2738
Mercaptopurine/C5(gas)	30.9354	141.1790
Mercaptopurine/S3(water)	449.6962	471.2190
Mercaptopurine/C5(water)	31.4963	138.6185
Mercaptopurine/S3(methanol)	450.5648	470.1660
Mercaptopurine/C5(methanol)	31.4782	138.7161
Mercaptopurine/S3(ethanol)	451.0528	469.5676
Mercaptopurine/C5(ethanol)	31.4691	138.725
Adenine/C3(gas)	44.6806	137.6755
Adenine/N2(gas)	185.6648	65.2140
Adenine/C3(water)	43.2411	140.0954
Adenine/N2(water)	184.7770	63.5996
Adenine/C3(methanol)	43.2865	140.0396
Adenine/N2(methanol)	184.8562	63.6911
Adenine/C3(ethanol)	43.3116	140.0083
Adenine/N2(ethanol)	184.8986	63.7408

Table 3: Donor and acceptor NBO for tow structures and the level of B3LYP/ 6-31G*in different solvents

Donor NBO (i)	Acceptor NBO(j)	E2(kcal/mol)
Mercaptopurine /Gas/LP(1) S3	BD*(1) N1-C5	3.48
Mercaptopurine /Gas/LP(2) S3	BD*(2) N1-C5	23.49
Mercaptopurine /Water/ LP(1) S3	BD*(1) N1-C5	3.39
Mercaptopurine /Water/ LP(2) S3	BD*(2) N1-C5	22.25
Mercaptopurine /Methanol/ LP(1) S3	BD*(1) N1-C5	3.40
Mercaptopurine /Methanol/ LP(2) S3	BD*(2) N1-C5	22.29
Mercaptopurine /Ethanol/ LP(1) S3	BD*(1) N1-C5	3.40
Mercaptopurine /Ethanol/ LP(2) S3	BD*(2) N1-C5	22.31
Adenine /Gas/LP(1) N2	BD*(2) C3-N9	56.61
Adenine /Water/ LP(1) N2	BD*(2) C3-N9	56.68
Adenine /Methanol/ LP(1) N2	BD*(2) C3-N9	56.68
Adenine /Ethanol/ LP(1) N2	BD*(2) C3-N9	56.68

Table 4: Energy(kcal/mol) and hybrid for C5-S3 bonding of Mercaptopurine and C3-N2 bonding of adenine

DFT/B3LYP/ 6-31G*	Bond	Hybrid	Energy
Mercaptopurine /Gas/S3-C5	BD(1)	S3=Sp4.57d0.05	
		C5=sp2.62	-0.66008
Mercaptopurine /Water/ S3-C5	BD(1)	S3=sp4.44d0.04	
		C5=sp2.65	-0.66750
Mercaptopurine /Methanol/ S3-C5	BD(1)	S3=sp4.45d0.04	
		C5=sp2.65	-0.66722
Mercaptopurine /Ethanol/ S3-C5	BD(1)	S3=sp4.45d0.04	
		C5=sp2.65	-0.66707
Adenine /Gas/N2-C3	BD(1)	C3=sp2.29	
		N2=sp1.55	-0.83829
Adenine /Water/ N2-C3	BD(1)	C3=sp2.29	
		N2=sp1.55	-0.83954
Adenine /Methanol/ N2-C3	BD(1)	C3=sp2.29	
		N2=sp1.55	-0.83949
Adenine /Ethanol/ N2-C3	BD(1)	C3=sp2.29	
		N2=sp1.55	-0.83947

the filled NBO of the natural Lewis structure are well adapted to describe covalency effects in molecules. Since the non-covalent delocalization effects are associated with $\sigma > \sigma^*$ interactions between filled (donor) and unfilled (acceptor) orbitals, it is natural to describe them as being of donor–acceptor, charge transfer, or generalized "Lewis base-Lewis acid" type. The antibonds represent unused valence-shell capacity and spanning portions of the atomic valence space that are formally unsaturated by covalent bond formation. Weak occupancies of the valence antibonds signal irreducible departures from an idealized localized Lewis picture, i.e. true "delocalization effects". As a result, in the NBO analysis, the donor–acceptor (bond–antibond) interactions are taken into consideration by examining all possible interactions between 'filled' (donor) Lewis-type NBO and 'empty' (acceptor) non-Lewis NBO and then estimating their energies by second-order perturbation theory. These interactions (or energetic stabilizations) are referred to as 'delocalization' corrections to the zeroth-order natural Lewis structure.

The most important interaction between "filled" (donor) Lewis-type NBO and "empty" (acceptor) non-Lewis is reported in Table (3) the level of B3LYP/ 6-31G* basis set at the DFT theory., we observed between the LP(1) N2 and $\sigma^*(2)$ of C3-N9 of adenine and LP(1) S3 and $\sigma^*(1,2)$ of N1-C5 of Mercaptopurine and finally we reported the energy and hybrid for C5-S3 bonding of Mercaptopurine and C3-N2 bonding of adenine in Table (4), by same level.

CONCLUSION

In this research we have calculated quantum calculations on anticancer drug such as Opt, NMR, NBO that the results of these calculations have been summarized in tables 1-4.The main difference of Adenine and Mercaptopurine is in C3-N2, C5-S3 bonds (Fig. 1) and the structural details of these bonds have been reported in tables which are on the base of our calculations. In fact these calculations considered as a model and if molecule has these properties which have been mentioned in this paper and the data calculations of them be similar to data calculations of this paper we can call it as a new anticancer drug and in the next stage for more surety it is possible to test and synthesis it in laboratory.

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