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Molecular electrostatic potential, partial atomic charges and geometry optimized energy of streptozocin, a DNA alkylating agent

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Abstract

Streptozocin is a glucosamine-nitrosourea compound. It is an alkylating agents within the nitrosourea category. Streptozocin is used for treating metastatic cancer of the pancreatic islet cells. Conformational analysis and geometry optimization of streptozocin was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's, lowest unoccupied molecular orbital's and electrostatic potential (ESP) mapped onto electron density. The optimized geometries, Mulliken atomic charges and Zero Differential Orbital (ZDO) atomic charges were calculated. The energy values for the HOMO and LUMO of streptozocin are -2.800000 and -0.152550 eV respectively. The results of Mulliken and ZDO atomic charges showed that the negative charges in streptozocin can act as nucleophiles. The most feasible position for the drug to interact with the receptor was found to be -139.373619 au (-87458.345800 kcal/mol). The modeling and the calculations does not only presented to us the opportunity to take a critical look at this anticancer drug but has also given us the opportunity to compile fundamental result on properties that cannot be calculated in the laboratory.

Keywords: Streptozocin, ArgusLab, Electrostatic, Optimization

1. Introduction

Streptozocin is a chemical that is significantly hepatotoxic to the insulin-producing beta cells of the exocrine gland in mammals. It is a medication for treating cancers of the Islets of Langerhans. Streptozocin is approved by the U.S. Food and Drug Administration (FDA) for treating pathological process cancer of the exocrine gland isle cells. Since it carries a considerable risk of toxicity and infrequently cures the cancer, its use is usually restricted to patients whose cancer cannot be removed by surgery. In these patients, streptozotocin will scale back the growth size and scale back symptoms (especially hypoglycaemia attributable to excessive endocrine secretion by insulinomas) [1]. Due to its high toxicity to beta cells, in scientific researches, streptozocin has conjointly been long used for inducement insulitis and polygenic disorder on experimental animals [2].

Streptozocin is a glucosamine-nitrosourea compound. It is an alkylating agents within the nitrosourea category, it is hepatotoxicity to cells is by inflicting injury to the desoxyribonucleic acid, although alternative mechanisms may contribute. Desoxyribonucleic acid injury induces activation of poly ADP-ribosylation [3]. Streptozotocin is comparable enough to aldohexose to be transported into the cell by the aldohexose transport macromolecule, however it is not recognized by other aldohexose transporters. This explains its relative toxicity to beta cells, since these cells have comparatively high levels of glucose transport protein, GLUT2 [4, 5]. Streptozocin was

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originally known within the late Fifties as an antibiotic [6]. The drug was discovered in strain of the soil microorganism Streptomyces achromogenes by scientists at the pharmaceutical company Upjohn (now a part of Pfizer) in town, Michigan. The soil sample within which the microorganism turned up had been taken from Blue Rapids, Kansas, which may so be thought-about as the birthplace of streptozocin. Upjohn pharmaceutical company filed for patent protection for the drug in August 1958 and U.S. Patent 3,027,300 was granted in March 1962.

In the mid-1960s streptozotocin was found to be by selection hepatotoxic to the beta cells of the exocrine gland islets, the cells that commonly regulate glucose levels by manufacturing the internal secretion endocrine. This instructed the drug's use as animal model of polygenic disorder [7, 8], and as a medical treatment for cancers of the beta cells [9]. Within the nineteen Sixties and seventies the National Cancer Institute investigated streptozocin's use in cancer therapy. Upjohn pharmaceutical company filed for authority approval of streptozocin as a treatment for exocrine gland isle cell cancer in 1976, and approval was granted in 1982. The drug was marketed as Zanosar. Streptozotocin is currently marketed by the drug company Sicor (Teva). The structure of streptozocin is shown in Figure 1.

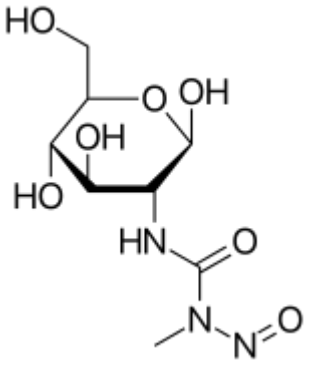

Figure 1: Structure of streptozocin

Electrostatic potential has been used as a parameter to probe molecular charge, molecular interactions and chemical activity of molecules [10]. We hereby present the molecular electrostatic potential, partial atomic charges and geometry optimized energy of streptozocin, a DNA alkylating agent.

.2. Materials and Methods

Geometry optimization study was performed on a window based computer using ArgusLab [11]. The chemical structure of streptozocin was generated by ArgusLab, minimization was performed with semi-empirical Austin Model 1 (AM1) parameterization. The minimum potential energy was calculated by using geometry convergence function in ArgusLab software. Surfaces created to visualize the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and electrostatic potential mapped on electron density surface. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map. Mulliken and Zero differential overlap (ZDO) atomic charges were calculation using quantum Mechanical AM1 in Arguslab software.

3. Result and Discussion

The Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO), electrostatic potential mapped onto electron density surface and the geometry convergence graph of streptozocin are shown in Figures 2 – 5 respectively. Partial atomic charges, optimized bond length and Optimized bond angles of streptozocin are shown in Tables 1 - 3 respectively.

Table 1: Partial atomic charges of streptozocin

Atoms	Mulliken atomic charges	ZDO atomic charges
1 O	-0.1611	-0.1284
2 C	0.3404	0.3018
3 C	-0.3084	-0.2974
4 C	-0.3713	-0.3507
5 C	-0.3374	-0.3527
6 C	0.9794	0.5548
7 C	0.1833	0.1499
8 O	-0.3204	-0.2935
9 O	-0.0770	0.1820
10 O	-0.0523	0.0692
11 O	-0.2050	-0.1766
12 N	-0.3919	-0.3596
13 C	0.2656	0.1679
14 N	-0.3297	-0.1677
15 N	0.3464	0.3328
16 O	-0.3251	-0.3241
17 O	-0.4907	-0.4812
18 C	0.2553	0.1733

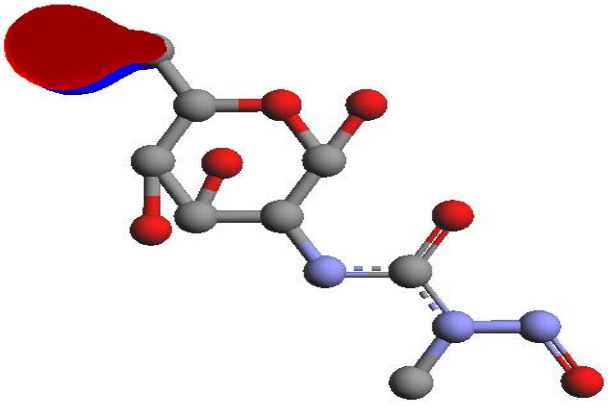

Figure 2: Highest Occupied Molecular Orbital (HOMO) of streptozocin

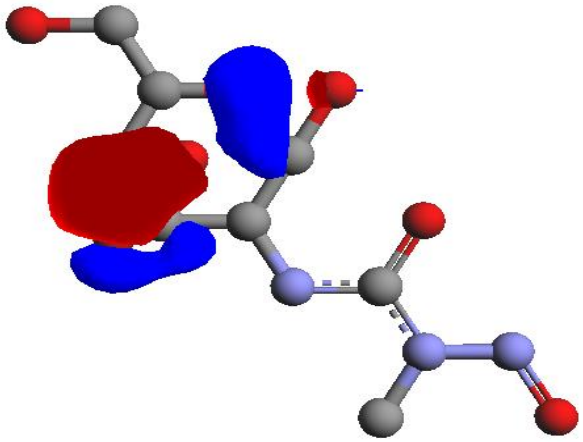

Figure 3: Lowest Unoccupied Molecular Orbital (LUMO) of streptozocin

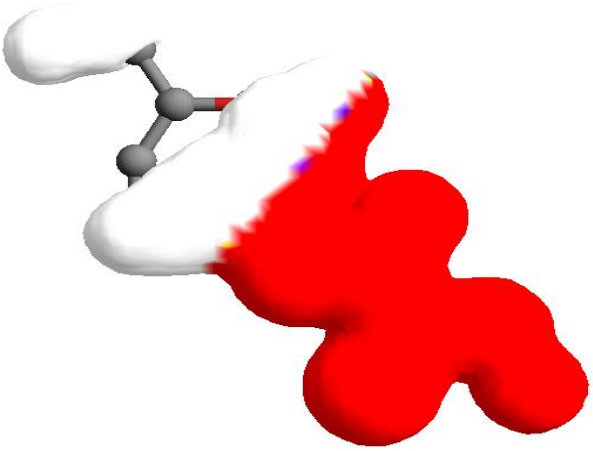

Figure 4: Electrostatic potential mapped onto electron density surface of streptozocin

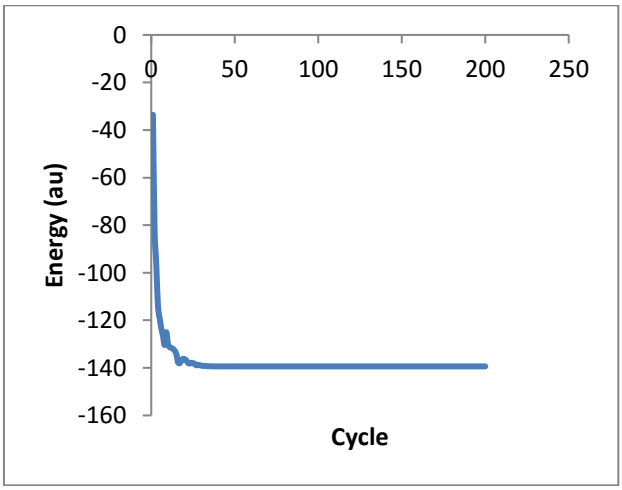

Figure 5: Geometry convergence graph of streptozocin

Table 2: Optimized bond length of streptozocin

Atoms	Bond length (pm)
1 2 (O)(C)	1.386426
1 3 (O)(C)	1.386426
2 4 (C)(C)	1.464000
2 11 (C)(O)	1.410739
3 5 (C)(C)	1.489000
3 7 (C)(C)	1.464000
4 6 (C)(C)	1.489000
4 12 (C)(N)	1.422764
5 6 (C)(C)	1.514000
5 9 (C)(O)	1.436155
6 10 (C)(O)	1.436155
7 8 (C)(O)	1.410739
12 13 (N)(C)	1.346235
13 14 (C)(N)	1.346235
13 17 (C)(O)	1.260307
14 15 (N)(N)	1.370000
14 18 (N)(C)	1.422764
15 16 (N)(O)	1.201824

Table 3: Optimized bond angles of streptozocin

Atoms	Bond angles (°)
2 1 3 (C)-(O)-(C)	120.000000
1 2 4 (O)-(C)-(C)	120.000000
1 2 11 (O)-(C)-(O)	120.000000
1 3 5 (O)-(C)-(C)	120.000000
1 3 7 (O)-(C)-(C)	120.000000
4 2 11 (C)-(C)-(O)	120.000000
2 4 6 (C)-(C)-(C)	120.000000
2 4 12 (C)-(C)-(N)	120.000000
5 3 7 (C)-(C)-(C)	120.000000
3 5 6 (C)-(C)-(C)	109.470000
3 5 9 (C)-(C)-(O)	109.470000
3 7 8 (C)-(C)-(O)	120.000000
6 4 12 (C)-(C)-(N)	120.000000
4 6 5 (C)-(C)-(C)	109.470000
4 6 10 (C)-(C)-(O)	109.470000
4 12 13 (C)-(N)-(C)	120.000000
6 5 9 (C)-(C)-(O)	109.470000
5 6 10 (C)-(C)-(O)	109.470000
12 13 14 (N)-(C)-(N)	120.000000
12 13 17 (N)-(C)-(O)	120.000000
14 13 17 (N)-(C)-(O)	120.000000
13 14 15 (C)-(N)-(N)	120.000000
13 14 18 (C)-(N)-(C)	120.000000
15 14 18 (N)-(N)-(C)	120.000000
14 15 16 (N)-(N)-(O)	120.000000

Austin Model 1 (AM1), is a semi-empirical concept that is rooted on the Neglect of Differential Diatomic Overlap integral approximation. It is used in computational chemistry for calculations of molecular electronic structure. Specifically, we can say that it is based on modified neglect of differential diatomic overlap approximation. This semi-empirical method was proposed by Michael Dewar and co-workers in their 1985 publication [12]. The results from AM1 parameterizations are often seen as the beginning of forcefields calculations

in molecular modeling. The number of atoms involve in AM1 parameterizations is between 13 – 16.

The HOMO of streptozocin (Figure 2) is the orbital of highest energy that is still occupied, thus energetically it is the best to eliminate electrons from this orbital. This may be just donating electron to create a bond. The LUMO of streptozocin (Figures 3) is the lowest lying orbital that is empty, thus energetically it is the best to receive electrons into this orbital. The energy values for the HOMO and LUMO of Streptozocin are -2.800000 and -0.152550 eV respectively.

ArgusLab [11] was utilized in generating electrostatic potential mapped onto the negatron density surface of streptozocin (Figure 4). Electrostatic potential maps are three dimensional diagrams of molecules. It permits us to check the charge distributions of molecules and charge connected properties of molecules. They together allow us to study dimensions and form of molecules. In natural science, electrostatic potential maps are valuable in predicting the behavior of advanced molecules [13]. Electrostatic potential mapped onto the electron density of streptozocin gave information regarding the electron distribution of the molecule, the properties of the nuclear charge and nature of static energy [13]. For simplicity, think about moving a charge on the spherical isosurface of atom. The charged nucleus emits a radially constant field of force. The area above than average electrostatic potential energy indicates the presence electrons or a weaker negative charge. Given the consistency of the nucleus electric charge, the upper potential energy worth indicates the absence of negative charges, which might mean that there are fewer electrons during this region. Therefore a strong electrostatic potential indicates the relative absence of electrons while weak electrostatic potential indicates an abundance of electrons. To accurately analyze the charge distribution of a molecule, a really great quantity of electrostatic potential energy values should be calculated [13]. The most effective way to convey this knowledge is to visually represent it, as electrostatic potential map [13]. The red region of the streptozocin surface is the lowest electrostatic potential energy while the blue region is the highest. Electrostatic potential surfaces are valuable in computer-aided drug design because they assist in understanding electrostatic interactions between the macromolecule and the drug [14 – 17]. These surfaces can be used to compare different inhibitors with substrates. Electrostatic potential surfaces will be either displayed as isocontour surfaces or mapped onto the molecular negatron density. The shape of a molecule is decided by the negatron density of the molecule. The minimum energy was calculated after geometry optimization. The geometry convergence curve is shown in Figure 5. The geometry optimized energy for streptozocin -139.373619 au (-87458.345800 kcal/mol) respectively. This is the best feasible position for streptozocin to act as an anticancer alkylating agent.

Similar results were reported recently by Ikpeazu and Co-workers [18]. They reported the electrostatic potential-mapped electron density surface and conformation analysis of an antidepressant, mirtazapine. In their study, electrostatic potential-mapped electron density surface showed the areas of the molecule that would be susceptible to nucleophilic and electrophilic attack. The predicted geometry energy was -90.575172 au (-56836.830000 kcal/mol). Khalida and Co-workers reported [19] the Conformational analysis and geometry optimization of Prasugrel as P2Y12 receptor antagonist. Conformational analysis and geometry optimization of Prasugrel was performed according to Hartree-Fock calculation method using Arguslab software. Their results indicated that the best conformation of the molecule -99561.2642 kcal/mol. At that point the molecule will be more active as P2Y12 receptor antagonist and reduce platelets aggregation more effectively [19]. Conformational Analysis of a Potent Anticancer Drug 3-(4-amino-1-oxo-1, 3-dihydro-H-isoindol-2-yl) Piperidine-2, 6-Dione (Lenalidomide) have also been published [14]. Computational conformation analysis of lenalidomide was performed according to the Hartree-Fock (HF) calculation method by ArgusLab 4.0.1 software. The minimum heat of formation was calculated by geometry convergence function by ArgusLab software. The most feasible position for the drug to interact with the receptor was found to be -23.107576 au (-14500.236400 kcal/mol).

The results of optimized bond length, bond angles, Mulliken and ZDO atomic charges are shown in Table 1-3 respectively.. The atoms with the negative charges can act as nucleophiles. They are able to donate electrons to an electrophile to form a chemical bond in relation to a reaction. They are sometimes called Lewis bases. Streptozocin has the ability to be involved in nucleophilic reaction because there are lots of negative charges in the molecule.

4. Conclusion

This research showed that the best conformation of **s**treptozocin was calculated to be -139.373619 au (-87458.345800 kcal/mol) which is the minimum potential energy calculated by Argus Lab software. At this point **s**treptozocin, will be more active as an anticancer alkylating agent. Finally all geometric variables were completely optimized and the lowest energy conformations were used in molecular modelling studies. The optimized geometries, Mulliken atomic charges and ZDO atomic charges were calculated. The modelling and the calculations does not only present to us the opportunity to take a critical look at this novel compound but has also given us the opportunity to compile fundamental result on properties that cannot be calculated in the laboratory.

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