Int. J. Chem. Sci.: 8(2), 2010, 1135-1145

DENSITY FUNCTIONAL STUDIES ON THE ELECTRONIC STRUCTURE OF GLUCOSAMINE AND ITS SALTS

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ABSTRACT

DFT (B3LYP)/6-31G calculations have been performed on the electronic structure of glucosamine and its salts. Net atomic charges, bond length, dipole moment and total energy of glucosamine and its salts were compared in order to explore the finer details of these molecules. Comparison shows that redistribution of charges on glucosamine sulphate is over larger range (- 1.413 to 1.413) as compared to glucosamine and its other salts, which favours the experimental results of pharmacokinetic studies, that glucosamine sulphate is better preferred to osteoarthritis than any of the salt of glucosamine. Further comparison of total energy from the ADMP calculations with DFT (B3LYP) at 6-31G level explains the stability and high reactivity of glucosamine sulphate.

Keywords: Quantum chemical calculations, Glucosamine salts, Electronic structure, Net atomic charges, Bond length, Dipole moment.

INTRODUCTION

Semi-empirical methods are relatively inexpensive and can be practically applied to very-very large molecular systems, because they are characterized by their use of parameters derived from experimental data in order to simplify this approximation to the Schrodinger equation. Therefore, in the recent past, it was realized that for a very large systems, one might run a semi-empirical optimization to obtain a starting structure for HF or DFT optimization. Although encouraging results were obtained by using semi-empirical methods to a reliable degree of accuracy specially for certain ground state properties but fail to reproduce all the experimental results. Since parameters suitable for some properties were not exactly suitable for other indices. Also, different sets of parameters were often suggested

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in the same approximation by different workers[1]. Furthermore, different approximate methods[2] were searched out giving varying degree of reliability and success. However, scientists working in the field were of the opinion that semi-rigorous procedures are no longer adequate for molecular electronic structure calculations[3]. The availability of quantum chemical programs (G-03W and GAUSS VIEW 4.1 VERSION)[4], which include all electrons of the systems and in which all electron integrals are evaluated without approximation, promoted us to use quantum chemical programs to explore the finer details of the electronic structure of moderate size molecules (Glucosamine and its salts) of biological importance to provide reliable and fairly accurate information on the electronic structure of these molecules. Electronic structure theory is one of the broad area within which the computational chemistry devoted to the structure of molecules and reactivity. It provides information about molecular systems and chemical reactions, which is probably not possible to obtain through observation. The study of the electronic structure and spectra[5] of these molecules have been chosen on the grounds that we wanted to search out a better treatment or proper remedy for osteoarthritis, which was a long awaited question in the mind of chemists. The first drug used in the treatment of osteoarthritis was aspirin. It is often quite effective in relieving both; the pain and inflammation and is also fairly inexpensive but because of relatively high toxicity, it is not preferred. There are other nonsteroidal anti-inflammatory drugs (NSAIDs) in the market but should not be preferred as they appear to suppress the symptoms but accelerate the progression of osteoarthritis[6-11]. In such situations, a naturally occurring substance found in high concentrations in joint structures appears to be nature's best remedy for osteoarthritis and this compound is glucosamine sulphate. But why and how it works better than any other glucosamine salts and NSAIDs, it remains a big question and therefore, a knowledge of the electronic structure of glucosamine and its related salts with DFT(B3LYP)/6-31G is of basic importance for a deeper understanding of their reactivities and spectral properties, as it includes electron correlation, which accounts for the instantaneous interactions of pairs of electrons with opposite spin, and it also provide the benefits of some more expensive *ab initio* methods at essentially Hartree-Fock cost. Therefore, we have given more emphasis on the study of their electronic properties. Several features of the electronic structure can be understood with help of ADMP calculations. Detailed analysis of electronic properties of organic molecules has also played an important role for a long time determining their molecular structures, intermolecular and intramolecular forces.

Computational method

Ab initio HF/6-31G method was used for initial geometry optimization and then DFT(B3LYP)/6-31G optimization of glucosamine and its hydrochloride, n-acetyl, sulphate salts was performed in order to include terms accounting for both; exchange energy and the

electron correlation, which has not been included in Hartree-Fock theory. Besides other electronic properties, ADMP calculations of glucosamine and all its salts at DFT (B3LYP)/6-31G are also calculated. A classical trajectory calculation[12-15] using the Molecular Dynamics Model[16-18], provides equivalent functionality to Born-Oppenheimer Molecular Dynamics at considerably reduced computational cost. All calculations in the present work were carried out in the Department of Physics, Paliwal (P.G.) College, Shikohabad on Pentium IV using G-03W and GAUSS VIEW 4.1 VERSION (4) of *ab initio* quantum mechanical program.

RESULTS AND DISCUSSION

The values of the net charges at various atomic sites in the units of 'e' are shown in Table 1. These are obtained through Mulliken Population Analysis using DFT(B3LYP)/6-31G method. The positive and negative values of the net charges at various atomic sites in a molecule are indicative of the fact that, the total charges on the orbitals after the molecule is formed are less or more than the free atomic charges. All the carbon of the glucosamine have less or more positive charges attached to electrophilic –OH group and all oxygen have negative charges, which shows that there is a migration of charges from carbon to the phenolic oxygen. More the charges given to the substitutents, more they will be free to react, means greater is the +I effect, greater will be reactivity. Further, more the +ve charge on the 'H' attached to the ring, more the reactive site, it will be. But because of the steric hinderance of the ring to the NH_2, the hydrogens of NH_2 are less electropositive as compared to H_{19}. Bond lengths of O_{17}-H_{19}, N_{16}-H_{22}, N_{16}-H_{23} are 1.0003Å, 1.0169 Å and 1.0169 Å, respectively. Among all –O-H, O_{17} has most negative charge and O_{17}-H_{19} has the greatest bond length. Similarly, N also has greater degree of negative charge and N_{16}-H_{22}, N_{16}-H_{23} bond lengths are more than any the of O-H bond length, which shows that these are the most reactive sites of glucosamine.

Table 1: Net atomic charges (in units of electron)

Glucosamine	Glucosamine hydrochloride	N-Acetyl glucosamine	Glucosamine sulphate
C_1 0.285136	C_1 0.255190	C_1 0.271133	C_1 0.293929
O_2 -0.526874	O_2 -0.516249	O_2 -0.547313	O_2 -0.543787

Cont…

Glucosamine	Glucosamine hydrochloride	N-Acetyl glucosamine	Glucosamine sulphate
C_3 0.063780	C_3 0.092874	C_3 0.105941	C_3 0.141855
C_4 0.113115	C_4 0.099319	C_4 0.089514	C_4 0.09585
C_5 0.0.052566	C_5 0.081620	C_5 0.057003	C_5 0.107786
C_6 0.008944	C_6 -0.023384	C_6 0.032308	C_6 -0.014441
H_7 0.147419	H_7 0.232950	H_7 0.176938	H_7 0.157987
C_8 0.011249	C_8 -0.009571	C_8 -0.048031	C_8 -0.097148
O_9 -0.616408	O_9 -0.621821	O_9 -0.622496	O_9 -0.628549
H_{10} 0.198852	H_{10} 0.177529	H_{10} 0.183315	H_{10} 0.156909
H_{11} 0.160093	H_{11} 0.214273	H_{11} 0.209898	H_{11} 0.154009
O_{12} -0.607430	O_{12} -0.614031	O_{12} -0.599177	O_{12} -0.647233
H_{13} 0.154330	H_{13} 0.170413	H_{13} 0.161066	H_{13} 0.188192
H_{14} 0.140374	H_{14} 0.165911	H_{14} 0.157460	H_{14} 0.156408
O_{15} -.613532	O_{15} -0.607412	O_{15} -0.606256	O_{15} -0.626226
N_{16} -0.739055	N_{16} -0.742137	N_{16} -0.667464	N_{16} -0.711199

Cont…

Glucosamine	Glucosamine Hydrochloride	N-Acetyl Glucosamine	Glucosamine Sulphate
O_{17} -0.654400	O_{17} -0.653186	O_{17} -0.617243	H_{17} 0.225307
H_{18} 0.126057	H_{18} 0.166494	H_{18} 0.143911	H_{18} 0.426982
H_{19} 0.406690	H_{19} 0.390955	H_{19} 0.373347	H_{19} 0.295154
H_{20} 0.166306	H_{20} 0.180015	H_{20} 0.202313	H_{20} 0.294083
H_{21} 0.372465	H_{21} 0.388449	H_{21} 0.376181	H_{21} 0.384298
H_{22} 0.315806	H_{22} 0.356164	H_{22} 0.357195	H_{22} 0.374875
H_{23} 0.299091	H_{23} 0.293226	C_{23} 0.520194	O_{23} -0.516035
H_{24} 0.363115	H_{24} 0.373349	H_{24} 0.366331	S_{24} 1.412964
H_{25} 0.372310	H_{25} 0.378299	H_{25} 0.378100	O_{25} -0.596012
	Cl_{26} -0.648299	C_{26} -0.475373	O_{26} -0.500136
	H_{27} 0.417375	O_{27} -0.481921	O_{27} -0.596584
		H_{28} 0.143237	H_{28} 0.407247
		H_{29} 0.182895	H_{29} 0.204209
		H_{30} 0.176992	

Table 2: Bond length (in units of Å)

Glucosamine		Glucosamine hydrochloride		N-Acetyl glucosamine		Glucosamine sulphate	
Bonded atoms	**Bond length**	**Bonded atoms**	**Bond length**	**Bonded atoms**	**Bond length**	**Bonded atoms**	**Bond length**
C_1-O_2	1.4309	C_1-O_2	1.444	C_1-O_2	1.4535	C_1-O_2	1.4535
C_1-C_6	1.532	C_1-C_6	1.5295	C_1-C_6	1.5378	C_1-C_6	1.5279
C_1-H_7	1.0963	C_1-H_7	1.0932	C_1-H_7	1.0922	C_1-H_7	1.0946
C_1-O_{12}	1.4506	C_1-O_{12}	1.4424	C_{1O}-O_{12}	1.4407	C_1-O_{12}	1.4359
O_2-C_3	1.4947	O_2-C_3	1.4768	O_2-C_3	1.4836	O_2-C_3	1.4716
C_3-C_4	1.5316	C_3-C_4	1.5374	C_3-C_4	1.5341	C_3-C_4	1.529
C_3-C_8	1.528	C_3-C_8	1.5194	C_3-C_8	1.5411	C_3-C_8	1.5152
C_3-H_{13}	1.0951	C_3-H_{13}	1.0959	C_3-H_{13}	1.0941	C_3-H_{13}	1.094
C_4-C_5	1.5359	C_4-C_5	1.5396	C_4-C_5	1.5311	C_4-C_5	1.5478
C_4-O_9	1.447	C_4-O_9	1.4497	C_4-O_9	1.4504	C_4-O_9	1.4555
C_4-H_{14}	1.0985	C_4-H_{14}	1.0956	C_4-H_{14}	1.096	C_4-H_{14}	1.0954
C_5-C_6	1.556	C_5-C_6	1.5493	C_5-C_6	1.55	C_5-C_6	1.553
C_5-H_{10}	1.0903	C_5-H_{10}	1.0919	C_5-H_{10}	1.0918	C_5-H_{10}	1.0935
C_5-O_{15}	1.4611	C_5-O_{15}	1.4571	C_5-O_{15}	1.462	C_5-O_{15}	1.4514
C_6-H_{11}	1.0995	C_6-H_{11}	1.0918	C_6-H_{11}	1.0939	C_6-H_{11}	1.1022
C_6-H_{16}	1.4768	C_6-N_{16}	1.5039	C_6-N_{16}	1.4599	C_6-N_{16}	1.4602
C_8-O_{17}	1.44	C_8-O_{17}	1.4684	C_8-O_{17}	1.46	C_8-H_{17}	1.0922
C_8-H_{18}	1.1006	C_8-H_{18}	1.0951	C_8-H_{18}	1.0962	C_8-O_{23}	1.4908
C_8-H_{20}	1.0923	C_8-H_{20}	1.0934	C_8-H_{20}	1.0892	C_8-H_{29}	1.0925
O_9-H_{25}	0.9799	O_9-H_{25}	0.9792	O_9-H_{25}	0.9801	O_9-H_{22}	0.978
O_{12}-H_{21}	0.9788	O_{12}-H_{21}	0.977	O_{12}-H_{21}	0.9781	O_{12}-H_{18}	0.9893

Cont…

Glucosamine		Glucosamine hydrochloride		N-Acetyl glucosamine		Glucosamine sulphate	
Bonded atoms	**Bond length**	**Bonded atoms**	**Bond length**	**Bonded atoms**	**Bond length**	**Bonded atoms**	**Bond length**
O_{15}-H_{24}	0.9816	O_{15}-H_{24}	0.982	O_{15}-H_{24}	0.981	O_{15}-H_{21}	0.9848
N_{16}-H_{19}	1.8175	N_{16}-H_{22}	1.0219	N_{16}-H_{22}	1.0158	N_{16}-H_{19}	1.0121
N_{16}-H_{22}	1.0169	N_{16}-H_{23}	1.1207	N_{16}-C_{23}	1.3711	N_{16}-H_{20}	1.0125
N_{16}-H_{23}	1.0169	,N_{16}-H_{27}	1.0419	O_{17}-H_{19}	0.9817	H_{18}-O_{25}	1.8306
O_{17}-H_{19}	1.0003	O_{17}-H_{19}	0.9749	O_{17}-H_{22}	2.012	O_{23}-S_{24}	1.7964
		H_{23}-Cl_{26}	1.8229	C_{23}-C_{26}	1.5153	O_{24}-O_{25}	1.6321
				C_{23}-O_{27}	1.2534	S_{24}-O_{26}	1.6065
				C_{26}-H_{28}	1.0938	S_{24}-O_{27}	1.7879
				C_{26}-H_{29}	1.0957	O_{27}-H_{28}	0.9914
				C_{26}-H_{30}	1.0933		

The effect of the HSO_4^- (Hydrogen sulphate) group at C_8 of the alkyl group can be seen on all the carbons of glucosamine sulphate, that migration of charges from all the ring carbons to the corresponding oxygen of –OH attached to them; thereby, making them more negative and hence, hydrogens of –OH becomes more +ve means glucosamine sulphate has more reactive sites as compared to glucosamine, glucosamine hydrochloride and N-acetyl glucosamine. A molecular property closely related to the asymmetry and charge distribution in a molecule is its electric dipole moment. This property is of fundamental importance not only because experimental values of this quantity help in establishing the validity of the calculated charge distributions but also changes in the normal coordinates determine the intensity of the band observed in the infrared spectrum of the molecule. It is known that the dipole moment should increase with the increasing electronegativity of the substituent, the calculated dipole moments presented in Table 3 show similar results. It was found that the magnitude of the dipole moment depends on the substituent being in the order Cl >OH >$NHCOCH_3$ > HSO_4^-. From this we can say that glucosamine sulphate is more symmetric molecule as compared to its other salts because it has the least dipole moment. As ADMP requests the classical trajectory calculation using atom centered density Matrix Propagation Molecular Dynamics Model. ADMP belongs to the extended Lagrangian approach to molecular dynamics using Gaussian basis function and propagating the density matrix. It

shows the trajectory of breaking the molecule with the time. If energy is supplied to glucosamine upto-666.974870 Hatree, then within 3.90 femtosecond six hydrogen (H_{11}, H_{14}, H_{24}, H_{25}, H_{19}, H_{20}) detaches from their respective positions. There is only deformation of glucosamine hydrochloride structure but no detachment of hydrogen from it even upto 5 femtosecond and -1127.792613 Hatree, which shows that more energy is required to break glucosamine hydrochloride. N-Acetyl glucosamine shows four detachments of hydrogen (H_{10}, H_{19}, H_{30}, H_7) upto 3.90 femtosecond and -819.595042 Hatree after 3.90 femtosecond rejoining of atoms occur and in case of glucosamine sulphate, there are detachment of five hydrogens (H_{10}, H_{13}, H_{19}, H_{22}, H_{29}) upto 3.10 femtosecond and -1290.51997 Hatree after this there is rejoining of detached atoms to the molecule. From the above observations and the total energy curves of glucosamine and its salts, it is found that the energy required to release the hydrogens from glucosamine and its salts are in the order glucosamine > N-Acetyl glucosamine > Glucosamine hydrochloride > Glucosamine sulphate. Therefore, it is concluded that glucosamine sulphate is more reactive as compared to glucosamine and its other salts. Thus, we can say that our theoretical electronic study of glucosamine and its salts, the glucosamine sulphate is most reactive and stable biomolecule, which favours the results of pharmacokinetic[19,20] study on animals and human being, that up to 98% of glucosamine sulphate is absorbed and it is better preferentially taken up by cartilage and other joint structures, where it then simulates the manufacture of other mucopolysaccharides.

Table 3: Dipole moments (in units of Debye)

Molecules	Glucosamine	Glucosamine hydrochloride	N-Acetyl glucosamine	Glucosamine sulphate
Dipole moment	4.7557	9.9642	3.3225	1.4872

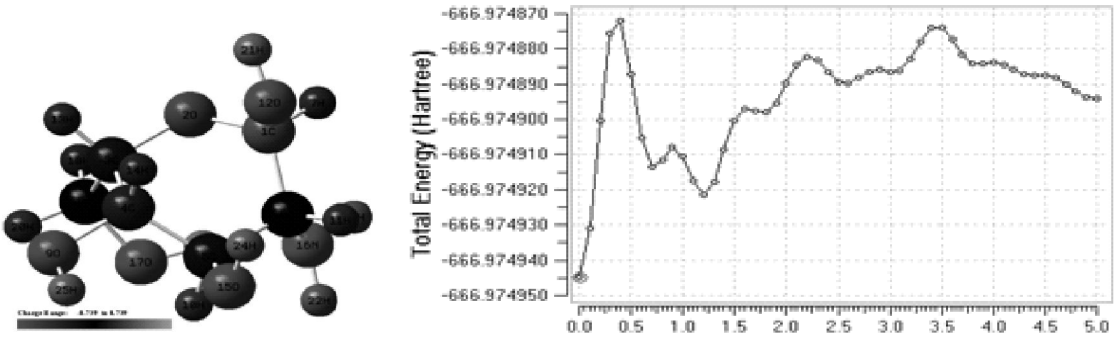

Fig. 3 (a): Total energy vs time trajectory curve of glucosamine

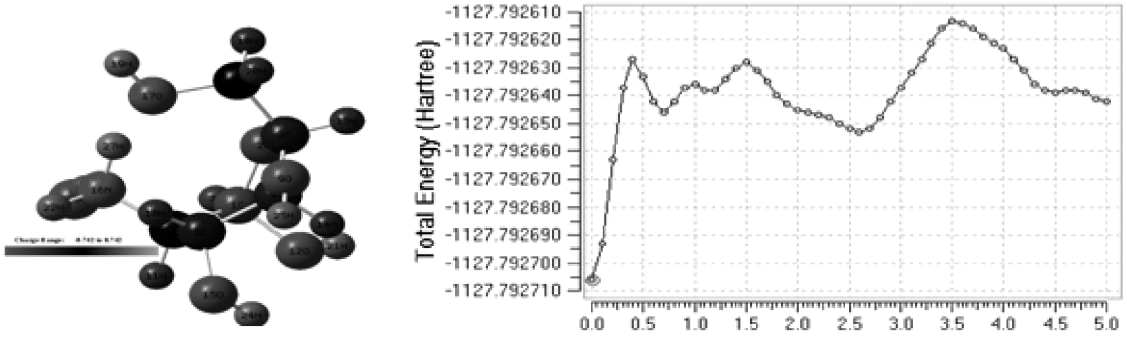

Fig. 3 (b): Total energy vs time trajectory curve of glucosamine hydrochloride

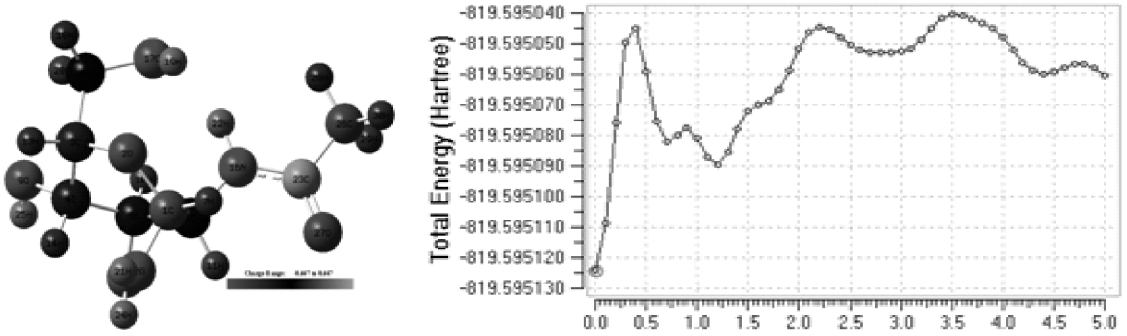

Fig. 3 (c): Total energy vs time trajectory curve of N-acetyl glucosamine

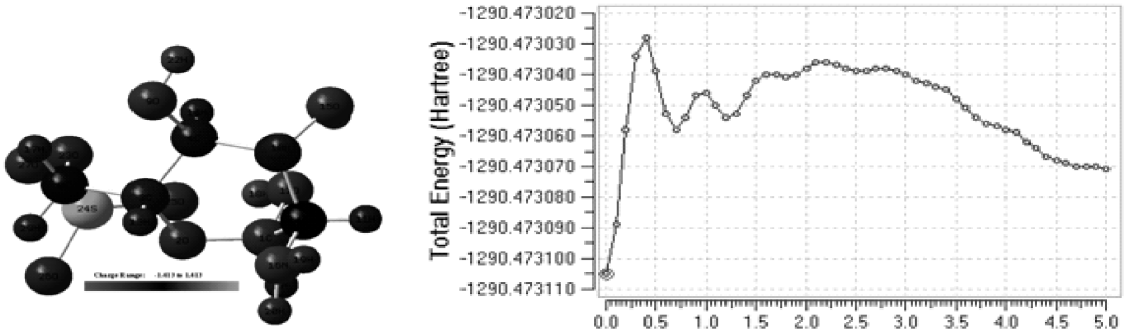

Fig. 3 (d): Total energy vs time trajectory curve of glucosamine sulphate

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Accepted : 19.12.2009