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Molecular Optimization Study of Gentamicin Drug

Abbas A-Ali Drea* and Marwa Kamil Jalil

University of Babylon, College of Science, department of Chemistry, Hilla-Iraq

Abstract: Molecular optimization have been carried out in vacuumed to investigate the energetic properties of geometry optimized structure of Gentamicin drug. Theoretical methods like, Semi empirical methods and Density functional method have been performed to estimate the chemical reactivity through calculations of Energy gap, Binding energy, Heat of formation and Zero point energy. The reactivity of the molecule has been investigated using Surface potential energy calculations through PM3-Single point Configuration Interaction (3*3), Microstate method to examination chemical bound stability of main bounds in Gentamicin drug molecule through bond angle, bond length and torsion angle. The vibration spectrum and electronic spectrum have been calculated by semi empirical CNDO method and DFT (Minimal STO-3G level). The best conformations of Gentamicin molecule has been studied through rotation of most reactive bound torsion angle C_{19}-N_{26}-C_{27}-H_{62}.

They found, the energetics values of total energy , MP2 Correlation Energy, E_{gap} and Zero point according to DFT(Minimal STO-3G level of theory) are equal to -298643.889, -1553.812, 1.37284,and -3763.39691 respectively at kCal/mol units. The N_{26}-C_{19} bond in Gentamicin represented the most probable to break down and shared in various reactions than other duo to the lowest bond dissociation energy value (75.734 kCal/mol). The conformations has most stable energy through energetic value equal to -6835.4145 kCal/mol.

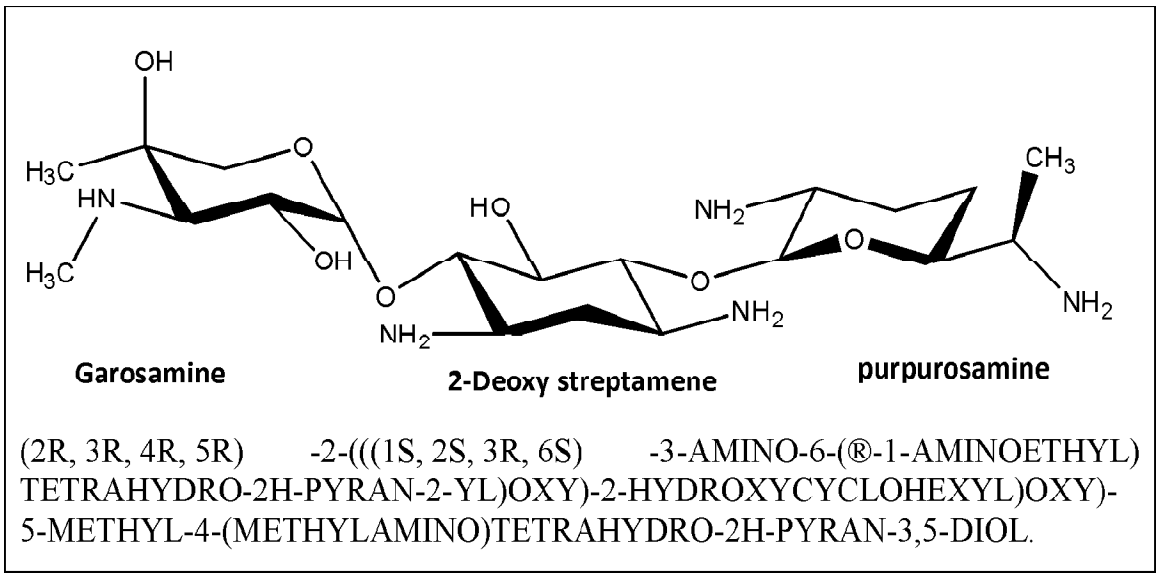
Key words: Gentamicin, potential energy surface, Geometry optimization, Single point calculations, DFT, Semi-empirical.

Introduction

Gentamicin is the antibiotic of first choice for treatment serious bacterial infections in bone, respiratory, skin, urinary tract, stomach, soft tissue, blood and heart in form of injection, ointment, cream, suspension and also used in Veterinary Medicine in many developed and industrialized countries[1-3]. Gentamicin has been discovered in 1963 by Marvin Weinstein's set at Schering Plough through isolated from various species of the micro mono sporia echinospora [4, 5]. Gentamicin is a commonly used as aminoglycoside antibiotics [6]. Gentamicin has been designed from three rings purpose amine, 2-deoxy strep amine and gentos amine or garos amine ring [7], since the major compounds of

Corresponding author: aadreab22@yahoo.com*

Gentamicin are differ in purpose amine component. The four major compounds of complex mixture for Gentamicin are C, C1a and C2a, a 6´-C-epimer of C2 [8, 9]. The other minor compounds that present include Gentamicin's A,A1,A2,A3,C2a,C2b,A4,B,B1and X2, and JI-20A,JI-20B,Sisomicin and G-418 have been described which are other antibiotics structurally related to Gentamicin[10,11]. It was one of few antibiotics thermally-stable that remains active until after sterilization process [12]. Gentamicin drug fundamentally acts by binding to the 30S subunit of the bacterial ribosome stopping the continuous progress of protein synthesis [13].The two hydroxyl groups of deoxystreptamine(2-DOS) linked to Garosamine (3-methyl amino-3-deoxy-4-C-methyl-β-L-arabinose) and purpurosamine (2,6-diamino-2,3,4,6,7_pentadeoxyheptopyranose) amino sugars by glycosides' bonds, the amino groups in the two surges attached to (2-DOS) profoundly influence on the biological activity but presence or absence of hydroxyl groups not have a clear effect on the activity of aminoglycosides antibiotics. Figure 1. Show two dimensional view of the Gentamicin molecule [14-16].



(2R, 3R, 4R, 5R) -2-(((1S, 2S, 3R, 6S) -3-AMINO-6-(®-1-AMINOETHYL) TETRAHYDRO-2H-PYRAN-2-YL)OXY)-2-HYDROXYCYCLOHEXYL)OXY)-5-METHYL-4-(METHYLAMINO)TETRAHYDRO-2H-PYRAN-3,5-DIOL.

Figure 1: Two dimensional view of the Gentamicin molecule [14-16]

They found several types of Gentamicin with different chemical activities due their structures, that's related to energetics properties and energy gaps for each of these stractures. The aim of the present work tend to find the molecular optimized structure towards the chemical activity of Gentamicin. The quantum mechanics calculation methods have been used, since different methods of semi-empirical and DFT- STO-3G at level of theory, to estimate the geometry optimization, heat formation, total energy, HOMO&LUMO, Energy gap, vibration spectrum, and electronic spectrum. Also Surface potential energy was used to investigate the reactivity of main chemical bonds that's consistent gentamicin molecule structure [17].

Computational Details

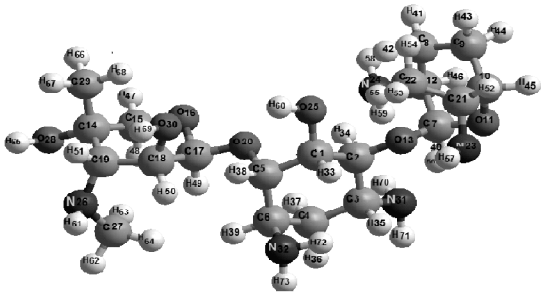
Computations have been done using quantum methods that's implemented at Hyperchem program version 8.0.2 [18-20]. DFT, Minimal STO-3G at level of theory have been used to find out Geometrical properties, likes electrostatic potential, total charge density, HOMO and LUMO energy, Zero point energy, vibration spectrum and electronic spectrum [21]. Semiempirical calculation have been performed using several methods like MNDO, CNDO, INDO, MNDO3, AM1 and RM1 and to estimate energetic properties, that's followed by using DFT, Minimal STO-3G at level of theory for the same manner[22]. Potential energy stability of bond length, bond angle and torsion angle have been examined using PM3 method CI (3*3) Microstate to estimate the chemical reactivity of main bound in Gentamicin drug[23].

Results and Discussion

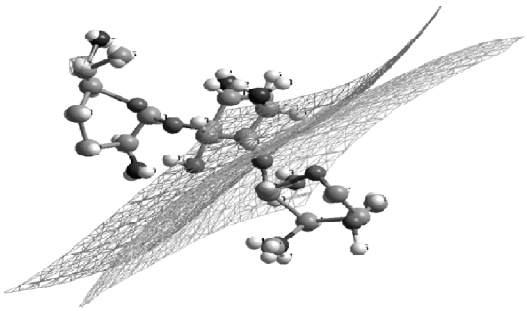
The Geometry optimization structure of gentamicin molecule is represented in figure 1. They found that properties such electrostatic potential and their molecular orbitals are distributed at different active sites. The chemical structure is consisted from three different sugar rings and chemical reactivity of the substituted functional groups on these ring are differ at different orientations due their different induced field effect, such amine groups, hydroxyl groups, and methyl amine . Table 1. Involved energetic values of optimized gentamicin, the total energy value with full MP2 -300197.701 kCal mol^{-1} is comes due geometry optimization process in vacuumed. Zero point energy (ZPE) value is calculated as a result of vibrational spectrum data that's equal to -3763.39691 kCal mol^{-1} is much stabilized structure and relax molecules due to this low value of ZPE. The cost time of calculus is 542 hours, 54 mints and 31 second. The red color regions of electrostatic potential that observed in figure 1&2 show high electron density on oxygen atoms due to the high electronegativity, while the green color reigns represented the low electron density of carbon atoms. The HUMO and LUMO energies have been appeared in red and green color, the negative part of wave function has been given by red color (subject attacked by an electrophile) and the green color represented the positive part of wave function (subject attacked by nucleophile), this behavior determine chemical effectiveness of Gentamicin molecule toward the substitution reaction [24-27].

Table 1
Energetic properties of Gentamicin molecule calculated at DFT Minimal STO-3G at level of theory

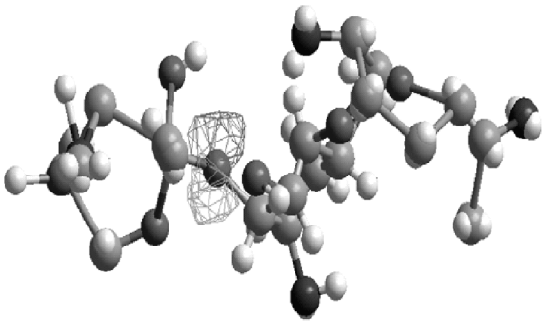
Total energy (kCal/mol)	-298643.889
Total energy with MP2 (kCal/mol)	-300197.701
MP2 Correlation Energy (kCal/mol)	-1553.812
LUMO (eV)	55.92773
HOMO (eV)	54.55486
Energy gap (eV)	1.37284
Zero point energy (kCal/mol)	-3763.39691
Time of calculus (hr.min.sec)	542:54:31



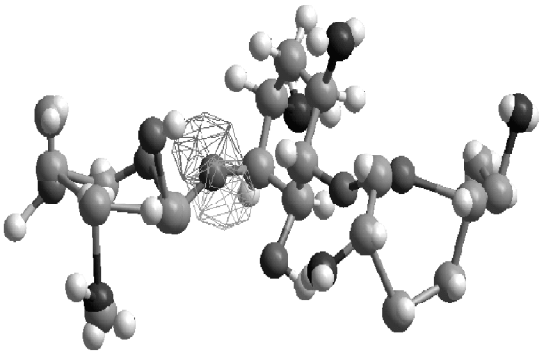
Geometry optimization



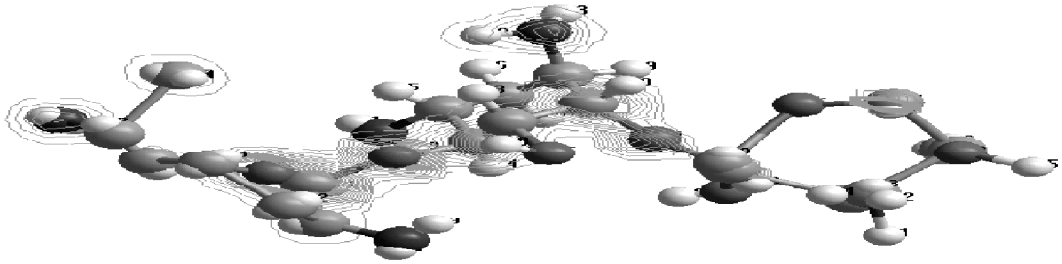
Electrostatic potential



LUMO at three dimensions



HOMO at three dimensions



Total charge density

Figure 2: Geometrical optimization properties of Gentamicin molecule calculated by DFT, Minimal STO-3G at level of theory

Surface Potential energy calculation have been used to investigated the stability of bond length and bond angle for the bounds of Gentamicin molecule through PM3 Configuration Interaction microstate (3*3), as shown in Table. They found that's bonds of C_{14}-O_{28} and C_{18}-O_{30} were more stable than other bonds with 108.354 and 104.548 kCal/mol respectively of dissociation energy values than other bounds. From other view Figure 2. Shows the four bond with lowest chemical stability than other chemical bounds of Gentamicin molecule, since the red color on C_{14}-O_{28} and C_{18}-O_{30} bonds appears their higher

stability than other two bonds C_{19}-N_{26} and C_{10}-C_{21} bonds in yellow color. The lowest chemical stability due to the induced effect field of substituted functional groups that found in the molecule (N atom have electronegativity less than O atom, leads to weak hydrogen linkage in the amines group compared with a hydroxyl group and thus easily broken and shared in important reactions).

Table 2
Surface Potential energy calculation of chemical bonds Semiemprical-PM3 method CI (3*3) Microstate

Bonds	**Equilibrium energy*	***Equilibrium bond length*	**Dissociation energy*	***Dissociation bond length*	**Energy difference*
C_2-O_{13}	-6835.467	1.927	-6751.963	2.326	83.504
C_7-O_{13}	-6835.302	1.427	-6751.080	2.826	84.222
C_5-O_{20}	-6835.450	1.427	-6748.511	2.627	86.939
C_{17}-O_{20}	-6835.146	1.427	-6737.786	2.327	97.36
C_{21}-N_{23}	-6834.811	1.527	-6753.967	2.627	80.844
C_6-N_{32}	-6834.801	1.527	-6754.999	2.627	79.802
C_3-N_{31}	-6834.985	1.527	-6754.030	2.627	80.955
C_{12}-N_{24}	-6834.914	1.527	-6742.434	2.827	92.48
C_{19}-N_{26}	**-6834.991**	**1.527**	**-6759.257**	2.627	**75.734**
C_{10}-C_{21}	-6835.109	1.527	-6759.148	2.827	75.961
C_{14}-O_{28}	-6835.449	1.427	-6727.095	2.427	108.354
C_{18}-O_{30}	-6835.181	1.427	-6730.633	**2.427**	104.548
C_1-O_{25}	-6835.192	1.427	-6737.128	2.827	98.064
C_{21}-C_{22}	-6835.439	1.527	-6747.763	2.827	87.676
C_{14}-C_{29}	-6835.394	1.527	-6752.386	2.827	83.008
N_{26}-C_{27}	-6834.412	1.527	-6751.304	2.527	83.108

* kCal/mol units. ** Angstrom units

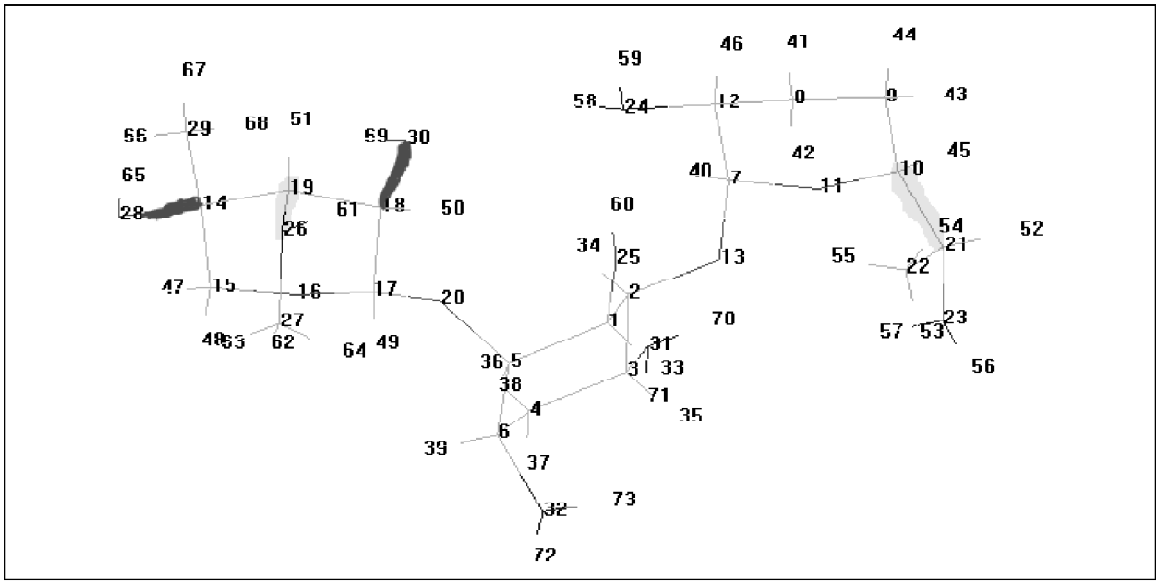


Figure 3: The lowest chemical stability bonds of Gentamicin molecule (active bonds)

Figure 4. Illustrates the potential energy stability of bonds at Gentamicin molecule. The C_2-O_{13} bond is lowest stable and more active toward the reactions than other bond, since bond length equal to 1.927 ú. The difference in the stability of the bonds depends on the nature of substituted functional groups (tendency to donate or draw electrons) and also their steric effects of each bond in the bulk structure.

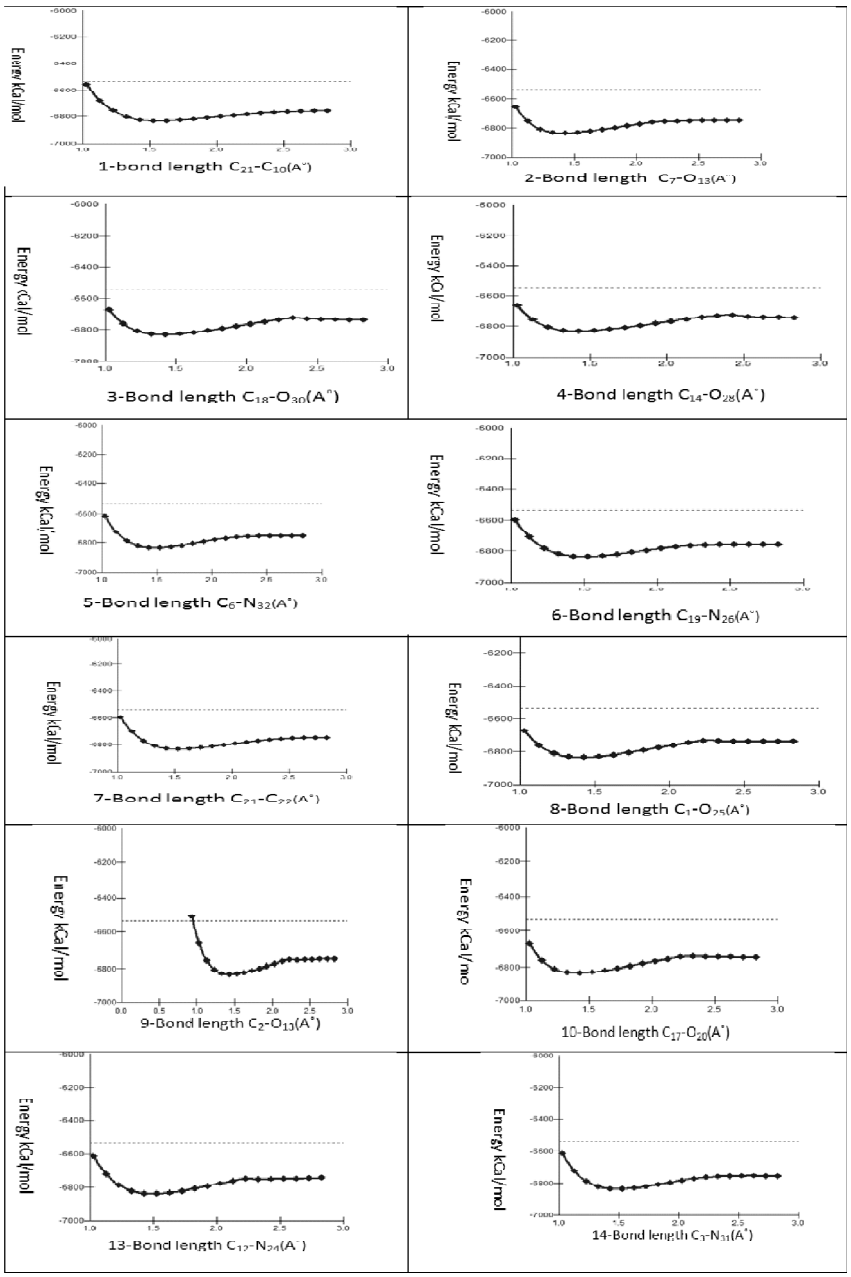


Figure 4: Potential energy stability curves of bond length in Gentamicin molecule calculated at semi emprical PM3 CI.Microstate (3*3)

Table 3. Show the calculation of bound angle stability toward the torsion energy stresses and their related equilibrium configuration as active site at Gentamicin structure. Comperes between all the chemical bounds described that, bond angle O_{13}-C_7-C_{11} angle is more stable than other bond angles due their dissociation energy value of 615.711 kCal/mol [28].

Table 3
Surface Potential energy investigation of Gentamicin bond angle calculated at semi empirical –PM3, CI (3*3) Microstate

Bond angle	**Equilibrium bound energy*	***Equilibrium bond angle*	**Dissociation bond energy*	***Broking bond angle*	**Energy difference*
C_{21}-C_{10}-C_9	-6834.4438	110	-6807.3588	140	27.085
C_{21}-C_{10}-C_{11}	-6834.2270	120	-6806.6005	140	27.627
N_{23}-C_{21}-C_{10}	-6835.4672	110	-6800.2763	140	35.191
C_{29}-C_{14}-C_{28}	-6835.3413	110	-6790.5341	140	44.807
N_{26}-C_{19}-C_{18}	-6834.5932	110	-6803.9326	140	30.661
N_{26}-C_{19}-C_{14}	-6834.7910	110	-6805.7739	140	29.017
C_{27}-N_{26}-C_{19}	**-6834.9833**	**120**	**-6822.2983**	**140**	**12.685**
O_{30}-C_{18}-C_{19}	-6835.3989	110	-6803.3569	140	32.042
O_{30}-C_{18}-C_{17}	-6834.8481	110	-6810.2363	140	24.612
N_{23}-C_{21}-C_{22}	-6834.7915	110	-6789.6723	140	45.119
C_{19}-C_{14}-C_{28}	-6835.1088	110	-6803.7934	140	31.315
C_{29}-C_{14}-C_{15}	**-6835.4667**	110	-6801.0942	140	34.373
N_{32}-C_6-C_4	-6834.6279	110	-6813.6079	140	21.02
N_{32}-C_6-C_5	-6835.4580	110	-6802.7153	140	32.743
O_{25}-C_1-C_5	-6835.4526	110	-6794.6425	140	40.810
O_{25}-C_1-C_2	-6833.9047	120	-6810.5952	140	23.309
N_{31}-C_3-C_4	-6835.3852	110	-6796.5888	140	38.796
N_{31}-C_3-C_2	-6835.4658	110	-6804.6333	140	30.833
N_{24}-C_{12}-C_7	-6835.4399	110	-6804.6567	140	30.783
C_2-O_{13}-C_7	-6834.901	120	-6820.601	140	14.300
C_{17}-O_{20}-C_5	-6834.779	110	-6819.388	140	15.392
C_{18}-O_{17}-C_{20}	-6835.323	110	- 6806.133	140	29.19
O_{20}-C_{17}-O_{16}	-6835.0009	100	-6775.118	140	59.882
O_{20}-C_5-C_6	- 6835.164	110	-6787.224	140	47.94
C_3-C_2-O_{13}	-6835.416	110	-6730.334	140	105.082
O_{13}-C_2-C_1	-6834.943	110	-6783.069	140	51.875
O_{13}-C_7-C_{11}	**-6835.456**	**100**	**-6219.745**	**130**	**615.711**
O_{13}-C_7-C_{12}	-6833.747	120	-6811.620	140	22.127
O_{20}-C_5-C_1	-6835.466	110	-6803.631	140	31.835

Table 4 shows the Potential energy stability of the mean torsion angles in Gentamicin molecule. The bound angle C_2-O_{13}-C_7-C_{12} is represented more stable bound than other bounds due to their requirements for 3037.6617 kCal/mol to break down, also the dissociation energy value of the bound angle C_{19}-N_{26}-C_{27}-H_{62} is equal to 3.231 kCal/mol,

so that it's represented the lowest stable than other angles of gentamicin [29]. Figure 5 Show comparison between these two bonds, the high stable bond defined in red color and the lowest stable in yellow color.

Table 4
Potential energy stability and dissociation of Gentamicin Torsion angle by Semiemprical-PM3 method CI(3*3)

Bond Torsion angles	**Equilibrium energy*	***Equilibrium Torsion angle*	**Dissociation energy*	***Broking Torsion angle*	**Dissociation energy of angle*
C_6-C_5-O_{20}-C_{17}	-6834.7261	120	-6736.3330	180	98.3931
C_{18}-C_{17}-O_{20}-C_5	-6834.9556	130	-6829.4888	180	5.4668
C_2-O_{13}-C_7-C_{12}	**-6834.5577**	**90**	**-3796.8960**	**180**	**3,037.6617**
C_1-C_5-O_{20}-C_{17}	-6831.0410	180	-6752.6841	60	78.3569
C_7-O_{13}-C_2-C_1	-6803.3691	180	-6118.7456	100	684.6235
C_{22}-C_{21}-C_{10}-C_9	-6834.4434	170	-6829.2099	110	5.2335
C_3-C_2-O_{13}-C_7	-6834.0347	110	-6444.9834	180	389.0513
C_{11}-C_7-O_{13}-C_2	-6821.1719	180	-5192.0469	70	1,629.125
O_{16}-C_{17}-O_{20}-C_5	-6826.2759	180	-6761.5801	90	64.6958
C_{27}-N_{26}-C_{19}-C_{18}	-6832.7802	140	-6820.0845	180	71.2001
N_{23}-C_{21}-C_{10}-C_9	-6834.4331	130	-6824.4809	100	9.9522
N_{23}-C_{21}-C_{10}-C_{11}	-6834.3843	160	-6828.9585	110	5.4258
C_{27}-N_{26}-C_{19}-C_{14}	-6834.3779	60	-6828.5972	150	5.7807
C_{22}-C_{21}-C_{10}-C_{11}	-6832.6406	60	-6828.61377	180	4.02683
C_{19}-N_{26}-C_{27}-H_{62}	**-6835.4145**	**180**	**-6832.1835**	**140**	**3.231**
C_{19}-N_{26}-C_{27}-H_{63}	-6833.7505	60	-6829.4551	140	4.2954
C_{19}-N_{26}-C_{27}-H_{64}	-6834.4927	60	-6830.1133	140	4.3794

The C_{19}-N_{26}-C_{27}-H_{62} torsion angle represented the more stable from other in Potential energy stability value by -6835.4145 kCal/mol in 180^{Ú} due to the functional groups that found in the molecule. Different optimized structures (configurations) can be occurs at Gentamicin through different transitions torsion angle states into C_{19}-N_{26}-C_{27}-H_{62} angle. Figure 5 Show that the torsion angle of C_{19}-N_{26}-C_{27}-H_{62} in Gentamicin molecule includes the presence of several cases of branches transition to vibrate bond chemical angle in different energies for getting the best situation stabilizing steric optimum , it's have several stationary point such as A, C and E are minimal . Points such as B and D are maximum energetic states. Only structures at points A, C and E represented the stable conformations for this torsion angle. the lowest energy conformation was the anti-conformation in structure E, it was the most stable from other by -6835.4145 kCal/mol in 180^{Ú} due to the molecule arranged its groups to adopt the alleviated torsional strain and reduced the electron repulsion in the torsion angle [31].

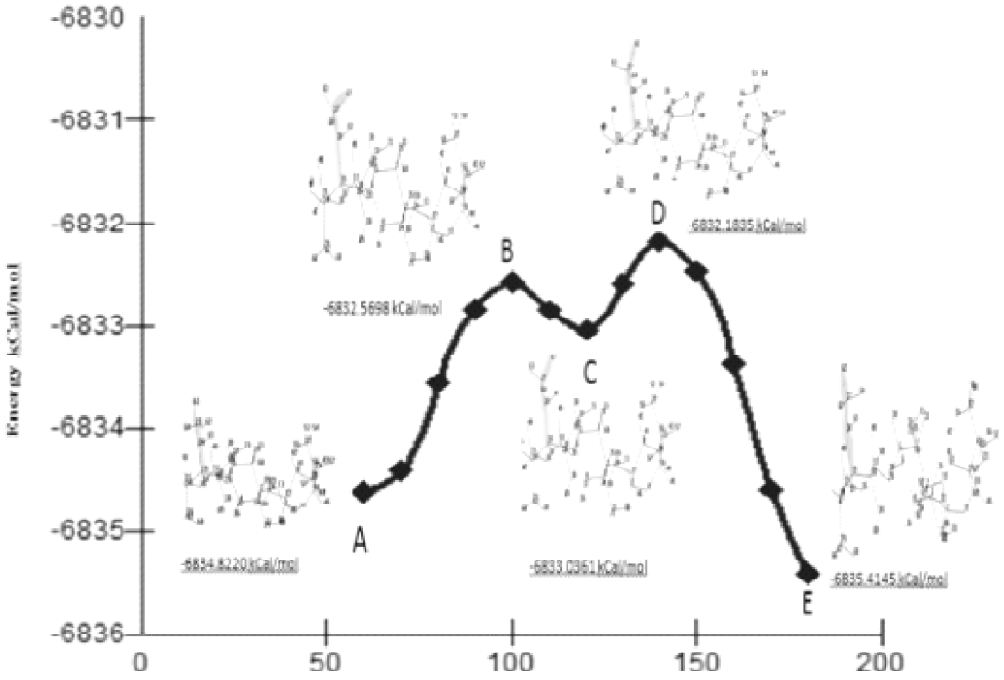


Figure 5: Surface potential energy curve of torsion angle C_{19}-N_{26}-C_{27}-H_{62} of Gentmicine

CONCLUSIONS

- The Energetic properties of Gentamicin molecule have been found by using several semi empirical methods and DFT calculations.
- The chemical reactivity of the molecule appeared the N_{26}-C_{19} bond length the most probable to break down by using S.P.E calculations duo to the less value of bond dissociation energy (75.734kCal/mol)of functional group (methyl amine) at Garosamine.
- The bond angle O_{13}-C_7-C_{11} angle is more stable than other bond angles due their dissociation energy value of 615.711 kCal/mol.
- The bound angle C_2-O_{13}-C_7-C_{12} is more stable bound than other bounds due to their requirements for 3037.6617 kCal/mol to break down.
- The C_{19}-N_{26}-C_{27}-H_{62} is the most stable angle than others in Gentamicin with Potential energy stability value of -6835.4145 kCal/mol in $180^{Ú}$.

References

[1] W. Lesniak, W. R. Harris, J. Y. Kravitz, J. Schacht, and V. L. Pecoraro , Solution Chemistry of Copper(II)-Gentamicin Complexes: Relevance to Metal-Related Aminoglycoside Toxicity, Inorg. Chem., 42(2003), 1420-1429, DOI: 10.1021/ic025965t

[2] S.M. Dizaj, F. Lotfipour, M. Barzegar-Jalali, M.-H. Zarrintan, K. Adibkia, Physicochemical characterization and antimicrobial evaluation of gentamicin-loaded $CaCO_3$ nanoparticles prepared via microemulsion method, J.Drug Delivery Science and Technology. (2016), DOI: 10.1016/j.jddst.2016.05.004.

[3] N. C. Megoulas, Mi. A. Koupparis, Development and validation of a novel LC/ELSD method for the quantitation of gentamicin sulfate components in pharmaceuticals, J. Pharmaceutical and Biomedical Analysis. 36 (2004) 73–79, DOI:10.1016/j.jpba.2004.05.018.

[4] J. E. Davies, "Aminoglycosides: Ancient and Modern", J. Antibiot. 59(2006) 529–532.

[5] Ch. Chen, Y. Chen, P. Wu, B. Chen, Update on new medicina applications of gentamicin: Evidence-based review, J .the Formosan Medical Association 113 (2014) 72-82, *http://dx., DOI.org/10.1016/j.jfma.2013.10.002*.

[6] A. MansoorInasab, A. Morsali, M.M. Heravi and S. A. Beyramabadi, Quantum Mechanical Study on the Adsorption of Drug Gentamicin onto ã-Fe2O3 nanoparticles,.J.chem.3 (2015) 1509-1513, *http://dx.doi.org/10.13005/ojc/310329.*

[7] G. Hariprasad & M. Kumar & K. Rani &P. Kaur & A. Srinivasan, Aminoglycoside induced nephrotoxicity: molecular modeling studies of calreticulin-gentamicin complex, J .Mol Model .18 (2012) 2645–2652, DOI 10.1007/s00894-011-1289-8.

[8] Yawen Gu, Xianpu Ni, Jun Ren, Huiyuan Gao, Da Wang, and Huanzhang Xia, Biosynthesis of Epimers C2 and C2a in the Gentamicin C Complex, ChemBioChem .16 (2015)1933 – 1942, *http://dx.doi.org/10.1002/cbic.201500258*.

[9] G. Seidl, H. P. Nerad, Gentamicin C: Separation of C1, C1 a, C2, C2a and C2b Components by HPLC Using Isocratic Ion-Exchange Chromatography and Post-Column Derivatisation, Chromatographi .3 (1988). DOI: 10.1007/BF02316439.

[10] J. Berdy, J. Kadar Pauncz, ZS. Mesfalvivajna, Gy. Horvath, J. Gyimesi and I. KOCZKA, Metabolites of Gentamicin-Producing Micromonospora species 1. Isolation and identifiction of metabolites, J. antibiotic. 11(1977), DOI: 10.7164/antibiotics.30.945.

[11] R.T Testa and B.C. Tilley, Biotransformatio , A new Approach to Aminoglycoside biosynthisis:: II Gentamicin, Antibiotic .2(1976), DOI: 10.7164/antibiotics.29.140.

[12] A. Mansoorinasab, A. Morsali, M. M. Heravi, and S. A. Beyramabadi, Quantum Mechanical Study on the Noncovalent Adsorption of DrugGentamicin Onto Pristine and COOH Functionalized Carbon Nanotubes, J. Comput. Theor. Nanosci .12(2015), 4935–4941, DOI:10.1166/jctn.2015.4462.

[13] S. Yoshizawa, D. Fourmy, and J.D. Puglisi, Structural origins of gentamicin antibiotic action, The EMBO J.22 (1998) 6437-6448, DOI: 10.1093/emboj/17.22.6437.

[14] M. Himabindu and A. Jetty, Microbial Biosynthesis and Applications of Gentamicin A Critical Appraisal, Biotechnology .Rev.28 (2008)173–212, DOI: 10.1080/07388550802262197.

[15] A. Chmielewsiu, A. Konowae, and A.Zamojski, The Synthesis of Racemic purpurosamine B, Carbohydrate Research, 70 (1979) 275-282.

[16] R. Benveniste and J. Davies, Structure-Activity Relationships among the Aminoglycoside Antibiotics: Role of Hydroxyl and Amino Groups, Antimicrobial agents and chemotherapy, 4(1973) 402-409.

[17] Aqyl. Alaa -Hussein, and Abbas. A-Ali Drea, Theoretical investigations of photolysis for Halon-2402 in stratospheric layer, Basra Journal of Science (C) 30 (2012) 132-146.

[18] Abbas A- Ali Drea, Theoretical study to synthesis 1, 3, 5,-triglycerol benzene using Semi empirical and Ab-Initio calculation methods, National Journal of Chemistry, 39(2010) 481- 498.

[19] Aqyl. Alaa Hussein, and Abbas A-Ali Drea, Theoretical investigation study of Bromine radical reaction with ozone stratospheric layer, J. Applicable Chemistry, 1(2012) 453-459.

[20] HyperChem 8.0.2. 2, Hypercube Inc.

[21] Duaa. Muayad, Saudon. A. Aowda and A.A-Ali Drea, Simulation Study of Oxidation for Oleic acid by KMnO4 Using Theoretical Calculations. Applicable Chemistry. 2 (2013) 42-49.

[22] Abbas. A-Ali Drea, Photolysis of Raxil DS2 in aqueous solution by sun light through transition state computational study National Journal of Chemistry, 37(2010), 86 -100.

[23] Fathel. O. Essa, Kathtem. J. Kadhum, and Abbas. A-Ali Drea , Estimation of transition state and Synthesis of Barbituric Acid with their derivatives of 1,3,4-Thiadiazole, J. Applicable Chemistry, 1(3)(2012)344-351.

[24] Abbas. A-Ali Drea and Raua -Hussien, Simulation study of ozone depletion through photolysis mechanism of HCFC-124, 7 (2016) 99-110.

[25] Hyffa. Adnan, Saudon. A. Aowda and Abbas A-Ali Drea, Simulation Study of alkylation reaction of resorcinol, 3 (2014) 2365-2371.

[26] Hyfa. T. Mohammed, and A. A-Ali Drea, Prodrug Design methods to treat Parkinson's disease, 7(2)(2016) 111-117.

[27] Raual-Hussein, Theoretical Investigation of Photolysis Reactions Mechanisms for Halo-Hydrocarbon Compounds in Stratospheric Layer, MSC thesis, 2017.

[28] Abbas A-Ali Drea and Aqyel Hussein Alkhaffagi, Theoretical Study of Reaction Mechanism for Ozone with Light Halohydrocarbons , MSC thesis, 2012.

[29] H. T. Mohammed, and Abbas A-Ali Drea, Prodrug Design methods to treat Parkinson's disease, 7(2)(2016) 111-117.

[30] [29] Abbas A-Ali Drea and Aqyel Hussein Alkhaffagi, Theoretical Study of Reaction Mechanism for Ozone with Light Halohydrocarbons , MSC thesis, 2012.

[31] Abbas A-Ali Drea and Aqyel Hussein Al-khaffagi, Theoretical Study of Reaction Mechanism for Ozone with Light Halo hydrocarbons, MSC thesis, 2012.