A DFT Study of Diazepam Derivative

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Abstract

Diazepam is a drug used to treat mild to moderate anxiety and tension and to relax muscle. It falls under benzodiazepine class. A simple diazepam derivative is chosen for the present study. Gaussian 16 software is used for the present research. Bond angle, bond length, tetrahedral angle, Mulliken charges, electrostatic potential and contour diagram are studied under Becke 3- parameter (exchange), Lee, Yang and Parr using 6-31G basis set.

Keywords: *Physical parameters, Mulliken charges, electrostatic potential, contour diagram, Density functional theory, Diazepam, DFT*

1.Introduction

Anxiety and depression is a common severe brain disorder affecting the world wide population[1]. Benzodiazepines is a group of psycoactive drugs and it acts on central nervous system, having anxiolytic, sedative and hypnotics effects[2]. It is also used to treat alcohol withdrawl syndrome, relief of muscle spams, seisures disorders, trouble sleeping and restless legs syndrome [3]. The Diazepines derivatives shows various pharmacological activities and it is the backbone of several antifungal, antibacterial, antiviral, analgesic, antiulcer and anti inflammatory drugs[4]. Diazepam is a positive allosteric modulators of the GABA type A receptor It acts on the brain and cetral nerveous system to produce a calming effect[5].

2. Review of Literature

B. Sylaja[6] *et.al.,* has been studied the structural parameters and vibrational frequency of Diazepam by quantum chemical methods. Theoretical calculations are carried out by B3LYP/6-311G(d,p) method using the Gaussian 03 W program package. VEDA program has been used to calculate the Potential energy distribution (PED) from quantum chemically calculated vibrational frequencies. The ^{13}C and ^{1}H NMR chemical shift has been calculated by DFT method and compared with experimental data. The NLO parameters polarizability, dipole moment and first order hyperpolarizability are calculated using B3LYP/6-311G(d,p) method along with HOMO and LUMO energies and molecular electrostatic potential for DPM has been studied. The optimized geometrical parameters like bond length, bond angle and dihedral angle of DPM are determined and compared with experimental data. Molecular docking studies is used to determine DPM acts as an inhibitor against nervous disorder.

A. J. Palace Carvalho[2] *et.al.,* have been studied A DFT study on the adsorption of benzodiazepines to vermiculite surfaces. In this work, electronic structure calculations based on the density functional theory (DFT) are presented on the interaction computational details A theoretical study of the interactions between adsorbing molecules of diazepam (DZP) and alprazolam with a vermiculite surface was carried out by density functional theory (DFT) calculations. When comparing the two adsorbates, the calculations suggest that DZP has a stronger affinity for the vermiculite surface. Bader charges analysis showed that in both cases a small charge is transferred from the molecules to the surface. Both of which can provide the bridging effects that have been observed in this work and, consequently, a strong interaction between the adsorbates and the surface. This study suggests vermiculite as a promising and cheap alternative for removal of these drugs from waters and wastewaters through adsorption processes.

3. Materials and Methods

The density functional theory studies are carried out using the Gaussian- 16 Revision B. 01 software[7] and visualised by Gaussview-6 software. The DFT-B3LYP/6-31G basis set is adopted to calculate the physical properties of 2,7-diphenyl-1,4-diazepan-5-one molecule in this work.

4. Results and Discussion
4.1 Optimized geometry

2,7-diphenyl-1,4-diazepan-5-one is a chemical compound with molecular formula $C_{17}H_{1.8}N_2O$. It is a 38 atoms, 142 electrons, singlet system. It is a neutral molecule.

The 2D and 3D representations are given in Figure 1. The atom numbering scheme for the title compound is shown in Table 1
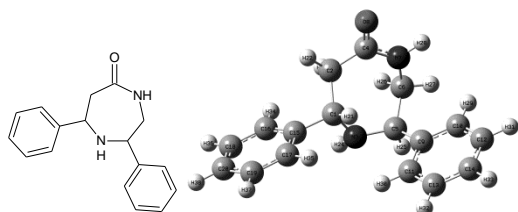

Fig. 1 The 2D and 3D structure for 2,7-diphenyl-1,4-diazepan-5-one

Table 1: The list of atoms of optimized Diazepam by DFT/B3LYP

1	2	3	4	5	6	7	8
C	C	N	C	C	C	N	O
9	10	11	12	13	14	15	16
C	C	C	C	C	C	C	C
17	18	19	20	21	22	23	24
C	C	C	C	H	H	H	H
25	26	27	28	29	30	31	32
H	H	H	H	H	H	H	H
33	34	35	36	37	38		
H	H	H	H	H	H		

The Table 1 shows the list of atoms of diazepam. The carbons 1, 2, 4, 5, 6 are present in seven membered ring. The other carbons are present in six membered aromatic rings.

The bond distance, bond angle and dihedral angle for the molecule are computed at DFT/ B3LYP/6-31G basis set.

Table 2: The Bond distance of optimized Diazepam by DFT/B3LYP

Code No	Atoms set	Bond distance (A°)
R1	(C1,C2)	1.5636
R2	(C1,N3)	1.4754
R3	(C1,C15)	1.5248
R4	(C1,H21)	1.0969
R5	(C2,C4)	1.5195
R6	(C2,H22)	1.0922
R7	(C2,H23)	1.099
R8	(N3,C5)	1.4693
R9	(N3,H24)	1.0134
R10	(C4,N7)	1.3735
R11	(C4,O8)	1.2518
R12	(C5,C6)	1.5542
R13	(C5,C9)	1.5359
R14	(C5,H25)	1.1019
R15	(C6,N7)	1.4639

R16	(C6,H26)	1.0988
R17	(C6,H27)	1.0938
R18	(N7,H28)	1.0111
R19	(C9,C10)	1.4056
R20	(C9,C11)	1.4056
R21	(C10,C12)	1.3996
R22	(C10,H29)	1.085
R23	(C11,C13)	1.3986
R24	(C11,H30)	1.0841
R25	(C12,C14)	1.3986
R26	(C12,H31)	1.0857
R27	(C13,C14)	1.3994
R28	(C13,H32)	1.0859
R29	(C14,H33)	1.0854
R30	(C15,C16)	1.4059
R31	(C15,C17)	1.404
R32	(C16,C18)	1.3993
R33	(C16,H34)	1.0866
R34	(C17,C19)	1.3989
R35	(C17,H35)	1.0861
R36	(C18,C20)	1.3995
R37	(C18,H36)	1.0857
R38	(C19,C20)	1.3996
R39	(C19,H37)	1.0855
R40	(C20,H38)	1.0854

The distance between the nuclei of two bonded atom is called bond length. From the Table 2, it is clear that the shortest bond is R18 (N7-H28) (1.0111Å) and the longest bond is R1 (C1-C2) (1.5636 Å).

Table 3: The Bond angle of optimized Diazepam by DFT/B3LYP

Code No	Atoms set	Bond angle (°)
A1	A(2,1,3)	114.9201
A2	A(2,1,15)	111.4914
A3	A(2,1,21)	107.1914
A4	A(3,1,15)	108.1469
A5	A(3,1,21)	106.9136
A6	A(15,1,21)	107.8673
A7	A(1,2,4)	113.4848
A8	A(1,2,22)	109.7089
A9	A(1,2,23)	109.4512
A10	A(4,2,22)	105.7945
A11	A(4,2,23)	110.347
A12	A(22,2,23)	107.8586
A13	A(1,3,5)	121.2096
A14	A(1,3,24)	113.3654
A15	A(5,3,24)	114.2453
A16	A(2,4,7)	117.3863
A17	A(2,4,8)	121.7724
A18	A(7,4,8)	120.834
A19	A(3,5,6)	113.1805
A20	A(3,5,9)	111.7953
A21	A(3,5,25)	104.674
A22	A(6,5,9)	114.1593
A23	A(6,5,25)	105.055
A24	A(9,5,25)	107.0691
A25	A(5,6,7)	115.3108
A26	A(5,6,26)	107.3686
A27	A(5,6,27)	110.1342

A28	A(7,6,26)	110.1805
A29	A(7,6,27)	107.1087
A30	A(26,6,27)	106.4017
A31	A(4,7,6)	127.0694
A32	A(4,7,28)	114.2776
A33	A(6,7,28)	118.6381
A34	A(5,9,10)	122.1763
A35	A(5,9,11)	119.488
A36	A(10,9,11)	118.239
A37	A(9,10,12)	120.9272
A38	A(9,10,29)	120.5712
A39	A(12,10,29)	118.5011
A40	A(9,11,13)	120.9269
A41	A(9,11,30)	118.2083
A42	A(13,11,30)	120.8647
A43	A(10,12,14)	120.2678
A44	A(10,12,31)	119.6253
A45	A(14,12,31)	120.1066
A46	A(11,13,14)	120.2987
A47	A(11,13,32)	119.6603
A48	A(14,13,32)	120.0409
A49	A(12,14,13)	119.3386
A50	A(12,14,33)	120.2633
A51	A(13,14,33)	120.398
A52	A(1,15,16)	121.1803
A53	A(1,15,17)	120.223
A54	A(16,15,17)	118.5775
A55	A(15,16,18)	120.7397
A56	A(15,16,34)	120.0536
A57	A(18,16,34)	119.2034
A58	A(15,17,19)	120.8231
A59	A(15,17,35)	119.2714
A60	A(19,17,35)	119.9055
A61	A(16,18,20)	120.1417
A62	A(16,18,36)	119.7874
A63	A(20,18,36)	120.07
A64	A(17,19,20)	120.1226
A65	A(17,19,37)	119.7883
A66	A(20,19,37)	120.0891
A67	A(18,20,19)	119.5948
A68	A(18,20,38)	120.1822
A69	A(19,20,38)	120.2226

Bond angle is the formation of angle between the three adjacent atom in a molecule. From the Table 3, it is clear that the largest bond angle is A31 (C4-N7-C6) with an angle of 127.0697° and the shortest bond angle is A21 (N3-C5-H25) with an angle of 104.674°.

Table 4: The Dihedral angle of optimized Diazepam by DFT/B3LYP

Code No	Atoms	Dihedral angle (°)	Conformation
D1	D(3,1,2,4)	-77.7443	SC
D2	D(3,1,2,22)	164.1639	AP
D3	D(3,1,2,23)	46.001	SC
D4	D(15,1,2,4)	158.7496	AP
D5	D(15,1,2,22)	40.6578	SC
D6	D(15,1,2,23)	-77.5052	SC
D7	D(21,1,2,4)	40.9113	SC
D8	D(21,1,2,22)	-77.1805	SC
D9	D(21,1,2,23)	164.6566	AP
D10	D(2,1,3,5)	61.2918	SC
D11	D(2,1,3,24)	-80.4068	SC
D12	D(15,1,3,5)	-173.4405	AP
D13	D(15,1,3,24)	44.8609	SC
D14	D(21,1,3,5)	-57.5192	SC
D15	D(21,1,3,24)	160.7822	AP
D16	D(2,1,15,16)	51.7946	SC
D17	D(2,1,15,17)	-129.8222	AC
D18	D(3,1,15,16)	-75.4769	SC
D19	D(3,1,15,17)	102.9063	AC
D20	D(21,1,15,16)	169.2251	AP
D21	D(21,1,15,17)	-12.3917	SP
D22	D(1,2,4,7)	62.0098	SC
D23	D(1,2,4,8)	-117.0135	AC
D24	D(22,2,4,7)	-177.6568	AP
D25	D(22,2,4,8)	3.3199	SP
D26	D(23,2,4,7)	-61.2456	SC
D27	D(23,2,4,8)	119.7311	AC
D28	D(1,3,5,6)	-57.3481	SC
D29	D(1,3,5,9)	73.2477	SC
D30	D(1,3,5,25)	-171.19	AP
D31	D(24,3,5,6)	84.0422	SC
D32	D(24,3,5,9)	-145.362	AC
D33	D(24,3,5,25)	-29.7997	SP
D34	D(2,4,7,6)	1.9229	SP
D35	D(2,4,7,28)	-176.6377	AP
D36	D(8,4,7,6)	-179.0442	AP
D37	D(8,4,7,28)	2.3952	SP
D38	D(3,5,6,7)	71.7849	SC
D39	D(3,5,6,26)	-51.429	SC
D40	D(3,5,6,27)	-166.8832	AP
D41	D(9,5,6,7)	-57.6162	SC
D42	D(9,5,6,26)	179.1698	AP
D43	D(9,5,6,27)	63.7157	SC
D44	D(25,5,6,7)	-174.6034	AP
D45	D(25,5,6,26)	62.1827	SC
D46	D(25,5,6,27)	-53.2714	SC
D47	D(3,5,9,10)	-157.5159	AP
D48	D(3,5,9,11)	26.1233	SP
D49	D(6,5,9,10)	-27.4252	SP
D50	D(6,5,9,11)	156.214	AP
D51	D(25,5,9,10)	88.3938	SC
D52	D(25,5,9,11)	-87.967	SC
D53	D(5,6,7,4)	-64.5386	SC
D54	D(5,6,7,28)	113.9664	AC
D55	D(26,6,7,4)	57.1725	SC
D56	D(26,6,7,28)	-124.3225	AC
D57	D(27,6,7,4)	172.5068	AP
D58	D(27,6,7,28)	-8.9882	SP
D59	D(5,9,10,12)	-176.7431	AP
D60	D(5,9,10,29)	2.9933	SP
D61	D(11,9,10,12)	-0.3388	SP
D62	D(11,9,10,29)	179.3976	AP
D63	D(5,9,11,13)	176.9407	AP
D64	D(5,9,11,30)	-2.9498	SP
D65	D(10,9,11,13)	0.4369	SP
D66	D(10,9,11,30)	-179.4535	AP
D67	D(9,10,12,14)	-0.0194	SP
D68	D(9,10,12,31)	-179.8043	AP
D69	D(29,10,12,1)	-179.7612	AP

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D70	D(29,10,12,3)	0.454	SP
D71	D(9,11,13,14)	-0.1776	SP
D72	D(9,11,13,32)	179.9053	AP
D73	D(30,11,13,1)	179.7099	AP
D74	D(30,11,13,3)	-0.2072	SP
D75	D(10,12,14,1)	0.2862	SP
D76	D(10,12,14,3)	-179.7281	AP
D77	D(31,12,14,1)	-179.93	AP
D78	D(31,12,14,3)	0.0557	SP
D79	D(11,13,14,1)	-0.1889	SP
D80	D(11,13,14,3)	179.8254	AP
D81	D(32,13,14,1)	179.7279	AP
D82	D(32,13,14,3)	-0.2578	SP
D83	D(1,15,16,18)	178.2728	AP
D84	D(1,15,16,34)	- 2.3868	SP
D85	D(17,15,16,1)	-0.1363	SP
D86	D(17,15,16,3)	179.204	AP
D87	D(1,15,17,19)	-178.5136	AP
D88	D(1,15,17,35)	1.5691	SP
D89	D(16,15,17,1)	-0.0888	SP
D90	D(16,15,17,3)	179.994	AP
D91	D(15,16,18,20)	0.2211	SP
D92	D(15,16,18,36)	179.8677	AP
D93	D(34,16,18,20)	-179.1248	AP
D94	D(34,16,18,36)	0.5218	SP
D95	D(15,17,19,20)	0.2299	SP
D96	D(15,17,19,37)	-179.6869	AP
D97	D(35,17,19,20)	-179.8533	AP
D98	D(35,17,19,37)	0.2299	SP
D99	D(16,18,20,1)	-0.0788	SP
D100	D(16,18,20,3)	179.6933	AP
D101	D(36,18,20,1)	-179.7244	AP
D102	D(36,18,20,3)	0.0478	SP
D103	D(17,19,20,1)	-0.1445	SP
D104	D(17,19,20,3)	-179.9166	AP
D105	D(37,19,20,1)	179.772	AP
D106	D(37,19,20,3)	-0.0001	SP

The dihedral angle is the angle between planes through two sets of three atoms, having two atoms in common. From the Table 4, it is clear that the synperiplanar (SP), antiperiplanar (AP), synclinal (SC) and anticlinal (AC) conformation are present in the target molecule.

4.2 Mulliken's Charge distribution

The charge distribution of the molecule was calculated on the base of Mulliken's method using B3LYP/6-31G basis set [8].

Table 5: Mulliken's charge of target molecule

Atom number	Mulliken charge B3LYP/6-31G (a.u)
C 1	-0.067837
C2	-0.301020
N3	-0.568909
C4	0.495051
C5	-0.052635

C6	-0.091020
N7	-0.617625
O8	-0.465035
C9	0.122889
C10	-0.153426
C11	-0.152440
C12	-0.132647
C13	-0.128854
C14	-0.118005
C15	0.123923
C16	-0.157325
C17	-0.149781
C18	-0.128032
C19	-0.128102
C20	-0.119303
H21	0.158684
H22	0.174293
H23	0.138073
H24	0.283660
H25	0.151451
H26	0.142131
H27	0.146536
H28	0.323540
H29	0.103819
H30	0.155326
H31	0.124437
H32	0.124293
H33	0.125246
H34	0.121223
H35	0.134228
H36	0.127029
H37	0.128619
H38	0.127546

From the Table 5, the atoms C1, C2, N3, C5, C6, N7, O8, C10, C11, C12, C13, C14, C16, C17, C18, C19, C20 atoms are having negative charge and C4, C9, C15 atoms are having positive charge. All the hydrogen atoms are having positive charge. The N3 and N7 atoms show negative values. N7 is more negative than N3. The presence of C=O group near N7 enhances the negative value at N7. The C4 carbon exerts more positive value since it lies between O8 and N7. In aromatic rings the carbon (C9, C15) which are joined to seven membered ring system exerts positive charge and other aromatic carbons show negative charge due to the delocalisation of electrons. In the seven membered ring all the carbon shows negative charge[8]. The Bar diagram of Mulliken charge distribution is presented in the Figure 2.
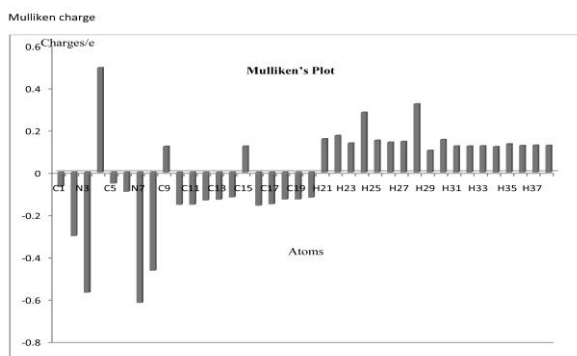
Fig. 2: The Mulliken atomic charge distribution of target molecule

4.3 Dipole moment, Quadrupole moment and Energy

The dipole moment is the first derivative of the energy with respect to an applied field. It is a measure of the antisymmetry in the molecular charge distribution and is given as a vector in three dimensions.

The predicted dipole moment (in Debye) is shown in Table 6. The total dipole moment obtained by B3LYP/6-31G basis set is calculated as 4.2416 D.

Table 6: The predicted dipole moment of optimized Diazepam

B3LYP/631G basis set (D)			
X	Y	Z	Total
0.0130	-1.1976	-4.0690	4.2416

The predicted quadrupole moment (in Debye-Ang) is shown in Table 7. From the Table 7, it is clear that the target molecule is slightly elongated along the ZZ axis. The energy of the molecule is found to be -843.1594 a.u.

Table 7: The predicted Quadrupole moment of optimized Diazepam

B3LYP/631G basis set (Debye-Ang)		
XX	YY	ZZ
-102.6841	-120.1259	-122.8944

Electrostatic potential Map (ESP)
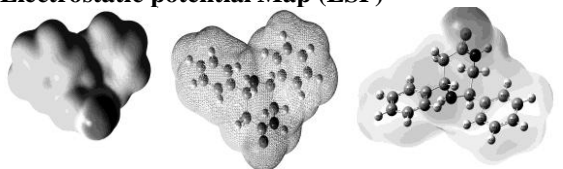
Solid view   **Mesh view**   **Transparent view**

Fig. 3: Electrostatic potential of Diazepam

ESP gives the electrostatic potential at location on a particular surface. Most commonly a surface of electron density to over all molecular size. In this Diazepam derivative near to (–C=O) group represent large negative values [electron rich] near (-NH) group represent large positive values [electron poor] [10].
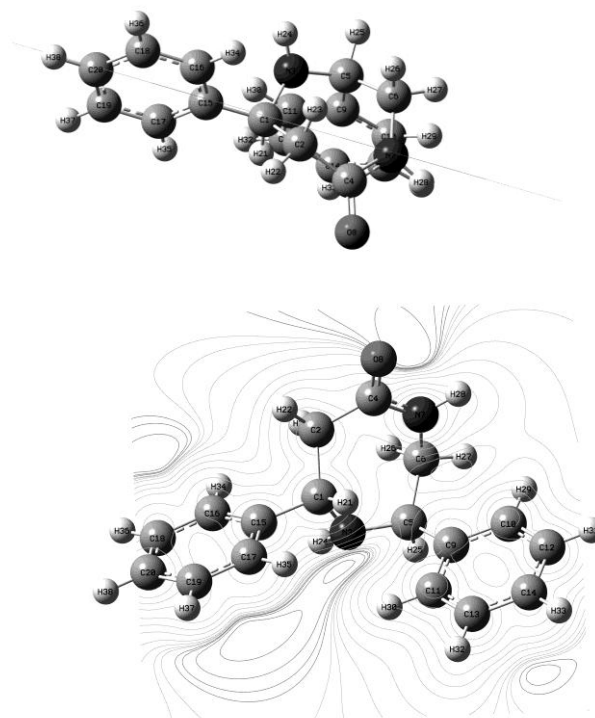

Fig. 4: Contour diagram of Diazepam

From the Figure 4, it is clear that the N3-H24 group occupying above the plane. The C4-O8 group occupying below the plane and the N7, C1, C15, C20, H38 atoms lies in the plane.

5. Conclusions

In the present work, we have performed the theoretical study of diazepam derivative using Gaussian 16 software and viewed by Gaussview- 6. The bond length, bond angle, dihedral angle, Mulliken charge distribution, Electrostatic potential and Contour diagram are calculated DFT/B3LYP/6-31G level.

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