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A DFT study of Edaravone

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Abstract

Edaravone is a novel neuroprotective agent that was approved for the acute therapy of embolic stroke, and has great potential to protect against toxicity induced by various radicals. In this study, physical properties of edaravone is discussed. Gaussian 16 software is used for the present research and Gaussview 6 is used to visualize the molecule. Bond angle, bond length, tetrahedral angle, Mulliken charges, ESP, contour diagram are investigated under B3LYP/6-31G basis set using DFT.

Keywords: *Bond angle, bond length, tetrahedral angle, Mulliken charges, ESP, contour diagram, Edaravone, DFT*

1. Introduction

The Chemical name of Edaravone is 3-methyl-1-phenyl-2-pyrazolin-5-one. It is a prescription medicine permitted by the United States Food and Drug Administration to treat people with amyotrophic lateral sclerosis (ALS). [1,2] Edaravone is an antipyrine derivative that functions as a free radical scavenger and neuroprotective agent.[3] It has been previously investigated for the treatment of ischemic stroke, reperfusion insult, and acute myocardial infarction as it possesses antioxidant and anti-apoptotic features. Since it possesses a low molecular weight with good quality water and lipid-soluble properties, it is therapeutically beneficial in crossing the blood-brain barrier to intervene cognitive enhancers and neuroprotective effects. Oral formulation of edaravone is currently under development.[4] Edaravone is used to help people recuperate from stroke in Japan,[5] and is used to treat amyotrophic lateral sclerosis (ALS) in the US and Japan.[6,7] It is given by intravenous infusion.[6] There is no data on whether it is secure for pregnant women to obtain, and it is unknown if edaravone is secreted in breast milk.[6] The drug is identified to be an antioxidant, and oxidative stress has been hypothesized to be part of the process that kills neurons in people with ALS.[7] The half-life of edaravone is 4.5 to 6 hours and the half-lives of its metabolites are 2 to 3 hours. It is metabolized to sulfate and glucuronide conjugate, neither of which are active. It is mainly excreted in urine as the glucuronide conjugate form.[6]

2. Materials and Methods

Computational method calculation

The density functional theory studies were carried out using the Gaussian software and visualized by Gauss view-6 software.[8] The geometry optimization was performed with DFT method using Becke's hybrid three parameters exchange functional of non local correlation functional of Lee Yang and Parr (B3LYP).[9]

3. Results and Discussion

Optimized geometry

3-Methyl-1-phenyl-2-pyrazolin-5-one is a chemical compound with molecular formula [$C_{10}H_{10}N_{2O}$]. It is a 23 atoms, 92 electrons, neutral, singlet system.

The atom numbered scheme for the compound is shown in Table 1. The 2D and 3D representation are given in Figure 1. The carbons 2,5,7 are present in 5 membered ring. The other carbons are present in the six membered aromatic ring.

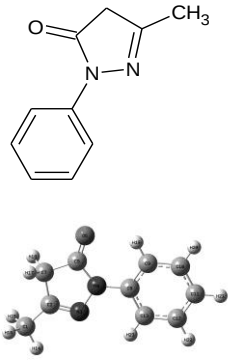

Figure 1 : The 2D and 3D optimized structure of Edaravone.

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Atom list

Table 1 : The list of atoms of optimized Edaravone

1	**2**	**3**	**4**	**5**	**6**
C	C	N	N	C	O
7	**8**	**9**	**10**	**11**	**12**
C	C	C	C	C	C
13	**14**	**15**	**16**	**17**	**18**
C	H	H	H	H	H
19	**20**	**21**	**22**	**23**	
H	H	H	H	H	

Table 2 : The bond distance of optimized Edaravone

Code No	Atoms set	Distance (A°)
R1	R(1,2)	1.4908
R2	R(1,14)	1.0925
R3	R(1,15)	1.0976
R4	R(1,16)	1.0976
R5	R(2,3)	1.3013
R6	R(2,7)	1.5055
R7	R(3,4)	1.4307
R8	R(4,5)	1.3958
R9	R(4,8)	1.4216
R10	R(5,6)	1.2428
R11	R(5,7)	1.5272
R12	R(7,17)	1.0966
R13	R(7,18)	1.0966
R14	R(8,9)	1.4069
R15	R(8,13)	1.4059
R16	R(9,10)	1.3981
R17	R(9,19)	1.0805
R18	R(10,11)	1.3988
R19	R(10,20)	1.0855
R20	R(11,12)	1.3998
R21	R(11,21)	1.0851
R22	R(12,13)	1.3961
R23	R(12,22)	1.0855
R24	R(13,23)	1.0812

Bond distance is the distance between the nuclei of the two bonded atoms. From the Table 2, it is found that the shortest bond is R17 (C9-H19) with a distance of 1.0805Å and the longest bond is R11 (C5-C7) with a distance of 1.5272 Å.

Table 3: The bond angle of optimized Edaravone

Code No	Atoms set	Bond angle (°)
A1	A(2,1,14)	110.0742
A2	A(2,1,15)	111.0838
A3	A(2,1,16)	111.0839
A4	A(14,1,15)	108.6995
A5	A(14,1,16)	108.6995
A6	A(15,1,16)	107.1036
A7	A(1,2,3)	121.7208
A8	A(1,2,7)	125.8698
A9	A(3,2,7)	112.4094
A10	A(2,3,4)	108.1864
A11	A(3,4,5)	112.0364
A12	A(3,4,8)	118.5784
A13	A(5,4,8)	129.3852
A14	A(4,5,6)	127.3587
A15	A(4,5,7)	105.1059
A16	A(6,5,7)	127.5353
A17	A(2,7,5)	102.2619
A18	A(2,7,17)	113.1256
A19	A(2,7,18)	113.1257
A20	A(5,7,17)	110.69
A21	A(5,7,18)	110.69
A22	A(17,7,18)	106.9791
A23	A(4,8,9)	120.7273
A24	A(4,8,13)	119.159
A25	A(9,8,13)	120.1137
A26	A(8,9,10)	119.2625
A27	A(8,9,19)	119.8412
A28	A(10,9,19)	120.8963
A29	A(9,10,11)	121.0193
A30	A(9,10,20)	118.91
A31	A(11,10,20)	120.0707
A32	A(10,11,12)	119.2341
A33	A(10,11,21)	120.3921
A34	A(12,11,21)	120.3738
A35	A(11,12,13)	120.6942
A36	A(11,12,22)	120.1346
A37	A(13,12,22)	119.1712
A38	A(8,13,12)	119.6762
A39	A(8,13,23)	119.3212
A40	A(12,13,23)	121.0026

The formation of angle between the three adjacent atom in a molecule is called bond angle. From the Table 3, it is clear that the largest bond angle is A13 (C5-N4-O6) with an angle of 129.3852° and the shortest bond angle is A17 (C2-C7-C5) with an angle of 102.2619°.

Table 4 : The dihedral angle of optimized Edaravone

Code No	Atoms	Dihedral angle(°)	Conformation
D1	D(14,1,2,3)	0.0003	SP
D2	D(14,1,2,7)	-179.9997	AP
D3	D(15,1,2,3)	-120.4455	AC
D4	D(15,1,2,7)	59.5544	SC
D5	D(16,1,2,3)	120.4462	AC
D6	D(16,1,2,7)	-59.5538	SC
D7	D(1,2,3,4)	179.9999	AP
D8	D(7,2,3,4)	0.0	SP
D9	D(1,2,7,5)	-179.9999	AP
D10	D(1,2,7,17)	60.9241	SC
D11	D(1,2,7,18)	-60.9239	SC
D12	D(3,2,7,5)	0.0	SP
D13	D(3,2,7,17)	-119.0759	AC

D14	D(3,2,7,18)	119.076	AC
D15	D(2,3,4,5)	0.0	SP
D16	D(2,3,4,8)	180.0	AP
D17	D(3,4,5,6)	-180.0	AP
D18	D(3,4,5,7)	0.0	SP
D19	D(8,4,5,6)	0.0001	SP
D20	D(8,4,5,7)	-179.9999	AP
D21	D(3,4,8,9)	179.9998	AP
D22	D(3,4,8,13)	-0.0002	SP
D23	D(5,4,8,9)	-0.0002	SP
D24	D(5,4,8,13)	179.9998	AP
D25	D(4,5,7,2)	0.0	SP
D26	D(4,5,7,17)	120.7777	AC
D27	D(4,5,7,18)	-120.7778	AC
D28	D(6,5,7,2)	180.0	AP
D29	D(6,5,7,17)	-59.2223	SC
D30	D(6,5,7,18)	59.2223	SC
D31	D(4,8,9,10)	180.0	AP
D32	D(4,8,9,19)	0.0	SP
D33	D(13,8,9,10)	0.0	SP
D34	D(13,8,9,19)	-180.0	AP
D35	D(4,8,13,12)	-180.0	AP
D36	D(4,8,13,23)	0.0	SP
D37	D(9,8,13,12)	0.0	SP
D38	D(9,8,13,23)	180.0	AP
D39	D(8,9,10,11)	0.0	SP
D40	D(8,9,10,20)	180.0	AP
D41	D(19,9,10,11)	180.0	AP
D42	D(19,9,10,20)	0.0	SP
D43	D(9,10,11,12)	0.0	SP
D44	D(9,10,11,21)	180.0	AP
D45	D(20,10,11,12)	-180.0	AP
D46	D(20,10,11,21)	0.0	SP
D47	D(10,11,12,13)	0.0	SP
D48	D(10,11,12,22)	180.0	AP
D49	D(21,11,12,13)	-180.0	AP
D50	D(21,11,12,22)	0.0	SP
D51	D(11,12,13,8)	0.0	SP
D52	D(11,12,13,23)	-180.0	AP
D53	D(22,12,13,8)	180.0	AP
D54	D(22,12,13,23)	0.0	SP

The dihedral angle is the angle between planes through two sets of 3 atoms, having two atoms in common. From the Table 4, it is clear that the synperiplanar (SP) conformation antiperiplanar (AP) as anti or trans; and synclinal (SC) and anticlinal (AC) as gauche or skew conformations are present in the target molecule.

Mulliken charges distribution

The charge distribution of the molecule was calculated on the base of Mulliken's method using B3LYP/6-31G basis set.[9]

Table 5: Mulliken charges for target molecule

Atom numbering	Mulliken charge B3LYP/631G
C1	-0.455889
C2	0.272005
N3	-0.173638
N4	-0.655618
C5	0.562532
O6	-0.437811
C7	-0.427737
C8	0.331472
C9	-0.121901
C10	-0.154185
C11	-0.106908
C12	-0.145514
C13	-0.125388
H14	0.178870
H15	0.162699
H16	0.162698
H17	0.206634
H18	0.206634
H19	0.184235
H20	0.127276
H21	0.122492
H22	0.124486
H23	0.162557

From the Table 5, C1, N3, N4, O6, C7, C9, C10, C11, C12, C13 atoms are having negative charge, and C2, C5, C8 atoms are having positive charge. All the hydrogen atoms are in positive charge. The N3 and N4 shows negative values, but N4 is more negative than N3. Since the presence of C=O group near N4 enhances the negative value. The C5 carbon shows more positive value since its lies between O6 and N4. In aromatic rings the carbon (C8) which is joined to a 5 membered ring system has positive charge feels positive charge and all other aromatic carbons shows negative charges due to delocalisation of electron.[10] The Bar diagram of Mulliken charge distribution is shown in the Figure 2.

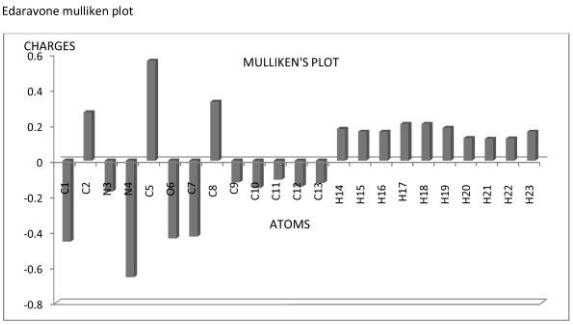

Figure 2 : The Mulliken atomic charge distribution of target molecule.

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 asymmetry 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 3.6078 D.

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Table 6: The predicted dipole moment of optimized Edaravone

B3LYP/631G basis set (D)			
X	Y	Z	Total
-3.0591	-1.9127	0.0004	3.6078

The predicted quadrupole moment (in Debye-Ang) is given in Table 7. From the Table 7, it is clear that the target molecule is slightly elongated along the YY axis. The energy of the molecule is found to be **=-571.6380542 a.u.**

Table 7: The predicted quadrupole moment of optimized Edavarone

B3LYP/631G basis set (Debye-Ang)		
XX	YY	ZZ
-55.6027	-81.2176	-76.9822

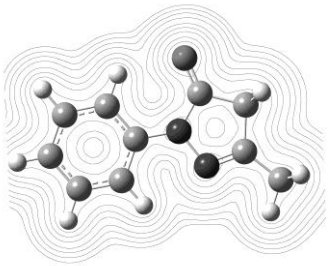
Electrostatic potential map (ESP) of Edaravone

Solid view **Mesh view** **Transparent view**

Figure 3 : Electrostatic potential of Edaravone

ESP gives the electrostatic potential at location on a particular surface most commonly a surface of electron density to over all molecular size. From the Figure 3, it is clear that C=O has large negative values[electron rich] whereas the five membered ring has large positive values [electron poor] In this target molecule Edaravone, the colors near red represent large negative values [electron rich] .[11]

Contour diagram



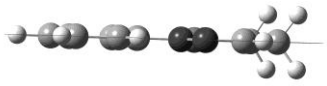


Figure 4 : Contour diagram of Edaravone in different views

From Figure 4 it is clear that H18, H15 atoms are occuping above the plane. The H14, H17 atoms lies below the plane. All the other atom are along the plane.

4. Conclusions

In the presence work, we have performed the theoretical study of Edaravone derivative using Gaussian 16 software. The bond length, bond angle, dihedral angle, Mulliken charge distribution are calculated by DFT/B3LYP/6-31G level.

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