24. Synthesis and DFT studies of 4-(3,4-dimethoxyphenyl)-2-(4-fluorophenyl)-2,3-dihydro-1H-1,5-benzodiazepine

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Abstract

The 4-(3,4-dimethoxyphenyl)-2-(4-fluorophenyl)-2,3-dihydro-1H-1,5-benzodiazepine has been synthesizedby using condensation reaction of ortho phenylenediamine with (2E)-1-(3,4-dimethoxyphenyl)-3-(4-fluorophenyl) prop-2-en-1-one in ethanol as solvent. The structure of synthesized compound was characterized by UV, FT-IR and ^{1}H NMR spectroscopic methods.The physical parameters like molecular structure, molecular geometry, bond lengths, bond angels, dipole moment, atomic charges, vibrational frequencies, molecular orbital energies etc. are theoretically examined by Density Functional Theory (DFT) using B3LYP method at 6-311++G(d,p) basis set with the help of Gaussian-03(W) package. Various thermodynamic properties of titled compound also investigated at same level of theory. Theoretically computed vibrational frequencies were compared with the experimental frequencies.

Keywords: Benzodiazepine, FT-IR, DFT, B3LYP.

Introduction

Chalcones are important starting materials for the synthesis of various heterocyclic compounds such as pyrazolines, pyrimidines, thiazines, flavones, benzodiazepines etc. Most of these heterocycles are highly biological active and are widely used in the pharmaceutics. Benzodiazepines derivatives are important class of nitrogenic heterocycles because of their promising biological activities (1). They show anticancer(2), anticonvulsant (3), antimicrobial, antioxidant and antibacterial activities (4). Due to their wide range of pharmacological, industrial and synthetic applications the synthesis of 1,5-benzodiazepines has received considerable

attention. Benzodiazepine derivatives are also commercially used as dyes for cyclic fibers. Moreover 1,5-benzodiazepines derivatives are valuable synthons for preparation of other fused ring compounds such as triazolo, oxazino or furanobenzodiazepines.Density functional theory (DFT) is the one of the popular method for computational study of compounds. The B3LYP method at 6311++G(d,p) basis set exhibit good performance on geometry, vibrational frequencies and other theoretical properties of molecule. By considering the importance of this functions,in the present work we have calculated structural parameters, thermodynamic functions, vibrational frequencies of titled compound.

Materials and Methods

All the chemicals needed for synthesis were obtained from commercial source (AR grade with purity > 99%) and used without further purification. Melting point of the compound were determined in open capillary tubes and are uncorrected, IR spectra were recorded on Shimadzu FT-IR spectrometer using potassium bromide pellets. 1H NMR was determined on Bruker Avance II 400 MHz spectrometer against TMS as internal standard. The purity of compound was checked by thin layer chromatography (TLC).

Synthesis of chalcone: A mixture of 3,4-dimethoxy acetophenone (0.01 mol) and 4-fluoro benzaldehyde (0.01 mol) in ethanol (15 ml) was stirred together for 24 hrs in the presence of 40% NaOH (10 ml). The reaction mixture was then poured into crushed ice and acidified with dilHCl. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol.

Synthesis of 1,5-benzodiazepine: A reaction mixture of chalcone (1mmol) and ortho phenylenediamine (1 mmol) in DMF (10 ml) and few drops of piperidine was refluxed for 4-6 hrs. The progress of reaction was monitored by TLC. After completion of reaction the reaction mixture was distilled to remove excess solvent and poured into crushed ice. The solid obtained was filtered, washed, dried and recrystalized from ethanol to get pure titled compound.

Yield: 86% and m.p. 190-192^{0}C. FT-IR (KBr, in cm^{-1}): 3410 (N-H stretching), 2926 (Ar-H stretching), 1589 (C=N stretching), 1155 (Ar-F stretching).

Experimental ^{1}H NMR: δ 7.10-7.85 (m, 11H, Ar-H), δ 5.38 (s, 1H, N-H), δ 3.85-4.30 (s, 6H, 2-OCH$_3$)

Scheme of synthesis
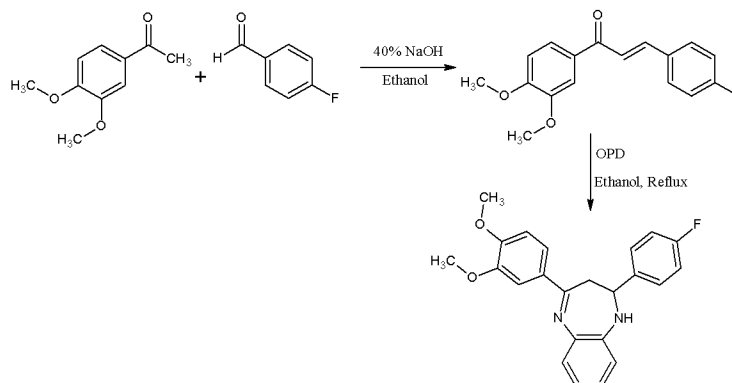
4-(3,4-dimethoxyphenyl)-2-(4-fluorophenyl)-2,3-dihydro-1H-1,5-benzodiazepine

Computational details: All the computational calculations are determined in gas phase by using Gaussian-03(W) package. In order to analyzed the theoretical parameters of titled compound geometry optimized by DFT/B3LYP method with 6-311 ++ G(d,p) basis set. Optimized structure of titled compound was used for the frequency calculations by using same level of theory. For a good agreement between a theoretical and experimental data the calculated frequencies were scaled using the Pulay scaled quantum mechanical force field methodology

Result and Discussion

Molecular geometry: Geometry optimization of titled compound carried out in ground state by DFT/B3LYP, 6311++G(d,p) basis set. The optimized geometrical parameters bond lengths, bond angles and Mullikan atomic charges are listed in table 1, 2 and 3 respectively. Optimized structure with numbering scheme given in Fig.1
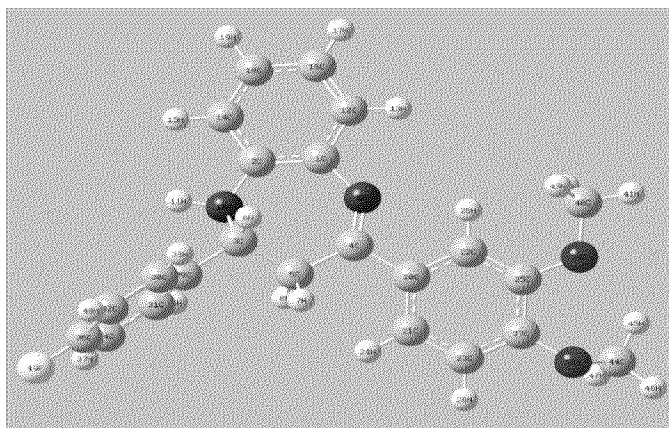
Fig. 1: Optimized structure and atomic labeling of titled compound.

Table 1: Bond lengths

Bond	Bond Length(Å)	Bond	Bond Length(Å)
C1-C2	1.4207	C22-C25	1.3880
C1-N9	1.3956	C22-H26	1.0799
C1-C12	1.4109	C23-C27	1.3878
C2-N10	1.3949	C23-H28	1.0837
C2-C14	1.4056	C25-C27	1.4149
C3-C5	1.5330	C25-O39	1.3658
C3-H6	1.0986	C27-O38	1.3692
C3-N10	1.4690	C29-C30	1.3974
C3-C29	1.5188	C29-C31	1.4009
C4-C5	1.5180	C30-C32	1.3941
C4-N9	1.2836	C30-H33	1.0848
C4-C20	1.4965	C31-C34	1.3925
C5-H7	1.0938	C31-H35	1.0843
C5-H8	1.0955	C32-C36	1.3848
N10-H11	1.0113	C32-H48	1.0828
C12-H13	1.0833	C34-C36	1.3865
C12-C16	1.3849	C34-H37	1.0830
C14-H15	1.0863	C36-F49	1.3554
C14-C18	1.3864	O38-C44	1.4338
C16-H17	1.0834	O39-C40	1.4229
C16-C18	1.3965	C40-H41	1.0889
C18-H19	1.0842	C40-H42	1.0950
C20-C21	1.3994	C40-H43	1.0947
C20-C22	1.4070	C44-H45	1.0909
C21-C23	1.3944	C44-H46	1.0895
C21-H24	1.0816	C44-H47	1.0956

Table 2: Bond angles

Bond	Bond angle(°)	Bond	Bond angle(°)
C2-C1-N9	128.71	C20-C22-H26	117.21
C2-C1-C12	117.52	C25-C22-H26	121.22
N9-C1-C12	113.64	C21-C23-C27	121.28
C1-C2-N10	122.45	C21-C23-H28	120.87
C1-C2-C14	118.99	C27-C23-H28	117.85
N10-C2-C14	118.53	C22-C25-C27	119.62
C5-C3-H6	108.21	C22-C25-O39	124.24

C5-C3-N10	111.02	C27-C25-O39	116.13
C5-C3-C29	110.56	C23-C27-C25	118.87
H6-C3-N10	109.69	C23-C27-O38	118.67
H6-C3-C29	107.81	C25-C27-O38	122.32
N10-C3-C29	109.47	C3-C29-C30	120.59
C5-C4-N9	128.27	C3-C29-C31	120.83
C5-C4-C20	115.63	C30-C29-C31	118.57
N9-C4-C20	116.10	C29-C30-C32	121.21
C3-C5-C4	116.32	C29-C30-H33	119.64
C3-C5-H7	107.76	C32-C30-H33	119.15
C3-C5-H8	108.60	C29-C31-C34	121.06
C4-C5-H7	108.21	C29-C31-H35	119.77
C4-C5-H8	109.17	C34-C31-H35	119.17
H7-C5-H8	106.32	C30-C32-C36	118.42
C1-N9-C4	132.21	C30-C32-H48	121.67
C2-N10-C3	119.30	C36-C32-H48	119.90
C2-N10-H11	111.67	C31-C34-C36	118.52
C3-N10-H11	111.66	C31-C34-H37	121.67
C1-C12-H13	116.34	C36-C34-H37	119.81
C1-C12-C16	122.90	C32-C36-C34	122.21
H13-C12-C16	120.74	C32-C36-F49	118.94
C2-C14-H15	118.42	C34-C36-F49	118.85
C2-C14-C18	121.88	C27-O38-C44	116.90
H15-C14-C18	119.69	C25-O39-C40	118.37
C12-C16-H17	120.35	O39-C40-H41	105.73
C12-C16-C18	118.93	O39-C40-H42	11.44
H17-C16-C18	120.71	O39-C40-H43	11.24
C14-C18-C16	119.73	H41-C40-H42	1.9.49
C14-C18-H19	119.66	H41-C40-H43	109.47
C16-C18-H19	120.60	H42-C40-H43	109.39
C4-C20-C21	122.51	O38-C44-H45	111.35
C4-C20-C22	119.28	O38-C44-H46	105.85
C21-C20-C22	118.20	O38-C44-H47	110.31
C20-C21-C23	120.44	H45-C44-H46	109.87
C20-C21-H24	121.21	H45-C44-H47	109.98
C23-C21-H24	118.34	H46-C44-H47	109.39
C20-C22-C25	121.56	-	

Table 3: Mullikan atomic charges

Atom	Charge	Atom	Charge
C1	0.27867	H26	0.21571
C2	-0.15051	C27	-0.65871
C3	-0.28024	H28	0.19540
C4	-0.01285	C29	1.04291
C5	-1.23521	C30	-0.22642
H6	0.22180	C31	-0.29849
H7	0.13559	C32	0.12208
H8	0.19512	H33	0.16086
N9	0.27501	C34	0.16702
N10	0.06116	H35	0.20850
H11	0.22966	C36	-0.68527
C12	-0.08779	H37	0.21076
H13	0.14683	O38	-0.16100
C14	-0.07430	O39	-0.17794
H15	0.12516	C40	-0.32920
C16	-0.56756	H41	0.17904
H17	0.16372	H42	0.16818
C18	-0.32691	H43	0.15940
H19	0.16316	C44	-0.29368
C20	1.41264	H45	0.16307
C21	-0.017467	H46	0.15442
C22	0.28195	H47	0.12971
C23	-0.35268	H48	0.21419
H24	0.15972	F49	-0.17054
C25	-1.07747	-	-

HOMO-LUMO: The study of highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and their energy gap of the organic compounds are important for determining the reactivity of molecule. The HOMO, LUMO with their energies of titled molecule have been calculated by DFT using B3LYP/6-311G++(d,p) method. E_{HOMO} and E_{LUMO} are -0.20672 and-0.06359 eV respectively. The HOMO-LUMO energy gap for titled compound is -0.14313 eV.Fig. 2 shows the pictorial presentation of HOMO and LUMO.
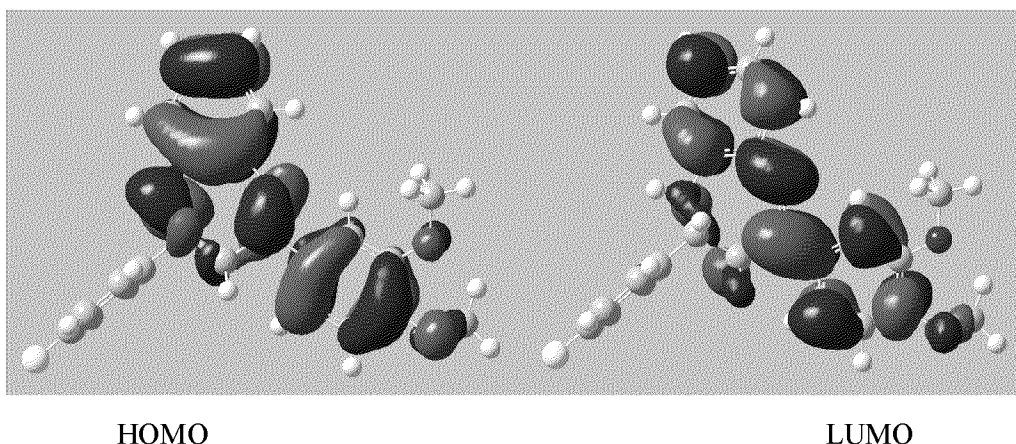
HOMO   LUMO

Fig.2: HOMO-LUMO of titled compound

Vibrational assignments: There are total 49 atoms in titled molecule with 141 fundamental modes of vibration. The experimental FT-IR spectrum has been recorded and theoretically frequencies are predicted by DFT/B3LYP method using 6-311 ++ G(d,p) basis set. The theoretically predicted vibrational frequencies are scaled by an empirical factor 0.9613. The selected experimental and theoretical vibrational frequencies of titled compound with their assignments are listed in the Table 4.

Table 4: Selected experimental and theoretical vibrational assignments calculated at B3LYP/6-311++G(d,p) level

Mode	Calculated scaled frequencies (cm^{-1})	IR Intensity (km) mol^{-1}	Experimental frequencies (cm^{-1})	Assignment
141	3571	13.74	3410	N-H str
124	2911	18.46	2926	C-H straro.
123	2897	83.81	2815	CH$_3$str (C44)
122	2893	43.64		CH$_3$str (C40)
121	2867	21.36		C3-H str
120	1611	72.90	1589	C=N str
115	1542	11.35	1523	Ring A C=C straro.
114	1540	1.09	1514	Ring B C=C straro.
111	1468	32.67	1416	N-H bending
106	1428	3.91	1345	CH$_3$ bend(C44)
105	1423	10.02		CH$_3$ bend (C40)
87	1192	173.73	1155	C-F str

Abbreviations: str-stretching, bend-bending,aro- aromatic Ring A: 3,4-dimethoxyphenyl ring, Ring B: 4-fluorophenyl ring.

Conclusion

The method adopted for the synthesis of biologically active fluorinated 1,5 benzodiazepine in this investigation is simple, efficient and yield of product is excellent. The structural, electronic and vibrational investigations along with molecular orbital analysis of titled compound is determined using DFT with B3LYP/6-311++G(d,p) basis set. The calculated frequencies show good agreement with experimental frequencies.

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