

Experimental and Theoretical Studies on a Derivative of Tetrahydro-1H-Benzodiazepine

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N-Cyclohexyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,5]diazepine-2-carboxamide (5) was synthesized using an efficient, highly recyclable and eco-friendly catalyst heteropolyacid/triethoxysilyl)propyl]isonicotinamide (HPA/TPI-Fe₃O₄ nanoparticles) in one-pot. The compound 5 was characterized by FT-IR, ¹H NMR, ¹³C NMR, mass spectra and elemental analysis. The theoretical calculations on 5 were carried out at the M06-2X and B3LYP methods with a 6-311++G(2d,p) basis set. The structural parameters and the IR data of 5 were analyzed and compared with the corresponding experimental data. The results show fair correlation between the calculated ¹³C chemical shifts with B3LYP/6-311++G(2d,p) level and experimental data. Theoretical studies on the frontier molecular orbitals, mapped molecular electrostatic potential (MEP) and corresponding graphs and charge delocalization of 5 were also carried out.

Keywords: DFT, NBO, MEP, N-Cyclohexyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,5]diazepine-2-carboxamide

INTRODUCTION

Benzodiazepine compounds have various pharmaceutical properties including anxiolytic, anticonvulsant, hypnotic, sedative, and skeletal muscle relaxant properties [1,2,3,4]. 1,5-Benzodiazepine can be synthesized *via* MCRs approach [5]. 1,5-Benzodiazepine structure of 5 was prepared from a novel one-pot pseudo-five-component condensation reaction between cyclohexyl-isocyanide, benzenediamine and 3-oxopentanedioic acid.

Multicomponent reactions (MCRs) are combined with three or more reagents to give a single heterocyclic products in a single step [6,7]. Herein, we investigate a novel and efficient method for one-pot synthesis of bifunctional diazepine. Heteropolyacids (HPAs) are promising green solid acids which have been widely used as catalysts in both homogeneous and heterogeneous conditions [8]. Due to environmentally friendly and highly efficient synthesis of

new organic compounds, the heterogeneous materials with supported HPW, such as HPW/C [9,10], HPW/CNTS [11], HPW/TiO₂ [12] have been investigated. Meanwhile, the paramagnetic Fe₃O₄ nanoparticles have attracted much attention and have been investigated widely because of the easy extraction of the catalyst [13,14]. In this research, N-cyclohexyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo [b][1,5] diazepine-2-carboxamide (5) is synthesized using an efficient, highly recyclable and eco-friendly catalyst heteropolyacid/triethoxysilyl)propyl] isonicotinamide (HPA/TPI-Fe₃O₄ nanoparticles) in one-pot. The experimental and theoretical spectra FT-IR, ¹H and ¹³C NMR chemical shifts are interpreted and compared.

EXPERIMENTAL

General Method

The reactions were monitored by IR, ¹H NMR and ¹³C NMR spectra, and mass spectra data. Melting point was measured on an electro-thermal 9200 apparatus. The IR

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spectra were measured on a Shimadzu IR-470 spectrometer. The ^1H NMR spectra (DMSO-d_6) were recorded on a Bruker DRX-300 Avance instrument at 300.13 MHz and ^{13}C NMR spectra were recorded on 75.47 MHz. Mass spectra were recorded on a Finnign-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The elemental analyses were performed by an Elementar Analysensys-teme GmbH VarioEL.

Synthesis of N-cyclohexyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,5] Diazepine-2-carboxamide

A solution of *o*-phenylenediamine (2.00 mmol) and 3-oxopentanedioic acid (4.40 mmol) was stirred in the presence of the HPA/TPI- Fe_3O_4 nanoparticles (0.02 g) for 4 h in the presence of 10% HCl at room temperature, and then, isocyanocyclohexane (2.00 mmol) and water (3.0 ml) were added to the reaction mixture. 3 ml of ethanol was added to the reaction mixture and the mixture was heated at 60 °C. The reaction completion was monitored by TLC (ethyl acetate/n-hexane, 1/1). The catalyst was extracted using an external magnet. The precipitate was filtered off and washed with hexane, and then crystallized in ethanol to give product 5 with high yield of 95%. The possible mechanism for synthesis of product 5 is shown in Fig. 1. The characterization data are given below.

Colorless crystals; m.p.: 210-211 °C. IR (KBr) cm^{-1} : 3375, 3330, 2930, 2862, 1602, 1502, 1478. ^1H NMR (300.13 MHz, DMSO-d_6) δ : 1.00-2.00 (21H, m, 5 CH_2 of cyclohexyl and 3 CH_3), 2.28 (2H, s, CH_2), 4.12 (m, br s, CH of cyclohexyl), 6.57 (1H, br s, NH), 6.70-6.80 (2H, m, H-Ar), 7.12 (1H, d, $J = 7.2$ Hz, H-Ar), 7.50 (1H, d, $J = 7.2$ Hz, H-Ar), 8.86 (1H, d, $J = 7.9$ Hz, NH), 11.56 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ : 21.2, 24.7, 24.9, 25.1, 31.1, 52.0, 53.0, 118.8, 123.3, 123.9, 125.9, 126.5, 128.6, 134.5, 159.8. MS m/z : 440 (M $^+$, 21), 189 (47), 173 (100), 90 (25), 55 (35), 37 (24). Anal. Calcd. for $\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}$: C, 72.34; H, 9.27; N, 13.32; found C, 72.34; H, 9.20; N, 13.42.

Computational Details

In this research, the quantum chemical calculations were carried out at the DFT level using the Gaussian 09 program [15]. The global optimized configuration of 5 is shown in Fig. 2. Full geometry optimization and subsequent

frequency calculations were performed using the B3LYP and M06-2X methods. The proton and carbon chemical shifts of 5 were calculated based on gauge-independent atomic orbital (GIAO) approach [16]. The ^1H and ^{13}C chemical shifts (δ) of 5 were calculated by subtracting the calculated isotopic value of the shielding tensor σ_{cal} from that of TMS: $\delta = \sigma_{\text{TMS}} - \sigma_{cal}$ (ppm). Also, ^1H and ^{13}C chemical shifts of structure were simulated by GaussView software [17]. Thermodynamic and physico-chemical properties of this compound were also calculated. The structural characterization such as geometrical optimization of 5 was investigated using experimental and DFT (B3LYP and M06-2X) methods with 6-311++G(2d,p) basis set. The data obtained via the M062X method moved to the Supplementary section since the data obtained *via* M06-2X is closer to the B3LYP method.

The main reason for selecting the B3LYP method is that this is a more widely used and popular method whose results is usually closer to the experimental data [18,19]. The 6-311++G(2d,p) basis set was used to add more flexibility to the basis set available for elements H and heavy atoms.

RESULTS AND DISCUSSION

Experimental Section

In the experimental section, the reusability of the catalyst is discussed.

Catalytic activity of HPA/TPI- Fe_3O_4

To determine the reusability of HPA/TPI- Fe_3O_4 nanoparticles the nanocatalyst was readily separated from the reaction mixture by an external magnet and washed with dichloromethane. Then, the nanocatalyst was dried and put in a vacuum oven at 80 °C for 3 h to reactivate the nanocatalyst. At last, the recovery catalyst was reused for sequence reaction. The results revealed that the catalytic activity of nanocatalyst remains constant as the fresh catalyst. Table 1 indicates that the yields of the reactions are not decreased through identical reaction conditions.

Theoretical Section

In this section, the vibrational assignments, chemical shift analysis, frontier molecular orbital analysis, molecular

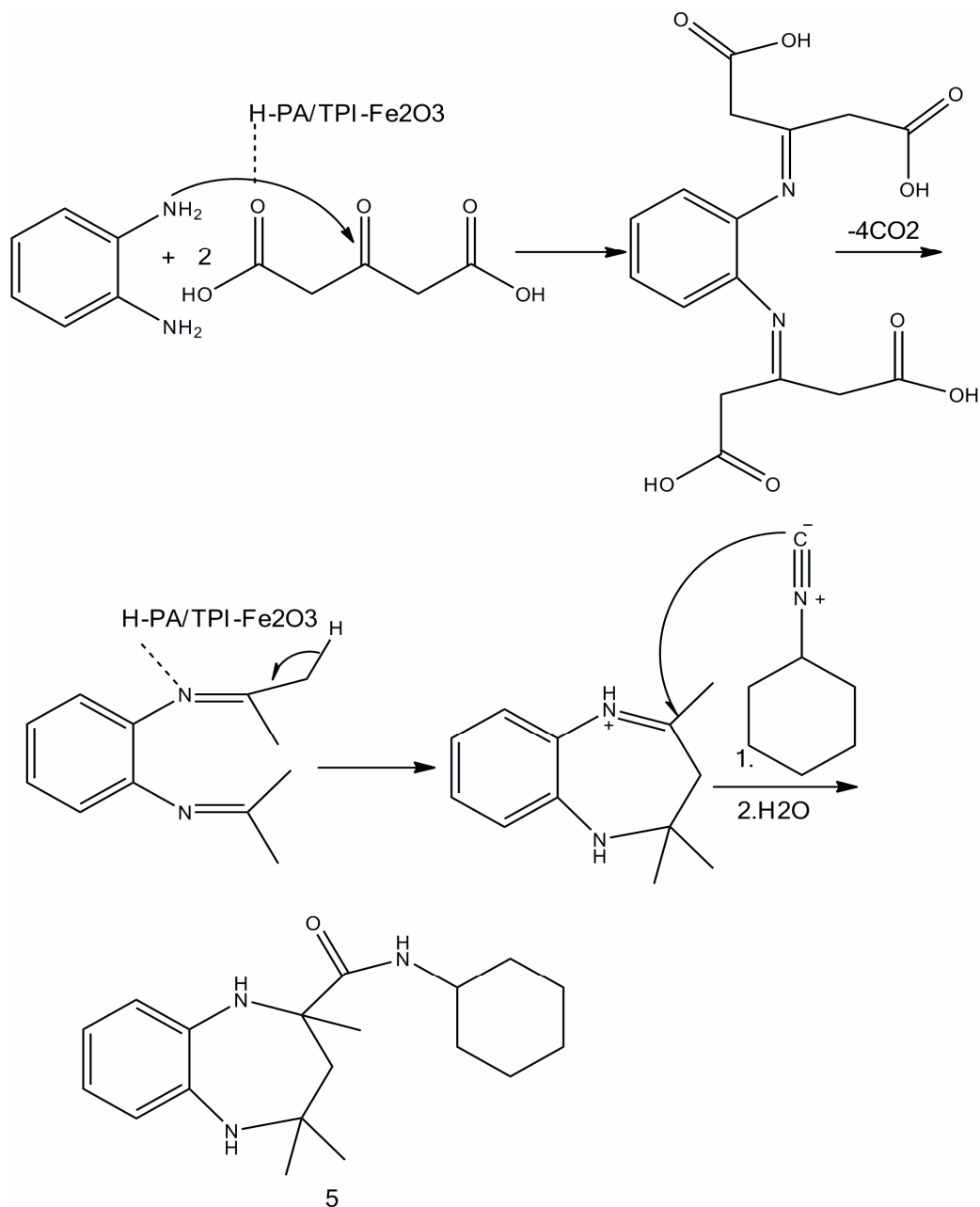


Fig. 1. Possible mechanism for the synthesis of product 5 which catalyzed by HPA/TPI-Fe₃O₄.

electrostatic potential map, thermodynamic and physico-chemical properties, charges on atoms and NBO analysis are discussed.

Vibrational Assignments

The experimental and calculated FT-IR spectra of 5 are

shown in Fig. 3. According to the theoretical calculations, the structure of 5 has the C₁ point group symmetry. This compound consists of 52 atoms. The number of vibration modes of 5 is 139 in normal vibration, 99 in-plane and 40 in out-of-plane. The bands that are in the plane of the molecule are represented as A', while out of the plane bands are

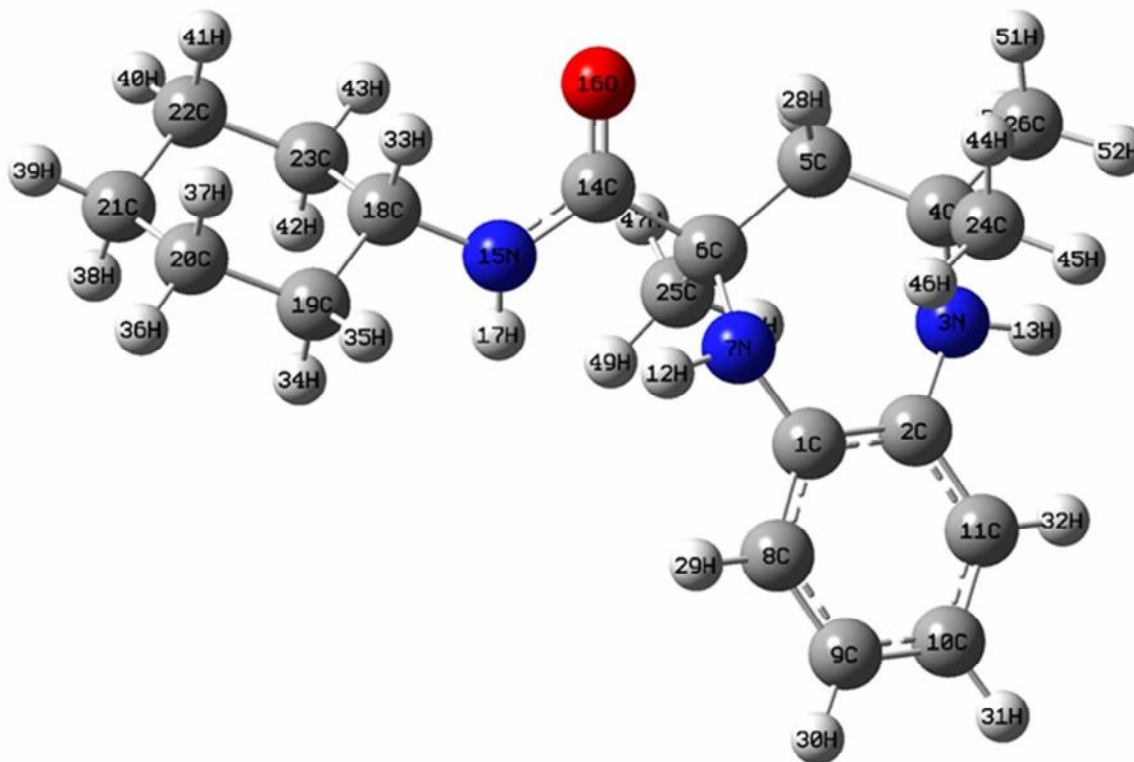


Fig. 2. The global optimized configuration of 5.

Table 1. Recycle of the Catalyst HPA/TPI-Fe₃O₄ Nanoparticles

Cycle	Cat. (g)	Yields (%)
1	0.020	95
2	0.020	95
3	0.020	95
4	0.020	95
5	0.020	93
6	0.020	93

assigned as A". Thus, 139 normal modes of vibrations of 5 are distributed as $\Gamma_{\text{vib}} = 99A' + 40A''$. Relationship between the experimental and computed frequencies of 5 was obtained by the M06-2X and B3LYP methods. From Fig. 4,

it is found that the results obtained by B3LYP ($R^2 = 0.998$) method are in good agreement with the experimental values. DFT calculations clarified that the results of the B3LYP method is in good agreement with the experimental values.

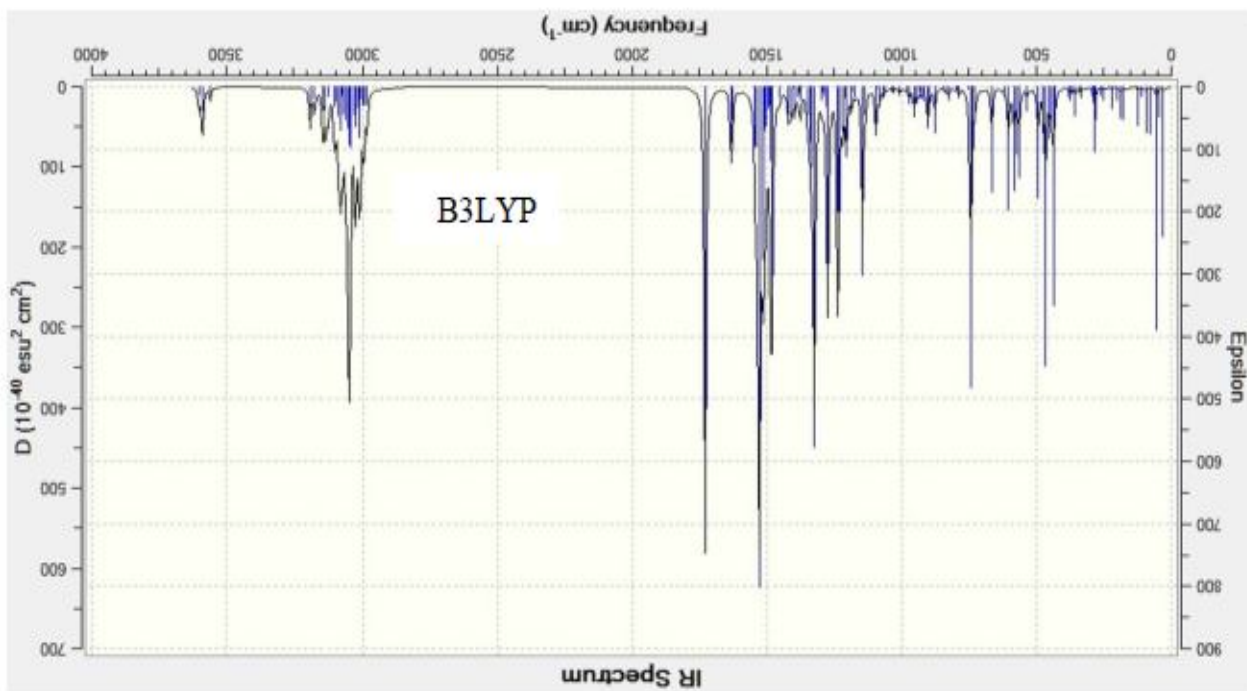
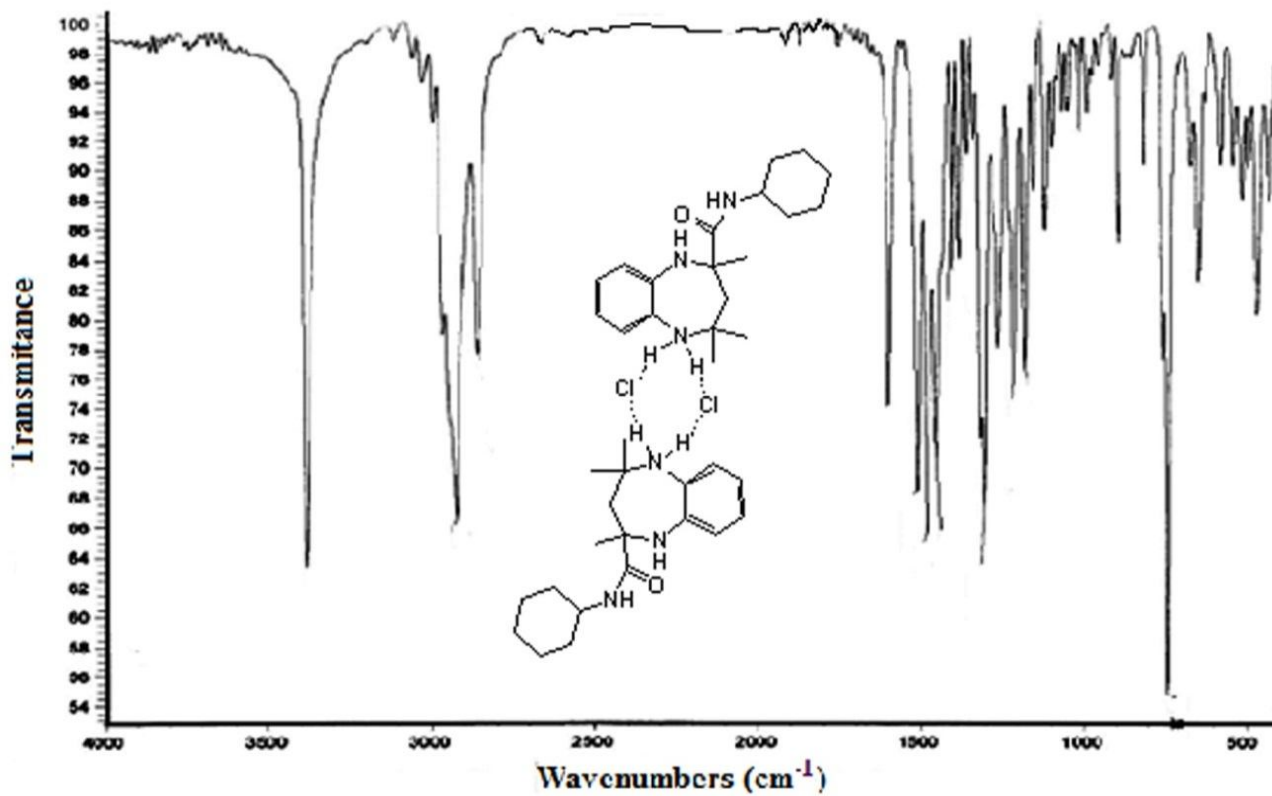


Fig. 3. Experimental and calculated IR spectra for 5.

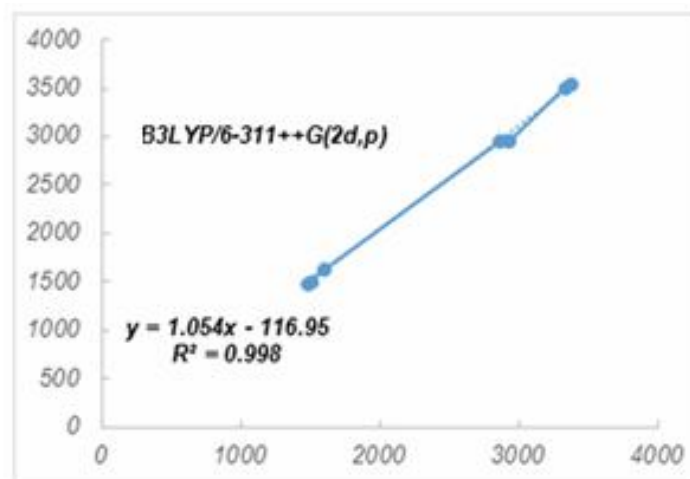


Fig. 4. Relationship between the experimental and computed frequencies of 5.

Recently, Asadi *et al.* have reported experimental and theoretical study on a novel derivative of 1,3,4-oxadiazepin [20]. They found that the physical properties and spectroscopic data of 1,3,4-oxadiazepin are in good agreement with the experimental data using B3LYP/6-311++G(d,p) level which justifies using B3LYP as a suitable method.

C-H Vibrations

The C-H stretching vibration in alkanes and aromatic structure are in the regions of 2850-3000 cm^{-1} and 3000-3100 cm^{-1} , respectively [21,22]. The FT-IR bands observed for the C-H stretching vibrations were at 3375, 3330, 2930 and 2862 cm^{-1} . The calculated C-H stretching vibrations appeared at 3554.7, 3510.7, 2958.5 and 2953.6 cm^{-1} at the B3LYP/6-311++G(2d,p) level.

C=C Vibrations

The C=C bond in aromatic is assigned in the region of 1400-1600 cm^{-1} [22]. In this structure, the C=C bond was seen at 1602 cm^{-1} . The FT-IR bands for the C=C stretching vibrations observed at 1602 cm^{-1} . At the B3LYP/6-311++G(2d,p) level, the calculated C=C stretching vibration appeared at 1571.7 cm^{-1} .

H-C-H Bending Vibrations

The H-C-H bending absorption appears in the region of

1440-1500 cm^{-1} [22]. In this structure, the H-C-H bending is observed at 1478 cm^{-1} . At the B3LYP/6-311++G(2d,p) level, the calculated H-C-H bending vibrations appeared at 1454.9 cm^{-1} .

H-N-C Bending Vibrations

The H-N-C bending absorption appears in the region of 1510-1550 cm^{-1} [22]. In this structure, the H-N-C bending is observed at 1502 cm^{-1} . The calculated H-N-C bending vibrations appeared at 1475.2 cm^{-1} by the B3LYP/6-311++G(2d,p) level.

C=O Vibrations

The region of 1630-1690 cm^{-1} is assigned to C=O bond in amides [21,22]. In title compound, 1668 cm^{-1} was assigned to the C=O bond of amide functional group. The calculated C=O stretching vibration appeared at 1498.7 cm^{-1} for amide at the B3LYP/6-311++G(d,p) level.

Chemical Shift Analysis

Proton chemical shift analysis, ^1H NMR. The experimental and calculated ^1H NMR spectra of 5 are shown in Fig. 5. It was found that the ^1H chemical shift values (with respect to TMS) occurred at 1.34-7.40 ppm at the B3LYP level, whereas the experimental shifts were in the range of 1.0-11.56 ppm. The cyclohexyl protons (H33-43) experimentally resonated at 1-4.12 ppm as a multiplet

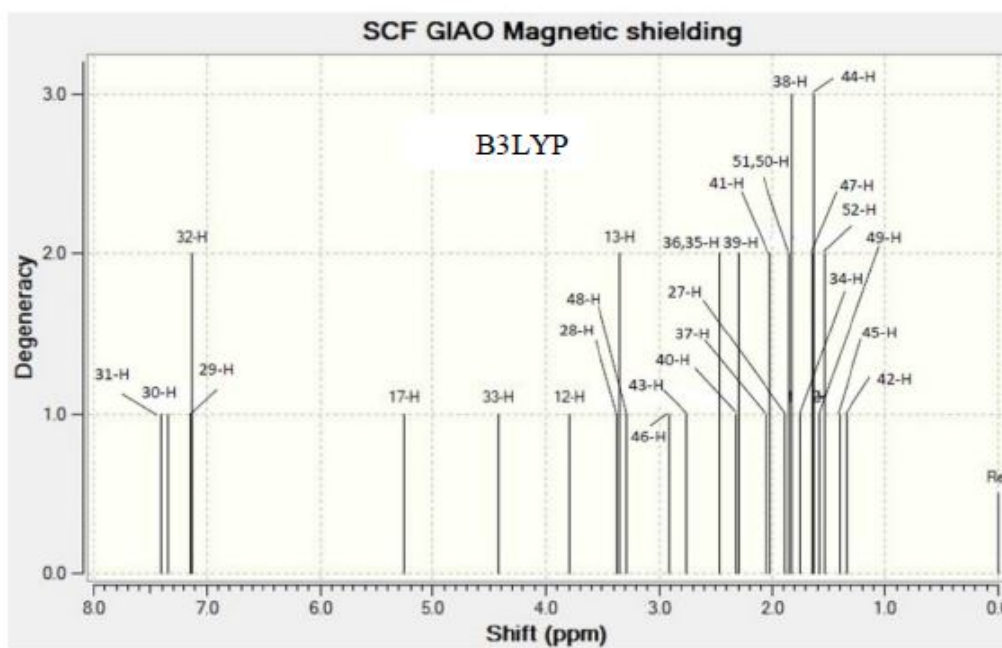
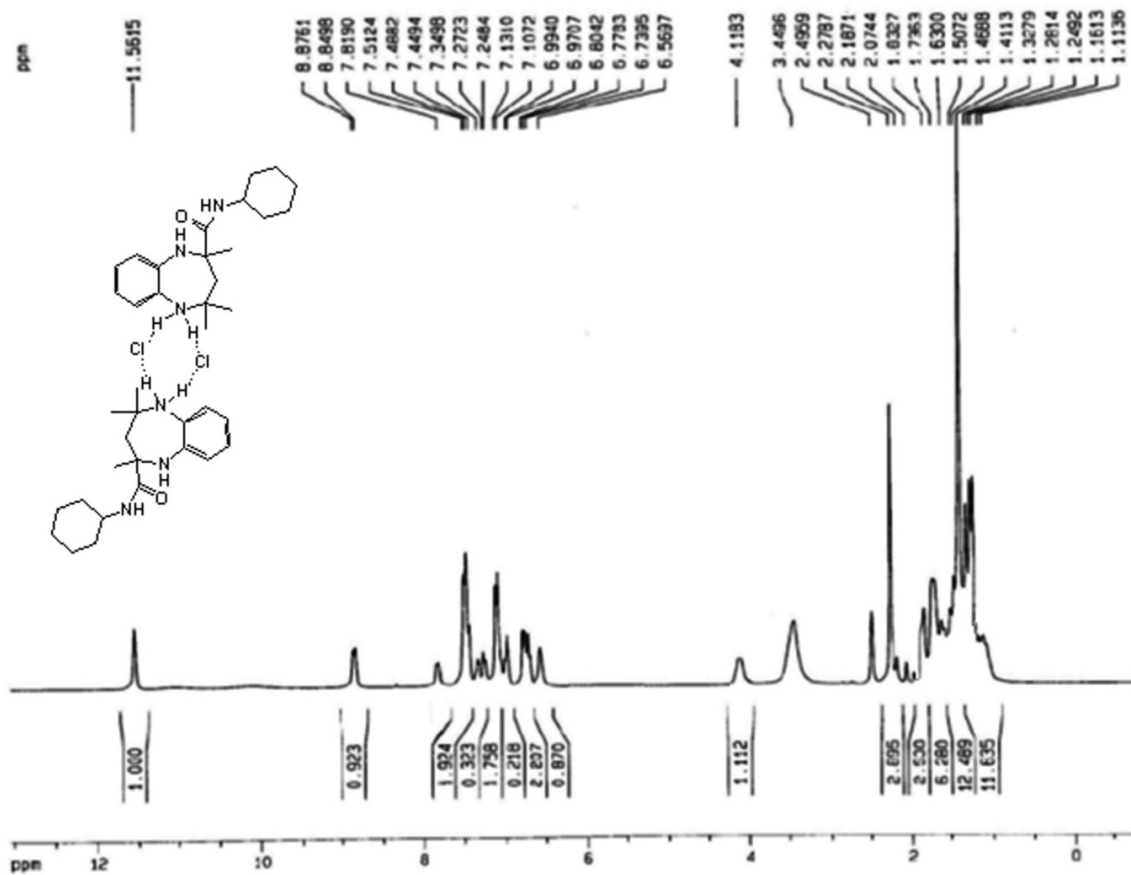


Fig. 5. Experimental and calculated ^1H NMR spectra of 5.

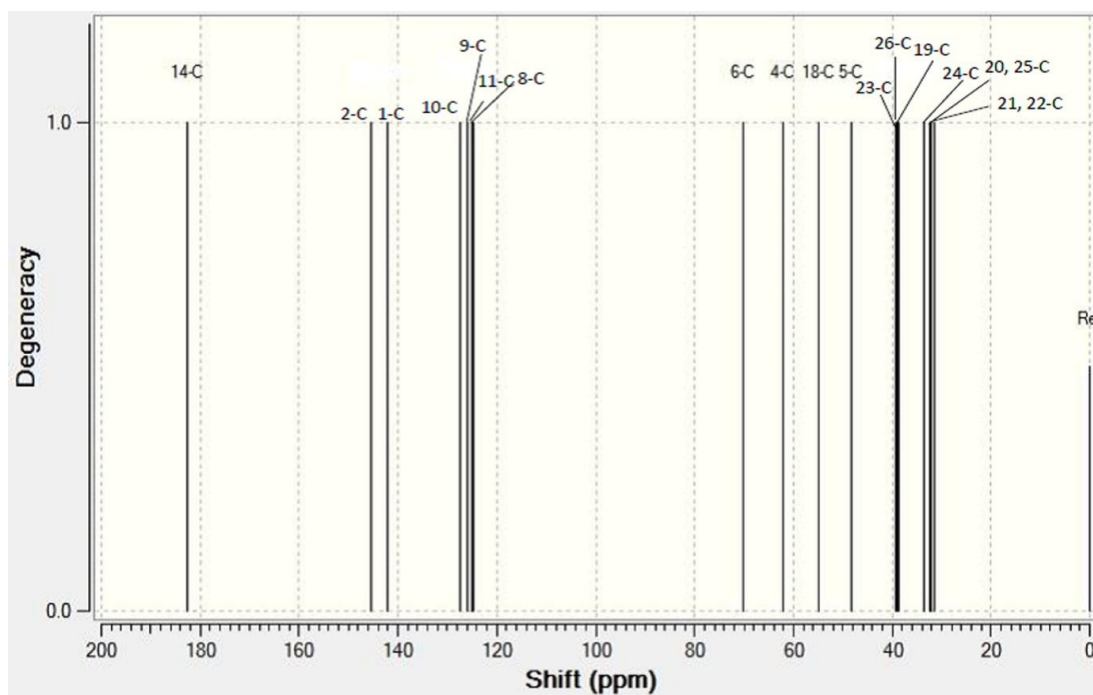
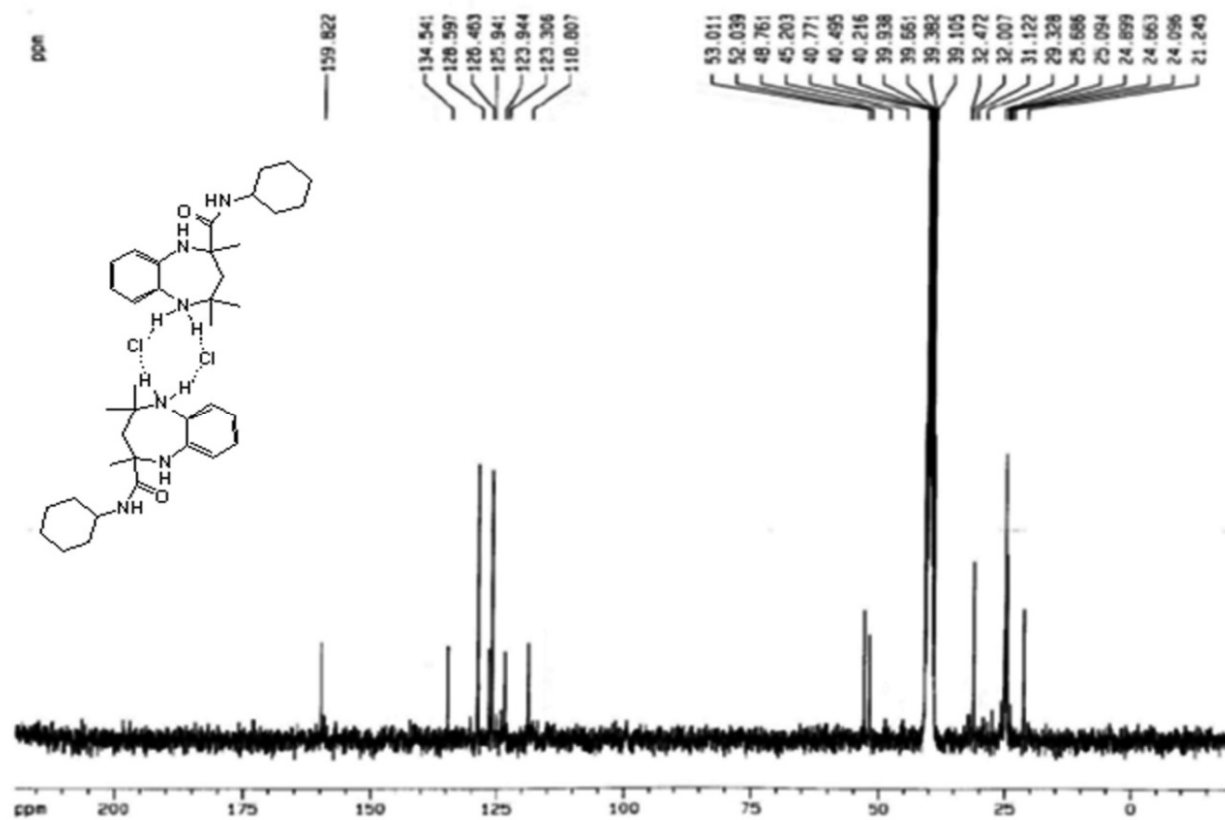


Fig. 6. Experimental and calculated ^{13}C NMR spectra of 5.

whose chemical shifts were theoretically predicted in the range of 1.34-4.42 at the B3LYP level. The signal in the range of 1.0-2.0 ppm was assigned to methyl protons (H44-H52) whose chemical shifts were theoretically predicted in the range of 1.40-3.28 at the B3LYP level. The NH protons (H12, H13 and H17) of the title compound were experimentally identified at 8.86, 6.57, 11.56 ppm. These chemical shifts theoretically occurred at 3.79, 3.34, 5.25 ppm at the B3LYP level of theory. The multiplet at 6.70-7.50 ppm corresponded to the aromatic protons (H29-32) that were calculated at 7.12-7.40 ppm by the B3LYP level. The B3LYP values of the chemical shift for ¹H NMR were found to be in a fair agreement with the experimental values.

Carbon chemical shift analysis, ¹³C NMR. The experimental and calculated ¹³C NMR spectra of 5 are shown in Fig. 6. The ¹³C chemical shifts (with respect to TMS) were assigned in the range of 31.62-182.45 ppm by the B3LYP level, while the corresponding experimental data were observed in the range of 21.2-159.8 ppm. The largest deviation between the calculated and experimental ¹³C NMR chemical shifts ($|\delta_{\text{exp}} - \delta_{\text{B3LYP}}|$) was observed for C4 with 56.68 ppm at the B3LYP level. The chemical shifts of C22, C21, C20 and C25 are experimentally located in the 21.2, 21.2, 24.7 and 24.9 ppm, respectively. The theoretical chemical shift values of these atoms were assigned at 31.62 (error approx. -10.42 ppm), 31.95 (error approx. -10.75 ppm), 32.51 ppm (error approx. -7.81 ppm) and 32.46 ppm (error approx. -7.56 ppm) at B3LYP level. The B3LYP values of the chemical shift for ¹³C NMR were found to be in a fair agreement with the experimental values.

Frontier Molecular Orbital Analysis

The energy difference between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) is called HOMO-LUMO energy gap that shows the chemical activity of the molecule. These data can be utilized as a simple indicator of kinetic stability. It should be noted that the larger amount of energy gap shows the higher kinetic stability.

Saeidian *et al.* have reported the DFT (B3LYP/6-31G) calculations of novel 1,5-bis(N-substituted-1,2,3-triazole) benzodiazepinedione scaffolds [23]. They have reported the energy of 0.137 *a.u.* for HOMO-LUMO gap of

benzodiazepinedione in which HOMO is localized on whole of the molecule while LUMO is localized only on the diazepinedione ring due to bearing two electron withdrawing carbonyl groups; these results confirm our obtained data. L. Kosychova *et al.* have reported the synthesis and theoretical calculations of a novel 1,5-diazepine [24]. Their DFT calculations clarified that the HOMO density of *N*-(1,5-benzodiazepin-4-yl)benzohydrazide intermediate resides mainly on the N1 atom of the diazepine as a nucleophilic site, in consistent with our results. Meanwhile, the LUMO density is localized mainly on the carbon atom of the C=O group of the diazepine as the most probable electrophilic site. In our study, the calculated energy gap of the title compound was 5.779 eV at the B3LYP/6-311++G (2d,p) level.

Molecular Electrostatic Potential Map

The molecular electrostatic potential (MEP) is a reactivity map displaying most probable regions for the electrophilic attack of charged point-like reagents on organic molecules [25]. The MEP map of 5 is shown in Fig. 7. Blue colors indicate positive MEP regions, while red colors correspond to negative MEP regions. The MEP map of 5 was in the range from -0.101 to +0.157 au. This picture showed that N7 has almost more negative MEP region compared with other atoms. This means that nitrogen atom can undergo protonation reaction with acidic reagents.

Calculated Thermodynamic and Physico-chemical Properties

The thermodynamic parameters including total energies, zero-point vibrational energies (ZPVE), entropies and some other thermodynamic parameters were calculated for 5 (Table 2). The logarithm of the partition coefficient for *n*-octanol/water (logP values) of 5 was calculated using two commercially available programs (ChemBioOffice Ultra 11.0 [26] and ACD/LogP [27]). As indicated in Table 2, the B3LYP calculated dipole moment of 5 is 2.178 Debye.

Charges on Atoms

Calculated Mulliken atomic charges showed that some of the atoms of this molecule have positive charge while some of them have negative charge. Calculated NBO atomic charges showed that the largest value of positive charge,

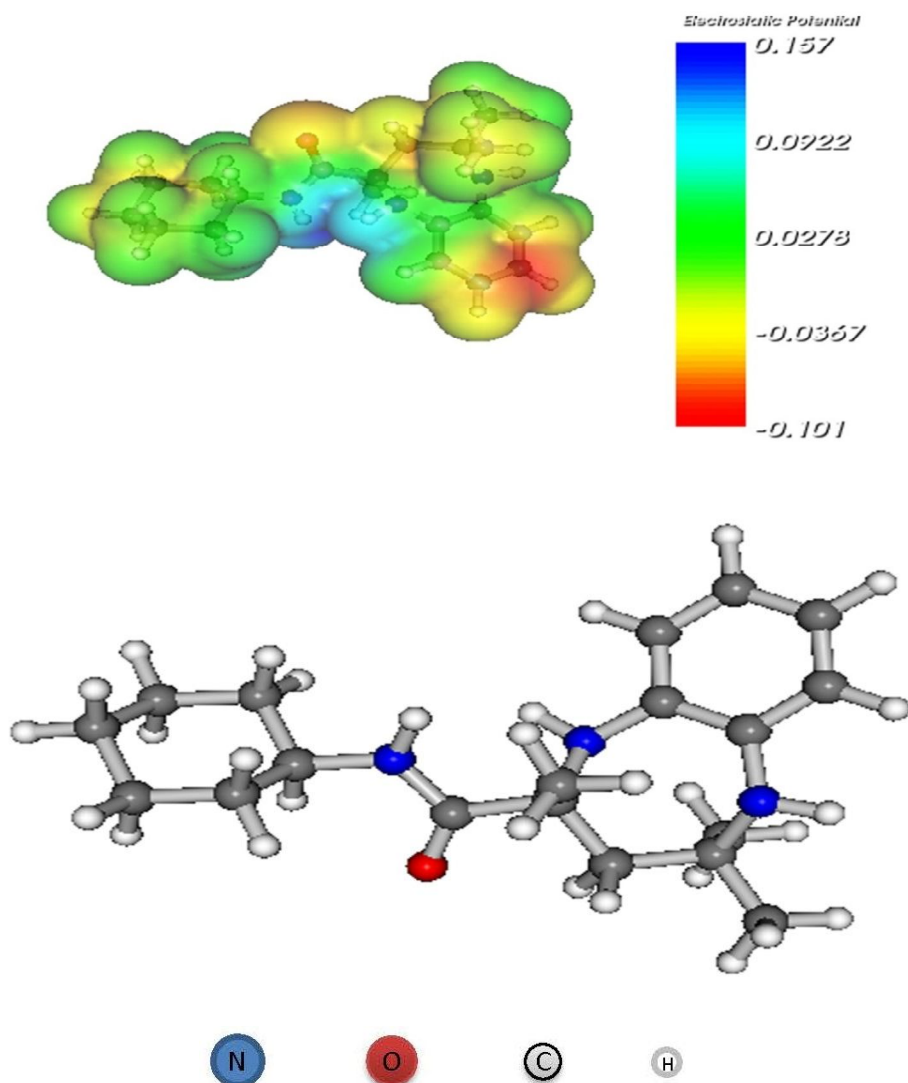


Fig. 7. Molecular electrostatic potential (MEP) diagram for 5.

+0.711, is located on the C₁₄ atom at the B3LYP level. The nitrogen N₇ atom has the most negative charge of -0.669 at the B3LYP level (Fig. 8).

NBO Analysis

The natural bond orbital (NBO) calculations investigated the inter- and intra-molecular bonding interactions among bonds, and intra-molecular charge transfer (ICT) or hyperconjugative interactions for 5 (Table 3). Through NBO analysis, we can obtain information about the energy of the interactions between filled Lewis type molecular

orbital and empty non-Lewis type. Second order perturbation theory is suitable for NBOs and estimating their energy. In this theory, two parts of donor and acceptor. Donor is a filled bonding or lone pair orbital and acceptor is a vacant anti-bonding or lone pair orbital. The stabilization energy E₂ associated with each donor NBO (i) and acceptor NBO(j) delocalization is calculated from the second order perturbation approach by the following equation [28]:

$$E(2) = \Delta E_{ij} = q_i \times F_{ij}^2 / \epsilon_j - \epsilon_i$$

Table 2. Theoretically Computed Total Energies (kcal mol⁻¹), Zero-point Vibrational Energies (kcal mol⁻¹), Rotational Constants (GHz), Entropies (cal mol⁻¹ K⁻¹), Enthalpies (kcal mol⁻¹), Gibbs-free Energies (kcal mol⁻¹), Dipole Moment (Debye) and some Physico-chemical Properties at B3LYP 6-311G++(2d,p) Level

Parameters	B3LYP 6-311G++(2d,p)
Total energy	-615754.835
Zero-point energy	-615466.975
Rotational constants	0.4751173 0.1348808 0.1140796
Entropy	
Total	154.695
Translational	43.140
Rotational	35.040
Vibrational	76.514
Enthalpy	-615452.490
Gibbs-free energy	-615498.611
Dipole moment (D)	
X	-1.2853
Y	1.3154
Z	1.1668
Total	2.1780
Properties	
	Molar refractivity (cm ³) ^a
	Molar volume (cm ³) ^a
	Parachor (cm ³) ^a
	Index of refraction ^a
	Surface tension (dyne cm ⁻¹) ^a
	Density (g cm ⁻³) ^a
	Polarizability (cm ³) ^a
	LogP

^aACD/ChemSketch, ^bChemBioOffice Ultra.

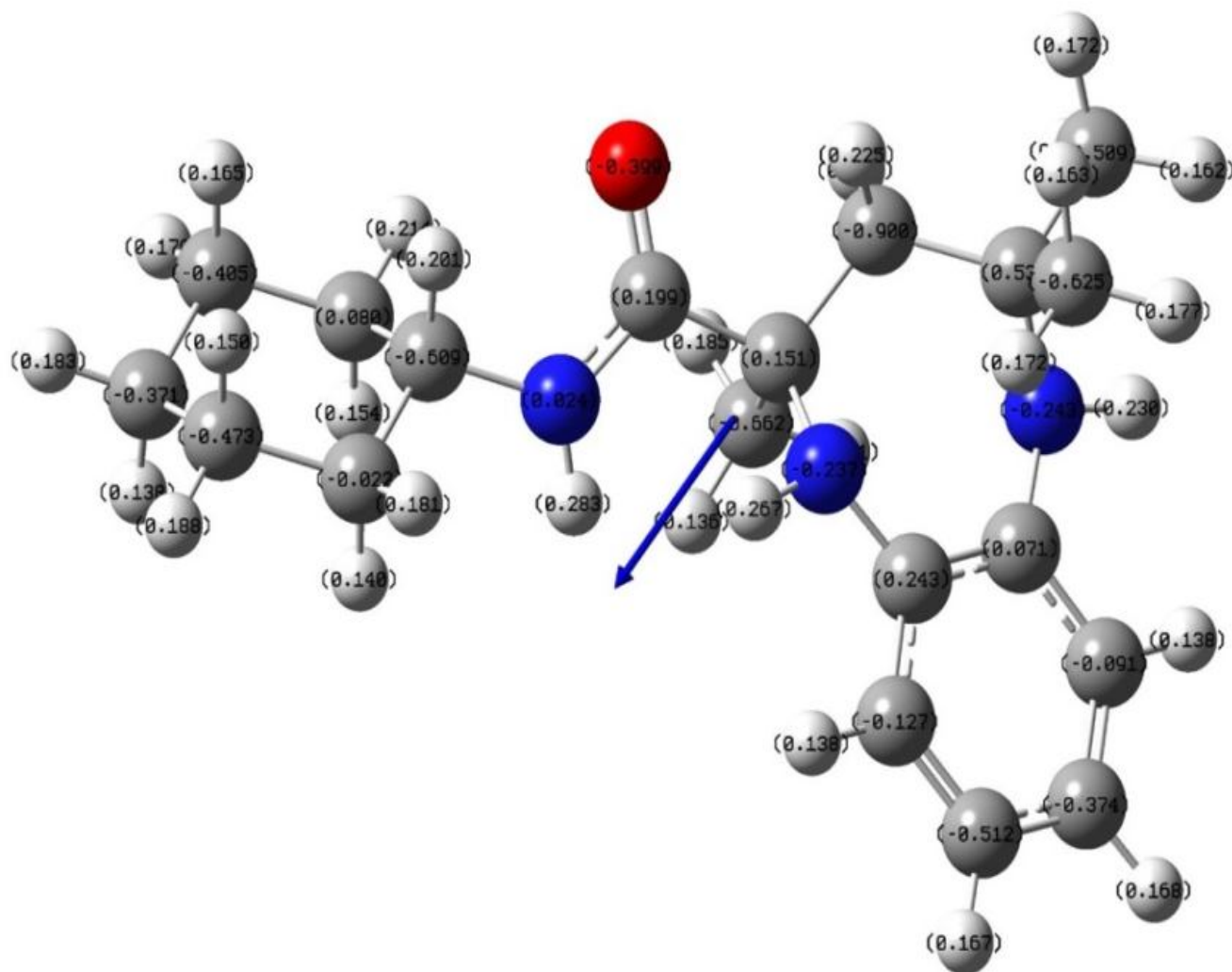


Fig. 8. Charges on atoms of 5 calculated at the B3LYP/6-311++G(2d,p) level.

where q_i is the donor orbital occupancy, E_i and E_j are the diagonal elements (orbital energies) and F_{ij} is the off diagonal NBO Fock matrix element. The larger $E(2)$ value in the NBO analysis shows the dependent intramolecular interactions between electron-donors and electron-acceptors; the greater the value of $E(2)$, the more efficient the calculation method for stability compound. In this work, the NBO analysis was performed for 5. The results showed that six interactions from phenyl group lead to the stability of the compound. Also, delocalization of lone pair electrons on N_3 toward phenyl ring gave the stability of $E_2 = -87.13$ at the B3LYP level. Delocalization of lone pair electrons on N_{15} toward the $C_{14}-O_{16}$ bond gained the stability of

$E_2 = -59.50$ at the B3LYP level. Meanwhile, the stability of $E_2 = -26.06$, at the B3LYP level, showed a strong interaction between the O_{16} atom and $\sigma^*(C_{14}-N_{15})$.

CONCLUSIONS

The title compound 5 was synthesized *via* MCR reactions between *o*-phenylenediamine, 3-oxopentanedioic acid and isocyanocyclohexane. The structure of 5 was determined and characterized by elemental analysis, FT-IR, 1H and ^{13}C NMR. Comparison between the calculated and experimental values indicated that the calculated vibrational wavenumbers at the B3LYP method were in good

Table 3. Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis for 5 at the B3LYP Method with 6-311++G(2d,p) Basis Set

Donor NBO(I)	Acceptor NBO (j)	E2 (kcal mole ⁻¹) B3LYP	Ej-Ei (a.u.) B3LYP	F(i,j) (a.u.) B3LYP
$\pi(\text{C1-C2})$	$\pi^*(\text{C9-C8})$	24.22	0.23	0.067
$\pi(\text{C1-C2})$	$\pi^*(\text{C10-C11})$	19.73	0.28	0.067
$\pi(\text{C8-C9})$	$\pi^*(\text{C1-C2})$	35.04	0.26	0.088
$\pi(\text{C8-C9})$	$\pi^*(\text{C10-C11})$	19.53	0.27	0.066
$\pi(\text{C10-C11})$	$\pi^*(\text{C1-C2})$	21.33	0.21	0.063
$\pi(\text{C10-C11})$	$\pi^*(\text{C8-C9})$	27.03	0.23	0.072
Lp(1)N3	$\pi^*(\text{C1-C2})$	87.13	0.34	0.166
Lp(1)N3	$\sigma^*(\text{C4-C24})$	5.56	0.74	0.059
Lp(1)N7	$\sigma^*(\text{C4-C26})$	20.39	0.29	0.072
Lp(1)N15	$\pi^*(\text{C14-O16})$	59.50	0.29	0.117
Lp(1)N15	$\sigma^*(\text{C18-C23})$	7.05	0.64	0.064
Lp(2)O16	$\sigma^*(\text{C14-N15})$	26.06	0.72	0.124
Lp(2)O16	$\sigma^*(\text{C6-C14})$	20.14	0.61	0.1

agreement with the experimental values. Meanwhile, the obtained ¹H and ¹³C NMR data showed that the B3LYP method are in a fair agreement with the experimental data. The NBO analysis showed that the six interactions arising from the phenyl group, and lone pair electrons on the N₃, N₁₅ and O₁₆ atoms are effective in the stability of 5.

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