

Synthesis, Physico-Chemical, Hirschfield Surface and DFT/B3LYP Calculation of Two New Hexahydropyrimidine Heterocyclic Compounds

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ABSTRACT: *Two new hexahydropyrimidine compounds were prepared in high yield by condensation of an equimolar amount of 1,3-diamine with 2-dipyridylketone at room temperature in dichloromethane. The desired hexahydropyrimidine structures were confirmed on the basis of their UV-Visible, elemental analysis, FT-IR, ¹H-NMR, TG/DTG and EI-MS data. Hirschfield and DFT/B3LYP theoretical analyses were performed and their output results were compared to experimental data.*

KEYWORDS: *Hexahydropyrimidine; Hirschfield surface; NMR; DFT.*

INTRODUCTION

The hexahydropyrimidine heterocyclic group is existent in many pharmaceutical and natural agents [1]. Hexahydropyrimidines are playing an important role in the medical area, like fungicide, anti-inflammatory

parasiticide, antivirals and anti-bacterial [2]. Several hexahydropyrimidines and their derivatives served as a reagent for the stabilization of polymers [3].

Moreover, hexahydropyrimidines agents act as novel

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ligand due to the presence of nitrogen atom donors in their backbone, since it binds the metal centers through mono-, or polydentate coordination mode [4-7].

The synthetic procedure of heterocyclic compounds and hexahydropyrimidines through a dehydration reaction of ketone or aldehydes with diamines consider being a typical synthetic method [7-17]. Spirohexahydropyrimidines ligands were recently synthesized *via* one-pot condensation of formaldehyde, anilines, and cyclohexanones through Mannich-type reaction using proline as a catalyst [18]. Such a procedure classified as a vital C-C coupling process therefore, it was broadly applied to the preparation of diverse spirohexahydropyrimidines derivatives [19].

Multicomponent hexahydropyrimidines compounds were successfully synthesized without side products through one/multi-pot synthesis procedures which only smoothly performed by using iron(III) chloride as a catalyst [19].

Nevertheless, two prospect outcomes may produce such condensation reaction, the wanted products hexahydropyrimidine or Schiff bases unwanted products, control reaction conditions may favor over each other [13].

Generally, aliphatic carbonyls were employed in the producing of hexahydropyrimidines, while aromatic carbonyls were served to synthesize Schiff bases [20, 21]. Because the hexahydropyrimidine compounds easy de-structured to their carbonyl and diamine starting materials under diluted acidic reaction conditions, it can be used in organic assembly as effective protective functional groups [13].

In this work, two new hexahydropyrimidine such as 2,2-di(pyridin-2-yl)hexahydropyrimidine (**1**) and 6,6-di(pyridin-2-yl)-5,7-diazaspiro[2.5]octane (**2**) were prepared and spectrally characterized, the X-ray structure of **1** and other derivatives were currently published [6-13]. The optimized parameters of **1** were matched with the crystallographic data. The intermolecular forces in the packed crystal lattice were also confirmed by Hirshfeld surface analysis calculations. The nucleophilic and electrophilic sites were mapped in MEP analysis. Electronic absorption UV-VIS./TD-SCF, HOMO/LUMO, H-NMR analysis were computed and compared to their experimental results. The thermal stability and thermal decomposition behavior of **2** were experimentally evaluated by TG/DTG analysis in an open atmosphere.

RESULTS AND DISCUSSION

The hexahydropyrimidine compounds were made

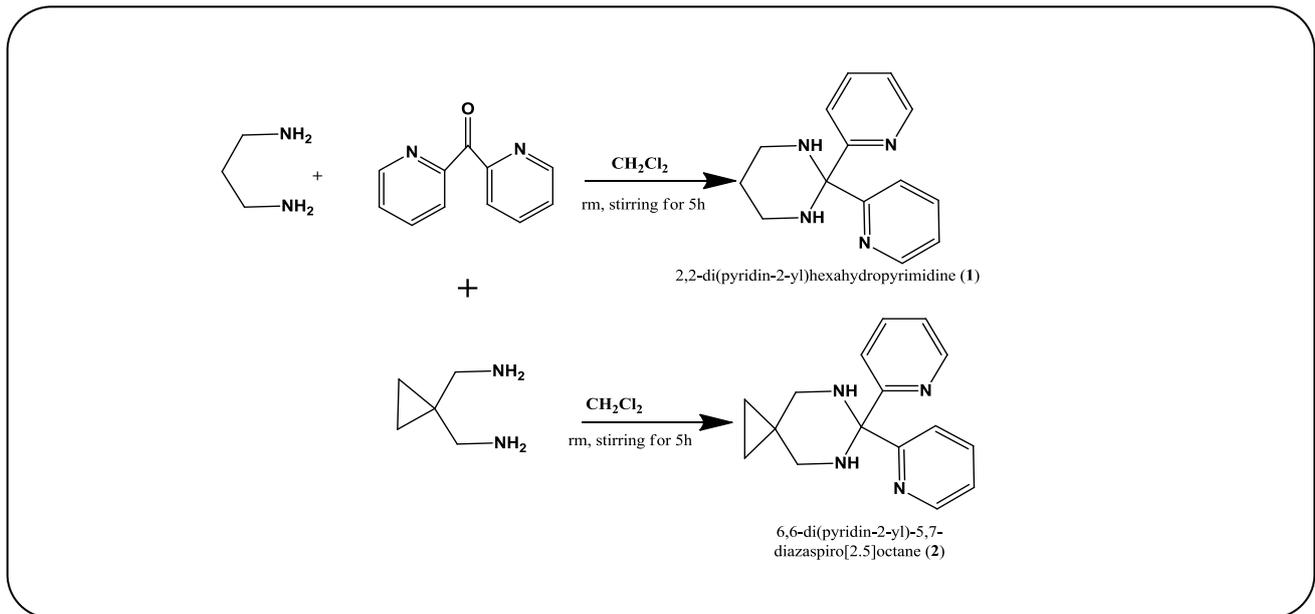
available by mixing an equimolar amount of 1,3-diamine with 2-dipyridine ketone in dichloromethane solvent, as shown in Scheme 1. The condensation reaction was processed in a bath of cyclization to produce hexahydropyrimidine and not the Schiff bases product [13]. Due to the stoichiometry, solvents and temperature, we have found critical points in synthesis to avoid the formation of Schiff base or incomplete hexahydropyrimidine: (a) slight excess of ketone (or aldehyde) over the diamine quantities. (b) The solvent should be slightly polar, for example, alcohol is suitable but dichloromethane found to be the best choice (c) the reaction is performed at room temperature without heating (d) absent of acidic condition. The colorless product which was collected at the end of the reaction, it was re-dissolved in diethyl ether, non-soluble impurities or unwanted products were filtrated out. The diethyl ether solvent was evaporated from the solution mixture in order to crystalline the hexahydropyrimidine desired product in high yield.

The elemental analyses are consistent with the molecular formulas of the desired compounds, compound **1** (Calcd. for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.77; H, 6.61; N, 23.25), compound **2** (Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.02; H, 6.77; N, 21.01). EI-MS spectrum [M^+] m/z of **1** = 240.14 (240.2 theoretical), EI-MS spectrum of **2** = 266.15 (266.3 theoretical). MS results are in good agreement with the molecular ion.

The IR spectrum of hexahydropyrimidine revealed several absorption bands related to structural vibration of several functional groups. The main absorption bands at 3405-3380, 3080-3060, 2980-2700 cm^{-1} are cited to N-H, C-H_{py}, C-H_{aliph} stretching vibration, respectively.

The experimental and theoretical 1H -NMR spectra are consistent with the proposed structures of the desired compounds, signals of aliphatic and aromatic protons are assigned to their expected chemical shifts positions, as seen in Fig. 1. For the comparative reason, the theoretical 1H -NMR was plotted against the experimental one, as illustrated in Fig. 1a and 1b. The correlation coefficient value $R^2 = 0.9981$ for the plot of protons chemical shifts determined by computed 1H -NMR versus experimental one disposed of an excellent linear relation between theoretical and experimental 1H -NMR (Fig. 1c).

The theoretical optimization of **1** was performed at the DFT (Density Functional Theory) level of theory and



Scheme 1: Synthesis of hexahydropyrimidine.

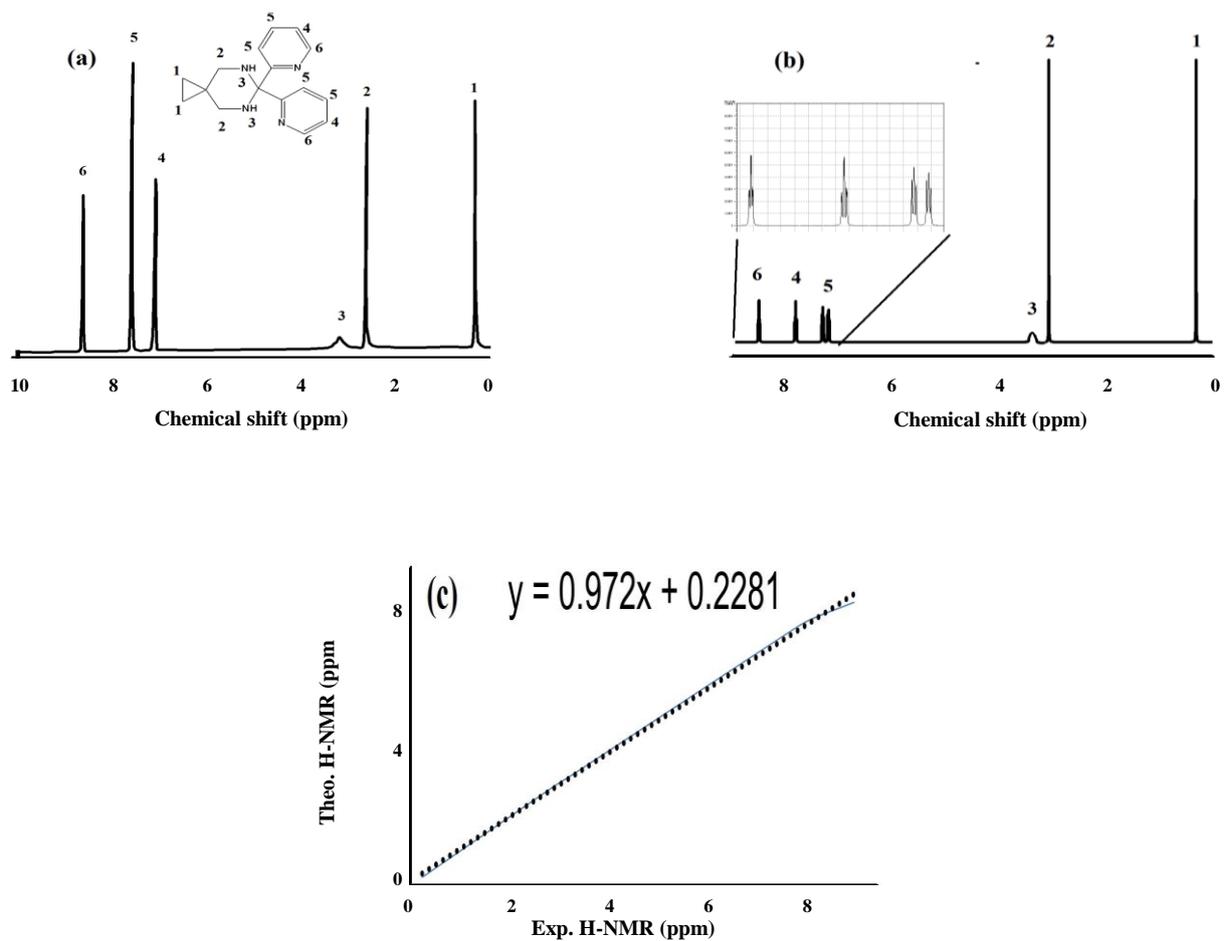
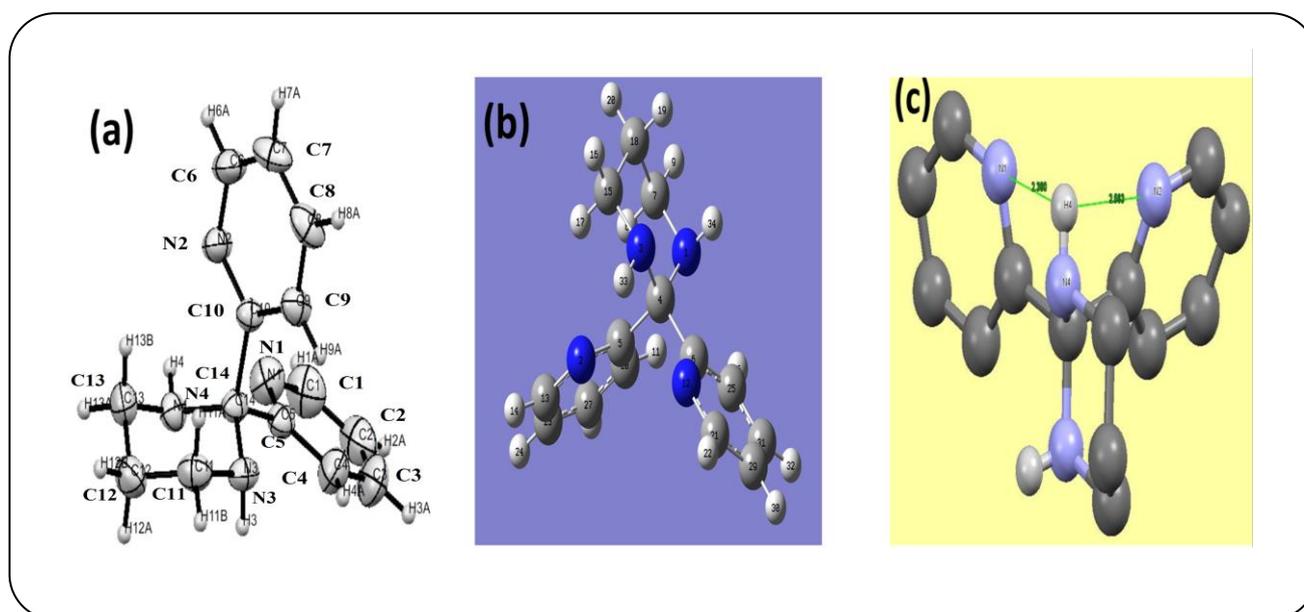


Fig. 1: (a) Experimental ^1H NMR spectrum of 2 in CDCl_3 at RT, (b) Theoretical ^1H NMR in vacuum (c) Experimental in comparison to the theoretical.

Table 1: Calculated and experimental bond lengths and angles (°) around N_2CPy_2 carbon of **1 at B3LYP/3-21G levels of theory.**

Bond Å	Experimental	DFT/B3LYP
C-N1	1.464	1.477
C-N2	1.464	1.477
C-C _{Py1}	1.546	1.540
C-C _{Py2}	1.530	1.540
Angle (°)		
N1-C-N2	110.82	110.35
C _{Py1} -C- C _{Py2}	106.98	109.61
N1-C- C _{Py1}	107.52	109.32
N2-C- C _{Py2}	109.52	109.22

**Fig. 2: (a) ORTEP of **1** with thermal ellipsoids drawn at 50% probability level (b) optimized DFT-B3LYP structure and (c) ball and stick intra-H-bond.**

compared to the X-ray structure data, as seen in Fig. 2a and b. The geometrical parameters such as bond lengths and bond angles in the optimized structure around the tetrahedral N_2CPy_2 carbon center was compared to the X-ray solved structure data, as listed in Table 1.

The total bond lengths and bond angles belong to molecule **1** was extracted from the crystal information file of the solved crystal data and illustrated in Table 2.

An optimized geometry of **1** possesses C1 symmetry. The hexahydropyrimidine unit was found to have chair conformation favored structure with one equatorial and one axial H-N functional group, two intra H-bonds were detected in N-H_{eq}.....2N_{py} with 2.380 and 2.668 Å

length (Fig. 2c), such bonds play a critical role in crystal structure stabilization and building 3D H-bonds network.

The electronic absorption of the desired compounds was performed in MeOH. The compounds revealed UV electronic absorption activities only at $\lambda_{max} = 250-320$ nm which attributed to $\pi-\pi^*$ intra-ligand transitions. Fig. 3 showed the UV spectrum and TD-SCF DFT/B3LYP theoretical calculation of **1** in a gaseous state. Intense transition band at $\lambda_{max} = 290$ nm with $\epsilon = 2.2 \times 10^4 \text{ M}^{-1}\text{L}^{-1}$ (Fig. 3a), while time-dependence DFT/B3LYP UV-Vis. spectrum revealed a major band with $\lambda_{max} = 310$ nm, as shown in Fig. 3b.

An excellent match between the theoretical- TD-SCF DFT/B3LYP and the experimental UV-measurement

Table 2: The experimental bond lengths (Å) and angles (o) extracted from **1** structure.

Bonds		Experimental Length Å	Angles			Experimental value (°)
H3	N3	0.88(2)	C2	C1	N1	124.0(2)
H4	N4	0.92(2)	C2	C3	C4	119.4(2)
C1	C2	1.361(3)	C3	C4	C5	118.5(2)
C1	N1	1.335(3)	C4	C5	C14	122.5(2)
C2	C3	1.365(3)	C4	C5	N1	122.2(2)
C3	C4	1.384(3)	C14	C5	N1	115.3(1)
C4	C5	1.382(3)	C7	C6	N2	124.1(2)
C5	C14	1.527(2)	C6	C7	C8	118.4(2)
C5	N1	1.334(2)	C7	C8	C9	118.5(2)
C6	C7	1.366(2)	C8	C9	C10	120.1(2)
C6	N2	1.343(2)	C9	C10	C14	121.0(1)
C7	C8	1.372(3)	C9	C10	N2	121.7(1)
C8	C9	1.373(2)	C14	C10	N2	117.2(1)
C9	C10	1.379(2)	C12	C11	N3	113.1(1)
C10	C14	1.546(2)	C11	C12	C13	109.2(2)
C10	N2	1.340(2)	C12	C13	N4	109.5(1)
C11	C12	1.514(3)	C5	C14	C10	107.0(1)
C11	N3	1.467(2)	C5	C14	N3	109.5(1)
C12	C13	1.511(2)	C5	C14	N4	107.4(1)
C13	N4	1.469(2)	C10	C14	N3	107.8(1)
C14	N3	1.464(2)	C10	C14	N4	114.1(1)
C14	N4	1.464(2)	N3	C14	N4	110.9(1)
			C1	N1	C5	117.6(2)
			C6	N2	C10	117.1(1)
			H4	N4	C13	111(1)
			C13	N4	C14	113.4(1)
			C11	N3	C14	112.2(1)

the analysis was observed, and perhaps the slight ~20 nm shift may be due to the solvent effect [22-24].

The HOMO/LUMO energy level data are very useful to estimate the physio-chemical behavior of compounds. Several chemical parameters like symmetry, electrophilicity, chemical potential, hardness, quantum chemistry terms and electronegativity [24]. Fig. 4 shows the HOMO/LUMO orbital shapes together with their energy levels of **1** in the gaseous phase, the HOMO response at -0.19121 a. u. while the LUMO is located at -0.01860 a. u. with ~ 0.18 a. u. energy gap. The calculated

energy gap value revealed the easiness of electron excitation from HOMO to LUMO. HOMO and LUMO gap is related to the chemical reactivity or kinetic stability since both have negative values that decide the chemical stability of the ligand [23].

MEP of **1**

The MEP is a helpful technique to calculate the interaction of the molecule with its neighbors. It is also useful for evaluating points in molecules activities for electrophilic and biological attacks depending

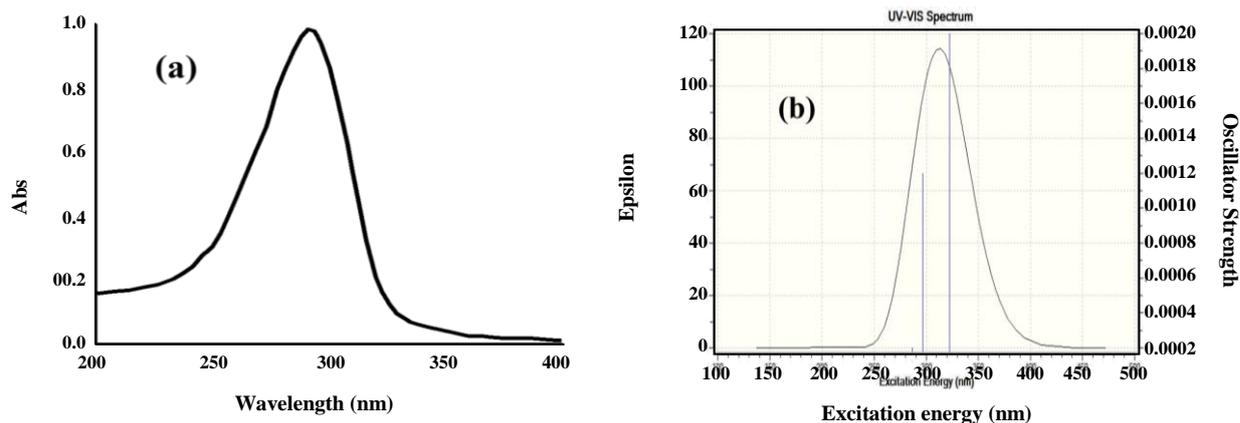


Fig. 3: Experimental UV spectrum of 1 in methanol $\lambda_{max} = 290$ nm (a) and theoretical TD-DFT/B3LYP in the gaseous state with $\lambda_{max} = 310$ nm (b).

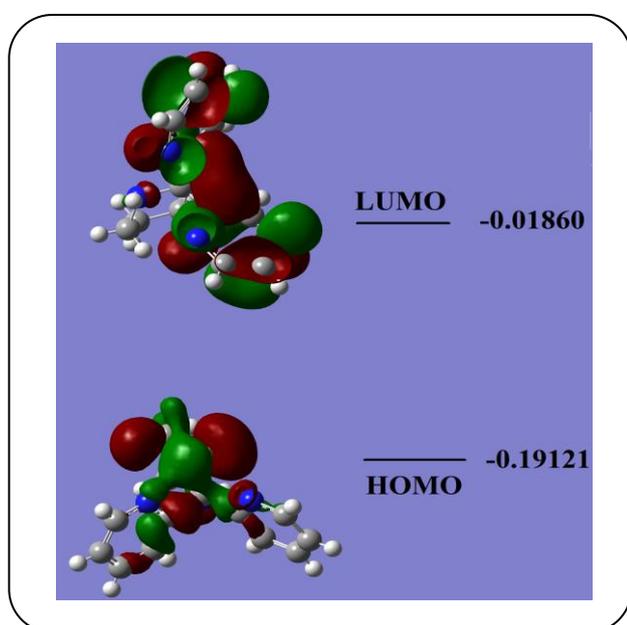


Fig. 4: HOMO/LUMO of 1.

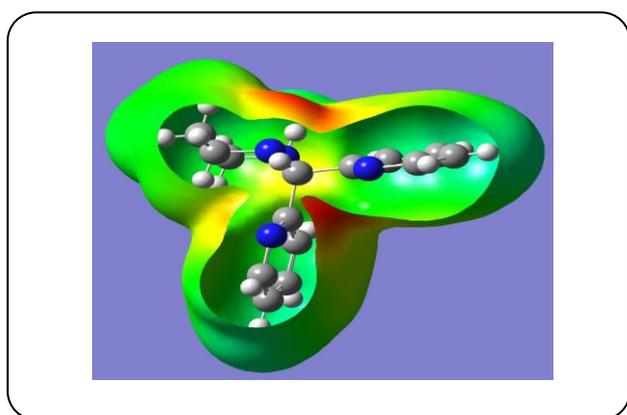


Fig. 5: MPE surface of 1.

on the polarity of the molecule [24]. In order to estimate the nucleophilic and electrophilic sites in molecule compound **1**, MEP/B3LYP was performed as shown in Fig. 5. The electrostatic potential is illustrated by different colors; red as most negative, while blue as the least in negative. The values of the electrostatic decreased in the order of red>orange>yellow>green>blue.

In compound **1**, the most negative atoms around are N atoms (red), with their unshared lone pair of electrons, are classified as preferred sites for electrophilic attacked, on the other hand, the maximum e-poor atoms which are nucleophilic moderate attacked sites that are cited to alkyl and aromatic H-C groups (green). No blue color was detected in the MEP, which reflected no sharp electronic shortage in the molecule; meanwhile, the presence of the red and orange colors supported the compound to be as an excellent e-donor ligand.

Hirshfeld surface analysis

Hirshfeld surface of compound **1** is depicted in Fig. 6. The red points over the surface indicate the types of intercontacts that are involved mostly as hydrogen bonds [24-27]. The big-red spots on d_{norm} presence as the strongest H-bonds, while other intermolecular interactions are in small-red points indicate weak connections. Four red spots were recorded per molecule; the two strong interactions were detected around N-H functional group (strong nucleophilic group) which is consistent with the MEP results.

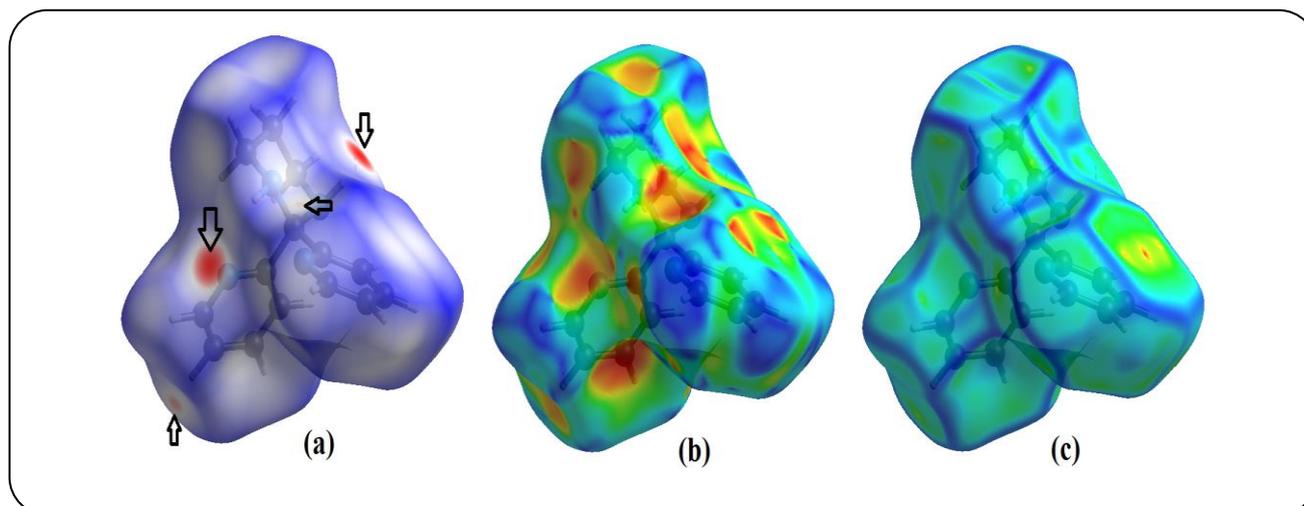


Fig. 6: d_{norm} mapped (a), shape index (b) and curvedness (c) on the Hirshfeld surface of **1**.

The 2D Finger print plots over the Hirshfeld surfaces showed the presence of inter-contacts H...H (63.5%)>H...C (9.9%)>H...N (6.5%) with H...all (79.9%) as depicted in Fig. 7.

TG/DTG

The TG/DTG thermal analysis of **2** was performed in an open atmosphere room temperature in the range of 25–300 °C with 10 °C/min rate of heat, as seen in Fig. 8. Typical one step thermal decomposition was detected in the range ~ 75–140°C. No intermediate product or residue was detected at the end of the decomposition process, which confirmed that such material is decomposed with one step mechanism.

Experimental Section

The IR data were obtained collected using PerkinElmer FT-IR Spectrophotometer. $^{13}\text{C}\{^1\text{H}\}$ and ^1H -NMR were measured on Bruker DRX 250 spectrometer. The UV spectrum was recorded on TU-1901 UV-visible spectrophotometer. EI-MS spectra were recorded using PerkinElmer Finnigan 711A (8 kV) spectrometer.

20 mmol of the 1,3-propanediamine in 20 mL of dichloromethane was added to 20 mmol of 2-dipyridylketone dissolved in 30 mL of dichloromethane was sealed and stirred for 8 h. The resulting mixture was evaporated under an open atmosphere. The solid powder product was re-dissolved in diethyl ether, unwanted material was removed by filtration, while the product was obtained after evaporation of diethyl ether as crystalline

material, the product was washed with distilled water several times.

Compound **1**, yield 88%, Mp: 98 °C; Colorless, ^1H NMR (ppm, CDCl_3 , 250 MHz): 1.21 (s, CH_3 , 6H), 3.49 (br, NH, 2H), 3.67 and 3.66 (br, CH_2 , 4H), 7.10–8.70 (3m, Py, 10H),

Compound **2**, yield 90%, Mp: 84 °C; Colorless, ^1H NMR (ppm, CDCl_3 , 250 MHz): 0.32 (d, 2CH_2 , 4H), 2.82 (br, CH_2 , 4H), 3.24 (br, NH, 2H), 7.00–8.85 (3m, Py, 10H).

CONCLUSIONS

The 2,2-di(pyridin-2-yl)hexahydropyrimidine (**1**) and 6,6-di(pyridin-2-yl)-5,7-diazaspiro[2.5]octane (**2**) were prepared in high yield, physicochemically and thermally characterized. The condensation reaction was performed with an equimolar amount from the corresponding 1,3-diamine with 2-dipyridylketone under specific conditions to avoid the formation of unwanted side products. The structures of the desired products were deduced from UV-visible, elemental analysis, TG, FT-IR, ^1H -NMR and EI-MS analysis. The X-ray structure data of **1**, Hirschfeld surface and DFT/B3LYP theoretical analysis were matched well when they compared together.

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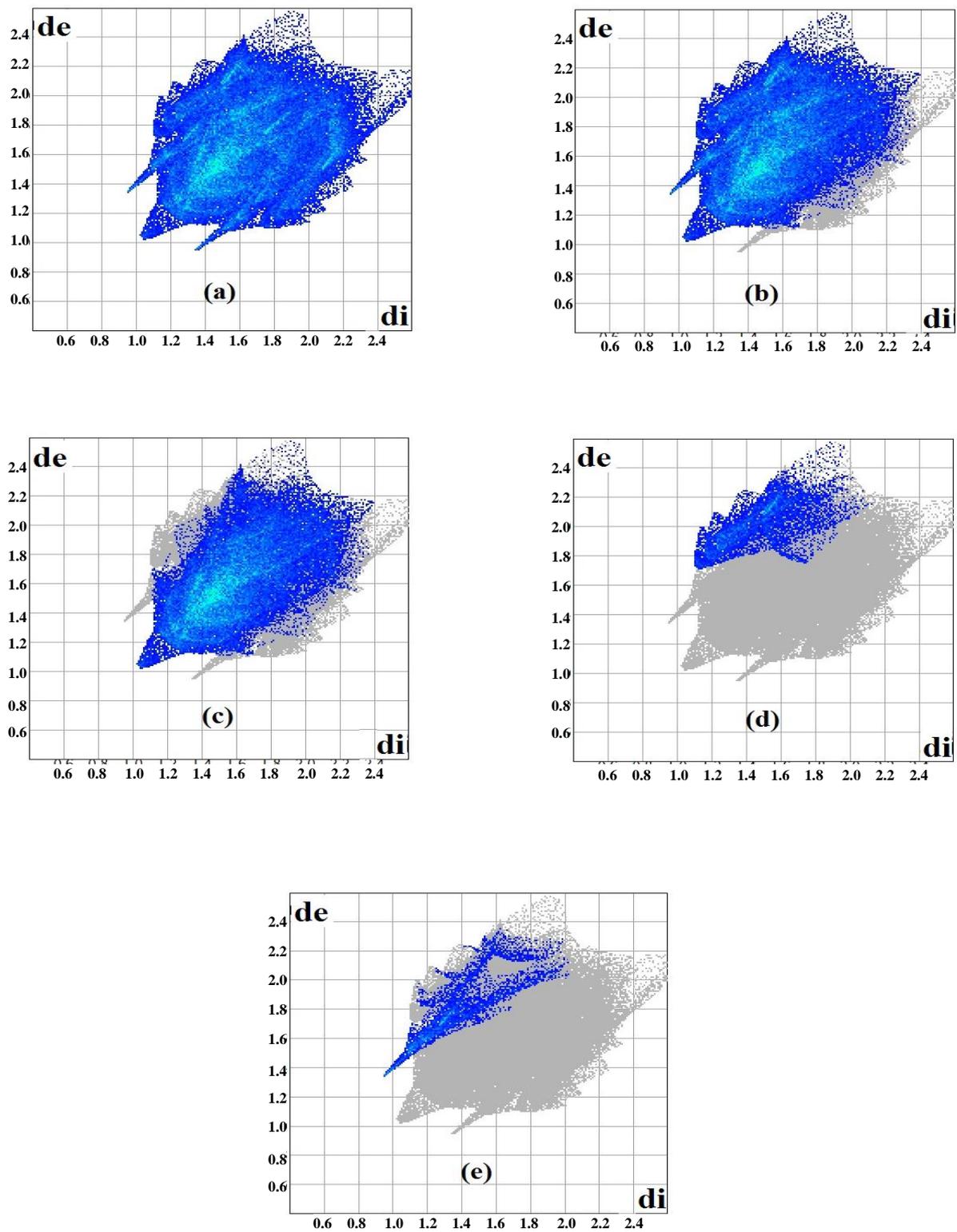


Fig. 7: Fingerprint of 1 inside...outside atoms, (a) all...all, (b) H...all, (c) H...H, (d) H...C and (e) H...N.

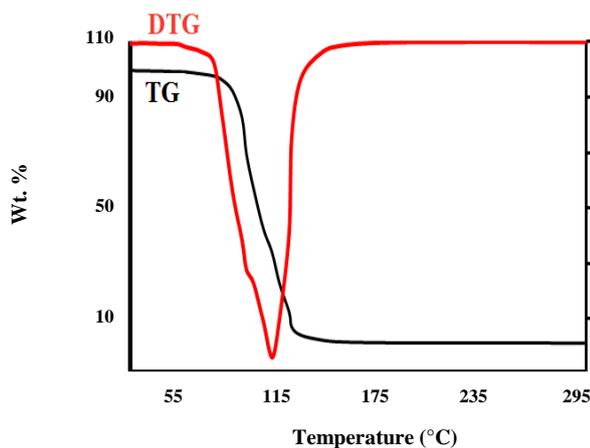


Fig. 8: TG/DTG of 6,6-di(pyridin-2-yl)-5,7-diazaspiro[2.5]octane

Authors Contribution

M.A, O.A., and I.A, performed the experiments; A.B. carried out the DFT; S.R., R.T. and H.E. performed the spectral and analyzed it: NMR, EA, MS and XRD; T.B and A.Z helped in the results and discussion; I. W. wrote the manuscript.

Supplementary Material

An XRD structural analysis was deposited with the Cambridge crystallographic data center, CCDC No. 953976. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from thee CCDC, 12 union Road, Cambridge CB2 IEZ, UK; fax: +44-1223-33633; e-mail: deposit@ccdc.ac.uk)”.

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