Synthesis, characterization, and molecular structure investigation of new tetrahydrobenzo[*b*]thiophene-based Schiff bases: A combined experimental and theoretical study

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Abstract

Five new heterocyclic Schiff base derived from tetrahydrobenzo[*b*]thiophene were synthesized by condensation reaction of 2-amino-4, 5, 6, 7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile with aromatic aldehydes in dimethylformamide containing $ZnCl_2$. The new Schiff bases were characterized on the basis of FT-IR, ^{1}H NMR, and ^{13}C NMR spectral data. In addition, the optimized geometries and assignment of the ^{1}H NMR chemical shifts of the synthesized compounds were computed using the density functional theory (DFT) approaches. Good agreement between the DFT-calculated ^{1}H NMR chemical shifts and the corresponding experimental values confirms suitability of the optimized geometries for the synthesized Schiff bases. Characteristics of the bonding interactions have been explored using the quantum theory of atoms in molecule (QTAIM) analysis.

Keywords: AIM; DFT; Schiff base; tetrahydrobenzo[*b*]thiophenes.

Introduction

The Schiff bases firstly proposed by the German chemist Hugo Schiff [1] refer to the compounds having an imine or azomethine functional group prepared by a condensation reaction between an aldehyde or ketone and a primary amine. The general formula for Schiff base is RR'C=NR" where R, R', and R" could be variously substituted with alkyl, aryl, or heterocyclic groups. The -C=N- imine bond with electrophilic carbon and nucleophilic nitrogen provides excellent binding opportunities with different nucleophiles and electrophiles and plays a unique role in conferring broad-spectrum biological activities to these compounds. It has been known that certain Schiff bases, either alone or in a metal chelated form, possess important biological activities such as anticancer [2], antibacterial [3], antihypertensive [4], anticonvulsant [5], and antimicrobial [6] properties. These compounds are also

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applied in nonlinear optical materials [7], corrosion inhibitors [8], and synthesis of nano-compounds [9-12]. Some of them have also inhibitory activities against α-glucosidase [13], carbonic anhydrase [14,15], urease [16], cholinesterase [17], glutathione reductase [18]. Schiff bases also serve as versatile ligands for coordinating a variety of transition metal ions in different coordination geometries and oxidation states [19,20]. Therefore, Schiff bases have been known to form complexes with most metals of d-block as well as with lanthanides [21-23]. The easy preparation, synthetic flexibility, and biological applications make further investigations for the synthesis of new Schiff bases essential.

The presence of thiophene motif, either alone or as a fused ring with other heterocyclic moieties, in a number of biological significant molecules has made it prime target for scientific research. It has been known that certain thiophenes possess important biological properties such as anticancer [24], antimicrobial [25], antioxidant [26], antitubercular [27], anti-inflammatory [28], and anti-HCV [29] activities. Certain thiophenes are known as potential inhibitors of D-amino acid oxidase [30], tyrosine phosphatase 1B [31], TNF-α [32], and carbonic anhydrase [33]. Moreover, a number of thiophenes have been employed as apoptosis inducing agents [34] and constitute the structural unit of a series of natural products [35]. Because of the importance of this heterocycle moiety, we became interested in the synthesis of new tetrahydrobenzo[b]thiophene-based Schiff bases.

Nowadays, the computational approaches, such as density functional theory (DFT) calculations, are used as a complementary or alternative method for the experimental ones. The computational chemistry is useful in several aspects of the chemical compounds and chemical reactions such as the optimized geometry, spectral behaviors, kinetics and mechanism of the reactions and so on [36-49].

In light of these findings and due to our interest in the synthesis of new heterocyclic compounds [50-53], in this paper, we wish to report the synthesis of some new heterocyclic Schiff bases derived from tetrahydrobenzo [b] thiophenes **3a-3e** by condensation reaction of 2-amino-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carbonitrile **1** with aromatic aldehydes **2a-2e** in dimethylformamide (DMF) containing $ZnCl_2$ (Scheme 1). DFT calculations were also employed to identify the obtained stereoisomers. Furthermore, characteristics of the bonding interactions were investigated using the QTAIM analysis.

a: Ar = 2-$O_2NC_6H_4$
b: Ar = 2-ClC_6H_4
c: Ar = 3-ClC_6H_4
d: Ar = 3-BrC_6H_4
e: Ar = 4-MeC_6H_4
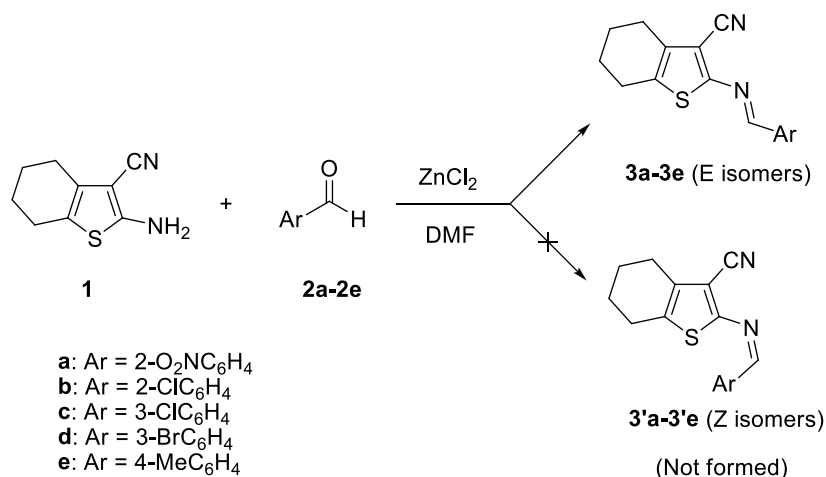
Scheme 1. Synthesis of new tetrahydrobenzo[*b*]thiophene-based Schiff bases **3a-3e**.

Experimental

Chemicals and apparatus

All chemicals were purchased from Merck and Aldrich and used without additional purification. Melting points were measured on a Stuart SMP3 melting point apparatus. Fourier transform infrared (FT-IR) spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 FT spectrometer at 300 and 75 MHz frequencies, respectively, in DMSO-d$_6$ as the solvent using tetramethyl silane (TMS) as internal standard. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

Computational methods

All of the DFT calculations have been performed using the B3LYP functional [54] as implemented in the Gaussian 03 program [55]. The 6-311++G(d,p) basis sets were used. Firstly, geometries of the investigated species which were fully optimized had no imaginary frequency of the Hessian. The zero-point corrections and thermal corrections were considered in evaluation of the electronic and the Gibbs free energies. In addition, the ^{1}H NMR chemical shifts were computed using the GIAO method [56] with respect to the tetramethylsilane.

The quantum theory of atoms in molecules (QTAIMs) has been based on the topological analysis of the electron density, ρ(r) [57]. Several quantities of the electron density are used to explore nature of the bonds such as the kinetic energy density (G_b), the potential energy density (V_b), the total energy density (H_b), the electron density (ρ), and its Laplacian ($\nabla^2\rho$) at a bond critical point (BCP). The QTAIM was used to study the nature of important bonds. The AIM calculations have been done employing the AIMALL package [58].

General experimental procedure for the synthesis of (E)-2-(arylideneamino)-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carbonitriles 3a-3e

A mixture of 2-amino-4, 5, 6, 7-tetrahydrobenzo [*b*] thiophene-3-carbonitrile **1** (0.178 g, 1 mmol) and aromatic aldehydes **2a-2e** (1 mmol) in DMF (5 mL) in the presence of ZnCl$_2$ (0.109 g, 0.8 mmol) was heated under reflux for 2-3 h. Upon completion, monitored by TLC, the mixture was cooled to room temperature and poured into cold water (15 mL). The crude product was collected and recrystallized from 96% ethanol (7 mL) to afford the pure compounds **3a-3e** in high yields.

(E)-2-(2-Nitrobenzylideneamino)-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3a). Yellow crystals. Yield 83%. M.p. 150-152 °C. FT-IR (*v*, cm^{-1}): 2222 (CN), 1524 and 1346 (NO$_2$). ^{1}H NMR (δ, ppm): 1.75-1.87 (m, 4H, 2CH$_2$), 2.56-2.64 (m, 2H, CH$_2$), 2.69-2.78 (m, 2H, CH$_2$), 7.80 (td, 1H, *J* = 7.6, 1.5 Hz, H$_{Ar}$), 7.90 (t, 1H, *J* = 7.5 Hz, H$_{Ar}$), 8.14 (dd, 1H, *J* = 8.0, 1.1 Hz, H$_{Ar}$), 8.19 (dd, 1H, *J* = 7.7, 1.3 Hz, H$_{Ar}$), 8.90 (s, 1H, CH==N). ^{13}C NMR (δ, ppm): 21.89, 22.89, 24.21, 25.12, 108.13, 114.26, 125.40, 129.43, 129.85, 133.17, 134.47, 135.14, 135.43, 149.68, 156.95, 158.82.

(E)-2-(2-Chlorobenzylideneamino)-4, 5, 6 ,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3b). Light brown crystals. Yield 91%. M.p. 153-156 °C. FT-IR (*v*, cm^{-1}): 2207 (CN). ^{1}H NMR (δ, ppm): 1.77-1.85 (m, 4H, 2CH$_2$), 2.57-2.64 (m, 2H, CH$_2$), 2.69-2.76 (m, 2H, CH$_2$), 7.50-7.58 (m, 1H, H$_{Ar}$), 7.60-7.64 (m, 2H, H$_{Ar}$), 8.16 (d, 1H, *J* = 7.2 Hz, H$_{Ar}$), 8.82 (s, 1H, CH==N). ^{13}C NMR (δ, ppm): 21.90, 22.90, 24.21, 25.12,

108.12, 114.27, 125.41, 129.44, 129.87, 133.18, 134.48, 135.14, 135.44, 149.70, 157.01, 158.84.

(E)-2-(3-Chlorobenzylideneamino)-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3c). Light brown crystals. Yield 82%. M.p. 138-139 °C. FT-IR (v, cm^{-1}): 2216 (CN). ^{1}H NMR (δ, ppm): 1.76-1.86 (m, 4H, 2CH$_2$), 2.56-2.63 (m, 2H, CH$_2$), 2.68-2.76 (m, 2H, CH$_2$), 7.58 (t, 1H, J = 7.9 Hz, H$_{Ar}$), 7.65 (dt, 1H, J = 8.0, 2.1 Hz, H$_{Ar}$), 7.93 (dt, 1H, J = 7.5, 1.3 Hz, H$_{Ar}$), 7.98 (t, 1H, J = 1.7 Hz, H$_{Ar}$), 8.65 (s, 1H, CH==N). ^{13}C NMR (δ, ppm): 21.92, 22.95, 24.21, 25.10, 107.44, 114.52, 128.22, 128.90, 131.49, 132.56, 134.30, 134.31, 135.10, 137.37, 159.32, 159.52.

(E)-2-(3-Bromobenzylideneamino)-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3d). Light brown crystals. Yield 89%. M.p. 146-147 °C. FT-IR (v, cm^{-1}): 2216 (CN). ^{1}H NMR (δ, ppm): 1.74-1.85 (m, 4H, 2CH$_2$), 2.54-2.62 (m, 2H, CH$_2$), 2.66-2.75 (m, 2H, CH$_2$), 7.50 (t, 1H, J = 7.8 Hz, H$_{Ar}$), 7.76 (dt, 1H, J = 7.5, 1.0 Hz, H$_{Ar}$), 7.95 (d, 1H, J = 7.8 Hz, H$_{Ar}$), 8.11 (t, 1H, J = 1.6 Hz, H$_{Ar}$), 8.61 (s, 1H, CH==N). ^{13}C NMR (δ, ppm): 21.92, 22.94, 24.19, 25.10, 107.45, 114.51, 122.75, 128.55, 131.69, 131.80, 134.26, 135.07, 135.40, 137.56, 159.29, 159.35.

(E)-2-(4-Methylbenzylideneamino)-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3e). Light yellow crystals. Yield 90%. M.p. 141-143 °C. FT-IR (v, cm^{-1}): 2217 (CN). ^{1}H NMR (δ, ppm): 1.75-1.85 (m, 4H, 2CH$_2$), 2.39 (s, 3H, CH$_3$), 2.54-2.60 (m, 2H, CH$_2$), 2.65-2.73 (m, 2H, CH$_2$), 7.35 (d, 2H, J = 8.0 Hz, H$_{Ar}$), 7.85 (d, 2H, J = 8.0 Hz, H$_{Ar}$), 8.58 (s, 1H, CH==N). ^{13}C NMR (δ, ppm): 21.81, 21.97, 23.00, 24.23, 25.05, 106.18, 114.74, 129.83, 130.20, 132.70, 133.01, 134.78, 143.59, 160.41, 160.95.

Results and discussion

Synthesis

The starting material 2-amino-4, 5, 6, 7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile **1** was prepared according to the literature method [59,60]. First, the reaction between this compound and 2-nitrobenzaldehyde **2a** was selected as the test reaction to determine suitable reaction conditions. Among the tested solvents; including, EtOH, MeOH, CH$_2$Cl$_2$, and DMF in the absence or presence of a catalyst such as glacial acetic acid, H$_2$SO$_4$, and ZnCl$_2$, the reaction was more facile and proceeded to give the highest yield of the product, using ZnCl$_2$ in DMF at reflux temperature. Consequently, all the reactions for the synthesis of other Schiff base products were carried out in these optimized conditions. Monitoring of the reaction with thin-layer chromatography (TLC) showed the formation of only one product in each case which was isolated from the reaction mixture as described in Experimental section. The structural elucidation of the isolated products was based upon spectral data. For example, the ^{1}H NMR spectrum of the compound isolated from the reaction of the compound **1** with 2-nitrobenzaldehyde **2a** in DMSO-d$_6$ showed a singlet at δ = 8.90 ppm for the CH=N group as well as the characteristic signals in aromatic region as a triplet of doublet (7.80 ppm, 1H), a triplet (7.90, 1 H), and two doublet of doublet (8.14 and 8.19 ppm, 2H) for the *ortho-* substituted aromatic moiety. These new signals along with other signals in aliphatic region belonging to the four methylene groups indicated the formation of a Schiff base as the result of a condensation reaction. Furthermore, the ^{13}C NMR spectrum showed the characteristic signals at δ = 21.89, 22.89, 24.21, 25.12, 108.13, 114.26, 125.40, 129.43, 129.85, 133.17, 134.47, 135.14, 135.43, 149.68, 156.95, and 158.82 ppm for the aliphatic as well as the SP^2

carbons. In accord with these data, two stereoisomers **3a** (E) and **3'a** (Z) are possible for the isolated product (Scheme 1).

DFT calculations

Since NMR spectra indicated formation of only one product, it was important to identify the obtained stereoisomer. However, based on the above-mentioned spectral and microanalytical data, the specific stereoisomer cannot be assigned. Therefore, to identify the obtained stereoisomer, DFT calculations were used. First, all of the geometries for E and Z species were fully optimized i.e. in compounds **3a** (E) and **3'a** (Z) the optimized forms are shown in Figure 1

with labeling of atoms. In the all optimized geometries, the thiophene and benzene rings are planar; however, each of them is in a separate plane. The geometries **3a-E1**, **3a-E2**, **3a-E3**, and **3a-E4** have E configuration, where the thiophene and benzene rings are trans to each other, whilst in the **3'a-Z1** and **3'a-Z2**, the orientation of thiophene and benzene rings are cis and the configuration is Z. The geometries for the other stereoisomers **3b-3e** (E) and **3'b-3'e** (Z) were also optimized. Relative energies of the all forms are gathered in Table 1. As seen, for all of the investigated compounds, the E forms are more stable than Z forms.
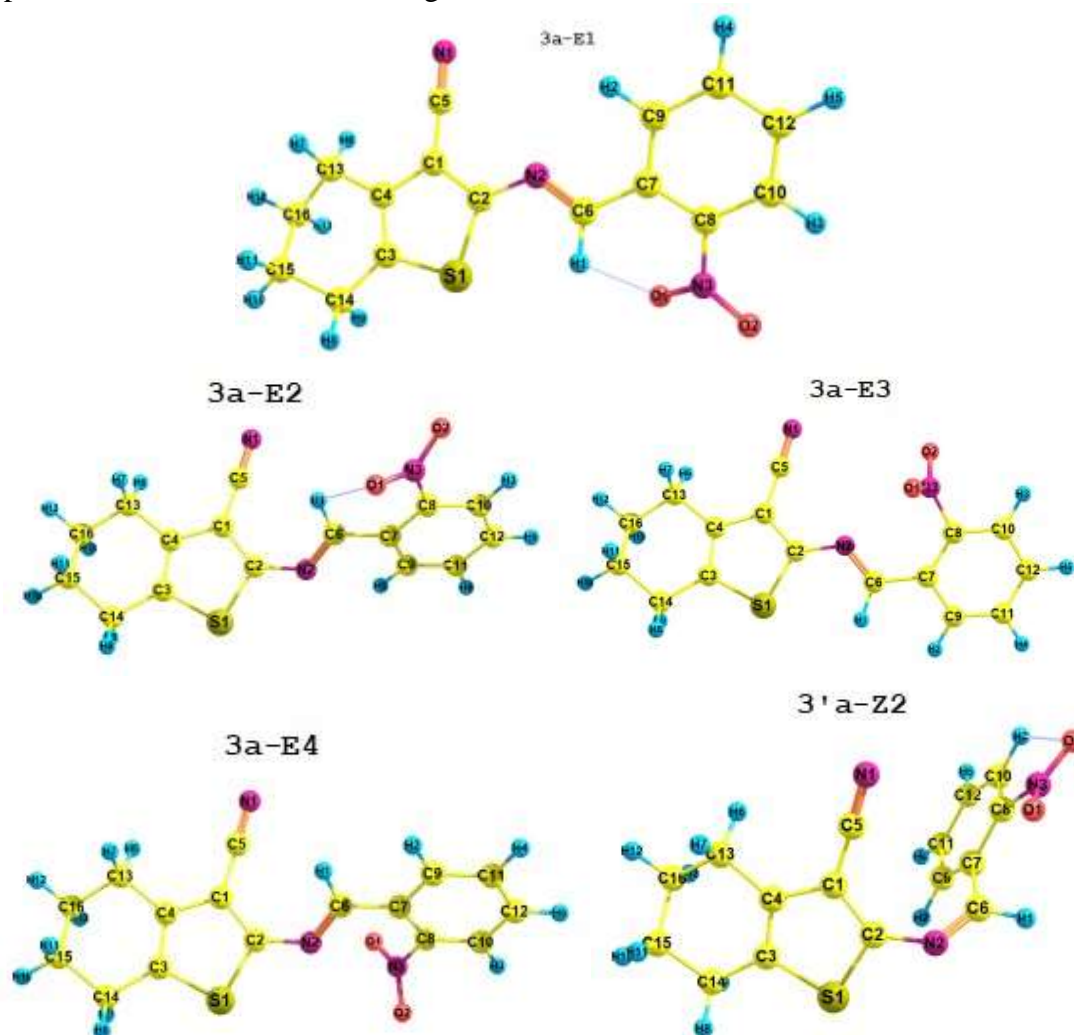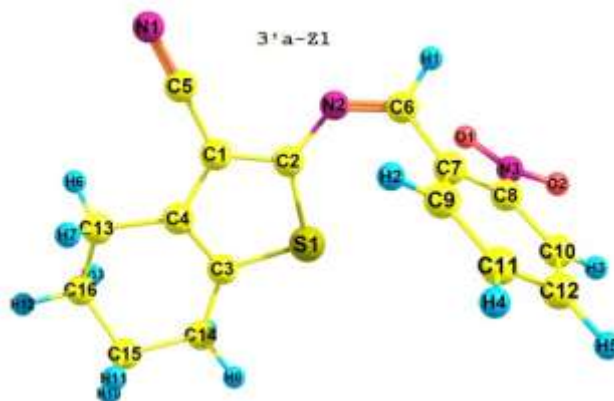
Figure 1. Optimized geometries for compounds **3a** (E) and **3'a** (Z)

Table 1. Relative energies (E+ZPE) of the optimized stereoisomers **3a-3e** (E) and **3'a-3'e** (Z)

Geometry	Stereoisomer									
	3a	**3'a**	**3b**	**3'b**	**3c**	**3'c**	**3d**	**3'd**	**3e**	**3'e**
E1	00.00	----	00.00	----	00.00	----	00.00	----	00.00	----
E2	12.00	----	11.93	----	11.82	----	11.61	----	10.94	----
E3	07.03	----	07.56	----	07.49	----	07.74	----	----	----
E4	17.85	----	18.12	----	16.86	----	16.27	----	----	----
Z1	----	26.81	----	33.25	----	36.13	----	36.03	----	33.22
Z2	----	33.41	----	36.43	----	37.36	----	37.34	----	----

For the most stable forms in the **3a** and **3'a**, **3a-E1** and **3'a-Z1** respectively, the ^{1}H NMR chemical shifts have been computed. The obtained results are given in Table 2. As can be seen, the observed chemical shifts are closer to the DFT-calculated values for the **3a-E1** than the **3'a-Z1**. These data are well in agreement with the calculated energies in Table 1, and confirm that the isolated stereoisomer has E configuration.

Table 2. The comparison of the experimental (Exp.) ^{1}H NMR chemical shifts data (δ, ppm) with those obtained from the calculated (Cal.) values for the **3a-E1** and the **3'a-Z1**

Position of H	^{1}H NMR				
	Exp.	Cal.		Deviation $|\delta_{Exp} - \delta_{Cal}|$	
		3a-E1	**3'a-Z1**	**3a-E1**	**3'a-Z1**
H1	8.90	8.93	8.73	0.03	0.17
H2	8.14	8.76	7.43	0.62	0.71
H3	8.19	8.26	8.61	0.07	0.42
H4	7.90	8.07	7.64	0.17	0.26
H5	7.80	7.83	7.50	0.03	0.30
H6	2.56-2.64	2.80	2.91	0.16-0.24	0.27-0.35
H7	2.56-2.64	2.65	2.51	0.01-0.09	0.05-0.13
H8	2.69-2.78	2.86	2.33	0.08-0.17	0.36-0.45
H9	2.69-2.78	2.86	2.58	0.08-0.17	0.11-0.20
H10	1.75-1.87	2.04	1.80	0.17-0.29	0.05-0.07
H11	1.75-1.87	1.92	1.58	0.05-0.17	0.17-0.29
H12	1.75-1.87	1.74	1.86	0.01-0.13	0.01-0.11
H13	1.75-1.87	1.69	1.58	0.06-0.18	0.17-0.29

Important structural parameters of the **3a-E1** form are depicted in Table 3. As seen, all of the calculated parameters are in the expected range. Except of the

tetrahydrobenzene ring, the molecule is roughly planar. The cyano substituent and the azomethine group are in the same plane with the thiophene and benzene rings. However, the nitro group makes a dihedral angle of about 30° with the benzene ring. The length of C6-N2 bond is 128.6 pm which is correspond to a C=N double bond, whilst the C2-N2 bond length is 136.6 pm, corresponding to a C-N single bond.

Table 3. Selected structural parameters of the **3a-E1** form

| Bond	Bond length (pm)	Angle	(°)	Dihedral angle	(°)
C5-N1	115.8	C1-C5-N1	178.5	C13-C16-C15-C14	-62.1
C5-C1	141.9	C5-C1-C4	123.6	N1-C5-C1-C4	1.5
C1-C4	143.4	C1-C4-C13	125.7	C5-C1-C4-C3	-179.8
C4-C3	136.9	C4-C13-C16	11.3	C1-C4-C3-S1	-0.4
C3-C14	150.2	C1-C4-C3	112.0	C4-C3-S1-C2	0.1
C3-S1	174.7	C4-C3-S1	112.3	C3-S1-C2-N2	-180.0
C2-S1	176.3	C3-S1-C2	91.7	C1-C2-N2-C6	-175.4
C2-N2	136.6	S1-C2-N2	126.8	C4-C1-C2-N2	179.7
C6-N2	128.6	C1-C2-N2	123.6	C1-C2-N2-C6	-175.5
C6-C7	146.7	C2-N2-C6	122.5	C2-N2-C6-C7	-177.1
C7-C8	141.1	N2-C6-C7	120.5	N2-C6-C7-C8	-167.2
C8-N3	147.2	C6-C7-C8	124.0	C6-C7-C8-N3	6.8
N3-O1	122.9	C7-C8-N3	121.4	C7-C8-N3-O1	31.8
O1-H1	228.6	C8-N3-O1	118.3	C8-N3-O1-H1	-51.2
C10-C12	138.9	O2-N3-O1	123.8	C7-C8-C10-C12	-1.5
C15-C16	153.4	C7-C8-C10	122.5	C1-C4-C13-C16	165.0

The strength and characteristic of a bond are related to the molecular electronic charge density ($\rho(r)$) and its Laplacian ($\nabla^2\rho$), respectively. The signs of $\nabla^2\rho$ and H_b at the BCP exhibit additional information about the nature of the interactions. The interaction will be strong, medium and weak, when ($\nabla^2\rho < 0$, $H_b < 0$), ($\nabla^2\rho > 0$, $H_b < 0$) and ($\nabla^2\rho > 0$, $H_b > 0$), respectively [61]. The character of a bond can be determined by the $-G_b/V_b$ value. **The $-G_b/V_b > 1$, $0.5 < -G_b/V_b < 1$ and $-G_b/V_b < 0.5$** represent the noncovalent, partially covalent and covalent characters, respectively.

The molecular graph of the **3a-E1** form is shown in Figure 2, where small-green spheres are corresponded to the BCPs. Also, the hydrogen bond energies are computed by $E_{HB} = 1/2V_b$ [62]. In the **3a-E1** form, there is an intramolecular H1…O1 hydrogen bond between the azomethine hydrogen and O1 atom of the nitro group. The $\nabla^2\rho(r)$, H_b and $-G_b/V_b$ values of this bond are 0.063448, 0.002292 and 1.20321 H, respectively, confirming that the H1…O1 H-bond is a weak and noncovalent interaction. This issue is also true for the H1…Cl intramolecular H-bond in structure of the 3b-E1 form, where the $\nabla^2\rho(r)$, H_b and $-G_b/V_b$ values are 0.052024, 0.002315 and 1.276121 H, respectively. Energies of the H1…O1 and H1…Cl H-bonds of the **3a-E1** and **3b-E1** species are 0.006786 and 0.00535 H, respectively. As seen in Figure 2, there are four rings in **3a-E1**: the tetrahydrobenzene, thiophene and benzene rings together with a six membered ring involving the H1…O1 bond. The ring critical point (RCP) of these rings is shown by small-red spheres. The values of $\rho(r)$ for these rings

are 0.018845, 0.037288, 0.021615 and 0.012966 C.Bobhr⁻³, respectively. Therefore, the thiophene ring involves

the highest electron density. The electron density isosurface map of the **3a-E1** form is shown in Figure 3.
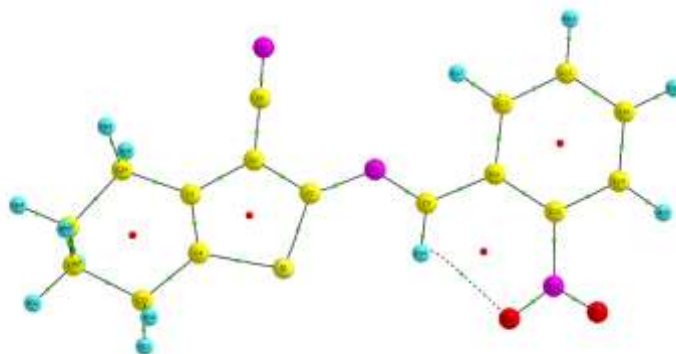
Figure 2. AIM molecular graph of the **3a-E1**.
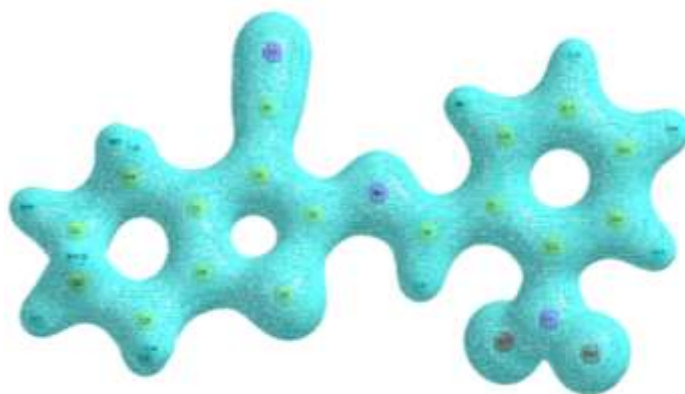
Figure 3. Electron density isosurface map of the **3a-E1**.

Conclusion

In summary, we have reported the synthesis of five new Schiff bases derived from tetrahydrobenzo [*b*]thiophene by the reaction of 2-amino-4, 5, 6, 7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile with aromatic aldehydes in DMF containing ZnCl₂. The new Schiff bases were characterized on the basis of IR, ¹H NMR, and ¹³C NMR spectral data. The structure of the isolated stereoisomers was confirmed using the DFT calculations. For all of the investigated Schiff bases, the E configuration is the most stable stereoisomer. Good consistency between the experimental ¹H NMR chemical shifts and the corresponding DFT-calculated values approves suitability of

the optimized geometry of the **E1** form in all compounds. Based on the QTAIM results, the intramolecular H-bond of the compounds **3a** and **3b** is a weak and noncovalent interaction. Moreover, the results showed that the thiophene ring involves the highest electron density.

Acknowledgements

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