ISSN 1070-4280, Russian Journal of Organic Chemistry, 2021, Vol. 57, No. 1, pp. 100–107. © Pleiades Publishing, Ltd., 2021.

Experimental and Theoretical Investigations Regarding the Thione–Thiol Tautomerism in 4-Benzyl-5-(thiophene-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

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Received September 4, 2020; revised October 9, 2020; accepted October 20, 2020

Abstract—The title compound was synthesized by ring-closure reaction of thiophene-2-carbohydrazide with benzyl isothiocyanate and characterized using spectroscopic methods (NMR and FT-IR). Quantum chemical calculations at the B3LYP/6-311++G(*d*,*p*) level were carried out to examine its molecular and spectroscopic properties, thione–thiol tautomerism, and proton transfer reaction. The structural and spectroscopic results were well consistent with the experimental data. The solvent effect on the proton transfer reaction was examined using three solvents (acetone, ethanol, and dimethyl sulfoxide) through the polarizable continuum model (PCM) approximation (direct solvent effect) and solvent-assisted mechanism. A high energy barrier was determined for the interconversion of the thione and thiol forms in both gas and solution phases. Even though the presence of solvent molecules significantly reduced the barrier to proton transfer, it was insufficient for the reaction to occur. The corresponding thermodynamic parameters and the energy difference between the HOMO and LUMO of the thione and thiol tautomers were calculated.

Keywords: 1,2,4-triazole, thione–thiol tautomerism, solvent effect, theoretical calculations, DFT

DOI: 10.1134/S1070428021010140

INTRODUCTION

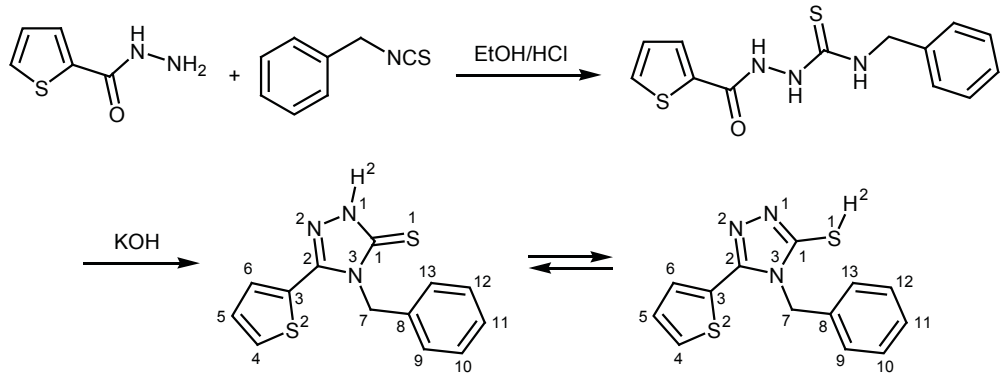
Tautomerization and proton transfer processes attract much attention from researchers due to their widespread occurrence in biology and role in mechanisms of various reactions [1–4]. It is also known that the role of solvent in these processes is very important. Thus, numerous experimental and theoretical studies have been conducted to increase the knowledge about the mechanisms of proton transfer, tautomeric equilibria, and related processes [5–14]. 1,2,4-Triazoles may exist in two major tautomeric forms having different reactivities. The thione–thiol tautomerism of these compounds has been still a matter of debate since it is difficult to identify which one of the two forms exists. The prototropic tautomerism of parent 1,2,4-triazole-3-thione and its disubstituted derivatives containing thiophene and benzyl groups is crucial in many biochemical and chemical areas [15–17]. The information about the relative stabilities of tautomeric forms and their interconversion is also significant in terms of structural chemistry. Moreover, the effect of solvents on molecular stability and reactivity is determined by the change of the energy of tautomerization in various solvents.

In this study, the title compound, 4-benzyl-5-(thiophene-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**1**), was newly synthesized via the ring-closure reaction of thiophene-2-carbohydrazide with benzyl isothiocyanate (Scheme 1) and was characterized by spectroscopic techniques (NMR, FT-IR). The thione–thiol tautomerism of this compound was theoretically studied at the DFT/B3LYP level of theory using 6-311++G(*d*,*p*) basis set. Solvent effects were considered through the polarized continuum model (PCM) by directly involving solvent molecules at the same calculation level.

RESULTS AND DISCUSSION

Spectroscopic characterization. Table 1 contains the experimental IR frequencies of 4-benzyl-5-(thiophene-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**1**)

Scheme 1.



and those calculated for its thione and thiol tautomers (see also Supplementary Materials). An acceptable agreement was observed between the theoretical vibrational frequencies and experimental ones. Stretching vibrations of N–H and S–H bonds are commonly observed in the region above 2500 cm^{-1}, in particular at 3100–3400 (N–H) and 2550–2600 cm^{-1} (S–H) [18]. The calculated N–H stretching frequency for compound **1** was 3240 cm^{-1} against experimentally found 3195 cm^{-1}. The experimental and calculated S–H stretching frequencies were 2650 (weak) and 2641 cm^{-1}, respectively. Some other characteristic vibration bands were those of C=N, C–S, and C=S stretching modes. The C–S and C=S vibrations usually appear in the regions 700–600 and 1275–1030 cm^{-1}, respectively [18]. In the experimental IR spectrum, the C–S and C=S vibrations were observed at 530 and 1230 cm^{-1}, while the calculated frequencies are 545 and 1195 cm^{-1}, respectively. Furthermore, the C=N stretching frequency 1574 cm^{-1} matched the calculated value 1561 cm^{-1}. These findings clearly indicated that the title compound had the thione rather than thiol structure in the solid state.

Nuclear magnetic resonance was used to characterize the structure of **1** in solution (Table 2). For this purpose, the correlations between the experimental ^1H and ^{13}C NMR spectra and those calculated for the thione and thiol tautomers were analyzed by using a linear regression model.

One of the characteristic ^1H NMR peaks was the SH/NH signal which could appear as a singlet in the range δ 13.80–9.0 ppm [19]. It was observed in the experimental ^1H NMR spectrum at δ 14.6 ppm, i.e., at a lower field than theoretically predicted for both SH (δ 13.05 ppm) and NH protons (δ 9.0 ppm). Another characteristic peak is that for the benzylic protons, which was found experimentally as a singlet at δ 5.48 ppm against δ 5.39 ppm for the thiol tautomer and δ 5.20 ppm for the thione form. Aromatic protons of the benzyl group appeared as a multiplet in the range δ 7.10–7.74 ppm, while their theoretical positions were estimated at δ 6.81–7.62 (thiol) and 6.80–7.69 ppm (thione).

In the ^{13}C NMR spectrum, the first characteristic peak was the C=N peak which appeared at δ_C 146.7 ppm experimentally and was predicted theoretically at δ_C 163.4 ppm. The second was the C=S peak observed experimentally at δ_C 168.2 ppm; its calculated position is δ_C 171.6 ppm. Aromatic carbons of the benzyl substituent resonated at δ_C 126.6–130.2 ppm in the experimental spectrum, while the calculated resonance regions are δ_C 131.1–141.3 ppm for the thiol tautomer and δ_C 129.8–141.2 ppm for the thione tautomer.

The experimental and theoretical NMR data were then analyzed using the linear regression model. The following equations were found for the thione form:

$$^1H: \delta_{exp} = (-4.444\pm3.049) + (1.686\pm0.423)\delta_{calc};$$
$$R^2 = 0.638;$$
$$^{13}C: \delta_{C,exp} = (-0.378\pm2.364) + (0.961\pm0.017)\delta_{C,calc};$$
$$R^2 = 0.996.$$

The corresponding correlations for the thiol tautomer are as follows:

$$^1H: \delta_{exp} = (-0.989\pm0.385) + (1.137\pm0.049)\delta_{calc};$$
$$R^2 = 0.983;$$
$$^{13}C: \delta_{C,exp} = (-3.609\pm5.154) + (0.999\pm0.038)\delta_{C,calc};$$
$$R^2 = 0.983.$$

The results are consistent with literature data [17, 20, 21]. Table 2 compares the theoretical ^1H and ^{13}C NMR chemical shifts calculated for the thiol and

Table 1. Experimental and calculated (VEDA) vibrational frequencies of the title compound

Vibrational mode	Unscaled B3LYP/6-311(*d*,*p*)		Experimental
	thione	thiol	
Stretching			
N^1H^2/S^1H^2	3240 (N^1H^2)	2641 (S^1H^2)	3195 (N^1H^2)/2650 (S^1H^2)
N^2C^2	1620, 1547, 1469	1511, 1449, 1366, 1274	–
C^4C^5	1547, 1499, 1469, 1110	1511, 1461, 1113	–
C^3C^6	1620, 1547, 1374, 1250	1599, 1366, 1250	1590
$C^{10}C^9$	1649, 1108	1647, 1352, 1109	1654
$C^{11}C^{10}$	1629, 1051	1051, 1018	–
$C^{11}C^{12}$	1326, 1051, 1018	1628, 1051	–
$C^{12}C^{13}$	1649, 1353	1352,109	–
C^8C^9	1629, 1326	–	–
N^1C^1	1561,1549,1514	1256, 1195	1574
C^5C^6	1374, 1080	1449, 1078	–
N^3C^1	1353, 1326, 940	1414, 1389	1380
C^2C^3	1620, 290	1599, 1511, 306	1588
N^1N^2	1280, 1125, 1110	1097, 1078	1089
C^7C^8	1217, 828	1222, 823	–
N^3C^7	1195, 792, 726	1274, 786	–
C^1S^1	1195, 575	545, 513	530, 1230
S^2C^4	859, 752, 658	857, 750, 656	–
Bending			
$C^2N^2N^1$	1422, 964	–	–
$C^{11}C^{12}C^{13}$	1018, 635	1018, 823, 634	–
$S^2C^4C^5$	680	656	669
$H^2N^1N^2/H^2S^1C^1$	1499, 1485, 1256	963, 962, 944	–
$C^4C^5C^6$	859, 752	857, 750	–
$C^2C^3C^6$	376, 162, 108	365, 178, 106	–
$N^1C^1N^3$	1195	–	–
$N^2C^2C^3$	522, 108	1274, 306	–
$C^1N^1N^2$	1053, 940	1202	–
$S^1C^1N^1$	464, 376, 251, 211	459, 241,160	–
Torsional			
$H^2N^1N^2C^2/H^2S^1C^1N^3$	679, 551	182, 160	–
$C^1N^1C^2N^2$	735, 376, 365	688	700
$C^9C^{10}C^{11}C^{12}$	940, 792, 712, 712	713	–
$N^3C^2C^3C^6$	108	–	–
Out-of-plane			
$S^1N^3N^1C^1$	679, 551	288, 241, 160	–
$C^3N^3N^2C^2$	735, 365, 75	731, 373, 73	–
$C^7C^1C^2N^3$	251, 211	178	–

Table 2. Experimental and theoretical ^{1}H and ^{13}C NMR chemical shifts (δ, δ_C, ppm, downfield from TMS) for the title compound

Atom[a]	Experimental	Calculated	
		thiol	thione
C^1	146.7 (thiol)/168.2 (thione)	163.4	171.6
C^2	135.8	157.2	155.3
C^3	130.3	135.2	133.1
C^4	130.3	135.2	133.1
C^5	129.3	131.1	131.7
C^6	129.3	131.3	133.3
C^7	47.2	50.0	49.3
C^8	130.2	141.3	141.2
C^9	127.9	131.1	133.2
C^{10}	129.1	133.3	132.4
C^{11}	126.6	132.5	131.9
C^{12}	129.1	132.3	132.8
C^{13}	127.9	132.4	129.8
$NC\mathbf{H}_2C_6H_5$	5.48 s (2H)	5.39	5.20
H_{arom}, H_{Th}	7.10–7.74 (8H)	6.81–7.62	6.84–7.69
SH/NH	14.6	13.05	9.0

[a] For atom numbering, see Scheme 1.

thione tautomers of **1** with those found experimentally (see also Supplementary Materials).

Thione–thiol tautomerism. The thione and thiol tautomers of **1** could be converted to each other via intramolecular proton transfer. Proton migration from the N^1 nitrogen atom to the S^1 sulfur atom (i.e., the transformation of the thione tautomer to thiol) is accompanied by some variations of structural parameters. The N^1–C^1 bond shortens from 1.356 to 1.309 Å for the isolated molecule, from 1.350 to 1.310 Å in acetone, and from 1.350 to 1.311 Å in ethanol and DMSO; simultaneously, the S^1–C^1 distance increases from 1.356 to 1.766 Å for the isolated molecule and from 1.687 to 1.765 Å in acetone, ethanol, and DMSO. This is consistent with breaking of the S=C double bond and formation of N=C double bond.

The thione–thiol transformation involves increase of the N^1–N^2 distance, shortening of the N^3–C^1 bond, contraction of the $S^1C^1N^1$, $C^1N^1N^2$, and $C^1N^3C^2$ bond angles, and expansion of the $S^1C^1N^3$, $N^1N^2C^2$, and $N^1C^1N^3$ angles (see Supplementary Materials). Figure 1 shows the energy profile of the single proton transfer process (thione–thiol tautomerism). The tautomerization energy was calculated as the energy differences between the tautomers and the transition state. The energy differences between the two tautomers were 71.86 kJ/mol in the gas phase, 62.74 kJ/mol in acetone, 65.83 kJ/mol in ethanol, and 66.00 kJ/mol in DMSO. Comparison of the ground state energies of the thione and thiol tautomers, as well as tautomerization energies, showed that the thione form was more stable than thiol in both gas phase and solution. The energies

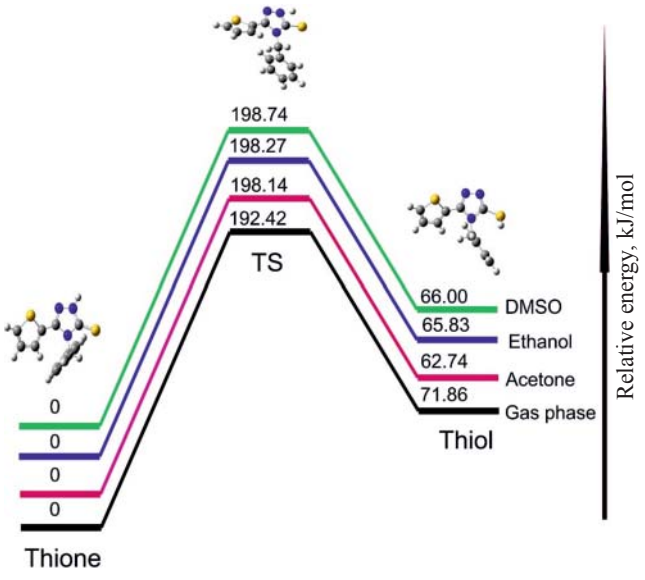


Fig. 1. Relative energy profile of the single proton transfer process (thione–thiol tautomerism) in the gas phase and various solvents.

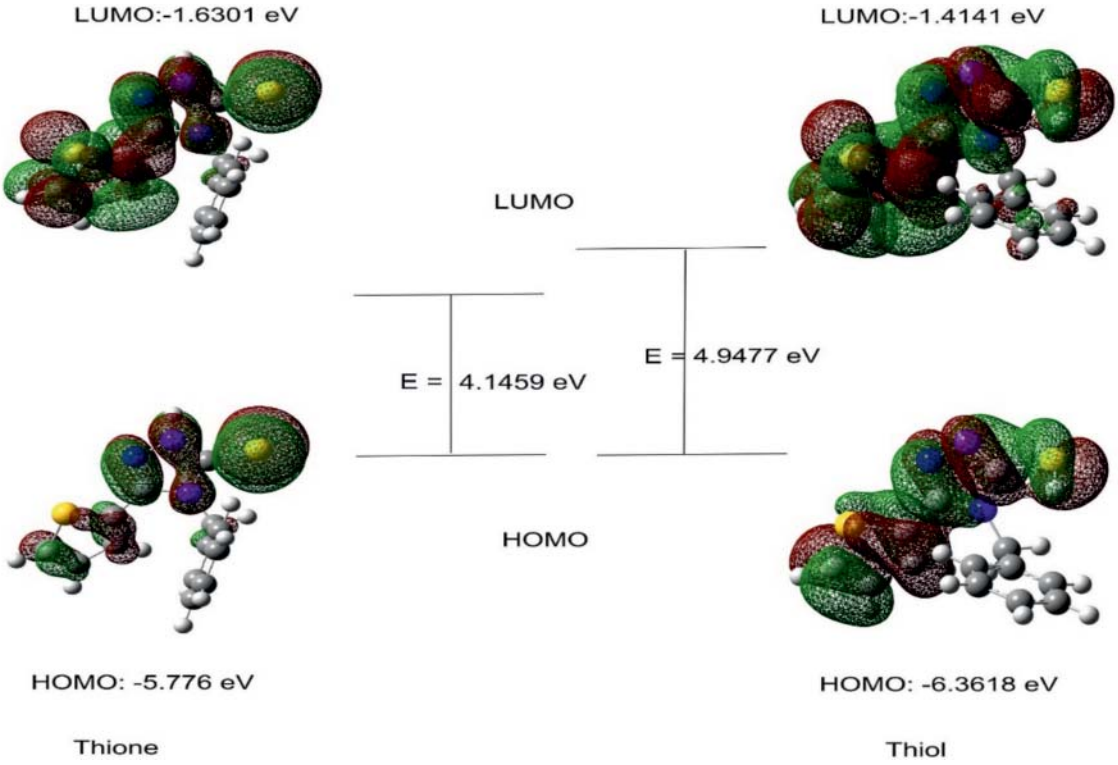


Fig. 2. Structures and energies of the HOMO and LUMO of the thione and thiol forms of the title compound.

of the transition states (TS) relative to the thione tautomer were 192.42, 198.14, 198.27, and 198.74 kJ/mol, and the reverse energy barriers were 120.14, 135.40, 132.44, and 132.74 kJ/mol in the gas phase, acetone, ethanol, and DMSO, respectively. These values indicate that both forward and reverse proton transfer reactions require a fairly high energy. In both cases, the barrier height increased in going from the gas phase to DMSO solution. The high energy barriers suggest that tautomeric transformations are unfavorable in both gas phase and solution. The barrier to the proton transfer process increases in parallel with the dipole moment of the solvent. The free energy changes and large positive standard enthalpies for both forward and reverse proton transfer indicated that both thione–thiol and thiol–thione processes are highly endothermic in both gas phase and solution. Therefore, the proton transfer reaction can be regarded as a quite unfavorable process which is unlikely to occur spontaneously.

HOMO–LUMO energies and density of states data. The HOMO/LUMO energies of the thiol and thione tautomers were calculated using B3LYP/6-311G++(*d*,*p*) approximation for the gas phase and solutions in acetone, ethanol, and DMSO. The structures of the HOMO and LUMO are shown in Fig. 2. There are some differences between the HOMO and LUMO orbitals of the thione and thiol forms. The thione HOMO is localized on the 1,2,4-triazole ring, and the LUMO, on the 1,2,4-triazole and thiophene rings; the thiol HOMO is contributed mainly by the 1,2,4-triazole and thiophene rings, and the thiol LUMO is spread over the entire molecule. The HOMO/LUMO energy gap in the thione form is 4.1459 eV in the gas phase, 4.4759 eV in acetone, 4.4852 eV in ethanol, and 4.5311 eV in DMSO. The corresponding values for the thiol form are 4.9477, 4.7337, 5.0184, and 5.0179 eV, respectively. These data suggest that the HOMO–LUMO transition in the thione tautomer should be easiest in the gas phase and most difficult in DMSO. The HOMO–LUMO transition in the thiol form is most favorable in acetone and unfavorable in ethanol. In this respect, the thione tautomer appears to be more reactive than the thiol form. However, consideration of only the HOMO and LUMO may not provide a realistic description of the frontier orbitals, since in the boundary region neighboring orbitals may show quasi-degenerate energy levels. For this reason, the density of states (DOS) was calculated for both gas and solutions in acetone, ethanol, and DMSO by using GaussSum 3.0 software. Figure 3 represents the DOS plot of the 4-benzyl-5-(thiophene-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione molecule.

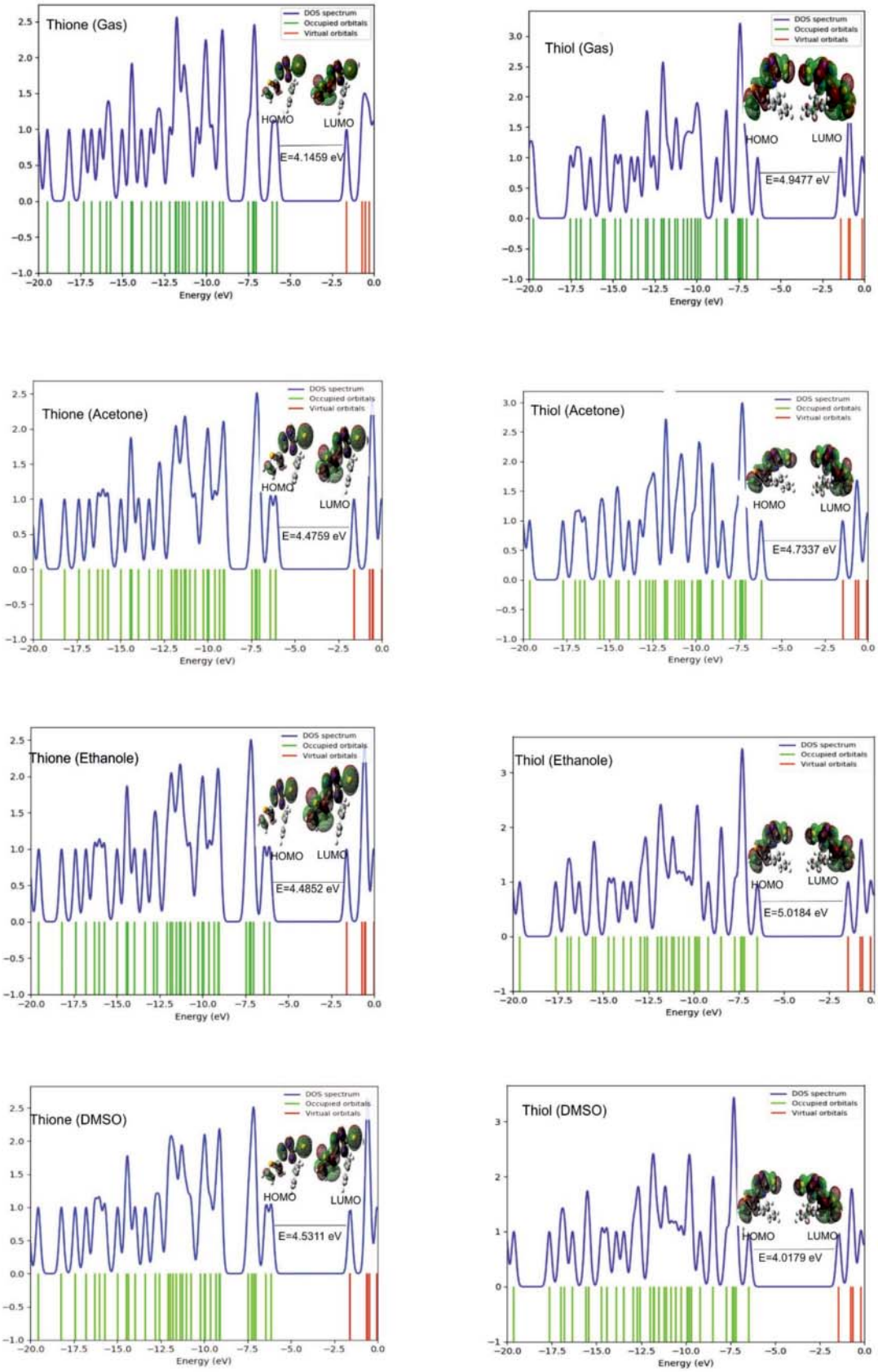


Fig. 3. Density of states diagrams for the thione and thiol tautomers of the title compound in different solvents.

EXPERIMENTAL

Computational methods. All theoretical calculations were performed using GaussView 5 and Gaussian 09 software [22, 23]. The ^{1}H and ^{13}C NMR chemical shifts were computed using the GIAO approach [24]. The harmonic vibrational frequencies were assessed for the optimized structure, and the theoretical frequencies were scaled by 0.964 [25]. The potential energy distribution (PED) of the title compound was calculated using VEDA 4 program [26]. The density of states (DOS) was calculated by GausSum 3.0.2 software [27]. Solvent effects (acetone, ε = 20.7; ethanol, ε = 24.3; DMSO, ε = 45) were examined at the same level via the polarizable continuum model [28–30]. Chemicals were purchased from Aldrich or Merck. Melting points were determined on a Gallenkamp melting point apparatus. The infrared spectra were recorded with a Perkin Elmer Spectrum One FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were taken on a Bruker Ascend 400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C.

4-Benzyl-5-(thiophene-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (1). A mixture of thiophene-2-carbohydrazide (**I**) (0.01 mol), ethanol (50 mL), and benzyl isothiocyanate was refluxed for 3 h. After ~4 h, solid *N*-benzyl-2-(thiophene-2-carbonyl)hydrazine-1-carbothioamide began to separate from the solution. Potassium hydroxide (0.15 mol) was then added, and the mixture was refluxed for 6 h, cooled, acidified to pH 3–4 with aqueous HCl, and poured onto crushed ice while stirring. The resulting solid was filtered off, dried, and recrystallized from ethyl alcohol. Yield 65%, mp 145–147°C. IR spectrum (KBr), ν, cm^{-1}: 3064–3102 (C–H_{arom}), 2854, 2967 (C–H), 1574 (C=N), 1274 (C=S), 705 (C–S–C). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 5.48 s (2H, C**H**$_2$C$_6$H$_5$), 7.10–7.74 (8H, H_{arom}), 14.16 s (1H, SH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ_C, ppm: 47.2, 126.6, 127.9, 129.1, 129.3, 130.3, 135.8, 146.7.0, 168.2. Found, %: C 57.02; H 4.15; N 15.07; S 23.21. $C_{13}H_{11}N_3S_2$. Calculated, %: C 57.12; H 4.06; N 15.37; S 23.46.

CONCLUSIONS

4-Benzyl-5-(thiophene-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione was synthesized and its spectroscopic characteristic (IR, ^{1}H and ^{13}C NMR) were determined experimentally and calculated theoretically for the thione and thiol tautomers. The thione–thiol tautomerism via intramolecular proton transfer was studied in both gas phase and solutions in different solvents (acetone, ethanol, dimethyl sulfoxide). The experimental and theoretical data consistently showed the thione structure of the title compound. The energy difference between the thione and thiol tautomers and the energy of activation for the tautomerization process suggested both kinetic and thermodynamic unfavorableness of intramolecular proton transfer reaction both in the gas phase and in solution. However, inclusion of more solvent molecules, as well as the effect of the bulk would probably reduce the barrier to proton transfer.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1070428021010140.

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