Research Article

Structural and Vibrational Study on Monomer and Dimer Forms and Water Clusters of Acetazolamide

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Experimental IR and Raman spectra of solid acetazolamide have been analysed by computing the molecular structures and vibrational spectra of monomer and dimer forms and water clusters of acetazolamide. The possible stable conformers of free acetazolamide molecule in the ground state were obtained by scanning the potential energy surface through the dihedral angles, D₁ (1S-2C-6S-9N), D₂ (4N-5C-12N-14C), and D₃ (5C-12N-14C-16C). The final geometry parameters for the obtained stable conformers were determined by means of geometry optimization, carried out at DFT/B3LYP/6-31G++(d,p) theory level. Afterwards the possible dimer forms of the molecule and acetazolamide-H₂O clusters were formed and their energetically preferred conformations were investigated using the same method and the same level of theory. The effect of BSSE on the structure and energy of acetazolamide dimer has been investigated. The assignment of the vibrational modes was performed based on the potential energy distribution of the vibrational modes, calculated by using GAR2PED program. The experimental vibrational wavenumbers of solid acetazolamide are found to be in better agreement with the calculated wavenumbers of dimer form of acetazolamide than those of its monomeric form. NBO analysis has been performed on both monomer and dimer geometries.

1. Introduction

Acetazolamide, C₄H₆N₄O₃S₂ (1,3,4-thiadiazole-2-sulfonamide, 5-acetamido), is a sulfonamide derivative and carbonic anhydrase inhibitor used clinically to lower intraocular pressure in glaucomatous patients. It is also used as a diuretic agent for treating acute high-altitude sickness and used for the treatment of epilepsy, and most frequently it is used as a drug for the prophylaxis of high-altitude disorders [1–3]. Recently, it has played a major role as a remedy against respiratory diseases and it has been used to prevent adverse effects of drugs in the treatment of influenza [4] and epilepsy and as diuretic [5]. Traditionally, carbonic anhydrase inhibitors derived from acetazolamide were shown to inhibit the growth of several tumor cell lines in vitro and in vivo [6, 7].

Acetazolamide is known to exist in two crystal forms (modifications I and II), which was first reported by Pala in 1956 [8]. Mathew and Palenik solved the crystal structure of

triclinic acetazolamide (polymorphic form A, modification II) [9]. Griesser et al. [10] reported the crystal structure of acetazolamide polymorphic form B (modification I) and notified that crystal polymorphism of acetazolamide was based on changes in the spatial molecular arrangement and in the connectivities of hydrogen bonds. The experimental and calculated vibrational spectra [11] and crystal structure [12] of an acetazolamide derivative (5-amino-1,3,4-thiadiazole-2-sulfonamide; Hats) have been reported. The experimental vibrational spectra of the two polymorphic forms (A, B) of acetazolamide were reported by Baraldi et al. [13]. The structure and spectroscopic behaviours of some 1,3,4-thiadiazole ligands containing –SO₂NH₂ groups and their metal clusters were examined [14–23]. Recently, Brandan et al. [24] calculated the harmonic vibrational wavenumbers for the optimized geometry of acetazolamide, using DFT/B3LYP method with the 6-31G* and 6-311++G** basis sets. Chaturvedi et al. [25] reported calculated vibrational spectra of monomer and dimer forms of acetazolamide,

but the calculations were performed on the most stable conformer, obtained by geometry optimization, and on three possible dimers. The basis set superposition error (BSSE) correction was not taken into account on the dimer forms. In the present work, we have extended the investigation of the possible stable conformers of title molecule by means of torsion potential energy surface scan studies through dihedral angles, D_1 (1S-2C-6S-9N), D_2 (4N-5C-12N-14C), and D_3 (5C-12N-14C-16C), and calculated the vibrational modes and wavenumbers of the most stable conformer. Moreover, the structures and vibrational wavenumbers of four energetically favorable dimers and ten H_2O clusters of acetazolamide were investigated and the effect of basis set superposition error (BSSE) on the structure and energy of acetazolamide dimers has been evaluated. Acetazolamide is very slightly soluble in water. However, its solubility is significantly important and its slight changes affect the bioavailability of acetazolamide [10]. The aims of this study are to elucidate the conformational preferences of acetazolamide and the effect of hydrogen bonding in the formation of molecular dimers and upon interaction with water molecules.

2. Experimental and Computational Methods

2.1. Experimental Part. The acetazolamide molecule was purchased from Sigma-Aldrich ($\geq 99\%$) with CAS number 59-66-5 and used as received. The FT-IR spectra of KBr disc (for solid sample) and aqueous solution (between ZnSe plates) of the molecule were recorded on a Jasco FT/IR-6300 spectrometer in the range $400\text{--}4000\text{ cm}^{-1}$ with a resolution of 2 cm^{-1} based on averaging 200 samples and 100 background scans. The Raman spectrum of the sample was taken with a Jasco NRS-3100 micro-Raman spectrometer (1800 lines/mm or 1200 lines/mm grating and high sensitivity cooled CCD). Sample was excited with a 531.96 nm diode laser. The Raman system was calibrated with a silicon semiconductor using the Raman peak at 520 cm^{-1} . A $20\times$ microscope objective (Olympus) was used to focus the laser and collect Raman scattering on the sample. Spectral resolution was 1.08 cm^{-1} and 100 spectra were accumulated.

2.2. Computational Part. All of the calculations were carried out by using the Gaussian03© program suite [26]. Due to success in calculating the electronic structure and energy, the calculations were carried out by using the hybrid density functional theory (DFT/B3LYP) method. For the calculations of monomer, dimer forms of acetazolamide and acetazolamide-water clusters $6\text{-}31++\text{G(d,p)}$ basis set was used. The X-ray crystallographic results [9] of acetazolamide molecule were used as initial input geometrical data. The minimum energy conformers of acetazolamide were identified by scanning the potential energy surface by varying D_1 (1S-2C-6S-9N), D_2 (4N-5C-12N-14C), and D_3 (5C-12N-14C-16C) dihedral angles. The final geometry parameters for the obtained stable conformers were determined by means of geometry optimization carried out at DFT/B3LYP/6-31G++(d,p) level of theory. Furthermore, acetazolamide dimers were constructed by bringing two identical acetazolamide monomers

FIGURE 1: The most stable geometry, atom numbering, and searched dihedral angles of acetazolamide.

together in possible configurations, and energetically preferred conformations of dimers were investigated using the same method and the same level of theory. In order to correct overestimation between unscaled and observed wavenumbers dual scaling factors were used. We scaled all the computed harmonic wavenumbers under 1800 cm^{-1} with the scale factor 0.977 and wavenumbers greater than 1800 cm^{-1} with the scale factor 0.955 [27]. The potential energy distribution (PED) of the vibrational modes of the molecules was calculated with GAR2PED program [28], and the fundamental vibrational modes were characterized by their PED values.

3. Result and Discussion

3.1. Conformational Analysis and H-Bonding Interactions. The molecular model of acetazolamide with the atom numbering scheme is given in Figure 1. Stable low energy conformers of free acetazolamide molecule were obtained firstly by potential energy surface scan studies by iteratively varying D_1 (1S-2C-6S-9N), D_2 (4N-5C-12N-14C), and D_3 (5C-12N-14C-16C) dihedral angles with step angle of 60° . PES scan for acetazolamide calculated with D_1 (1S-2C-6S-9N), D_2 (4N-5C-12N-14C), and D_3 (5C-12N-14C-16C) dihedral angles at the B3LYP/6-31G++(d,p) method is shown in Figure S1 (see Figure S1 in Supplementary Materials available online at <http://dx.doi.org/10.1155/2013/538917>). The 45 conformers were identified between 0 and 10 kcal/mol relative energy intervals. Their dihedral angles and relative energies were given in Table S1. The geometry optimization was then performed on the lowest energy conformer. The estimated four most stable conformers of acetazolamide dimers are illustrated in Figure 2. All possible conformations of acetazolamide interacting with one water molecule were investigated, and acetazolamide interacting with five water molecules was determined as the final possible conformation of acetazolamide-water cluster. Figure 3 demonstrates the geometries of the 10 stable acetazolamide-water clusters obtained using DFT method with B3LYP/6-31++G(d,p) basis set. The energies of the four most stable dimers (I–IV) and energetically preferred H_2O -acetazolamide clusters are given in Table 1. It is known that the basis set superposition error

FIGURE 2: The energy minimized structures of four low energy conformers (I–IV) of the dimer forms of the acetazolamide, (I–IV), respectively.

TABLE 1: (a) The calculated energies of monomeric, dimeric (I–IV), and H_2O clusters (I–IX). (b) The counterpoise uncorrected and corrected interatomic distance (Å) and binding energy (kcal/mol) of dimer I.

(a)				
	Calculated energy (kcal/mol)	Energy differences (kcal/mol)		
Monomer	−876645.7	—		
<i>Dimer I</i>	−1753308.7	0		
Dimer II	−1753299.4	9.3		
Dimer III	−1753297.9	10.8		
Dimer IV	−1753301.5	7.2		
Cluster I	−924613.6	6.1		
Cluster II	−924617.1	2.6		
Cluster III	−924613.6	6.0		
Cluster IV	−924614.6	5.1		
Cluster V	−924619.1	0.6		
<i>Cluster VI</i>	−924619.7	0		
Cluster VII	−924619.1	0.6		
Cluster VIII	−924612.9	6.7		
Cluster IX	−924614.6	5.1		
(b)				
	BSSE uncorrected		BSSE corrected	
	<i>R</i> (5C–22C) (Å)	ΔE (kcal/mol)	<i>R</i> (5C–22C) (Å)	$\Delta(E + \text{BSSE})$ (kcal/mol)
<i>Dimer I</i>	4.23	17.4	4.25	16.1

FIGURE 3: The energy minimized structures of ten low energy conformers (I–X) of H_2O clusters of the acetazolamide (I–X), respectively.

(BSSE) effect is rather significant on the structure and energy of dimer forms, so removing this effect is very important. Therefore, optimization of the dimer I was also carried out along with the counterpoise correction scheme proposed by Boys and Bernardi [29]. The BSSE uncorrected and corrected distances between two acetazolamide units $\{R(5\text{C}-22\text{C})\}$ (Å) and binding energy (ΔE) of acetazolamide dimer $\{\Delta E = 2^*E_{\text{monomer}} - E_{\text{dimer}}\}$ are given in Table 1(b). As seen in Table 1(b), the energy of dimer I is found to be 17.39 kcal/mol

lower than total energy of the two monomer (2^*E_{monomer}) units, indicating that intermolecular hydrogen bonding plays an important role in stabilization of the molecule.

The predicted geometrical parameters such as bond lengths and bond angles of the stable conformation of acetazolamide monomer, dimer (dimer I), and water cluster (VI and X) of acetazolamide, calculated at B3LYP method with 6-31G++(d,p), are presented in Table S2 in accordance with the atom numbering scheme as given in Figure 1. By

FIGURE 4: Experimental FT-IR (a) and micro-Raman spectra (b) of acetazolamide in the regions $3600\text{--}2800\text{ cm}^{-1}$ and $1800\text{--}200\text{ cm}^{-1}$, respectively.

FIGURE 5: Experimental FT-IR (solid) and calculated (scaled) absorption intensity spectra of acetazolamide in the regions $3600\text{--}2600\text{ cm}^{-1}$ (a) and $1800\text{--}400\text{ cm}^{-1}$ (b), respectively.

comparing theoretical and experimental bond lengths [9], it is easily seen that the computed bond lengths at B3LYP/6-31++G(d,p) method were slightly longer since the theoretical calculations were performed on isolated molecule in the gaseous state, whereas the experimental results are for the solid phase of the molecule [9, 10, 12]. Main differences between crystal structure [9] and monomer acetazolamide occur in H containing bond lengths and angles, and this is probably due to insufficient predictions for light atoms in the crystal structure study done in 1974 [9]. The theoretical results are mainly consistent with reports of other studies [11, 24]. Comparison of the geometry parameters of monomer form with those of dimer and water cluster of acetazolamide clearly shows the effects of intermolecular hydrogen bonding.

The intra- and intermolecular hydrogen bonds of the dimer forms (I–IV) of the four low energy conformations together with those of ten energetically preferred water clusters are tabulated in Table 2. The lowest energy conformer of dimer form (dimer I) makes stronger interhydrogen bonding interactions.

3.2. Vibrational Analysis. The experimental FT-IR (a) and micro-Raman spectra (b) of acetazolamide are given in Figure 4. The experimental FT-IR and Raman spectra of the solid acetazolamide are also given in comparison with those of calculated gas phase spectra in Figures 5 and 6, respectively.

The calculated wavenumbers, the calculated Raman intensities, and the potential energy distributions of the

FIGURE 6: Experimental (solid) and calculated (scaled) Raman intensities spectra of acetazolamide in the regions 3600–2800 cm^{-1} (a) and 1800–200 cm^{-1} (b), respectively.

vibrational modes of monomer and dimer (I) forms of acetazolamide and acetazolamide- H_2O cluster (VI and X) are given in Table 3, in comparison with the experimental vibrational spectra of the investigated molecule. The calculated wavenumbers of the four low energy dimers of acetazolamide are given in Table S3 comparatively. The assignment procedure for the dimers was done according to the potential energy distribution of dimer I.

When acetazolamide goes from the monomer form to the dimer or to the water cluster, alterations in the vibrational spectra, due to formation of H-bonds, are estimated. The NH_2 , NH , $\text{C}=\text{O}$, and SO_2 vibrational modes provide useful information on the intermolecular H-bonding interaction for the acetazolamide. On the other hand, NH stretching vibrations have anharmonic behavior [30–32]. Thus, in harmonic approximation procedure, NH_2 stretching wavenumbers are overestimated due to neglect of anharmonicity [33]. The calculated values of $\nu(\text{NH})$ stretching wavenumbers were 3451, 3035–2995 and 3221 cm^{-1} and 3099 cm^{-1} for monomer and dimer (dimer I) forms and water cluster (VI and X), respectively. As seen from Table 3, due to the participation of the $-\text{NH}$ group in hydrogen bonds, $\nu(\text{NH})$ in dimer I (with two $\text{N}\cdots\text{H}$ bonds; Figure 2) and water clusters VI and X (Figure 3) showed negative shifts, 456–416 and 230 cm^{-1} and 352 cm^{-1} , respectively. The highest shifts (456 and 416 cm^{-1}) were obtained for the dimer I. The calculated values suggest the presence of relatively strong $\text{N}\cdots\text{H}$ and $\text{NH}\cdots\text{N}$ hydrogen bond interactions in dimer I. The differences in hydrogen bonding strengths are responsible for these different wavenumber shifts. On the other hand $\text{C}=\text{O}$, and SO_2 groups do not involve hydrogen bonding interaction in both dimer I form and water cluster VI, and we do not observe a remarkable change in this wavenumber on going from monomer form to dimer or cluster form.

The acetazolamide $\text{C}-\text{N}$ ring stretching modes were recorded at 1540 cm^{-1} , 1425 cm^{-1} , and 1275 cm^{-1} as strong

intense bands in the IR and at 1425 cm^{-1} and 1260 cm^{-1} in Raman spectra of solid acetazolamide by Chufan et al. [19]. However, in other studies, these modes were obtained at 1498 cm^{-1} and 1450 cm^{-1} [11] and at 1571 cm^{-1} and 1452 cm^{-1} [34]. In the present study, the 1550, 1420, 1384, and 1311 cm^{-1} in IR and 1555, 1428, 1370, and 1308 cm^{-1} in Raman spectrum of solid acetazolamide are assigned to $\text{C}-\text{N}$ stretching vibrations. The 1550 cm^{-1} (IR) $\text{C}-\text{N}$ stretching mode is estimated to shift to higher wavenumber in both dimer and water cluster forms due to contribution of δ_{CNH} mode.

The $\nu_{\text{as}}(\text{SO}_2)$ stretching mode was observed at 1345 cm^{-1} and 1347 cm^{-1} in IR and Raman spectra, respectively, and was calculated at 1312 cm^{-1} , 1314 cm^{-1} , 1296 cm^{-1} , and 1319 cm^{-1} for monomer, clusters (VI and X), and dimer structure, respectively. Cami et al. [11] observed this mode at 1342 cm^{-1} and Baraldi recorded this mode at 1343 cm^{-1} and at 1348 cm^{-1} in IR and Raman spectra, respectively [13].

The mixing of $\delta_{\text{CNH}} + \nu(\text{C}-\text{N})$ modes was observed at 1234 and 1226 cm^{-1} as a strong band in the IR spectrum and at 1241 cm^{-1} in Raman spectrum as a medium band. This mode is calculated at 1197, 1223, 1319, and 1232–1226 cm^{-1} for free, clusters (VI and X), and dimer forms of acetazolamide, respectively.

The bands at 1174 cm^{-1} and 1140 cm^{-1} were assigned to $\nu(\text{N}-\text{N})_{\text{ring}}$ stretching and νSO_2 symmetric stretching vibrations, respectively, by Cami et al. [11]. In this study we observed a strong band at 1167 cm^{-1} in IR and 1165 cm^{-1} in Raman spectra and assigned it to $\nu\text{SO}_2 + \nu(\text{N}-\text{N})$ mode according to PED calculations. The PED result of this mode shows us that SO_2 stretching and $(\text{N}-\text{N})$ stretching contributions are 59% and 44%, respectively.

The strong band at 1095 cm^{-1} in the IR and Raman spectra is assigned to NH_2 rocking mode, in agreement with PED. The corresponding mode was assigned at 1097 cm^{-1} [11] and at 1090 cm^{-1} [34] in previous studies. But Baraldi et al.

TABLE 3: Experimental FT-IR (solid and aqueous solution) and Raman and calculated wavenumbers (cm^{-1}) of the global conformations of monomeric, dimeric, and H_2O clusters (V1 and X) forms of acetazolamide molecule.

This work	Assignment	This work				This work calculated by DFT/6-31++G(d,p)									
		Experimental		Experimental		Free		Cluster V1		Cluster X		Dimer I		PED ($\geq 5\%$)	
	[13]	IR _{Solid}	IR _{aq}	Raman	IR _{Solid}	Raman	ν_{sc}	ν_{uns}	Raman Int. Mono	ν_{sc}	ν_{sc}	ν_{sc}	Raman Int. Dimer I	Free acetazolamide	
$\nu_{\text{as}}(\text{N}-\text{H})$	$\nu_{\text{as}}\text{N}-\text{H}$	3339 vs	—	3337 vw	3331 m ^a ; 3301 s ^b	—	3473	3637	631	3474	3433	3484; 3484	1169; 22	$\nu_{\text{NH2}}(\text{asym.})$ (100)	
$\nu(\text{N}-\text{H})$	$\nu\text{N}-\text{H}$	3234 s	3193	3225 m	3227 m ^a ; 3179 m ^b	3230 w ^a ; 3183 sh ^b	3451	3614	1980	3221	3099	3035 ; 2995	28; 4931	ν_{NH} (100)	
$\nu_{\text{s}}(\text{N}-\text{H})$	$\nu_{\text{s}}\text{N}-\text{H}$	3151 s	—	3145 w	3148 m ^a ; 3093 w ^b	3152 w ^a ; 3089 s ^b	3361	3520	1690	3360	3334	3364; 3364	119; 3162	$\nu_{\text{NH2}}(\text{sym.})$ (100)	
$\nu_{\text{as}}(\text{CH}_3)$	νCH_3	3004 s	—	—	3001 vw ^a ; 3014 vv ^b	3014 ^b	3007	3149	1564	3011	3018	3015; 3014	181; 26336	$\nu_{\text{CH3}}(\text{asym.})$ (100)	
$\nu_{\text{as}}(\text{CH}_3)$	νCH_3	2948 m	—	2979 sh	2916 w ^a ; 2985 vw ^b	2941 vs ^a ; 2985 ^b	2996	3138	1759	2995	2982	2992; 2992	3199; 575	$\nu_{\text{CH3}}(\text{asym.})$ (99)	
$\nu_{\text{s}}(\text{CH}_3)$	νCH_3	2923 m	—	2933 vs	2932 ^b	2932 ^b	2924	3061	5191	2924	2914	2923; 2923	7119; 3177	$\nu_{\text{CH3}}(\text{sym.})$ (100)	
$\nu(\text{C}=\text{O})$	$\text{C}=\text{O}$	1699 vs	1694	1707 s	1698 s ^a ; 1680 s ^b	1708 m ^a ; 1677 w ^b	1724	1765	3123	1720	1719	1721; 1720	45; 5313	ν_{OC} (77) + ν_{CC} (6) + δ_{CNC} (7)	
$\delta\text{NH}_2(\text{scis.})$	$\delta\text{NH}_{\text{ip}}$	1558 sh	1569	—	1574 w ^b	1571 ^b	1562	1599	173	1560	1619	1554; 1554	200; 145	$\delta_{\text{NH2}}(\text{scis.})$ (96)	
$\nu(\text{C}=\text{N}) + \delta_{\text{CNH}}$	$\nu_{\text{as}}\text{C}=\text{N}_{\text{ring}}$	1550 vs	1552 s	1555 m	1542 vs ^a ; 1553 vs ^b	1558 ^b	1519	1554	6783	1546	1575	1581 ; 1565	2005; 15	ν_{CN} (60) + δ_{CNH} (28)	
$\delta_{\text{as}}(\text{CH}_3)$	—	1457 w	1457	—	1454 sh ^b	1455 sh ^b	1460	1494	749	1459	1479	1463; 1462	72; 1099	δ_{CHH} (74) + δ_{CHC} (13)	
$\delta_{\text{as}}(\text{CH}_3)$	$\nu_{\text{s}}\text{C}=\text{N} + \delta_{\text{a}}\text{CH}_3$	1437 s	1435	1442 vs	1436 m ^a ; 1437 m ^b	1443 vs ^a ; 1434 m ^b	1440	1474	932	1443	1451	1449; 1448	611; 204	δ_{CHH} (81) + δ_{CHC} (8) + ν_{CN} (8)	
$\nu_{\text{as}}(\text{C}=\text{N})_{\text{ring}}$	$\nu_{\text{s}}\text{C}=\text{N} \delta_{\text{a}}\text{CH}_3$	1420 sh	1418	1428 sh	1426 sh ^b	1422 ^b	1442	1476	2472	1449	1443	1456; 1456	7540; 1329	ν_{CN} (77) + δ_{CHH} (6)	
$\nu_{\text{s}}(\text{C}=\text{N})_{\text{ring}}$	$\delta_{\text{s}}\text{CH}_3$	1384 sh	1387	1370 w	1376 sh ^b	1386 ^b	1409	1442	5198	1424	1428	1439; 1435	72; 16412	ν_{CN} (54) + δ_{CNH} (23) + δ_{CNN} (6)	
$\delta_{\text{s}}(\text{CH}_3)$	$\nu_{\text{as}}\text{SO}_2$	1365 s	1363	—	1368 vs ^b	1373 ^b	1376	1409	1144	1377	1388	1379; 1379	1312; 42	δ_{CHH} (92) + ν_{CC} (6)	
$\nu_{\text{as}}(\text{SO}_2)$	$\nu_{\text{as}}\text{C}-\text{N}-\text{C}$	1346 vs	1344	1347 m	1343 vs ^a ; 1322 s ^b	1348 ^a	1312	1343	750	1314	1296	1319; 1319	1226; 690	$\nu_{\text{SO2}}(\text{asym.})$ (90) + δ_{SNH} (6)	
$\nu(\text{C}-\text{N})$	$\nu\text{C}-\text{N}_{\text{ring}}$	1282 s	—	1308 w	1280 m ^a ; 1286 m ^b	1242 w ^a ; 1289 ^a	1291	1322	109	1299	1249	1300; 1298	11; 186	ν_{CN} (62) + ν_{CS} (13) + δ_{NCN} (7) + δ_{CCN} (5)	
δ_{CNH}	—	1234 s	1234	1241 m	1227 s ^a	—	1197	1225	629	1223	1319	1232 ; 1226	2041; 15	ν_{CN} (29) + δ_{CNH} (19) + ν_{CC} (13) + δ_{NCO} (12) + δ_{CCH} (9)	
$\nu_{\text{s}}(\text{SO}_2) + \nu_{\text{s}}(\text{N}-\text{N})_{\text{ring}}$	$\nu_{\text{s}}\text{SO}_2$	1168 vs	1166	1165 s	1163 vs ^a ; 1176 vs ^b	1167 s ^a ; 1168 ^b	1121	1147	1022	1133	1100	1134; 1132	186; 1905	ν_{OS} (59) + ν_{NN} (34)	
$\nu_{\text{s}}(\text{SO}_2) + \nu_{\text{s}}(\text{N}-\text{N})_{\text{ring}}$	$\delta_{\text{ip}}\text{CNNC}$	1105 m	1106	1103 sh	1122 m ^b	1121 ^b	1100	1126	5630	1104	1140	1105; 1104	10516; 439	ν_{OS} (42) + ν_{NN} (39)	
$\rho(\text{NH}_2)$	“Ring mode”	1096 s	1097	1094 s	1095 s ^a ; 1087 m ^b	1097 s ^a ; 1085 m ^b	1071	1096	323	1070	1171	1063; 1063	14; 778	ρNH_2 (91)	
$\delta_{\text{ring}} + \nu_{\text{ring}}$	“Ring mode”	1038 w	1038	—	1045 m ^a ; 1045 m ^b	1041 ^b	1042	1066	538	1045	1048	1046; 1045	139; 1528	δ_{SCN} (44) + ν_{CS} (42)	
$\rho(\text{CH}_3)$	—	—	—	—	1011 ^a ; 1014 ^b	1016 ^b	1031	1055	10	1033	1045	1036; 1036	9; 29	δ_{CCH} (72) + δ_{CHH} (10) + ν_{CNCO} (16)	

TABLE 3: Continued.

Assignment	This work		This work calculated by DFT/6-31++G(d,p)				PED (≥5%) Free acetazolamide				
	Experimental		Free		Cluster VI			Dimer I			
This work	[13]	Experimental		Experimental		Free	Raman Int. Mono	Cluster X	Dimer I	Raman Int. Dimer I	
		IR _{solid}	IR _{aq}	Raman	IR _{solid}						Raman
ρ(CH ₃)	ν(N-N)	996 m	995	998 w	975 m ^b	955 m ^a , 968 ^b	276	1000	1014	1009; 1007	δ _{CCH} (55) + ν _{CC} (18)
ν(C-N) + ν(C-C)	νS-N	944 s	947	956 m	939 s ^a , 913 m ^b	916 ^b	854	954	963	953; 949	ν _{CN} (25) + ν _{CC} (18) + ν _{NN} (9) + δ _{CCN} (15) + δ _{CCH} (8) + δ _{OCN} (7) + δ _{NCN} (6)
ν(S-N)	“Ring mode”	813 m		807 vw	813 w ^a , 844 w ^b	—	2623	821	829	817; 817	ν _{SN} (55) + ν _{S-NH₂} (15)
δ _{ring} + ν _{ring}	“Ring mode”	783 m		—	780 m ^a , 817 m ^b	821 ^b	24	792	793	798; 786	ν _{CS} (17) + ν _{CC} (7) + δ _{CCN} (12) + δ _{NNC} (42)
ν _{as} (C-S) _{ring}	ν _a (C-S) _{ring}	705 m	719	709 s	705 w ^a , 710 w ^b	712 m ^a , 711 ^b	1385	681	682	683; 681	ν _{CS} (58) + ν _{CC} (9) + δ _{NCO} (9) + δ _{NCC} (12)
w(NH ₂)	ν _s (C-S) _{ring}	675 s	668	680 vs	674 s ^a , 673 s ^b	684 vs ^a , 680 ^b	408	667	988	626; 624	ν _{S-NH₂} (36) + ν _{SN} (19) + ν _{CS} (16) + δ _{NSO} (13)
ν ₂ (C-S) _{ring} + δ _{ring}	—	644 m	643	647 sh	643 ^a , 651 w ^b	645 ^b	5062	648	661	661; 659	δ _{CSC} (23) + ν _{CS} (23) + ν _{S-NH₂} (16) + ν _{NS} (6) + δ _{NSO} (6)
Γ _{as} (ring)	δ _{ip} N-C=O	621 vs	618	637 w	620 s ^a , 622 s ^b	636 w ^a , 624 ^b	225	639	636	635; 635	Γ _{NNGS} (44) + ν _{NNGS} (30) + ν _{CCNO} (11)
ν _{OCNC}	—	608 sh		610 vw	613 ^b	607 ^b	16	778	591	597; 595	ν _{CNCO} (24) + ν _{NNGS} (16) + Γ _{NNGS} (20) + Γ _{NCNO} (13) + Γ _{NCNH} (11) + ν _{CCNH} (8) + δ _{CHC} (7)
Γ _s (ring)	δSO ₂	582 m		580 w	584 m ^b	588 ^b	65	593	575	578; 576	Γ _{NCSC} (50) + ν _{NNGS} (10) + ν _{SCSN} (21) + δ _{CSO} (6)
δ(C-C=O)		573 m	575	—	574 m ^b	578 m ^a , 574 ^b	392	576	611	573; 570	δ _{CCO} (19) + ν _{S-NH₂} (10) + ν _{CS} (16) + ν _{CC} (8) + δ _{OSC} (7) + δ _{NCN} (5)
w(SO ₂) + w(NH ₂)	δO=C-C	—		—	554 m ^b	560 ^b	279	535	524	532; 531	δ _{NSO} (34) + δ _{CCO} (10) + δ _{CSN} (10) + ν _{S-NH₂} (12) + ν _{NS} (5)
ν(N-H)	—	508 s	881	507 w	520 s ^b	507 ^b	97	778	878	881; 864	ν _{CNCH} (25) + Γ _{OCNH} (20) + ν _{CCNO} (16) + Γ _{NNGS} (10) + Γ _{NCNH} (8)
δ _{sciss} (SO ₂)	wag SO ₂	457 vw	545	453 w	458 m ^b	450 w ^a , 453 ^b	1731	469	514	470; 470	δ _{OSO} (40) + δ _{NSO} (25) + ν _{NS} (11) + ν _{CS} (5)
ρ(SO ₂) + t(NH ₂)	ρSO ₂	406 vw		413 w	411 w ^b	417 w ^a , 406 ^b	208	435	468	433; 433	δ _{NSO} (48) + ν _{S-NH₂} (16) + Γ _{NCNH} (7) + Γ _{CSN} (7) + δ _{SNH} (7)
t(NH ₂) + t(SO ₂)	—	—		—	398 ^b	395 sh ^b	245	406	440	400; 400	δ _{NSO} (51) + Γ _{OSNH} (18) + Γ _{NSCN} (9)
δ _{CCO} + δ _{OSO}	Lattice vib.	—		373 w	—	374 m ^a , 368 ^b	1489	388	404	386; 384	δ _{CCO} (21) + δ _{NCN} (18) + δ _{OSO} (16) + δ _{SCS} (7) + δ _{CCN} (13) + ν _{CS} (7) + ν _{CN} (6)

TABLE 3: Continued.

Assignment		This work				This work calculated by DFT/6-31++G(d,p)								
This work	[13]	Experimental		Experimental		Free	Cluster VI		Cluster X	Dimer I	PED (≥5%) Free acetazolamide			
		IR _{solid}	IR _{aq}	Raman	IR _{solid}	Raman	ν _{sca.}	ν _{uns}	Raman Int. Mono	ν _{sca.}	ν _{sca.}	Raman Int. Dimer I		
δ _{CCN}	—	—		326 w	—	328 w ^a , 330 ^b	346	354	298	353	364	360; 355	15; 364	δ _{CCN} (41) + δ _{NCS} (23) + ν _{CS} (5)
ν(NH ₂)	—	—		267 m	—	270 s ^a , 270 ^b	291	298	503	302	386	316; 315	34; 594	δ _{CSN} (19) + δ _{OSN} (19) + Γ _{HNSO} (19) + Γ _{NCS} (6)
ν(NH ₂)	—	—		253 sh	—	256 m ^a , 258 ^b	274	280	363	274	—	275; 275	12; 952	Γ _{HNSC} (23) + δ _{CSN} (17) + δ _{CSO} (9) + δ _{NSO} (8) + Γ _{CSN} (9)
ν _{C-S}	—	—		—	—	230 ^b	235	241	4727	237	270	237; 233	5884; 325	ν _{CS} (42) + δ _{CSN} (25) + δ _{NCC} (13) + δ _{CSO} (6)
Γ _{CSNH}	—	—		195 w	—	192 ^b	219	224	291	230	231	243; 241	4402; 112	δ _{OSN} (32) + Γ _{HNSC} (32) + Γ _{NCS} (18)
δ _{CSN}	—	—		160 w	—	136 ^b	163	166	425	176	197	165; 163	1835; 12	δ _{CSN} (55) + δ _{CNC} (29)
ν _{C-S}	—	—		116	—	118 ^b	123	126	1587	127	133	138; 132	4227; 114	ν _{CSN} (33) + δ _{CSO} (27) + ν _{CCNH} (15) + Γ _{OCHN} (10)
δ _{SCS}	—	—		105	—	105 ^b	90	92	887	87	130	102; 100	567; 764	δ _{SCS} (44) + δ _{CNC} (13) + Γ _{CNCN} (14)
Γ _{NCNH}	—	—		—	—	—	88	90	295	98	104	118; 104	57; 25	Γ _{NCNH} (54) + Γ _{CNCO} (9) + ν _{CSN} (7) + δ _{CSN} (6)
ν(CH ₃)	—	—		—	—	—	56	57	1122	50	116	78; 62	817; 1641	ν _{S-NH₂} (36) + Γ _{NCCH} (18) + ν _{NCCH} (10) + ν _{NCSN} (6) + Γ _{NCS} (6)
ν(CH ₃)	—	—		—	—	—	39	40	2415	43	106	51; 48	459; 3691	Γ _{NCCH} (69) + ν _{NCCO} (17) + δ _{HCH} (6)
Γ _{SCSN}	—	—		—	—	—	11	11	1622	21	13	31; 12	572; 4369	Γ _{SCSN} (65) + ν _{SCSN} (15)

^aRef [13], ^bRef [24].

assigned this strong intense band at 1095 cm^{-1} to a “ring mode” (1,3,4 thiadiazolic ring) [13]. Our assignments are in agreement with those of Cami et al. [11, 34].

Cami et al. [11] assigned the 1058 cm^{-1} and 795 cm^{-1} bands to ring bending vibrations with contribution from $\nu(\text{C-S})$ [11]. In this study, ring bending and ring stretching modes were found to be mixed and assigned to 1038 cm^{-1} and 782 cm^{-1} bands observed in IR spectrum as weak bands. We do not observe any band in the Raman spectrum attributable to these modes.

We assigned the $\nu(\text{S-N})$ mode to the medium and weak bands observed at 812 cm^{-1} and 807 cm^{-1} in the IR and Raman spectra, respectively, according to the calculated results. This mode was assigned to the medium band at 872 cm^{-1} in [34], whereas Cami et al. [11] assigned the $\nu(\text{S-N})$ +wagging (NH_2) complicated mode to 944 cm^{-1} [11] and Baraldi et al. assigned it to 939 cm^{-1} [13].

The $\nu_{\text{as}}(\text{C-S})_{\text{ring}}$ was observed at 704 cm^{-1} as a medium band in the IR and at 709 cm^{-1} as strong band in the Raman spectra. The $\nu_{\text{s}}(\text{C-S})_{\text{ring}}$ stretching was mixed with ring bending and observed at 644 cm^{-1} and 647 cm^{-1} in IR and Raman spectra, respectively. The bands at 782 cm^{-1} and 679 cm^{-1} were assigned to $\nu(\text{C-S})$ asymmetric and symmetric stretchings, respectively, by Cami et al. [34].

In this study, the band located at 675 cm^{-1} in the IR and at 680 cm^{-1} in the Raman spectrum was assigned to $w(\text{NH}_2)$ mode. This mode with a contribution of CH bending vibration was assigned to 636 cm^{-1} by Cami et al. [11]. There was no assignment corresponding to the $w(\text{NH}_2)$ mode in [13].

The ring torsion modes were expected in the region $530\text{--}650\text{ cm}^{-1}$. We assigned the 621 cm^{-1} and 582 cm^{-1} bands in IR spectrum and 637 and 580 cm^{-1} bands in the Raman spectrum to the ring torsion modes. These modes were observed at 650 cm^{-1} and 534 cm^{-1} by Cami et al. [11]. Baraldi et al. did not assign ring torsion modes [13]. However, the bands at 621 cm^{-1} in the IR spectrum and at 637 cm^{-1} in Raman spectrum were identified as $\delta_{\text{ip}}(\text{N-C=O})$ mode [13], and the band at 584 cm^{-1} in IR spectrum and at 588 cm^{-1} in the Raman spectrum was assigned to δSO_2 [24].

The acetazolamide SO_2 wagging mode, coupled with NH_2 wagging mode, was calculated at 535 cm^{-1} for free form. We did not observe this mode in the experimental IR or Raman spectra, but it was observed at 588 cm^{-1} [34] and at 552 cm^{-1} [11] in previous studies. This mode was assigned to 458 cm^{-1} in IR and 453 cm^{-1} in Raman spectra [24]. Rocking and twisting SO_2 vibrations were situated at 416 cm^{-1} and 315 cm^{-1} [11]. In this study, corresponding values of these modes were assigned at 406 cm^{-1} and at 413 cm^{-1} .

The assignment in the range of $500\text{--}250\text{ cm}^{-1}$ is difficult due to the presence of several overlapping weak bands. These bands are associated with vibrational and lattice modes and most of them are strongly overlapped.

The experimental micro-Raman (solid) and calculated (scaled) Raman intensity spectra and the experimental FT-IR (solid) and calculated (scaled) absorption intensity spectra of acetazolamide dimer (I–IV) are given in Figures 7 and 8.

FIGURE 7: Experimental micro-Raman (solid) and calculated (scaled) Raman intensity spectra of acetazolamide dimer (I–IV) in the region $1800\text{--}200\text{ cm}^{-1}$, respectively.

FIGURE 8: Experimental FT-IR (solid) and calculated (scaled) absorption intensity spectra of acetazolamide dimer (I–IV) in the region $1800\text{--}400\text{ cm}^{-1}$, respectively.

$\nu\text{C=O}$, $\nu\text{C=N}$, $\nu_{\text{a}}\text{SO}_2$, and $\nu_{\text{s}}\text{SO}_2$ vibrations are observed at 1699 , 1550 , 1346 , and 1168 cm^{-1} , respectively, in the IR spectrum of solid acetazolamide, but they are observed at 1694 ($\Delta = \nu_{\text{aq.}} - \nu_{\text{solid}} = -5\text{ cm}^{-1}$), 1552 ($\Delta = \nu_{\text{aq.}} - \nu_{\text{solid}} = +2\text{ cm}^{-1}$), 1344 ($\Delta = \nu_{\text{aq.}} - \nu_{\text{solid}} = -2\text{ cm}^{-1}$), and 1166 ($\Delta = \nu_{\text{aq.}} - \nu_{\text{solid}} = -2\text{ cm}^{-1}$) respectively, in that of aqueous solution. The water cluster structure (X) of Figure 3 simulates best the aqueous environment for the molecule. The experimental FT-IR (solid and aqueous solution) and calculated (scaled) absorption intensity spectra of H_2O clusters (I–X) of acetazolamide in the region of $1800\text{--}800\text{ cm}^{-1}$ are given in Figure S2.

3.3. HOMO-LUMO and NBO Analysis. The frontier molecular orbitals are important in determining the molecular reactivity. The highest occupied molecular orbital (HOMO) energy characterizes the ability of electron giving, the lowest unoccupied molecular orbital (LUMO) energy characterizes the ability of electron accepting, and the gap between HOMO and LUMO characterizes the molecular stability. The HOMO

and LUMO energies of acetazolamide are calculated by DFT method at B3LYP/6-31G** level of theory, and the atomic orbital compositions of the frontier molecular orbitals for acetazolamide are shown in Figure S3. LUMO is located over the ring, the methyl group, and C–N bond which is located on the chain of the molecule. The HOMO is located over the ring, carbonyl group, and amine group, and consequently the homo-lumo transition implies an electron density transfer to ring, methyl group, and C–N bond from the carbonyl group and amine group. The computed low HOMO-LUMO energy gap (–5.497 eV) shows the charge transfer interactions, taking place within the molecule.

The NBO analysis of acetazolamide molecule is calculated by DFT method at B3LYP/6-31G** level of theory. The nature and credibility of the intermolecular hydrogen bonding can be analysed by searching the changes in electron density in the environments of N $\cdots$ H hydrogen bonds. The NBO analysis of acetazolamide clearly explains the evidence of the formation of strong H-bonded interaction between the LP(N) and $\sigma^*(\text{N-H})$ antibonding orbitals. The hyperconjugative interactions $\text{CR}(\text{N}_4) \rightarrow \sigma^*(\text{H}_{20}-\text{N}_{21})$, $\text{LP}_1(\text{N}_4) \rightarrow \sigma^*(\text{H}_{20}-\text{N}_{21})$, and $\text{CR}(\text{N}_{25}) \rightarrow \sigma^*(\text{N}_{12}-\text{H}_{13})$, $\text{LP}_1(\text{N}_{25}) \rightarrow \sigma^*(\text{N}_{12}-\text{H}_{13})$ are obtained as 0.37, 23.34, 0.37, and 23.34 kcal/mol, respectively, and are shown in Table S4. The differences in E^2 energies are reasonably due to the fact that the accrual of electron density is in the N–H bonds.

The comparison of NBO analysis between dimer and monomer forms of acetazolamide indicates the formation of two H-bonded interactions between nitrogen lone electron pairs and $\sigma^*(\text{N-H})$ antibonding orbitals.

The magnitudes of charge transfer from lone pairs of $n(\text{N}_4)$ and $n(\text{N}_{25})$ of the hydrogen-bonded N atoms into the antibonds $\sigma^*(\text{N}_{21}-\text{H}_{20})$ and $\sigma^*(\text{N}_{12}-\text{H}_{13})$ increased upon dimerization (0.05298e and 0.05299e) (see Table S5). Similar conclusion can be obtained while considering the energy of each orbital. The electron density in the N–H antibonding orbitals $\sigma^*(\text{N}_4-\text{C}_5)$ and $\pi^*(\text{N}_4-\text{C}_5)$ is increased significantly (0.00291e and 0.04037e, resp.) because of the dimerization. The elongation (0.02 Å) thereby weakens the bond. This is associated with the downshifts of stretching frequency (Table S2 and Table 3).

The intramolecular hyperconjugative interaction $\sigma(\text{N}_4-\text{C}_5)$ distribution to $\sigma^*(\text{C}_5-\text{N}_{12})$ and $\sigma^*(\text{N}_{12}-\text{C}_{14})$ caused less stabilization of 1.09 and 2.06 kcal/mol. This interaction of $\pi(\text{N}_4-\text{C}_5)$ with $\pi^*(\text{C}_2-\text{N}_3)$ leads to strong delocalization of 14.11 kcal/mol. There occurs a strong intramolecular hyperconjugative interaction from $n(\text{N}_{12})$ to $\sigma^*(\text{N}_4-\text{C}_5)$ and $\sigma^*(\text{C}_{14}-\text{O}_{15})$ with 47.21 and 54.82 kcal/mol (Table S4). The increased electron density at the N_{12} atom leads to the elongation of N–H bond and a lowering of the N–H stretching wavenumber (see Table S2 and Table 3).

4. Conclusion

In this study, the monomer and dimer forms and water clusters of acetazolamide were studied by using the DFT method at B3LYP/6-31G++(d,p) level of theory. The effect of basis set superposition error (BSSE) on the structure and

energy of acetazolamide dimer has been investigated. The most stable structure of the dimer (dimer I) possesses interaction energy of 16.116 kcal/mol after the basis set superposition error (BSSE) correction. The difference between the BSSE corrected (16.116 kcal/mol) and uncorrected (17.390 kcal/mol) interaction energies indicates the magnitude of error caused due to the basis set superposition. The energy of dimer I is found to be lower than the total energy of the two monomer (2^*E_{monomer}) units, indicating that intermolecular hydrogen bonding plays an important role in stabilization of the molecule. The wavenumbers associated with the related molecule are in a good agreement with [11, 34]. The comparison of NBO analysis between dimer and monomer forms of acetazolamide indicates the formation of two H-bonded interactions between nitrogen lone electron pairs and $\sigma^*(\text{N-H})$ antibonding orbitals. Increasing of the electron density in the N–H antibonding orbitals upon dimerization can be associated with the downshifts of N–H stretching frequency.

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