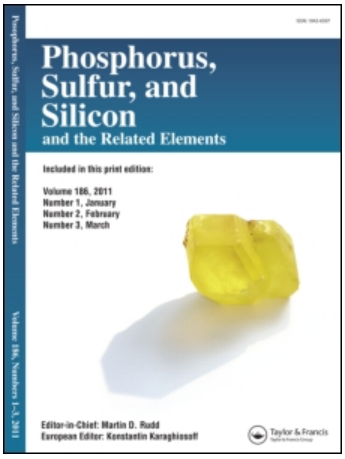

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GIAO/DFT ^{13}C NMR Chemical Shifts of 1,3,4-Thiadiazoles

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^{1}H, ^{13}C and ^{15}N NMR spectra of 2-acetylamino-1,3,4-thiadiazole and its 5-substituted derivatives have been measured and assigned based on reference data, as well as homo- and heteronuclear 2 D NMR experiments. In addition, the GIAO/DFT approach at the B3LYP level of theory using the 6-311G basis set was used to calculate the ^{13}C NMR chemical shifts. Although this method gives reliable results for 2-arylhydrazones of 1,3-diphenylpropanetrione, 2-phenacylpyridines, (Z)-2-(2-hydroxy-2-phenylvinyl)pyridines, 4-fluoroanilines, (1Z,3Z)-1,4-di(pyridin-2-yl)buta-1,3-dienediols and their tautomeric forms, the calculated chemical shifts for the 1,3,4-thiadiazoles studied are less satisfactory. Presence of the sulfur atom(s) seems to be responsible for such behavior.

Keywords 1,3,4-Thiadiazoles; ab initio calculations; NMR chemical shifts

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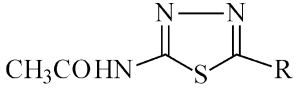
INTRODUCTION

Theoretically calculated NMR parameters are shown to be very helpful in distinguishing between two (or more) related forms of the same compound, *e.g.* isomers or tautomers. In our recent papers,[1–9] the NMR signals were correctly assigned for acylmethyl derivatives of pyridine and their prototropomers by comparing the experimental and calculated chemical shifts. Since the thiadiazole ring contains two carbon, two nitrogen and one heavier sulfur atoms, calculation of their NMR chemical shifts is an interesting way to test the validity of the procedure used for prediction of the NMR data. Therefore, 2-acetylamino-1,3,4-thiadiazole and its 5-substituted derivatives showing interesting biological activities were chosen to be studied for the present article. 2-Acetylamino-5-sulfonylamino-1,3,4-thiadiazole (acetazolamide), **5** (Scheme 1), is a potent inhibitor of carbonic anhydrase.[10,11] It is used clinically for treating glaucoma.[12] 2-Acetylamino-1,3,4-thiadiazole, **1**, was reported to show antitumor activity.[13] There are some interesting inter-and intramolecular interactions in these compounds. The molecules of 2-acetylamino-5-sulfonylamino-1,3,4-thiadiazole, **5**, are held together in the crystal by strong N–H...O and N–H...N hydrogen bonds.[14] The 1,3,4-thiadiazole ring in this compound is planar but both side chains are bent out of the ring planes.[14] The C–S bonds in the ring have some double character resulting from delocalization of the π electrons in the thiadiazole ring.[14] The molecules of bis(5-acetylamino-1,3,4-thiadiazole-2-sulfonyl)amine, **6**, consist of two nearly planar acetylaminothiadiazolesulfonyl units which are parallel.[15] Coplanarity of the acetylamino groups and the thiadiazole rings is a consequence of π-electron delocalization over these groups and by non-bonding S···O interactions.[15] In this paper multinuclear magnetic resonance of 2,5-disubstitued 1,3,4-thiadiazoles were described and experimental and GIAO/DFT ^{13}C NMR data were compared.



No	1	2	3	4	5
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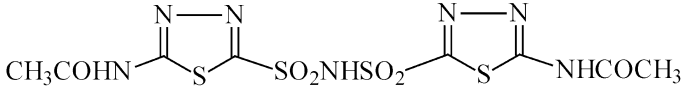

6

SCHEME 1

RESULTS AND DISCUSSION

Experimental ^{1}H, ^{13}C and ^{15}N NMR chemical shifts of **1–6** are collected in Table I. It contains also the ^{13}C NMR chemical shifts calculated at B3LYP/6-311G//RHF/3-21G level.

Since ^{15}N NMR chemical shifts of non-quaternary nitrogen atoms containing the lone electron pair are known to be sensitive to solvent, concentration and temperature[17] nitrogens are not included in theoretical considerations. Similarly, protons locating on the periphery of the molecule are also subjected to more efficient intermolecular (solvent-solute) effects than the carbon atoms[18] and are left away from the theoretical treatment.

Geometry optimizations with the HF3-21G, 6-31G, and 6-31G** basis sets are known to have comparable effects on the calculated (GIAO) chemical shifts.[19–21] Thus, the minimum basis set, 3-21G, was used to provide satisfactory molecular geometries for reproduction of the ^{13}C NMR chemical shifts. These were calculated for all

TABLE I Experimental ^{1}H, ^{13}C, and ^{15}N and Calculated ^{13}C NMR (in Italics)[a] Chemical Shifts (δ/ppm) for 0.1–0.2 M DMSO-d_6 Solutions at 303 K of 1–6

Nucleus	1	2	3	4	5	6
N**H**	~ 12.5s (broad)	~ 12.6s (broad)	12.26s	12.47s	~ 12.6s (broad)	12.93s
C**H**$_3$	2.18s	2.20s	2.08s	2.17s	2.20s	2.22s
H in R	9.11s	—	13.91s	D	8.24s	8.26s
C2	168.69	169.34	169.45	169.12	169.61	161.24
	155.12	*158.49*	*156.99*	*163.48*	*161.82*	*161.82*
C5	148.46	147.90	152.31	159.54	161.39	169.49
	144.18	*153.68*	*157.49*	*163.06*	*169.57*	*169.57*
CH$_3$	22.43	22.17	22.33	22.53	22.51	22.42
	21.95	*21.89*	*21.83*	*22.08*	*22.03*	*22.03*
C = O	158.55	159.61	183.72	167.72	164.51	164.39
	161.84	*161.18*	*160.89*	*161.84*	*161.78*	*161.78*
N**3**	−58.4[b]	[c]	[c]	[c]	[c]	[c]
N4	−22.8[b]	[c]	[c]	[c]	[c]	[c]
CO**N**H	−245.3	−241.5	−242.9	−244.1	−242.7	−242.6

[a] B3LYP/6-311G//RHF/3-21G.

[b] Assignment is based on the ^{15}N NMR shift of unsubstituted 1,3,4-thiadiazole -7.9 ppm in DMSO-d.[16] In PFG ^{1}H,^{15}N HMBC H-5 of **1** shows cross-peaks with both ring nitrogens, the cross-peak with the signal at -22.8 ppm being more intensive supporting the above assignment.

[c] Not observed because H-5 is missing in these compounds and side chain NH is too far and its signal is too broad to give any cross-peaks with the ring nitrogens.

TABLE II ^{13}C NMR Chemical Shifts (δ/ppm) for Compound 1 Calculated[a] with Different Basis Sets

	C2	C5	CH_3	C = O
B3LYP/6-31G(d,p)[b]	132.20	150.02	148.46	22.81
	131.69	*149.24*	*147.32*	*22.88*
B3LYP/6-31G(2d,p)[b]	133.54	151.54	150.86	23.11
	133.08	*150.83*	*149.80*	*23.18*
B3LYP/6-31G(2d,2p)[b]	134.54	152.94	152.38	23.83
	134.09	*152.23*	*151.32*	*23.89*

[a] Chemical shifts obtained with HF/6-31G(d,p) and HF/6-31G(2d,p) methods of geometry optimization are given in regular font and italic, respectively.
[b] Basis set used in calculation of chemical shifts.

carbon atoms, *i.e.* **C**2, **C**5, $\mathbf{C}_{\text{methyl}}$ and $\mathbf{C}_{\text{carbonyl}}$. The correlation for the side chain C_{methyl} is satisfying. However, it is easily seen that especially for $\mathbf{C}_{\text{carbonyl}}$ of **3** and **4** (which contain sulfur atom in the substituent at C5) the calculated parameters differ significantly from the experimental ones although all ^{13}C shifts correlated by a satisfying way for 2-aryl-hydrazones of 1,3-diphenylpropanetrione,[3] 2-phenacylpyridines and (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines,[5] 4-fluoroanilines,[4] (1*Z*,3*Z*)-1,4-di(pyridin-2-yl)buta-1,3-dienediols, and their tautomeric forms.[8,9] For the ring carbons C2 and C5 adjacent to sulfur atom the correlations were also poor. So, it is obvious that the used theoretical model does not take into account heavy sulfur atom(s) in a proper way. As it can be seen in Table II, more sophisticated 6-31G basis sets give more satisfying results for C5 and $\mathbf{C}H_3$ only.

In conclusion we can point out that a GIAO/DFT approach at the B3LYP level of theory using the 6-311G basis set does not reliably reproduce the experimental ^{13}C NMR chemical shifts for 2-acetylamino-1,3,4-thiadiazoles and its 5-substituted derivatives. Presence of the sulfur atom(s) in these molecules seems to be responsible for such a behavior. In the near future, we are going to use more sophisticated calculation methods to obtain a better agreement between the experimental and calculated chemical shifts for these compounds.

EXPERIMENTAL

Satisfactory analytical data (± 0.3 % for C, H, and N) were obtained for all new compounds.

2-Acetylamino-1,3,4-thiadiazole (1)

This compound was obtained by modification of the known method.[22] A mixture of 9.0 g (0.10 mol) of thiosemicarbazide and 16.6 ml (14.82 g, 0.10 mol) of ethyl orthoformate was heated for 2 h at the boiling water bath. The reaction mixture was then diluted with 250 mL of acetonitrile and allowed to boil for a short time. The hot mixture was filtered off to remove the solid impurities, and the filtrate obtained was cooled down. The precipitate formed (1-ethoxymethylenethiosemicarbazide) was collected by suction (24%). The mixture of 3.0 g (0.02 mol) of this compound and 14.2 mL (15.31 g, 0.15 mol) of acetic anhydride was heated at 90°C for 1h. The black solid obtained was recrystallized from water. 2-Acetylamino-1,3,4-thiadiazole obtained (90%) melts at 265–267°C (lit. 268–269°C).[23–27]

2-Acetylamino-5-chloro-1,3,4-thiadiazole (2)

10.0 mL (0.33 mol) of 30% hydrogen peroxide was added portionwise to 80.0 mL (2.59 mol) of 36% hydrochloric acid (during addition the temperature of the reaction mixture should be kept below 10°C). 8.04 g (0.05 mol) of 2-acetylamino-5-mercapto-1,3,4-thiadiazole (**3**, POLPHARMA S.A., Poland) and 75.0 mL (1.32 mol) of 96% acetic acid were then added to this mixture and whole was stirred for 8 h at 10–15°C. The solid product was collected, washed with plenty of water and recrystallized from ethanol. It melts at 245–246°C (lit. 245–246°C).[28] Yield: 4.32 g (53%).

2-Acetylamino-5-mercapto-1,3,4-thiadiazole (3)

5.30 g of anhydrous sodium carbonate and 9.20 g (0.12 mol) of carbon disulphide were added to 9.10 g (0.1 mol) of thiosemicarbazide suspended in 35 mL of anhydrous ethanol. The obtained mixture was refluxed with stirring for 1 h at temperature ca 50°C and then heated for 4 h on a steam bath. Solvent was removed by distillation, and the obtained residue dissolved in 40 mL of water (40 mL) and acidified with ca 8 mL of conc. hydrochloric acid to give 10.9 g (80%) of 2-amino-5-mercapto-1,3,4-thiadiazole. It melts at 232–233°C [lit. 232°C (decomp.)].[28] Subsequently, 10.90 g (9.4 mL, 0.1 mol) of acetic anhydride was added portionwise to the mixture of 6 mL of glacial acetic acid and 10.9 g (0.08 mol) of 2-amino-5-mercapto-1,3,4-thiadiazole. The mixture was refluxed with stirring for 5 h. Precipitate (9.8 g, 70 %) obtained after addition of water and cooling of the obtained solution was recrystallized from water. It melts at 288–290°C (lit. 290–293°C),[29] 293–294°C.[30]

2-Acetylamino-5-sulfo-1,3,4-thiadiazole (4)

The mixture of 24.9 mL (26.12 g, 0.435 mol) of glacial acetic acid, 28.7 mL (0.93 mol) of 36% hydrochloric acid, 8.06 g (0.046 mol) of 2-acetylamino-5-mercapto-1,3,4-thiadiazole and 24.1 mL (0.786 mol) of 30% hydrogen peroxide was stirred for 2 h at 5-10°C. The obtained solid was filtrated, washed with plenty of water and recrystallized from water. The product melts at 282–283°C. Yield: 5.4 g (53%).

2-Acetylamino-5-sulfonylamino-1,3,4-thiadiazole (5)

80 mL (2.64 mol) of 30% hydrogen peroxide was added portion wise to stirred 36% hydrochloric acid (50 mL, 1.62 mol). During addition temperature of the reaction mixture was kept at 10–15°C. 5.0 g (0.029mol) of 2-acetylamino-5-mercapto-1,3,4-thiadiazole was then added to reaction mixture in the same manner. The obtained solid of 2-acetylamino-5-sulfochloro-1,3,4-thiadiazole was collected at the Büchner funnel and washed with ice water. This crude byproduct was added as small portions to the stirred 25% aqueous ammonia at temperature not exceeding 20°C. Reaction mixture was then heated for 2 h at 50°C (to remove excess of ammonia) and refluxed for ten minutes with charcoal. The filtrate obtained after removing the charcoal was cooled down and acidified with conc. hydrochloric acid to pH 1. The obtained precipitate was collected and recrystallized from water. It melts at 256–257°C (lit. 258–259°C).[31] Yield: 2.05 g (32%).

Bis(5-acetylamino-1,3,4-thiadiazole-2-sulfonyl)amine (6)

2-Acetylamino-5-sulfochloro-1,3,4-thiadiazole was obtained in the following manner. 80 mL (2.64 mol) of 30% hydrogen peroxide was added to 50 mL of 36% hydrochloric acid 5–10°C. To this mixture were added successively: 5.0 g (0.029 mol) of 2-acetylamino-5-mercapto-1,3,4-thiadiazole and 50.4 mL, 52.84 g (0.88 mol) of glacial acetic acid. The obtained reaction mixture was then stirred for 2 h at 5–10°C. The solid 2-acetylamino-5-sulfochloro-1,3,4-thiadiazole formed was filtrated off and washed with ice water. This wet by-product was added at 5–10°C directly to the suspension of 2.2 g (0.01 mol) of 2-acetylamino-5-sulfamino-1,3,4-thiadiazole in the solution of 0.4 g (0.01 mol) of sodium hydroxide in 100 mL of water at 5–10°C. Stirring at the same temperature was continued for additional 1.5 h. Non-reacted starting materials were removed and the filtrate treated with 40% aqueous solution of sodium hydroxide (to pH 12). The solid formed after 24 h was collected and dissolved in minimum amount of water.

36% hydrochloric acid was then added to this (hot) solution to pH 1. After cooling down the white crystals precipitate from the solution. The product melts at 307–311°C (lit. 318°C).[32] Yield: 0.65 g (16%).

Spectra

All NMR spectra were recorded for 0.1–0.2 M solutions in DMSO-d_6 solutions at 303 K with a Bruker Avance DRX 500 FT NMR spectrometer equipped with an inverse detection 5-mm diameter broad-band probe head and z-gradient accessory working at 500.13 MHz (^{1}H), 125.76 MHz (^{13}C) and 50.59 MHz (^{15}N), respectively. In ^{1}H NMR experiments the spectral width was 8500 Hz (17 ppm), the number of data points 65 K, the flip angle 30°, and the number of scans 32. The FIDs were multiplied by an exponential window function of the digital resolution (0.13 Hz) prior to Fourier Transform (FT). The ^{1}H NMR chemical shifts are referenced to the trace signal of $CHCl_3$ ($\delta = 7.26$ ppm from internal TMS).

In proton composite pulse decoupled (Waltz-16) ^{13}C NMR experiments the spectral width was 30300 Hz (240 ppm), the number of data points 65 K, the flip angle 30°, and the number of scans typically >10000 in order to observe reliably also the weak signals of the possible minor contributors. The FIDs were multiplied by an exponential window function of the digital resolution (0.92 Hz) prior to Fourier Transform (FT). The ^{13}C NMR chemical shifts are referenced to the center peak of solvent $CDCl_3$ ($\delta = 77.00$ ppm from TMS).

In order to distinguish the spin systems belonging to possible different tautomeric forms as well as to assign the ^{1}H NMR spectra reliably also the 2 D double quantum filtered (DQF) ^{1}H,^{1}H COSY[33–34] experiments were run. In these experiments the data matrix size was 1024 points (f_2-axis) × 128 points (f_1-axis), which was zero filled to 512 points along the f_1-axis prior to FT. 32 scans were accumulated for every f_1-increment (f_2-spectrum). A shifted sine-bell window function was used along both axes prior to FT.

2 D pulsed field gradient (PFG) selected ^{1}H,^{13}C HMQC[35,36] and ^{1}H,^{13}C HMBC[37] experiments were run to assign reliably the ^{13}C NMR spectra. In HMQC the matrix size was typically 2500 Hz/512 points (^{1}H = f_2-axis) × 10000 Hz/512 points (^{13}C = f_1-axis), which was multiplied by a sine-bell window function along both axes prior to FT. The number of scans was 32 and a composite pulse decoupling (graph) was used to remove proton couplings. In HMBC measurements, 64 scans were accumulated for each f_1-increment; the matrix size and windowing were the same as in HMQC. A low-pass filter (to remove correlations transmitted *via* direct couplings) and a 50 msec delay [for an evolution of ^nJ(C,H) couplings] were included in the HMBC pulse sequence.

In order to determine the ^{15}N NMR chemical shifts, PFG ^{1}H,^{15}N HMBC experiments were run. In these experiments, the size of data matrix was 2500 Hz/512 points (^{1}H) × 22500 Hz/1024 points (^{15}N-axis). The ^{15}N NMR chemical shifts were referenced to an external neat nitromethane ($\delta = 0.0$ ppm) sample in a 1 mm diameter capillary tube inserted coaxially inside the 5 mm NMR sample tube. A sine-bell multiplication was done along both axes prior to FT. 64 scans were accumulated for every $^{15}N = f_1$-increment. A 50 msec delay for an evolution of $^{n}J(N,H)$ couplings was included in this HMBC pulse sequence.

Calculations

Quantum chemical calculations were performed at the HF and B3LYP levels of theory with the Gaussian 03 package.[38] Geometries were optimized to the global minima at the *ab initio* HF level with the 3-21G basis set using C1-symmetry (no symmetry constraint). The GIAO/DFT calculations for ^{13}C chemical shifts were performed at the B3LYP level with 6-311G basis set as in our previous paper.[5] Chemical shifts are referenced to TMS.

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