Carbon-13 Nmr Spectra of 1,2,3-Thiadiazoles

James H. Looker, Nazir A. Khatri, Ronald B. Patterson and Charles A. Kingsbury

Department of Chemistry, The University of Nebraska, Lincoln, Nebraska 68588

Received March 20, 1978

Natural abundance ^{13}C nmr spectra are reported for 1,2,3-thiadiazole and nine derivatives. The spectra are discussed in terms of α- and β-effects of substituent groups and compared with corresponding spectra of alkene and benzene derivatives. ^{13}C nmr spectra of four 1,3,4-thiadiazoles are presented. Spectral data indicate that in dimethylsulfoxide solution 2-mercapto-5-methyl-1,3,4-thiadiazole exists predominantly as the thione tautomer.

J. Heterocyclic Chem., 15, 1383 (1978)

In previous papers, we have reported ^{13}C nmr spectra of oxygen heterocycles, γ-pyrones (1) and flavones (2). For several years, synthesis of 1,2,3-thiadiazoles has been in progress in this laboratory (3). Quite recently, at least two papers from other laboratories have reported ^{13}C nmr spectra of 1,3,4-thiadiazoles (4,5a), and one the spectra of cycloalkeno-1,2,3-thiadiazoles (5b). In the present paper we report ^{13}C nmr data for ten 1,2,3-thiadiazoles synthesized for spectral analysis, and for four commercially available 1,3,4-thiadiazoles.

In Table I are listed ^{13}C nmr data for the parent 1,2,3-thiadiazole and nine derivatives (Chart I). All substances were prepared by literature procedures, and possessed physical properties in reasonable agreement with previously reported values. However, 4-methyl-1,2,3-thiadiazole, prepared by a minor modification of one literature procedure (6), resulted in a solid, m.p. 87-89°, instead of an oil (6,14).

Chart I

I: R = R' = H
II: R = Ph, R' = H
III: R = CH_3, R' = H
IV: R = COOH, R' = H
V: R = COOH, R' = D
VI: R = $CONH_2$, R' = H
VII: R = $CONH_2$, R' = D
VIII: R = COCl, R' = H
IX: R = CN, R' = H
X: R = CH_3, R' = $COOC_2H_5$

In this study, initial assignment of ^{13}C resonances of I was made by comparing its spectrum with spectra of pyrazole, 1,2,3-triazole, and thiophene (7). In both pyrazole and triazole, the resonance of the carbon atom *alpha* to a nitrogen atom is downfield relative to the resonance of the α-carbon of thiophene. Accordingly, the line at 147.35 ppm is assigned to carbon-4, and that at 135.83 to carbon-5. These assignments have been confirmed by substituent effects, including deuteration, and by the off-resonance spectrum of III (sequel).

Of the substances soluble in deuteriochloroform, substitution of either methyl or phenyl (II and III) causes a marked downfield shift of the *ipso*-carbon resonance (α-effect), and an upfield shift of the C (5) resonance (β-effect). The chlorocarbonyl group (VIII) also exerts a downfield influence on the *ipso*-carbon, and in contrast to methyl and phenyl groups, causes a downfield shift also in the C (5) resonance. In the ester (X), the carboethoxy group causes a downfield shift of the *ipso*-carbon resonance through an apparent strong α-effect, which more than compensates for the expected influence of the methyl group, which could cause an upfield shift through its β-effect. Addition of DMSO-d_6 to the deuteriochloroform mixture of IX was necessary to effect solution. Cyano is the only group at C (4) which resulted in an upfield shift of the *ipso*-carbon resonance. This group caused a rather large downfield shift in the C (5) resonance of IX.

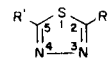
In order to confirm the assignments made for C (4) and C (5) resonances of 1,2,3-thiadiazole derivatives, an off-resonance spectrum of III was obtained. A quartet was observed at 12.9, a doublet at 133.45, and a singlet at 157.89 ppm. Since a hydrogen atom is known to be at C (5), the doublet at 133.45 provides convincing evidence that this line is indeed the C (5) resonance in III.

The solubility of IV and VI dictated use of DMSO-d_6 as solvent. Both carboxyl and carbamoyl groups cause downfield shifts in both the C (4) and C (5) resonances, although the magnitude of the shifts could be caused in part by the change in solvent. 5-Deuterio-1,2,3-thiadiazole-4-carboxylic acid (V) was prepared from deuterated pyruvic acid by the Hurd-Mori reaction (8), and contained approximately 80% of the deuteration product (from mass spectral analysis). The deuterated amide VII was prepared from V *via* the acid chloride. The ^{13}C nmr spectra of V and VII contained lines very close to those in the spectra of IV and VI. But the peaks at 144.56 and 141.79 were broadened and reduced in intensity, and hence are the C (5) resonances in the spectra of these deuteration products. In the decoupled ^{13}C nmr spectrum of 2-deuteriothiophene, the C (2) resonance was not present at all (9).

A comparison of the ^{13}C nmr spectral properties of 1,2,3-thiadiazole derivatives with spectra of similarly substituted benzenes (10) and alkenes (11) has been made. It is apparent that the α-effects of phenyl, methyl, carboxyl, and chlorocarbonyl are similar to the corresponding α-effects in either benzenes or alkenes, but the carboethoxy α-effect is more like that in alkenoates than in aroates. Cyano, although showing a negative α-effect, nonetheless is similar to cyano α-affects in either benzenes

Chart II

XI XIa



XII: R = NH_2, R' = H
XIII: R = NH_2, R' = CH_3
XIV: R = R' = CH_3

or alkenes. The β-effect of phenyl and cyano is intermediate between that of these groups on benzene *vis-a-vis* alkenes. Methyl appears to resemble alkenes in its β-effect.

^{13}C nmr data for four commercially available 1,3,4-thiadiazoles (Chart II) are presented in Table II. The value of the chemical shift for C (2) indicates that in dimethylsulfoxide solution XI actually is the thione tautomer XIa, and is in agreement with recent findings that certain alkylamino- and arylamino-1,3,4-thiadiazoline-2-thiones have the thione carbon resonance near 185 ppm (5a). Thione tautomers also have been observed as predominant in several structurally related 4-thiazoline-2-thiones, in which the C (2) resonance appears in the 185-190 ppm range (12).

Coupled spectra of the 1,2,3-thiadiazole derivative (II) and the 1,3,4-thiadiazole (XII) were examined in order to determine certain carbon-proton coupling constants. In the spectrum of II, $^{1}J_{C5\text{-}H5}$ was 189.4 Hz, a value which correlates well with $^{1}J_{C2\text{-}H2}$ near 188.0 Hz in bromothiophene derivatives (15), and was seen to be larger than the $^{1}J_{CH}$ value of ~ 159 Hz for benzene (16). From the spectrum of XII, a $^{1}J_{C5\text{-}H5}$ value of 214.5 Hz was determined. Long-range carbon-proton coupling was evident in the C (2) resonance, which was split by 3.8 Hz. Presumably this splitting resulted from coupling of C (2) with the proton at the 5-position, through the hetero sulfur atom.

EXPERIMENTAL

1,2,3-Thiadiazoles.

Thiadiazoles were prepared by literature methods, as follows: I (8), II (8), IV (8), VI (13), VIII (13), IX (13), and X (14).

4-Methyl-1,2,3-thiadiazole (III) (6,14).

Acetone *N*-(carboethoxy)hydrazone (11.5 g.) was added in small portions to 50 ml. of thionyl chloride, cooled in ice. The reaction mixture then was stirred at room temperature for 6 hours, and excess thionyl chloride evaporated. The residue solidified on standing 20 hours at room temperature. Addition of benzene-petroleum ether (b.p. 38-46°) to the residue gave the crude thiadiazole (7.3 g.), m.p. 76-80°. Attempts at recrystallization by solution in several solvents gave an oil. The compound was purified by trituration twice with benzene-petroleum ether (1:10 volume), m.p. 87-89°; ms: m/e calcd. for $C_3H_4N_2S$: 100.14;

Table I

^{13}C Nmr Chemical Shifts of 1,2,3-Thiadiazoles

1,2,3-Thiadiazole	Substituent at C(4)	Substituent at C(5)	Solvent	Chemical Shift (a) δ(C_4)	Chemical Shift (a) δ(C_5)	Δδ C(4)	Δδ C(5)	δ Other Carbon Atoms
I	H	H	Deuteriochloroform	147.34 (b)	135.83 (c)	---	---	
II	Ph	H	Deuteriochloroform	163.92	130.90	+16.58	-4.91	130.22, 129.54, 129.3, 127.5 (Ph)
III	CH_3	H	Deuteriochloroform	157.86	133.45	+10.52	-2.38	12.9 (CH_3)
IV	COOH	H	DMSO-d_6	155.56	144.88	+ 8.22	+9.05	160.56 (COOH)
V	COOH	D	DMSO-d_6	154.92	144.56	+ 7.58	+8.73	160.55 (COOH)
VI	$CONH_2$	H	DMSO-d_6	157.7	141.98	+10.36	+6.15	160.24 ($CONH_2$)
VII	$CONH_2$	D	DMSO-d_6	157.74	141.79	+10.4	+5.96	160.16 ($CONH_2$)
VIII	COCl	H	Deuteriochloroform	154.68	142.57	+ 7.34	+6.74	160.02 (COCl)
IX	CN	H	Deuteriochloroform-DMSO-d_6	133.69	145.43	-13.69	+9.6	110.51 (CN)
X	CH_3	CO_2Et	Deuteriochloroform	159.44	139.21	+12.1	+3.38	13.77 and 14.01 (Two CH_3 groups) 62.34 (CH_2), 161.9 (COOR)

(a) Ppm downfield from TMS. (b) Lit. (5b) value, 147.5. (c) Lit. (5b) value, 136.3.

Table II

^{13}C Nmr Chemical Shifts of 1,3,4-Thiadiazoles

Compound	Solvent	Chemical Shifts (a) δ C_2	δ C_5	δ Other Carbon Atoms
XIa	DMSO-d_6	188.41	159.24	15.95 (CH_3)
XII	DMSO-d_6	168.17	142.65	---
XIII	DMSO-d_6	168.37 (b)	153 (b)	15.27 (CH_3)
XIV	Deuteriochloroform	164.88	164.88	15.20 (CH_3)

(a) Ppm downfield from TMS. (b) Tentative assignment.

found: 100.0096; ^1H nmr (deuteriochloroform): δ 2.81 (s, 3, methyl), 8.28 (s, 1, 5-H), lit. (14) ^1H nmr values, δ 2.78, 8.27.

5-Deuterio-1,2,3-thiadiazole-4-carboxylic Acid (V).

Pyruvic acid (12.67 g.) was deuterated in 23 ml. of deuterium oxide containing 1.42 g. of anhydrous potassium carbonate. The reaction was monitored by ^1H nmr, and proton resonances noted as absent after 2.5 hours reflux. Excess deuterium oxide and water were removed by vacuum distillation, and 2 ml. of sulfuric acid added to the residue. Vacuum distillation gave 7.9 ml. of deuterated pyruvic acid. The thiadiazole (V) then was prepared from deuterated pyruvic acid *via* the *N*-carboethoxyhydrazone by the method of Hurd and Mori (8).

5-Deuterio-1,2,3-thiadiazole-4-carboxamide (VII).

5-Deuterio-1,2,3-thiadiazole-4-carboxylic acid was converted to the crystalline acid chloride, m.p. 35.5-36.5°, by the method of Pain and Slack (13). To cold concentrated ammonium hydroxide (25 ml.) was added, dropwise, a solution of 1.09 g. of 5-deuterio-1,2,3-thiadiazole-4-carbonyl chloride in 20 ml. of dry acetone. The reaction mixture was stirred 15 minutes, then water was added. The resulting white precipitate was collected by filtration, washed with water, and finally recrystallized from water to give 5-deuterio-1,2,3-thiadiazole-4-carboxamide (0.54 g.), m.p. 219-220° [lit. (3) m.p. 219.5-220.5°].

1,3,4-Thiadiazoles.

The thiadiazoles XI, XIII, and XIV were obtained from Aldrich Chemical Co., and XII from ICN Pharmaceuticals, Inc., K & K Labs Division. All 1,3,4-thiadiazoles were used as received.

^{13}C Nmr Spectra.

The spectra were determined at 25.2 MHz on a Varian XL-100 instrument at normal probe temperatures. The concentration of the samples was approximately 300 mg./3 ml. of deuteriochloroform or DMSO-d_6. The error in signal position, as indicated by the computer, was ± 1.25 Hz. In most runs 5000 transients were collected. The approximate tipping angle used was 50°. In a typical spectrum, a 5K spectral width was used, with a 0.8 s acquisition time, and a 0.2 s pulse delay; 5 watts of decoupling power were used with a band-width of 1-1.5K. The center peak of the deuteriochloroform signal was used as standard, which was taken as 76.9 ppm from TMS. In DMSO-d_6 solutions, the solvent again was taken as standard, at 39.4 ppm from TMS. The gated mode of decoupler operation was used for coupled spectra (17).

Acknowledgement.

The NMR instrument used in this investigation was purchased with funds from NSF grant GP 10293, which is gratefully acknowledged.

REFERENCES AND NOTES

(1) C. A. Kingsbury, M. Cliffton, and J. H. Looker, *J. Org. Chem.*, 41, 2777 (1976).

(2) C. A. Kingsbury and J. H. Looker, *ibid.*, 40, 1120 (1975).

(3) J. H. Looker and L. W. Wilson, *J. Heterocyclic Chem.*, 2, 348 (1965).

(4) G. L'abbe', G. Verhelst, L. Huybrechts, and S. Toppet, *ibid.*, 14, 515 (1977).

(5a) J. R. Bartels-Keith, M. T. Burgess, and J. M. Stevenson, *J. Org. Chem.*, 42, 3725 (1977); (b) H. P. Braun and H. Meier, *Tetrahedron*, 31, 637 (1975).

(6) S. I. Ramsby, S. Ö. Green, S. B. Ross, and N. E. Stjernström, *Acta. Pharm. Suec.*, 10, 285 (1973).

(7) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N. Y., 1972, pp. 253-254.

(8) C. D. Hurd and R. I. Mori, *J. Am. Chem. Soc.*, 77, 5359 (1955).

(9) T. F. Page, T. Alger, and D. M. Grant, *ibid.*, 87, 5333 (1965).

(10) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", John Wiley & Sons, New York, N. Y., 1972, p. 81.

(11) Ref. 7, p. 184.

(12) I. W. J. Still, N. Plavac, D. M. McKinnon, and M. S. Chauhan, *Can. J. Chem.*, 54, 1660 (1976); *cf.* this paper for references to studies by R. Faure and co-workers with sulfur heterocycles.

(13) D. L. Pain and R. Slack, *J. Chem. Soc.*, 5166 (1965).

(14) R. Raap and R. G. Micetich, *Can. J. Chem.*, 46, 1057 (1968).

(15) Ref. 10, p. 104.

(16) P. C. Lauterbur, *J. Am. Chem. Soc.*, 83, 1838 (1961); K. Tori and T. Nakagawa, *J. Phys. Chem.*, 68, 3163 (1964); F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, 89, 2967 (1967).

(17) O. A. Gansow and W. Schittenhelm, *ibid.*, 93, 4294 (1971).