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Proton Magnetic Resonance Spectra of Thiazoles

Chemical Shifts and Substituent Effects

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The proton magnetic resonance spectra of twelve 2-substituted, four 4-substituted and nine 5-substituted thiazoles have been recorded at 60 Mc/s. The values of the chemical shifts and the coupling constants of these compounds in different solvents are reported. The effects of substituents on the chemical shifts of the ring-hydrogens are similar to those in the corresponding thiophenes, except for the 4-hydrogen shifts in $+M$ 2-substituted thiazoles, which are twice as large as the 4-hydrogen shifts of the corresponding 2-substituted thiophenes.

It has been shown that linear relations exist between the 3- and 5-hydrogen shifts in 2-substituted thiophenes and the corresponding shifts in 2-substituted furans.[1] The proportionality constants indicate much less effective transmission of the substituent effects in furans. On the other hand, a quantitative correlation between the *ortho*, *meta*, and *para* hydrogen shifts of monosubstituted benzenes and the 3-, 4-, and 5-hydrogen shifts of the corresponding 2-substituted thiophenes was not observed.[2] A consequence of the non-proportionality of the thiophenic and benzenic shifts is that the Hammett values cannot in general be used in the thiophene series (*cf.* Ref. 3). In the benzene series, however, proportionality between the *para* hydrogen shifts and the σ values of the substituents has been demonstrated.[4]

Interesting differences between the shifts of the substituted π-excessive five-membered heterocycles and the six-membered strongly π-deficient pyrimidines were also observed.[5] Especially sulphur-containing substituents caused anomalous shifts in the pyrimidines.[5]

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It was therefore of interest to study the chemical shifts of substituted thiazoles, which in geometry are similar to furan and thiophene, but which are much less π-excessive. Also our earlier NMR studies on the structures of dimeric 2-thiazolones,[6] dimeric 2-aminothiazole,[7] and 2-phenyl-4-thiazolone and related compounds [8] induced us to investigate more closely the chemical shifts of the various hydrogen atoms in substituted thiazoles. The NMR spectra of a number of thiazoles substituted in the 2-, 4-, and 5-positions were therefore recorded.

RESULTS

It would have been desirable to obtain the shifts of the substituted thiazoles in cyclohexane at infinite dilution in order to make the results strictly comparable with those obtained for benzenes, thiophenes, and furans. However,

Table 1. Chemical shifts (τ-values) and coupling constants (c/s) of thiazoles.

Solvent	Acetone				Cyclohexane			
Substituent	H_2	H_4	H_5	J	H_2	H_4	H_5	J
H	1.00	2.07	2.35	$J_{45} = 3.2$ $J_{25} = 2.1$	1.30	2.16	2.78	$J_{25} = 2.0, J_{45} = 3.0$
2-CHO		1.93	2.04	$J_{45} = 2.8$ $J_{CHO-5} = 1.3$		2.25	2.68	$J_{25} = 1.3, J_{45} = 3.1$
4-CHO	0.76		1.41	$J_{25} = 1.87$				
5-CHO	0.70	1.35		$J_{CHO-2} = 1.0$	0.92	1.47		$J_{CHO-2} = 0.9$
2-COOH		2.03	2.03					
4-COOH	0.79		1.40					
5-COOH	0.74	1.52						
2-$CO_2C_2H_5$		1.99	2.07	$J_{45} = 3.1$		2.11	2.44	$J_{45} = 3.06$
4-$CO_2C_2H_5$	0.93		1.57	$J_{25} = 2.5$	1.19		1.85	
5-CO_2CH_3	0.72	1.52			1.25	1.63		
2-NO_2		1.85	2.07	$J_{45} = 3.6$				
5-NO_2	0.67	1.24		$J_{24} = 0.75$				
2-Br		2.36	2.36			2.56	2.89	
5-Br	0.95	2.11			1.46	2.35		
2-Cl		2.38	2.38			2.58	2.92	
2-SC_2H_5		2.31	2.51	$J_{45} = 3.3$		2.48	3.00	$J_{45} = 3.4$
5-SC_2H_5	0.92	2.12			1.30	2.25		
2-$SO_2C_2H_5$		1.85	1.85					
5-$SO_2C_2H_5$	0.58	1.55						
2-CH_3		2.37	2.64	$J_{45} = 3.2$		2.53	3.08	$J_{45} = 3.3$
4-CH_3	1.15		2.86	$J_{CH_3-5} = 0.9$ $J_{25} = 1.6$	1.50		3.30	$J_{25} = 1.8$, $J_{CH_3-5} = 1.0$
5-CH_3	1.27	2.43		$J_{CH_3-4} = 1.4$	1.56	2.56		
2-CH_2OH		2.24	2.48	$J_{45} = 3.2$				
2-NH_2		3.01	3.47	$J_{45} = 3.7$				
2-OCH_3		2.84	3.10	$J_{45} = 3.6$		3.04	3.54	$J_{45} = 3.7$
5-OCH_3	1.65	2.77			1.93	2.92		
2-CO_2CH_3,4-CH_3			2.48	$J_{CH_3-5} = 0.8$			2.91	$J_{CH_3-5} = 0.8$
2-COOH,4-CH_3			2.48	$J_{CH_3-5} = 0.8$				
2-NH_2,5-Br		3.02						

Table 2. Chemical shifts (τ-values) and coupling constants (c/s) of some thiazoles in dimethyl sulphoxide solution.

Substituent	H_2	H_4	H_5	J
H	0.85	2.03	2.25	$J_{45} = 3.15$, $J_{25} = 1.95$
2-NO_2		1.70	1.93	$J_{45} = 3.5$
5-NO_2	0.58	1.10		$J_{24} = 0.8$
2-CHO		1.76	1.76	
2-COOH		1.90	1.90	
4-COOH	0.76		1.44	$J_{25} = 2.35$
5-COOH	0.65	1.42		$J_{24} = 0.5$
2-CH_2OH		2.35	2.46	
2-$CO_2C_2H_5$		2.18	2.18	
2-CO_2CH_3, 4-CH_3			2.26	$J_{CH_3-5} = 0.8$

as was the case with the pyrimidines, the low solubilities of many thiazoles precluded this, so chemical shifts were in most cases determined in dilute acetone solution (5—10 %), and where possible, in cyclohexane solution. A few compounds were also measured in dimethyl sulphoxide.

The shifts and coupling constants of thiazole and of 2- and 4-methylthiazole have been reported before,[9] but these data are not strictly comparable with our results as they were obtained with the neat liquids, water serving as external standard. The shifts obtained are given in Tables 1 and 2. It is obvious that the solvents influence the resonance positions of the thiazolic hydrogens. Especially the 2- and 5-hydrogen resonances are shifted towards lower field in the more polar solvents.

The monosubstituted thiazoles show very simple spectra, mostly two doublets, except in those cases when additional long-range couplings to methyl or formyl side-chain hydrogens are observed.

The large difference between the 2-hydrogen shift on the one hand and the 4- and 5-hydrogen shift on the other in thiazole makes the assignment very easy in 4- and 5-substituted thiazoles. In 2-substituted thiazoles the broader doublet lines are assigned to the 4-hydrogen resonance. The broadening is caused by its coupling to the nitrogen nuclei and the fairly rapid quadrupole relaxation of the nitrogen nuclei.[10] Similar broadening was earlier observed for the 4- and 6-hydrogen bands in 2-substituted pyrimidines.[5] The coupling constant J_{45} falls between 2.8—3.7 c/s and J_{25} between 1.6—2.5 c/s; J_{24} is in most cases too small to be resolved except in 5-nitrothiazole and 5-thiazolecarboxylic acid, where it was found to be 0.8 c/s and 0.5 c/s, respectively.

The long-range couplings show similar patterns as in thiophenes and furans.[1,11] In 4-methylthiazole and 4-methyl-2-thiazolecarboxylic acid and its ester, coupling to the 5-hydrogen has a value of 0.8—0.9 c/s. In 5-methylthiazole the long-range coupling to the 4-hydrogen is 1.4 c/s.

In 2-thiazolealdehyde, the formyl hydrogen shows long-range coupling to the 5-hydrogen and a similar coupling to the 2-hydrogen is observed in 5-thiazolealdehyde. No longe-range coupling was observed in 4-thiazolealdehyde where, by analogy with 3-thiophenealdehyde,[11] a coupling to the 2-hydrogen could have been expected.

Table 3. Chemical shifts (ppm) of substituted thiazoles relative to the shifts of the 2-, 4- and 5-hydrogens of unsubstituted thiazole in dilute acetone solution.

	2-substituted thiazoles		4-substituted thiazoles		5-substituted thiazoles	
Substituent	δ_4	δ_5	δ_2	δ_5	δ_2	δ_5
$SO_2C_2H_5$	−0.22	−0.50			−0.42	−0.52
CHO	−0.14	−0.31	−0.24	−0.94	−0.30	−0.72
COOH	−0.04	−0.32	−0.21	−0.95	−0.26	−0.55
$COOC_2H_5$	−0.08	−0.28	−0.07	−0.78		
$COOCH_3$					−0.28	−0.55
NO_2	−0.22	−0.28			−0.33	−0.83
Br	+0.29	+0.01			−0.05	+0.04
Cl	+0.31	+0.03				
CH_3	+0.30	+0.29	+0.15	+0.51	+0.27	+0.36
NH_2	+0.94	+1.12				
OCH_3	+0.77	+0.75			+0.65	+0.70
CH_2OH	+0.17	+0.13				
SC_2H_5	+0.24	+0.16			−0.08	+0.05

DISCUSSION

In Table 3, the chemical shifts of the substituted thiazoles relative to the hydrogens of unsubstituted thiazole are given. As in the aromatic compounds

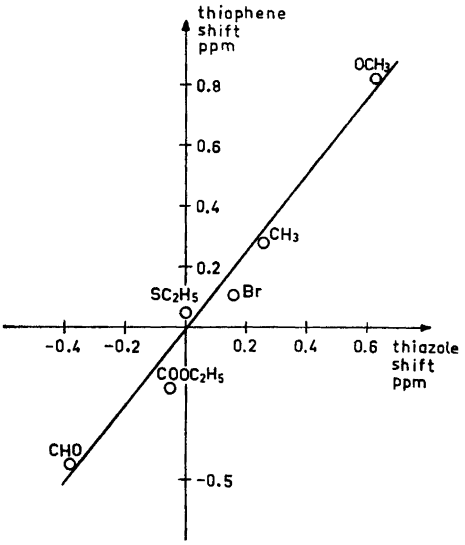

Fig. 1. Plot of the relative shifts of the 5-hydrogens in 2-substituted thiophenes *vs.* the 2-hydrogen shifts in 5-substituted thiazoles in cyclohexane solution.

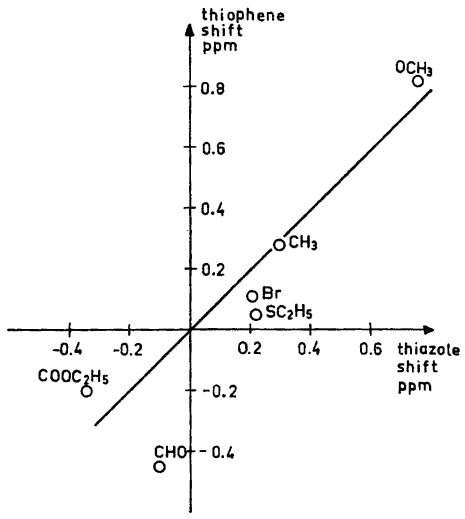

Fig. 2. Plot of the relative shifts of the 5-hydrogens in 2-substituted thiophenes *vs.* the 5-hydrogen shifts in 2-substituted thiazoles in cyclohexane solution.

studied earlier $-I$, $-M$ substituents cause shifts towards lower field while the stronger $+M$ substituents shift up-field, the shifts following the known mesomeric order.

Alkylthio groups cause similar shifts as in furans and thiophenes and do not show the deviations noted in the pyrimidine series.[5] The 5-shifts in 2-substituted thiophenes are similar to the 2-shifts in 5-substituted thiazoles (Fig. 1) and the 5-shifts in 2-substituted thiazoles (Fig. 2), and follow approximately the relation $\delta_{\text{thiophene}} = \delta_{\text{thiazole}}$, although deviations are noticed for some substituents (*cf.* 5-hydrogen shifts in 2-thiophenealdehyde and 2-thiazolealdehyde).

Similarly, the 3-shifts in 2-substituted thiophenes and the 4-shifts in 5-substituted thiazoles are of the same magnitude (Fig. 3). On the other hand, there are large deviations between the 2-shifts in 3-substituted thiophenes and the 4-shifts in the 5-substituted thiazoles.

Too few data are available for a comparison of the 5-shifts in 4-substituted thiazoles with the corresponding 2-shifts in 3-substituted thiophenes. However, in the few compounds studied, these shifts are very similar.

Comparing the "meta"-shifts, *e.g.* the 4-shifts in 2-substituted thiazoles, with the 4-shifts in 2-substituted thiophenes, it is seen that these are always larger in $-I$, $+M$ substituted thiazoles, leading to the relation δ_4 (thiophene)= $0.5 \times \delta_4$ (thiazole) (Fig. 4). The reason for this could be the following. We

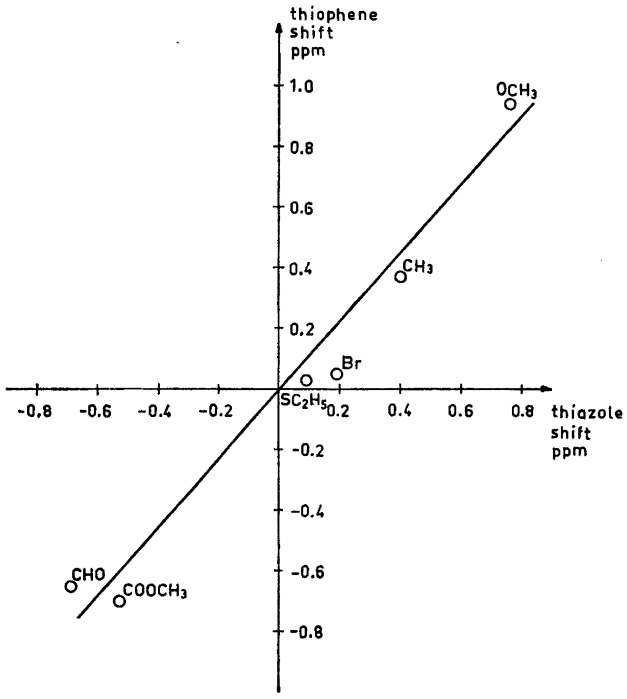

Fig. 3. Plot of the relative shifts of the 3-hydrogens in 2-substituted thiophenes *vs.* the 4-hydrogen shifts in 5-substituted thiazoles in cyclohexane solution.

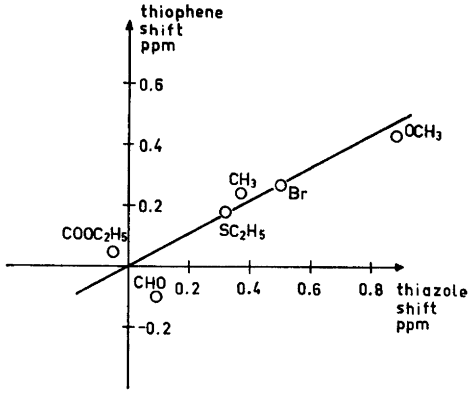

Fig. 4. Plot of the relative shifts of the 4-hydrogens in 2-substituted thiophenes *vs.* the 4-hydrogen shifts in 2-substituted thiazoles in cyclohexane solution.

have earlier explained the up-field shift of the 4-hydrogens in $+M$ 2-substituted thiophenes by assuming that a portion of the charge located on the 3- and 5-positions (as illustrated by resonance formulas I and II) is inductively relayed to the 4-position.[2]

I *II* *III* *IV*

Now due to electronegativity differences between nitrogen and carbon, resonance structure III in the thiazole system is of greater weight than the corresponding structure I and a greater relay of charge to the 4-position can thus be expected in the 2-substituted thiazoles. As in the pyrimidines, $-I$, $-M$ substituents appear to cause larger down-field shifts of the *meta* hydrogens in 2-substituted thiazoles than in the thiophenes.

Table 4. Chemical shifts (ppm) of substituted thiazoles relative to the shifts of the 2-, 4-, and 5-hydrogens of unsubstituted thiazole in dilute cyclohexane solution.

	2-substituted thiazoles		4-substituted thiazoles		5-substituted thiazoles	
Substituent	δ_4	δ_5	δ_2	δ_5	δ_2	δ_4
CHO	+0.09	−0.10			−0.38	−0.69
$COOC_2H_5$	−0.05	−0.34	−0.11	−0.93		
$COOCH_3$					−0.05	−0.53
Br	+0.50	+0.21			+0.16	+0.19
Cl	+0.42	+0.14				
CH_3	+0.37	+0.30	+0.20	+0.52	+0.26	+0.40
OCH_3	+0.88	+0.76			+0.63	+0.76
SC_2H_5	+0.32	+0.22			+0.00	+0.09

It is interesting to note that in all the solvents investigated, the 4- and 5-hydrogen resonances of 2-thiazolecarboxylic acid coincide. This could possibly indicate rapid tautomerism between the "normal" and zwitterionic structure of 2-thiazolecarboxylic acid. The latter structure is assumed to be responsible for the rapid decarboxylation of this acid. However, the similar shift of the acid and ester speaks against it.

EXPERIMENTAL

The NMR spectra were obtained on a Varian Associates DP-60 model V-4302 NMR spectrometer operating at 60 Mc/s and a 12″ Varian magnet V-4012A, equipped with integrator and background stabilizer. The magnet sweep was calibrated using the modulation side-band technique. The variable frequency was obtained from a Hewlett Packard wide range oscillator model 200CD and measured with a Beckman Model 6146 Universal EPUT timer. The accuracy of the shift values given in Tables 1—3 is better than ±0.04 ppm and the coupling constants is better than ±0.2 c/s.

Materials. Commercial *2-aminothiazole* (Fluka) was recrystallized from ethanol, m.p. 90—92°. The following compounds were prepared according to procedures described in the literature: *thiazole*,[12] b.p. 115°; *2-amino-5-bromothiazole*,[13,14] m.p. 90°; *2-bromothiazole*,[15] b.p. 54°/9 mm; *5-bromothiazole*,[14] b.p. 45—47°/7 mm; *2-chlorothiazole*,[15] b.p. 144—146°; *2-ethylthiothiazole*,[16] b.p. 86°/12 mm; *2-methoxythiazole*,[17] b.p. 148—150°; *2-methylthiazole*,[18] b.p. 127—130°; *4-methylthiazole*,[15] b.p. 129—130°; *5-methylthiazole*,[18] b.p. 55°/30 mm; *4-methyl-2-thiazolecarboxylic acid*,[19] m.p. 95° (decomp.); *methyl 4-methyl-2-thiazolecarboxylate*,[19] m.p. 65°; *2-nitrothiazole*,[20] m.p. 77—78°; *5-nitrothiazole*,[21] m.p. 63—65°; *4-thiazolealdehyde*,[22] b.p. 98—102°/17 mm; *2-thiazolecarboxylic acid*,[14,23] m.p. 95° (this acid decarboxylated very easily in solution, which could be followed in the NMR spectrum); *ethyl 2-thiazolecarboxylate*,[23] b.p. 128°/19 mm; *4-thiazolecarboxylic acid*,[24] m.p. 197°; *ethyl 4-thiazolecarboxylate*,[22] m.p. 46°; *5-thiazolecarboxylic* acid,[14] m.p. 199° (decomp.); *methyl 5-thiazolecarboxylate*,[22] b.p. 87—90°/10 mm.

Ethyl 2-thiazolyl sulphone. To 3.6 g (0.025 mole) of 2-ethylthiothiazole in 50 ml of acetic acid was added dropwise 12.5 ml of 30 % hydrogen peroxide and the solution heated at 100° for 90 min. It was then poured onto ice, made alkaline with conc. sodium hydroxide solution and extracted four times with ether, the extracts being combined. The ethereal solution was fried over magnesium sulphate and distilled, yielding 0.75 g (17 %) of ethyl 2-thiazolyl sulphone, b.p. 114—119°/0.05 mm. (Found: C 34.11; H 4.46; N 8.07; S 35.76. Calc. for $C_5H_7NO_2S_2$: C 33.88; H 3.99; N 7.90; S 36.17). No attempts were made to increase the yield in this and the two following experiments as enough material for running the NMR spectra was obtained.

5-Ethylthiothiazole. To a solution prepared from 1.2 g of sodium and 40 ml of methanol was added dropwise 3.1 g of ethyl mercaptan dissolved in 10 ml of methanol. A solution of 8.2 g of 5-bromothiazole in 20 ml of methanol was added dropwise to this solution and the mixture refluxed for 4 h. After filtration, an equal volume of water was added to the filtrate, which was then extracted four times with ether. The dried ether extract was fractionated *in vacuo* yielding 1.0 g (14 %) of 5-ethylthiothiazole, b.p. 93°/14 mm. (Found: C 40.84; H 4.90; N 9.62; S 44.07. Calc. for $C_5H_7NS_2$; C 41.34; H 4.86; N 9.64; S 44.14). In some experiments, 2-ethylthiothiazole could be detected by gas chromatography and NMR spectroscopy in the product, although no 2-bromothiazole could be detected in the gas chromatogram or in the NMR spectrum of the starting material.

Ethyl 5-thiazolyl sulphone, b.p. 116—120°/0.1 mm, was obtained in 5 % yield when 5-ethylthiothiazole was treated with hydrogen peroxide as described above for the 2-isomer. A satisfactory elemental analysis could not be obtained for this compound.

5-Methoxythiazole. To a solution prepared from 6.0 g of sodium and 75 ml of anhydrous methanol was added 0.01 g of potassium iodide, 3.73 g of cupric oxide and 15.1 g of 5-bromothiazole and the mixture refluxed for 5 h. After filtration, an equal volume of water was added to the filtrate, and the aqueous phase extracted with ether. The ethereal solution was washed with water, dried over magnesium sulphate and fractionated *in vacuo* to give 7.1 g (70 %) of 5-methoxythiazole, b.p. 65—68°/12 mm.

2-Thiazolealdehyde was prepared in a new way through reaction of 2-thiazolyllithium with N-methylformanilide: A solution of 20.2 g (0.12 mole) of 2-bromothiazole in 100 ml of anhydrous ether at −70°C was treated with 213 ml of 0.75 N butyllithium cooled to −70°C, the latter being pressed over with nitrogen. After stirring under nitrogen for additional 10 min at −70°C, the solution was pressed over with nitrogen into a solution of 18.4 g (0.14 mole) of N-methylformanilide in 100 ml of anhydrous ether. The mixture was stirred for 3 h at room temperature and allowed to stand overnight. The reaction mixture was hydrolyzed with 150 ml of 1 N hydrochloric acid, the aqueous layer extracted several times with chloroform and the combined organic layers washed with bicarbonate solution, dried and fractionated, yielding 6.2 g (46 %) of 2-thiazolealdehyde, b.p. 64–70°C/10 mm (lit.[25] b.p. 36–37°/3 mm). Acidic work-up was necessary as otherwise the corresponding alcohol was obtained.

2-Hydroxymethylthiazole. When the hydrolysis in the preceding experiment was carried out with water, this alcohol was isolated in 10 % yield from the chloroform extract. M.p. 68° after recrystallization from ether. (Found: C 41.95; H 4.72; N 12.46; S 27.79. Calc. for C_4H_5NOS: C 41.70; H 4.35; N 12.17; S 27.82).

5-Thiazolealdehyde, b.p. 90°/18 mm (lit.[22] b.p. 92–94°/16 mm) was obtained in 5 % yield from 5-bromothiazole, butyllithium, and N-methylformanilide in the same way as described for the 2-aldehyde. The low yield may be due to the great instability of 5-thiazolyllithium.

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