Proton and Carbon-13 Nuclear Magnetic Resonance Studies of Conformations of 1,3-Dipyridylthioureas

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Studies of ^{1}H and ^{13}C chemical shifts and of ^{1}H–^{1}H, ^{13}C–^{1}H coupling constants of 1,3-di-(2-pyridyl)-thiourea and its substituted derivatives indicate the occurrence of topomerisation between two internally hydrogen-bonded conformers, with a $Z,E \rightleftharpoons E,Z$ interconversion barrier of *ca.* 55.0 kJ mol^{-1}.

1,3-Disubstituted thioureas in solution exist as an equilibrium mixture of three conformational isomers (Figure 1). No evidence has been reported for the existence of the *E,E*-isomer.[1] The *E,Z*- and *Z,E*-isomers are equivalent if the substituents are identical. Reports of many ^{1}H and ^{13}C dynamic n.m.r. studies of alkylated thioureas have been published.[2–15] The spectroscopic results have been supported by total energy calculations on 1,3-dimethylthiourea.[16] Studies on arylthioureas are few.[9–12] In this work we examine both ^{1}H and ^{13}C n.m.r. spectra of 1,3-di-(2-pyridyl)thiourea (**1**) and its substituted derivatives (**2**)—(**6**).

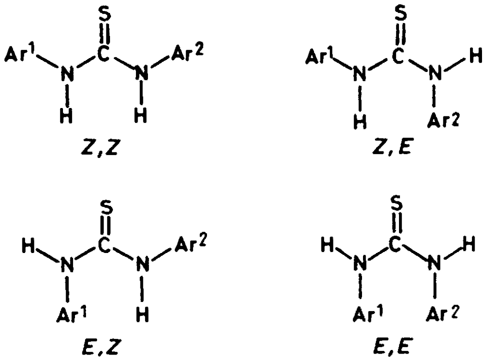

Figure 1. Conformational isomers of 1,3-disubstituted thioureas

$\mathrm{Ar^{1}NHCSNHAr^{2}}$

(**1**) Ar^{1} = Ar^{2} = 2-pyridyl
(**2**) Ar^{1} = Ar^{2} = 4-methyl-2-pyridyl
(**3**) Ar^{1} = 2-pyridyl, Ar^{2} = 3-methyl-2-pyridyl
(**4**) Ar^{1} = 2-pyridyl, Ar^{2} = 4-methyl-2-pyridyl
(**5**) Ar^{1} = 2-pyridyl, Ar^{2} = 5-methyl-2-pyridyl
(**6**) Ar^{1} = 2-pyridyl, Ar^{2} = 6-methyl-2-pyridyl

Results and Discussion

The ^{1}H n.m.r. spectra of compounds (**1**)—(**6**) at ambient temperature were complex, but at sub-ambient temperatures were clearly resolved. The ^{1}H chemical shifts for solutions in $\mathrm{CDCl_3}$ are assembled in Table 1. The spectra of (**1**) and (**2**) show two N*H* signals, at δ *ca.* 9.5 and 14.5, whereas those of (**3**)—(**6**) display four signals in this region. Variations of temperature and concentration had little effect on the extreme low-field signal, suggesting the presence of strong internal hydrogen bonding.[17–19] Dreiding models show that the *E,Z*- (or *Z,E*-) isomer possesses ideal geometry for the formation of a strong intramolecular $\mathrm{N{-}H \text{ - - - } N_{py}}$ hydrogen bond. Also, the signal at δ *ca.* 14.5 appeared consistently in the temperature range (310—210 K) investigated. Further, the spectra of (**1**)—(**6**) exhibit distinct signals of equal intensity for the pyridyl group in the two orientations. The results can be interpreted by assuming that the amidic N–H proton bonds to the basic pyridine nitrogen in the *E,Z*- (or *Z,E*-) form. The results also indicate an interesting topomerisation process between two intramolecularly hydrogen-bonded conformers which is fast at ambient temperature and slow at lower temperatures (see Figure 2). Concerted rotation in a disrotary fashion about the two amide $\mathrm{C} \overset{\text{---}}{=} \mathrm{N}$ bonds is the probable mechanism for the dynamic exchange. The thermodynamic stability of the hydrogen-bonded isomer confers conformational stability on the system.

The data recorded in Table 1 are consistent with the foregoing inference. The presence of $\mathrm{N{-}H \text{ - - } N_{py}}$ hydrogen bonding demands that the pyridyl ring in the *E*-form be coplanar with the thioureide plane, thereby increasing conjugative interaction with the amide nitrogen lone pair and causing the pyridyl ring protons to resonate at relatively higher fields. This structure also accounts for the extreme low-field shift of the 3-H of the pyridyl group in the *Z*-form (δ 8.6—8.88); this is due to the anisotropic deshielding effect of the C=S moiety. In contrast, the chemical shift of the 3-H of the pyridyl in the *E*-form group is similar to that of the corresponding proton in simple 2-substituted pyridines (δ 6.5—7.0).[20]

The analyses of the chemical shifts and the coupling constants of the 2-pyridyl group were carried out by using LAOCOON I and LAOCOON II programs[21] with a DEC 1090 computer. The program in its first part computes the spectrum from guessed values of chemical shifts and spin–spin coupling constants. In the second part, the parameters are derived iteratively such that a best fit between calculated and observed line positions is obtained. Similar analyses of ^{1}H n.m.r. spectra of several 2-substituted pyridines have been reported.[22–24] The initial coupling constants for the four-spin pyridine system were obtained from ref. 22. The proton spin–spin coupling constants for (**1**) and (**2**) are shown in Table 2. The spectra of the heterogeneously substituted thioureas (**3**)—(**6**) are too complicated for the coupling constants to be obtained. The signals of H-6 appear at lower field than those of H-4 and H-5 owing to the magnetic anisotropy of the ring nitrogen atom. The observed chemical shifts and coupling constants are similar to those in *N*-(2-pyridyl)thioacetamide,[25] which exists in a stable *Z*-conformation and the parameters of which are quoted in Tables 1 and 2 for comparison.

The ^{13}C n.m.r. spectra of compounds (**1**)—(**6**) at ambient temperature are complex as a result of exchange broadening. At lower temperatures (below 233 K), the individual carbon resonances of the pyridyl and methylpyridyl rings in the *E*- and *Z*-orientations are separated. The assignment of the carbon resonance lines is based on comparison of the signal patterns observed with complete proton decoupling with those obtained in the proton-coupled spectra measured by use of gated de-

Table 1. ^{1}H Chemical shifts (δ) for solutions in CDCl$_3$^{a}

		(Pyridyl)$_Z$				(Pyridyl)$_E$							
Compd.	T/K	H-3	H-4	H-5	H-6	H-3	H-4	H-5	H-6	(CH$_3$)$_Z$	(CH$_3$)$_E$	(NH)$_Z$	(NH)$_E$
(1)	213	8.84	7.86	7.21	8.51	7.06	7.73	7.07	8.37			9.78	14.56
	293		7.70	7.08	8.40		7.70	7.08	8.40			8.96	14.29
(2)	213	8.58		7.00	8.32	6.67		6.86	8.22	2.44	2.37	9.73	14.39
	273											9.02	14.22
(3)	233	8.82	7.82	7.19	8.50	7.05	7.72	7.07	8.37			10.56	14.76
			7.49	7.28	8.46		7.70	7.06	8.12	2.45	2.32	8.33	14.58
(4)	233	8.80	7.85	7.21	8.48	7.05	7.75	7.09	8.32			10.03	14.73
		8.58		7.01	8.35	6.62		6.86	8.22	2.37	2.28	9.90	14.66
(5)	233	8.79	7.86	7.25	8.49	7.05	7.75	7.12	8.30			10.25	14.75
		8.61	7.63		8.32	6.94	7.52		8.16	2.37	2.31	8.73	14.10
(6)	233	8.83	7.82	7.20	8.51	7.06	7.72	7.09	8.32			10.42	14.78
		8.53	7.72	7.04		6.78	7.59	6.89		2.60	2.50	9.12	14.09
NPTA	293	8.79	7.82	7.20	9.08							10.89	

[a] For **(3)**—**(6)**, the values for the 2-pyridyl group are listed first, followed by those for methylpyridyl; NPTA = *N*-(2-pyridyl)thioacetamide.[25]

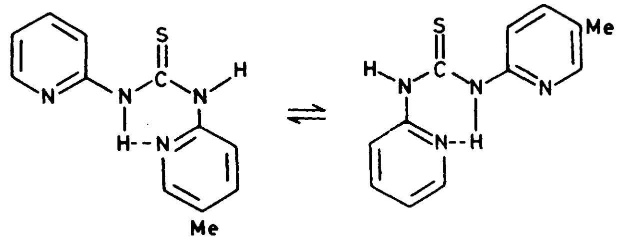

Figure 2. Interconverting forms of 1,3-dipyridylthioureas [shown for **(5)**]

Table 2. Proton coupling constants (J_{HH}/Hz)

Compound	Solvent	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
(1)	CDCl$_3$	8.61	0.32	0.25	7.22	1.94	5.12
NPTA	CDCl$_3$	8.51	0.45	0.50	7.45	1.42	5.06
(2)	CDCl$_3$		0.38	0.0			5.32 (*cis*)
			0.40	0.0			5.33 (*trans*)

coupling. Analysis of the fine splittings observed for methylpyridines also helps in this endeavour. The C-5 signal appears as an unsymmetric triplet instead of a quartet as a result of its coupling with H-3 (^3J) and H-6 (^2J); the coupling constants are nearly of equal magnitude. The proton-coupled spectra were analysed on a first-order basis; the absolute values of the direct coupling ($^1J_{CH}$) were determined. The long-range ^{13}C–^{1}H coupling constants (^2J, ^3J) were calculated by the procedure of Takeuchi.[26] For this purpose, the low-temperature spectra of **(1)** and **(2)** in CDCl$_3$ were utilized. The ^{13}C–^{1}H coupling constants were not obtained for the unsymmetrical thioureas since the spectra were very complicated.

The ^{13}C chemical shifts and their assignments are shown in Table 3. The chemical shifts for the pyridyl (or methylpyridyl) group in the *E*-form occur upfield relative to the analogous ones for the ring in the *Z*-orientation as a result of increased mesomeric interaction of the thioureide nitrogen lone pair with the pyridyl (or methylpyridyl) group consequent on the formation of an intramolecular hydrogen bond. The assignments of the chemical shifts for the 2-pyridyl and methylpyridyl methyl carbon atoms are compatible with the values reported for substituted pyridines.[26,27]

The values of the direct and long-range ^{13}C–^{1}H coupling constants are reported in Table 4. Excessive overlapping occurs for all the coupling constants not listed. The magnitudes of the coupling constants are compatible with the values reported for methylpyridines by Takeuchi.[26] The value of ^3J(C-2,H-6) is relatively high, indicating the influence of the nitrogen lone pair on the coupling constant. The coupling constants over one bond are all similar and in the range 160—180 Hz for the pyridyl ring carbon atoms. The observed chemical shifts and coupling constants for the pyridyl groups in the *Z*-form are similar to those for *N*-(2-pyridyl)thioacetamide, which has a stable *Z*-conformation;[25] the parameters for the latter are quoted in Tables 3 and 4 for comparison.

The interconversion barriers for **(1)** and **(2)** were obtained from variable-temperature n.m.r. data. Rate constants at the coalescence temperature were obtained by using the conventional relationship $k_c = \pi \Delta\nu/\sqrt{2}$ ($\Delta\nu$ denotes the maximum separation of the signals), applied under favourable conditions since the natural linewidths are small and the two isomers are present in a (nearly) 1:1 ratio. The free energy of activation at the coalescence temperature[28,29] ($\Delta G_{T_c}^{\ddagger}$) was calculated from the Eyring equation in which the transmission coefficient was set at ½. The frequency difference ($\Delta\nu$) between the two exchanging sites is large, particularly in ^{13}C n.m.r., as a result of which the coalescence temperatures are fairly high. The $\Delta G^{\ddagger}$ values at the coalescence temperature (T_c) determined for **(1)** and **(2)**, together with all the pertinent data, are listed in Table 5. The errors in $\Delta G^{\ddagger}$ are less than 0.5 kJ mol^{-1} in any one method. There are many factors which account for the differences in $\Delta G^{\ddagger}$ values determined by ^{1}H and ^{13}C n.m.r. spectra. The coalescence temperatures for **(3)**—**(6)** could not be determined confidently since the spectra were highly complicated. The free energy barrier to internal rotation for 1,3-dimethylthiourea[9,15] determined by the coalescence method is 47.7 kJ mol^{-1}. In contrast to 1,3-dialkylated thioureas, the pyridyl groups of 1,3-dipyridylthioureas compete with the amide nitrogen lone pair (cross-conjugation). The stabilization by internal hydrogen bonding however is the chief factor promoting the increase in the barrier in 1,3-dipyridylthioureas.

Table 3. ^{13}C Chemical shifts (δ) for solutions in $CDCl_3$[a]

Compd.	T/K	(Pyridyl)$_Z$ C-2	C-3	C-4	C-5	C-6	(Pyridyl)$_E$ C-2	C-3	C-4	C-5	C-6	$(CH_3)_Z$	$(CH_3)_E$	C=S
(**1**)	213	152.8	117.3	139.0	120.9	148.3	151.9	112.7	137.7	118.7	145.8			176.9
	293	152.7	112.5	138.4	118.6	146.9	152.7	112.5	138.4	118.6	146.9			177.2
(**2**)	213	152.9	117.6	148.5	122.1	150.7	152.0	112.6	147.9	120.2	149.4	21.5	21.8	180.0
	293	159.8	108.6	147.3	114.0	147.8	159.8	108.6	147.3	114.0	147.8			180.4
(**3**)	233	153.1	117.1	138.9	123.3	148.2	152.8	112.8	137.7	120.8	145.7			176.8
		151.1	131.3		119.5	146.6	150.3	123.9	139.8	118.6	143.6	16.7	14.3	177.2
(**4**)	233	152.9	118.1	137.6	120.8	148.2	152.0	112.8	135.9	118.6	145.2			177.0
		155.2	117.6	148.5	121.9	150.4	153.2	112.9	145.6	119.9	149.0	21.6	21.3	176.9
(**5**)	233	153.0	117.1	137.6	123.8	148.5	150.0	112.8	136.7	119.6	145.1			177.2
		154.1	116.6	139.6	129.8	148.0	151.4	112.9	137.8	127.5	144.8	18.8	17.7	176.9
(**6**)	233	153.1	117.5	137.6	121.8	148.2	153.0	112.8	136.7	119.6	145.2			177.2
		152.2	114.5	139.1	120.4	157.4	151.4	109.4	137.9	118.1	155.5	24.2	23.8	176.9
NPTA	293	152.3	116.4	137.5	121.4	148.2								

[a] As Table 1.

Table 4. Direct and long-range $^{13}C-^{1}H$ coupling constants (Hz)

	(**1**)	NPTA	(**2**)
^1J(C-3,H-3)	167.18	169.36	108.63
^1J(C-4,H-4)	163.03	164.14	
^1J(C-5,H-5)	164.53	166.06	162.49
^1J(C-6,H-6)	180.45	179.67	173.70
^3J(C-2,H-4)	9.03	9.35	
^3J(C-2,H-6)	11.50	11.32	12.10
^3J(C-3,H-5)	6.98	6.71	6.05
^3J(C-4,H-6)	6.65	6.10	6.05
^3J(C-5,H-3)	6.98	7.14	9.89
^3J(C-6,H-4)	7.08	7.42	
^3J(C-6,H-5)	3.58	3.85	
^2J(C-5,H-6)		7.69	12.51
^2J(C-6,H-5)			3.30
^3J(C-3,4-CH_3)			4.95
^3J(C-4,4-CH_3)			6.05
^3J(C-5,4-CH_3)			4.95

Table 5. Barriers to interconversion ($\Delta G^{\ddagger}$)

Compd.	Solvent	T_c/K	Δv source	$\frac{\Delta v}{\text{Hz}}$	$\frac{\Delta G^{\ddagger}}{\text{kJ mol}^{-1}}$
(**1**)	$CDCl_3$	268	H-4	34.56	51.0
	$CDCl_3$	283	C-3	309.39	53.6
(**2**)	$CDCl_3$	297	H-5	89.89	59.4
	$CDCl_3$	293	C-3	338.85	55.7

Experimental

Materials.—The dipyridylthioureas (**1**) and (**2**) were prepared according to a known method[30] and recrystallized from ethanol [Found: (**1**) C, 57.65; H, 4.6; N, 24.25. Calc. for $C_{11}H_{10}N_4S$: C, 57.35; H, 4.4; N, 24.35%. Found: (**2**) C, 60.3; H, 5.5; N, 21.8. Calc. for $C_{13}H_{14}N_4S$: C, 60.45; H, 5.45; N, 21.7%.]

Compounds (**3**)—(**6**) were synthesized by the following method. To a mixture of 2-pyridylamine (1 mol) and the appropriate methylpyridine (1 mol) dissolved in absolute ethanol, carbon disulphide (0.15 mol), and NaOH (0.1 mol) were added. The mixture was refluxed for 36 h; H_2S was evolved. The mixture was cooled to room temperature, concentrated, poured into an excess of water, and made acidic with HCl (2N); the precipitated sulphur (if any) was filtered off. The filtrate was neutralized with sodium hydrogen carbonate and extracted with chloroform. The product left after removal of the chloroform was purified by preparative t.l.c. [chloroform–ethyl acetate (4:1 v/v)]: m.p.s (°C) (**1**) 152—154, (**2**) 187—189, (**3**) 168—170, (**4**) 177—179, (**5**) 179—181, (**6**) 174—176 [Found: (**3**) C, 59.05; H, 4.85; N, 23.1. (**4**) C, 59.3; H, 5.0; N, 22.7. (**5**) C, 58.85; H, 4.7; N, 23.25. (**6**) C, 59.2; H, 5.2; N, 22.7. $C_{12}H_{12}N_4S$ requires C, 59.0; H, 4.95; N, 22.95%].

N.m.r. Measurements.—^1H N.m.r. spectra were recorded at 270 MHz with a Bruker WH-270 instrument in the Fourier transform mode (pulse width 15 μs, pulse angle 67°, spectral width 4 000 Hz, acquisition time 30 s, number of pulses 20—30). ^{13}C Spectra were obtained with the same instrument at 67.89 MHz; chemical shifts were obtained under proton-noise-decoupling conditions (typical spectral parameters: spectral width 17 240 Hz, acquisition time 3.0 s, pulse width 15 μs, pulse angle 67°, number of pulses 100—400). All measurements were made relative to internal tetramethylsilane, with $CDCl_3$ as solvent. The spectrometer was fitted with a variable-temperature accessory capable of maintaining temperature to within ±1 K, and was attached to a computer with 20 K memory.

References

1 M. L. Martin, M. L. Filleux-Blanchard, G. J. Martin, and G. A. Webb, *Org. Magn. Reson.*, 1980, **13**, 396.
2 R. H. Sullivan, P. Nix, E. L. Summers, and S. L. Parker, *Org. Magn. Reson.*, 1983, **21**, 293.
3 R. H. Sullivan and E. Price, *Org. Magn. Reson.*, 1975, **7**, 143.
4 W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70**, 517.
5 P. Hanson and D. A. R. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1973, 2162.
6 A. M. Giuliani, *J. Chem. Soc., Dalton Trans.*, 1970, 492, 497.
7 J. S. Hartman and G. S. Schrobilgen, *Can J. Chem.*, 1973, **51**, 99.
8 R. K. Gosavi, U. Agarwala, and C. N. R. Rao, *J. Am. Chem. Soc.*, 1967, **89**, 235.
9 H. Kessler and D. Liebfritz, *Tetrahedron Lett.*, 1970, 1595.
10 M. L. Filleux-Blanchard, *Org. Magn. Reson.*, 1977, **9**, 125.
11 M. L. Filleux-Blanchard and A. Durrand, *Bull. Soc. Chim. Fr.*, 1972, 4710.
12 W. Walter and K. P. Ruess, *Justus Liebigs Ann. Chem.*, 1971, **746**, 54.
13 B. T. Rown and G. F. Katekar, *Tetrahedron Lett.*, 1969, 2343.
14 R. F. Hobson, L. W. Reeves, and K. N. Shaw, *J. Phys. Chem.*, 1973, **77**, 1228.

15 C. D. Freeman and D. L. Hooper, *J. Phys. Chem.*, 1974, **78**, 961.
16 M. V. Andreocci, M. Bossa, G. Ramunni, M. Scazzocchio, D. Gattegno, and A. M. Giuliani, *J. Chem. Soc., Dalton Trans.*, 1974, 41.
17 M. D. Joesten and L. J. Schaad, 'Hydrogen Bonding,' Dekker, New York, 1974, pp. 39—45.
18 B. Brzezinski, *Org. Magn. Reson.*, 1979, **12**, 432.
19 D. B. Davies and A. Rabczenko, *J. Chem. Soc., Perkin Trans. 2*, 1981, 82.
20 D. W. Aksnes and H. Kryvi, *Acta Chem. Scand.*, 1972, **26**, 2255.
21 J. D. Swalen, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1966, **2**, ch. 3.
22 W. Brugel, *Z. Electrochem.*, 1962, **66**, 159.
23 V. J. Kowalewski and D. G. De Kowalewski, *J. Chem. Phys.*, 1962, **37**, 2603.
24 W. B. Smith and J. L. Roark, *J. Phys. Chem.*, 1969, **73**, 1049.
25 L. V. Sudha, S. Manogaran, and D. N. Sathyanarayana, *J. Mol. Struct.*, 1985, **129**, 137.
26 Y. Takeuchi, *Org. Magn. Reson.*, 1975, **7**, 181; *J. Chem. Soc., Perkin Trans. 2*, 1978, 285.
27 L. Stefanaik, *Org. Magn. Reson.*, 1979, **12**, 379.
28 D. K. Dalling, D. M. Grant, and L. R. F. Johnson, *J. Am. Chem. Soc.*, 1971, **93**, 3678.
29 D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 1971, 656.
30 N. P. Buu-Hoi, N. D. Xuong, and N. H. Nans, *J. Chem. Soc.*, 1955, 253.

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