

Carbon-13 NMR Chemical Shifts of Some New N,N-Disubstituted Thioureas of Potential Biological Interest

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Résumé

Les déplacements chimiques par RMN du ^{13}C de quinze nouveaux dérivés de thiourée N,N-bisubstitués sont présentés.

Abstract

The carbon-13 NMR chemical shifts of fifteen new N,N-disubstituted thiourea derivatives of potential biological interest are reported.

Introduction

A large number of N,N-diaryl thioureas were synthesized by Buu-Hoi *et al.* (1,2) and were reported to show tuberculostatic activity and inhibitory properties against influenza virus. A number of thiourea derivatives have also been reported to exhibit marked antituberculous, antibacterial and fungicidal activities (3-6). Recently, the chemical structure and antiviral activity of N,N-diphenyl thioureas was studied through the synthesis and testing of model compounds (6). These findings encouraged us to prepare new disubstituted thioureas for biological activity testing (7).

There is little information in the literature on the effect of substituents on the carbon-13 chemical shift of the thiocarbonyl group, and no carbon-13 chemical shifts have been reported before for substituted thioureas. This paper reports the carbon-13 chemical shifts of a series of new disubstituted thiourea derivatives (Figure 1).

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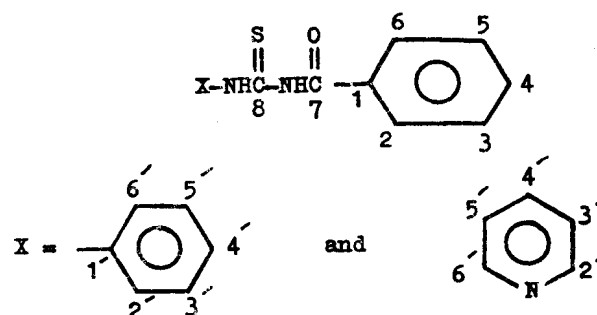


Figure 1. Structure and numbering of carbon atoms of N,N-disubstituted thiourea derivatives. For compounds 1-15, X represents (1) phenyl; (2) *p*-nitrophenyl; (3) *p*-chlorophenyl; (4) *p*-diethylaminophenyl; (5) *p*-methoxyphenyl; (6) *p*-CH₃CONH-phenyl; (7) *o*-methoxyphenyl; (8) *o*-chlorophenyl; (9) *o*-nitrophenyl; (10) 2'-pyridyl; (11) 4-methyl-2-pyridyl; (12) 5'-chloro-2-pyridyl; (13) 6'-methyl-2-pyridyl; (14) 6'-methoxy-3'-pyridyl; (15) 3'-pyridyl.

Experimental

The compounds were synthesized by the reaction of phenyl and benzoyl isothiocyanates with various substituted anilines (7). The IR and NMR spectra and elemental analyses were consistent with the assigned structures.

Carbon-13 NMR Spectra

The samples were prepared in 5-mm NMR tubes in dimethyl sulphoxide-*d*₆ (15-20% w/v). A small amount of TMS was added as an internal standard. The carbon-13 NMR spectra were recorded at ambient temperature on a Varian FT 80 A NMR spectrometer operating at 20 MHz. All spectra were recorded with the following parameters: spectral width, 4 KHz; flip angle, 45°; acquisition time, 1 s; delay time, 3.5 s; number of transients, 3000-9000. The chemical shifts are accurate to ± 0.06 ppm.

Table I. Carbon-13 Chemical Shifts (ppm) of Some New N,N-Disubstituted Thioureas.

Comp.	δ_1	$\delta_2 = \delta_6$	$\delta_3 = \delta_5$	δ_4	δ_7	δ_8	$\delta_{1'}$	$\delta_{2'}$	$\delta_{3'}$	$\delta_{4'}$	$\delta_{5'}$	$\delta_{6'}$
1 Phenyl	133.22	128.78	128.56	132.26	168.40	179.25	138.12	124.41	128.56	126.41	128.56	124.41
2 p-nitro-ph	133.34	128.82	128.53	132.06	168.18	179.37	144.09	124.35	124.03	144.41	124.03	124.35
3 p-Cl-ph	133.19	128.62	128.49	132.14	168.25	179.42	137.03	126.21	128.74	130.33	128.74	126.21
4 p-(NC ₂ H ₅) ₂ -ph	133.03	128.65	128.47	132.30	168.29	178.10	125.93	125.40	111.06	145.93	111.06	125.40
5 p-OCH ₃ -ph	133.13	128.71	128.51	132.25	168.31	179.15	130.80	125.94	114.33	156.81	114.33	125.94
6 p-CH ₃ C(=S)-ph	133.18	128.75	128.51	132.26	168.41	179.01	132.72	124.71	119.26	135.81	119.26	124.71
7 o-OCH ₃ -ph	133.15	128.78	128.46	132.15	168.44	178.03	123.72	155.81	114.16	126.51	120.86	124.51
8 o-Cl-ph	133.32	128.86	128.53	131.98	168.62	180.32	135.41	127.32	128.23	128.39	129.58	131.90
9 o-NO ₂ -ph	133.35	128.88	128.53	132.23	168.34	181.05	131.92	127.84	133.82	129.93	124.94	144.09
10 2-pyridyl	133.14	128.54	128.54	132.44	167.90	177.91		151.27	115.35	138.29	121.08	148.06
11 4-CH ₃ -2-py	133.28	128.73	128.54	132.62	167.75	177.83		151.75	115.66	147.60	122.17	149.51
12 5-Cl-2-py	133.21	128.66	128.46	132.10	168.21	177.98		149.85	116.43	137.72	127.06	146.61
13 6-CH ₃ -2-py	133.12	128.57	128.57	132.85	168.23	177.60		151.09	112.07	138.68	120.32	156.53
14 6-OCH ₃ -3-py	133.13	128.71	128.71	132.12	168.29	180.79		143.36	120.43	136.90	109.99	180.79
15 3-py	133.23	128.74	128.51	132.12	168.21	180.50		146.13	135.14	132.62	123.44	147.00

Table II. Substituents Induced Shifts and Deviations from Additivity Rule Values, $\Delta\delta_{AL}$, (ppm) for compounds 1-14.

Compds	$\delta_{1'}$	$\delta_{2'}$	$\delta_{3'}$	$\delta_{4'}$	$\delta_{5'}$	$\delta_{6'}$
2	5.97 (-1.03)	-0.06 (-1.66)	-4.53 (-1.50)	18.00	-4.53	-0.06
3	-1.09 (0.11)	1.80 (-0.20)	0.18 (-0.98)	3.92	0.18	1.80
4	-12.19 (0.81)	0.99 (0.00)	-17.5 (0.22)	19.52	-17.50	0.99
5	-7.80 (0.48)	1.53 (1.23)	-14.23 (-2.00)	30.40	-14.23	1.53
6	-5.40 (0.00)	0.30 (0.00)	-9.30 (-1.60)	9.40	-9.30	0.30
7	-14.40 (0.39)	31.4 (5.06)	-14.4 (-0.49)	0.10 (1.01)	-7.70 (1.01)	0.10 (-2.21)
8	-2.71 (-2.81)	2.91 (0.91)	-0.33 (-0.02)	1.98 (0.92)	1.02 (0.92)	7.49 (2.59)
9	-6.20 (-1.30)	3.43 (1.83)	5.26 (1.92)	3.52 (1.28)	-3.62 (1.28)	19.68 (0.18)
11	-	0.48 (3.52)	0.31 (0.09)	9.31 (0.43)	1.09 (0.43)	1.45 (1.56)
12	-	-1.42 (0.48)	1.08 (-0.97)	-0.57 (-0.32)	5.98 (-0.32)	-1.45 (-1.80)
13	-	-0.18 (2.58)	-3.28 (0.49)	0.39 (-1.56)	-0.76 (-1.56)	8.47 (-4.04)
14	-	-2.77 (-4.35)	-14.71 (3.39)	4.28 (-0.17)	-13.45 (-0.17)	33.79 (1.28)

Values in parentheses represents deviations from the additivity rule values, $\Delta\delta_{(AL)}$ (Equation 1).

Results and Discussion

The carbon-13 substituent chemical shifts (SCS) for the disubstituted thiourea derivatives, measured in DMSO-d₆ solution, are shown in Table I. Proton coupled and decoupled carbon-13 spectra were recorded. The assignment of the chemical shifts for

compounds 1-15 was based on the following considerations: (a) thiocarbonyl carbon atoms are deshielded relative to carbonyl carbons, (b) the chemical shifts of benzaldehyde, aniline and methyl anilide (9) were used as a guide in the assignment of compounds 1-9, and those of pyridine and substituted amino pyridine (10) in the assignment of compounds 10-15, (c) differentia-

tion between quaternary carbons and proton-bearing carbons was based on the intensity in proton-decoupled spectra; some proton-coupled spectra were also used for this purpose, (d) the substituent induced shift (SIS) of different substituents (11) and the additivity rule were used to calculate chemical shift values for compounds 1-15 which were compared with the observed chemical shifts.

From Table I, it is obvious that the nature of the substituents on X has little effect on the carbon chemical shift of the "COPh" moiety in compounds 1-15. On the other hand, the effect of these substituents on the thiocarbonyl chemical shift is variable. The change in the thiocarbonyl chemical shift in going from compound 1 to 2, then to 5 is quite small, indicating that the electronic effect on the thiocarbonyl chemical shift is quite small. In compounds 14 and 15, where the thiourea moiety is *meta* to the nitrogen atom of the pyridine ring, the thiocarbonyl chemical shifts are 180.79 ppm and 180.50 ppm, respectively. The thiocarbonyl is shifted to high field relative to compound 1 in compounds 10-13, where the nitrogen atom is *ortho* to the thiourea moiety. This change in chemical shift could be due to the fact that the electronic interaction between the thiocarbonyl group and the nitrogen lone pair is minimal in compounds 14 and 15 and increases in compounds 10-13. This change is much larger than that observed for the carbonyl chemical shift in going from pyridine-2-carbaldehyde to pyridine-3-carbaldehyde (10).

The carbon-13 chemical shifts of carbons 1'-6' in compounds 2-9 and 11-15 were calculated using the additivity rule and the SIS of the substituent groups on X with the values of the C-13 chemical shifts of compounds 1 and 10 which were chosen to serve as model compounds. The deviation from the additivity rule $\Delta\delta_{AL}$ (12,13) was calculated from eq. 1 (Table II):

$$\Delta\delta_{AL} = \delta_{exp} - \delta_{calc} \quad (1)$$

This deviation is very small for compounds 2-6 and compound 15. It is larger for compounds 7-9 and 10-14. This deviation is a combination of steric (14,15) and electronic effects (12,16). This conclusion is supported by the fact that in these compounds the change in the thiocarbonyl chemical shift, relative to that of compound 1, ranges from 1.8 ppm in compound 9 to -1.65 ppm in compound 13.

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ity would be a tax on profits remitted out of the country, which could be offset against research done here. While such a scheme might not be fool-proof, it would not be open to the massive abuse of the SRTC. For companies inside Canada, the problem is as much one of bureaucracy as fundamentally new initiatives.

Secondly, we must have an expanding program in basic and applied research in the universities and government laboratories. This is not just the whining of a deprived researcher: *all* the companies quoted in the recent Financial Post survey agree. I am not even requesting more money immediately: for a start the scientific infrastructure is so run down that we would have trouble coping with a massive influx of money. What would allow one to have some hope for the future would be a commitment by the government that support for scientific research would rise at twice the rate of inflation for the next ten years. If such a commitment were in place, the space program would have been paid for without the agony and futility of the present round of NRC cuts.

Thirdly, we need a new idea. A suggestion by Richard Slobodrian, from Laval, is worth considering seriously. A tax of 5¢ a litre on gasoline would raise the price to less than what we were paying a year ago, and it would fund *all* scientific research in Canada. But what politician would ever propose a new tax, even if it did offer the country a chance of economic survival into the 21st. century?

Or maybe we should just assume that the world owes us a living?

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