^{13}C NMR Spectral Assignments of Chlorpromazine and Its 5-Oxide. Literature Correction

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The ^{13}C chemical shift assignments of title compounds were made on the basis of their coupled and decoupled spectra. The size of the *ipso* and allylic ^{13}CH coupling constants establish unequivocally the identity of symmetry related carbon pairs and show that several assignments reported previously are incorrect.

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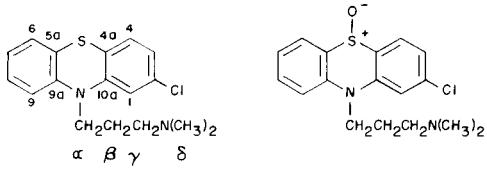
The ^{13}C nmr chemical shift assignments of carbon resonances of the widely-used tranquilizer chlorpromazine, **1**, (commercially known as thorazine) and its 5-oxide, **2**, have been reported [1]. Those investigators used the models,



1 2

10-(3-dimethylaminopropyl)phenothiazine and 10-(3-dimethylaminopropyl)phenothiazine 5-oxide, single frequencies off-resonance decoupling experiments (SFORD) and aromatic substituent effects for the ^{13}C chemical shift assignments of the titled compounds, **1** and **2**. Many of the problems in the nmr literature at present are the results of misassignments made on the basis of single frequency off-resonance decouplings. Since the ^{1}H spectra of **1** and **2** are not well resolved and the authors did not do single frequency *on* resonance decouplings, their spectral assignments may be in error.

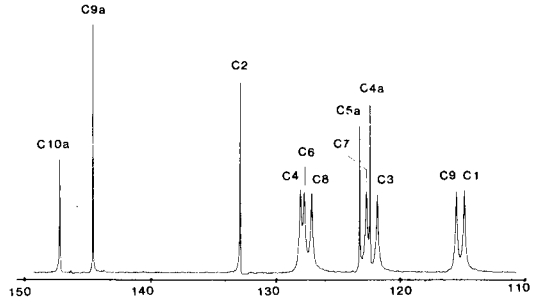


Figure 1. 50.3 MHz ^{13}C-nmr ^{1}H-decoupled spectrum of chlorpromazine hydrochloride, **1**, in DMSO-d_6, 2000 Hz expansion of the aromatic region.

Recently, we prepared several phenothiazine related molecules for *in vivo* biomedicinal studies and assigned their ^{13}C chemical shifts on the basis of coupling patterns and aromatic substituent effects [2]. In addition, tertiary

Table 1

^{13}C Chemical Shifts of Chorpromazine, Chlorpromazine 5-Oxide and Some Model Compounds [a,b]

Compound	C_1	C_2	C_3	C_4	C_{4a}	C_{5a}
1	115.7	132.4	122.2	127.9	122.7	123.5
1 [ref 1]	116.4 [c]	132.5	123.1 [c]	128.1	122.9	123.6
2	116.9	138.4	122.4	132.8	125.3	123.9
2 [ref 1]	117.2 [c]	137.4	122.5 [c]	132.4 [c]	123.6 [c]	125.1 [c]
3 [ref 2] [d]	114.2	133.1	122.0	127.3	121.7	122.9
4 [ref 2] [d]	114.6	126.5	125.2	127.6	127.3	122.3
	C_6	C_7	C_8	C_9	C_{9a}	C_{10a}
1	127.6	123.0	127.1	116.3	143.5	146.0
1 [ref 1]	127.8	122.3 [c]	127.2	115.8 [c]	143.6	146.1
2	133.7	123.0	131.1	117.5	137.8	139.5
2 [ref 1]	130.7 [c]	121.9 [c]	133.1 [c]	116.5 [c]	137.9	139.1
3 [ref 2] [d]	127.4	122.6	126.9	114.1	144.8	146.7
4 [ref 2] [d]	127.1	122.6	127.0	114.1	144.4	145.3

[a] (ppm). [b] Measured downfield from TMS and using the solvent as double reference standard; DMSO-d_6 = 39.5 ppm. [c] Chemical shifts erroneously assigned. [d] In deuteriochloroform (77.0 ppm).

Table 2

^{13}C-^{1}H Spin-coupling Constants of Chlorpromazine (**1**) [a]

Resonance	$^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$
1	C_1H_1 = 165.6		C_1H_3 = 4.6
2		C_2H_3 = 5.5 [b]	C_2H_4 = 9.9
3	C_3H_3 = 169.7		C_3H_1 = 4.5
4	C_4H_4 = 164.9		$C_{4a}H_3$ = 8.2 [c]
4a			$C_{4a}H_1$ = 6.6 [c]
5a			$C_{5a}H_{7(9)}$ = 6.5
6	C_6H_6 = 162.1		C_6H_8 = 7.9
7	C_7H_7 = 163.7		C_7H_9 = 7.0
8	C_8H_8 = 162.8		C_8H_6 = 8.1
9	C_9H_9 = 161.3		C_9H_7 = 7.7
9a			$9_{9a}H_{7(9)}$ = 7.4
10a			$C_{10a}H_4$ = 7.8
	Chlorpromazine 5-Oxide (**2**) [a]		
1	C_1H_1 = 167.2		C_1H_3 [d]
2		C_2H_3 = 2.5 [b,e]	C_2H_4 = 10.1
3	C_3H_3 = 171.9		C_3H_1 = 3.1
4	C_4H_4 = 165.2		
4a			$C_{4a}H_3$ = 10.2 [c]
			$C_{4a}H_1$ = 6.6 [c]
5a			$C_{5a}H_{7(9)}$ = 6.9
6	C_6H_6 = 163.7		C_6H_8 = 7.4
7	C_7H_7 = 166.0		C_7H_9 = 6.0
8	C_8H_8 = 163.3		C_8H_6 [d]
9	C_9H_9 = 163.3		C_9H_7 = 6.4
9a			$C_{9a}H_{7(9)}$ [f]
10a			$C_{10a}H_4$ = 7.5

[a] In Hz. [b] May represent $^{2}J_{C_2H_1}$ which could be confirmed by spin population transfer at a field strength sufficient to give a first order spectrum for the benzenoid protons. [c] The two couplings were distinguished from each other by partial decoupling of benzenoid protons. [d] The value could not be determined accurately. [e] Estimated value. [f] $^{3}J_{CH}$ couplings were not observed due to ^{14}N quadrupole broadening.

carbon resonances were distinguished from those of secondary and primary carbons by using an INEPT pulse sequence [3] in which *ipso* couplings of tertiary carbons are absent. Our results indicated that some of the previously reported ^{13}C assignments of **1** and **2** were incorrect.

Thus, we obtained the ^{1}H-decoupled and coupled ^{13}C spectra of the hydrochloride salts of **1** and **2** in DMSO (Figures 1-4) and assigned chemical shifts according to our procedure. The ^{1}H-decoupled and coupled ^{13}C spectra of the free base of **2** in deuteriochloroform (Figures 5a-b) are also included for comparison. The ^{13}C chemical shifts of chlorpromazine, **1**, chlorpromazine 5-oxide, **2**, and some model compounds are listed in Table 1. The ^{13}C-^{1}H spin-coupling constants of **1** and **2** are listed in Table 2. The tertiary carbon atoms are identified from the other carbon resonances by comparing the coupled and decoupled spectra of **1**. The absence of the single-bond ^{13}C-^{1}H coupling (*ipso* coupling) and small long-range ^{13}C-^{1}H coupling constants (< 15 Hz) allow the narrow multiplets due to bridgehead and substituted carbon atoms (C_{4a}, C_{5a}, C_{9a}, C_{10a}, and C_2) to appear at the resonance frequencies assigned to their decoupled signals (Figure 1). The resonances of the sp^2 carbon atoms in Figures 1 and 3 are paramagnetically broadened since the spectra are those of the hydrochloride salts of **1** and **2**. Interestingly, paramagnetic

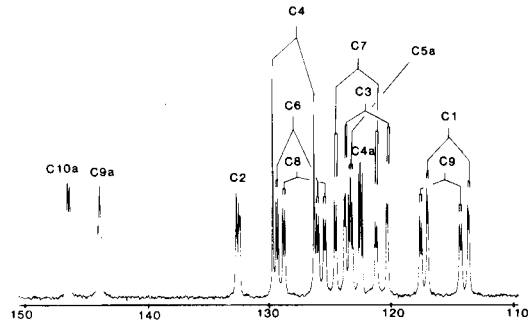


Figure 2. 50.3 MHz ^{13}C-nmr ^{1}H-coupled spectrum of chlorpromazine hydrochloride, **1**, in DMSO-d_6, 2000 Hz expansion of the aromatic region.

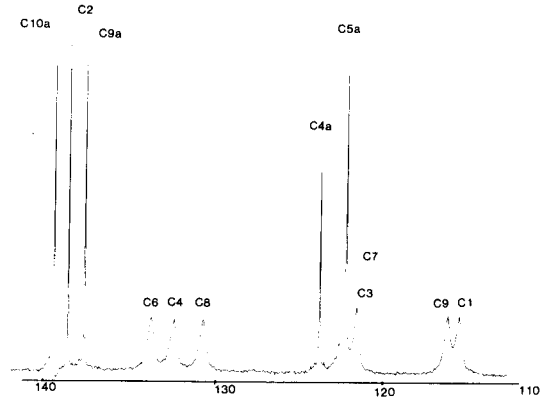


Figure 3. 50.3 MHz ^{13}C-nmr ^{1}H-decoupled spectrum of chlorpromazine 5-oxide hydrochloride, **2**, in DMSO-d_6, 1500 Hz expansion of the aromatic region.

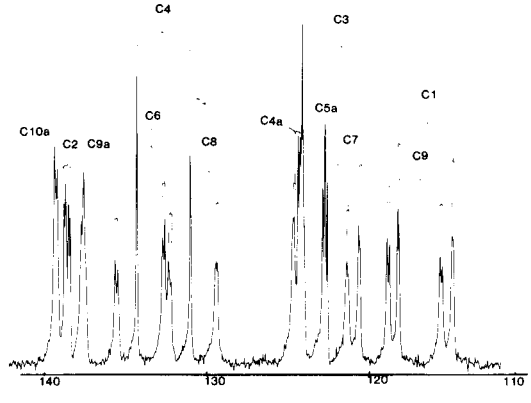


Figure 4. 50.3 MHz ^{13}C-nmr ^{1}H-coupled spectrum of chlorpromazine 5-oxide hydrochloride, **2**, in DMSO-d_6, 1500 Hz expansion of the aromatic region.

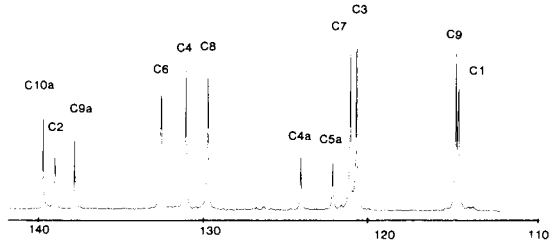


Figure 5a. 50.3 MHz ^{13}C-nmr ^{1}H-decoupled spectrum of free base of **2** in deuteriochloroform, 1500 Hz expansion of the aromatic region.

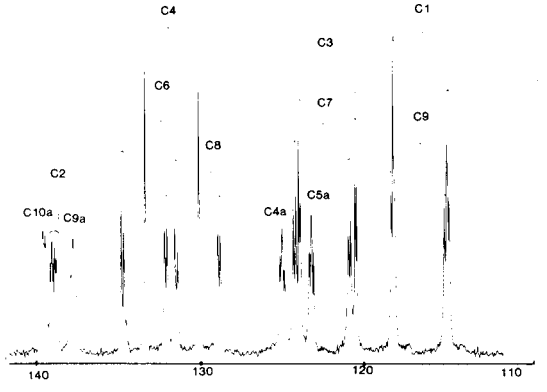


Figure 5b. 50.3 MHz ^{13}C-nmr ^{1}H-coupled spectrum of free base of **2** in deuteriochloroform, 1500 Hz expansion of the aromatic region.

line broadening was observed for the sp^2 ^{13}C nmr signals of 10-arylphenothiazinium radical cations [4].

The ^{1}H-decoupled spectrum of the free base of **2** (Figure 5a) shows that the carbon resonances of the quaternary carbon resonances (C_2, C_{4a}, C_{5a}, C_{9a} and C_{10a}) have lower relative intensities than those of the aromatic C-H carbon resonances which is the result of the longer relaxation times of the former as compared to the latter resonances. By decreasing the duration of the relaxation delay, which further saturates the quaternary carbon resonances, the discrimination between the quaternary and the aromatic C-H carbon resonances was found to be even more clear.

The size and presence or absence of the allylic ^{13}C-^{1}H coupling constants also confirmed the tertiary carbon assignments. For instance, the narrow doublet at 146.1 ppm (compound **1**) is assigned to C_{10a} due to its coupling with H_4, the 2-position being substituted with a chlorine atom. Similarly, C_{9a} is slightly shielded with respect to C_{10a} and appears as a narrow triplet since it is coupled to two allylic hydrogens, H_6 and H_8; the poorer resolution of this triplet is due to the ^{14}N quadrupolar broadening. Thus, our assignments of this carbon pair agree with those reported previously [1].

However, such agreement is not observed for the C_1, C_9 and C_3, C_7 carbon pairs. The analysis of the coupled and decoupled spectra in Figure 1 and Figure 2 indicates that the chemical shift assignments of the two carbon atoms in each carbon pair are the reverse of those assigned previously for compound **1**. Thus, the *ipso* ^{13}C-^{1}H coupling of carbons ortho to chlorine, C_1 (165.6 Hz) and C_3 (169.7 Hz) is larger than the typical phenothiazine coupling constants for C_7 (163.7 Hz) and C_9 (161.3 Hz). Also, the three-bond allylic ^{13}C-^{1}H couplings of C_1 (4.6 Hz) and C_3 (4.4 Hz) are smaller than those of C_7 (7.0 Hz) and C_9 (7.7 Hz). This interdependence between substituents and coupling constants is well known [5] and was observed in the spectra of all substituted phenothiazines which we had analyzed [2].

The other carbon chemical shifts were assigned by similar analogy. The appearance of C_2 as a narrow doublet of triplets at 132.5 ppm is indicative of halogen substitution [5,9] and was interpreted in terms of additional *ortho* two-bond coupling (C_2H_1 and C_2H_3).

The previous assignment of the symmetry related pair C_4, C_6 agrees with ours. However, two very important points should be made concerning the former method which limits its use for assigning chemical shifts to carbon atoms of this type. Their use of chlorine substituent effects on aromatic chemical shifts on *ortho, meta*, and *para* carbons of benzene for assigning chemical shifts of the phenothiazine ring carbon atoms is very tenuous since its effect is very small. Also, chemical shift "cross-over" occurs in phenothiazines by minor variations of substituents on the tricyclic ring [2]. For example, the chemical shifts of C_1 and C_9 overlap in 10-methyl-2-chlorophenothiazine, **3**, and completely "cross-over" in 10-methyl-3-chlorophenothiazine, **4**. The chemical shifts of the carbons in the C_4, C_6 symmetry related carbon pairs are readily distinguished from each other in that C_4 appears as a doublet at the lower field because of the absence of C_4H_2 coupling and C_6 appears as doublet of doublets at the higher field due to C_6H_6 and C_6H_8 coupling. The doublet at 129.8 ppm and 126.5 ppm in Figure 2, thus differentiates unambiguously the chemical shift of C_4 from that of all other carbons, particularly that of C_6. A similar observation has been made by Gampe and co-workers [6].

The chemical shift assignments for the 5-oxide, **2**, were made similarly. In this case, the chlorine substituent effect is much smaller than that observed in **1** and approaches the experimental error (0.05-0.10 ppm) and as such should not be used for the ^{13}C chemical shift assignments. The analysis of the coupled and decoupled spectra of **2** in Figure 3 and Figure 4 shows that the chemical assignments of atoms of the four symmetry-related pairs, C_1, C_9; C_3, C_7; C_4, C_6 and C_{4a}, C_{5a} are also the reverse of those reported in reference 1.

The first two pairs were again analyzed by the criteria outlined earlier. That is, the *ipso* C_1H_1 and C_3H_3 couplings

are larger than the respective coupling of C_9H_9 and C_7H_7 counterpair. Also, the allylic coupling of carbons next to chlorine substituent (C_1H_3 and C_3H_1) are much smaller than C_9H_7 and C_7H_9 couplings, respectively. The overlapping signals of C_7 and C_{5a} in Figure 3 are clearly distinguished as two separate resonances in the ^1H-decoupled ^{13}C nmr spectrum of the free base in Figure 5a.

The utility of this method is exemplified further by the detailed analysis of the coupled spectrum in Figure 4. The resonance at the lower field (133.7 ppm) is due to C_6 and the one at 132.8 ppm to C_4 since the latter does not show the allylic coupling and appears as two singlets in the coupled spectrum of **2**. Therefore, the cross-over of C_4 and C_6 in **2** as compared to the spectrum of **1** is readily established; C_6 is more deshielded than C_4 in chlorpromazine 5-oxide, **2**, and the reverse is true for compound **1**. The distinction between C_6 and C_8 was made based on the well-established chemical shift changes induced by the sulfoxide functionality [7,8].

Chemical shift of C_{4a} in **2** has also crossed over those of C_3 and C_7 relative to compound **1**. In addition, C_{4a} is further upfield in **1** and in effect is reversed with the signal of C_{5a} in compound **2**. Both signals appear at their respective resonances in the decoupled spectrum of chlorpromazine 5-oxide, **2**, but only the one at the upper field (123.9 ppm) shows as a narrow triplet ($C_{5a}H_7$ and $C_{5a}H_9$) whereas the one at 125.3 ppm appears as the uneven multiplet due to the additional perturbations induced by chlorine atom at C_2. Therefore, chemical shift assignments of C_4, C_6 and C_{4a}, C_{5a} for compound **2** must also be reversed from those reported earlier [1]. The partial overlap of C_{4a} and C_3 in Figure 4 obscures the two signals, but the same signals are clearly separated as two distinct sets of multiplets in Figure 5b.

Lastly, the cross-over also occurs with C_{9a} and C_2 in the spectrum of **2** but the two chemical shifts are readily distinguished by their coupling

EXPERIMENTAL

Chlorpromazine (**1**) was obtained through the courtesy of Smith, Kline and French Laboratories. Chlorpromazine sulfoxide hydrochloride, **2**, was prepared by oxidation of **1** with sodium nitrite in dichloromethane/-acetic acid medium and its hydrochloride prepared by precipitating the free-base with 10% hydrochloric acid.

The coupled and decoupled ^{13}C spectra were obtained using 1.2-1.5 *M* solutions in DMSO-d_6 or deuteriochloroform as specified by the figure caption using the solvent and TMS as double standard references. The spectra were run on a WP 200-SY Bruker spectrometer operating at the frequency of 50.327 MHz. Spectral widths of 200 ppm were employed using 1-4 second relaxation delays and data collected with 16 K data points. The expanded spectra with smaller spectral widths were used to evaluate the coupling constants; typically relaxation delay times of 2 seconds with pulse width of 8 microseconds and a tip angle of 45° were used.

REFERENCES AND NOTES

[1] D. B. Staiger, R. J. Warren, J. E. Zarembo, A. Post and E. L. Anderson, *J. Heterocyclic Chem.*, **18**, 101 (1981).

[2] M. V. Jovanovic and E. R. Biehl, *Org. Magn. Reson.*, **22**, 491 (1984).

[3] Inept sequence program software provided by IBM instruments Inc., Orchard Park, P. O. Box 332, Danbury, Connecticut 06810.

[4] M. V. Jovanovic and E. R. Biehl, *J. Org. Chem.*, **48**, 1905 (1984).

[5] G. C. Levy, R. L. Lichter and G. L. Nelson, "Carbon-13 Magnetic Resonance Spectroscopy", Wiley, New York, 2nd ed, 1980, p 127.

[6] R. T. Gampe, Jr., G. E. Martin, A. C. Pinto and R. A. Hollins, *J. Heterocyclic Chem.*, **18**, 155 (1981).

[7] A. L. Ternay, Jr., J. Hermann, B. A. Hayes and P. Joseph-Nathan, *J. Org. Chem.*, **45**, 189 (1980).

[8] D. F. Ewing, *Org. Magn. Reson.*, **12**, 499 (1979).

[9] A. R. Tarpley, Jr. and J. H. Goldstein, *J. Mol. Spectrosc.*, **37**, 432 (1971).