^{13}C NMR Spectral Analysis of Chlorpromazine, Chlorpromazine Sulfoxide and Related Models (1)

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The natural abundance carbon-13 nmr spectra of chlorpromazine, chlorpromazine sulfoxide and related models were obtained and assigned. The chemical shift effects from sulfoxidation of the carbon skeleton will be discussed. Assignments were made on the basis of models, single frequency off-resonance decoupling experiments, additivity rules based on benzene substituent effects, and general symmetry considerations.

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Analogs of the phenothiazine based compounds have been studied extensively for their antipsychotic activity. This work has led to studies in their mechanism of action and structural character (2-6). We have analyzed and assigned ^{13}C nmr spectra of 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride, (chlorpromazine, I) and 10-3-dimethylaminopropyl)-2-chlorophenothiazine-*S*-oxide hydrochloride, (chlorpromazine sulfoxide, II). In addition, two structurally related models, 10-(3-dimethylaminopropyl)phenothiazine (III) and 10-(3-dimethylaminopropyl)phenothiazine sulfoxide (IV), have been assigned. Our objective is to report the ^{13}C nmr assignments of the above four compounds and to illustrate the effect of sulfoxidation on the chemical shifts of the carbon skeleton. Chemical shift assignments of I and II were made on the basis of comparison to related phenothiazine models, single frequency off-resonance decoupling (SFORD) experiments, aromatic substituent effects and molecular symmetry considerations.

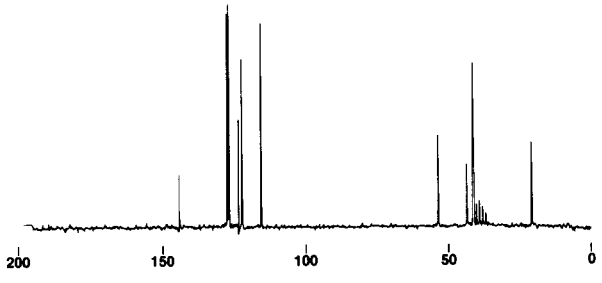

Figure 1. 400 Hz Spectrum of the Model 10-(3-Dimethylaminopropyl)phenothiazine; III.

The symmetrical model 19-(3-dimethylaminopropyl)-phenothiazine, (III) produced a simplified spectrum of six aromatic carbon resonances which were assigned on the basis of additivity rules of substituted aromatic compounds (7,8). The nitrogen atom attached to the phenyl ring shields the carbons in the *ortho* and *para* positions.

Table I

C-13 Chemical Shifts of Chlorpromazine and Chlorpromazine Sulfoxide

	Chlorpromazine											
	Cl Substituted Phenyl						Unsubstituted Phenyl					
	11	12	1	2	3	4	13	14	6	7	8	9
Model, III	144.4	123.8	115.9	127.1	122.6	127.6	123.8	144.4	127.6	122.6	127.1	115.9
Cl Effect (a)	+1.3	−1.9	+0.4	+6.2	+0.4	+1.3						
Theoretical, I	145.7	121.9	116.3	133.3	123.0	128.9	123.8	144.4	127.6	122.6	127.1	115.9
Observed, I	146.1	122.9	116.4	132.5	123.1	128.1	123.6	143.6	127.8	122.3	127.2	115.8
Δ (b)	0.4	1.0	0.1	0.8	0.1	0.8	0.2	0.8	0.2	0.3	0.1	0.1
	Chlorpromazine Sulfoxide											
Model, IV	137.8	124.5	116.7	133.1	121.9	130.9	124.5	137.8	130.9	121.9	133.1	116.7
Cl Effect	+1.3	−1.9	+0.4	+6.2	+0.4	+1.3						
Theoretical, II	139.1	122.6	117.1	139.3	122.3	132.2	124.5	137.8	130.9	121.9	133.1	116.7
Observed, II	139.1	123.6	117.2	137.4	122.5	132.4	125.1	137.9	130.7	121.9	133.1	116.5
Δ	0.0	1.0	0.1	1.9	0.2	0.2	0.4	0.1	0.2	0.0	0.0	0.1

(a) F. W. Wehrll and T. Wirthlin, Heydon and Son, Ltd., 1976, p. 47. (b) Δ = [δ, ppm (experimental) - δ, ppm (model)].

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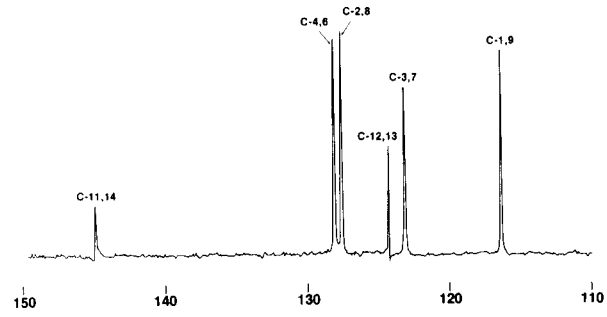

Figure 2. 800 Hz Scale Expansion of Aromatic Region of 10-(3-Dimethylaminopropyl)phenothiazine Hydrochloride, Compound III.

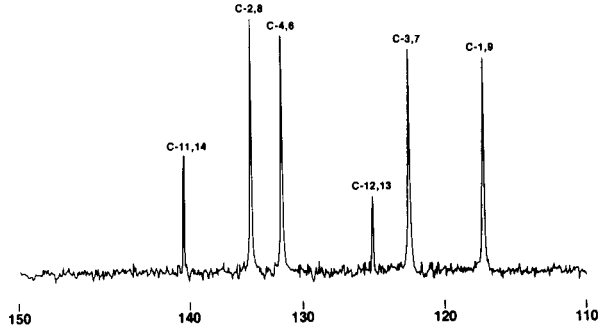

Figure 3. 800 Hz Scale Expansion of Aromatic Region of 10-(3-Dimethylaminopropyl)phenothiazine 5-Oxide Hydrochloride, Compound IV.

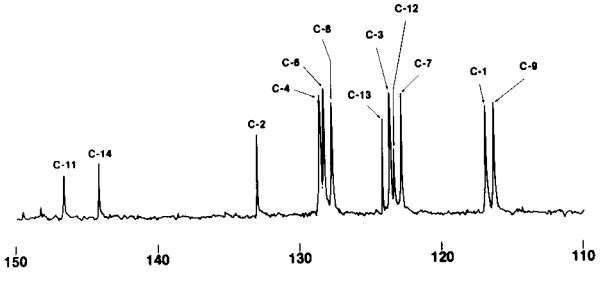

Figure 4. 800 Hz Scale Expansion of Aromatic Region of Chlorpromazine Hydrochloride, Compound I.

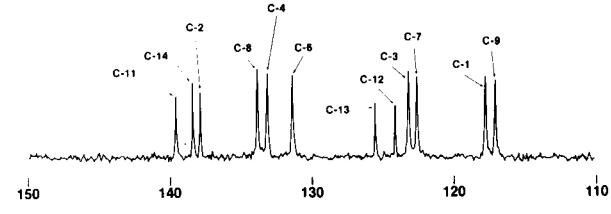

Figure 5. 800 Hz Scale Expansion of Aromatic Region of Chlorpromazine Sulfoxide, Hydrochloride, Compound II.

Thus, carbons 1,9 and 3,7 are found at 115.86 ppm and 122.63 ppm, respectively, whereby the former exhibits the largest shielding effect. Carbon resonances, 11,14 and

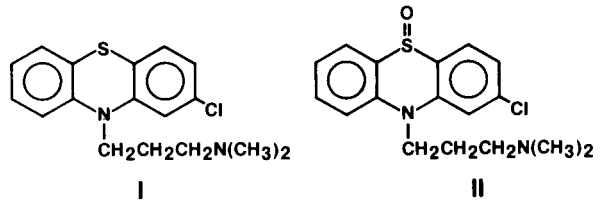

Figure 6. Chlorpromazine and Chlorpromazine Sulfoxide.

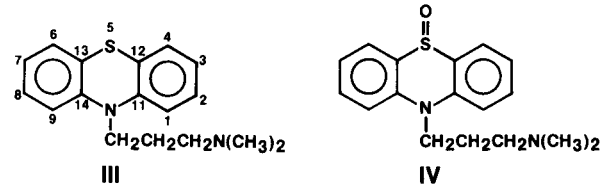

Figure 7. Symmetrical Models: Compound III, 10-(3-Dimethylaminopropyl)phenothiazine and Compound IV, 10-(3-Dimethylaminopropyl)phenothiazine Sulfoxide.

12,13 were confirmed as quaternaries by the SFORD. The former pair were assigned to the carbon bearing the nitrogen at 144.35 ppm. As literature data on aromatic sulfur compounds are relatively sparse (9), ^{13}C nmr spectra were obtained on diphenyl sulfide and thioanisole to remove the ambiguity concerning the assignments of carbons *ortho* (5,6) and *para* (3,9) to the sulfur. On the basis of the unequivocal assignments of these models, the more shielded signal of the remaining unassigned pair in the symmetrical phenothiazine, III, is due to the carbon *para* to the sulfur. Thus carbons 2,8 and 2,6 are at 127.58 ppm, respectively. In the case of 10-(3-dimethylaminopropyl)-phenothiazine *S*-oxide (IV); however, the carbon *para* to the sulfoxide functionality is more deshielded relative to the *ortho* carbon based on the unequivical assignments of the model compound diphenylsulfoxide. All other assignments for the phenothiazine sulfoxide were arrived at by the same rationale.

Matching the model carbon resonances to those obtained in the monochloro substituted analog in a best-fit manner, results in assignments for the phenyl carbons 6,7,8,9,13 and 14, assuming the chloro substituent has little, if any, effect on the chemical shifts across the heteroatom bridges.

The chloro substituent effect on aromatic chemical shifts (*ortho, meta* and *para*) was used in assigning the chloro substituted phenyl in chlorpromazine (I) and the corresponding sulfoxide (II). The electronic effect of a chlorine substituent is relatively small, i/e.; 0.4 at the *ortho* position, 1.3 at the *meta* position and -1.9 at the *para* position (7). In our case we maintain the principle by using the chemical shifts of the model as a base and correct the positions *ortho, meta* and *para* to the chlorine substituent. This eliminates the necessity of calculating the effect of

sulfur and nitrogen along with chlorine and leads to more accurate shift estimates for our objective compounds. Thus, the resulting chemical shifts of the chloro substituted phenyl portion of chlorpromazine (I) and chlorpromazine sulfoxide (II), were obtained by algebraically combining the appropriate value of the effect to the observed chemical shift of the model, resulting in assignments for carbons 1,2,3,4,11 and 12.

For chlorpromazine (I) and chlorpromazine sulfoxide (II), the chemical shifts derived from the model are in excellent agreement with the observed chemical shifts of these compounds. Table I lists this data. One may view the term; delta, Δ, as a measure of the agreement between the derived and observed carbon resonances. A value of less than 1.0 ppm represents a probably assignment and approaches experimental error (0.2-0.3 ppm) for the conditions under which the spectrum was taken.

EXPERIMENTAL

All ^{13}C nmr spectra were obtained in deuterated dimethylsulfoxide using tetramethylsilane as reference. A Varian CFT-20 instrument operating at 20 MHz for carbon-13 and 80 MHz in the proton decoupling frequency were used. Proton noise decoupled (PND) spectra were collected using 8k data points in conjunction with a Varian 620 L-100 computer. The spectral width was 4000 Hz with an acquisition time for one second and pulse width of eight microseconds (about a 50° flip angle). Since each compound is characterized by assigning the aromatic resonances, the aromatic regions were expanded by displaying full scale at 800 Hz. The promazine side chain varies only slightly and therefore is shown only for the model compound, III.

Substituted aromatic carbons were determined by single frequency off-resonance decoupling experiments. These served as a check in using relative signal intensities from the proton noise decoupled spectrum as a means to differentiate quarternary carbons.

The compounds used in this study were either prepared in these labs or obtained from commercial sources (Aldrich Chemical Co.).

REFERENCES AND NOTES

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