Correlation of Dihedral Angles with ^{13}C Chemical Shifts of Quaternary Carbon Atoms of Some Phenothiazine Derivatives

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A direct relationship between the ^{13}C nmr chemical shifts of the quaternary carbon atoms of the central ring of phenothiazine and the dihedral angle of the respective derivatives has been observed. This correlation allows for the useful and quick estimation of the dihedral angles of novel phenothiazines from readily obtainable ^{13}C nmr solution measurements. In addition, the change in the dihedral angle appears to be directly related to the S-C_{4a}-C_{10a} bond angle; however, the C_{4a}-S-C_{5a} bond angle is not affected by changes in the dihedral angle. This indicates that the "flattening" of the phenothiazine tricyclic ring system is compensated for by the vertical displacement of the sulfur atom, by changes in hybridization of N_{10}, and by other angular distortions of the middle ring.

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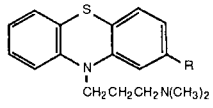
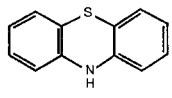
Introduction.

The pharmacological activity of several neuroleptic phenothiazine derivatives appear to depend, in part, on the dihedral angle (θ) of the butterfly structure of the tricyclic ring. The dihedral angle is defined as the folding angle between the planes of the two benzo rings of the tricyclic ring system. For example, the increased planarity resulting from replacement of the 2-chloro-group of chlorpromazine, **1a** (θ = 159.2°) [1] with a 2-methoxy substituent to give 2-methoxypromazine, **1b**, (θ = 157.4°) [2] is accompanied with complete loss of pharmacologic activity [3]. Phenothiazine, itself, which has dihedral angles in the monoclinic (153.3° [4]) and orthorombic (158.5° [5]) forms, **1c**, that are similar to that of **1b**, is also an ineffective neuroleptic agent.



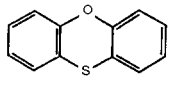
1a R = Cl

1b R = OCH_3



1c

Martin and coworkers have shown that the dihedral angles of phenoxathiin analogs, **2**, can be correlated with the ^{13}C nmr chemical shifts of the sulfur-bearing 1a carbon atom [6]. The statistical evaluation of the limited available data (five compounds) gave a correlation coefficient, r = 0.959. In principal, such relationships should provide a convenient means for the preliminary estimation of dihedral angles from solution ^{13}C nmr measurements, after suitable parameterization, of other heterotricyclic systems of medicinal interest.



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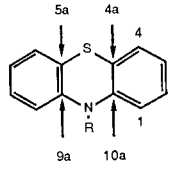
This paper reports on our study to determine if the X-ray/^{13}C nmr relationship observed in phenoxathiins can be extended to phenothiazine derivatives. In addition, the investigation of the relationship between the dihedral angles and various internal bond angles is discussed.

Results and Discussion.

The structure and numbering of the parent compound, **3**, is shown below, Table 1 lists the dihedral angles and the



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^{13}C nmr chemical shifts of the sulfur-bearing 4a carbon atom for several phenothiazine derivatives. The data for phenothiazine compounds which exist as one independent

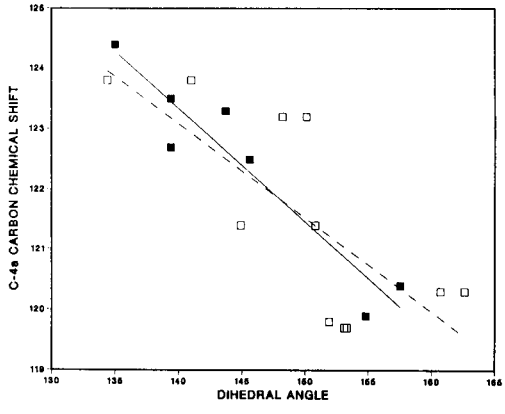


Figure 1. Least square plot of the ^{13}C nmr chemical shifts of the C_{4a} carbons of phenothiazines *vs.* the dihedral angles; compounds with two independent molecules in a unit cell are represented by empty square symbols and dash line curve.

Table 1

Comparison of the ^{13}C-NMR Chemical Shifts of the C_{4a} Carbon Atom (δ ppm) of Phenothiazines with the Corresponding Dihedral Angles (°)

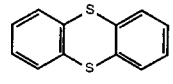
Compound No.	Derivative	$^{13}C_{4a}$ [a]	Dihedral Angle (°) [b]
5	10-methyl	123.3	143.7 [10]
6	10-ethyl	124.4	135.0 [11]
7 [c]	2-chloro-10-(dimethylaminopropyl) -Chlorpromazine [d]	122.7 123.5 [e]	139.4 [1]
8	10-(2'-nitrophenyl)	119.9	154.8 [13]
9	10-(2'-methoxyphenyl)	120.4	157.5 [14]
10	10-(4'-methylphenyl)	119.8	151.9 [15]
11	3,4',7-tribromo-10-phenyl	122.5	145.6 [16]
12 [f]	10-benzyl	123.2	148.2 [17] 150.1
13 [f]	10-(dimethylaminopropyl) -Promazine [d]	123.8	134.4 [18] 141.0
14 [f]	10-(4'-bromophenyl)	121.4	144.9 [19] 150.8
15 [f]	2-chloro-10-phenyl	119.7	153.1 [20] 153.3
16 [f]	10-phenyl	120.3	160.7 [g] [21] 162.6

[a] Taken from ref [9]. [b] Literature reference for the crystallographically determined dihedral angle is given in parentheses. [c] ^{13}C-nmr data taken from ref [12]. [d] Common name. [e] Chemical shift of symmetry related carbon atoms (C_{5a}). [f] Phenothiazines with two independent molecules in a unit cell. [g] Reported as 150.7, but verified as a typographical error.

molecule in the single crystal are illustrated by the full-line curve in Figure 1. Statisticial evaluation of the data of this curve in Figure 1 gives a correlation coefficient, r = 0.943. That the shielding of the sulfur-bearing atoms of the middle ring of the phenothiazines is directly related to dihedral angle indicates that the mesomeric interaction between N_{10} and the middle ring increases as the tricyclic ring flattens. The slope of this plot is opposite in sign to that observed for phenoxathiin and isosterically related systems (δ). We are unable to explain this difference at present.

The dashed curve in Figure 1 is a plot of the dihedral angles *vs.* the ^{13}C chemical shifts of the phenothiazines which exist as two crystallographic independent molecules in an asymmetric unit of a single crystal lattice. The slope of the plots of both curves are approximately the same which indicates that the dihedral angle of both sets of phenothiazines can be estimated from appropriate ^{13}C nmr data.

Martin [7] has noted that the variations in the dihedral angle in a series of analogs of thianthrene, **4**, appear to be related to changes in the C-C-S bond angle of the middle



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ring and not to the C-S-C bond angle. The latter values are fairly constant [7]. A determination of the generality of

Table 2

Bond Angles of the Middle Ring of Selected Phenothiazines (Supplements Figure 2) [a,b]

Compound No.		S-C_{4a}-C_{10a}	S-C_{5a}-C_{9a}	N-C_{10a}-C_{4a}	N-C_{9a}-C_{5a}
5		119.8	119.8	120.0	120.0
12 [c]	Molecule A	120.2	119.9	120.5	120.6
	Molecule B	120.1	119.8	120.0	120.3
9		121.3	121.0	120.8	120.9
14 [c]	Molecule A	120.3	120.0	119.5	120.1
	Molecule B	120.5	120.3	120.7	121.0
15 [c]	Molecule A	121.2	120.6	119.9	120.7
	Molecule B	121.4	121.4	120.2	120.2
10		120.4	120.7	120.6	120.7
11		120.4	118.9	120.6	121.3
6		118.3	118.3	118.3	119.0
16 [c]	Molecule A	120.8	122.2	121.9	120.7
	Molecule B	119.7	120.8	120.5	119.7
8		120.9	121.5	121.3	119.9
7		119.7	120.9	118.1	116.9
13 [c]	Molecule A	117.0	118.8	121.8	119.1
	Molecule B	121.7	121.5	118.1	118.1

[a] For the source of literature data see references in Table 1. [b] Remaining points in Figure 2 can be obtained from refs [5,9,11]. [c] Phenothiazines with two independent molecules in a unit cell.

this relationship was precluded by the paucity of x-ray data available on thianthrene analogs.

We have plotted various bond angles of the middle ring of the selected phenothiazines [8] against the dihedral angle to see if the behavior observed by Martin in the thianthrene analogs is carried over into the phenothiazine system. The data listed in Table 2 show that there is a good correlation between the dihedral angle and the S-C-C bond angle of the middle ring if the phenothiazine derivatives are divided into two classes, one which consists of electron-releasing substituents (full line-curve A in Figure 2) and the other which contains electron-withdrawing groups (dash line Curve B in Figure 2). Statistical evaluation of these two plots taken from data listed in Table 2 gives correlation coefficients, r = 0.937 and 0.967, respectively, indicating that a better fit is obtained for those phenothiazines substituted with electron-withdrawing groups. McDowell [5] has commented previously on the constancy of the C-S-C bond angles in phenothiazines [5].

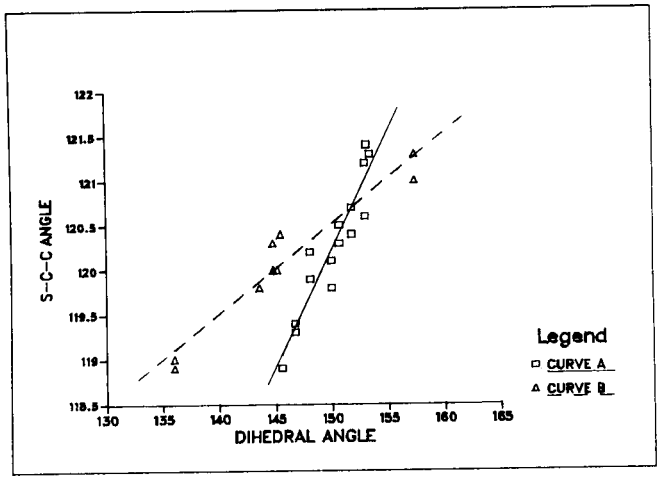

Figure 2. Plot of the dihedral angles of phenothiazines *vs.* the corresponding S-C-C angle of the middle ring. Phenothiazines containing electron-withdrawing groups in one of the benzo rings are represented by empty triangle symbols and dashed line curve.

We are investigating currently the relationship between the dihedral angle, ^{13}C nmr chemical shifts, and various bond angles of the middle ring of pyrido[3,2-*b*][1,4]benzothiazines which will be reported subsequently.

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