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The Carbon-13 NMR Spectra and Electronic Structure of 3*H*-Phenothiazin-3-one and Its Methyl Derivatives

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The ^{13}C NMR chemical shifts of 3*H*-phenothiazin-3-one (**1**) and eleven of its methyl derivatives are reported. The effect of including sulfur 3d orbitals is discussed in relation to the ^{13}C chemical shifts. The chemical shifts of **1** can be explained in terms of both the successive polarization of the long π-conjugated framework promoted by the carbonyl group and the contribution of the sulfur d-orbitals. The ^{13}C chemical shifts gave a better correlation with the CNDO/2 π- and total electron densities calculated by means of the *sp*-basis set than by means of the *spd*-basis set, but an improved correlation was obtained by reducing the extent of d-orbital participation on sulfur. From the correlation of the ^{13}C chemical shifts with the CNDO/2 *sp* π- and the total electron densities of all the carbons of **1** and monomethyl derivatives, the proportionality constants of −300 and −180 ppm/e respectively were obtained.

There have been extensive studies of phenothiazines in connection with medical chemistry, with particular reference to the correlation of the psychopharmacological activities with the molecular structures such as the electronic and steric properties of substituents and the conformational change in the parent molecule.[1] It is well known that phenothiazines can be used as neuroleptics and that they depress the vital function of the dopamine receptor in the central nervous system.[2] Although phenothiazine itself is not an effective neuroleptic, its pharmacological activity is increased by the introduction of both electron-withdrawing group such as Cl or CF_3 at the 2-position and the *N*-side chain such as *N*-[3-(dimethylamino)propyl], *N*-[3-(4-methyl-1-piperazinyl)propyl], or *N*-[3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl] group (for example, trifluoperazine, chlorpromazine, fluphenazine, and perphenazine).[1a,c]

From X-ray analysis[3—9] and the determination of the dipole moment and the molar Kerr constant,[10] phenothiazines are known to have a folded structure about the N–S axis and a quasi-equatorial substituent on the nitrogen. The dihedral angles between the two planes of the benzenoid rings of phenothiazines in a solid vary from 134.4° for thioridazine to 158.5° for orthorhombic phenothiazine.[3] In a solution, however, *N*- and ring inversions take place with butterflylike flapping motion, and the population of the *N*-quasi-axial substituent seems to increase with an increase in the bulkiness of the *N*-substituent.[11]

Although phenothiazin-3-ones have been used as enzyme inhibitors, anthelmintics, stabilizers, antioxidants, dyestuffs, and indicators,[12—22] their relative difficulty of preparation has limited the number of compounds examined. 3*H*-Phenothiazin-3-one (**1**) inhibits the activities of succinoxidase, cytochrome oxidase, and glyoxalase as well as phenothiazine.[13] On the other hand, 3*H*-phenoxazin-3-one is well known to be the chromophore part of actinomycin D, which binds to double-helical DNA and specifically inhibits RNA synthesis.[23]

Whereas many papers have been devoted to the study of the electronic and conformational properties of phenothiazines by means of the ^{13}C NMR[11] and ^{1}H NMR[24—28] chemical shifts, the dipole moments,[10] the molar Kerr constants,[10] the EPR and polarographic oxidation potentials,[29] X-ray crystal analyses,[3—9] and molecular orbital calculations,[11,29] there have been few corresponding data on **1** and its derivatives.

This paper will deal with the ^{13}C NMR spectra of **1** and eleven of its methyl derivatives in order to elucidate how the presence of *p*-benzoquinone monoimine type and the methyl group influences the electronic properties of phenothiazines. The ^{13}C chemical shifts of 3*H*-phenothiazin-3-ones give an index of the electronic densities of their carbons for the ground state and would seem to be useful for any future discussion of their pharmacological properties and reactivities.

Experimental

Materials. **1** was synthesized by the cyclization of *o*-aminothiophenol with *p*-benzoquinone according to the method of Bodea and Raileanu;[30] mp 162—163 °C (lit, 161—162 °C). The monomethyl-3*H*-phenothiazin-3-ones were prepared by the method of Terdic:[31] 1-methyl-(**2**), mp 146—148 °C (lit, 145—147 °C); 2-methyl- (**3**), mp 182—183 °C (lit, 181—183 °C); 4-methyl- (**4**), mp 142—143 °C (lit, 141—143 °C); 6-methyl- (**5**), mp 192—193 °C (lit, 190—192 °C); 7-methyl- (**6**), mp 210—211 °C (lit, 208 °C); 8-methyl- (**7**), mp 181—182 °C (lit, 180—182 °C); 9-methyl- (**8**), mp 179—180 °C (lit, 171—173 °C). Dimethyl- and trimethyl-3*H*-phenothiazin-3-ones were synthesized from *o*-aminothiophenol and the corresponding methyl derivatives of *p*-benzoquinone; 1,2-dimethyl- (**9**), mp 191—192 °C; 1,4-dimethyl- (**10**), mp 146—148 °C; 2,4-dimethyl- (**11**), mp 164—165 °C; 1,2,4-trimethyl- (**12**), mp 160—161 °C. Found for **10**: C, 69.33; H, 4.54; N, 5.97%. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80%. Found for **11**: C, 69.50; H, 4.32; N, 5.65%. Found for **12**: C, 70.43; H, 5.08; N, 5.42%. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49%. All the compounds were purified by TLC and column chromatography and checked by means of their IR and ^{1}H NMR spectra. The *N*-chloro-*p*-benzoquinone monoimine was commercially obtained (guaranteed reagent) and used without further purification.

Procedures. The ^{13}C NMR spectra were recorded on a JEOL FX-100 Fourier-transform spectrometer at room temperature at 25.00 MHz, using a deuterium lock. Samples were prepared in the 9:1 $CDCl_3$–CD_3OD solvent system, with tetramethylsilane as an internal reference, in 5-mm spinning tubes because these compounds were not soluble enough in $CDCl_3$. The melting points were determined on a

Yanagimoto micromelting apparatus and are uncorrected.

Theoretical

The quantum chemical calculations were carried out by the CNDO/2 method[32] and using parametrizations without further modification. The convergence was judged from the electron-density criterion of 10^{-4} in the density matrix. The CNDO/2 program suppled by QCPE[33] Program No. 141 was modified to accommodate atomic orbital matrices greater than seventy. The dihedral angles associated with the inner thiazine ring of **1** in the butterfly structure were calculated by using QCPE[33] Program No. 397. Computations were carried out on a HITAC M-200H computer at the Computer Center of the Institute for Molecular Science.

For Runs 2, 4—13, and 19 in the CNDO calculations of **1** shown in Table 3, the X-ray data for the bond lengths and bond angles of the benzenoid ring and the *p*-benzoquinone imine portion of the actinomycin D obtained from light-atom analysis were used to those for the corresponding bond lengths and bond angles of **1**, except that the bond length of C-6—C-7 was 1.41 Å; for the other runs, their bond angles were assumed to be 120°. For the hydrogen bonding of the carbonyl group of **1** with methanol, the atomic distance between the carbonyl oxygen and the alcoholic hydrogen was presumed to be 1.61 Å, and the hydroxyl group was arranged on the extension line of the carbonyl bond. The geometry of **1** has been transferred to the monomethyl derivatives. The atomic coordinates of the methyl group and methanol were determined from the following bond distances and bond angles: C–C (methyl), 1.51 Å; C–O, 1.43 Å; olefinic (or aromatic) C–H, 1.08 Å; methyl C–H, 1.09 Å; O–H, 1.02 Å; ∠COH, 110°; ∠OCH=∠CCH=109.5°. The bond lengths and angles of planar *N*-chloro-*p*-benzoquinone monoimine were: C=O, 1.23 Å; C=N, 1.33 Å; C=C, 1.32 Å; C–C, 1.49 Å, N–Cl, 1.75 Å; C–H, 1.08 Å; ∠C–C–C, 116°; ∠C=C–C, 122°; ∠C=N–Cl= ∠C=C–H =120°.

Results and Discussion

*^{13}C Chemical Shifts of 3*H*-Phenothiazin-3-one.* A reasonably self-consistent set of assignments for the chemical shifts of the 3*H*-phenothiazin-3-ones and the substituent-induced chemical shifts (SCS) of the methyl group are summarized in Tables 1 and 2 respectively. The carbon resonances of **1** can be assigned not directly, but on the basis of the off-resonance decoupling technique and the methyl-substituent effects on benzenes[34] and olefins.[35]

The signal for the carbonyl nuclei in **1** appeared at 183 ppm; it is shifted to a magnetic field higher by 4 ppm relative to those (187.0 and 186.5 ppm, respectively) in *p*-benzoquinone[36] and *N*-chloro-*p*-benzoquinone monoimine.[37] The chemical shifts of carbonyl carbons increase in the order of: **1**

TABLE 1. ^{13}C NMR CHEMICAL SHIFTS OF 3*H*-PHENOTHIAZIN-3-ONE AND ITS METHYL DERIVATIVES

Substituent	Chemical shift, δ												
	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a	Me
Nil (**1**)	139.9	134.9	182.6	119.6	135.8	123.8	125.1	131.3	128.2	134.0	139.1	146.1	
1-Me[a] (**2**)	[147.9][b]	132.9	182.5	118.9	135.7	123.9	124.7	131.0	127.8	134.1	138.5	145.8	18.4
2-Me (**3**)	136.5	[144.2]	182.8	119.5	134.9	123.4	125.0	130.6	127.9	133.7	139.2	146.4	16.5
4-Me (**4**)	139.8	134.3	181.7	[127.4]	131.3	124.6	125.4	130.8	128.1	133.7	138.8	146.7	16.5
6-Me (**5**)	139.9	135.0	182.9	119.8	136.1	123.3	[133.7]	132.2	127.5	132.7	139.3	145.6	18.7
7-Me (**6**)	140.1	134.6	182.8	119.3	136.0	124.0	125.1	[143.0]	129.7	133.9	137.4	145.1	21.8
8-Me (**7**)	139.9	134.8	182.5	119.2	136.0	120.7	124.7	132.7	[138.6]	134.0	139.0	145.9	20.9
9-Me (**8**)	140.2	134.4	182.6	118.8	135.9	123.8	122.7	131.0	129.5	[142.8]	137.4	144.4	18.1
1,2-Me$_2$ (**9**)	[142.9]	[140.1]	182.2	118.6	134.9	123.5	124.7	130.4	127.6	134.0	138.8	145.9	14.3(1-Me), 13.0(2-Me)
1,4-Me$_2$ (**10**)	[147.4]	132.2	181.3	[126.2]	130.9	124.4	124.8	130.4	127.6	133.7	137.9	146.1	18.2(1-Me), 11.9(4-Me)
2,4-Me$_2$ (**11**)	136.3	[143.2]	181.7	[127.0]	130.5	124.1	125.3	130.2	127.8	133.2	138.8	146.4	16.8(2-Me), 12.6(4-Me)
1,2,4-Me$_3$ (**12**)	[145.8]	[139.1]	181.1	[125.8]	130.1	124.2	124.8	129.8	128.4	133.5	138.5	142.5	14.2(1-Me), 13.3(2-Me), 12.5(4-Me)

a) Methyl group. b) Square brackets denote positions of methyl substituents.

TABLE 2. EFFECT OF METHYL SUBSTITUTION OF 3*H*-PHENOTHIAZIN-3-ONE

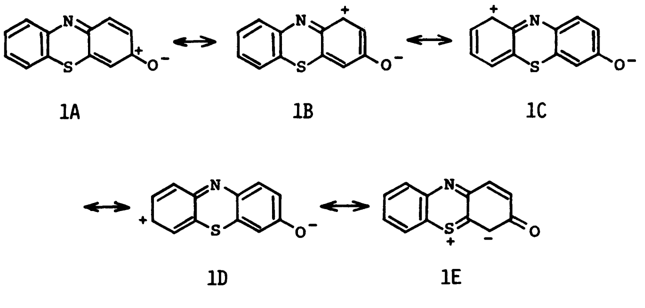
Substituent	Methyl substituent-induced chemical shift[a)]/ppm											
	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a
1-Me[b)] (**2**)	[8.0][c)]	−2.0	−0.1	−0.7	−0.1	0.1	−0.4	−0.3	−0.4	0.1	−0.6	−0.3
2-Me (**3**)	−3.4	[9.3]	0.2	−0.1	−0.9	−0.4	−0.1	−0.7	−0.3	−0.3	0.1	0.3
4-Me (**4**)	−0.1	−0.6	−0.9	[7.8]	−4.5	0.8	0.3	−0.5	−0.1	−0.3	−0.3	0.6
6-Me (**5**)	0.0	0.1	0.3	0.2	0.3	−0.5	[8.6]	0.9	−0.7	−1.3	0.2	−0.5
7-Me (**6**)	0.2	−0.3	0.2	−0.3	0.2	0.2	0.0	[11.7]	1.5	−0.1	−1.7	−1.0
8-Me (**7**)	0.0	−0.1	−0.1	−0.4	0.2	−3.1	−0.4	1.4	[10.4]	0.0	−0.1	−0.2
9-Me (**8**)	0.3	−0.5	0.0	−0.8	0.1	0.0	−2.4	−0.3	1.3	[8.8]	−1.7	−1.7
1,2-Me$_2$ (**9**)	[3.0]	[5.2]	−0.4	−1.0	−0.9	−0.3	−0.4	−0.9	−0.6	0.0	−0.3	−0.2
1,4-Me$_2$ (**10**)	[7.5]	−2.7	−1.3	[6.6]	−4.9	0.6	−0.3	−0.9	−0.6	−0.3	−1.2	0.0
2,4-Me$_2$ (**11**)	−3.6	[8.3]	−0.9	[7.4]	−5.3	0.3	0.2	−1.1	−0.4	−0.8	−0.3	0.3
1,2,4-Me$_3$ (**12**)	[3.6]	[4.2]	−1.5	[6.2]	−5.7	0.4	−0.3	−1.5	−0.8	−0.5	−0.6	−0.3

a) Relative to parent. b) Methyl group. c) Substituted carbons indicated by square brackets.

(182.6)<1,4-naphthoquinone (184.7)[38]<*p*-benzoquinone (187.0)[36] <cyclohexenone (198.9)[39]<cyclohexanone (208.8).[40] This order suggests that the upfield shift is closely associated with the delocalization of the partial possitive charge of the carbonyl carbon so long as the steric perturbation is negligible.

The chemical shifts of C-1 and C-2 in **1** move 3—4 ppm to a lower field than those of the corresponding carbons of *N*-chloro-*p*-benzoquinone monoimine. In the *p*-benzoquinone imine framework of **1**, the fact that the signal for the C-4a is more shielded than that for the C-1, in spite of the replacement of sulfur atom more electronegative than hydrogen, may be explained in terms of the normal character of phenyl vinyl sulfides and/or the contribution of the d-orbitals of the sulfur atom. The chemical shifts of the C-4 and C-4a in **1** moved downfield by 4—5 ppm in comparison with those of the corresponding vinyl group of phenyl vinyl sulfide.[41] This deshielding effect may be due to the change in the vinyl group to the olefinic double bond of a cyclic compound because the difference in chemical shifts between ethylene and the olefinic carbons of cyclohexene[42] was observed to be 5 ppm. As will be shown below, the CNDO/2 calculation of **1** suggests that the participation of sulfur d-orbitals results in the enhancement and lowering of the total electron densities of the odd-numbered carbons except for the C-9a and the even-numbered carbons except for the C-4a respectively; especially, the increased total electron densities of C-4a and C-5a adjacent to the sulfur atom are mainly based on the remarkably increased $2p_x$ orbital densities of their carbons.

The biggest differences between the benzenoid carbon shieldings of **1** and phenothiazine are the chemical shifts of C-7 and C-9. The C-7 and C-9 nuclei in the former are more deshielded than those for the corresponding carbon nuclei in the latter by 10 and 20 ppm respectively. As the C-7 and C-9 carbons are meta-carbons relative to the sulfur atom, their chemical shifts are strongly affected not by the sulfur atom, but the polar and electron-withdrawing characteristics of the imino group, promoted by the powerful polarizing carbonyl group, even if the internal olefinic double bond attenuates the transmission effect. The deshielding of C-7 and C-9 reflects the relative importance of the polar canonical forms, 1C and 1D, which have the partial positive charge on the 7 and 9 positions of the aromatic ring attributable to the electron-withdrawing carbonyl group. As a result, the signals for the C-7 and C-9 shifted to a lower field because of their positions para and ortho respectively relative to the imino group.



1A 1B 1C

1D 1E

The nitrogen atom of phenothiazine forms the apex of a flattened pyramid, with the two ipso carbons of the benzenoid moiety and hydrogen as the base. According to the classical resonance theory, a hybrid orbital containing the lone-pair electrons of the nitrogen atom has a perpendicular orientation on the base plane of the pyramid; this orientation is convenient for overlapping the $2p_\pi$ orbitals of the aromatic ring because their orbitals are relatively parallel. Therefore, a part of the lone-pair electrons flows the ortho- and para-carbons of the benzenoid ring through the π-conjugation. In the case of **1**, however, the sp^2 hybrid orbital of the lone-pair electrons is almost perpendicular to the $2p_\pi$ orbitals of the benzenoid ring. Therefore, the delocalization of lone-pair electrons is very poor. The electron-attracting nature of the imino group is facilitated by a fair overlapping between the $2p_\pi$ orbitals of nitrogen and benzenoid carbons, since the C–N bond length of the 3*H*-phenoxazin-3-one skeleton of actinomycin D has been found to be 1.36 Å; this value is smaller than that (1.399 Å) of phenothiazine.[3] The relatively high shielding of C-5a, the bridgehead quaternary carbon linking to the sulfur atom, may be due to the d-orbital contribution of the sulfur atom.

Methyl-subsituent Effect. The methyl substitution on the aromatic ring caused a shift of the ipso carbon downfield by 9—12 ppm and a shift of the para benzenoid carbon upfield by 1—3 ppm. The ortho carbon farther from the thiazine ring shifted downfield by 0.9—1.5 ppm, and another ortho carbon, upfield by 0.0—1.7 ppm. The introduction of the methyl group resulted in an upfield shift of the meta carbon, making it remoter from the thiazine ring, by 0.1—0.7 ppm, but the nearer meta carbon was only slightly affected in the range of −0.1—0.2 ppm. The upfield shift of para carbon induced by methyl substitution was enhanced as the para position approached the sulfur atom.

When a methyl group is introduced on any of the aromatic moiety except for the C-6, the signals for the 2, 4, and 10a carbons, *i.e.*, the even-numbered carbons, in the quinone imine ring shift to a field higher by 0.1—1.7 ppm, while the shielding of the other carbons, *i.e.*, the odd-numbered carbons and the C-4a, in the quinonoid ring is either unaffected or moved only slightly downfield; the substituent effect is transmitted mainly through its π-conjugated framework by means of alternation.

The replacement of the hydrogen of quinone imine by a methyl group caused a deshielding of α-carbon by 8—9 ppm and a shielding of olefinic β-carbon by 2—4.5 ppm, but the chemical shift of β-carbonyl carbon was almost unaffected. The carbonyl carbons of **1** and eleven of its methyl derivatives absorb over a fairly narrow range, *ca.* 2 ppm, or from $\delta_c = 181$ to 183. This remarkable insensitivity of carbonyl carbons to substituents has also been observed in methyl-*p*-benzoquinones[36] and 3-substituted and 2-cyclohexenones.[39] The magnitude of the β-effect of methyl group bonded to the 4-position carbon was larger than that of the other monomethyl-3*H*-phenothiazin-3-ones. The magnitude for the β-effect of the 2-methyl group is similar to that of 2-methyl-*p*-benzoquinone.[36]

The chemical shift of methyl carbon increased in the following sequence: 4-methyl = 2-methyl < 9-methyl < 1-methyl < 6-methyl < 8-methyl < 7-methyl. This order suggests that the shielding of methyl carbon increases when the methyl carbon is spatially near to the more electronegative heteroatom. The electrostatic interaction between the heteroatom and the nearest hydrogen of the methyl group enhances the polarization of the methyl $C^{\delta-}$–$H^{\delta+}$ bond and the resulting higher shielding of methyl carbon. As the methyl group can be treated as a pseudo-π-electron system, the polarization of the C–H bond of the methyl group affects the chemical shifts of α- or ipso carbon as an inductive effect through the σ-bond and those of β- or ortho and para carbons as a resonance effect through the π-bond. The magnitudes of the C_α and C_{ipso}-SCS of the methyl group decrease with an increase in the shielding of the methyl carbon, except for the methyl C_α-SCS greater than that expected at the C-2; this trend suggests that the α-effect of the methyl group is attenuated by the dispersion of the partially negative charge on the methyl carbon through the C–C σ bond. The deviation of the methyl C_α-SCS on the C-2 may be due to the more important contribution of the π-electron delocalization.

The chemical shifts of dimethyl- and trimethyl-3*H*-phenothiazin-3-ones agreed roughly with the values estimated from the data of monomethyl derivatives by using the additivity relationship, except that those of the C-1 and the C-2 in 1,2-dimethyl- and 1,2,4-trimethyl-3*H*-phenothiazin-3-ones appeared at a field higher by 2 ppm than the estimated values. The magnitude of the difference is responsible for the steric compression effects, which have been found in the chemical shifts of spatially crowded carbons, such as *o*-xylene[34,43] and 1,2- and 2,3-dimethylindoles.[44] Similarly, the chemical shift of methyl carbons is upfield in the sterically more compressed form.

Table 3. Total energies and dipole moments of 3*H*-phenothiazin-3-one in various conformations[a]

Run	Bond length /Å								Fashion	Total energy/a.u.		Dipole moment/D	
	C–N	C=N	C=O	C-4a–S	C-5a–S	Aromatic	Quinone			*spd*	*sp*	*spd*	*sp*
							C–C	C=C					
1	1.40	1.37	1.24	1.76	1.76	1.39	1.49	1.32	Planar(120°, 125°, 125°, 126°)[b]	-131.42_0	−131.11	3.34	4.10
2	1.36	1.34	1.24	1.76	1.661	1.39—1.43	1.42—1.36		Planar(120°, 124°, 126°, 124°)[c]	-131.42_1	−131.07	3.58	5.26
3	1.36	1.36	1.15	1.71	1.66	1.39	1.40	1.38	Planar(116°, 120°, 120°, 120°)[b]	−131.33		2.83	
4	1.36	1.34	1.24	1.55	1.563	1.39—1.43	1.42—1.36		Planar(120°, 124°, 126°, 124°)[b]	−131.34		5.34	
5	1.36	1.34	1.24	1.76	1.76	1.39—1.43	1.42—1.36		Planar except for S(ψ_1=−20.85°)[d]	−131.41	-131.09_5	3.60	4.88
6	1.36	1.34	1.24	1.78	1.76	1.39—1.43	1.42—1.36		Planar except for S(ψ_1=−20.88°)[d]	−131.41	-131.09_9	3.63	4.84
7	1.36	1.34	1.24	1.669	1.76	1.39—1.43	1.42—1.36		Twisted[e] (ψ_2=5°)[d]	-131.42_1	−131.07	3.57	5.22
8	1.36	1.34	1.24	1.76	1.76	1.39—1.43	1.42—1.36		Twisted[f] (ψ_2=15°)[d]	−131.41	-131.09_5	3.75	4.78
9	1.36	1.34	1.24	1.74	1.76	1.39—1.43	1.42—1.36		Twisted[f] (ψ_2=17.8°)[d]		-131.08_6		4.75
10	1.36	1.34	1.24	1.76	1.76	1.39—1.43	1.42—1.36		Twisted[e] (ψ_2=18.59°)[d]	−131.41	−131.08	3.41	4.81
11	1.36	1.34	1.24	1.71	1.751	1.39—1.43	1.42—1.36		Twisted[f] (ψ_2=19°)[d]	−131.40	−131.06	3.75	4.78
12	1.36	1.34	1.24	1.76	1.766	1.39—1.43	1.42—1.36		Twisted[f] (ψ_3=155°)[d]	−131.40	−131.07	3.89	4.41
13	1.36	1.34	1.24	1.76	1.702	1.39—1.43	1.42—1.36		Twisted[f] (ψ_3=160°)[d]	−131.41		4.19	
14	1.38	1.34	1.15	1.76	1.76	1.39	1.44	1.34	Butterfly(116°, 52.90°; 120°, −49.85°; 120°, 35.56°; 100°, −19.31°; 120°, 21.84°; 120°, −40.24°)[g]	−131.31		2.34	
15	1.35	1.35	1.15	1.71	1.71	1.39	1.40	1.38	Butterfly(120°, 25.15°; 120°, −26.69°; 120°, −16.88°; 92°, 47.05°; 120°, −48.71°; 120°, 19.95°)[g]	−131.32		3.17	
16	1.36	1.36	1.15	1.76	1.76	1.39	1.43	1.34	Butterfly(116°, 56.15°; 120°, −45.63°; 120°, 3.13°; 100°, 23.51°; 120°, −15.13°; 120°, −21.20°)[g]	−131.33		2.98	
17	1.40	1.38	1.15	1.76	1.76	1.39	1.44	1.34	Butterfly(116°, 56.70°; 120°, −36.24°; 120°, −7.88°; 100°, 29.22°; 120°, −12.23°; 120°, −27.13°)[g]	−131.34		2.93	
18	1.43	1.34	1.23	1.76	1.76	1.39	1.49	1.32	Butterfly(116°, 50.16°; 120°, −46.66°; 120°, 36.69°; 100°, −23.82°; 120°, 26.78°; 120° −42.52°)[g]	−131.39		3.22	
19	1.36	1.34	1.24	1.76	1.76	1.39—1.43	1.42—1.36		Butterfly(118°, 30.31°; 123°, −41.02°; 123°, 19.03°; 98°, 8.64°; 123°, −17.60°; 123°, 1.02°)[g]	Not converged(both *spd* and *sp*)			

a) More detailed information on molecular geometries are described in the Theoretical section. b) Bond angles of N, C-10a, C-4a, and C-9a. c) Bond angles of N, C-10a, C-5a, and C-9a. d) The bond angles of N, C-4a, C-10a, and C-9a, except for C-5a instead of C-4a for Runs 7 and 9, are equal to the corresponding data for Run 4. ψ_1 represents the dihedral angle between the N—C-10a and the C-4a—S bonds; ψ_2, that between the C-9a—N and the C-10a—C-4a bonds, and ψ_3, that between the N—C-10a and the C-9a—C-5a bonds. e) Sulfur coplanar to the benzenoid ring. f) Sulfur coplanar to the quinonoid ring. g) The bond angles and the approximate dihedral angles of atoms varying from N to C-9a in a clockwise direction on the inner thiazine ring. The angles are defined as shown in Fig. 1 of Ref. 50.

*CNDO/2 Calculation of 3*H*-Phenothiazin-3-ones.* None of the crystal structures of **1** have been reported in spite of a detailed clarification of the medicinally more important phenothiazine and its derivatives. On the other hand, in the case of 3*H*-phenoxazin-3-one, the molecular geometry can be presumed from that of actinomycin D, about which detailed stereochemical information with the DNA helix served to clarify the cancer-inhibiting mechanism.[23] X-ray crystal analysis showed the quinonoid portion of the 3*H*-phenoxazin-3-one ring system to be slightly twisted in a propeller-like fashion with respect to the aromatic portion of the chromophore.

In general, the C–S bond is longer than the C–O bond, whereas the interior angle of C–S–C is smaller than that of C–O–C.[45] If the inside thiazine ring of **1** is a planar structure in order to enhance the resonance stabilization between the benzene and the quinone rings, the bond lengths and/or bond angles among C, N, and S atoms must, at least in part, lie outside normal ranges.

There are various possible conformations of **1**, for example; (i) a planar structure, (ii) a twisted quinone fashion, and (iii) a butterfly structure such as phenothiazine. Therefore, CNDO/2 calculations of the above possible molecular structures were carried out in order to obtain information on the conformation with the lowest total energy, the correlation of the ^{13}C chemical shifts with CNDO/2 charge densities, and the magnitude of the sulfur-d-orbital contribution.

Table 3 lists the CNDO/2 total energies and dipole moments of various molecular geometries of **1**. In the *spd* approximation, the total electronic energies of **1** for the (i), (ii), and (iii) structures varied from −552.7 to −566.3 a.u., whereas the total energy for those structures changed only slightly between −131.3 and −131.4 a.u. The inclusion of d-orbitals on the sulfur atom in **1** resulted in a lowering of the total energy of 0.3—0.4 a.u. and of the dipole moment of 0.5—1.6 debye in comparison with the case of the exclusion of d-orbitals. The sulfur 3d orbitals reduce the dipole moment by introducing a *pd* polarization in the opposite sense to the *sp* polarization. The *sp* and *spd* calculations for **1** suggest that Runs 1 and 7 have the lowest total energies, −131.1133 and −131.4210 a.u. respectively; generally, (i) and (ii) are more stable than (iii) unless the repulsion of the cores increases abnormally because of the shorter bond length. The molecular geometry for Run 1 is the ideal geometry considered to maintain the planarity of the inner thiazine ring having the C–S bond length of 1.76 Å observed in phenothiazine[3] under the normal geometries of benzene and *p*-benzoquinone[46] frameworks. Run 7 is responsible for the slightly twisted, semiactual but ideal structure between the benzene and the *p*-quinone imine rings, whose bond lengths and angles are referred to the corresponding data of the 3*H*-phenoxazin-3-one geometry of actinomycin D.

Table 4 shows the CNDO/2 π and total electron densities of **1** and its methyl derivatives for the planar and twisted structures. The ^{13}C chemical shifts gave a better correlation with the π- or total ($\sigma+\pi$) electron densities calculated by the *sp*-basis set rather than the *spd*-basis set except for the α-carbons of the sulfur atom. As Table 4 shows, the *spd* approximation underestimated the total density on the C-4 and results

TABLE 4. CNDO/2 π AND TOTAL ELECTRON DENSITIES OF 3*H*-PHENOTHIAZIN-3-ONE AND ITS METHYL DERIVATIVES[a)]

Substituent	Fashion	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a
Nil (**1**)	Planar[b)]	3.9874	4.0423	3.7631	4.0748	3.9314	3.9568	4.0053	3.9876	3.9983	4.0055	3.9133	3.9148
		π 0.9702	1.0044	0.8583	1.0574	0.9521	1.0020	1.0138	0.9921	1.0057	1.0012	1.0067	0.9746
Nil (**1**)[c)]	Planar	3.9925	4.0379	3.7721	4.0268	3.9853	4.0106	3.9673	4.0021	3.9820	4.0185	3.8779	3.8901
		π 0.9691	1.0019	0.8650	1.0052	0.9529	1.0077	0.9801	1.0090	0.9808	1.0132	0.9722	0.9545
Nil (**1**)[d)]	Planar	3.9817	4.0474	3.7476	4.0806	3.9273	3.9553	4.0060	3.9855	3.9985	4.0027	3.9140	3.9221
		π 0.9612	1.0122	0.8351	1.0663	0.9430	0.9999	1.0145	0.9884	1.0059	0.9976	1.0101	0.9858
1-Me (**2**)	Planar	3.9478	4.0663	3.7655	4.0743	3.9336	3.9569	4.0057	3.9875	3.9986	4.0054	3.9132	3.9240
		π 0.9417	1.0431	0.8555	1.0538	0.9557	1.0003	1.0141	0.9917	1.0064	1.0011	1.0074	0.9805
2-Me (**3**)	Planar	4.0151	3.9961	3.7708	4.0772	3.9317	3.9584	4.0051	3.9896	3.9979	4.0071	3.9117	3.9136
		π 1.0131	0.9707	0.8611	1.0605	0.9487	1.0057	1.0132	0.9955	1.0049	1.0039	1.0025	0.9651
4-Me (**4**)	Planar	3.9871	4.0446	3.7705	4.0272	3.9575	3.9591	4.0055	3.9892	3.9983	4.0068	3.9116	3.9142
		π 0.9670	1.0075	0.8615	1.0238	0.9954	1.0031	1.0139	0.9946	1.0057	1.0032	1.0035	0.9677
6-Me (**5**)	Planar	3.9880	4.0419	3.7634	4.0748	3.9356	3.9747	3.9661	4.0062	3.9924	4.0158	3.9080	3.9128
		π 0.9703	1.0039	0.8579	1.0582	0.9500	1.0305	0.9821	1.0186	0.9934	1.0177	0.9952	0.9707
7-Me (**6**)	Planar	3.9865	4.0445	3.7629	4.0767	3.9305	3.9507	4.0242	3.9490	4.0167	3.9988	3.9230	3.9208
		π 0.9688	1.0076	0.8573	1.0600	0.9512	0.9881	1.0406	0.9600	1.0313	0.9876	1.0228	0.9844
8-Me (**7**)	Planar	3.9879	4.0420	3.7633	4.0751	3.9317	3.9652	3.9997	4.0054	3.9605	4.0241	3.9089	3.9135
		0.9704	1.0039	0.8581	1.0581	0.9512	1.0182	1.0018	1.0171	0.9754	1.0281	0.9956	0.9718
9-Me (**8**)	Planar	3.9872	4.0433	3.7632	4.0761	3.9308	3.9506	4.0157	3.9814	4.0169	3.9647	3.9318	3.9172
		0.9697	1.0059	0.8574	1.0593	0.9510	0.9904	1.0304	0.9788	1.0323	0.9687	1.0326	0.9794
Nil (**1**)	Twisted[e)]	3.9960	4.0433	3.7565	4.0797	3.9263	3.9669	4.0050	3.9868	3.9932	4.0085	3.9127	3.9018
Nil (**1**)[c)]	Twisted	3.9997	4.0391	3.7648	4.0286	3.9849	4.0256	3.9666	4.0015	3.9769	4.0222	3.8771	3.8744
Nil (**1**)[d)]	Twisted	3.9882	4.0508	3.7392	4.0876	3.9191	3.9631	4.0062	3.9823	3.9944	4.0038	3.9163	3.9096
1-Me (**2**)	Twisted	3.9546	4.0690	3.7569	4.0789	3.9277	3.9666	4.0052	3.9867	3.9936	4.0088	3.9131	3.9103
2-Me (**3**)	Twisted	4.0251	3.9968	3.7633	4.0833	3.9255	3.9693	4.0044	3.9897	3.9924	4.0113	3.9101	3.8978
4-Me (**4**)	Twisted	3.9948	4.0468	3.7635	4.0301	3.9544	3.9696	4.0051	3.9891	3.9930	4.0109	3.9103	3.8981
6-Me (**5**)	Twisted	3.9964	4.0430	3.7567	4.0802	3.9286	3.9863	3.9629	4.0070	3.9869	4.0189	3.9074	3.9001
7-Me (**6**)	Twisted	3.9944	4.0464	3.7555	4.0823	3.9243	3.9595	4.0248	3.9464	4.0121	4.0011	3.9238	3.9080
8-Me (**7**)	Twisted	3.9965	4.0428	3.7568	4.0798	3.9269	3.9751	3.9999	4.0039	3.9568	4.0277	3.9078	3.9000
9-Me (**8**)	Twisted	3.9946	4.0459	3.7558	4.0822	3.9242	3.9597	4.0164	3.9800	4.0141	3.9636	3.9316	3.9055
Nil (**1**)	Planar except	3.9945	4.0443	3.7570	4.0750	3.9285	3.9596	4.0089	3.9856	3.9956	4.0066	3.9155	3.9019
	for S[f)]	π 0.9751	1.0052	0.8678	1.0521	0.9513	0.9893	1.0077	0.9853	1.0086	0.9952	1.0139	0.9888
Nil (**1**)[c)]	Planar except	3.9985	4.0397	3.7646	4.0254	3.9905	4.0213	3.9701	4.0004	3.9785	4.0211	3.8816	3.8751
	for S	π 0.9711	1.0033	0.8747	0.9970	0.9454	0.9964	0.9707	1.0041	0.9833	1.0084	0.9771	0.9647

a) Calculated by *sp* approximation. b) Molecular geometry referred to Run 1. c) *Spd* calculation. d) Hydrogen bonding of the carbonyl group to methanol. e) Geometry associated with Run 8. f) Molecular structure in connection with Run 6.

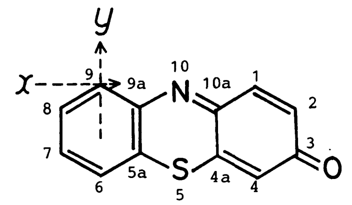


Fig 1. Numbering and coordinate systems for **1**. The z axis is perpendicular to this paper.

generally in a lowering of the total electron densities on the β- and δ-carbons numbered from the sulfur atom, and the enhancement of those on the α- and the γ-carbons; the former is mainly attributable to the decreased π-electron density, and the latter, to increases in the σ-electron density and the π-electron density. As has been described above, in the ^{13}C NMR spectrum of **1**, the signal of the C-4 appeared in the highest magnetic field; this trend is in agreement with the theoretical data calculated by means of the *sp* approximation; in the *spd* calculation, the most electron-rich carbon is not the C-4, but the C-2.

The values of the correlation coefficient, *r*, between the ^{13}C chemical shifts of all the carbons in **1** and their total electron densities, calculated in Runs 1, 5, 6, 8, and 10 by means of *sp*- and *spd*-basis sets, are 0.88 and 0.85—0.86 respectively. If it is reasonable that the linear relationship holds between the electron densities calculated by means of the *sp*- and *spd*-basis sets, the value of *r* is enhanced up to 0.89 by evaluating the degree of sulfur-d-orbital participation as 28—36%. From the linear correlation of the ^{13}C chemical shifts with the π-electron densities of the over-all carbons of interest, the best value of *r* is 0.94 for Run 1 when the *spd* contributions are somewhere between 43 and 44%, and a proportionality constant of −350.8±39.6 ppm/e was obtained for the π-electron system composed of *sp* 56% and *spd* 44%.

In the *sp* calculation of **1** in a twisted form, it is the most stable structure that the quinonoid portion is twisted at a torsional angle of 15° with respect to the aromatic ring, where the X-ray-diffraction data of actinomycin D were adopted for the bond lengths and bond angles of these rings. In this case, the value of *r* for their total electron densities is equal to 0.884, enhanced to 0.887 when the carbonyl group is weakly bonded to the solvent by means of hydrogen bonding.

From the linear relationship between the ^{13}C chemical shifts of all the carbons of **1** and its monomethyl derivatives, except for methyl carbons and their CNDO/2 *sp* electron densities in the case of a planar structure carried out in Run 1, the proportionality constants of −297.6±13.8 ppm/e ($r=0.912$) and −179.5±10.2 ppm/e ($r=0.875$) were obtained for the π- and the total electron systems respectively. Improved correlations could be obtained for only quinonoid carbons: −300.7±15.5 ppm/e ($r=0.944$) for the π-system and −181.5±9.6 ppm/e ($r=0.941$) for the total electron system. Similar *sp* calculations on the twisted structure with the torsional angle of 15° gave a

Table 5. Charge distribution in the atomic orbitals of 3*H*-phenothiazin-3-one[a)]

Atom	Atomic orbital	Run 1 Planar		Run 6 Planar except for S		Run 8 Twisted	
		spd	*sp*	*spd*	*sp*	*spd*	*sp*
C-4	2s	1.0198	1.0209	1.0135	1.0152	1.0130	1.0141
	$2p_x$	1.2036	1.0203	1.0360	1.0311	1.0334	1.0306
	$2p_y$	0.9783	0.9762	0.9789	0.9767	0.9814	0.9801
	$2p_z$	1.0052	1.0574	0.9970	1.0521	1.0008	1.0549
C-4a	2s	1.0340	1.0398	1.0343	1.0415	1.0291	1.0379
	$2p_x$	1.0263	0.9873	1.0331	0.9783	1.0261	0.9762
	$2p_y$	0.9721	0.9522	0.9776	0.9574	0.9738	0.9581
	$2p_z$	0.9529	0.9521	0.9454	0.9513	0.9559	0.9541
S	3s	1.7991	1.7886	1.8149	1.8074	1.8079	1.7995
	$3p_x$	0.8242	1.1465	0.8295	1.2126	0.8664	1.2183
	$3p_y$	1.0920	1.2187	1.2346	1.3202	1.2816	1.3701
	$3p_z$	1.9174	1.9163	1.7165	1.7435	1.6474	1.6887
	$3d_{z^2}$	0.0481		0.0636		0.0721	
	$3d_{xz}$	0.0793		0.1011		0.1070	
	$3d_{yz}$	0.0472		0.0555		0.0508	
	$3d_{x^2-y^2}$	0.1004		0.0977		0.0975	
	$3d_{xy}$	0.1811		0.1695		0.1587	
C-5a	2s	1.0241	1.0312	1.0396	1.0463	1.0428	1.0497
	$2p_x$	0.9951	0.9411	1.0115	0.9495	1.0144	0.9531
	$2p_y$	0.9837	0.9824	0.9738	0.9746	0.9795	0.9881
	$2p_z$	1.0077	1.0020	0.9964	0.9893	0.9890	0.9830
C-6	2s	1.0031	1.0067	1.0097	1.0129	1.0092	1.0126
	$2p_x$	1.0135	1.0167	1.0201	1.0205	1.0192	1.0206
	$2p_y$	0.9706	0.9681	0.9697	0.9678	0.9701	0.9680
	$2p_z$	0.9801	1.0138	0.9707	1.0077	0.9681	1.0039

a) z axis is perpendicular to the benzenoid plane.

slightly less good correlation of -170.8 ± 9.9 ppm/e ($r=0.931$) for the total electron system.

In the case of phenothiazine, the fair linear relationship between the ^{13}C chemical shifts and the CNDO/2 total electron densities gave a proportionality constant of -127.7 ± 7.1 ppm/e ($r=0.985$).[47] A slope of -171.1 ± 25.0 ppm/e ($r=0.908$) was obtained for the π-electron system;[47] this value is approximately equal to the generally accepted value of -160 ppm/e for the π-electron of aromatics.[48,49] The correlation of the ^{13}C chemical shifts of the *N*-chloro-*p*-benzoquinone monoimine used as a reference compound for the quinone portion of **1** with their charge densities was also examined. An excellent correlation with the experimental results was obtained; the proportionality constants for the π- and total electrons were -458.2 ± 36.1 ppm/e ($r=0.988$) and -224.8 ± 5.3 ppm/e ($r=0.999$) respectively. These results indicate that the proportionality constants of **1** are close to the arithmetic mean values between those of *N*-chloro-*p*-benzoquinone monoimine and phenothiazine in the cases of both π- and total electrons.

Table 5 shows the distribution of charges among the atomic orbitals from the C-4 to the C-6 of **1** in the planar and twisted fashions. The sulfur total electron densities of **1** were evaluated to be 6.05—6.08 and 6.09—6.11 by means of the *sp* and *spd* approximations respectively. The summation of the electron densities of the five d-orbitals calculated varies from 0.46 to 0.53 and decreases as the distance of the C–S bond becomes longer and/or the conformation of **1** approaches the planar structure. The participation of the 3d orbital in bonding brings about a remarkable decrease in the electron density of sulfur $3p_\sigma$ orbitals, chiefly the $3p_x$ orbital; the reverse was found for the $3p_x$ orbitals of C-4a and C-5a adjacent to the sulfur atom. The perturbation of the charge densities of even-numbered carbons non-adjacent to the sulfur by the d-orbitals occurs through the $2p_\pi$ orbitals, as can be clear in Tables 4 and 5. In particular, the $2p_\pi$ electron density on the non-nearest-neighbor carbon, C-4, is strikingly decreased. As has been described above, however, the electron densities calculated by the *spd*-basis set did not fit the observed values of the ^{13}C chemical shifts well. A significantly improved correlation was obtained by reducing the extent of sulfur d-orbital participation to less than 50%.

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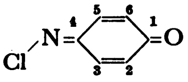
37) When the carbons of *N*-chloro-*p*-benzoquinone monoimine are numbered as:



the ^{13}C chemical shifts, δ, of their carbons in $CDCl_3$ are as follows: C-1, 186.5; C-2, 127.2; C-3, 134.6; C-4, 167.2; C-5, 137.4; C-6, 130.8. The CNDO/2 *spd* π- and total electron densities of their carbons are as follows: C-1, 0.8699, 3.7689; C-2, 0.9863, 4.0274; C-3, 0.9770, 3.9948; C-4, 0.8981, 3.8559; C-5, 0.9841, 3.9905; C-6, 0.9818, 4.0246.

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