Time-Resolved Resonance Raman and Density Functional Study of the Radical Cation of Chlorpromazine

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We have obtained a resonance Raman spectrum of the radical cation of promazine. We have also carried out density functional theory calculations to find the structures, hyperfine coupling constants (hfcc's), spin densities, and vibrational frequencies for the ground electronic states of the neutral chlorpromazine molecule and its radical cation. Preliminary vibrational assignments were made for all of the observed bands in the resonance Raman spectrum of the radical cation of chlorpromazine and in the FT-Raman spectrum of the neutral chlorpromazine molecule. Our results indicate that the radical cation of chlorpromazine has a nonplanar structure similar to that of the radical cation of promazine. However, the chlorine atom at the 2 position in chlorpromazine appears to noticeably change the hfcc's and spin densities of the radical cation compared to the radical cation of promazine. This is possibly due to conjugation and/or through-bond interactions of the chlorine atom with the central-ring heterocycle.

Introduction

Phenothiazine derivatives with *N*-aminopropyl side chains, such as promazine and chlorpromazine, are of interest due to their applications as tranquilizers and neuroleptic agents[1−4] as well as their potential use in solar energy applications.[5] It has been suggested that phenothiazine, promazine, and chlorpromazine act as good electron donors and possibly function as a charge transfer or electron donor at drug receptor sites,[6] which is consistent with the generation of charge-transfer complexes of phenothiazine-like compounds with various acceptor molecules.[7] The radical cations of phenothiazine and its derivatives are relatively stable, and it has been suggested that they play a role in the biological function of phenothiazine-like compounds.[8] Because the phenothiazine class of drugs are greatly sensitive to changes in molecular structure, detailed information about the electronic structure and geometries are needed to better understand how the small changes in these molecules and radical cations influences their biological functions and activities.

Houk and co-workers measured the photoelectron spectra of phenothiazine and four biologically active derivatives and found very little variation in their ionization potentials, which suggests that there is not a direct correlation between the neuroleptic activity and the ionization potential.[10] Several EPR investigations suggest that the biological activities of the phenothiazine class of drugs are related to the ability of the aromatic moiety to make a molecular complex at the receptor site.[11,12] A time-resolved absorption spectroscopy investigation of the radical cations of promazine and chlorpromazine showed that the radical cations are formed by a direct photoionization process.[13] This study found that the chlorpromazine radical could also be formed by the loss of the chlorine atom from the triplet state.[13] Chlorpromazine is about 10 times more toxic than promazine,[14] and it has been suggested that this is due to the formation of the radical by dechlorination of chlorpromazine. A time-resolved absorption and fluorescence study of the reactions of phenothiazine, and several of its derivatives, with chloroalkanes indicated that an electron-transfer or charge-transfer interaction takes place when the radical cation is present.[15]

The molecular structure of the neutral phenothiazine molecule and its derivatives depends on the side chain and other substituents connected to the phenothiazine moiety.[16] For example, the neutral phenothiazine molecule is folded about the N−S axis with two planes of the rings having a dihedral angle of 158.5°. This dihedral angle transforms to ∼140° for promazine and ∼139° for chlorpromazine. The radical cations of phenothizaine and its derivatives noticeably open up their structures relative to their neutral molecules. The results of photoionization work,[10] EPR experiments,[17] and recent ab initio density functional theory (DFT) calculations and experimental Raman spectra[18] indicate that the radical cation of phenothiazine is planar (or nearly so) in its ground state, with a dihedral angle ∼180°. EPR experiments on the radical cations of promazine and chlorpromazine suggest that they are nonplanar, and the folding dihedral angle of chlorpromazine radical cation was estimated to be ∼169.9°.

Several Raman studies have been performed for phenothiazine and its photochemical reactions.[18−20] The triplet state and radical cations of phenothiazine and 2-chlorphenothiazine were examined with nanosecond time-resolved resonance Raman spectroscopy by Takahashi and co-workers.[20] They found that the spin density is mainly localized on the S atom in the T_1 triplet state. Raman and ab initio DFT calculations have been reported for the neutral molecules and radical cations of phenothizaine and promazine.[18,21] These investigations found that the ground electronic states of the neutral molecules of phenothiazine and promazine have nonplanar structures with dihedral angles of ∼153° and ∼147.1°, respectively, while the radical cation of phenothiazine is planar (with a dihedral angle ∼180°) and the radical cation of promazine is nonplanar, with a dihedral angle ∼172°. The DFT calculations[18,21] suggest that the radical cation of promazine has noticeably more spin density on nitrogen, compared to sulfur, but the radical cation of phenothiazine

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radical cation has more spin density on sulfur than on nitrogen. The promazine DFT calculated HOMO and LUMO electron densities exhibit differences in both the central ring and the side chain upon excitation.[21]

In this paper, we present a resonance Raman spectrum of the radical cation of chlorpromazine. We also report ab initio DFT calculations for both the neutral chlorpromazine molecule and its radical cation. The optimized structures, electron spin distributions, and vibrational frequencies were computed for the neutral chlorpromazine molecule and its radical cation. Preliminary vibrational assignments are given for the experimentally observed Raman bands of chlorpromazine and its radical cation. The structural and vibrational frequency shifts observed upon the production of the radical cation from the neutral molecule of chlorpromazine are discussed with the computed electronic structures. We compare our results for the chlorpromazine molecule and radical cation with those previously found for phenothiazine and promazine. We discuss the varying structures and biological acitivities of phenothiazine, promazine, and chlorpromazine.

Experiment

We have previously described the experimental methods and apparatus used to acquire nanosecond time-resolved resonance Raman spectra,[18,21−24] so we shall only give a brief account here. The excitation wavelengths for the pump and probe laser beams were provided by the hydrogen Raman-shifted laser lines from the harmonics of a pulsed nanosecond Nd:YAG laser. The pump and probe beams were spatially overlapped and lightly focused on a flowing liquid stream of sample using a near collinear geometry. An optical delay was used to provide the time delay between the pump and probe pulses. The Raman scattered light was collected with a backscattering geometry and reflective optics. The reflective optics imaged the Raman signal through a depolarizer and the entrance slit of a 0.5 m spectrograph onto a grating that dispersed the light onto a liquid-nitrogen-cooled CCD detector. The CCD acquired the Raman signal (for about 60 × 10 s) before being readout to a PC computer, and ∼10−15 of these readouts were summed to obtain the resonance Raman spectrum. The FT-Raman spectra of the neutral chlorpromazine molecule were obtained using a commercial FT-Raman spectrometer (Bio-Rad) with cw 1064 nm excitation.

Chlorpromazine, spectroscopic grade methanol, and carbon tetrachloride were purchased from Aldrich and used to make samples for the Raman experiments. The time-resolved resonance Raman experiments used concentrations of $\sim 5 \times 10^{-3}$ M chlorpromazine in a 10:2 methanol/CCl_4 mixed solvent. The mixed solvent system was used to quench the chlorpromazine fluorescence and to efficiently form the radical cation of chlorpromazine because of the interactions of the S_1 state of the molecule with the chloroalkanes.[15] The chlorpromazine radical cation has an absorption band ∼520 nm (which is close to our probe excitation wavelength of 532 nm), according to laser flash photolysis experiments.[13]

Calculations

The optimized structures, electron spin distribution, hfcc's, and vibrational frequencies of neutral chlorpromazine and its radical cation were calculated using DFT computations and the Gaussian program suites.[25] The DFT computations used Becke's three-parameter hybrid method using the Lee−Yang−Parr correlation functional (B3LYP)[26] and the 6-31G* split valence plus polarization basis set. The gradients and vibrational frequencies were obtained analytically, and no imaginary frequencies were observed at the optimized structures of either the radical cation of chlorpromazine or the neutral chlorpromazine molecule. The potential energy distributions (PED) obtained from the NMODE program[27] and visual inspections of the animated normal modes from the Molden program[28] were used to find descriptions of the vibrational modes. Vibrational frequency isotopic shifts for ^{34}S- and ^{15}N-substituted derivatives of chlorpromazine were also calculated to help make some tentative vibrational assignments from comparison to experimental isotopic data available for the structurally similar phenothiazine molecule and calculated isotopic data for promazine. Hartree−Fock (HF) computations were also done for the ground state of chlorpromazine using the Gaussian programs[25] for comparison purposes.

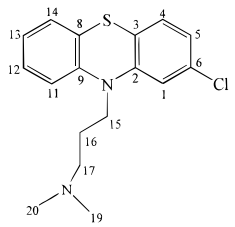

Figure 1. Diagram of the chlorpromazine molecule with the carbon and nitrogen atoms numbered 1−20. The numbering corresponds to the atom numbers used in Tables 1, 2, 5, and 6.

Results and Discussion

Figure 1 displays a simple diagram of the chlorpromazine molecule with the carbon, sulfur, and nitrogen atoms numbered 1−20, corresponding to the numbers used to denote the atoms in Tables 1 and 2. Table 1 lists the chlorpromazine structural parameters obtained from the RHF/6-31G* and DFT B3LYP/6-31G* calculations, and these results are compared to the experimental values obtained from X-ray crystallography measurements.[29] Both the experimental and the computational dihedral angles of chlorpromazine between the two lateral rings indicate that the ground electronic state of chlorpromazine is folded along the N−S axis, and this is similar to analogous results for promazine.[21] The introduction of the $(CH_2)_3N(CH_3)_2$ side chain at the N-atom position of the phenothiazine group, to form the promazine derivatives, gives rise to smaller dihedral angle values. This suggests that the degree of folding increases for large substituents at N-substituted derivatives, such as promazine and chlorpromazine, because of interactions between the side chain and the central ring system of the phenothiazine group. In contrast, the chlorine substitution that forms chlorpromazine from promazine has little effect on the dihedral angle. Examination of Table 1 shows that the HF and DFT computational results have similar values for both the bond lengths and the bond angles for the ground electronic state. The computational results of Table 1 generally display reasonable agreement with the experimental (X-ray) results. Comparison of the CSC and CNC bond angles in Table 1, for chlorpromazine with the corresponding values for phenothiazine,[16,17] indicates that the introduction of the side chain in chlorpromazine has little effect on these bond angles.

The structural parameters of the radical cation of chlorpromazine, computed from UHF and DFT calculations, are compared with results derived from X-ray diffraction experiments in Table 2. The DFT calculations and the experimental results shown in Tables 1 and 2 indicate that the dihedral angle increases upon going from the parent molecule to the radical cation of chlorpromazine (146° to 171.7°, DFT; 139.4−69.9°, experi-

TABLE 1: Structural Parameters for the Ground State of the Neutral Chlorpromazine Molecule Calculated Using HF and DFT Methods with a 6-31G* Basis Set and a Comparison to Experimental Values Determined by X-ray Diffraction[a]

parameters	RHF calcd	DFT/B3LYP calcd	X-ray expt[b]
dihedral angle (S−N)	147	146	139.4
dihedral ($C_{16}-C_{15}-N-C_2$)	−82.9	−82.2	
dihedral ($C_{17}-C_{16}-C_{15}-N$)	161.8	160.6	
dihedral ($C_{19}-N_{18}-C_{17}-C_{16}$)	82.8	81.7	
C_3-S-C_8	98.8	99.2	97.3
C_2-N-C_9	120.7	121.6	118.4
C_3-S	1.768	1.776	1.75
C_8-S	1.770	1.779	1.75
C_2-N	1.404	1.41	1.40
C_9-N	1.412	1.418	1.41
$C_{15}-N$	1.460	1.467	1.51
C_1-C_2	1.393	1.406	1.4
C_2-C_3	1.40	1.413	1.4
C_3-C_4	1.382	1.394	1.42
C_4-C_5	1.385	1.395	1.38
C_5-C_6	1.376	1.388	1.39
C_6-C_1	1.383	1.394	1.4
$C_{15}-C_{16}$	1.541	1.546	1.53
$C_{16}-C_{17}$	1.531	1.536	1.55
$C_{17}-N_{18}$	1.456	1.468	1.45
$N_{18}-C_{19}$	1.449	1.459	1.46
$N_{18}-C_{20}$	1.449	1.460	1.49
C_1-H_1	1.067	1.079	
C_4-H_4	1.075	1.086	
C_5-H_5	1.073	1.084	
C_6-Cl	1.745	1.762	1.74
C_2-N-C_{15}	119.6	118.8	117.8
C_9-N-C_{15}	118.5	117.9	117.7
C_2-C_3-S	119.9	120.4	119.7
C_3-C_2-N	120.9	121.3	118.1
$S-C_3-C_4$	119.1	118.6	
$C_2-C_1-H_1$	121.2	121.2	
$C_1-C_2-C_3$	117.4	117.4	120.3
$C_2-C_3-C_4$	120.8	120.8	119.3
$C_3-C_4-H_4$	118.9	118.9	
$C_3-C_4-C_5$	121.4	121.5	121.7
$C_4-C_5-H_5$	121.3	121.3	
$C_4-C_5-C_6$	117.6	117.6	117
C_5-C_6-Cl	119.5	119.6	118.7
$C_5-C_6-C_1$	122.0	122.0	119.8

[a] Bond lengths are in Å and bond angles are in degrees. [b] Values are from X-ray diffraction experimental results reported in ref 29.

TABLE 2: Structural Parameters for the Ground State of the Radical Cation of Chlorpromazine, Calculated Using HF and DFT Methods with a 6-31G* Basis Set and a Comparison to Experimental Values Determined by X-ray Diffraction for Chlorpromazine[a]

parameters	RHF calcd	DFT/B3LYP calcd	X-ray expt[b]
dihedral angle (S−N)	170.4	170.5	169.9
dihedral ($C_{16}-C_{15}-N-C_2$)	−89.5	−89.6	−88.4
dihedral ($C_{17}-C_{16}-C_{15}-N$)	−160.5	−155.8	−178.4
dihedral ($C_{19}-N_{18}-C_{17}-C_{16}$)	82.3	85.1	54.5
C_3-S-C_8	100.1	102.4	99.6
C_2-N-C_9	124.0	124.1	123.5
C_3-S	1.749	1.739	1.733
C_8-S	1.751	1.742	1.776
C_2-N	1.387	1.396	1.391
C_9-N	1.382	1.400	1.442
$C_{15}-N$	1.501	1.487	1.459
C_1-C_2	1.422	1.414	1.414
C_2-C_3	1.417	1.423	1.361
C_3-C_4	1.401	1.407	1.392
C_4-C_5	1.390	1.380	1.385
C_5-C_6	1.400	1.407	1.358
C_6-C_1	1.384	1.385	1.360
$C_{15}-C_{16}$	1.534	1.541	1.499
$C_{16}-C_{17}$	1.533	1.538	1.527
$C_{17}-N_{18}$	1.455	1.468	1.509
$N_{18}-C_{19}$	1.456	1.466	1.453
$N_{18}-C_{20}$	1.455	1.466	1.453
C_1-H_1	1.066	1.079	
C_4-H_4	1.074	1.086	
C_5-H_5	1.072	1.084	
C_6-Cl	1.727	1.736	1.729
C_2-N-C_{15}	118.3	118.3	118.7
C_9-N-C_{15}	117.4	117.6	117.6
C_2-C_3-S	123.0	123.4	125.0
C_3-C_2-N	122.3	122.3	122.6
$S-C_3-C_4$	117.0	116.0	113.4
$C_2-C_1-H_1$	121.6	121.1	
$C_1-C_2-C_3$	118.2	117.4	117.6
$C_2-C_3-C_4$	119.8	120.5	121.5
$C_3-C_4-H_4$	118.9	119.1	
$C_3-C_4-C_5$	121.5	121.1	120.5
$C_4-C_5-H_5$	120.8	121.0	
$C_4-C_5-C_6$	118.8	118.6	117.3
C_5-C_6-Cl	119.8	119.3	118.4
$C_5-C_6-C_1$	120.6	121.5	119.7

[a] Bond lengths are in Å and bond angles are in degrees. [b] Values are from X-ray diffraction experimental results reported in ref 11.

mental). The radical cation of chlorpromazine has a nonplanar structure, and this is consistent with previous electron spin resonance (ESR) studies that suggest that the promazine and chlorpromazine radical cations are nonplanar.[11,17] The change in oxidation affects the folding dihedral angle, mainly due to the change in heteroatom hybridization. An inspection of Tables 1 and 2 reveals that several bond lengths and bond angles associated with the central ring group change noticeably upon formation of the radical cation from the neutral parent chlorpromazine: the C−S bond length decreases by 0.04 Å, the C−N bond length decreases by 0.018 Å, the CSC bend angle increases from 99.2° to 102.4°, and the CNC bend angle increases from 121.6° to 124.1°. The phenyl ring bond lengths (C_1-C_2, C_2-C_3, and C_5-C_6) increase upon formation of the radical cation from the neutral chlorpromazine molecule.

Table 3 compares calculated and experimental proton hfcc's for the radical cations of phenothiazine, promazine, and chlorpromazine. Because UHF and MP2 ab initio methods are known to be deficient in computing accurate hfcc's and spin densities, due to severe spin contamination of the ground-state wave function,[30] we only compare the hybrid HF/DF B3LYP results to the experimental results. Several investigations on other organic radicals have shown that gradient corrected BP86, BLYP, and hybrid HF/DF B3LYP methods produce calculated hfcc's that are close to the values obtained from ESR experiments.[31−33] Examination of Table 3 shows that there is reasonable agreement between the DFT computed results and the experimental ESR results (note, the experiments determine only the magnitude and not the sign of the hfcc's). The ratio of $\alpha(N)/\alpha(H_5)$ is interpreted in terms of the dihedral folding angle of the radicals in response to the type of substituent.[17] The relative value of this ratio for side chains attached with primary or secondary carbons is consistent with the steric requirements of the side chains (e.g., the more hindered the aminum center, the greater the fold angle induced in the central heterocycle). It is interesting to note that the calculated value of $\alpha(N)$ decreases

TABLE 3: Hyperfine Coupling Constants[a] (hfcc's) Calculated Using DFT Methods with a 6-31G* Basis Set and a Comparison to Experimental Values for Phenothiazine (PHT), Promazine (PRZ), and Chlorpromazine (CPRZ) Radical Cations

	DFT/B3LYP calcd			expt		
parameter	PTH	PRZ	CPRZ	PTH[b]	PRZ[c]	CPRZ[c]
α(N)	5.45	9.41	6.56	6.34	7.08	6.85
$\alpha(\beta$H)	−7.94	3.53	3.36	7.29	3.52	3.42
$\alpha(H_1)$	0.74	−1.39	−0.64	1.13	0.92	1.01
$\alpha(H_4)$	−0.98	0.94	0.45	0.50	0.40	0.50
$\alpha(H_5)$	−2.66	−2.84	−2.43	2.49	1.92	1.89
$\alpha(H_6)$	−0.66	−0.24	0.25	0.50	0.80	
α(N)/$\alpha(H_5)$	2.06	3.32	2.70	2.55	3.612	3.62

[a] Hyperfine coupling constants are in Gauss units. [b] Values from ref 17. [c] Values from ref 11.

TABLE 4: Spin Density Dsitributions for the Radical Cations of Phenothiazine (PTH), Promazine (PRZ), and Chlorpromazine (CPRZ), Calculated Using DFT Methods with a 6-31G* Basis Set

	DFT/B3LYP calcd		
parameter	PTH	PRZ	CPRZ
ρ_S	0.27	0.23	0.26
ρ_N	0.26	0.33	0.28
ρ_{C1}	0.02	0.04	0.01
ρ_{C2}	0.04	−0.01	0.01
ρ_{C3}	0.12	0.12	0.12
ρ_{C4}	−0.05	−0.06	0.01
ρ_{C5}	0.10	0.11	0.09
ρ_{C6}	0.01	−0.01	0.02
ρ_{C8}	0.12	0.13	0.11
ρ_{C9}	0.04	0.01	0.03

going from the promazine radical cation (9.41) to the chlorpromazine radical cation (6.56), and the value of $\alpha(\beta$H) for the radical cation of chlorpromazine also decreases in comparison with the value for promazine. The same qualitative trends are also observed for the α(N) and $\alpha(\beta$H) changes between the promazine and chlorpromazine radical cations for the experimental values of Table 3. The differences found for the hfcc's between the promazine and chlorpromazine radical cations indicate that the redistribution of charge and spin density of the unpaired electron are related to the presence of the chlorine atom. Solvent interaction with the chlorine atom may indirectly affect the hfcc's. For example, solvent effects on the radical cations of promazine and chlorpromazine were reported by Soria and co-workers[11] in a series of ESR experiments. They found that the electronic effect of the chlorine atom substituent is likely perturbed by solvent interaction with the chlorpromazine radical cation through hydrogen bonding with the chlorine atom. The ESR experimental results also found that the decrease in the $\alpha(\beta$H) coupling constant is related to the decrease of the π spin density (α(N)).

Table 4 presents the calculated spin densities of the carbon, sulfur, and nitrogen atoms of the radical cations of phenothiazine, promazine, and chlorpromazine, determined using a Mulliken population analysis of the B3LYP DFT results. Mulliken population analyses give atomic charge spin densities that noticeably depend on the particular basis set and computational methods employed.[34] Thus, the spin densities given in Table 4 should be used with some caution. However, the qualitative features of the calculated spin densities in Table 4 are interesting to compare. The magnitude of the spin density at N (0.28) for chlorpromazine radical cation is smaller than that at N (0.33) for the promazine radical cation, while the spin density at S (0.26) for chlorpromazine radical cation increases

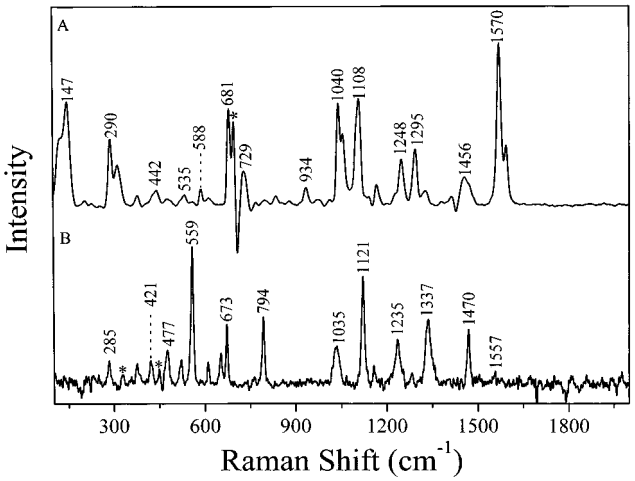

Figure 2. (A) FT-Raman spectrum of neutral chlorpromazine molecule in the solution phase. The spectrum has been solvent and background subtracted. The asterisk marks a solvent subtraction artifact, and the larger Raman bands are labeled. (B) Time-resolved resonance Raman spectrum of the radical cation of chlorpromazine in the solution phase. The spectrum has been solvent and background subtracted, and the larger Raman bands are labeled.

moderately compared to the value for the promazine radical cation (0.23). This qualitative behavior of the S- and N-spin densities is consistent with our calculated hfcc's and previously reported ESR experimental results,[11,17] which suggest that the redistribution of charge and spin density of the unpaired electron occurs in the radical cation of chlorpromazine because of the interaction of the chlorine atom substituent. The values of the spin densities at C_3 (0.12) and C_8 (0.11) are larger than those of other carbon atoms, and this is consistent with the ESR experimental results,[11,17] which indicate that the side-chain interaction with the central ring of the phenothiazine group in promazine and chlorpromazine displays preferences for particular conformations along the C−N bond.

Figure 2A shows the FT-Raman spectrum of the neutral chlorpromazine molecule in its ground electronic state. Table 5 presents a comparison of the experimental Raman vibrational frequencies with the RHF- and DFT-calculated vibrational frequencies for chlorpromazine. Table 5 also lists the DFT/B3LYP calculated isotopic shifts for several ^{34}S- and ^{15}N-substituted derivatives of chlorpromazine. A comparison of the HF and DFT calculations with the experimental values shows that the DFT-calculated vibrational frequencies exhibit reasonable agreement without scaling, while the HF values need to be scaled (and generally do not agree as well as the DFT results). This is similar to other comparisons of ab initio calculated vibrational frequencies with experimental results for other organic molecules.[35,36] However, we note that there is a somewhat larger discrepancy between the ring C−C stretch and the C−H stretch DFT-calculated values and the experimental values, which is similar to the DFT results for tetrachlorinated dibenzodioxins reported by Rauhut and Pulay.[37] A moderate amount of scaling for the ring C−C and C−H stretch modes (scaling of these modes by 0.9614[38] gives the values shown in parentheses in Tables 5 and 6) can improve the agreement between the DFT and the experimental values. We shall refer to the DFT calculation results when making preliminary assignments for the experimental Raman vibrational bands in the succeeding section.

The DFT calculated ring C−C stretch modes at 1606 and 1659 cm^{-1} are assigned to the experimental Raman bands at 1570 and 1594 cm^{-1}, respectively (similar to previous assign-

TABLE 5: Vibrational Frequencies[a] of the Neutral Chlorpromazine Molecule Calculated Using HF and DFT/B3LYP Methods with a 6-31G* Basis Set

approximate description	calcd RHF	calcd DFT	expt[b]	^{34}S-subst DFT	$^{15}N_{10}$-subst DFT	$^{15}N_{18}$–subst DFT
central-ring def (out-of-plane butterfly-like mode)	56	55				
central ring boat def.	85	87				
ring def (out-of-plane) + $CCCN_{18}$ torsion	101	107	116 w			
ring def (out-of-plane)	142	149	147 m			
central ring boat def	163	169				
$N_{10}CCC$ torsion	208	219	207 vw			
central ring chair def + $CCCN_{18}$ torsion	221	237	228 vw			
central ring boat def	283	290	290 s			
$CN_{18}C$ wag	291	307	315 m			3.1
central ring def + $NC_{15}C_{16}$ wag	319	333		1.5		
$CN_{10}C$ wag	370	393	378 w		2.1	1
CCN_{18} wag	389	408				
$CN_{18}C$ bend	413	432	429 w			0.8
Central ring def	422	441				
CSC bend	434	455	442 w	3		
ring def (out-of-plane)	471	468	478 w			
ring def (out-of-plane)	490	489	535 w			
C−Cl stretch	527	543	589 w			
CCC bend + CCN_{10} bend	612	609	614 vw		1.8	
$CN_{10}C$ bend	650	674	681 vs ?		3.1	
CCC bend	677	698	681 vs ?			
CCC bend	702	725	727 vw ?		1	
CH_2 rock	714	735	727 vw ?			
C−H bend (out-of-plane)	766	763	768 vw			
C−H bend (out-of-plane)	781	785	799 vw			
CH_2 rock	811	842	836 w			
$C_{15}C_{16}$ stretch	848	884	882 vw ?			
C−H bend (out-of-plane)	873	890	882 vw ?			
CH_2 twist + C_9NC_{15} bend + C−Cl str	899	932	934 w		7.1	
C−H bend (out-of-plane)	921	978	973 vw			
$CN_{18}C$ stretch + C_{16}−C_{17} stretch	967	1005				5.7
C−H bend (out-of-plane)	1008	1019				
ring breathing	1032	1074	1040 vs			
CH_3 wag	1051	1084	1056 s			
CSC sym stretch	1074	1125	1110 vs	1		
CH_3 wag	1101	1139	1139 w			
C−H bend	1128	1175	1165 m			
C−H bend	1142	1191				
C−H bend + CH_2 twist	1170	1210				
ring def	1193	1235				
CH_2 twist	1221	1258	1248 m ?			
$CN_{10}C$ sym stretch	1244	1281	1248 m ?		7.9	
C−H bend + CH_2 twist	1259	1301	1294 s			
CH_2 twist + CN_{18} stretch	1292	1331	1327 w			6
CH_2 twist	1310	1346				
C−H bend + CH_2 twist	1354	1400				
CH_2 wag	1380	1421	1410 vw			
CH_2 wag	1393	1434				
C−H bend + CCC sym stretch	1407	1452	1457 m			
CH_3 sym def	1436	1486	1467 m			
CH_3 sym def	1459	1505				
CH_3 bend	1473	1527				
CH_2 bend	1483	1542				
CH_3 bend	1495	1556				
CH_2 bend	1501	1567				
ring CC stretch	1574	1606 (1544)	1570 vs			
ring CC stretch	1589	1634 (1570)				
ring CC stretch	1611	1659 (1595)	1594 s			
C−H stretch	2784	2936 or (2822)				
C−H stretch	2795	2952 or (2838)				
CH_2 sym stretch	2874	3060 or (2942)				
CH_3 sym stretch	2895	3090 or (2971)				
CH_2 asym stretch	2917	3111 or (2991)				
CH_3 asym stretch	2935	3135 or (3014)				
ring CH asym stretch	3003	3199 or (3076)				
ring CH asym stretch	3014	3210 or (3086)				
ring CH sym stretch	3033	3228 or (3103)				
ring CH sym stretch	3052	3253 or (3127)				
ring C−H stretch	3071	3244 or (3119)				
ring C−H stretch	3110	3292 or (3165)				

[a] The calculated frequencies are compared to experimental values where available. [b] This work. Experiment intensity description: vs = very strong; s = strong; m = medium; w = weak; vw = very weak. DFT calculated values in parentheses are C−C stretch and C−H stretch frequencies scaled by 0.9614 (see text).

TABLE 6: Vibrational Frequencies[a] of the Radical Cation of Chlorpromazine Calculated Using UHF and DFT/B3LYP Methods with a 6-31G* Basis Set

approximate description	calcd UHF	calcd DFT	expt[b]	^{34}S-subst DFT	$^{15}N_{10}$subst DFT	$^{15}N_{18}$-subst DFT
ring def (out-of-plane)	60	62				
central ring boat def	89	96				
ring def (out-of-plane) + $CCCN_{18}$ torsion	101	104				
central ring def + C−Cl def	158	165				
ring def (out-of-plane)	200	217				
ring CCCC wag	223	235				
$CN_{18}C$ wag	274	293	285 w	1.2		2.3
central ring boat def	312	328		1.7		
central ring chair def	359	382	377 w	2.7	1	
ring def (out-of-plane)	402	426	421 m			
CSC bend	436	453	477 m	2.5		
ring CCC wag	453	488				
ring def (out-of-plane)	505	545	522 w		1.6	
C−Cl stretch	525	558	559 vs	2.3	1.4	
ring CCC wag	576	617	611 w		2	
ring CCC bend	597	637	653 m			
$CN_{10}C$ bend	650	677	673 s		3.1	
C−H bend (out-of-plane)	690	729				
C−H bend (out-of-plane) + C_{15}−N_{18} stretch	717	746				1.5
C−H bend (out-of-plane)	749	758				
C−H bend (out-of-plane)	760	802	794 s			
$CN_{18}C$ sym stretch + CH_2 rock	815	845				
C−H bend (out-of-plane)	820	858				
C_{15}−C_{16} stretch	852	890				
C−H bend (out-of-plane)	871	922				
CCC bend + C_9N stretch	886	943			6.2	
C_{16}−C_{17} stretch + N_{18}−C_{17} stretch	947	997			4.8	3
C_{15}−N_{10} stretch	971	1043	1035 m ?		4.1	
ring breathing	1013	1065	1035 m ?			
CH_3 wag + CH_2 rock	1042	1077				
CH_2 rock + CH_3 wag	1069	1107				
CSC sym stretch	1080	1120	1121 vs	1		
CH_3 wag	1098	1134				
C−H bend	1122	1178	1157 w			
C−H bend + CN_{10} stretch	1133	1235	1235 m ?		2.5	
$CN_{10}C$ sym stretch	1156	1263	1235 m ?		4	2.5
C−H bend	1177	1298	1283 vw			
C−H bend	1231	1309				
CH_2 twist	1265	1324	1337 s			
CH_2 wag	1298	1380			4	
CH_2 twist	1315	1385				
CH_2 wag	1337	1391				
C−H bend	1351	1442				
CH_2 wag	1369	1409				
CH_2 wag	1389	1427				
C−H bend	1425	1496	1470 s ?			
CH_3 sym def	1438	1509	1470 s ?			
ring CC stretch	1460	1496				
CH_2 bend	1480	1532				
ring CC stretch	1493	1581 (1520)	1557 vw			
ring CC stretch	1503	1611 or (1549)				
ring CC stretch	1543	1643 or (1580)				
CH stretch	2818	2982 or (2867)				
CH_2 sym stretch	2834	2993 or (2877)				
CH_2 sym stretch	2884	3069 or (2951)				
CH_3 sym stretch	2899	3096 or (2979)				
CH_2asym stretch	2925	3113 or (2992)				
CH_3 asym stretch	2941	3143 or (3021)				
CH_2 sym stretch	2960	3122 or (3001)				
CH_2 asym stretch	3017	3169 or (3047)				
ring C−H asym stretch	3029	3223 or (3099)				
ring C−H stretch	3043	3232 or (3107)				
ring C−H sym. stretch	3053	3249 or (3123)				
ring C−H stretch	3160	3297 or (3170)				

[a] The calculated frequencies are compared to experimental values where available. [b] This work. DFT calculated values in parentheses are C−C stretch and C−H stretch frequencies scaled by 0.9614 (see text).

ments made for phenothiazine and promazine). The experimental Raman bands at 1467 and 1457 cm^{-1} are assigned to the DFT calculated 1484 cm^{-1} (CH_3 sym Def) and 1434 cm^{-1} (C−H bend + CCC sym Stretch) vibrational modes. The experimental 1410, 1327, and 1165 cm^{-1} Raman bands are assigned to the nominal CH_2 wag (DFT calculated 1421 cm^{-1}) and two C−H

bend modes (DFT calculated 1331 and 1165 cm^{-1}), respectively. The 1248 cm^{-1} experimental Raman band is assigned to the DFT calculated $C-N_{10}-C$ symmetric stretch mode at 1283 cm^{-1} and/or the CH_2 twist at 1258 cm^{-1}, while the 1110 cm^{-1} experimental band is assigned to the C−S−C symmetric-stretch vibration (DFT-calculated frequency of 1127 cm^{-1}). The calculated isotopic shifts for the ^{34}S- and ^{15}N-substituted chlorpromazine derivatives in Table 5 for the C−S−C and C−N−C symmetric stretch modes are similar to experimental isotopic shifts observed for the corresponding modes in 2-chlorphenothiazine molecules.[20] The Raman bands at 442 and 429 cm^{-1} are assigned to the CSC bend and the central ring deformation and/or $CN_{18}C$ bend modes, respectively. Using a comparison to the promazine and 2-chlorophenothiazine molecules, the experimental chlorpromazine bands at 535 and 589 cm^{-1} are assigned to the out-of-plane ring deformation and C−Cl stretch modes, respectively. We have also made preliminary assignments of the other Raman bands observed, and they are given in Table 5. The two experimental Raman bands at 681 and 727 cm^{-1} assignments are somewhat ambiguous because of the two possible assignments for each of these modes. However, further experimental data, using the $^{15}N_{10}$ substituted derivative, could likely distinguish the two possible assignments for the 681, 727, and 1248 cm^{-1} Raman bands because one possible assignment is predicted to shift noticeably in frequency, while the other possible assignment would not shift in frequency. Similarly, the isotopic shifts for other derivatives of chlorpromazine could be used to improve or better determine the vibrational assignments of other experimentally observed vibrational bands as has been done previously for the related phenothiazine and 2-chlorophenothiazine compounds.[20]

Figure 2B displays a time-resolved resonance Raman spectrum of the radical cation of chlorpromazine. Table 6 gives a comparison of the UHF and DFT/B3LYP calculated vibrational frequencies with the observed Raman vibrational frequencies. We have made preliminary assignments for the experimentally observed Raman bands (given in Table 6) of the radical cation of chlorpromazine, and we shall focus on some of the highlights here. One of the largest resonance Raman bands is the nominal C−Cl stretch vibrational mode at 559 cm^{-1}, and this frequency is close to that observed in the resonance Raman spectra of 2-chlorophenothiazine (553 cm^{-1}).[20] The experimental Raman bands at 1121, 673, 477, 421, and 285 cm^{-1} are assigned to the nominal CSC symmetric stretch, $CN_{10}C$ bend, CSC bend, ring deformation (out-of-plane) + $N_{10}CCC$ torsion, and $CN_{18}C$ wag modes, respectively. A few of the observed Raman bands, such as the 1235 and 1035 cm^{-1} bands, are not easy to assign because they each have two plausible assignments. However, experimental isotopic derivative vibrational spectra for the radical cation of chlorpromazine can likely be used to distinguish the between the two possible assignments because of the differing isotopic shifts of their vibrational modes (such as the $^{15}N_{18}$ derivative for the 1235 cm^{-1} band and the $^{15}N_{10}$ derivative for the 1035 cm^{-1} band).

It is revealing to compare the chlorpromazine radical cation Raman spectrum with that for the neutral parent molecule. The vibrational frequencies of the CSC bend and the CSC symmetric stretch modes increase by 35 and 11 cm^{-1}, respectively, upon changing from the neutral chlorpromazine molecule to its radical cation. This suggests that the dihedral angle along the S−N axis becomes greater in the radical cation than in the parent neutral molecule, and this is consistent with the results of both the DFT ab initio calculations presented here and the ESR experiments for chlorpromazine previously reported.[11,17] Results derived from photoelectron spectra[10] also imply that the dihedral angle change, upon production of the radical cation, leads to better π-orbital overlap between the C and the N atoms and between the ring C and the ring S atoms to give larger aromatic resonance stabilization of the radical cation. This would be expected to affect the C−S and C−N bonds' electron density more than it would affect the two phenyl rings. It is interesting that the $CN_{10}C$ bend and $CN_{10}C$ symmetric stretch vibrational frequencies of the radical cation remain close to the values for the neutral chlorpromazine molecule (681 and 1248 cm^{-1} for neutral chlorpromazine and 673 and 1235 cm^{-1} for the radical cation) and have a moderate lowering of frequency (−8 and −13 cm^{-1}, respectively). This is in contrast to the case of phenothiazine, for which these two modes increase in frequency significantly in the radical cation compared to the neutral parent molecule.[18] The phenothiazine radical cation displays substantial increases in the vibrational frequencies of the $CN_{10}C$ bend, $CN_{10}C$ symmetric stretch, CSC bend, and CSC symmetric stretch modes, compared to the neutral phenothiazine molecule, which is consistent with a planar structure of the radical cation.[18] However, the $CN_{10}C$ bend and $CN_{10}C$ symmetric stretch modes for both promazine and chlorpromazine radical cations lack the frequency increases (and even display moderate decreases in frequency), relative to the neutral parent molecules, and this implies that these radical cations still have a nonplanar structure. This implication is corroborated by the chlorpromazine radical cation DFT-calculated dihedral angle of 171°, the calculated hfcc $\alpha(N)/\alpha(H_5)$ ratio, and the ESR results (shown in Table 3).[11,17]

We have also made a semiquantitative comparison of the calculated vibrational normal modes of the chlorpromazine radical cation with those of the promazine radical cation, using the ViPA program[39,40] (this program provides quantitative analysis of the vibrational modes of one molecule for comparison with those of a structurally similar molecule). The decomposition of the calculated (UHF) mode at 525 cm^{-1} into promazine modes (5.6%, 328 cm^{-1} + 2.6%, 406 cm^{-1} + 7.0%, 454 cm^{-1} + 3.9%, 591 cm^{-1}) does not have any contribution greater than 10% from the promazine radical cation modes. This is consistent with its assignment to the nominal C−Cl stretch mode. Similar results are found for the calculated 158 cm^{-1} mode, and this is consistent with its assignment to the ring deformation (out-of-plane) plus the C−Cl bend deformation. The C−C stretch and C−H stretch normal modes for chlorpromazine radical cation are very similar to those of the promazine radical cation. For example, the ring C−C stretch at 1543 cm^{-1} of the chlorpromazine radcial cation is described as 90% of the 1543 cm^{-1} mode of the promazine radical cation. However, some of the lower frequency modes of the chlorpromazine radical cation are different from those of the promazine radical cation because their structures are noticeably different from each other. Generally, these lower frequency chlorpromazine radical cation modes have a large contribution from the promazine radical cation mode that is very close in frequency to the chloropromazine radical cation vibration. The decomposition of the chlorpromazine radical cation modes into the promazine radical cation normal modes, determined using the ViPA program,[39,40] is available as Supporting Information.

The resonance Raman intensity patterns of the radical cations of chlorpromazine and promazine are very different from one another. This implies that the excited electronic states of the radical cations of promazine and chlorpromazine undergo significantly different structural changes relative to their ground electronic state structures. The C−Cl stretch and CSC symmetric

stretch are substantially larger than the $CN_{10}C$ bend and $CN_{10}C$ symmetric stretch modes and do not change much in intensity in the chlorpromazine radical cation resonance Raman spectra compared to the promazine radical cation resonance Raman spectrum. The significant intensity of the C−Cl stretch mode in the chlorpromazine radical cation is very similar to the T_1 to T_n resonance Raman spectra for 2-bromonaphthalene, which displays substantial intensity in the C−Br in-plane deformation and C−Br stretch fundamentals and noticeable intensity in their combination bands with the intense C−C stretch mode (analogous to the ν_{5a} mode in naphthalene).[22,41] The T_1 state of 2-bromonaphthalene does not readily undergo debromination and is relatively stable, but the T_n state undergoes efficient debromination (probably via a predissociative mechanism).[22,41] Chlorpromazine is about 10 times more phototoxic and photoallergic than promazine, and this has been suggested to be due to photoinduced dechlorination.[14,42−44] Takahashi and coworkers[20] observed a similar resonance Raman spectrum for 2-chlorophenothiazine, which had substantial intensity in the C−Cl stretch fundamental. They also observed an unidentified transient in their transient absorption spectra for the radical cation of chlorophenothiazine that could be due to the phenothiazinyl neutral radical formed by photoinduced dechlorination.[20] Our resonance Raman spectra for the radical cation of chlorpromazine is consistent with a photoinduced dechlorination reaction similar to the "reluctant" carbon−halogen bond cleavage reactions observed for other haloaromatic compounds (such as 2-bromonaphthalene) and the possible dechlorination reaction found for 2-chlorophenothiazine.

One of the more intriguing aspects of the phenothiazine derivatives, such as promazine and chlorpromazine, is their pattern of biological activity. To have high neuroleptic activity, it is necessary to have an electronegative substituent at the 2 position.[10,45−47] However, the biological activity does not follow a simple trend with the degree of electronegativity of the substituent: weak electron-withdrawing substituents, such as chlorine and thiomethyl, have similar neuroleptic activity (chlorpromazine and thiordazine, respectively). A stronger electron-withdrawing group like methylsulfinyl gives a lower neuroleptic activity (mesoridazine), and the very strong electron-withdrawing group of trifluoromethyl produces very strong neuroleptic activity (trifluoperazine).[45−47] This suggests that there is some optimum structural and electron density for the drug to achieve the largest biological activity and that these 2-position substituents noticeably tune the structure and electron density. Our DFT results for promazine and chlorpromazine, and their radical cations, suggest that the radical cation structures and the spin densities are significantly perturbed by the 2-position chlorine substitution. This can account for the substantial difference in neuroleptic activity between promazine and chlorpromazine and may show a good correlation with the neuroleptic activities of phenothiazine derivatives in general. Further work on thiordazine, mesoridazine, and trifluoperazine is planned to test this hypothesis for the correlation of biological activity with the perturbation of the structure and spin densities of the radical cations of the phenothiazine derivatives.

It is interesting to examine how the 2-position substituent may perturb the structure and spin densities of the radical cations of the phenothiazine derivatives. Inspection of Tables 1 and 2 shows that the formation of the radical cation of chlorpromazine from the neutral molecule leads to a longer $N-C_9$ bond (from 1.41 to 1.442 Å), a shorter $N-C_2$ bond (from 1.40 to 1.391 Å), a longer C_1-C_2 bond (from 1.40 to 1.414 Å), a shorter C_1-C_6 bond (from 1.40 to 1.36 Å) and a shorter C_6-Cl bond (from 1.74 to 1.729 Å). This suggests an increase in conjugation of the C_6-C_1 bond with the $N-C_2$ bond and could allow the Cl atom attached to the C_1-C_6 bond to interact noticeably with the central-ring heterocycle. This is consistent with the ESR and DFT results, which show that the Cl atom causes noticeable perturbation of the hfcc's (Table 3) and the spin densities (Table 4). The interaction of the side chain attached to the central-ring nitrogen atom appears to be a conjugative and/or inductive through bond effects for promazine[21] and appears similar to the interaction of the 2-position substituent with the central-ring heterocycle. The balance between the interaction of the side chain and the 2-position substituent with the central-ring heterocycle may play an important role in determining the interesting trends in the biological activities of the phenothiazine derivatives and further work is needed to assess the importance of these interactions.

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Supporting Information Available: Comparison of the UHF/6-31G* (from calculated normal modes of the chlorpromazine radical cation) with those of the promazine radical cation. The decomposition of the chlorpromazine normal modes into components of the promazine radical cation normal modes were determined using the ViPA program described in refs 39 and 40. This material is available free of charge via the Internet at http://pubs.acs.org.

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