Photoelectron Spectra of Psychotropic Drugs. 2. Phenothiazine and Related Tranquilizers[1]

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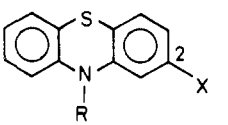
Abstract: Photoelectron spectra of phenothiazine, *N*-methylphenothiazine, and four biologically active derivatives—promazine, chlorpromazine, thioridazine, and trifluoperazine—have been measured. Assignments of various ionization potentials (IP's) to particular molecular orbitals have been made on the basis of qualitative models, correlations with IP's of similar molecules, substituent effects, and CNDO/2 calculations. In contrast to previous deductions from calculations, solution oxidation potentials, or charge-transfer spectra, these studies show that N-alkylation of phenothiazine lowers the first, as well as higher, π ionization potentials: phenothiazine (IP_1 = 7.26 eV), *N*-methylphenothiazine (7.15 eV), and promazine (7.20 eV). The discrepancies between gas-phase ionization potentials and solution oxidation potential and charge-transfer studies are attributed to differential solvation effects rather than conformational effects. There are also significant discrepancies between ionization potentials measured here and orbital energies obtained by CNDO/2 and ab initio calculations. The first ionization potentials, as well as averages of the first five π ionization potentials, for the pharmacologically active phenothiazines fall in the order trifluoperazine (7.31 eV), promazine (7.20 eV), chlorpromazine (7.16 eV), and thioridazine (7.00 eV) and do not correlate with antipsychotic activity based on dosage data for man.

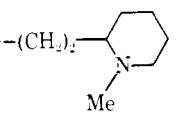
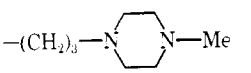
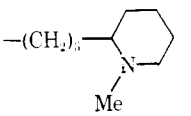
Introduction

A principal goal of molecular pharmacology is to determine how the structure of a molecule influences its biological activity. The shapes and conformations (topographies) of molecules, as well as the reactivities of molecules towards different types of reagents, are determined by their electronic structures. Considerable progress has been made in the calculation of conformations of drugs, and various activity indices, calculated quantum mechanically, have shed light on the electronic features required for various types of drug activity. We have attempted to complement computational data of this type with experimental measurements of the electronic properties of pharmaceutically important molecules. Our photoelectron spectroscopic investigations of hallucinogenic phenethylamines and tryptamines indicated that this technique not only provides valuable information about the electronic structures of these psychotropic drugs, but that the ionization potentials of these compounds are reasonably well correlated with hallucinogenicity in man and various animal indices of activity.[1] We have now extended these investigations to a series of clinically important phenothiazine tranquilizers and related molecules.

Phenothiazines with an *N*-aminopropyl side chain and various ring substituents are potent neuroleptics.[3] Although a great deal of information has been accumulated concerning the substituents necessary for activity in a variety of biological tests, the influence of these substituents on the electronic structure of the phenothiazine has not been clearly delineated. In 1959, Karreman, Isenberg, and Szent-Györgi suggested that phenothiazine tranquilizers were good electron donors and might act as charge- or electron-transfer donors at drug receptor sites.[4] This suggestion was based on calculations of the highest occupied molecular orbital (HOMO) energies by the Hückel method. Since that time, charge-transfer complex formation between phenothiazines and various acceptors has been successfully demonstrated.[4,5] Phenothiazines also form rather stable radical cations, and it has been suggested that these radicals may be of some importance in the biological activities of phenothiazines.[6]

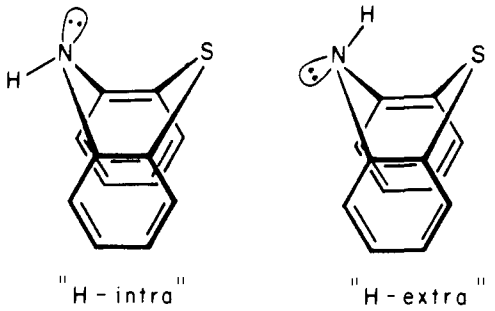
Although phenothiazine, **1**, and a variety of substituted phenothiazines readily form charge-transfer complexes, phenothiazine itself is not active as a central nervous system (CNS) depressant. The aminoalkyl side chain of pharmacologically active phenothiazines, such as **3–7**, is necessary for receptor binding and determines the type of activity that these



	R	X	
1	H	H	Phenothiazine
2	Me	H	*N*-Methylphenothiazine
3	$-(CH_2)_3NMe_2$	H	Promazine
4	$-(CH_2)_3NMe_2$	Cl	Chlorpromazine
5		SCH_3	Thioridazine
6		CF_3	Trifluoperazine
7		$SOCH_3$	Mesoridazine

multiply biologically active compounds will display, e.g., antipsychotic, anti-Parkinsonian, or antihistamine activity.[3] The amino group must be separated from the phenothiazine nucleus by a three-carbon side chain for tranquilizing activity, and this implies that the phenothiazine nucleus and the ammonium group interact with two sites of fixed relative disposition in the receptor.[3] This is likely a topographic rather than electronic effect, although without experimental evidence on the influence of the side chain on electronic structures, this conclusion is tentative.

An *N*-alkylamino side chain not only provides, after protonation at physiological pH, an ammonium group which can hydrogen-bond with an electron-rich site of a biological receptor, but may cause considerable changes in the preferred conformation of the phenothiazine at the ring nitrogen. Thus, Malrieu and Pullman proposed that N-alkylation converts the preferred "H-intra" conformation of the parent phenothiazine to a preferred "H-extra" conformation, the alkyl group taking the place of hydrogen.[7] In accord with their Hückel calculations for these conformations, *N*-alkylphenothiazines have higher oxidation potentials[8] and higher energy charge transfer (CT) transitions in complexes with acceptors[9] than the parent



does. These abnormal effects, which indicate that ionization potentials of *N*-alkylphenothiazines are higher than that of the parent, seem to require a change in conformation upon substitution, since alkyl groups ordinarily lower ionization potentials. One goal of our studies was to determine whether the gas phase ionization potentials of *N*-alkylphenothiazines were higher than that of phenothiazine, since one might also attribute higher oxidation potentials and blue-shifted CT maxima to solvation effects.

An electronegative substituent at position 2 is necessary for high neuroleptic activity, as well as for activity in a variety of biological tests. However, the types of substituents at position 2 which activate the drug do not follow the types of reactivity orders usually found in organic reactions. Chlorine and thiomethyl, which are weakly electron-withdrawing substituents,[10] give neuroleptic drugs of similar activity (chlorpromazine and thioridazine, respectively).[11] The methylsulfinyl group, a potent electron withdrawer,[10] gives a less potent drug (Mesoridazine), while an even more potent electron withdrawer, trifluoromethyl, gives a drug of high activity (trifluoperazine).[11] The second goal of our research was to determine the influence of substituents on the electronic structures of phenothiazines, with the long range goal of elucidating the mechanism of drug activation or deactivation by the 2 substituent.

Although solid-state ionization potentials (IP's) of phenothiazine have been measured by photoelectric threshold measurements,[12] and solution IP's have been estimated from charge-transfer transition energies,[9] photoelectron spectroscopy is a more precise method than these. We have shown earlier that the activity of phenethylamine and tryptamine psychotomimetics is not accounted for by the first IP's, but if higher (especially second) IP's are also taken into account, correlations with activities are obtained.[1] This was rationalized on the basis that all high-lying occupied orbitals of a donor can contribute to charge-transfer, dispersion, or polarization stabilization of a complex with an acceptor, and the two highest energy occupied MO's not only are most important due to their high energies, but changed energy more than the others upon substitution. A photoelectron spectrum provides all IP's below 21 eV, and, when properly assigned, indicates the character of the orbital from which the electron was removed. This information is significant since the π-like orbitals are more likely to be involved in charge transfer complex formation than σ- or n-like orbitals. However, a correlation between the charge on the side-chain nitrogen and the neuroleptic activity of phenothiazine drugs has been proposed.[13] If the side-chain basicity is important in determining activity, then the nitrogen lone-pair ionization potentials may be found to correlate with activity.

This paper reports a study of the PE spectra of phenothiazine (**1**) and five of its derivatives, *N*-methylphenothiazine (**2**), promazine (**3**), chlorpromazine (**4**), thioridazine (**5**), and trifluoperazine (**6**), the last four of which have significant neuroleptic activity.[3,12]

Molecular Orbitals of Phenothiazines

The π-molecular orbitals (MO's) of phenothiazine can be constructed formally from the π-MO's of benzene and the nitrogen and sulfur π-type lone pair orbitals of a dialkyl amine and a dialkyl sulfide, respectively. For this crude model, we shall assume that Koopmans' theorem[14] is valid, so that the negatives of SCF orbital energies, ϵ_j^{SCF}, are assumed to be good approximations to photoelectron ionization potentials, IP_j.

$$IP_j = -\epsilon_j^{SCF}$$

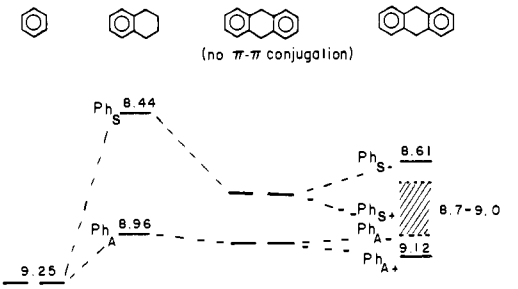
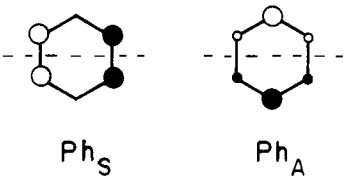


Figure 1. Molecular orbital energy levels for benzene and substituted benzenes.

The highest occupied MO's of benzene are degenerate and give rise to an IP of 9.25 eV.[15] Ortho-dialkylation of benzene to give, for example, benzocyclohexene, splits this degeneracy and gives rise to a first IP of 8.44 eV, arising from the "Ph_S" orbital, and a second IP of 8.96 eV due to the "Ph_A" orbital.[16] These designations refer to the symmetry of these orbitals with respect to the plane of symmetry perpendicular to the molecular plane of benzocyclohexene.



If two benzene rings are symmetrically linked by substituent bridges that transmit little or no conjugative interaction between the two ring systems, the orbital eneriges of the linked system are expected to be similar to those of the separated disubstituted benzenes themselves. For example, the first four IP's of 9,10-dihydroanthracene, **8**, fall in the 8.6 to 9.1 eV region (8.61, 8.7–9.0 (2 bands), 9.12 eV).[17] These arise from the orbitals corresponding to the bonding and antibonding combinations of Ph_S and Ph_A orbitals of the two benzene rings. Because of the small coefficients in the Ph_A orbitals at the site of fusion, the inductive lowering of the Ph_A orbitals upon substitution of the more electronegative benzo group for the ethano group is expected to be small. This is shown diagrammatically in Figure 1, where the Ph_S and Ph_A energies that 9,10-dihydroanthracene would have, if there were no conjugation between the phenyl groups, are estimated.

The Ph_S orbitals are expected to be influenced more by the inductive effect, due to the larger coefficients at the site of ring fusion. The large difference in inductive effects on the two orbitals is reasonable, if it is realized that the "inductive" effect of the benzo group probably results mainly from the lowering of the energies of the CH_2 π-like orbitals, and these are known (cf. benzene → benzocyclohexene) to influence the Ph_S orbitals much more than the Ph_A.

The Ph_A orbitals will interact to a small extent via through-space or through-bond interactions, and give rise to IP's around 9.0 and 9.12 eV, while the Ph_S orbitals can interact more strongly due to the larger coefficients at fused positions. Assuming that through-space interactions dominate over through-bond interactions (the latter would reverse the assignments), we have assigned the 8.61 eV band to the Ph_S–

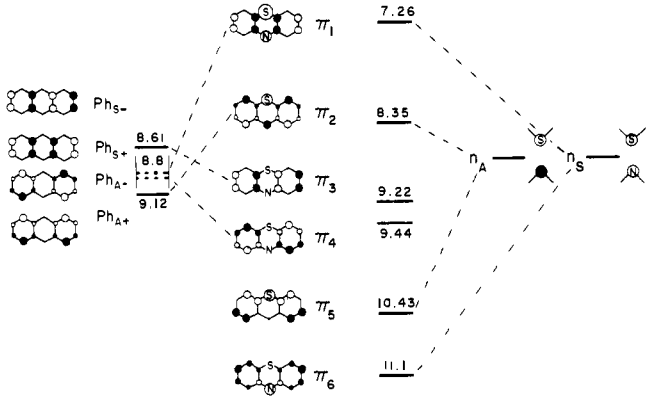


Figure 2. Correlations between the molecular orbitals of phenothiazine and those of the aromatic and heteroatom lone-pair fragments.

orbital and the ~8.9 eV band to the Ph_{S+}. These orbitals are shown schematically on the left side of Figure 2.

As a second step in the formal construction of phenothiazine MO's, we consider bringing a sulfur lone pair orbital (dimethyl sulfide lone pair IP = 8.65 eV)[18] into the vicinity of an amine lone pair (dimethylamine lone pair IP = 8.94 eV).[19] An in-phase combination, n_S, and an out-of-phase combination, n_A, will be generated as the lone-pair orbitals overlap. Because of the similarity in IP's of these two types of lone pairs, both n_S and n_A will contain more or less equal contributions from the two lone pair centers and will be approximately symmetric (n_S) or antisymmetric (n_A) with respect to a plane bisecting a line joining these atoms (right side of Figure 2).

Finally, interaction of the π-MO's of 9,10-dihydroanthracene with the lone-pair combinations, n_S and n_A, will give the highest energy phenothiazine MO's, π_1–π_6, shown in the center of Figure 2.

The dihydroanthracene orbitals Ph_{S-} and Ph_{A-}, which have a node through the central atoms cannot interact conjugatively with the lone pair orbitals because of the symmetry mismatch. These orbitals should be stabilized by the inductive effects of the S and N atoms. In the CNDO/2 calculations carried out on the x-ray crystallographic coordinates of phenothiazine,[20] the Ph_{S-} and Ph_{A-} orbitals correlate with π_3 and π_4 of phenothiazine (Figure 2). Comparing the IP's of these orbitals in 9,10-dihydroanthracene and phenothiazine indicates that Ph_{S-} has been stabilized by 0.6 eV, while Ph_{A-} has been stabilized by 0.4 eV.

The remaining shapes and energies of phenothiazine valence MO's obtained from CNDO/2 calculations are also shown in Figure 2. The calculations give results in good accord with qualitative ideas about orbital interactions. The Ph_{S+} and Ph_{A+} orbitals are of the proper symmetry to interact with the lone pair orbitals, but the approximate S and A symmetry of these orbitals will lead to strong mixing only between Ph_{S+} and n_S on the one hand, and between Ph_{A+} and n_A, on the other. These interactions lead to bonding combinations, $Ph_{S+} + n_S$ and $Ph_{A+} + n_A$, which are π_6 and π_5, respectively, in the CNDO/2 calculations. These orbitals are heavily aromatic, π_5 having only 24% of its electron density on S and 2% on N, and π_6 having less than 1% electron density on S and 32% on N. The antibonding orbitals, $Ph_{S+}-n_S$ and $Ph_{A+}-n_A$, are π_1 and π_2, respectively, in the CNDO/2 calculations (Figure 2). Both the π_1 and π_2 orbitals are more heavily localized on S than on N (42% and 18% in π_1, and 28% and 17% in π_2, for S and N, respectively). The lower energy orbitals, π_5 and π_6, do not retain familiar shapes, because they are composed of contributions not only from the fragment orbitals discussed, but from lower energy aromatic orbitals as well. However, the qualitative model does adequately account for the order of orbital energies obtained from calculations. That is, π_3 and π_4 are similar in energy to Ph_{S-} and Ph_{A-} of dihydroanthracene, π_1 and π_6 are Ph_{S+}-type and are very different in energy due to the substantial overlap between Ph_{S+} and n_S orbitals arising from the large coefficients on the aromatic rings at the site of substitution, and π_2 and π_5 are less split due to the smaller coefficients on the aromatic moieties at the sites of substitution.

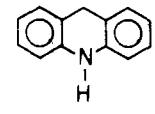
The same order of MO's predicted for phenothiazine is found by Hückel MO calculations on anthracene and CNDO/2 calculations on 9,10-dimethylanthracene. Because these molecules have two fewer π electrons than phenothiazine, the orbital corresponding to the HOMO of phenothiazine corresponds to the lowest unoccupied MO of the anthracenes.

The finding of an antibonding HOMO for phenothiazine in the Hückel calculations by Karreman, Isenberg, and Szent-Györgi[4] was corrected by Orloff and Fitts by using sulfur d-orbitals in the calculations.[21] More recently, Kaufman and Kerman's CNDO/2 calculations for a number of substituted phenothiazines indicate that the HOMO is, in each case, a bonding orbital.[13a] Popkie and Kaufman have also carried out extensive ab initio calculations on chlorpromazine and phenothiazine.[13b]

Photoelectron Spectra of Phenothiazines

Photoelectron spectra were recorded on a Perkin-Elmer PS-18 photoelectron spectrometer, operating with a resolution of about 25 meV. All of the compounds studied here were sublimed in the target chamber at temperatures of 85–135 °C. Xenon and argon were used as calibrants.

The photoelectron spectra of phenothiazine (**1**), *N*-methylphenothiazine (**2**), and promazine (**3**), are shown in Figure 3, while those of chlorpromazine (**4**), thioridazine (**5**), and trifluoperazine (**6**) are shown in Figure 4. The ionization potentials of the phenothiazines and related compounds are tabulated in Table I. Band assignments for the phenothiazines were made by comparison with the photoelectron IP's of diphenyl sulfide (measured here), diphenylamine, 9,10-dihydroanthracene, and acridan, **9**, and by comparison with CNDO/2 orbital energies.



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Phenothiazine, *N*-methylphenothiazine, and promazine have four well-resolved bands before the onset of σ ionizations at 10.5 eV. However, the shoulder on the high IP side of the third band in the *N*-methylphenothiazine spectrum indicates that this band consists of two overlapping ionizations. This conclusion is also consistent with the CNDO/2 calculations and the qualitative model discussed in the previous section of this paper. The assignments which we have made for the various ionizations are plotted in Figure 5. The shaded areas represent error limits on our measurements of vertical (band maxima) ionization potentials. The reasoning used to make these assignments is discussed below.

Phenothiazine. The band at 7.26 eV in the PES of phenothiazine is assigned as π_1 (Figure 2). This value is similar to that found for the first IP of acridan (7.33 eV)[22] which arises from an orbital similar to that calculated for π_1. Although it has been suggested that the strong electron donor properties of phenothiazines are due to the S atom,[23] Bloor and coworkers, in their studies of charge transfer complexes, have concluded that the S atom produces no dramatic changes in electron donor strength of phenothiazines and related compounds, while the introduction of the amino group enhances the electron donor properties significantly.[5b] The small dif-

Table I. Photoelectron Ionization Potentials of Phenothiazines and Models

		Reference
Phenothiazine (**1**)	7.26 ± 0.08, 8.35 ± 0.05, 9.22 ± 0.05, 9.44 ± 0.10, 10.43 ± 0.08	This work
N-Methylphenothiazine (**2**)	7.15 ± 0.07, 8.23 ± 0.05, 9.06 ± 0.05, 9.25 ± 0.20, 10.24 ± 0.09, 10.43 ± 0.20, 11.12 ± 0.14	This work
Promazine (**3**)	7.20 ± 0.06, 8.26 ± 0.05, 9.00 ± 0.06, 9.25 ± 0.07, 9.44 ± 0.10, 10.26 ± 0.07	This work
Chlorpromazine (**4**)	7.16 ± 0.08, 8.25 ± 0.05, 8.99 ± 0.08, 9.27 ± 0.07, 10.22 ± 0.09, 11.24 ± 0.06	This work
Thioridazine (**5**)	7.00 ± 0.08, 7.98 ± 0.12, 8.41 ± 0.06, 8.95 ± 0.05, 9.40 ± 0.06	This work
Trifluoperazine[a] (**6**)	7.31 ± 0.08, 8.41 ± 0.07, 9.32 ± 0.11, 9.42 ± 0.20, 10.52 ± 0.13	This work
Acridan[b] (**7**)	7.33, 8.83, 9.13, 10.86	Reference 22
Diphenyl sulfide	7.86, 8.46, 9.25, 9.25, 10.2, 10.5	This work
Diphenylamine	7.44, 9.04, 9.25	Reference 22

[a] Three ionizations fall within the 8.41-eV band. [b] A band with no reported IP falls in the 8.83 to 9.13-eV region.

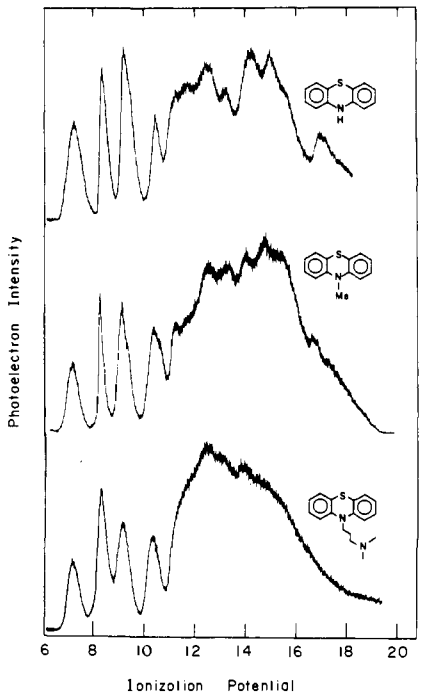

Figure 3. Photoelectron spectra of phenothiazine, *N*-methylphenothiazine and promazine.

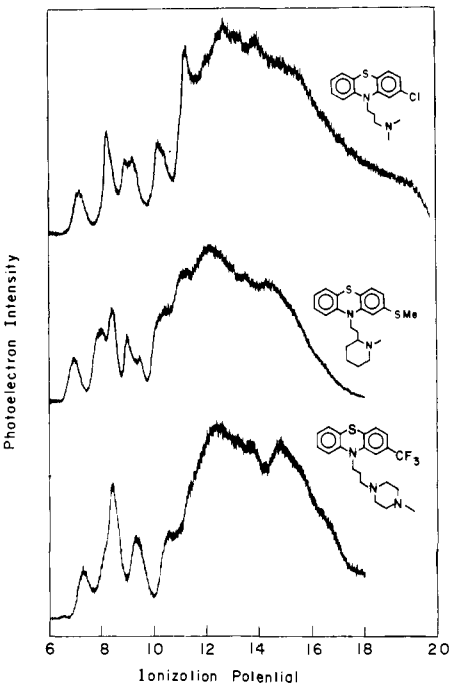

Figure 4. Photoelectron spectra of chlorpromazine, thiordiazine, and trifluoperazine.

ference in the first IP of acridan (7.33 eV) and phenothiazine (7.26 eV) is consistent with Bloor's conclusion. Additionally, a comparison of the IP's of diphenyl sulfide (7.86 eV) and diphenylamine (7.44 eV)[22] reveals the larger effect of the amino bridge over the S bridge in lowering IP_1.

The shape of the first band is also consistent with substantial N lone-pair character. That is, alkylamines generally have broad ionization bands, because the ground state (pyramidal) and radical cation (planar) geometries differ significantly.[25] Aromatic π ionization bands are generally sharper, due to larger Franck-Condon factors for the 0–0 transition.[15] A comparison of the shapes of the first five bands for phenothiazine indicates that the first ionization potential is most heavily amine-lone-pair in character, and that the amine portion of phenothiazine is pyramidal in the neutral ground state, and planar in the radical cation ground state. The CNDO/2 calculations described earlier (Figure 2) do not indicate unusually high amine lone-pair character in π_1, and further apparent disagreements between empirical deductions and CNDO/2 calculations are apparent in higher energy bands, as discussed below.

The band at 8.35 eV is assigned as π_2. Ionization from this orbital occurs at 0.5–0.8 eV less than ionization from the analogous acridan orbital. The second band in phenothiazine and substitued analogs is considerably sharper than the other bands. Because lone pair ionizations of various relatively rigid sulfides are generally quite sharp, with very strong 0–0 bands, and rapidly decreasing intensity in higher vibrational bands,[24] it appears that the second IP of phenothiazines and substituted derivatives arises from an orbital which is most heavily S-lone-pair in character. This conclusion, like the conclusion that π_1 is heavily amine-lone-pair in character, conflicts with the deductions from CNDO/2 calculations described earlier. The ab initio calculations of Popkie and Kaufman would provide a better theoretical prediction than CNDO/2 for the character of the π_1 and π_2 orbitals, but in the absence of eigenvector information in their paper,[13b] we conclude from the band shapes in the PE spectra that IP_1 arises from an orbital heavily amine-lone-pair-like, and π_2 from an orbital more S-lone-pair-like. However, as shown by substituent effects discussed below, both of these orbitals are significantly delocalized.

The band at 9.22 eV is assigned as $\pi_{3(4)}$ and the shoulder at

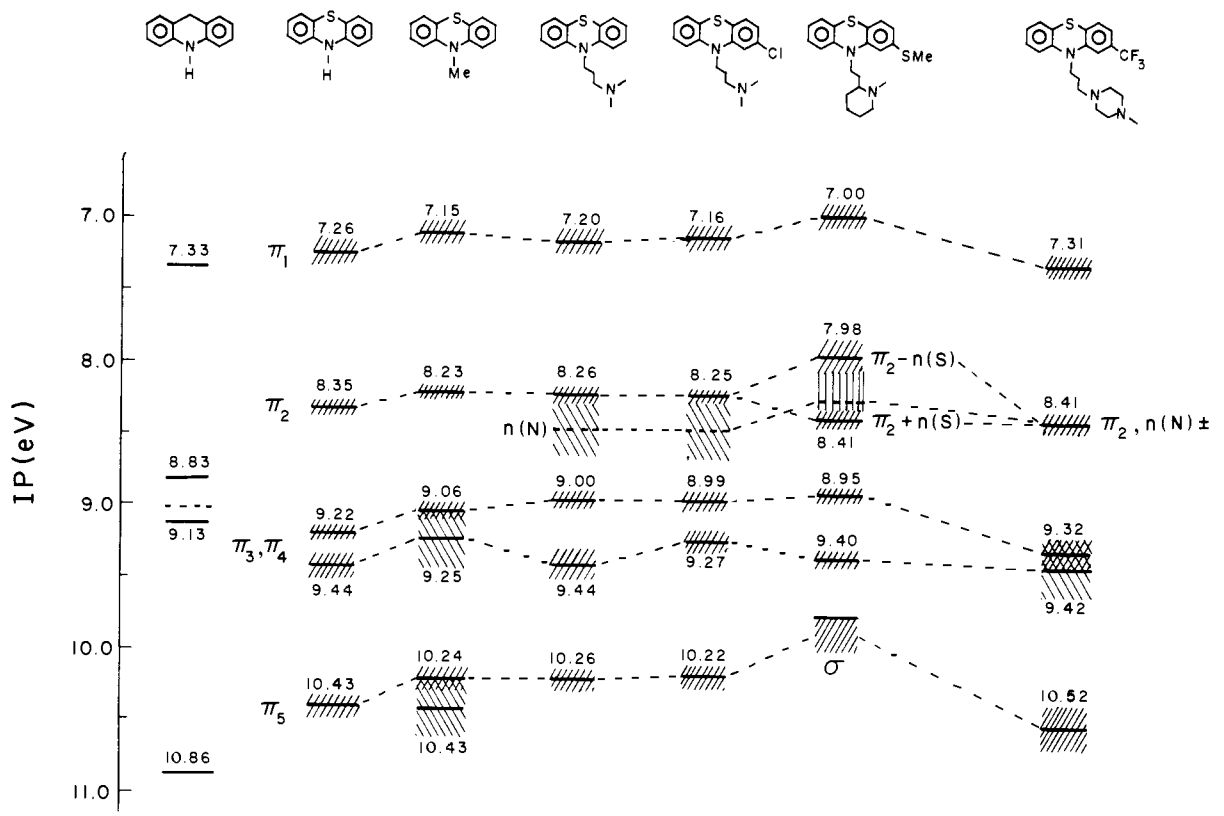

Figure 5. Correlation diagram for the molecular orbitals of phenothiazines. (Shaded areas represent limits of error.)

9.44 eV as $\pi_{4(3)}$. Because of the lack of resolution of the bands, and the unreliability of CNDO/2 calculations (or, indeed, other semiempirical SCF calculational methods) for prediction of the correct order of IP's for two orbitals so close in energy, we cannot make a definitive assignment of the order of IP's arising from orbitals labeled π_3 and π_4 in Figure 3. The assignments of $\pi_{3(4)}$ and $\pi_{4(3)}$ to the 9.22 and 9.44 eV ionizations shows that there is a slight stabilization of these orbitals relative to the analogous orbitals of acridan, which are reported at 8.8–9.13 eV. This assignment is consistent with the presence of a node through N and S so that these atoms only inductively stabilize π_3 and π_4.

The band at 10.43 eV is assigned as arising from π_5. This IP is 0.43 eV lower than that in acridan, consistent with the relatively large donor influence of sulfur, for low energy orbitals. Sulfur should also give rise to a second IP due to the in-plane lone pair. However, this appears at 11.17 eV in dimethyl sulfide,[24] and above 11 eV in thioanisole,[28] so that this IP is expected in the σ envelope above 11 eV.

N-Methylphenothiazine. The spectra of phenothiazine and *N*-methylphenothiazine are extremely similar, but the IP's of the latter are lower (0.1–0.2 eV) than those of phenothiazine, and the third band of the *N*-methyl compound is more nearly resolved into two maxima. The close correspondence between the phenothiazine and *N*-methylphenothiazine spectra indicates that the same assignments are appropriate for the two compounds. The first band in *N*-methylphenothiazine is slightly broader than that in phenothiazine, while the second band has become sharper upon N-methylation. This supports further the contention that π_1 is amino-like and π_2 is sulfide-like. That is, the alkyl group lowers the amine lone pair ionization potential so that "n_A" (Figure 2) becomes more N centered and "n_S" more S centered.

By contrast to the conclusions drawn from Hückel calculations, oxidation potentials, and charge-transfer transition energies, the gas-phase ionization potential of *N*-methylphenothiazine is lower than that of phenothiazine. The methyl group exerts its normal electron-donor effect, and if conformational differences are important, they result in an increase in first ionization potential which only partially cancels out the effect of electron donation by methyl. The effect of N-methylation is much smaller here than that in less conjugated amines (cf. the change in going from dimethylamine (8.94 eV) to trimethylamine (8.50 eV)[19] or *N*-methylaniline (7.73 eV) to *N*,*N*-dimethylaniline (7.51 eV)).[26,27] The methyl effect on all IP's is approximately constant, increasing somewhat on the higher IP bands, so that no additional information on assignments can be obtained from a comparison of the IP's of **1** and **2**.

Promazine. The PES of promazine is remarkably similar to those of phenothiazine and *N*-methylphenothiazine. In fact, the IP's of promazine and *N*-methylphenothiazine are the same within experimental error, except for that of the π_4 band. The slightly higher first IP of promazine (7.20 eV) as compared to that of *N*-methylphenothiazine (7.15 eV) probably arises from a slight change in band shape, which causes a shift in the band maximum. Thus, the aminopropyl and methyl groups affect the phenothiazine nucleus to the same extent.

The maximum of the third band of promazine is shifted to a lower ionization potential than that in phenothiazine, and there is considerably less separation between the second and third bands. It can be crudely estimated that $\pi_{3(4)}$ and $\pi_{4(3)}$ appear around 9.0 and 9.4 eV, and an additional band due to ionization of the side-chain tertiary amine lone-pair IP should appear in this region (~8.5 eV), at a value near those of trimethylamine (8.5 eV)[26] and *N*,*N*-dimethylphenethylamine (8.43 eV).[1]

Chlorpromazine. The spectrum of chlorpromazine is very similar to those of promazine and phenothiazine. The third band is now barely resolved into two bands, but the shapes of the various ionization bands are remarkably similar to those in the simpler analogs. Only a small shift is observed for π_1, which now occurs at 7.16 eV, while the remaining π orbitals show no significant shifts; e.g. π_2, 8.25 eV; $\pi_{3(4)}$, 8.99 eV; $\pi_{4(3)}$,

9.27 eV; and π_5, 10.22 eV. The lone-pair orbital of the side-chain N still appears to be at approximately 8.5 eV. The band at 11.24 eV can be assigned as a lone pair orbital on chlorine by comparison with the analogous orbital of chlorobenzene (11.42 eV).[15]

Kaufman's CNDO/2 calculations on promazine and chlorpromazine in their crystallographic conformations predict lower orbital energies for chlorpromazine than for promazine, by approximately 0.16 eV per orbital, for the three highest occupied MO's,[13a] and ab initio calculations indicate a 0.1–0.3 eV increase in the first five IP's by the 2-Cl substituent, in contrast to our experimental observations, which indicate essentially no IP change except for the 0.17 eV decrease in the fifth IP. PES studies on benzene and chlorobenzene show that the chlorine substituent on the aromatic ring inductively increases the IP of the orbital with a node at the site of substitution (benzene 9.25 eV; chlorobenzene 9.71 eV),[15] but causes little change in the first IP which arises from the orbital having a large coefficient at the chlorine site. In the latter, the inductive raising of the IP is offset by a conjugative lowering effect so that this IP of chlorobenzene (9.31 eV) is about the same as that of benzene itself (9.25 eV).[15] This same effect is observed in the photoelectron spectra of phenol (8.75, 9.45 eV) and *p*-chlorophenol (8.69, 9.76 eV).[26a] Rao and co-workers have found that chlorine increases the first four IP's of dimethylaniline by 0.15–0.20 eV,[26b] while the first IP of benzamide is decreased by about 0.1 eV by either a para or meta chlorine.[26c] As noted by Rao,[26b] halogens may either serve as donors or as acceptors (IP lowering or raising, respectively), depending on the other substituent on the aromatic ring.

Thioridazine. The PE spectrum of thioridazine, **5,** is similar to that of the promazines, **3** and **4,** but has an additional broad band at 7.98 eV and a larger separation between the two bands near 9 eV. The first band (7.00 eV) is assigned as π_1 and has the lowest IP of the compounds studied in this work; it is approximately 0.2 eV lower than π_1 of promazine. The thiomethyl group is a strong donor, which lowers the IP of benzene (9.25 eV) by 1.18 eV to a value of 8.07 eV in thioanisole.[28] The thiomethyl leaves the second orbital of benzene essentially unchanged (IP = 9.28 eV in thioanisole), while the third orbital of thioanisole, consisting of the bonding combination of the benzene HOMO (9.25 eV) and the sulfur lone pair (IP of dimethyl sulfide = 8.67 eV), gives rise to an IP of 10.15 eV. In thioanisole, the band due to ionization from an orbital which is principally S lone pair in character is relatively broad, due to the nearly equal energy of two rotamers, which have different IP's. The second band in the thioridazine spectrum has a similar appearance to the first of thioanisole.

The thiomethyl lone pair destabilizes the promazine HOMO by 0.2 eV. This is close to the destabilization of the thioanisole HOMO (0.14 eV) upon substitution of a second thiomethyl, but is much lower than the HOMO destabilization (1.18 eV) of benzene caused by the first thiomethyl group.[28a] The sulfur lone pair should be stabilized by this interaction, but will also be destabilized by mixing with lower-lying π orbitals of the phenothiazine skeleton. One of the principal interactions should involve the sulfur lone pair, n(S), and π_2 of promazine, whose IP is nearly the same as that of the sulfur lone pair in dimethyl sulfide. For this reason, we label the second (7.98 eV) and third (8.41 eV) π ionization potentials as $\pi_2 - n(S)$ and $\pi_2 + n(S)$, although there should be mixing of n(S) with all the π orbitals of phenothiazine. By comparison with the N lone pair IP of *N*-methylpiperidine (8.29 eV),[29] the side chain n(N) band of **4** probably falls near 8.3 eV, under the second and third bands.

The first band of thioridazine has sharpened very slightly relative to that in chlorpromazine, and this is compatible with the first IP being due to an orbital more heavily centered on the ring sulfur in thioridazine than in chlorpromazine. Kaufman and Kerman's CNDO/2 calculations on thioridazine predict an 0.06 eV increase in the first IP of thioridazine as compared to promazine, and 0.61 and 0.83 eV decreases in the second and third IP's.[13a] There seems to be little correspondence between CNDO/2 calculations and experiment in these systems.

Trifluoperazine. The strong electron withdrawal by the trifluoromethyl groups is manifested in the higher IP's of trifluoperazine, **6,** as compared to promazine. The first IP of **6** is 0.1 eV higher than that of promazine. The second band (π_2) now overlaps with two additional nitrogen lone-pair IP's from the side-chain piperazine moiety. For comparison, we measured the PES of *N,N'*-dimethylpiperazine, and found a single broad band at 8.42 eV whose shape is similar to that of the 8.41 eV band in **6**. The IP's arising from π_3 and π_4 in **6** appear at about 9.32 eV, indicating that these are raised by 0–0.3 eV as compared to these bands in promazine. The 10.52-eV band corresponds to π_5, raised by 0.3 eV as compared to promazine. Kaufman and Kerman's CNDO/2 calculations predict 0.40, 0.43, and 0.01 eV increases in IP's one through three upon conversion of promazine to trifluoperazine.[13a] The results here are in the right direction, but the first IP of trifluoperazine increased much less experimentally than was predicted by the calculations.

Comparisons of Gas-Phase Ionization Potentials with Charge-Transfer Maxima and Oxidation Potentials

The stability of charge-transfer complexes between phenothiazines and several types of aromatic electron acceptors is reduced by the presence of electron-withdrawing groups on the phenothiazine ring and by alkylation of the phenothiazine nitrogen. Charge-transfer complex formation studies indicate that the donor abilities of phenothiazines decrease in the order: phenothiazine > promazine > chlorpromazine.[5,9] Bloor and co-workers predicted IP's of 7.02 eV for phenothiazine and 7.18 eV for promazine based on frequencies of charge-transfer band maxima in CH_2Cl_2 solvent.[5b] By contrast, the direct measurements of IP's in the gas phase reported here indicate that chlorpromazine (7.16 eV) slightly surpasses promazine (7.20 eV) in electron donor ability, and promazine is very similar to, but slightly better than, phenothiazine (7.26 eV) as an electron donor. This conclusion is true whether the first IP's or the first five IP's are compared.

In Table II, various previous estimates of ionization potentials of phenothiazines are compared to those obtained here. Additional data on stability constants of charge-transfer complexes are also included in the table. The curious feature of these comparisons is the decrease in donor ability of phenothiazine upon N-alkylation or 2-chlorination, as measured by photoelectric threshold measurements (IP(p)),[12] CT maxima,[5,9] or solution oxidation potentials.[8] These data contrast with the IP's measured here, which *decrease* upon N-alkylation or 2-chlorination, indicating increased donor ability.

Further anomalies are observed with other charge-transfer complexes. For 2-substituted phenothiazines, charge-transfer complexes of phenothiazine with tetracyanoethylene give transition energies of 1.433, 1.408, 1.458, and 1.493 eV for the parent, 2-thiomethyl- 2-chloro, and 2-trifluoromethyl compounds, respectively.[30] Thus, in this series, the thiomethyl appears to lower the first IP by 0.025 eV (cf. our value of 0.20 eV from the comparison of promazine with thioridazine). The trifluoromethyl raises the apparent IP by 0.06 eV (cf. our value of 0.11 eV from the promazine, trifluoperazine comparison), and the chloro raises the IP by 0.025 eV (cf. our *decrease* of 0.04 eV from the promazine, chlorpromazine comparison). Thus, the changes in charge-transfer transition energies in CT complexes with TCNE and changes in gas phase ionization potentials are considerably different. With chlorpromazine,

Table II. Ionization Potentials, Oxidation Potentials, and Charge-Transfer Spectra of Phenothiazines.

Compound	IP(PES)[a]	IP(p)[b]	E_{ox} (mV)[c]	λ_{max}(CT)[e]	IP(CT)[f]	$K_{eq}(CHCl_3)$[h]	$K_{eq}(CCl_4)$[h]
Phenothiazine (**1**)	7.26	6.7	0.696	575 nm	7.02(7.28)[g]		
N-Methylphenothiazine (**2**)	7.15			543 nm	7.17		
Promazine (**3**)	7.20	6.8	0.540[d]	540 nm	7.18	0.293	1.40
Chlorpromazine (**4**)	7.16	6.7				0.205	1.19

[a] Photoelectron spectroscopy, this work. [b] Photoelectric threshold (ref 12a). A solid state IP of 4.36 eV has been measured for phenothiazine.[12b] [c] E_{ox} vs. sce, ref 8. [d] This value is for *N*-(*N*-β-hydroxyethylpiperazinyl)propylphenothiazine. [e] Complex with tetracyanobenzene.[5b] [f] From CT maxima with tetracyanobenzene using IP(CT) = $0.147\nu_{CT}$ + 4.463 eV.[5b] [g] From CT complex with bromanil using $h\nu_{CT}$ = 0.85IP − 4.32 eV.[9c] Values of 6.82–7.10 are obtained using other acceptors.[30] [h] Equilibrium constant with *p*-dinitrobenzene. For comparison, *N*,*N*′-dimethylaniline (IP = 7.51 eV) has an equilibrium constant about half that of promazine.[9b]

reaction with TCNE precludes observation of a charge-transfer complex.[31]

The differences in solution phase and gas phase donor abilities of phenothiazines may arise from several effects. The ability of a molecule to enter into charge- transfer complexation will depend on its shape and the extent of overlap of its donor orbitals with those of the acceptor. The shapes of these phenothiazines are not all the same; in the crystalline state, the dihedral angles between the benzene ring planes are 153° for phenothiazine,[20] 151° for *N*-methylphenothiazine,[32] 140° for promazine hydrochloride,[33] and 139° for chlorpromazine.[34] The opening of the dihedral angle should raise the energy of π_1 and π_2, and lower that of π_3 and π_4. Our IP measurements do not show this effect, but instead indicate that donors raise all orbital energies, and acceptors lower all orbital energies. The change in dihedral angles appears insignificant as far as influence on IP changes is concerned.

The extent of overlap possible between donor and acceptor orbitals may diminish as the side-chain size is increased, preventing close approach of the two addends. However, the most important difference between gas phase and solution measurements probably arises from differential solvation of different species. That is, as the side-chain size is increased, there may be inhibition of solvation of the phenothiazine moiety. For example, the Baker–Nathan order of carbonium ion stabilities (cation stabilities decreasing with substitution of larger alkyl group) is known to arise from solvation phenomena, because the intrinsic gas-phase stability of cations increases as the size of the alkyl substituent increases.[35] For the N-alkyl phenothiazines, solvent may be less able to stabilize the partially positive phenothiazine moiety in charge-transfer complexes, or the radical cation formed in oxidation.

Finally, we note that our observation of a difference between trends in donor ability in solution and in the gas-phase removes the necessity for suggesting a change in phenothiazine conformation upon alkylation. That is, N-methylation of phenothiazine lowers the intrinsic IP of the molecule in the gas-phase. At the same time, this molecule becomes more difficult to oxidize and a poorer charge-transfer donor in solution.

The suggestion by Malrieu and Pullman that the conformation of *N*-alkylphenothiazines differs from that of the parent compound has been found not to be the case in the crystalline compounds,[20,32] and our results imply that these molecules are very similar—i.e., have the same conformation—in the gas phase.

At the temperatures of 85–135° used to volatilize the phenothiazines for PE spectra, the phenothiazines are undergoing conformational changes, so that our spectra undoubtedly represent the IP's of mixtures of conformational isomers. Nevertheless, the relative sharpness of the bands arising from the aromatic moieties indicate that conformational isomers, if present, probably involve mainly gauche and anti side-chain conformations, rather than the "H-intra" and "H-extra" type of conformations of Malrieu and Pullman,[7] since these conformations would be expected to have substantially different IP's.

Relationships between the Electronic Structures of Phenothiazines and Their Biological Activities

The photoelectron spectra and calculations described in this paper provide considerably more data about the electronic structure of phenothiazine and its antipsychotic derivatives than has been previously available. The most obvious conclusions of this work are: (1) phenothiazine and its derivatives are potent electron donors, but there is little difference in electron-donor ability between the antipsychotic agents differing in clinical potency; (2) the various side chains present in active compounds have essentially no influence upon the electronic structure of the aromatic portion of these molecules; (3) the 2-substituents act as electron donors (IP decreasers) in the order, MeS > Cl ≈ H > CF_3, and this influence is felt more or less equally on all the valence orbitals.

The fact that the side chain does not directly influence the electronic structure of the aromatic portion of the molecule is fully in accord with the idea that the side chain amino group, which is protonated at physiological pH, and the aromatic phenothiazine nucleus, coordinate to different sites at the receptor(s). Thus, the main function of the side chain is to fix the relative spatial disposition of these two moieties.[36] A β-aminoethyl side chain leads to antihistamine or anti-Parkinson activity, while a variety of γ-aminopropyl side chains produce antipsychotic activity.[37] Thus, subtle changes in the relative disposition of the ammonium and aromatic moieties cause significant differences in pharmacological behavior, and our results indicate this is not due to differences in electronic structures of the aromatic moieties.

Because of the variations in activity with variations in side chain, it is difficult to directly compare the IP's of the phenothiazine portion of the molecule to activity. That is, for the compounds studied here, the dosages used to control acute paranoia have been reported as (in μmol/day); chlorpromazine (~1000); thioridazine (~400); trifluoperazine (~300),[38] while simple phenothiazines are less effective as neuroleptics. Cole cites Gardos' clinical estimates of potency as 1:1:12 for the former three compounds.[39] Other common clinical phenothiazine neuroleptics (Gardos' potencies in parentheses) include mesoridazine, **7** (2), fluphenazine (50), and perphenazine (11), the last two of which have 2-CF_3 and 2-Cl substituents, respectively, and β-hydroxyethyl substituents in place of the nitrogen *N*-methyl.[37,39] When promazines with various 2-substituents are compared in animal tests (suppression of rat conditioned avoidance response), activity increases in the series: H = $CONHNH_2$ = OMe < Ac < Cl < CF_3.[40,41] A variety of other data are available to substantiate this order of activity. Thus, 2-trifluoropromazine (triflupromazine) is three times more active than chlorpromazine,[39] and fluphenazine, perphenazine, and acetophenazine, have the relative potencies of 8:2:1.[39] However, it is notable that all of the clinically useful phenothiazines are very similar in activity. Although Cole ranks the clinical potencies as thioridazine < chlorpromazine < perphenazine < fluphenazine, he notes that there is little to choose among these compounds, with greater differences be-

tween them being manifested in side effects.[39] Thus, there seems little doubt about the order of antipsychotic or various in vivo[40,41] activities, but the scale is very compressed, with 2-substituents causing less profound changes in activity than side-chain variation.

It is tempting, if over-optimistic, to suggest that all of the phenothiazines are very good electron donors, and that the various 2-substituents cause very small changes in IP's, as well as small changes in activity. The changes in molecular complexation ability caused by the 2-substituent may well be less than changes in transport and partitioning properties.

For example, the partitioning of several phenothiazines between dodecane and water at pH 7 has been measured.[42] Of the compounds studied here, chlorpromazine, trifluoperazine, and promazine have partition coefficients of 366, 97, and 42, respectively.[42] This suggests that trifluoperazine is even more inherently active than is suggested by dosage data, while part of the relative ineffectiveness of promazine may be attributed to the relatively low affinity of this compound for lipid membranes.

Thus, we have neither sufficient electronic data nor biological data to rule out that the influence of IP's on activity is not caused by decreases in IP's. Thus, the molecule with the highest IP's, trifluoperazine, is the most active, that with the lowest IP's, thioridazine, is also quite active, and promazine and chlorpromazine, which differ substantially in activity, have essentially identical IP's.

One conclusion that could be made is a negative one: the difference in activities of various 2-substituted phenothiazines does not arise from differences in abilities of the aromatic ring of phenothiazines to participate as donors in molecular complex formation at the active site. This negative conclusion is supported by the good correlations between IP's and activities of hallucinogens.[1] In the latter case, we pointed out that the ability of a molecule to serve as a donor in molecular complex formation was related to IP's of the molecule, regardless of the mechanism—charge transfer, polarization, or dispersion—by which the complex is stabilized.

If not an increase in IP, what could the electronic function of the 2-substituent be, if, indeed, it is an electronic, and not a steric effect? It has been suggested that a direct interaction between receptor and the 2-substituent occurs.[38] However, another likely possibility, we feel, is that it is the electron-withdrawing character of the 2-substituent which is responsible for the activation of the promazine nucleus. That is, all of the common substituents in clinically important antipsychotics will lower the LUMO and other vacant orbital energies, and may make the aromatic ring a better charge-transfer acceptor, or may deactivate certain portions of the phenothiazine ring toward attack, preventing metabolic destruction. The energy of the LUMO of the aromatic ring could also be important if dispersion energy stabilized a molecular complex between the aromatic ring and the receptor.[1]

This proposition gains support, slim as it is, from our CNDO/2 calculations on phenothiazine, which indicate that the LUMO and the next two vacant orbitals all have more electron density on the sulfur atom and the 2-position than on any other position on the ring. Thus, attachment at the 2-position of a substituent which lowers vacant orbital energies, rather than at the 1-, 3-, or 4-positions, will have the largest vacant orbital lowering effect. If it is the LUMO of phenothiazines which is important in activity, then there should be a general trend toward increasing activity with increasing IP. This would result from the correlation between increasing IP and increasing EA from simple donor and acceptor substituents.[43] However, thiomethyl and chlorine both decrease IP's (raise occupied energies) and increase electron affinities (lower vacant orbitals energies),[43] so that these compounds show a decrease in IP vs. promazine even though they are more active. A more well-behaved series of substituents which both lower IP's and EA's (e.g., Me_2N–, MeO–, Me–) or both raise IP's and EA's (e.g., –COMe, –CN, –SOMe, $–SO_2Me$, $–CF_3$, –NO) would provide a better test of the relationships between electron structure (and IP's) and antipsychotic activity.

As noted before, the 2-methyl and 2-methoxy promazines have antipsychotic activity.[37] These substituents have essentially no effect on the first electron affinity of benzene, and slightly lower the second,[44] so that the 2-substituted promazines should be similar to promazine in activity, unless partition constants are substantially different.

Acceptors at the 2-position are well situated to withdraw electron density from sulfur, and a possible role of these groups is to deactivate the sulfur toward in vivo oxidation, which diminishes or eliminates activity.[45] Alternatively, the 2-substituent may protect the 3-position from attack by electrophiles. That is, if metabolism and deactivation of the phenothiazine were to occur by attack of, or complexation by, an electrophilic species at the 3-position of phenothiazine, which is known to be the most nucleophilic site in these molecules,[46] the Cl, SMe, and CF_3 groups should all deactivate this position by diminishing the HOMO coefficient at C-3. Substituents at C-4 will be much less effective due to the near node at C-4 in the phenothiazine HOMO (Figure 2). These speculations on the role of the 2-substituent are subject to experimental test, and by accumulating detailed information about the electronic structures of a more extensive series of neuroleptically active and inactive phenothiazines, we hope to gain insight into those electronic features common to the clinically active neuroleptics.

Finally, although no direct relationship has been found between ionization potentials and neuroleptic activity in a limited series of phenothiazines, it is of interest that the ionization potentials of two promazines are good predictors of the ability of these molecules to displace d-LSD from high-affinity binding sites in rat brain homogenates.[47] Thus, the averages of the first and second IP's of dopamine, mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM), dimethyltryptamine, promethazine,[48] chlorpromazine and LSD are 8.54, 8.16, 8.15, 7.90, 7.73, 7.71, and 7.65, respectively,[1] while the relative potencies ($-\log ED_{50}$) of these compounds are 3.52, 4.40, 5.30, 6.52, 7.00, 7.00, and 8.22, respectively.[47]

Surprisingly, even for compounds of the phenethylamine, tryptamine, and phenothiazine classes taken together, decreasing ionization potential parallels increasing binding ability. This lends some support to the idea that the activities of phenothiazines with the appropriate side chain is related to the IP of these molecules, and, thus, to the ability of the aromatic moiety to enter into molecular complex formation at the receptor site. Further small changes in activity caused by the variations of the 2-substituent do not appear, however, to be related to IP variations.

With guarded optimism, in light of the pitfalls open to the unwary,[49] we are pursuing the investigation of correlations between ionization potentials and activity, and of the electronic structures of psychotropic drugs.

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