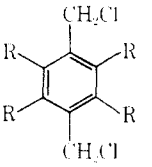
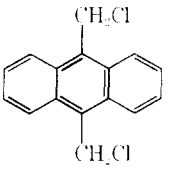
included in the table are 9,10-dimethylanthracene and 10-hydroxymethyl-9-methylanthracene. They are inactive. The "right" kind of chemical reactivity is possessed by **18** and **19**, but apparently the aromatic character is insufficient for more than minimal activity. Compound **17** lacks both qualifications. In view of the profound variation seen in Table I, other structural and substitutional investigations seem worthwhile. These findings appear to us to support further the mechanism of activity proposed in the preceding paper,[5] namely that these chemicals serve as DNA cross-linking agents whereby intercalation of the aromatic portion of the molecule is followed by chemical reaction between the alkylating group and one of the nucleophiles present in the DNA helix.

In the bifunctional series (Table IB) the comparison between **1** and **2** reinforces in a clear-cut manner the paramount contributions of geometry to activity of a molecule, a point emphasized in the preceding paper.[5] The enhancement of activity by administration in sesame oil reveals moderate activity in a simple benzene derivative (IV, R = Me), where none at all exists in the absence of the four Me groups (IV, R = H). Our view is that this activity derives from the ability of these groups partially to mimic the two outer rings of the very active anthracene (V; **4** in Table IB). The activity of V is such that the total dosage at the lower end of its active range is approximately 2 μg, divided among 3 doses.



IV



V

Table II shows corresponding figures for some of the most active compounds against the S-37 mouse ascites tumor, which is not cured by any mustard compound, including those in clinical use. In a few isolated instances, 50–60% increases in survival were formerly obtained—a degree value of 1.5–1.6. Table II generally, but not uniformly, presents a parallel to the figures in Table I showing a moderately less curable tumor with the curative range shifted upward at both ends—the compounds are appreciably less potent but usually slightly less toxic compared to their use against the Ehrlich tumor. The same protocol of 0.3 ml of sesame oil in both controls and experimentals was used with this tumor, although sesame oil had no appreciable effect on the controls' mean survival time, in contrast to its effect on the Ehrlich tumor-bearing mice.

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Electron-Donating Properties of Phenothiazine and Related Compounds

John E. Bloor,

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916

B. R. Gilson, R. J. Haas,

Chemistry Department, University of Virginia, Charlottesville, Virginia 22901

and Charles L. Zirkle

Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania

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The relative electron-donating properties of phenothiazine and related compounds containing C, N, O, and S atoms have been determined by measuring the maximum of the charge transfer band on complexation with tetracyanobenzene. Phenothiazine does not display exceptional donor ability and also the N and not S is largely responsible for the observed moderate electron-donating properties. It is suggested that good tranquilizing activity is more likely to be conferred by flexibility of the active molecules or by the ability of S to form complexes with the localized electrons rather than by the electron-donating properties of the molecule as a whole. Self-consistent field Pariser–Parr–Pople molecular orbital calculations are also carried out for many of the molecules and used to interpret the observed uv spectra and ionization potentials.

The idea that the S atom in phenothiazine derivatives confers upon them exceptional electron-donating power,[1] has been very widely accepted[2] as has also the concept that the psychopharmacological behavior of certain phenothiazines is related to this remarkable electron-donating power.[2,3] In view of this wide acceptance and because the original ideas were founded on some very approximate Hückel molecular orbital calculations[1,4] it was thought worth while to carry out a systematic experimental determination of the relative electron-donating properties of a number of phenothiazines and related substances in order to either confirm or to disprove the original contention that the phenothiazines are indeed exceptional electron donors. Previous studies of the electron-donating properties of phenothiazines have been confined to solid state studies,[5] which are difficult to interpret in terms of the

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properties of the individual molecule, and to some recent measurements of the charge transfer absorption bands and association constants[6-9] of a few phenothiazine derivatives with a number of different electron acceptors.

Measurement of Electron-Donating Properties.—It is generally accepted that a measure of the electron-donating properties of π electrons in delocalized systems is the ionization potential.[9] It is however very difficult to measure this quantity directly for complex molecules and instead it has become common practice[9-11] to measure the maximum frequency (ν_{CT}) of the charge transfer band observed for a series of donors and one given acceptor. The ionization potentials [I (exp)] of the donors are then obtained from a linear relationship of the type

$$\text{I (exp)} = K\nu_{CT} + C \qquad (1)$$

where K and C are obtained from reference molecules of known ionization potentials. In this study we have adopted this indirect procedure, although we recognize that anomalous results can occur in certain cases because of specific interactions between donor and acceptor.[9] A number of acceptors [trinitrobenzene, chloranil, tetracyanoethylene (TCNE), and 1,2,4,5-tetracyanobenzene (TCNB) were used in our preliminary measurements. From these results we chose tetracyanobenzene for our final measurements. The acceptor tetracyanoethylene which has been used by many previous workers[8-10] was deemed unsuitable for the present work because (a) it reacted chemically with some of the donors and (b) it often manifested more than one charge transfer band so that, because of band overlapping, it was difficult to measure the true ν_{CT} for the first charge transfer band. The measurements were all made using CH_2Cl_2 as solvent and using 1-cm cells in a Bausch and Lomb Spectronic 505 spectrophotometer. The results are tabulated in Tables I and II. The I (exp) values of the tables were calculated using benzene and naphthalene as reference molecules; *i.e.*, in eq 1 we used $K = 0.147$ eV and $C = 4.463$ eV.

Discussion of Electron-Donating Properties.—Table I lists the charge transfer bands for a number of compounds containing N, S, and O and which are closely related to phenothiazine. These results clearly establish that there is no remarkable change in electron-donating properties on introducing an S atom into a conjugated system and that in general S atoms enhance the electron-donating properties much less than the amino (NH) group (compare **8** and **9**, **11** and **12**). The results for the diphenylene compounds containing two heteroatoms (**13**–**16**) show that one of the two heteroatoms must be N for the compound to be even a moderately good [I (exp) < 7.5 eV] electron donor. The relatively small effect of the second hetero atom, when the first one is an amino N, is demonstrated by the comparison of the ionization potentials for acridane [**11**, I (exp) = 7.08 eV] with that of othiphenazine [**15**, I (exp) = 7.02 eV] and phenoxazine [**16**, I (exp) = 6.98 eV].

Table I
Charge Transfer Bands of Phenothiazine and Related Compounds with Tetracyanobenzene

Compounds[a]	No.	λ_{CT} (mμ)[b]	I (exp), e.V.	I (calcd), e.V.
Benzene	1	307	(9.24)[c]	(9.24)[c]
Anisole	2	400	8.14	8.40[d]
Thioanisole	3	419	7.96	7.99[d]
Aniline	4	474	7.55	7.90[d]
N-Methylaniline	5			7.34[d]
N,*N*-Dimethylaniline	6	539	7.18	7.15[d]
Diphenyl ether	7	360	8.54	8.44
Diphenyl thioether	8	414	8.01	7.84
Diphenylamine	9	508	7.35	7.43
Xanthene	10	411	8.04	
Acridan	11	560	7.08	
Thioxanthene	12	435	7.84	
Diphenylene dioxide	13	440	7.80	7.85
Thianthrene	14	424	7.93	7.00
Phenothiazine	15	575	7.02	6.82
Phenoxazine	16	584	6.98	7.08
Phenoxathiin	17	466	7.62	7.32
N,*N*′-Tetramethyl-phenylenediamine	18	719	6.50	6.25[d]

[a] All compounds were prepared and purified by standard methods at Smith, Kline, and French Laboratories, Philadelphia, Pa. [b] The wavelength measurements were made using a Bausch and Lomb 505 spectrophotometer using CH_2Cl_2 as a solvent. [c] Used as reference compound. [d] Taken from ref 15.

Table II
The Effect of Nitrogen Side Chain Substitution on Electron-Donating Properties

Side chain	Parent	No.	λ_{CT} (mμ)	I (exp), e.V.
Me	Diphenylamine	19	532	7.22
	Acridan	20	580	6.99
	Phenoxazine	21	625	6.81
	Phenothiazine	22	543	7.17
Dimethylamino-propyl	Diphenylamine	23	546	7.15
	Phenoxazine	24	560	7.09
	Phenothiazine	25	540	7.18
2-Hydroxymethylcyclopropyl	Acridane	26	555	7.11
	Phenoxazine	27	595	6.93
	Phenothiazine	28	550	7.13

The fact that although phenoxazine **16** is a slightly better electron donor than phenothiazine **15** the O analogs of promazine and chlorpromazine possess only very weak transquilizing action compared with the corresponding S compounds[12] shows that there is propably no simple direct relationship between electron-donating power and psychopharmacological action.

All the pharmacologically active compounds possess side chains on N so that it is important to know how the presence of the side chain affects the electron-donating properties. The side chain effect is demonstrated by the data in Table II. It is expected that the electronic effect of replacing the amino H by Me would enhance the electron-donating properties. This enhancement is in fact observed for the *N*-Me derivatives of diphenylamine (**19**), acridan (**20**), and phenoxazine (**21**). However, for *N*-methylphenothiazine (**22**) the electron-donating power is reduced. This anomalous effect for phenothiazine has been noted previously[2,3,13] from

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studies on polarographic oxidation potentials[2] and has been satisfactorily explained in terms of steric interactions which result in increased folding of the molecule and a corresponding reduction of the interaction of the N lone pair with the π electrons of the rest of the molecule.[3,13] For phenoxazine the normal electronic enhancement of electron-donating properties on *N*-Me substitution is observed and this can be interpreted as being due to the fact that the presence of the O atom increases the rigidity of the molecule compared to the S analog to such an extent that the steric interactions introduced by *N*-Me substitution are not sufficient to cause folding about the N and O axis. We suggest that this resistance to molecular deformation in phenoxazine derivatives could be responsible for their lack of tranquilizing action compared to the more flexible phenothiazine derivatives, *i.e.*, we suggest that this flexibility is desirable for strong binding at the drug receptor site. Further support for the idea that S compounds are more flexible than O compounds can be found in some recent molecular orbital calculations of the change in the total energy for 1,4-dioxadiene and 1,4-dithiadine with change in shape using the extended Hückel method, which includes all valence electrons.[14] Predictions were made that the most stable shape for the O compound was the planar one and that the energy increased quite sharply on folding the molecule about the O–O axis. For the S compound, on the other hand, the plot of the total energy *vs.* CSC angle gives a shallow minimum at a CSC angle of 140°, thus indicating that S compounds of this type would bend more easily than the corresponding O compounds.

The finding that the introduction of the dimethylaminopropyl group (**23**–**25**), or the cyclopropyl group (**26**–**28**) reduces the electron-donating power for all the molecules studied, except for **23** and **25**, indicates that, as steric interactions are increased, a point is reached at which even the O compound will deform. On protonation of the Me_2N group a sharp falling off of electron-donating properties is observed. As is shown by the observation that in **24** and **25** and in chlorpromazine, hydrochloride formation causes the charge transfer bands to move to shorter wave lengths by 40–60 mμ and to become very weak and broad. This would indicate that, if there is any connection at all between tranquilizing action and electron-donating properties, the hydrochloride is converted into the free base before exerting its electron-donating action.

SCF Molecular Orbital Calculations.—The original proposal that chlorpromazine is an outstanding electron donor was based on calculations made using the simple Hückel MO method.[1,4] Today this has largely been superseded by the more sophisticated Pariser–Parr–Pople self-consistent field molecular orbital (PPP) method.[15] This method has recently been used quite successfully to predict ionization potentials and to interpret the electronic spectra of a number of heterocyclic compounds containing N, O, and S.[16–18] We have now extended this work to some of the compounds of Table I.

The PPP calculations were performed using the methods described previously.[16] Initially we used the two sets of parameters summarized in Table III. In our previous work on compounds containing 5-membered S and O rings we found set A to give the best results. However, in the compounds considered here we found this set to predict far too many low-lying transition energies whereas set B gave good results. Consequently all the results reported in Tables I and IV were carried out using parameter set B.

Table III
Parameters for SCF MO Calculations

	Set A (in eV)			Set B (in eV)		
Atom	R_X+^a	I_X+^b	β_{CX}[c]	R_X[a]	I_X[b]	β_{CX}[c]
C	11.13	11.6	−2.32	11.13	11.16	−2.32
N	16.76	24.8	−1.8	12.34	21.0	−1.80
O	21.53	33.0	−1.8	15.23	26.7	−1.80
S	13.05	22.2	−1.5	10.01	19.16	−1.50

[a] One center coulomb integrals as in ref 16. [b] Valence state ionization potentials as in ref 16. [c] Resonance integrals between C and atom X.

Table IV
Calculated and Experimental[a] Electronic Spectra

Compound	No.[b]	λ (mμ)	log ϵ	λ_{calcd} (mμ)	f[c]	Pol[d]
Diphenylamine	21	282	4.24	295	0.54	X
				295	0.04	Y
				286	0.09	X
Diphenyl thioether	8	274	4.1	260	0.19	X
		250	3.76	257	0.11	X
				214	0.16	Y
Diphenyl ether	7	227	4.0	244	0.06	Y
				222	0.6	X
Diphenylene dioxide	13	295	3.87	266	0.25	X
		228	4.73	213	1.26	X
		222	4.64	196	0.84	Y
Phenoxazine	16	313	3.86	337	0.12	X
		238	4.68	224	1.03	X
Phenothiazine	15	320	3.64	319	0.34	X
		253	4.64	460	1.11	X
Phenoxthiin	17	295	3.60	299	0.05	X
		238	4.5	286	0.28	X
		241		220	1.03	X
Thianthiin	14	275	3.36 (sh)	341	0.55	X
		257	4.63	335	0.33	Y
		242	4.22	254	0.5	X

[a] Experimental values taken from "Organic Electronic Data," Vol. 1-4. Interscience, New York, N. Y., 1946–1959. [b] Numbering from Table I. [c] f is the calculated oscillator strength (ref 16). [d] The polarization axes are defined by choosing the C_2 axis of symmetry passing through the hetero atom(s) as the Y axis.

For geometries we assumed planar structures with standard C–C bond lengths of 1.397 Å, C–N and C–O lengths of 1.36 Å, and a C–S bond length of 1.78 Å. The singlet transition energies and oscillator strengths were the results of configuration interaction calculations in which the lowest ten singly excited configurations were included.

The calculated ionization energies [I (Calcd)] of Table I, column 5, were obtained using the relationship

$$I\ (Calcd) = [-E\ (HO) - 1.04]\ eV$$

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where E (HO) is the calculated energy of the highest occupied MO and the constant −1.04 eV was obtained by fitting the equation to predict correctly the ionization potential of benzene.

Discussion

There has been no previous attempt to assign the observed uv bands of phenothiazine and similar compounds to particular electronic transitions using SCF MO theory. Even though our theory is still very crude (particularly our assumptions about the geometry of the molecules) the main features of the observed spectra (Table IV) are, except for thianthrene, predicted very successfully. The calculations predict that for Ph_2NH there is a very intense band at 280 mμ while for Ph_2S the predictions are that the strong absorption will move to shorter wavelengths and a weaker band will appear as a long wavelength shoulder to the strong band. These predictions are in agreement with experiment. The theory agrees with experiment in predicting that in phenothiazine and in phenoxazine, phenoxathiin and diphenylene oxide the uv spectra will exhibit two absorption bands, one moderately intense in the 270- to 290-mμ region followed by a very strong one at about 240 mμ.

In our calculations we assumed planar geometry and we may infer from the good agreement between experiment and theory that the molecules under study are either near planar permanently or that the time-weighted average configuration is planar or close to planar. For thianthrene, however, the agreement between experiment and theory is poor. The observed spectra is different from the other phenylene compounds in that it possesses no long wavelength absorption band above 280 mμ. Also, the calculated ionization potential is high by 1.0 e.V. We interpret this gross discrepancy between theory and experiment as evidence that, of the compounds of Table IV, only thianthrene exists permanently in a bent form in the free state. From the results of dipole moment studies it has been previously suggested that phenoxazine also permanently exists in a bent form.[19] However, if we take into consideration the previously neglected[19] lone pair (or hybridization) moment of the O (1.35 Debyes),[20] we find that the π dipole moment is reinforced by about 0.52 D. If we also make the reasonable assumption that the dipole moment from the two C–C σ bonds will be approximately cancelled out by the moments of the two C–N bonds plus the moment of the N–H bond, then we arrive at a calculated moment of 1.87 D for a planar structure. This is in excellent agreement with the experimental value of 1.93 D.[19] Whereas the closeness of the calculated and experimental values is almost certainly fortuitous, it does demonstrate that it is perfectly reasonable for planar phenoxazine to possess a dipole moment of the same order of magnitude as the observed. This conclusion is compatible with the good electron donating properties of this compound which also indicates that the heteroatoms must be exerting their full conjugating power.

Conclusions.—Our experimental measurements of ionization potentials demonstrate that phenothiazine and related compounds are only moderately good electron donors (of the same order of magnitude as anthracene, [I (exp) = 7.2 eV)], and that they do not possess the potent electron-donating action previously assumed.[1-3] From both our results, and the recent findings of Millie, *et al.*,[11] that substituted indoles and methyl lysergate, also possess only moderate electron-donating powers, we must conclude that the evidence for a relationship between the psychotropic properties of molecules and electron-donating action is very tenuous.

The results of Table I show very clearly that the unique role of S in tranquilizers, such as chlorpromazine, is not connected with the electron-donating properties since these are largely determined by the N. One possible suggestion is made that the role of the S atom may be in conferring a flexibility on the molecule which is absent, for example, in the corresponding inactive O compound. The possible importance of conformational factors in influencing psychotropic activity for psychotomimetic drugs has been discussed recently.[21] Another possible role of S, which we are investigating, is its great ability (compared to O) to form complexes utilizing its localized lone pair. Of course, there is also the possibility that the O analogs of the phenothiazines are inadequate because of a different rate of absorption, distribution, or metabolism.

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