(54) S. F. Ting, S. M. Wang, and N. C. Li, *Can. J. Chem.*, **45**, 425 (1967).
(55) L. W. Reeves and C. P. Yue, *ibid.*, **48**, 3307 (1970).
(56) J. A. Glasel, *J. Am. Chem. Soc.*, **92**, 372 (1970).
(57) K. J. Packer and D. J. Tomlinson, *Trans. Faraday Soc.*, **67**, 1302 (1971).
(58) G. Akerlof, *J. Am. Chem. Soc.*, **54**, 4125 (1932).
(59) J. J. Lindberg and J. Kenttamaa, *Suom. Kemistil., B*, **33**, 104 (1960).
(60) F. E. Critchfield, J. A. Gibson, and J. L. Hale, *J. Am. Chem. Soc.*, **75**, 1991 (1953).
(61) A. N. Paruta and S. A. Irani, *J. Pharm. Sci.*, **54**, 1334 (1965).
(62) J. B. Hasted, "Aqueous Dielectrics," Chapman & Hall, London, England, 1973, chap. 7.
(63) D. Martin, A. Weise, and H.-J. Niclas, *Angew. Chem.*, **79**, 340 (1967).
(64) D. E. Bowen, M. A. Priesand, and M. P. Eastman, *J. Phys. Chem.*, **78**, 2611 (1974).
(65) E. A. Symons, *Can. J. Chem.*, **49**, 3940 (1971).
(66) D. Eisenberg and W. Kauzmann, "The Structure and Properties of Water," Oxford University Press, New York, N.Y., 1969, chap. 4.
(67) H. S. Frank, *Science*, **169**, 635 (1970).
(68) A. T. Hagler, H. A. Scheraga, and G. Nemethy, *J. Phys. Chem.*, **76**, 3229 (1972).
(69) R. E. Powell, W. E. Roseveare, and H. Eyring, *Ind. Eng. Chem.*, **33**, 430 (1941).
(70) L. Korson, W. Drost-Hansen, and F. J. Millero, *J. Phys. Chem.*, **73**, 34 (1969).

Spectra of Radical Cations of Phenothiazine Derivatives in Solution and Solid State

A. ORTIZ, A. PARDO, and J. I. FERNÁNDEZ-ALONSO ˣ

Received July 21, 1978, from the *Departamento de Química Física y Química Cuántica, Centro Coordinado CSIC-UAM, Facultad de Ciencias C-XIV, Cantoblanco, Madrid 34, Spain.* Accepted for publication October 1, 1979.

Abstract □ The UV and visible spectra of radical cations of several phenothiazine derivatives were studied using different solvents. The establishment of a relationship between these bands and the R_2 and R_{10} substituents was attempted. The influence of the disolvents on the bands also was studied. The characteristic charge transfer band was observed in the solid state using diffuse reflectance spectroscopy. The R_2 substituent did not appear to influence the band, while the R_{10} substituent influenced the band considerably, probably due to steric effects.

Keyphrases □ Phenothiazine—derivatives, spectra in solution and solid state, effect of R_2 and R_{10} substituents □ Psychotropic drugs—phenothiazine derivatives, spectra in solution and solid state, effect of R_2 and R_{10} substituents □ Spectroscopy—UV and visible spectra of phenothiazine derivatives, solution and solid state

Psychotropic drugs are fundamental in the treatment of mental disorders. Increased knowledge of the physicochemical properties of these products would help in understanding their interaction with live organisms.

One important property of these drugs is that they are oxidized easily (1). The idea that phenothiazines could act in humans in an oxidized form (2) was supported by the fact that several oxidized compounds are observed in the degradation products (3). This paper describes a study of the oxidized form of these phenothiazine derivatives in solution and in the solid state.

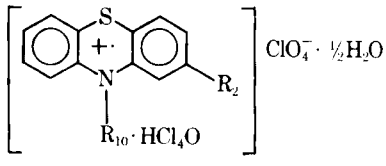
An attempt was made to relate the derivatives according to their R_2 and R_{10} substituents, semiconductor properties, dissociation constants (4), and ability to form complexes (5). The phenothiazine derivative cation radicals were prepared in a solid state, and their diffuse reflectance spectra were studied. The UV and visible spectra of these radicals in solution also were studied.

EXPERIMENTAL

Materials—Phenothiazine derivatives with R_2 and R_{10} substituents were used (Table I). The products were pharmacologically pure and were used as supplied commercially. Perchloric acid (70%) and potassium dichromate were the oxidizing agents. The solvents were distilled water, acetonitrile, and sulfuric acid (2 and 9 *N*).

A UV–visible spectrophotometer was used to obtain the solution spectra; for the diffuse reflectance spectra, the corresponding attachment was used.

Method—A literature method (6) was used to obtain the cation radicals in the solid state. The proposed formula for these products is (6):



The melting points of the products ranged from 175 to 223°. The radicals rapidly dissolved in all of the solvents used. An intense color appeared, corresponding to the oxidized form. The radicals remained indefinitely stable only with 9 *N* H_2SO_4 due to its high acidity.

The formation of charge transfer complexes in the solid state was studied by diffuse reflectance spectroscopy. Tablet preparation was the same as that used for the IR method except that naphthalene (7) was the solvent.

RESULTS

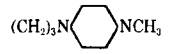
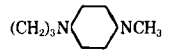
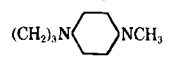
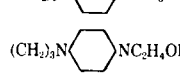
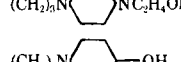
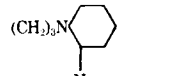
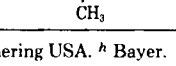
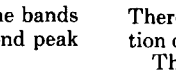
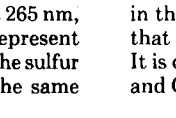
Solutions were prepared from polycrystalline powder of the cation radicals in 9 *N* H_2SO_4. Table II gives the wavelengths corresponding to the absorption peaks of the radicals in 9 *N* H_2SO_4, both in the visible and the UV range (Fig. 1). The reference used to study the effect of the substituents was promazine.

UV Spectra—The UV spectra of derivatives with a constant R_2 substituent and various R_{10} substituents were studied. Derivatives with R_2 = H and various R_{10} substituents (I–V) showed no change from the reference spectrum. This observation showed that the R_{10} substituent does not influence the UV electron transitions. In derivatives with R_2 = Cl and various R_{10} substituents, the R_2 substituent caused a bathochromic shift of 4 nm throughout the spectrum (Table II). The second peak in the spectra of derivatives with R_2 = CF_3 and various R_{10} substituents disappeared.

Derivatives with a constant R_{10} substituent and various R_2 substituents were considered. The effect of the R_2 substituent was observed in the promazine (I and VI–VIII) and perazine (V and X–XIII) families (Table II). The chlorine derivatives featured a 4-nm bathochromic shift in all bands. The other substituents caused more pronounced shifts throughout the spectrum, together with the disappearance of the second peak [derivatives with R_2 = OCH_3 or $SO_2N(CH_3)_2$].

0022-3549/80/0400-0378$01.00/0

Table I—Products and Their Characteristics

	Product	R_2	R_{10}	Salt	Clinical Use
I	Promazine[a]	H	$(CH_2)_3N(CH_3)_2$	HCl	Tranquilizer
II	Trimeprazine[b]	H	$CH_2CHCH_2N(CH_3)_2$ | CH_3	Tartrate	Antipruritic
III	Ethopropazine[b]	H	$CH_2CHN(CH_2CH_3)_2$ | CH_3	HCl	Antiparkinsonian, anticholinergic
IV	Diethazine[b]	H	$(CH_2)_2N(CH_2CH_3)_2$	HCl	Antiparkinsonian, anticholinergic
V	Perazine[c]	H		HCl	Tranquilizer
VI	Chlorpromazine[b]	Cl	$(CH_2)_3N(CH_3)_2$	HCl	Tranquilizer
VII	Triflupromazine[d]	CF_3	$(CH_2)_3N(CH_3)_2$	HCl	Tranquilizer
VIII	Methoxypromazine[b]	OCH_3	$(CH_2)_3N(CH_3)_2$	Maleate	Tranquilizer
IX	Methotrimeprazine[b]	OCH_3	$CH_2CHCH_2N(CH_3)_2$ | CH_3	Maleate	Analgesic
X	Prochlorperazine[e]	Cl		HCl	Tranquilizer
XI	Trifluoperazine[d]	CF_3		2 HCl	Tranquilizer
XII	Thiethylperazine[f]	SCH_2CH_3		Dimaleate	Antiemetic
XIII	Thioproperazine[b]	$SO_2N(CH_3)_2$		Maleate	Tranquilizer
XIV	Perphenazine[g]	Cl		HCl	Tranquilizer
XV	Fluphenazine[a]	CF_3		2 HCl	Tranquilizer
XVI	Properiziazine	CN		Base	—
XVII	Thioridazine[h]	SCH_3		HCl	Tranquilizer

[a] Rhodia. [b] Specia. [c] Promonta. [d] Squibb. [e] Upjohn. [f] Sandoz. [g] Schering USA. [h] Bayer.

In derivatives where $R_2 = CF_3$, no shift was produced in the bands compared to the same derivatives with $R_2 = H$, but the second peak disappeared.

For derivatives where $R_2 = SCH_3$ or SC_2H_5, an intense bathochromic shift was present in the first peak, the second peak remained at 265 nm, and a transition peak appeared (245–228 nm) that seemed to represent a vibratory structure. This transition could have been caused by the sulfur atom in the substituent [the same bands also appeared at the same wavelengths in the spectra of identical neutral products (8)].

Visible Spectra—The influence of the R_2 substituent on the first band was studied.

For the molecular series of I and VI–VIII, the results in Table II indicate that the substituents caused bathochromic shifts except for $R_2 = CF_3$, where a hypsochromic effect existed in the first band. The same shift occurred with the perazine-derived molecules (V and X–XIII).

The effect of the R_{10} substituent in the first band of the visible zone was observed in I–V. The values in Table II for these compounds show that not only the reduction in the number of carbons between the two nitrogens of the alkyl chain and of the nucleus, but also the introduction of substituents in the chain, produced small bathochromic shifts.

For the second and third bands, where a vibratory structure appeared to exist, the R_{10} substituent produced bathochromic effects. Contrary to the case with the first band, the R_2 substituent did not exert such a pronounced effect as the R_{10} substituent (5).

Analysis of Spectra with Different Solvents—A comparison of spectra using different solvents showed that the characteristic bands did not undergo any change. As a result, it was deduced that a difference in the polarity of the solvent did not produce a shift in the bands assigned to these compounds. It follows that the transition cannot be of the $n-\pi$ type where any influence of the solvent polarity would be pronounced. Therefore, these bands correspond to $\pi-\pi^*$ transitions (with the exception of the SR type, which was not studied).

The bathochromic shifts could have been produced by an instability in the fundamental state caused by the substituent and possible stability in the excited state. Where bands remained unaltered, it was assumed that the substituents did not interact with the π-structure of the ring. It is difficult to explain the effect of certain substituents, such as OCH_3 and CF_3, which caused the disappearance of some bands. The influence

Table II—UV and Visible Spectra of the Radical Cations of Some Phenothiazines Derivatives in Solution

Product	UV λ_{max}, nm	Visible λ_{max}, nm
I	272, 264, 212	518, 775–865
II	272, 265, 212	520, 780–875
III	271, 264, 210	520, 792–890
IV	272, 265, 212	523, 785–882
V	272, 265, 212	517, 774–860
VI	276, 268, 212	534, 775–865
VII	272, 214	505, 770–858
VIII	282, 228	573, 760s–820
IX	282, 224	575, 770s–825
X	276, 268, 217	535, 775–865
XI	272, 212	505, 775–860
XII	296, 268, 246, 224, 210	405, 465s–493, 650, 830s, 910
XIII	276, 216	525, 778–865
XIV	276, 268, 215	537, 775–867
XV	272, 212	505, 775–860
XVI	278, 230, 208	530, 775–860
XVII	295, 265, 244, 232, 210	363, 400s–470, 495, 650, 830, 900

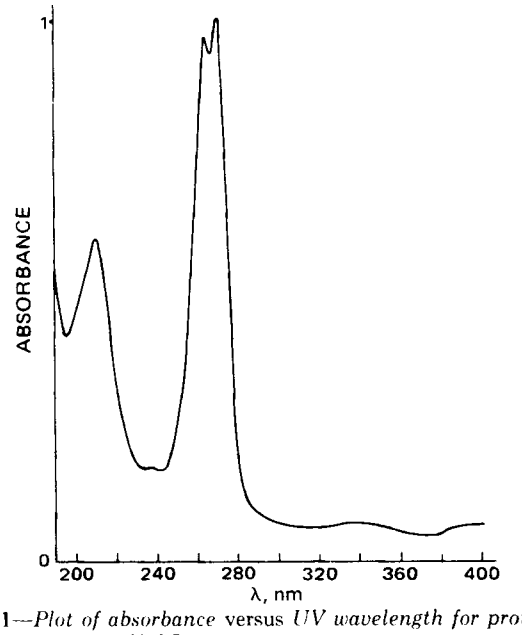


Figure 1—*Plot of absorbance* versus *UV wavelength for promazine radical cation in 9* N H_2SO_4.

of the R_{10} substituent appears on the electronic transition of the lowest energy transitions (with vibrational structure) in the visible range. This fact was attributed to the effect of the R_{10} interaction on the vibrational states.

Solid-State Spectra of Cation Radicals—The diffuse reflection spectra contained one band at 500 nm and another very wide band of equal intensity at 600–1200 nm. There were no other transitions in the field until 2000 nm.

A comparison was made with the visible spectrum of a cation radical in solution (curve e, Fig. 2). The location of the first band corresponded with the spectrum of the same radical in solution (515 nm), although it was slightly displaced toward the blue zone. These transitions of the monomer were affected by the field of the other cations and caused a shift in the π–π^* bands. The second band, wide and equal in intensity to the first band, was attributed to a charge transfer transition and appeared to superimpose on the electronic transition of the monomer in solution that appeared at 750–870 nm. This band exhibited the typical characteristics of a charge transfer; it was wide and without defined maxima.

To study the influence of the R_{10} substituent, I, II, IV, and V were considered (Fig. 2). If the maximum of this band is considered to be ~1000 nm, the promazine and perazine maxima were shifted toward the blue zone while the maxima of trimeprazine and diethazine were shifted toward the red zone.

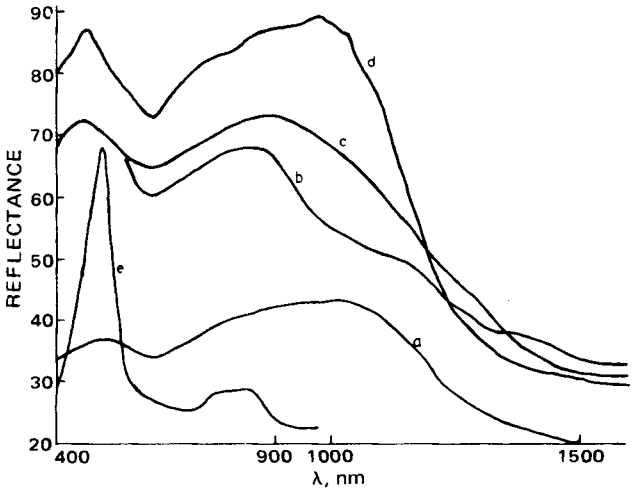


Figure 2—*Solid-state reflectance spectra of radical cations* (*reflectance* versus λ). *Key: a, diethazine; b, promazine; c, perazine; and d, trimeprazine. The visible spectrum of the perazine radical cation in sulfuric acid also is shown (e).*

Study of the influence of the R_2 substituent in the perazine family showed that the absorption peak varied slightly from 900 nm. Therefore, the R_{10} lateral chain appears to exert a greater effect than the R_2 substituents in the solid state. The influence of the R_{10} chain could be due to steric effects. This steric effect is augmented by an increase in the chain length and the different configurations that may result. This chain could insert itself between two radicals in the same column and the separation between them would increase, thus diminishing the possibility of a charge transfer and shifting the maximum toward the blue zone. Magnetic susceptibility studies could be conducted to verify this supposition. Promazine and perazine compounds should exhibit greater paramagnetism than the trimeprazine and diethazine compounds[1].

The transition was attributed to a charge transfer in the solid state and is thought to be caused through those ion radicals that are sufficiently close to overlap their half-complete π-orbitals.

Phenothiazine and its derivatives in neutral form are puckered by the heteroatoms (9).

In phenothazine oxidation, the positive charge is distributed throughout the nucleus, and the phenothiazine ion subsequently has to adopt a plane spatial structure for stability. On the other hand, it was concluded from electron–proton resonance studies (10, 11) that the positive charge is centered on the hetero ring. A definitive solution could be achieved by an X-ray diffraction study of these ions in the solid state. These ions could be in the form of infinitely long columns (12); this type of structure has been proposed for several ion salts (13).

The columns are believed to be formed by equidistant ion radicals (14). The separation of these ion radicals within the same column also could be studied by X-ray analysis. The columnar structure and the interplanar distance between the ions comprising the column can lead to charge transfer complexes. Here, the bond can be described as being formed by the overlap of half-complete π-orbitals of a donor molecule, *D*, and an acceptor, *A*. In this case, *A* and *D* are equal, and it follows that each molecule participates in the formation of overlapping orbitals. With two identical radicals, greatest interaction would take place when the two ions are superimposed.

The existence of distinct substituents capable of producing a large steric effect when interposed between two radicals of the same column appeared to have a marked influence on the packing distance of the cation derivatives in this study.

The apparent opposition that exists between the formation of solid structures with the participation of charge transfer bonding forces and the existence of unpaired electrons of these ion radicals, which in turn exhibit semiconductor properties associated with the unpaired electrons (15), should be considered. Likewise, the decrease in paramagnetic properties as a result of charge transfer interactions should be noted.

REFERENCES

(1) J. P. Billon, *Bull. Soc. Chim. Fr.*, **1960**, 1884. *Ibid.*, **1961**, 1923.

(2) A. Sentz-Gyorgi, "Introduction to Submolecular Biology," Academic, New York, N.Y., 1960.

(3) I. Forrest and M. Berger, *Biochim. Biophys. Acta*, **29**, 442 (1958).

(4) A. Pardo, S. Vivas, F. España, and J. I. Fernández-Alonso, *Afinidad*, **29**, 640 (1972).

(5) A. Pardo, F. Tomás, and J. I. Fernández-Alonso, *An. Quím.*, **73**, 20 (1977).

(6) F. H. Merkle and C. A. Discher, *J. Pharm. Sci.*, **53**, 965 (1964).

(7) Y. Iida, *Bull. Chem. Soc. Jpn.*, **45**, 624 (1972).

(8) J. González and J. I. Fernández-Alonso, *An. Fis. Quím.*, **66B**, 919 (1970).

(9) B. Pullman and A. Pullman, *Biochim. Biophys. Acta*, **35**, 525 (1969).

(10) D. W. Schieser and L. D. Tuck, *J. Phys. Chem.*, **51**, 7 (1962). M. Kamiya and A. Akahori, *Chem. Pharm. Bull.*, **18**, 11 (1970).

(11) G. Lagercrantz, *Acta Chem. Scand.*, **15**, 1545 (1961).

(12) Y. Iida, *Bull. Chem. Soc. Jpn.*, **45**, 624 (1972). *Ibid.*, **45**, 105 (1972).

(13) *Ibid.*, **43**, 772 (1969).

(14) R. G. Kepler, *J. Chem. Phys.*, **39**, 3528 (1963). Y. Matsunaga, *Bull. Chem. Soc. Jpn.*, **41**, 2615 (1968).

(15) A. Ortiz, A. Pardo, J. Llabrés, and J. I. Fernández-Alonso, *Mol. Pharmacol.*, in press.

[1] To be published.