MOLECULAR PHARMACOLOGY, 16, 1040–1045

A Study of the Semiconductivity of Cation Radicals of Certain Phenothiazine Derivatives

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(Received October 9, 1978)
(Accepted July 16, 1979)

SUMMARY

ARRUFAT, A. ORTIZ, J. I. FERNÁNDEZ-ALONSO, A. PARDO AND J. LLABRÉS. A study of the semiconductivity of cation radicals of certain phenothiazine derivatives. *Mol. Pharmacol.* **16**: 1040–1045 (1979).

This paper describes an experimental study on the electrical conductivity of cation radical samples, of phenothiazine derivatives, in solid phase. All samples studied exhibited semiconductor properties. Conductivity at room temperature varied between 10^{-4} and 10^{-9} $(\Omega \cdot cm)^{-1}$. We proved the dependence of the conductivity on the length of the R_{10} and R_2 substituents. The relationship between the parameters defining the electric conductivity and the pharmacological activity was also shown.

INTRODUCTION

The physico-chemical study of phenothiazines has increased greatly during recent years. One of the most common properties of phenothiazine and its derivatives is their oxidation capacity (1–3), which gives rise to the idea that the phenothiazines could act in their oxidized form in humans or produce a redox reaction. This idea was further supported by the fact that various oxidized compounds were found (4) among metabolic degradation products. Based on this, Sentz Gyorgi (5) proposed that certain products act in the human body by means of an energy or electron transfer.

Various studies have been carried out on biomolecules as energy transporters (5–7) and the field of organic semiconductors contributes considerably to the study of electronic flow in neurones and other cells. The phenothiazines can act as electron donors where there are adequate acceptors. This property, together with the steric or conformational bonding of the different chemical species, gives rise to the well known beneficial effects (8).

The cation radicals of the phenothiazine derivatives were first obtained in 1913 by Pummerer and Gassner (9). From this moment, research concentrated upon the salts of these compounds and, in particular, on the solutions of these salts (10). Only recently the solid phase of these radicals has been studied (11, 12). These cation radicals have interesting properties: those derived from the electronic structure and those due to the form in which the radical is packed in the solid state. It is assumed that the cation radicals pack together as solids in columns (12) in such a way that the partially filled π orbital of each radical overlaps

0026-895X/79/061040-06$02.00/0

forming energy bands belonging to the crystalline complex (13). The solid phase can be described thus:

$$[Q^{+} \ldots Q^{+} \ldots Q^{+} \ldots][\ldots Q^{\circ} \ldots Q^{+} \ldots . Q^{-} \ldots Q^{\circ}]$$

where Q^{+} is a phenothiazine radical.

The present paper describes a study of the electronic conductivity of these cation radicals in the solid phase. It should be pointed out that because of the impossibility of obtaining sufficiently large monocrystalline samples, we used the classical technique of compressed powders and have worked continuously under the same experimental conditions; we could thus carry out a comparative analysis of the prepared samples. The conductivity values obtained from randomly oriented grains can be considered as the average conductivity in all directions (14) or, as in the TCNQ (14), only the lowest conductivity components determine the value of this variable.

EXPERIMENTAL

The compounds under study are given in Table 1. The phenothiazines were obtained from the sources shown in the table. In order to obtain the cation radicals we followed the Merckle method (15). Extremely brittle crystals were obtained. The melting points of these products are between 175 and 223°.

Conductivity measurements. Conductivity measurements were taken using samples of pressed powder. The Masuda method (16) was used and measurements were taken in a continuous current. The applied voltage varied between 2 and 20 volts. Temperature varied between room temperature and 60°.

RESULTS AND DISCUSSION

Figure 1 shows the σ versus $1/T$ graph for promazine. It is observed that the cation radicals obey the equation:

$$\sigma = \sigma_0 \cdot \exp^{(-E_a/KT)} \quad (1)$$

where σ_0 is the conductivity for $T \rightarrow \infty$ and E_a the activation energy of the electrical conduction. The results show that the electrode-sample contacts behave ohmically. Figure 2 shows the σ versus V graph at different temperatures, in the temperature ranges studied and a voltage range of 0–20 volts. It is observed that the ohmic behavior is maintained (similar graphs were obtained for the other compounds). Table 2 gives values for σ_0, σ (at room temperature) and for E_a for each of the compounds under study.

The values of σ measured at room temperature varied from 10^{-9} to 10^{-4} $(\Omega \cdot \text{cm})^{-1}$, indicating that the compounds studied exhibited an intermediate-type conductivity (17). The activation energies varied between 0.37 and 0.11 eV. Chlorpromazine showed anomalous behavior as previously described by Gutmann in chlorpromazine neutra (18). We attempted to prove the existence of an optical transition for the wavelengths corresponding to the associated energies of the electronic activation processes. The attempt, however, proved negative.

An interesting characteristic regarding the charge transfer in the solid state is the evaluation of the mobility of the carrier densities. The Hall effect is the usual technique for studying inorganic semiconductors. Organic semiconductors exhibit very low values for electronic mobilities and the technique cannot, therefore, be used. The carrier density was then determined from the plasma frequency. This equals $\lambda \sim 1200$ nm and corresponds to a density of $n = 10^{20}$ e/cc. This value shows that each molecule contributes an electron to a hypothetical conduction band. Therefore, using this value for n and the expression:

$$\sigma = n \cdot e \cdot \mu$$

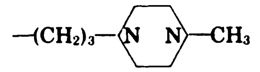
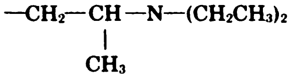
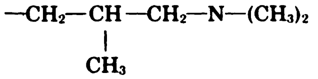
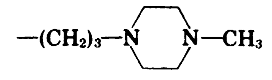
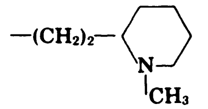
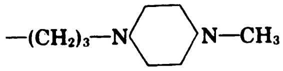
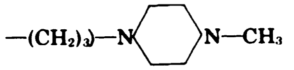
where e is the elemental charge and μ the electron mobility, μ can be calculated. Values obtained were within the range of 10^{-4} to 10^{-2} cm/V·sec and are typical for aromatic compounds when measurements are made on pressed powder. This suggests, in agreement with Many *et al.* (19), that the conduction mechanism can be of the "quantum hopping" type.

Influence of the Structure of Organic Compounds on their Electrical Behavior

The most important difference between organic and inorganic semiconductors arises from the fact that the molecules in

TABLE 1

Products, substituents R_2 and R_{10}, salts and clinical activity in several phenothiazine derivatives

Product	R_2	R_{10}	Salt	Clinical activity	Source
I Promazine	—H	$-(CH_2)_3-N-(CH_3)_2$	ClH	T	Rhodia
II Perazine	—H		Tartrate	T	Promonta
III Isothiazine	—H	 $-CH_2-\underset{CH_3}{CH}-N-(CH_2CH_3)_2$	ClH	AP, AH	Specia
IV Alimemazine	—H	 $-CH_2-\underset{CH_3}{CH}-CH_2-N-(CH_3)_2$	ClH	T, AH	Specia
V Diethazine	—H	$-(CH_2)_2-N-(CH_2CH_3)_2$	ClH	AH, AP	Specia
VI Chlorpromazine	—Cl	$-(CH_2)_3-N-(CH_3)_2$	ClH	T	Specia
VII Prochlorperazine	—Cl		ClH	T	Upjohn
VIII Metoxipromazine	$-OCH_3$	$-(CH_2)_3-N-(CH_3)_2$	Maleate	T	Specia
IX Thioridazine	$-SCH_3$		ClH	T	Sandoz
X Thietilperazine	$-SCH_2CH_3$		Dimaleate	AEm	Sandoz
XI Trifluorperazine	$-CF_3$		—2ClH	T	Squibb

the crystalline state are held together by small forces and are fixed at relatively long distances from each other (on the order of 3.4 Å). In many organic solids this restricts the intermolecular transport or charges. Dark conductivity and photoconductivity properties are related to the electronic and structural behavior of pure organic compounds, as are those in the polycrystalline state (20).

In our case each compound is made up of a tricyclic nucleus, a relatively long R_{10} lateral chain and a R_2 substituent as well as the ClO_4^- ion, which is common to all derivatives studied. With the idea of relating the variation in conductivity with the structure of these radicals, separate studies were carried out on the influence of the R_2 and R_{10} on the conductivity.

1. *Influence of the R_{10} substituent.* There are five compounds with R_2 = H which differ in the R_{10} substituent. The E_a (Table 2) of the five compounds varies from 0.3 to 0.4 eV. At room temperature the order in increasing conductivity is:

$$I \simeq II < III < IV \simeq V$$

It is known that the steric effects result from the internal molecular geometry and the nature of the substituents play an important role in intermolecular charge transfer because of the packing of adjacent radicals in the solid state (21). Thus we can say that the differences in conductivity of the five compounds could be related to the length of the R_{10} lateral chain and to the steric effect due to the chain being located between two neighboring radicals.

From theoretical studies (22) it is known that the R_{10} lateral chain, as in I and II, is capable of rotating and acquiring different configurations. This could be the reason why the steric effect is increased by the interposition of this chain between two ad-

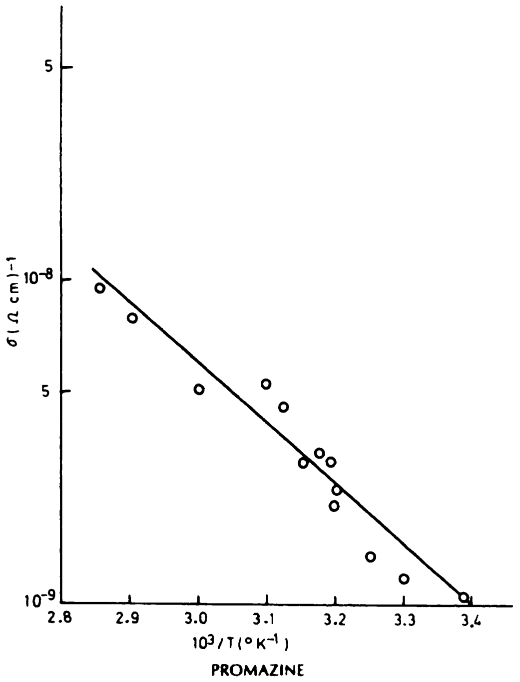


FIG. 1. *Promazine semiconductivity, versus 1000/ $T(°K^{-1})$*

jacent cation radicals which impedes the current flow. This can explain the decrease in conductivity which is observed experimentally. In compounds IV and V, the chain is shorter with only two carbon atoms between the two nitrogen atoms. Due to this, the steric effect is diminished with a resulting increase in conductivity.

In alimemazine, the methyl group of the second atom of the R_{10} affects the possible rotation of the chain (23) and the steric effect should be less than in the previous products, thus giving rise to a slight increase in the conductivity which, in fact, was observed. It is therefore deduced that a shortening of the lateral chain produces a decrease in the steric effect, which gives rise to an increase in conductivity as confirmed by the experimental results.

2. *Influence of the R_2 substituent.* Dark conductivity and photoconductivity are closely connected with the number and degree of delocalization of the π electrons, an increase in the number of aromatic rings or R substitution affects the conductivity. This is enhanced by increasing the electron donating power of the group R (24). From Table 2 it is observed that the conductivity can be substantially increased by varying the R_2 substituent. With compounds II, VII, X and XI where the R_{10} is the peperazinic group, it is observed that the conductivity follows the sequence:

$$R_2 \; -H, \; -SCH_2CH_3, \; -Cl, \; -CF_3$$

$$\sigma \; II < X < VII < XI$$

The increase in σ is probably due to the effect of the R_2 substituent on the π electron

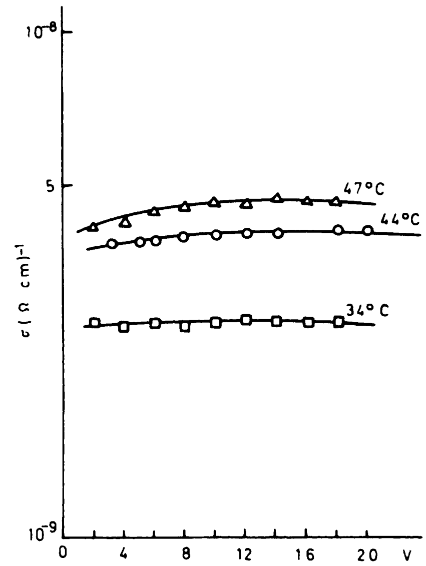


FIG. 2. *Promazine semiconductivity, versus voltage at different temperatures*

TABLE 2

Products, conductivity at room temperature (σ) extrapolated conductivity (σ_0) and activation energy in phenothiazine derivatives

Product	σ	σ_0	E_a
	$(\Omega\cdot cm)^{-1}$	$(\Omega\cdot cm)^{-1}$	(eV)
I Promazine	$2.06\cdot10^{-9}$	$4.8\cdot10^{-3}$	0.37
II Perazine	$4.6\cdot10^{-9}$	$5.4\cdot10^{-3}$	0.37
III Alimemazine	$2.15\cdot10^{-8}$	$6.7\cdot10^{-2}$	0.37
IV Isothiazine	$7.18\cdot10^{-7}$	$3.7\cdot10^{-1}$	0.35
V Diethazine	$3.12\cdot10^{-7}$	—	—
VI Chlorpromazine	$7.51\cdot10^{-6}$	1.5	0.32
VII Prochlorperazine	$5.32\cdot10^{-6}$	—	—
VIII Metoxiproximazine	$1.36\cdot10^{-4}$	$5.5\cdot10^{-2}$	0.18
IX Thioridazine	$1.45\cdot10^{-7}$	$2.5\cdot10^{-4}$	0.19
X Thietilperazine	$4.42\cdot10^{-7}$	$3.2\cdot10^{-1}$	0.36
XI Trifluorperazine	$1.94\cdot10^{-5}$	$1.4\cdot10^{-3}$	0.11

system of the phenothiazine nucleus. Those derivatives with the highest conductivity are metopromazin (VIII) and trifluorperazin (XI). Product VIII with the R_2 = $-OCH_3$ has a strong electron donating power upon the π electron system of the phenothiazine nucleus. This in turn exhibits a slight excess in electron charge which facilitates conductivity. Product XI, the electrophylic nature of the R_2, gives rise to an electronic defect in the phenothiazine nucleas. This should diminish the conductivity, but we find experimentally that this does not take place and can, perhaps, be explained by the fact that can be formed a dipole species of the cation radical (24) favoring this way σ.

3. *Conductivity-pharmacological activity relationship.* Finally, in this study of the conductivity of certain phenothiazines, we have attempted to enlarge upon the relationship between conductivity and pharmacological activity. First, we discuss the effect of the R_{10} lateral chain. In order for a compound of this family to act as a tranquilizer, its R_{10} chain must have three carbon atoms between the two nitrogen atoms (25). A lateral chain with fewer than three carbon atoms can exhibit other pharmacological properties but not those of a neuroleptic.

We have previously observed that the conductivity varies with the length of the chain, decreasing as the length or branching of the chain increases. We can assume, therefore, that the neuroleptic activity of these compounds varies inversely with σ. If we keep R_{10} constant, we can observe the effect of R_2. Taking the piperazine series as an example, it is observed that the conductivity varies thus: perazine < thietilperazine < prochlorperazine < trifluorperazine (26). This variation in σ parallels the neuroleptic effect of these compounds.

ACKNOWLEDGMENTS

The authors wish to thank Drs. F. Rueda and J. M. Martinez Duart (U.A.M.) for their helpful cooperation.

REFERENCES

1. Billon, J. Proprietés electrochimiques de la phenothiazine. *Bull. Soc. Chim. France* 1784, 1960.
2. Billon, J. Proprietés electrochimiques de la phenothiazine. *Bull. Soc. Chim. France* 1923, 1961.
3. Bloor, J. E. and B. R. Gilson. Electron donating properties of phenothiazine and related compounds. *J. Med. Chem.* **18:** 922-925, 1970.
4. Forrest I. and M. Berger. Free radicals as metabolites of drugs derived from phenothiazine. *Biochem. Biophys. Acta* **29:** 442, 1958.
5. Gyorgi, Sentz. Introduction to Submolecular Biology. Academic Press, New York, 1960.
6. Kasl, M. and B. Pullman. Horizons in Biochemistry. Academic Press, New York, 1961, 295.
7. Ely, D. D. Horizons in Biochemistry. Academic Press, New York, 1962, 376.
8. Hawkins D., and L. Pauling (Eds), "Orthomolecular Psychiatry", W. H. Freeman. San Francisco (1973).
9. Pummerer, R. and S. Gassner. Uber die Desmotropie o- and p-chinoider salze in thiazin rehie. *Berichte* **46:** 2310, 1913.
10. Michaelis, L., S. Granich and M. P. Schubert. Another type of free radicals in the group of thiazines and same others related compounds. *J. Am. Chem. Soc.* **63:** 351, 1941.
11. Shine, H. S. and E. E. Mach, Ion radicals *v.* phenothiazine phenothiazine 5-oxide and phenothiazine-3 in acid solutions. *J. Org. Chem.* **30:** 2130–2139, 1965.
12. IIda, Y. The cation radical salts of phenothiazine and related compounds. *Bull. Chem. Soc., Japan* **64:** 663–667, 1971.
13. Fox, D. Electrical Conductivity in Organic Solids (Ed. H. Hallman and M. Silver). Interscience, New York, 1960.
14. Gutmann, F. and L. E. Lyons. Organic Semiconductors. John Wiley and Sons, Inc., New York, p. 168.
15. Merkle, F. H. and C. A. Disher. Separation and investigation of a stable solid free radical of chlorpromacine. *J. Pharm. Soc.* **53:** 965, 1964.
16. Masuda, K. and J. Hanna Guchi. Electric conduction of α-α'diphenil-β picrylhydrazyl single crystal. *J. Phys. Soc. Jap.* **20:** 358–363, 1965.
17. Siemons, W. J. and R. G. Kepler. Electronic properties of a new class of highly conductive organic solids. *J. Chem. Phys.* **39:** 12, 1963.
18. Gutmann, F. and A. Netschay. Electrical properties of chlorpromazine. *J. Chem. Phys.* **36:** 9, 1962.
19. Many, A., E. Harnik and D. Gelich. *J. Chem. Phys.* **23:** 1733, 1955.
20. H. Meier. Organic Semiconductors: Dark and Photoconductivity of Organic Solids. Weinheim, Verlag Chemie, 1975.
21. Yannoni, N. F. and L. G. Hanscon. Soll Cells. *Proc. Int. Colloq*, 1970, p. 175.
22. Kaufmann, J. J. and E. Kerman. Quantum chemical and theoretical techniques for the understanding of the action of drugs which affect the

C.N.S. Jerusalem Symposium on Quantum Chemistry and Biochemistry, VI, Jerusalem, 1974.

23. Gordon, N. Phenothiazines, Psychopharmacological Agents. Academic Press, New York, 1967, pp. 119–130.
24. Meier, H. Semiconductor Properties of Dyes. Springer-Verlag, Basel, 1976, pp. 107–108.
25. Janssen, P. A. J., IV Reuni du College International de Neuro-Psychopharmacologie. Birmingham (1964). Janssen, P. A. J. Abstrat., 36, 158th National American Chemical Soc. Meeting Sept, 1969. Ibid (1970).
26. Burker, J. C. and Piala, J. and H. Yale., "Meeting Soc. Pharmacol. Exptl. Therap. (1956) French Dick. Indiana.