

RAMAN SPECTRA OF PHENOTHIAZINE AND SOME PHARMACEUTICAL DERIVATIVES

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Phenothiazines are widely used as antipsychotic drugs and for this reason there has been much effort devoted to the spectroscopic characterization of these compounds. Although the infrared spectra of phenothiazines have been well characterized,¹ there have been no reports of the Raman spectra. Raman spectrometry appears useful in the identification of phenothiazines because of the presence of carbon-sulphur bonds and because the technique is well suited to the examination of solids, the physical form of most pharmaceutical preparations. In the present communication we report the spectra of several solid phenothiazines in the 600-1600-cm⁻¹ region and present preliminary assignments of the major bands.

EXPERIMENTAL

The formulae of the substituted phenothiazines studied are presented in Table 1. Compounds **I** (trifluorpromazine hydrochloride) and **II** were obtained from the Squibb Institute. Compounds **III** and **IV** were obtained from Searle Laboratories. These compounds were used without further purification. Unsubstituted phenothiazine (Aldrich Chemical Co.) was recrystallized from benzene.

Raman spectra were recorded on a Spex 1401 double monochromator equipped with a cooled RCA C31034 photomultiplier and both photon-counting and d.c. detection systems. He-Ne 632.8-nm excitation (25-35 mW at

the sample) was employed. Samples were irradiated for about 30 min in the laser beam to remove residual fluorescence. Samples were introduced into the laser beam as powders contained in standard glass melting-point capillaries. All spectra were recorded with 10 cm⁻¹ resolution.

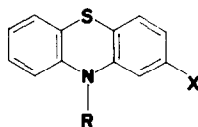
RESULTS AND DISCUSSION

The Raman spectra of the phenothiazines examined are presented in Table 2. Because the samples were examined as polycrystalline solids, depolarization ratios were not taken.

The phenothiazine spectra can be interpreted as derived from the spectra of diphenylamine, diphenyl sulphide and the various saturated compounds which make up the side-chains. Such an approach is valid, since the phenothiazine is known to be folded about the S-N axis, with a dihedral angle between the phenylene rings of about 140-154°, depending on the substitution pattern.^{2,3} Thus, the two phenylene rings are more or less independent and the spectra will be closely related to those of simpler substituted benzenes. The ring mode dominated by symmetric phenylene-sulphur stretching appears at 670-680 cm⁻¹ for the phenothiazines investigated. In diphenyl sulphide (liquid) this vibration occurs at 668 cm⁻¹.⁴ The differences may be attributed to both the difference in the phase and to the presence of an *ortho*-substituent in phenothiazine and possibly to the difference in the C-S-C bond angle. This band is in the same region as the C-C out-of-plane deformation, which is responsible for the infrared absorption

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Table 1 Formulae of substituted phenothiazines



Compound	X	R
I	CF ₃	-(CH ₂) ₃ N(CH ₃) ₂ .2HCl
II	CF ₃	$ \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ \diagup \quad \diagdown \\ \text{-(CH}_2\text{)}_3\text{-N} \quad \text{N-CH}_2\text{-CH}_2\text{-O-C(=O)-(CH}_2\text{)}_5\text{CH}_3 \\ \diagdown \quad \diagup \\ \text{CH}_2\text{-CH}_2 \end{array} $.2HCl.H ₂ O
III	Cl	$ \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ \diagup \quad \diagdown \\ \text{-(CH}_2\text{)}_3\text{-N} \quad \text{CH-C(=O)-NH-CH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)}_2 \\ \diagdown \quad \diagup \\ \text{CH}_2\text{-CH}_2 \end{array} $.2HCl
IV	Cl	$ \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ \diagup \quad \diagdown \\ \text{-(CH}_2\text{)}_3\text{-N} \quad \text{N-CH}_2\text{-C(=O)-CH}_3 \\ \diagdown \quad \diagup \\ \text{CH}_2\text{-CH}_2 \end{array} $.2HCl

Table 2. Raman spectra of phenothiazines

Phenothiazine	I	II	III	IV	Assignment
				605w	
	610w	610w		610w	
			620m	620w	
			645m		
	660w		670w		
685w	680s	680s	685s	675vs	Symmetric Ph-S-Ph stretch
	700w	705w		700m	
720w	720w	725w		720w	
		735w	735w		
750w	740w		745w		
	760w			760w	
	775w	770m	795m	780w	
	850w	800w			Symmetric C-N-C stretch, tert. aliphatic amines
		810w	815m	820m	
	840w	825w	840w	835w	
			855w	850w	
		870w		865w	
	880w		880w		
890w			890w		
			905w	900w	
		925w	930m	925w	
	940w	940m	945w		
		970w	955w	960w	
			980s		
			1010m	995w	
			1040s	1015w	
1040vs	1040s	1040vs	1040s	1045vs	CH ring deformation
	1060m	1055m	1060m		
1085w	1088w	1080w	1070w	1075w	Asymmetric Ph-S-Ph stretch
	1110vs	1110s	1110vs	1100vs	Asymmetric C-N-C stretch
1130w		1125m	1130w	1125w	
	1145w	1150w	1145w	1145m	
1165w	1165w	1160w	1170m	1175w	CH ring deformation
		1180w			
		1185w			
			1195m	1200w	
			1210m		
		1220w		1220w	
			1235m		
1250m	1245w	1240w	1250w	1250s	symmetric Ph-N-Ph stretch
	1260w	1260w			
			1270m	1280w	
	1290w		1290w	1295m	
			1300m		
	1310m	1315s	1325w	1320w	methylene twisting
		1340m	1335m	1335w	
	1365m				
			1370m		
				1380w	
			1410w	1405w	
			1420w	1425m	
	1435w	1430m			
		1445m	1440m		
	1465w		1460w	1465w	
			1475m	1475w	
		1500w			
			1525m	1520w	
1570m	1570s	1580s	1570s	1570s	ring stretching
	1590m	1595m	1590w	1590w	ring stretching
1605m	1605m	1605m	1605sh	1605sh	ring stretching

in the 690-cm^{-1} region.^{4,5} Overlap with this mode, which is active in *ortho*-disubstituted benzenes,⁶ cannot be ruled out.

The asymmetric phenylene-sulphur stretches occur in the $1070\text{--}1090\text{-cm}^{-1}$ region. In diphenyl sulphide this band occurs at around 1080 cm^{-1} .^{4,5}

The medium intensity symmetric phenylene-nitrogen stretch is found at $1240\text{--}1250\text{ cm}^{-1}$. In solid diphenylamine, this vibration is observed in the infrared at 1250 cm^{-1} .

The intense 1040-cm^{-1} band we assign to a C-H ring deformation. This is a strong band at 1040 cm^{-1} for diphenylamine and at 1026 cm^{-1} for diphenyl sulphide.⁴ A weaker C-H deformation occurs at $1165\text{--}1175\text{ cm}^{-1}$ and is observed at 1153 cm^{-1} for diphenyl sulphide.⁴

In the spectrum of unsubstituted phenothiazine a pair of ring modes occurs at 1570 and 1605 cm^{-1} . These are the two components of a ring-stretching mode (l and k in Whiffen's notation). In the spectra of the ring-substituted phenothiazines, three bands occur in this region, owing to the non-equivalence of the two phenylene rings. We have not attempted detailed assignments of the bands due to vibrations of the alkyl side chains. We present only a few general assignments, but do not attribute bands to individual amines or alkyl groups.

The pharmaceutical derivatives have a group of bands between 800 and 900 cm^{-1} , due to symmetric C-N-C stretches of the tertiary amino groups.⁸ The asymmetric C-N-C stretches appear as strong bands at $1100\text{--}1110\text{ cm}^{-1}$. Similarly, the band at $1310\text{--}1325\text{ cm}^{-1}$ is assignable to a methylene twisting mode of the alkyl chains common to all of the substituted phenothiazines.⁹

Summary—The laser-Raman spectra of several phenothiazines in the region $600\text{--}1600\text{ cm}^{-1}$ are reported. The major bands are assigned to ring modes or to vibrations of the alkyl side-chains.

Further refinement of these spectra and their extensions to higher and lower frequencies are in progress and will be reported at a later date.

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THE DETERMINATION OF METALLIC IRON IN THE PRESENCE OF FAYALITE

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A current investigation in these laboratories, into the treatment of low-grade tin ores, involved the reduction of tin calcines under various conditions. During the analysis of these reduced calcines difficulty was encountered in determining metallic iron. The reduced samples contained metallic iron, tin and tin-iron alloys, tin and iron oxides, aluminium-iron oxides (hercynite), and iron silicate (fayalite, $2\text{FeO}\cdot\text{SiO}_2$).

It was confirmed that metallic iron can be determined satisfactorily in the presence of iron oxides (both ferrous, ferric and complex oxides such as hercynite) by methods such as those of Kraft and Fischer¹ or Blum and Searl² whereby the sample is treated with bromine in methanol under reflux conditions. The oxide residue is subsequently filtered off, washed with methanol, and, following the evaporation of alcohol from the filtrate, the iron equivalent to the metallic iron content is determined in dilute hydrochloric acid solution.

The method above, however, does not give accurate results for metallic iron when iron silicates such as fayalite are present in the sample to be analysed. The errors arise because fayalite is attacked by hydrogen bromide which apparently forms in the alcoholic solution of bromine even when moisture is rigorously excluded.³ In Fig. 1, (a) and (b), are shown portions of the X-ray diffraction patterns of a synthetic sample containing iron (II) oxide, silica, and approximately 6% fayalite before and after treatment with bromine in methanol. It is clear that most of the fayalite has been dissolved during this treatment.

Several variations of the method of Kraft and Fischer¹ were studied in order to overcome this problem. It was found that whereas iodine in methanol did not attack the fayalite, the metallics—tin, iron, and iron-tin alloys—were halogenated only slowly. A more satisfactory variation was to treat the sample with bromine alone under reflux, then evaporate all excess of bromine before extracting the iron