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MATERIALS AND METHODS

This chapter is divided into Section A, which describes the properties and importance of the materials used in the investigations and Section B provides details of the instrumental methods and techniques employed for the synthesis and characterization of the materials with respect to Elemental, TGA, UV-Vis, IR, electrical, X-ray diffraction and the like.

SECTION A: MATERIALS

1) Phenothiazine, (PTZ): Phenothiazine, also called dibenzothiazine or thiodiphenyl amine was first synthesized by Bernthsen in 1883 [1]. It is a yellow green crystalline solid melting at 186 °C. It is insoluble in water but soluble in most of the organic solvents such as acetone, ethanol, acetonitrile, methanol, benzene, etc. It is a photo sensitive compound. The structure of phenothiazine can be written as in Fig.1.

![Fig. 1 Phenothiazine](image)

The ionization potential of phenothiazine is very low as indicated indirectly by charge-transfer spectra [2-3]. Under certain condition it gives triply charged ions [4]. McDowell had determined the structure of phenothiazine using 1046 diffractometer [5]. The space
group is orthorhombic with \( a = 7.916 \pm 0.01 \), \( b = 20.974 \pm 0.01 \) and \( c = 5.894 \pm 0.01 \) Å. The C-S-C angle is \( 100.9 \pm 0.3 \) Å and there are four molecules in the unit cell.

2) 2-Chlorophenothiazine, (CP): The synthesis of CP involves two stages [6]. It is a greenish yellow compound melting at 180 °C. It is insoluble in water but soluble in organic solvents like acetone, ethanol, benzene, dimethyl formamide, etc. It undergoes slow photochemical oxidation. It is identified by IR and UV spectra [7]. The influence exerted by the substituent, chlorine located in the benzene ring of the phenothiazine is very small. The literature concerning CP is meagre. The structure of CP is as given in Fig. 2.

![Fig. 2 2-Chlorophenothiazine](image)

3) Promethazine hydrochloride, (PH): Promethazine hydrochloride, 10- [2-dimethylamino] propyl]-phenothiazine hydrochloride known as phenergan, is an important phenothiazine tranquilizer.

![Fig. 3 Promethazine Hydrochloride](image)
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It is a first generation H1 receptor antagonist, antihistamine and antiemetic medication.

Paul Charpentier developed a method for the synthesis of PH by employing 10- (2-propyl) phenothiazine in methanol, mercury (II) sulphate, dimethyl amine-dioxane, sulphuric acid and Raney nickel [8]. It can also be synthesized by other method [9]. Promethazine has the structure as shown in Fig. 3. by powder X-ray diffraction [10]. It is a white amorphous powder melting at 222 °C. It is soluble in water, acetone, ethanol, acetonitrile, but insoluble in chloroform, benzene and ether.

4) Promazine hydrochloride, (PMH): It is prepared by heating phenothiazine, 3-dimethyl amino-1-chloropropane in xylene [11]. It is a white crystalline photosensitive substance with a melting point of 182 °C. It oxidizes upon prolonged exposure to air and acquires blue or pink colour, incompatible with alkalies, heavy metals and oxidizing agents. It is soluble in water, methanol, acetone and ethanol but insoluble in benzene and ether. Falkenberg and Ringertz have reported single crystal X-ray data of promazine hydrochloride, recrystallised from slow evaporation from ether at about 4°C [12]. The structure of promazine hydrochloride is as shown below:

![Promazine Hydrochloride](image_url)

Fig. 4 Promazine Hydrochloride.
5) Chlorpromazine hydrochloride, (CPH): It is a white crystalline compound which melts at 196 °C. It is sold under trade names, Largactil and Thorazine. It was synthesized by Charpentier [13]. It is soluble in water, methanol, ethanol, acetone and acetonitrile, practically insoluble in benzene and ether. It has the following structure:

![Fig. 5 Chlorpromazine Hydrochloride](image)

6) Triflupromazine hydrochloride, (TPH): 10-(3-dimethyl amino propyl)-2-trifluromethyl hydrochloride, TPH, was discovered and developed by Squib Institute for Medical Research. It is an improved drug through fluoridation of the basic phenothiazine. It is commercially known as vesprin. Its structure is shown below:

![Fig. 6 Triflupromazine Hydrochloride](image)

It is a white crystalline powder easily soluble in water, methanol, alcohol, acetonitrile and acetone and melts at 174 °C. Phelps and Cordes have reported the single crystal X-ray data of TPH [14].
7) Dioxopromethazine hydrochloride, (DPH): A method for preparing DPH is explained elsewhere [15]. It is a white crystalline compound with melting point 298 °C, soluble in water, acetone, acetonitrile, ethanol and methanol. Its structure is shown below:

![Dioxopromethazine Hydrochloride](image)

Fig. 7 Dioxopromethazine Hydrochloride

8) Diethazine hydrochloride, (DH): DH, 10-(2-ethyl amino ethyl)phenothiazine is a white crystalline light sensitive solid. It melts at 180 °C. It has the following structure:

![Diethazine Hydrochloride](image)

Fig. 8 Diethazine Hydrochloride

It is soluble in water, methanol, ethanol and acetonitrile but insoluble in ether. It can be used as complexing agent for Ni (II) and Co (II) complexes in potentiometry and as redox indicator in vanadimetry [16-17].
9) Ethopropazine hydrochloride, (EPH): Ethopropazine hydrochloride, N,N Diethyl α methyl 10 H phenothiazine -10 ethanamine, is used in the treatment of Parkinson’s disease. It is also used to control severe reactions to certain medicines such as reserpine. It is a white crystalline compound soluble in water, methanol, ethanol, acetonitrile and insoluble in chloroform and ether. The crystal structure of this compound has been reported by Klein et al. [18]. It melts at 206 °C.

Fig. 9 Ethopropazine Hydrochloride

10) Mepazine hydrochloride monohydrate, (MH): 10-[(1-Methyl- Piperidinyl) methyl ]-10 H phenothiazine hydrochloride monohydrate has the following structure:

Fig. 10 Mepazine Hydrochloride monohydrate.

It is a white crystalline powder insoluble in ether and benzene but soluble in water, methanol, acetone, alcohol. It was synthesized by Schuler using 3-bromo methyl-1-methyl
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piperidine, phenothiazine and sodamide in xylene [19]. The presence of one molecule of water has been confirmed in the TGA and elemental analysis. It melts at 180 °C. It is a photosensitive compound.

11) Methdilazine hydrochloride, (MDH): It is an off-white crystalline powder, soluble in water, methanol, ethanol and acetonitrile. It is a photosensitive compound and has the following structure:

![Methdilazine Hydrochloride](image1)

12) Fluphenazine dihydrochloride, (FPH): 4-[3-(2-trifluoromethyl-10H-phenothiazine-10-yl)-propyl-1-piperazine ethanol dihydrochloride, FPH, was synthesized by Yale

![Fluphenazine Dihydrochloride](image2)
and Sowinski using 2-trfluromethyl phenothiazine, sodamide and 1-(3-chloropropyl)-4-methyl piperazine [20]. It belongs to the piperazine class of phenothiazines and is extremely potent. It is a white crystalline powder, melting at 236 °C. It is commercially known as Anatensol and is soluble in water, ethanol, chloroform and DMSO. Its structure is as shown in Fig. 12.

13) Acetophenazine dimaleate, (APM): The synthesis of APM has been reported by Ermakova and Grifenko [21]. It melts at 168 °C. It is soluble in acetone, methanol, ethanol and water. It has the following structure:

![Fig. 13 Acetophenazine Dimaleate](image)

14) Trifluoperazine dihydrochloride, (TFP): 10-[3-(4-methyl-1-piperazinal) propyl] -2-trifuro-methyl phenothiazine, TFP, is a typical antipsychotic drug of phenothiazine group.

![Fig. 14 Trifluoperazine Dihydrochloride](image)
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It is more potent than chlorpromazine. Zhuravlev et al. have reported the synthesis of TFP [22]. It is a white amorphous compound commercially known as stelazine or eskazine. The free base is sparingly soluble in water but its hydrochloride is soluble in water, methanol, ethanol, acetone and acetonitrile. It melts at 242 °C. McDowell has reported the single crystal X-ray data of this compound [23].
SECTION B: METHODS AND INSTRUMENTATION

The analytical instruments like elemental analyzer, UV-Visible, FT-IR spectrometer, thermogravimetric analyser and single crystal X-ray diffractometers were used for the characterization of pure phenothiazine derivatives and its charge-transfer complexes with picric acid and chloranil. The electrical conductivity measurements were carried out using two probe techniques.

Elemental Analysis

Elemental analysis for carbon, hydrogen, nitrogen and sulphur were done using Vario EL III CHNS analyser, Fig. 15. Suitable quantity of sample (5-10 mg) was used along with the catalyst tungsten oxide for the determinations. The analytical balance used was very sensitive, and was capability of measuring upto third decimal places.

Fig. 15 Vario EL III Elemental analyzer
UV-Visible spectra

A microprocessor based Systronics-117 UV-Visible spectrophotometer, Ahmedabad, India, Fig. 16, with matched quartz cells of 1.0 cm path length was used for UV-Visible spectral measurements.

Fourier Transform Infrared spectra (FTIR)

FTIR spectra were recorded using JASCO FT/IR-4100A spectrometer, Japan, Fig. 17. Samples were recorded using both Nujol mull and KBr disc techniques. Spectroscopic grade KBr obtained from Merck, Darmstadt, Germany and Nujol obtained from Acros Organics, New Jersey, USA, were used to record the spectra.
**Powder X-Ray Diffraction**

Powdered samples of phenothiazine and its derivatives were studied using a Rigaku Miniflex diffractometer, model IGC-2, Rigaku Denki Co. Ltd., Japan. X-Ray tube of 1.5 kW with Cu target was used.

**PROCEDURAL DETAILS**

The sample was finely ground to the grain size of 2–5 μ. Suitable amount of the sample was placed on the glass sample holder which has the effective window area 14 × 14 mm with depth of 0.45 mm and compressed it uniformly using a thick glass plate to get even measuring surface. The sample was loaded on the goniometer. The shutter was opened. The approximate peak profile of the measuring range and selection of the operation conditions were checked by rapid scanning. Goniometer was driven from the starting position by constant speed scanning synchronizer with a recorder. The goniometer was stopped after constant speed scanning of the measuring range. A schematic representation of the X-ray diffractometer is given in Fig. 18.
Fig. 18: Schematic diagram of X-ray diffractometer. 

(A) 1) X-ray generator, 2) Automatic shutter mechanism, 3) X-ray tube, 4) Goniometer, 5) Goniometer protective cover, 6) Specimen, 7) Detector, 8) Radiation enclosure for main console, 9) Counting and measuring unit and 10) Recorder. 

(B) Glass sample holder.

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Stoe single crystal X-ray diffractometer

Since its introduction, Stoe single crystal X-ray diffractometer (Fig. 19), the CCD area detector has revolutionized the field of small molecule crystallography, reducing data collection times by several orders of magnitude. This instrument is equipped with a programmable low temperature apparatus and structural determinations are typically performed at -100°C. Data are reduced/integrated offline on a locally networked PC and work-up then proceeds to structure solution using the latest version of the SHELX software suite.

![Fig. 19 Siemens SMART CCD X-ray Diffractometer.](image)

Thermogravimetric Analysis

Thermogravimetric studies were performed in air atmosphere with a flow rate of 100 ml/min and dynamic heating rate of 10°C/min from ambient to 700°C. A Perkin-Elmer TGA - 7 Analyser was used to record the thermograms of all the complexes, Fig. 20. A known weight of about 5-10 mg of each sample was dried in a desiccator before the analysis was done.
Fig. 20 Perkin-Elmer thermogravimetric analyser.

**Electrical conductivity**

Perkin-Elmer KBr Die (Fig. 21a and 21b), Perkin-Elmer Corporation, USA, and a compact laboratory hydraulic press, Techno Search Instruments, Mumbai, India, were used for making pellets. Compact portable precision instrument digital micro/milli ohmmeter of model DOT - 402 and Digital Insulation Tester of model DOT - 425 from DOT technologies, Bangalore, India, were used for all electrical conductivity measurements (Fig. 22). Resistance measurements were carried out using a two-probe electrical conductivity setup.
Fig. 21(a): KBr Die Cut-away View. 1) Plunger, 2) C – Ring, 3) O – Ring, 
4) O – Ring Cap, 5) Barrel, 6) Barrel O - Ring, 7) Base, 8) Hose Nipple, 
9) Powder and 10) Anvil.

Fig. 21 (b) Hydraulic press
Suitable quantity of phenothiazine sample was pressed in the form of pellets of 1.3 cm diameter and 0.15–0.2 cm thickness in a KBr die, applying a pressure of 500 kg/cm². Conducting silver paint ELTECKS silver preparation No. 1228/C, ELTECKS Corporation, Bangalore, India, was coated on both the surfaces of the pellets and the electrical contacts of the samples were made to the electrodes using the same silver paint. The electrical contacts were checked to verify Ohmic connection, and the electrical measurements were done from the ambient to suitable high temperature range using the above meters.
References


