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In memoriam prof. dr. Ioan A. Silberg

MICROWAVE-ASSISTED SYNTHESIS AND ELECTROCHEMICAL BEHAVIOUR OF PHENOTHIAZINE-FORMALDEHYDE POLYMER DERIVATIVE

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ABSTRACT. Phenothiazine-formaldehyde polymer was obtained by condensation reaction of 10*H*-phenothiazine with formaldehyde in the presence of acid catalysts. The synthesis was performed both under classical heating and microwave assisted heating conditions. Two different microwave installations were employed for optimizing the reaction conditions. Modified electrodes were prepared by adsorption of this polymer material on spectrographic graphite and the electrochemical parameters were estimated.

Keywords: phenothiazine, MAOS, modified electrodes, cyclic voltammetry

INTRODUCTION

During the last decade, the microwave heating became a popular alternative to conventional conductive heating not only for domestic food processing, but also for chemical synthesis purposes. The increasing number of scientific reports dedicated to the microwave-assisted organic synthesis (MAOS) shows that this technique is very convenient for the processing of organic matter. A survey of literature data shows that MAOS was applied to almost all of previously conventionally heated reactions [1-4]. Due to certain advantages, particularly shorter reaction times, which offer the possibility of rapid optimization of chemical reactions, MAOS became an experimental technique applied for the syntheses of a large number of organic fine chemicals. MAOS also joins some of the major principles of the *green chemistry* such as: *the increase of energy efficiency* by effective *in situ* conversion of the electromagnetic energy into heat which avoids energy loss, and *the use of safer solvents and reaction conditions* by avoiding the use of toxic solvents in solvent-free reactions, or the use of water and other solvents under supercritical conditions (reaction pressures of 2-3 Mpa which

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would facilitate temperatures in the order of 200 ^{o}C for common solvents such as methanol, ethanol, acetone, all which boil below 85 ^{o}C at atmospheric pressure).

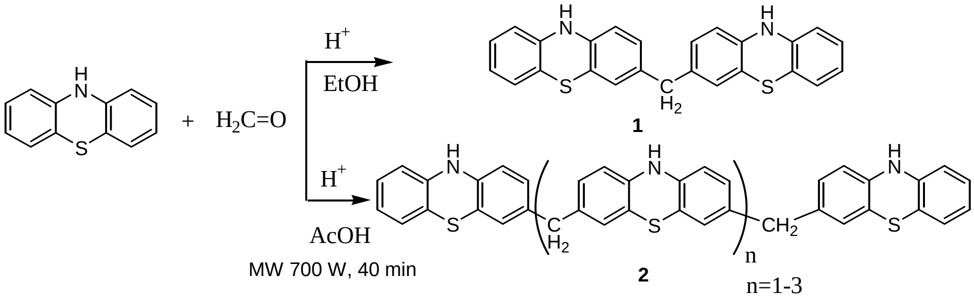
The synthesis and electrochemical characterization of several phenothiazine derivatives was a constant interest for our research group during last years [5-8]. In this paper, we present the microwave assisted synthesis and the electrochemical characterization of a phenothiazine-formaldehide polymer derivative based on *bis*-(phenothiazin-3-yl)-methane moiety. A comparison between classical synthesis and the microwave assisted syntheses performed using two different experimental techniques was attempted. The electrochemical behaviour was studied by simple adsorption on graphite electrode surface, using cyclic voltammetric (CV) measurements and an explanation of the electrochemical parameters was attempted. An electrochemical study can be performed using two methods: (i) the investigated compound dissolved in solution [9-16] or (ii) the investigated compound adsorbed on an electrode surface [17-19]. We choosed the second method because the investigation of the adsorbed systems requires small quantities of organic compounds, so that modified electrodes can be easily obtained at laboratory scale and the observed properties may recommend them as electrocatalysts for the obtaining of sensors / biosensors, etc.

RESULTS AND DISCUSSION

Synthesis

Phenothiazine dimer or higher oligomer obtaining by the condensation reaction of phenothiazine with aldehydes such as formaldehyde, acetaldehyde or benzaldehyde, was already reported [20-21]. The condensation of phenothiazine with formaldehyde in solution, in the presence of an acid catalyst leads to *bis-(*10*H*-phenothiazin-3-yl)-methane **1** accompanied by oligomers **2** (Scheme 1). The catalytic activity of hydrochloric acid, methanesulfonic acid and respectively trifluoroacetic acid were compared. Best results were obtained in the presence of hydrochloric acid.

The reaction conditions can be optimized in order to change the relative ratios of the reaction products. Thus, when acetic acid was employed as solvent, *bis-(*10*H*-phenothiazin-3-yl)-methane **1** was obtained in lower amounts and oligomers **2** appeared as major reaction products. The condensation products **1**, **2** precipitated from the reaction mixture and were easily separated by filtration. The conversion of the phenothiazine was about 90%. **1** was removed by dissolution in THF. The mixture of oligomers **2** is a dark powder highly unsoluble in organic solvents such as ethanol, acetone, ether, toluene.



Scheme 1

The structure assignment of **1** is supported by spectroscopic data. EI mass spectrum shows the molecular peak situated at 410 m/e**.** The substitution in position 3 of the phenothiazine units was unambiguously assigned by ^{1}H-NMR spectroscopy; thus, in the 2D ^{1}H-^{1}H homocorrelation COSY–45 spectrum, the cross peaks of the signals situated in the 6.6-6.9 ppm range reveals the aromatic protons coupling patterns. For the methylene bridge,^{13}C-NMR spectrum shows one signal situated at 40 ppm.

For the polymer structure **2,** FT-IR spectroscopy indicate the stretching vibration of N-H bonds by the absorption band situated at 3230 cm^{-1}. 300 MHz ^{1}H-NMR spectrum shows a singlet signal situated at 3.5 ppm for the equivalent methylene protons and a singlet signal situated at 8.5 ppm assigned to the protons in the NH groups of the equivalent phenothiazine units. Unfortunately, the signals of the protons attached to the heteroaromatic ring give an overlapping multiplet in the 6.6-7 ppm range. The analogy with the well resolved spectrum of parent compound **1** enables us to suggest the same substitution pattern for oligomer **2**.

Microwave assisted synthesis of phenothiazine-formaldehyde polymer derivative 2

The experimental techniques applied for the microwave-assisted syntheses of phenothiazine-formaldehyde polymer derivatives described below, are based on two different microwave installations:

a) dynamic microwave power system designed by INCDTIM Cluj-Napoca [22], as a mono-mode cavity reactor for open vessel operating conditions. The advantage of the single-mode cavity is the uniform heating pattern, higher field strengths and reproducible conditions in small reactors. The disadvantage is due to small sample volumes and to the fact that only one reaction vessel can be irradiated at the time.

b) microwave installation *Synthos 3000* designed by Parr instrument company as a multimode cavity reactor for high pressure operating conditions. Reproducible operating conditions are ensured in the reactor equipped with temperature and pressure sensors, built-in magnetic stirrer, cooling mechanisms, power control and software operation. The advantage relies on the fact that parallel syntheses can be performed in several reaction vessels which can be irradiated simultaneously in multivessel rotors.

Two different reaction techniques were employed:

a) "Dry media" procedure, which involved solventless conditions and the reagents were preadsorbed onto a more or less microwave transparent inorganic support (silica gel, alumina or clay). This solvent free approach is appropriate for MAOS in open vessel conditions.

b) Pressurized systems procedure, where the reaction was carried out in standard organic solvents under sealed vessel conditions.

Table 1 presents a comparison between the experimental conditions employed and the results obtained in the microwave-assisted synthesis of **2**. Classical heating by thermal convection and microwave heating of the reaction mixture in acetic acid solvent affords similar reaction yields of **2**, but significantly shorter reaction times are requested by MAOS. Dry media procedure generated lower yields due to the immobilization of the highly unsoluble reaction product on the solid support.

Table 1.

Experimental conditions for the synthesis of phenothiazine-formaldehyde polymer derivative **2**

Procedure	Heating type	Solvent/ Support	Temp. [^{0}C]	Time [min]	Yield [%]
Classical	Thermal convection	AcOH	60	120	78
Dry media	Single-mode MW cavity	Al_2O_3	60	15	38
Pressurized systems	Multi-mode MW cavity	AcOH	60	40	75

Electrochemical behaviour of phenothiazine-formaldehyde polymer derivative 2

The electrochemical behavior of **2** was studied by simple adsorption on a graphite electrode surface, using cyclic voltammetric (CV) measurements. The modified graphite electrodes were obtained by spreading onto the electrode surface a solution 1 mM of **2** in dimethylsulfoxide and leaving them to dry at room temperature. Before immersion in the test solution the modified electrodes were carefully washed with water. For each electrode, the surface coverage (Γ, mol cm^{-2}) was estimated from the under peak areas, recorded during the CV measurements at low scan rate (< 10 mV s^{-1}), and considering as 1 the surface redox valency [23]. The presented results are the average of three identically prepared electrodes.

Figure 1 shows the voltammetric response corresponding to compound **2** adsorbed on the surface of a graphite electrode in a phosphate buffer solution (pH 7) and the stability of the modified electrode expressed by the time dependence of the surface coverage for the obtained modified electrode.

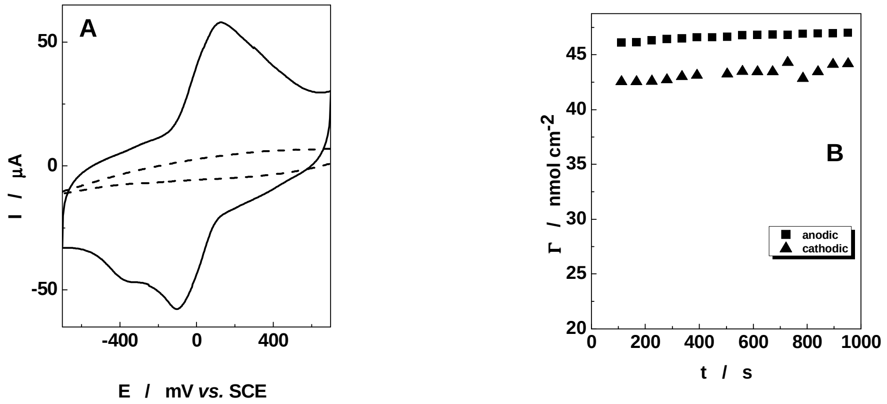
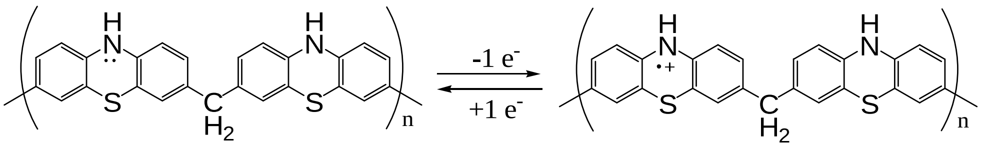


Figure 1. (A) Cyclic voltammograms of graphite electrode (---) and of compound **2** adsorbed on graphite (—). (B) Time dependence of surface coverage for compound **2** adsorbed on graphite.
Experimental conditions: starting potential -0.700 V/SCE; potential scan rate 50 mV s^{-1}; supporting electrolyte, 0.1M phosphate buffer, pH 7.

The voltammogram of compound **2** (fig. 1A) shows an oxidation wave ($E_{pa}^{0/+1}$= 74 mV *vs.* SCE), which can be assigned to the formation of stable radical cations generated by the phenothiazine structural units present in the molecular structure (scheme 2).



Scheme 2

The width at half peak height (E_{FWHM} values given in table 2) was different to the one corresponding to the ideal case (E_{FWHM} = 90.6/n mV, where n is the number of electrons). The observed discrepancies might prove the existence of repulsive interactions between the adsorbed redox species (radical cations generated in the anodic process) [23,25]. Compound **2** exhibits the relative current ratio I_{pa}/I_{pc} close to one, specific to adsorbed conditions [23]. The electrochemical stability was studied by cycling the electrode potential in phosphate buffer solution during 20 cycles. It was observed that the shape of the voltammogram remained unchanged (results not shown) and the peak parameters were not affected by the surface coverage. The modified electrode presents a good electrochemical stability as shown in figure 1B, due to good adsorption properties of the polymer derivative.

Table 2

Electrochemical parameters of the voltametric response for graphite electrode modified with **2**. Experimental conditions as in Fig1.

Cpd *	E_{pa} [mV] *vs*SCE	E_{pc} [mV] *vs*SCE	E^0 [mV] *vs*SCE	ΔE_{peak} [mV]	E_{FWHM} [mV]		$\frac{I_{pa}}{I_{pc}}$	Γ 10^8mol cm^{-2}
					anodic	cathodic		
2	74	-70	2	144	272	235	1.24	5.4

*Compound **2**

CONCLUSIONS:

The two microwave installations employed in the microwave-assisted synthesis of **2** offered an efficient heating of the reaction mixture and comparison with the conventional synthetic methods demonstrates advantages related to shorter reaction times. In this particular case, *dry media* procedure presented the disadvantage of lower yields, due to the immobilization of the highly unsoluble reaction product on the solid support.

The electrochemical behavior of a graphite electrode modified with phenothiazine-formaldehyde polymer derivative **2**, shows redox activity and good adsorption properties of this compound.

EXPERIMENTAL PART

The reactions were performed using:
a) dynamic microwave power system designed by INCDTIM Cluj-Napoca
b) microwave installation *Synthos 3000* designed by Parr instruments
Reagents from Merck were used.
TLC was used to monitor the reaction progress (Merck silica gel F 254 plates).
NMR spectra were recorded using a 300 MHz Brucker NMR spectrometer.
FT-IR spectra were recorded using a Brucker Vector 22 FT-IR spectrometer.

Phenothiazine-formaldehyde polymer 2

a) Phenothiazine 0,5 g (2,5 mmol) was solved in acetic acid (50 mL), conc. hydrochloric acid (0.5 mL) was added and then formaldehyde (4mmol, 0.32 mL aqueous solution 36%) was added drop wise under vigorous stirring at room temperature. After 30 minutes, a dark precipitate start to accumulate and the reaction is perfected for 2 hours at 60 ^{0}C. The dark grey precipitate was filtered and washed several times with warm methanol; the precipitate was suspended in THF and then filtered. 0.4 g dark powder was obtained, yield 78%.

b) Phenothiazine (0,5 g 2,5 mmol) was solved in acetone (30 mL) and aluminium oxide (0.5 g) was added to the clear solution. The solvent was then removed under vacuum by rotary evaporator. Formaldehyde (4 mmol, 0.32 mL aqueous solution 36%) and conc. hydrochloric acid (0.1 mL) were added to the phenothiazine adsorbed on the solid support. The mixture was subjected to microwave irradiation in the resonance cavity of the dynamic microwave power system designed by INCDTIM, with prescribed power level 700 W and temperature monitoring. TLC was used to monitor the reaction progress. After 15 minutes total time of irradiation the solid material was extracted 3 times with DMF (10 mL). The product precipitated when water was added to the reunited DMF solutions. 0.2 g dark powder precipitate was obtained by filtration, yield 38%.

c) Phenothiazine 0,5 g (2,5 mmol), formaldehyde (4 mmol) aqueous solution 36% 0.32 mL, conc. hydrochloric acid 0.5 mL and acetic acid 20 mL were introduced in a quartz reaction vessel which was then sealed and subjected to microwave irradiation in the resonance cavity of the microwave *Synthos 3000* instrument with controlled heating at 60 ^{0}C and after 40 minutes generated a dark grey precipitate which was filtered from the reaction mixture and then washed several times with warm methanol; the precipitate was solubilized in THF and filtered. 0.38 g dark powder was obtained, yield 75%.

^{1}H-NMR (300MHz, DMSO-d$_6$**):** δ=3.57 ppm (s, 2H), 6.61-7 ppm (m, 12H), 8.5 ppm (s, 2H).
IR (cm^{-1}): 3328, 1595, 1487, 1314, 798, 743.

Electrode preparation

A spectrographic graphite rod (Ringsdorff-Werke, GmbH, Bonn-Bad Godesberg, Germany), of ~ 3 mm diameter, was wet polished on fine (grit 400 and 600) emery paper (Buehler, Lake Bluff, Ill., USA). Then, a graphite piece of suitable length was carefully washed with deionized water, dried, and finally press-fitted into a PTFE holder in order to obtain a graphite electrode having, in contact with the solution, a flat circular surface of ~ 0.071 cm^2.

The modified graphite electrode was obtained by spreading onto the electrode surface 2 µl of 1 mM derivative **2** solution in dimethylsulfoxide, and leaving them for one day at room temperature to evaporate the solvent. Before immersion in the test solution the modified electrodes were carefully washed with deionized water.

Electrochemical measurements

CV measurements were carried out in a conventional three-electrode electrochemical cell. A saturated calomel electrode (SCE) and a coiled Pt wire served as reference and counter electrode, respectively. The cell was connected to a computer-controlled voltammetric analyzer (Autolab-PGSTAT10, Eco Chemie, Utrecht, Netherlands).The supporting electrolyte was a 0.1 M phosphate buffer, pH 7 prepared using $K_2HPO_4 \cdot 2H_2O$ and $KH_2PO_4 \cdot H_2O$ from Merck (Darmstadt, Germany).

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