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In memoriam prof. dr. Liviu Oniciu

SYNTHESIS AND ELECTROCHEMICAL BEHAVIOUR OF *BIS*-(10-ETHYLPHENOTHIAZINYL)-PHENYLMETHANE

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ABSTRACT. *Bis*-(10-ethylphenothiazinyl)-phenylmethane was obtained by the condensation of 10-ethyl-phenothiazine with benzaldehyde in the presence of acid catalysts. The electrochemical behavior of *bis*-(10-ethylphenothiazinyl)-phenylmethane adsorbed on spectrographic graphite has been investigated. Cyclic voltammetric measurements performed in aqueous buffer solutions at different potential scan rates pointed out to a quasi-reversible, surface-confined redox process, with a negative formal standard potential of -55 mV *vs.* SCE (10 mV s^{-1}). The voltammetric response involves the transfer of $1e^-$, with a heterogeneous rate constant of 18.9 s^{-1} (pH 7). The modified electrodes showed a good electrochemical stability.

Keywords*: 10-alkylphenothiazine, modified electrodes, cyclic voltammetry*

INTRODUCTION

The condensation reaction of phenothiazine with aromatic aldehydes (benzaldehyde, *o-, m-* and *p*-nitrobenzaldehyde) in acid media was already reported [1]. The mild electrophile generated by the aldehyde in the presence of methanesulfonic acid is responsible for the substitution of the phenothiazine ring and *bis-(*10*H*-phenothiazin-3-yl)-methane derivatives were obtained as major reaction products. 10*H*-Phenothiazine is characterized by enhanced reactivity towards electrophilic substitution, but the introduction of alkyl functional groups at different positions affects both orientation of subsequent substitution and the overall reactivity [2]. Thus, 10-alkylphenothiazine is a "slightly deactivated" substrate for electrophilic substitution. Theoretical explanations are based on both electronic and steric effects. Due to the sp^3 hybridization state of the two heterocyclic heteroatoms (nitrogen and sulfur), phenothiazine molecular structure is folded about S-N axis with a dihedral angle of about 150^0 [3], influenced by the presence of substituents. According

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to the spatial position of the substituent attached to nitrogen with respect to the dihedral angle, two distinct configurations may appear as it can be seen in figure 1.

10*H*-Phenothiazine is characterized by an "*intra*" orientation of the hydrogen atom (by pointing inside with respect to the dihedral angle, figure 1a), while 10-ethylphenothiazine preferentially adopts an "*extra*" orientation of the ethyl group due to steric reasons (figure 1b).

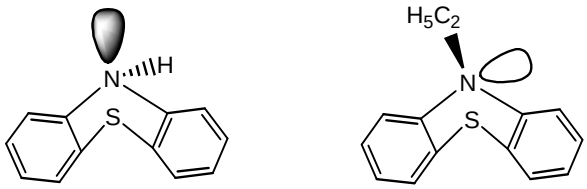


Figure 1. Configurations of phenothiazine derivatives
a) 10H-Phenothiazine, b) 10-Ethylphenothiazine

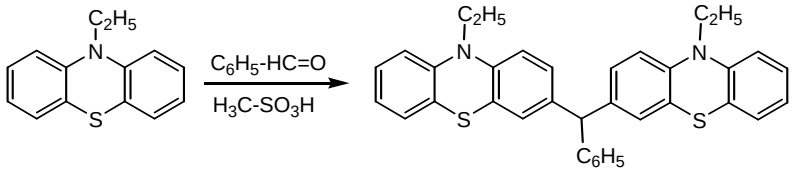
These two configurations are not electronically equivalent, according to the possibility of conjugation of the nitrogen lone pair of electrons with the adjacent benzene π system. In 10*H*-phenothiazine, the transmission of the electronic effects is very efficient and electrophilic substitution occurs easily. The reduced participation of the nitrogen lone pair to the extended π system in 10-ethylphenothiazine structure due to steric hindrance explains the decreased reactivity in electrophilic substitution.

In this paper, we describe the synthesis of *bis*-(10-ethylphenothiazin-3-yl)-phenylmethane (**1**)**,** a new product obtained by the condensation between 10-ethylphenothiazine and benzaldehyde. The electrochemical behavior and electrochemical stability of **1** adsorbed on spectrographic graphite were investigated by cyclic voltammetric (CV) measurements performed at different scan rates. The heterogeneous electron transfer rate constant (k_s) was estimated using Laviron treatment [4].

RESULTS AND DISCUSSIONS

Synthesis

The condensation of 10*H*-phenothiazine with benzaldehyde generated *bis-(*10*H*-phenothiazin-3-yl)-phenylmethane in good yields, when methane sulfonic acid was employed as catalyst and the reaction mixture was heated to reflux in ethanol solution [1]. These reaction conditions were modified in order to perform the condensation of less reactive 10-ethylphenothiazine with benzaldehyde. *Bis-(*10-ethylphenothiazin-3-yl)-phenylmethane (**1**) was obtained using acetic acid as a solvent (Scheme 1). After refluxing the reaction mixture several hours, the condensation product **1** precipitated from the reaction mixture and was easily separated by filtration.



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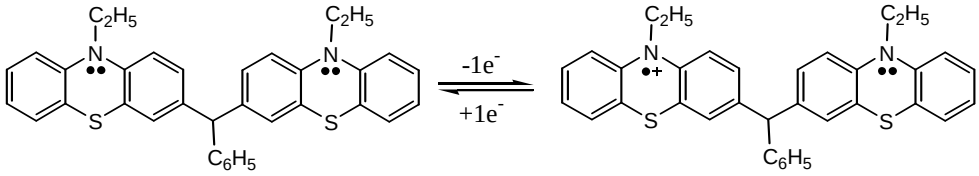
Scheme 1

The structure assignment of **1** is supported by NMR spectroscopic data. The presence of the ethyl substituent was revealed by the coupled signals situated at 1.2 ppm (t, 6H) and 3.1 ppm (q, 4H) and the proton in the methine bridge generated a singlet signal situated at 3.8 ppm.

Electrochemical behaviour of bis-(10-ethylphenothiazin-3-yl)-phenylmethane-modified graphite electrode

The electrochemical behavior of **1** adsorbed on spectrographic graphite (G***/*1**) was investigated using CV measurements, at different potential scan rates. As it can be seen from figure 2A, the cyclic voltammogram recorded for G***/*1** electrode presents a peak pair with the formal standard potential placed at -55 mV *vs.* SCE (pH 7). It is the most negative value recorded in a series of phenothiazine derivatives based on bis-(10*H*phenothiazin-3-yl)-methane and bis-(10*H*phenothiazin-3-yl)-phenylmethane [5]. This suggests that compound **1** participates easier to oxidation processes and is explained by the reduced participation of the nitrogen lone pair to the extended π system in the 10-ethylphenothiazine unit responsible for redox equilibria. The oxidation wave ($E_{pa}^{0/+1}$= -43 mV *vs.* SCE) can be assigned to the radical cation formation of one phenothiazine unit in the molecular structure. Scheme 2 shows the proposed reaction scheme for the electrochemical processes occurring during the voltammetric experiments.



Scheme 2

The electrochemical parameter ΔE indicates a quasi-reversible redox process, taking into consideration its value of 24 mV, as criterion for the process reversibility. This value is smaller than those obtained for the related compounds mentioned above [5], suggesting a more reversible electron transfer.

The width at half peak height (E_{FWHM}) was different to the corresponding ideal case (E_{FWHM} = 90.6/n mV, where n is the number of electrons). The observed discrepancies (140 and 33 mV for anodic and cathodic process, respectively) prove the existence of repulsive interactions between the adsorbed redox species (radical cations generated in the anodic process) and attractive ones (neutral molecules or dimers formed during the cathodic process) [5,6].

As expected for surface confined redox active species [4], the cyclic voltammograms recorded for a wide range of potential scan rates (0.01 – 0.8 V s^{-1}) showed a linear dependence of the peak currents (I_p) on the electrode potential scan rate (v). The slope of log I_p *vs.* log v dependence was close to one (0.88 ± 0.03 and 0.98 ± 0.04 for anodic and cathodic process, respectively), confirming once again the existence of adsorbed species. The number of electrons involved in the redox process, estimated from I_p *vs.* v dependence [7] was found close to 1 (within ± 10%), in accordance with the predicted value for the cation formation.

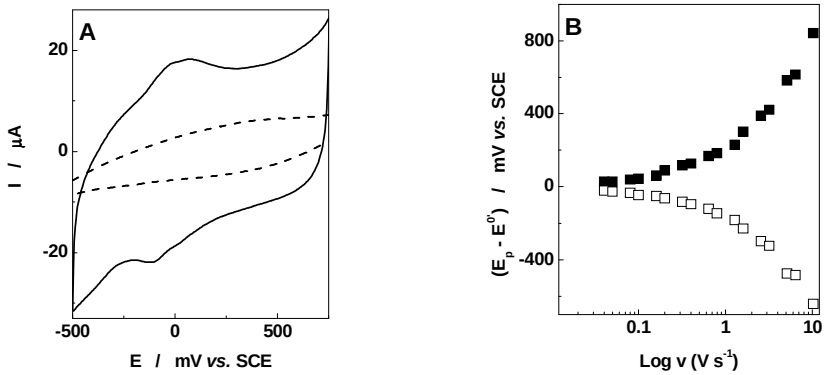


Figure 2. (A) Cyclic voltammograms of graphite electrode (---) and of compound **1** adsorbed on graphite (—) and (B) experimental dependence of (E_p - $E^{o'}$) on the scan rate, corresponding to **1** adsorbed on graphite electrodes. Experimental conditions: starting potential, -500 mV *vs.* SCE; potential scan rate, 100 mV s^{-1} (A); supporting electrolyte, 0.1 M phosphate buffer (pH 7).

The heterogeneous electron transfer rate constant (k_s, s^{-1}) was estimated at pH 7, using the treatment proposed by Laviron [4] (figure 2B) and it was found equal to 18.9 s^{-1}, while the transfer coefficient (α) was 0.52. The k_s value is higher than those determined for phenothiazine (1.7 s^{-1}) [8], which proves that compound **1** is more active electrochemically than phenothiazine.

The stability of modified electrodes was tested by measuring the variation of phenothiazine electrochemical signal in a defined time range. It is known that the immobilization stability of a compound on graphite electrode is decided by the number of conjugated aromatic rings from the molecule. Thus, the electrochemical stability tests of the G/**1** were performed in potentiodynamic conditions: the electrode potential was continuously cycled within the potential range covering the domain of the phenothiazine redox activity, in phosphate buffer solution, pH 7. From the recorded voltammograms a progressive decrease of the electrode surface coverage was observed, while the voltammogram shape remains invariant (results not shown). This behaviour proves the G/**1** good electrochemical stability and its relatively strong adsorption on the graphite surface.

The kinetic interpretation of the deactivation process showed that it obeys first-order kinetics. The slopes of kinetic plots were used to determine the values of the deactivation rate constants, as an average of the anodic and cathodic process and a value of $3.45 \cdot 10^{-13}$ mol cm^{-2} s^{-1} was obtained. The value of deactivation rate constant is smaller in comparison with other phenothiazine derivatives, octachloro-phenothiazinyl and heptachloro-hydroxy-phenothiazine (k_{deact} = $27.5 \cdot 10^{-10}$ mol cm^{-2} s^{-1} and $1.3 \cdot 10^{-8}$ mol cm^{-2} s^{-1}, respectively) [9]. This is due to the structure of **1**, which is favorable for increasing the electrochemical stability of modified graphite electrode.

CONCLUSIONS

The condensation of 10-ethylphenothiazine, a slightly deactivated phenothiazine substrate, with benzaldehyde in the presence of acid catalysts generated *bis-(*10-ethylphenothiazin-3-yl)-phenylmethane (**1**) in good yields. Modified electrodes were prepared by adsorption of **1** on graphite. Electrochemical data show that oxidation process occurs easier for **1** as compared to related *bis-(*10*H*-phenothiazin-3-yl)-methane derivatives [4], as well as other derivatives containing phenothiazine units which were previously studied under the same conditions [8,9]. The linear dependence between peak current (I_p) and the potential scan rate (v) proves the existence of a redox couple adsorbed on electrode surface involving $1e^-$.

The graphite electrodes modified with **1** presented a good electrochemical stability.

EXPERIMENTAL SECTION

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.

Bis(10-ethylphenothiazin-3-yl)-phenylmethane (1)
10-Ethylphenothiazine 0,5 g (2,5 mmol) was solved in acetic acid (50 mL), methanesulfonic acid (0.5 mL) was added and then benzaldehyde (1.5 mmol) was added drop wise under vigorous stirring at room temperature. The reaction mixture was heated to reflux for 4 hours. The pink precipitate accumulated was filtered and washed several times with warm methanol; the precipitate was suspended in THF and then filtered. 0.4 g powder was obtained, yield 67%.
^{1}H-NMR (300MHz, DMSO-d_6)**:** δ=1.2 ppm (t, 6H), 3.1ppm (q, 4H), 3.8 ppm (s, 1H), 6.61-7.2 ppm (m, 19H).
IR (cm^{-1}): 3100, 1595, 1487, 1314, 794, 740.

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 **1** 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.
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}). The presented results are the average of 3 identically prepared electrodes.

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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