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Electrochemical Degradation and Thermal Deactivation of Valproic Acid Drug

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Electrochemical degradation of valproic acid drug (VAc) was studied by direct and indirect electrochemical oxidation processes using platinum electrode. The effect of halide counteranions on oxidation of valproic acid and its electrochemical mineralization in hydro-alcoholic solution was investigated. The electrochemical behavior of valproic acid was studied by cyclic voltammetry and spectrophotometrical assisted electrolysis in the presence of fluoride, chloride and bromide anions. Bromide electromediated was shown to be the most efficient degradation process. A plausible mineralization mechanism was proposed. In addition, thermal deactivation of valproic acid was studied by simultaneous thermogravimetry/differential scanning calorimetry (TG/DSC).

Keywords: valproic acid, electrodegradation, spectrophotometry, thermochemistry

1. INTRODUCTION

Valproic acid (VAc) and its sodium salts, given intravenously or by mouth, are medications specially used to treat partial or generalized seizures, epilepsy, bipolar disorder, migraine headaches, schizophrenia and epilepsy [1-5]. The main side effects of its administration are organic effects such as serious liver problems, pancreatitis, vomiting, sleepiness or psychological effects like increased suicide risk [1-5]. During controlled therapy, the VAc concentrations in human plasma are in a range of 20–100 mg/L [1-5]. Acute intoxications, such as overdoses with concentrations greater than 150 mg/L VAc in plasma, can result in coma, metabolic acidosis and even death. VAc and its hepatotoxic 4-ene metabolite were quantified by high performance liquid chromatography-ultraviolet (HPLC-UV) for over than 60 Chinese epileptic patients [1]. VAc was successfully determined, in the presence of asenapine, by isocratic chromatography with reversed-phase column after liquid-liquid extraction [6]. VAc determination in human serum or plasma by HPLC method was achieved with or without

derivatization, in association with mass spectrometry [7-9], flame ionization detection [10], by capillary electrophoresis [11, 12], fluorescence spectroscopy, UV-Vis spectrophotometry [13], thermochemoluminescence method [14], electrochemical method [15].

In last decades, the increased misuse of drugs or inappropriate elimination can lead to an increased content of pharmaceutical compounds from wastewater. Drugs are partially metabolized after their administration and consequently are excreted as initial form or as metabolites with more or less toxicity [16-20]. Among others, electrochemical methods are effective methods to water treatment due to degradation of toxic and/or recalcitrant pollutants [21-25]. Relatively low amount of drugs in wastewater and aquatic media could cause significant changes in biosphere and microorganism. Electrochemical degradation parameters include substrate concentration, solvent nature, supporting electrolyte, time, temperature, anode and cathode material, working potential / current density, cell nature / type / dimensions.

In the present study, we report the valproic acid (VAc) electrochemical degradation on platinum electrode. We investigate the influence of halide ions (F^-, Cl^-, Br^-) as supporting electrolyte on the electrochemical behavior of valproic acid. The individual effect of F^-, Cl^- and Br^- on the electrodegradation of VAc was investigated in order to elucidate the most probable mechanism of electrochemical degradation. Thermal analysis of VAc was also used as alternative method for VAc deactivation.

2. MATERIALS AND METHODS

2.1. Materials

Valproic acid was purchased as Convulex 500 mg pills (gastroresistant soft capsules). Sodium halides (sodium fluoride, sodium chloride and sodium bromide) and ethyl alcohol were purchased from Sigma Aldrich. Stock solutions of 1.0 $mol \cdot L^{-1}$ NaX (X = F, Cl, Br) were prepared by dissolving the corresponding amount of sodium halide in double distilled water. A stock solution of 10^{-1} $mol \cdot L^{-1}$ VAc was prepared by diluting of corresponding volume of VAc in hydro-ethyl solvent (H_2O:C_2H_5OH) = (9:1). Working solution containing both VAc $8.3 \cdot 10^{-2}$ $mol \cdot L^{-1}$ and NaX 10^{-1} $mol \cdot L^{-1}$ was freshly prepared for each experiment by diluting appropriate volume of stock solutions with hydro-ethyl solvent.

2.2. Methods

All electrochemical experiments were performed in a glass single-chamber electrochemical cell with a working volume of 100 mL in a dynamic regime provided by a magnetic stirrer (300 rpm). Platinum electrodes with an active area of 2 cm^2 were employed as anode and cathode. The reference $Ag|AgCl|KCl_{sat}$ electrode was also used. These electrodes were connected to a VoltaLab potentiostat-galvanostat to generate and measure the potential / current density carried out in the working electrode. The VoltaLab equipment was controlled with a PC running the VoltaMaster4 software in order to

obtain the experimental data. Cyclic voltammograms were recorded using a scan rate of 50 $mV \cdot s^{-1}$. All experiments were conducted in the electrolytic cell open to air and at room temperature. The electrochemical mineralization experiments were carried out under galvanostatic conditions of constant current density (50 $mA \cdot cm^2$).

All the measurements were carried out in the spectral range from 400 to 200 nm.

A Varian 50 Conc UV-Vis Spectrophotometer with 1x1x4 cm quartz cells was used for all absorbance measurements. The UV-Vis spectra were registered using the Cary WinUV software in wavelength range from 200 to 800 nm.

The association between the UV-Vis spectrophotometry and cyclic voltammetry was successfully used for the analysis of electrode processes of biologically active compounds like the drugs [26, 27].

Thermogravimetric analysis (TG) and differential scanning calorimetry (DSC) are used to characterize the thermal deactivation of valproic acid in a controlled nitrogen gas atmosphere. Both working and reference crucible, made from aluminum, served as containers during thermoanalytical measurements. These crucible guarantees that the sensor was not contaminated by VAc probe. The measurements were performed using a Diamond Thermogravimetric / Differential Thermal Analyzer from PerkinElmer instruments with Pyris software. Thermogravimetric and calorimetric analyzes were used to identify the thermo-stability range of some biologically active compounds [28, 29] indicating the safety of their use, as well as the identification of the phase transformations. The VAc sample was heated using a temperature scanning rate of 5 $°C \cdot min^{-1}$, from room temperature to 500 °C.

3. RESULTS AND DISCUSSION

3.1. Electrochemical Behavior of Valproic Acid Drug on Platinum Electrodes

The catalytic function of the platinum electrode surface in the electroactivity of valproic acid drug was first studied by cyclic voltammetry. The cyclic voltammograms of Pt electrode in 10^{-1} $mol \cdot L^{-1}$ NaX, $8.3 \cdot 10^{-2}$ $mol \cdot L^{-1}$ VAc alongside the voltammetric behaviour of the Pt electrode in the corresponding blank solutions are presented in Figure 1 (X= F-a, Cl-b, Br-c).

The cyclic voltammograms of the Pt electrode registered with an initial anodic scan changed in the presence of VAc compared to voltammetric response of the electrode in the blank solutions in that the current density significantly decreased. In the presence of fluoride (Figure 1a) and chloride (Figure 1b), the voltammograms were modified between -0.9 V and -1.1 V due to the adsorption of VAc molecules on electrode surface. There are no significant differences between the voltammograms obtained with the electrolyte solutions containing the fluoride anions and chloride as support electrolyte. In contrast, when the electrolyte solution contains both the bromide anions and the valproic acid molecules, the anode current density increases from about 8 $mA \cdot cm^{-2}$ to 50 $mA \cdot cm^{-2}$. This is an indicative of the increase in the rate of oxidation of biologically active molecules of valproic acid to the surface of the electrode in the presence of bromide anions.

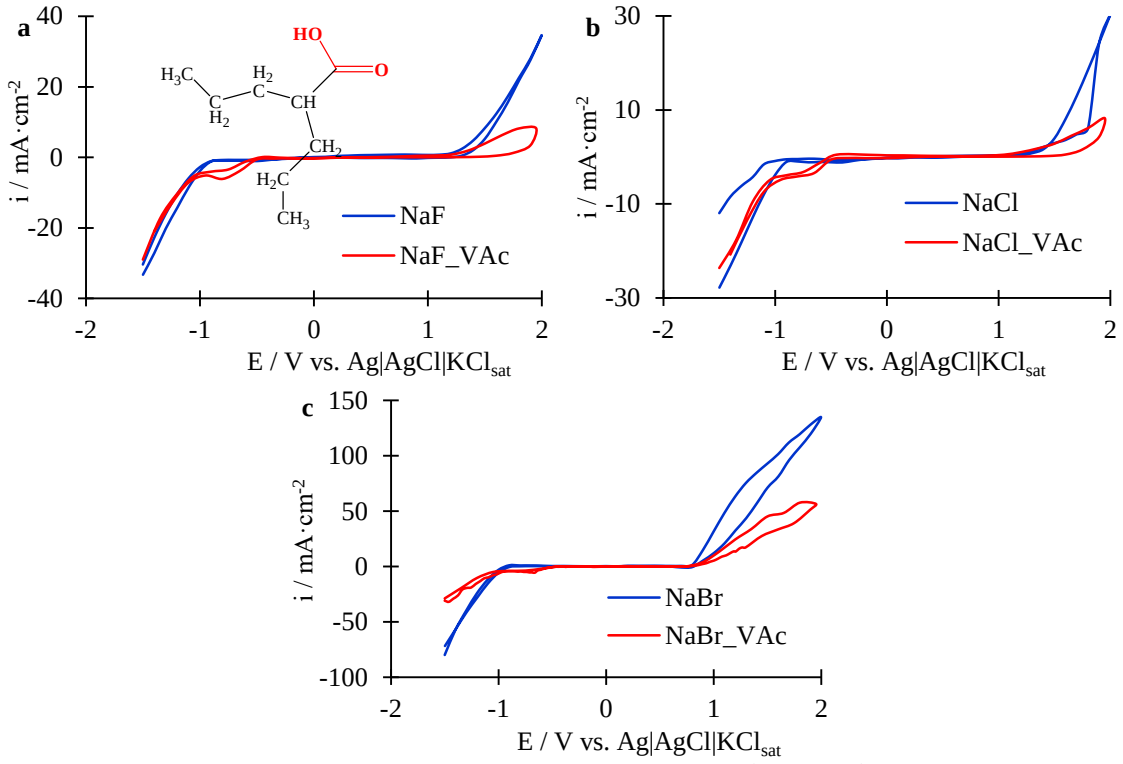


Figure 1. Cyclic voltammograms on Pt electrode recorded in 10^{-1} mol·L^{-1} NaX solutions (X = F$^-$, Cl$^-$, Br$^-$) in the absence (blue line) and in the presence of $8.3 \cdot 10^{-2}$ mol·L^{-1} VAc (red line).

The fluoride anion is electrochemically inactive in the range of potentials analyzed; it does not participate in the charge transfer processes at the surface of the electrode while the chloride and bromide anions can participate in the electrode processes by forming the corresponding oxygenated anions;

$$2X^- - 2e \rightarrow X_2$$

$$X_2 + H_2O \rightarrow HOX + HX \quad \text{(X = Cl, Br)}$$

Both chloride and bromide anions undergo electrochemical oxidation at the electrode surface and generate oxidant oxygenated species that may change the mechanism of electrochemical degradation of valproic acid [18-24]. Reduction/oxidation potential values provide information on the viability of electron transfer in vivo. The values of reduction potentials were determined for progabide, pyridazines and zonisamide anticonvulsants [30]. The results of this study indicated that for grater values then 0.6 V the compound can act as an electron acceptor from a cellular donor. The composition of the supporting electrolyte has a significant role on the degradation processes of biologically active compounds on the electrode surface. Chloride and bromide anions participate in the processes on the electrode surface that lead to the formation of active species with strong oxidizing capacity [27, 31]. Comparative studies using different halides anions indicate that in some cases degradation processes occur at a higher rate in the presence of chloride anions, while in other cases in the presence of bromide anions. For example, the electrochemical degradation of metribuzin pesticide reaches a maximum value of 89.3% in the presence of bromide anions, while the presence of chloride ions

reaches a lower degree of degradation of 47.5% after 1.0 hours of electrolysis. Similarly, the degradation of Chocolate Brown HT food coloring molecules leads to a higher rate in the presence of bromide anions [31]. The direct consequence of the formation of hypochlorite and hypobromite anions consists of valproic acid oxidation in homogenous phase (indirect electrochemical oxidation). Knowing the strong oxidative action of hypochlorite and hypobromite anions, it is expected that valproic acid molecules will be degraded much faster. The presence of these ions in the electrolyte solution changes as the reaction mechanism and the rate of the reaction. For all three different supporting electrolytes, the pH value was almost close to neutral.

Comparing the three figures (1a, 1b and 1c) at high potentials of the working electrode, in the presence of fluoride and chloride anions, low current density value of 8 $mA \cdot cm^{-2}$ was reached, whereas for the solution containing bromide anions, current density reached high value about 50 $mA \cdot cm^{-2}$.

Antipsychotics and anticonvulsants drugs can be evaluated by electrochemical methods such as cyclic, linear and differential voltammetry [32-35]. The study of electrochemical behavior of six compounds of antiepileptic drug class (o-aminobenzamides and quinazolines-2,4-diones) revealed that the oxidation potential depends on the length and the type of functional group [32]. Cyclic voltammetry was also used to study the correlation between the biological activity and the ability to participate at electron transfer processes [32]. Glassy carbon and boron-doped diamond electrodes were used to study the electrochemical behavior of antipsychotic drugs including breviscapine, chlorpromazine and thioridazine [33-35]. These studies provide information about the possibility of a selective determination of antipsychotic drugs from biological samples and pharmaceutical formulations.

The electrolyte solutions containing valproic acid were analyzed by UV-Vis spectrophotometry before and after the recording of cyclic voltammograms and the results are shown in Figure 2. These spectra are presented in comparison with the UV-Vis spectra of the supporting electrolyte solutions, in the absence of valproic acid, recorded under the same experimental conditions.

The experimental data from Figure 2 demonstrate the different electrochemical behavior of valproic acid molecules in the presence of the halide anions. The absorbance maximum increase in the presence of bromide anions, at aproximately 260 nm is most likely due to the chemical and electrochemical formation of intermediary species, absorbing in the same UV range as VAc molecule. The fluorine anion is electrochemically inactive, as shown by the results presented in Figure 2a. The experimental results obtained for the NaF 10^{-1} $mol \cdot L^{-1}$ supporting electrolyte solution show that the UV-Vis spectrum initially recorded is identical to that obtained after cyclic voltammetry. UV-Vis spectra of NaCl supporting electrolyte does not show significant changes in absorbance or wavelength values. This is due to the very short time of the analysis. However, a closer analysis of the UV-Vis spectra corresponding to the supporting electrolyte (Figure 2b) shows fine changes in the absorption values at wavelengths less than 250 nm (NaCl before / after CV).

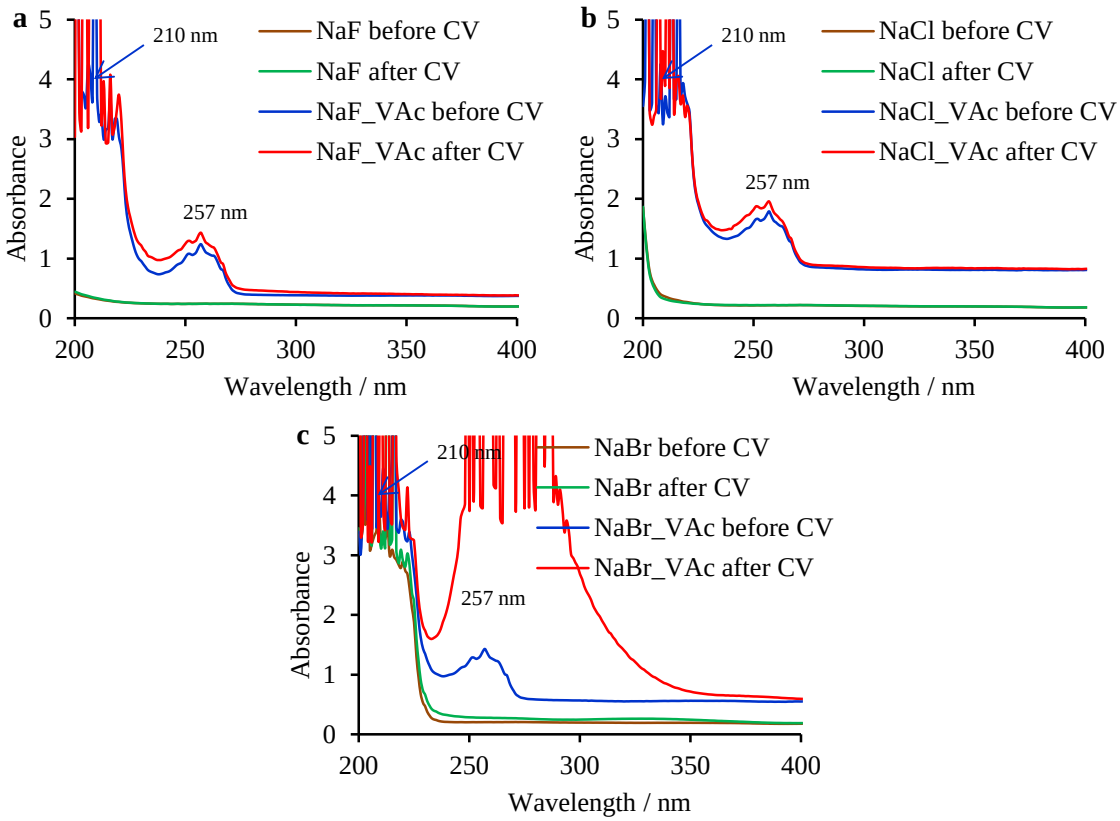


Figure 2. UV-Vis spectra of saline solution, in the presence and in the absence of valproic acid, before and after cyclic voltammetry performing.

Under experimental conditions identical to the previous ones, spectrophotometric analysis of the bromide support electrolyte indicate the electrochemical generation of the active oxy-bromide species (Figure 2c, NaBr before / after CV). The UV-Vis spectrum of the bromide solution obtained after cyclic voltammogram recording shows changes in the wavelength range 350-300 nm and at wavelengths less than 270 nm.

UV-Vis spectrophotometric analysis of electrolyzed solutions at constant current density of 50 $mA \cdot cm^{-2}$ (Figure 3) indicates two absorption maxima recorded at 257 nm and 210 nm corresponding to valproic acid [36].

The electrochemical behavior of carbamazepine, an anticonvulsant drug used in the treatment of neuropathic pain and epilepsy, on the gold electrode in phosphate buffer solution allows its determination in a wide range of concentrations in solid dosage forms [37]. The electrochemical processes of carbamazepine were studied by employing different electrochemical techniques. Also, the interaction of this drug with calf thymus DNA was used to determine the carbamazepine in bulk and tablets samples [38]. Another anticonvulsant drug studied by electrochemical methods was oxcarbazepine [39, 40]. The authors invetigated the influence of the supporting electrolyte, the solvent, the potential scanning rate and the pH on the voltammetric behavior. The authors proposed both a mechanism of electrochemical degradation of oxcarbazepine and a differential pulse voltammetric method to determine it [39, 40].

In the presence of fluoride anions, the electrolysis process was observed for 60 min. and exhibits an increase in the maximum absorption intensity but also the wavelength shifts from 257 nm to 250 nm (Figure 3a). The mechanism of the electrochemical degradation of VAc is influenced to a lesser extent by the fluoride anions. According to Figure 3b, it can be stated that during the electrolysis (30 minutes) of the supporting electrolyte solution (NaF), there are no changes of the UV-Vis spectra. In the presence of fluoride anions, the degradation of VAc molecules takes place through a heterogeneous mechanism directly at the active centers on the working electrode surface. In the presence of chloride anions, an increase in the absorption maximum intensity shifted to lower wavelengths, can be observed (Figure 3c).

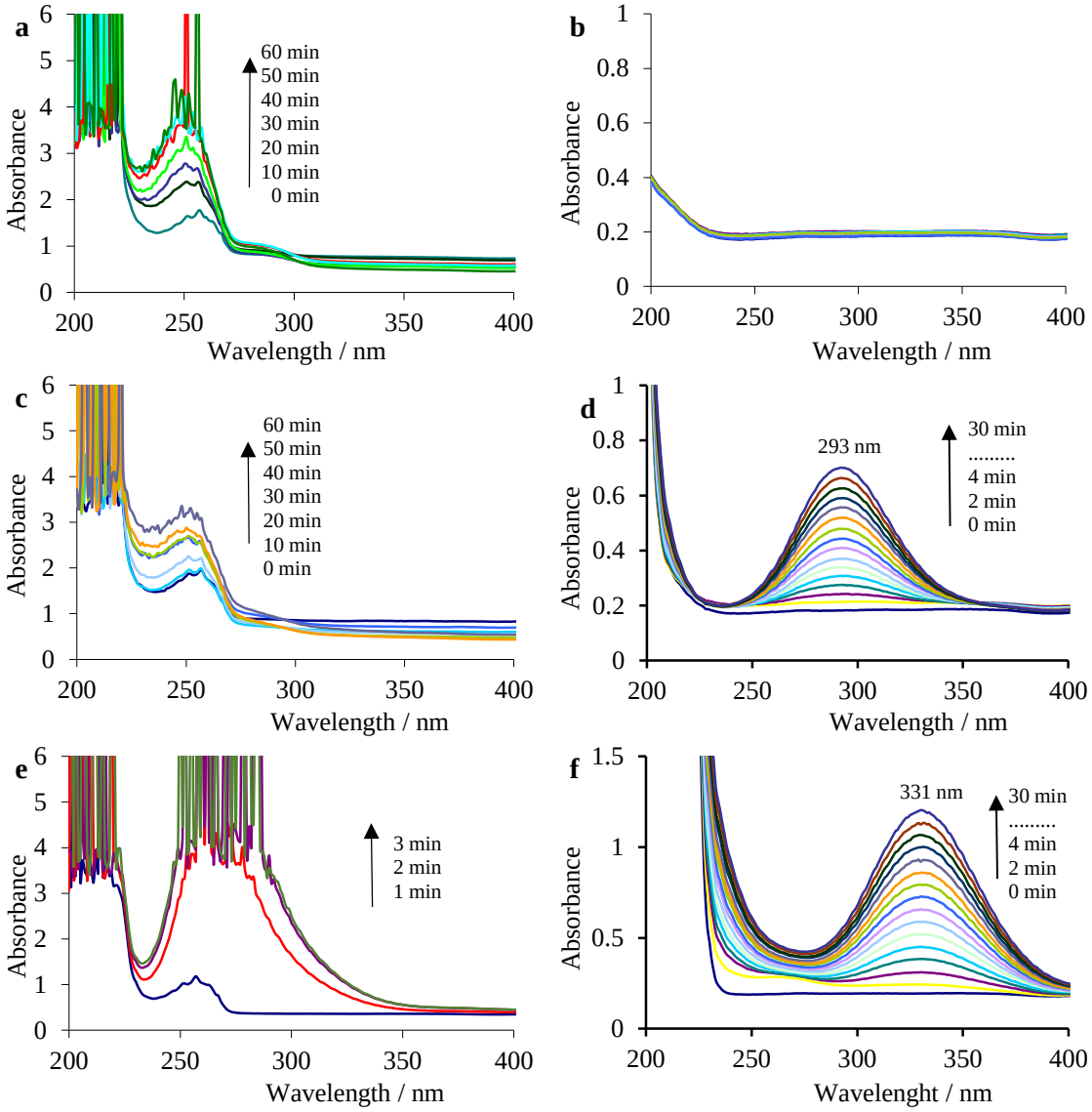


Figure 3. UV-Vis spectra of 10^{-1} mol·L^{-1} NaX solutions ($X = F^-, Cl^- \text{ and } Br^-$) in the absence and in the presence of $8.3 \cdot 10^{-2}$ mol·L^{-1} VAc, registered at different times of electrolysis; a) NaF_VAc, b) NaF, c) NaCl_VAc, d) NaCl, e) NaBr_VAc, f) NaBr.

Analyzing the Figures 3a and 3c, it can be stated that, in the presence of chloride anions, VAc molecules are electrochemically degraded. It is observed that, under the same experimental conditions, the absorbance values are lower in the presence of chloride anions corresponding to the maximum absorption λ = 257-250 nm. Another feature of UV-Vis spectra is that the electrogenerated active species of chlorine at λ = 293 nm are not highlighted, as Figure 3d indicates, which shows that these species are consumed as they are formed. The mechanism of electrochemical degradation of VAc, in the presence of chloride anions, arises both directly at the electrode surface and indirectly within the electrolyte solution under the action of oxychlorinated species ($\boldsymbol{ClO_n^-, n = 1,2,3,4}$) (Figure 3d).

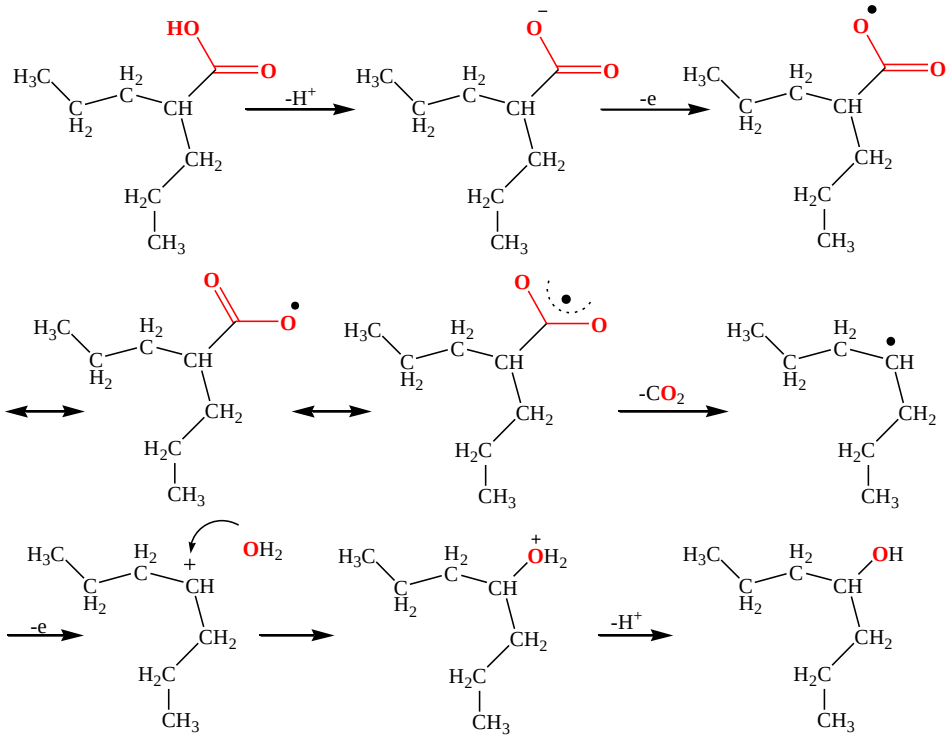
In the presence of bromide anions, the electrolysis process could not be followed for more than 3 minutes, the absorption maxima becomes wider, it is shifted to higher wavelengths and is attributed to degradation products of valproic acid (Figure 3c). Constant current electrolysis of the NaBr 10^{-1} mol·L^{-1} supporting electrolyte solution (Figure 3f) shows the formation of the active oxy-bromide species ($BrO_n^-, n = 1,2,3,4$). These species being identified according to the maximum absorption at the wavelength λ = 331 nm. When the electrolyte solution contains the supporting electrolyte and the biologically active compound (Figure 3e), a very high absorption maximum is recorded, centered at the wavelength λ = 275 nm. This maximum is attributed to the degradation products of VAc molecules. Because UV-Vis spectra indicate the highest degree of degradation and a minimum time, in this case, it can be stated that the degradation rate in the presence of bromide anions is the highest. Similar behavior has been observed for electrochemical degradation of a widely used food additive such as Chocolate Brown HT [31]. Electrochemical studies in combination with spectrophotometric analysis showed that the rate of electrochemical degradation of Chocolate Brown HT varies in the order: Br > Cl > F.

Electrochemical degradation of VAc molecule in the presence of fluoride anions involves a direct electrochemical mineralization that is initiated at the electroactive sites by the attack of electrogenerated hydroxyl radicals. Electrochemical degradation of VAc molecule in the presence of bromide anions involves a mineralization that is initiated in the bulk solution by the electrogenerated oxyhalogenated species.

It can be concluded that different anions exhibit different electrochemical behaviors and implicitly may favor the participation of valproic acid molecules in the charge transfer processes at the surface of the electrode or on the contrary may have a retarding effect on the oxidation processes of these molecules.

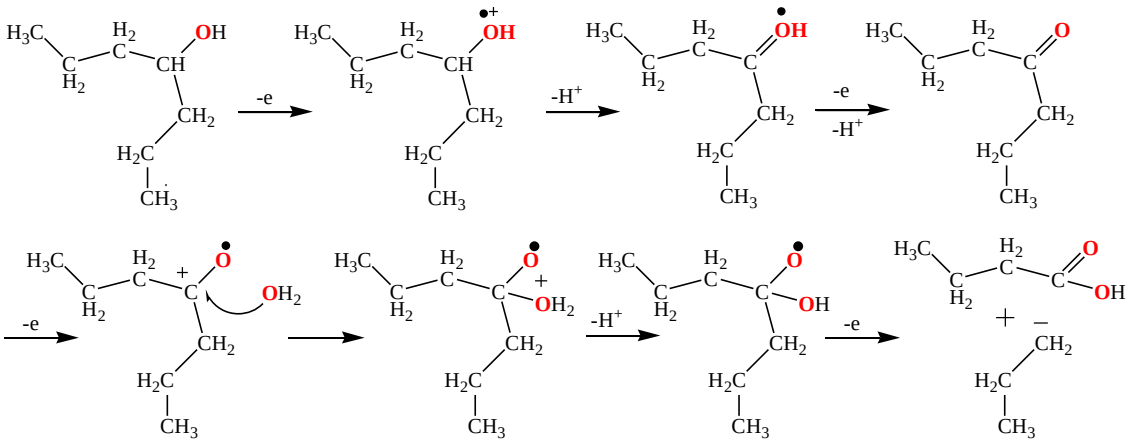
Proposed mechanism for electrochemical oxidation of VAc drug was studied assuming that the oxidizing species are either hydroxyl radical or oxyhalogenated species. This mechanism is a possible way to transform valproic acid molecules into electrochemically degraded compounds. Electrochemical oxidation pathway may depends on several experimental factors such as, the pH and composition of the electrolyte solution, the electrocatalytic properties of the electrodes and the electrochemical method approached. Certainly the degradation mechanism is different from the metabolic one. Both valproic acid and its metabolites were determined by gas chromatography - mass spectrometry from biological urine samples [41 - 43]. Electrochemical degradation mechanism can be observed in scheme 1-3. Among others, carboxyl group is an easily ionisable group with a strong

nucleophilic character. Fragmentation mechanism is initiated by an oxidative decarboxylation of VAc molecule as is presented in Scheme 1.



Scheme 1. The mechanism of electrochemical oxidative decarboxylation of valproic acid.

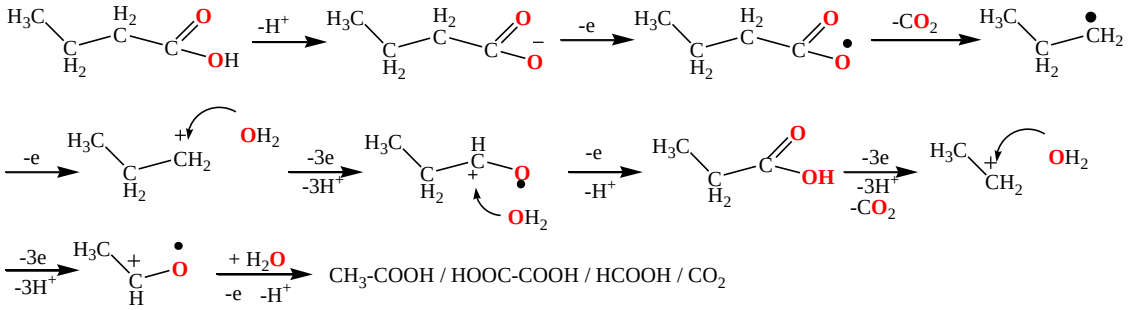
Hydroxy intermediate species is consequently oxidized to the corresponding keto derivative followed by a C-C bond cleavage resulting in a small molecule formation (Scheme 2).



Scheme 2. The electrochemical mechanism of 4-heptanol oxidative degradation.

There is a stepwise oxidation mechanism of C atoms leading to lower toxicity compounds; acetic acid, oxalic acid, formic acid, CO_2 and H_2O. The proposed mechanism takes into account both the experimental results obtained by cyclic voltammetry and by spectrophotometric analysis, as well as the inductive and electromeric effects which are presented in the valproic acid molecule and in

intermediates formed during the electrochemical degradation process. This mechanism takes place through the 4-keto intermediate, a compound identified by gas chromatographic analysis - mass spectrometry as the metabolite present in the largest amount in urine [42].



Scheme 3. The mechanism of electrochemical degradation of butanoic acid.

The study of experimental parameters in electrochemical analysis of biologically active compounds from the class of drugs [21-23, 25-27], food additives [24, 31], corrosion inhibitors [44, 45] etc. is important because it provides information on stability to oxidation and reduction reactions, how to interact with other compounds, by extrapolation to in vivo conditions.

3.2 Thermal Behavior of Valproic Acid Drug in Nitrogen Atmosphere

The results obtained for the study of the thermal behavior of valproic acid in the temperature range from room temperature (25 °C) to 300 °C are shown in Figure 4.

In Figure 4, the thermogravimetric curve (TG) shows an asymptotic variation of the sample mass, starting from 95 °C to 185 °C. The first order derivative of the thermogravimetric curve (dTG curve) indicates a maximum process temperature at a value of 175 °C. Very wide temperature range, about 90 °C, indicates several concerted processes such as thermal degradation of valproic acid with the elimination of carbon dioxide (decarboxylation), thermal degradation with the removal of small molecular weight fragments such as hydrogen and acetylene, but these processes may also be accompanied by partial evaporation of VAc. At the end of this thermal effect (185 °C) in the crucible is recorded a mass of 2.1 % of the initial value represented by small fragments and ash resulting from the combustion process. At temperatures above 240 °C there is a decrease in the mass from 2.1 to 1.8 % of the initial value corresponding to the degradation of small molecule intermediate compounds.

At the end of the experiment (300 °C) in the crucible is a residue representing 0.8 % of the initial value of the sample mass.

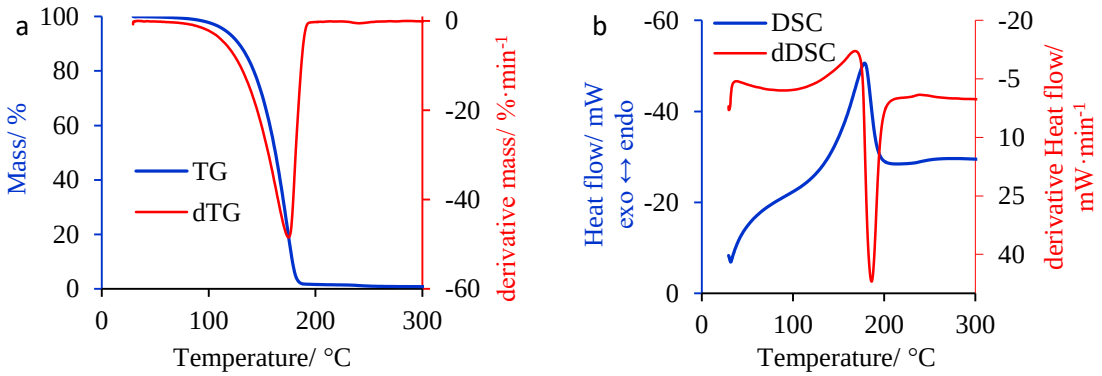


Figure 4. Thermograms (TG / DSC) of VAc in nitrogen inert atmosphere.

The calorimetric analysis (DSC and dDSC curves) of the sample indicates three successive thermal effects: a minor endothermic heat effect, recorded in the temperature range of 25 °C to 90 °C due to the heating of the sample and / or the initiation of a partial evaporation; a major endothermic heat effect with a maximum temperature of 175 °C corresponding to the advanced degradation of the VAc molecule; a minor endothermic effect (240 °C) corresponding to the degradation of small molecule intermediate compounds.

4. CONCLUSIONS

Mineralization of valproic acid drug by electro-generated oxidants was investigated in simulated polluted hydro-alcoholic solution in the presence of different halide anions (F, Cl, Br). Was demonstrated that electrogenerated oxidizing intermediates obtained by constant current density electrolysis of halide anions can be successfully used for mineralization of this type of drug.

According to analysis of spectrophotometric results, the chemical oxidation of valproic acid in the bulk solution prevails over electrochemical reactions at the electrode / electrolyte interface, especially in the presence of bromide anions.

The electrochemical oxidation of VAc drug in the presence of bromide anions using Pt electrode showed that the degradation is almost complete after 2-3 min of electrolysis. The electrochemical degradation of valproic acid considerably increased upon the addition of bromide ions.

Thermal analysis of valproic acid in an inert atmosphere of nitrogen gas indicates the presence of overlapping thermal processes in the temperature range 170-190 °C. At temperatures above 240 °C, degradation of small intermediate compound molecules occurs, resulting in a residue at the end of the experiment of 0.8% of the initial mass.

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