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The Effect of Electrochemically Synthesized Aqueous Sodium Persulfate on the Biotransformation of Certain Psychoactive Medications

Mogely Sh. Khubutiya[*], Vladimir A. Kolesnikov[**], Anatoly K. Evseev[§], Mark M. Goldin[§], Alexey D. Davydov[§§], Michael M. Goldin[†]

* *Member of the Russian Academy of Sciences, N. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russian Federation*
***D.I. Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation*
§ *N. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russian Federation*
§§ *A.N. Frumkin Institute of Physical Chemistry and Electrochemistry of the Russian Academy of Sciences, Moscow, Russian Federation*
† *Liberty University, Lynchburg, Virginia, USA*

ABSTRACT. The psychotropic drugs amitriptyline, tisercin and carbamazepine were used as models for the investigation of the oxidizing activity of electrochemically synthesized sodium persulphate. Derivatives of phenothiazines, xanthene and benzodiazepines were oxidized by the persulphate-containing solution, and the oxidation products were low in toxicity. The oxidation products were identical to well-known products of biotransformation (metabolites) of drugs in living organisms. *© 2015 Bull. Georg. Natl. Acad. Sci.*

Key words: *detoxification, oxidative biotransformation, psychoactive drugs, sodium persulphate, sodium hypochlorite.*

Modern approaches to designing high-performance methods for treatment of acute poisonings, kidney failure, and liver failure use artificial detoxification methods that replicate aspects of the physiological mechanisms of self-purification of organism for exo- and endo-toxicants [1]. Perhaps the most promising of these are devices that reproduce the overall integral effect of treatment by modeling the physicochemical principles of physiological detoxification [2]. The best-known methods are hemodialysis [1,3], plasmapheresis [3], hemosorption [4]; however, a simpler method of so-called "oxidative therapy" is being used quite widely at present [5]. The essence of "oxidative therapy" is the use of detoxifying solutions containing "active" oxygen donors that can oxidize endo- and exogenous toxicants in blood, converting them into non-toxic products.

In recent years, electrochemically synthesized aqueous sodium hypochlorite solutions [6] found uses in oxidative therapy alongside the previously

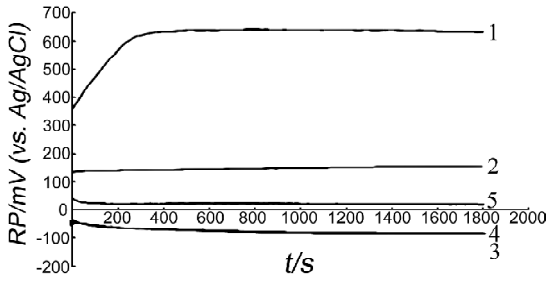

Fig. 1. The variation of redox potential of blood serum with different oxidants as a function of time: 1 – 8 mM NaClO, 2 – anolyte (1.4 mM $Na_2S_2O_8$), 3 – blood serum + 0.15 M NaCl (10:1), 4 – blood serum with a 10% addition of a 1.41 mM solution of $Na_2S_2O_8$ produced at a current density of 0.4 A/cm^2, 5 – blood serum with 10% of a 8 mM solution of NaClO.

utilized hydrogen peroxide and dissolved ozone. However, sodium hypochlorite has a major limitation in its use in medical practice due to its high oxidizing activity. Additionally, toxic organic chloride impurities may be present in solutions of sodium hypochlorite (and may result in the formation of dioxins) due to the technology used in the synthesis of these solutions [7].

Taking into account the above considerations it was suggested that a more promising option may involve the use of persulfate (peroxydisulfate) anions as donors of active oxygen, since this "active" oxygen donor can be synthesized using a chloride-free sulfate electrolyte. This option was chosen because electrochemically synthesized aqueous solutions of sodium persulfate at concentrations below 1×10^{-3} M were shown not to injure blood cells, important biochemical components of blood do not change under the influence of these solutions [8-11], and the precursor sulfate anions are non-toxic even at significantly high concentrations [12].

The electrosynthesis of sodium persulfate was carried out in a diaphragm filter-press electrolyzer. A porous titanium diaphragm separated the cathode and anode chambers, with a titanium-plate cathode and a titanium plate covered with iridium dioxide as the anode. The electrolyte (0.28 M aqueous sodium sulfate) was continuously circulated by a peristaltic pump. Current densities were in the range of 0.08-0.64 A/cm^2.

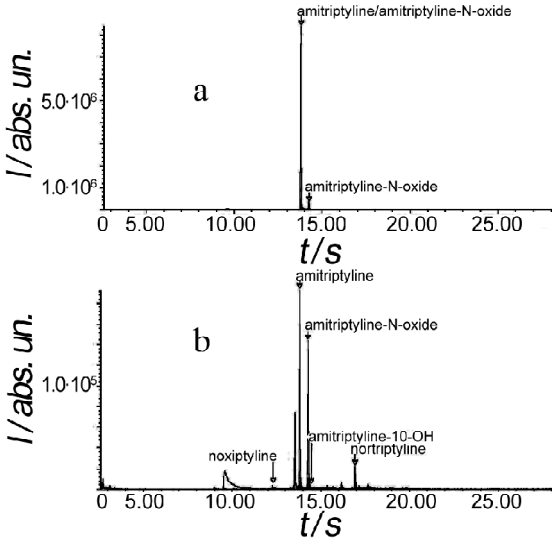

Fig. 2. A representative GC/MS result for the oxidation products for an aqueous solution of amitriptyline: a – oxidation by a 10% addition of 1.41 mM $Na_2S_2O_8$ prepared at a current density of 0.4 A/cm^2, b – oxidation by a 10% addition of 8 mM NaClO.

The electrochemically synthesized solutions were pH-corrected to 7.3 (a physiologic value) and added to blood serum containing a psychoactive medication (amitriptyline at 25 mg/L; tisercin, generic name levomepromazine, at 25 mg/L; and carbamazepine at 20 mg/L) in order to determine the oxidizing activity of the solutions. The results were obtained by monitoring the redox potential (RP) of blood serum and the concentrations of the drugs and their biotransformation products by gas chromatography-mass spectrometry (GC/MS) [13,14].

The RP variation for 8.0 mM NaClO and 1.4 mM $Na_2S_2O_8$ solution produced electrochemically at a current density of 0.4 A/cm^2 is shown in Fig. 1, curves *1* and *2*, respectively. These data show that the hypochlorite solution is a stronger oxidizing agent than the persulfate solution. Indeed, the addition of 8.0 mM sodium hypochlorite solution to blood serum led to a considerable positive shift in its RP, over +100 mV (Fig. 1, curve *5*). Such a drastic change in the oxidizing activity of blood serum is undesirable for organism [15]. At the same time, the addition of sodium persulfate solution to the blood serum did not result in a significant change, with the RP value shifting by not more +4.0 mV (Fig. 1, curve *4*). There-

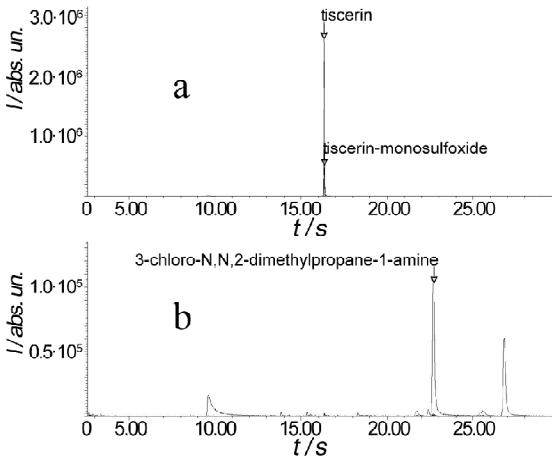

Fig. 3. A representative GC/MS result for the oxidation products for an aqueous solution of tisercin: a – oxidation by a 10% addition of 1.41 mM $Na_2S_2O_8$ prepared at a current density of 0.4 A/cm^2, b – oxidation by a 10% addition of 8 mM NaClO.

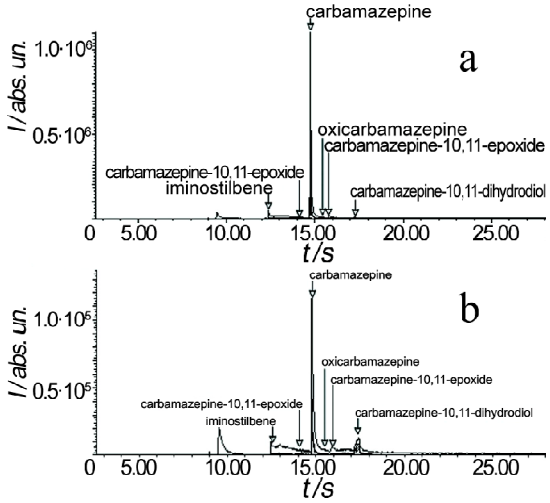

Fig. 4. A representative GC/MS result for the oxidation products for urine with carbamazepine: a – initial urine with 10% addition of physiological solution (0.15 M NaCl), b – oxidation by a 10% addition of 1.41 mM $Na_2S_2O_8$ prepared at a current density of 0.4 A/cm^2.

fore, the addition of persulfate as an oxidizing agent to blood serum did not result in any noticeable change in its redox properties.

Next, the oxidizing activity of electrochemically synthesized persulfate solution towards psychoactive medications was determined. The data presented in Fig. 2a show that the addition of aqueous sodium persulfate to a solution of amitriptyline clearly led to the formation of amitriptyline-N-oxide, which is much less toxic than the initial amitriptyline. Moreover, the physiological biotransformation of amitriptyline in organism also leads to formation of amitriptyline-N-oxide [16]. At the same time, the oxidation of amitriptyline by NaClO (Fig. 2b) led to the formation of noxiptyline, amitriptyline-10-OH, and nortriptyline in addition to amitriptyline-N-oxide. It should be noted that nortriptyline is highly cardiotoxic [17]. Likewise, for tisercin, sodium hypochlorite (Fig. 3b) produces a highly toxic chloroamine oxidation product (3-chloro-N,N,2-dimethylpropane-1-amine), whereas sodium persulfate (Fig. 3a) produces a much more benign tisercin monosulphoxide.

The effect of sodium persulfate solution on the level of carbamazepine and its metabolites in urine proved particularly interesting. The data in Fig. 4b show that the concentration of carbamazepine decreased, and the level of its inactive derivative, carbamazepine-10,11-dihydrodiol, increased. This is a very important observation because carbamazepine-10,11-dihydrodiol is the end product of natural oxidation of carbamazepine in organism via the epoxide-diol metabolic pathway [18]. It can be deduced that the electrochemically synthesized aqueous sodium persulfate is a medicinal preparation capable of mimicking the functions of liver monooxygenase. Therefore electrochemically produced sodium persulfate provides an additional resource to beneficially control the kinetics of detoxification of organism from carbamazepine through acceleration of the biotransformation of toxicants.

The effect of electrochemically produced sodium persulfate on the oxidation of amitriptyline, tisercin (levomepromazine) and carbamazepine was elucidated *in vitro*; the products of persulfate oxidation of these toxicants are the same as the products of their natural biotransformation. In contrast, sodium hypochlorite tended to produce several highly toxic species from the same drugs.

Thus, it was found that the products of oxidation of psychoactive drugs by persulfate and hypochlorite solutions have very different toxic prop-

erties, i.e. toxicity of products of biotransformation depends on oxidative activity of oxidative solution.

Electrochemically produced sodium persulfate is a more effective, and potentially clinically acceptable, agent for biotransformation of psychotropic drugs, as compared with the sodium hypochlorite despite the lower oxidative activity.

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სამედიცინო მეცნიერებანი

ელექტროქიმიურად სინთეზირებული წყლიანი ნატრიუმ პერსულფატის გავლენა გარკვეული ფსიქოტროპული პრეპარატების ბიოტრანსფორმაციაზე

მ. ხუბუტია[*], ვ. კოლესნიკოვი[**], ა. ევსეევი[§], მარკ. მ. გოლდინი[§], ა. დავიდოვი[§§], მიხაილ მ. გოლდინი[†]

* *რუსეთის მეცნიერებათა აკადემიის წევრი, ნ. სკლიფოსოვსკის სახ. გადაუდებელი სამედიცინო დახმარების კვლევითი ინსტიტუტი, მოსკოვი, რუსეთი*
** *დ. მენდელეევის სახელობის რუსეთის ქიმიური ტექნოლოგიის უნივერსიტეტი, მოსკოვი, რუსეთი*
§ *ნ. სკლიფოსოვსკის სახ. გადაუდებელი სამედიცინო დახმარების კვლევითი ინსტიტუტი, მოსკოვი, რუსეთი*
§§ *ა. ფრუმკინის სახელობის რუსეთის მეცნიერებათა აკადემიის ფიზიკური ქიმიისა და ელექტროქიმიის ინსტიტუტი, მოსკოვი, რუსეთი*
† *ლიბერთის უნივერსიტეტი, ლინჩბურგი, ვირჯინია, აშშ*

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