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Short communication

Electrochemical, quantum-chemical and antioxidant properties of antipyrine and its derivatives

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Abstract

Electrochemical, quantum-chemical and antioxidant properties of antipyrine and its derivatives have been investigated in this work.

New quantum-chemical parameter such as difference of formation heats of a molecule and its cation radical ($\Delta\Delta H_{cat}$) has been used in order to describe properties of the investigated substances. Electrochemical properties (oxidation, reduction potentials) have been investigated. Correlation between the calculated $\Delta\Delta H_{cat}$ and the experimentally obtained oxidation potentials for antipyrine and its derivatives has been found.

Keywords: Antioxidant; Antipyrine; Antipyrine derivatives; Quantum-chemical parameters; Voltammetry

1. Introduction

Protection of human against oxidative stress as well as prophylactic of cancer and other incurable diseases are important directions in medicine and biochemistry over the world. Oxidative stress arises in a biological system after an increased exposure to oxidants, a decrease in the antioxidant capacity of the system, or both. It often leads to the generation of reactive oxygen species (ROS), including free radicals [1]. Antioxidants play a major role in protecting biological systems against many incurable diseases. The antioxidants have been widely used in different fields of industry and medicine as substances, which interrupt radical-chain oxidation processes, improve general health, help cell rejuvenation and prevent cancer [2].

The interest in antioxidants is constantly growing. However, many problems are not resolved. Investigation of the relation between electrochemical properties and structures of antioxidants seems to be very interesting problem. It could be a key to comprehension of mechanisms of biochemical oxidation of these substances in tissues.

Quantum-chemical parameters help to describe properties of antioxidants in detail. Data of distribution of charge density over the molecule structure would help to determine active atoms groups, which are responsible for oxidation of whole molecule. Difference of formation heats of a molecule and its cation radical ($\Delta\Delta H_{cat}$) could be used as parameter of cation radical stability of the substances. On the other hand, oxidation electrode potential of the substance is important thermodynamic parameter of oxidation process. Investigation of the relation between quantum-chemical parameters of the substance and its electrochemical properties would predict various substance characteristics and their oxidation mechanisms [3,4].

In this work, antipyrine and its derivatives have been investigated as antioxidants. Over the last few years, these compounds have been widely used in different fields of medicine. New antipyrine derivatives such as amides of 4-aminoantipyrine and 9,10-substituted stearinic acids are effective pharmaceuticals for prophylactic and treatment of virus diseases. They have antimutagen action. It was confirmed by clinical test.

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Electrochemical and antioxidant properties of antipyrine and its derivatives have been investigated in this work.

Antioxidant properties of antipyrine derivatives have been determined by voltammetry. Voltammetry is convenient methodology for studying antioxidant properties and determining antioxidant activity of the biological systems. Nowadays the development of bioelectroanalytical chemistry is successful and is conditioned by the nature of the matter, because electrochemical mechanisms make up the base of the majority of biochemical processes. Investigations the influence of pharmaceuticals on the process of quasi-reversible electrochemical oxygen reduction (ER O_2) and its kinetics could be treated as the modeling of antioxidant activity of the samples in vitro. The ER O_2 proceeds at the electrode in several stages with formation of the reactive oxygen-derived species. It is similar to the reduction oxygen in tissues [5]:

$$O_2 + e^- \overset{k}{\rightleftarrows} O_2^{\bullet -} \quad (1)$$

$$O_2^{\bullet -} + H^+ \rightleftarrows HO_2^{\bullet} \quad (2)$$

$$HO_2^{\bullet} + H^+ + e^- \rightleftarrows H_2O_2 \quad (3)$$

$$H_2O_2 + 2H^+ + 2e^- \rightleftarrows 2H_2O. \quad (4)$$

Thus, antioxidant interaction with oxygen and the ROS proceeds at the electrode according to the general mechanism:

$$R{-}H + O_2 = R + HO_2^{\bullet} + e^- + H^+ = R + H_2O_2 \quad (5)$$

which includes preceding protonation reaction of oxygen by antioxidant. Visually it is observed as decrease of electrochemical reduction current of oxygen and shift of peak potential toward to the negative values. Objectively oxygen concentration decreases due to preceding protonation reaction; therefore, according to the classic Nernst equation for electrode process [5]:

$$E_{O_2/HO_2^{\bullet}} = E^{\circ}{}_{O_2/HO_2^{\bullet}} + \frac{RT}{zF} \ln \frac{C_{O_2}}{C_{HO_2^{\bullet}}} \quad (6)$$

potential become less. On the other hand, slow preceding protonation reaction stops the main process of ER O_2 because of the decrease of electroactive form at the electrode surface. Thus, electrochemical reduction current of oxygen decreases since it is directly proportional to the substance concentration at the electrode surface.

Degree of changes of the ER O_2 current in dependence on the antioxidant concentration in the solution has been suggested as a coefficient of the antioxidant activity (K):

$$K = \frac{\Delta I}{I^{\circ} \Delta C} \quad (7)$$

where ΔC is the change of the antioxidant concentration in g/ml, ΔI is the change of the ER O_2 current density with the antioxidant addition, I° is the limiting current density of the ER O_2 without antioxidants in the solution.

This work is also designed to serve as a basis for investigating of the relation between antioxidant properties and the oxidation behaviour of the substances.

2. Experimental

2.1. Electrochemical properties studies

Potentials of anodic oxidation of antipyrine derivatives have been determined by cyclic voltammetry. This method involves the recording of cyclic voltammograms of the substances by means of voltammetric analyzer using differential voltammetry under the following conditions: potential rate scan 0.02 V/s, potential range $E = 0$ to +1.5 V. The three-electrode cell ($V = 10$ ml) is connected to the analyzer and consists of a working carbon glass microelectrode, a silver–silver chloride reference electrode with KCl saturated ($Ag|AgCl|KCl_{sat}$), a carbon glass auxiliary electrode and a nitrogen (or inert gas) supply tube.

Because of solubility problems all of the electrochemical studies were carried out in nonaqueous media, namely in ethanol, using sodium perchlorate (0.1 M) as supporting electrolyte. The solutions of antipyrine derivatives were prepared from the chemically pure corresponding substances by solving in ethanol.

2.2. Quantum-chemical calculations

Quantum-chemical calculations were carried out using a semiempirical method MNDO (HyperChem Pro 6). Differences of formation heats of a molecule and its cation radical ($\Delta\Delta H_{cat}$) and electron density have been calculated for investigated substances.

2.3. Antioxidant activity determinations

The principle of the method was described earlier [5,6]. It involves the recording of voltammograms of the cathodic reduction of oxygen by means of any voltammetric analyzer using differential voltammetry under the following conditions: potential rate scan 0.02 V/s, potential range $E = 0$ to -0.6 V.

The electrochemical cell ($V = 10$ ml) is connected to the analyzer and consists of a working mercury film electrode (MFE), a silver–silver chloride reference electrode with KCl saturated ($Ag|AgCl|KCl_{sat}$), a carbon glass auxiliary electrode and a nitrogen (or inert gas) supply tube. An open type cell can be used in this investigation. The reference electrode is either separated from the working electrode or both the electrodes are held in the electrochemical cell. The working electrode potential is initially set at 0 V for about 30 s. During this step the solution is stirred by a magnetic stirrer. After the stirring is stopped, the potential is scanned negatively, causing oxygen reduction, which gives a current first wave in this potential range. Supporting electrolyte is 0.1 M $NaClO_4$ in

ethanol. Its value is proportional to the amount of oxygen in the solution.

3. Results and discussion

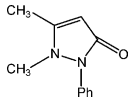
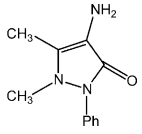
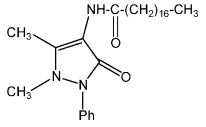
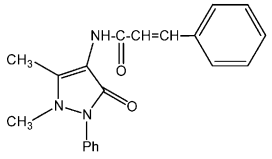
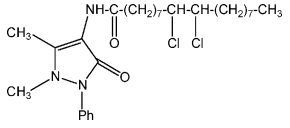
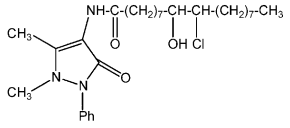
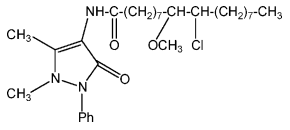
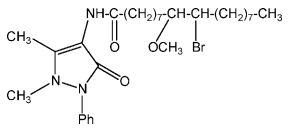
Electrochemical properties of antipyrine and its seven derivatives (Table 1) have been investigated in this work.

Cyclic voltammograms of these substances have been recorded (Fig. 1). It should be noted that the various substituted of 4-steroylaminoantipyrines (substances 5–8) have the same cyclic voltammograms. Obviously general oxidation mechanism of these compounds is identical.

The obtained voltammograms indicate on the complicated oxidation mechanisms of antipyrine derivatives, including two processes (at $E = 0.57$ V and $E = 1.2$–1.3 V). As for aminoantipyrine, appearance of the oxidation peak at $E = 0.57$ V is associated with oxidation of NH_2-group. Disappearance of oxidation peak at $E = 0.57$ V for substances 3 and 4 could be explained by difficulty of hydrolysis of NH-group. On the contrary, for substances 5–8 hydrolysis of NH-group is catalyzed by halogens ions in the molecule structure. Cyclic voltammograms at $E = 1.2$–1.3 V for all substances indicate on the oxidation of antipyrine ring and –N–N– bond in it.

For confirmation of this assumption data of distribution of charge density over the molecule structure have been calculated for antipyrine and its derivatives. For example electron structure of 4-(3-phenylacriloyl)-aminoantipyrine is presented in the Fig. 2.

Table 1
Structures of antipyrine and its derivatives

N	Substance name	Structure
1	Antipyrine	
2	4-Aminoantipyrine	
3	4-Steroylaminoantipyrine	
4	4-(3-phenylacriloyl)-Aminoantipyrine	
5	4-(8,9-dichlorstearoyl)-Antipyrine	
6	4-(8(9)-hydroxy-9(8)-chlorstearoyl)-Antipyrine	
7	4-(8(9)-methoxy-9(8)-chlorstearoyl)-Antipyrine	
8	4-(8(9)-methoxy-9(8)-bromstearoyl)-Antipyrine	

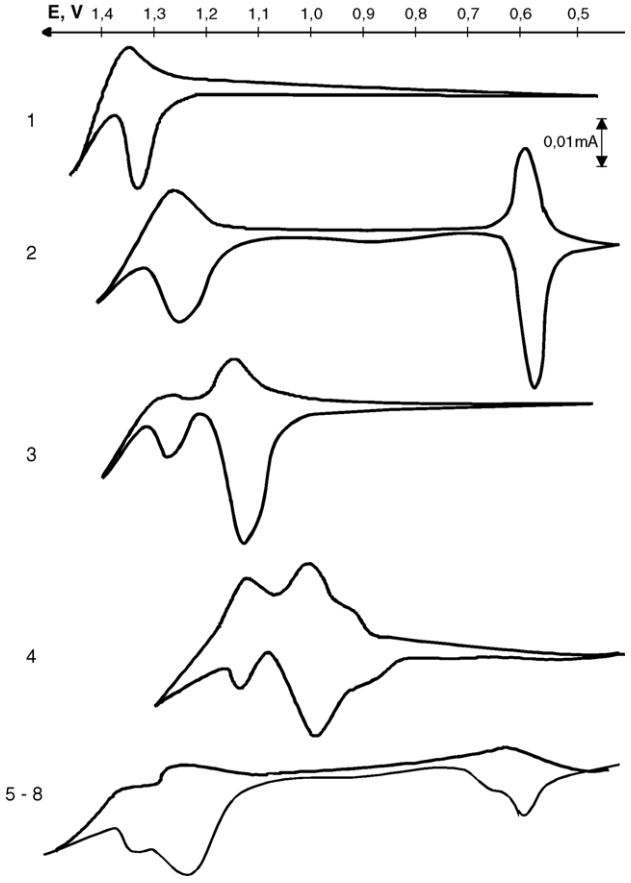


Fig. 1. Cyclic voltammogramms of antipyrine and its derivatives.

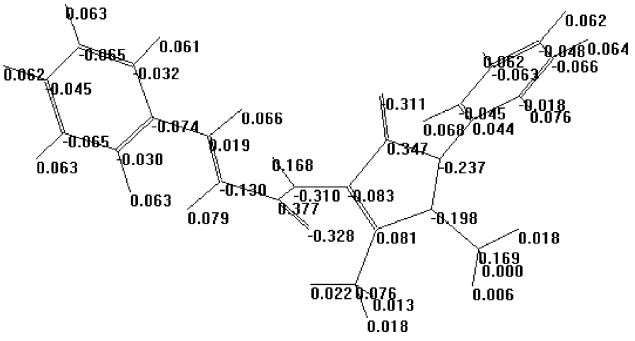
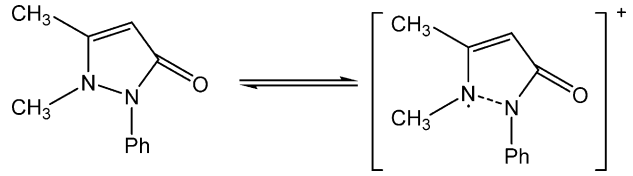


Fig. 2. Distribution of charge density over the molecule of 4-(3-phenylacriloyl)-aminoantipyrine.

Fig. 2 shows that high electron density is located near –N–H– (−0.310) and –N–N– (−0.237, −0.198) bonds in molecule structure. It gives possibility to propose that these atom groups in the molecule are subject to oxidation and give oxidations peaks at E = 0.57 V (oxidation –N–H– group) and at E = 1.2–1.3 V (oxidation –N–N– group).

Moreover cyclic voltammograms at E = 1.2–1.3 V indicate on the reversibility of the oxidation processes for all investigated substances, that could be connected with the stability of cation radicals of the substances. Quantum-chemical calculation of difference of formation heats of a molecule and its cation radical ($\Delta\Delta H_{cat}$) has been used as argument of this approach (Table 2).

The calculations indicate on the correlation between oxidation potential of the substances and their $\Delta\Delta H_{cat}$. Obviously oxidation of the investigated substances at E = 1.2–1.3 V proceed via cation radical formation and reversible process according following mechanism:



Correlation between the calculated differences of formation heats of a molecule and its cation radical $\Delta\Delta H_{cat}$ and the experimentally obtained oxidation potentials for antipyrine and its derivatives (with the exception of 4-(3-phenylacriloyl)-aminoantipyrine) is presented in the Fig. 3.

In addition antioxidant activity of the investigated substances have been determined. For this aim, voltammograms of the oxygen reduction current in the supporting electrolyte at the mercury film electrode (MFE) without and with antioxidant have been recorded (Fig. 4).

Curves of the relative change of the ER O_2 current density (I/I°) against antioxidant concentration have been plotted. The slope angle tangent of straightforward lines (in the range of small antioxidant concentrations) is suggested as a coefficient of the antioxidant activity K (according to 7).

As a result, coefficients of the antioxidant activity (K) of the investigated samples have been determined in this work. As it is expected all substances have shown antioxidant activity (Table 3). 4-Steroylaminoantipyrine

Table 2
Quantum-chemical and electrochemical properties of antipyrine and its derivatives

N	Substance name	$\Delta\Delta H_{cat}$ (kcal/mol)	E (V)
1	Antipyrine	190.95	1.35 ± 0.04
2	4-Aminoantipyrine	175.06	1.24 ± 0.02
3	4-Steroylaminoantipyrine	179.45	1.29 ± 0.02
4	4-(3-phenylacriloyl)-Aminoantipyrine	177.10	1.13 ± 0.02
5	4-(8,9-dichlorstearoyl)-Antipyrine	177.99	1.28 ± 0.02
6	4-(8(9)-hydroxy-9(8)-chlorstearoyl)-Antipyrine	179.38	1.29 ± 0.03
7	4-(8(9)-methoxy-9(8)-chlorstearoyl)-Antipyrine	180.70	1.30 ± 0.02
8	4-(8(9)-methoxy-9(8)-bromstearoyl)-Antipyrine	180.78	1.31 ± 0.02

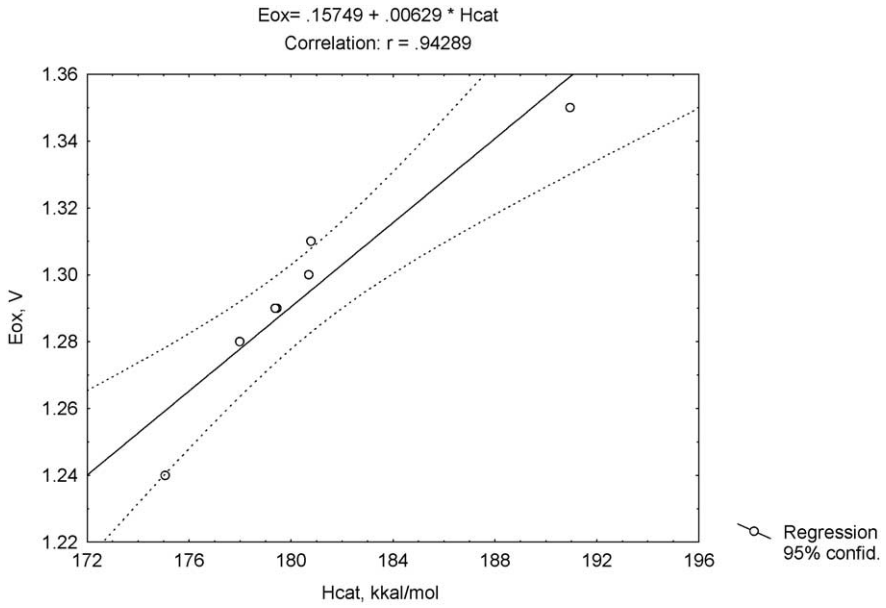


Fig. 3. Dependence of oxidation potentials E_{ox} against difference of formation heats of a molecule and its cation radical $\Delta\Delta H_{cat}$ for antipyrine and its derivatives.

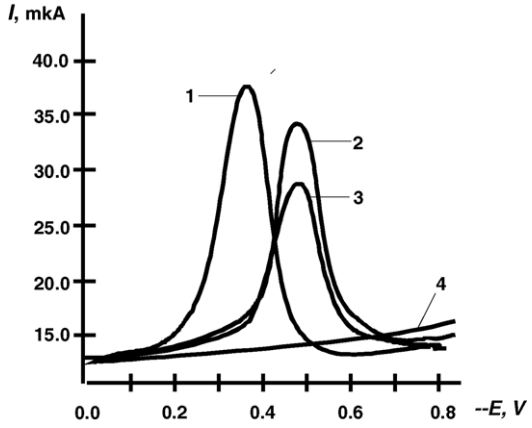


Fig. 4. Voltammograms of the electrochemical oxygen reduction current in the 0.1 M $NaClO_4$ in ethanol at the MFE without (1) and with antipyrine with concentration 0.12 g/ml (2) and 0.24 g/ml (3). Curve 4 is the residual current without oxygen in the solution.

and 4-(3-phenylacriloyl)-aminoantipyrine have demonstrated excellent antioxidant activity in comparison with the standard antioxidant—methyl-2,6-di-tert-buthyl-phenol ($K = 58.99 \pm 0.34$).

Table 3
Coefficients of the antioxidant activity (K) of the investigated samples

N	Substance name	K (ml/g)
1	Antipyrine	24.15 ± 0.34
2	4-Aminoantipyrine	41.18 ± 0.22
3	4-Steroylaminoantipyrine	163.30 ± 0.34
4	4-(3-phenylacriloyl)-Aminoantipyrine	161.70 ± 0.22
5	4-(8,9-dichlorstearoyl)-Antipyrine	79.71 ± 0.26
6	4-(8(9)-hydroxy-9(8)-chlorstearoyl)-Antipyrine	41.82 ± 0.39
7	4-(8(9)-methoxy-9(8)-chlorstearoyl)-Antipyrine	63.73 ± 0.22
8	4-(8(9)-methoxy-9(8)-bromstearoyl)-Antipyrine	63.25 ± 0.22

4. Conclusions

Electrochemical, quantum-chemical and antioxidant properties of the antipyrine and its derivatives have been investigated in this work. It was noted on the complicated oxidation mechanism of the substances. Quantum-chemical calculations confirmed the assumption of stability of cation radicals of the substances and expectable mechanism of their oxidation. Correlation between differences of formation heats of a molecule and its cation radical $\Delta\Delta H_{cat}$ and the oxidation potentials of antipyrine and its derivatives has been found. It was established that the more $\Delta\Delta H_{cat}$ value the greater E_{ox} value of substance. Moreover, all investigated substances have shown good antioxidant activity.

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