Electrochemical transformations and antiradical activity of asymmetrical RS-substituted pyrocatechols

I. V. Smolyaninov,[a,b]★ O. V. Pitikova,[c] A. I. Poddel'sky,[d] and N. T. Berberova[a]

[a]*Astrakhan State Technical University,*
16 ul. Tatishcheva, 414056 Astrakhan, Russian Federation.
E-mail: ivsmolyaninov@gmail.com
[b]*Southern Scientific Center, Russian Academy of Sciences,*
41 ul. Chekhova, 344006 Rostov-on-Don, Russian Federation
[c]*Ingineering Centre LLC "Gazprom dobycha Astrakhan,"*
Building 8, 6 ul. Savushkina, 414056 Astrakhan, Russian Federation
[d]*G. A. Razuvaev Institute of Organometallic Chemistry, Russian Academy of Sciences,*
49 ul. Tropinina, 603137 Nizhni Novgorod, Russian Federation

Redox transformations of sulfides **1**—**8** combining a fragment of sterically hindered pyrocatechol with alkyl, cycloalkyl, and aromatic substituents were studied. The first step of electrooxidation of thioethers affords *o*-benzoquinones. The introduction of the redox-active thioether group extends the range of redox properties of pyrocatechols. In the second step, the thioether fragment is involved in the quasi-reversible anodic process, and the number of electrons participating in the electrode reaction depends on the structure of the hydrocarbon group bonded to the sulfur atom. The reactivity of compounds **1**—**8** toward $O_2^{\bullet -}$ was evaluated on the basis of the electrochemical data. Cyclopentyl, phenyl, or benzyl substituents in the thioether group exert a greater effect on the antiradical activity than the alkyl moieties. The formation of an *o*-semiquinolate radical anion in the reaction of pyrocatechol thioethers with KO_2 was detected by the ESR method. It was shown using the reaction with the stable 2,2-diphenyl-1-picrylhydrazyl radical as an example that RS-functionalized pyrocatechols show a higher antiradical activity compared to 3,5-di-*tert*-butylpyrocatechol.

Key words: cyclic voltammetry, catechol thioethers, redox transformations, antiradical activity, *o*-benzoquinones.

Pyrocatechol fragment is contained in the structures of physiologically active compounds including flavonoids, amines, and alkaloids. It is known that pyrocatechols and hydroquinones, on the one hand, are inhibitors of free radical processes.[1,2] On the other hand, they act as generators of reactive oxygen species (ROS), such as superoxide radical anion and hydrogen peroxide. Pyrocatechols exhibit antibacterial, antitumor, and cytotoxic activity.[3—6] Sulfides are referred to antioxidants involved in the destruction of hydroperoxides without radical species formation.[7] Thioethers prevail in the structures of biologically active compounds and pharmaceuticals.[8] Sulfides containing aromatic groups are suitable building blocks for the synthesis of potent drugs,[9] organic materials, and polymers.[10]

The introduction of chalcogens (S, Se, and Te) into the structures of phenolic antioxidants, synthetic derivatives of tocopherols, and flavonoids, including those containing pyrocatechol moieties, provides new possibilities for the design of polyfunctional antioxidants.[11—13] The majority of antioxidants are electrochemically active compounds and, therefore, the introduction of an additional redox center as a thioether group leads to the extension of the range of redox properties. The oxidation of sulfides forms sulfoxides and sulfones thus favoring an increase in their biological activity.[14]

Antioxidants with thioether groups evoke special interest in the recent time.[15,16] Phenols and hydroquinones, being redox-active compounds, participate in electron transfer reactions. Sulfur-containing *o*- and *p*-benzoquinones have biological activity[17—19] and unusual physicochemical properties,[20—23] due to which they are attractive for using as ligands in coordination chemistry.[24,25]

Electrochemical methods are universally recognized for studying the properties and preparation of redox-modulating agents[26,27] and are considered as a useful tool for modeling biological (metabolic) redox reactions.[28,29] Electrochemical approaches make it possible to evaluate the potential antiradical activity[30,31] and also to explain a possible mechanism of action of the studied compounds.[32,33] In the presence of oxygen, cyclic redox transformations pyrocatechol/*o*-benzoquinone result in

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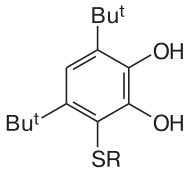
the anti/prooxidant activity of this redox pair due to the possibility of formation of superoxide radical anion.[34]

The present study is aimed at studying the electrochemical transformations of 3-alkylsulfanyl-, 3-cycloalkylsulfanyl-, 3-arylsulfanyl-, and 3-benzylsulfanyl-substituted pyrocatechols **1**—**8**, establishing the mechanism of their oxidation, and evaluating the influence of the thioether group on the reactivity toward superoxide radical anion, KO_2, and diphenylpicrylhydrazyl.



H_2Cat—S—R (**1**—**8**)

1—**8:** R = Bu^n (**1**), C_5H_{11} (**2**), C_6H_{13} (**3**), C_7H_{15} (**4**), C_8H_{17} (**5**), *cyclo*-C_5H_9 (**6**), Ph (**7**), Bn (**8**)

Experimental

Commercially available reagents, *viz.*, 3,5-di-*tert*-butyl-*o*-benzoquinone (98+%, Alfa Aesar), 3,5-di-*tert*-butylpyrocatechol (98%, Aldrich), 1-butanethiol, 1-pentanethiol, 1-hexanethiol, 1-heptanethiol, 1-octanethiol, cyclopentanethiol, thiophenol (98+%, Alfa Aesar), benzylthiol (99%, Alfa Aesar), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical (Aldrich), potassium peroxide KO_2 (Acros Organics), *cis*-dicyclohexano-18-crown-6 (98%, Aldrich), and $Bu_4NOH \cdot 30H_2O$ (>99%, Sigma-Aldrich) were used as received. The solvents used were purified and dehydrated according to standard procedures.[35]

^1H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker AVANCE DPX-200 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. IR spectra were measured on an FSM 1201 FTIR spectrometer in KBr pellets.

Elemental analysis was carried out on Euro EA 3000 (C, H, N) and Analytik Jena multi EA 5000 (C, S, N, Cl) elemental analyzers.

ESR spectra were detected on a Bruker EMX spectrometer (working frequency ~9.5 GHz). Hyperfine coupling constants were determined using simulation of theoretical spectra by the WINEPR Simfonia 1.25 program (Bruker). Electronic absorption spectra were recorded on SF-103 and SF-104 spectrophotometers (in a range of 300—1100 nm) at room temperature.

Electrochemical transformations of compounds **1**—**8** were studied by cyclic voltammetry (CV) in a three-electrode cell with an IPC-pro potentiostat under argon. The supporting electrolyte, 0.1 *M* Bu_4NClO_4 (99%, Acros), was twice recrystallized from aqueous EtOH and dried *in vacuo* at 50 °C for 48 h. The concentration of the studied compounds was 0.5—6.0 mmol L^{-1}. A stationary glassy carbon (GC) electrode (d = 2 mm) (or platinum electrode (Pt) (d = 2 mm)) served as a working electrode, a platinum wire (S = 18 mm^2) was the auxiliary electrode, and Ag/AgCl/KCl with a water-impermeable membrane was the reference electrode.

Microelectrolysis of thioethers **1**—**8** was performed on a PI-50-1.1 potentiostat at stationary platinum electrodes, which were plates with a surface area of 30 mm^2, in a 5-mL undivided three-electrode cell under anaerobic conditions. The Ag/AgCl/KCl electrode with a conducting water-impermeable membrane was used as a reference electrode. Pyrocatechol was added to an electrochemical cell containing a solution of the supporting electrolyte (0.1 *M* Bu_4NClO_4) in acetonitrile. Electrolysis was performed in the potentiostatic mode at a potential of 1.40 V. Microelectrolysis of thioethers **1**—**8** in the presence of oxygen was carried out in the potentiostatic mode at a potential of −1.20 V for 30 min. Thioethers (C = 3 mmol L^{-1}) were introduced into an aerated solution of the supporting electrolyte (0.1 *M* Bu_4NClO_4) in acetonitrile.

The reaction with the electrogenerated superoxide radical anion was performed in acetonitrile under the conditions of CV experiment as follows. Oxygen was preliminarily passed through the solution for 10 min to saturation (3 mmol L^{-1}).[36] Cyclic voltammograms of oxygen reduction were detected in the range from −0.5 to −1.20 V at a potential scan rate of 0.2 V s^{-1} in the absence of pyrocatechols for the determination of the primary current values of the anodic and cathodic peaks. The concentration of pyrocatechols **1**—**8** was varied from 0.5 to 6.0 mmol L^{-1}. The efficiency of superoxide radical anion scavenging by pyrocatechols was estimated from the IC_{50} value (concentration of pyrocatechol necessary for decreasing the superoxide radical anion concentration by 50% (from the initial level based on current)), which depends on the change in the anodic current of superoxide radical anion reoxidation in the presence of additives of pyrocatechols ΔI_{pa} ($\Delta I_{pa} = ((I^i_{pa} - I^0_{pa})/I^0_{pa}) \cdot 100\%$), where I^0_{pa} and I^i_{pa} are the current values of the reoxidation peak of the superoxide radical anion to oxygen in the absence of the studied (I^0_{pa}) compound and in the presence of this compound in concentration i (I^i_{pa}).[37] As the current of the reoxidation peak of the superoxide radical anion decreases by 50% of the initial value, 50% of the electrogenerated superoxide radical anion detected at the reverse CV branch were consumed in the reaction with pyrocatechols. The IC_{50} value was determined from the dependence of ΔI_{pa} of the superoxide radical anion on the pyrocatechol concentration.

Spectroelectrochemical studies were carried out in a three-electrode cell (quartz cuvette). A platinum wire (S = 3 cm^2) was placed in a cuvette containing a 0.1 *M* solution of Bu_4NClO_4 and pyrocatechols **1** or **8** (C = 0.5 mmol L^{-1}), and absorption spectra were recorded in the UV and visible ranges (340—840 nm) using an SF-103 spectrophotometer. The platinum wire served as an auxiliary electrode. The Ag/AgCl/KCl electrode with a conducting water-impermeable membrane was used as a reference electrode.

The reaction of pyrocatechol **2** (C = 1 mmol L^{-1}) with KO_2 (C = 2 mmol L^{-1}) was conducted in anhydrous DMF in the presence of *cis*-dicyclohexano-18-crown-6 (C = 0.05 mol L^{-1}) in order to increase the solubility of KO_2, and the formation of the reaction products was monitored by the ESR method. Electronic absorption spectra were recorded on an SF-104 spectrophotometer in a range of 300—600 nm at room temperature. The reactions of thioethers **4** and **5** (C = 1 mmol L^{-1}) with 1 equiv. KO_2 were carried out in anhydrous DMF in a spectrophotometric cell in the presence of *cis*-dicyclohexano-18-crown-6 (C = 0.05 mol L^{-1}).

The main parameters of the antiradical activity (EC_{50}, TEC_{50}, AE, n_{DPPH}) of the compounds in the reactions with the DPPH

radical were detected in acetonitrile at 298 K. The EC_{50} value (concentration of the antioxidant necessary for decreasing the amount of the DPPH radical by 50% compared to the initial value) was determined after achieving the equilibrium state, which was established in 30—60 min after beginning of the reaction. To determine EC_{50}, the dependence of the residual concentration of the stable radical on the molar ratio expressed in the number of moles of the antioxidant per 1 mole of the stable radical was plotted. The concentration of compounds **1**—**8** was varied from 5 to 50 μmol L^{-1}.

The number of molecules of transformed DPPH radical (n_{DPPH}) was calculated by the equation $n_{DPPH} = C_0(DPPH)/2 \cdot EC_{50}$, where $C_0(DPPH)$ is the initial concentration of the DPPH radical (C = 50 μmol L^{-1}). The antiradical efficiency (AE) was calculated by the equation $AE = 1/(EC_{50} \cdot TEC_{50})$, where TEC_{50} is the time of achievement of the equilibrium state at the antioxidant concentration equal to EC_{50}.

Compounds 1—8 were synthesized using the modified known procedure.[38] A solution of thiol (4.5 mmol) in ethanol (10 mL) was added dropwise to a solution of 3,5-di-*tert*-butyl-*o*-benzoquinone (0.66 g, 3.0 mmol) in ethanol (20 mL) over 4—5 h at room temperature under argon to the complete bleaching of the reaction mixture. The solvent was evaporated under reduced pressure. The formed precipitate was recrystallized from acetonitrile.

4,6-Di-*tert*-butyl-3-(butylsulfanyl)benzene-1,2-diol (1). The yield was 0.41 g (44%). White powder, m.p. 65—67 °C. IR, ν/cm^{-1}: 3502, 3325 (O—H), 2989, 2958, 2930, 2909, 2870 (C—H). ^{1}H NMR, δ: 0.94 (t, 3 H, CH_3, Bu^n, $^3J_{H,H}$ = 7.2 Hz); 1.40 (s, 9 H, Bu^t); 1.45 (m, 2 H, CH_2, Bu^n); 1.49 (s, 9 H, Bu^t); 1.67 (m, 2 H, CH_2, Bu^n); 2.66 (t, 2 H, CH_2, Bu^n, $^3J_{H,H}$ = 7.4 Hz); 5.56 (br.s, 1 H, OH); 6.90 (s, 1 H, C_6H_1); 7.28 (s, 1 H, OH). ^{13}C NMR, δ: 13.67, 22.18, 29.32, 31.47, 35.10, 36.84, 37.58, 115.89, 115.92, 135.85, 140.56, 143.17, 145.23. Found (%): C, 69.96; H, 9.10; S, 10.31. $C_{18}H_{28}O_2S$. Calculated (%): C, 70.08; H, 9.15; S, 10.39.

4,6-Di-*tert*-butyl-3-(pentylsulfanyl)benzene-1,2-diol (2). The yield was 0.42 g (43%). White powder, m.p. 45—77 °C. IR, ν/cm^{-1}: 3502, 3320 (O—H), 2991, 2954, 2927, 2866, 2870 (C—H). ^{1}H NMR, δ: 0.92 (t, 3 H, CH_3, *n*-pentyl, $^3J_{H,H}$ = 6.4 Hz); 1.42 (s, 9 H, Bu^t); 1.25—1.50 (m, 4 H, CH_2, *n*-pentyl); 1.50 (s, 9 H, Bu^t); 1.55—1.85 (m, 2 H, CH_2, *n*-pentyl); 2.67 (t, 2 H, S—CH_2, $^3J_{H,H}$ = 7.4 Hz); 5.58 (s, 1 H, OH); 6.92 (s, 1 H, C_6H_1); 7.30 (s, 1 H, OH). ^{13}C NMR, δ: 13.89, 22.30, 29.09, 29.31, 31.15, 31.46, 35.09, 36.83, 37.84, 115.87, 115.93, 135.82, 140.54, 143.13, 145.20. Found (%): C, 70.72; H, 9.33; S, 9.95. $C_{19}H_{30}O_2S$. Calculated (%): C, 70.76; H, 9.38; S, 9.94.

4,6-Di-*tert*-butyl-3-(hexylsulfanyl)benzene-1,2-diol (3). The yield was 0.50 g (49%). White powder, m.p. 48 °C. IR, ν/cm^{-1}: 3502, 3275 (O—H), 2991, 2957, 2930, 2917, 2866 (C—H). ^{1}H NMR, δ: 0.90 (t, 3 H, CH_3, J = 6.2 Hz); 1.20—1.40 (m, 6 H, CH_2); 1.41 (s, 9 H, Bu^t); 1.50 (s, 9 H, Bu^t); 1.55—1.80 (m, 2 H, CH_2); 2.66 (t, 2 H, CH_2S, J = 7.4 Hz); 5.58 (br.s, 1 H, OH); 6.91 (s, 1 H, C_6H_1); 7.29 (s, 1 H, OH). ^{13}C NMR, δ: 13.99, 22.48, 28.68, 29.31, 29.39, 31.40, 31.47, 35.09, 36.83, 37.87, 115.87, 115.94, 135.82, 140.55, 143.14, 145.20. Found (%): C, 71.32; H, 9.50; S, 9.50. $C_{20}H_{32}O_2S$. Calculated (%): C, 71.38; H, 9.58; S, 9.53.

4,6-Di-*tert*-butyl-3-(heptylsulfanyl)benzene-1,2-diol (4). The yield was 0.47 g (45%). White powder, m.p. 47 °C. IR, ν/cm^{-1}: 3495, 3320 (O—H), 2991, 2988, 2957, 2927, 2863 (C—H). ^{1}H NMR, δ: 0.90 (t, 3 H, CH_3, J = 6.0 Hz); 1.20—1.40 (m, 8 H, CH_2); 1.41 (s, 9 H, Bu^t); 1.49 (s, 9 H, Bu^t); 1.55—1.75 (m, 2 H, CH_2); 2.66 (t, 2 H, CH_2S, J = 7.4 Hz); 5.57 (br.s, 1 H, OH); 6.91 (s, 1 H, C_6H_1); 7.28 (s, 1 H, OH). ^{13}C NMR, δ: 14.03, 22.57, 28.87, 28.98, 29.32, 29.42, 31.47, 31.66, 35.10, 36.83, 37.86, 115.88, 115.94, 135.82, 140.55, 143.14, 145.21. Found (%): C, 71.92; H, 9.74; S, 9.13. $C_{21}H_{34}O_2S$. Calculated (%): C, 71.95; H, 9.78; S, 9.15.

4,6-Di-*tert*-butyl-3-(octylsulfanyl)benzene-1,2-diol (5). The yield was 0.72 g (66%). White powder, m.p. 65—67 °C. IR, ν/cm^{-1}: 3496, 3319 (O—H), 2984, 2957, 2924, 2852 (C—H). ^{1}H NMR, δ: 0.89 (t, 3 H, CH_3, J = 6.1 Hz); 1.20—1.40 (m, 10 H, CH_2); 1.41 (s, 9 H, Bu^t); 1.49 (s, 9 H, Bu^t); 1.55—1.80 (m, 2 H, CH_2); 2.66 (t, 2 H, CH_2S, J = 7.4 Hz); 5.56 (br.s, 1 H, OH); 6.91 (s, 1 H, C_6H_1); 7.27 (s, 1 H, OH). ^{13}C NMR, δ: 14.05, 22.61, 29.02, 29.10, 29.17, 29.32, 29.41, 31.47, 31.77, 35.10, 36.83, 37.87, 115.88, 115.94, 135.82, 140.54, 143.15, 145.21. Found (%): C, 72.50; H, 9.91; S, 8.80. $C_{22}H_{36}O_2S$. Calculated (%): C, 72.48; H, 9.95; S, 8.79.

4,6-Di-*tert*-butyl-3-(cyclopentylsulfanyl)benzene-1,2-diol (6). The yield was 0.67 g (70%). White powder, m.p. 68 °C. IR, ν/cm^{-1}: 3485, 3275 (O—H), 2957, 2907, 2867 (C—H). ^{1}H NMR, δ: 1.42 (s, 9 H, Bu^t); 1.50 (s, 9 H, Bu^t); 1.55—1.85 (m, 6 H, CH_2, cyclopentyl); 1.90—2.15 (m, 2 H, CH_2, cyclopentyl); 3.14 (q, 1 H, CH, cyclopentyl, $^3J_{H,H}$ = 7 Hz); 5.58 (s, 1 H, OH); 6.92 (s, 1 H, C_6H_1); 7.27 (s, 1 H, OH). ^{13}C NMR, δ: 24.47, 29.31, 31.70, 33.93, 35.08, 36.93, 51.07, 115.80, 115.99, 135.80, 140.43, 143.28, 145.62. Found (%): C, 71.18; H, 8.76; S, 9.94. $C_{19}H_{28}O_2S$. Calculated (%): C, 71.21; H, 8.81; S, 10.00.

4,6-Di-*tert*-butyl-3-(phenylsulfanyl)benzene-1,2-diol (7). The yield was 0.62 g (63%). White powder, m.p. 85—87 °C. IR, ν/cm^{-1}: 3536, 3374 (O—H), 3073, 3055 (C—H аром.), 3001, 2961, 2913, 2869 (C—H). ^{1}H NMR, δ: 1.44 (s, 9 H, Bu^t); 1.46 (s, 9 H, Bu^t); 5.61 (s, 1 H, OH); 6.82 (s, 1 H, C_6H_1); 6.88—7.02 (m, 2 H, Ph); 7.06 (s, 1 H, OH); 7.10—7.35 (m, 3 H, Ph). ^{13}C NMR, δ: 29.30, 31.30, 35.28, 36.78, 110.89, 116.59, 125.27, 125.48, 129.14, 136.34, 137.28, 140.94, 144.03, 145.44. Found (%): C, 73.10; H, 7.40; S, 9.74. $C_{20}H_{24}O_2S$. Calculated (%): C, 73.13; H, 7.37; S, 9.76.

3-(Benzylsulfanyl)-4,6-di-*tert*-butylbenzene-1,2-diol (8). The yield was 0.48 g (46%). White powder, m.p. 90—92 °C. IR, ν/cm^{-1}: 3486, 3259 (O—H), 3089, 3062 (C—H arom.), 2958, 2910, 2870 (C—H). ^{1}H NMR, δ: 1.43 (s, 9 H, Bu^t); 1.53 (s, 9 H, Bu^t); 3.84 (s, 2 H, CH_2); 5.56 (br.s, 1 H, OH); 6.95 (s, 1 H, C_6H_1); 7.30 (s, 1 H, OH); 7.24—7.36 (m, 5 H, Ph). ^{13}C NMR, δ: 29.31, 31.54, 35.15, 36.90, 42.22, 115.30, 116.05, 127.65, 128.79, 128.90, 136.28, 136.84, 140.74, 143.30, 145.40. Found (%): C, 73.60; H, 7.68; S, 9.30. $C_{21}H_{26}O_2S$. Calculated (%): C, 73.64; H, 7.65; S, 9.36.

4,6-Di-*tert*-butyl-3-(pentylsulfanyl)-*o*-benzoquinone (9) was synthesized by the oxidation of pyrocatechol **2** (0.3225 g, 0.001 mol) in diethyl ether (40 mL) with an aqueous solution of $K_3Fe(CN)_6$ (5 equiv.) in an alkaline medium of KOH (0.112 g). The product was extracted with diethyl ether and washed with water twice. Pure *o*-benzoquinone **9** was obtained by chromatography of the reaction mixture using a hexane—ethyl acetate (1 : 1) mixture as an eluent. The yield was 0.195 g (61%), m.p. 15—17 °C. IR, ν/cm^{-1}: 1655, 1672, 1736 (C=O), 2873, 2931, 2961 (C—H). ^{1}H NMR, δ: 0.75—0.85 (m, 3 H, CH_3); 1.18 (s, 9 H, Bu^t); 1.20—1.35 (m, 6 H, 3 CH_2, C_5H_{11}); 1.43 (s, 9 H, Bu^t); 2.45—2.60 (m, 2 H, SCH_2, C_5H_{11}); 6.92 (s, 1 H, C_6H_1). ^{13}C NMR, δ: 12.86, 21.11, 26.60, 27.58, 28.73, 30.22, 34.05, 36.09, 40.14, 116.55, 135.91, 146.62, 159.98, 178.81, 181.23. Found (%): C, 70.81; H, 9.30; S, 9.98. $C_{19}H_{30}O_2S$. Calculated (%): C, 70.76; H, 9.38; S, 9.94.

Results and Discussion

Many works are devoted to electrosynthesis of pyrocatechol thioethers containing various heterocyclic fragments.[39—43] However, data on the redox properties and mechanism of electrochemical transformations of similar compounds are lacking. In this work, a series of asymmetrical thioethers **1**—**8** was obtained by the reactions of 3,5-di-*tert*-butyl-*o*-benzoquinone with various thiols.[44] The electrochemical properties of thioethers **1**—**8** were studied by cyclic voltammetry (CV) in acetonitrile at the GC electrode. The redox potentials of the studied compounds are presented in Table 1. The electrooxidation of sulfides **1**—**8** proceeds similarly in two consecutive steps in acetonitrile at the potential scan to +1.80 V (Fig. 1).

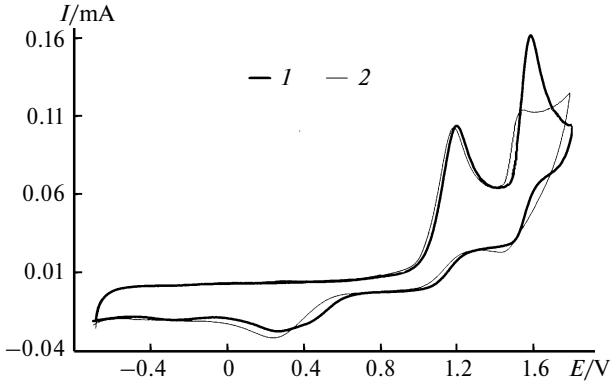


Fig. 1. CV curves of the oxidation of thioethers **4** (*1*) and **8** (*2*) in the potential scan range from −0.7 to +1.8 V (MeCN, GC anode, Ag/AgCl/KCl, 0.1 *M* NBu_4ClO_4, *C* = 3 mmol L^{-1}, *v* = 0.2 V s^{-1}, argon).

The first two-electron peak is irreversible and corresponds to the oxidation of the pyrocatechol fragment. The length of the alkyl group does not affect the values of oxidation potentials of compounds **1**—**5**. On going from compound **3** to compound **7**, the oxidation potential insignificantly shifts to the anodic region (0.04 V). The presence of the thioether group in the pyrocatechol fragment favors the anodic shift of the oxidation potentials of compounds **1**—**8** compared to 3,5-di-*tert*-butylpyrocatechol (+1.11 V), which indicates its electron-acceptor character. The cathodic peak observed on the reverse branches of voltammograms in the range from 0.44 to 0.30 V presumably corresponds to the reduction of the H^+Q—S—R species formed due to the chemical reaction following the electron transfer.[45] The ECE mechanism takes place for pyrocatechols in aprotic organic solvents, and two EC steps (E is the electrochemical stage, and C is the chemical stage) converge into one electrode process.[45,46] The electrochemical oxidation of thioethers **1**—**8** primarily results in the generation of an unstable dication undergoing partial deprotonation in a solution (Scheme 1).

The use of the platinum anode made it possible to detect the reduction peak for the H^+Q—S—R species and proton (−0.03 V), which was identified by the addition of concentrated perchloric acid. The values of oxidation potentials for sulfides **1**—**8** at the GC or Pt anodes are almost identical.

The introduction of the thioether group results in the extension of the range of redox properties of the studied compounds due to the appearance of an additional redox transition at 1.54—1.63 V (see Table 1). It is known that the electrochemical oxidation of sulfides, depending on the structure, solvent nature, and the presence of a nucleophilic reagent, proceeds as one- or two-electron process.[47] The studied thioethers can be divided into two groups. The first group contains compounds **1**—**5**

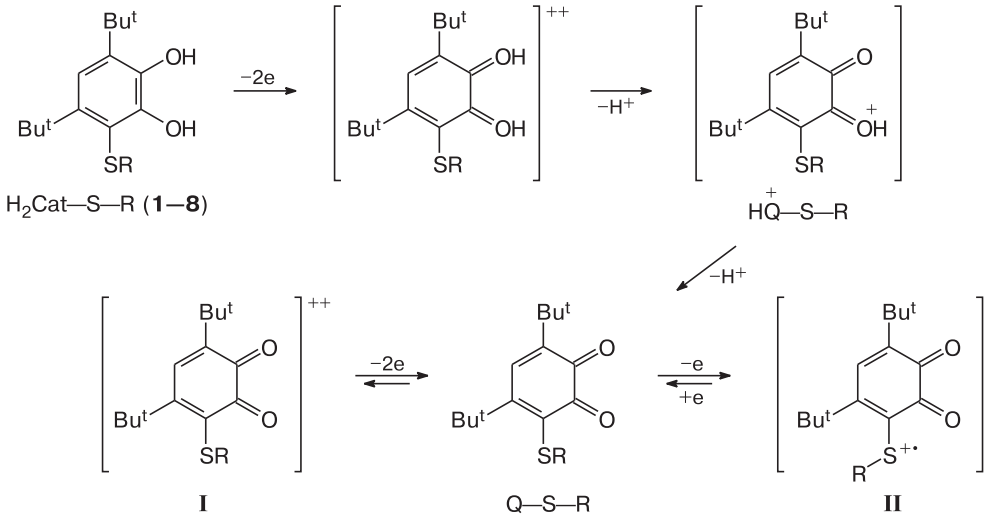
Table 1. Oxidation potentials of compounds **1**—**9** according to the CV data*

Compound	E^{ox1}	E^{ox2}	$E^{ox}_{1/2}$	I_c/I_a	$-E^{red}_{1/2}$(Q/SQ)/V	E^{ox}(CatH—S—R)/V
	V					
1	1.20	1.60	1.55	0.38	0.40	−0.07
2	1.21	1.59	1.54	0.33	0.41	−0.06
3	1.19	1.60	1.55	0.33	0.40	−0.07
4	1.20	1.59	1.55	0.40	0.39	−0.08
5	1.20	1.59	1.54	0.39	0.40	−0.08
6	1.21	1.59	1.55	0.58	0.41	−0.06
7	1.23	1.63	1.60	0.40	0.37	0.01
8	1.18	1.54	1.51	0.70	0.40	−0.05
9	1.58	—	—	—	0.41	—

Note. E^{ox1} and E^{ox2} are potentials of the anodic peaks, $E^{ox}_{1/2}$ is the half-wave potential for the second quasi-reversible oxidation peak, I_c/I_a is the ratio of currents of the reverse cathodic and direct anodic peaks, $E^{red}_{1/2}$(Q/SQ) is the half-wave potential for the reduction of electrogenerated *o*-benzoquinones (Q) to *o*-benzosemiquinones (SQ), and E^{ox}(CatH—S—R) is the potential of the oxidation peak of the singly deprotonated form of pyrocatechol thioethers.

* GC electrode, MeCN, *v* = 0.20 V s^{-1}, 0.1 *M* NBu_4ClO_4, *C* = 3 mmol L^{-1}, Ar, Ag/AgCl/KCl (sat.).

Scheme 1



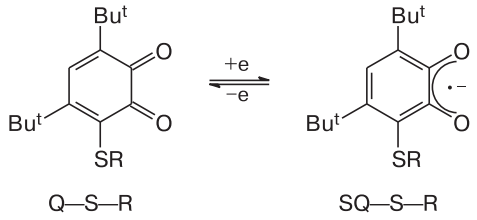
(see Fig. 1, curve *1*), which are characterized by the participation of two electrons in the second anodic process (see Scheme 1, dication **I**), and thioethers **6**—**8** characterized by the one-electron level based on current are in the second group (see Fig. 1, curve *2*).

The low stability of dications **I** generated by the electrooxidation of compounds **1**—**5** (see Table 1, ratio I_c/I_a) indicates the chemical step following the electron transfer: the C—S bond cleavage and formation of sulfoxides, sulfones, or sulfonium salts.[47] The formation of relatively stable radical cations (see Scheme 1, radical cation **II**) is detected for the compounds with the cyclopentyl or benzyl groups. A similar electrochemical pattern was observed earlier in dimethylformamide at a potential of 1.65 V ($I_c/I_a = 0.53$) for 3,6-di-*tert*-butyl-*o*-benzoquinone containing annelated 1,2-diethiete ring.[22]

Microelectrolyses of compounds **1**—**8** (2 h) at a controlled potential value +1.40 V were conducted to confirm the formation of *o*-quinones. A considerable decrease in the intensity of the first oxidation peak at the pyrocatechol fragment (conversion reaches 80%) is observed in the CV curves of the electrolysis products, and the second anodic peak remains unchanged by current and potential (Fig. 2). The cathodic region exhibits the quasi-reversible one-electron peak corresponding to the redox transition *o*-benzoquinone/*o*-benzosemiquinone (Q—S—R/SQ—S—R) (Scheme 2).

The bands corresponding to stretching vibrations of the C=O bonds of *o*-quinones (1640—1670 cm^{-1}) are observed in the IR spectra of the electrolysis products. The UV-visible absorption spectrum of the electrolysis products exhibits an intense absorption maximum at 500—510 nm. The spectroelectrochemical studies of compounds **1** and **8** at an oxidation potential of +1.40 V are accompanied by the appearance in the visible range of an

Scheme 2



absorption maximum at 505 nm, whose intensity increases with time, confirming the formation of the corresponding *o*-benzoquinones (Figs 3 and 4).

Compounds containing quinonoid fragment and thioether group are considered as efficient phototriggers, the mechanism of action of which is based on the intramo-

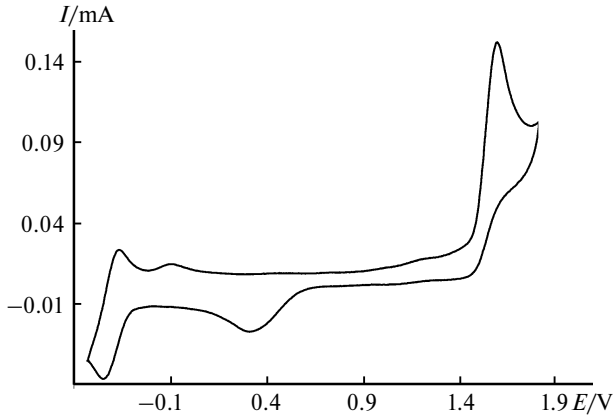


Fig. 2. CV curve of the oxidation of the product of exhaustive electrolysis of thioether **2** (2 h) obtained at an electrolysis potential of 1.40 V (MeCN, GC electrode, Ag/AgCl/KCl, 0.1 *M* NBu_4ClO_4, $C(\mathbf{2}) = 3$ mmol L^{-1}, $v = 0.2$ V s^{-1}, argon).

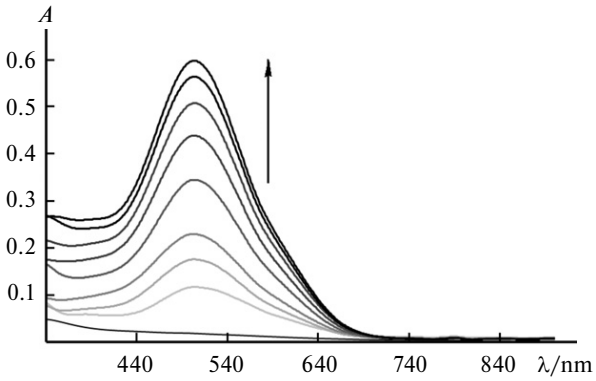


Fig. 3. Changes in the electronic absorption spectrum of compound **1** during electrolysis (45 min) at a controlled potential of +1.40 V (Ag/AgCl/KCl) (C = 0.5 mmol L^{-1}, MeCN).

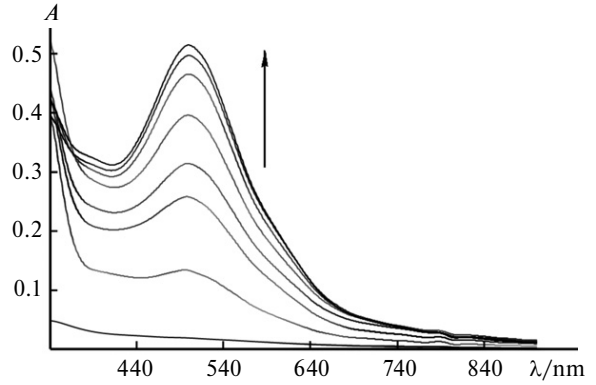


Fig. 4. Changes in the electronic absorption spectrum of compound **8** during electrolysis (60 min) at a controlled potential of +1.40 B (Ag/AgCl/KCl) (C = 0.5 mmol L^{-1}, MeCN).

lecular redox reaction of benzoquinones with the sulfide bridge. The broad absorption bands in the visible spectral range is a characteristic feature of this type of compounds.[48] The absorption band in the visible spectral range for electrogenerated *o*-benzoquinones corresponds to the partial intramolecular charge transfer between the boundary redox orbitals (HOMO—LUMO) involving the thioether group and *o*-quinone fragment.[21,22,48] The energy band gap value (ΔE) calculated from the spectral data (parameter of absorption edge of the absorption spectrum) is 2.2 eV, on the average, for the synthesized *o*-quinones. The electrochemical data can be used for the determination of $\Delta E = E^{ox}_{1/2} - E^{red}_{1/2}$ only for the *o*-quinones generated from compounds **6**—**8**, which are characterized by one-electron oxidation. As a result, values of 1.96, 1.97, and 1.91 eV close to those calculated by the spectral data were obtained for compounds **6**, **7**, and **8**, respectively.

For electrogenerated *o*-quinones, the nature of the hydrocarbon group at the sulfur atom exerts no pronounced effect on the potential values for the redox pair *o*-quinone/*o*-semiquinone. The introduction of the sulfur atom into the *o*-quinonoid ring results in the shift of the reduction potential to the anodic range by 0.04 V compared to 3,5-di-*tert*-butyl-*o*-benzoquinone, which agrees with the electron-acceptor effect of the heteroatom. The electrochemical activity of 4,6- di-*tert*-butyl-3-pentylthio-*o*-benzoquinone (**9**) obtained by the counter synthesis is analogous to that of the electrolysis product generated by the electrooxidation of compound **2** (see Table 1).

Quinonoid/pyrocatechol (hydroquinone) fragment is a moiety of many natural compounds with diverse biological activity. The presence of the sulfide fragment, which is transformed into sulfone upon oxidation, makes it possible to enhance the pharmacological activity of quinonoid compounds.[14] The redox potential value of the quinone/hydroquinone (pyrocatechol) pair is used for the prediction of anti/prooxidant activity. The ratio of the oxidized/reduced forms affects the balance of cytotoxic and cytoprotector properties of compounds of this type.[49,50] One of intermediates involved in the redox cycle of quinones is superoxide radical anion, which includes in the pull of reactive oxygen species. Superoxide radical anion finds use in electrocatalysis and synthesis of organic compounds and is also applied for neutralization of dangerous chemical waste.[51,52] Owing to this, the reactions of pyrocatechol thioethers with superoxide radical anion were studied under the conditions of CV experiment using spectral methods (UV-visible and ESR spectroscopy), as well as their reactions with KO_2. The CV method enables one to monitor changes in oxygen or analyte in the course of the reaction.

The electrochemical pattern changes upon the introduction of pyrocatechols into the solution (Figs 5 and 6). A prepeak (*A*) appears in the direct branch of the voltammogram at the potential shifted to the anodic region. In the reverse branch of the voltammogram, the anodic peak of superoxide radical anion oxidation (*C*) decreases by current and an additional peak (*B*) appears in the potential range from −0.08 to 0.01 V. An increase in the pyrocatechol concentration decreases the reversibility of oxygen reduction with a decrease in the anodic peak current (*C*). This fact is explained by the participation of the electrogenerated superoxide radical anion in the homogeneous chemical reaction in a solution. The changes observed allow one to evaluate the reactivity of pyrocatechol thioethers toward superoxide radical anion from a change in the IC_{50} parameter.

To estimate the efficiency of $O_2^{\bullet -}$ scavenging, we used the equation proposed earlier[37] for the calculation of IC_{50} from a change in the anodic current of oxidation of the superoxide radical anion in the presence of pyrocatechol additives: $\Delta I_{pa} = ((I^i_{pa} - I^0_{pa})/I^0_{pa}) \cdot 100\%$. When the initial peak current value of the reoxidation of superoxide radical anion to oxygen (I^0_{pa}) decreases by 50% in the presence of pyrocatechol, 50% of formed $O_2^{\bullet -}$ detected on the reverse branch of the voltammogram were consumed

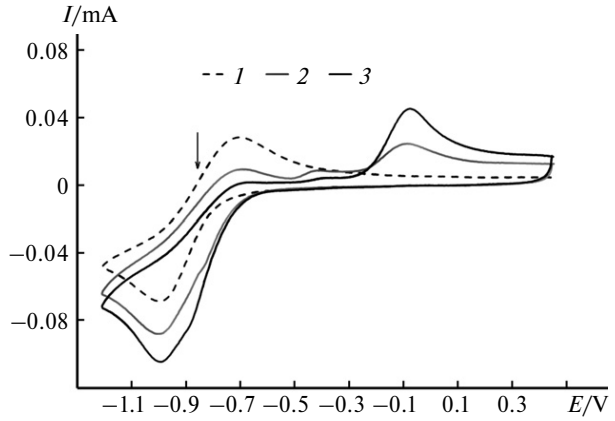


Fig. 5. CV curves of oxygen reduction in the absence (*1*) and in the presence of compound **4** in concentrations of 2 (*2*) and 4 mmol L^{-1} (*3*). Potential scan range from +0.5 to −1.20 V (MeCN, GC electrode, Ag/AgCl/KCl, 0.1 *M* NBu_4ClO_4, $v = 0.2$ V s^{-1}). Here and in Fig. 6, arrow shows the direction of an intensity decrease in the current of superoxide radical anion reoxidation with an increase in the concentration of introduced pyrocatechol.

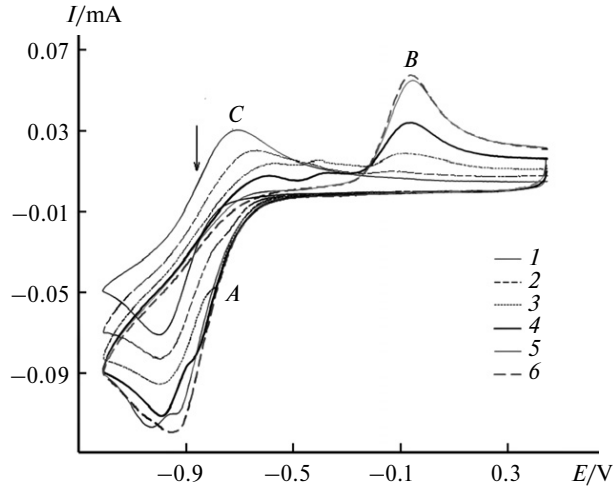


Fig. 6. CV curves of oxygen reduction in the absence (*1*) and in the presence of compound **2** in concentrations of 0.5 (*2*), 1 (*3*), 2.5 (*4*), 4 (*5*), and 5 mmol L^{-1} (*6*) (MeCN, GC electrode, Ag/AgCl/KCl, 0.1 *M* NBu_4ClO_4, $v = 0.2$ V s^{-1}).

in the reaction with pyrocatechol. Therefore, the concentration of pyrocatechols (*i*) necessary for achieving this ΔI_{pa} value can be considered as IC_{50}. The parameter of IC_{50} for catechol thioethers **1**—**5** was registered in the narrow range from 3.8 to 4.2 mmol L^{-1}, as well as for 3,5-di-*tert*-butylpyrocatechol (3.8 mmol L^{-1}). The minimum values of IC_{50} were obtained for sulfides **6** and **7** and are equal to 3.6 and 3.2 mmol L^{-1}, respectively. For compound **8**, IC_{50} is 4.5 mmol L^{-1}. Sterically hindered pyrocatechol and its thioethers **1**—**8** manifest moderate activity toward $O_2^{\bullet -}$, being at the level of retinoic acid and biotin and exceeding the data for α-tocopherol.[37]

The value of conversion of pyrocatechols to *o*-benzoquinones under the microelectrolysis conditions (−1.20 V, 30 min) was used as an additional parameter that characterizes the reactivity of compounds **1**—**8** toward $O_2^{\bullet -}$. The conversion of compounds **1**—**8** was estimated by a decrease in the anodic peak current at 1.18—1.20 V corresponding to the oxidation of the pyrocatechol moiety. It was found that with the elongation of the alkyl group the conversion of pyrocatechols to *o*-benzoquinones increases as follows: 44% (**1**) < 47% (**2**) < 50% (**3**) < 59% (**4**) < 65% (**5**). The maximum value equal to 77% was obtained for compound **6** containing the cyclopentane residue. The replacement of alkyl groups by phenyl (compound **7**) or benzyl (compound **8**) substituents decreases the conversion to 40%. The conversion for 3,5-di-*tert*-butylpyrocatechol is 45%, which is close to the results obtained for compound **1**. Therefore, the introduction of the thioether group with linear (C_6—C_8) or cyclic (cyclopentyl) alkyl substituents leads to the enhancement of the reactivity of sulfides toward $O_2^{\bullet -}$ compared to 3,5-di-*tert*-butylpyrocatechol.

The prepeak (*A*) in the CV curves was earlier detected for flavonoids containing pyrocatechol fragment and pyrocatechols with electron-acceptor groups.[53,54] The formation of this peak was explained[54] by the formation of a complex stabilized by hydrogen bonds between the oxygen radical anion and substrate. The quantum chemical calculations performed recently for unsubstituted pyrocatechol also confirmed the existence of a similar complex.[55] The peak of oxidation of the reaction product (*B*) was observed in the present study along with the prepeak (*A*) in the CV curves of oxygen reduction in the presence of pyrocatechol thioethers **1**—**8**.

To elucidate the nature of the formed intermediate (*B*), we studied the reactions of compounds **1**—**8** with tetrabutylammonium hydroxide. The introduction of 2 equiv. NBu_4OH into a solution of pyrocatechols **1**—**8** leads to the disappearance of the redox transition for the pyrocatechol fragment and the appearance of a new oxidation peak in the potential range from 0.01 to −0.08 V. It should be mentioned that the second anodic step corresponding to the oxidation at the sulfur atom remains unchanged (Fig. 7). The introduction of 1 equiv. NBu_4OH favors a twofold decrease in the current of the oxidation peak of the pyrocatechol group and the appearance of an anodic peak identical to that appeared upon the addition of 2 equiv. NBu_4OH. A similar behavior was earlier observed for 3,5-di-*tert*-butylpyrocatechol, which is explained by monoanion formation.[56] The dianion can be formed as a result of the disproportionation of the *o*-semiquinone radical or during its one-electron reduction at the electrode. The highly basic dianion is protonated to the monoanion by ethanol or trace amounts of water present in the solvent. The potentials of the oxidation peaks of the monoanions (see Table 1) are identical to the potentials of the oxidation peaks (*B*) detected in the reverse branches

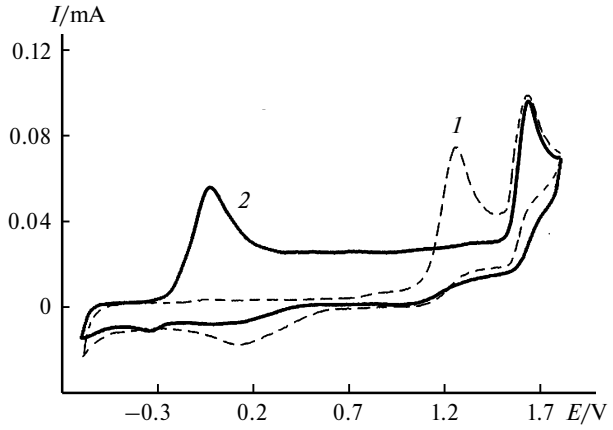


Fig. 7. CV curves of the oxidation of pyrocatechol **1** in the absence (*1*) and in the presence of a solution of 2 equiv. NBu_4OH in EtOH (*2*) (MeCN, C(**1**) = 2 mmol L^{-1}, GC anode, Ag/AgCl/KCl, 0.1 M NBu_4ClO_4, v = 0.2 V s^{-1}).

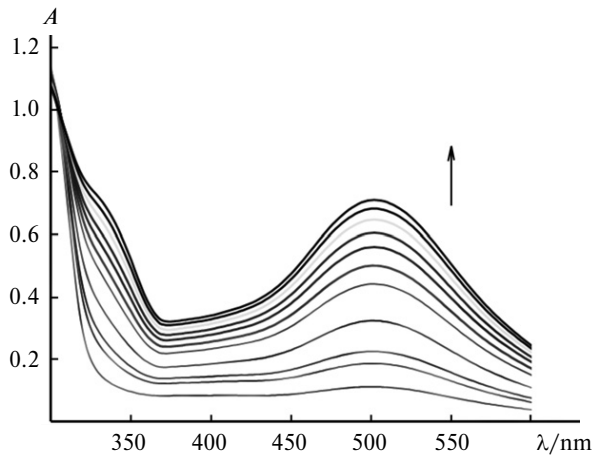


Fig. 9. Changes in the electronic absorption spectrum of compound **5** (C = 1 mmol L^{-1}) during 90 min after the addition of 1 equiv. KO_2 in the presence of *cis*-dicyclohexano-18-crown-6 (C = 0.05 mol L^{-1}) (298 K, solvent DMF).

of the CV curves (see Figs 5 and 6). In the presence of a base, the pulse potential scan from −0.75 to 0.30 V made it possible to establish the quasi-reversible redox transition at a potential of −0.40 V (Fig. 8) corresponding to the reduction of *o*-benzoquinone.

The reactions of pyrocatechol thioethers **4** and **5** with KO_2 were studied in dimethylformamide in the presence of *cis*-dicyclohexano-18-crown-6. The introduction of KO_2 into a solution of pyrocatechol **4** leads to the coloration of the solution within 30—90 min, which is accompanied by fast changes in the absorption spectrum (Fig. 9) in which a broad band at λ = 500—510 nm and a shoulder in a range of 320—330 nm appear. These changes are similar to those considered above and correspond to the formation of *o*-quinone and the corresponding monoanion.[56]

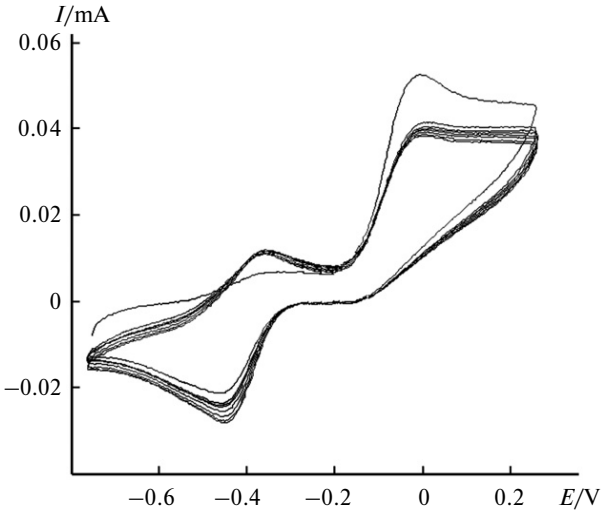


Fig. 8. CV curves of the oxidation of pyrocatechol **8** in the presence of a solution of 2 equiv. NBu_4OH in EtOH supplying pulses in the potential scan range from −0.75 to 0.30 V (MeCN, C(**8**) = 2 mmol L^{-1}, GC anode, Ag/AgCl/KCl, 0.1 M NBu_4ClO_4, v = 0.2 V s^{-1}) (see text).

o-Benzoquinones observed in the reactions are the final products of the reactions of the superoxide radical anion with pyrocatechols and, hence, the question about the mechanism of their formation remains principal. 2-Hydroxyphenoxyl radical formed upon hydrogen atom transfer or *o*-semiquinone radical anion generated by the one-electron transfer coupled with the abstraction of two protons can act as the major intermediates. The reactions of pyrocatechols with KO_2 in DMF were studied by the ESR method for compound **2** used as an example.

The reaction with potassium peroxide leads to the oxidation of pyrocatechol to form the corresponding *o*-semiquinone derivative, whose ESR spectrum represents a doublet with the isotropic g factor equal to 2.0049 (Fig. 10). The hyperfine coupling constant (HFC) of a lone electron with the proton in position 5 of the aromatic ring of the *o*-semiquinone radical is $a_i(^1H)$ = 2.95 Oe. The spectrum intensity decreases rapidly with time and becomes lower by approximately 20 times within 15 min, which is explained by the disproportionation of the *o*-semiquinone radical to *o*-quinone.

Thus, this is the *o*-semiquinone radical anion the formation of which was detected. This fact together with the electrochemical and spectral data provides understanding of the mechanism of the reactions of the superoxide radical anion with the studied pyrocatechols (Scheme 3).

The complex between the superoxide radical anion and pyrocatechol is primarily formed and detected only during the CV experiment, and then electron and two protons are transferred leading to the *o*-semiquinone radical anion. The disproportionation of the latter favors the generation of *o*-quinone observed in the UV-visible spectrum and in

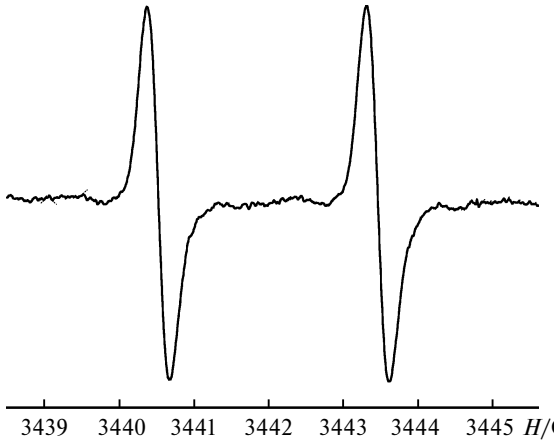


Fig. 10. ESR spectrum of potassium *o*-semiquinolate (derivative of $H_2Cat—S—C_5H_{11}$) formed by the reaction of compound **2** (C = 1 mmol L^{-1}) with KO_2 (C = 2 mmol L^{-1}) in DMF in the presence of *cis*-dicyclohexano-18-crown-6 (C = 0.05 mol L^{-1}) (293 K).

the voltammograms, as well as the dianion easily protonated to the monoanion, the oxidation of which is observed in the reverse branches of the CV curves. The scheme proposed for transformations of pyrocatechol thioethers is consistent with the recent results taking into account the electron transfer coupled with the abstraction of two protons.[54,55]

Various substituents in the thioether group of pyrocatechols **1**—**8** affect their reactivity toward superoxide radical anion. It seemed interesting to study whether a similar dependence exists in the case the stable 2,2-diphenyl-1-picrylhydrazyl radical scavenging often used for the estimation of antiradical activity of mono- and polyphenolic compounds.[57] The reactions of thioethers **1**—**8** with DPPH were carried out in a deaerated solution of MeCN (298 K). The introduction of compounds **1**—**8** into the solution containing DPPH radical results in a decrease in the intensity of the absorption maximum at 517 nm. The antiradical activity of thioethers was determined from changes in EC_{50}, TEC_{50}, and antiradical efficiency (AE) as a complex parameter capable of estimating both the ability of a compound to abstract oxygen atom and the rate of its reaction with DPPH radical. The comparative data on the antiradical activity are presented in Table 2. As a whole, pyrocatechol thioethers exhibit a fairly high antiradical activity comparable with that of gallic acid esters.[58] The minimum EC_{50} values were obtained for compounds **6**—**8**, which is consistent with the data on their reactions with the superoxide radical anion.

An increase in the number of carbon atoms in the hydrophobic alkyl group for thioethers **1**—**5** does not lead to a significant change in EC_{50} and TEC_{50} parameters. The presence of the thioether group in the pyrocatechol structure favors a decrease in the time of achievement of the equilibrium state compared to 3,5-di-*tert*-butylpyrocatechol, which indicates an increase in the antiradical activity of thioethers. It should be mentioned that a decrease in the TEC_{50} parameter for thioethers **6**—**8** would considerably affect their reactivity toward short-lived free radicals formed in biological systems, which is confirmed in the reactions with the superoxide radical anion. The

Scheme 3

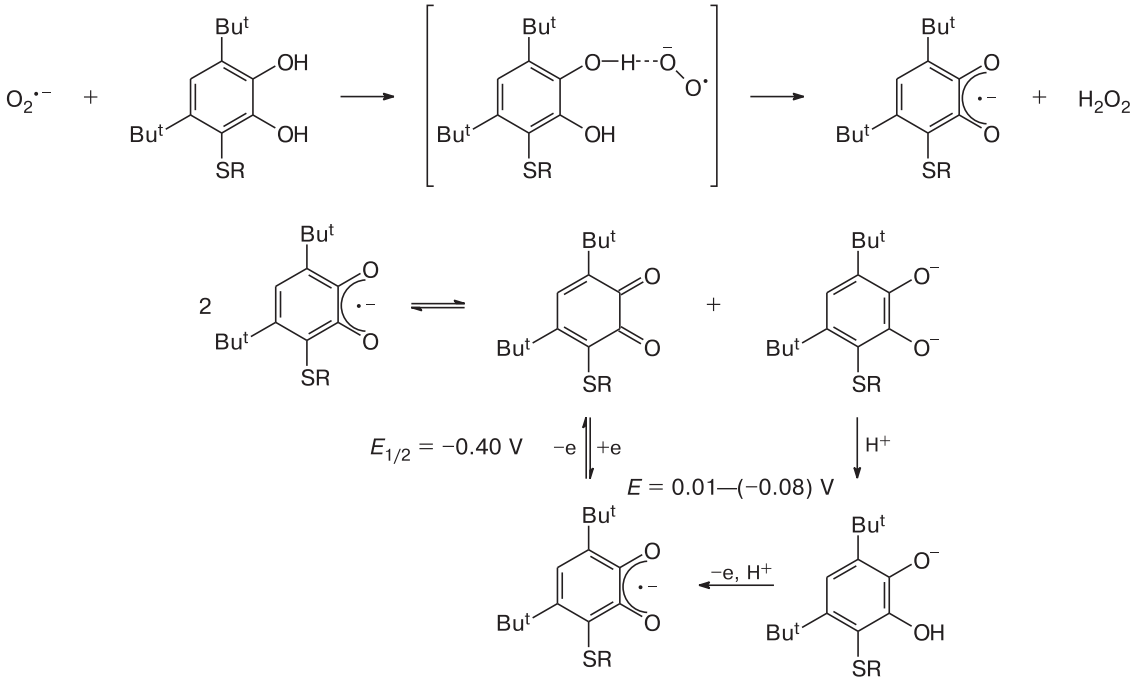


Table 2. Parameters of antiradical activity of compounds **1—8** and 3,5-di-*tert*-butylpyrocatechol in the test with the DPPH radical (MeCN, 298 K)

Compound	EC_{50} /μmol L^{-1}	TEC_{50} /min	$AE \cdot 10^3$
1	12.0±0.5	50	1.67
2	16.0±0.4	40	1.56
3	15.9±0.7	40	1.57
4	12.8±0.3	50	1.56
5	14.5±0.6	40	1.72
6	11.1±0.9	35	2.57
7	12.0±0.7	40	2.08
8	11.5±0.4	32	2.71
3,5-Di-*tert*-butylpyrocatechol	13.1±1.3	60	1.33

number of transformed molecules of diphenylpicrylhydrazyl (n_{DPPH}) for compounds **2**, **3**, and **5** is less than two. The most part of compounds have the value of $n_{DPPH} \geq 2$. The obtained results agree with the electrochemical data on the number of electrons transferring in the first anodic step. The AE (antiradical efficiency) parameter enables one to evaluate the studied compounds in comparison. According to the previously proposed classification,[59] thioethers **1—8** are characterized by a medium AE ($AE > 1 \cdot 10^{-3}$). In the case of compounds **6—8**, the presence of the thioether group in combination with cyclopentyl, phenyl, or benzyl substituent results in an increase in the reactivity of the pyrocatechol moiety toward both superoxide radical anion and DPPH.

To conclude, in this work we studied the influence of the thioether fragment on the electrochemical properties and antiradical activity of the series of asymmetrical pyrocathehol thioethers. It is shown that the introduction of the thioether functional group favors the extension of the range of redox properties of compounds **1—8** due to the possibility of sulfide bridge oxidation. In the first step, the electrooxidation of thioethers affords *o*-benzoquinones for which the reduction potentials of the redox pair *o*-benzoquinone/*o*-benzosemiquinone were determined. The second oxidation step involves the thioether fragment, and the number of electrons participating in the electrode reaction depends on the structure of the hydrocarbon group bonded to the sulfur atom. The reactions of compounds **1—8** with the superoxide radical anion and KO_2 were studied using a combination of electrochemical and spectral methods. A comparative evaluation of the reactivity enabled us to establish that cyclopentyl, phenyl, and benzyl substituents in the thioether group exert a higher effect on the antiradical activity than alkyl fragments do. The mechanism was proposed for the reaction of the superoxide radical anion with pyrocatechols taking into account the one-electron transfer coupled with the abstraction of two protons. The main parameters of antiradical activity of compounds **1—8** were determined in the test with the DPPH radical. It was found that the presence of the thioether group favors a decrease in the reaction time and, hence, an increase in the radical scavenging efficiency. Sulfides **1—8** exhibit a higher antiradical activity than 3,5-di-*tert*-butylpyrocatechol.

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