Russian Journal of General Chemistry, Vol. 71, No. 3, 2001, pp. 457–463. Translated from Zhurnal Obshchei Khimii, Vol. 71, No. 3, 2001, pp. 494–500.
Original Russian Text Copyright © 2001 by Plemenkov, Yanilkin, Morozov, Palei, Maksimyuk, Ngo Bakopki.

Reactions of Single-electron Oxidation and Reduction of Sulfides of the Azulene Series

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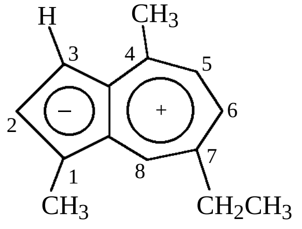
Received September 27, 1999

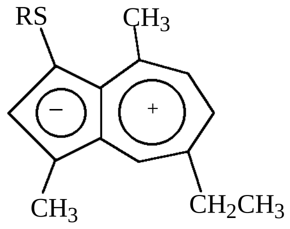
Abstract—Single-electron oxidation in acetonitrile and reduction in DMF of sulfides of 3-RS-1,4-dimethyl-7-ethylazulenes (R = Me, Et, Ph, *p*-MeC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *N*-1-phenyltetrazolyl) leads to stable radical cations and radical anions, respectively. The found reduction potentials of sulfides of the azulene series are close to those of natural and synthetic bioantioxidants. In the radical cations the unpaired electron is essentially delocalized over the cyclopentadienyl fragment of the molecule, and the sulfide group in large measure defines the distribution of spin density. In the radical anion spin density is delocalized in the tropylium cycle, and the influence of the sulfide group is insignificant. Electrochemical oxidation of unsubstituted 1,4-dimethyl-7-ethylazulene results in the formation of a dimeric radical cation.

It is known that processes of oxidation, which are vitally important to a living system, are at the same time fatal to it (hydroperoxide destruction of cell membranes, mutagenic effects). Living organisms themselves to some extent produce substances protecting them from excess oxidants, sulfur- and selenium-containing enzymes in the first place (glutathione-peroxidase, as one example). Of high antioxidant activity are also some vitamins which are exogenic for living organisms antioxidants, retinol, ascorbic acid, and tocopherol in their number. In medical practice, synthetic antioxidants, sterically hindered phenols and their derivatives in particular, are also widely used. It should be noted that phenol compounds with pronounced antioxidant activity are found in many plants (flavanoids, hydroxycinnamic acids). In addition to this class of compounds, in plants there are found also other substances which to some extent exhibit reductive properties, mainly isoprenoids [1, 2]. Among them we should single out 1,4-dimethyl-7-azulene and prepared on its basis sulfide derivatives as potential bioantioxidants in view of their high electron-donor power (IP$_1$ 7.0–7.3 eV [3]) and very low toxicity (LD$_{50}$ 3000 mg/kg [4]).

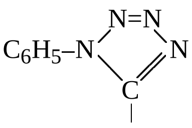
Earlier [5, 6] we reported on the methods of isolation in the pure state from yarrow (*Achillea*) a biologically active substrate, 1,4-dimethyl-7-ethylazulene, as well as on its enzymatic concentration and chemical modification by the reactions with sulfenyl chlorides. The presence in the molecules of the obtained sulfides of the azulene series of the tropilium moiety with its high electron affinity and the cyclopentadienyl fragment combined with the thio group which are powerful electron donors allow one to consider these compounds as potential redox deactivators of various highly active radicals generated in living organisms under external effects. Chemical as well as biochemical properties of compounds are to a great extent defined by the characteristics of boundary orbitals. By Michaelis postulate [7], multi-electron redox processes involve successive acts of single-electron transfer. By now the postulate has gained a sufficient experimental support and quantum-mechanical substantiation [8].



I



II–VII

R =  (**II**), Ph (**III**), *p*-MeC$_6$H$_4$ (**IV**),

p-MeOC$_6$H$_4$ (**V**), Et (**VI**), Me (**VII**).

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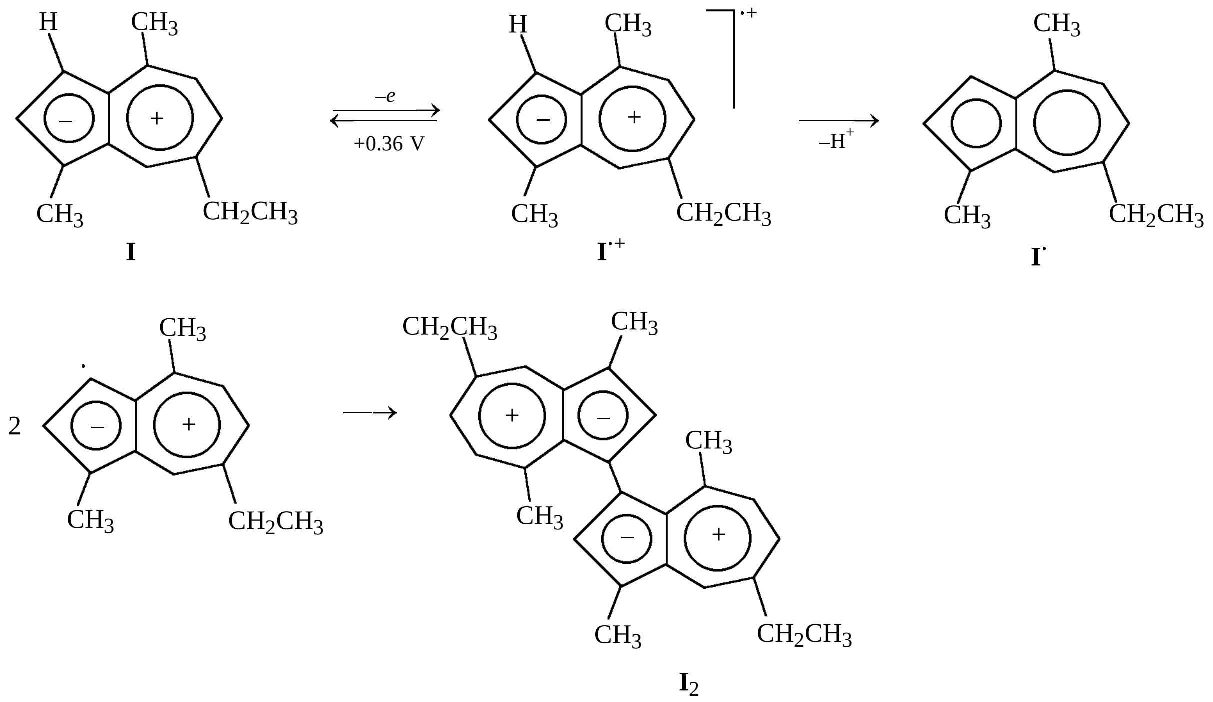
In the present study we report on the results of investigation by means of voltammetry, electrolysis, and ESR spectroscopy of single-electron transfer oxidation and reduction of 1,4-dimethyl-7-ethylazulene (**I**) and its sulfides (**II**–**VII**).

Electrochemical oxidation. In cyclic voltammograms of 1,4-dimethyl-7-ethylazulene (**I**) taken with a platinum electrode in acetonitrile (0.1 M Et_4NClO_4) there is a single irreversible oxidation peak (E_p = +0.36 V). The peak current corresponds to the transfer of two electrons per molecule. In the back wave of the voltammogram curves are registered two reduction peaks at the potentials of $E_p^{1,red}$ +0.17 and $E_p^{2,red}$ = +0.04 V (Fig. 1). In electrolysis at the potential of +0.5 V by means of electrolysis combined with ESR spectroscopy registered a stable paramagnetic species with Δ**H** ~1.2 mT, its spectrum is presented in Fig. 2. On the strength of all the results this paramagnetic reaction product can be identified as a dimeric radical anion $\mathbf{I}_2^{\cdot+}$, and the overall process of oxidation of 1,4-dimethyl-7-ethylazulene **I** can be thus depicted by the following scheme:



$$\mathbf{I}_2 \underset{+0.04\ \mathrm{V}}{\overset{-e}{\rightleftarrows}} \mathrm{I}_2^{\cdot+} \underset{+0.17\ \mathrm{V}}{\overset{-e}{\rightleftarrows}} \mathbf{I}_2^{++}$$

$$\mathbf{I}_2^{++} + \mathbf{I} \rightleftarrows \mathbf{I}_2^{\cdot+} + \mathbf{I}^{\cdot+}$$

The transfer of the first electron results in the formation of the radical cation ($\mathbf{I}^{\cdot+}$) which rapidly splits off proton to transform into the radical ($\mathbf{I}^{\cdot}$). Dimerization of the latter leads to the dimer of 1,4-dimethyl-7-ethylazulene ($\mathbf{I}_2$), which easier than the starting 1,4-dimethyl-7-ethylazulene **I** donates two electrons in succession to give finally the dication ($\mathbf{I}_2^{++}$). Under homogeneous conditions the dimeric dication oxidizes 1,4-dimethyl-7-ethylazulene **I** to be reduced itself to the dimeric radical cation registered by ESR. The above scheme makes it possible to give account of the two-electron level of the irreversible oxidation peak, the appearance of the dimeric radical cation, and the absence of the subsequent oxidation peaks, since the dication is hard to oxidize.

Unlike the case with 1,4-dimethyl-7-ethylazulene **I**, electrochemical oxidation of sulfides of 1,4-dimethyl-7-ethylazulene **II**–**VII** in acetonitrile with 0.1 M Et_4NClO_4 as a background proceeds as a multistep process (see the table). At the first step in the low potentials region (0.24–0.52 V) occurs a rever-

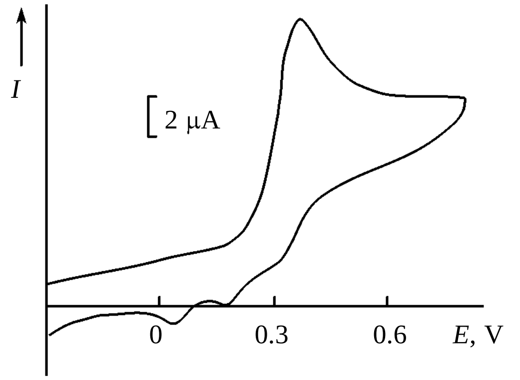


Fig. 1. Cyclic voltammogram of a 5×10^{-3} M solution of 1,4-dimethyl-7-ethylazulene (**I**) in MeCN/0.1 M Et_4NClO_4 at a platinum electrode; *V* 100 mV/s, 22°C.

Fig. 2. ESR spectrum of the radical cation of the 1,4-dimethyl-7-ethylazulene dimer ($\mathbf{I_2}$) generated by the electrochemical oxidation at a platinum electrode of a 5×10^{-3} M solution of 1,4-dimethyl-7-ethylazulene (**I**) in MeCN/0.1 M Et_4NClO_4 at the potential of +0.5 V.

sible transfer of one electron resulting in the formation of radical cations stable in the time scale of voltammetric measurements (seconds). At the potential sweep rates of 20–200 mV/sec in the cyclic voltammogram curves symmetric anode–cathode peaks (Fig. 3, i_p^c/i_p^a 1.0) are registered indicative of high stability of the products of single-electron oxidation of compounds **II**–**VII**. Further oxidation of the radical cations at the potentials of the subsequent waves proceeds irreversibly. Radical cations of compounds **II**–**VII** were registered by means of ESR at the controlled potential of the first wave.

The spectra of the radical cations of compounds **II**, **IV**, and **V** display a ten-component structure with a binominal ratio of line intensities (Fig. 4). The spectrum of the radical cation of compound **VI** consists of twelve components (Fig. 5). By analogy with the literature data for similar radical cations [3, 9] the spectrum of compound ($\mathbf{II}^{\cdot+}$) can be analyzed as one resulting from the interaction with the protons of the methyl group in the position 3 (*a* ~0.88 mT), with the proton in the position 7 (*a* ~0.39 mT), and with the methylene protons in the position 5 (*a* ~0.36 mT) and roughly equal contants of hyperfine interaction with the protons in the positions 2 and 6 (*a* ~0.08 mT). Splittings from the protons of the methyl group in the position 3 are sensitive to the electron-donor properties of the substituents, characterized by the oxidation potentials of compounds, and decrease with decreasing oxidation potential.

With compound **VII**, additional interactions with the methylene protons at the atom of sulfur are appended. In the order of magnitude they are the same as the interaction with protons in the positions 5 and 7. Participation of the orbitals of sulfur in the distribution of spin density is also reflected in a noticeble deviation of the *g*-factor [for compound ($\mathrm{V}^{\cdot+}$) equal

Characteristics of the reduction and oxidation waves of the sulfides of 1,4-dimethyl-7-ethylazulene (**II**–**VII**)[a]

Comp. no.	Reduction			Oxidation		
	$-E_{1/2}^{red}$, V[b]	*n*[c]	i^a/i^c[d]	$-E_{1/2}^{ox}$, V[b]	*n*[c]	i_p^c/i_p^a[e]
I	1.86	1.0	0.70	0.36	2.0	0.0
	2.70	1.0	0.00			
II	1.80	1.0	0.60	0.52	1.0	1.0
	2.63	4.6	0.00	1.11	1.0	0.0
III	1.86			0.48	1.0	1.0
	1.84			1.03	1.0	0.0
				1.53	2.0	0.0
IV	1.86	1.0	0.77	0.36	1.0	1.0
	2.87	1.0	0.00	0.90	1.0	0.0
				1.31	2.0	0.0
V	1.86	1.0	0.62	0.32	1.0	1.0
	2.86	1.3	0.00	0.82	1.0	0.0
				1.16	1.5	0.0
				1.38	2.0	0.0
VI	1.84	1.1	0.66	0.29	1.0	1.0
	2.85	0.9	0.00	0.92	1.0	0.0
VII	2.00	1.0	0.71	0.24	1.0	1.0
	2.92	1.2	0.00	0.82	1.0	0.0

[a] Reduction by polarography in DMF/0.1 M Bu_4NI at a mercury drop electrode, oxidation by cyclic voltammetry in MeCN/0.1 M Et_4NClO_4 at a platinum electrode. [b] Potentials are measured relative to $Ag/AgNO_3$ 0.01 M in MeCN. [c] The number of electrons is estimated by comparison with one-electron limiting reduction and oxidation currents of reference compounds. [d] Ratio between anode commutated current and limiting cathode current, *f* 10 Hz, theoretical value for reversible processes 0.78. [e] Ratio between the currents of the corresponding cathode and anode peaks obtained by cyclic voltammetry.

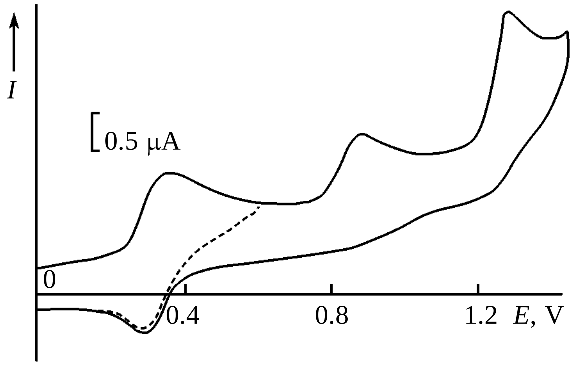


Fig. 3. Cyclic voltammogram of 1×10^{-3} M solution of compound **IV** in MeCN/0.1 M Et_4NClO_4 at a platinum electrode; *V* 100 mV/sec, 22°C.

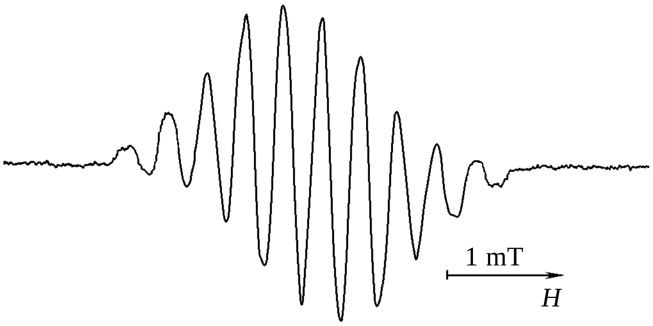
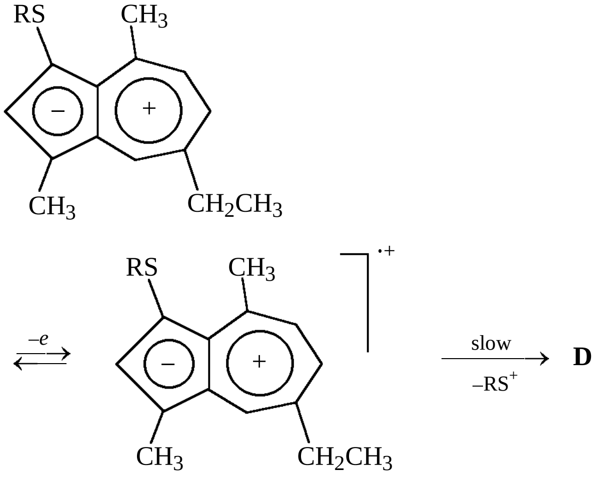


Fig. 4. ESR spectrum of the radical cation of compound **IV** generated by electrochemical oxidation of 5×10^{-3} M solution of compound **IV** in MeCN/0.1 M Et_4NClO_4 at a platinum electrode at a potential of +0.6 V.

to 2.0042] from the value common to the radical cations of aromatic compounds.

A correlation between the oxidation potentials of 1,4-dimethyl-7-ethylazulene (**I**) and its sulfides **II**–**VII** shows that introduction of the RS group in the position 3 of the molecule of 1,4-dimethyl-7-ethylazulene (**I**) results in promotion or hampering of the process of oxidation, depending on the nature of R. The electron-donor properties of the RS groups decrease in the following order of R: Me > Et > *p*-$MeOC_6H_4$ > *p*-MeC_6H_4 > Ph > *N*-1-phenyltetrazolyl.

Noteworthy is the fact that alkyl sulfides **VI**, **VII** are oxidized more readily than the corresponding aryl derivatives, while dialkyl sulfides are more hard to oxidize than diaryl sulfides [9]. In all likelihood, this is due to the fact that, as distinct from R_2S where sulfur acts as a reaction center, the RS group in dimethylethylazulenes at the first two stages of oxidation is but a substituent, and in acetonitrile it undergoes transformations only at the potentials of the subsequent waves. After a prolonged electrooxidation (≥30 min) of the sulfides of the azulene series **II**–**VII** at the potentials of the first peak and upon the subsequent bringing the potential down, a spectrum of the dimeric radical cation is registered by ESR. It seems likely that slow elimination of the RS^+ group



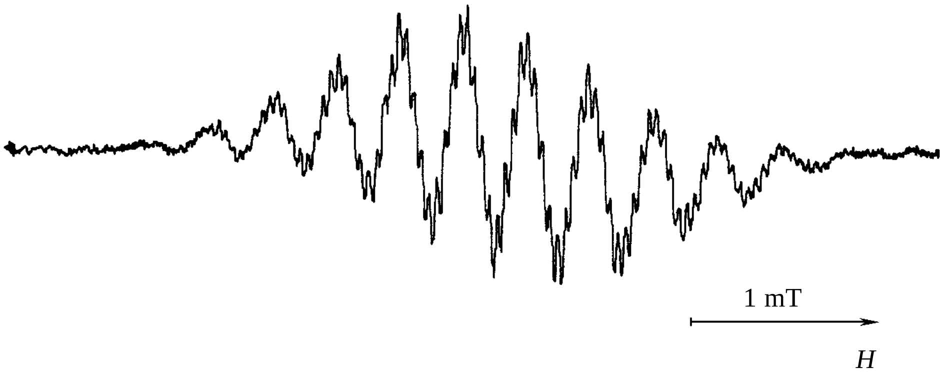


Fig. 5. ESR spectrum of the radical cation of compound **VI** generated by electrochemical oxidation of 5×10^{-3} M solution of compound **VI** in MeCN/0.1 M Et_4NClO_4 at a platinum electrode at a potential of +0.6 V.

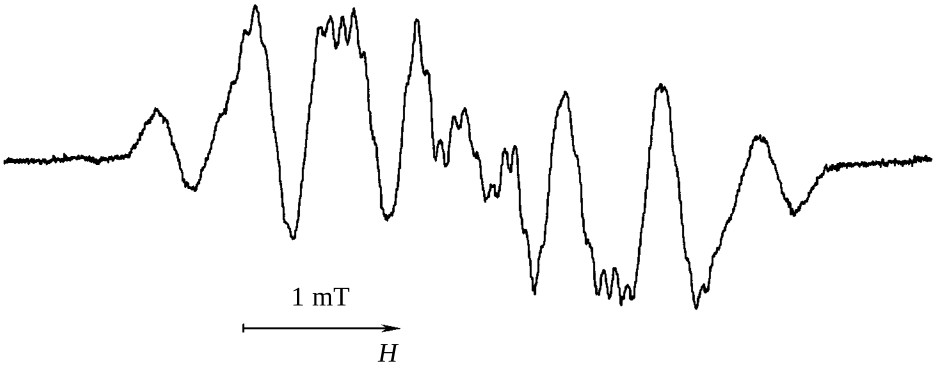


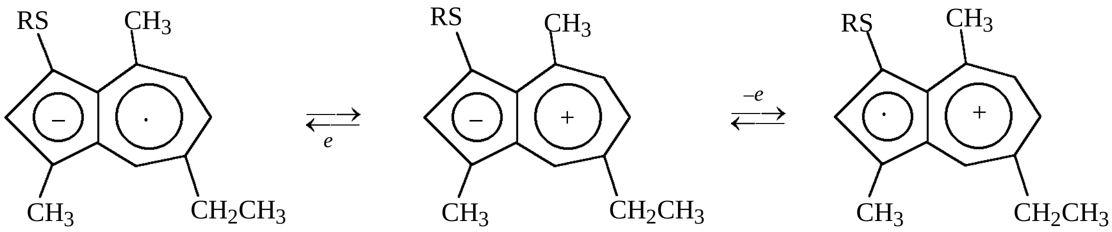
Fig. 6. ESR spectrum of radical anions generated by the electrochemical reduction of 5×10^{-3} M solution of 1,4-dimethyl-7-ethylazulene (**I**) in MeCN/0.1 M Et_4NClO_4 at a platinum electode at the potential of –2.1 V.

takes place from the radical cations to give the radical (**I**$^{\cdot}$), which further undergoes the same transformations as in the oxidation of 1,4-dimethyl-7-ethylazulene.

Electrochemical reduction. 1,4-Dimethyl-7-ethylazulene (**I**) and its sulfides **II**–**VII** in DMF against a background of 0.1 M Bu_4NI are reduced in a way similar to azulene [10]. In the polarograms two reduction waves observed (see the table). At the first stage occurs a reversible transfer of one electron resulting in the formation of fairly stable radical anions registered by ESR in the electrolysis at the potentials of the first wave directly in the resonator of the ESR spectrometer.

The ESR spectrum of the radical anion of 1,4-dimethyl-7-ethylazulene (**I**) is characterized by a complex multiplet structure (Fig. 6). By analogy with the radical anion of azulene [3,10], the multiplets can be attributed to the splittings from the protons at the C^6 atom (a ~1.11 mT), in the position 4 (a ~0.61 mT), from three protons in the methyl group in the position 8 (a ~0.55 mT), and from the protons in the position 2 (a ~0.27 mT). The found value of the g-factor is specific to aromatic radical anions (g 2.0026). The spectra of the substituted 3-RS-1,4-dimethyl-7-ethylazulenes **II**, **IV**, **V**, and **VI** closely resemble each other, the expanse of the spectra sligthly decreasing in proportion to the increase in the electron-acceptor properties of the substituents characterized by their reduction potentials, which reflects diminishing spin density on the tropylium ring. The influence of varied substituents is insignificant, since the substitutent is located in the node of the HOMO. At the potentials of the second wave radical anions irreversibly accept one electron in the case of compounds **I**, **IV**–**VII** and four electrons in the case of sulfide **II**. In contrast to the process of oxidation, the effect of substituents in reduction is less pronounced. As an example, for compounds **IV** and **V** the reduction potentials are practically the same, while the oxidation potentials differ by 40 mV. However, in general, substituents R exert similar effect on the reduction and oxidation potentials: those decreasing the oxidation potential increase the reduction potential, i.e., shift the reduction and oxidation potentials in the same direct ion.

Different sensitivity of radical cations and radical anions and their ESR spectra to the influence of substituents and the oxidation and reduction potentials is apparently due to the fact that it is the cyclopentadienyl fragment which acts as a reaction center in the electrochemical oxidation. The unpaired electron is largely delocalized over this fragment, and the sulfide group takes part in the delocalization of the charge and spin density which is reflected in the observed rather strong effect on E_p^{ox}. In the reduction, an electron is transferred on the tropylium fragment, and the sulfide group practically does not participate in the delocalization of the spin density. If the starting molecule is conceived as a bipolar structure, then the processes of oxidation and reduction can be conventionally described by the following scheme:



I–**VII**

In summary we should note some points which permit the sulfides of 1,4-dimethyl-7-ethylazulene to be considered as promising inhibitors of radical processes in biological systems. In living organisms under the action of various factors highly active free radicals are formed which can lead to pathologic changes or the death of the organism as a result of a chain reaction [11]. The results of the electrochemical reduction and oxidation of the derivatives of 1,4-dimethyl-7-ethylazulene show that these compounds efficiently deactivate many radicals by SET-mechanism. Their reasonably low reduction potentials indicate that these compounds are efficient interceptors of solvated electrons, no active radical species forming in the process, which is testimony to the possibility of their using as radioprotectors. Of particular promise is their use as antioxidants which is determined by several considerations.

(1) 1,4-Dimethyl-7-ethylazulene **I** and its sulfides **II**–**VII** are oxidized in the same region of potentials or even easier than known antioxidants (e.g., for α-tocopherol in acetonitrile E_p 0.53 V [12]), and so will reduce radicals with not lower, and probably with greater efficiency.

(2) All these compounds are relatively inert to atmospheric oxygen and will obviously not be consumed in undesirable processes.

(3) The products of oxidation are inert and do not continue the chains of radical reactions.

(4) The processes of reduction and oxidation of the dimeric species are to a high degree reversible. In principle, one may expect deactivation of radicals of various types. The oxidized form deactivates radicals capable of oxidation, e.g., solvated electron or superoxide ion $O_2^{-\cdot}$, and the reduced form deactivate radicals prone to reduction, e.g. hydroperoxide radicals or radical cations of polycyclic hydrocarbons which are the immediate products of transformation of carcinogenes [13]. In this case 1,4-dimethyl-7-ethylazulene and its sulfides are not consumed but play the role of electron carriers between the different types of radicals.

(5) The presence in the molecules of 1,4-dimethyl-7-ethylazulenesulfides of the sulfur atom with a high affinity to oxygen and carbon makes it possible deeactivation of radicals by way of their addition, their reduction being retained.

EXPERIMENTAL

The study of electrochemical oxidation of 1,4-dimethyl-7-ethylazulene **I** and its sulfides **II**–**VII** was carried out in actonitrile on the background of 0.1 M Et_4NClO_4 by cyclic voltammetry at a platinum disk electrode 0.5 mm in diameter with the use of a PI-50-1 potentiostat. As a reference electrode we used a silver electrode Ag/0.01 M $AgNO_3$ in MeCN, and platinum wire was an ancillary electrode. The potential sweep rate was varied within the interval of 20–200 mV/sec. The electrochemical reduction was studied by classical and commutation polarography in DMF on the background of 0.1 M Bu_4NI with the use of a PU-1 polarograph. Parameters of the capillary: m 0.71 mg/sec, t_1 0.5 sec. Switching rate was 10 Hz. The solvent was deaerated with argon. The substrate concentration was 10^{-3} M, temperature 22°C.

The procedures of purification of solvents and background salts and polarographic measurements were described earlier [14].

The electrolysis-ESR studies were performed with the use of a set comprised of an ESR spectrometer and a potentiostat and making it possible for the electrochemical process to be carried out immediately in the resonator of the ESR spectrometer. We used a special-purpose three-electrode cell devised in the Arbusov IOC of the KSC, RAS [14].

As a working electrode we used a platinum plate, an ancillary electrode was a platinum wire, the reference electrode was a silver wire. The ESR spectra were registered on a RadioPAN SE/X-2544 spectrometer. Deaeraition of the solution was carried out by three-fold freezing–evacuation–unfreezing of the cell.

ACKNOWLEDGMENTS

The study was carried out in the framework of the program INCO-Copernicus (project no. IC 15CT98-0150).

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