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REVIEW

Kinetic EPR-Studies of the Anti-Peroxyl Radical Reactivities with Various Metallochelates of 3,5-Di-Iso-Propylsalicyalte and Salicylidene Schiff Base

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Abstract

Copper(II)-, Fe(III)-, Zn(II)-, and Mn(II)-3,5-di-*iso*-propylsalicylate (3,5-DIPS) chelates and $Cu(II)_2$(acetyl-3,5-DIPS)$_4$, and 3,5-DIPS, salicylidene Schiff base chelates Mn(III), Co(II), Ni(II), were kinetically examined as antioxidants in the scavenging of *tert*-butyl peroxyl radical (*tert* − butylOO$^\bullet$) in non-polar and polar aprotic solvents. Using kinetic EPR method absolute rate constants and corresponding Arrhenius parameters were determined for reactions of *tert* − butylOO$^\bullet$ with these chelates in the temperature range from − 63 to − 11 °C. It was established that the order of anti-*tert* − butylOO$^\bullet$ reactivity is: Mn(II)(3,5-DIPS)$_2$ >> $Cu(II)_2$(3,5-DIPS)$_4$ > Fe(III)(3,5-DIPS)$_3$ > Zn(II)(3,5-DIPS)$_2$ >> $Cu(II)_2$(acetyl-3,5-DIPS)$_4$ and 3,5-DIPS acid. Mn(II)(3,5-DIPS)$_2$ caused the most rapid removal rate for *tert* − butylOO$^\bullet$ as a result of the oxidation of Mn(II) to Mn(III) by *tert* − butylOO$^\bullet$. The reaction of *tert* − butylOO$^\bullet$ with $Cu(II)_2$(3,5-DIPS)$_4$, Zn(II)(3,5-DIPS)$_2$ and Fe(III)(3,5-DIPS)$_3$ is due only to hydrogen atom abstraction from the ligand phenolic OH group by *tert* − butylOO$^\bullet$, owing to their activation by the metalloelement through weakening the intramolecular hydrogen bond. High reactivity of *tert* − butylOO$^\bullet$ with Mn(III) and Co(II) salicylidene Schiff base chelates was established. These salicylidene Schiff base chelates react in a 1:1 stoichiometric ratio with *tert* − butylOO$^\bullet$ without free radical formation and with the single-electron oxidation of central metalloelements. It is concluded that removal of alkylperoxyl radical by Cu(II)-, Fe(III)-, Zn(II)-, and Mn(II)-3,5-di-*iso*-propylsalicylate chelates, Mn(III) and Co(II) salicylidene Schiff base chelates may partially account for their biological activities.

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1 Introduction

It has been clearly shown that essential metalloelement (Cu, Fe, Zn, Ni, Co and Mn) chelates exhibit properties of efficient bioactive antioxidants with potential for the prevention and/or treatment of various pathological disease states [1–7]. These co-ordination compounds show a great diversity in action. Metal coordination can be used to enhance the activity of biologically active molecules. These activities have been related to their superoxide dismutase (SOD)-mimetic, catalase-mimetic, P450 modulating, protein kinase modulating, cyclo-oxygenase modulating, and nitric oxide synthase modulating activities as well as their respective facilitation of specific metalloelement-dependent enzyme syntheses [1–7]. Stable, controllable in biosystems and relatively nontoxic metalloelement-chelates of 3,5-di-*iso*-propylsalicylate (3,5-DIPS) and salicylidene Schiff base chelates thoroughly studied as bioactive compounds and antioxidants [1, 2, 8–11] are considered as particularly perspective in this regard. Essential metalloelement salicylidene Schiff base chelates and metalloelement chelates of 3,5-di-*iso*-propylsalicylateare pharmaceutically acceptable compositions and therefore potentially useful as efficient antioxidants for various biological applications, for prevention and/or treatment of diseases caused by free radicals [1, 2, 11, 12]. These properties have been mainly related to their superoxide dismutase (SOD)-mimetic and catalase-mimetic reactivities [1, 2, 8, 9]. There are also data suggesting that manganese salicylidene Schiff base chelates prevent lipid peroxidation induced by acidosis [8]. The last mentioned property of chelates is very substantial as it was found that a number of human pathologies are associated with the intensification of lipid peroxidation [13].

To offer a more complete explanation of the antioxidant properties of these chelates in preventing peroxidative alterations of bio-membrane lipids and other oxidizable cellular and extracellular components, it was viewed as important to study the antioxidant and antiradical reactivities of these lipophilic chelates in organic media. From this standpoint the Electron Spin/Paramagnetic Resonance (ESR/EPR) spectroscopy is one of the most informative methods in studying free radical reactions in the elemental level [14].

It is of special importance in studying the reactions of antiradical activity of metallo-complexes. Such investigations carrying out in complex reaction systems are complicated because of multifunctionality of metallo-complex antioxidants, associated with simultaneous participation in many elementary chemical steps. Under noncomplicated conditions the EPR kinetic method enables to reveal on the level of elementary reactions two significant characteristics of the antiradical potency of antioxidants:

- Rate constants of the antioxidants with free radicals, characterizing their antiradical activity,
- Antiradical capacity of antioxidants characterizing the number of radicals scavenged by one molecule of the antioxidant.

The EPR kinetic method is complementary with other research methods that allows in addition to quantitative characteristics to obtain information about the mechanism of antiradical potency of the antioxidants.

In this study a brief review of our investigations dedicated to revealing the reactivity of these chelates with peroxyl radicals using EPR spectroscopy is presented.

Indeed, the reaction of peroxyl radicals with metallochelates, which serve as antioxidants, is a reasonable approach to understand their chain-breaking reactivity in preventing lipid peroxidation. This in turn further characterizes the antioxidant properties of these chelates. Direct kinetic investigations of alkylperoxyl radical reactions with metallochelates are a well-established approach to understand their antioxidant reactivity in biologically relevant lipid media [15–18].

The antioxidant activity of the metallo-complexes was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) method test [3, 7, 11, 12]. In the reactions on hydrogen atom abstraction from phenolic antioxidants by the radicals responsible for removal of free radicals, a linear correlation between the reactivity of DPPH and the high reactive alkoxyl radical $RO^{\bullet}$ in relation to hydrogen atom-donor phenolic antioxidants was observed [19]. Nevertheless, redox characteristics of model stable radicals DPPH and chain carried radicals of lipid peroxidation peroxyl radicals differ significantly. $E^{\circ}(tert-\text{butylOO}^{-}/tert-\text{butylOO}^{\bullet})=0.71$ V at pH 7 [20], while $\text{DPPH}^{-}/\text{DPPH}^{\bullet}$ redox couple for biamperometric determination is equal to 0.23 V at pH 7.4 [21]. This may lead to vital inaccuracy at modelling antiperoxiradical, antilipidperoxidation ability of metallochelates by means of DPPH. The question becomes of special urgency if metalloelement of the antioxidant acts as antiradical reaction center. In this case it improves the properties of metallochelate antioxidant through intermolecular electron transfer. Therefore, revelation of the antiradical ability and chemical action mechanism of metalloelement antioxidants in relation to lipidperoxidation chain carrier lipoperoxyl radicals is of special importance. Consequently, its influence on the antiradical reactivity of Cu(II), Fe(III), Zn(II), Ni(II), Mn(II) and Mn(III) chelates was also of interest and provided additional information concerning the mechanism of *tert*-butylperoxyl radical ($tert-\text{butylOO}^{\bullet}$) reaction with these chelates and clarifies their relative antioxidant reactivity. This information was also viewed as very useful in predicting structures of more effective metalloelement containing bio-active antioxidants. The objective of the present work was to present direct kinetic measurements, using EPR spectroscopy for reactions of $tert-\text{butylOO}^{\bullet}$ with chelates in non-polar lipophilic organic media [22, 23].

The anti-$tert-\text{butylOO}^{\bullet}$ reactivities of these chelates are presented as the absolute rate constants (k_{react}) and antioxidant free-radical capacities (f_R), the number of $tert-\text{butylOO}^{\bullet}$ that react with one molecule of chelate, under the employed experimental conditions. Simultaneously, FT-IR and electrochemical measurements [23–29] are presented along with kinetic EPR studies aimed at complex understanding the antiperoxyradical effect of the selected metallochelates.

2 Experimental

2.1 Kinetic EPR Measurements with Pulse Reagent Introduction

Kinetic EPR measurements with pulse reagent introduction [22] were performed using the experimental setup shown in Fig. 1. Measurements of absolute rate constants for the reaction of *tert* – butylOO$^{\bullet}$ with antioxidant were performed in the temperature range of – 63 to ÷ 11 °C. The quartz cell was divided into compartments by means of a septal membrane. *tert* – butylOO$^{\bullet}$ was generated by photolytic irradiation (220–400 nm) of a 10^{-3}–10^{-2} M *tert* – butylOOH solution in the quartz EPR cell with a 500 W mercury lamp. Photolytic cleavage of the O–O bond of *tert* – butylOOH leads finally to the formation of *tert* – butylOO$^{\bullet}$ as shown below:

$$tert - \text{butylOOH} \xrightarrow{h\nu} tert - \text{butylOO}^{\bullet} +^{\bullet} \text{OH},$$

$$tert - \text{butylOO}^{\bullet} +^{\bullet} \text{OH} + 2tert - \text{butylOH} \xrightarrow{\text{fast}} tert - \text{butylOH} + \text{H}_2\text{O} + 2tert - \text{butylOO}^{\bullet}.$$

Under the conditions of these kinetic experiments these reactions occurred within 30 s, so that the studied metallochelates did not have sufficient time to react with *tert*-butylhydroperoxide. The absence of a reaction of the *tert* – butylOOH with studied metallochelates was established by observing no change in visible spectra obtained with heptane solutions. Additional support for this comes from the absence of any EPR signal following mixing of these chelates with a solution of *tert* – butylOOH in the absence of UV irradiation. In the case of Mn(II)L_2,

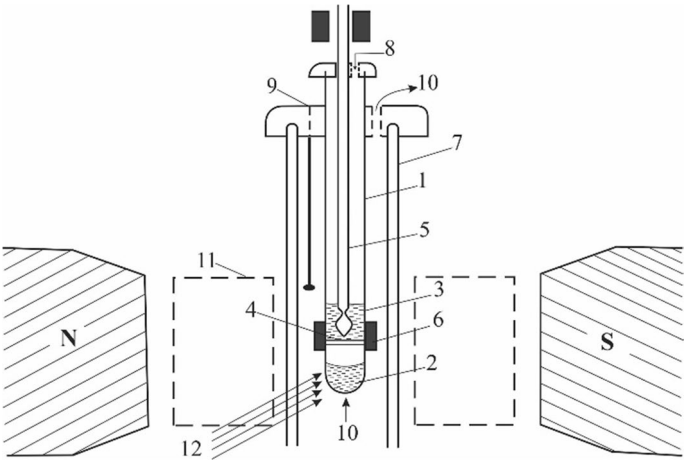


Fig. 1 Experimental setup: (1) quartz cell; (2) solution of *tert* – butylOOH; (3) solution of antioxidant, chelate or phenolic compound; (4) teflon membrane; (5) quartz stirring rod; (6) teflon joint; (7) dewar; (8) dry air inlet; (9) thermocouple; (10) thermostating gas; (11) EPR cavity; and (12) UV irradiation photolysis source, [22, 23]

the absence of a reaction with *tert* – butylOOH was demonstrated by the observation that there was no change in the EPR spectrum of a solution of $Mn(II)L_2$ upon addition of *tert* – butylOOH. After photolytic-generation of*tert* – butylOO$^{\bullet}$, and turning off the irradiation source, a solution of antioxidant phenols or chelate was added to the solution of *tert* – butylOO$^{\bullet}$ by breaking the membrane separating these two solutions. The magnetic field was then adjusted to maximize the amplitude of the EPR signal for the resultant solution of *tert* – butylOO$^{\bullet}$ during a period of 2–10 s before the membrane breakage. This signal is due to the singlet state of the *tert* – butylOO$^{\bullet}$, which has a *g*-value of 2.0143 ± 0.0006. Kinetics of *tert* – butylOO$^{\bullet}$ consumption was recorded with an EPR-B spectrometer operating at 9.4 GHz with 100 kHz modulation (built in Moscow, Institute of Chemical Physics). Plots of the change in concentration of *tert* – butylOO$^{\bullet}$ due to its reaction with the added antioxidant (AO) are shown in Fig. 2. Analysis of these kinetic plots revealed that the rate of *tert* – butylOO$^{\bullet}$ reaction with these AO-s is proportional to the concentration of the reacting species and described by the following second-order equation:

$$-d\left[tert - \text{butylOO}^{\bullet}\right]/dt = k_{\text{eff}}\left[tert - \text{butylOO}^{\bullet}\right][\text{AO}],$$

where $k_{\text{eff}} = m_{\text{st}}k_{\text{react}}$, and m_{st} is the stoichiometric coefficient showing how many times k_{eff} differs from the absolute k_{react} under the reaction conditions. The m_{st} parameter often coincides with antiradical capacity f_R, the number of molecules of *tert* – butylOO$^{\bullet}$ that react with one molecule of antioxidant under the reaction conditions. The reactions were performed with an excess of these antioxidants, establishing pseudo-first order conditions (Fig. 2).

Respective k_{eff} values were determined from a linear least-squares fitted plot obtained for each kinetic plot according to the following equation:

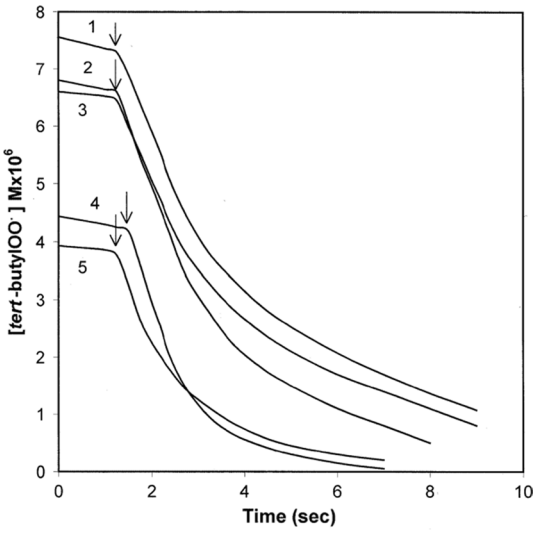


Fig. 2 Kinetics of decrease in concentration of *tert* – butylOO$^{\bullet}$ due to reaction with the added antioxidant at – 31.5 °C. Arrows indicate the time of addition of antioxidant solution to the solution of *tert* – butylOO$^{\bullet}$: (1) 5×10^{-5} M BHT;(2) 10^{-4} M HT;(3) 10^{-2} M $Fe(III)L_3$; (4) 2×10^{-2} M $Cu(II)_2L_4$; and (5) 2.5×10^{-4} M $Mn(II)L_2$ in 10% (v/v) toluene in heptane, [23]

$$k_{\text{eff}}\left(\text{M}^{-1}\text{s}^{-1}\right) = \frac{2.303\log\left(\left[tert-\text{butylOO}^{\bullet}\right]_0/\left[tert-\text{butylOO}^{\bullet}\right]_t\right.}{t[\text{AO}]_0},$$

where t is the time interval for change in the initial concentration of $tert-\text{butylOO}^{\bullet}$, $[tert-\text{butylOO}^{\bullet}]_o$, to the current concentration, $[tert-\text{butylOO}^{\bullet}]_t$, and $[\text{AO}]_o$ is the initial concentration of antioxidant. A change in the reaction mixture volume with temperature was taken into consideration when k_{eff} was determined. Usually the accuracy of k_{eff} measurement is ± 10% of the value presented in Table 1. The Arrhenius activation energies for the second-order rate constants, $\log k = \log A - E/RT$, were determined from the relationship of $\log k_{\text{eff}}$ versus $1/T$ according to the Arrhenius equation, where A is the pre-exponent, E is the activation energy, and R is the universal gas constant. At reasonably high values of k_{react}, as was found to be true for Mn(II)L_2 and phenolic antioxidants, HT and BHT, this method allows to measure the free-radical capacity, f_R, for each the antioxidant. This value is obtained by introducing the antioxidant into the reaction solution at a concentration less than that of $tert-\text{butylOO}^{\bullet}$. The conditions for the reaction are selected so that after the kinetic curve of the corresponding reaction between peroxyl radicals, when the antioxidant is introduced, its fast consumption takes place. Further, due to deficiency of the antioxidant again slow reaction between the peroxyl radicals is observed. In this case the amount of $tert-\text{butylOO}^{\bullet}$ radical consumed during the reaction with the antioxidant is determined by EPR, as shown in Fig. 3. Then:

$$f_R = \Delta\left[tert-\text{butylOO}^{\bullet}\right]/[\text{AO}]_{\text{O}},$$

where $[\text{AO}]_0$ is the initial concentration of the antioxidant, in this case characterizing its quantity consumed completely.

This method allows to measure the free radical capacity, f_R for each chelate and their comparison with the f_R obtained for BHT [22, 23].

2.2 Electrochemical Measurements

Differential pulse voltametric (DPV) experiments were performed by using a Bioanalytical Systems 100 B/W electrochemical analyzer (BAS, USA) with a conventional three-electrode system at 20 ± 0.1 °C. The working electrode was a glassy carbon electrode with an area of ~ 0.09 cm^2, which was cleaned before voltammetric determinations by polishing with 0.5-μm size alumina powder. The reference electrode was filled with a solution containing 0.01 M of AgNO_3 and 0.1 M of TBAP in MeCN with a platinum wire as the auxiliary electrode. All electrodes were BAS electrodes. Differential pulse voltammograms were recorded from 400 to 1350 mV. TBAP (0.1 M) in methylene chloride was used as a supporting electrolyte. The solutions were purged by passing a stream of high purity solvent-saturated nitrogen for about 20 min and the nitrogen atmosphere was then maintained over the solution during these measurements. Background current for solvent and supporting electrolyte correction were obtained for all measurements. The operation of the electrochemical analysis system was checked with a $\text{K}_3\text{Fe(CN)}_6$ solution for which a linear calibration correlation coefficient of 0.9995 was obtained.

Table 1 The values of second-order absolute rate constants for reaction of *tert* − butylOO• with antioxidants in organic medium [23]

Rate constant, $k_{eff} = m_{st} \times k_{react}$ M^{-1} s^{-1}										
Temperature (°C)										
Antioxidant	−63	−52.5	−42	−31.5	−21.5	−11	37[a]	f_R[b]	E (kJ mol^{-1})[d]	Log A[e]
3.5-DIPS acid	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	–	–	–	–
$Cu(II)_2(L)_4$	9.3	15.86	26	37.76	46.14	57.6	203	–	16.65	5.05
$Cu(II)_2$(acetyl-3,5-DIPS)$_4$	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	–	–	–	–
Fe(III) $(L)_3$	16.34	23.3	25	28.7	33.08	41.24	66	–	7.40	3.07
$Mn(II)(L)_2$	1532	1653	1873	1969	2257	2302	3085	0.34 ± 0.03	3.83	4.10
Mn(II) $(L)_2$ in 0.256 M ethylacetate in heptane	1850	2293	3600	4066	5245	6420	14,000	0.44 ± 0.03[c]	10.97	6.01
$Zn(II)(L)_2$	–	–	–	9.0	–	–	–	–	–	–
HT	1858	2728	2820	3735	4727	7005	13,077	2 ± 0.02	10.69	5.92
HT in 5.1 M ethylacetate in heptane	54.6	108	139	212	268	386	1500	–	16.80	5.97

[a]Values extrapolated by Arrhenius equation

[b]For phenolic antioxidants m_{st} equals f_R for Cu(II), Zn(II) and Fe(III)3,5-DIPS chelates f_R equals ~ 2 for $Mn(II)(L)_2$ $m_{st} = 2$ in 10% (v/v) toluene in heptanes

[c]In heptanes and 10% (v/v) toluene and 50% (v/v) ethylacetate

[d]Arrhenius activation energy

[e]Pre-exponent. The correlation factor, r^2, for values of the Arrhenius equation varied from 0.98 to 0.99

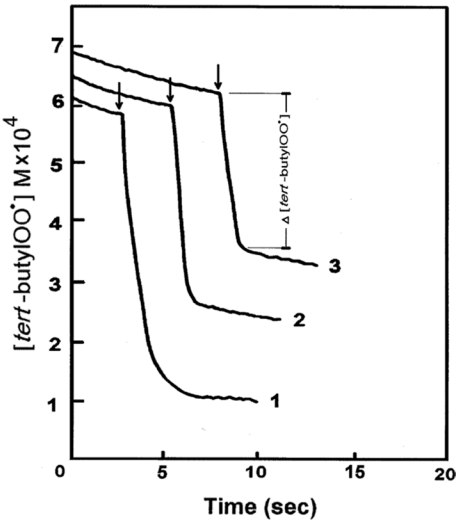


Fig. 3 Measuring the free radical capacity, f_R. Kinetics of decrease in concentration of *tert* – butylOO• due to the reaction with added antioxidant: (1) 2.5×10^{-4} M HT in heptane; (2) 8×10^{-4} M Mn(II)L_2 10% (v/v) toluene and 50% (v/v) ethylacetate in heptane; (3) 8×10^{-4} M Mn(II)L_2 in 10% (v/v) toluene in heptane at – 63 °C. Arrows indicate the time of antioxidant solution addition to the solution of *tert* – butylOO•, [23]

2.3 FT-IR Spectra for Metallochelates and for the Products of their Reaction with Cyano-*Iso*propylperoxyl Radical

Potassium bromide discs or Nujol mulls were used to obtain infrared spectra of 3,5-DIPS and its Cu(II), Mn(II), Zn(II) and Fe(III) chelates through the 4000–200 cm^{-1} spectral region with a Perkin–Elmer 1600 FTIR spectrophotometer. The concentration of chelates in respect to the phenolic OH group was approximately the same, 10^{-5} mol per 100 mg KBr or in Nujol: 2.62 mg for Mn(II)L_2, 2.63 mg for Cu(II)$_2L_4$, 2.64 mg for Zn(II)L_2, 2.39 mg for Fe(III)L_3, and 2.2 mg for 3,5-DIPS. IR investigations for the reaction of Cu(II)-, Mn(II)-, Zn(II)-, or Fe(III)-3,5 DIPS chelates with cyano-*iso*-propylperoxyl radical were performed as follows [23]. The thermal azoinitiator AIBN (10^{-2} M) and the metallochelate were dissolved in 10 ml of benzene to give a final concentration of 3×10^{-3} M 3,5-DIPS ligand, [Cu(II)$_2L_4$] = 7.5×10^{-4} M, [Fe(III)L_3] = 1×10^{-3} M, [Zn(II)L_2] = 1.5×10^{-3} M, and [Mn(II)L_2] = 1.5×10^{-3} M. Solutions were heated at 70 °C for 36 h, with a continuous provision of oxygen.

Benzene is measurable in the given conditions and does not enter into the reaction with R• and ROO• radicals [30]. The conversion of AIBN to cyano-*iso*-propylperoxyl radical exceeded 99.9% under these conditions. After the designated reaction time, the formed precipitate was collected by filtration at room temperature. The filtrate was heated at 70 °C in a vacuum (15 mmHg) rotating evaporator for 1 h and the solid was removed to obtain an IR spectrum using KBr discs and Nujol mulls as described above. Control experiments with each of the studied chelates were performed in the absence of AIBN.

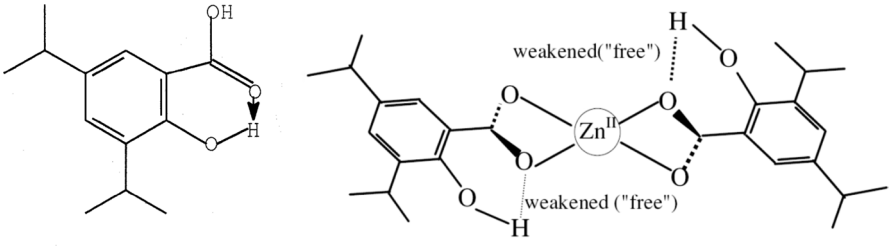
3 Results and Discussion

3.1 Kinetic Investigations of the *tert* − butylOO• Reactivities of Cu(II)-, Mn(II)-, Zn(II)- and Fe(III)-3,5-DIPS Chelates

Absolute rate constants for the chemical reduction of *tert* − butylOO• to *tert* − butylOOH by these antioxidant chelates and commonly used phenolic antioxidant HT are presented in Table 1 [23, 28]. The data presented include experimentally measured values for the antiradical capacities, f_R, for the most active antioxidants: Mn(II)L_2, HT, (as shown in Table 1). Cu(II), Fe(III), Zn(II), and Mn(II) 3,5-DIPS chelates exhibit anti-radical activity with respect to *tert* − butylOO• in an organic medium. The observed order of anti-*tert* − butylOO• reactivity was: Mn(II)L_2 >> Cu(II)$_2L_4$ > Fe(III)L_3 > Zn(II)L_2. The Cu(II)$_2$(3,5-DIPAS)$_4$ and 3,5-DIPS acid had no measurable reactivity. Only the antiradical activity for the most active among these metallochelates, Mn(II)L_2, was close to activities of phenolic antioxidant HT in non-polar medium.

3.2 IR Studies of 3,5-DIPS and its Cu(II), Fe(III), and Mn(II) Metallochelates

Since the metalloelement in each of these 3,5-DIPS chelates as well as the phenolic groups of the 3,5-DIPS ligands can serve as reaction centers removal of *tert* − butylOO•, infrared spectra were obtained for each of them, as well as for 3,5-DIPS acid to examine the nature of the bonding of the phenolic OH group in each of these compounds [23]. Unlike the 3,5-DIPS acid where strong intramolecular is present the broad absorption through the range of 3650–3100 cm^{-1} with an apparent maximum at 3200 cm^{-1} for these chelates, in the absence of a carboxyl OH group, suggests the presence of weakened, more "free" phenolic OH. The relative absorption intensities for these chelates through the range of 3650–3100 cm^{-1} were Mn(II)L_2 > Cu(II)$_2L_4$ ≈ Fe(III)L_3 ≈ Zn(II)L_2. There was no absorption centered at 2700 cm^{-1} in spectra of these chelates, consistent with weakened of intramolecular hydrogen bonding shown in Scheme 1 [23, 29].



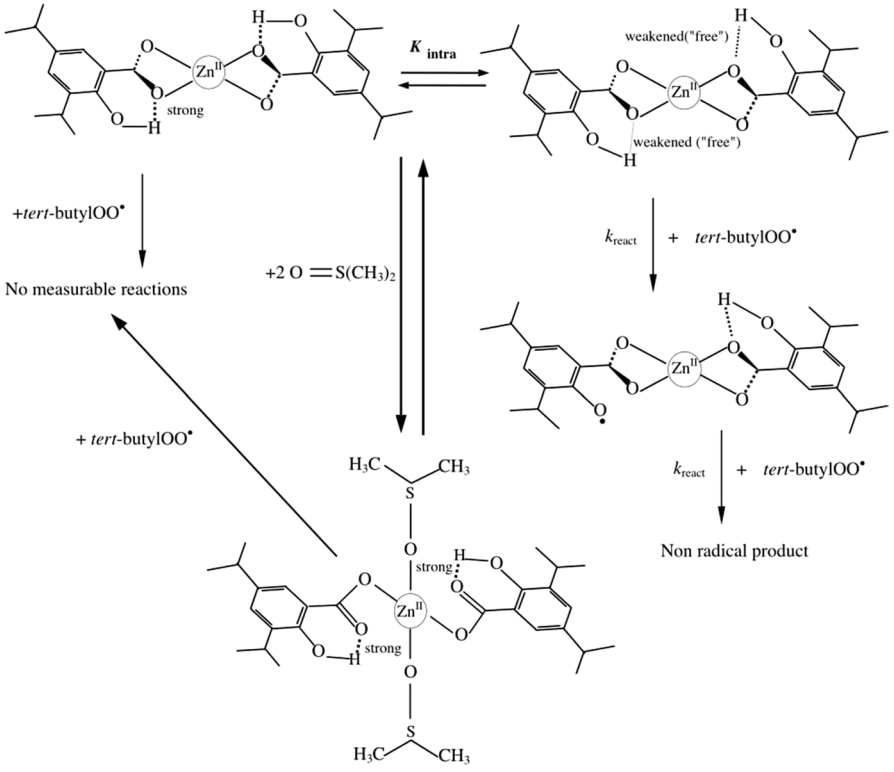
Scheme 1 Illustration of intramolecular hydrogen bonding in 3,5-DIPS acid (1) and its reduction or loss resulting in an increase in the free phenolic OH group in going from 3,5-DIPS acid to a metallochelate of 3,5-DIPS (2) [29]

Studies of products from the reaction of cyano-*iso*-propylperoxyl radical with these chelates also established the participation of the phenolic OH group in the reaction with *tert* – butylOO•. Heating a solution containing an azo thermoinitiator, AIBN, in an oxygen rich atmosphere brings about the following sequence of reactions, resulting in the formation of cyano-*iso*-propylperoxyl radical as shown:

$$R' - N = N - R' \rightarrow \left[R'N_2R'\right]_{\text{solvent cage}} \rightarrow 2R' + N_2,\ R'^{\bullet} = \left(CH_3\right)_2C^{\bullet}CN,$$

$$R'^{\bullet} + O_2 \xrightarrow{\text{very fast}} \text{cyano} - iso - \text{propylOO}^{\bullet}.$$

The reactions of cyano – *iso* – propylOO• with $Cu(II)_2L_4$, $Fe(III)L_3$, and $Mn(II)L_2$ are analogous to the reaction sequence shown in Scheme 2 for *tert* – butylOO•. Infrared absorption bands for the phenolic OH group were no longer present in spectra obtained for products of the reaction with cyano – *iso* – propylOO•. This once more testifies to the participation of phenolic OH group of the 3,5-DIPS ligand in the reaction with the peroxyl radical. This conclusion is supported by the report that



Scheme 2 Mechanism for the reaction of *tert* – butylOO• with the phenolic OH group of the 3,5-DIPS ligand by the example of Zn(II)L_2 and axial bonding of electron pair donors such as DMSO to $Zn^{II}(3,5\text{-DIPS})_2$ act indirectly increases the intramolecular hydrogen bonding of the ligand and prevents the participation of salicylic phenol OH groups inthe reaction with the peroxyl radicals [28]

Fe(III) and Cu(II) acetylacetonates [18] and $Cu(II)_2$(acetyl-3,5-DIPS)$_4$, as shown in Table 1, have no measurable anti-*tert* – butylOO$^{\bullet}$ reactivity because of lack a phenolic OH group.

3.3 Voltammetric Measurements on the Primary Importance of Non-Hydrogen-Bonded Salicylic OH Hydrogen Atoms as the Initial Site of Peroxyl Radical Reactivity

Differential pulse voltammetric studies have allowed to distinguish clearly the two types of salicylic OH groups on the basis of distinctive peak oxidation potentials in these molecules of substituted Cu(II) salicylates [27]. As shown in Fig. 4, there are two distinctly different peak potentials for the oxidation of salicylic OH groups in the substituted Cu(II) salicylates. The more intense and significantly greater oxidation peak potentials between 1000 and 1200 mV versus Ag/Ag+correlate with

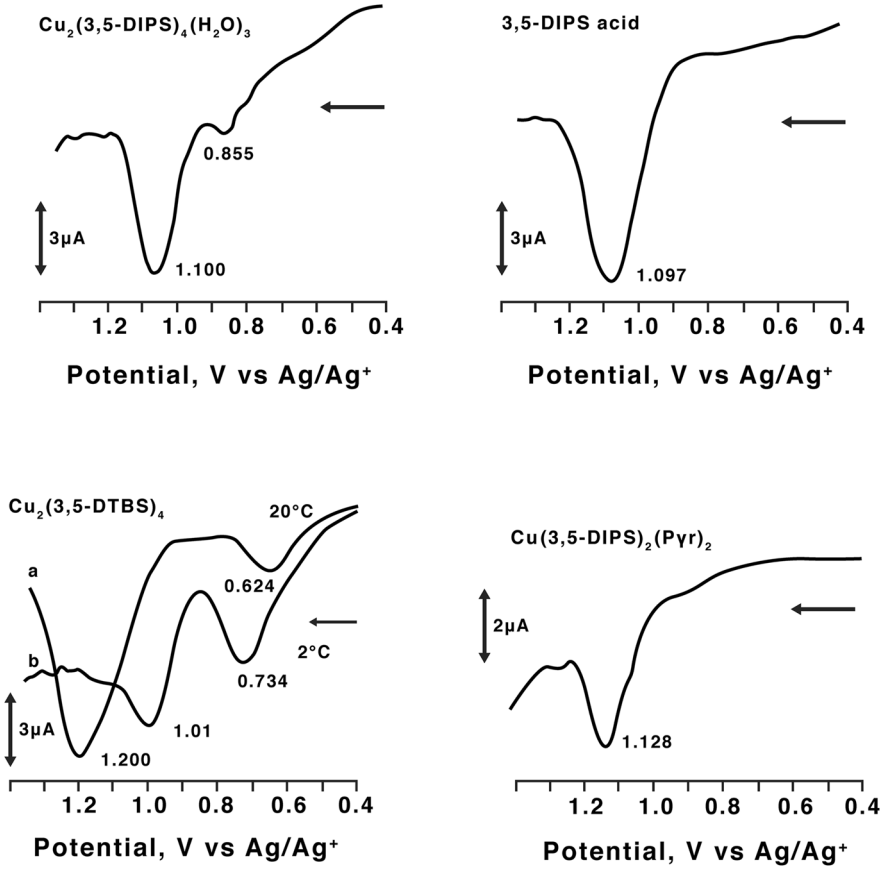


Fig. 4 Differential pulse voltammograms of 0.1 mM of Cu(II) salicylates and 0.4 M of 3,5-DIPS acid in CH_2Cl_2. Supporting electrolyte, 0.1 mM of TBAP; initial potential, 400 mV; final potential, 1350 mV; scan rate, 20 mV s^{-1}; pulse amplitude, 50 mV; pulse width, 50 ms; and pulse period, 200 ms, [27]

the intramolecularly hydrogen-bonded salicylic OH hydrogen atoms. Significantly less intense oxidation peak potentials are observed between 600 and 900 mV versus Ag/Ag+ and correlate with salicylic OH groups that are weakened ("free") intramolecularly hydrogen bonded, while oxygen atoms are coordinate covalently bonded to the Cu(II) atom. The magnitude of oxidation peak potential in the former mentioned range is characteristic for phenolic AOs. For example, an anodic oxidation peak potential of 850 mV versus Ag/Ag+ was found for BHT using our experimental conditions.

These observations suggest that the reactivity of substituted Cu(II) salicylates with respect to peroxyl radical is due to the availability of salicylic OH hydrogen atoms that are not strong intramolecularly hydrogen bonded to carboxylate oxygens. The significantly higher oxidation potentials of intramolecularly hydrogen-bonded salicylic OH hydrogen atoms testify about their less availability and reactivity with respect to peroxyl radical, as measured under our experimental conditions. Their oxidation potentials are very close to those of the salicylic OH hydrogen atoms in the 3,5-DIPS acid (Fig. 4), which are strongly intramolecularly hydrogen bonded and unavailable for reaction with *tert* − butylOO$^{\bullet}$ (Table 1).

Increasing the reaction temperature also affected the ratio of unavailable intramolecularly bonded hydrogen atoms to available hydrogen atoms weakened ("free") of intramolecular hydrogen bonding for H-transfer reaction. The increase in the k_{eff} values with the temperature is also conditioned by certain contribution of more available salicylic OH hydrogen atoms. Structure–reactivity relationships in reactions of substituted Cu(II) salicylates with *tert*-butylperoxyl radical correlated with a magnitude significantly less intense oxidation peak potentials are observed between 600 and 900 mV versus Ag/Ag+ [27].

The voltammetric data allowed also to arrive at the conclusion on the dramatically negative impact on rate constants of the reactions between substituted Cu(II) salicylates and peroxyl radicals due to the axial stronger Lewis base such as pyridine, leads to the disappearance of the lower oxidation potential peak. This explains the marked no measurable in reactivity of Cu(II)(3,5-DIPS)$_2$(pyridine)$_2$ with peroxyl radical. This fact is in accordance with the concept of so-called mediated kinetic medium effect in the reaction observed at axial coordination of a stronger Lewis base, dimethylsulfoxide (DMSO), with the Zn(II) atom of Zn(II)(3,5-DIPS)$_2$, leading to mediated strengthening of intramolecularly bonded hydrogen atoms of phenolic hydroxyl groups of the ligand, and consequently to dramatic fall in their antiradical capacity shown in Scheme 2 [28, 29].

3.4 Mechanism of the Reaction of *tert* − butylOO$^{\bullet}$ Radicals with the Cu(II)$_2$L$_4$, Fe(III)L$_3$, Zn(II)L$_2$ and Mn(II)L$_2$

The mechanism of the anti-*tert* − butylOO$^{\bullet}$ reactivity of these chelates involves abstraction of the hydrogen atom from the phenolic O–H group of the 3,5-DIPS ligand with the formation of an intermediate "chelatephenoxyl radical" and subsequent formation of nonradical products, as shown in Scheme 2.

It can be concluded from the above reactions that the maximal possible free-radical capacity of Cu(II), Zn(II) and Fe(III) metallochelates is equal to twice the number of phenolic OH groups in these molecules. This result is explained by the distinctive mechanism of $Mn(II)L_2$ which involves both coordination of the phenolic oxygen and weakening of the phenolic O–H bond, as well as the oxidation of Mn(II) to Mn(III) in its reaction with *tert* – butylOO•. Based upon our experimental data for the *tert* – butylOO• system, $Mn(II)L_2$ is clearly a more effective antioxidant than the Cu(II), Zn(II) or Fe(III) chelates. With regard to $Cu(II)_2L_4$, $Zn(II)L_2$ and $Fe(III)L_3$, the central metalloelements: Cu(II), Zn(II) and Fe(III) are not easily oxidized to their next higher oxidation state, Cu(III) or Fe-(IV), while Mn(II) is easily oxidized to Mn(III). This is evidenced by the large negative oxidation potential of Cu(II), $E°[Cu(II)/Cu(III)] = -2.6$ V at pH 7 [31], and Fe(III), $E°[Fe(III)/Fe(IV)] = -1.4$ V at pH 7 [32], while the oxidation potential of Mn(II), $E°[Mn(II)/Mn(III)] = -0.1$ V at pH 7 [33], is much smaller and close to the oxidation potential of *tert* – butylOO•, $E°(tert - butylOO^- / tert - butylOO^•) = 0.71$ V [20]. The large oxidation potentials required for the oxidation of Cu(II) to Cu(III) and Fe(III) to Fe(IV) constitute a barrier for their oxidation by *tert* – butylOO• due to the less than required oxidizing capacity of *tert* – butylOO•. A similar situation involving high anti-*tert* – butylOO• reactivity has been reported for Mn(II) (1,10-phenanthroline)$(stearate)_2$, a complex which is devoid of a phenolic OH group [18]. The reductive properties of Mn(II) chelates account for their reactivity as anti-*tert* – butylOO•, electron transfer reactants [16–18]. This reaction pathway, shown below, for the oxidation of $Mn(II)(3,5\text{-}DIPS)_2$ predominates over the mechanism involving abstraction of a hydrogen atom from a phenolic OH group. This mechanism is also corroborated by the disappearance of the EPR signal for $Mn(II)L_2$ during the course of the reaction with *tert* – butylOO• as shown in Fig. 5. The EPR spectrum exhibits a broad signal without fine or hyperfine structure. This signal suggests that dipolar interactions between manganese ions exist [7]. With the oxidation of Mn(II) to Mn(III) by *tert* – butylOO• radical additional reactions occur [18]:

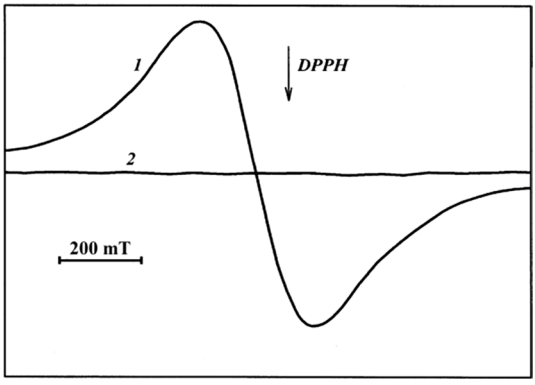
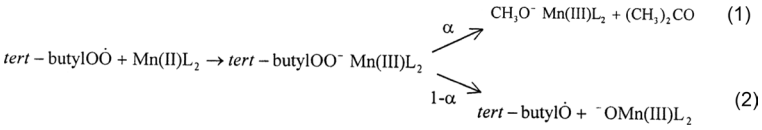


Fig. 5 EPR spectrum of Mn(II) L_2 in 10% (v/v) toluene in heptane (1) before reacting with *tert* – butylOO• at – 31.5 °C (2) after reaction. The arrow indicates peak position for 1,1-diphenyl-2-picrylhydrazyl-radical (DPPH). EPR conditions for spectrum: 9.4 GHz microwave frequency, 0.8 mW microwave power, 0.5 mT modulation amplitude, 100 kHz modulation frequency [23]



$$tert-\text{butylO}^{\bullet} + tert-\text{butylOOH} \rightarrow tert-\text{butylOH} + tert-\text{butylOO}^{\bullet}(\text{Regeneration}). \quad (3)$$

And then most probably,

$$\text{Mn(II)L}_2 + -\text{OMn(III)L}_2 \rightarrow \text{L}_2\text{Mn(II)OMn(III)L}_2. \quad (4)$$

As mentioned above, the value of the rate constant for reaction of $tert-\text{butylOO}^{\bullet}$ with Mn(II)L_2 is increased when ethylacetate is added to the reaction medium (Fig. 6), while adding an electron-donor solvent, ethyl acetate, to the reaction system containing Fe(III)L_3, $\text{Cu(II)}_2\text{L}_4$ or Zn(II)L_2 leads to a decrease in rate constant for reaction of $tert-\text{butylOO}^{\bullet}$. It was shown by the example of Zn(II)L_2 [29] what occurs as a result of bonding of ethyl acetate to Zn(II) via ester carbonyl oxygen atoms with ternary complex formation, that leads to weakening of carboxylate coordinate bonding to Zn(II) and strengthening of intramolecular hydrogen bonding between hydrogen atom of salicylic OH groups and carboxylate oxygens. Subsequent addition of two or three additional equivalents of ethyl acetate leads to intermolecular hydrogen bonding with participation of the hydrogen atom of salicylic OH groups.

This result lends support, once again, to the possibility that the reaction of $tert-\text{butylOO}^{\bullet}$ with Mn(II)L_2 is mechanistically different from the reaction with the Cu(II) and Fe(III) chelates, since in this case ethyl acetate, an electron donor and polar solvent, facilitates the dominant reaction pathway of electron transfer for the reduction of $tert-\text{butylOO}^{\bullet}$. The electron donating and polar character of ethyl acetate stabilizes the charge on the oxygen atom of $tert-\text{butylOO}^{\bullet}$ and leads to a change in oxidation potential for Mn(II)/Mn(III) which would lead to a faster rate of reaction. It should be noted that in the presence of ethyl acetate the ability of Mn(II)L_2 to behave as a $tert-\text{butylOO}^{\bullet}$ scavenger is more than one order of magnitude larger than the activity of *para*-methylphenol (HT) or butylated hydroxytoluene (BHT) (Fig. 2; Table 1). According to reactions (1)–(4), the fraction of reactions resulting in peroxyl radical scavenging, is equal to α:

$$\alpha = \frac{2f_R}{1+f_R}.$$

The values of α calculated by using the measured f_R values for the fraction of reaction (1) are presented in the foot notes to Table 1. However, the occurrence of reaction (2) does not hinder the antioxidant reactivity of Mn(II)L_2 in preventing lipid peroxidation for the following reason. When alpha hydrogen is present

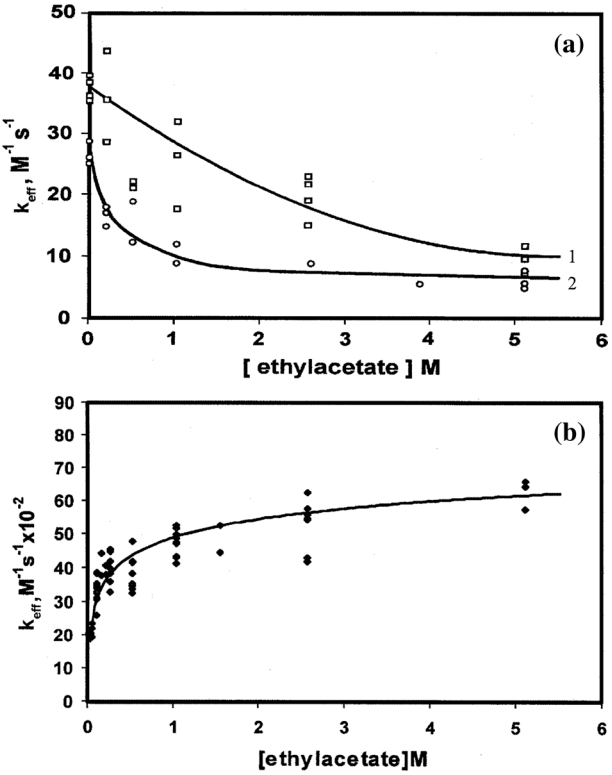


Fig. 6 The kinetic solvent effect of ethyl acetate addition on the value of second-order rate constants for reaction of *tert* – butylOO• with chelate antioxidant.: **a** $Cu(II)_2L_4$ (1) and $Fe(III)L_3$ (2); **b** $Mn(II)L_2$ in 10% (v/v) toluene in heptane in the presence of ethyl acetate at – 31.5 °C [23]

in the structure of the lipoperoxyl radicals, they react with the metallochelates under consideration would occur practically without formation of new free radicals: $\alpha \approx 1$.

$$R_1R_2CHOO^{\bullet} + Mn(II)L_2 \rightarrow HO - Mn(III)L_2 + R_1R_2 = O.$$

Copper(II), iron(III), zinc(II), and manganese(II) 3,5-di-*iso*-propylsalicylate chelates also were investigated to determine their ability to inhibit the free radical initiated chain reactions leading to the peroxidation of model lipids: isopropyl benzene and ethylbenzene. Quantitative kinetic studies of these chelates established the same order of antioxidant, and correspondingly antiradical reactivities, as in kinetic EPR measurements [24].

Thus, Cu(II), Fe(III), Zn(II) and Mn(II) metallosalicylates act as hybrid antioxidants: (i) metallo elements play the role of reaction centers responsible for catalase- and superoxide dismutase-mimetic activity; (ii) phenolic OH group of the ligand "activated" by metalloelement acts as a antiradical center on removal of free radicals by reaction of H-atom transfer; (iii) in case of $Mn(II)L_2$ the central metalloelement

additionally acts as a reaction center on removal of the peroxyl radical by its one-electron reduction. A similar antiradical ligand activation was observed in complexes of metalloelements with flavonoids due to additional stabilization by metalloelements the phenoxyl radicals and quinolide structures [4–6] formed in the reactions of H-atom transfer.

3.5 Reactivity of *tert*-Butylperoxyl Radical with Manganese(III), Cobalt(II), and Nickel(II) Salicylidene Schiff Base Chelates

Schiff bases represent a special class of ligands with a variety of donor atoms exhibiting interesting coordination modes towards transition metals. Schiff-bases have been widely used as ligands because of high stability of the coordination compound, as well as good solubility in common solvents [9].

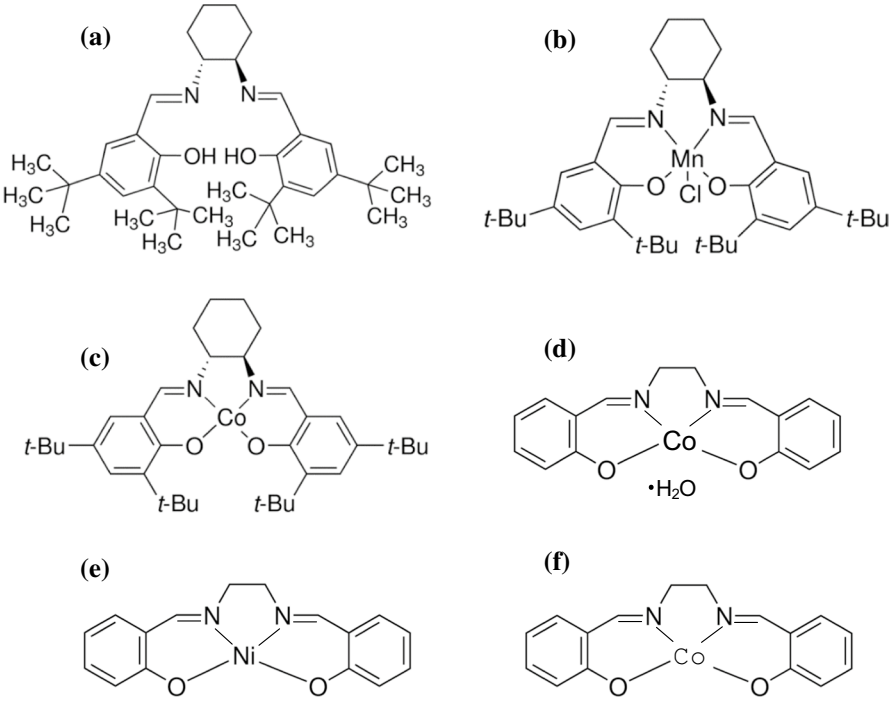
Some of these compounds are identified as having high capacity in scavenging free radicals by the example of DPPH radicals [3, 11, 34].

The objective of the present section was to kinetically study the anti-*tert*-butylperoxyl radical (*tert* – butylOO•) (chain carriers in biomemrane peroxidation reactions) reactivities of Mn(III), Co(II), and Ni(II) salicylidene Schiff base chelates, demonstrated in the Scheme 3. This task was achieved by direct kinetic measurements using an EPR spectroscopy method for reactions of *tert* – butylOO• with the mentioned chelates in a nonpolar lipid mimetic medium [26]. The chemical mechanism of the reaction of *tert* – butylOO• with the chelates was also examined. This information along with kinetic characteristics of the considered reactions may be useful in predicting metalloelement chelate reactivity as bioactive antioxidants.

The value for k_{react} was determined taking into consideration the change in reaction mixture volume with temperature. Usually, the k_{eff} measurement accuracy was 7% of the value presented in Table 2.

3.6 Differential Pulse Voltammetric Studies of the Reaction of *tert*-ButylOO• with Salicylidene Schiff Base Chelates

Differential pulse voltammetric studies through the potential range of 0.1–1.4 V [26] revealed antioxidant reactivity for these chelates. Oxidation peaks were observed at $E_{01} = 0.703$ V, $E_{02} = 0.909$ V, $E_{03} = 1.040$ V, $E_{04} = 1.217$ V vs. Ag/Ag^+ non-aqueous for bschdaMn(III) and $E_{01} = 0.760$ V, $E_{02} = 0.965$ V for bschdaCo(II) as shown in Fig. 7. These results correlate with the oxidation of Mn(III) to Mn(IV) and Co(II) to Co(III). Characteristic peaks in this potential range were not observed for, bsetdaCo(II), bsetdaCo(II)(H_2O), and bsetdaNi(II) as shown in Fig. 7. This explains the large difference in antiperoxyl radical reactivity of bschdaMn(III) and compared with bsetdaCo(II), bsetdaCo(II)(H_2O), and the absence of measurable antiperoxyl radical reactivity of Ni(II)salen chelates. High antiperoxyl radical reactivity of bschdaCo(II) in comparison with bsetdaCo(II), bsetdaCo(II)(H_2O) is conditioned by considerable electron-donating effect of the four *tert*-butyl substitutes and 1,2-ciclohexane fragment in the ligand structure, which significantly reduces the oxidative potential of central metalloelement. The characteristic metalloelement



Scheme 3 Structures of Mn(III), Co(II) and Ni(II), salicylidene Schiff base chelates: **a** (*R*,*R*)-(–)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (bschda). **b** (*R*,*R*)-(–)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (bschdaMn(III)). **c** (*R*,*R*)-(–)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (bschdaCo(II)). **d** *N*,*N*'-bis(salicylidene)ethylenediaminoaquacobalt(II) ≡ *N*,*N*'-Bis(salicylidene)ethylenediaminocobalt(II) hydrate (bschdaCo(II)(H2O)). **e** *N*,*N*'-bis(salicylidene)ethylenediaminonickel(II) (bsetdaNi(II)). **f** *N*,*N*'-Bis(salicylidene)ethylenediaminocobalt(II) (bsetdaCo(II))

oxidation peaks were lost as a result of the reaction of the bschdaMn(III) and Co(II) chelates with *tert* – butylOO• as shown in Fig. 7. These results show that bschdaMn(III) and bschdaCo(II) undergo one-electron oxidations: Co(II) → Co(III) and Mn(III) → Mn(IV).

DPV studies of the reaction products of *tert* – butylOO• with bschdaCo(II) and bschdaMn(III) chelates demonstrated that Co(II) and Mn(III) are oxidized to Co(III) and Mn(IV), respectively, and that the mechanism of the anti-*tert* – butylOO• reactivity of these chelates involves an electron transfer from the central metalloelement to the peroxyl radical. As a result, *tert* – butylOO• is chemically reduced by bschdaCo(II) and bschdaMn(III) as shown:

$$tert - \text{butylOO}^{\bullet} + \text{bschdaM(n+)} \rightarrow tert - \text{butylO}^{-}\text{M(n + 1)+)bschda.}$$

Oxidation of the central metalloelement in bschdaMn(III) and bschdaCo(II) chelates is related to their low oxidation potentials. It is evident that the oxidizing

Table 2 The values of second-order absolute rate constants for reaction of anti-*tert* − butylOO• with antioxidants in organic medium [27]

Rate constant, $k_{react} \times 10^{-2}$ M^{-1} s^{-1}									
Temperature (°C)									
Antioxidant	− 52.5	− 42	− 31.5	− 21.5	− 11	37[a]	f_R	E (kJ mol^{-1})[b]	Log A[c]
BschdaMn(III)	69.2	75.7	102.3	107.5	125.6	227.9	1	8.72	5.87
BschdaCo(II)	188.4	289.5	491.1	730.4	1078	4799.2	1	21.51	9.31
BsetdaCo(II)[d]	0.47	0.62	1.23	2.30	2.94	14	–	22.36	6.92
BsetdaCo(II)(H_2O)[d]	0.13	0.19	0.79	0.82	1.9	7.43	–	25.42	7.16
BHT	27.3	28.2	37.4	47.8	70.1	130.8	2	12.49	6.49

[a]Values obtained by extrapolation of the Arrhenius equation

[b]Arrhenius activation energy

[c]Pre-exponent. The correlation factor, r^2, for values of the Arrhenius equation varied from 0.98 to 0.99

[d]Reaction mixture was composed of heptanes containing 5% toluene, 32% chlorobenzene, and 10% v/v *n*-butanol

capacity of *tert* − butylOO• is sufficient to oxidize Mn(III) and Co(II) in the bschda Schiff base chelates, but not the bsetda Schiff base ligands nor the Ni(II) chelates.

Strict stoichiometric relationships for the reaction of bschdaCo(II) and bschdaMn(III) with *tert* − butylOO• are also consistent with values of $f_R = 1$ for these reactions. These results differ from f_R values of 0.20–0.44 observed for the reaction of *tert* − butylOO• with Co(II)(acetylacetonate)$_2$, as well as Mn(II)(1,10-phenanthroline)(stearate)$_2$, Co(II)(1,10-phenanthroline)(stearate)$_2$, and Mn(II)(3,5-di-*iso*propylsalicylate)$_2$ [18, 23]. The values smaller than 1 for f_R are described for the formation of free radicals along with nonradical products formed with the removal of *tert* − butylOO•.

4 Conclusions

Metal complexes offer a platform for design of therapeutic compounds. The basic ideas for the synthesis and developing various processes in metal complexes is under progress. Copper(II)-, Fe(III)-, Zn(II)-, and Mn(II)-3,5-di-*iso*-propylsalicylate (3,5-DIPS) chelates and Mn(III), Co(II), and Ni(II) salicylidene Schiff base chelates were kinetically examined as antioxidants in the scavenging of *tert*-butylperoxyl radical. Using kinetic EPR methods absolute rate constants and corresponding Arrhenius parameters were determined for reactions of *tert* − butylOO• with these chelates in the temperature range − 63 to − 11 °C. It was established that the order of anti-*tert* − butylOO• reactivity is: Mn(II)(3,5-DIPS)$_2$ >> Cu(II)$_2$(3,5-DIPS)$_4$ > Fe(III)(3,5-DIPS)$_3$ > Zn(II)(3,5-DIPS)$_2$ >> Cu(II)$_2$(acetyl-3,5-DIPS)$_4$ and 3,5-DIPS acid. Mn(II)(3,5-DIPS)$_2$ caused the most rapid rate of removal of *tert* − butylOO• as a result of the oxidation of Mn(II) to Mn(III) by *tert* − butylOO•. The reaction of *tert* − butylOO• with Cu(II)$_2$(3,5-DIPS)$_4$, Zn(II)(3,5-DIPS)$_2$ and Fe(III)(3,5-DIPS)$_3$

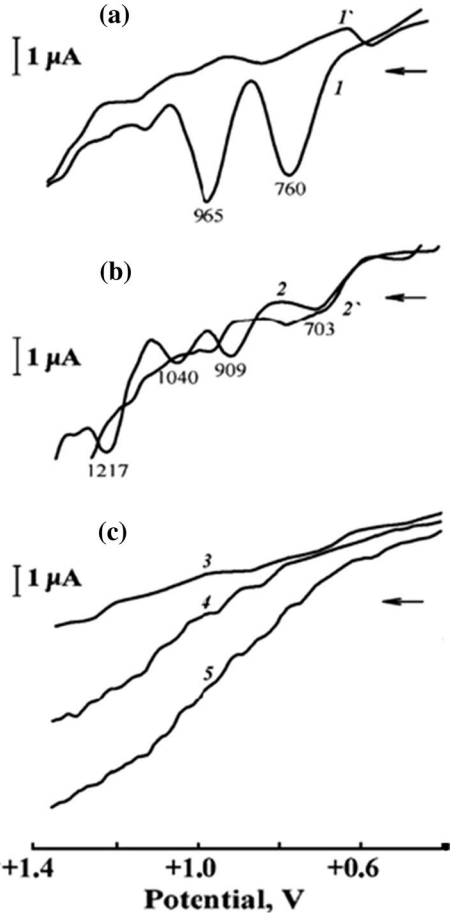


Fig. 7 Differential pulse voltammograms of 8.7×10^{-2} mM bschdaCo(II) (1), bschdaMn(III) (2), bsetdaNi(II) (3), bsetdaCo(II)(H_2O) (4), and bsetdaCo(II) (5) for anodic reduction processes. For bschdaCo(II) and bschdaMn(III) before (1,2) and after (1′,2′) reaction with *tert* – butylOO•. The supporting electrolyte was 0.1 M TBAP in CH_2Cl_2. The initial $E = 100$ mV and final $E = 1400$ mV, the scan rate was 20 mV s^{-1}, sample width = 20 ms, pulse amplitude = 50 mV, pulse width = 50 ms, and pulse period = 200 ms [27]

is due only to hydrogen atom abstraction from the ligand phenolic OH group by *tert* – butylOO•, as a result of their activation by the metalloelement through weakening the intramolecular hydrogen bond. Essentially, the metalloelement salicylates are hybrid antioxidants: the metalloelement exhibits superoxide dismutase (SOD)-mimetic, catalase-mimetic catalytic antioxidant activities, and in the case of Mn(II) antiradical activity too. Simultaneously, the activated OH bond of the ligand acts as a phenolic antiradical center.

High reactivity of *tert* – butylOO• with Mn(III) and Co(II) salicylidene Schiff base chelates was established. These salicylidene Schiff base chelates react in a 1:1 through one-electron transfer reaction stoichiometric ratio with *tert* – butylOO• without free radical formation. Differential pulse voltammetry established that the rapid removal rate of *tert* – butylOO• by these chelates is the result of Mn(III) oxidation to Mn(IV) and Co(II) oxidation to Co(III) by *tert* – butylOO•. It is concluded that the mechanism of alkylperoxyl radical removal by Cu(II)-, Fe(III)-, Zn(II)-, and Mn(II)-3,5-di-*iso*-propylsalicylate (3,5-DIPS) chelates, Mn(III) and Co(II)

salicylidene Schiff base chelates provides valuable information for targeted design in terms of sustainability, activity, redox characteristics and the hybrid action mechanism of bioantiradical metallochelates.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Compliance with Ethics Requirements This article does not contain any studies with human or animal subjects.

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