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Kinetics and Mechanism of Reactions of Aliphatic Stable Nitroxide Radicals in Chemical and Biological Chain Processes

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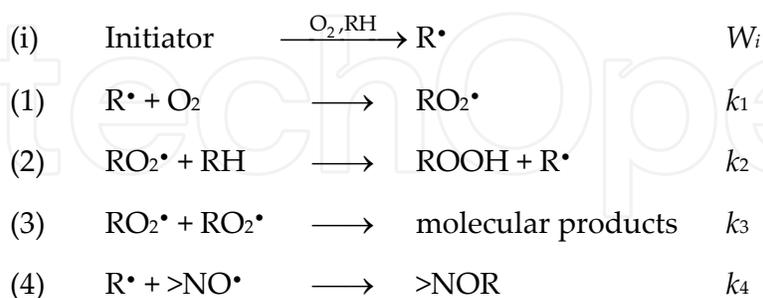
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1. Introduction

Stable nitroxide radicals (>NO•) play very important role in experimental studies and in theoretical analysis of chemical and biochemical processes' mechanism for over 50 years.

For a long time it was believed that cyclic stable nitroxide radicals (piperidine, pyrroline, and imidazoline >NO•) inhibit oxidation of hydrocarbons (RH) and 1- and 1,1- ethylene substituted monomers (M) only via reaction with substrate's alkyl radicals in accordance with Scheme 1 (Buchachenko, 1965; Denisov & Afanas'ev, 2005; Mogilevich & Pliss, 1990). If substrate is M then chains are propagated by polyperoxide radicals (MO₂•) through its addition to monomer's double bond in accordance with the reaction: MO₂• + M → M• (Mogilevich & Pliss, 1990).



Scheme 1. Classical mechanism of organic compounds oxidation inhibited by nitroxide radicals

At the same time a probability of direct reaction of nitroxide with peroxide radicals is considered in a number of works (Barton, 1998; Goldstein & Samuni, 2007; Offer & Samuni, 2002; Pliss et al., 2010a, 2010b, 2012). Therefore it is necessary to review the most significant results in the field of kinetics and mechanism of elementary reactions of piperidine,

pyrroline, and imidazoline $>\text{NO}^\bullet$ with active particles of chemical and biochemical oxidation processes. Such an attempt has been made in this review.

Structures of nitroxide radicals and corresponding hydroxylamines which reactions' mechanisms were analyzed in this work are presented in Figure 1.

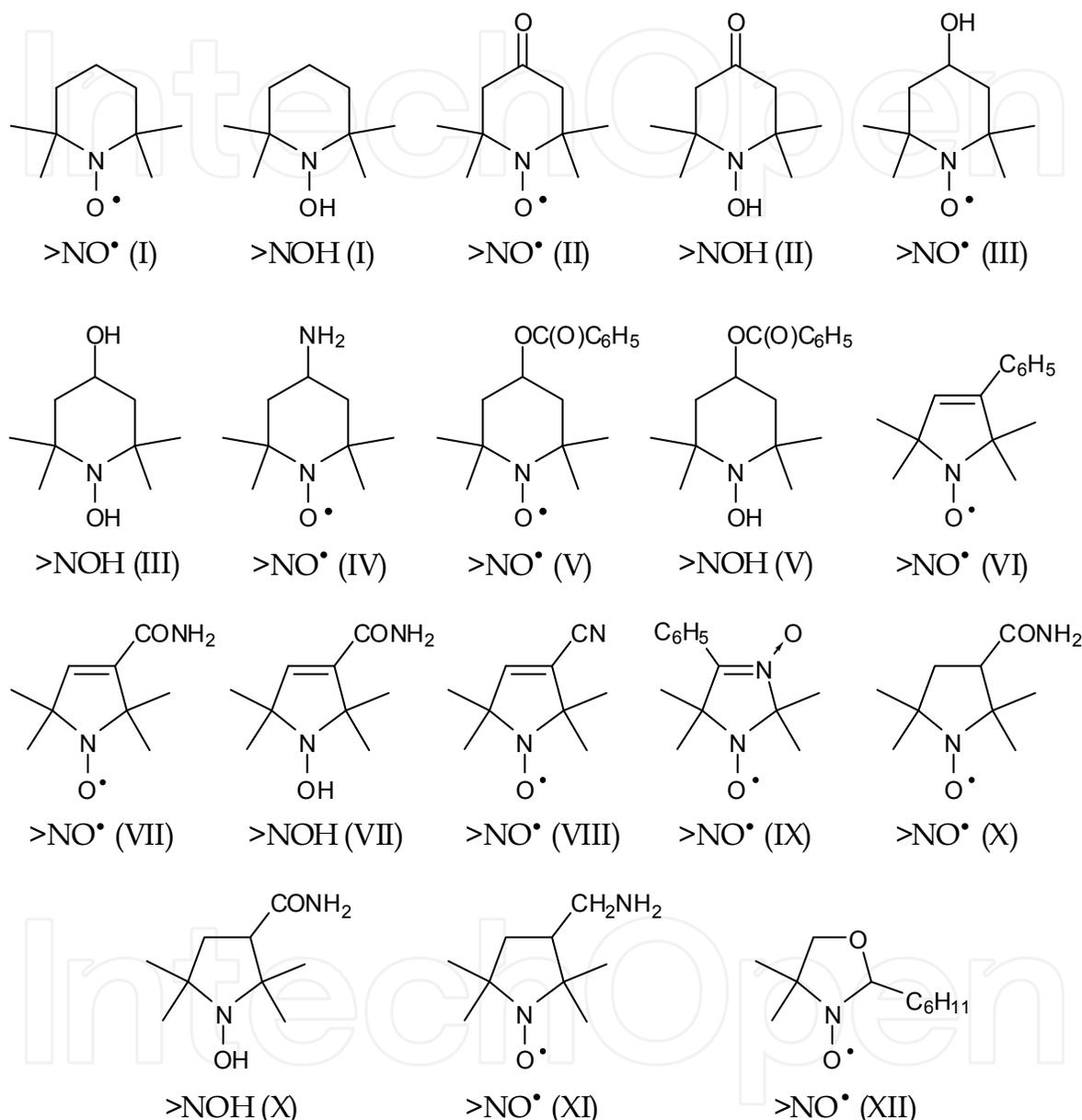


Figure 1. Structures of nitroxide radicals and corresponding hydroxylamines

2. Classical mechanism of organic compounds liquid phase oxidation inhibited by stable nitroxide radicals

For the first time Scheme 1 was proposed by A. Buchachenko with staff to describe the oxidation of ethylbenzene in presence of $>\text{NO}^\bullet$ (II) and (III) (Buchachenko, 1965). k_4/k_1 Values (Table 1) were obtained from kinetic data of some organic compounds' initiated

oxidation in presence of $>\text{NO}\cdot$. It can be seen that nitroxide radicals inhibit oxidation of methacrylic and acrylic ethers more effectively rather than oxidation of alkylaromatic compounds: k_4/k_1 values on average an order of magnitude greater for methacrylates and acrylates as compared with styrene, benzene, and cumene (Table 1).

At the same time k_4/k_1 value for methyl methacrylate (0.36) is close to that for cyclohexyl methyl ether (0.33) (Kovtun et al., 1974). Such results prove an important role of polar effects in reactions of $>\text{NO}\cdot$ with alkyl radicals during vinyl monomers oxidation.

So it should be noted that inhibiting activity of $>\text{NO}\cdot$ increases along with length of methacrylic ethers' alkyl substitute: k_4/k_1 value increases more than 3 times from methyl ether to ionic ether. The similar trend also takes place for acrylic ethers (Table 1).

M• (R•)	k_4/k_1 Value		Reference
	$>\text{NO}\cdot$ (I)	$>\text{NO}\cdot$ (II)	
$\sim\text{CH}_2\text{C}\cdot\text{HC}_6\text{H}_5$	—	0.10	(Browlie & Ingold, 1967)
$\sim\text{CH}_2\text{C}\cdot(\text{CH}_3)\text{COOCH}_3$	0.36	0.37	(Pliss & Aleksandrov, 1977)
$\sim\text{CH}_2\text{C}\cdot(\text{CH}_3)\text{COO}-n\text{-C}_4\text{H}_9$	0.72	0.72	(Pliss & Aleksandrov, 1977)
$\sim\text{CH}_2\text{C}\cdot(\text{CH}_3)\text{COO}-iso\text{-C}_4\text{H}_9$	0.72	0.72	(Pliss & Aleksandrov, 1977)
$\sim\text{CH}_2\text{C}\cdot(\text{CH}_3)\text{COO}-n\text{-C}_9\text{H}_{19}$	1.20	1.20	(Pliss & Aleksandrov, 1977)
$\sim\text{CH}_2\text{C}\cdot\text{HCOOCH}_3$	2.27	2.27	(Pliss & Aleksandrov, 1977)
$\sim\text{CH}_2\text{C}\cdot\text{HCOO}-n\text{-C}_4\text{H}_9$	5.20	5.20	(Pliss & Aleksandrov, 1977)
$\text{CH}_3\text{C}\cdot\text{HC}_6\text{H}_5$	0.04	—	(Browlie & Ingold, 1967)
$(\text{CH}_3)_2\text{C}\cdot\text{C}_6\text{H}_5$	0.05	—	(Kovtun et al., 1974)

Table 1. k_4/k_1 Values in oxidizing monomers and hydrocarbons at 323 K

Absolute k_4 values were measured in (Aleksandrov et al., 1979) by ESR spectroscopy method (Table 2). We note that $>\text{NO}\cdot$ is one of the strongest acceptors for alkyl radicals. k_4 Values are close to ones for molecular oxygen addition to alkyl radicals ($k_1 \geq 1 \cdot 10^7 \text{ M}^{-1} \cdot \text{s}^{-1}$ (Aleksandrov et al., 1979)). k_4 Values for reactions of $>\text{NO}\cdot$ (I) – (VII) with alkyl radicals of methyl methacrylate at 323 K are within a limits of $(0.8 - 2.0) \cdot 10^7 \text{ M}^{-1} \cdot \text{s}^{-1}$ (Table 2). Even higher k_4 values for the reaction of $>\text{NO}\cdot$ (I) with R• of low molecular weight at 291 K were obtained in (Bowry & Ingold, 1992) by laser flash photolysis method: these values are within a limits of $1 \cdot 10^6 - 2 \cdot 10^9 \text{ M}^{-1} \cdot \text{s}^{-1}$.

The probability of $>\text{NO}\cdot$ participation in chain initiation process via its reaction with monomer's π -bond was estimated in (Ruban et al., 1967) using the reaction of $>\text{NO}\cdot$ (I) and (III) with styrene and α -methyl styrene as example. Reaction



at 393 K proceeds with constant rate value which equals to $4.6 \text{ M}^{-1} \cdot \text{s}^{-1}$ in styrene, but in α -methyl styrene this reaction doesn't proceed at all even at 453 K (Ruban et al., 1967). It's clear that $>\text{NO}\cdot$ initiating function completely suppresses by its participation in reaction (4).

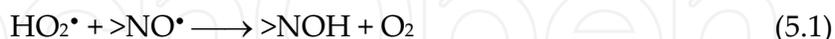
Further we will see that reaction (4) is not the only one in oxidation inhibition by nitroxide radicals.

M•	>NO•	$k_4, M^{-1}\cdot s^{-1}$
$\sim CH_2C\cdot HC_6H_5$	I	$8.0\cdot 10^6$
$\sim CH_2C\cdot (CH_3)COOCH_3$	I	$1.2\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COOCH_3$	II	$0.8\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COOCH_3$	III	$0.8\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COOCH_3$	V	$1.4\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COOCH_3$	VI	$1.6\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COOCH_3$	VII	$1.2\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COOCH_3$	VIII	$2.0\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COO-n-C_4H_9$	I	$1.2\cdot 10^7$
$\sim CH_2C\cdot (CH_3)COO-iso-C_4H_9$	I	$0.9\cdot 10^7$
$\sim CH_2C\cdot HCOOCH_3$	I	$3.0\cdot 10^7$
$\sim CH_2C\cdot HCOO-iso-C_4H_9$	I	$1.8\cdot 10^7$
<i>cyclo-C</i> • ₆ H ₁₁	I	$3.0\cdot 10^7$
(CH ₃) ₂ C•CN (in benzene)	I	$8.6\cdot 10^7$

Table 2. Rate constants for the reaction M• (R•) + >NO• at 323 K (Aleksandrov et al., 1979)

3. Multiple chain-breaking by stable nitroxide radicals

It was proved on oxidation of a number of compounds that oxidation chains propagate by peroxide radicals which possess redox properties. These are HO₂• radicals (cyclohexadiene (Howard & Ingold, 1967), 1,2-ethylene substituted and 1,4-butadiene substituted monomers (Mogilevich & Pliss, 1990)), >C(OH)O₂• (alcohols (Kharitonov & Denisov, 1967)), and >CH-CH(OO•)N< (aliphatic amines (Aleksandrov, 1987)). Dual reactivity of these radicals results in multiple >NO• participation in chain termination processes (Denisov, 1996). So for hydroperoxide radical this process can be described with the following reactions (Denisov, 1996):



Let's perform the analysis of oxidation mechanism with >NO• regeneration and one without it.

3.1. Analysis of oxidation mechanism without nitroxide radical regeneration

In accordance with Scheme 1 initial rate process (W) without >NO• regeneration would be described by the following equation ($W = W_0$ when $[>NO\cdot]_0 = 0$):

$$W_i \left(\frac{W_0}{W} - \frac{W}{W_0} \right) = \frac{k_4 [>NO\cdot]_0 W_0}{k_1 [O_2]} \quad (1)$$

If $k_4[>\text{NO}\cdot]_0 \gg k_3[\text{RO}_2\cdot]$ then

$$W = \frac{k_1[\text{O}_2]}{k_4[>\text{NO}\cdot]_0} W_i \quad (2)$$

So the rate process in linear termination mode (high $[>\text{NO}\cdot]_0$) is directly proportional to the partial oxygen pressure (P_{O_2}). Therefore if oxygen is substituted by air the oxidation rate is to decrease 5 times. Such results were gained in (Browlie & Ingold, 1967; Pliss & Aleksandrov, 1977). But here is one important circumstance. From literature data (Aleksandrov, 1987) it's known that the reduction of nitroxide to corresponding hydroxylamine ($>\text{NOH}$) occurs via the reaction of aminoalkyl radical $>\text{N}-\text{C}\cdot\text{H}-\text{CH}<$ with nitroxide radical as $>\text{NO}\cdot$ attack to $\beta\text{-C}-\text{H}$ bond of alkyl radical.

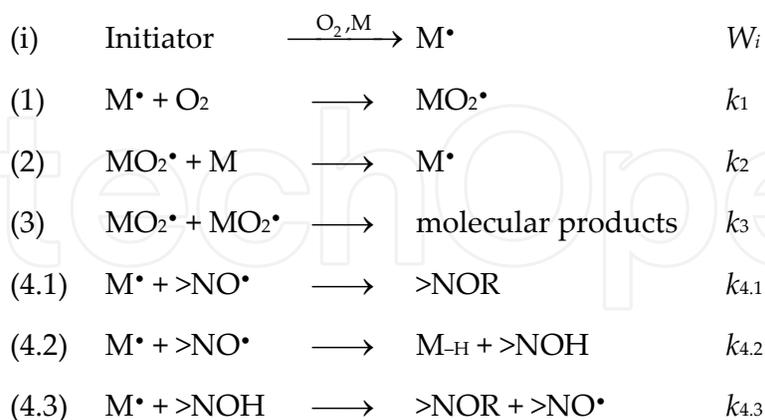


The hydroxylamines being formed are thermally stable under experimental conditions (Aleksandrov, 1987). If we assume that $>\text{NOH}$ is able to react with $\text{R}\cdot$



then $>\text{NO}\cdot$ stoichiometric coefficient must be more than 1.

Let's consider the probability of $>\text{NO}\cdot$ cross-disproportionation with other alkyl radicals. Such a consideration is quite useful cause at physiological P_{O_2} values in body tissues of higher animals and humans (5 – 50 torus) oxygen concentration is less than $1 \cdot 10^{-4}$ M (Porter & Wujek, 1984). In this case inequality $[\text{RO}_2\cdot] \gg [\text{R}\cdot]$ is not satisfied and it's necessary to take into account alkyl radicals' participation contribution. This can be done by modifying Scheme 1 for vinyl monomers' oxidation (Scheme 2).



Scheme 2. Mechanism of organic compounds oxidation inhibited by nitroxide radicals taking into account $\text{M}\cdot$ with $>\text{NO}\cdot$ disproportionation

Let's estimate $>\text{NO}\cdot$ recombination and disproportionation shares ratio according to reactions (4.1) and (4.2). There's almost no any experimental data for such estimation, so we have to use the results of quantum-chemical calculations.

Table 3 represents the values of quantum energies of $>\text{NO}^\bullet$ reactions¹ with peroxyalkyl radicals $\sim\text{OOM}^\bullet$ (DFT B3LYP/6-31G* calculation similar to one in (Becke, 1993)). As a structural unit we've used $-\text{OOCH}_3$ fragment. As can be seen from the table, such operation is quite acceptable: substitution of $-\text{OOCH}_3$ to $-\text{CH}_2\text{CH}_3$ or to $-\text{CH}_2\text{CH}_2\text{CH}_3$ doesn't result in significant changes in energy values calculated.

It should be noted that in accordance with calculated results recombination's probability is significantly greater as compared with disproportionation's one: mean difference in energies is greater or equal of 30 kJ/mol. However, cross-disproportionation in liquid phase also can not be excluded: polar effects may have a significant effect especially if there are polar groups in conjugation with $\beta\text{-C-H}$ bond (Roginskii, 1987). Recombination and disproportionation energies lowering during methyl group addition to α -position of radical center $\sim\text{OOM}^\bullet$ also seem to be a logical cause as a steric effects appear in this case.

M $^\bullet$	Reaction type	
	M $^\bullet$ + $>\text{NO}^\bullet \rightarrow \text{MON}$	M $^\bullet$ + $>\text{NO}^\bullet \rightarrow \text{M-H} + >\text{NOH}$
$\text{C}_6\text{H}_5\text{CH}^\bullet\text{CH}_2\text{OOCH}_3$	-121	-77
$\text{C}_6\text{H}_5\text{CH}^\bullet\text{CH}_2\text{CH}_3$	-136	-69
$\text{C}_6\text{H}_5\text{CH}^\bullet\text{CH}_2\text{CH}_2\text{CH}_3$	-125	-70
$\text{C}_6\text{H}_5\text{C}^\bullet(\text{CH}_3)\text{CH}_2\text{OOCH}_3$	-79	-70
$\text{C}_6\text{H}_5\text{C}^\bullet(\text{CH}_3)\text{CH}_2\text{CH}_3$	-94	-68
$\text{C}_6\text{H}_5\text{C}^\bullet(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$	-69	-67
$\text{CH}_3\text{OC}(=\text{O})\text{CH}^\bullet\text{CH}_2\text{OOCH}_3$	-127	-111
$\text{CH}_3\text{OC}(=\text{O})\text{CH}^\bullet\text{CH}_2\text{CH}_3$	-172	-145
$\text{CH}_3\text{OC}(=\text{O})\text{CH}^\bullet\text{CH}_2\text{CH}_2\text{CH}_3$	-144	-93
$\text{CH}_3\text{OC}(=\text{O})\text{C}^\bullet(\text{CH}_3)\text{CH}_2\text{OOCH}_3$	-79	-61
$\text{CH}_3\text{OC}(=\text{O})\text{C}^\bullet(\text{CH}_3)\text{CH}_2\text{CH}_3$	-93	-75
$\text{CH}_3\text{OC}(=\text{O})\text{C}^\bullet(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$	-88	-79
Mean value	-111	-82

Table 3. Reaction energies of alkyl radicals with $>\text{NO}^\bullet$ (I) (kJ/mol)

Reactions (4.2) and (4.3) rates ratio can be estimated on the basis of experimental kinetic data of $>\text{NO}^\bullet$ (I) consumption in cumene, styrene, or methyl methacrylate in inert atmosphere. Experiment conditions: 323 K, atmosphere of argon, $[>\text{NO}^\bullet(\text{I})]_0 = 5 \cdot 10^{-3}$ M, initiator – azobisisobutyronitrile, $W_i = 1 \cdot 10^{-7}$ M \cdot s $^{-1}$. The dynamic equilibrium is to set over time in case of reactions (4.2) and (4.3) and observed residual ESR signal value is to increase along with $[>\text{NO}^\bullet]_0$ growth since the following equalities are valid during that equilibrium:

¹ In chemical thermodynamics quantum-chemically calculated reaction energy is used. It is a difference between full energies of reaction's products and reagents. This value often correlates with experimental value – enthalpy of reaction (<http://cccbdb.nist.gov/>).

$$k_{4.2}[\overline{R^\bullet}][\overline{>NO^\bullet}] = k_{4.3}[\overline{R^\bullet}][\overline{>NOH}]$$

$$[\overline{>NOH}] = [\overline{>NO^\bullet}]_0 - [\overline{>NO^\bullet}]$$

$$[\overline{>NO^\bullet}] = \frac{k_{4.3}[\overline{>NO^\bullet}]_0}{k_{4.2} + k_{4.3}}, \text{ whence } \frac{k_{4.2}}{k_{4.3}} = \frac{[\overline{>NO^\bullet}]_0}{[\overline{>NO^\bullet}]} - 1$$

After completely $>NO^\bullet$ consumption the residual ESR signal amplitude doesn't exceed a noise level under experimental conditions. This corresponds to potential stationary $>NO^\bullet$ concentration of less than 10^{-7} M (ESR spectrometer Adani CMS 8400). In this case $[\overline{>NOH}] \approx [\overline{>NO^\bullet}]_0$ and at $[\overline{>NO^\bullet}]_0 = 5 \cdot 10^{-4}$ M we have the following value of $k_{4.2}/k_{4.3}$ ratio:

$$k_{4.2}/k_{4.3} = (5 \cdot 10^{-4} / 1 \cdot 10^{-7}) - 1 \approx 5 \cdot 10^4$$

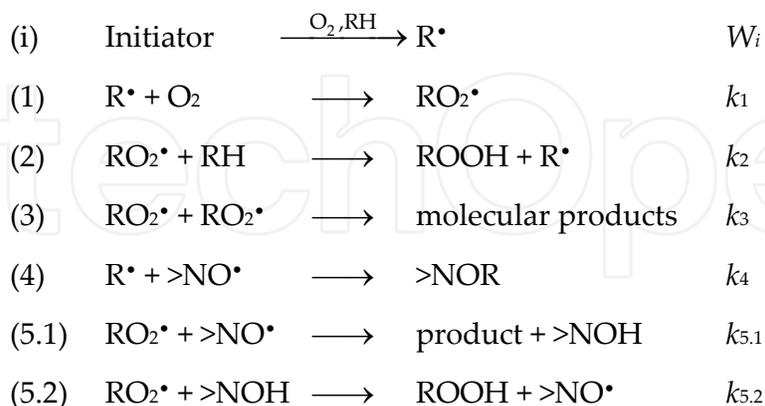
And now the ratio of (4.3) to (4.2) reaction rates can be estimated:

$$\frac{W_{4.3}}{W_{4.2}} = \frac{k_{4.3}[\overline{>NOH}]}{k_{4.2}[\overline{>NO^\bullet}]} \approx 2 \cdot 10^{-5} \frac{[\overline{>NOH}]}{[\overline{>NO^\bullet}]}$$

Therefore in range of up to 99% of $>NO^\bullet$ consumption reaction's (4.3) share is less than 1% of reaction (4.2), so practically there's no any $>NO^\bullet$ regeneration at all. That is $f = 1$ in inert atmosphere and in these substrates' medium. It's obvious that reaction (4.2) would be completely suppressed by reaction of $>NOH$ with RO_2^\bullet at $[O_2] > 1 \cdot 10^{-4}$ M.

3.2. Analysis of oxidation mechanism with nitroxide radical regeneration

In case of $>NO^\bullet$ regeneration the oxidation's mechanism describes by Scheme 3.



where $RO_2^\bullet = HO_2^\bullet, >C(OH)O_2^\bullet, \text{ or } >CH-CH(OO^\bullet)N<$

Scheme 3. Mechanism of organic compounds oxidation inhibited by nitroxide radicals taking into account $>NO^\bullet$ regeneration

The following equation is valid for this scheme:

$$W_i \left(\frac{W_0}{W} - \frac{W}{W_0} \right) = \frac{k_4 [>NO^\bullet]_0 W_0}{k_1 [O_2]} + \frac{2k_5 [>NO^\bullet]_0 W_i^{0.5}}{k_3^{0.5}} \quad (3)$$

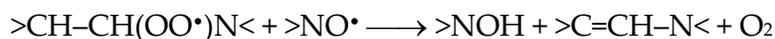
where $k_5 = (k_{5.1} [>NO^\bullet] + k_{5.2} [>NOH])/2 [>NO^\bullet]_0$.

Kinetic analysis shows that at $[O_2] \sim 1 \cdot 10^{-2}$ M and $[>NO^\bullet]_0 < 10^{-4}$ M the contribution of reaction (4) to chain termination process is negligible, and then

$$\frac{W_0}{W} - \frac{W}{W_0} = \frac{2k_5 [>NO^\bullet]_0}{(W_i k_3)^{0.5}} \quad (4)$$

With the drop of P_{O_2} and small share of quadratic chain termination the oxidation rate will decrease not linearly, but slower. Such facts were found for instance in (Pliss & Aleksandrov, 1977; Ruban et al., 1967).

Reaction (5.1) proceeds as disproportionation of nitroxide and peroxide radicals (Denisov, 1996):



$>NO^\bullet$ regeneration and multiple chain termination processes are caused just by subsequent reaction (5.2). Measured kinetic inhibiting factors² for different nitroxide radicals and substrates presented for example in review (Denisov, 1996). The most of f values greater than ten and reflects just a lower bound of this value.

4. Specific features of nitroxide and peroxide radicals reactions in biological systems and in liquid phase organic substrates

Like transition metals, nitroxide radicals can easily transform both to oxidized (oxoammonium cation) and to reduced (hydroxylamine) forms (Berliner, 1998; Sen' & Golubev, 2009; Zhdanov, 1992). This fact, along with $>NO^\bullet$ ability to penetrate through cell membranes and with its paramagnetic properties, suggests that nitroxide radicals poses a number of unique features unlike the compounds of any other class. Like antioxidants and mimetics of superoxide dismutase enzyme, $>NO^\bullet$ are able to supply an effective protection for cells and tissues (Denisov & Afanas'ev, 2005; Soule et al., 2007; Wilcox, 2010). Nitroxide radicals inhibit oxidation of lipids in fatty acids' micelles (Damiani et al., 2002; Noguchi et al., 1999), liposome membranes (Damiani et al., 2002; Wilcox, 2010), lipoproteins (Damiani et al., 1994), and in low density microsomes (Antosiewicz et al., 1995; Nilsson et al., 1990). At the moment there's not enough information concerning $>NO^\bullet$ reactions with redox peroxide

² Inhibiting factor is ratio of real induction period (t) to theoretical period of inhibitor conversion (φ), i.e. $f_{inh} = t/\varphi$, where $\varphi = f [>NO^\bullet] / W_i$ (f – stoichiometric inhibiting factor).

radicals to understand such reactions' mechanisms. In fact, there is no any certain agreement on this reaction, so some authors consider it as unlikely one (Blough, 1988; Browlie & Ingold, 1967; Damiani et al., 2002; Denisov, 1996).

Our recent results concerning reactions of $>\text{NO}\cdot$ (I) – (VII) with $\text{MO}_2\cdot$ radicals of 1,1-substituted ethylenes allows suggestion that such reaction's probability is quite high.

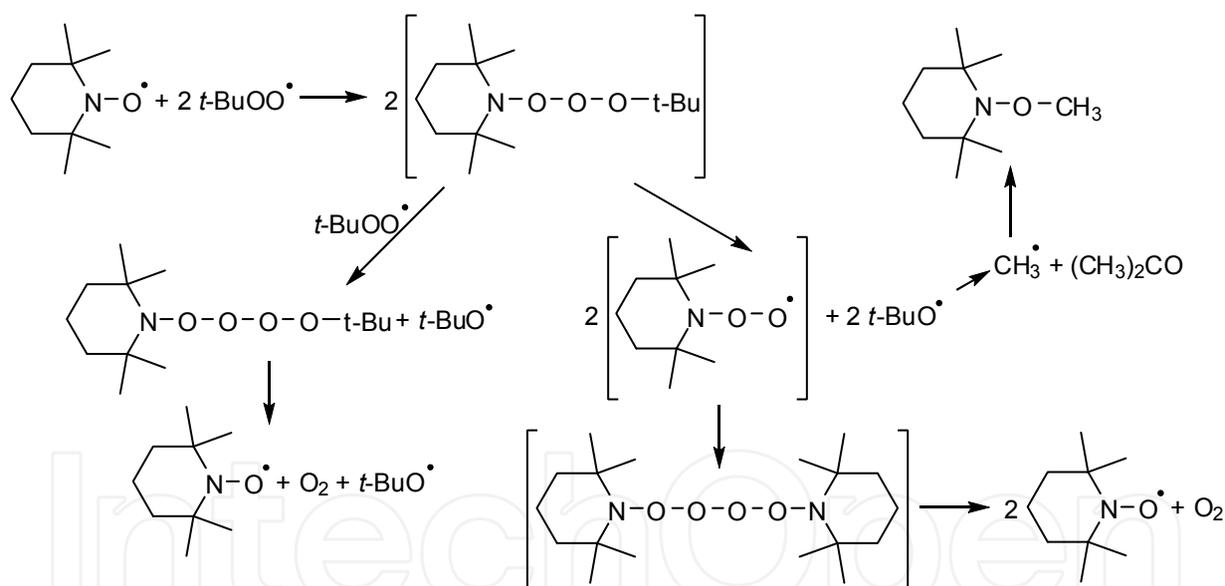
Let's review some experimental data in this field to understand the situation.

4.1. Nitroxide and peroxide radicals reaction under conditions modeling biological systems

Barton et al. assumed that in reaction of $>\text{NO}\cdot$ (I) with $(\text{CH}_3)_3\text{COO}\cdot$ the formation of quite stable intermediate should take place (Barton et al., 1998):



Further this intermediate should decompose to a number of products with concomitant formation of molecular oxygen and $>\text{NO}\cdot$ regeneration according to the following very speculative scheme (Scheme 4) with no any kinetic evidence (Barton et al., 1998).



Scheme 4. Mechanism of nitroxide with tert-butyl peroxide radicals reaction according to (Barton et al, 1998)

Stipa attempted to prove this scheme with *ab initio* quantum-chemical calculations (Stipa, 2001). The calculations were performed using Gaussian 98 Hartree-Fock method and complete basis set CBS-QB3. $\text{H}_2\text{NO}\cdot$ Radical was used as a model of $>\text{NO}\cdot$ (I) in view of available computer resources limitations (work was submitted in April 2001). The calculations' results indicate the possibility of Scheme 4.

This conclusion seems to be quite controversial since radical $\text{H}_2\text{NO}\cdot$ can not provide an adequate $>\text{NO}\cdot$ (I) model. For example, standard enthalpy calculated for the first reaction

stage was -1.794 kcal/mol (table 2 in (Stipa, 2001)), i.e. this value is not very different from zero within the quantum-chemical calculations accuracy. This suggests that the studied trioxide apparently must be thermodynamically unstable structure. At the same time, radical $\text{H}_2\text{NO}^\bullet$ is much more active than simulated $>\text{NO}^\bullet$ (I). It's easy to show with Density Functional Theory (DFT) calculations (Becke, 1993). Quantum energy values of radicals $\text{H}_2\text{NO}^\bullet$ and $>\text{NO}^\bullet$ (I) recombination with $\text{CH}_3\text{O}^\bullet$ and $\text{CH}_3\text{OO}^\bullet$ were calculated by DFT B3LYP/6-31G* (similar calculation is shown in Table 3). The results are shown below.

Radical	Recombination energy, kJ/mol	
	$>\text{NO}^\bullet$ (I)	$\text{H}_2\text{NO}^\bullet$
HO^\bullet	-28.3	-98.4
HOO^\bullet	48.1	-20.4
CH_3^\bullet	-150.6	-232.8
$\text{CH}_3\text{O}^\bullet$	11.5	-58.2
$\text{CH}_3\text{OO}^\bullet$	60.3	9.92

Table 4.

Even this simple example shows that stable nitroxide radical $>\text{NO}^\bullet$ (I) is significantly less active than $\text{H}_2\text{NO}^\bullet$.

Offer and Samuni also suggest that stable trioxide formation proceeds in reaction of tert-amidinopropyl radicals with $>\text{NO}^\bullet$ (I) and (III) in phosphate buffer at pH 7.4 and 310 K (Offer & Samuni, 2002):



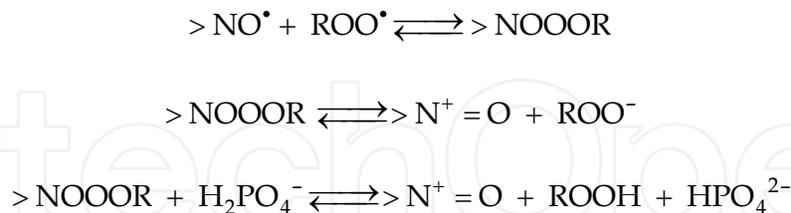
This reaction was studied with combination of ESR-spectroscopy method and cyclic voltammetry, but no any kinetic evidences of product formation and its subsequent transformation were provided.

Brede et al. studied the reaction of $n\text{-C}_{17}\text{N}_{35}\text{OO}^\bullet$ with $>\text{NO}^\bullet$ (I) with pulse radiolysis at room temperature (Brede et al., 1998). The rate constant value $k < 10^5 \text{ M}^{-1}\cdot\text{s}^{-1}$ was specified but the reaction's mechanism wasn't discussed.

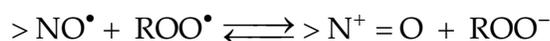
Goldstein S. and Samuni also determined the rate constants of reactions of $\text{CH}_3\text{OO}^\bullet$, $(\text{CH}_3)_3\text{COO}^\bullet$, $\text{CH}_2(\text{OH})\text{OO}^\bullet$, and HO_2^\bullet with $>\text{NO}^\bullet$ (I) – (IV), (X) – (XII) with pulse radiolysis at room temperature (Goldstein & Samuni, 2007). The values obtained are shown in Table 4. The mechanism of $\text{RO}_2^\bullet + >\text{NO}^\bullet$ reaction was discussed; therefore let's consider this paper in more detail.

It was shown that nitroxide with peroxide radicals' reaction mainly results in formation of corresponding oxoammonium cations. In case of $(\text{CH}_3)_3\text{COO}^\bullet$ the formation of stable cation radical $>\text{NO}^\bullet$ (I) and decay products of relatively unstable cation radical $>\text{NO}^\bullet$ (II) was spectrophotometrically detected. In case of HOO^\bullet the reaction with piperidine nitroxide radicals is catalyzed by anion H_2PO_4^- as noted in (Goldstein & Samuni, 2007). Therefore under physiological conditions (pH 7.4 and $5 \cdot 10^{-2} \text{ M}$ phosphate) observed rate constants for piperidine nitroxide radicals are slightly greater than those shown in Table 4. Moreover,

catalysis by H_2PO_4^- anions implies that nitroxide with peroxide radicals' reaction proceeds according to inner-sphere electron transfer mechanism when $>\text{NOOR}$ adduct's decomposition can undergo general acid catalysis:



It's obvious that in absence of catalysis the adduct's formation may also occur, but inner-sphere electron transfer mechanism still can not be excluded:



Known rate constants of reaction $\text{HO}_2^\bullet (>\text{C}(\text{OH})\text{O}_2^\bullet) + >\text{NO}^\bullet$ (I) and (III) in organic solvents are in the range of $1.1 \cdot 10^4 - 2.1 \cdot 10^5 \text{ M}^{-1} \cdot \text{s}^{-1}$ at 323 K (Aleksandrov, 1987; Wilcox, 2010), which is two-three orders of magnitude lower than values shown in Table 5. Such a huge difference may hardly be explained only by the reaction's specificity in phosphate buffer. Further reaction of radicals HO_2^\bullet and $\text{CH}_2(\text{OH})\text{OO}^\bullet$ with $>\text{NO}^\bullet$ proceeds, as is well known, as disproportionation rather than recombination (Denisov, 1996; Denisov & Afanas'ev, 2005; Mogilevich & Pliss, 1990).

$>\text{NO}^\bullet$	$\text{CH}_3\text{OO}^\bullet$	$(\text{CH}_3)_3\text{COO}^\bullet$	$\text{CH}_2(\text{OH})\text{OO}^\bullet$	⁾ HO_2^\bullet
I	$2.8 \cdot 10^7$	$5.1 \cdot 10^7$	$1.0 \cdot 10^8$	$1.1 \cdot 10^8$
II	$2.8 \cdot 10^5$	$5.4 \cdot 10^5$	—	$<6 \cdot 10^6$
III	$3.3 \cdot 10^6$	$5.4 \cdot 10^6$	$4.4 \cdot 10^7$	$2.7 \cdot 10^7$
IV	$1.0 \cdot 10^6$	$1.5 \cdot 10^6$	—	$<1 \cdot 10^7$
X	$8.1 \cdot 10^5$	$1.1 \cdot 10^5$	$9.0 \cdot 10^6$	$1.1 \cdot 10^6$
XI	$9.6 \cdot 10^5$	$1.5 \cdot 10^6$	—	$1.1 \cdot 10^6$
XII	$5.0 \cdot 10^4$	$6.7 \cdot 10^4$	—	$1.6 \cdot 10^5$

⁾ Calculated on the base of (Goldstein et al., 2003; Goldstein & Samuni, 2007).

Table 5. Rate constants ($\text{M}^{-1} \cdot \text{s}^{-1}$) of $\text{ROO}^\bullet + >\text{NO}^\bullet$ reaction (Goldstein & Samuni, 2007).

It's important that authors (Goldstein & Samuni, 2007) on the base of experimental data suggested that rate constant of reaction $\text{RO}_2^\bullet + >\text{NOH}$ doesn't exceed $1 \cdot 10^5 \text{ M}^{-1} \cdot \text{s}^{-1}$, i.e. this reaction is much slower as compared with $\text{RO}_2^\bullet + >\text{NO}^\bullet$ (Table 4). Thereby we note that, as it well known (Denisov, 1996; Denisov & Afanas'ev, 2005; Mogilevich & Pliss, 1990), upon a competition of reactions (5.1) and (5.2) (see Scheme 2) the rate-limiting reaction is just the first one.

As can be seen from the results above, the mechanism of nitroxide with peroxide radicals' reactions in biological systems isn't elucidated at all. The authors of works analyzed are inclined to possibility of $>\text{NO}^\bullet$ reaction not only with peroxide radicals poses redox

properties: HO_2^\bullet , $>\text{C}(\text{OH})\text{O}_2^\bullet$, but with RO_2^\bullet which are oxidants only: $(\text{CH}_3)_3\text{COO}^\bullet$, $n\text{-C}_{17}\text{H}_{35}\text{OO}^\bullet$ (Barton et al., 1998; Brede et al., 1998; Goldstein et al., 2003; Goldstein & Samuni, 2007; Offer & Samuni, 2002; Stipa, 2001). It is assumed that such a reaction occurs as recombination with formation of trioxide. According to the authors of papers cited, nitroxide radicals are able to provide protection against oxidation at extremely low concentrations due to the regeneration process resulting from the reaction of corresponding oxoammonium cations with common biological reducing agents.

Hereby it's interesting to consider the reaction of $>\text{NO}^\bullet$ with RO_2^\bullet which are only oxidants under conditions when oxoammonium cations' formation is improbable, i.e. during an oxidation in organic phase.

4.2. Nitroxide radicals reactions with peroxide radicals of 1- and 1,1- ethylene substituted monomers

As it has already been mentioned above, reactions of $>\text{NO}^\bullet$ with peroxide radicals of 1- and 1,1- ethylene substituted monomers were discovered recently (Pliss et al., 2010a, 2010b, 2012). Authors (Pliss et al., 2010a, 2010b) on the basis of kinetic data of styrene's and (meth)acrylates' oxidation in presence of piperidine, pyrroline, and imidazoline $>\text{NO}^\bullet$ suggested that nitroxide radicals inhibit the oxidation process via $>\text{NO}^\bullet$ reaction with substrate's both alkyl and peroxide radicals, and moreover $>\text{NO}^\bullet$ regeneration occurs during chain termination process in accordance with reactions:



The following results served grounds for these assumptions: oxygen consumes linearly in presence of $>\text{NO}^\bullet$ for all monomers for a long period of time. That period is greater than the theoretical induction period, and if P_{O_2} reduces to five times (from $1 \cdot 10^5$ to $0.2 \cdot 10^5$ Pa) the oxidation rate decreases to less than two times (Pliss et al., 2010a, 2010b). But of course it is unacceptable to make any definite conclusions about detailed mechanism just on the basis of the oxygen consumption kinetic data only.

In (Pliss et al., 2012) $>\text{NO}^\bullet$ antioxidant activity was studied during styrene's oxidation using a complex of kinetic methods in combination with quantum-chemical calculations and kinetic modeling. The choice of styrene is caused by the following circumstances. Firstly, the reaction of styrene's inhibited oxidation is not complicated by complexation process as it is in case of many other vinyl compounds (acrylic monomers for example). Secondly, high reactivity of styrene's double bond makes it possible to study this process under long chains conditions even if oxidation is quite strongly inhibited. Thirdly, in case of styrene the rate constants of elementary stages are known for many key reactions, and this knowledge makes kinetic modeling significantly easier to carry out.

Let's consider the results of this work and some of our new data.

Oxidation kinetics was studied in area of initial O_2 consumption rates in temperature range of 310 – 343 K with highly sensitive capillary microvolumometer according to technique (Loshadkin et al., 2002). Initial $>NO\bullet$ concentrations were in range of 10^{-7} – 10^{-3} M. Experiments were carried out at $P_{O_2} = 20$ or 100 kPa. In special cases oxygen-argon mixes were prepared to obtain the oxidation rates dependences on $[O_2]$. Initiation rate W_i was determined with inhibition method by detection of induction period ending time τ_{ind} and application of known equation $W_i = 2[InH]_0/\tau_{ind}$. 6-Hydroxy-2,2,5,7,8-pentamethylbenzochroman was used as inhibitor (InH). Kinetic modeling was performed as described in (Loshadkin et al., 2002).

Values of styrene's oxidation rates inhibited by different $>NO\bullet$ under oxygen and air saturation conditions and when quadratic termination share is no more than 25% are presented in Table 6. As seen from the table, the oxidation's rate for different $>NO\bullet$ from oxygen to air decreases substantially less than five times. This fact according to (Aleksandrov, 1987; Denisov & Afanas'ev, 2005; Kharitonov & Denisov, 1967; Kovtun et al., 1974; Mogilevich & Pliss, 1990; Pliss & Aleksandrov, 1977; Denisov, 1996) suggests that nitroxide radicals react with both $M\bullet$ and $MO_2\bullet$.

Kinetics of $>NO\bullet(III)$ consumption at its different initial concentrations are presented in Figure 2. From this data it follows that according to inhibition by reaction (4) $>NO\bullet$ should consume much faster than it happens in fact. With special experiments it was shown that value of inhibiting factor e.g. for $>NO\bullet(III)$ and $>NO\bullet(IV)$ is more than 7 (Pliss et al., 2012), so it suggests that $>NO\bullet$ regeneration process occurs upon chain termination. We note that this effect doesn't depend on styrene's concentration.

$[>NO\bullet]_0 \cdot 10^5, M$	$W \cdot 10^6, M \cdot s^{-1}$		W_{O_2} / W_{air}
	$P_{O_2} = 1 \cdot 10^5 Pa$ (oxygen)	$P_{O_2} = 0.2 \cdot 10^5 Pa$ (air)	
0	11.0	11.0	1.00
$>NO\bullet(I)$			
2.8	4.75	2.58	1.84
4.1	4.37	2.84	1.54
$>NO\bullet(II)$			
4.2	3.76	2.12	1.78
14	2.88	1.17	2.45
$>NO\bullet(III)$			
5.7	4.34	2.19	1.98
18	3.13	1.30	2.40
$>NO\bullet(IV)$			
4.0	5.67	4.09	1.38
8.0	5.07	2.20	2.30
$>NO\bullet(V)$			
5.9	4.90	3.21	1.53
17	2.38	0.78	3.06

Table 6. Kinetic parameters of styrene's oxidation inhibited with $>NO\bullet$; $W_i = 1.0 \cdot 10^{-8} M \cdot s^{-1}$ (Pliss et al., 2012)

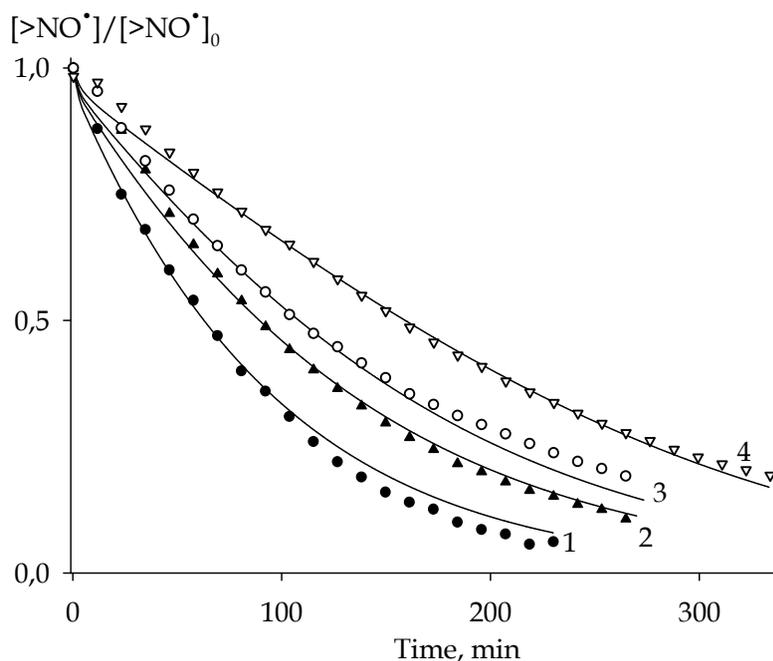


Figure 2. Kinetics of $>\text{NO}\cdot$ (III) consumption during styrene oxidation (in relative coordinates); points: experimental data, curves: a result of simulation. $P_{\text{O}_2} = 20 \text{ kPa}$; $W_i = 1.0 \cdot 10^{-8} \text{ M}\cdot\text{s}^{-1}$; $[>\text{NO}\cdot]_0$, M: 1 – $2.3 \cdot 10^{-6}$, 2 – $5.9 \cdot 10^{-6}$, 3 – $1.2 \cdot 10^{-5}$, 4 – $2.8 \cdot 10^{-5}$ (Pliss et al., 2012).

Styrene's oxidation can be effectively inhibited by hydroxylamines. This assertion confirms with distinct induction period on oxygen consumption's kinetic curve (typical one represented at Figure 3 (Pliss et al., 2012)). Rate constants of such antioxidants' reactions with peroxide radicals can be determined from inhibited oxidation's rate dependence on time according to the following equation (Loshadkin et al., 2002):

$$F = \ln \frac{1 + W / W_0}{1 - W / W_0} - \frac{W_0}{W} = \frac{k_{5.2} W_0}{k_2 [M]} t + \text{const} \quad (5)$$

But the problem is that oxidation rate remains significantly lower than W_0 after the inhibiting period (see Figure 3) since $>\text{NO}\cdot$ being formed is an inhibitor of oxidation itself. However the kinetic modeling shows that in this case in equation (5) we can substitute W_0 value to the value of oxidation's rate at after-induction period. Herewith $k_{5.2}$ determination error is less than 10%. Calculated $k_{5.2}$ mean value at 323 K for $>\text{NOH}$ (III), equal to $4 \cdot 10^6 \text{ M}^{-1}\cdot\text{s}^{-1}$ (Pliss et al., 2012), was later used in mechanism's kinetic modeling.

Dependences of $>\text{NO}\cdot$ consumption and its accumulation from corresponding $>\text{NOH}$ on time during styrene's oxidation at $P_{\text{O}_2} = 20 \text{ kPa}$ presented at Fig. 4 (ESR-spectroscopy method). It's seen that hydroxylamine being injected quickly transforms to $>\text{NO}\cdot$ and its maximum concentration differs from $[>\text{NO}\cdot]_0$ by less than 10%. It's important that hereafter consumption rates of injected $>\text{NO}\cdot$ and one being formed from hydroxylamine are almost the same (see curves 1 and 2 at Fig. 4).

As already been mentioned (see Section 3), if chains propagates by $\text{HO}_2\cdot$, $>\text{C}(\text{OH})\text{O}_2\cdot$, or $>\text{CH}-\text{CH}(\text{OO}\cdot)\text{N}<$ radicals then inhibition proceeds as disproportionation of these radicals

with $>\text{NO}\cdot$. Herewith hydroxylamine being injected quickly transforms to $>\text{NO}\cdot$ which almost doesn't consume but effectively inhibits an oxidation of corresponding substrates. So in this case the inhibiting factor values are more than 100 (Kovtun et al., 1974). Therefore it should be considered that in case of styrene's oxidation the way of irreversible $>\text{NO}\cdot$ consumption is reaction (4).

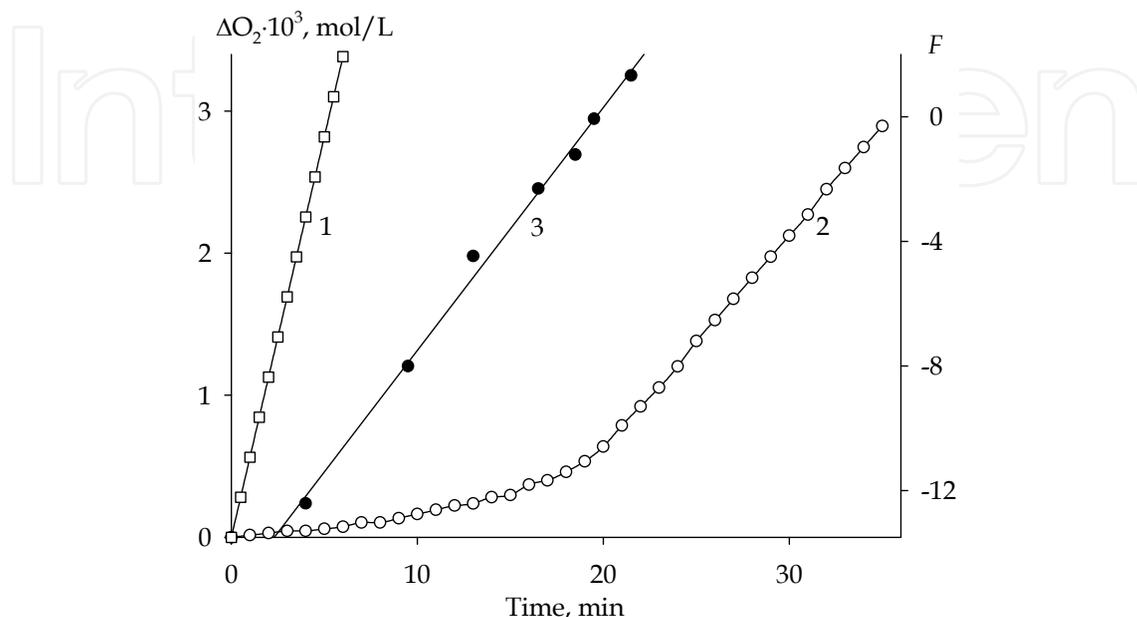


Figure 3. Kinetics of O_2 consumption during styrene's oxidation: 1 – without inhibitor; 2 – $[\text{>NOH (III)}] = 2 \cdot 10^{-5} \text{ M}$; 3 – anamorphous of curve 2 in coordinates of equation (5); $P_{\text{O}_2} = 20 \text{ kPa}$; $W_i = 1.0 \cdot 10^{-8} \text{ M} \cdot \text{s}^{-1}$ (Pliss et al., 2012)

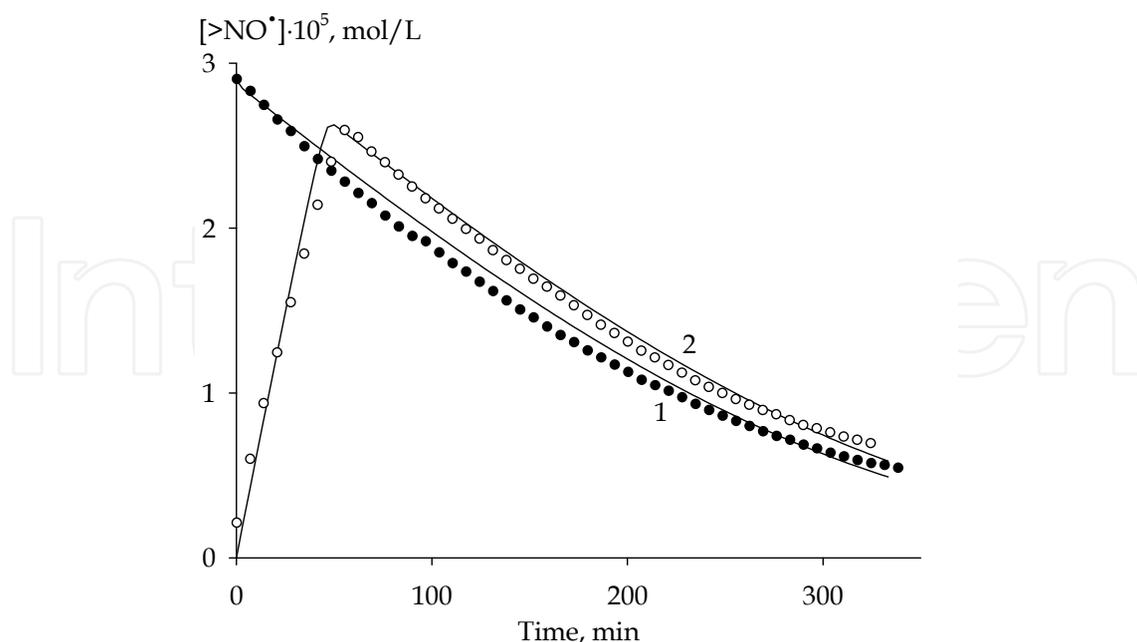


Figure 4. Kinetics of $>\text{NO}\cdot$ (III) consumption (1) and its accumulation from corresponding hydroxylamine (2) during styrene's oxidation: dots – experimental data, curves – modeling results; $[\text{>NO}\cdot \text{ (III)}]_0 = [\text{>NOH (III)}]_0 = 2.9 \cdot 10^{-5} \text{ M}$; $P_{\text{O}_2} = 20 \text{ kPa}$; $W_i = 1 \cdot 10^{-8} \text{ M} \cdot \text{s}^{-1}$ (Pliss et al., 2012)

As it was mentioned above (see section 3.1), reaction (4) may proceed both as recombination and as disproportionation. Target experiment's results presented at Figure 5. Rate of $>\text{NO}\cdot$ (III) consumption in styrene (atmosphere of argon) during initiated oxidation was equal to initiation rate, and this $>\text{NO}\cdot$ consumption was proceeded up to detection limit of ESR-spectrometer ($\leq 1 \cdot 10^{-7}$ M). After that argon was substituted to oxygen and, as can be seen at Figure 5, $>\text{NO}\cdot$ signal was appeared again.

These cycles were repeatedly detected several times until we reached the spectrometer's detection limit. Each time $>\text{NO}\cdot$ was recrudesced in share about 25–30% of its initial concentration. This fact confirms the assumption that reaction (4) also may proceed as disproportionation due to β -C-H bond of styrene's alkyl radical ($\sim\text{CH}_2\text{C}\cdot\text{HC}_6\text{H}_5$) with olefin's formation $\sim\text{CH}=\text{CHC}_6\text{H}_5$ (M-H):



Thus $>\text{NO}\cdot$ signal may appear due to the reaction (5.2) upon oxygen blow (see Scheme 5 below).

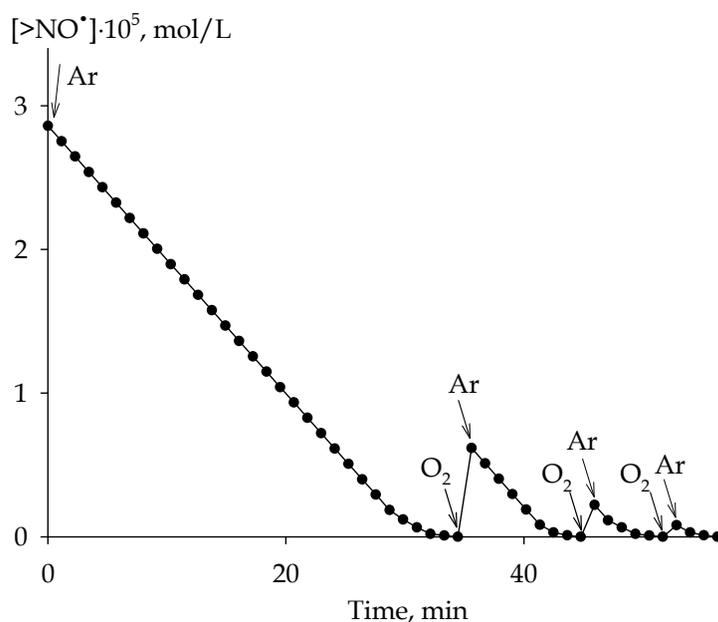
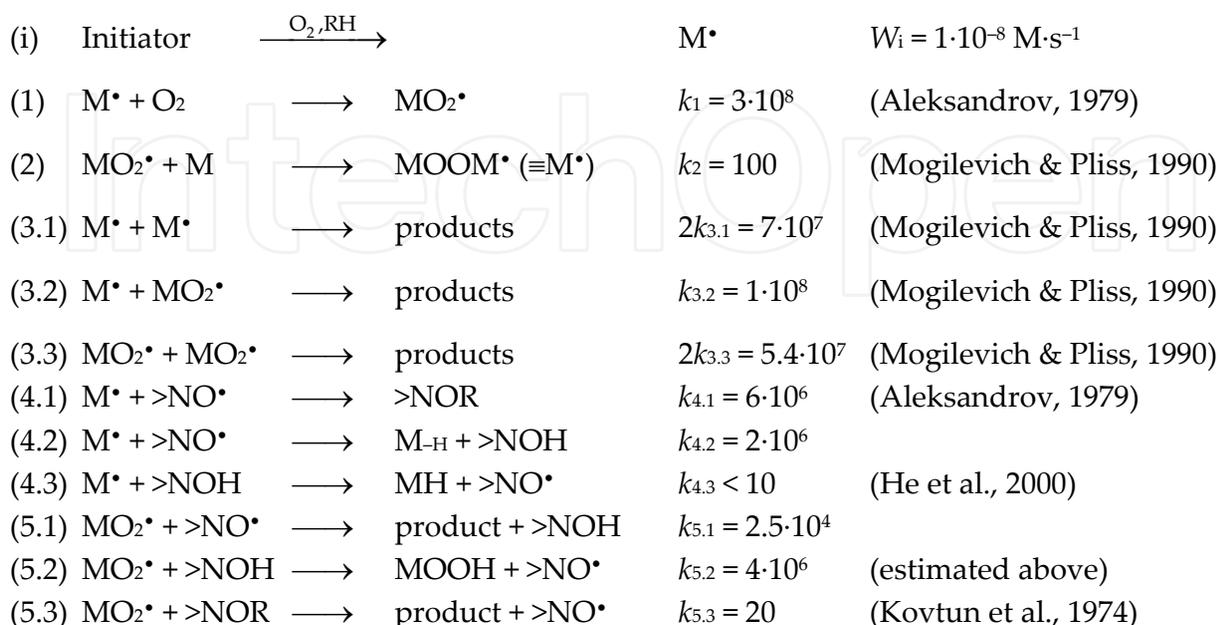


Figure 5. Kinetics of $>\text{NO}\cdot$ (III) consumption in styrene: $[>\text{NO}\cdot \text{ (III)}]_0 = 2.8 \cdot 10^{-5}$ M; $W_i = 1 \cdot 10^{-8}$ M \cdot s $^{-1}$ (Pliss et al., 2012)

Another one probable reason of this effect (Figure 5) is reaction $\text{MO}_2\cdot + >\text{NOR} \rightarrow \text{product} + >\text{NO}\cdot$ (5.3) that was first proposed in (Denisov, 1982). As $>\text{NO}\cdot$ regeneration source, this reaction was studied in detail for reactions of some alkoxyamines $>\text{NO}\cdot$ (I) with peroxide radicals of cumene and cyclohexylmethyl ether at 338 K (Kovtun et al., 1974). Obtained $k_{5.3}$ values ($1 - 26$ M $^{-1}\cdot$ s $^{-1}$) suggest that $>\text{NOR}$ being studied in (Kovtun et al., 1974) are weak inhibitors. This conclusion also is confirmed with the dependences of styrene's oxidation rates on $>\text{NOR}$ (I) and $>\text{NO}\cdot$ (III) concentrations (Pliss et al., 2012).

All of the experimental data and our previous results (Pliss et al., 2010a, 2010b, 2012) allow us to provide the following formal kinetic scheme of styrene's oxidation inhibited by aliphatic stable nitroxide radicals:



Scheme 5. Detailed mechanism of vinyl monomers oxidation inhibited by nitroxide radicals

We've used this scheme for kinetic modeling (Pliss et al., 2012). Values of $k_1 - k_{4.1}$, $k_{4.3}$, $k_{5.3}$ ($M^{-1} \cdot s^{-1}$) were taken from the literature and values of $k_{4.2}$ and $k_{5.1}$ were obtained from modeling. Figures 2 and 4 shows that calculated curves are of satisfactorily consistent with experimental data. This indirectly confirms the reliability of Scheme 5.

Kinetic analysis shows that $[M^\bullet] \ll [MO_2^\bullet]$ when $[O_2] \sim 1 \cdot 10^{-2} \text{ M}$. In this case reactions (3.1), (3.2), (4.2), (4.3), and (5.3) can be neglected. Then the scheme including reactions (i), (1), (2), (3.3), (4.1), (5.1), and (5.2) can be described by equation:

$$W_i \left(\frac{W_0}{W} - \frac{W}{W_0} \right) = \frac{k_4 [>NO^\bullet]_0 W_0}{k_1 [O_2]} + \frac{2k_5 [>NO^\bullet]_0 W_i^{0.5}}{k_{3.3}^{0.5}},$$

where $k_5 = (k_{5.1} [>NO^\bullet] + k_{5.2} [>NOH]) / 2 [>NO^\bullet]_0$. If $[>NO^\bullet] < 10^{-4} \text{ M}$ then chain termination by reaction (4) can be neglected, therefore that scheme can be described by equation:

$$\frac{W_0}{W} - \frac{W}{W_0} = \frac{2k_5 [>NO^\bullet]_0}{(W_i k_{3.3})^{0.5}}. \quad (6)$$

Previously (Pliss et al., 2010a, 2010b) we've analyzed a simplified scheme including reaction (i), (1), (2), (3.3), (5.1), and (5.2). We've calculated the values of $k_5 = (5 \pm 3) \cdot 10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$ for $>NO^\bullet$ (I) – (V) in oxidizing vinyl monomers at 323 K and $P_{O_2} = 1 \cdot 10^5 \text{ Pa}$. These values are close enough to estimated in this present work value $k_{5.1} = 2.5 \cdot 10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$.

A fundamental question about the detailed mechanism of the reaction (5.1) remains open. By analogy with the oxidation of 1,2-substituted ethylenes and 1,4-substituted butadienes (Mogilevich & Pliss, 1990) we can assume that hydroxylamine's formation is facilitated by conjugation of β -C–H bond with peroxide bridge of styrene's polyperoxide radical:



Peroxide bridge is an important structural unit of $\sim\text{MO}_2\cdot$ radical. It alters the reaction center's electronic characteristics and increases the electrostatic term's contribution to the transition state's total energy (Denisov, 1996; Denisov & Afanas'ev, 2005; Mogilevich & Pliss, 1990). Probable reason of this effect is the difference in the triplet repulsion, which is close to zero in transition state of disproportionation reaction of $\text{MO}_2\cdot$ with $>\text{NO}\cdot$ and is sufficiently large for the reaction of $>\text{NO}\cdot$ with nonconjugated C–H bond of hydrocarbon (Denisov, 1996). The latter probably explains the fact that aliphatic nitroxide radicals inhibit the hydrocarbon's oxidation via reaction with alkyl radicals only.

The results obtained in the present study draws attention to the results gained for biological systems where it is assumed that reaction of aliphatic $>\text{NO}\cdot$ with peroxide radicals proceeds via $>\text{NOOOR}$ adduct formation decomposing to corresponding oxoammonium cations (Barton et al., 1998; Goldstein & Samuni, 2007; Offer & Samuni, 2002). The probability of such intermediate's existence is also considered in quantum-chemical analysis (Hodgson & Coote, 2010; Stipa, 2001). Further regeneration of nitroxide radicals may be due to reaction of oxoammonium cations with common biological reducing agents (Goldstein & Samuni, 2007; Offer & Samuni, 2002).

Direct reaction $\text{MO}_2\cdot + >\text{NO}\cdot \longrightarrow \text{MOOON}<$ that results to stable trioxide's formation is seems quite doubtful for aliphatic $>\text{NO}\cdot$ in organic phase at moderate temperatures (≤ 373 K). First, it's easy to reject on the base of kinetic reasons cause in this case the kinetics of $>\text{NO}\cdot$ consumption and stoichiometry of chain termination would have a different nature than those observed in numerous studies (Browlie & Ingold, 1967; Kovtun et al., 1974; Pliss et al., 2010a, 2010b, 2012; Pliss & Aleksandrov, 1977). Second, it's easy to refute by direct quantum-chemical calculations (DFT B3LYP/6-31G*, Table 7). It's easy to see that peroxide radicals' addition to $>\text{NO}\cdot$ is thermodynamically unfavorable.

Radical	H•	HO•	HOO•	•CH ₃	CH ₃ O•	CH ₃ OO•
Energy	-243.4	-28.3	48.1	-150.6	11.5	60.3

Table 7. Energy of some radicals' addition to $>\text{NO}\cdot$ (I), kJ/mol

5. Conclusions

Thus, we must conclude that reaction of nitroxide with peroxide radicals plays an important role during styrene's oxidation in presence of aliphatic stable $>\text{NO}\cdot$. This reaction proceeds probably as disproportionation and results to a partial $>\text{NO}\cdot$ regeneration.

At the same time we emphasize that detailed mechanism of chemical and biological oxidation processes inhibited by stable nitroxide radicals is still far from being established. Therefore kinetic experiments on the key reactions involving nitroxide radicals and its conversion products (hydroxylamines, alkoxyamines, oxoammonium cations) in solutions of organic substrates and in biological systems must be carried out to solve this problem.

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