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Free-Radical Generation Mechanism and Antimalarial Activity of Cyclohexyl Endoperoxides

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Abstract—A kinetic analysis has been carried out for a cascade of intramolecular oxidation reactions of free radicals generated in the redox reactions of substituted cyclohexyl endoperoxides (15 compounds) with the Fe^{2+} ion. Each radical conversion reaction has been characterized by its enthalpy, activation energy, and rate constant. Kinetic characteristics have been calculated by the intersecting parabolas method. Depending on their structure, cyclohexyl endoperoxides generate one to three radicals. There is a linear empirical correlation between the number of radicals generated by a peroxide and its molar antimalarial activity (IC_{50}/M, where M is the molar mass of the peroxide). The peroxides that generate no more than one radical show no antimalarial activity.

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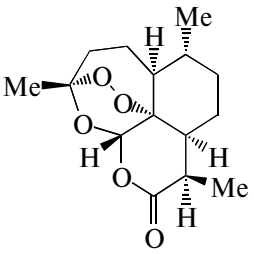
Artemisinin and its derivatives have proved to be very effective antimalarials [1–6]. They actively suppress the *Plasmodium falciparum* clones that are resistant to quinine, chloroquinine, and other quinoline-based drugs. Structurally, artemisinin is a tricyclic sesquiterpene with a peroxide bridge [1]:



Artemisinin

Its therapeutic effect is based on its ability to generate free radicals via the following redox reaction involving a Fe(II) chelate [7–9]:

$$ROOR + Fe(II) \longrightarrow RO^{\bullet} + RO^{-} + Fe(III).$$

Because the iron chelate concentration in the organism of a malaria parasite is 20 times higher than in the human organism, peroxide decomposition into radicals takes place mainly in the plasmodium cell [5]. A kinetic analysis of the reactions involving artemisinin radicals demonstrated the following [10, 11]. The alkoxyl radicals generated by the endoperoxide isomerize into alkyl radicals ($RO^{\bullet} \rightarrow R^{\bullet}$), and the latter react with O_2, initiating a cascade of intramolecular oxidation reactions. The polyatomic hydroperoxide resulting from these reactions reacts with Fe(II), generating a series of free radicals. Among these species, hydroxyl radicals play the key role in the killing of the malaria parasite [12–15].

The therapeutic activity of artemisinin and its derivatives depends strongly on the peroxide structure and even peroxide conformation [12]. High therapeutic activity is displayed by the compounds in which a cascade of free-radical reactions yields a series of hydroxyl radicals [13–15]. Kinetic investigation of the free-radical reactions of artemisinin posed the following questions:

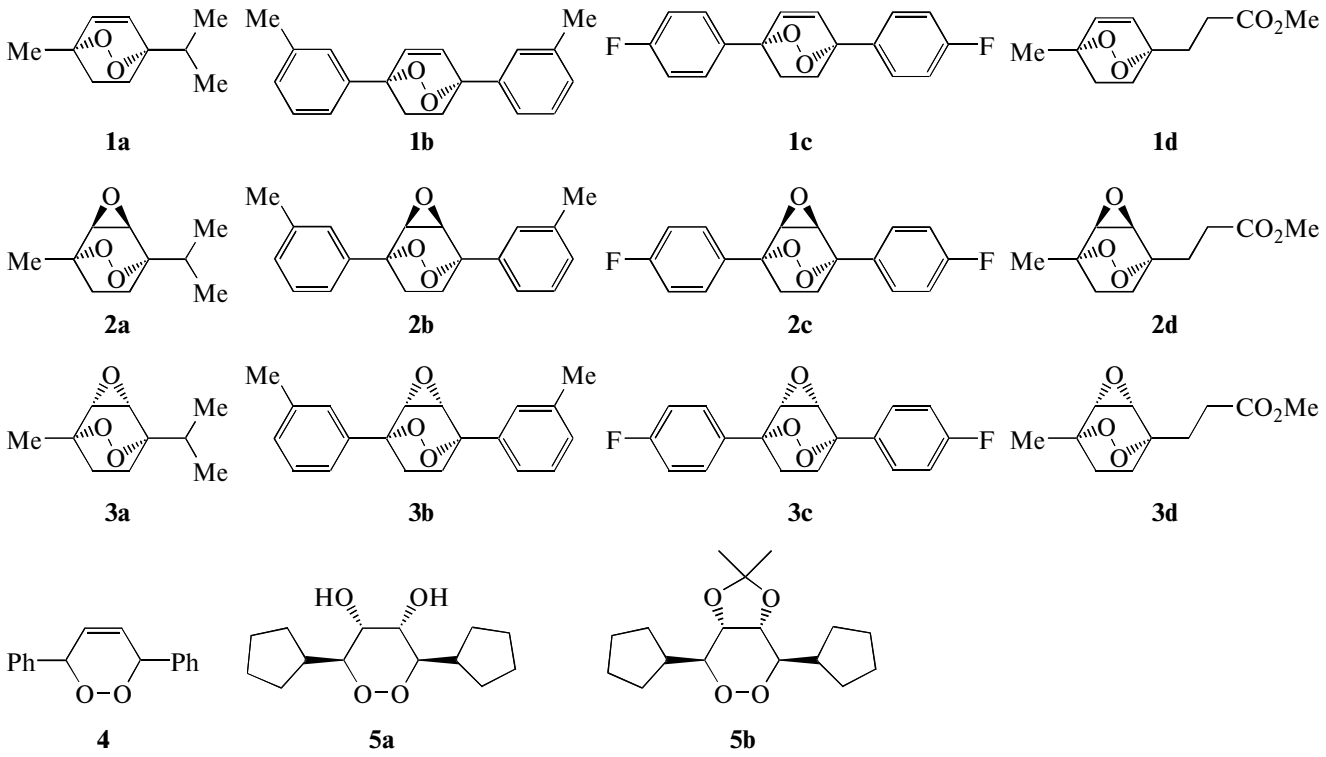
(1) Do the compounds generating not only hydroxyl radicals, but also other ones ($RO^{\bullet}$, $RO_2^{\bullet}$, $HO_2^{\bullet}$, etc.), show antimalarial activity?

(2) What is the role of the polycyclic structure of artemisinin?

(3) Do structurally different monocyclic peroxides differ in the way they generate free radicals?

(4) How is the antimalarial activity of monocyclic peroxides correlated with their initiation power?

In order to elucidate these issues, we undertook a kinetic study of free-radical reactions of 15 monocyclic endoperoxides, whose structures [16] are presented below. These compounds are well-known antimalarials, whose activity will be characterized in terms of IC_{50}, which is the relative weight dose of a drug that reduces the number of malaria parasite cells by half.



COMPUTATIONAL PROCEDURE

The kinetic schemes of the free-radical reactions of the above endoperoxides were constructed using the semiempirical intersecting parabolas method [17, 18]. In this method, each class of free-radical reactions is characterized by the following parameters: atomic structure of the reactive site of the transition state, e.g., O...H...C for the $RO^{\cdot} + RH$ and $RO_2^{\cdot} + RH$ reactions; coefficients b and b_f for the bond being attacked and for the forming bond, respectively ($2b^2$ is the force constant of the bond); zero-point energies of these bonds, $0.5hN_A\nu$ and $0.5hN_A\nu_f$, respectively (h is the Planck constant, N_A is Avogadro's number, and ν and ν_f are the stretching frequencies of these bonds); total extension of the reacting bonds in the transition state, r_e; preexponential factor A per equireactive bond being attacked. We will also consider the following quantities derived from the above parameters: coefficient $\alpha = b/b_f$ and product br_e. Any particular reaction is characterized by its classical enthalpy ΔH_e,

$$\Delta H_e = \Delta H + 0.5hN_A(\nu - \nu_f), \quad (1)$$

where ΔH is the enthalpy of the reaction, and by the classical potential barrier

$$E_e = E + 0.5hN_A\nu - 0.5RT, \quad (2)$$

where E is the Arrhenius activation energy ($E = RT\ln(k/A)$. The numerical values of these parameters for the classes of reactions that are involved in the conversions of the above peroxides are listed in Table 1.

Activation energy was calculated using the following equation [17]:

$$E = B^2\left\{1 - \alpha\sqrt{1 - \frac{\Delta H + 0.5hN_A(\nu - \nu_f)}{Bbr_e}}\right\}^2 - 0.5h\nu N_A + 0.5RT, \quad (3)$$

where $B = br_e/(1-\alpha^2)$.

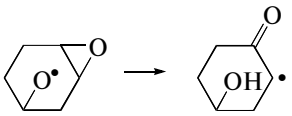
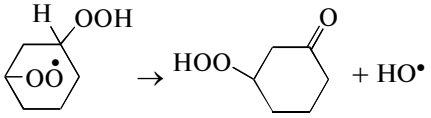
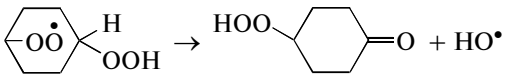
The enthalpies of radical abstraction and radical isomerization with H atom transfer were determined from the dissociation energies of the breaking (i) and forming (f) bonds:

$$\Delta H = D_i - D_f. \quad (4)$$

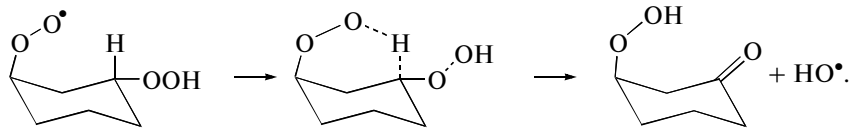
The values of these energies [25] are listed in Table 2. The enthalpy of decomposition of radicals was calculated using Benson group increment theory [26]. The values of group increments are presented in a review by Cohen [27].

Isomerization via H atom abstraction from the α-hydroperoxy–C–H bond is accompanied by the fragmentation of the molecule through O–O bond breaking [23]:

Table 1. Kinetic parameters of different classes of reactions [19–24]

Reaction class	α	br_e, $(kJ/mol)^{1/2}$	$0.5hN_A\nu_i$, kJ/mol	$0.5hN_A\Delta\nu$, kJ/mol	log$A$ [s^{-1}]
$RO^\bullet \rightarrow R^\bullet$	0.796	13.13 ($B = 35.84$)	17.4	−4.3	12.74 (9.3)[a]
	0.796	18.20 ($B = 49.67$)	17.4	−4.3	12.74 + D[b]
$RO^\bullet \rightarrow$ decyclization	0.748	9.84 ($B = 22.34$)	6.2	−2.1	13.00
$RO^\bullet$ + LSH	0.707	11.67 ($B = 23.27$)	15.1	−6.6	7.30[c]
$RO_2^\bullet \rightarrow R^\bullet$	0.814	13.23 ($B = 39.21$)	17.4	−3.8	12.14 (9.3)[a]
	0.814	18.38 ($B = 54.47$)	17.4	−3.8	12.14 + Δ[b]
	0.814	18.58 ($B = 55.07$)	17.4	−3.8	12.14 + Δ[b]
$R^1R^2C(OH)OO^\bullet \rightarrow HO_2^\bullet + R^1R^2C(O)$	1.022	14.07	21.7	2.1	10.00
$RO_2^\bullet$ + LSH	0.722	11.94 ($B = 24.94$)	15.1	−6.1	7.30[c]

Note: [a] The number in parentheses refers to the A value for the linear (acyclic) radical.
[b] The term $\Delta = 0.5\log(2RT/\pi E)$ accounts for the probability of the activation energy being accumulated at the two breaking bonds.
[c] For this bimolecular reaction, $A = A_0$[LSH].



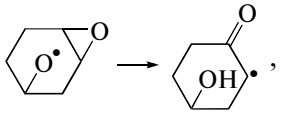
Therefore, the dissociation energy of this bond is equal to the algebraic sum of the dissociation and formation energies of the bonds involved in the reaction, and the enthalpy of the isomerization reaction is

$$\Delta H = D_{C-H}(> C-H(OOH) + D_{O-H} - D_{C=O}(\pi). \quad (5)$$

For activation of the radical in this reaction, it is necessary that the energy be concentrated at the C–H and O–O bonds. As a consequence, the classical activation barrier of the thermoneutral reaction is high ($E_{e0} = 102.7$ kJ/mol [23]) and the preexponential factor includes the multiplier $(2RT/\pi E)^{1/2}$, which accounts for the probability of energy concentration at the two bonds [24]. The rate constant of the isomerization reaction is

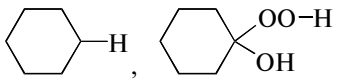
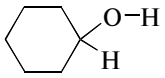
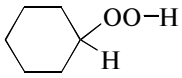
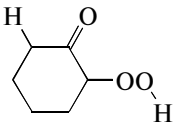
$$k = A\exp(-E/RT) = n_{C-H}A_0\sqrt{\frac{2RT}{\pi E}}\exp(-E/RT), \quad (6)$$

where n_{C-H} is the number of C–H bonds accessible to the attacking radicals and A_0 is the preexponential factor typical of this class of reactions. A similar situation takes place in the isomerization reaction



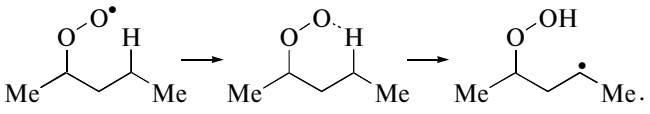
in which the abstraction of the H atom from the H–C–O bond is also accompanied by bond rearrangement. As a consequence, the reaction is very exothermic and likely takes place in one step. The kinetic parameters of this reaction were calculated under the assumption that its classical activation energy is again

Table 2. Dissociation energies of the C–H and O–H bonds [25]

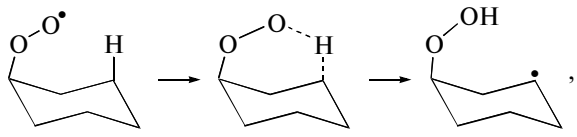
Compound	D_{C-H}, kJ/mol	D_{O-H}, kJ/mol
	408.8	362.1
	388.4	438.5
	248.1	365.5
	394.1	369.8
R^1R^2CH-H, $R^1R^2CHOO-H$	412.0	365.5
$R^1R^2C-H(O-H)$	390.5	431.9
PhC–H(OH)Me	366.4	438.2

E_{e0} = 102.7 kJ/mol [23]. The values of these kinetic parameters are given in Table 1.

The preexponential factors for the isomerization reactions $RO^{\cdot} \rightarrow {}^{\cdot}R'$ and $RO_2^{\cdot} \rightarrow {}^{\cdot}R'$ vary, depending on whether they occur in a cyclic or linear radical [19]. This is due to the fact that this isomerization proceeds via the formation of a six-membered cyclic transition state, such as



The formation of this transition state structure is accompanied by a considerable decrease in entropy ($\Delta S^{\neq} = -48$ J mol^{-1} K^{-1} because of rotation about four bonds being hindered [19]. In the case of isomerization occurring in a ring, e.g.,



rotation about a single C–O bond is hindered in the transition state and, accordingly, the decrease in entropy is fairly small ($\Delta S^{\neq} \approx -12$ J mol^{-1} K^{-1}) and the reaction proceeds at a higher rate (Table 2).

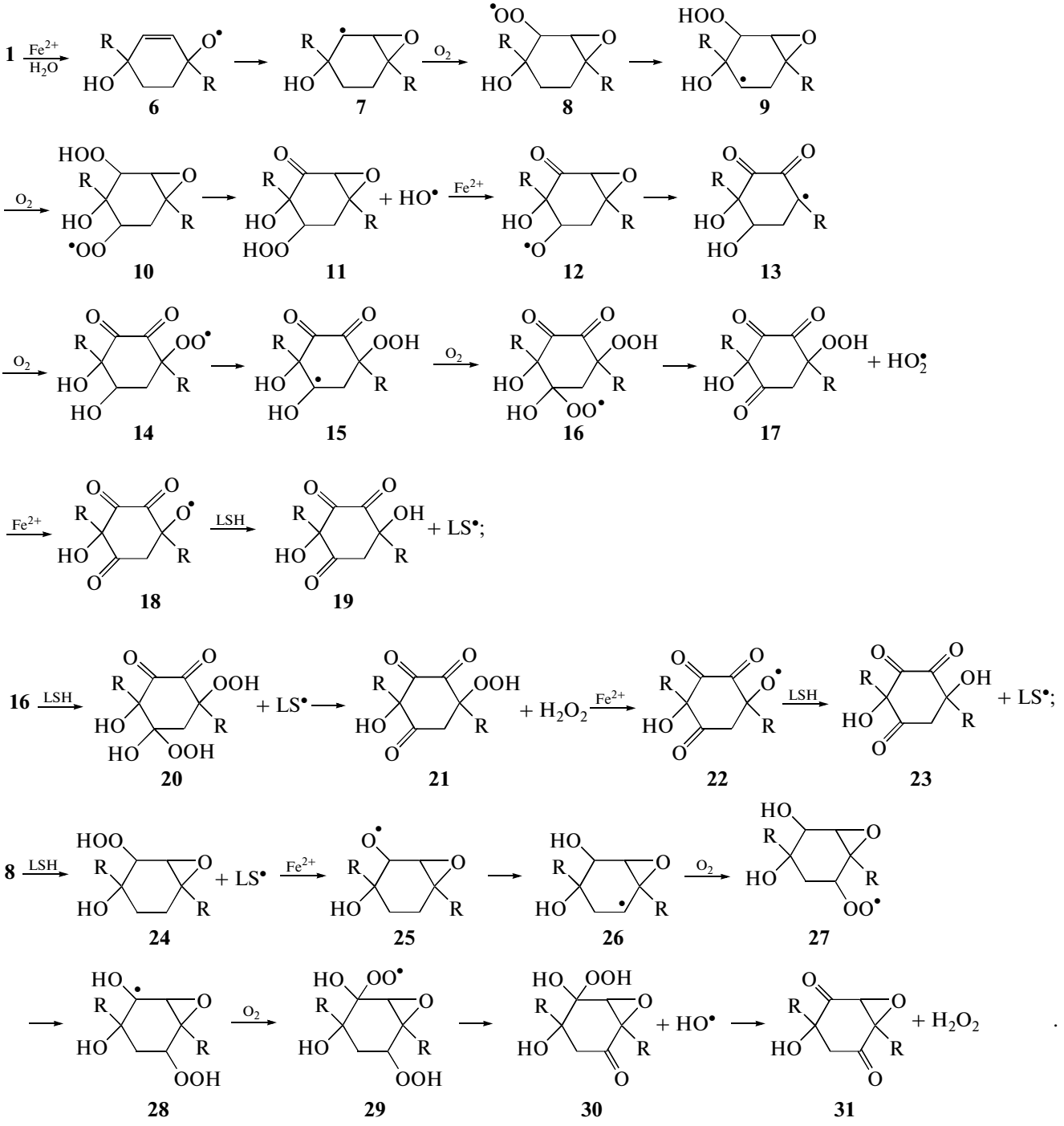
The addition reaction

$$R^{\cdot} + O_2 \longrightarrow RO_2^{\cdot}$$

is very exothermic [28], and its rate constant is diffusion-controlled (in methyl oleate, $k = 1.5 \times 10^9$ L mol^{-1} s^{-1} [28]). In the methyl oleate medium (analogue of the lipid phase in the cell) under aerobic conditions ($p_{O_2} = 0.21$ atm), $[O_2] = \gamma_{O_2} \times 0.21 = 1.12 \times 10^{-2} \times 0.21 = 2.35 \times 10^{-3}$ mol/L, so the specific rate of this reaction is $k[O_2] = 3.5 \times 10^6$ s^{-1}. Any other bimolecular reaction between an alkyl radical and a biological substrate takes place much less rapidly [29]. The reactions of alkoxyl and peroxyl radicals with biological substrates were analyzed in earlier works [10, 11, 29]. The most rapid reactions are those of $RO^{\cdot}$ and $RO_2^{\cdot}$ with the thio group of L-cysteine (LSH), whose residues are components of proteins (D_{S-H} = 360 kJ/mol [22]). For this reason, just this reaction was considered to be the key step of the bimolecular reactions that is in competition with the unimolecular $RO^{\cdot}$ and $RO_2^{\cdot}$ isomerization and decomposition reactions.

RESULTS AND DISCUSSION

The scheme of free-radical reactions of endoperoxides **1a**–**1d** is presented below (Scheme 1). Since the substituents R in the 3- and 6-positions are uninvolved in the free-radical reactions, this scheme is the same for all of the four compounds.



Scheme 1.

Alkoxyl radicals result from the decomposition of an endoperoxide by a Fe(II) chelate via the following redox reaction:

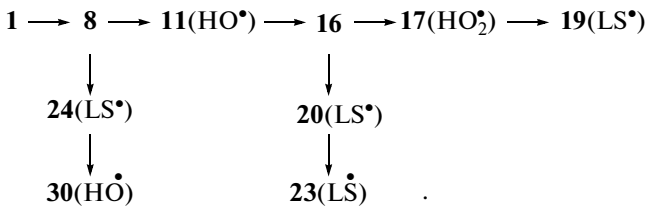
$$Fe^{2+} + ROOR \longrightarrow Fe^{3+} + RO^{\cdot} + RO^{-}.$$

They isomerize rapidly into alkyl radicals, and the latter turn rapidly into peroxyl radicals in the presence of oxygen [30]. All parallel reactions were considered for each reaction step, and the most rapid of them are included in Scheme 1. The enthalpy (ΔH), activation energy (E), and rate constant (k) at 310 K for each reaction step are listed in Table 3.

In the cases in which the rate constants of two parallel reactions are comparable (their ratio is no larger than 5), both reactions are included in Table 3. This situation takes place for radicals **8**, **16**, and **29**. The reaction scheme presented in Scheme 1 suggests that the generation of free radicals via the decomposition of peroxides **1a**–**1d** occurs in the following way:

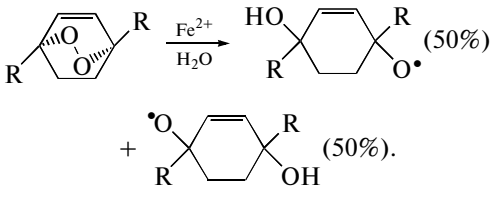
Table 3. Kinetic parameters of the conversions of the radicals generated by the endoperoxides

Reaction	ΔH, kJ/mol	E, kJ/mol	k at 310 K, s^{-1}
6 → 7	−25.9	1.4	6.0×10^{12}
7 → 8, 9 → 10, 13 → 14, 15 → 16, 26 → 27, 28 → 29	−142.6	1.4	3.5×10^{6}
8 → 9	43.3	56.3	4.6×10^{2}
10 → 11	−117.4	40.5	2.5×10^{4}
12 → 13	−144.8	32.8	4.1×10^{6}
14 → 15	29.8	49.6	2.4×10^{4}
16 → 17	22.4	41.1	2.3×10^{2}
18 → 19, 22 → 23, 36 → 37, 42 → 43	−78.5	5.8	2.1×10^{6}
16 → 20, 46 → 48	−2.1	30.9	1.2×10^{2}
8 → 24, 34 → 35, 40 → 41	−5.5	29.5	2.1×10^{2}
25 → 26	−29.7	39.7	1.3×10^{6}
27 → 28	22.9	46.1	1.4×10^{4}
29 → 30	−114.0	43.8	1.1×10^{4}
32 → 33	−47.4	17.5	4.5×10^{9}
33 → 34, 39 → 40, 45 → 46	−155.4	1.4	3.5×10^{6}
38 → 39	−33.2	1.4	6.0×10^{12}
44 → 45	−41.4	19.4	1.1×10^{6}
46 → 47	19.5	39.5	4.4×10^{2}
44 → 50	−71.9	7.4	1.1×10^{6}



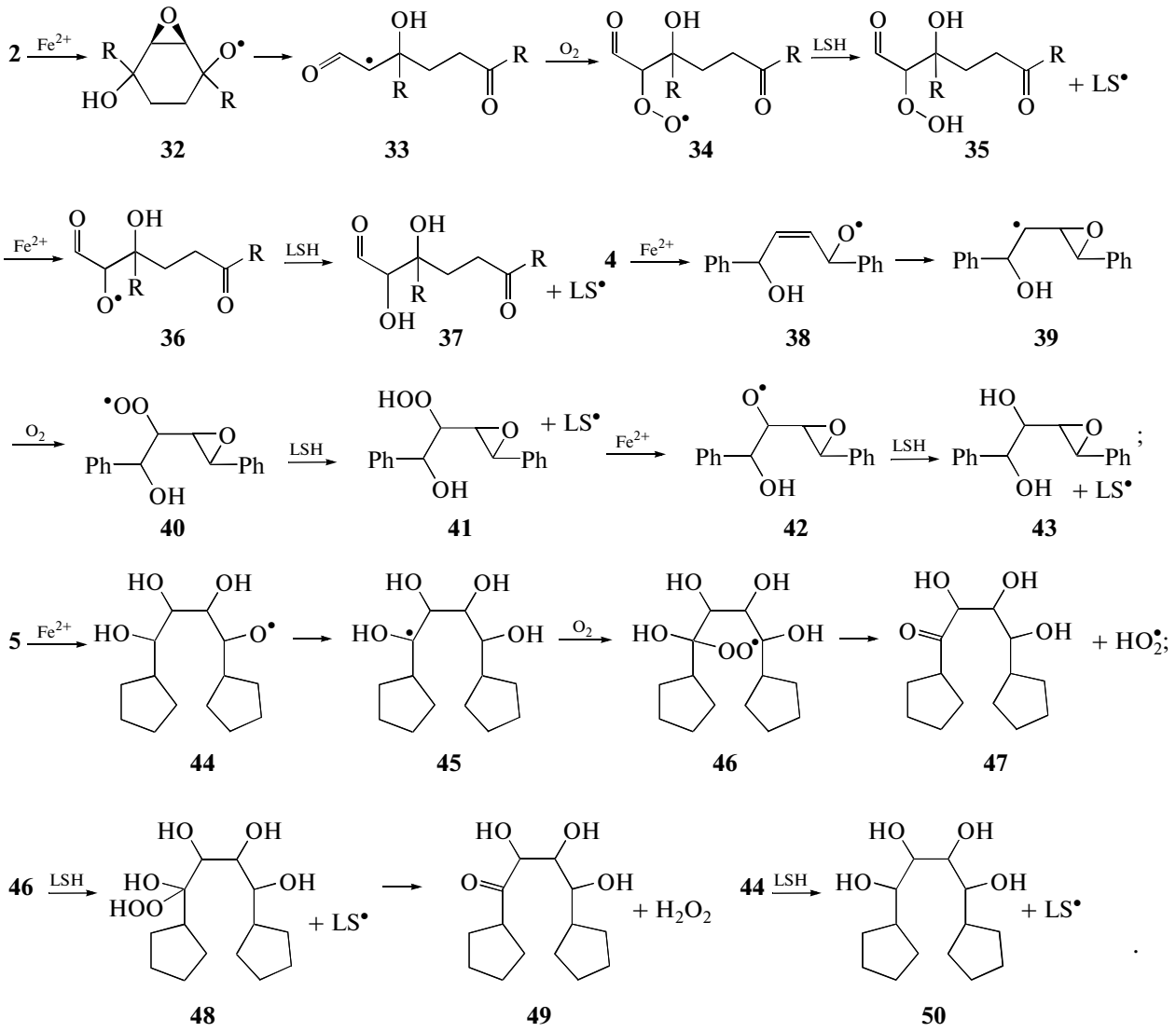
Scheme 2.

According tom this scheme, the decomposition of type **1** peroxides (**1a**–**1d**) yields 100% hydroxyl radicals, 45% hydroperoxyl radicals, and 124% thiyl radicals. The $RO_2^{\bullet}$ radical is the one that reacts most rapidly with the thio group of L-cysteine in the organism of the malaria parasite, turning into the thiyl radical. The total free-radical yield from the conversions of the alkoxyl radical from peroxide **1** is $n_{\Sigma R} = 2.69$. The hydrogen peroxide resulting from the **20 → 21** and **30 → 31** reactions is most likely decomposed by catalase without producing free radicals. Peroxide **1** decomposes via two parallel reactions yielding one of the following two alkoxyl radicals:



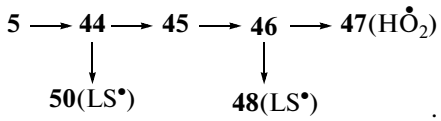
These radicals are identical, so the schemes of their free-radical reactions are also identical and, accordingly, the free-radical yield per molecule is the same as the free-radical yield per radical.

The free-radical reactions of peroxides **2a**–**2d**, **4**, **5a**, and **5b** are presented in Scheme 3. The substituents R in the 3- and 6-positions are uninvolved in the free-radical reactions, so the reaction scheme is the same for all of the compounds of this group.



Scheme 3.

The cascade of the reactions of radical **32**, which forms from peroxide **2**, consists of five consecutive steps yielding two thiyl radicals. Of the four CH and CH_2 groups of this peroxide, only one undergoes oxidation. The mechanism of the conversion of peroxides **3a**–**3d**, which are stereo analogues of compounds **2a**–**2d**, is the same, and so is the free-radical yield: $n_{\Sigma R}$ = 2.0. The conversion of peroxide **4** consists of six steps. Two thiyl radicals escape into the bulk as a result of the cascade reactions of the resulting radicals: $n_{\Sigma R}$ = 2.0. The generation of free radicals in the decomposition of peroxides **5a** and **5b** occurs via the following consecutive and parallel reactions:



The decomposition of the peroxide finally yields 0.6 $HO_2^{\bullet}$ and 0.4 $LS^{\bullet}$, and the total free-radical yield is $n_{\Sigma R}$ = 1.0. Thus, the above five peroxides generate one to three free radicals. The hydroxyl radical, which is crucially important for the therapeutic action of an antimalarial drug, forms only from peroxide **1**, and its yield is 1.

It is pertinent to correlate the antimalarial activity of the peroxides with the free-radical yield. A measure of antimalarial activity is IC_{50}, which the drug dose per kilogram of the organism that reduces the number of plasmodium cells by 50%. The IC_{50} data for the peroxides, as well as the artemisinin dose IC_{50}(A), were reported by Crespo et al. [16]. Relative *P. falciparum* suppression activity is characterized by the IC_{50}(A)/IC_{50}(N) ratio, where N is the designation of a drug (N = **1a, 1b**, etc.). Because IC_{50} is a weight characteristic and each particular drug has its own molar

mass M_N that differs significantly from the molar mass of artemisinin (M_A = 282.2 g/mol), it is correct to compare the molar effectivenesses of the peroxides in terms of the $M_A IC_{50}(N)/M_N IC_{50}(A)$ ratio. The results of this comparison are presented in Table 4. Clearly, peroxides characterized by the same free-radical yield differ in their antimalarial effectiveness. Averaging of the $\ln[M_A IC_{50}(N)/ M_N IC_{50}(A)]$ values yielded the following results:

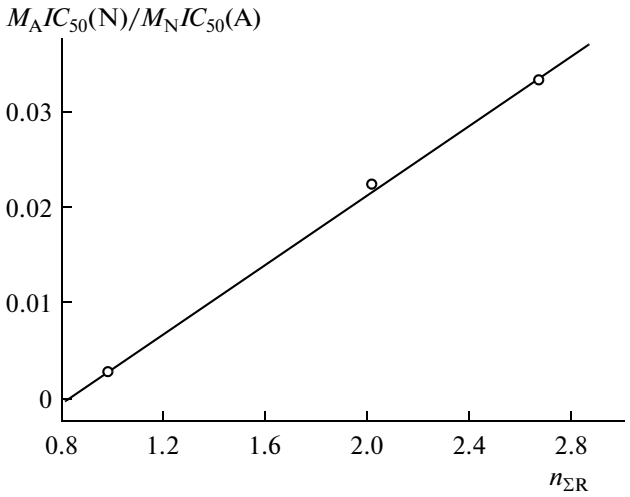
$n_{\Sigma R}$	1	2	2.68
$M_A IC_{50}(N)/M_N IC_{50}(A)$	2.3×10^{-3}	2.3×10^{-2}	3.3×10^{-2}

The antimalarial effectiveness of the peroxides depends linearly on the radical yield (figure) and can be fitted to the linear equation

$$M_A IC_{50}(N)/M_A IC_{50}(A) = (1.85 \pm 0.16) \times 10^{-2}(n_{\Sigma R} - 0.84). \quad (7)$$

Thus, the antimalarial activity of the monocyclic endoperoxides increases with an increasing total free-radical yield per unit amount of peroxide decomposed. The $M_A IC_{50}(A)/M_N IC_{50}(N)$ ratio is a linear function of the total free-radical yield. The peroxides characterized by $n_{\Sigma R} \le 1$ show almost no antimalarial activity. The above empirical relationship between the antimalarial effectiveness and $n_{\Sigma R}$ provides an explanation for the fact that the linear peroxides ROOR and ROOH are inactive against malaria [1]. The activity of the monocyclic endoperoxides is only 0.2–3% of the activity of artemisinin. The results reported here will augment insight into the correlation between free-radical generation and the antimalarial action of peroxide drugs. We will now compare the structural and kinetic characteristics of monocyclic peroxide drugs to those of polycyclic ones, to which artemisinin derivatives belong.

Cyclohexyl endoperoxides (this work)	Artemisinin and its derivatives [12–15]
Monocyclic structure	Polycyclic structure
Domination of the $RO_2^{\bullet} + LSH \rightarrow ROOH + LS^{\bullet}$ reaction because of the low rate of the $RO_2^{\bullet} \rightarrow R^{\bullet}$ reaction in the linear radical	Domination of the $RO_2^{\bullet} \rightarrow R^{\bullet}$ reaction because of the high reaction rate in the cyclic radical
Short intramolecular oxidation chain (1 or 2 steps)	Long intramolecular oxidation chain (2–6 steps)
Free-radical yield of 1 to 3	Free-radical yield of up to 6
$HO^{\bullet}$ yield of 0 to 1	$HO^{\bullet}$ yield of 2 to 4
one or 2 OOH groups formed	Up to six OOH groups formed
Linear dependence of IC_{50} on $n_{\Sigma R}$	Exponential dependence of IC_{50} on n_{OH}
Relative antimalarial activity of 0–3%	Relative antimalarial activity of 20–200%



Relative molar antimalarial activity of endoperoxides, $M_A IC_{50}(N)/M_N IC_{50}(A)$, as a function of the number of radicals they generate.

Clearly, the great difference in initiation behavior and therapeutic action between the monocyclic and polycyclic peroxides is due to the fact that the radicals of the former undergo comparatively slow intramolecular oxidation, while the radicals of the latter do this rapidly. Why does the polycyclic structure of artemisinin and its derivatives ensure multiple recurrence of the $R^{\bullet} \longrightarrow RO_2^{\bullet} \longrightarrow R^{\bullet}$ reaction? This question can be elucidated by comparing the schemes of the free-radical conversions of artemisinin and peroxides **2**–**5**. As was noted above (Table 1), the isomerization reaction $RO_2^{\bullet} \longrightarrow R^{\bullet}$ in the cyclic structure is accompanied by a slight decrease in entropy and, as a consequence, is characterized by a large preexponential factor of $A = 1.4 \times 10^{12}\ s^{-1}$. Monocyclic alkoxyl radical often decompose to yield linear radicals (Scheme 3). The $RO_2^{\bullet}$ radicals forming from the latter isomerize at a low rate because of the high negative activation entropy (for these reactions, $A = 2.0 \times 10^9\ s^{-1}$). As a consequence, the linear peroxyl radicals more readily enter into the bimolecular reaction $RO_2^{\bullet} + LSH \longrightarrow ROOH + LS^{\bullet}$, so the peroxide does not turn into a polyatomic hydroperoxide, and this has adverse implications for its therapeutic action. For example, for the **34** $\longrightarrow$ **35** reaction, $k[LSH] = 210\ s^{-1}$, while for the competing reaction

34 $\longrightarrow$ $CH(O)CH(OOH)CR(OH)C^{\bullet}HCH_2C(O)R$,

$k = 0.65\ s^{-1}$. A similar situation is observed in the isomerization of cyclic and linear alkoxyl radicals.

The results of this study supplement earlier data concerning free–radical conversions of artemisinin and its derivatives [12–15]. The antimalarial activity of the endoperoxides is mainly determined by two factors. The major factor is generation of hydroxyl radi-

Table 4. Correlation between the kinetic parameters of the conversions of the endoperoxide radicals and the antimalarial activity of the endoperoxides

N	n_{HO}	n_{HO_2}	n_{LS}	$n_{\Sigma R}$	$M_A IC_{50}(N)/M_N IC_{50}(A)$	
					clone D10	clone K1
1a	1.00	0.45	1.24	2.69	2.1×10^{-2}	4.4×10^{-2}
1b	1.00	0.45	1.24	2.69	1.7×10^{-2}	–
1c	1.00	0.45	1.24	2.69	4.8×10^{-2}	5.1×10^{-2}
1d	1.00	0.45	1.24	2.69	1.9×10^{-3}	–
2a	0	0	2	2.00	2.9×10^{-2}	6.0×10^{-2}
2b	0	0	2	2.00	5.7×10^{-2}	3.1×10^{-2}
2c	0	0	2	2.00	1.5×10^{-1}	1.6×10^{-1}
2d	0	0	2	2.00	7.3×10^{-3}	–
3a	0	0	2	2.00	1.1×10^{-2}	1.9×10^{-2}
3b	0	0	2	2.00	7.2×10^{-3}	–
3c	0	0	2	2.00	4.0×10^{-2}	7.7×10^{-2}
3d	0	0	2	2.00	1.5×10^{-3}	–
4	0	0	2	2.00	1.1×10^{-3}	8.4×10^{-3}
5a	0	0.40	0.60	1.00	2.4×10^{-3}	–
5b	0	0.40	0.60	1.00	2.2×10^{-3}	–

cals by the polyatomic hydroperoxides that result from the chain intramolecular oxidation of the drug. The higher the $HO^{\cdot}$ yield, the higher the antimalarial activity of the compound. The IC_{50} value depends on n_{OH} in an exponential way [13–15]. The other, less significant factor is generation of other radicals ($RO^{\cdot}$, $RO_2^{\cdot}$, $HO_2^{\cdot}$), which also kill the plasmodium, but do this less effectively. In terms of IC_{50}, these radicals are 1–2 orders of magnitude less effective than the hydroxyl radical. The IC_{50} value depends linearly on $n_{\Sigma R}$. The peroxides generating a single radical are practically inactive against the plasmodium. The possible ways in which the radicals act on biological substrates and enzymes were considered in a number of reviews [1–9, 12].

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