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PAPER

An important role of intramolecular free radical reactions in antimalarial activity of artemisinin and its analogs†‡

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The kinetic schemes of intramolecular reactions of five analogs of artemisinin were built. The method of intersecting parabolas was used for the calculation of activation energies and rate constants of each elementary step of these schemes. The competition between monomolecular and bimolecular free radicals was taken into account. It was evidenced that the intramolecular oxidation of these compounds proceeds as a cascade of consecutive free radical reactions with the formation of hydroperoxide groups. The latter decompose *via* reactions with the Fe(II) complexes generating free radicals. Among the radicals formed, the hydroxyl radical was proved to play the key role. A correlation between the yield of hydroxyl radicals n_{OH} and antimalarial activity of compounds (IC_{50}) was observed. The dependence of index IC_{50} on n_{OH} is linear in the logarithmic coordinates: $\ln[IC_{50}(\text{Artemisinin})/IC_{50}(\text{Compound})] = -14.10 + 3.85 \times n_{OH}$. The proposed scheme explains and demonstrates a strong dependence of the antimalarial effectiveness of a drug on the chemical structure.

Introduction

Malaria is a deadly disease, affecting hundreds of millions of people in tropical countries.[1] Alkaloids, such as quinine and chloroquine, have been efficient as antimalarial drugs. However, considerable resistance have been developed by malaria parasites to such alkaloids. Artemisinin (**1**) and its analogs are widely used now as new antimalarial remedies against drug-resistant *Plasmodium falciparum* malaria.[2–8] Artemisinin is a naturally occurring sesquiterpene, the essential feature of which is the peroxy group. This group was shown to react with Fe^{2+} and Fe^{3+} ions generating free radicals.[2–9] However, many other peroxides initiating free radicals were found to be inactive as antimalarial drugs.[2–4] So, the peroxy group of **1** is important for antimalarial activity but there are other peculiarities in structure **1** important for an efficient antimalarial effect. As shown recently, this peculiarity is hidden in the mechanism of intramolecular reactions of oxidation of **1** with the important role of free radical isomerization.[8,10,11] Artemisinin produces alkoxy radicals by the reaction with Fe(II) complexes. The latter are transformed into alkyl radicals. Isomerization of alkyl and alkoxy radicals plays an important role in this kind of free radical transformations.[10–11]

The free radical chemistry of cyclization and decyclization of free radicals was successfully developed by Athel Beckwith. During the last 20 years, he investigated a great number of these reactions with free radicals of different structures.[12–17] His findings (peculiarities of structure, activation energies and rate constants of free radical decyclizations) became a valuable scientific ground for developing the semiempirical theory and evaluating the kinetic parameters of these reactions in the scope of the intersecting parabolas model (IPM).[18] These data appeared to be very important to build up the full kinetic scheme of free radical transformations of **1** in the presence of Fe(II) complexes and oxygen. As a result of these studies, the kinetic scheme of transformations of **1** appeared to be a consecutive cascade of free radical reactions of isomerization and oxidation with the formation of a polyatomic hydroperoxide.[10,11] The latter generates a line of free radicals due to the reactions with the Fe(II) and Fe(III) complexes, transforming **1** into a polyatomic initiator. This initiator generates radicals of different structure: alkoxy, peroxy, and hydroxy. So, the next step of this study is to clear up what kind of initiated free radicals is important for curing effect of **1**. To solve this problem, we chose five sesquiterpenes (**2–6**) with peroxide groups close to the structure of **1** and decided to build up the kinetic schemes of free radical reactions for each compound in the presence of Fe(II) and oxygen and to compare the yield of free radicals with the antimalarial activity. This paper is devoted to this study.

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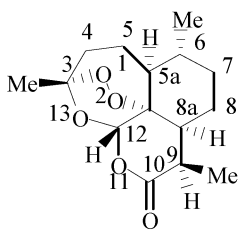
† This paper is devoted to the blessed memory of Athel Beckwith, brilliant scientist, who broadened the borders of modern free radical chemistry.

‡ Electronic supplementary information (ESI) available: Schemes for free radical oxidation cascade reactions of compounds **3–6**. See DOI: 10.1039/c0ob01150a

Method of calculation

Calculation of the enthalpy of the reaction

The enthalpy ΔH of intramolecular hydrogen transfer in cyclic alkoxy and peroxy radicals was calculated as the difference of the



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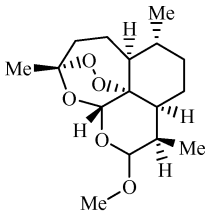

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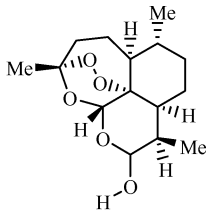

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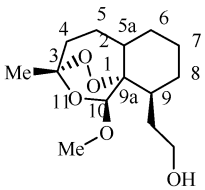

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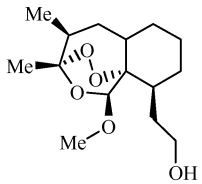

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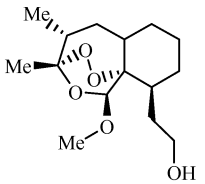

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dissociation energy of the initial attacked (D_i) and formed (D_f) bonds

$$\Delta H = D_i - D_f. \quad (1)$$

The dissociation energies of the C–H bonds in molecules **1–6** and the O–H bonds in the RO–H and ROO–H bonds formed were taken as the same as in the analogous molecules and are presented in Table 1.

The average error in estimation of the dissociation energies of the C–H and O–H bonds is ± 2 kJ mol^{-1}.[22] The calculated values of ΔH were used for the estimation of the activation energies and rate constants of isomerization of the free radicals formed.

Intersecting parabolas method

The activation energy E and rate constant k were calculated by the IPM method. This method has been described elsewhere.[18,21] The free radical reaction is characterized in the scope of this method by the following parameters: (1) classical enthalpy ΔH_e that includes the difference between the zero-point energies of the attacked and formed bonds

$$\Delta H_e = D_i - D_f + 0.5hN_A(\nu - \nu_f), \quad (2)$$

where ν and ν_f are the frequencies of stretching vibrations of the reacting bonds in s^{-1}, and h and N_A are Planck's constant and Avogadro's number, respectively; (2) the classical potential barrier E_e relates to the experimentally determined Arrhenius activation energy $E = RT\ln(A/k)$ by the equation

$$E_e = E + 0.5(hN_A\nu - RT); \quad (3)$$

(3) coefficients b and b_f describing the dependence of the potential energy on the amplitude of atomic vibration along the valence bond ($2b^2$ and $2b_f^2$ are the force constants of the attacked and formed bonds, respectively); the ratio $b/b_f = \alpha$, (4) the parameter r_e characterizing the total extension of two reacting bonds in the transition state; (5) the pre-exponential factor A = constant for the chosen class of free radical reactions.

The activation energy was calculated from the enthalpy of the reaction by eqn (4)

$$E = B^2\left\{1 - \alpha\sqrt{1 - \frac{\Delta H_e}{Bbr_e}}\right\}^2 - 0.5(hN_A\nu_i - RT) \quad (4)$$

where $B = br_e/(1 - \alpha^2)$, $\alpha = b_i/b_f$. The values of α, br_e, $0.5hN_A\nu_i$, $0.5hN_A(\nu_i - \nu_f)$, and A for the chosen classes of reactions are given

Table 1 Dissociation energies of C–H and O–H bonds in artemisinin, its analogs, and hydroperoxides[19,20]

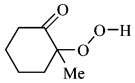
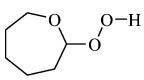
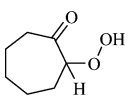
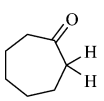
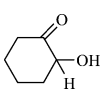
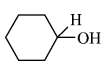
Bond	D_{C-H}, D_{O-H} (kJ mol^{-1})	Bond	D_{C-H}, D_{O-H} (kJ mol^{-1})
O^1–H, O^2–H	D_{O-H} = 438.5	C^4–H(OOH) (**1–4**), C^5–H(OOH) (**1–6**)	D_{C-H} = 370.9
C^4–H (**1–4**), C^5–H	D_{C-H} = 403.9	C^6–H(OOH) (**4–6**), C^7–H(OOH), C^8–H(OOH)	D_{O-H} = 375.8
C^4–H (**5–6**), C^{5a}–H	D_{C-H} = 390.0	>CHOO–H	D_{O-H} = 365.5
C^6–H (**1–3**)	D_{C-H} = 395.5	>CROO–H	D_{O-H} = 358.6
C^6–H(**4–6**), C^7–H, C^8–H	D_{C-H} = 408.8	C^9OO–H (**1**)	D_{O-H} = 362.9
C^{8a}–H (**1–3**)	D_{C-H} = 387.6	C^{10}OO–H (**2–6**)	D_{O-H} = 358.4
C^9–H (**1**)	D_{C-H} = 385.3	C^{12}OO–H (**1–3**)	D_{O-H} = 358.4
C^9–H (**2–3**)	D_{C-H} = 390.8		D_{O-H} = 362.9
C^9–H (**4–6**)	D_{C-H} = 396.8		D_{O-H} = 367.6
C^{10}–H (**4–6**), C^{12}–H	D_{C-H} = 378.1		D_{C-H} = 356.2
RCH(OH)–H	D_{C-H} = 399.5		D_{C-H} = 389.2
	D_{C-H} = 373.7		D_{C-H} = 388.4

Table 2 Kinetic parameters of classes of free radical reactions calculated in this study[18,21,23]

Class reactions	α	br_e (kJ mol^{-1})$^{1/2}$	$0.5hN_A\nu_i$	$0.5hN_A(\nu_I - \nu_f)$ (kJ mol^{-1})	lg(A/s^{-1})
RO$^\bullet$ → R$^\bullet$	0.796	13.13	17.4	−4.3	12.6
RO$^\bullet$ → Decyclization	0.748	9.84	6.2	−2.1	13.0
RO$^\bullet$ + LSH	0.707	11.67	15.1	−6.6	7.3[a]
$RO_2^\bullet$ → R$^\bullet$ (n = 6)[b]	0.814	13.23	17.4	−3.8	12.74
$RO_2^\bullet$ → R$^\bullet$ (n = 7)[b]	0.814	13.43	17.4	−3.8	12.74
$R_iO_2^\bullet$ → $R_jO_2^\bullet$	1.000	13.13	21.2	0.0	11.54
$RO_2^\bullet$ + LSH	0.722	11.94	15.1	−6.1	7.3[a]

[a] For this bimolecular reaction, $A = A_0$[LSH], [LSH] = 0.02 mol l^{-1}. [b] Here n is the number of atoms forming the transition state cycle.

in Table 2. The mean square error of activation energy calculation was as low as 1.5 kJ mol^{-1}.[21]

The rate constant was calculated *via* the Arrhenius equation

$$k = A \exp(-E/RT) \quad (5)$$

When the values of rate constants of two parallel reactions were close (their ratio < 4), both reactions were taken into account.

Results and discussion

Competing reactions in the free radical chemistry of artemisinin

The parallel reactions of free radicals formed from **1** play an important role in the kinetics of free radical reactions of **1** and its analogs. This competition was studied elsewhere.[10,11] When an alkoxy radical is generated by the reaction of the peroxide group with Fe(II), it can react with any biological substrate. The values of the rate constants of possible reactions are compared in Fig. 1.

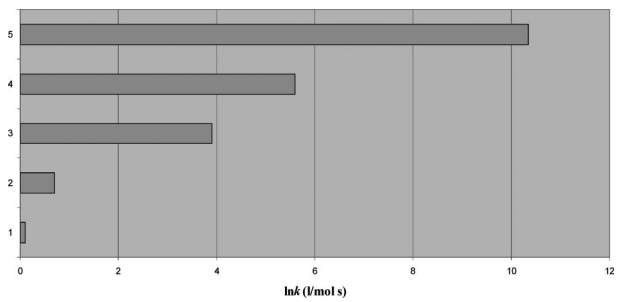


Fig. 1 Rate constants of bimolecular reactions of the peroxy radicals of **1** with different substrates: 1—glycerol, 2—methyl oleate, 3—methyl linoleate, 4—glucose, 5—L-cysteine.[11]

One can see that the fastest is the reaction of RO$^\bullet$ with the S–H groups of L-cysteine. The same situation is observed for the reactions of peroxyl radicals.[11] The next step in the kinetic analysis of competing reactions is given by intramolecular reactions of the alkoxy radical formed. There are two types of these reactions: isomerization with hydrogen atom transfer and decyclization.

The values of ΔH, E, and k(310 K) were calculated by the IPM method. The reactions of isomerization with hydrogen atom transfer appeared to be much faster then the reaction of RO$^\bullet$ with L-cysteine (LSH).[8,11] So, the calculation of the rate constants of all competing reactions helps to choose the main route of transformation of the formed free radical.

The alkyl radical R$^\bullet$ formed from RO$^\bullet$ participates, in turn, in a few parallel reactions. The addition of O_2 with the formation of peroxyl radical $RO_2^\bullet$ appeared to be the fastest: it proceeds with the diffusion-controlled rate constant ($k = 1.5 \times 10^9$ l mol^{-1} s^{-1}).[22] and dominates when its concentration is 10 or 100 times lower than the air-equilibrium concentration.[11] As a rule, the intramolecular hydrogen transfer in $RO_2^\bullet$ proceeds more rapidly than its reaction with L-cysteine if there are C–H bonds accessible for isomerization. The peculiarities of the competing reactions described above were taken into account in constructing kinetic schemes of free radical oxidation of compounds **2–6**. Among the parallel reactions of any peroxy radical, the reaction with the lower enthalpy proceeds more rapidly. An example of such competition is given in Table 3.

Table 3 Comparison of the kinetic characteristics of parallel reactions of peroxy radical $R^{5a}OO^\bullet$ (**2**)

Reaction	ΔH (kJ mol^{-1})	E (kJ mol^{-1})	k(310 K) (l mol^{-1} s^{-1})	%
$R^{5a}OO^\bullet \rightarrow R^{12\bullet}$	19.5	44.3	1.8×10^5	84.0
$R^{5a}OO^\bullet \rightarrow R^{8a\bullet}$	29.0	48.9	3.2×10^4	15.0
$R^{5a}OO^\bullet \rightarrow R^{4\bullet}$	45.3	57.2	1.3×10^3	0.6
$R^{5a}OO^\bullet \rightarrow R^{7\bullet}$	50.2	59.9	4.4×10^2	0.2
$R^{5a}OO^\bullet \rightarrow R^{8\bullet}$	50.2	61.5	2.4×10^2	0.1
$R^{5a}OO^\bullet$ + LSH	−5.5	26.7	3.0×10^2	0.1

It is seen from Table 3 that reaction $R^{5a}OO^\bullet \rightarrow R^{12\bullet}$ is the main reaction and other reactions can be neglected.

Kinetic scheme of the cascade oxidation of compound 2

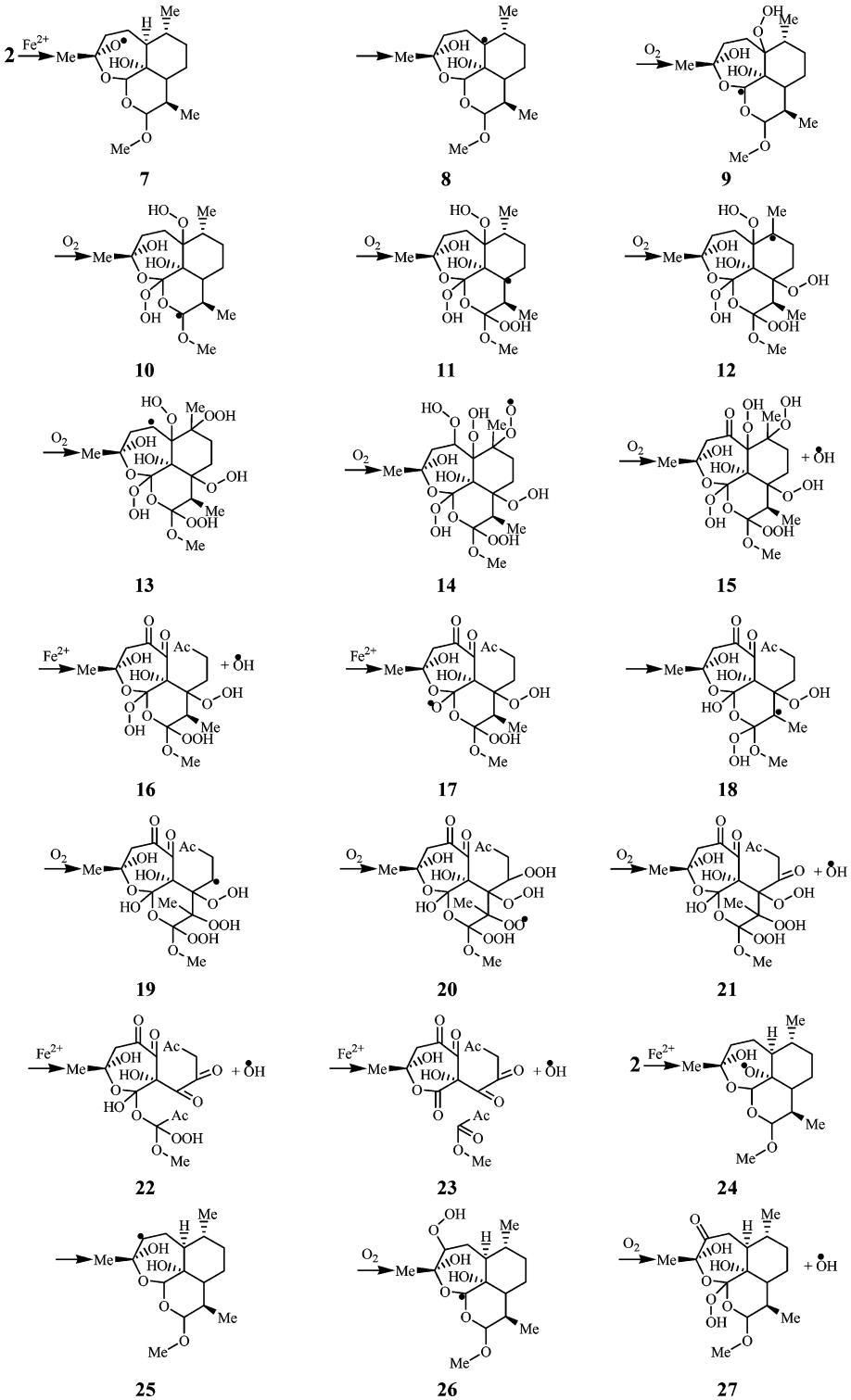
The kinetic scheme of transformations of free radicals formed from compound **2** is presented below. Each reaction is characterized by the enthalpy, activation energy, and rate constant at T = 310 K calculated by the method of IPM (see Table 4).

The probabilities of generation of alkoxy radicals $RO^{1\bullet}$ and $RO^{2\bullet}$ from compound **2** are supposed to be equal. Five hydroxyl radicals are generated due to the oxidation of radical $RO^{2\bullet}$. Radical $RO^{1\bullet}$ is isomerized in parallel to alkyl radicals $R^{4\bullet}$ and $R^{7\bullet}$ with the ratio of rate constants 2 : 1 (see Schemes 1 and 2). The oxidation and destruction of $R^{4\bullet}$ produces three hydroxyl and two LS$^\bullet$ radicals, and the oxidation of $R^{7\bullet}$ produces two hydroxyl and one thiyl radical. The total yield of radicals per molecule of **2** is equal to 3.83 hydroxyl radicals and 0.83 LS$^\bullet$ radicals.

Reaction schemes for free radical oxidation cascade reactions of compounds **3–6** are presented in the ESI.‡

The antimalarial activities (ln[IC_{50}(**1**)/IC_{50}(**i**)]) of five studied compounds **2–6** are compared with the total yield of free radicals and the yield of hydroxyl radicals n_{OH} (see Table 5).

We observe no correlation between the activity and general yield of free radicals (compare **1** and **2**, **3** and **5**, **1** and **6**). On the contrary,



Scheme 1 Stages of intramolecular oxidation of compound **2**.

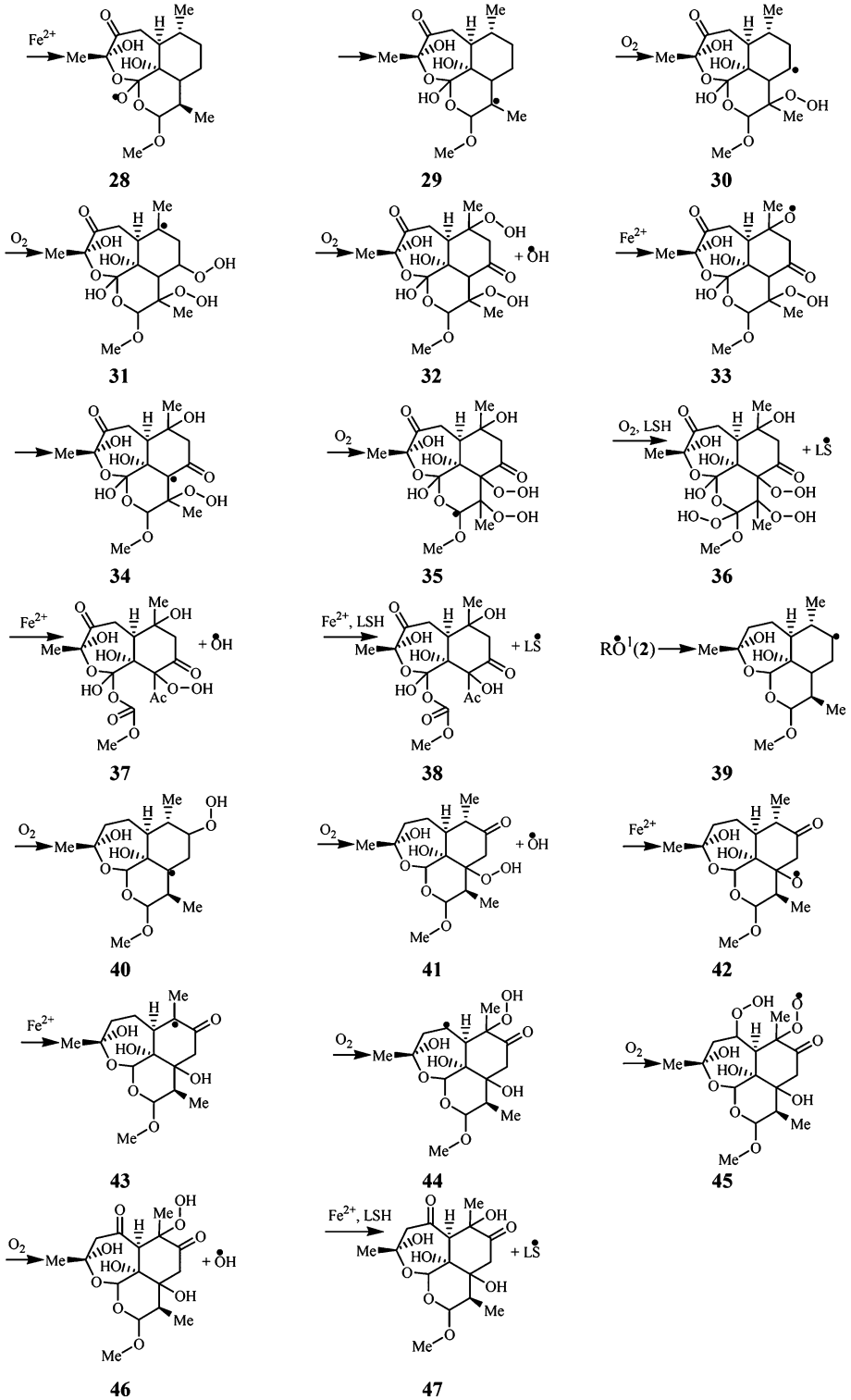
there is a dependence of the antimalarial activity on the number of initiated hydroxyl radicals (see Fig. 2). This dependence of $\ln(IC_{50})$ on the yield of hydroxyls is linear and can be expressed by eqn (6)

$$\ln\{IC_{50}(\mathbf{1})/IC_{50}(\mathbf{i})\} = -14.10 \pm 0.86 + (3.85 \pm 0.24) \times n_{OH}. \quad (6)$$

Reactions of generation of hydroxyl radicals

The hydroxyl radicals are generated in the following three types of elementary steps.

1. Hydroxyl is formed by decay of the hydroperoxyalkyl radical that succeeds the reaction of hydrogen atom transfer.

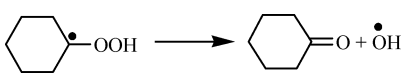


Scheme 2 Stages of intramolecular oxidation of compound **2**.

$$>C(OO^{\bullet})CH_2CH(OOH)- \rightarrow >C(OOH)CH_2C^{\bullet}(OOH)-$$

$$>C(OOH)CH_2C^{\bullet}OOH- \rightarrow >C(OOH)CH_2C(O)- + HO^{\bullet}$$

The decay of the hydroperoxyalkyl radical is a very exothermic reaction. For example, the reaction proceeds with the enthalpy $\Delta H = -164.2$ kJ mol^{-1}.



2. Radical HO$^{\bullet}$ is generated as a result of decomposition of the cyclic α-hydroperoxyoxyl radical formed from diatomic hydroperoxide.

Table 4 Enthalpies, activation energies and rate constants of free radical reactions of Schemes 1 and 2 calculated by the IPM method

Reaction	ΔH (kJ mol^{-1})	E (kJ mol^{-1})	k(310 K) (s^{-1})
7 → **8**	− 48.5	17.0	5.46 × 10^{9}
8 → **9**	19.5	44.3	1.79 × 10^{5}
9 → **10**, **34** → **35**	19.7	44.5	1.74 × 10^{5}
10 → **11**	29.2	49.5	2.51 × 10^{4}
11 → **12**	36.9	54.6	3.47 × 10^{4}
12 → **13**, **43** → **44**	45.3	57.3	1.22 × 10^{3}
13 → **14**, **19** → **20**, **44** → **45**	−6.9	19.8	4.15 × 10^{6}
14 → **15**	−2.4	34.3	9.13 × 10^{6}
17 → **18**, **28** → **29**	−43.0	18.4	3.17 × 10^{9}
18 → **19**	53.4	61.7	2.21 × 10^{2}
20 → **21**	20.4	44.8	1.55 × 10^{5}
24 → **25**	−34.6	21.8	8.51 × 10^{8}
25 → **26**, **26** → **27**	12.6	42.7	3.53 × 10^{5}
29 → **30**	50.2	60.0	4.27 × 10^{2}
30 → **31**	30.0	49.4	2.61 × 10^{4}
31 → **32**, **40** → **41**	17.2	43.2	2.88 × 10^{5}
33 → **34**	−53.2	14.9	1.23 × 10^{10}
35 → **36**	1.6	32.4	6.95 × 10
37 → **38**, **46** → **47**	−78.5	5.8	2.06 × 10^{2}
7 → **39**	−29.7	23.6	4.26 × 10^{8}
39 → **40**	22.1	45.7	1.10 × 10^{5}
42 → **43**	−54.7	14.2	1.61 × 10^{10}
45 → **46**	12.3	42.6	3.65 × 10^{5}

Table 5 Comparison of the relative antimalarial activity of compound {IC_{50}(**1**)/IC_{50} (Compound)} with the number of generated hydroxy radicals n_{OH}

Compound	n_{OH}	n_{LS}	Σn	IC_{50}(**1**)/IC_{50}(**i**)	Reference
1	3.17	1.17	4.34	1.00	24
2	3.83	0.83	4.66	2.28	24
3	4.33	0.50	4.83	7.40	24
4	3.00	1.50	4.50	0.09	25
5	3.75	1.50	5.25	1.4; 1.8; 2.2	25
6	2.50	1.50	4.00	0.008	25

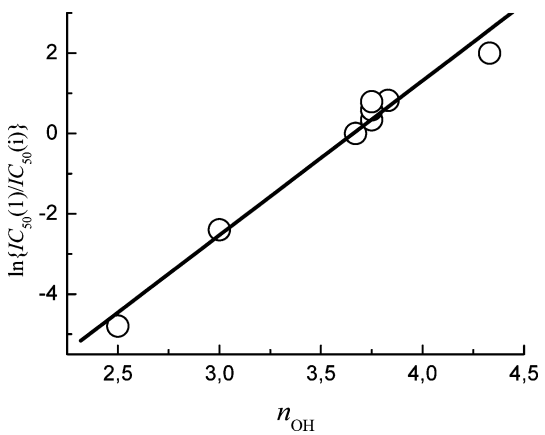
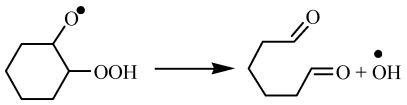


Fig. 2 Correlation of ln{IC_{50}(**1**)/IC_{50}(Compound)} with the number hydroxyl radicals n_{OH} initiated by the compound in intramolecular oxidation.

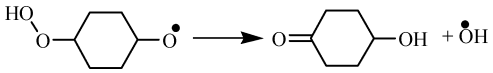
$$Fe^{2+} + >C(OOH)C(OOH)< \rightarrow FeOH^{2+} + >C(O^{\bullet})C(OOH)<$$

$$>C(O^{\bullet})C(OOH)< \rightarrow >C{=}O + >C{=}O + HO^{\bullet}$$

This decay is very exothermic too. For example, the enthalpy of decomposition



is $\Delta H = -128.7$ kJ mol^{-1}.3. Hydroxyl radical is generated also as a result of isomerization of the alkoxy radical with the hydroperoxyl group in the γ-position, for example,



Hydroxyl radical is known to be an extremely active intermediate that participates very rapidly in the reactions of hydrogen atom abstraction and addition to double bonds.[26] Hence, it can attack any of biological targets in a malaria parasite. These targets may be Fe chelates of enzymes of plasmodium, proteins, carbohydrates, lipids, *etc.*[27–30] The exponential dependence of IC_{50} of a drug on n_{OH} demonstrates the cumulative character of the hydroxyl radical effect and explains the very strong influence of the chemical structure on the antimalarial effectiveness of the compound (compounds with $n_{OH} < 2$ have very low effectiveness and that with $n_{OH} > 3.5$ demonstrates very high effectiveness).

Conclusions

The results of this study give the ground for the formulation of the following hydroxyl mechanism of the action of **1** and its analogs as antimalarial drugs. The concentration of the Fe chelates in malarial plasmodium is 20 times higher than that in human body. That is why the initiation of free radicals proceeds preferentially inside a malarial parasite. The latter lives inside the red blood cells that transport oxygen. The alkyl radicals formed from **1** react instantly with O_2 and are transformed into peroxy radicals. The isomerization of $RO_2^{\bullet}$ into $R^{\bullet}$ leads to a consecutive cascade of oxidation and isomerization of formed free radicals producing polyatomic hydroperoxide. The decay of the formed hydroperoxide groups initiates new free radicals. Among them, the hydroxyl radicals play a key role. They damage the biological substrates of the malaria parasite and kill it. The yield of hydroxyl radicals and, hence, the effectiveness of an antimalarial drug depend strongly on its structure. The empirical dependence of the effectiveness of antimalarial action on the yield of hydroxyl radicals formed as a result of the cascade of free radical reactions of the drug is exponential.

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