Hydroxyl mechanism of the antimalarial effect of artemisinin and its analogs

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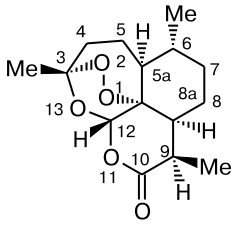
Kinetic schemes for the intramolecular oxidation of four artemisinin analogs, which are used as drugs against malaria, were developed. Each stage of the kinetic scheme is characterized by the enthalpy, activation energy, and rate constant calculated using the model of intersecting parabolas. The competition of mono- and bimolecular radical reactions was taken into account when developing the schemes. The hydroperoxide groups are formed as a result of the intramolecular oxidation of these compounds and generate free radicals in the reaction with Fe^{II}. Among these free radicals, hydroxyl radicals play the key role, since their yield (n_{OH}) correlates with the antimalarial activity of the peroxide compound. The efficiency of the drug (index IC_{50}) exponentially depends on n_{OH} and is expressed by the formula $IC_{50}(\text{Artemisinin})/IC_{50}(\text{Compound}) = 1.54 \cdot 10^{-6}\exp(3.9n_{OH})$. The elementary reactions resulting in the generation of hydroxyl radicals are considered. It is supposed that DNA of a malaria parasite is the main biological target for hydroxyl radicals.

Key words: artemisinin, artemisinin analogs, antimalarial activity, hydroxyl radical, DNA, isomerization of radicals, kinetic scheme, rate constant, model of intersecting parabolas, activation energy, enthalpy of reaction.

Artemisinin (**1**) is a highly efficient drug, which is successfully used against malaria plasmodium (*Plasmodium falciparum*) resistant to quinine and its analogs of the alkaloid type.[1—3] The curing effect of compound **1** is due to the generation of free radicals. Structure **1** is a sesquiterpene endoperoxide (see below). The peroxide bridge in structure **1** generates free radicals *via* the redox reaction with chelates of divalent iron

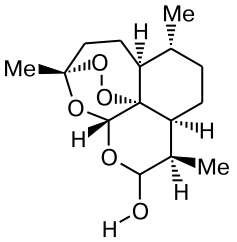
$$ROOR + Fe^{2+} \longrightarrow RO^{\cdot} + RO^{-} + Fe^{3+},$$

which, as it is believed, results in the death of the parasite. It was assumed for a long time that the mechanism of the antimalarial effect of compound **1** is reduced to this reaction, *i.e.*, compound **1** "works" as a usual initiator.[1,3—10] However, the synthesis and testing of its analogs to antimalarial activity showed that the whole structure of molecule **1** rather than its peroxide bridge only plays an important role.[1,2] Using the kinetic analysis of the reactions occurring after the cleavage of the peroxide bridge in compound **1** in the presence of oxygen, it was proposed that the radicals formed are involved in a cascade of consecutive transformations with participation of oxygen.[11—16] As a result, compound **1** is transformed into polyatomic hydroperoxide. The latter generates free radicals *via* the reaction with Fe^{II}, which results in the death of the parasite. The kinetic analysis of radical transformations of



1

$(IC_{50})_{rel} = 1.00$



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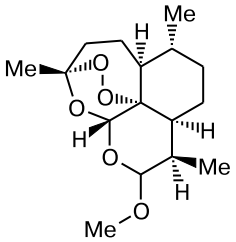
$(IC_{50})_{rel} = 7.40$



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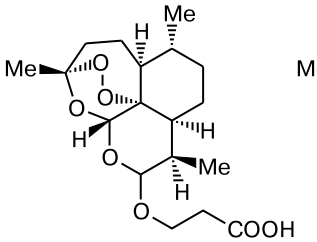
$(IC_{50})_{rel} = 1.78$



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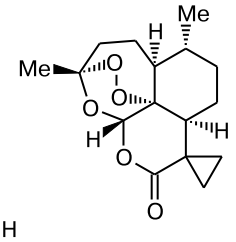
$(IC_{50})_{rel} = 1.78$



5

$(IC_{50})_{rel} = 0.08$

Note. $(IC_{50})_{rel} = IC_{50}(\mathbf{1})/IC_{50}(i)$.

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a series of analogs of compound **1** established that the efficiency of their action is determined by the number of hydroxyl radicals generated by one molecule of the drug rather than the total number of generated radicals.[2,17–21] This result was obtained for a series of structures with the same or lower antimalarial activity (compared to that of **1**). The antimalarial activity is characterized by index IC_{50}, the dose of the drug that decreases the concentration of a malaria parasite by 2 times (it is expressed in ng g^{-1}). The present work is devoted to the kinetic analysis of analogs of compound **1** that manifest a higher activity than the activity of compound **1**.[22] The radical transformations of drugs **2**—**4** and compound **5** were considered. Compound **5** is an analog of **1** in which the C—H group in position 9 is "switched off" (>CH is replaced by the >C-*cyclo*-C_3H_5 group).

The present study is aimed at revealing whether the generation of hydroxyl radical plays the key role in the antimalarial effect of these highly efficient drugs and at refining the dependence of the antimalarial activity of such drugs on the yield of hydroxyl radicals.

Calculation Procedure

The method of intersecting parabolas was used for the calculation of the activation energy E and rate constant k of mono- and bimolecular radical reactions.[23–25] In terms of this method, each class of radical reactions is characterized by the following parameters: the atomic structure of the reaction center of the transition state, for example, O...H...C for the reactions RO$^{\cdot}$ + RH or $RO_2^{\cdot}$ + RH, coefficients b for the attacked bond and b_f for the formed bond ($2b^2$ is the force constant of the bond), zero-point valence vibration energies of these bonds $0.5hN_A\nu$ and $0.5hN_A\nu_f$, respectively (h is Planck´s constant, N_A is Avogadro´s number, and ν and ν_f are the frequencies of stretching vibrations of these bonds), total elongation of reacting bonds in the transition state r_e, and pre-exponential factor A per one equireactive attacked bond. The derivatives of these parameters are coefficient $\alpha = b/b_f$ and product br_e. The values of these parameters for the reactions, which are observed for the oxidation of the compounds considered, are given in Table 1.

An individual reaction is characterized by the classical enthalpy $\Delta H_e = \Delta H + 0.5hN_A(\nu - \nu_f)$ (ΔH is the enthalpy of the reaction) and classical potential barrier $E_e = E + 0.5hN_A\nu - 0.5RT$. The activation energy of the reaction was calculated through the enthalpy of the reaction ΔH by the reaction

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

where $B = br_e/(1 - \alpha^2)$. The enthalpy of the isomerization and bimolecular abstraction of the H atom was calculated as the difference of the dissociation energies of the attacked bond D_{C-H}

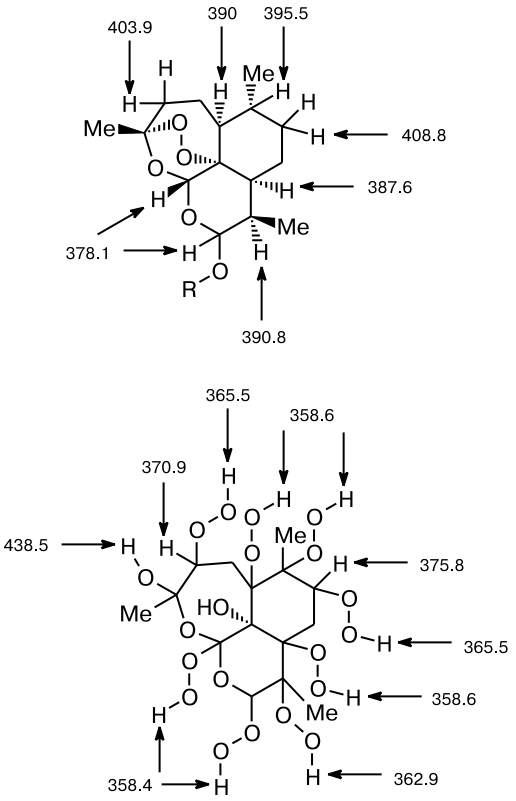


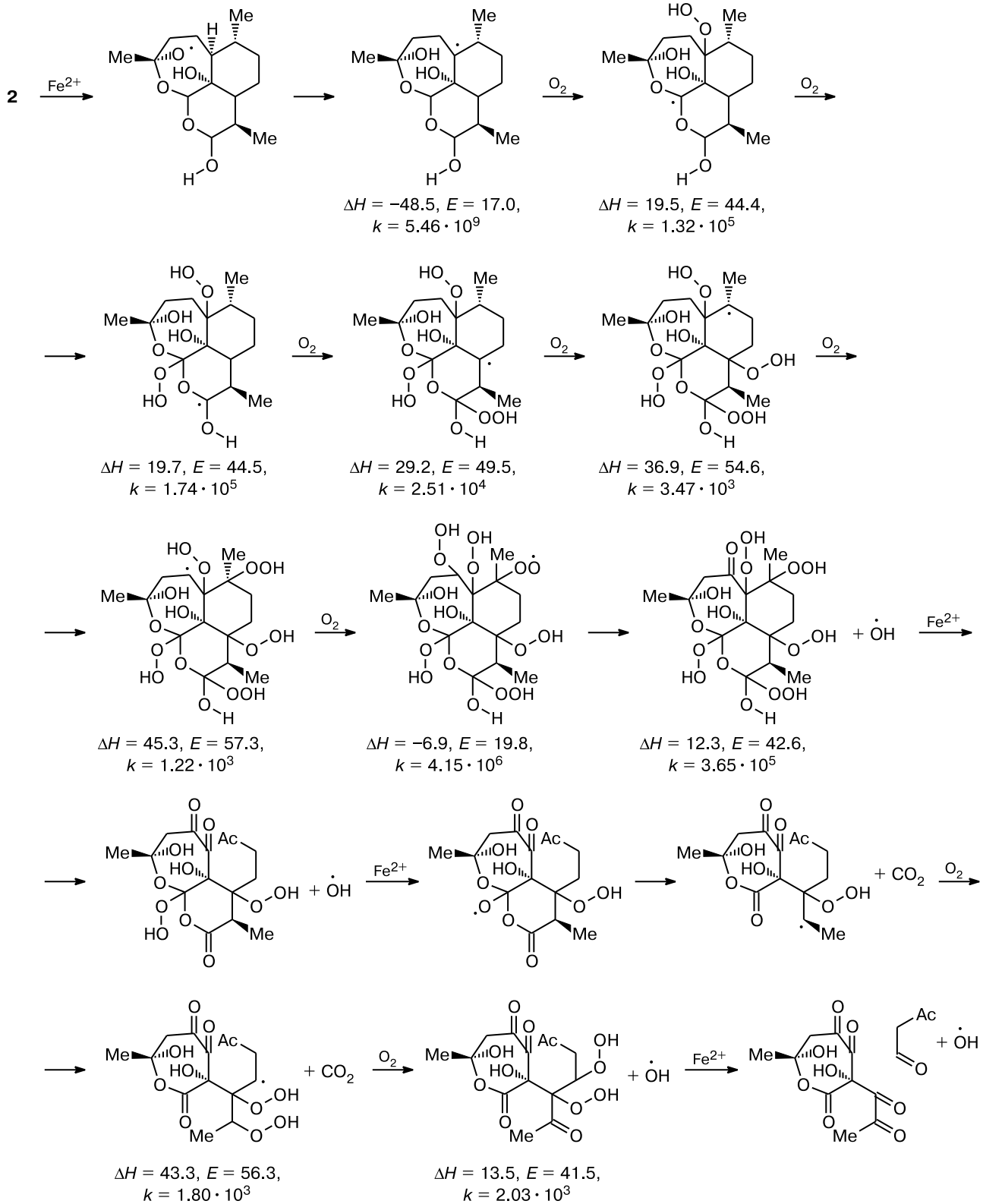
Table 1. Kinetic parameters of the reaction classes[26–28]

Reaction class	α	br_e/kJ$^{0.5}$ mol$^{-0.5}$	$0.5hN_A\nu_i$	$0.5hN_A(\nu_I - \nu_f)$	log(A/s^{-1})
			kJ mol^{-1}		
RO$^{\cdot}$ → R$^{\cdot}$	0.796	13.13	17.4	−4.3	12.6
RO$^{\cdot}$ → Decyclization	0.748	9.84	6.2	−2.1	13.0
RO$^{\cdot}$ + LSH	0.707	11.67	15.1	−6.6	7.3*
$RO_2^{\cdot}$ → R$^{\cdot}$ (n = 6)**	0.814	13.23	17.4	−3.8	12.74
$RO_2^{\cdot}$ → R$^{\cdot}$ (n = 7)**	0.814	13.43	17.4	−3.8	12.74
$R_fO_2^{\cdot}$ → $R_fO_2^{\cdot}$	1.000	13.13	21.2	0.0	11.54
$RO_2^{\cdot}$ + LSH	0.722	11.94	15.1	−6.1	7.3*

* For this bimolecular reaction $A = A_0$[LSH].

** n is the number of atoms in the cycle of the transition state.

Scheme 1



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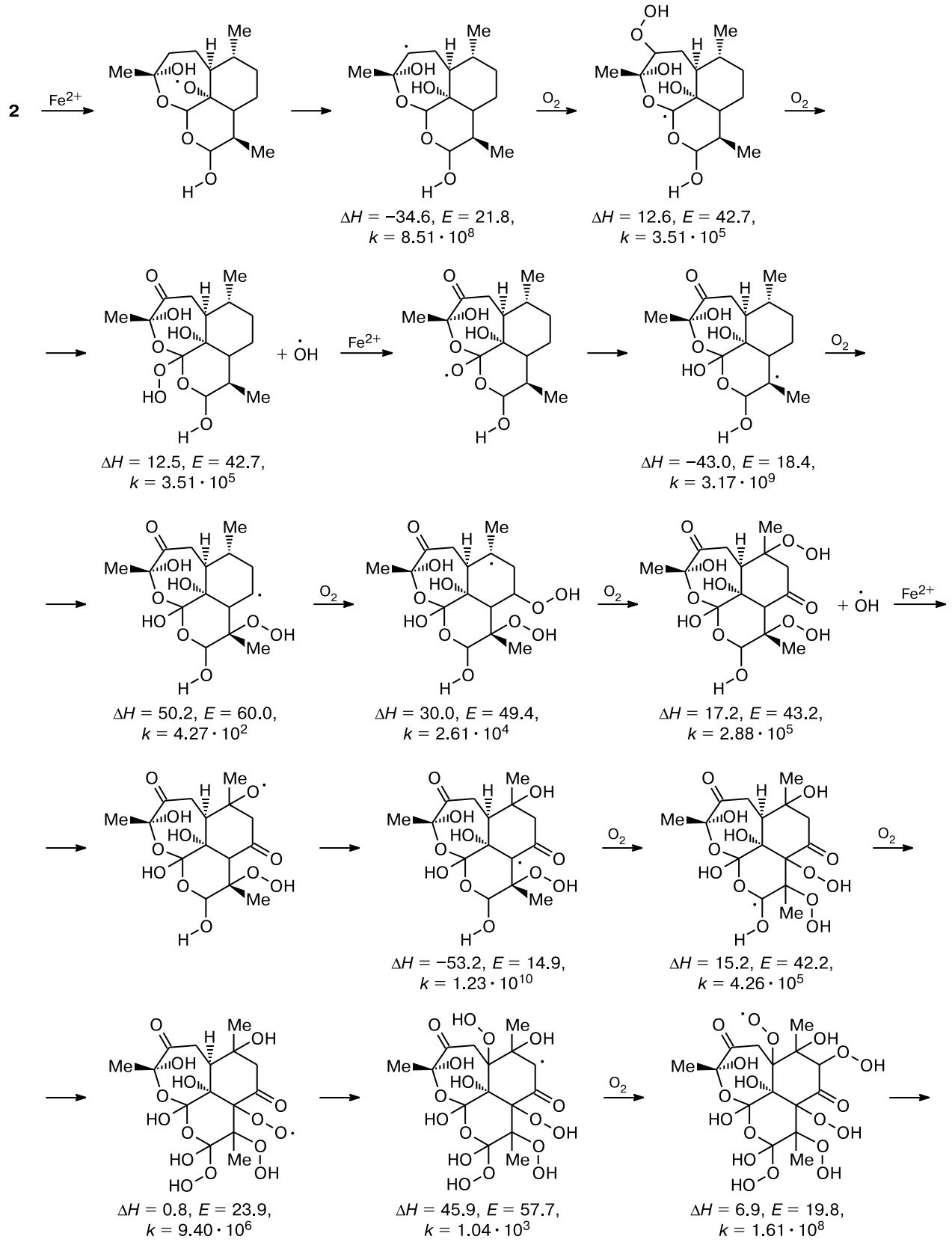

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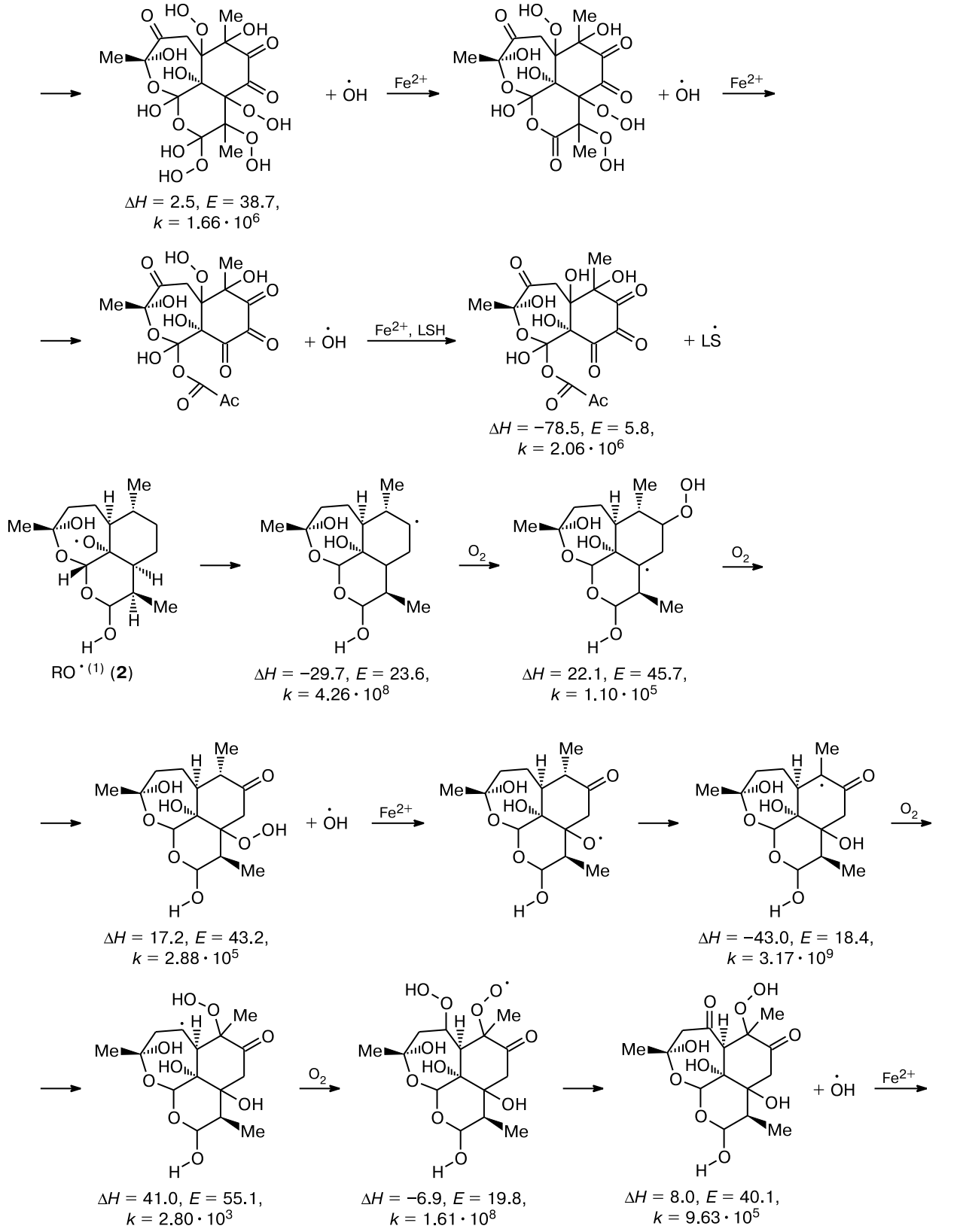

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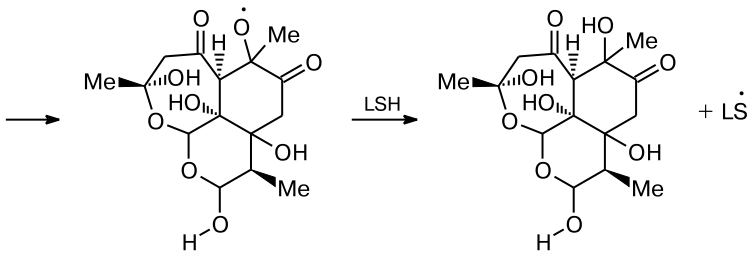


ΔH = −78.5, E = 5.8,
$k = 2.06 \cdot 10^6$

(or D_{S-H}) and the formed bond D_{O-H}: $\Delta H = D_{C-H} - D_{O-H}$. The values of D_{C-H} and D_{O-H} (kJ mol^{-1}) used in the calculation are presented below.[29—32]

The strength of the S—H bond in L-cysteine is D_{S-H} = = 360 kJ mol^{-1}.[28] Among all substrates, these are the thio groups of L-cysteine in the composition of proteins that are attacked most rapidly by radicals RO$^{\cdot}$ and RO$_2^{\cdot}$.[12,15]

The calculation of k of radical reactions is necessary for taking into account the competition of parallel reactions and composing the sequence of radical transformations. Two parallel reactions were taken into account if the ratio of their constants k_1/k_2 did not exceed 5, which corresponds to the difference in activation energies $\Delta E = E_2 - E_1 = 4$ kJ mol^{-1} at equal A_1 and A_2. For instance, the rate constant for H atom abstraction from position C(4) by radical RO$^{(2)\cdot}$ is k(C(4)H) = $8.51 \cdot 10^8$ s^{-1} (310 K), whereas that from position C(7) is k(C(7)H) = $4.26 \cdot 10^8$ s^{-1}. The ratio k(C(4)H)/k(C(7)H) is 2.0, and the both reactions were taken into account (Schemes 1—3, ΔH and E are presented in kJ mol^{-1}, and k(310 K) are presented in s^{-1}). The addition of oxygen to the alkyl radical occurs very rapidly with the diffusion rate constant.[25] The specific rate constant of this reaction in the lipid phase $k[O_2]$ is $3.5 \cdot 10^{-6}$ s^{-1}.[15] Thus, the reaction considered occurs much more rapidly than any other reaction involving the alkyl radical.[15]

Results and Discussion

The kinetic scheme of radical transformations of compound **2** and kinetic characteristics for each stage are presented in Scheme 1. Each stage involving the peroxyl radical includes two consecutive elementary acts: the fast addition of oxygen to the alkyl radical (see above) and the intrinsic fast reaction involving RO$_2^{\cdot}$ formed.

This scheme shows that alkoxyl radical RO$^{(2)\cdot}$ formed from compound **2** isomerizes exclusively to alkyl radical R$^{(5a)\cdot}$. The single parallel reaction of RO$^{(2)\cdot}$ with LSH is by three orders of magnitude slower (k[LSH] = $1.0 \cdot 10^6$ s^{-1}).[12] As a result of a chain of successive radical transformations, R$^{(5a)\cdot}$ generates four hydroxyl radicals. Since only 50% of the molecules reacted with Fe^{II} generates radicals RO$^{(2)\cdot}$, the yield of radicals HO$^{\cdot}$ per molecule **2** *via* this radical is equal to 2. The transformation of radical RO$^{(1)\cdot}$ proceeds *via* two parallel channels. The isomerization RO$^{(1)\cdot} \rightarrow$ RO$^{(4)\cdot}$ followed by transformations of R$^{(4)\cdot}$ affords five hydroxyl radicals and one thiyl radical. The ratio k(RO$^{(1)\cdot} \rightarrow$ R$^{(4)\cdot}$)/[k(RO$^{(1)\cdot} \rightarrow$ R$^{(4)\cdot}$) + k(RO$^{(1)\cdot} \rightarrow$ $\rightarrow$ R$^{(7)\cdot}$)] is 0.67. Taking into account that 50% of molecules **2** are transformed in the reaction **2** $\rightarrow$ RO$^{(1)\cdot}$, we have that the yield of radicals *via* this channel is n_{OH} = 1.67 and n_{LS} = 0.33. The reaction RO$^{(1)\cdot} \rightarrow$ RO$^{(7)}$ results in the transformation of 0.33 RO$^{(1)\cdot}$ radical. A chain of successive transformations of radical R$^{(7)\cdot}$ gives rise to two hydroxyl radicals and one thiyl radical, and the yields are n_{OH} = 0.33 and n_{LS} = 0.17 per one molecule **2**. The total yield of radicals ($n_{\Sigma R}$) per one molecule **2** is $n_{\Sigma R}$ = 4.5, of which n_{OH} = 4 and n_{LS} = 0.5.

The kinetic Scheme 2 shows the sequence of transformations of radicals, which are formed due to the reactions following the cleavage of the peroxide bridge in compound **3**.

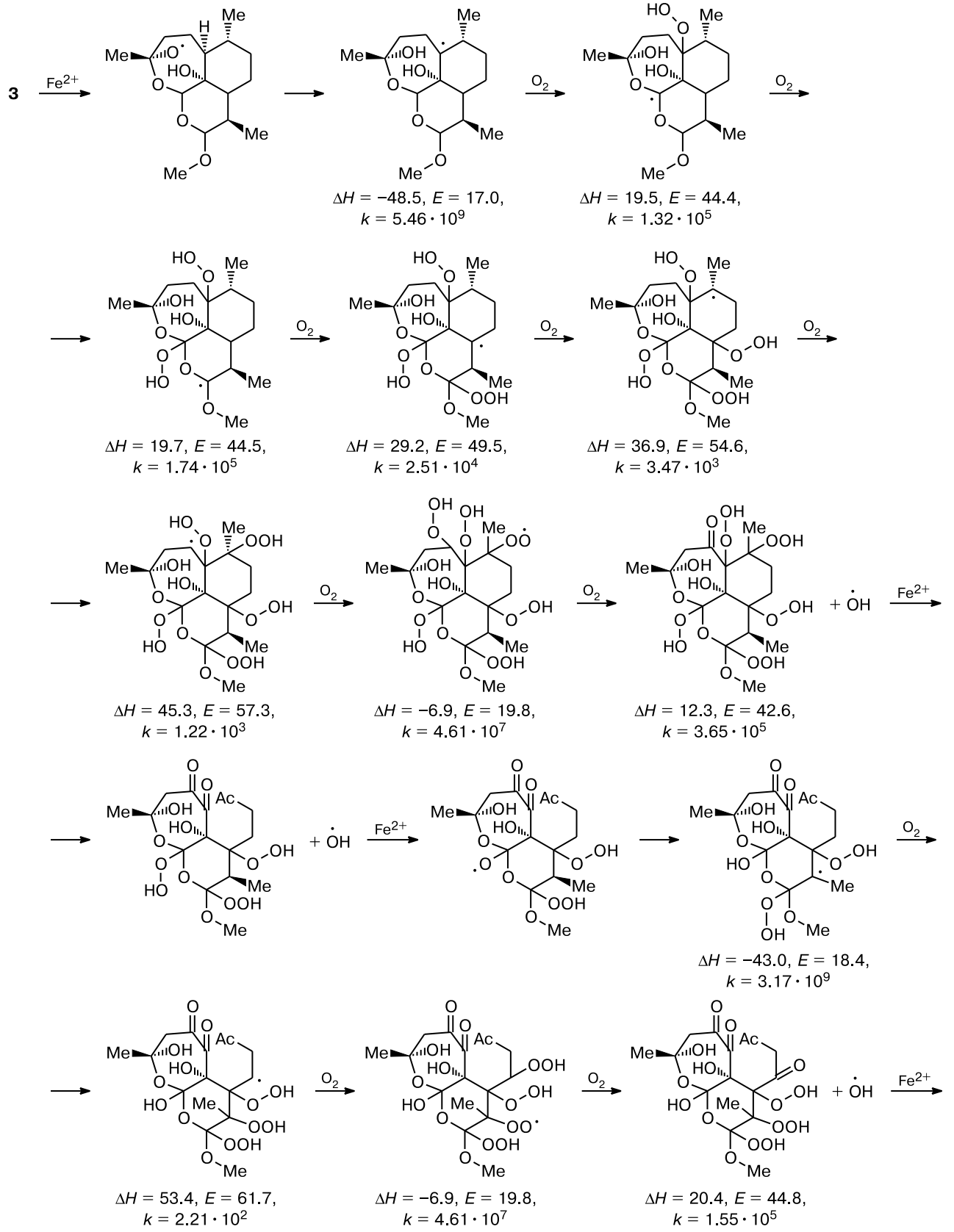
In Scheme 2, as in Scheme 1, each stage involving the alkyl radical includes the fast addition of oxygen and isomerization of the peroxyl radical formed. Taking into account the parallel reactions involving peroxyl radicals, we obtained the following parameters for the generation of radicals by molecule **3**: n_{OH} = 3.83, n_{LS} = 0.83, and $n_{\Sigma R}$ =4.66. The kinetic scheme of transformations of compound **4** has the same network of reactions and finally the same yield of radicals per one molecule.

The introduction of the cyclopropyl substituent in artemisinin into position C(9) switches off the group C(9)—H from the cascade of radical transformations. This drastically changes the yield of hydroxyl radicals upon the oxidative destruction of compound **5** (see Scheme 3).

Radical C(12)O$^{\cdot}$ cannot attack the group C(9)H because of its absence, and the cascade of subsequent reactions with the elimination of CO_2 and decyclization of the cyclopropane ring results in the generation of a series of radicals LS$^{\cdot}$ (instead of HO$^{\cdot}$ during the oxidation of compounds **1**—**4**). As a result of the oxidation of compound **5**, the yield of radicals HO$^{\cdot}$ n_{OH} is as low as 1.67.

For a more complete consideration of the role of radicals LS$^{\cdot}$ and HO$^{\cdot}$ in the antimalarial effect of the analogs of **1**, Table 2 includes the kinetic analysis results for compounds **2**—**5** and also other analogs of compound **1** considered earlier,[17—21] namely, compounds **6**—**13**, whose structures are given below.

Scheme 2



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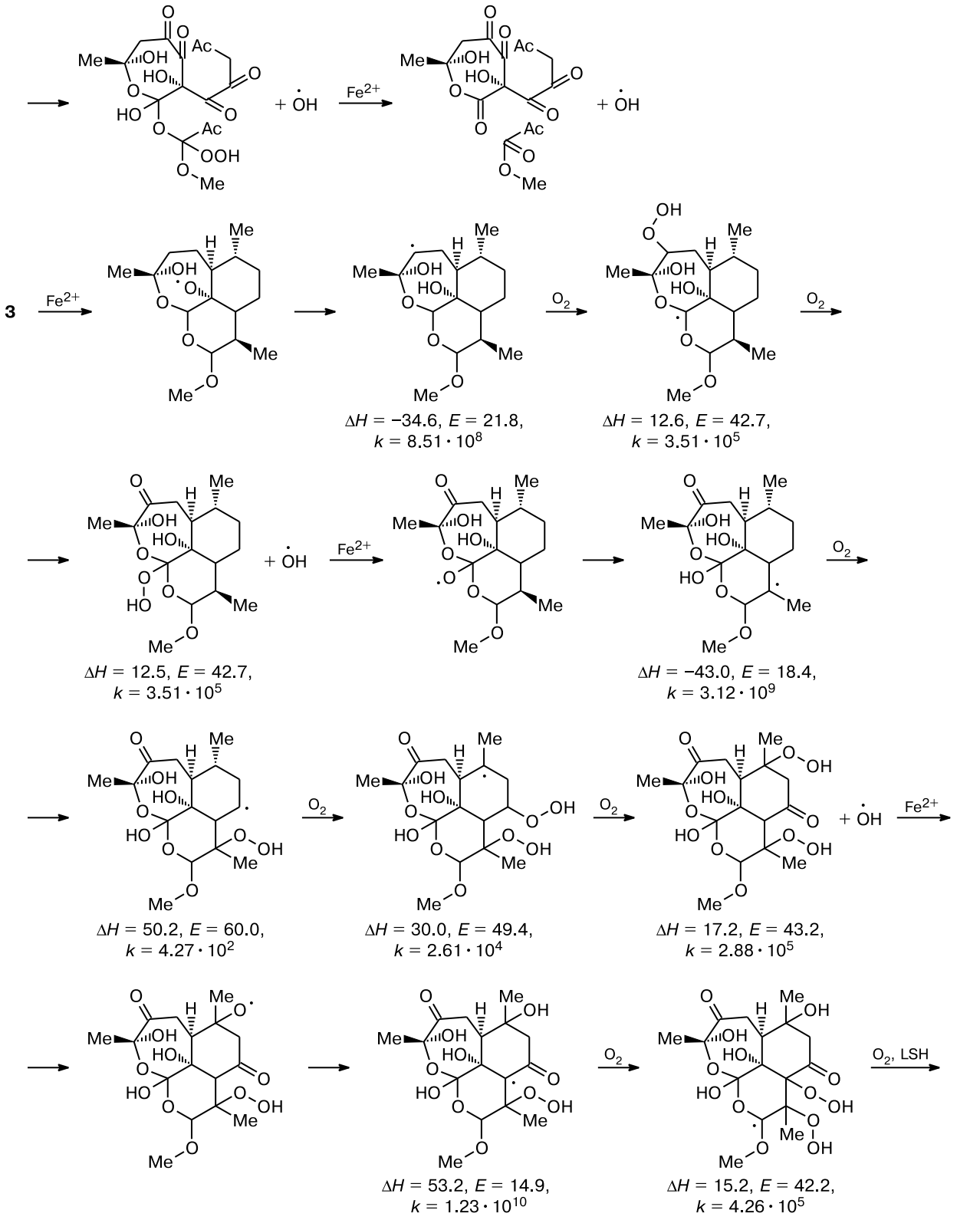
Scheme 2 (*continued*)



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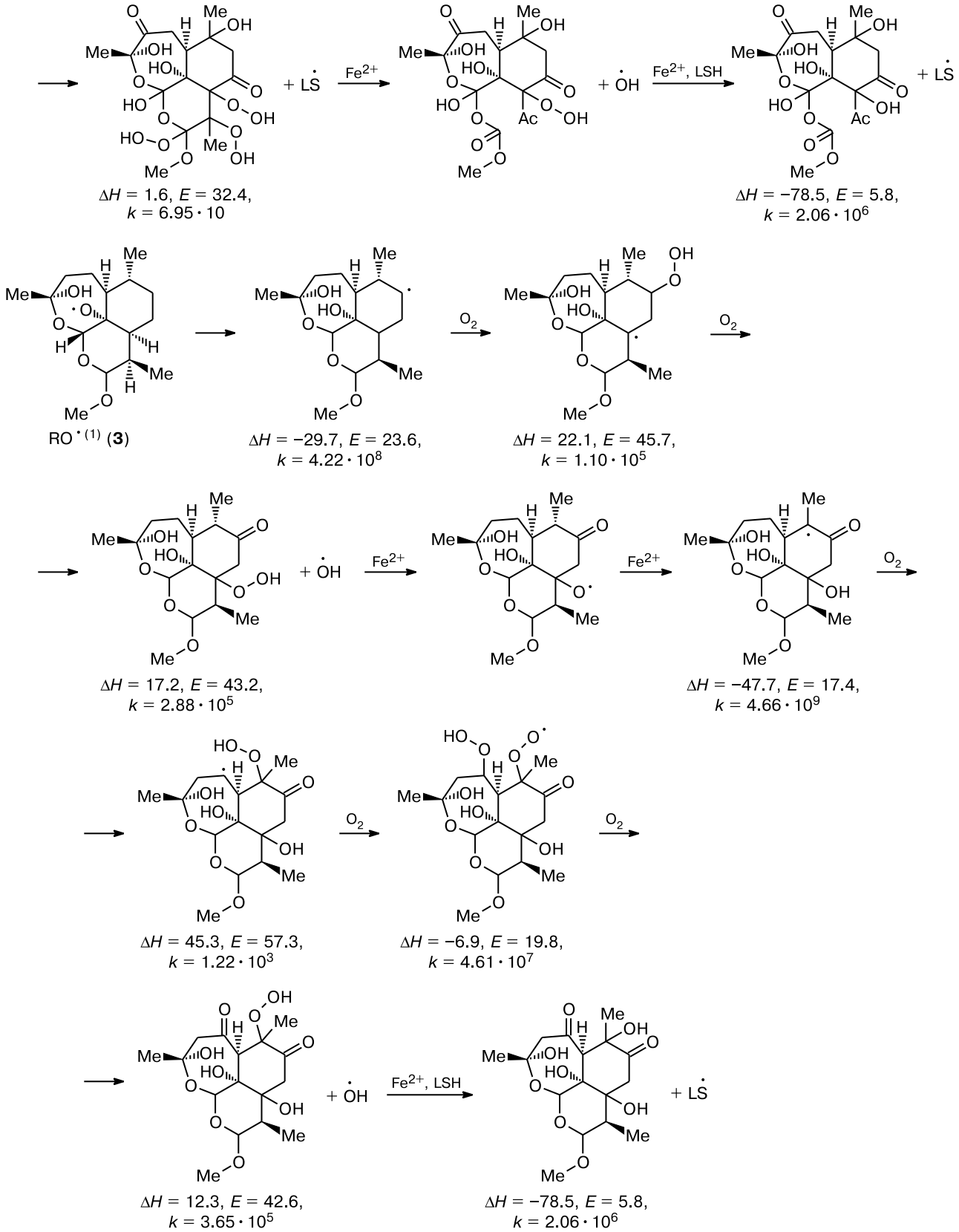
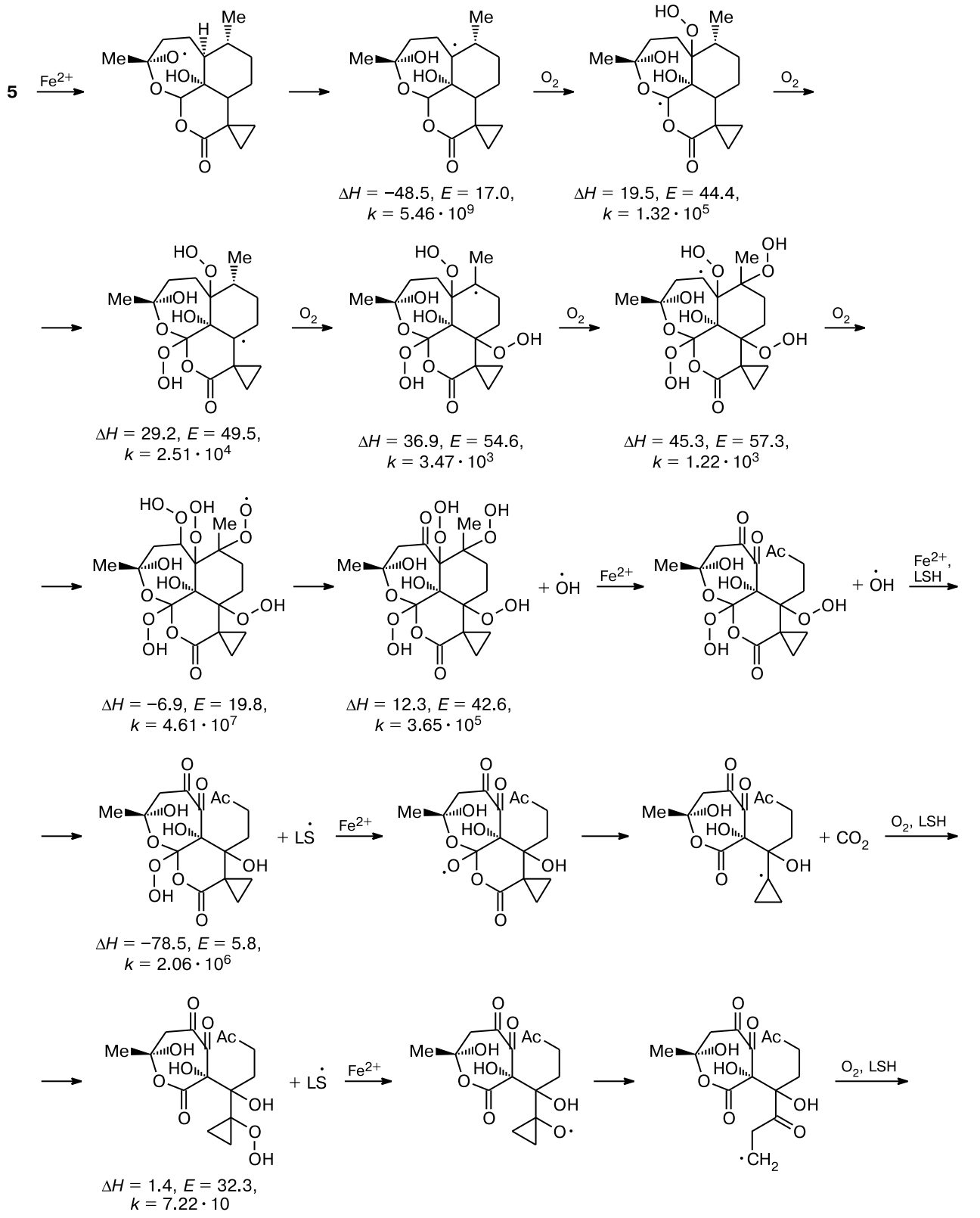


Scheme 3



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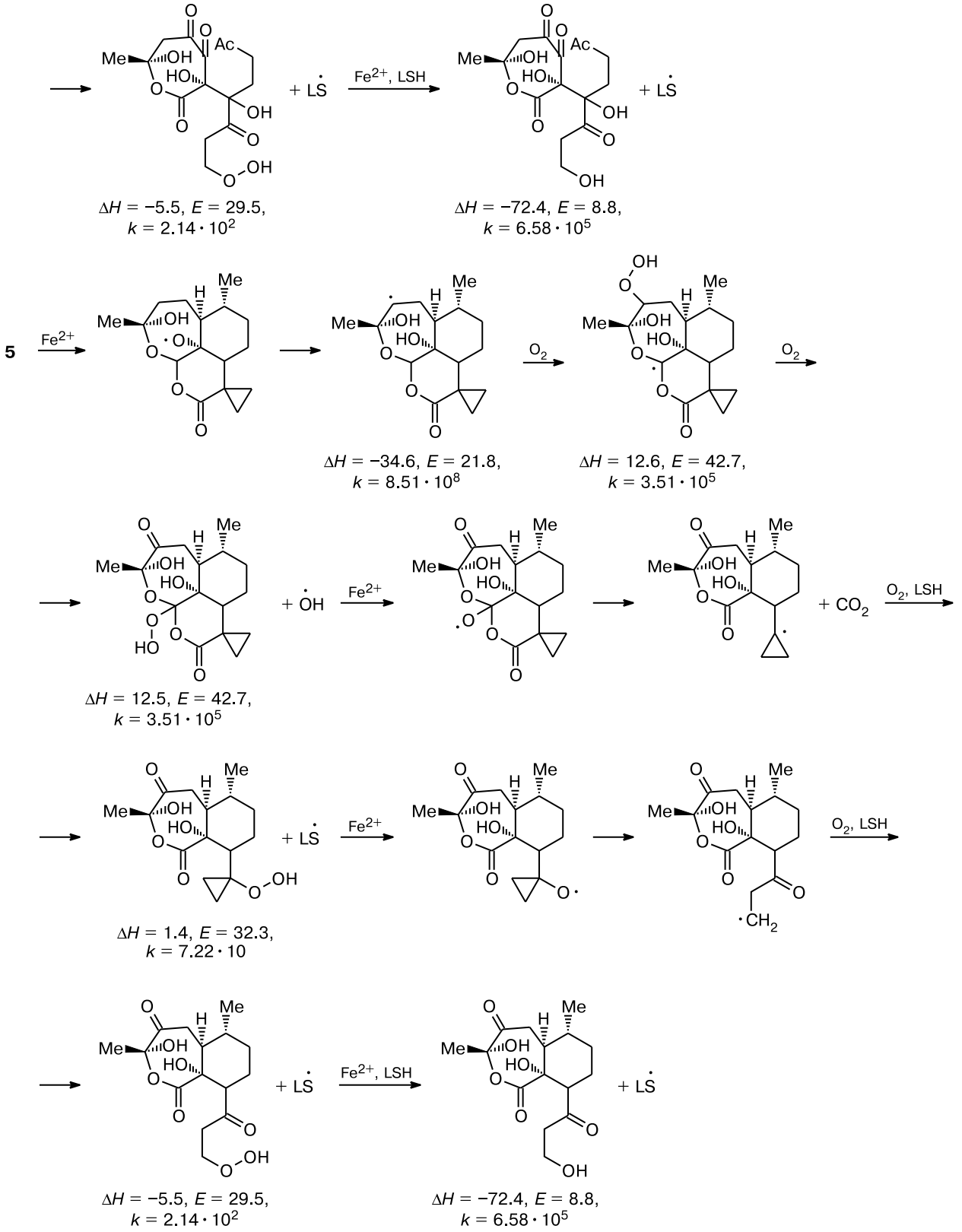
Scheme 3 (*continued*)



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Scheme 3 (*continued*)

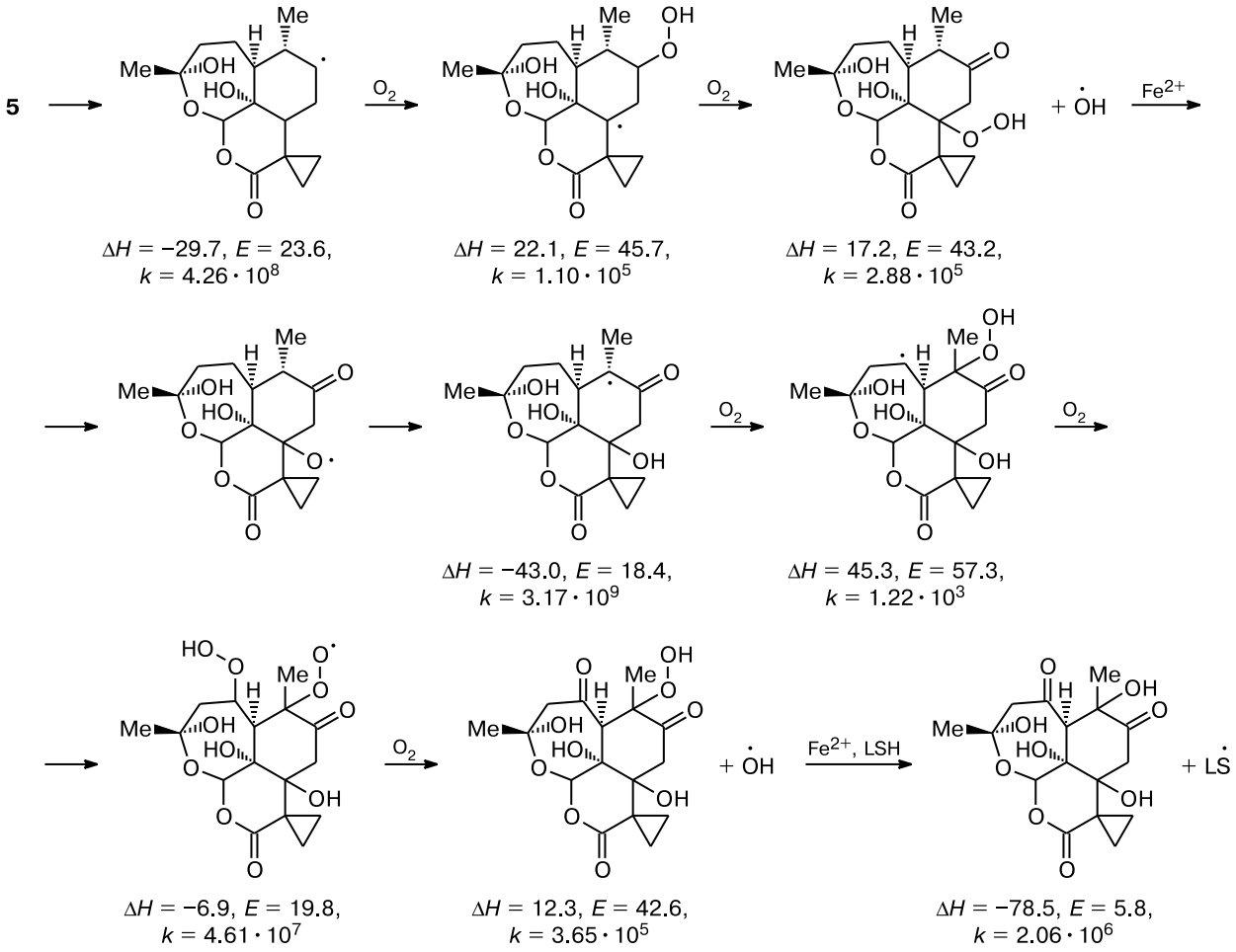


Table 2. Comparison of the antimalarial activity of compound **1** and its analogs **2**—**13** (see Refs 8—10) with the number of hydroxyl radicals n_{OH}, which are formed due to their intramolecular oxidation[16—21]

Compound	n_{OH}	$N_{\Sigma R}$	$IC_{50}(\mathbf{1})/IC_{50}(i)$	$\ln[IC_{50}(\mathbf{1})/IC_{50}(i)]$
1	3.17	4.00	1.00	0.00
2	4.00	4.50	7.40	2.00
3	3.83	4.66	2.28	0.82
4	3.83	4.66	1.78	0.58
5	1.67	4.33	0.08	−2.53
6	3.00	5.00	0.20	−1.61
7	3.30	4.30	1.08; 0.75*	0.08; −0.29
8	3.00	6.00	0.14	−1.97
9	0.50	1.00	0.00; 0.00*	—
10	2.83	4.50	0.09	−2.41
11	3.50	4.00	2.20; 1.80; 1.40 *	0.79; 0.59; 0.34
12	2.50	3.00	0.016	−4.13
13	2.50	3.00	0.016	−4.13

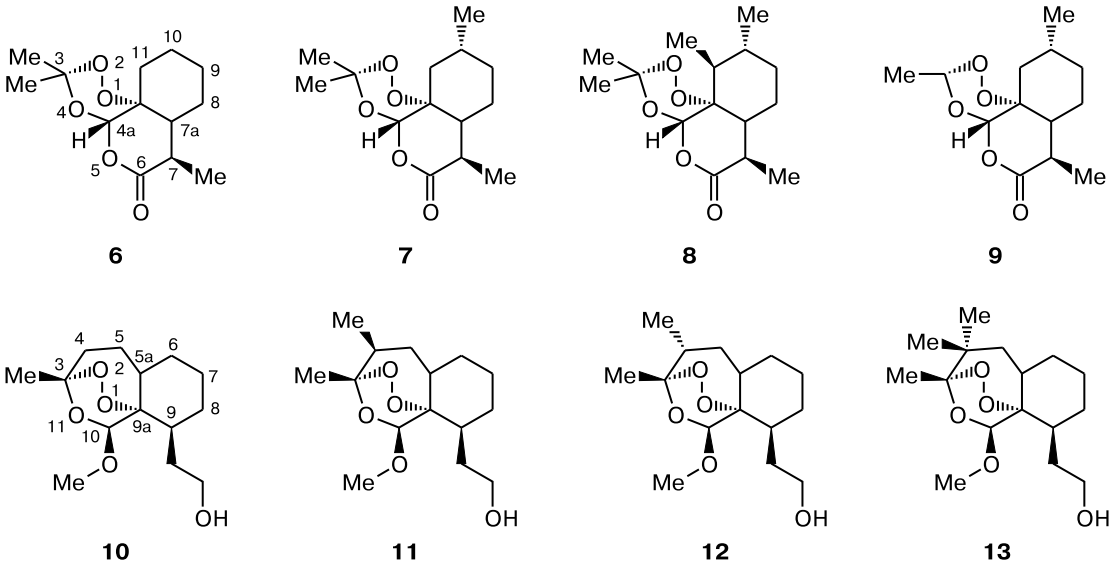
* Index IC_{50} was measured on various clones of plasmodium *P. falciparum*.

In Table 2 n_{OH} and $n_{\Sigma R}$ are compared with the antimalarial-effect index IC_{50}.

When discussing the mechanism of action of compound **1**, it is often assumed that compound **1** plays the exclusive role of the free-radical initiator.[1,3,8—10] If the total number of radicals is significant, *i.e.*, the total yield of all radicals per one molecule of the peroxide compound, one may expect a correspondence between $IC_{50}(\mathbf{1})/IC_{50}(i)$ and the total yield of radicals $n_{\Sigma R}$. This comparison is performed in Fig. 1.

It is clearly seen that any correlation is absent. On the one hand, there are compounds with $n_{\Sigma R}$ equal to 3.5 and 5 among highly efficient antimalarial drugs. On the other hand, the compound with $n_{\Sigma R} = 6$ turned out to be low efficient. Therefore, the high yield of radicals does not indicate that the drug is efficient.

Another situation was observed when we compared IC_{50} with the yield of hydroxyl radicals, which has already been mentioned earlier.[17—21] In this work, we compared the concentration index IC_{50} with the yield of hydroxyl radicals n_{OH} for each of compounds **1**—**13**. The results of



comparison of $\ln\{IC_{50}(\mathbf{1})/IC_{50}(i)\}$ and n_{OH} are presented in Fig. 2, indicating a linear dependence between these values with a correlation coefficient of 0.97 and the root-mean-square deviation SD = 0.5. This means that the curing effect of the peroxide compounds is caused by the generation of hydroxyl radicals that destroy malaria plasmodium.

Thus, the dependence of IC_{50} on n_{OH} is exponential

$$\ln[IC_{50}(\mathbf{1})/IC_{50}(i)] = -13.4\pm1.0 + (3.9\pm0.3)n_{OH} \quad (2)$$

or

$$IC_{50}(\mathbf{1})/IC_{50}(i) = 1.5\cdot10^{-6}\exp(3.9n_{OH}). \quad (3)$$

Drugs that are more active than compound **1** should provide the yield of hydroxyl radicals exceeding 3.3.

Why do precisely the hydroxyl radicals cause the death of the malaria parasite? They are very reactive due to the high exothermicity of radical abstraction reactions involving these radicals. This is seen from the comparison of the O—H bond strength in various compounds.[29–31]

Compound	*sec*-ROO—H	PhO—H	MeO—H	HO—H
D_{O-H} /kJ mol^{-1}	365.5	369.0	436.0	499.0

For this reason, hydroxyl reacts with many reactants with a diffusion rate constant and is poorly selective. The reaction of hydroxyl addition is also very fast. In particular, it reacts with organic bases composing DNA with diffusion rate constant. The values of $k(HO^{\cdot}$ + base) in H_2O are presented below.[33]

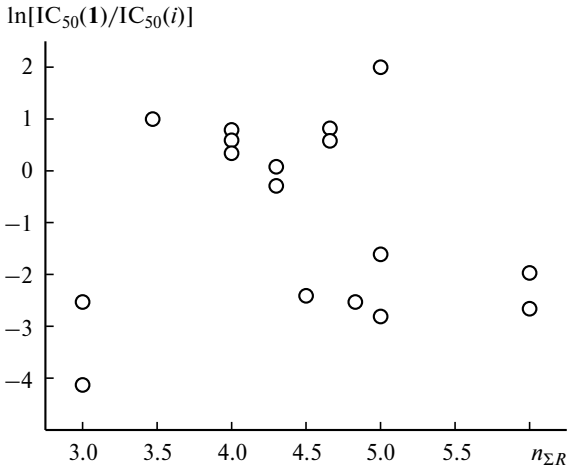


Fig. 1. Logarithm of the relative antimalarial activity of the drugs ($IC_{50}(\mathbf{1})/IC_{50}(i)$) *vs* total number of radicals ($n_{\Sigma R}$) generated by the drug due to its oxidation.

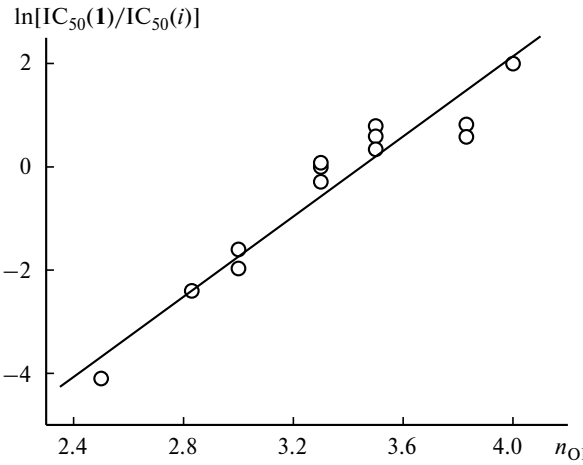


Fig. 2. Logarithm of the relative antimalarial activity of the drugs ($IC_{50}(\mathbf{1})/IC_{50}(i)$) *vs* number of hydroxyl radicals (n_{OH}) generated by the drug due to its intramolecular oxidation.

Base	Adenine	Guanine	Thymine	Cytosine
$k \cdot 10^{-9}$ (398 K) /L mol^{-1} s^{-1}	5.8	9.2	5.5	5.8
pH (H_2O)	5.7	10.0	6.0	7.0

It is most likely that it is the DNA of malaria plasmodium that is the biological target, whose reaction with OH radicals results in the death of the parasite. It was experimentally shown that in the presence of iron ions of compound **1** caused the destruction of DNA plasmodium.[1,34,35] A favorable circumstance is the fact that red blood corpuscles, where DNA is absent, form the biotope of malaria plasmodium.[1] It is not excluded that radicals HO$^{\cdot}$ also attack other biological targets (protein and iron-containing enzymes), but these damages are secondary.

An analysis of Schemes 1—3 allows us to distinguish two types of reactions *via* which hydroxyl radicals are generated from compound **1** and its analogs.

The oxidation of methylene groups affords groups >CH(OOH) in which the C—H bond is weakened by the influence of the adjacent hydroperoxide group. This is induced by the stabilization of the radical >$^{\cdot}$COOH due to the interaction of the unpaired electron with the p-electrons of the oxygen atoms of the peroxide group. Therefore, the isomerization of the peroxyl radicals in the β-position to such a group proceeds predominantly with the cleavage of the C—H bond of the peroxide group. The radicals >$^{\cdot}$COOH, appeared in this process, are thermally unstable and decompose rapidly with the O—O bond cleavage *via* the exothermic reaction

$$>CH(OO^{\cdot})CH_2CH(OOH)R \longrightarrow$$
$$\longrightarrow >CH(OOH)CH_2C^{\cdot}(OOH)R \longrightarrow$$
$$\longrightarrow >CH(OOH)CH_2C(O)R + HO^{\cdot}.$$

The enthalpies of decomposition of such three radicals are presented below.

Radical	$Me_2C^{\cdot}OOH$	*cyclo*-$C_6H_{10}^{\cdot}OOH$	*cyclo*-$C_7H_{12}^{\cdot}OOH$
$-\Delta H$ /kJ mol^{-1}	142.6	131.8	132.6

Totally eight hydroxyl radicals are formed *via* reactions of this type in the kinetic scheme of transformations of compound **2**.

The intramolecular oxidation of compounds **1**—**5** affords diatomic hydroperoxides with the OOH groups in the α-position (>C(OOH)C(OOH<). In the reaction with the iron chelates they generate alkoxy radicals >C(O$^{\cdot}$)C(OOH)<. The latter are thermally unstable and decompose rapidly in the exothermic reaction with the C—C bond cleavage and generation of radicals $^{\cdot}$OH.

$$>C(O^{\cdot})C(OOH) \longrightarrow >C{=}O + >C{=}O + O^{\cdot}H$$

For example, the decomposition of the 2-hydroperoxycyclohexyloxyl radical occurs with $\Delta H = -136.9$ kJ mol^{-1}, and the decomposition of the analogous 2-hydroperoxycycloheptyloxyl radical occurs with $\Delta H = -163.2$ kJ mol^{-1}. Two hydroxyl radicals are formed in this reaction due to the intramolecular oxidation of compound **2** (see Scheme 1).

Thus, an analysis of the intramolecular oxidation reactions of compounds **2**—**5** in combination with the published data[17—21] makes it possible to formulate the following mechanism of action of the peroxide antimalarial drugs, analogs of compound **1**. Under the action of the Fe^{II} chelates the compound containing the O—O group is transformed into the alkoxyl radical. This radical isomerizes to the alkyl radical, which further undergoes intramolecular relay-race oxidation. This oxidation results in polyatomic hydroperoxides, which, in turn, generates radicals in the reaction with Fe^{II}. The next cascade of radical reactions generates very reactive hydroxyl radicals, whose sources are peroxyl and alkoxyl radicals with hydroperoxide fragments. The higher the yield of hydroxyl radicals n_{OH}, the more efficient the drug. The dependence of the antimalarial activity of the *i*th drug $IC_{50}(\mathbf{1})/IC_{50}(i)$ in the yield radicals OH n_{OH} is nonlinear (exponential). The compounds with $n_{OH} \geq 3.3$ are efficient. The most important biological target for hydroxyl radicals is DNA of the malaria parasite. The efficient antimalarial effect of the peroxide drugs is favored by the fact that the content of the iron chelates in malaria plasmodium is 20 times higher than that in the human organism and red blood corpuscles, oxygen mediators containing no DNA, are the biotope of the parasite. The hydroxyl model of transformation of compound **1** and its analogs formulated in the present work makes it possible to explain the influence of the structure of the drug on its efficiency and provides a new approach to prediction of efficient antimalarial drugs.

References

1. Y. Li, H. Huang, Y.-L. Wu, in *Medicinal Chemistry of Bioactive Natural Products*, Eds X.-T. Liang, W.-S. Fang, J. Wiley and Sons, New York, 2006, 183.
2. E. T. Denisov, S. L. Solodova, T. G. Denisova, *Usp. Khim.*, 2010, **79**, 1065 [*Russ. Chem. Rev.* (*Engl. Transl.*), 2010, **79**, 981].
3. S. R. Meshnick, T. E. Taylor, S. Kamchonwongpaisan, *Microbiol. Rev.*, 1996, **60**, 301.
4. W. Asawamahasakda, I. Ittarat, Y.-M. Pu, H. Ziffer, S. R. Meshnick, *Antimicrob. Agents Chemother.*, 1994, **38**, 1854.
5. P. M. O´Neill, G. H. Posner, *J. Med. Chem.*, 2004, **47**, 2945.
6. P. A. Berman, P. A. Adams, *Free Radical Biol. Med.*, 1997, **22**, 1283.
7. B. Meunier, A. Robert, *Acc. Chem. Res.*, 2010, **43**, 1444.
8. D. J. Creek, W. N. Charman, F. C. K. Chiu, R. J. Prankerd, K. J. McCullough, Y. Dong, J. L. Vennerstrom, S. A. Charman, *J. Pharmaceut. Sci.*, 2007, **96**, 2945.
9. M. A. Avery, F. Gao, W. K. M. Chong, T. F. Hendrickson, W. D. Inman, P. Crews, *Tetrahedron*, 1994, **50**, 957.
10. G. H. Posner, D. Wang, J. N. Cumming, C. H. Oh, A. N. French, A. L. Bodley, T. A. Shapiro, *J. Med. Chem.*, 1995, **38**, 2273.

11. E. T. Denisov, T. G. Denisova, F. M. D. Ismail, *Int. J. Chem. Kinet.*, 2005, **37**, 554.
12. S. L. Solodova, E. T. Denisov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2006, 1502 [*Russ. Chem. Bull.*, *Int. Ed.*, 2006, **55**, 1557].
13. S. L. Solodova, E. T. Denisov, *Kinet. Katal.*, 2007, **48**, 220 [*Kinet. Catal.* (*Engl. Transl.*), 2007, **48**, 204].
14. S. L. Solodova, E. T. Denisov, T. G. Denisova, *Mendeleev Commun.*, 2008, **18**, 24.
15. S. L. Solodova, E. T. Denisov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2008, 267 [*Russ. Chem. Bull.*, *Int. Ed.*, 2008, **57**, 274].
16. S. L. Solodova, E. T. Denisov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2009, 760 [*Russ. Chem. Bull.*, *Int. Ed.*, 2009, **58**, 777].
17. E. T. Denisov, *Proc. EUCHEM Conf. on Organic Free Radicals (Bologna, Italy, June 28—July 2, 2010)*, Bologna, 2010, 53.
18. E. T. Denisov, T. G. Denisova, *Izv. Akad. Nauk*, *Ser. Khim.*, 2010, 1831 [*Russ. Chem. Bull.*, *Int. Ed.*, 2010, **59**, 1881].
19. E. T. Denisov, T. G. Denisova, *Butlerov. Soobshch.* [*Butlerov´s Reports*], 2010, **23**, No. 15, 11 (in Russian).
20. S. L. Solodova, E. T. Denisov, *Sb. tr. IPKhF RAN "Fizika i khimiya protsessov, orientirovannykh na sozdanie novykh naukoemkikh tekhnologii, materialov i oborudovaniya"* [*Collection of Works of the Institute of Chemical Physics of the Russian Academy of Sciences "Physics and Chemistry of Processes Oriented at the Development of Novel Science Intensive Technologies, Materials, and Equipment*], IPKhF, Chernogolovka, 2007, 264 (in Russian).
21. E. T. Denisov, *Org. Biomol. Chem.*, 2011, **9**, 4219.
22. D. J. Creek, W. N. Charman, F. C. K. Chiu, R. J. Frankerd, Y. Dong, J. L. Vennerstrom, S. A. Charman, *Antimicrob. Agents Chemother.*, 2008, **52**, 1291.
23. E. T. Denisov, *Usp. Khim.*, 1997, **66**, 953 [*Russ. Chem. Rev.* (*Engl. Transl.*), 1997, **66**, 859].
24. E. T. Denisov, in *General Aspects of the Chemistry of Radicals*, Ed. Z. B. Alfassi, Wiley, Chichester, 1999, 79.
25. E. T. Denisov, I. B. Afanas´ev, *Oxidation and Antioxidants in Organic Chemistry and Biology*, CRC Press, Taylor and Francis Group, Boca Raton, FL, 2005, 981 pp.
26. E. T. Denisov, T. G. Denisova, *Usp. Khim.*, 2004, **73**, 1181 [*Russ. Chem. Rev.* (*Engl. Transl.*), 2004, **73**, 1091].
27. T. G. Denisova, E. T. Denisov, *Kinet. Katal.*, 2006, **47**, 124 [*Kinet. Catal.* (*Engl. Transl.*), 2006, **47**, 121].
28. E. T. Denisov, C. Chatgilialoglu, A. F. Shestakov, T. G. Denisova, *Int. J. Chem. Kinetics*, 2009, **41**, 284.
29. E. T. Denisov, T. G. Denisova, T. S. Pokidova, *Handbook of Free Radical Initiators*, Wiley-Interscience, Hoboken, New Jersey, 2003, 879 pp.
30. T. G. Denisova, E. T. Denisov, *Neftekhimiya,* 2004, **44**, 278 [*Petroleum Chemistry* (*Engl. Transl.*), 2004, **44**].
31. E. T. Denisov, V. E. Tumanov, *Usp. Khim.*, 2005, **74**, 905 [*Russ. Chem. Rev.* (*Engl. Transl.*), 2005, **74**, 825].
32. Y.-R. Luo, *Handbook of Bond Dissociation Energies in Organic Molecules*, CRC Press, Boca Raton, 2003, 380 pp.
33. G. V. Buxton, C. L. Greenstock, W. Ph. Helman, A. B. Ross, *J. Phys. Chem. Ref. Data*, 1988, **17**, 513.
34. Y.-L. Wu, H.-B. Chen, K. Jiang, Y. Li, F. Shan, D.-Y. Wang, Y.-F. Wang, W.-M. Wu, Y. Wu, Z.-J. Yao, Z.-Y. Yue, C.-M. Zhou, *Pure Appl. Chem.*, 1999, **71**, 1139.
35. W.-M. Wu, Z.-J. Yao, Y.-L. Wu, K. Jiang, Y.-F. Wang, H.-B. Chen, F. Shan, Y. Li, *J. Chem. Soc., Chem. Commun.*, 1996, **18**, 2213.

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