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Radical chemistry of artemisinin

E T Denisov, S L Solodova, T G Denisova

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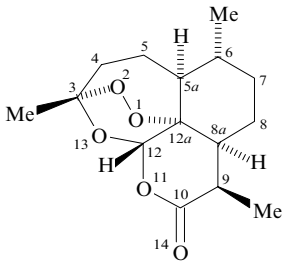
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Abstract. The review summarizes physicochemical characteristics of the natural sesquiterpene peroxide artemisinin. The kinetic schemes of transformations of artemisinin radicals under anaerobic conditions are presented and analyzed. The sequence of radical reactions of artemisinin in the presence of oxygen is considered in detail. Special emphasis is given to the intramolecular chain oxidation resulting in the transformation of artemisinin into polyatomic hydroperoxide. The kinetic characteristics of elementary reaction steps involving alkyl, alkoxyl, and peroxyl radicals generated from artemisinin are discussed. The results of testing of artemisinin and its derivatives for the antimalarial activity and the scheme of the biochemical synthesis of artemisinin in nature are considered. The bibliography includes 125 references.

I. Introduction

Malaria is a severe common disease. Nowadays, from 300 to 500 million people suffer from this disease, and up to 3 million people die from this disease every year, 40% of those being children.[1,2] Malaria is caused by the microorganism Plasmodium malariae. There are four types of human malaria parasites: *Plazmodium vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*. The infection is transmitted through the bites of infected mosquitoes (*Anopheles* sp.), the life cycle of malaria parasites occurring in part in mosquitoes and in part in the human organism.[3]

In the mid-20th century, the use of quinine and its derivatives resulted in a substantial reduction in the number of malaria-infected patients. However, in the 1960s malaria returned because the Plasmodium malariae (*P. falciparum*) resistant to quinine, chloroquine, mefloquine, and other quinine-based drugs developed in Thailand and South America and then spread to other areas.[3,4] Hence, there is an urgent need for new effective antimalarial drugs. Artemisinin (**1**) is one of such drugs.†



1

This unique compound was discovered in China,[5,6] where the program called 'Project 523' was launched in

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† Hereinafter, the conventional atomic numbering system of artemisinin is used.

1967. A part of this program endeavored to explore and use traditional Chinese medicine. The large-scale screening of the antimalarial activity of wild plants was carried out. The screening of more than 1000 plants revealed Chinese wormwood (sweet wormwood) *Artemisia annua* (the Chinese name is qinghao) as a possible sources of antimalarial components. This plant was utilized as the antimalarial agent in traditional Chinese medicine for more than two thousand years. The earliest report of this plant dates back to 168 B.C, and its use for the treatment of malaria was mentioned in 'Handbook of Prescriptions for Emergency Treatment' written by Ge Hong (281 – 340 AD). This plant came to the attention of Chinese phytochemists involved in the 'Project 523'. Almost simultaneously, in 1972, three research teams (from Beijing and the Yunnan and Shandong (Shantung) provinces) isolated a white crystalline compound from leaves of sweet wormwood. This compound exhibited high antimalarial activity in animal tests and was called artemisinin (the Chinese name is qinghaosu). The artemisinin content in dried leaves of wormwood varies from 0.01% to 1.6% based on the leaf dry weight depending on the collection time and area. In 1991, China produced $\sim$5 tonnes of artemisinin, and Vietnam produced $\sim$3 tonnes of this compound.[7]

The discovery of artemisinin has stimulated research on the mechanism of action, medical use, and the synthesis of its derivatives and analogues. More than 1000 publications on the chemistry and biochemistry of compound **1** appeared up to 2005,[5] and numerous reviews were published (see, for example, Refs 6 – 19). It appeared that compound **1** and its derivatives have diverse biological activities. These compounds are effective against certain types of malignant tumours [5, 20 – 22] and fungi.[23]

The therapeutic activity of artemisinin is closely related to the presence of the peroxide bridge in the molecule. In spite of extensive research of compound **1** as a medication, the mechanism of its action is poorly understood. All known schemes are qualitative in character and often include hypothetical steps (see the above-mentioned reviews and references therein).

This review considers aspects that are not adequately covered in the literature, such as the physical chemistry of compound **1** and the kinetics of transformations of radicals generated from **1**. It should be noted that we have recently formulated the first quantitative kinetic scheme of the reactions of these radicals.[24 – 29] This scheme provides a new approach to the study and prediction of the properties of artemisinin derivatives, as well as to the synthesis of drugs based on these compounds.

II. Structure of artemisinin

The structure of compound **1** was determined in 1979.[5] Studies by elemental analysis, X-ray diffraction, and NMR and IR spectroscopy showed that artemisinin belongs to sesquiterpene endoperoxides. The presence of the peroxide bridge was confirmed also by chemical experiments (release of I_2 from NaI in an acetic acid solution and the reaction with PPh_3). Interatomic distances, bond angles, and dihedral angles in the artemisinin molecule are given in Table 1.

As can be seen from these data, the results of quantum chemical calculations are in good agreement with the X-ray

Table 1. Structural characteristics of artemisinin (**1**).

Interatomic distances and angles	Experimental data		Quantum chemical calculations	
	see [a]	see [b]	B3LYP/16-31G(dp) [30]	B3LYP/16-31G(dp) [32]
O(1) – O(2)	1.472 ± 0.003	1.456	1.460	1.460
O(1) – C(12*a*)	1.456 ± 0.006	1.458	1.456	1.455
O(2) – C(3)	1.417 ± 0.003	1.415	1.414	1.414
O(13) – C(3)	1.448 ± 0.004	–	1.442	–
O(13) – C(12)	1.384 ± 0.004	–	1.396	–
C(3) – C(4)	–	–	–	1.546
C(12) – C(12*a*)	1.526 ± 0.003	–	1.539	–
∠O(1) – O(2) – C(3)	108.3 ± 0.3	–	108.3	108.3
∠O(2) – C(3) – O(13)	106.8 ± 0.3	–	108.5	–
∠C(3) – O(13) – C(12)	113.8 ± 0.3	–	114.1	–
∠O(13) – C(12) – C(12*a*)	114.2 ± 0.2	–	113.3	–
∠C(12) – C(12*a*) – O(1)	110.5 ± 0.2	–	111.4	–
∠C(12*a*) – O(1) – O(2)	111.5 ± 0.3	–	111.6	111.6
∠O(2) – C(3) – C(4)	–	–	111.9	–
∠O(1) – C(12*a*) – C(5*a*)	–	–	105.8	–
∠C(3) – C(4) – C(5)	–	–	114.1	–
∠O(1) – O(2) – C(3) – O(13)	−75.5 ± 0.2	–	−74.0	–
∠O(2) – C(3) – O(13) – C(12)	36.1 ± 0.3	–	32.9	–
∠C(3) – O(13) – C(12) – C(12*a*)	26.0 ± 0.3	–	27.4	–
∠O(13) – C(12) – C(12*a*) – O(1)	−51.0 ± 0.3	–	–	–
∠C(12) – C(12*a*) – O(1) – O(2)	12.5 ± 0.3	–	11.6	–
∠C(12*a*) – O(1) – O(2) – C(3)	47.7 ± 0.3	–	48.0	47.9
∠O(1) – O(2) – C(3) – C(4)	–	–	–	46.8
∠O(2) – O(1) – C(12*a*) – C(5*a*)	–	–	–	250.8
∠O(2) – C(3) – C(4) – C(5)	–	–	–	265.4
∠O(1) – C(12*a*) – C(5*a*) – C(5)	–	–	–	68.5

Note. The interatomic distances are given in Ångstroms; the bond angles and the dihedral angles are in degrees. [a] According to the X-ray diffraction data;[30] [b] spectroscopic data.[31]

Table 2. Atomic vibration frequencies of compound **1** in the IR and Raman spectra.[31]

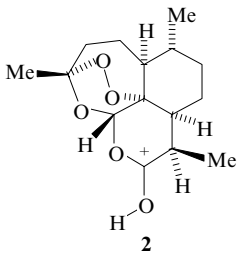
Bond	ν /cm^{-1}	Bond	ν /cm^{-1}
C(12)–C(12*a*), C(8*a*)–C(12*a*)	700	C(6)–CH$_3$, C(4)–C(5), C(5)–C(5*a*)	1077
C(3)–O(13), C(3)–C(4)	724	C(12)–O(11), C(6)–CH$_3$	1100
C(10)–O(11), C(10)–C(9)	793	C(5*a*)–C(12*a*), C(12)–O(13)	1116
O(1)–O(2)	882	C(6)–C(7), C(8*a*)–C(12*a*), C(9)–CH$_3$	1132 [a]
C(12)–O(11), C(12)–O(13), C(7)–C(8)	993	C(12)–O(13)	1137, 1150 [a]
C(4)–C(5), C(5)–C(5*a*)	1052, 1053		

[a] Quantum chemical data.

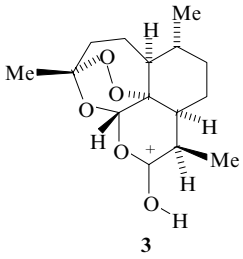
diffraction and Raman spectroscopy data. A comparison with dialkyl peroxides, where r_{O-O} = 1.48 Å,[33] shows that the peroxide bond in compound **1** has almost the same length (1.47 Å), but the C–O bond (r_{C-O} = 1.41–1.42 Å) is slightly shorter (r_{C-O} = 1.44–1.46 Å).[33]

The stretching vibrational frequencies of artemisinin are given in Table 2. The frequencies were identified by comparing the IR and Raman spectra of compound **1** with the corresponding spectra of model compounds (cyclohexane, valerolactone, and oxepane containing the peroxide bridge).[31] The examination of the IR spectrum of protonated artemisinin in the gas phase showed that the protonation occurs at the carbonyl oxygen atom O(14),[34] the interatomic O(1)–O(2) distance in the peroxide bridge being slightly longer (1.481 Å). The protonation of compound **1** affords conformers **2** and **3**, whose energies of the formation (ΔH) differ by 15.7 kJ mol^{-1} (calculations at the B3LYP/6-31G* level of theory); ΔH(**3**) > ΔH(**2**).

The addition of an electron *in vacuo* to one of the two oxygen atoms of the peroxide bridge leads to an increase in the O(1)–O(2) distance by 50%.



2



3

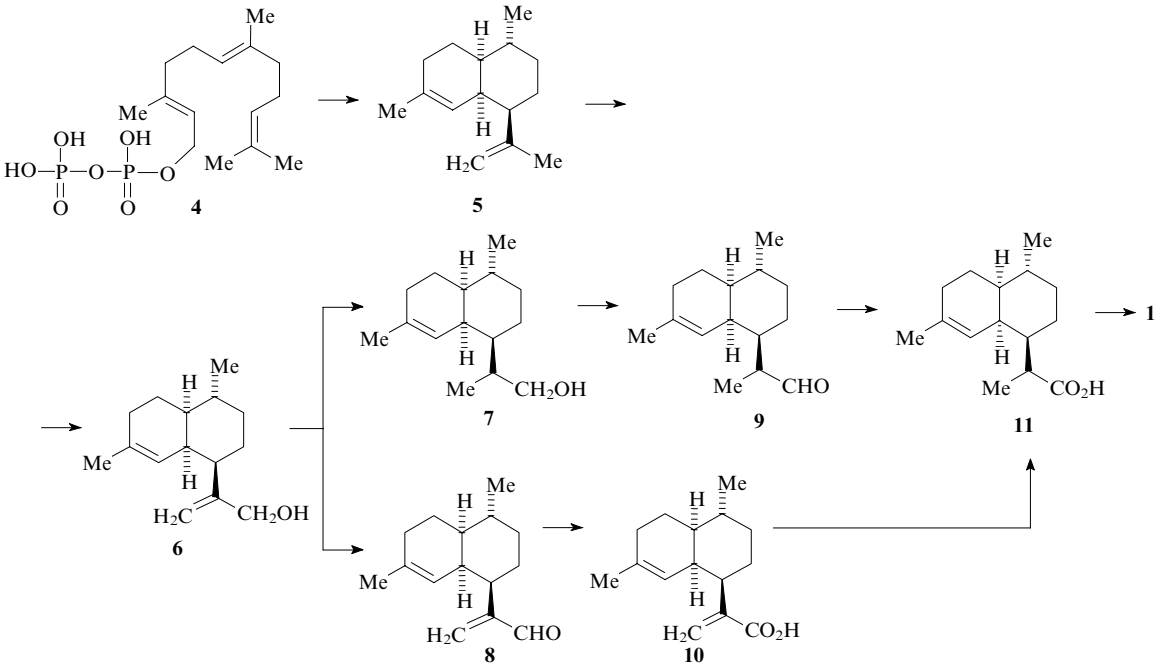
III. Synthesis of artemisinin

The synthesis of compound **1** in nature is an interesting question. How is such a complex molecule constructed in plants? Main steps in the biosynthesis have been elucidated in the recent past (Scheme 1).[5,19,35] Apparently, diphosphate of the unsaturated compound (farnesyl diphosphate, **4**) is the starting compound, whose cyclization affords terpene **5** followed by the successive oxidation to alcohol (**6** or **7**), aldehyde (**8** or **9**), and acid (**10** or **11**). The oxidation of dihydroartemisininic acid (**11**) gives artemisinin. The transformation of acid **11** into compound **1** can follow alternative paths: the enzymatic photooxidation by atmospheric oxygen and the oxidation of the acid to hydroperoxide followed by the transformation into endoperoxide.[5]

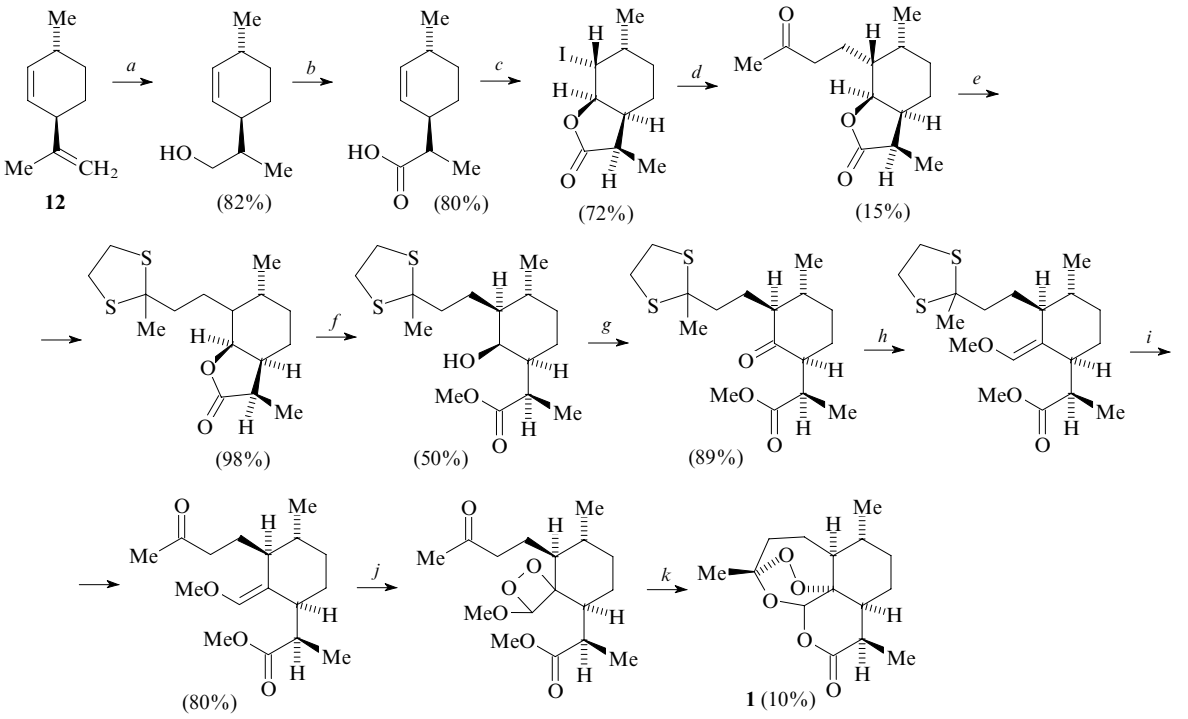
The chemical synthesis of artemisinin from (+)-isolimonene (**12**) was a breakthrough.[36] The sequence of transformations, the reaction conditions, and the yields of the reaction products are presented in Scheme 2.

The synthesis of compound **1** from acid **10** was documented.[37–40] The transformation of hydroperoxide **13** into

Scheme 1



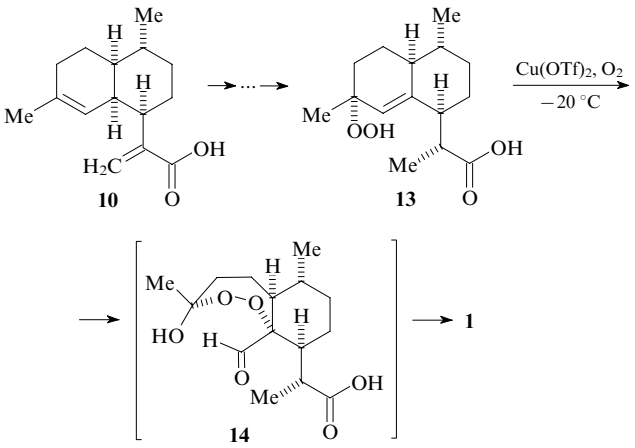
Scheme 2



(*a*) (cyclo-C_6H_{11})$_2$BH, THF, 0 °C, 7 days; (*b*) CrO_3, H_2SO_4, Me_2CO, 0 °C; (*c*) I_2 + KI, $NaHCO_3$ (aqueous), in the dark, 48 h; (*d*) $AcCH{=}CH_2$, Bu^n_3SiH, azobis(isobutyronitrile) (AIBN), PhMe, Δ; (*e*) $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C; (*f*) 1) 10% NaOH, MeOH, Δ; 2) HCl (gas), −24 °C; 3) CH_2N_2, Et_2O; (*g*) diperoxycumyl carbonate, CH_2Cl_2, 0 °C; (*h*) $MeOCH_2PPh_3Cl$, potassium hexamethyldisilazide, THF, 50 °C, 24 h; (*i*) $HgCl_2$ + $CaCO_3$, MeCN–H_2O (9 : 1); (*j*) O_2, *hv*, Pink Bengal, −78 °C, 4 h; (*k*) HCl (gas), 70% $HClO_4$, Et_2O, 28 h.

hemiacetal **14** is the key step that occurs in the presence of oxygen and is catalyzed by copper salts (Scheme 3).

Scheme 3



Nowadays, artemisinin is produced commercially by the extraction from dried leaves of wormwood.

IV. Derivatives and analogues of artemisinin

The discovery of artemisinin led to an increase in the number of studies on the synthesis of its analogues.[5, 7–9, 22, 23, 41–64] Many of these compounds exhibited high activity against the Plasmodium malariae *P. falciparum* resistant to quinine and its derivatives (see compounds **15**–**24** and Table 3).

As can be seen from the above data, certain compounds showed activity in tests 10–20 times higher than that of compound **1**.

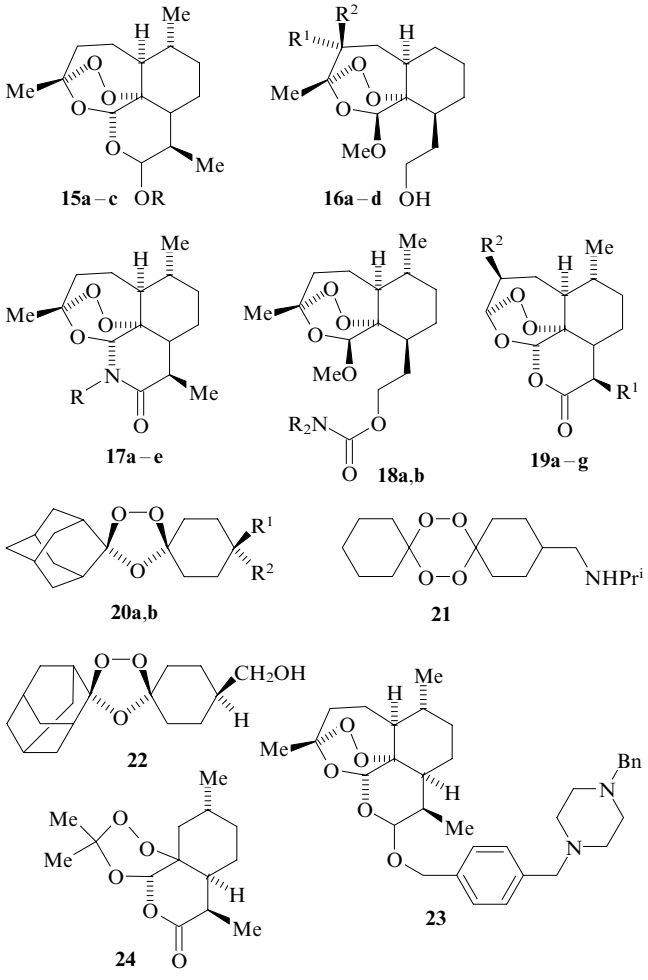


Table 3. Antimalarial activity of artemisinin derivatives.

Compound	Substituents	Parasite *P. falciparum* clone	Relative activity [a]	Ref.
15a	H	K-1	7.4	65
15b	Me	K-1	2.3	65
15c	$C(O)(CH_2)_2CO_2H$	K-1	1.8	65
16a	$R^1 = H$, $R^2 = Me$	W-2	1.8	43
		D-6	2.3	43
16b	$R^1 = R^2 = H$	see [b]	0.09	44
16c	$R^1 = Me$, $R^2 = H$	see [b]	1.4	44
16d	$R^1 = Bn$, $R^2 = H$	see [b]	1.0	44
17a	H	see [b]	1.0	46
17b	Bu^i	see [b]	9.0	46
17c	Me	see [b]	2.6	46
17d	CH_2Py-2 [c]	see [b]	22.0	46
17e	CH_2CHO	see [b]	26.0	46
18a	Et	D-6	2.3	66
18b	Ph	D-6	4.3	66
19a	$R^1 = H$, $R^2 = Me$	W-2	21.0	47
19b	$R^1 = H$, $R^2 = CO_2Et$	W-2	2.3	47
19c	$R^1 = H$, $R^2 = CMe_2Ph$	W-2	2.2	47
19d	$R^1 = Bu^n$, $R^2 = Me$	W-2	1.8	47
19e	$R^1 = Bu^n$, $R^2 = CO_2Et$	W 2	13.8	47
19f	$R^1 = (CH_2)_2NO_2$,	D-6	0.75	67
	$R^2 = H$	W-2	0.77	67
19g	$R^1 = CH_2CH(CN)Fc$, [d] $R^2 = H$	see [b]	5.0	68
20a	$R^1 - R^2 = O$	K-1	3.3	54
		NF-54	3.8	54
20b	$R^1 = CH_2NH_3^+$, $R^2 = H$	see [b]	5.7	65
21	–	D-6	1.0	22
		W-2	1.1	22
22	–	see [b]	2.0	65
23	–	K-1	3.9	69
24	–	D-6	1.1	70
		W-2	0.75	70

[a] The relative activity is the ratio $IC_{50}(\mathbf{1})/IC_{50}$(sample), where IC_{50} is the concentration of the compound required to kill 50% of parasites; [b] the clone was not mentioned in the original study; [c] Py is pyridyl; [d] Fc is ferrocenyl.

The assumption on the key role of the peroxide group in the therapeutic activity of artemisinin has inspired interest in the synthesis of cyclic peroxides. Examples of these peroxides are given in Table 3. The action of synthetic peroxides as antimalarial agents has been considered in more detail in the reviews.[14, 19, 71] It should be noted that the QSAR programme has found use in recent years for the prediction of promising structures of this class of compounds.[58, 72–76]

V. Physicochemical characteristics of artemisinin

Enthalpy of formation. In 2007, the heats of combustion of artemisinin and its derivatives **15b**,**c** were measured by calorimetry.[77] Table 4 gives the densities (ρ), the heats of combustion (Q), and the calculated enthalpies of formation (ΔH_f^{298}) for compounds **1** and **15b**,**c** in the crystalline state.

Thermal stability. The thermal stability of artemisinin and its derivatives **15b**,**c** was studied by thermogravimetry.[77] Table 4 presents the results of thermogravimetric analysis: the temperature of the onset of decomposition (T_{onset}) and the temperature of the destruction at a maximum rate (T_{max}).[77] The substantial weight loss for all three compounds is observed after their melting at $T > 420$ K. Formic acid and succinic anhydride were detected among decomposition products of compound **1** by IR spectroscopy.

Redox potential and thermal decomposition. The electrochemical reduction of artemisinin in *N*,*N*-dimethylformamide was studied by cyclic voltammetry.[78] Under these conditions, compound **1** undergoes irreversible dissociative reduction, with the anodic peak potential (E_{max}) dependent on the scan rate. Thus, E_{max} is -1.68 V at a rate of 1 V s^{-1}. The standard reduction potential (E°_{diss}) of compound **1** in *N*,*N*-dimethylformamide is -0.89 V. This potential corresponds to the O–O bond dissociation energy (D_{O-O}) equal to 98.3 ± 2.1 kJ mol^{-1}. This value is substantially lower than D_{O-O} for dialkyl peroxides (162 ± 3 kJ mol^{-1}).[33] However, the activation energy of thermal decomposition of artemisinin in a neutral solvent (n-octane) is 168 kJ mol^{-1} (Ref. 79), which is very similar to the dissociation energy of the O–O bond in dialkyl peroxides.[33]

The thermal decomposition of the model cyclic peroxide, *viz*., 3,3-dimethylhexahydrobenzo-1,2,4-trioxacyclohexane (**25**), was investigated.[79] The kinetic parameters of its decomposition in different solvents, such as the rate constant (k), the activation energy (E), and the Arrhenius preexponential factor (A), are given in Table 5. It can be seen that the rate constant of decomposition of peroxide **25** varies in a wide range from 2.6×10^{-5} to 4.6×10^{-2} s^{-1}

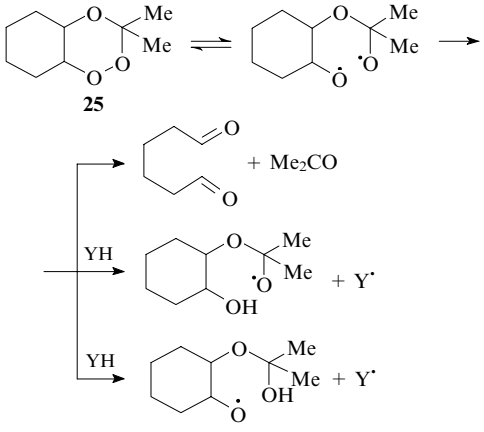


Table 4. Thermodynamic characteristics of artemisinin and its derivatives in the crystalline state.[77]

Compound	Molecular formula	ρ /g cm^{-3}	Q /kJ mol^{-1}	$-\Delta H_f^{298}$ /kJ mol^{-1}	T_{onset} /K	T_{max} /K
1	$C_{15}H_{22}O_5$	1.300	7546.53 ± 3.24	1492.81 ± 7.62	421.43	480.53
15b	$C_{16}H_{26}O_5$	1.215	7282.28 ± 3.09	2419.75 ± 7.52	357.13	405.49
15c	$C_{19}H_{28}O_8$	1.316	8150.75 ± 4.24	3320.12 ± 9.90	412.81	444.56

Table 5. Kinetic parameters of the decomposition of peroxide **25** in different solvents.[79]

Solvent	k(433 K) /s^{-1}	E /kJ mol^{-1}	A /s^{-1}
n-Octane	2.57×10^{-5}	167.7	4.36×10^{15}
Benzene	2.93×10^{-5}	160.7	7.13×10^{14}
Toluene	1.43×10^{-3}	149.6	1.59×10^{15}
Dioxane	4.57×10^{-2}	140.6	4.18×10^{15}
Propan-2-ol	6.82×10^{-5}	132.1	5.88×10^{11}
Methyl cellosolve	1.19×10^{-4}	106.7	8.84×10^{8}

depending on the nature of the solvent. For the comparison, it should be noted that the constant k of the decomposition of dialkyl peroxides (Bu^tOOBu^t, $PhMe_2COOCMe_2Ph$, *etc.*) depends only slightly on the nature of the solvent. For example, the rate constant of decomposition of Bu^tOOBu^t in the gas phase at 433 K is 5.7×10^{-4} s^{-1} (Ref. 33). The decomposition of cyclic peroxide **25** occurs apparently by the cascade mechanism involving the solvent (YH).

In solvents containing strong C–H bonds, such as benzene (D_{C-H} = 474 kJ mol^{-1}) and n-octane (D_{C-H} = 412 kJ mol^{-1}), the intramolecular destruction is apparently the main reaction, whereas in toluene containing a weak C–H bond (D_{C-H} = 375 kJ mol^{-1}),[80] the bimolecular reaction of the biradical with YH plays an important role as well. In polar solvents, the decomposition is influenced by the solvation of the starting peroxide and the resulting biradical. The thermal decomposition of compound **1** occurs most likely in a similar way.

Solubility. Artemisinin is poorly soluble in water, but is sufficiently soluble in organic solvents. Table 6 gives the solubility (x_1) of artemisinin at 283 K in different solvents. The solubility was measured as the mole fraction of compound **1** calculated by the equation[81]

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_S/M_S}, \qquad (1)$$

where m_1 and m_S are the weights of dissolved compound **1** and the solvent, respectively; M_1 and M_S are the corresponding molecular weights. The solubility was measured in the temperature range 283–323 K. The temperature dependence is described by the empirical equation[81]

$$\ln(10^4\times x_1) = A + \frac{B}{T} + C\times\ln T. \qquad (2)$$

The coefficients A, B, and C are also given in Table 6.

Of the solvents examined, compound **1** has the highest solubility in chloroform (x_1 = 0.0486) and toluene (x_1 = 0.0374), whereas the lowest solubility is observed in acetonitrile ($x_1 \approx 2\times10^{-4}$). The solubility of compound **1** increases with increasing temperature. For example, x_1 = 0.286 in chloroform at 323 K, *i.e.*, it is 5.9 times higher than that at 283 K. The solubility of artemisinin in water at pH 7.2 and room temperature is only 63 mg litre^{-1} ($x_1 = 4.02\times10^{-6}$).[18] The solubility of compound **1** in liquid carbon dioxide was studied at a pressure from 10 to 27 MPa in the temperature range 310–338 K.[83] This dependence is described by the following empirical equation:

$$\ln x_1 = 2.162\times\ln(\rho T) + 0.00224\,\rho - \frac{2795}{T} - 26.31, \qquad (3)$$

where ρ is the density (kg m^{-3}).

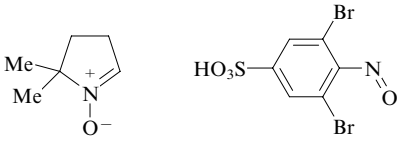
VI. Generation of radicals by reactions of artemisinin with iron(II) compounds

The peroxide group plays a key role in the therapeutic action of artemisinin, because its reduction leads to the disappearance of the this action.[5,8,84] It is known that peroxides readily decompose by the homolytic mechanism. Thus, the redox reactions of peroxide compounds with iron(II) ions and complexes result in the generation of free radicals.[33,85,86]

Use of radical acceptors. The formation of radicals in the reactions of compound **1** with Fe^{II} was established by the spin trapping method.[5,8,15,87–89] In the study,[87] Fe^{II} was used as the complex with ethylenediaminetetraacetate (EDTA), and the reaction was performed in a MeCN–H_2O mixture (1 : 1) at room temperature in the presence of free radical traps, such as 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO, **26**) and 3,5-dibromo-4-nitrosobenzenesulfonic acid (DBNBS, **27**).

Table 6. Solubility of artemisinin in different solvents and the constants from Eqn (2).[81,82]

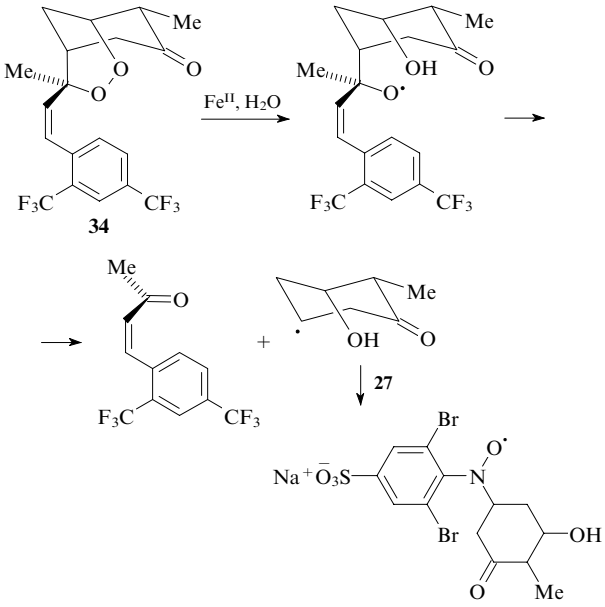
Solvent	Fraction of alcohol in a mixture	$x_1\times10^4$ (283 K)	A	B	C
MeOH	–	5.587 ± 0.564	13.3084	−5178.1	1.1866
AcOEt	–	52.529 ± 2.719	18.5010	−5375.7	0.7997
Me_2CO	–	38.806 ± 1.471	14.4142	−4222.2	0.7412
MeCN	–	1.978 ± 0.162	−264.858	6929.4	42.6982
cyclo-C_6H_{12}	–	4.401 ± 0.379	0.8660	−3832.9	2.5120
PhMe	–	374.506 ± 3.8960	4.5587	−2215.1	1.6281
$CHCl_3$	–	486.848 ± 8.0264	18.7247	−3958.6	0.2574
EtOH–H_2O	0.138	0.576 ± 0.292	−73.36	−215	11.4
	0.273	1.409 ± 0.274	55.15	−6299	−7.397
	0.467	5.653 ± 1.98	−3.028	−3862	1.629
	0.771	8.698 ± 3.23	−135.12	2373	21.22
	1.000	13.530 ± 4.01	−123.96	2041	19.51



26 **27**

Both O- (**28**, **29**) and C-centred alkyl radicals (**30**, **31**) are generated in the reactions of compound **1** with Fe^{II}. After the trapping (for example, by DBNBS), the radicals are transformed into stable nitroxides **32** and **33**. The structures of the nitroxides were determined from the hyperfine splitting of lines in their EPR spectra. Scheme 4 shows examples of reactions giving radicals **32** and **33**.[87]

The reaction of the artemisinin derivative arteflene (**34**) with Fe^{II} also affords C-centred radicals detected by the spin trapping method.[90]



34

Reaction products. The generation of alkyl radicals by the reaction of artemisinin with Fe^{II} is consistent also with the formation of the products of their addition to glutathione (R′SH) by the reactions:[91]

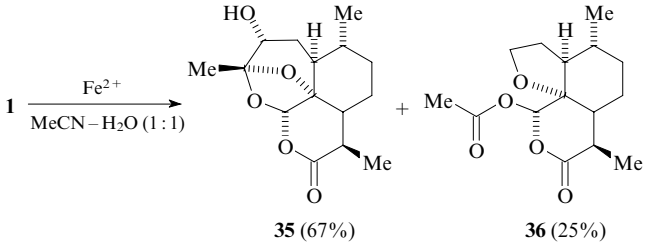
$$\mathbf{1} + Fe^{II} \longrightarrow R^{\bullet} + Fe^{III},$$

$$R^{\bullet} + R'SH \longrightarrow RH + R'S^{\bullet},$$

$$R^{\bullet} + R'S^{\bullet} \longrightarrow R'SR.$$

This is confirmed also by the fact that in the presence of iron complexes, compound **1** catalyzes the oxidation of lipids in cell membranes.[92]

The molecular products of the transformation of artemisinin in the presence of iron(II) ions are also indicative of their formation from free radicals. In *in vitro* experiments under anaerobic conditions, it was found that this reaction gives compounds **35** and **36**.[5]

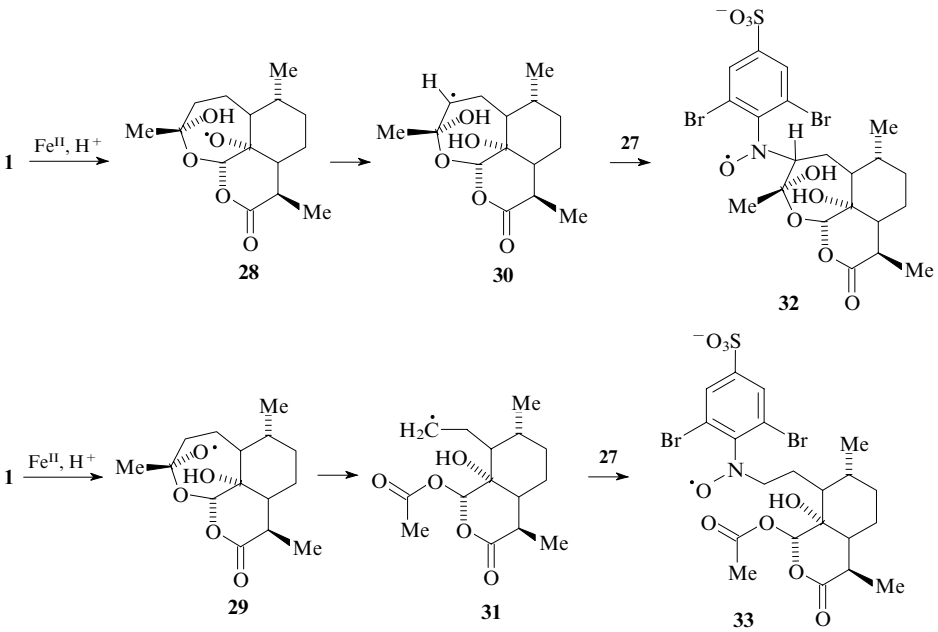


35 (67%) **36** (25%)

Similar results were obtained also for artemisinin derivatives **15a**–**c**.[5,93] The kinetic schemes of the formation of products **35** and **36** will be discussed in the next section.

Kinetics of the reaction. The rate constants for the reactions of artemisinin with Fe^{II} salts involving the peroxide bridge are given in Table 7. As can be seen from Table 7, the anion has an effect on the rate of reduction of the peroxide group. Thus, iron gluconate reacts most rapidly with compound **1**. The Fe^{III} ion also has catalytic activity. The composition of the products depends on the nature of both the anion and the solvent.

Scheme 4



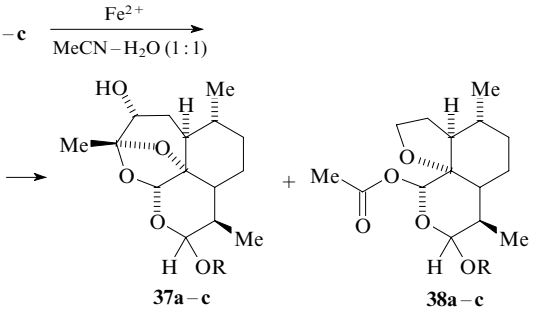
28 **30** **32**

29 **31** **33**

Table 7. Rate constants for the decomposition of the peroxide bridge in compound **1** by the reaction with Fe^{II}/Fe^{III} at 309 K.[94]

Salt	Solvent	k /litre mol^{-1} s^{-1}	Ratio **35** : **36**
Fe^{2+} Gluconate	MeCN – H_2O (1 : 1)	$(5.55 \pm 0.7) \times 10^{-2}$	2.7
$FeSO_4$	MeCN – H_2O (1 : 1)	$(5.00 \pm 0.55) \times 10^{-3}$	0.9
$FeCl_2$	MeCN – H_2O (1 : 1)	$(2.87 \pm 0.18) \times 10^{-3}$	0.5
$FeBr_2$	MeCN – H_2O (1 : 1)	$(2.41 \pm 0.28) \times 10^{-3}$	0.3
$Fe(ClO_4)_2$	MeCN – H_2O (1 : 1)	$(2.22 \pm 0.18) \times 10^{-3}$	0.2
$FeCl_3$	MeCN – H_2O (1 : 1)	$(1.02 \pm 0.37) \times 10^{-3}$	–
$FeSO_4$	dioxane – H_2O (1 : 1)	1.33×10^{-3}	–
	MeOH – H_2O (1 : 1)	1.54×10^{-3}	–
	H_2O	2.06×10^{-2}	
	$MeC(O)NH_2$ – H_2O (1 : 1)	8.94×10^{-2}	–
	Me_2SO – H_2O (1 : 1)	0.14×10^{-2}	–
	H_2O (pH 7.25)	10.0 ± 0.5 [a]	–
$Fe_2(SO_4)_3$	H_2O (pH 7.25)	8.5 ± 2.0 [a]	–

Note. The concentrations of compound **1** and Fe^{II} are 0.03 and 0.03 mmol litre^{-1}, respectively. [a] At 298 K.[95]



Compound	R	Yield (%)	
		37	**38**
a	H	46	25
b	Me	45	37
c	$C(O)(CH_2)_2CO_2H$	23	45

The decomposition of the peroxide bridge is accompanied by the change in the oxidation state of the iron ions: Fe^{II} is transformed into Fe^{III} and *vice versa*.[95] This is in good agreement with the following kinetic scheme of the redox reactions:[33]

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

$$RO^{\bullet} \xrightarrow{\text{ring opening}} (R^1)^{\bullet},$$

$$(R^1)^{\bullet} + Fe^{3+} \longrightarrow (R^1)^+ + Fe^{2+},$$

$$(R^1)^+ + H_2O \longrightarrow R^1OH + H^+$$

(hereinafter, ROOR stands for artemisinin, and R^i is the moiety of artemisinin).

The enol form of compound **1** can also serve as a reducing agent, which reacts with the Fe^{3+} ion:[96]

$$R^1CH{=}C(OH)R^2 + Fe^{3+} \longrightarrow R^1C^{\bullet}HC(O)R^2 + Fe^{2+} + H^+.$$

The high efficacy of artemisinin and its derivatives as antimalarial agents, on the one hand, and their low toxicity, on the other hand, are determined by the fact that the content of iron complexes in the Plasmodium malariae is two orders of magnitude higher than that in the human organism. Hence, the generation of radicals in cells of the Plasmodium malariae occurs much more rapidly than that in the human organism. The question is whether the rate of generation of radicals is the main factor determining the efficacy of the therapeutic action of compound **1** and its analogues (Fig. 1)?

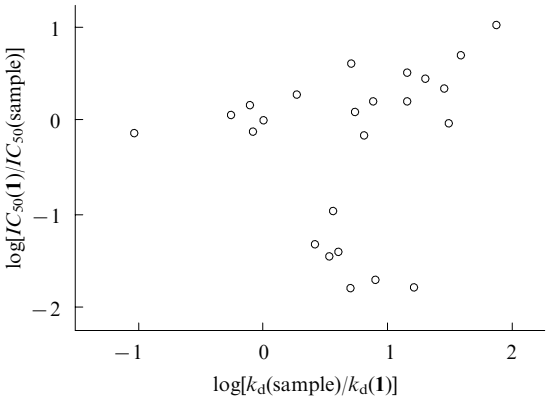


Figure 1. Plot of the antimalarial activity of artemisinin derivatives described by $\log[IC_{50}(\mathbf{1})/IC_{50}(\text{sample})]$ *versus* the relative rate constant for the reaction of the peroxide group with iron ions (Fe^{II}/Fe^{III}) at 310 K in logarithmic coordinates.[97]

As can be seen from Fig. 1, there is no correlation between the antimalarial activity of the compounds and their ability to generate radicals by the reaction with iron ions. However, the reduction of the peroxide group, as mentioned above, leads to the inactivation of the molecule. Consequently, the presence of the peroxide group in the molecule is a necessary but not sufficient condition for the effective therapeutic action of the drug. (Many simple peroxides do not have therapeutic action at all.[5]) Evidently, there are also other structural factors responsible for the antimalarial activity of the substance.

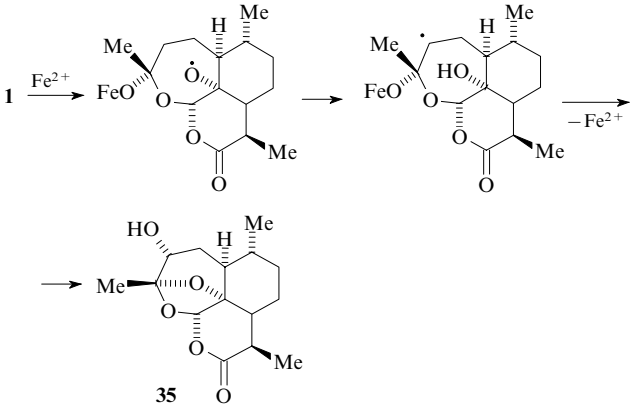
VII. Transformation products of alkoxyl radicals generated from artemisinin under anaerobic conditions

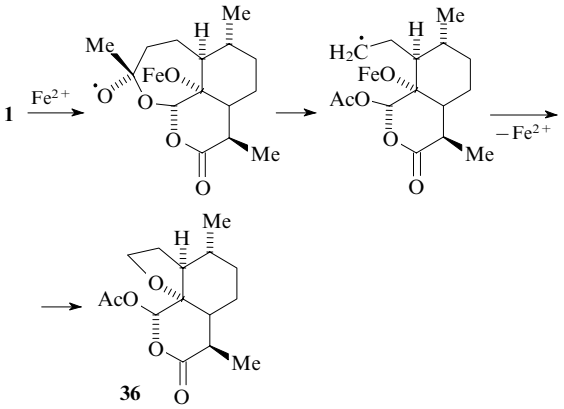
Products generated in the redox reactions of artemisinin with iron(II) salts confirm the radical mechanism. The decomposition affords alkoxyl radicals with free valences at the O(1) and O(2) atoms. The O–O bond cleavage is preceded by the formation of the coordination bond between one of the oxygen atoms and the hemin iron atom, as was determined by spectroscopic methods.[98] This is also evident from the influence of the anion on the rate constant of the reaction of compound **1** with Fe^{2+} (see Table 7). The equilibrium constant also depends on the nature of the anion (X):

$$\mathbf{1} + Fe(H_2O)_5X \rightleftharpoons \mathbf{1}\cdot Fe(H_2O)_4X + H_2O.$$

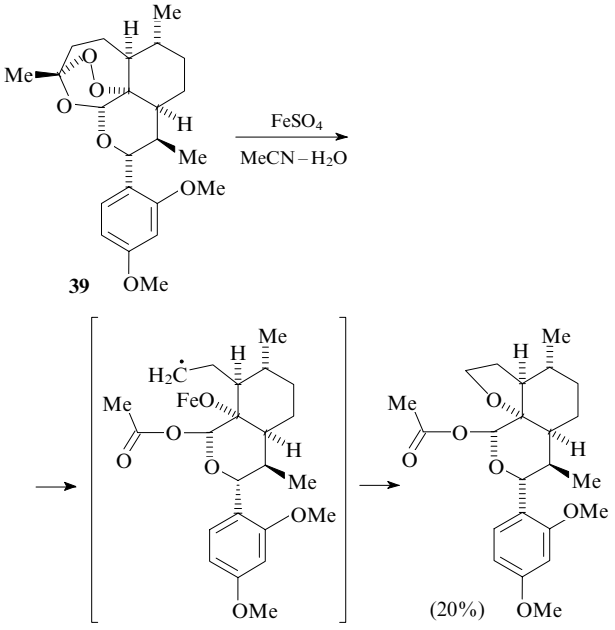
The monitoring of the change in the oxidation state of the iron atom in the course of decomposition of the

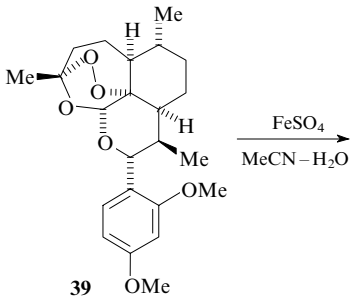
peroxide group in compound **1** showed that Fe^{II} is oxidized to Fe^{III}, and Fe^{III} is again reduced to Fe^{II}. Consequently, the decomposition of peroxide occurs as the catalytic redox reaction.[95] The electrochemical reduction of artemisinin in the presence of the Fe^{II}/Fe^{III} pair gives the same molecular products as those obtained after the catalytic decomposition.[99] The radical mechanism of the formation of compounds **35** and **36** can be described by the following schemes.[5, 88, 93, 100, 101]

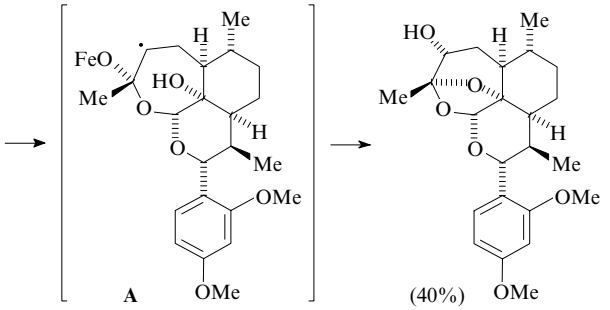




Artemisinin derivative **39** is involved in similar reactions.[88]

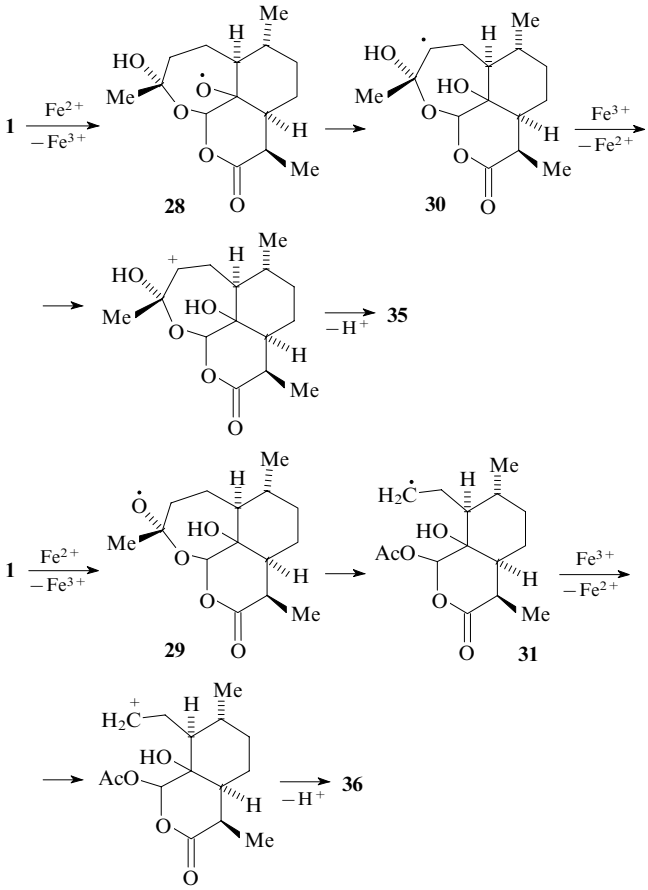






It was suggested that the C—O—C bridge is formed not as a result of the intramolecular heterolytic reaction between two hydroxyl groups of the intermediate **A**, but as a result of the oxidation of the peroxide group by the two-electron mechanism through the intermediate formation of the ferryl ion FeO^{2+} (Ref. 88, 93, 100, 101). However, this assumption was not experimentally confirmed and remains hypothetical.[4] The formation of products **35** and **36** is attributed to the transformations involving Fe^{2+} and Fe^{3+}

Scheme 5



ions; each step has the reliably identified analogous reactions (Scheme 5).[33]

VIII. Quantum chemical calculations for reactions of alkoxyl radicals generated from artemisinin

Alkoxyl radicals actively react with compounds containing C–H bonds. All these reactions are exothermic because $D_{O-H} > D_{C-H}$.[102] For example, the enthalpy and the activation energy of the reaction of the radicals $Me_3CO^{\bullet}$ with the CH_2 group of cyclohexane are $\Delta H = -40$ kJ mol^{-1} and $E = 22.6$ kJ mol^{-1}, respectively.[103]

The alkoxyl radicals are rapidly involved in the intramolecular hydrogen atom transfer reaction. For example, for the reaction

$$Me_2C(O^{\bullet})(CH_2)_3Me \longrightarrow Me_2C(OH)(CH_2)_2C^{\bullet}HMe$$

$E = 23.4$ kJ mol^{-1} and $k = 1.3 \times 10^5$ s^{-1} (350 K).[104] There is reason to believe that these reactions also occur rapidly in the case of alkoxyl radicals generated from artemisinin (hereinafter, artemisinin radicals) and its analogues. Quantum chemical calculations confirmed this assumption.

Table 8 presents the results of quantum chemical calculations for the following two types of reactions of alkoxyl radicals: the hydrogen atom transfer and the ring opening. As can be seen from Table 8, the calculated values of ΔH for the hydrogen atom transfer reactions vary in a wide range from -22 to -91 kJ mol^{-1}, whereas the thermochemical calculations from the dissociation energies of the corresponding bonds give $\Delta H = -35 \pm 2$ kJ mol^{-1}. The activation energy of these reactions varies in the range of 17–112 kJ mol^{-1}. The similar situation is observed for the ring opening, Thus, ΔH varies in the range from -77 to 35 kJ mol^{-1} (the thermochemical calculations give $\Delta H = -9$ kJ mol^{-1}), and the activation energy varies in

Table 8. Energies of the hydrogen atom transfer and the ring opening in alkoxyl radicals generated from compound **1** and its analogues calculated by quantum chemical methods.

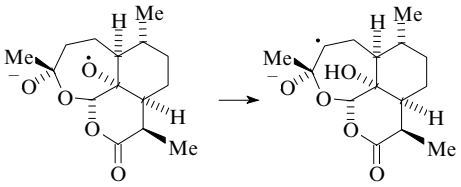
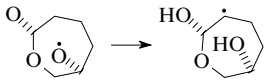
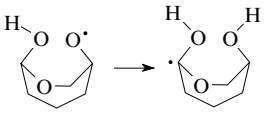
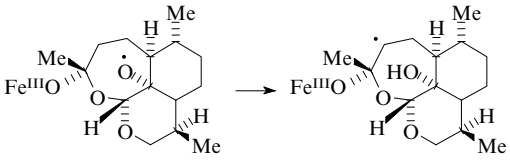
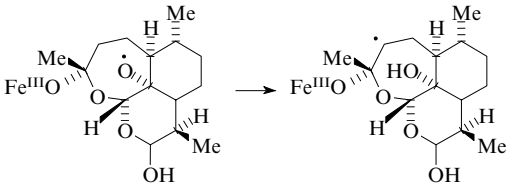
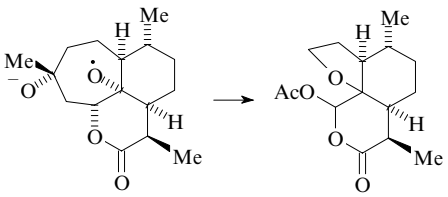
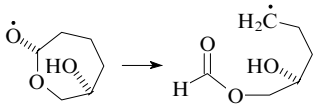
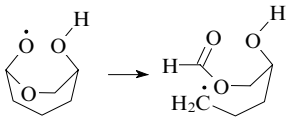
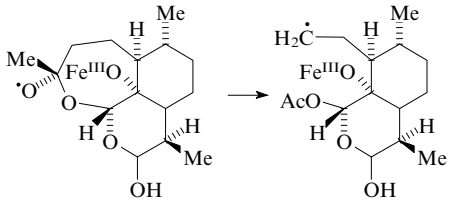
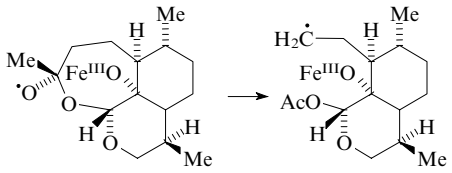
Reaction	$-\Delta H$/kJ mol^{-1}	E/kJ mol^{-1}	Method	Ref.
Hydrogen atom transfer				
	91.4	90.7	AM 1	105
	58.4	112.1	PM 3	105
	37.2	60.6	B3LYP	106
	21.6	30.2	B3LYP/6-31G(d)	107
	14.6	27.3	B3LYP/6-31G(d,p)	108
	40.0	17.4	B3LYP/6-31G(d,p)	32
	40.4	34.1	B3LYP/6-31G(d,p)	32
Ring opening				
	77.3	74.2	AM 1	105
	34.9	111.9	PM 3	105
	−35.2	70.4	B3LYP	106
	42.1	32.5	B3LYP/6-31G(d)	107

Table 8 (continued).

Reaction	$-\Delta H$ /kJ mol^{-1}	E /kJ mol^{-1}	Method	Ref.
Ring opening				
	67.7	35.2	B3LYP/6-31G(d,p)	108
	47.2	18.7	B3LYP/6-31G(d,p)	32
	35.6	20.7	B3LYP/6-31G(d,p)	32

the range of 19–112 kJ mol^{-1}. For the comparison, let us mention $E = 38.5$ kJ mol^{-1} for the ring opening in the cyclohexyloxyl radical.[104] Therefore, the quantum chemical results are in qualitative agreement with the fact of the formation of primary and secondary alkyl radicals from artemisinin; however, a large difference in the values of ΔH and E is indicative of the low precision of the the calculations. Evidently, the radicals derived from compound **1** are very complicated for quantum chemical calculations.

IX. Competition between mono- and bimolecular reactions of alkoxyl radicals generated from artemisinin

The kinetic analysis of monomolecular reactions of alkoxyl radicals (RO$^{\bullet}$) generated from compound **1** and the comparison of their parameters with those of bimolecular reactions with various biologically active compounds (hereinafter, substrates) were performed in the studies.[24,25] In these studies, the enthalpies of the competitive reactions, their activation energies, and the rate constants were calculated for the first time with the use of the parabolic model of radical reactions (the intersecting parabolas model, IPM). This model is based on experimental data and provides an estimation of the activation energies of radical reactions with an error of only 1.5 kJ mol^{-1} (Ref. 109, 110). The kinetic parameters calculated earlier for mono- and bimolecular reactions of alkoxyl radicals[104,111] were used in the calculations.

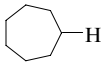
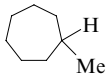
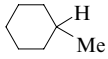
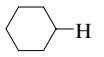
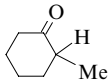
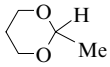
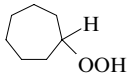
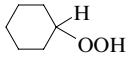
In the intramolecular hydrogen atom transfer reactions, the C–H bond that is attacked is cleaved (the strength of the bond D_{C-H}), and the O–H bond is formed (D_{O-H}). The enthalpy of this reaction is

$$\Delta H = D_{C-H} - D_{O-H}. \quad (4)$$

Table 9 gives the strengths of the bonds in the model compounds used for the calculation of the enthalpies of the mono- and bimolecular reactions of alkoxyl radicals.

The radicals RO$^{\bullet}$ generated from artemisinin are cycloalkylalkoxyl radicals. The analysis of the transformation products of compound **1** and the quantum chemical calcu-

Table 9. Dissociation energies of individual bonds D_{C-H} and D_{O-H}.[28,102,112]

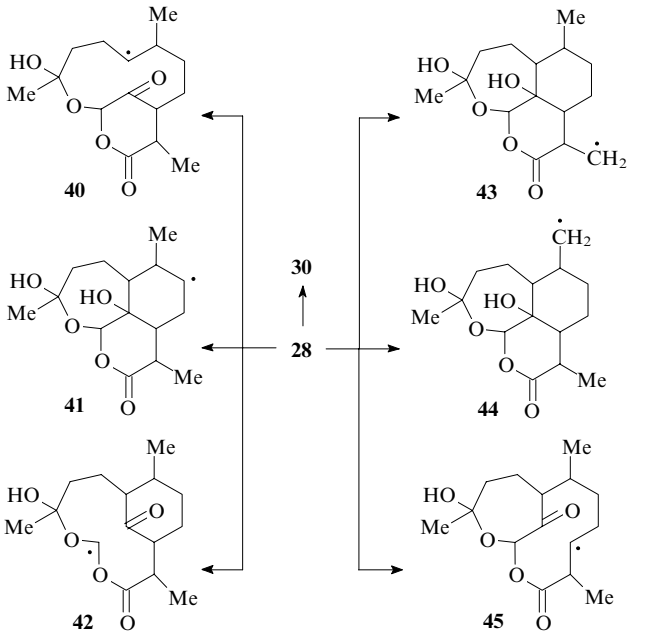
Bond in compound **1** and its derivatives	Bond in the model compound	D_{C-H} /kJ mol^{-1}
O(1)–H, O(2)–H		438.5[a]
C(4)–H, C(5)–H		403.9
C(5*a*)–H		390.0
C(6)–H		395.5
C(7)–H, C(8)–H		408.8
C(8*a*)–H		387.6
C(9)–H		385.3
C(12)–H		378.3
C(3 or 9)CH$_2$–H	AlkCH$_2$—H	422.0
C(4)(OOH)–H, C(5)(OOH)–H		370.9
C(7)(OOH)–H, C(8)(OOH)–H		375.8

[a] The energy D_{O-H} is given.

lations (see above) showed that these radicals are involved in intramolecular hydrogen atom transfer and ring opening reactions. The enthalpies of the latter reactions were calculated using the Benson group increment theory taking into account the strain energies of the starting and resulting rings.[25] Schemes 6 and 7 show the radical reactions of alkoxyl radicals **28** and **29** giving radicals **40**–**48**. Table 10 presents the calculated physicochemical parameters (ΔH, E, and k) of these reactions.[24, 25]

It can be seen that the hydrogen atom transfer from the γ position with respect to the weakest C–H bond is the most rapid reaction of alkoxyl radicals **28** and **29**. This is consistent with the experimental data on the composition of the products obtained in the reactions of artemisinin with Fe^{2+} under anaerobic conditions (see above).

Scheme 6



Scheme 7

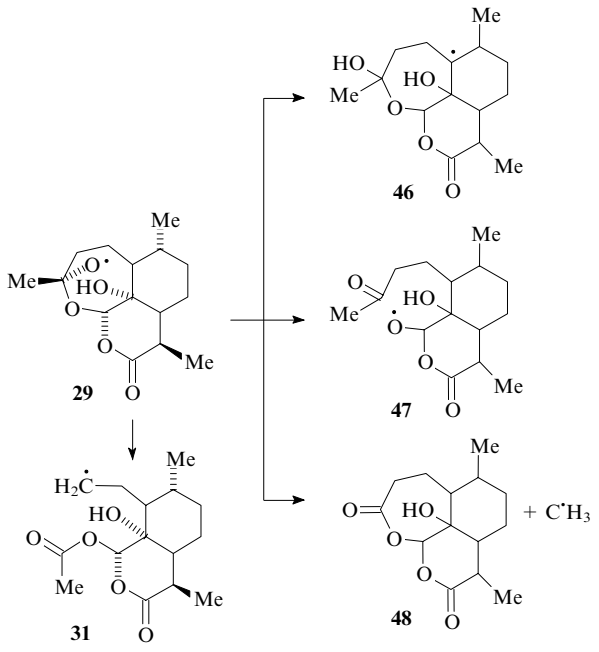


Table 10. Thermodynamic and kinetic parameters of the reactions of alkoxyl radicals **28** and **29** generated from artemisinin.

Reaction	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	k(310 K)/s^{-1}
Intramolecular hydrogen atom transfer			
28 ⟶ **30**	−34.6	21.8	1.67×10^9
28 ⟶ **41**	−29.7	23.6	8.36×10^8
28 ⟶ **43**	−16.5	28.6	1.81×10^8
28 ⟶ **44**	−16.5	28.6	1.81×10^8
29 ⟶ **46**	−48.5	16.0	8.01×10^9
Ring opening and decomposition			
28 ⟶ **40**	12.0	34.5	1.53×10^7
28 ⟶ **42**	69.9	71.2	1.01×10^1
28 ⟶ **45**	33.5	45.1	2.52×10^5
29 ⟶ **31**	−8.7	25.4	5.25×10^8
29 ⟶ **47**	58.5	65.8	8.18×10^1
29 ⟶ **48**	25.2	40.7	1.39×10^6

The alkoxyl radicals generated from compound **1** are very actively involved in the bimolecular hydrogen atom abstraction reactions with other compounds. To understand the mechanism of the biological action of artemisinin, it is important to know which processes occur more rapidly.

The following biologically active compounds were examined as substrates in bimolecular reactions: L-cysteine (D_{S-H} = 360.0 kJ mol^{-1}), *cis*–*cis*-methyl linoleate (D_{C-H} = 318.0 kJ mol^{-1}), *cis*-methyl oleate (D_{C-H} = 344.0 kJ mol^{-1}), glucose (D_{C-H} = 371.4 kJ mol^{-1}), and glycerol (D_{C-H} = 387.7 kJ mol^{-1}).[25] Figure 2 shows the calculated rate constants for the reactions of the alkoxyl radicals RO(1)˙ (**28**) and RO(2)˙ (**29**) generated from compound **1** with different compounds at 310 K.

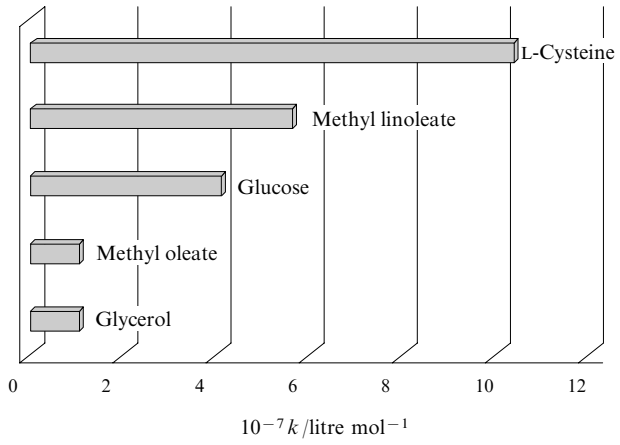


Figure 2. Rate constants for the bimolecular reactions of the alkoxyl radicals generated from compound **1** with different substrates at 310 K.[25]

The diagram shows that of the substrates under consideration, the artemisinin alkoxyl radicals react most rapidly with L-cysteine at the SH groups. The comparison of the rates of the mono- and bimolecular reactions of these alkoxyl radicals showed that the monomolecular reactions occur several orders of magnitude more rapidly than the bimolecular reactions.[25] This is attributed to the fact that

the entropy of activation of the bimolecular reaction ($\Delta S^{\neq}_{bim}$) $RO^{\bullet} + LH$ is much lower than $\Delta S^{\neq}_{mono}$, and, consequently, the pre-exponential factor A_{mono} is 4–5 orders of magnitude larger than A_{bim}.[104] Therefore, it was found that the free valence is retained at the C atom of artemisinin after the transformation of the alkoxyl radicals, *i.e.*, the cycloalkyl radical is formed.

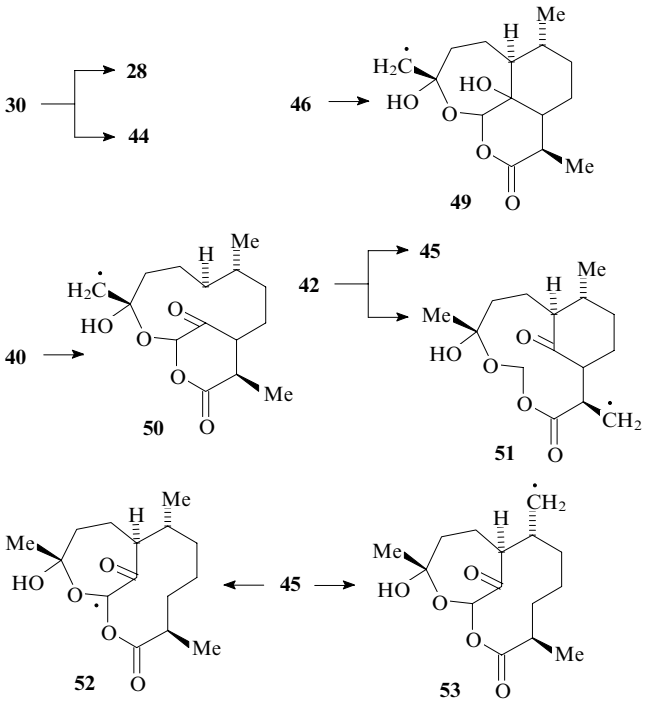
X. Reactions of alkyl radicals derived from artemisinin

As shown above, the alkoxyl radicals derived from compound **1** are transformed into the corresponding cycloalkyl radicals in particular intramolecular reactions. The cycloalkyl radicals can, in turn, be involved in monomolecular hydrogen atom transfer reactions, ring opening reactions,[104] and bimolecular reactions with different substrates. The competition between these reactions was analyzed in the study.[26] Scheme 8 shows the intramolecular hydrogen atom transfer in alkyl radicals giving radicals **49**–**53**. Table 11 presents ΔH, E, and k for these reactions calculated with the use of IPM.

Table 11. Thermodynamic and kinetic parameters of the intramolecular hydrogen atom transfer in artemisinin alkyl radicals.[26]

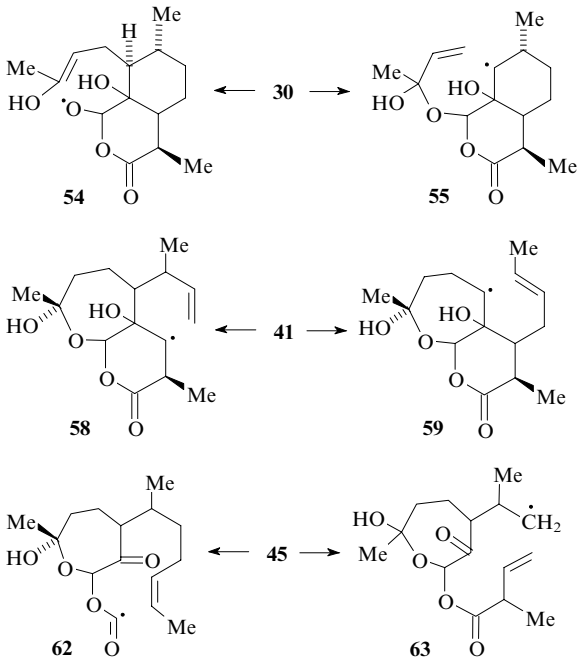
Reaction	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	k (310 K)/s^{-1}
30 → **28**	34.6	55.2	7.52×10^3
30 → **44**	18.1	45.3	1.05×10^6
40 → **50**	17.3	44.9	1.24×10^6
42 → **45**	−4.7	33.5	4.53×10^7
42 → **51**	34.0	54.3	1.07×10^4
45 → **52**	2.7	37.2	1.08×10^7
45 → **53**	17.3	44.9	1.24×10^6
46 → **49**	32.0	53.1	1.70×10^4

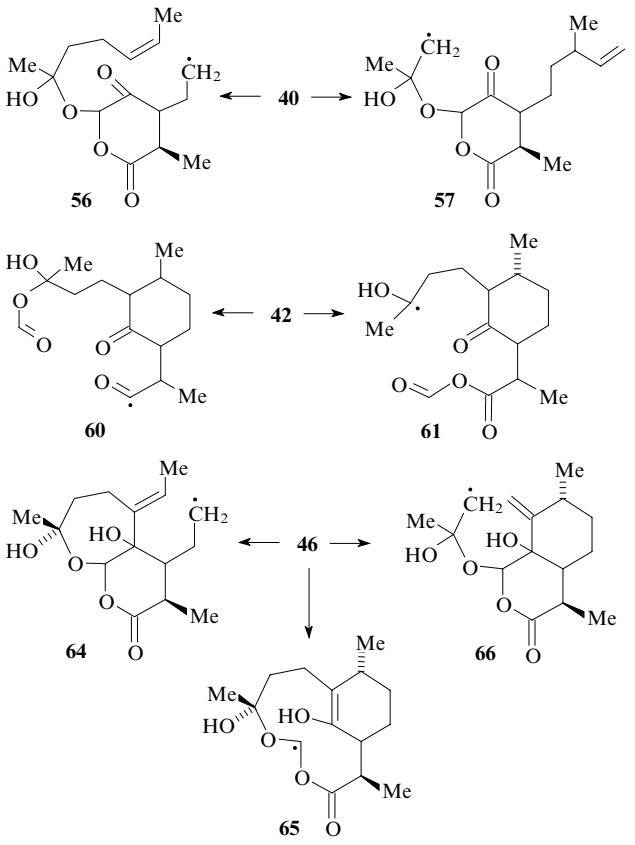
Scheme 8



It can be seen that depending on the structure of the cycloalkyl radical and the enthalpy of the reaction, the rate

Scheme 9





constant of the isomerization of alkyl radicals at 310 K varies in a wide range from 7.5×10^3 to 4.5×10^7 s^{-1}.

The ring opening reactions of cycloalkyl radicals generated from artemisinin are shown in Scheme 9. These transformations afford radicals **54**–**66**. All reactions are endothermic and occur rather slowly. Thus, the rate constant at 310 K varies from 7×10^{-9} to 3 s^{-1} (Table 12).

The artemisinin cycloalkyl radicals are involved in bimolecular reactions, whose rate depends on the enthalpy of the reaction, the structure of the reaction centre, and the concentration of the substrate. The alkyl radicals, like the alkoxyl radicals (see above), react most rapidly with the SH groups of L-cysteine (R′SH).[26] Table 13 gives the physicochemical parameters of the bimolecular reactions of cycloalkyl radicals **30**, **40**–**42**, **45**, and **46** with L-cysteine. Depending on the enthalpy, the rate constant varies from 7×10^5 to 1.0×10^7 litre mol^{-1} s^{-1}. It is interesting to compare the rates of these reactions with those of the most rapid isomerization reactions (k_{is}) of the same radicals (Table 14). The comparison shows that all radicals, except **46**, are involved mainly in the isomerization.

Table 12. Thermodynamic and kinetic parameters of the ring opening in artemisinin alkyl radicals.[26]

Reaction	ΔH, /kJ mol^{-1}	E /kJ mol^{-1}	k (310 K) /s^{-1}
30 ⟶ **54**	47.2	105.5	3.34×10^{-5}
30 ⟶ **55**	63.0	102.0	1.26×10^{-4}
40 ⟶ **56**	38.9	75.9	3.19
40 ⟶ **57**	51.0	82.5	0.25
41 ⟶ **58**	83.8	121.2	7.50×10^{-8}
41 ⟶ **59**	69.4	112.9	1.81×10^{-6}
42 ⟶ **60**	65.4	100.7	2.13×10^{-4}
42 ⟶ **61**	109.7	125.3	1.49×10^{-8}
45 ⟶ **62**	104.5	113.7	1.34×10^{-6}
45 ⟶ **63**	83.9	100.2	2.58×10^{-4}
46 ⟶ **64**	94.1	127.3	7.08×10^{-9}
46 ⟶ **65**	52.1	99.1	3.28×10^{-4}
46 ⟶ **66**	45.6	92.6	4.90×10^{-3}

Table 13. Thermodynamic and kinetic parameters of the reactions of artemisinin alkyl radicals with L-cysteine (R′SH).[26]

Radical	$-\Delta H$ /kJ mol^{-1}	E /kJ mol^{-1}	k /litre mol^{-1} s^{-1}	k[R′SH] /s^{-1}
30	43.9	13.5	5.31×10^6	2.65×10^5
40, **45**	44.7	13.2	5.92×10^6	2.96×10^5
41	48.8	11.8	1.03×10^7	5.15×10^5
42	31.0	18.2	8.42×10^5	4.21×10^4
46	30.0	18.6	7.25×10^5	3.63×10^4

Note. The concentration of cysteine was 0.05 mol $litre^{-1}$; the rate constants of the bimolecular reactions were calculated for the temperature of 310 K.

Table 14. Comparison of the kinetic characteristics of the isomerization and the reaction of alkyl radicals with L-cysteine (310 K) (see Tables 13 and 15).

Radical	k_{is} /s^{-1}	k[R′SH] /s^{-1}	k[R′SH]/(k_{is} + k[R′SH]) (%)
30	1.05×10^6	2.65×10^5	20.0
40	1.24×10^7	2.96×10^5	2.3
42	3.10×10^7	4.21×10^4	0.14
45	1.10×10^7	2.96×10^5	2.6
46	1.70×10^4	3.63×10^4	68.0

XI. Intramolecular chain oxidation reaction of artemisinin

Under aerobic conditions in the living organism, cycloalkyl radicals derived from artemisinin bind oxygen. The addition of O_2 to alkyl radicals is limited only by the self-diffusion of oxygen and occurs with a rate constant (k_{O_2}) of 10^9–10^{10} litre mol^{-1} s^{-1}. In lipids, the constant k_{O_2} is similar to those in linoleic acid esters ($k_{O_2} = 1.5 \times 10^9$ litre mol^{-1} s^{-1}).[86] The Henry coefficient of oxygen (γ_{O_2}) in this medium is 1.12×10^{-2} mol $litre^{-1}$ atm^{-1} (Ref. 86). Hence, the specific rate of the reaction of alkyl radicals with O_2 at $p(O_2) = 0.21$ atm (in air) is 3.5×10^6 s^{-1}. A comparison of this value with the specific rates of the reactions of artemisinin alkyl radicals with L-cysteine (see Table 14) shows that the oxygen addition is the major pathway of the transformation of the alkyl radicals in an aerobic medium resulting in the formation of peroxyl radicals. This conclusion was drawn in the studies.[27,28] A comparison of the oxygen addition with the monomolecular reactions of the artemisinin alkyl radicals (see Tables 11 and 12) shows that this reaction is the most rapid transformation channel for the majority of radicals. The exceptions are the reactions **42** → **45** and **45** → **52**, which proceed more rapidly than the oxygen addition. Nevertheless, the free valence at the carbon atom is retained in these cases as well. Therefore, under aerobic conditions there are the following main reaction channels of radicals generated from artemisinin:

$$\mathbf{1} \longrightarrow \mathbf{28} \longrightarrow (R^i)^{\bullet} \xrightarrow{O_2} R^iOO^{\bullet},$$

$$\mathbf{1} \longrightarrow \mathbf{29} \longrightarrow (R^j)^{\bullet} \xrightarrow{O_2} R^jOO^{\bullet}.$$

The further transformations of the artemisinin peroxyl radicals were analyzed for the first time in the studies.[27,28] The reactivity of peroxyl radicals depends on their structures and is related to the strength of both the C–H bond of the substrate that is attacked and the newly formed R^iOO–H bond.[112] Table 15 presents the structures of hydroperoxides **67**–**75**, which are the oxidation products of artemisinin, and the dissociation energies of the O–H bond of the hydroperoxyl groups in model compounds.

The thermodynamic and kinetic parameters (ΔH, E, k, and $k \cdot$[R′H]) for the reactions of the artemisinin peroxyl radicals generated from hydroperoxides **67**–**75** with different substrates (R′H) are summarized in Table 16. As can be seen from this table, the specific rate of the bimolecular reactions at 310 K varies from 1.5×10^{-2} to 2.2×10^3 s^{-1}. Among these reactions, the reaction of the peroxyl radicals with the compound containing SH groups, *viz*., L-cysteine, is the most rapid process.

The peroxyl radicals undergo the competitive intramolecular hydrogen atom transfer to form alkyl radicals containing the hydroperoxide group. The kinetic analysis

Table 15. Dissociation energies of the O—H bond in hydroperoxides generated from artemisinin.[113]

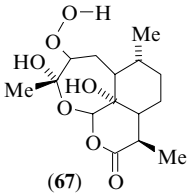
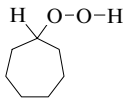
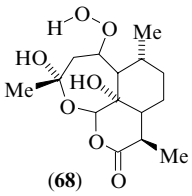
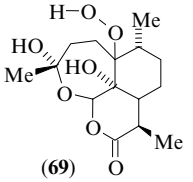
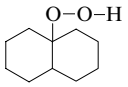
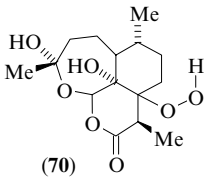
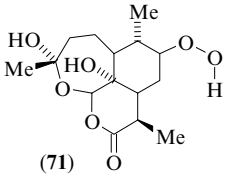
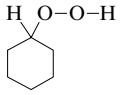
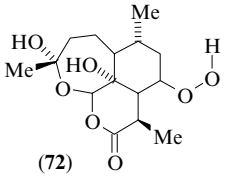
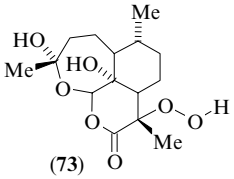
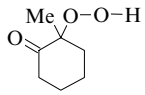
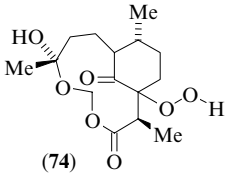
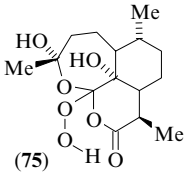
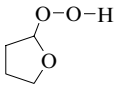
O—H Bond in hydroperoxide, the oxidation product of compound **1**	Model compound	D_{O-H} /kJ mol^{-1}
 (**67**)		365.5
 (**68**)		
 (**69**)		358.6
 (**70**)		
 (**71**)		365.5
 (**72**)		
 (**73**)		362.9
 (**74**)		
 (**75**)		367.6

Table 16. Thermodynamic and kinetic parameters of the bimolecular reactions of the peroxyl radicals derived from artemisinin with different substrates (R′H).[28]

R′H	[R′H] /mol litre^{-1}	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	A /litre mol^{-1} s^{-1}	k (310 K) /litre mol^{-1} s^{-1}	k[R′H] /s^{-1}
D_{O-H} = 365.5 kJ mol^{-1} (for hydroperoxides **67**, **68**, **71**, **72**)						
(*Z*)-Methyl oleate	2.95	−21.5	43.3	1.0×10^{7}	2.00	0.59×10^{1}
Methyl linoleate	3.02	−47.5	33.3	1.0×10^{7}	4.84×10^{1}	1.46×10^{2}
Glycerol	0.1	21.8	47.4	1.0×10^{8}	1.00	1.0×10^{-1}
Glucose	0.1	5.9	33.1	1.0×10^{8}	2.64×10^{2}	2.64×10^{1}
L-Cysteine	0.05	−5.5	26.7	1.0×10^{9}	3.12×10^{4}	1.56×10^{3}
D_{O-H} = 358.6 kJ mol^{-1} (for hydroperoxides **69**, **70**)						
(*Z*)-Methyl oleate	2.95	−14.6	46.2	1.0×10^{7}	6.66×10^{-1}	0.19×10^{-1}
Methyl linoleate	3.02	−40.6	35.9	1.0×10^{7}	1.80×10^{1}	5.44×10^{1}
Glycerol	0.1	28.7	50.8	1.0×10^{8}	2.71×10^{-1}	2.71×10^{-2}
Glucose	0.1	12.8	36.3	1.0×10^{8}	7.67×10^{1}	0.77×10^{1}
L-Cysteine	0.05	1.4	29.6	1.0×10^{9}	1.03×10^{4}	5.15×10^{2}
D_{O-H} = 362.9 kJ mol^{-1} (for hydroperoxides **73**, **74**)						
(*Z*)-Methyl oleate	2.95	−18.9	44.4	1.0×10^{7}	1.32	3.89
Methyl linoleate	3.02	−44.9	34.0	1.0×10^{7}	3.73×10^{1}	1.13×10^{2}
Glycerol	0.1	24.9	52.4	1.0×10^{8}	1.48×10^{-1}	1.48×10^{-2}
Glucose	0.1	8.5	42.8	1.0×10^{8}	6.14	5.59×10^{1}
L-Cysteine	0.05	−2.9	29.2	1.0×10^{9}	1.20×10^{4}	6.00×10^{2}

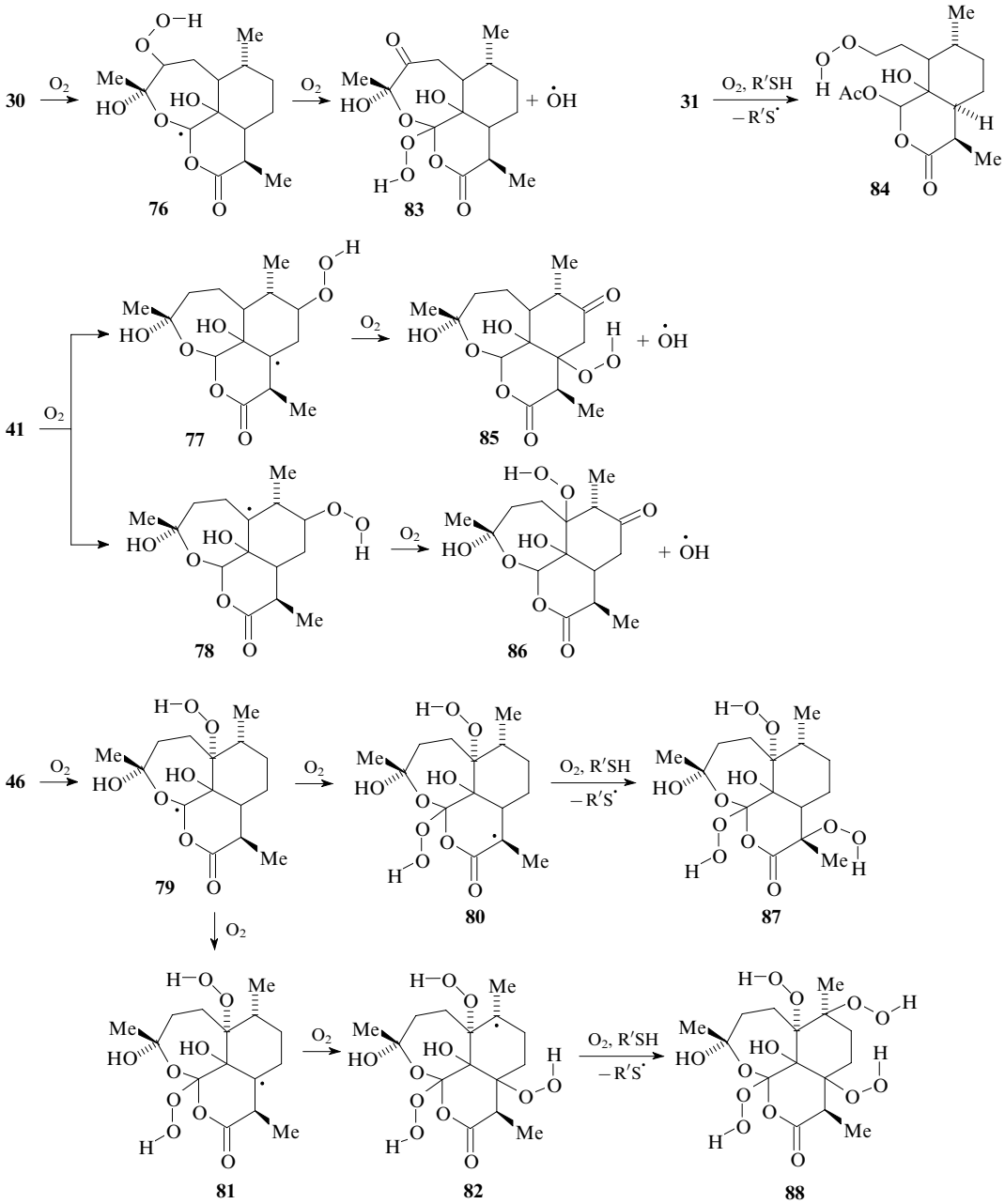
Table 16 (continued).

R′H	[R′H] /mol litre^{-1}	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	A /litre mol^{-1} s^{-1}	k (310 K) /litre mol^{-1} s^{-1}	k [R′H] /s^{-1}
D_{O-H} = 367.6 kJ mol^{-1} (for hydroperoxide **75**)						
(*Z*)-Methyl oleate	2.95	−23.6	42.5	1.0×10^7	2.80	0.70×10^1
Methyl linoleate	3.02	−49.6	32.6	1.0×10^7	6.49×10^1	1.96×10^2
Glycerol	0.1	19.7	46.4	1.0×10^8	0.15×10^1	1.5×10^{-1}
Glucose	0.1	3.8	32.1	1.0×10^8	3.82×10^2	3.82×10^1
L-Cysteine	0.05	−7.6	25.9	1.0×10^9	4.34×10^4	2.17×10^3

showed that these reactions are several orders of magnitude more rapid than the bimolecular reactions of $RO_2^{\cdot}$ with substrates.[27,28] As a result, after the cleavage of the peroxide bridge, artemisinin undergoes the intramolecular chain oxidation reaction to give finally multifunctional peroxide.

Each peroxyl radical is simultaneously involved in several reactions accompanied by the hydrogen atom trans-

Scheme 10



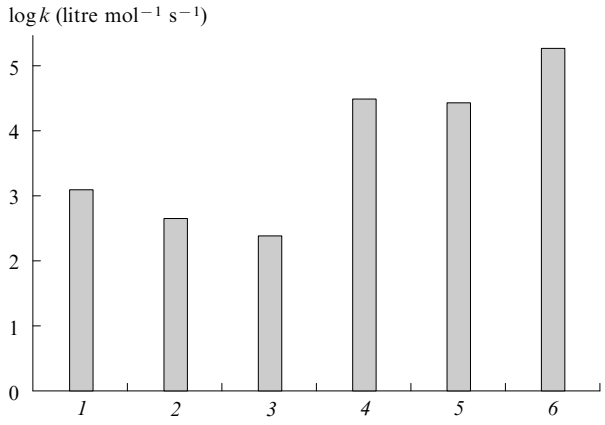


Figure 3. Rate constants (on the logarithmic scale) for the intramolecular hydrogen atom abstraction by the peroxyl radical generated from radical **46** as a result of the C–H bond cleavage in position 4 (*1*), 7 (*2*), 8 (*3*), 8*a* (*4*), 9 (*5*), and 12 (*6*). $T = 310$ K.[28]

fer. Among these competitive reactions, one (rarely two) reaction occurs most rapidly. For example, the peroxyl radical generated from radical **46** causes the abstraction of the H atom from the C(4)–H, C(7)–H, C(8)–H, C(8*a*)–H, C(9)–H, and C(12)–H bonds of artemisinin. As can be seen from Fig. 3, which presents the rate constants for these reactions on the logarithmic scale, the most rapid reaction corresponds to the bar *6*. This reaction affords 76% of hydroperoxide **69**.

Alkyl radicals **30** and **41** are the major isomerization products of alkoxyl radical **28** (66% and 33%, respectively); alkyl radicals **31** and **46** are the major isomerization products of alkoxyl radical **29** (16% and 83%, respectively). Scheme 10 shows the intramolecular transformations of these radicals under aerobic conditions. Each step consists of two successive elementary events. The former event involves the addition of the oxygen molecule to form radicals **76**–**82**, and the latter event involves the isomerization of the resulting peroxyl radical or its reaction with L-cysteine (R′SH) to give hydroperoxides **83**–**88**.

Table 17 gives the thermodynamic and kinetic parameters (ΔH, E, and k) for these reactions.

Table 18. Thermodynamic and kinetic parameters of the intramolecular hydrogen atom transfer in the alkoxyl and peroxyl radicals generated from peroxide **87**.[29]

Reaction	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	k (310 K) /s^{-1}
89 ⟶ **90**	−29.7	23.6	8.36×10^8
90 ⟶ **91**	30.0	49.7	2.32×10^4
91 ⟶ **92**	17.2	43.3	2.79×10^5
94 ⟶ **95**	−53.2	15.5	9.86×10^9
95 ⟶ **96**	45.9	58.1	8.83×10^2
96 ⟶ **97**	−5.5	26.7	1.60×10^3
97 ⟶ **98**	−8.0	25.8	4.48×10^8
98 ⟶ **100**	−220.0	∼0	$\sim 10^{13}$

XII. Oxidized artemisinin as a polyfunctional initiator

Each hydroperoxide group of polyatomic hydroperoxide generated from artemisinin (**1**), in turn, reacts with iron complexes and generates new alkoxyl radicals by the redox reactions

$$Fe^{2+} + ROOH \longrightarrow RO^{\bullet} + Fe^{3+} + HO^{-}.$$

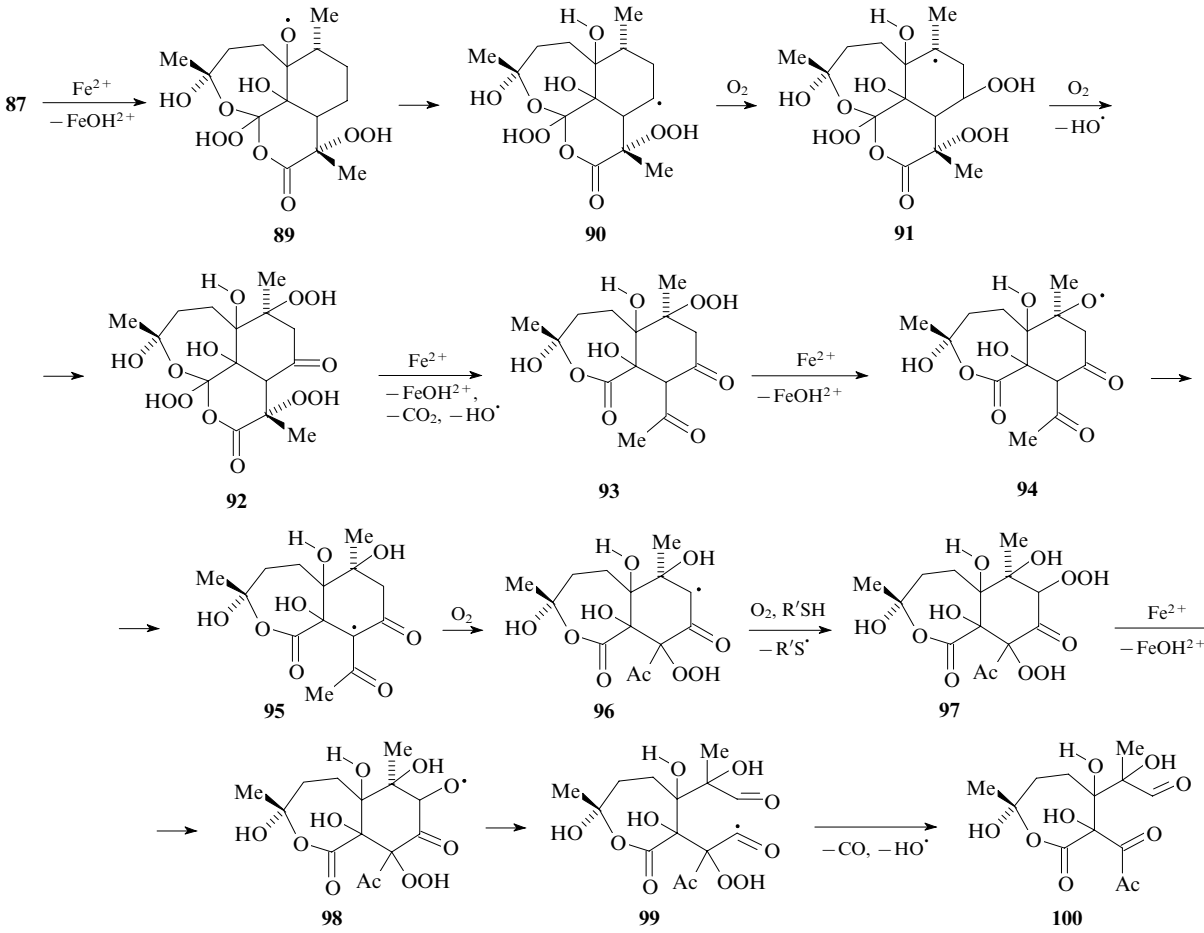
Therefore, the oxidation of artemisinin is followed by cascade radical transformations initiated by the hydroperoxide groups generated from artemisinin. The kinetic scheme of these transformations and the calculations of ΔH, E, and k (310 K) for each step with the use of IPM were described in the study.[29] The oxidative destruction sequence of triatomic hydroperoxide **87**, which is the oxidation product of alkyl radical **46**, is shown below as an example (Scheme 11). In this scheme, only the major (most rapid) pathways of the transformations of the alkoxyl and peroxyl radicals giving intermediates **89**–**100** are presented.

As can be seen from the above example, the cascade successive reactions involving the cleavage of the hydroperoxide groups of compound **87** and the oxidation of the alkyl radicals that formed result in the generation of three hydroxyl radicals and one thiyl radical from one molecule. The oxidative destruction of tetraatomic hydroperoxide **88** affords five free radicals.[29] Table 18 summarizes the thermodynamic and kinetic characteristics of all the steps considered above. The more complete scheme of trans-

Table 17. Thermodynamic and kinetic parameters of the intramolecular hydrogen atom transfer in the peroxyl radicals derived from artemisinin.[28]

Reaction	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	k (310 K)/s^{-1}	Reaction	ΔH /kJ mol^{-1}	E /kJ mol^{-1}	k (310 K)/s^{-1}
Radical **30**				Radical **46**			
30 ⟶ **76**	12.8	42.8	3.38×10^5	**46** ⟶ **79**	19.7	46.2	9.02×10^4
76 ⟶ **83**	3.3	38.4	1.82×10^6	**79** ⟶ **80**	17.7	45.2	1.34×10^5
Radical **31**				**80** ⟶ **87**	−9.8	25.0	3.04×10^3
31 ⟶ **84**	−5.5	21.5	7.89×10^2	**79** ⟶ **81**	20.0	44.7	1.62×10^5
Radical **41**				**81** ⟶ **82**	36.9	54.8	3.14×10^3
41 ⟶ **77**	22.1	45.7	1.09×10^5	**82** ⟶ **88**	1.4	29.6	5.15×10^2
77 ⟶ **85**	17.2	43.3	2.79×10^5				
41 ⟶ **78**	30.0	49.7	2.32×10^4				
78 ⟶ **86**	17.2	43.3	2.79×10^5				

Scheme 11



formations of the hydroperoxides generated from artemisinin was described in the study.[29]

As can be seen from Schemes 10 and 11, the decomposition of the hydroperoxide groups and the transformation of the resulting alkoxyl radicals afford peroxyl radicals as the major intermediates. The chain of transformations can be represented as follows:

$$ROOH \xrightarrow{Fe^{II}} RO^{\bullet} \longrightarrow R^1O_2^{\bullet} \longrightarrow R^1(OOH), \textit{ etc.}$$

The intramolecular chain oxidation reaction of artemisinin with the exposure of the free valence to the bulk can occur in several ways.

1. If C–H bonds accessible to the intramolecular attack are absent in the peroxyl radical generated from compound **1**, the radical reacts with other substrates (R′SH), the reaction with L-cysteine containing the thiol group occurring most rapidly.

$$RO_2^{\bullet} + HSCH_2CH(NH_2)COOH \longrightarrow$$
$$\longrightarrow ROOH + S^{\bullet}CH_2CH(NH_2)COOH.$$

2. If the intramolecular hydrogen atom transfer occurs by the reaction

$$RO_2^{\bullet} + \rangle CH(OOH) \longrightarrow ROOH + \rangle C^{\bullet}(OOH),$$

the resulting hydroperoxyalkyl radical rapidly decomposes to give the carbonyl compound and the hydroxyl radical, and the latter goes into the bulk and reacts with the substrate (R′H):

$$\rangle C^{\bullet}(OOH) \longrightarrow \rangle C{=}O + HO^{\bullet},$$

$$HO^{\bullet} + R'H \longrightarrow H_2O + (R')^{\bullet}.$$

3. If the oxidation of compound **1** affords two hydroperoxide groups in adjacent positions, the decomposition of one of these groups causes the dissociation of the C–C and O–O bonds and the generation of the hydroxyl radical. For example, peroxide **88** generates $HO^{\bullet}$ by the reactions

$$Fe^{2+} + \rangle C(5a)(OOH)C(6)(OOH) \langle \longrightarrow$$
$$\longrightarrow FeOH^{2+} + \rangle C(5a)(O^{\bullet})C(6)(OOH) \langle,$$

$$\rangle C(5a)(O^{\bullet})C(6)(OOH) \langle \longrightarrow \rangle C(5a){=}O + \rangle C(6){=}O + HO^{\bullet}.$$

4. If $RO_2^{\bullet}$ attacks the H atom in the group $\rangle CH(OH)$ by the reaction

$$ROO^{\bullet} + \rangle CH(OH) \longrightarrow ROOH + \rangle C^{\bullet}(OH),$$

the resulting hydroxyalkyl radical binds the O_2 molecule and is transformed into the hydroxyperoxyl radical, and the latter rapidly decomposes to give the carbonyl compound and $HO_2^{\bullet}$:[86,114]

$$\rangle C^{\bullet}(OH) + O_2 \longrightarrow \rangle C(OH)OO^{\bullet},$$

$$\rangle C(OH)OO^{\bullet} \longrightarrow \rangle C{=}O + HO_2^{\bullet}.$$

The simplified scheme of the stepwise oxidative destruction of artemisinin is shown in Scheme 12.

Scheme 12

$$\mathbf{1} + Fe^{2+} \longrightarrow RO^{\bullet}\ [RO(1)^{\bullet}\ \text{or}\ RO(2)^{\bullet}],$$

$$RO^{\bullet} \longrightarrow R^{\bullet},$$

$$R^{\bullet} + O_2 \longrightarrow ROO^{\bullet},$$

$$ROO^{\bullet} \longrightarrow R^{\bullet}(OOH) + nO_2 \longrightarrow \ldots \longrightarrow R(OOH)_nOO^{\bullet},$$

$$R(OOH)_nOO^{\bullet} \longrightarrow R(=O)(OOH)_{n-1} + HO^{\bullet},$$

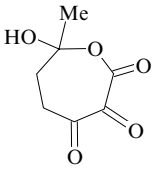
$$R(OOH)_{n-1}(OH)OO^{\bullet} \longrightarrow R(=O)(OOH)_{n-1} + HO_2^{\bullet},$$

$$R(OOH)_{n-1}OO^{\bullet} + R'SH \longrightarrow R(OOH)_n + R'S^{\bullet},$$

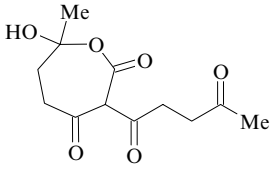
$$R(OOH)_n + Fe^{II} \longrightarrow R(OOH)_{n-1}O^{\bullet} + Fe^{III} + HO^{\bullet},$$

$$R(OOH)_{n-1}O^{\bullet} + R'SH \longrightarrow R(OOH)_{n-1}OH + R'S^{\bullet},\ \textit{etc.}$$

It can be seen that the oxidation of compound **1** followed by the decomposition of the hydroperoxide groups that are formed affords not one but several free radicals. On the average, one starting molecule generates from four to five radicals in the course of the oxidative destruction.[29] The oxidation of artemisinin followed by the decomposition of the hydroperoxide groups that are formed affords the radicals $R'S^{\bullet}$ and $HO_2^{\bullet}$ and the very reactive radical $HO^{\bullet}$. The successive oxidative destruction of artemisinin gives H_2O, CO_2, MeCHO, $AcCH_2CHO$, and compound **100** (seeScheme 11), as well as 7-hydroxy-7-methyl-2,3,4-trioxooxepane (**101**) and 7-hydroxy-7-methyl-2,4-dioxo-3-(1′,4′-dioxopentyl)oxepane (**102**).[29]

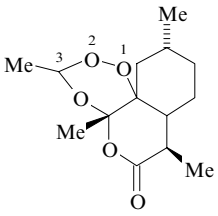


101

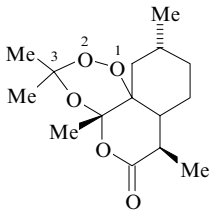


102

The scheme of the oxidative transformations of artemisinin explains why this compound exhibits high antimalarial activity, whereas many synthetic peroxides do not have this activity. Due to the polycyclic structure of compound **1** and the presence of the endoperoxide bridge, the oxidation of this compound results in not one radical reaction but cascade radical reactions in the organism of the Plasmodium malariae characterized by a high concentration of iron complexes. Compounds that do not undergo the intramolecular chain oxidation reaction after the formation of $RO^{\bullet}$ exhibit low (if at all) antimalarial activity. As an example, let us mention the results obtained in the study.[70] Among the analogues of artemisinin synthesized in the cited study, compound **103**, for example, appeared to be inactive,



103

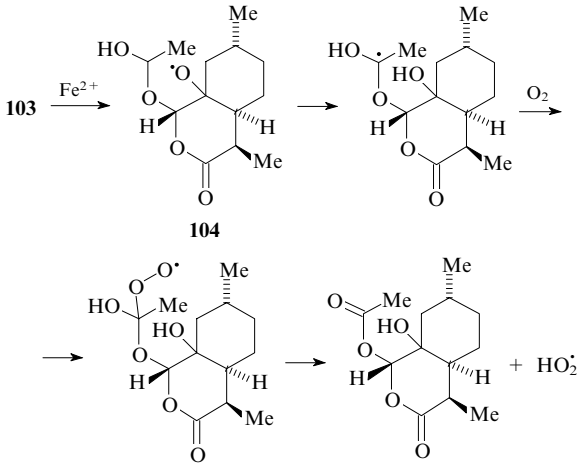


24

whereas compound **24** exhibited the activity similar to that of compound **1** (see Table 3).

The difference in these structures is, at the first glance, insignificant. These compounds differ by one methyl group in position 3. Consequently, the replacement of the H atom by the methyl group results in the appearance of the high antimalarial activity. Whether it is possible to explain this fact in terms of the intramolecular chain oxidation reaction of compounds **24** and **103**? The oxidative destruction sequence for compound **103** is shown in Scheme 13.

Scheme 13



104

$$HO_2^{\bullet} \rightleftharpoons H^+ + O_2^{-\bullet},$$

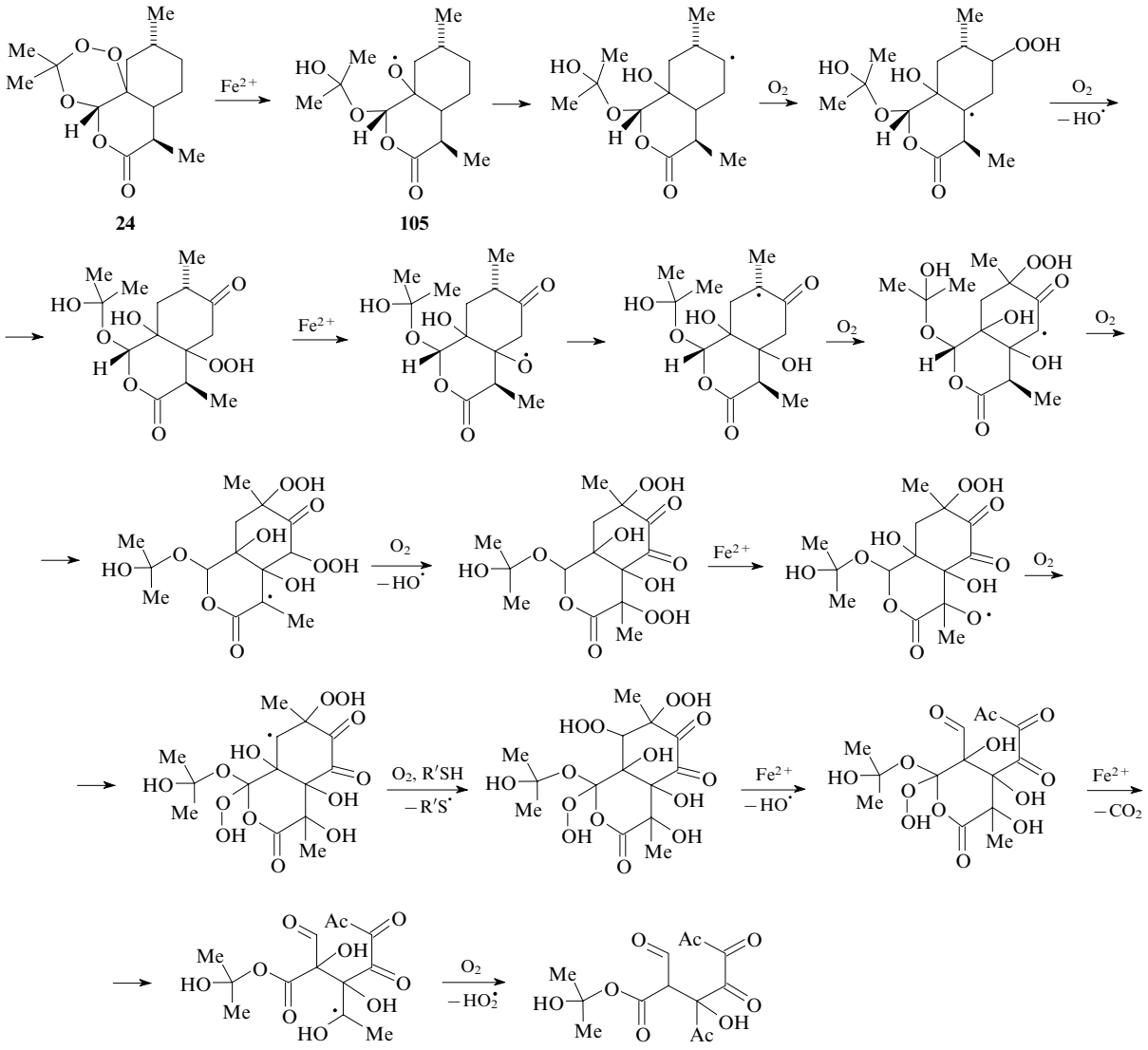
$$O_2^{-\bullet} + Fe^{3+} \longrightarrow O_2 + Fe^{2+}.$$

The redox reaction of **103** with Fe^{II} leads to the cleavage of the peroxide bridge and the formation of radical **104**. This radical contains two bonds accessible to the intramolecular attack. Thus, the weakest C(3)−H bond (D_{C-H} = 381.0 kJ mol^{-1}) is influenced by the adjacent hydroxy group, whereas the C−H bond in the cyclohexane ring is much stronger (D_{C-H} = 408.8 kJ mol^{-1}).[102] Hence, the radical $RO(1)^{\bullet}$ attacks the C(3)−H bond, and the hydroxyalkyl radical that is formed binds the O_2 molecule and is transformed into the α-hydroxyperoxyl radical $>C(OH)OO^{\bullet}$, which rapidly decomposes with the elimination of $HO_2^{\bullet}$.[114] The latter exists as the superoxide ion $O_2^{-\bullet}$ and is rapidly oxidized in the organism of parasites containing many iron complexes. Consequently, the active radicals have no time to be formed during oxidation of compound **103**. The alkoxyl radical containing the free valence at the O(2) atom due to the absence of the H atom in the γ position is forced to react with the substrate R′SH and, as a result, the intramolecular oxidation reaction does not proceed.

The replacement of the H atom in the γ position by the methyl group radically changes the kinetic scheme of the reaction. The oxidation of compound **24** involves the entirely different sequence of transformations (Scheme 14).

It can be seen that in the latter case alkoxyl radical **105** attacks the C−H bond of the cyclohexane ring. This, in turn, leads to cascade oxidative transformations with the successive formation of three very active hydroxyl radicals and the thiyl radical, which accounts for the high therapeutic activity of compound **24**. Therefore, the kinetic model of the intramolecular chain reaction of artemisinin provides insight into the relationship between the structure of the

Scheme 14



compound containing the peroxide group and its antimalarial activity. This approach can be used for the prediction of the most active structures having this activity.

XIII. Biochemical action of radicals derived from artemisinin

The reactions of radicals generated from compound **1** with biomolecules are extensively studied and discussed in the literature (see, for example, Ref. 5). After the oral administration to patients, artemisinin is rapidly absorbed into the blood, and its concentration in the blood reaches the peak value within one hour [115] or 1.8 h.[116] The half-life of artemisinin in the organism varies from 1.9 to 2.6 h. The half-life of artesunate **15c** in patients is much smaller (45 min).[117]

Evidently, the consequences of the reactions of artemisinin radicals with malaria parasite DNA are of great importance. In this respect, the specificity of the habital of the Plasmodium malariae plays an important role. Thus, in the human organism and organisms of warm-blooded animals the Plasmodium is concentrated in erythrocytes, where DNA is absent.[5] Hence, it is Plasmodium DNA that is subjected to the destructive action of the radicals. It was shown that compound **1** causes the DNA cleavage in the presence of Fe^{2+} ions in an $MeCN-H_2O$ mixture (1 : 1).[100, 101] The presence of cysteine or glutathione (R′SH) protects DNA from the radical destruction due to the reaction

$$R^{\bullet} + R'SH \longrightarrow RH + R'S^{\bullet}$$

in the absence of oxygen (see Ref. 5, p. 234) and due to the reaction

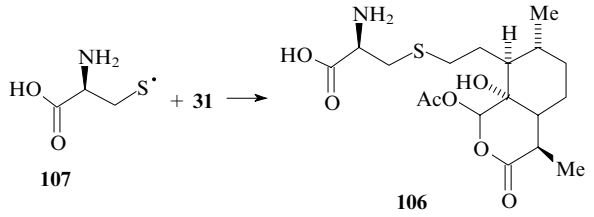
$$RO_2^{\bullet} + R'SH \longrightarrow ROOH + R'S^{\bullet}$$

in the presence of oxygen.

A series of studies by Meshnick and co-workers [118–120] provided evidence that artemisinin alkylates proteins in the presence of iron complexes under aerobic conditions, which also leads to the death of the Plasmodium malariae. More recently, it was shown that this leads also to the destruction of hemoglobin.[121, 122] Since the Plasmodium malariae has the limited ability to synthesize amino acids, the hemoglobin proteolysis is of considerable importance. Cysteine protease plays a key role in the hemoglobin proteolysis,[123] and its inactivation by the radicals derived from compound **1** kills the parasites. In addition, the reducing agent gluta-

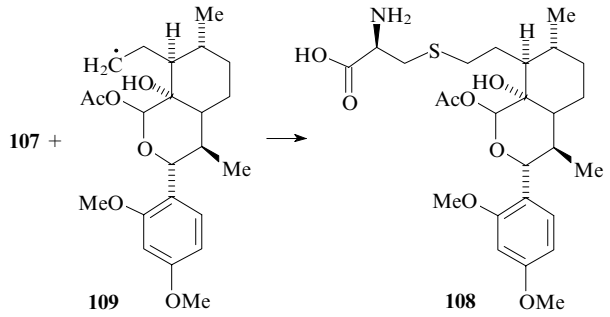
thione is vital to the parasite. The blockage of the action of glutathione reductase in cells of the parasite leads to its death.[124]

The study of the reactions of artemisinin with Fe^{2+} salts in the presence of cysteine showed that these reactions afford compound **106** as a result of the addition of alkyl radical **31** to the thiyl radical of cysteine (**107**).[91]



107 106

Related compound **108** was obtained by the reaction of radical **109** generated from phenyl derivative **39** with cysteine in the presence of Fe^{2+} (Ref. 5).



The reaction of glutathione with the **1**–Fe^{2+} system also gave a structurally similar product.[91] Evidently, a decrease in the concentration of glutathione in the organism of the parasite assists its death.

Hemin iron complexes are vital to the Plasmodium malariae. These complexes attack radicals generated from compound **1**. The formation of adducts of the radical derived from artemisinin **1** with the heme, in particular, mono- and dialkylated derivatives of the hemoglobin heme, were detected by mass spectrometry.[98,125] In the study of the reaction of manganese(II) tetraphenylporphyrin with radical **31** in dichloroethane,[11] it was shown that the manganese heme can be alkylated by the artemisinin radical. The addition product of the latter to porphyrin was identified. Apparently, the reaction occurs through the cleavage of the peroxide bridge in artemisinin followed by the decyclization of the alkoxyl radical and the addition of the C-centred radical to porphyrin. Therefore, compound **1** has a complex effect on the Plasmodium malariae. Thus, the radicals derived from compound **1** react with DNA, iron complexes, and proteins of the parasite.

XIV. Conclusions

Artemisinin is a unique drug having the high antimalarial activity. Nowadays, it is obvious that this action is a result of a combination of the factors associated, on the one hand, with the structure of artemisinin, and on the other hand, with the characteristic features of the vital activity of the malaria parasite.

The Plasmodium malariae is characterized by a very high concentration of enzymes containing iron complexes. In the cells of the Plasmodium, the concentration of iron complexes is two orders of magnitude higher than that in the human organism because the Plasmodium digests hemoglobin from erythrocytes. Radicals are generated predominantly in cells of the Plasmodium malariae by the reaction of the peroxide bridge of artemisinin with Fe^{II} complexes. However, the formation of the alkoxyl radical by this reaction is only the first event followed by the intramolecular chain oxidation reaction of compound **1** resulting in its transformation into a polyfunctional initiator containing several hydroperoxide groups. The decomposition of these groups in the presence of Fe^{II} leads to the additional cascade of oxidative transformations and the generation of new radicals. Therefore, in the presence of atmospheric oxygen and Fe^{2+} ions, artemisinin acts as a self-propagating radical initiator generating not one but several radicals. The groups $\geqslant$CH and $>CH_2$ in compound **1** are potential sites of the formation of new hydroperoxide groups and the radicals generated from these groups.

The groups $>CH_2$ in artemisinin play an important role. The oxidation of these groups affords secondary hydroperoxide groups, which generate highly reactive hydroxyl radicals:

$$RO_2^{\bullet} + >CH(OOH) \longrightarrow ROOH + >C^{\bullet}(OOH),$$

$$>C^{\bullet}(OOH) \longrightarrow >C{=}O + HO^{\bullet}.$$

Hydroperoxide groups in adjacent positions serve as another source of hydroxyl radicals. The decomposition of one of these groups results in the C–C bond cleavage and the decomposition of the adjacent OOH group to form hydroxyl radicals:

$$Fe^{2+} + >C(OOH)C(OOH)< \longrightarrow$$

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

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

The hydroxyl radicals attack DNA and chelate rings of the enzymes (Plasmodium malariae DNA), resulting in the parasite death.

The construction of the quantitative kinetic scheme of radical transformations of compound **1** and its analogues opens the possibility to develop the kinetic method for the preliminary estimation of the initiating ability of drugs containing the peroxide group. This method may be useful for the prediction of the antimalarial activity of synthetic peroxides.

Apparently, the lactone group –O–C(O)– in the artemisinin molecule also plays an important role, which deserves investigation. Artemisinin is dissolved mainly in the lipid phase. The hydrolysis of the lactone group leads to the transformation of compound **1** into acid, which goes to the parasite plasma, where it acts as the radical initiator. Evidently, the above data require the additional experimental validation and improvement, which should open a new approach to the synthesis and investigation of effective antimalarial drugs.

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