Competition between mono- and bimolecular reactions of artemisinin alkoxyl radicals

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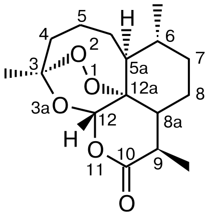
The competition between intramolecular and bimolecular reactions of alkoxyl radicals formed from artemisinin was theoretically analyzed. The enthalpies of these reactions were calculated. The activation energies and rate constants of reactions of intramolecular hydrogen atom transfer, decyclization, and decomposition of alkoxyl radicals of artemisinin and several its derivatives, as well as the activation energies and rate constants of reactions of these radicals with the C—H, S—H, and O—H bonds in biological substrates and their analogs were calculated by the intersecting parabolas method The fastest reactions of artemisinin alkoxyl radicals were identified. The full kinetic scheme of transformation of these radicals was proposed. Artemisinin radicals with the free valence on the carbon atom are predominantly formed due to the transformation of the artemisininoxyl radicals.

Key words: alkoxyl radical, artemisinin, bimolecular hydrogen atom abstraction, intramolecular hydrogen atom transfer, competitive reactions, rate constant, radical decyclization, intersecting parabolas method, activation energy, reaction enthalpy.

Presently, artemisinin (**1**) is the most efficient medicine against malaria.[1—4] Artemisinin is sesquiterpene with the peroxide bridge.



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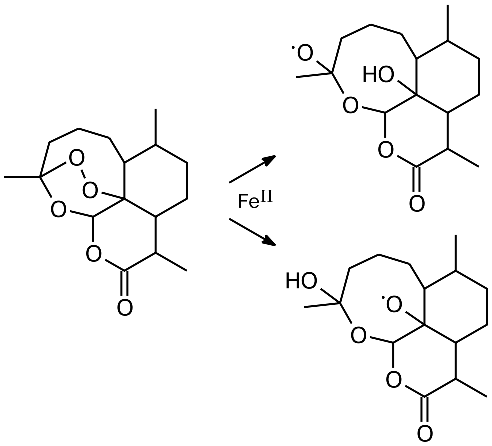
The peroxide group has been experimentally shown[5] to be crucial in the therapeutic effect of artemisinin: the curative effect disappears when this group is removed. It was also proved that artemisinin generates free radicals in a parasite organism resulting in its death. Free radicals are formed by the reduction of the peroxide bridge with the bivalent iron chelate (Scheme 1).

Scheme 1



The alkoxyl radicals that formed are assumed[4] to react with C—H bonds of lipids, and the resulting alkyl radicals add to the chelate ring of iron-containing enzymes and deactivate them.

The radical mechanism of the artemisinin effect was simulated[6—8] using quantum chemical calculations, which showed a possibility of intramolecular transformations of the artemisinin alkoxyl radicals with the H atom transfer and C—C bond cleavage.

Recent analysis[9] of intramolecular reactions of radicals formed from artemisinin showed that these reactions are rather diverse and some of them occur rapidly. Complete analysis of both intramolecular and bimolecular reactions of the artemisinin alkoxyl radicals proceeding in a body is necessary for the construction of the detailed kinetic scheme of reactions of radicals formed from artemisinin. In the present work we attempted to solve this problem. Artemisinin (see Scheme 1) and its therapeutically active derivatives **2—4** [1] were used in this study.

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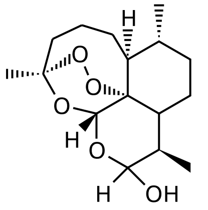

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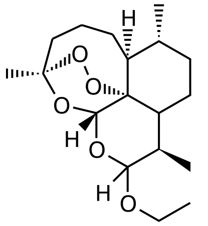

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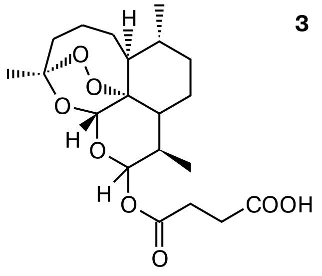

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The intramolecular transformations of two alkoxyl radicals (see Scheme 1) formed from artemisinin (**1**) and its derivatives (**2—4**) were considered.

In addition to the isomerization reactions, bimolecular reactions of these radicals with substrates HY are considered.

$$RO^{\cdot} + HY \longrightarrow ROH + Y^{\cdot}$$

We chose the following compounds as reactants HY: *cis*-methyl oleate (D_{C-H} = 344.0 kJ mol^{-1})[10], *cis—cis*-methyl linoleate (D_{C-H} = 318.0 kJ mol^{-1})[10], glycerol (D_{C-H} = 387.7 kJ mol^{-1})[10], glucose (D_{C-H} = 371.4 kJ mol^{-1})[11], D-ribose (D_{C-H} = 370.0 kJ mol^{-1})[11], L-cysteine (D_{S-H} = 360.0 kJ mol^{-1})[12], α-tocopherol (D_{O-H} = 330.0 kJ mol^{-1}),[13] and ubiquinol (D_{O-H} = 343.8 kJ mol^{-1})[13].

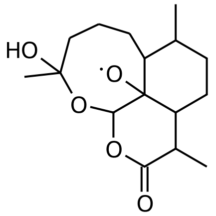
To calculate the activation energies and rate constants of bimolecular reactions, we used the equations and parameters of the intersecting parabolas model (IPM) as applied to both bimolecular[11,13—15] and intramolecular radical reactions.[16—18]

Calculation procedure

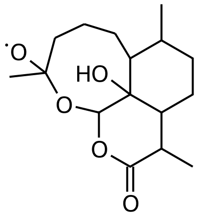
Enthalpy of bimolecular reactions and intramolecular hydrogen transfer reactions. The enthalpy of intramolecular hydrogen transfer in cyclic alkoxy radicals was calculated as the difference of dissociation energies of the initial attacked (D_i) and formed (D_f) bonds

$$\Delta H = D_i - D_f \tag{1}$$

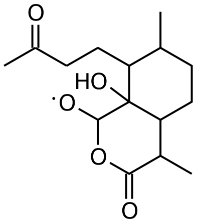
The dissociation energies of the C—H bonds of molecules of artemisinin and its derivatives taken the same as in analogous molecules are presented in Table 1. The dissociation energy of the formed O—H bond (D_{O-H}) for all the three considered artemisinin radicals shown below was accepted equal to 438.5 kJ mol^{-1} as in cyclohexanol.[19]



$R^1O^{\cdot}$



$R^2O^{\cdot}$

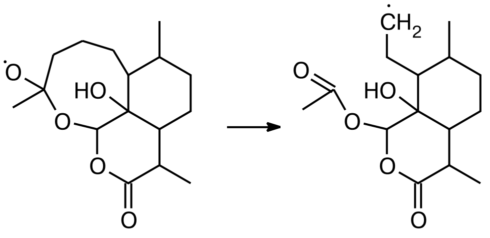


$R^3O^{\cdot}$

The average error in estimation of the dissociation energies of the C—H and O—H bonds is ±2 kJ mol^{-1} (see Ref. 10). The calculations are valid for the reactions in nonpolar solvents. The obtained ΔH values are given in Table 1. The enthalpies of bimolecular reactions of H atom abstraction by the artemisinin alkoxyl radicals were calculated similarly.

Enthalpy of decyclization reactions of the radicals. The enthalpy of decyclization reactions of artemisinin alkoxyl radicals was calculated by the Benson increment method[20]; the increments of the corresponding groups and ring strain energies were borrowed from the reference book.[21] The dissociation energies of the C—H bonds from the review[10] were used to calculate the enthalpies of groups containing the free valence. The average error in calculation of the reaction enthalpy is ±5 kJ mol^{-1}. The calculation of ΔH by the increment method was performed as follows. The [C—(O)(O$^{\cdot}$)(C)$_2$] and [C—(H)$_2$(C)$_2$] groups disappear and the [CO—(O)(C)] and [C$^{\cdot}$—(C)(H)$_2$] groups are formed in the decyclization reaction (Scheme 2). In addition, the seven-membered ring is opened, and its strain energy $E_{rsc}(C_7)$ disappears.

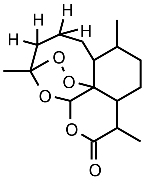
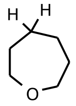
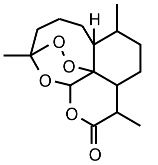
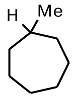
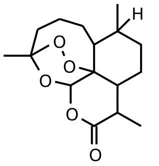
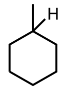
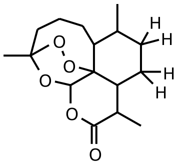
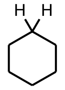
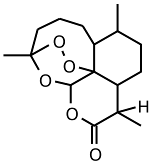
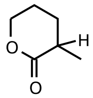
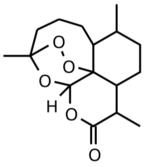
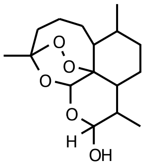
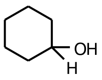
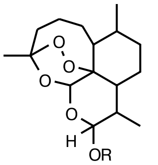
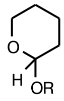
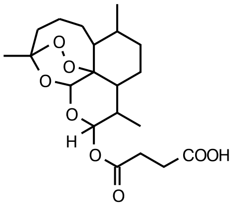
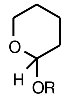
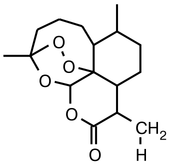
Scheme 2



As a result, the reaction enthalpy ΔH is the following:

$$\Delta H = \Delta H[\mathrm{CO{-}(O)(C)}] + \Delta H[\mathrm{C^{\cdot}{-}(C)(H)_2}] - \Delta H[\mathrm{C{-}(O)_2(C)_2}] - \Delta H[\mathrm{O^{\cdot}{-}(C)}] - \Delta H[\mathrm{C{-}(H)_2(C)_2}] - E_{rsc}(C_7). \tag{2}$$

Table 1. Dissociation energies of individual bonds in artemisinin and its derivatives and the enthalpies of intramolecular reactions that occur with H atom abstraction by the alkoxyl radicals of artemisinin

Compound	Analogous molecule	D_{C-H}	ΔH	Reference
		kJ mol^{-1}		
		403.9	−34.6	10
		390.0	−48.5	10
		395.5	−43.0	10
		408.8	−29.7	10, 11
		385.3	−53.2	11
	$(n\text{-}C_4H_9O)_2CHMe$	378.3	−60.2	10
		388.4	−50.1	10, 11
		386.0	−52.5	10
		386.0	−52.5	10
	R—CH$_2$—H	422.0	−16.5	11

The $\Delta H[C^{\bullet}-(C)(H)_2]$ increment is calculated from the $\Delta H[C-(C)(H)_3]$ increment:

$$\Delta H[C^{\bullet}-(C)(H)_2] =$$

$$= \Delta H[C-(C)(H)_3] + D_{C-H} - \Delta H[H^{\bullet}] =$$

$$= -42.26 + 422 - 218 = 161.74 \text{ kJ mol}^{-1}.$$

The $\Delta H[O^{\bullet}-(C)]$ increment is calculated from the $\Delta H[O-(C)(H)]$ increment:

$$\Delta H[O^{\bullet}-(C)] =$$

$$= \Delta H[O-(C)(H)] + D_{O-H} - \Delta H[H^{\bullet}] =$$

$$= -159.33 + 438.5 - 218 = 61.17 \text{ kJ mol}^{-1}.$$

The following value is obtained for the reaction enthalpy:

$$\Delta H = -137.24 + 161.74 + 53.56 - 61.17 + 20.63 - 26.34 =$$

$$= 11.18 \text{ kJ mol}^{-1}.$$

Equations of the intersecting parabolas method. In the framework of this method[13–15] the reaction of abstraction, for instance,

$$RO^{\cdot} + R_iH \longrightarrow ROH + R_i^{\cdot},$$

is considered as the result of intersection of two potential curves, one of which characterizes the stretching vibration of the attacked C—H bond and another curve characterizes the stretching vibration of the formed O—H bond in the reaction product. The stretching vibrations of the hydrogen atom in ROH and R_iH are considered harmonic. The reaction is characterized by the following parameters[15]: (1) classical enthalpy ΔH_e that includes the difference between the zero-point energies of the attacked and formed bonds ($\Delta H_e = D_i - D_f + 0.5hN_A(\nu_i - \nu_f)$), where D_i and D_f are the dissociation energies of the initial attacked (i) and formed (f) bonds, ν_i and ν_f are the frequencies of stretching vibrations of these bonds in s^{-1}, and h and N_A are the Planck constant and Avogadro's number, respectively; (2) classical potential barrier E_e related to the experimentally determined Arrhenius activation energy E by the equation

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

(3) coefficients b_i and b_f describing the dependence of the potential energy on the amplitude of atomic vibrations along the valence bond (parameter $b = \pi\nu(2\mu)^{1/2}$, where μ is the reduced mass of the atoms forming the bond, and ν is the frequency of the stretching vibration of the bond); (4) parameter r_e characterizing the total extension of two reacting bonds in the transition state.

In the IPM method these parameter are related as follows[15]:

$$br_e = \alpha(E_e - \Delta H_e)^{1/2} + E_e^{1/2}, \tag{4}$$

where $b = b_i$, *i.e.*, concerns the attacked bond in the molecule, and the coefficient $\alpha = b_i/b_f$. The reactions that belong to one class are characterized by the parameter br_e = const. The thermally neutral reaction belonging to this class ($\Delta H_{e0} = 0$) occurs[15] with the classical potential barrier equal to

$$\sqrt{E_{e0}} = \frac{br_e}{1+\alpha}. \tag{5}$$

This method well describes intramolecular reactions of hydrogen atom transfer[17] and decyclization of cyclic free radicals.[18] The values of α, br_e, and other parameters for these reactions are given in Table 2. Among possible reactions of intramolecular hydrogen transfer we took into account only the reactions that proceeded through the six-membered transition state. For these reactions the energy E_{e0} is minimum.[17]

The br_e parameter for decyclization of cycloalkoxyl radicals was obtained by analysis of the experimental rate constants of decyclization of the *cyclo*-$[(CH_2)_nCHO^\bullet]$ radicals, where n = 4, 5. The initial data and calculation results are presented below. The decyclization of the cyclopentyloxyl radical occurs with the rate constant $k(298\ K) = 3.02 \cdot 10^7\ s^{-1}$ (see Ref. 11) and $\Delta H = 29.8\ kJ\ mol^{-1}$, from which for this reaction we find the parameter $br_e = 10.60\ (kJ\ mol^{-1})^{1/2}$. The decyclization of the cyclohexyloxyl radical occurs with the rate constant $k(353\ K) = 1.10 \cdot 10^7\ s^{-1}$ (see Ref. 11) and $\Delta H = 36.5\ kJ\ mol^{-1}$, from which we find $br_e = 9.44\ (kJ\ mol^{-1})^{1/2}$. The br_e parameter is affected by the ring strain energy E_{rsc}; for cyclopentane $E_{rsc} = 26.75\ kJ\ mol^{-1}$, and for cyclohexane $E_{rsc} = 0.68\ kJ\ mol^{-1}$.[21] Assuming that the dependence of br_e on E_{rsc} is linear, we obtain the following empirical formula for br_e $(kJ\ mol^{-1})^{1/2}$:

$$br_e = 9.41 + 4.50 \cdot 10^{-2} E_{rsc}. \tag{6}$$

For the cycloheptane ring $E_{rsc} = 26.34\ kJ\ mol^{-1}$ (see Ref. 21) and, hence, for the decyclization of the artemisinin alkoxyl radicals $br_e = 10.60\ (kJ\ mol^{-1})^{1/2}$. The br_e parameters for other reactions were borrowed from Refs 15 and 16 (see Table 2).

The activation energies of the reactions considered were calculated by the equation[15]

$$\sqrt{E_e} = \frac{br_e}{1-\alpha^2}\left[1 - \alpha\sqrt{1 - \frac{1-\alpha^2}{(br_e)^2}\Delta H_e}\right]. \tag{7}$$

The pre-exponential factor of the intramolecular hydrogen transfer reaction depends on the number of the attacked C—H bonds n_{C-H} (for example, $n_{C-H} = 2$ for the CH_2 group, *etc.*). Therefore, the reaction rate constant was calculated by the equation

$$k = n_{C-H} \cdot A_0 \exp(-E/RT) = A\exp(-E/RT). \tag{8}$$

The A factor depends on the number of the CH_2 or CH groups that lose the ability of free rotation in the cyclic transition state. The empirical dependence of $\log A$ on m takes the following form (m is the number of fragments losing the ability to rotation in the transition state)[17]:

$$\log A = 13.30 - 0.60 \cdot m. \tag{9}$$

Geometric parameters of the transition state of bimolecular reactions. A method for calculation of interatomic distances in the transition state from the activation energy and reaction enthalpy values was developed[22,23] for bimolecular radical reactions. The method is based on a combination of the quantum chemical calculation and IPM formulas. The C...H and O...H interatomic distances in the transition state of the reaction $RO^\bullet + RH$ are calculated for each individual reaction from its activation energy and enthalpy using the formulas[22,23]

$$r^{\#}(C...H) = r(C-H) + \beta b^{-1}\sqrt{E_e}, \tag{10}$$

$$r^{\#}(O...H) = r(O-H) + \alpha\beta b^{-1}\sqrt{E_e - \Delta H_e}, \tag{11}$$

where r(C—H) and r(O—H) are the interatomic distances in RH and ROH, $r^{\#}$(C...H) and $r^{\#}$(O...H) are the interatomic distances in the transition state, and β is the proportionality coefficient between the bond elongations calculated by the quantum chemical and IPM methods. The values of bond lengths[24] and β coefficients[22,23] used in the present work are given below.

Table 2. Kinetic parameters br_e, $0.5hN_A\nu_i$, $\log A_{C-H}$, and E_{e0} for the considered reaction classes[15,16]

Reaction class	α	br_e /(kJ mol^{-1})$^{1/2}$	$0.5hN_A\nu_i$ /kJ mol^{-1}	$\log A_{C-H}$ /s^{-1}	E_{e0} /kJ mol^{-1}
$RO^\bullet + R^1H$	0.796	12.73	17.4	9.0	50.2
$RO^\bullet + R^2H$	0.796	13.96	17.4	8.0	60.4
$RO^\bullet + RSH$	0.707	11.67	15.1	9.0	46.7
$RO^\bullet + ArOH$	0.992	14.16	21.5	9.0	50.5
cyclo-$RO^\bullet \rightarrow R_f^\bullet$	0.796	13.13	17.4	12.6	53.4
cyclo-$RO^\bullet$ → decyclization	0.748	10.60	8.2	13.0	26.2
$R^1R^2CO^\bullet \rightarrow R^{1\bullet} + R^2C(O)$	0.748	13.37	8.2	14.54	58.5

R^1H and R^2H are aliphatic and unsaturated compounds, respectively.

Bond	C—H	O—H	S—H
Bond length ($\times 10^{10}$/m)	1.096	0.970	1.345
β	1.44	1.49	1.63

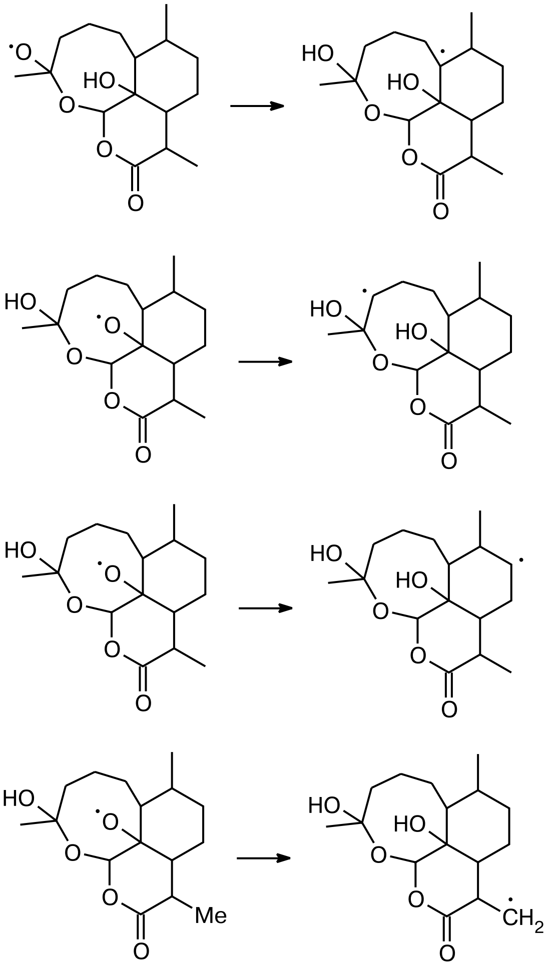
Results and Discussion

The reactions of intramolecular H atom transfer in the alkoxyl radicals of artemisinin and its derivatives are shown in Scheme 3, and the results of calculation of the activation energies and rate constants are given in Table 3.

As can be seen from the data in Table 3, intramolecular hydrogen transfer in alkoxyl radicals is an exothermic reaction that occurs very rapidly (k(310 K) $\approx$ $8.6 \cdot 10^{10}$—$1.3 \cdot 10^{9}$ s^{-1}). It occurs more rapidly in the $R_2O^{\bullet}$ alkoxyl radicals formed from artemisinin alkoxy derivatives **3** and **4** (see Scheme 3, reactions (8) and (9), k(310 K) = $2.5 \cdot 10^{10}$ s^{-1}).

The reactions of decyclization of the alkoxyl radicals are shown in Scheme 4, and their kinetic characteristics are presented in Table 4.

Scheme 3

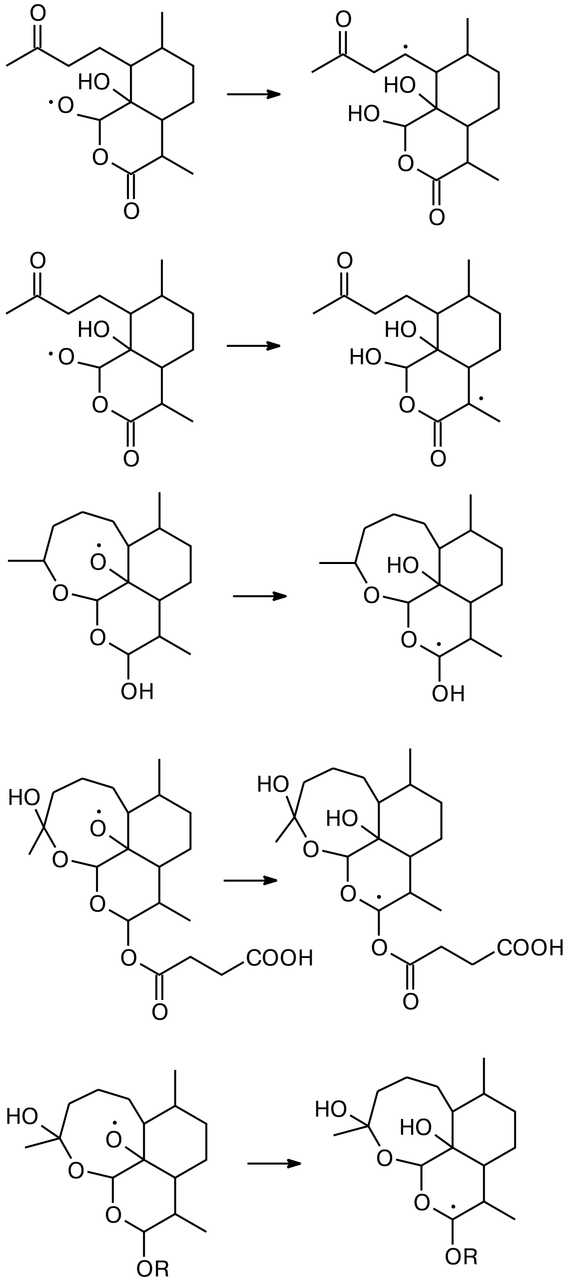


(1)

(2)

(3)

(4)



(5)

(6)

(7)

(8)

(9)

It is seen that in the $R_1O^{\bullet}$ radical the C(3)—O(3a) bond cleavage is the fastest (see the structure of compound **1**) to form alkoxyl radical $R_3O^{\bullet}$ (see Scheme 4, reaction (11), Table 4, k(310 K) = $1.4 \cdot 10^{8}$ s^{-1}). The decomposition of $R_1O^{\bullet}$ occurs very slowly to form the methyl radical (reaction (12), k(310 K) = $5.6 \cdot 10^{3}$ s^{-1}). All the three decyclization reactions of the $R_2O^{\bullet}$ radical occur with close rates (reactions (13)—(15), k(310 K) $\approx$ $(4.6$—$6.0) \cdot 10^{10}$ s^{-1}). The $R_3O^{\bullet}$ radical undergoes the fastest decyclization with the C(12)—C(12a) bond cleavage (see Scheme 4, reaction (16); k(310 K) = $1.0 \cdot 10^{9}$ s^{-1}). The results obtained in the present work agree satisfactorily with the data of quantum chemical calculations. For

Table 3. Enthalpies, activation energies, and rate constants of intramolecular H atom transfer reactions in alkoxyl radicals of artemisinin (see Scheme 3)

Reaction	ΔH	E	log$A$	n*	k(310 K) /s^{-1}
	kJ mol^{-1}				
(1)	−43.0	18.8	12.6	1	$2.59 \cdot 10^{9}$
(2)	−34.6	21.8	12.6	2	$1.67 \cdot 10^{9}$
(3)	−29.7	23.6	12.6	2	$8.36 \cdot 10^{8}$
(4)	−16.5	28.6	11.4	3	$1.14 \cdot 10^{7}$
(5)	−26.5	24.8	12.0	2	$1.34 \cdot 10^{8}$
(6)	−53.2	15.5	12.6	1	$9.85 \cdot 10^{9}$
(7)	−50.1	16.5	12.6	2	$1.34 \cdot 10^{10}$
(8)	−60.7	13.1	12.6	1	$2.47 \cdot 10^{10}$
(9)	−60.7	13.1	12.6	1	$2.47 \cdot 10^{10}$

* n is the number of attacked C—H bonds.

Table 4. Enthalpies, activation energies, and reaction rate constants of decyclization of alkoxyl radicals of artemisinin (see Scheme 4)

Reaction	ΔH	E	log$A$	k(310 K) /s^{-1}
	kJ mol^{-1}			
(10)	11.2	33.9	13.0	$1.93 \cdot 10^{7}$
(11)	−4.0	28.8	13.0	$1.39 \cdot 10^{8}$
(12)	29.3	64.0	14.54	$5.61 \cdot 10^{3}$
(13)	−43.7	13.5	13.0	$5.33 \cdot 10^{10}$
(14)	−42.4	13.9	13.0	$4.59 \cdot 10^{10}$
(15)	−21.8	13.2	13.0	$6.04 \cdot 10^{10}$
(16)	5.5	23.7	13.0	$1.01 \cdot 10^{9}$
(17)	20.2	30.7	13.0	$6.72 \cdot 10^{7}$
(18)	17.9	29.6	13.0	$1.03 \cdot 10^{8}$
(19)	−52.5	4.4	13.0	$1.78 \cdot 10^{12}$
(20)	−52.5	4.4	13.0	$1.78 \cdot 10^{12}$

instance, for the activation energy of reaction (2) (see Scheme 3) $E = 21.8$ kJ mol^{-1} in obtained in our work, in Ref. 6 $E = 27.5$ kJ mol^{-1}, and in Ref. 7 $E = 30.2$ kJ mol^{-1}; for reaction (10) (see Scheme 4) $E = 33.9$ kJ mol^{-1} was obtained in the present work, in Ref. 6 $E = 35.2$ kJ mol^{-1}, in Ref. 7 $E = 35.9$ kJ mol^{-1} (the error in estimation of E by the intersecting parabolas method is ±2 kJ mol^{-1}, and in the quantum chemical calculation it is higher than ±10 kJ mol^{-1}).

Table 5 presents the calculated values of ΔH, E, k, and specific rate $k[\mathrm{R_iH}]$ for the reactions of three alkoxyl radicals (they possess equal reactivity) with several substrates.

The alkoxyl radicals react most rapidly with the C—H bonds of unsaturated acids containing two double bonds and with the C—H bonds of the aldehyde groups of glucose and D-ribose. Comparison of the rate constants of intramolecular hydrogen transfer in the alkoxy radicals and specific rates of their reactions with the substrates shows that the former reactions occur much more rapidly (Scheme 6).

Scheme 4

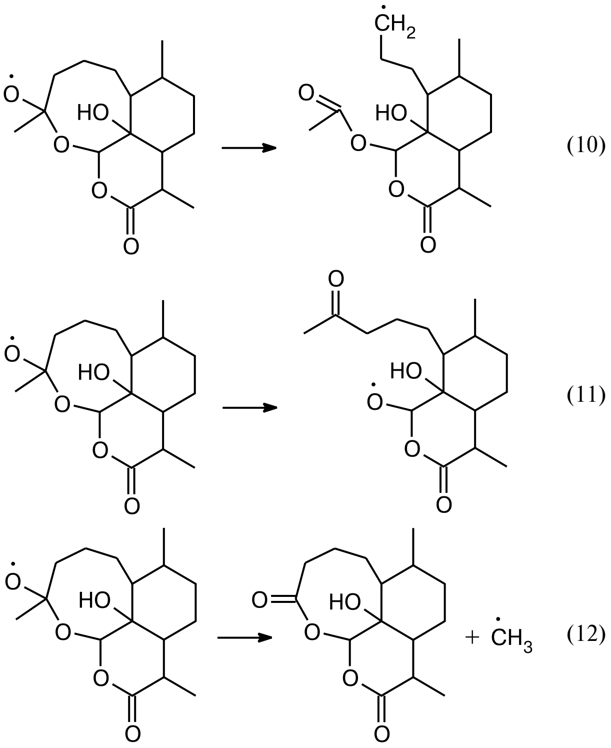
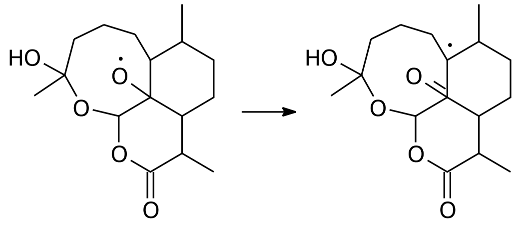


Table 5. Enthalpies, activation energies, and rate constants of bimolecular reactions of alkoxyl radicals of artemisinin ($\mathrm{R^1O^{\bullet}}$, $\mathrm{R^2O^{\bullet}}$, $\mathrm{R^3O^{\bullet}}$) with substrates HY

Substrate (HY)	E, /kJ mol^{-1}	k (310 K) /L (mol)$^{-1}$	[R$_i$H] /mol L^{-1}	k[R$_i$H] /s^{-1}	r(Y...H)$\cdot 10^{10}$	r(X...H)$\cdot 10^{10}$
					m	
Z-$C_7H_{15}CH_2{=}CH(CH_2)_7CO_2Me$	9.7	$9.44 \cdot 10^{6}$	2.95	$2.78 \cdot 10^{7}$	1.291	1.313
$C_5H_{11}CH{=}CHCH_2CH{=}CHC_7H_{14}CO_2Me$	3.3	$5.58 \cdot 10^{7}$	3.02	$1.68 \cdot 10^{8}$	1.265	1.339
$CH_2OHCHOHCH_2OH$	13.2	$5.87 \cdot 10^{6}$	13.69	$8.04 \cdot 10^{7}$	1.332	1.264
$C_6H_{12}O_6$	8.3	$3.99 \cdot 10^{7}$	8.57	$3.42 \cdot 10^{8}$	1.314	1.281
D-$C_5H_{10}O_5$	7.9	$4.65 \cdot 10^{7}$	8.57	$3.98 \cdot 10^{8}$	1.277	1.269
$HSCH_2CH(NH_2)COOH$	5.8	$1.03 \cdot 10^{8}$	0.50	$5.15 \cdot 10^{7}$	1.556	1.325
α-Tocopherol	1.8	$4.93 \cdot 10^{8}$	0.01	$4.93 \cdot 10^{6}$	1.075	1.317
Ubiquinol	2.0	$9.44 \cdot 10^{8}$	0.01	$9.44 \cdot 10^{6}$	1.091	1.301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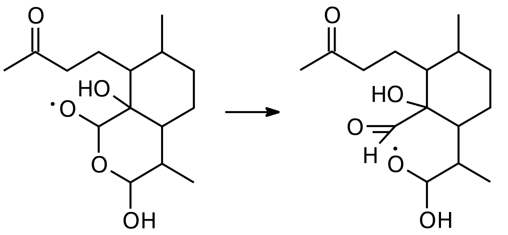
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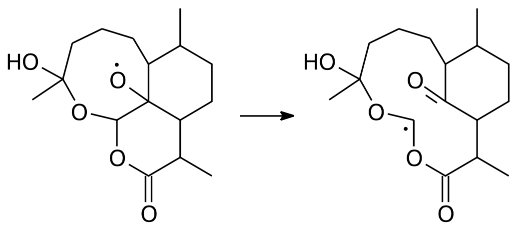
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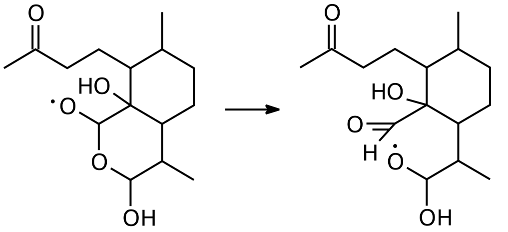
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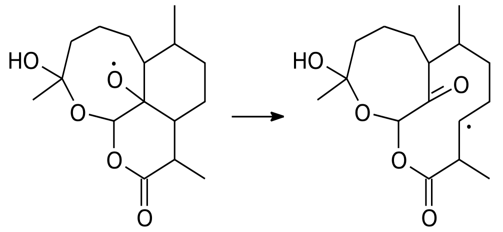
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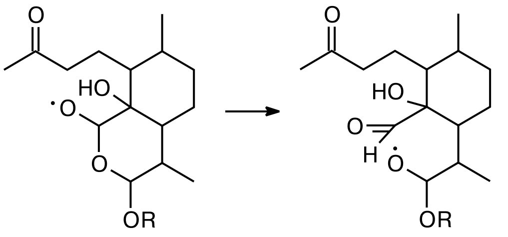
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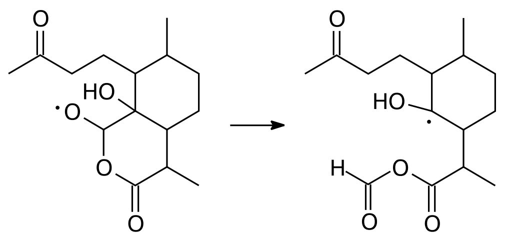
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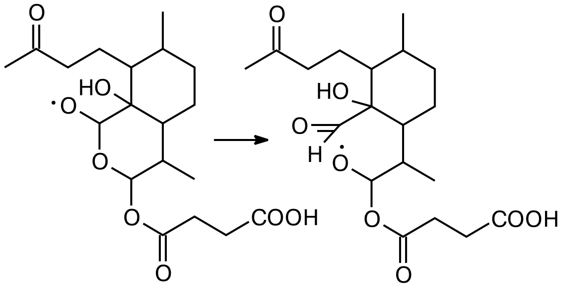
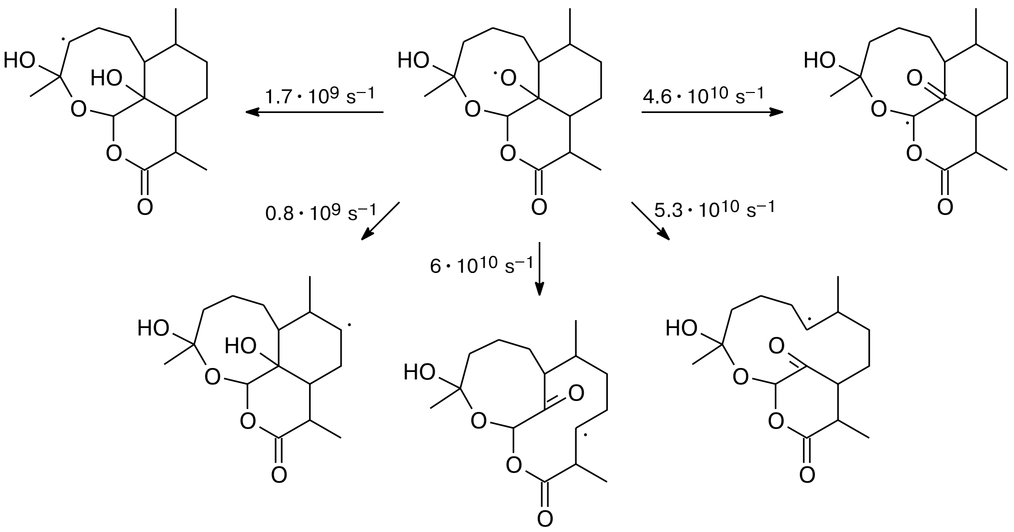
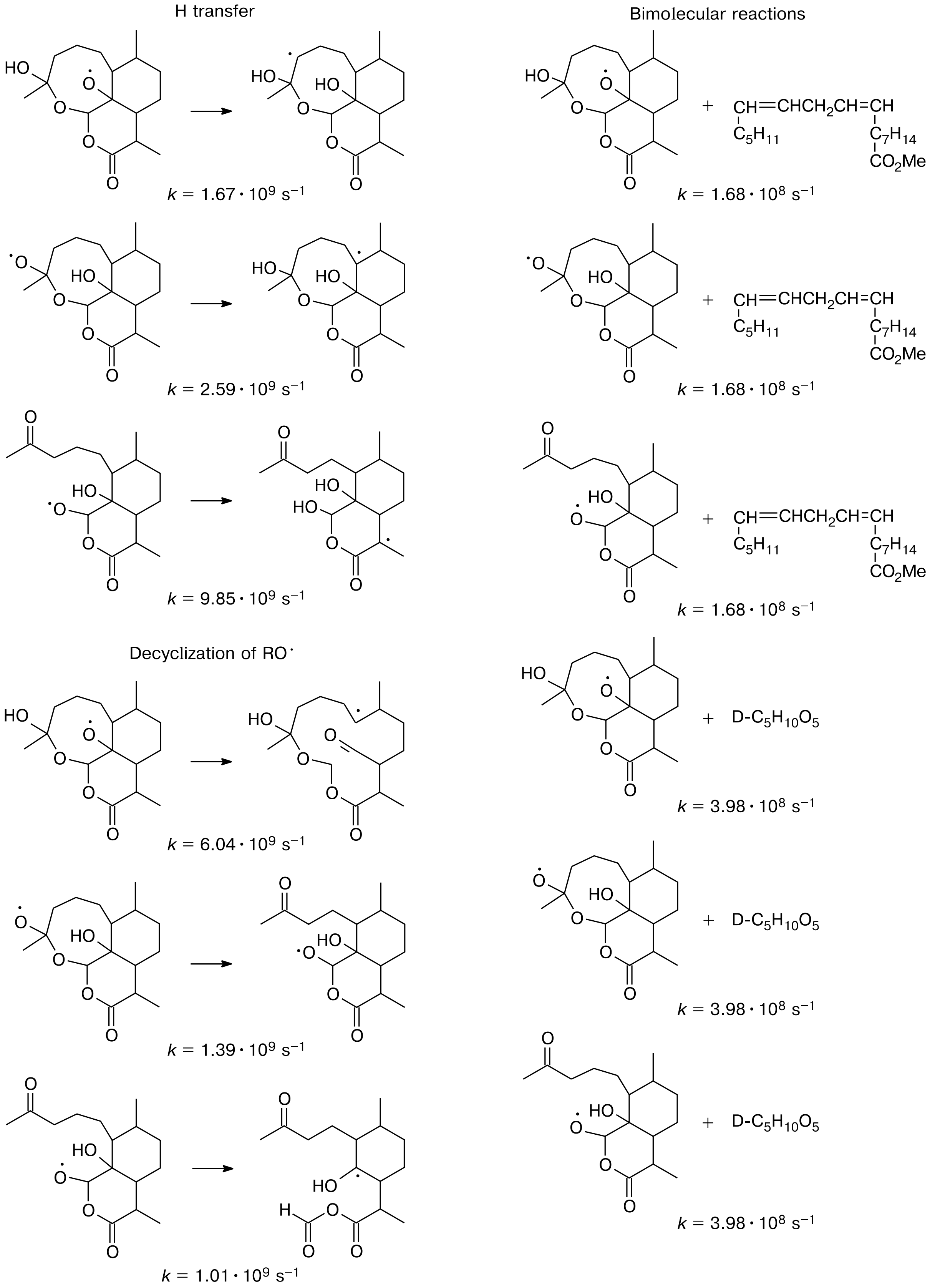

(20)

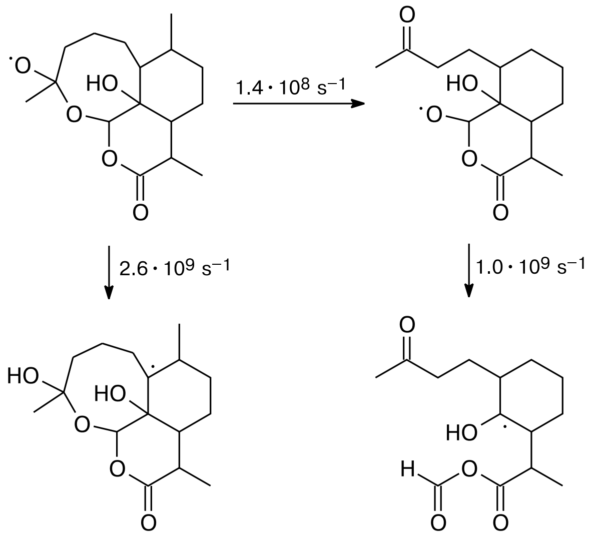
Scheme 5



Scheme 6


H transfer
Bimolecular reactions
k = 1.67 · 10^9 s^-1
k = 1.68 · 10^8 s^-1
k = 2.59 · 10^9 s^-1
k = 1.68 · 10^8 s^-1
k = 9.85 · 10^9 s^-1
k = 1.68 · 10^8 s^-1
Decyclization of RO·
k = 3.98 · 10^8 s^-1
k = 6.04 · 10^9 s^-1
k = 3.98 · 10^8 s^-1
k = 1.39 · 10^9 s^-1
k = 3.98 · 10^8 s^-1
k = 1.01 · 10^9 s^-1
+ CH=CHCH2CH=CH C5H11 C7H14 CO2Me
+ D-C5H10O5
HO
O
H

Scheme 7



The scheme of the main routes of transformation of the alkoxyl radicals formed from artemisinin thus takes the following form (Schemes 6 and 7).

Thus, the fastest reactions of transformation of the alkoxyl radicals are (see Scheme 5, Table 5) reaction (1) for $R_1O^\bullet$ (Scheme 3) and reactions (13), (14), and (15) (Scheme 4) for $R_2O^\bullet$. The alkoxyl radicals of the artemisinin derivatives enter very rapidly into reactions (7), (8), and (9) (see Scheme 3 and Table 3). The bimolecular reactions of the artemisinin alkoxyl radicals with methyl linoleate and D-ribose occur by two orders of magnitude more slowly.

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