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Competition of Monomolecular and Bimolecular Reactions of the Alkyl Radicals of Artemisinin

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Abstract—The competition between monomolecular and bimolecular reactions of alkyl radicals of artemisinin is considered theoretically. The enthalpies of these reactions are calculated. The activation energies and rate constants of intramolecular hydrogen atom transfer, of the decyclization of the alkyl radicals of artemisinin, and of the bimolecular reactions of these radicals with C–H, S–H, and O–H bonds of biological substrates and their analogues are calculated in the framework of the parabolic model. The intramolecular hydrogen transfer reactions proceed at the highest rate. The bimolecular reactions occur somewhat less rapidly. The fastest of them are the reactions of the alkyl radicals with the thio groups of cysteine. The decyclization reactions of all artemisinin alkyl radicals are very slow.

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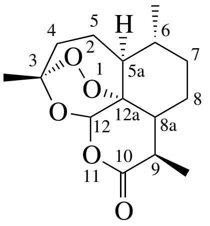
INTRODUCTION

At present, artemisinin and its derivatives are regarded as the most efficient and rapidly acting antimalarial drugs. The structure of artemisinin is rather complicated, and the curing effect of this medicine is due to the presence of a peroxide bridge [1–4].



In our previous study [5], we considered reactions of the alkoxyl radicals resulting from the reduction of the peroxide bridge of artemisinin by divalent iron chelates. The fast intramolecular transformation of the artemisininoxyl radicals results in the formation of artemisinin radicals with a free valence on the carbon atom. Such carbon-centered radicals are very reactive and can enter into various intramolecular and bimolecular reactions. For this reason, in the present work, we analyze the competition between the monomolecular and bimolecular reactions of the alkyl radicals forming from the primary alkoxyl radicals of artemisinin. The object of this study is seven carbon-centered artemisinin radicals resulting from the fastest intramolecular transformations of the artemisininoxyl radicals [5]. The dissociation energies of the attacked bonds ($D_{C–H}$) in these radicals are given in Table 1 [6–8].

Furthermore, we analyze the bimolecular reactions of the artemisinin alkyl radicals with a number of HY substrates:

$$R^{\cdot} + HY \longrightarrow RH + Y^{\cdot}.$$

The substrates were the following compounds: *cis*-methyl oleate ($D_{C–H}$ = 344.0 kJ/mol [6]), *cis-cis*-methyl linoleate ($D_{C–H}$ = 318.0 kJ/mol [6]), glycerol ($D_{C–H}$ = 387.7 kJ/mol [7]), glucose ($D_{C–H}$ = 371.4 kJ/mol [7]), *D*-ribose ($D_{C–H}$ = 370.0 kJ/mol [7]), *L*-cysteine ($D_{C–H}$ = 360.0 kJ/mol [9]), α-tocopherol ($D_{C–H}$ = 330.0 kJ/mol [10]), and ubiquinol ($D_{C–H}$ = 343.8 kJ/mol [10]).

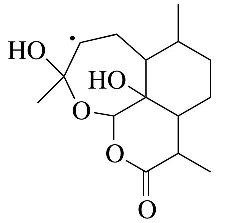
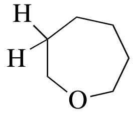
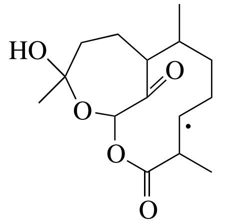
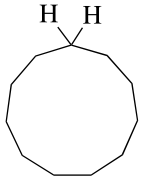
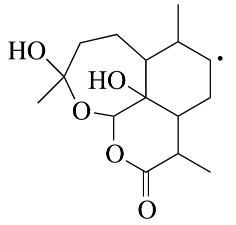
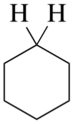
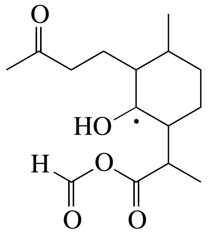
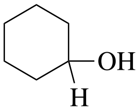
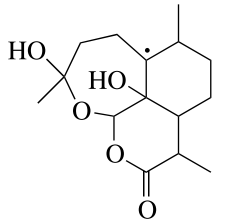
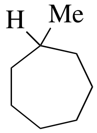
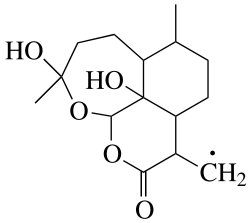
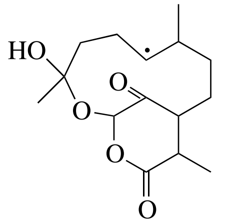
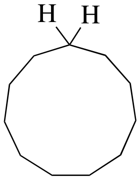
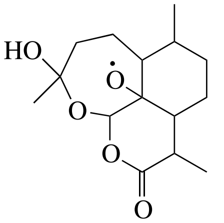
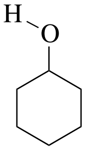
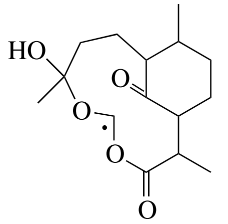
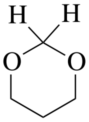
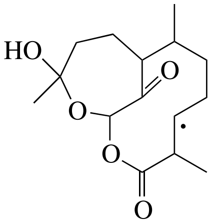
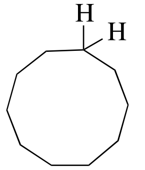
The activation energies and rate constants of the monomolecular and bimolecular reactions were calculated using the intersecting parabolas model (IPM) as applied to bimolecular [11, 12] and intramolecular [13] radical reactions.

COMPUTATIONAL PROCEDURE

Enthalpy of Bimolecular and Intramolecular Hydrogen Atom Transfer Reactions

The enthalpies (ΔH) of intramolecular hydrogen atom transfer in the artemisinin alkyl radicals and of the reactions of these radicals with the substrates were calculated as the difference between the dissociation energies of the breaking (D_i) and forming (D_f) bonds: $\Delta H = D_i - D_f$. The average error of estimation of the dissociation energies of the C–H bonds is ±2.0 kJ/mol [6].

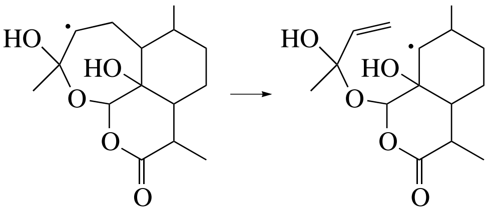
Table 1. Dissociation energies of individual bonds in the artemisinin alkyl radicals [6–8]

Radical	Formula	Analogous compound	$D_{C–H}$, kJ/mol	Radical	Formula	Analogous compound	$D_{C–H}$, kJ/mol
$R_1^{\bullet}$			403.9	$R_6^{\bullet}$			404.7
$R_2^{\bullet}$			408.8	$R_7^{\bullet}$			388.4
$R_3^{\bullet}$			390.0			R–CH$_3$	422.0
$R_4^{\bullet}$			404.7				438.5
$R_5^{\bullet}$			388.0				385.3

These calculations are applicable to reactions in nonpolar solvents.

Enthalpy of Radical Decyclization Reactions

The enthalpies of decyclization of artemisinin alkyl radicals were calculated using the Benson increment method [14]. The numerical values of the increments of the groups were taken from [15]. The enthalpies of the groups having a free valence were calculated using the dissociation energies of C–H bonds in structurally similar hydrocarbons (Table 1). The average error in the calculated enthalpies of reactions is approximately ±5 kJ/mol. An example of the calculation of the decyclization enthalpy by the increment method is given below. In the reaction



the C–(C)$_3$(H), C–(C)$_2$(H)$_2$, and C$^{\bullet}$–(C)$_2$(H) groups disappear and the C$_d$–(H)$_2$, C$_d$–(H)(C), and C$^{\bullet}$–(C)$_2$(H)

Table 2. Kinetic parameters α, br_e, $\log A_{C-H}$, and $E_{e,0}$ for the reactions considered [10, 12, 13, 16]

Type of reaction	α	br_e, (kJ/mol)$^{1/2}$	$\log A_{C-H}$ [s^{-1}]	$E_{e,0}$, kJ/mol
cyclo-$R^{\bullet} \longrightarrow R_f^{\bullet}$	1.00	14.42	13.6	52.0
cyclo-$R^{\bullet} \longrightarrow R_fO^{\bullet}$	1.256	16.46	8.0	53.2
Decylization of *cyclo*-$R^{\bullet}$	0.832	16.96	13.3	85.7
$R^{\bullet} + R^1H$	1.00	17.30	9.0	74.8
$R^{\bullet} + R^2H$	1.00	18.60	8.0	86.5
$R^{\bullet}$ + RSH	0.887	12.86	9.0	46.4
$R^{\bullet}$ + ArOH	1.247	17.61	8.0	61.5

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

groups are formed. In addition, the seven-membered cycle is opened and its strain energy disappears. Therefore, the enthalpy of this reaction is expressed as

$$\begin{aligned}\Delta H &= \Delta H[C_d\text{–}(H)_2] + \Delta H[C_d\text{–}(H)(C)] \\ &+ \Delta H[C^{\bullet}\text{–}(C)_2(H)] - \Delta H[C\text{–}(C)_3(H)] \qquad (1) \\ &- \Delta H[C\text{–}(C)_2(H)_2] - \Delta H[C^{\bullet}\text{–}(C)_2(H)].\end{aligned}$$

The $[C^{\bullet}\text{–}(C)_2(H)]$ increment can be derived from the $[C\text{–}(C)_2(H)_2]$ increment: $\Delta H[C^{\bullet}\text{–}(C)_2(H)] = \Delta H[C\text{–}(C)_2(H)_2] + D_{C-H} - \Delta H_f^0[H^{\bullet}] = -20.63 + 403.9 - 218 = 165.3$ kJ/mol. The $\Delta H[C^{\bullet}\text{–}(C)_2(H)]$ increment is calculated from the $\Delta H[C\text{–}(C)_2(H)_2]$ increment: $\Delta H[C^{\bullet}\text{–}(C)_2(H)] = \Delta H[C\text{–}(C)_2(H)_2] + D_{C-H} - \Delta H_f^0[H^{\bullet}] = -20.63 + 408.8 - 218 = 170.2$ kJ/mol. The enthalpy of the reaction is then $\Delta H = 26.32 + 36.32 + 170.2 + 1/17 + 20.63 - 165.3 - 26.34 = 63.0$ kJ/mol.

Equations of the Intersecting Parabolas Method

In the IPM [11–13], a radical abstraction reaction, for instance,

$$R^{\bullet} + R_iH \longrightarrow RH + R_i^{\bullet},$$

is viewed as resulting from the intersection of two potential curves, of which one characterizes the stretching vibrations of the bond being attacked and the other characterizes those of the bond forming in the reaction product. The reaction has the following parameters:

(1) The classical enthalpy ΔH_e, which includes the difference between the zero-point energies of the breaking bond (strength D_i) and the forming bond (strength D_f). In intramolecular H atom transfer reactions, these energies are equal and, hence, $\Delta H_e = \Delta H = D_i - D_f$.

(2) The classical potential barrier E_e, which is related to the experimental Arrhenius activation energy $E = RT\ln(A/k)$ by the equation

$$E_e = E + 0.5(hN_A\nu_i - RT), \qquad (2)$$

where h is Planck's constant, N_A is Avogadro's number, ν_i is the C–H stretching frequency, and $0.5hN_A\nu_i = 17.4$ kJ/mol.

(3) The coefficients b_i and b_f, which characterize the dependence of the potential energy on the amplitude of the vibrations of the atoms along the valence bond. For the C–H bond, $b = \pi\nu_i(2\mu)^{1/2} = 37.43 \times 10^{10}$ (kJ/mol)$^{1/2}$, where μ is the reduced mass of the bonded atoms. The parameter α is defined as $\alpha = b_i/b_f$.

(4) The parameter r_e, which characterizes the total extension of the two reacting bonds in the transition state.

In the IPM, these parameters are interrelated by the equation

$$br_e = \alpha(E_e - \Delta H_e)^{1/2} + E_e^{1/2}, \qquad (3)$$

where $b = b_i$ and, therefore, refers to the bond being attacked. Reactions of one class are characterized by a fixed br_e value. The classical potential barrier of a thermally neutral reaction ($\Delta H_{e,0} = 0$) is calculated using the formula

$$\sqrt{E_{e,0}} = \frac{br_e}{1+\alpha}. \qquad (4)$$

This method provides a good description both for intramolecular hydrogen atom transfer reactions [12] and for the decyclization of cyclic free radicals [13]. The values of α, br_e, and other parameters for the reactions considered here are listed in Table 2. Of the possible intramolecular hydrogen atom transfer reactions, we took into consideration only the reactions proceeding via a six-membered transition state and having the lowest activation energy $E_{e,0}$ [13].

The activation energies of the reactions were calculated using the equation [12]

$$\sqrt{E_e} = \frac{br_e}{1-\alpha^2}\left\{1-\alpha\sqrt{1-\frac{1-\alpha^2}{(br_e)^2}\Delta H_e}\right\}. \qquad (5)$$

The preexponential factor A for an intramolecular hydrogen atom transfer reaction depends on the number of groups that lose the ability to rotate freely in the cyclic transition state (m) [13]:

$$\log A_0 = 13.30 - 0.6m. \qquad (6)$$

Furthermore, the factor A depends on the number of C–H bonds being attacked, n_{C-H} (for the CH_2 group, $n_{C-H} = 2$). Accordingly, the rate constant was calculated using the equation

$$k = n_{C-H}A_0\exp(-E/RT) = A\exp(-E/RT). \qquad (7)$$

RESULTS AND DISCUSSION

The activation energies and rate constants of intramolecular hydrogen atom transfer reactions in the artemisinin alkyl radicals calculated by formulas (5)–(7) are given in Table 3.

The data listed in Table 3 suggest that reactions of the cyclo-$R^{\bullet} \longrightarrow$ cyclo-$R_f^{\bullet}$ type occur rather rapidly (at 310 K, k ranges from approximately 1.3×10^9 to 3.3×10^4 s^{-1}). By contrast, the reaction of H atom abstraction from the hydroxyl group (cyclo-$R^{\bullet} \longrightarrow$ cyclo-$R_f^{\bullet}$ type) is slow because of its endothermicity (at 310 K, $k_2 \approx 2.5 \times 10^3$ s^{-1}). Among the reactions considered, reactions (V) and (VII) are the fastest.

The ΔH, E, and k values for the decyclization reactions of the artemisinin alkyl radicals are presented in Table 4. All these reactions are endothermic and proceed several orders of magnitude less rapidly than the intramolecular hydrogen atom transfer reactions.

The ΔH, E, k, and specific rate values for the bimolecular reactions of the artemisinin alkyl radicals with a number of substrates are given in Table 5. Among the bimolecular reactions considered, the reactions of the alkyl radicals with S–H bonds of the biological substrates are the fastest (at 310 K, k[RH] $\approx 5.2 \times 10^5$–3.0×10^4 s^{-1}). The reactions of the alkyl radicals with the other substrates occur at a much lower specific rate.

The results of the calculation presented in this work suggest the following. The intramolecular hydrogen atom transfer in the artemisinin alkyl radicals occurs more rapidly than the bimolecular reactions of these radicals with substrates. The rate constants of the intramolecular hydrogen atom transfer reactions (their dimension is s^{-1}) decrease in the following order (see Table 3): $k_5 = 1.3 \times 10^9 > k_7 = 6.0 \times 10^7 > k_3 = 2.9 \times 10^6 > k_1 = 1.0 \times 10^6 \approx k_6 = 1.2 \times 10^6 \approx k_9 = 1.2 \times 10^6 > k_4 = 5.1 \times 10^4 > k_8 = 3.3 \times 10^4$. By contrast, the decyclization reactions of the artemisinin alkyl radicals occur much less rapidly than the bimolecular reactions (Table 4). Note that the decyclization of the artemisinin alkyl radicals is a much faster reaction [5].

The specific rates of the bimolecular reactions decrease in the following order (the specific rates of the reactions involving the $R_1^{\bullet}$ radicals at 310 K (s^{-1}) are given in parentheses: *L*-cysteine (2.6×10^5) > α-tocopherol (4.7×10^4) > ubiquinol (1×10^4) > methyl linoleate (2.8×10^3) > *D*-ribose (540) > glucose (420) > glycerol (85) > methyl oleate (66). Clearly, the bimolecular reactions of the artemisinin alkyl radicals, specifically, their reactions with protein thio groups are the most likely under anaerobic conditions.

The artemisinin alkyl radicals in reactivity in the reactions with *L*-cysteine are arranged in the following order: $R_2^{\bullet} > R_1^{\bullet} \approx R_4^{\bullet} \approx R_6^{\bullet} > R_5^{\bullet} \approx R_3^{\bullet} \approx R_7^{\bullet}$. Let us compare the rate constants of intramolecular H atom transfer to the rate constants of bimolecular H atom abstraction from the thio group of *L*-cysteine by various artemisinin alkyl radicals:

Radical	$R_1^{\bullet}$	$R_2^{\bullet}$	$R_3^{\bullet}$	$R_4^{\bullet}$, $R_6^{\bullet}$	$R_5^{\bullet}$	$R_7^{\bullet}$
k_{iso}, s^{-1}	1.05×10^6	2.91×10^6	1.30×10^9	1.24×10^6	6.05×10^7	0
k[RSH], s^{-1}	2.65×10^5	5.15×10^5	3.63×10^4	2.96×10^5	4.21×10^4	2.85×10^4
$\frac{k[\mathrm{RSH}]}{k_{iso} + k[\mathrm{RSH}]}$, %	20	15	0.003	19	0.07	100

Clearly, the $R_7^{\bullet}$ radical is not involved in isomerization and enters only into the bimolecular abstraction reaction. The $R_1^{\bullet}$, $R_2^{\bullet}$, $R_4^{\bullet}$, and $R_6^{\bullet}$ radicals participate simultaneously in both reactions, whereas the $R_3^{\bullet}$ and $R_5^{\bullet}$ radicals are mainly involved in the isomerization reactions.

Table 3. Enthalpies, activation energies, and rate constants of the intramolecular H atom transfer reactions in the artemisinin alkyl radicals

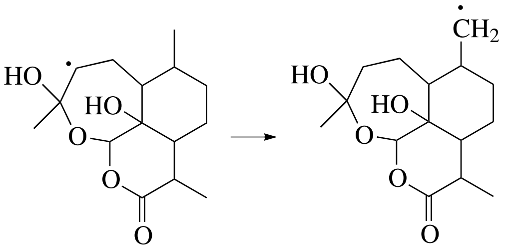
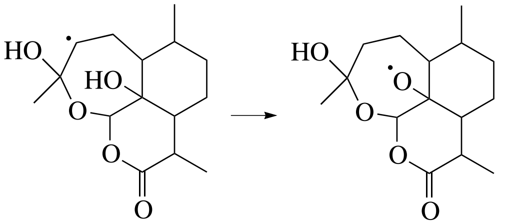
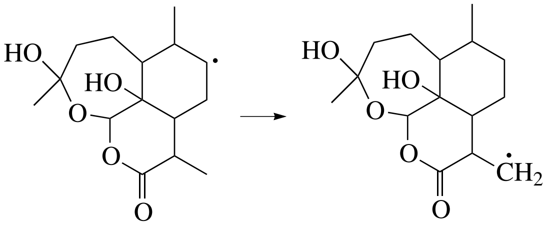
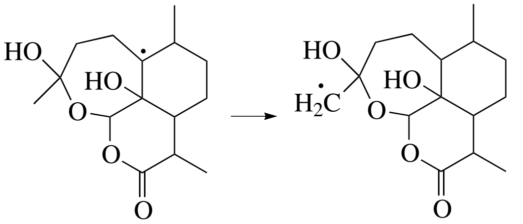
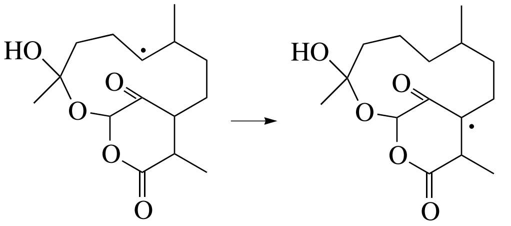
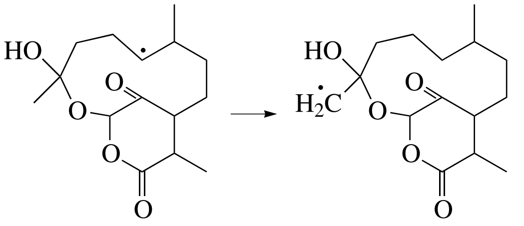
Reaction no.	Reaction	α	br_e, (kJ/mol)$^{1/2}$	log$A$ [s^{-1}]	ΔH	E	k (310 K), s^{-1}
					kJ/mol		
(I)		1.00	14.42	13.18	18.1	45.3	1.05×10^6
(II)		1.256	16.49	12.70	34.6	55.2	2.48×10^3
(III)		1.00	14.42	13.18	13.2	42.7	2.91×10^6
(IV)		1.00	14.42	13.18	32.0	53.1	5.11×10^4
(V)		1.00	14.42	13.60	–19.4	26.6	1.30×10^9
(VI)		1.00	14.42	13.18	17.3	44.9	1.24×10^6

Table 3. (Contd.)

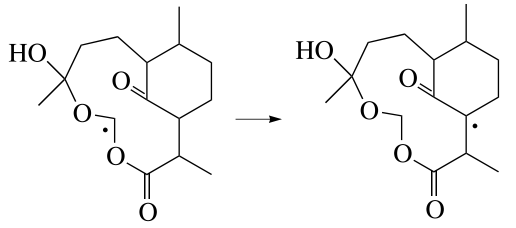
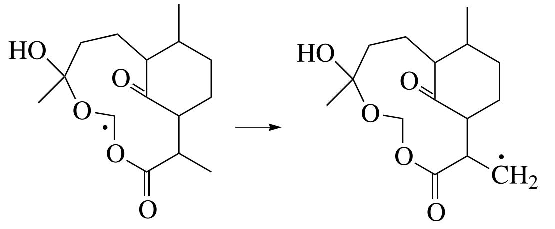
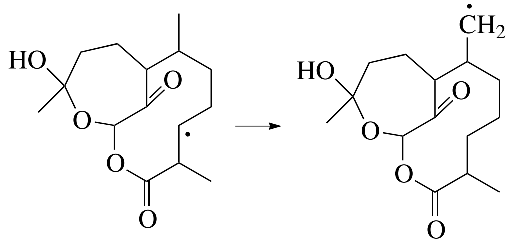
Reaction no.	Reaction	α	br_e, (kJ/mol)$^{1/2}$	log*A* [s^{-1}]	Δ*H*	*E*	*k* (310 K), s^{-1}
					kJ/mol		
(VII)		1.00	14.42	13.60	–2.7	34.5	6.05×10^{7}
(VIII)		1.00	14.42	13.18	34	54.3	3.26×10^{4}
(IX)		1.00	14.42	13.18	17.3	44.9	1.24×10^{6}

Table 4. Enthalpies, activation energies, and rate constants of decyclization of the artemisinin alkyl radicals

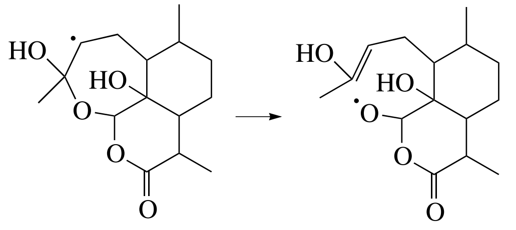
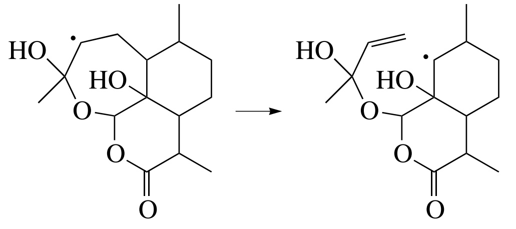
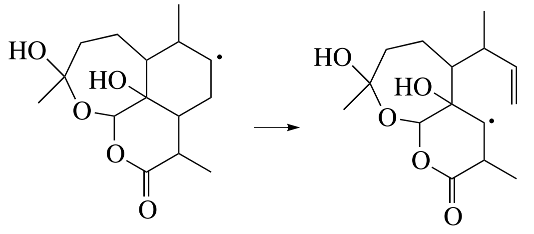
Reaction no.	Reaction	Δ*H*, kJ/mol	α	br_e, (kJ/mol)$^{1/2}$	*E*, kJ/mol	*k*, s^{-1}
(X)		47.2	0.728	15.29	92.3	5.66×10^{-3}
(XI)		63.0	0.832	15.29	94.1	2.78×10^{-3}
(XII)		83.8	0.832	16.96	121.2	7.53×10^{-8}

Table 4. (Contd.)

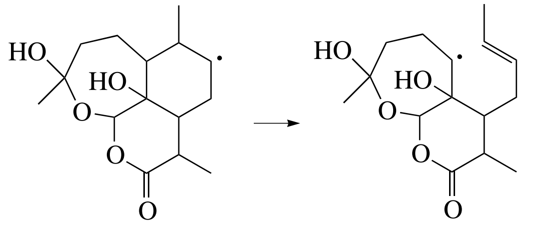
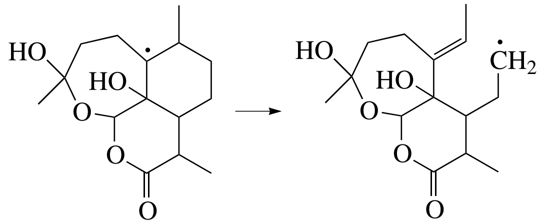
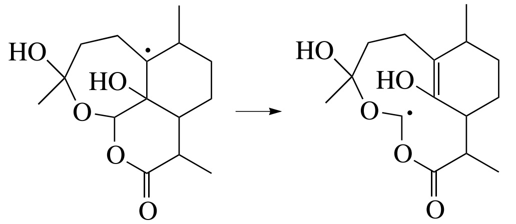
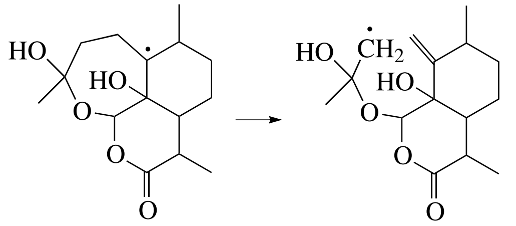
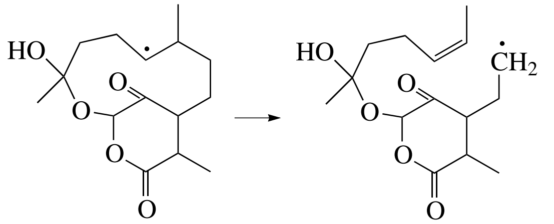
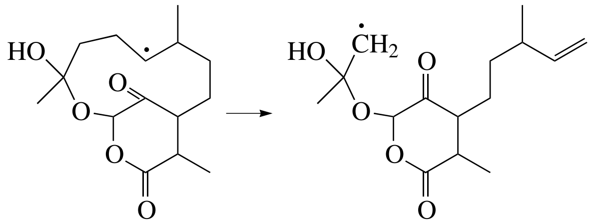
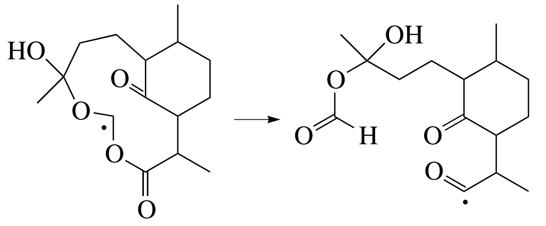
Reaction no.	Reaction	ΔH, kJ/mol	α	br_e, (kJ/mol)$^{1/2}$	E, kJ/mol	k, s^{-1}
(XIII)		69.4	0.832	16.96	112.9	1.81×10^{-6}
(XIV)		92.5	0.832	16.96	126.3	1.03×10^{-8}
(XV)		72.5	0.832	15.29	99.6	3.28×10^{-4}
(XVI)		76.3	0.832	15.29	101.8	1.37×10^{-4}
(XVII)		90.2	0.832	13.97	100.4	2.37×10^{-4}
(XVIII)		80.1	0.832	13.97	93.8	3.05×10^{-3}
(XIX)		65.1	0.654	13.97	93.2	3.88×10^{-3}

Table 4. (Contd.)

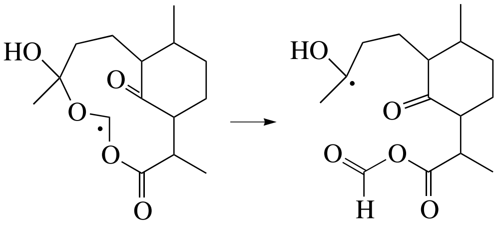
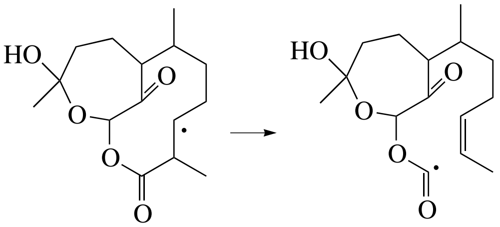
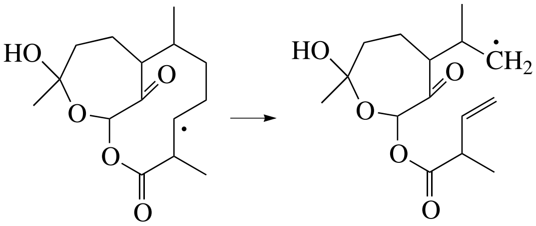
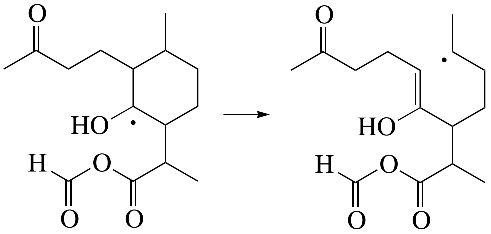
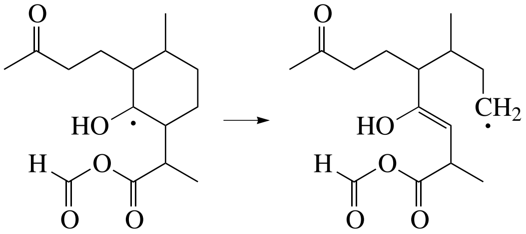
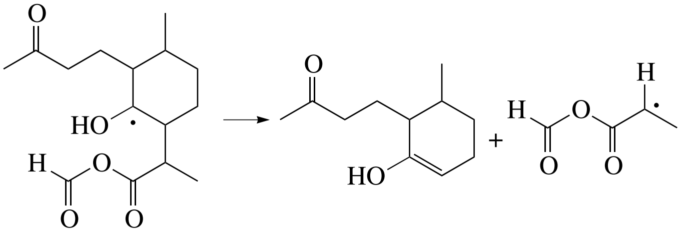
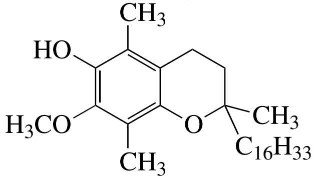
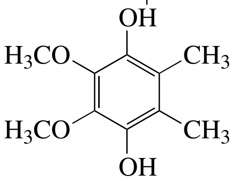
Reaction no.	Reaction	ΔH, kJ/mol	α	br_e, (kJ/mol)$^{1/2}$	E, kJ/mol	k, s^{-1}
(XX)		109.7	0.654	13.97	118.9	1.86×10^{-7}
(XXI)		104.5	0.832	13.97	110.2	5.32×10^{-6}
(XXII)		83.9	0.832	13.97	96.3	1.18×10^{-3}
(XXIII)		111.2	0.832	16.96	137.7	1.22×10^{-10}
(XXIV)		119.0	0.832	16.96	142.7	1.79×10^{-11}
(XXV)		116.8	0.832	13.37	119.1	1.70×10^{-7}

Table 5. Enthalpies, activation energies, and rate constants of the bimolecular reactions of the artemisinin alkyl radicals with the substrates

Reaction no.	Radical	ΔH, kJ/mol	E, kJ/mol	k (310 K), l mol^{-1} s^{-1}	[R$_i$H], mol/l	k[R$_i$H], s^{-1}
Z-$C_7H_{15}CH_2CH{=}CH(CH_2)_7CO_2Me$						
(XXVI)	$R_1^{\bullet}$	–59.9	43.0	2.25×10	2.95	6.64×10
(XXVII)	$R_2^{\bullet}$	–64.8	41.0	4.90×10	2.95	1.27×10^2
(XXVIII)	$R_3^{\bullet}$	–46.0	48.9	0.23×10	2.95	0.68×10
(XXIX)	$R_4^{\bullet}$, $R_6^{\bullet}$	–60.7	42.7	2.56×10	2.95	7.55×10
(XXX)	$R_5^{\bullet}$	–47.0	48.5	0.27×10	2.95	0.79×10
(XXXI)	$R_7^{\bullet}$	–44.4	49.6	0.18×10	2.95	0.47×10
$C_5H_{11}CH{=}CHCH_2CH{=}CHC_7H_{14}CO_2Me$						
(XXXII)	$R_1^{\bullet}$	–85.9	32.8	5.98×10^2	3.02	1.81×10^3
(XXXIII)	$R_2^{\bullet}$	–90.8	30.9	1.21×10^3	3.02	3.65×10^3
(XXXIV)	$R_3^{\bullet}$	–72.0	38.1	7.47×10	3.02	2.56×10^2
(XXXV)	$R_4^{\bullet}$, $R_6^{\bullet}$	–86.7	32.5	6.72×10^2	3.02	2.03×10^3
(XXXVI)	$R_5^{\bullet}$	–73.0	37.7	8.71×10	3.02	2.63×10^2
(XXXVII)	$R_7^{\bullet}$	–70.4	38.8	5.84×10^2	3.02	1.76×10^3
$CH_2(OH)CH(OH)CH_2OH$						
(XXXVIII)	$R_1^{\bullet}$	–20.8	48.7	0.62×10	13.69	8.49×10
(XXXIX)	$R_2^{\bullet}$	–25.7	46.4	1.49×10	13.69	2.04×10^2
(XL)	$R_3^{\bullet}$	–6.9	55.3	0.048×10	13.69	0.66×10
(XLI)	$R_4^{\bullet}$, $R_6^{\bullet}$	–21.6	48.3	0.72×10	13.69	9.86×10
(XLII)	$R_5^{\bullet}$	–7.9	54.8	0.058×10	13.69	0.79×10
(XLIII)	$R_7^{\bullet}$	–5.3	56.1	0.035×10	13.69	0.48×10
$C_6H_{12}O_6$						
(XLIV)	$R_1^{\bullet}$	–32.5	43.4	4.93×10	8.57	4.22×10^2
(XLV)	$R_2^{\bullet}$	–37.4	41.2	1.14×10^2	8.57	9.77×10^2
(XLVI)	$R_3^{\bullet}$	–18.6	49.7	0.42×10	8.57	3.59×10
(XLVII)	$R_4^{\bullet}$, $R_6^{\bullet}$	–33.3	42.9	5.66×10	8.57	4.85×10^2
(XLVIII)	$R_5^{\bullet}$	–19.6	49.2	0.50×10	8.57	4.28×10
(XLIX)	$R_7^{\bullet}$	–17.0	50.5	0.31×10	8.57	2.66×10
D-$C_5H_{10}O_5$						
(L)	$R_1^{\bullet}$	–33.9	42.7	6.28×10	8.57	5.38×10^2
(LI)	$R_2^{\bullet}$	–38.8	40.6	1.44×10^2	8.57	1.23×10^3
(LII)	$R_3^{\bullet}$	–20.0	49.1	0.54×10	8.57	4.63×10
(LIII)	$R_4^{\bullet}$, $R_6^{\bullet}$	–34.7	42.4	7.20×10	8.57	6.17×10^2
(LIV)	$R_5^{\bullet}$	–21.0	48.6	0.65×10	8.57	5.57×10
(LV)	$R_7^{\bullet}$	–18.4	49.8	0.41×10	8.57	3.51×10

Table 5. (Contd.)

Reaction no.	Radical	ΔH, kJ/mol	E, kJ/mol	k (310 K), l mol^{-1} s^{-1}	[R$_i$H], mol/l	k[R$_i$H], s^{-1}
L-HSCH$_2$CH(NH$_2$)COOH						
(LVI)	$R^{\bullet}_1$	–43.9	13.5	5.31×10^6	0.05	2.65×10^5
(LVII)	$R^{\bullet}_2$	–48.8	11.8	1.03×10^7	0.05	5.15×10^5
(LVIII)	$R^{\bullet}_3$	–30.0	18.6	7.25×10^5	0.05	3.63×10^4
(LIX)	$R^{\bullet}_4$, $R^{\bullet}_6$	–44.7	13.2	5.92×10^6	0.05	2.96×10^5
(LX)	$R^{\bullet}_5$	–31.0	18.2	8.42×10^5	0.05	4.21×10^4
(LXI)	$R^{\bullet}_7$	–28.4	19.2	5.69×10^5	0.05	2.85×10^4
						
(LXII)	$R^{\bullet}_1$	–73.9	7.9	4.70×10^6	0.01	4.70×10^4
(LXIII)	$R^{\bullet}_2$	–78.8	5.9	9.44×10^6	0.01	9.44×10^4
(LXIV)	$R^{\bullet}_3$	–60.0	13.7	4.97×10^5	0.01	4.97×10^3
(LXV)	$R^{\bullet}_4$, $R^{\bullet}_6$	–74.7	7.6	5.32×10^6	0.01	5.32×10^4
(LXVI)	$R^{\bullet}_5$	–61.0	13.2	5.88×10^5	0.01	5.88×10^3
(LXVII)	$R^{\bullet}_7$	–58.4	14.4	3.79×10^5	0.01	3.79×10^3
						
(LXVIII)	$R^{\bullet}_1$	–60.1	13.6	1.01×10^6	0.01	1.01×10^4
(LXIX)	$R^{\bullet}_2$	–65.0	11.5	2.27×10^6	0.01	2.27×10^4
(LXX)	$R^{\bullet}_3$	–46.2	19.9	8.94×10^4	0.01	8.94×10^3
(LXXI)	$R^{\bullet}_4$, $R^{\bullet}_6$	–60.9	13.3	1.15×10^6	0.01	1.15×10^4
(LXXII)	$R^{\bullet}_5$	–47.2	19.4	1.07×10^5	0.01	1.07×10^3
(LXXIII)	$R^{\bullet}_7$	–44.6	20.6	6.68×10^4	0.01	6.68×10^2

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