

Intramolecular Reactions of Free Radicals Formed from Artemisinin

EVGENY DENISOV,¹ TAISA DENISOVA,¹ FYAZ ISMAIL²

¹Institute of Problems of Chemical Physics, RAS, Chernogolovka, Moscow Region, 142432, Russia

²School of Pharmacy & Chemistry, Liverpool John Moores University, Liverpool, L3 3AF, UK

Received 22 July 2004; accepted 19 April 2005

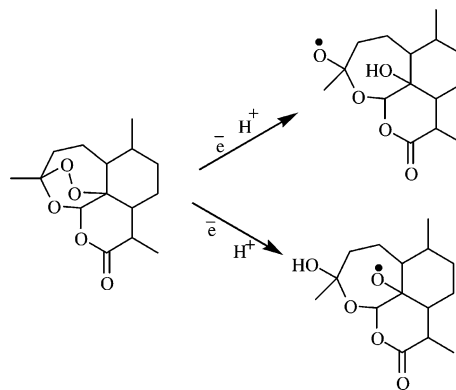
DOI 10.1002/kin.20112

Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Two cyclic alkoxy radicals are formed as a result of peroxide bridge scission in artemisinin. Intramolecular reactions of these radicals induce the cascade of reactions of isomerization, decyclization, and decomposition of formed free radicals. It includes 14 reactions of intramolecular free radical hydrogen transfer, 17 reactions of decyclization of alkoxy and alkyl radicals, and 4 reactions of decomposition of alkoxy, acyl, and carboxyl radicals. The enthalpies of these 35 reactions are calculated. Using intersection parabolas method, activation energies and rate constants of all these reactions are calculated. The most rapid reactions are selected for every intermediate free radical. © 2005 Wiley Periodicals, Inc. *Int J Chem Kinet* 37: 554–565, 2005

INTRODUCTION

Artemisinin (qinghaosu) and its derivatives are regarded now as the most effective remedy against malaria. Artemisinin possesses the chemical structure that strongly differs from other antimalarial drugs. The key structural fragment of artemisinin is 1,2,4-trioxane ring. A few hypotheses about action of artemisinin as antimalaria remedy were put forward [1–9]. Reduction of peroxide bridge by Fe(II) centers of enzymes was proposed as the first stage of action. Two alkoxy radicals of different structures can be produced via this reaction.



All possible intramolecular reactions of these alkoxy radicals as well as reactions of secondary formed radicals were analyzed.

The present study is devoted to thermodynamic and kinetic analysis of all possible intramolecular reactions of free radicals formed from artemisinin in its reactions with reducing agents. These reactions include hydrogen atom transfer in alkoxy and alkyl radicals, reaction

of decyclization of alkoxy and alkyl radicals, and decomposition of formed alkoxy, acyl, and carboxyl radicals (35 reactions). The values of reaction enthalpies are calculated using Benson's method of increments [10]. The semiempirical intersecting parabolas method (IPM) is used to calculate activation energies and rate constants of the studied reactions [11–15].

METHOD OF CALCULATION

Calculation of Enthalpy of Reactions

The enthalpy ΔH of intramolecular hydrogen atom transfer in cyclic alkoxy and alkyl radicals was calculated as the difference of dissociation energies (BDE) of cleaved (D_i) and formed (D_f) bonds

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

The values of BDE of C–H bonds were taken from [15], and BDE of formed O–H bond was taken as $D(\text{O–H}) = 438.5 \text{ kJ mol}^{-1}$ in cyclohexanol [16]. The mean uncertainty in BDE of C–H and O–H bonds is $\pm 2 \text{ kJ mol}^{-1}$ [15,16]. Calculations are valid for reactions in nonpolar media.

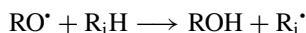
The enthalpy ΔH of decyclization of radical R_i^{\cdot} into radical R_f^{\cdot} was calculated as the difference

$$\Delta H = \Delta H(R_i\text{H}) + D_i - \Delta H(R_f\text{H}) - D_f, \quad (2)$$

where D_i is BDE of $R_i\text{–H}$ bond and D_f is BDE of $R_f\text{–H}$ bond. Enthalpies of molecules were calculated via combination of molecular enthalpies taken from [17] and Benson's method of increments [10]; the values of increments as well ring strain energies were taken from [18]. The mean uncertainty in evaluation of reaction enthalpy is approximately $\pm 6 \text{ kJ mol}^{-1}$.

Main Equations of IPM

The intersecting parabolas model (IPM) as a semiempirical model of an elementary bimolecular and intramolecular free radical reaction appeared to be very efficient in the calculation and analysis of activation energies for a wide variety of free radical abstraction and addition reactions [11–15]. In the IPM, the radical abstraction reaction, for example



in which the hydrogen atom is transferred from the initial molecule ($R_i\text{H}$) to the product (ROH), is regarded as the result of intersection of two potential curves; one of

which refers to the potential energy $U_i(r)$ of the vibration of the H atom along the bond being dissociated in the initial molecule, and another refers to the potential energy $U_f(r)$ of the vibration of the same atom along the bond being formed in the reaction product (U is the potential energy, and r is the amplitude of the atomic vibration along the valence bond). The stretching vibrations of the H atom in ROH and $R_i\text{H}$ are regarded as harmonic and are described by the parabolic law

$$\sqrt{U(r)} = br \quad (3)$$

The following parameters are used to characterize the elementary step [11–15]:

1. The enthalpy of reaction ΔH_e includes the difference between the zero-point energies of the broken and generated bonds

$$\Delta H_e = D_i - D_f + 0.5hN_A(\nu_i - \nu_f) \quad (4)$$

where D_i and D_f are the dissociation energies of the broken (i) and generated (f) bonds, ν_i and ν_f (s^{-1}) are the stretching vibration frequencies of these bonds, h and N_A are Planck and Avogadro constants, respectively.

2. The classical potential barrier E_e is related to the experimentally determined Arrhenius energy E by the equation:

$$E_e = E + 0.5(hN_A\nu_i - RT) \quad (5)$$

3. The coefficients b_i and b_f describe the dependence of the potential energy on the atomic vibration amplitude along the valence bonds. There is a parabolic relation between the potential energy and the vibration amplitude (see Eq. (3)). The parameter $2b^2$ is the force constant of the corresponding bond with $b = \pi\nu(2\mu)^{1/2}$, where μ is the reduced mass of the atoms forming the bond and ν is stretching vibration frequency of this bond.
4. The parameter r_e characterizes the distance between two minimum points of intersecting parabolas. This parameter is equal to the sum of amplitudes of vibration of two bonds transformed in the reaction. In the IPM, these parameters are related to the equation:

$$br_e = \alpha\sqrt{E_e - \Delta H_e} + \sqrt{E_e} \quad (6)$$

where $b = b_i$, i.e., refers to the attacked bond in the molecule, while $\alpha = b/b_f$. In the case of structurally isotypical reactions ($br_e = \text{const.}$), a thermally neutral reaction ($\Delta H_e = 0$) occurs with the

Table I Parameters of IPM for Different Types of Transition States [11,22]

Class of Reactions	α	$b \times 10^{-10}$ (kJ ^{1/2} mol ^{-1/2} m ⁻¹)	$0.5hN_A\nu_i$ (kJ mol ⁻¹)	$0.5hN_A(\nu_i - \nu_f)$ (kJ mol ⁻¹)
R [•] + H—C	1.000	37.43	17.4	0.0
RO [•] + H—C	0.796	37.43	17.4	-4.3
<i>cyclo</i> -R _i [•] → R _f [•]	0.832	44.83	8.2	-1.7
<i>cyclo</i> -R _i O [•] → R _f [•]	0.748	44.83	8.2	-2.1
RC [•] O → R [•] + CO	0.593	44.83	8.2	5.5
R ₃ CO [•] → R [•] + R ₂ C(O)	0.748	44.83	8.2	-2.1

classical potential barrier E_{e0} , which is determined by two parameters, namely, α and br_e (or r_e , b , and b_f):

$$\sqrt{E_{e0}} = \frac{br_e}{1 + \alpha} \quad (7)$$

The parabolic model is, in essence, empirical, because the parameter α is calculated from spectroscopic (ν_i and ν_f) and atomic (μ_i and μ_f) data, while parameter br_e (or E_{e0}) is found from the experimental activation energies E ($E = RT \ln(A/k)$), where A is the pre-exponential factor typical of the chosen group of reactions, and k is the rate constant in nonpolar solvent. The calculations showed that br_e is constant for structurally similar reactions. This method was proved to be

valid for intramolecular reactions of hydrogen transfer [19–22] and decyclization of cyclic free radicals. The values of α , br_e , and other parameters for reactions of different types are given in Tables I and II.

The parameter br_e for intramolecular reactions was evidenced to depend on strain energy E_{rsc} of the ring formed in transition state [19–22], and the last depends on number of atoms n forming the ring. This empirical dependence has the following form for intramolecular reactions:

(a) for reaction R_i[•] → R_f[•] (hydrogen transfer) [19]

$$br_e = 14.41 + 0.98 \times 10^{-2} E_{rsc} \quad (8)$$

(b) for reaction R_iO[•] → R_f[•] (hydrogen transfer) [19]

Table II Parameters of IPM for Different Classes of Intramolecular Reactions of Cyclic Free Radicals [11,22]

Radical	n	br_e (kJ ^{1/2} mol ^{-1/2})	E_{e0} (kJ mol ⁻¹)	E_{rsc} (kJ mol ⁻¹)	$\log A_{C-H}$ A_{C-H} (s ⁻¹)
Intramolecular reactions of H transfer in R [•] radicals					
<i>cyclo</i> -[RC [•] H(CH ₂) ₂ (C—H)HY]	5	17.03	72.5	26.7	13.60
<i>cyclo</i> -[RC [•] H(CH ₂) ₃ (C—H)HY]	6	14.42	52.0	0.7	13.60
<i>cyclo</i> -[RC [•] H(CH ₂) ₄ (C—H)HY]	7	17.04	72.6	26.8	13.60
Intramolecular reactions of H transfer in RO [•] radicals					
<i>cyclo</i> -[RCH(O [•])(CH ₂)(C—H)HY]	5	15.50	72.6	26.7	13.60
<i>cyclo</i> -[RCH(O [•])(CH ₂) ₂ (C—H)HY]	6	13.13	53.4	0.7	13.60
<i>cyclo</i> -[RCH(O [•])(CH ₂) ₃ (C—H)HY]	7	13.13	53.4	26.8	13.60
Decyclization of alkyl radicals					
R _i [•] → R _f [•]	5	15.30	69.7	26.7	13.60
R _i [•] → R _f [•]	6	16.96	85.7	0.7	13.60
R _i [•] → R _f [•]	7	15.29	69.6	26.8	13.60
R _i [•] → R _f [•]	11	13.97	58.1	47.56	13.60
Decyclization of alkoxy radicals					
R _i O [•] → R _f [•]	5	10.78	38.0	26.7	10.30
R _i O [•] → R _f [•]	6	9.84	31.7	0.7	10.30
R _i O [•] → R _f [•]	7	10.29	34.6	26.8	10.30
Decomposition of radicals					
RC [•] O → R [•] + CO		11.20	49.4		13.00
R ₃ CO [•] → R [•] + R ₂ C(O)		11.83	45.8		13.48

$$br_e = 13.13 \text{ (for } n = 6 \text{ and } n = 7) \quad (9)$$

$$br_e = 15.50 \text{ (for } n = 5)$$

(c) for reaction $R_i^* \rightarrow R_f^*$ (decyclization) [21]

$$br_e = 17.00 - 6.38 \times 10^{-2} E_{\text{rsc}} \quad (10)$$

(d) for reaction $R_iO^* \rightarrow R_f^*$ (decyclization) [22]

$$br_e = 9.81 + 3.61 \times 10^{-2} E_{\text{rsc}} \quad (11)$$

The calculation of activation energy of studied reactions was performed according the following equations [11–15]:

(1) for $\alpha = 1$

$$\sqrt{E_e} = \frac{br_e}{2} + \frac{\Delta H_e}{2br_e} \quad (12)$$

(2) for $\alpha \neq 1$

$$\sqrt{E_e} = \frac{br_e}{1 - \alpha^2} \left[1 - \alpha \sqrt{1 - \frac{1 - \alpha^2}{(br_e)^2} \Delta H_e} \right] \quad (13)$$

(3) for $\Delta H_e(1 - \alpha^2) \ll (br_e)^2$

$$\sqrt{E_e} = \frac{br_e}{1 + \alpha} + \frac{\alpha \Delta H_e}{2br_e} \quad (14)$$

$$E = E_e - 0.5hN_A\nu_i + 0.5RT \quad (15)$$

The uncertainty of activation energy estimation is around 2 kJ mol^{-1} [11]. Activation energies are calculated for reactions in nonpolar media.

Pre-exponential factor of intramolecular hydrogen transfer reaction depends on the number $n_{\text{C-H}}$ of attacked C–H bonds (for example $n_{\text{C-H}} = 2$ for CH_2 group etc.).

$$k = n_{\text{C-H}} \times A_0 \exp(-E/RT) = A \exp(-E/RT) \quad (16)$$

Besides this, it depends on the number of fragments that lose the ability of free rotation in the cyclic transition state. The empiric dependence has the following form (m = number of fragments frozen in transition state) [21]:

$$\log A = 13.30 - 0.60 \times m \quad (17)$$

RESULTS AND DISCUSSION

Enthalpies of Reactions

The strength of O–H bond in alcohols is higher than the strength of C–H bonds attacked by alkoxy radical. Therefore, intramolecular hydrogen transfer proceeds in alkoxy radicals as exothermic reaction. Reactions of hydrogen transfer in cyclic alkyl radical are close to thermoneutral (see Table III).

It is seen that decyclization of alkoxy radicals is exothermic. Decyclization of alkyl radicals with cleaving of C–O bond proceeds as exothermic reaction, however, that with cleaving of C–C bond as endothermic (see Table IV). Elimination of CO from acyl radical is endothermic reaction. On the contrary, elimination of CO_2 from carboxyl radical is exothermic reaction (see Table IV).

Activation Energy and Rate Constant of Reactions

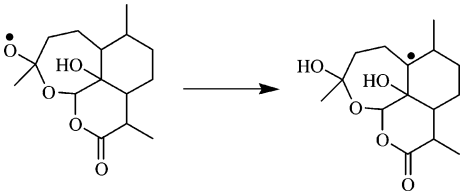
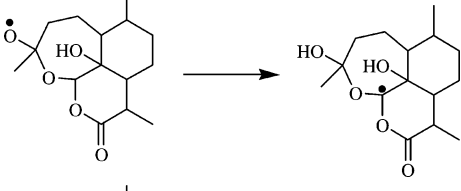
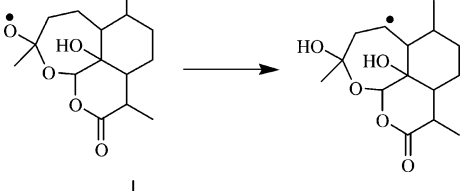
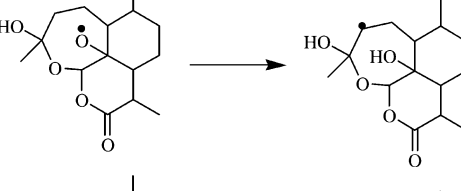
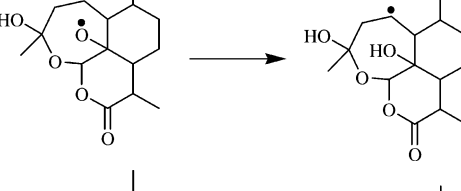
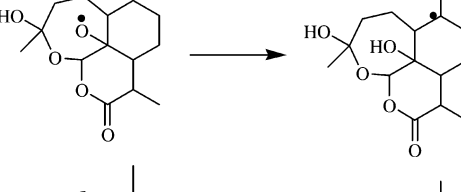
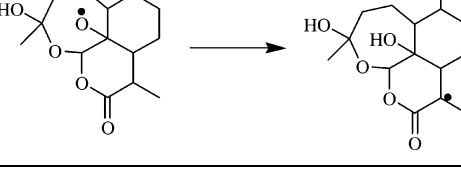
Two factors are important for activation of intramolecular hydrogen transfer, namely, reaction enthalpy ΔH and ring strain energy E_{rsc} in transition state [21,22]. The ring strain energy for six-membered transition state is close to zero [18]. Therefore, among reactions (1), (6), (7), and (11) with $\Delta H_e = -47.3 \text{ kJ mol}^{-1}$, the lowest activation energy is observed for reaction (1) with six-membered transition state ($E = 18.3 \text{ kJ mol}^{-1}$). For reactions with five-membered transition state, the lowest $E = 36.2 \text{ kJ mol}^{-1}$ is observed for reaction (2) with the lowest reaction enthalpy ($\Delta H_e = -55.6 \text{ kJ mol}^{-1}$). Among reactions with hydrogen transfer in cyclic alkyl radical, the reaction (13) with $n = 6$ appears the most rapid (see Table V).

Among seven reactions of RO^* decyclization, reactions (17) and (20) have the lowest activation energies and highest rate constants (see Table VI).

Rate constants of alkyl radical decyclization vary in very wide limits from 10^9 to 10^{-10} s^{-1} . Activation energy of these reactions depends on reaction enthalpy and transition state ring strain energy [21]. Reaction (24) as the most exothermic is the most rapid. Reactions of CO elimination are slow due to their endothermicity. Exothermic reaction of alkoxy radical decay with elimination of CH_3 is rapid due to its exothermicity. The exothermic reaction of carboxyl radical decay proceeds very rapidly too.

Enthalpy and activation energy of model reaction was calculated by quantum chemical methods [23].

Table III Enthalpies of Intramolecular Hydrogen Atom Transfer

No.	Reaction	D_i (kJ mol ⁻¹)	D_f (kJ mol ⁻¹)	ΔH (kJ mol ⁻¹)
Intramolecular reactions of H transfer in cyclic RO [•] radicals				
1		395.5	438.5	-43.0
2		387.2	438.5	-51.3
3		403.9	438.5	-34.6
4		403.9	438.5	-34.6
5		403.9	438.5	-34.6
6		395.5	438.5	-43.0
7		395.5	438.5	-43.0

Continued

Table III Continued

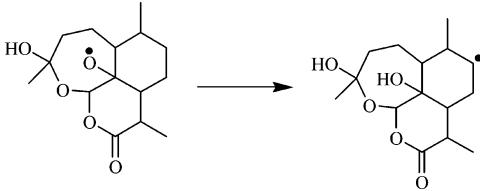
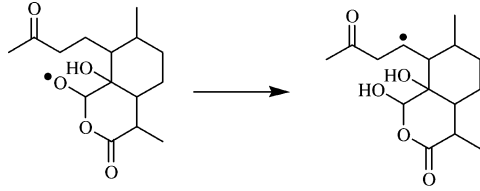
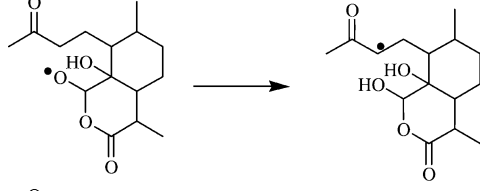
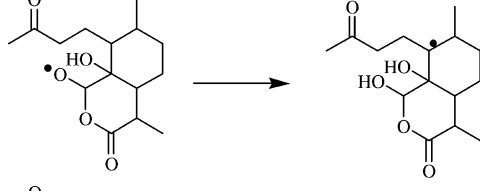
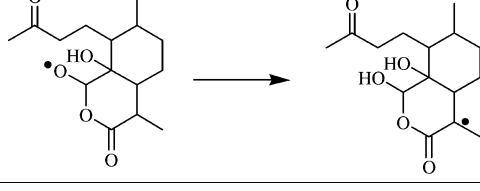
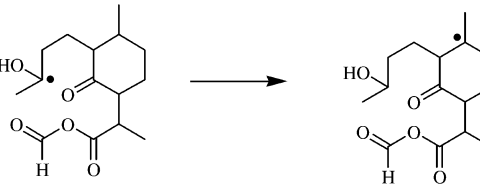
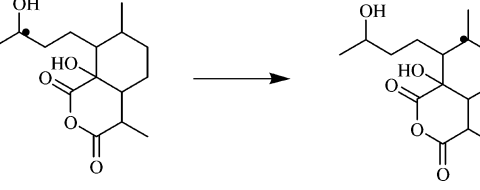
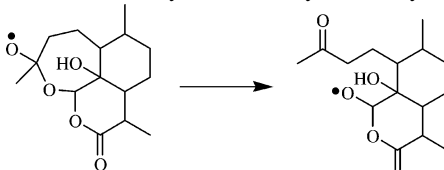
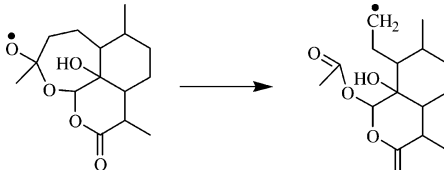
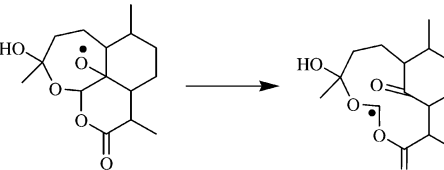
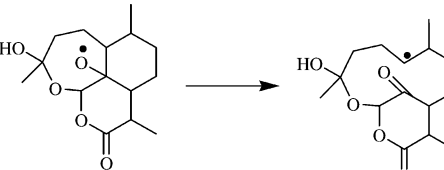
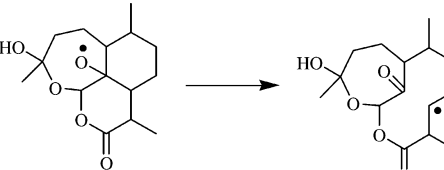
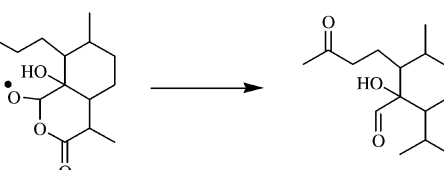
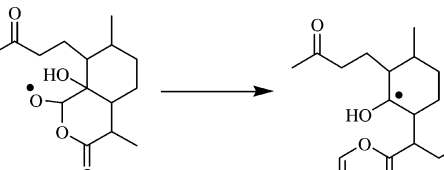
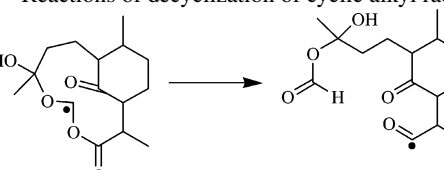
No.	Reaction	D_i (kJ mol ⁻¹)	D_f (kJ mol ⁻¹)	ΔH (kJ mol ⁻¹)
8		408.8	438.5	-29.7
9		412.0	438.5	-26.5
10		397.2	438.5	-41.3
11		395.5	438.5	-43.0
12		395.5	438.5	-43.0
Intramolecular reactions of H transfer in cyclic R [•] radicals				
13		395.5	390.5	5.0
14		395.5	390.5	5.0

Table IV Enthalpies of Decyclization of Alkoxy and Alkyl Radicals and Decay of Acyl and Alkoxy Radicals

No.	Reaction	ΔH (kJ mol ⁻¹)
Reactions of decyclization of cyclic alkoxy radicals		
15		-17.5
16		-89.2
17		-100.9
18		-22.0
19		8.1
20		-71.7
21		-64.5
Reactions of decyclization of cyclic alkyl radicals		
22		-117.5

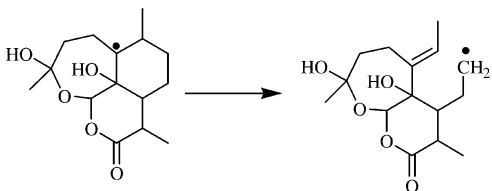
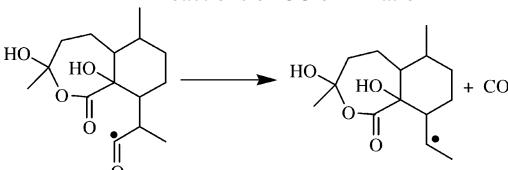
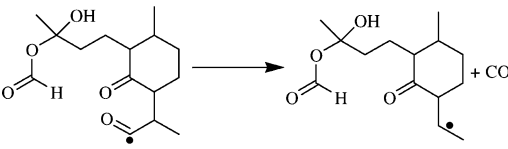
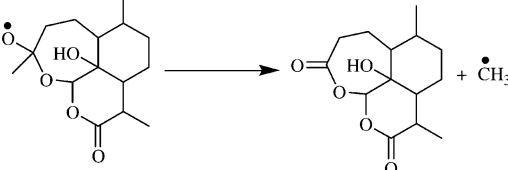
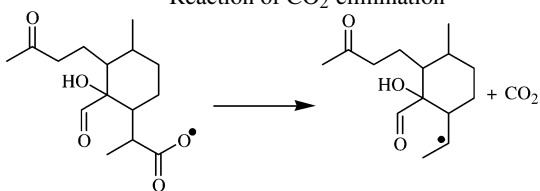
Continued

Table IV Continued

No.	Reaction	ΔH (kJ mol ⁻¹)
23		-88.6
24		-135.6
25		-94.9
26		74.8
27		74.8
28		108.3
29		82.7
30		87.8

Continued

Table IV Continued

No.	Reaction	ΔH (kJ mol ⁻¹)
31		92.2
Reactions of CO elimination		
32		47.9
33		47.9
Reaction of RO• decomposition		
34		-7.4
Reaction of CO ₂ elimination		
35		-40.1

The results of these calculations in comparison with our data are given below.

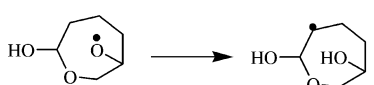
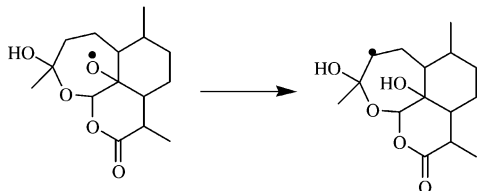
No.	Reaction	ΔH (kJ mol ⁻¹)	E (kJ mol ⁻¹)	Reference
		-21.6	30.2	[23]
4		-34.6	21.8	This work

Table V Activation Energies and Rate Constants of Hydrogen Transfer Reactions in Radicals Formed from Artemisinin

Reaction	<i>n</i> (Cycle)	ΔH_e (kJ mol ⁻¹)	<i>E</i> / (kJ mol ⁻¹)	log <i>A</i> <i>A</i> (s ⁻¹)	<i>k</i> (310 K) (s ⁻¹)
<i>R_iO[•] → R_f[•] (H transfer)</i>					
1	6	-47.3	18.8	13.6	2.67 × 10 ¹⁰
2	5	-55.6	36.2	13.6	3.16 × 10 ⁷
3	5	-38.9	42.3	13.9	5.82 × 10 ⁶
4	6	-38.9	21.8	13.9	1.70 × 10 ¹⁰
5	5	-38.9	42.3	13.9	5.82 × 10 ⁶
6	5	-47.3	39.2	13.6	9.88 × 10 ⁶
7	5	-47.3	39.2	13.6	9.88 × 10 ⁶
8	6	-34.0	23.6	13.9	8.52 × 10 ⁹
9	6	-30.8	24.7	13.3	5.36 × 10 ⁹
10	7	-45.6	19.4	12.7	2.70 × 10 ⁹
11	5	-47.3	39.2	13.6	9.88 × 10 ⁶
12	6	-47.3	38.5	13.6	1.30 × 10 ⁷
<i>R_i[•] → R_f[•] (H transfer)</i>					
13	6	5.0	38.4	13.60	1.34 × 10 ⁷
14	6	5.0	38.4	13.60	1.34 × 10 ⁷

Table VI Activation Energies and Rate Constants of Decyclization and Decay of Radicals Formed from Artemisinin

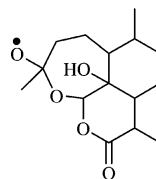
Reaction	<i>n</i> (Cycle)	ΔH_e (kJ mol ⁻¹)	<i>E</i> (kJ mol ⁻¹)	log <i>A</i> <i>A</i> (s ⁻¹)	<i>k</i> (310 K) (s ⁻¹)
<i>cyclo-R_iO[•] → R_f[•] (decyclization)</i>					
15	7	-19.6	19.9	10.30	8.87 × 10 ⁶
16	7	-91.3	2.2	10.30	8.52 × 10 ⁹
17	7	-103.0	1.3	10.30	1.21 × 10 ¹⁰
18	7	-24.1	18.5	10.30	1.53 × 10 ⁷
19	6	6.0	27.5	10.30	4.65 × 10 ⁵
20	6	-73.8	1.3	10.30	1.21 × 10 ¹⁰
21	6	-66.6	3.8	10.30	4.58 × 10 ⁹
<i>cyclo-R_i[•] → R_f[•] (decyclization)</i>					
22	11	-119.2	10.9	13.3	2.91 × 10 ¹¹
23	11	-90.3	18.3	13.3	1.65 × 10 ¹⁰
24	11	-137.3	7.0	13.3	1.32 × 10 ¹²
25	6	-96.6	41.3	13.3	2.20 × 10 ⁶
26	11	73.1	90.4	13.3	1.17 × 10 ⁻²
27	11	73.1	90.4	13.3	1.17 × 10 ⁻²
28	6	106.6	135.8	13.3	2.62 × 10 ⁻¹⁰
29	6	81.0	120.4	13.3	1.03 × 10 ⁻⁷
30	7	86.1	108.7	13.3	1.13 × 10 ⁻⁵
31	6	90.5	126.0	13.3	1.18 × 10 ⁻⁸
<i>RC[•](O) → R[•] + CO</i>					
32		53.4	66.4	13.0	64.6
33		53.4	66.4	13.0	64.6
<i>R₃CO[•] → R[•] + R₂C(O)</i>					
34		-9.5	35.0	13.5	4.00 × 10 ⁷
<i>RC(O)O[•] → R[•] + CO₂</i>					
35		-40.1	18.9	13.0	6.4 × 10 ⁹

We see that calculated values of ΔH and E are not in great difference for reaction of hydrogen transfer in cyclic alkoxy radicals.

CONCLUSION

We can now compare the different ways of transformation for each free radical formed from artemisinin.

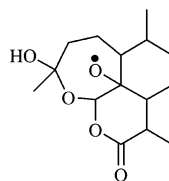
Radical



Reaction	1	2	3	15	16	34
k (310 K) (s^{-1})	2.7×10^{10}	3.2×10^7	5.8×10^6	8.9×10^6	8.5×10^9	1.3×10^7

The most rapid is the reaction (1) with H transfer from C to O atom of alkoxy radical.

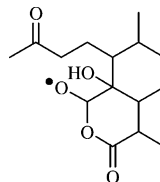
Radical



Reaction	4	5	6	7
k (310 K) (s^{-1})	1.7×10^{10}	5.8×10^6	9.9×10^6	9.9×10^6
Reaction	8	17	18	19
k (310 K) (s^{-1})	8.5×10^9	1.2×10^{10}	1.5×10^7	4.6×10^5

The most rapid is reaction (17) of decyclization with cleaving of C—C bond.

Radical



Reaction	9	10	11	12	20	21
k (310 K) (s^{-1})	5.4×10^9	4.2×10^{10}	9.9×10^6	2.7×10^{10}	1.2×10^{10}	4.6×10^9

The most rapid is reaction (10) with hydrogen transfer from C—H bond to oxygen atom.

Among reactions of hydrogen transfer in cyclic alkyl radicals reaction (13) proceeds more rapidly than reaction (14) (see Table V), reaction (22) more rapidly than (23), reaction (24) more rapidly than reaction (25), the

rate constants of reactions (26) and (27) are equal, and reactions (28)–(31) are very slow.

BIBLIOGRAPHY

- Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc Chem Res* 2002, 35, 167.

- Wu, Y. *Acc Chem Res* 2002, 35, 255.
- Meshnick, S. R. *Int J Parasitol* 2002, 32, 1655.
- Posner, G. H.; Park, S. B.; Conzalez, L.; Wang D.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A.; Bachi, M. D. *J Am Chem Soc* 1996, 118, 3537.
- Jung, M. *Curr Med Chem* 1994, 45.

6. Zhou, W.-S.; Xu, X.-X. *Acc Chem Res* 1994, 27, 211.
7. Klayman, D. I. *Science* 1985, 228, 1049.
8. Gu, J.; Chen, K.; Jiang, H.; Leszczunski, J. *J Phys Chem A* 1999, 103, 9364.
9. Eyler, G. N.; Canizo, A. I.; Mateo, C. M.; Alvarez, E. E.; Cafferata, L. F. R. *J Org Chem* 1999, 64, 8457.
10. Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.
11. Denisov, E. T. *Russ Chem Rev* 1997, 66, 859.
12. Denisov, E. T. In *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B. (Ed.); Wiley: London, 1999; pp. 79–137.
13. Denisov, E. T. *Russ Chem Rev* 2000, 69, 153.
14. Denisov, E. T.; Denisova, T. G. *Handbook of Antioxidants*; CRC Press: Boca Raton, FL, 2000.
15. Denisov, E. T.; Denisova, T. G.; Pokidova, T. S. *Handbook of Free Radical Initiators*; Wiley: Hoboken, NJ, 2003.
16. Denisova, T. G.; Denisov, E. T. *Kinet Catal.* (in press).
17. NIST Standard Reference Database 19A. *Positive Ion Energetics*. Ver. 2.02, 1994.
18. Domalski, E. S.; Hearing, E. D. *J Phys Chem Ref Data* 1993, 22, 816.
19. Denisova, T. G.; Denisov, E. T. *Kinet Catal* 2001, 42, 620.
20. Shestakov, A. E.; Denisova, T. G.; Denisov, E. T.; Emel'yanova N. S. *Russ Chem Bull* 2002, 51, 602.
21. Denisova, T. G.; Denisov, E. T. *Russ Chem Bull* 2002, 51, 949.
22. Denisov, E. T.; Denisova, T. G. *Russ Chem Rev* 2004, 73, 1091.
23. Gu, J.; Chen, K.; Jiang, H.; Leszczynski, J. *J Phys Chem A* 1999, 103, 9364.