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Artemisinin as a self-propagating radical initiator under aerobic conditions

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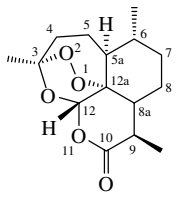
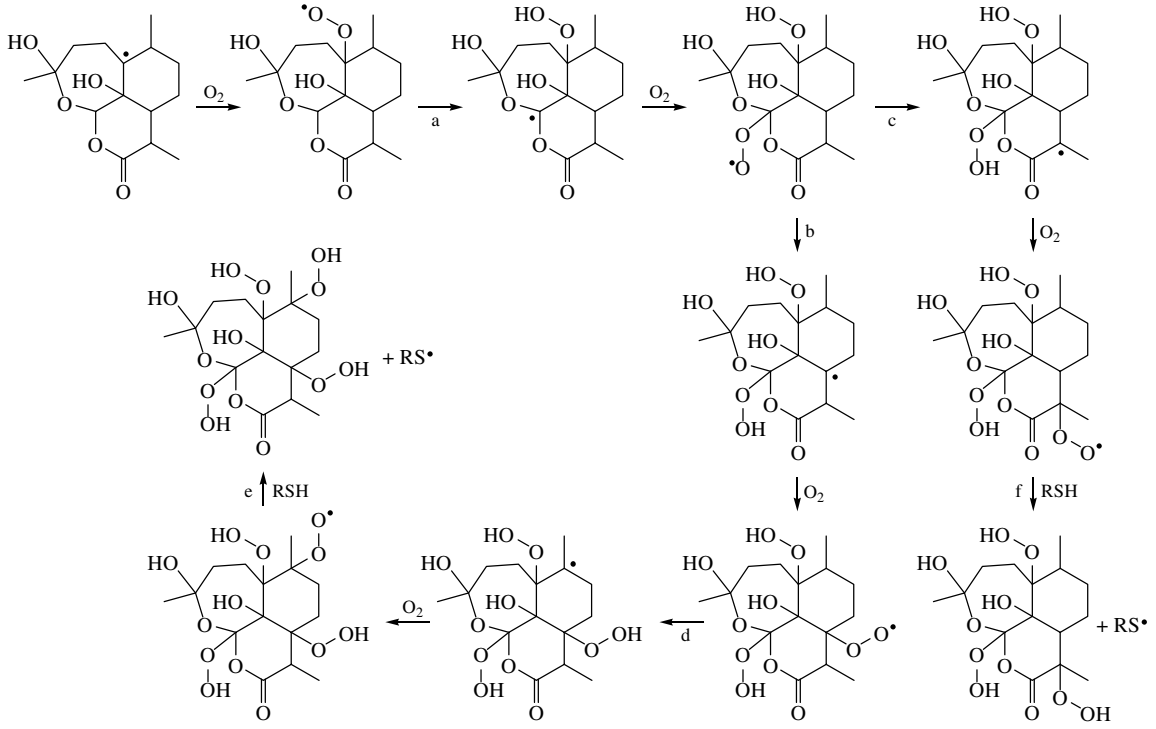
It has been shown theoretically using a parabolic model of radical reactions that alkyl radicals formed from artemisinin are involved in the rapid intramolecular chain oxidation of artemisinin to a polyfunctional initiator with several hydroperoxy groups.

Artemisinin and its derivatives are currently considered the most efficient drugs against malaria.[1–4] Artemisinin is a sesquiterpene with a peroxide bridge. Its therapeutic effect is explained by the formation of radicals in the reaction of chelated iron with the peroxide group.[5] The resulting radicals give rise to the formation of links in parasite's enzyme molecules resulting in the parasite's death.



Previously, we analysed the reactions of alkoxy and alkyl radicals formed from artemisinin and the competition of these reactions with the bimolecular reactions of the above radicals.[6,7] For alkoxy radicals, intramolecular hydrogen transfer and decyclisation predominate; as a result, a free valence is retained on artemisinin in the form of its alkyl radical. For alkyl radicals of artemisinin, intramolecular reactions also predominate over bimolecular reactions with substrates under anaerobic conditions. The C-centered artemisinin radicals resulting from such reactions can quickly add oxygen to give peroxy radicals. These reactions occur in a liquid phase with a diffusion rate constant of around 10^{10}–10^{9} dm^3 mol^{-1} s^{-1}.[8] The purpose of this work is to analyse theoretically the competition of intramolecular and bimolecular reactions of artemisinin peroxy radicals and to derive a kinetic scheme of transformations of these radicals.

We choose the following compounds as substrates for the bimolecular reactions of peroxy radicals: methyl *cis*-oleate ($D_{C–H}$ = 344.0 kJ mol^{-1}),[9] methyl *cis–cis*-linoleate ($D_{C–H}$ = = 318.0 kJ mol^{-1}),[9] glycerol ($D_{C–H}$ = 387.7 kJ mol^{-1}),[9] glucose ($D_{C–H}$ = 371.4 kJ mol^{-1}),[9] D-ribose ($D_{C–H}$ = 370.0 kJ mol^{-1}),[9] L-cysteine ($D_{S–H}$ = 360.0 kJ mol^{-1}),[10] α-tocopherol ($D_{O–H}$ = = 330.0 kJ mol^{-1})[11] and ubiquinol ($D_{O–H}$ = 343.8 kJ mol^{-1}).[11]



Scheme 1 $R^{5a\bullet}$ radical transformations.

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Table 1 Kinetic parameters α, br_e, $0.5hN_AH_i$ and $0.5hN_A(H_i - H_f)$ for the reaction types under consideration.[a,12,13]

Reaction type	α	br_e/ (kJ mol^{-1})$^{1/2}$	$0.5hN_AH_i$/ kJ mol^{-1}	$0.5hN_A(H_i - H_f)$/ kJ mol^{-1}
$RO_2^{\bullet} \rightarrow R^{\bullet}$ ($n = 6$)	0.814	13.23	17.4	–3.8
$RO_2^{\bullet} \rightarrow R^{\bullet}$ ($n = 7$)	0.814	13.43	17.4	–3.8
$RO_2^{\bullet} + R^1H$	0.814	15.20	17.4	–3.8
$RO_2^{\bullet} + R^2H$	0.814	15.20	17.4	–3.8
$RO_2^{\bullet} + RSH$	0.722	11.94	15.1	–6.1

[a] R^1H and R^2H are aliphatic and unsaturated compounds, respectively; $\alpha = b_i/b_f$, where b_i and b_f are coefficients describing the dependence of the potential energy on the amplitude of atoms' vibrations along the valence bond; r_e characterises the total elongation of the two reacting bonds in the transition state; $0.5hN_AH_i$ is the zero-oscillation energy of the bond; $0.5hN_A(H_i - H_f)$ is the difference between the zero-oscillation energies of the reacting bonds; and n is the number of atoms C in the cyclic transition state of the isomerization reaction.

To calculate the activation energies and reaction rate constants for artemisinin peroxy radicals, we used the equations and parameters of the intersecting parabolas method,[8,12,13] in which the radical elimination, for example,

$$RO_2^{\bullet} + R_iH \rightarrow ROOH + R_i^{\bullet},$$

is considered to be a result of the intersection of two potential curves, one of which characterises the stretching vibrations of the bond being attacked and the other characterises those of the bond formed in the reaction product.

The activation energies of the test reactions were computed using the following equations:[12]

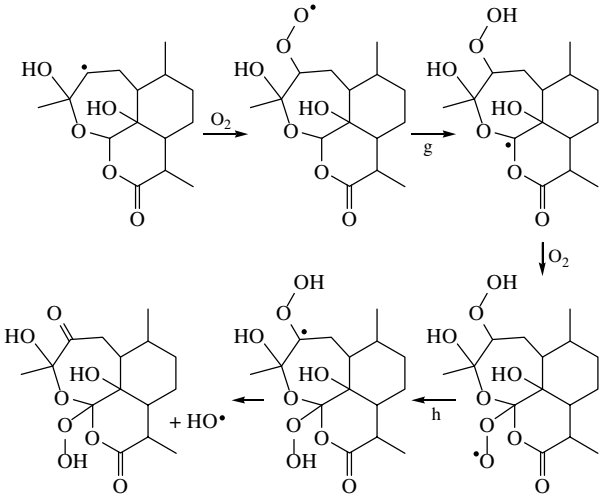
$$\sqrt{E_e} = \frac{br_e}{1-\alpha^2}\left\{1 - \alpha\sqrt{1 - \frac{1-\alpha^2}{(br_e)^2}\ \Delta H_e}\right\}, \quad (1)$$

$$E = E_e - 0.5(hN_AH_i - RT), \quad (2)$$

where E_e is the classical potential barrier and E is the activation energy of the reaction. The values of α, br_e and other parameters corresponding to the test reactions are given in Table 1.

Of the possible intramolecular hydrogen transfer reactions, only those were taken into account which occur *via* six- or seven-membered transition states, the activation energies of which are the smallest.[13] To calculate the enthalpies ΔH of intramolecular H transfer, we used the dissociation energies of C–H bonds in model compounds[9] and those of O–H bonds of structurally similar hydroperoxy groups.[14] The intramolecular oxidation of artemisinin results in a >CH(OOH) moiety, in which the α-C–H bond is weakened by the adjacent hydroperoxy group. The strength of this bond was calculated by a published method[15] based on experimental data on the reaction of the cyclohexylperoxy radical with the α-C–H bond in cyclohexylhydroperoxide.[16] The values of D_{C-H} and D_{O-H} for bonds used for the reaction enthalpy calculations are presented in Table 2.

The rate constant was calculated by the Arrhenius equation $k = A\exp(-E/RT)$. The preexponential factor A for intramolecular hydrogen transfer depends on the number m of groups that lose the ability for free rotation in the cyclic transition state; the relationship is described by the equation $\lg A_0 = 13.30 - 0.6m$.[13] In the transition state of intramolecular attack of $RO_2^{\bullet}$ to the C–H bond, the rotation of only one group is disabled, namely, that of the O–O$^{\bullet}$ bond in the $RO_2^{\bullet}$ radical; therefore, $A_0 = 5.5\times10^{12}$ s^{-1}. For bimolecular reactions, $A_0 = 1.0\times10^8$ dm^3 mol^{-1} s^{-1} for an aliphatic C–H bond, $A_0 = 1.0\times10^7$ dm^3 mol^{-1} s^{-1} for an allylic C–H bond, $A_0 = 3.2\times10^7$ dm^3 mol^{-1} s^{-1} for an O–H bond in phenol, and $A_0 = 1.0\times10^9$ dm^3 mol^{-1} s^{-1} for an S–H bond in L-cysteine.[11] Furthermore, the factor A depends on the number n_{C-H} of C–H bonds being attacked; therefore, the reaction rate constant was calculated by the equation $k = n_{C-H}\times A_0\exp(-E/RT) = A\exp(-E/RT)$.



Scheme 2 $R^{4a\bullet}$ radical transformations.

Calculations showed that, of all the substrates, peroxy radicals react most quickly with S–H groups of L-cysteine. In particular, *tert*-$RO_2^{\bullet}$ reacts with L-cysteine (R′SH) with $\Delta H = 1.4$ kJ mol^{-1}, $E = 29.6$ kJ mol^{-1} and $k(310\ K) = 1.03\times10^4$ dm^3 mol^{-1} s^{-1}; at [R′SH] = 0.05 mol dm^{-3}, k[R′SH] = 5.15×10^2 s^{-1}. The other bimolecular reactions proceed much slower. Thus, the rate constants k(310 K) are 2 (methyl oleate), 48 (methyl linoleate), 1.0 (glycerol), 260 (glucose) and 340 dm^3 mol^{-1} s^{-1} (D-ribose). It is evident from the data in Table 2 that most of reactions of intramolecular hydrogen transfer occur much rapidly. The most rapid reaction was selected from the concurrent reactions of intramolecular H transfer. For example, the $R^4O_2^{\bullet}$ radical abstracts a hydrogen atom from positions $R^{5a\bullet}$ ($k = 3.68\times10^4$ s^{-1}), $R^{6\bullet}$ ($k = 1.26\times10^4$ s^{-1}) and $R^{12\bullet}$ ($k = 3.30\times10^5$ s^{-1}). A comparison of the values of k shows that the main pathway of the transformations of this radical is the abstraction of H from the RH^{12} position. The bimolecular reaction of $R_iO_2^{\bullet}$ with artemisinin proceeds extremely slowly due to a very low (~10^{-6} mol dm^{-3}) concentration of artemisinin and a low rate constant (0.35 dm^3 mol^{-1} s^{-1}). Table 2 lists the enthalpies, activation energies and rate constants for these most rapid reactions.

The main pathways of transformations of two C-centered artimisinin radicals are shown in Schemes 1 and 2. It is evident from the kinetic schemes that the oxidation of artemisinin radicals predominantly occurs as an intramolecular chain reaction to give a molecule incorporating several hydroperoxy groups (2–4). In such a chain reaction, the free valence is removed from artemisinin either *via* a reaction with the substrate (most quickly, in the reaction with L-cysteine) or *via* the decomposition of the unstable α-hydroperoxyalkyl radical: >C$^{\bullet}$(OOH) → → >C=O + HO$^{\bullet}$, as a result of which a free valence is removed

Table 2 Dissociation energies of individual C–H bonds in artemisinin[6] and O–H bonds in its peroxides;[14] enthalpies, activation energies and rate constants of intramolecular H-atom transfer and k[R′SH] for bimolecular reactions of peroxy radicals with the S–H bond of L-cysteine calculated by equation (1).

Reaction	D_{C-H}/ kJ mol^{-1}	D_{O-H}/ kJ mol^{-1}	ΔH/ kJ mol^{-1}	E/ kJ mol^{-1}	k(310 K)/ s^{-1}
$R^{5a}O_2^{\bullet} \rightarrow R^{12\bullet}$ (a)	378.3	358.6	19.7	44.5	1.72×10^5
$R^{12}O_2^{\bullet} \rightarrow R^{8a\bullet}$ (b)	387.6	367.6	20.0	44.7	1.62×10^5
$R^{12}O_2^{\bullet} \rightarrow R^{9\bullet}$ (c)	385.3	367.6	17.7	45.2	1.34×10^5
$R^{8a\bullet}O_2^{\bullet} \rightarrow R^{6\bullet}$ (d)	395.5	358.6	36.9	54.8	3.14×10^3
$R^6O_2^{\bullet}$ + R′SH (e)	360.0	358.6	1.4	29.6	5.15×10^{2a}
$R^9O_2^{\bullet}$ + R′SH (f)	360.0	369.8	–9.8	25.0	3.04×10^{3a}
$R^4O_2^{\bullet} \rightarrow R^{12\bullet}$ (g)	378.3	365.5	12.8	42.8	3.30×10^5
$R^{12}O_2^{\bullet} \rightarrow R^4(OOH)^{\bullet}$ (h)	370.9	367.6	3.2	38.4	1.82×10^6

[a] k[R′SH] is reported; [R′SH] = 0.05 mol dm^{-3}.

from artemisinin as a hydroxy radical. The decomposition of the α-hydroperoxycyclohexyl radical is very exothermic; its enthalpy equals –92 kJ mol^{-1}. In turn, the hydroperoxy groups resulting from the oxidation decompose into radicals on treatment with an iron chelate. Thus, the generation of radicals from artemisinin is a more complex process than it was believed previously.[1,2] The alkoxy radical formed from artemisinin is converted into an alkyl radical, which is oxidised by a chain mechanism to give a polyatomic hydroperoxide, and the latter generates free radicals in a set of main reactions with Fe^{II}. Thus, artemisinin behaves as a repetitive initiator in the presence of oxygen. Apparently, this is one of the reasons for its high efficiency as a drug.

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