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Standard Molar Enthalpies of Formation and Thermal Stabilities of Artemisinin and Its Two Derivatives: Artemether and Artesunate

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The constant-volume energy of combustion of crystalline artemisinin and its two derivatives, artemether and artesunate, in oxygen at $T = 298.15$ K was determined to be $\{-(7546.53 \pm 3.24), -(7582.28 \pm 3.09)$, and $-(8150.75 \pm 4.24)\}$ kJ·mol^{-1} using combustion calorimetry, respectively. The derived standard molar enthalpies of formation of the three compounds in crystalline states at $T = 298.15$ K were $\{-(1492.81 \pm 7.62), -(2419.75 \pm 7.52)$, and $-(3320.12 \pm 9.90)\}$ kJ·mol^{-1}, respectively. The thermal stabilities of the three compounds were also investigated by thermal analysis combined with an FT-IR method.

Introduction

Artemisinin, artemether, and artesunate are all sesquiterpene lactone compounds with an endoperoxide function. Artemisinin was first isolated from the Chinese traditional herb *Artemisia annua* L. and its structure was confirmed by Chinese scientists in 1970s.[1−6] Artemisinin and its derivatives/analogues are currently regarded as a promising drugs against malaria, an ancient disease that once was thought to be near eradication in the 1950−1960s but has become a serious threat to humankind again as a result of the appearance of multidrug-resistant variants.[7] Its antimalarial mechanism is of great interest to the scientific community as its unique 1,2,4-trioxane structure of entirely incompatible with the traditional antimalarial structure−activity theory. Many researchers focused their efforts to elucidate its antimalarial mechanism and to synthesize its derivatives or analogues.[7−10] Artemether and artesunate are two derivatives of artemisinin. Their antimalarial effects are better than artemisinin because their water solubility were increased.[2] The molecular structure and basic information of the three compounds are summarized in Figure 1 and Table 1, respectively.

The thermochemical properties of a drug are very important for its development. The knowledge of the thermodynamics data can provide important experimental foundation for the quantum chemistry, computer-aided drug designs, and new materials. It will also afford a theoretical basis to establish the technological processes of synthesis and purification and to understand the biochemical reactions if quantitative studies on the energetic are to be performed. However, the thermodynamics properties of artemisinin and its derivatives were seldom reported. Only a few studies on their physical properties have been reported. The Chinese scientists in the research group on artemisinin and Lisgarten et al. confirmed the crystal structure and the absolute configuration of artemisinin,[5,6] artemether,[11,12] and artesunate[13] using X-ray diffraction analysis on crystals, respectively. Luo et al.[14] and Lin et al.[15] studied the thermal rearrangement and decomposition products of it, respectively. Chan et al. researched the polymorphism of artemisinin.[16] Xing et al.[17] and Coimbra et al.[18] studied the solubility of artemisinin in supercritical carbon dioxide, respectively.

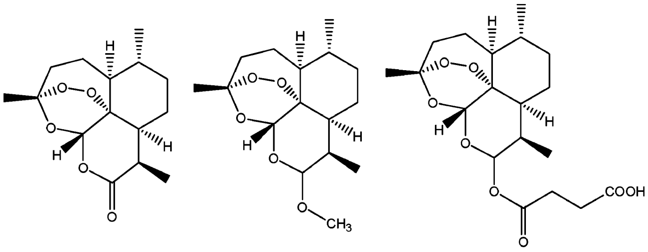

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Figure 1. Molecular structure of artemisinin (1), artemether (2), and artesunate (3).

Table 1. General Information and Density Values of Artemisinin, Artemether, and Artesunate[a]

compound	formula	CASRN	M/g·mol^{-1}	ρ/g·cm^{-3}	ref
artemisinin	$C_{15}H_{22}O_5$	63968-64-9	282.33	1.300	5, 6
artemether	$C_{16}H_{26}O_5$	71963-77-4	298.38	1.215	11, 12
artesunate	$C_{19}H_{28}O_8$	88495-63-0	384.42	1.316	13

[a] M is the molar mass. ρ is the density. They were calculated from the crystal lattice parameters determined by X-ray crystal analysis according to the literature.

In the present work, the enthalpies of combustion of artemisinin, artemether, and artesunate in crystal form were determined by rotating-bomb combustion calorimetry at $T = 298.15$ K and the standard molar enthalpies of formation in the crystalline state at $T = 298.15$ K were derived. The thermal stability of the three compounds were further examined by thermal analysis (TG-DTA) combined with FT-IR over the temperature range from (300 to 750) K, respectively.

Experimental Section

Materials. Artemisinin (CASRN: 63968-64-9) was supplied by Qingjiang Bioengineering Co. Ltd., Hubei Province, People's Republic of China. It was extracted from *Artemisia annua* L. and then purified. Artemether (CASRN: 71963-77-4) and artesunate (CASRN: 88495-63-0) were obtained from Chengdu Superman Plant & Chemical Development Co., Ltd., Sichuan

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Province, People's Republic of China. They were semisynthesized from artemisinin. The three compounds are all colorless needle crystals, and the purities of mass fraction are all above 0.995, which were determined by HPLC and XRD. Further purification was not performed. In the present calorimetric case, the mass of the sample was accurately weighed using a microbalance (Sartorius, ME215S) with a resolution of 0.01 mg. Nitrogen gas with a purity of 99.999 % was used in the TG-DTA and FT-IR tests.

Combustion Calorimetry. The constant-volume energy of combustion of the three title compounds were determined with a RBC-II type rotating-bomb combustion calorimeter, which was constructed in the Department of Chemistry, Northwest University, Xi'an 710069, People's Republic of China. The calorimeter mainly consisted of a water thermostat, a caloritube, a platinum thermometer, and an integrated circuit for temperature measurement and indication. More comprehensive descriptions about the calorimeter and detailed procedure can be found in the earlier literatures.[19−21]

The temperature of the water thermostat was kept at $T = (298.15 \pm 0.0005)$ K. The water temperature in the caloritube was subsequently adjusted to lower than that of the water thermostat, and the temperature difference between the water in the caloritube and the water thermostat was equal to half of the temperature increment of the calorimeter during the combustion reaction. A known mass of double-distilled water was added into the caloritube. When the sample was placed in the crucible fixed on the support in the rotating-bomb, the Ni−Cr wire was fixed in the bomb and the initial bomb-solution was then injected into the rotating-bomb. After the bomb was filled with 2.5 MPa oxygen gas, it was sealed. Before the calorimetric test, the calorimeter was set up well. It was important to keep up a constant temperature change rate in the calorimeter at the beginning of the experiment. In the early period of the experiment, the values of the temperature were recorded versus time typically with one entry every 30 s until the 11th one. From the 11th one, the sample was ignited, and the magnitudes of the temperature were recorded every 60 s till the main period of the combustion reaction was finished. In the later period of the experiment, the temperatures were recorded as in the early period of the experiment. After the experiment was accomplished, the final products of the combustion reaction were analyzed.

The gases formed in the combustion reaction were collected in a gas collecting bag. The amounts of gas were measured by a gas meter, which was joined between the bag and the apparatus for gas analysis. The apparatus for gas analysis had four absorption tubes connected with each other. The first one was filled with P_4O_{10} and $CaCl_2$ (anhydrous) to absorb the water vapor in gases; the second one was filled with active MnO_2 in order to absorb the nitrogen oxides; the third one was filled with alkali asbestos to absorb the CO_2, which is for determination; and the fourth one was also filled with P_4O_{10} and $CaCl_2$ (anhydrous) to absorb the water formed in the process of determination.

The gaseous CO_2 formed in the combustion reaction was absorbed by the pipe with alkali asbestos. The amount of CO_2 was determined through the mass increment of the tube. The amount of CO_2 dissolved in the final acidic solution was ignored.

Azo dyes were formed when NO_2 was absorbed by the absorption solution in the first flask. NO was oxided into NO_2 when it passed through an oxide tube. The formed NO_2 was absorbed by the absorption solution in the second flask. The amount of NO and NO_2 were obtained by determination the absorbance at a wavelength between (540 and 545) nm (Saltzman calorimetric analysis method).

The fitting and internal wall of the bomb was washed with double-distilled water, and the final solution (including the washing solution) was transferred into a conical flask and then heated to boiling to remove CO_2. After neutralization, the solution was cooled to room temperature in a volumetric flask. The amount of HNO_3 in the final solution in the bomb was determined by using Devarda's alloy method.[22]

The analytical results of the final solution showed that the combustion reactions were complete. Neither carbon deposits nor carbon monoxide was formed during the combustion reactions. The amount of NO_x in the final gas was insignificant.

The energy equivalent of the RBC-II calorimeter was calculated according to the following equation:

$$\epsilon = (Qa + Gb + 5.983c)/\Delta T \tag{1}$$

where ϵ is the energy equivalent of the calorimeter, Q is the energy of combustion of benzoic acid, a is the mass of benzoic acid, G is the heat of combustion of Ni−Cr wire for ignition (0.9 $\text{J}\cdot\text{cm}^{-1}$), b is the length of the actual Ni−Cr wire consumed, 5.983 J is the enthalpy of formation and solution of nitric acid corresponding to 1 cm^3 of 0.1000 $\text{mol}\cdot\text{dm}^{-3}$ solution of NaOH, c is the volume of 0.1000 $\text{mol}\cdot\text{dm}^{-3}$ solution of NaOH consumed, and ΔT is the corrected temperature increment.

The corrected value of the heat exchange is calculated by the following equation:

$$\Delta(\Delta T) = nr_{\text{f}} + (r_{\text{a}} - r_{\text{f}})/(\overline{T}_{\text{a}} - \overline{T}_{\text{f}})[(T_0 + T_{\text{a}})/2 + \sum_{i=1}^{n-1} T_i - n\overline{T}_{\text{f}}] \tag{2}$$

where $\Delta(\Delta T)$ denotes the corrected value of the heat exchange; n is the number of readings for the main (or reaction) period; r_{f} and r_{a} are the temperature change rate at the fore and after periods, respectively (r is positive when temperature decreased); $\overline{T}_{\text{f}}$ and $\overline{T}_{\text{a}}$ are the average temperature of the calorimeter at the fore and after periods, respectively; T_0 is the last value of the temperature of the fore period; T_{a} is the first reading of the after period; $\sum_{i=1}^{n-1} T_i$ is the sum of all values of the temperature of the main period, except for the last one of the main period; and $(r_{\text{a}} - r_{\text{f}})/(\overline{T}_{\text{a}} - \overline{T}_{\text{f}})$ must be constant.

The energy equivalent and the uncertainty of the rotating-bomb combustion calorimeter were calibrated by the combustion of benzoic acid (Standard Reference Material 39i, the National Institute of Standards and Technology).[23] The energy equivalent was determined to be (17775.09 ± 7.43) $\text{J}\cdot\text{K}^{-1}$, where the uncertainty quoted is the standard deviation of the mean of six calibration experiments.

Thermal Analysis. The TG-DTA tests were performed in a thermal analyzer, SDT Q600 from TA instrument, Waters LCC, USA. The 90 μL TA corundum crucibles were used, and the instrument was calibrated by indium before the tests. About a (7 to 10) mg sample was used at each time. The heating rate was 10 $\text{K}\cdot\text{min}^{-1}$, and the temperature range was from (300 to 750) K. The nitrogen gas flow rate was 200 $\text{mL}\cdot\text{min}^{-1}$ to ensure the gaseous decomposition products being quickly driven out from the furnace to the gas sample cell of the IR spectrometer. The IR spectrum of the off gas from the oven of the thermal analyzer was synchronously recorded by an FT-IR spectrometer, Nicolet 380 with a TGA/FT-IR interface from Thermo Electron Corporation, USA. The temperature of the gas transfer tube and the sample cell of the IR spectrograph were thermostated at

Table 2. Constant-Volume Energy of Combustion of Artemisinin, Artemether, and Artesunate in Oxygen at T = 298.15 K[a]

no.	m/g	Q_C/J	Q_N/J	ΔT/K	$-\Delta_C U_m^{\ominus}$(cr)/kJ·mol^{-1}
			Artemisinin		
1	0.84431	12.60	31.67	1.2728	7550.53
2	0.84722	12.60	31.42	1.2755	7540.66
3	0.84307	12.60	31.53	1.2702	7546.22
4	0.84604	12.60	31.29	1.2726	7534.02
5	0.84750	12.60	31.48	1.2782	7554.13
6	0.84616	12.60	31.60	1.2761	7553.61
mean					7546.53 ± 3.24
			Artemether		
1	0.82231	12.60	21.50	1.1783	7587.46
2	0.88225	12.60	20.69	1.2632	7582.59
3	0.86308	12.60	21.48	1.2350	7577.42
4	0.83492	12.60	21.60	1.1939	7571.91
5	0.82636	12.60	20.85	1.1850	7593.47
6	0.84766	12.60	21.36	1.2135	7580.81
mean					7582.28 ± 3.09
			Artesunate		
1	0.71304	12.60	21.30	0.8539	8164.70
2	0.75247	12.60	21.38	0.8999	8154.52
3	0.80352	12.60	20.96	0.9595	8143.45
4	0.81610	12.60	21.55	0.9741	8139.89
5	0.79085	12.60	20.88	0.9463	8159.91
6	0.83520	12.60	21.42	0.9971	8142.01
mean					8150.75 ± 4.24

[a] m is the mass of sample, which has been corrected from the apparent mass. $Q_C = Gb$ is the energy of combustion of igniting wire, and $Q_N = 5.983c$ is the heat of formation of nitric acid as described in eq 1. ΔT is the corrected temperature increment. $\Delta_C U_m^{\ominus}(\text{cr}) = -(\epsilon \Delta T\text{-}Q_C - Q_N)M/m$ is the constant-volume molar energy of combustion of sample, where M is the molar mass of the samples and ϵ is the corrected energy equivalent of the combustion calorimeter determined as (17775.09 ± 7.43) J·K^{-1}. The uncertainty quoted for $\Delta_C U_m^{\ominus}$(cr) corresponds to the standard deviation of the mean value.

453 K. The spectra were recorded with a time interval of 5 s in the wave number range from (4000 to 400) cm^{-1}, and each record was the Fourier transformation of 10 scans. The IR background was collected and subtracted before the measurement.

Results and Discussion

Standard Molar Enthalpies of Formation. The standard atomic masses recommended by the IUPAC Commission in 2005[24] were used in the calculation of all of the molar quantities. The density values summarized in Table 1 of the compounds were used to correct the apparent mass to mass. The standard-state corrections have been processed according to the "Washburn reduction".[25]

The constant-volume energy of combustion of the three crystalline compounds at T = 298.15 K, $\Delta_C H_m^{\ominus}$(cr), were determined by a rotating-bomb combustion calorimeter. The detailed results of combustion calorimetric experiment are summarized in Table 2. The standard molar enthalpies of combustion of the three compounds at T = 298.15 K, $\Delta_C H_m^{\ominus}$(cr), refers to the enthalpy of combustion reaction of the following ideal combustion reactions at T = 298.15 K and P = 101.325 kPa:

$$C_{15}H_{22}O_5(\text{cr}) + 18O_2(\text{g}) = 15CO_2(\text{g}) + 11H_2O(\text{l}) \tag{3}$$

$$C_{16}H_{26}O_5(\text{cr}) + 20O_2(\text{g}) = 16CO_2(\text{g}) + 13H_2O(\text{l}) \tag{4}$$

$$C_{19}H_{28}O_8(\text{cr}) + 22O_2(\text{g}) = 19CO_2(\text{g}) + 14H_2O(\text{l}) \tag{5}$$

The standard molar enthalpies of combustion of the compounds at T = 298.15 K were calculated from the experimental energy of combustion at T = 298.15 K by the following equation:

$$\Delta_C H_m^{\ominus}(\text{cr}) = \Delta_C U_m^{\ominus}(\text{cr}) + \Delta nRT \tag{6}$$

where n is the total amount of gas present as products or reactants, $\Delta n = n_{\text{product}} - n_{\text{reactant}}$, R = 8.314472 J·mol^{-1}·K^{-1},[26] and T = 298.15 K.

Table 3. Standard Molar Enthalpies of Combustion and Formation of Artemisinin, Artemether, and Artesunate

compound	$\Delta_C H_m^{\ominus}$(cr)/kJ·mol^{-1}	$\Delta_f H_m^{\ominus}$(cr)/kJ·mol^{-1}
artemisinin	−7553.97 ± 6.48	−1492.81 ± 7.62
artemether	−7592.20 ± 6.18	−2419.75 ± 7.52
artesunate	−8158.19 ± 8.48	−3320.12 ± 9.90

The standard molar enthalpies of formation of the three compounds at T = 298.15 K, $\Delta_f H_m^{\ominus}$(cr), were derived by Hess's law according to the following thermochemical equations:

$$\Delta_f H_m^{\ominus}(\text{cr, } C_{15}H_{22}O_5) = [15\Delta_f H_m^{\ominus}(CO_2\text{, g}) + 11\Delta_f H_m^{\ominus}(H_2O\text{, l})] - \Delta_C H_m^{\ominus}(\text{cr, } C_{15}H_{22}O_5) \tag{7}$$

$$\Delta_f H_m^{\ominus}(\text{cr, } C_{16}H_{24}O_5) = [16\Delta_f H_m^{\ominus}(CO_2\text{, g}) + 13\Delta_f H_m^{\ominus}(H_2O\text{, l})] - \Delta_C H_m^{\ominus}(\text{cr, } C_{16}H_{24}O_5) \tag{8}$$

$$\Delta_f H_m^{\ominus}(\text{cr, } C_{19}H_{28}O_8) = [19\Delta_f H_m^{\ominus}(CO_2\text{, g}) + 14\Delta_f H_m^{\ominus}(H_2O\text{, l})] - \Delta_C H_m^{\ominus}(\text{cr, } C_{19}H_{28}O_8) \tag{9}$$

where $\Delta_f H_m^{\ominus}(CO_2\text{, g}) = -(393.51 \pm 0.13)$ kJ·mol^{-1}, and $\Delta_f H_m^{\ominus}(H_2O\text{, l}) = -(285.83 \pm 0.04)$ kJ·mol^{-1}.[27,28] The standard molar enthalpies of combustion and formation of the compounds at T = 298.15 K were derived and summarized in Table 3. The

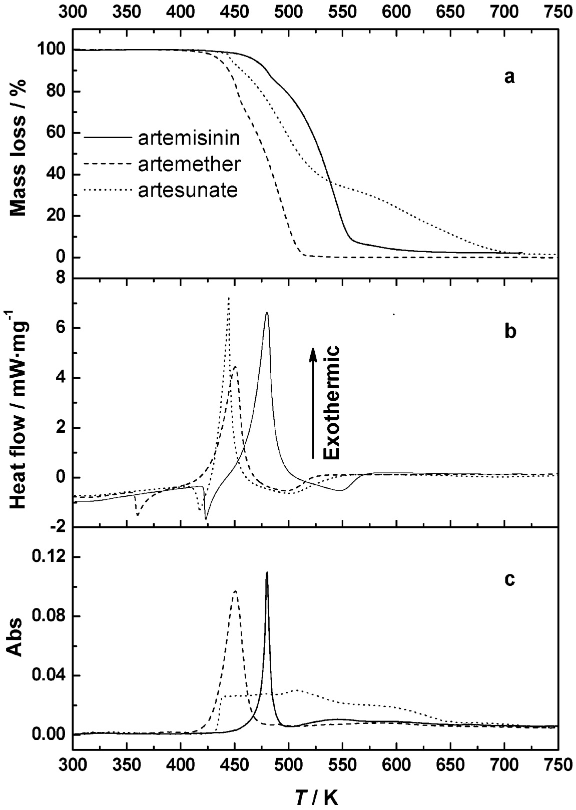

Figure 2. TG (a) and DTA (b) curve and the IR absorbance vs the furnace temperature (c) of artemisinin (solid lines), artemether (dashed lines), and artesunate (dotted lines).

Table 4. Onset and Peak Temperatures of the DTA Curves[a]

compound	T_{onset}/K	T_{peak}/K
artemisinin	421.43	480.53
artemether	357.13	450.49
artesunate	412.81	444.56

[a] T_{onset} is the onset temperature of the first endothermic peak, and T_{peak} means the peak temperature of the exothermic peak of the DTA curves.

uncertainties assigned to the values of $\Delta_C H_m^\Theta$(cr) and $\Delta_f H_m^\Theta$(cr) were calculated according to the literature[29] in accordance with the normal thermochemical practice. They were twice the overall standard deviation of the mean and include the uncertainties in calibration and in the values of auxiliary quantities used.

Thermal Stabilities. The TG-DTA measurements were carried out in N_2 atmosphere. The TG-DTA results were presented in Figure 2. It can be seen from the mass loss curves (Figure 2a) that the mass loss occurred above 420 K for all of the three compounds. There were two mass loss steps for artemisinin and artemether and three steps for artesunate. No residue was found in the crucible after the experiment was completed. Two peaks were observed from the DTA curves (Figure 2b). There were no mass loss at the first endothermic peaks, and they were associated with the fusion of the compounds. The second large exothermic peaks corresponded to the first mass loss, and they were associated with the thermal rearrangement and decomposition of the compounds. They started just after fusion. The onset temperature of the endothermic peaks and the peak temperature of the exothermic peaks were summarized in Table 4.

The IR spectrum of off gas was recorded by an FT-IR spectrometer continuously. The results are shown in Figures 2 and 3. It can be seen from Figure 2 that the peaks of the IR absorbency of gaseous decomposition products from artemisinin and artemether appeared at the first mass loss step; however, for artesunate, two absorbency peaks appeared at the first and second mass loss steps. The gaseous decomposition products may mainly be composed of formic acid (HCOOH) at the first mass loss step for the three compounds, and it may be succinic anhydride ($C_4H_4O_4$) at the second mass loss step of artesunate, respectively, by comparing the IR spectrums with the standard IR spectrum library as shown in Figure 3.

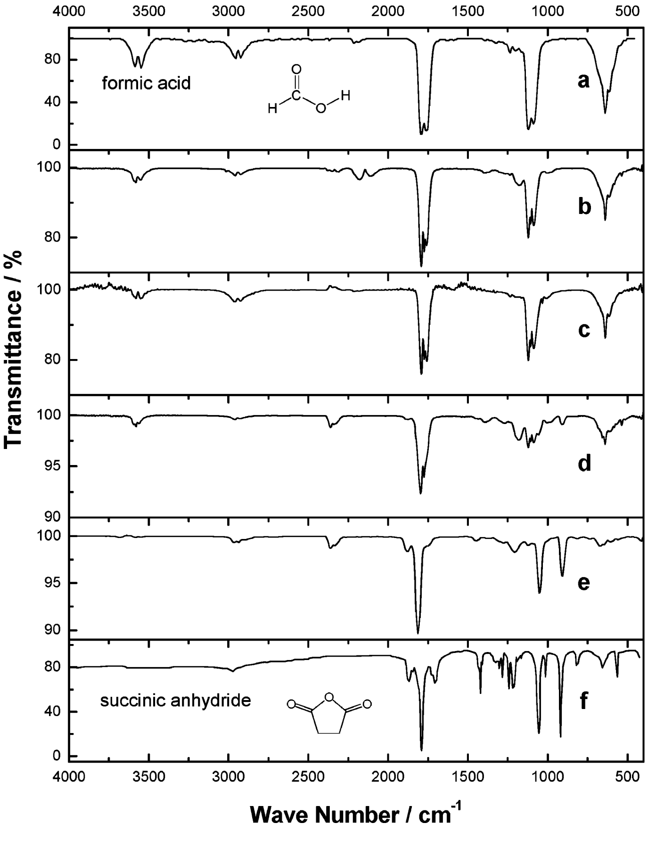

Figure 3. FT-IR spectra of the gaseous decomposition products. The standard IR spectra of formic acid (a) and succinic anhydride (f); the IR spectra of the gaseous decomposition product of artemisinin (b), artemether (c), artesunate at the first (d) and second (e) mass loss steps.

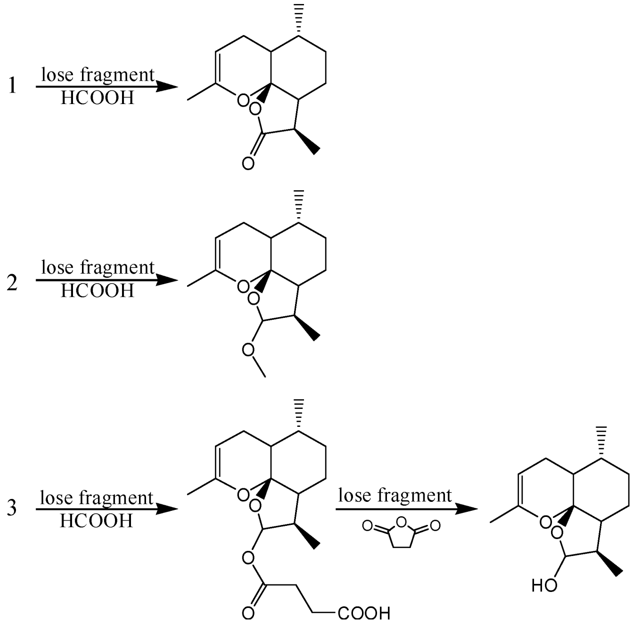

Figure 4. Proper decomposition schemes of artemisinin, artemether, and artesunate.

The thermal decomposition products and the possible decomposition scheme of artemisinin were described by Luo et al.[14] and Lin et al.[15] in the earlier literature that the lost fragment of the decomposition was formic acid. So the result in this work is congruous with the result in the literature very well. Artemether and artesunate may have the same decomposition scheme at this step because they have the same framework. The IR spectrum at the second mass loss steps of artemisinin and artemether were weak and not specific. It implied that the decomposition products at this step are complex and that it is not a simple decomposition step. For artesunate, the succinic ester group may form succinic anhydride and lose at the second mass loss step. The probable decomposition schemes of the compounds are shown in Figure 4.

Conclusions

This paper reports the constant-volume energies of combustion measured by using a rotating-bomb combustion calorimeter of crystalline artemisinin, artemether, and artesunate. The standard molar enthalpies of the three compounds were derived from the experimental results. The uncertainties of the standard molar enthalpies of formation obtained by combustion calorimetry were estimated to be less than 0.5 %. Additionally, the thermal stabilities of the three compounds were determined by thermal analysis (TG-DTA), and the gaseous decomposition products of them were characterized synchronously by combining with FT-IR. The possible decomposition schemes of the compounds are speculated by comparing this work with the earlier researchers' works. In the first mass loss step of the three compounds, the fragment of formic acid is lost, while in the second mass loss step of artesunate the fragment of succinic anhydride is lost.

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