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THERMODYNAMIC PROPERTIES OF SOME MONOTERPENES WITH PHARMACOLOGICAL APPLICATIONS

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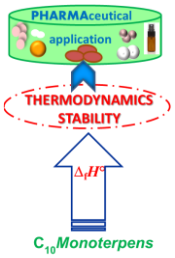
Solid-state thymol, liquid carvacrol and eugenol were characterized by using combustion calorimetry and thermal analysis-simultaneous thermogravimetry (TG) coupled with differential scanning calorimetry (DSC) techniques. The enthalpies of formation were calculated using the measured heat of combustion for the studied compounds. Our values were compared with the literature and calculated data. Information about the stability of the samples was reported. From DSC measurements, the temperatures of melting-decomposition and their corresponding enthalpies were calculated.



INTRODUCTION

The purpose of the present research is the calorimetric characterization of carvacrol, thymol and eugenol. Carvacrol, thymol and eugenol are monocyclic monoterpenes, presenting significant biological properties. Phenolic monoterpenes have antioxidant, analgesic and anti-inflammatory effects, being usual components of numerous essential oils (EOs).

Thymol (2-isopropyl-5-methylphenol) is a natural phenolic monoterpenoid extracted primarily from Thymus species. Pharmacological applications of thymol are concerned on its remarkable antimicrobial, antioxidant, anti-inflammatory and cicatrizing activities. Both thymol and thyme essential oil are expectorant, anti-inflammatory, antiviral, antibacterial and antiseptic agents being used in traditional medicine for the treatment of the upper respiratory system, but also for their anticancer activity against human gastric cancer cells.[1-2]

Due to its phenolic structure and redox properties, thymol has an antioxidant activity, playing an important role in adsorbing and neutralizing of free radicals or decomposing peroxides.[3]

Carvacrol (5-isopropyl-2-methylphenol) is originated from Thymus capitatus and Origanum vulgare and posses a wide antimicrobial activity.[4] Thyme essential oil and thymol are involved in recent studies for new directions of biological or therapeutic activities of natural plant substances. Current surveys have evidenced their antifungal, antiviral and anticancer properties. Also, their new therapeutic formulations, such as nanocapsules including these constituents, can be helpful in medicinal practice and generate opportunities for their expanded use. The employment of thymol and thyme essential oil in the healthcare sector is very encouraging but requires further research and analysis.[5]

Eugenol (4-allyl-2-methoxyphenol), also called clove oil, is an important constituent of clove

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essential oil, displaying antibacterial, analgesic and antioxidant properties. It is an anti-inflammatory, anaesthetic and analgesic agent (toothache and pulpitis treatment in dentistry), antibacterial and antineoplastic agent (apoptosis inducer) and inhibitor of some enzimes.[6]

Thymol is a colourless, crystalline compound with characteristics including strong odor and solubility in alcohol and other organic solvents, but it is only slightly soluble in water. Carvacrol is a colourless to pale yellow liquid, insoluble in water but highly soluble in ethanol, acetone.[5] Eugenol appears as clear colourless pale yellow or amber-colored liquid, odor of cloves and spicy pungent taste.[6] The present work will complete the data bases regarding the thermodynamic parameters of studied phenols and brings more information about their thermal behaviour.

RESULTS AND DISCUSSION

Refractive indices

Refractive indices of monocyclic monoterpenes at 20; 25°C are presented in Table 1 and compared with data from the literature.

Combustion energy

The data of combustion measurements for the studied compounds are shown in Tables 2, 3, 4. The corrections for the gelatine capsule, the cotton thread and filament used in the combustion experiments were calculated from the corresponding masses and energies of combustion. $\Delta_c u°_{(\text{gelatine capsule})}$= 19,294±3 J g^{-1} was determined in our laboratory (to be compared with the value certified by the fabricant 19.26 kJ g^{-1}), $\Delta_c u°_{(\text{cotton})}$ = 16,709±5 J g^{-1} checked in our laboratory, in agrement with literature value 16,240 J g^{-1} [9] and $\Delta_c u°_{(\text{Ni–Cr})}$ = 5.86 kJ g^{-1} (certified by the calorimeter's fabricant). In order to bring the experimental values of the energy of combustion to the standard state (T = 298.15 K and $P°$= 0.1 MPa), corrections were made with the Washburn approximate equation:[10]

$$\Pi\% = \frac{-0.3 \cdot a \cdot P_{initial}}{-\Delta U^{\text{exp}}} \left[1 - \frac{1.1 \cdot (b - 2 \cdot c)}{4 \cdot a} + \frac{2}{P_{initial}} \right] \quad (1)$$

where: P stands for the initial oxygen pressure and $-\Delta U^{\text{exp}}$ for the experimental energy of combustion; a, b, and c are the numbers of carbon, hydrogen and oxygen atoms from the chemical formula of the compound, $C_aH_bO_c$.

Table 1

Comparative data of refractive indices of monocyclic monoterpenes

Chemical Name (IUPAC)	n_D (this work)		n_D^{20} (literature)
	n_D^{20}	n_D^{25}	
Carvacrol (5-isopropyl-2-methylphenol)	1.52355	1.52418	1.5319[7]
Thymol (2-isopropyl-5-methylphenol)	-	-	1.5227[7]
Eugenol (4-allyl-2-methoxyphenol)	1.54112	1.53869	1.5405[8]

Table 2

Results for typical combustion experiments for liquid carvacrol*

Sample	1	2	3	4	5	6
m_{sample}/g	0.302585	0.256463	0.254957	0.304812	0.314505	0.316392
$m_{capsule}$/g	0.11525	0.11253	0.11102	0.1111	0.11335	0.115121
$m_{(Ni–Cr)}$/g	0.003225	0.004829	0.004821	0.004011	0.003725	0.004975
m_{cotton}/g	0.009471	0.01124	0.007424	0.008679	0.007821	0.008912
ΔT/K	1.3736	1.1996	1.1846	1.3736	1.4125	1.4259

Table 2 (continued)

$\varepsilon_{calor}(-\Delta T_c)$/J	-13810.72	-12061.25	-11910.44	-13810.72	-14201.83	-14336.56
$-m_{capsule}\Delta_c u°_{capsule}$/J	-2223.65	-2171.17	-2142.04	-2143.58	-2187.00	-2221.17
$-m_{wire}\Delta_c u°_{wire}$/J	-18.89	-28.29	-28.24	-23.49	-21.82	-29.14
$-m_{cotton}\Delta_c u°_{cotton}$/J	-158.25	-187.81	-124.05	-145.02	-130.68	-148.91
$-\Delta_c u$ /Jg^{-1}	-37708.15	-37720.77	-37716.59	-37723.65	-37717.48	-37729.60
$-\Delta_c u°$/Jg^{-1}	-37707.51	-37720.13	-37715.95	-37723.01	-37716.84	-37728.96
$<\Delta_c u°>$/ Jg^{-1}	-(37718.7±7.2)					

* m_{sample} – mass of compound burned in each experiment; $m_{capsule}$ – mass of gelatin capsule burned in each experiment; $m_{(Ni–Cr)}$ – mass of fire burned in each experiment; m_{cotton} – mass of cotton burned in each experiment; ΔT – temperature rise; ε_{calor} – the energy equivalent of the calorimeter; Δu_{cotton} – energy of combustion of the cotton fuse; Δu_{ign} – energy used to ignite the sample by means of a fire; $\Delta_c u$ – non-corrected massic energy of combustion of compound; $\Delta_c u°$– standard energy of combustion;$<\Delta_c u°>$ – mean value of standard massic energy of combustion; $u(\Delta_c u°)$ – uncertainties in this table are expressed as the standard deviation of the mean.

Table 3

Results for typical combustion experiments for solid thymol*

Sample	1	2	3	4	5	6
m_{sample}/g	0.833755	0.781068	0.789415	0.891447	0.752986	0.741529
$m_{capsule}$/g	0	0	0	0	0	0
$m_{(Ni–Cr)}$/g	0.007235	0.006204	0.005815	0.006371	0.002851	0.005863
m_{cotton}/g	0.001448	0.026225	0.019483	0.012792	0.007893	0.009057
ΔT/K	3.1273	2.9702	2.9907	3.3616	2.8336	2.794
$\varepsilon_{calor}(-\Delta T_c)$/J	-31443.11	-29863.56	-30069.68	-33798.85	-28490.13	-28091.98
$-m_{capsule}\Delta_c u°_{capsule}$/J	0	0	0	0	0	0
$-m_{wire}\Delta_c u°_{wire}$/J	-42.38	-36.34	-34.06	-37.32	-16.70	-34.34
$-m_{cotton}\Delta_c u°_{cotton}$/J	-24.19	-438.19	-325.54	-213.74	-131.88	-151.33
$-\Delta_c u$ /Jg^{-1}	-37632.8	-37626.7	-37635.6	-37633.0	-37638.9	-37633.5
$-\Delta_c u°$/Jg^{-1}	-37632.2	-37626.1	-37634.9	-37632.3	-37638.2	-37632.8
$<\Delta_c u°>$/ Jg^{-1}	-(37632.8±4)					

* The symbols have the same meaning as in Table 2

Table 4

Results for typical combustion experiments for liquid eugenol*

Sample	1	2	3	4	5	6
m_{sample}/g	0.368885	0.293601	0.291592	0.346758	0.416795	0.379503
$m_{capsule}/g$	0.111102	0.111012	0.112907	0.114985	0.114295	0.115923
$m_{(Ni–Cr)}/g$	0.007249	0.005461	0.006799	0.005829	0.006951	0.006296
m_{cotton}/g	0.009279	0.006094	0.01654	0.010861	0.009593	0.009956

Table 4 (continued)

ΔT/K	1.4366	1.1846	1.1996	1.3736	1.5995	1.4809
$\varepsilon_{calor}(-\Delta T_c)$/J	-14444.14	-11910.44	-12061.25	-13810.72	-16082.00	-14889.55
$-m_{capsule}\Delta_c u°_{capsule}$/J	-2143.62	-2141.89	-2178.45	-2218.54	-2205.23	-2236.64
$-m_{wire}\Delta_c u°_{wire}$/J	-42.46	-31.99	-39.83	-34.14	-40.72	-36.88
$-m_{cotton}\Delta_c u°_{cotton}$/J	-155.04	-101.82	-276.37	-181.48	-160.29	-166.35
$-\Delta_c u$ /Jg^{-1}	-32809.7	-32815.8	-32808.2	-32808.3	-32811.7	-32805.2
$-\Delta_c u°$/Jg^{-1}	-32809.0	-32815.0	-32807.5	-32807.6	-32811.0	-32804.5
$<\Delta_c u°>$/ Jg^{-1}	-(32809.1±3.6)					

* The symbols have the same meaning as in Table 2

The standard combustion enthalpy $\Delta_c H^o$ of compounds was calculated taking into account the following reaction:

$$\text{Carvacrol } C_{10}H_{14}O(l) + 13O_2(g) \longrightarrow 10CO_2(g) + 7H_2O(l) \quad (2)$$

$$\text{Thymol } C_{10}H_{14}O(s) + 13O_2(g) \longrightarrow 10CO_2(g) + 7H_2O(l) \quad (3)$$

$$\text{Eugenol } C_{10}H_{12}O_2(l) + 12O_2(g) \longrightarrow 10CO_2(g) + 6H_2O(l) \quad (4)$$

by using the equation:

$$\Delta_c H^o = \Delta_c U^o + \Delta nRT \quad (5)$$

where Δn is the change in the mole number of gaseous compounds during the combustion reaction:

$$\Delta n = \Sigma n_{\text{products,g}} - \Sigma n_{\text{reactants,g}} \quad (6)$$

The uncertainty associated with the molar enthalpy of combustion is given as twice the overall standard deviation of the mean, as recommended by Olofsson *et al.*[11] It includes the uncertainties associated with the calibration experiments (uncertainties of massic energy of combustion of benzoic acid, of capsules and of the energetic equivalent of the calorimeter) and with the auxiliary materials.

The following values were considered: $\Delta_f H^o_{CO2(g)}$= -393.51±0.13 kJ mol^{-1}, $\Delta_f H^o_{H2O(l)}$= -285.83±0.042 kJ mol^{-1} for calculating the enthalpy of formation.[12]

$$\Delta_f H^o = a\Delta_f H^o_{CO2(g)} + b/2\Delta_f H^o_{H2O(l)} - \Delta_c H^o \quad (7)$$

The obtained value of the standard molar enthalpy of formation of monocyclic monoterpenes is shown in Table 5, together with literature [13-15] and calculated values.[16,17]

Table 5

Thermochemical data at T= 298.15 K and P^o= 0.1 MPa for the studied monoterpenes

Compounds	$-\Delta_c U^o$/kJ mol^{-1}	$-\Delta_c H^o$/kJ mol^{-1}	$-\Delta_f H^o$/kJ mol^{-1}		$-\Delta_f H^o$/kJ mol^{-1}
	(this work)∗	(this work)∗	(this work)∗	(literature)	(calculated)
Carvacrol (liquid)	5666.11±1.4	5673.54±1.4	262.37±1.5	270.0[18]	283.21[16]
Thymol (solid)	5653.19±0.95	5660.63±0.95	275.28±1.04	280.0[18] 309.7[15]	294.58[16] 264.4[17]
Eugenol (liquid)	5387.25±1.1	5392.21±1.1	257.87±1.2		273.47[16]

∗Uncertainty is standard deviations and includes the uncertainties of the enthalpies of formation of the reaction products H_2O and CO_2.

The formation enthalpies in solid state of thymol and in liquid state for carvacrol and eugenol experimentally found were compared with those obtained by means of the group additivity method, with parameters recommended by Domalski and Hearing.[16] Another method developed by Salmon and Dalmazone[17] for prediction of thermodynamic properties of organic compounds in the solid standard state was used for thymol as well and a considerably different value was obtained.

In case of eugenol the insertion of a –O–CH_3 group in the aromatic ring of phenol creates a higher enthalpic effect of destabilization in ortho-position.

Thermal analysis

Differential scanning calorimetry (DSC)

The DSC curves obtained in closed aluminium crucibles are shown in Fig. 1. The thermochemical parameters of the studied compounds derived from calorimeter DSC8500 measurements are shown in Table 6.

The DSC curve for eugenol displays only one endothermic peak at 257ºC (in agreement with the results obtained by Monteiro *et al.* attributed to its volatilization.[19] In the DSC curve of thymol an endothermic peak corresponding to its melting point starting at 49.53ºC and ending at 51.7ºC is noticed. Zamani et al. reported a melting peak at 51.8ºC.[20] The first peak from curve of carvacrol at 0.77ºC is attributed to the melting process, the same value of about 1ºC was reported by Lide[21] and Tackenberg *et al.*[22]

In Fig. 2 are shown the data obtained from DSC scans performed in open crucibles with TG–DSC SETSYS Evolution 17 calorimeter, at the same heating rate.

For the experiments performed with open crucibles, the curve profiles were different being noticed two endothermic transitions. The first peak for eugenol starting at 73.8°C is ascribed to the water desorption and the second one at 162ºC to the decomposition of the eugenol. In the case of carvacrol, its volatilization starts at 55.5ºC and the decomposition process at 158.6ºC, with formation of gaseous products. Thymol presents first, a melting peak starting at 49ºC as reported in literature[20,23] and a second one being attributed to the decomposition process, the same behaviour as in the case of closed crucibles scans.

In Table 6 are shown for comparison, the DSC data obtained from calorimeter DSC8500 and TG–DSC SETSYS Evolution 17 for the three studied compounds.

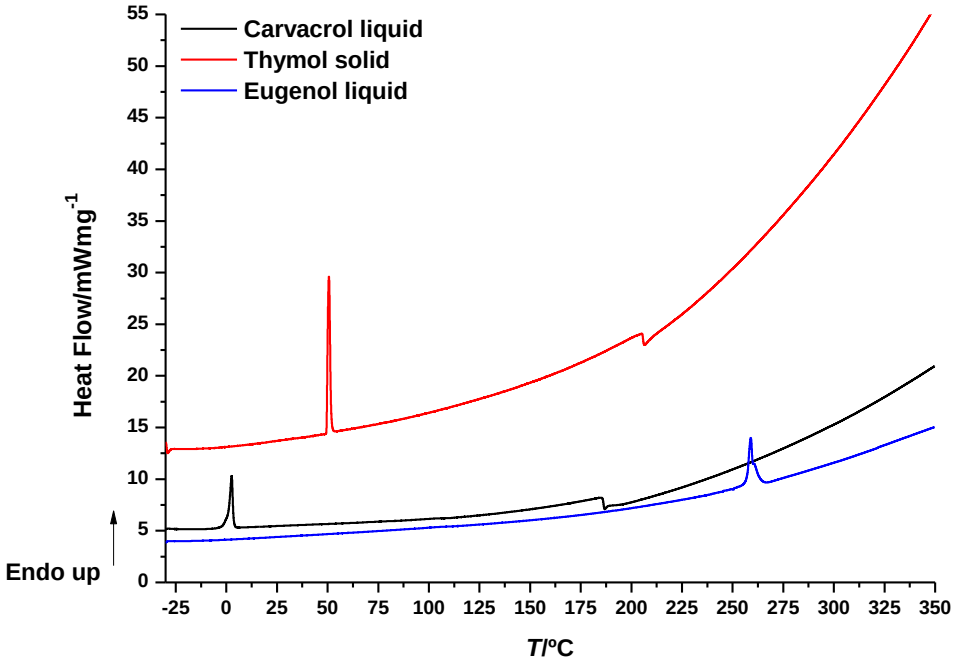

Fig. 1 – DSC scans of monocyclic monoterpenes obtained from calorimeter DSC8500.

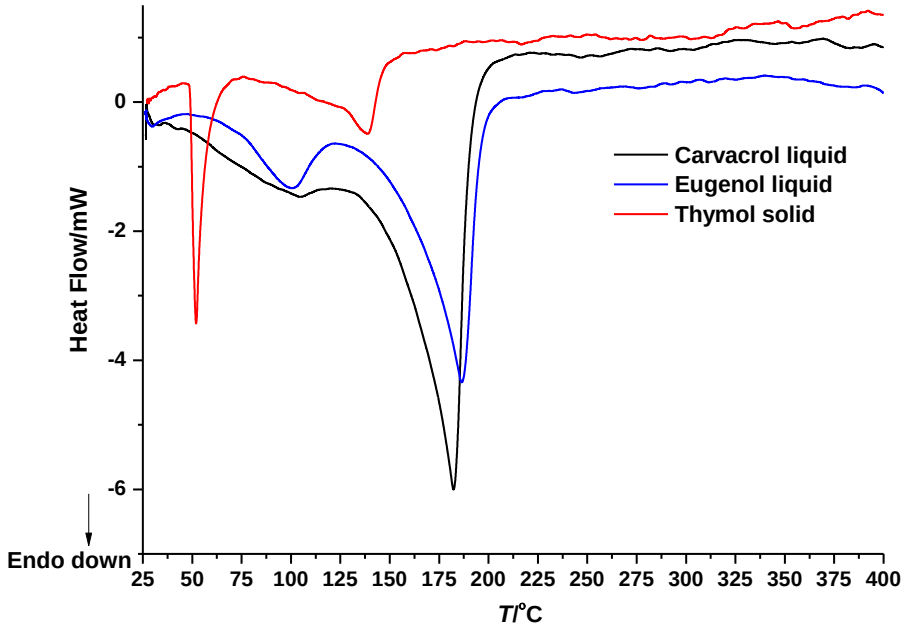

Fig. 2 – DSC scans of monocyclic monoterpenes obtained from calorimeter TG–DSC SETSYS Evolution 17.

Table 6

Comparative experimental values from DSC data for the three monocyclic monoterpenes

Properties		Compound					
		Carvacrol (liquid)		Thymol (solid)		Eugenol (liquid)	
	Method	DSC	TG/ DSC	DSC	TG/ DSC	DSC	TG/ DSC
T_{onset}/°C		0.77					
T_{max}/°C		2.62	-	-	-	-	-
T_{end}/°C		3.57					
ΔH/kJmol^{-1}		9.94					
T_{onset}/°C			55.5	49.53	49.0		73.8
T_{max}/°C		-	103.7	50.67	51.9	-	99.7
T_{end}/°C			115.6	51.7	56.3		115.7
ΔH/kJmol^{-1}			2.14	19.48	15.5		5.01
T_{onset}/°C		148.7	158.6	172.1	116.5	-	162.1
T_{max}/°C		185.6	182.3	204.8	139.0		186.5
T_{end}/°C		186.5	189.9	205.6	146.5		195.6
ΔH/kJmol^{-1}		30.1	24.23	14.83	21.9		26.4
T_{onset}/°C						257.05	
T_{max}/°C		-	-	-		258.97	-
T_{end}/°C						260.31	
ΔH/kJmol^{-1}						14.42	

Thermogravimetric analysis (TG/DSC)

In order to obtain information about the thermal stability and weight loss of the studied compounds, thermogravimetry (TG/DSC) method was employed. In Fig. 3 are shown the temperatures and weight losses in the TG and DTG curves for the studied monoterpenes. DSC curves of carvacrol showed two endothermic peaks up to 186ºC corresponding to its volatilization. The TG/DTG curves (Fig. 3) corroborate with this result show one step of weight loss of 91.87% up to 197ºC.[24] Thymol, like

carvacrol, presents a first step fast weight loss of 95% up to 182ºC follow by a continuous mass decrease of the sample of 99% up to 400ºC. From the DTG curve, another endothermic peak was noticed at 116ºC which was associated with thermal degradation. Base on derivative thermogravimetry (DTG) the maximum thermal decomposition was noticed at 199ºC.[25] In the TG thermogram of eugenol two steps of weight loss are noticed, first due to volatilization, in the range (30–116ºC) and the second due to eugenol decomposition, in the range (119–252ºC). These data are included in Table 7.

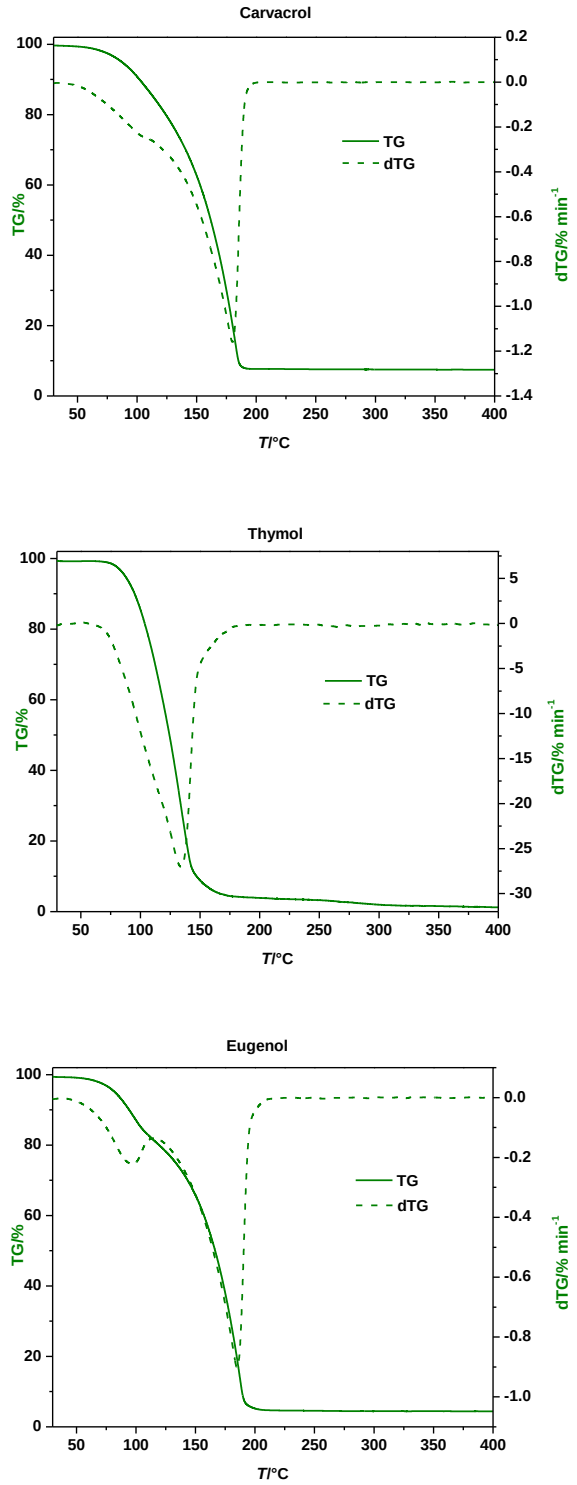

Fig. 3 – TG-DTG curves for monocyclic monoterpenes obtained from calorimeter TG–DSC SETSYS Evolution 17.

Table 7

Thermogravimetric data of the studied monocyclic monoterpenes

Properties	Compounds		
	Carvacrol (liquid)	Thymol (solid)	Eugenol (liquid)
Δm(%) / ΔT(°C)	-91.87/40–197	-95.02/62–182	-18.27/30–116
Δm(%) / ΔT(°C)	-	-3.00/182–400	-76.51/119–252
Δm(%)/RT-400°C	-92.55	-99.34	-95.08

From Table 7 it can be observed that at 400°C, a mass reduction of over 92% is recorded for all monoterpenes studied, which means that the decomposition process is complete.

EXPERIMENTAL

General information

Carvacrol (CA), Thymol (TY) and Eugenol (EU) were purchased from Sigma Aldrich Chemical and Merck Company and used without further purification. In Fig. 4 were represented structural formulas of the studied compounds. The chemical identifiers and provider purity of the used chemicals are given in Table 8.

Method and equipment

Refractive index determination

Refractive indices of monocyclic monoterpenes at 20; 25°C were measured at sodium D-line, λ_D = 589.3 nm, using a digital automatic refractometer (Anton Paar RXA 170) with an accuracy of ±0.01 K in temperature and of ±0.000001 for refractive index. The apparatus was calibrated with the certified reference liquid (CRM): tetrachloroethylene and was further checked out with deionized water at atmospheric pressure. Refractive index was obtained for water n_D^{20} =1.33302 and n_D^{25} =1.33249 according with literature.[26]

Combustion calorimetry

A Parr Instruments model 6200 microprocessor controlled isoperibol oxygen bomb calorimeter was used in combustion experiments. Temperature is measured with a high precision electronic thermometer using a specially designed thermistor sensor. Measurements were taken with 0.0001 K resolution. The jacket temperature is held constant for isoperibol operation. A microprocessor-based controller monitors both the temperatures of the bucket and of the jacket and performs the necessary heat leak corrections that result from differences between these two temperatures. These corrections are applied continuously throughout a test rather than as a final correction based on pre and post test measurements.

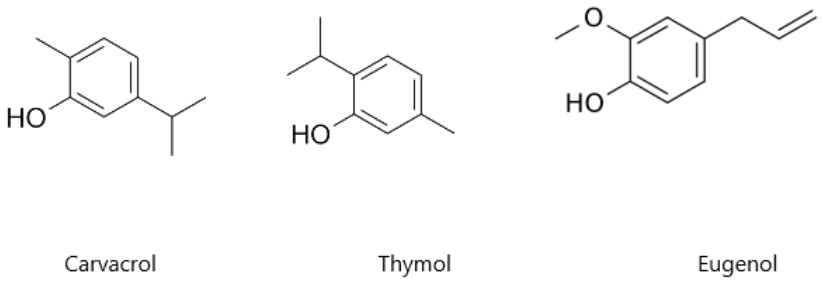

Fig. 4 – Structural formulas of the studied compounds.

Table 8

Specification of chemical compounds

Chemical Name (IUPAC)	CAS Number	Source	Initial mass fraction purity/ %*	Molecular weight/ gmol^{-1}
Carvacrol (5-isopropyl-2-methylphenol)	499-75-2	Sigma-Aldrich	98 %	150.22
Thymol (2-isopropyl-5-methylphenol)	89-83-8	Merck	99%	150.24
Eugenol (4-allyl-2-methoxyphenol)	97-53-0	Sigma-Aldrich	99 %	164.2

* The mass fraction purity is based on information provided by the supplier

The combustion calorimeter was calibrated by means of ten combustion experiments with benzoic acid (CAS 65-85-0) supplied by Parr Company, having the energy of combustion under certificate conditions ($\Delta_c u^o$ = -26434.5 J g^{-1}). The energy equivalent of our calorimeter was determined as ε_{calor}= (10054.4±1.4) J K^{-1}. The uncertainty associated with the average value of the energy equivalent is the standard deviation of mean.

The combustion bomb Parr Instruments standard type 1108 is a cylinder, with an internal volume of about 0.35 L, made of stainless steel, as well as its accessories. The samples burned in the oxygen filled bomb were enclosed in Parr 3601 Gelatine Capsules with maximum 0.9 mL volume. A cotton thread was used in order to ignite the samples. The completely equipped bomb (filament, fuse, gelatin capsule, sample, deionized water) was connected to the oxygen cylinder and flushed with oxygen. All combustion experiments were carried out in high purity oxygen 99.998% at 3.546 MPa and at T = 298.15 K and in the presence of 1 cm^3 of deionized water for saturation of the atmosphere.

Samples amounting between 0.25–0.45 g and gelatine capsules with a mass of 0.10–0.12 g were used in each experiment. The samples were weighed with a Mettler-Toledo microbalance with an accuracy of ±2·10^{-6} g.

Differential scanning calorimetry (DSC)

A Perkin Elmer power compensated DSC (model 8500) was used for the measurement of the enthalpies and temperatures of the processes occurring during heating. The calorimeter was calibrated with indium ($\Delta_{fus}H$ = 28.46 J g^{-1}). The areas of the peaks corresponding to the standard and studied substances were used to calibrate the instrument and calculate the thermal effects of the investigated processes, respectively. Samples of about 1–2 mg of phenols were sealed in aluminum pans. All samples were scanned at a heating rate of 10°C/min, in flowing nitrogen atmosphere (purity > 99.996%, 20 mL min^{-1}) from -30°C temperature up to 350°C. Samples were cooled and held isothermally at -30°C for 2 min, then heated to 350°C. The heat flow curves were processed by means of Pyris Software for Windows for calculating the thermal effects, namely melting/decomposition enthalpies. The purity of the compounds was verified by DSC (differential scanning calorimetry) method.[27]

Simultaneous thermogravimetry-differential scanning calorimetry (TG–DSC) measurements

Thermal properties (mass change, temperature and enthalpy of transformations) of compounds were measured by a simultaneous TG–DSC SETSYS Evolution 17 analyzer from Setaram, in the temperature range from 20 to 400 °C with 10°C min^{-1}, in alumina crucibles, in argon atmosphere. The sample mass for TG-DSC measurements was about 1-4 mg. The error of TG measurement is ± 0.154%. All thermal analysis (TG-DSC) data were processed using Calisto software.

CONCLUSIONS

Applying combustion and differential scanning calorimetry methods, reliable data were obtained for thymol, carvacrol and eugenol, such as melting, decomposition temperatures and the corresponding enthalpies of combustion and formation. The obtained results provide new information about the thermochemical stability, completing the data base in the field. For the first time, the combustion and formation enthalpy of eugenol have been measured by combustion calorimetry. The results could be used for a better explanation of the phenolic compounds behaviour when they are involved in different biological processes in the living bodies.

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