ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
https://www.icf.ro/rrch/

Rev. Roum. Chim.,
2026, *71*(5–6), 353–361
DOI: 10.33224/rrch.2026.71.5-6.06

Dedicated to Professor Alexandru T. Balaban
on the occasion of his 95th anniversary

THERMOCHEMICAL EVALUATION OF THE INCLUSION COMPLEXES BETWEEN 2-HYDROXYPROPYL-BETA-CYCLODEXTRIN WITH EUGENOL, THYMOL AND CARVACROL

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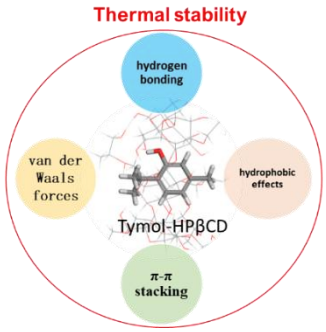
Received March 11, 2026

This work investigates solid-state inclusion complex formation between 2-hydroxypropyl-β-cyclodextrin (HPβ-CD) and three hydrophobic essential-oil phenolics: eugenol (EU), carvacrol (CA), and thymol (TY), aiming to improve the handling and performance of these bioactive compounds by addressing common limitations such as low water solubility, high volatility, and oxidative instability. Inclusion complexes (HPβ-CD/EU, HPβ-CD/CA, and HPβ-CD/TY) were prepared at a 1:1 molar ratio using a melting-in-solution method, followed by incubation and dehydration to obtain solid powders. The pure components and the resulting complexes were then characterized through ATR–FTIR spectroscopy, DSC/TG thermal analysis and oxygen bomb combustion calorimetry. The resulting structural, thermal, and energetic data provide experimental evidence of host–guest interactions and offer a useful basis for designing more stable and potentially more bioavailable cyclodextrin-based delivery systems for applications in foods, active packaging, and pharmaceutical formulations.



INTRODUCTION

Cyclodextrins, including HPβ-CD, cyclic oligosaccharides composed of α-(1→4)-linked D-glucopyranose units, forming a toroidal structure with a hydrophobic inner cavity and a hydrophilic outer surface, capable of forming non-covalent inclusion complexes with a variety of guest molecules.[1,2] The formation of inclusion complexes is primarily driven by hydrophobic interactions, van der Waals forces, and, in some cases, hydrogen bonding, with the spatial fit between host and guest being a critical determinant of complex stability. HPβ-CD is preferred over native β- and α-cyclodextrins for inclusion complex formation due to its vastly superior water solubility, lower toxicity, enhanced complexation efficiency, reduced aggregation, and broader regulatory acceptance. HPβ-CD is significantly more soluble in water, with a water solubility exceeding 500 mg/mL at 25°C, while unmodified β-cyclodextrin (β-CD) has very limited aqueous solubility, at approximately 18.5 mg/mL at 25°C. The hydroxypropyl substituents in HPβ-CD sterically hinder and break the regular intramolecular H-bond network between adjacent glucose units. This makes the molecule less rigid

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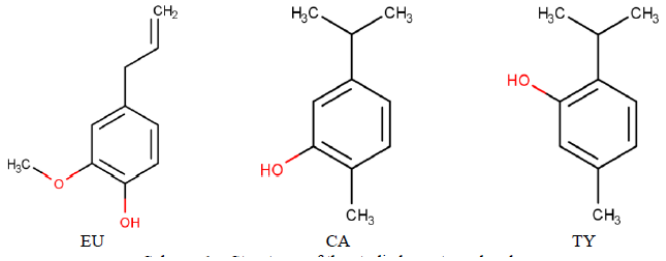
and reduces the crystal lattice energy. Moreover, HP-β-CD is usually a mixture of isomers with varying degrees and positions of substitution, this randomness prevents efficient crystal packing, resulting in an amorphous solid that has higher solubility than the crystalline native β-CD.[3]

The encapsulation process with HPβ-CD typically involves the insertion of the hydrophobic portion of the guest molecule into the cyclodextrin cavity, while polar functional groups may interact with the external hydroxypropyl groups of the HPβ-CD rim.[4,5] The hydroxypropyl substitutions disrupt the intramolecular hydrogen bonding of native β-CD, reducing its tendency to aggregate and enhancing its complexation capacity with lipophilic guests.[3] The interaction between 2-Hydroxypropyl-beta-cyclodextrin (HPβ-CD) and bioactive compounds such as eugenol (EU), carvacrol (CA), and thymol (TY) has garnered significant interest due to the potential of HPβ-CD to enhance the solubility, stability, and bioactivity of these hydrophobic molecules.

These inclusion complexes are particularly relevant in the context of food preservation, packaging, and delivery systems for volatile or poorly soluble compounds.[6] EU, CA and TY (Scheme 1) are all natural phenolic compounds found in essential oils, known for their strong antimicrobial, antioxidant, and anti-inflammatory properties.[7,8] While they share similar structural motifs, their specific molecular structures lead to differences in their aromatic profiles and precise biological activities.[9,10]



Scheme 1 – Structures of the studied guests molecules.

These compounds are major constituents of plants like cloves (Syzygium aromaticum), oregano (Origanum vulgare), and thyme (Thymus vulgaris), respectively. Structurally, eugenol (4-allyl-2-methoxyphenol) features a phenolic hydroxyl group, a methoxy substituent, and an allyl chain; carvacrol (5-isopropyl-2-methylphenol) and thymol (2-isopropyl-5-methylphenol) are isomeric phenols with isopropyl and methyl groups differing in position.[11] Despite their therapeutic potential, the practical application of these compounds is severely limited by their poor aqueous solubility (<1 mg mL^{-1}), high volatility, susceptibility to oxidation, and potential cytotoxicity at high concentrations.[12,13] These physicochemical drawbacks hinder their incorporation into aqueous-based formulations, such as oral rinses, topical gels, food preservatives, or nanomedicines.

Previous studies have revealed that the hydrophobic cavity of HPβ-CD (approximately 6.0–6.5 Å in diameter) can encapsulate the non-polar aromatic rings and alkyl chains of Eu, CA and TY while the polar phenolic OH groups remain partially exposed or interact with the cavity rim.[14] Phase solubility studies have demonstrated an A_L-type profile for these complexes, indicating 1:1 stoichiometry with stability constants ranging from 10^3 to 10^4 [1/M], depending on pH, temperature, and substitution patterns.[15–17] It was demonstrated that the complexation with EU increases its aqueous solubility by up to 100-fold, as confirmed by UV-Vis spectroscopy, differential scanning calorimetry (DSC), and Fourier-transform infrared (FT-IR) analyses, which reveal shifts in vibrational bands indicative of guest inclusion. [18] Studies have shown that eugenol forms inclusion complexes with both β-cyclodextrin and HPβ-CD, although the encapsulation efficiency is slightly lower for HPβ-CD compared to β-cyclodextrin (89.1% *vs* 90.9%).[19,20] The presence of the hydroxypropyl side chain in HPβ-CD may interfere with the optimal inclusion of eugenol within the cyclodextrin cavity, potentially reducing encapsulation efficiency.[19] Moreover, HPβ-CD/ eugenol formulations exhibit sustained antimicrobial activity against Staphylococcus aureus and Candida albicans due to controlled release.[21] Similarly, CA and TY form stable 1:1 complex with HPβ-CD, resulting in improved aqueous solubility and thermal stability, enhancing their retention in volatile environments and reducing dermal irritation in transdermal delivery systems.[22,23]

This article investigates the inclusion complexation of HPβ-CD with EU, CA, and TY using Fourier transform infrared spectroscopy (FT-IR), thermal analysis and combustion calorimetry. The physicochemical data resulted in this study aim to provide new data necessary for bioavailable formulations of these essential oil phenolics for different industries.

RESULTS AND DISCUSSION

FT-IR analysis

The FT-IR spectroscopy technique has been used for to investigate the interaction of guest (EU, CA, TY) and HPβ-CD and the Figs. 1a,b,c shows the FTIR-ATR spectra of HPβ-CD, EU, CA, TY and their 1:1 inclusion complex HPβ-CD/EU, HPβ-CD/CA and HPβ-CD/TY, in the solid state. The registered spectrum of pure HPβ-CD is corresponding to that previously presented in literature.[24]

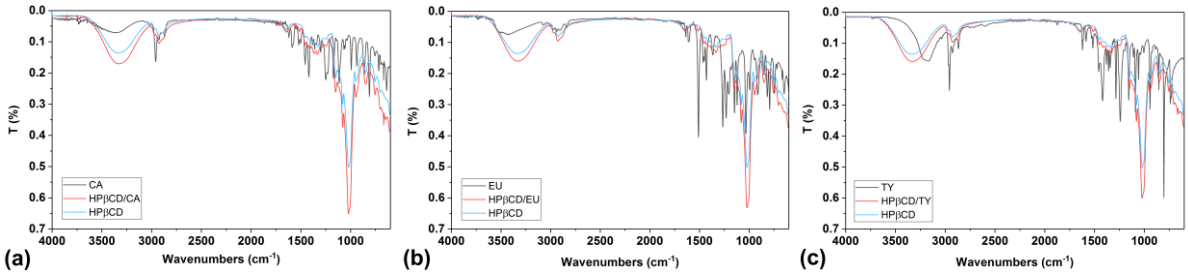


Fig. 1 – FT-IR spectra of solid powders of pure substances and inclusion complexes.

The pure compounds are strongly affected by the presence of HPβ-CD and the characteristic regions of the guest, EU[25,26], CA[27] or TY[24,27–29] are not present in the corresponding inclusion complex spectrum. In Fig. 1, the wide band of HPβ-CD with the absorption maximum at 3332 cm^{-1} is broadened for the obtained complexes and shifted only for HPβ-CD/TY at 3334 cm^{-1}which for the encapsulation of the TY is accomplished by involving much more the hydrogen bonds. Also, spectral changes are recorded in 1400–1200 cm^{-1} domain assigned to the absorption bands of the deformation vibrations of the C-H bonds in the primary and secondary hydroxyl groups of HPβ-CD, the peak at 1331 is shifted at 1338 ($\Delta\nu$=+7 cm^{-1}) for HPβ-CD/CA and HPβ-CD/TY complexes.

It should be noted that the disappearance of the guest (EU, CA, TY) bands under strong HPβ-CD absorptions may result not only from encapsulation of the guest molecule within the CD cavity but also from a guest fraction lower than 10–25%.[24,30] Therefore, in agreement with the proposed molar ratio of host: guest systems, it is expected that the FT-IR spectroscopic data to be in concordance with the results found on the calorimetry analyses.

Combustion energy

The data of the combustion measurements for the studied compounds are given in Table 1.

Table 1

Results for typical combustion experiments at T= 298.15 K and P^{o}= 0.1 MPa for HPβ-CD and the obtained complexes in solid state*

Parameters	HPβ-CD	HPβ-CD/CA	HPβ-CD/EU	HPβ-CD/TY
m_{sample} (g)	0.037172	0.025754	0.026841	0.027857
$m_{(Ni–Cr)}$ (g)	0.002398	0.005106	0.003326	0.006377
m_{cotton} (g)	0.004593	0.003012	0.003678	0.00292
ΔT (K)	0.3507	0.2698	0.2696	0.2883
$\varepsilon_{calor}(-\Delta T_c)$ (J)	–815.73	–627.56	–627.09	–670.59
$-m_{wire}\Delta_c u°_{wire}$ (J)	–14.05	–29.91	–19.48	–37.35
$-m_{cotton}\Delta_c u°_{cotton}$ (J)	–76.74	–50.33	–61.46	–48.79
$-\Delta_c u$ (Jg^{-1})	–19502.3	–21251.9	–20347.8	–20980.2
$-\Delta_c u°$ (Jg^{-1})	–19494.0	–21242.9	–20338.7	–20971.2

* m_{sample} – mass of compound 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.

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

HPβ-CD $C_{63}H_{12}O_{42}(s) + 45O_2(g) \longrightarrow 63CO_2(g) + 6H_2O(l)$ (1)

(Carvacrol+HPβ-CD) $C_{73}H_{26}O_{43}(s) + 58O_2(g) \longrightarrow 73CO_2(g) + 13H_2O(l)$ (2)

(Eugenol+HPβ-CD) $C_{73}H_{24}O_{44}(s) + 20.5O_2(g) \longrightarrow 73CO_2(g) + 12H_2O(l)$ (3)

(Thymol+ HPβ-CD) $C_{73}H_{26}O_{43}(s) + 58O_2(g) \longrightarrow 73CO_2(g) + 12H_2O(l)$ (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:

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

As recommended by Olofsson,[31] the uncertainty associated with the molar enthalpy of combustion is twice the overall standard deviation of the mean, and it includes the uncertainties associated with the calibration experiments (uncertainties of massic energy of combustion of benzoic acid and energetic equivalent of the calorimeter) and with the auxiliary materials.

The following values were considered

$\Delta_f H^o_{CO2(g)} = -393.51 \pm 0.13$ kJ mol^{-1},

$\Delta_f H^o_{H2O(l)} = -285.83 \pm 0.042$ kJ mol^{-1},[32]

for calculating the enthalpy of formation.

$$\Delta_f H^o = \Sigma \upsilon_p \Delta_c H^o_p - \Sigma \upsilon_r \Delta_c H^o_r \quad (7)$$

In order to bring the experimental values of the energy of combustion to the standard state (T = 298.15 K and P^o= 0.1 MPa), corrections were made with the Washburn approximate equation:[33]

$$\Pi\% = \frac{-0.3 \cdot a \cdot P_{initial}}{-\Delta U^{\exp}} \left[1 - \frac{1.1 \cdot (b - 2 \cdot c)}{4 \cdot a} + \frac{2}{P_{initial}} \right] \quad (8)$$

where P stands for the initial oxygen pressure and $-\Delta U^{\exp}$ 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, $C_aH_bO_c$. The Washburn correction Π is calculated in percents from the experimental value.

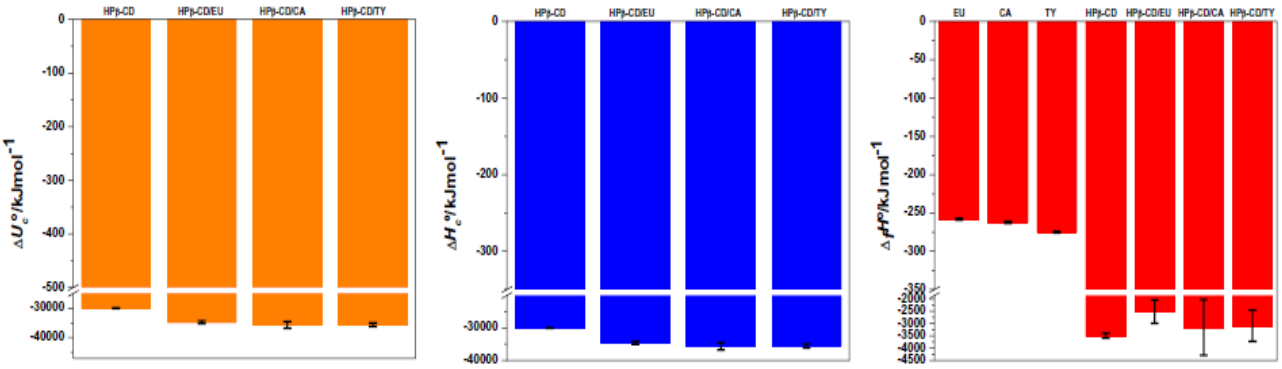


Fig. 2 – Chart of the energies, enthalpies of combustion and formation of (CA, EU, TY) [34], HPβ-CD and their inclusion compounds.

The obtained enthalpies of formation of the inclusion compounds indicate that EU, CA and TY are stabilized in presence of HPβ-CD. The most exothermic inclusion compound is HPβ-CD/CA which means that CA interacts strongly with HPβ-CD than EU or TY. EU is low exothermic due to allyl/phenol groups (*e.g.*, thymol's isopropyl para -OH ~50 kJ mol^{-1} exothermicity). EU's unsaturation hinders deep inclusion resulting in weaker binding with HPβ-CD.

Thermal analysis

Differential Scanning Calorimetry (DSC) is widely used to confirm the formation of inclusion complexes between guest molecules and cyclodextrins, including HPβ-CD. The thermal behavior and thermodynamic parameters corresponding to the pure EU, CA and TY were presented in our previous study.[34] specifying that the thermal signals were recorded with the same equipment used to carry out the thermal analysis in the present study. In this work, to investigate the inclusion compounds, the phase transitions presented by the pure compounds EU, CA and TY were considered in the temperature ranges of 25 to 500 for the power compensated calorimetry technique and in the range of 25 to 400 for the heat flow calorimetry technique, respectively.

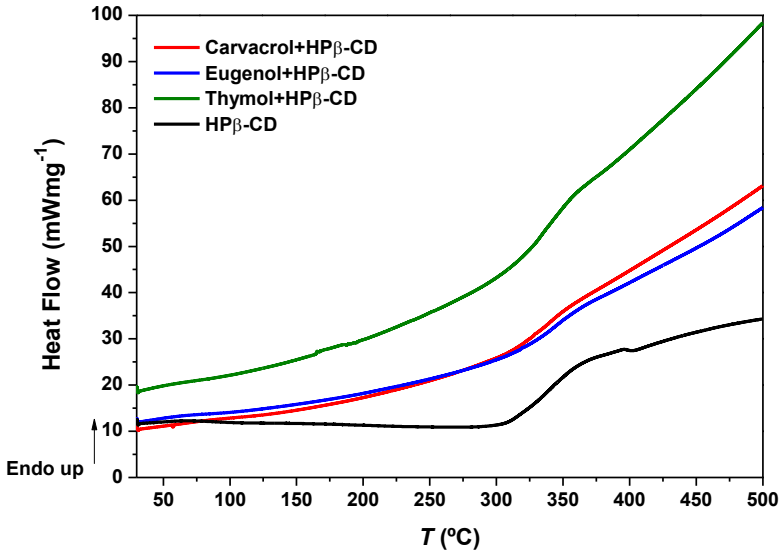


Fig. 3 – DSC curves of the inclusion compounds and HPβ-CD obtained by power compensated calorimetry technique, at 10 ºC min^{-1}.

The DSC curves obtained by power compensated calorimetry for EU, CA and TY in presence of HPβ-CD are presented in Fig. 3. Similar to EU, CA and TY the recorded thermograms show a gradual increase, indicating no characteristic endotherm for melting or other thermal transitions in presence of HPβ-CD. When a guest molecule is perfectly encapsulated within the HPβ-CD cavity, the characteristic melting, boiling, or sublimation peaks of the guest molecule typically shift, decrease in intensity, or disappear entirely in the DSC thermogram of the inclusion complex.[35–38] Thus, the presented thermograms in Fig. 3 suggest a strong interaction between guest molecules and HPβ-CD, thus proving the formation of stable inclusion complexes with an enhancing thermal stability of guests.

Instead, the DSC/TG curves in Fig. 4 show that the inclusion complex resembles that of HPβ-CD presenting only the endothermic event associated with the release of water from the HPβ-CD, and lacking the guest's thermal events.[35–38]

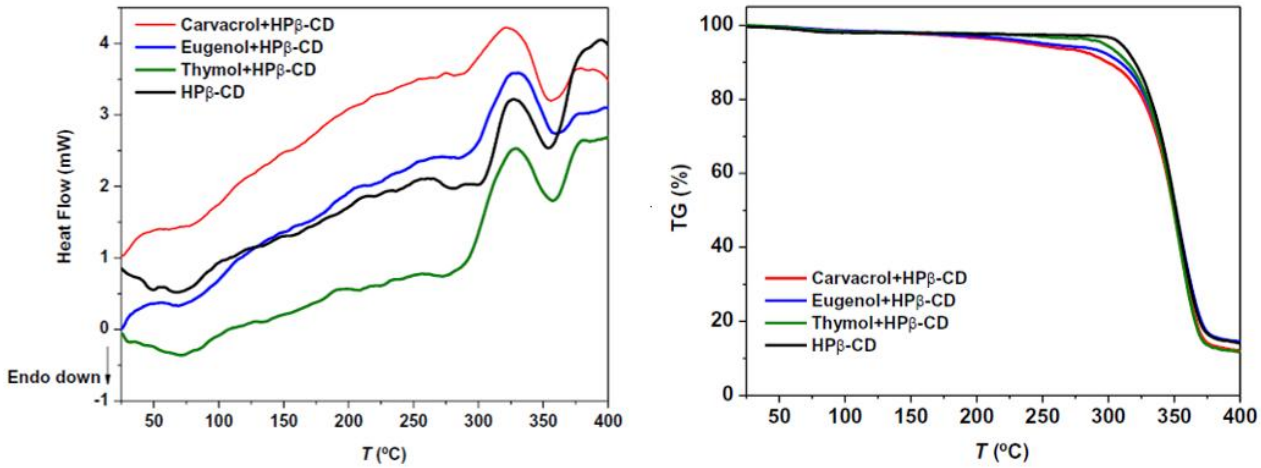


Fig. 4 – DSC (top panel) and TG (bottom panel) curves of the inclusion compounds and HPβ-CD obtained with calorimeter TG–DSC SETSYS Evolution 17, heating rate 10 ºC min^{-1}, under Argon flow.

HPβ-CD releases presents two water loss stages till temperature of 100.5 C (T_m = 49.9 °C and T_m =67.7 °C respectively), and decomposes at 304.7 °C. As presented in Fig. 4, the inclusion compounds release their water in a single step (for complexes of EU at T_m = 68.9 °C, of TY at T_m = 71.7 °C and of CA at T_m = 77.2 °C) and show the start temperature for decomposition at 266.4 °C, 274.1 °C and at 267.8 °C for complexes of EU, CA and TY respectively. The TG data indicated a

water loss of approximately 1.8% of complex mass for all the inclusion compounds and it was observed that the mass loss occurs faster for the inclusion complexes with EU and CA (at 203.2 °C) compared to complex with TY which starts to lose mass at 249.2 °C.

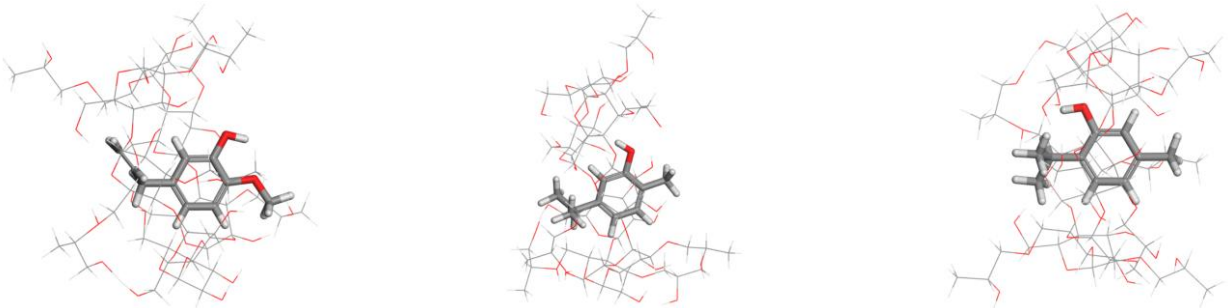
Table 2

Thermogravimetric data of the studied inclusion compounds, HPβ-CD and for the pure EU, CA, TY (In accordance with reference[34])

Sample	Temperature range (°C)	Weight loss (%)	Observation
HPβ-CD	25 – 135 135 – 284 284 – 400	2.36 0.75 83.11	–
EU	30 – 116 119 – 400	18.27 76.51	[34]
HPβ-CD/EU	25 – 135 135 – 192 192 – 278 278 – 399	1.76 1.07 3.0 79.6	–
CA	40 - 197	91.87	[34]
HPβ-CD/CA	25 – 135 135 – 195 195 – 278 278 – 400	1.98 1.27 3.63 80.99	–
TY	62 – 182 182 – 400	95.02 3.0	[34]
HPβ-CD/TY	25 – 135 135 – 231 231 – 400	1.94 0.52 85.83	–

Molecular modeling of the inclusion complexes

The spectroscopic and thermal data provided in this work for the inclusion complexes of the phenolic compounds EU, CA, TY prepared in a 1:1 molar ratio with HPβ-CD suggest that a stoichiometry of 1:1 (host-guest) is available for the investigated preparations. In these inclusion complexes, the interactions are primarily driven by van der Waals forces, hydrophobic effects, hydrogen bonding, and π-π stacking between the phenolic rings and cyclodextrin cavity glucose units.[1,2,4,5] Along with provided information in this work, literature data such as nuclear magnetic resonance studies, including ROESY spectra, have elucidated the inclusion modes: for TY and CA, the isopropyl group penetrates deeper into the cavity, while EU's allyl chain aligns along the primary rim.[39] Accordingly, in Fig. 5 are illustrated the investigated systems following the available information of complexation previously suggested. The functionalization degree of HPβ-CD is accordingly with literature.[40]



a) b) c)

Fig. 5 – Schematic representation of the inclusion complexes. Side view (primary rim of CD positioned to left side) of the spatial representation of the equilibrium geometries for 1:1 host-guest assemblies between a) – EU; b) – CA; c) – TY with HPβ-CD. The color correspondence is: blue for N atoms, grey for C atoms, light grey for H atoms, yellow for S atoms and red for O atoms.

EXPERIMENTAL

Materials and methods

Source and purity of samples

(2-hydroxypropyl)-β-cyclodextrin (HPβ-CD), eugenol (EU), carvacrol (CA) and thymol (TY) were purchased from Sigma Aldrich Chemical (Merck) Company and used without further purification. The chemical identifiers and provider purity of the used chemicals are given Table 3.

Table 3

Specification of chemical compounds

Chemical Name (abbreviation in this study)	CAS Number	Molecular weight (g mol^{-1})	Source	Initial mass fraction purity (%)
(2-hydroxypropyl)-β-cyclodextrin (HPβ-CD)	128446-35-5	~1396	Sigma-Aldrich	≥ 98%
Eugenol (EU)	97-53-0	164.2	Sigma-Aldrich	99%
Carvacrol (CA)	499-75-2	150.22	Sigma-Aldrich	98%
Thymol (TY)	89-83-8	150.24	Merck	99%

Inclusion compounds preparation method

The solid-state inclusion compounds HPβ-CD/EU, HPβ-CD/CA and HPβ-CD/TY were prepared in a 1:1 molar ratio of the host and guest using „melting in solution" method, procedure previously reported in literature. [41] The solid powder of HPβ-CD was dissolved in double distilled water then the corresponding quantity of guest (EU, CA and TY) was added in reaction. The mixture was gently stirred and incubated for 24h at room temperature. The complexes solid powders were resulted after dehydration at 50 °C.

Methods

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectral data of pure substances (HPβ-CD, EU, CA, TY) and synthesized solid inclusion complexes were recorded at room temperature by Nicolet iS10 FT-IR Spectrometer covering the range of 4000 to 600 cm^{-1}. The spectra were acquired with an average of 32 scans with spectral resolution of 4 cm^{-1} in attenuated total reflectance (ATR) mode.

Combustion calorimetry

A Parr Instruments model 6200 microprocessor controlled isoperibol oxygen bomb calorimeter was used. Samples were burned by using the semi-micro combustion kit of the calorimeter provided with a small bomb, inner volume 22 mL. The bomb was placed into the bucket, which contained 450 mL of water, filled from an automatic pipet. The temperature was measured with a high precision electronic thermometer using a specially designed thermistor sensor. Measurements were taken with resolution of 0.0001 K. Purity of the oxygen used for combustion was 99.998%.

The energy equivalent of the calorimeter, ε_{calor}= (2326.89±1.9) J K^{-1} (twice the standard deviation of the mean) was derived from combustion of the standard benzoic acid (CAS 65-85-0) supplied by Parr Company, from ten calibration experiments, using samples weighing between 0.10–0.19 grams. The massic energy of combustion under certificate conditions of benzoic acid was $\Delta_{benzoic\ acid}u^o$ = –26434 J g^{-1}.

The water volume added to the bomb for dissolution of combustion gases was 0.5 cm^3. The bomb was flushed with purified oxygen for 30 seconds, then sealed and filled with oxygen. The samples were burned in oxygen at a pressure of 3.546 MPa. The final solution from the bomb was analyzed for the presence of nitric acid (about 20% from the total nitrogen) by titration with 0.0709 N Na_2CO_3 solution. The heat due to nitric acid formation was obtained using the value of the molar internal energy of formation of nitric acid solution (0.1 M), $\Delta_f u°_{HNO3\ (aq)}$ = –58.8 kJ mol^{-1}.[42]

Auxiliary materials – cotton and Ni–Cr filament were used in combustion measurements. The corrections for the auxiliary materials, $q_{(cotton)}$ and $q_{(ign)}$ were calculated from the mass of cotton and the mass of the filament, the combustion enthalpy $\Delta_c u°_{(cotton)}$ = –(16709±5) J g^{-1} (determined in our laboratory, the value being in agreement with reference[42] and $\Delta_c u°_{Ni–Cr)}$ = –5.86 kJ g^{-1} (certified by the fabricant). Samples amounting between

0.03–0.05 g were used in each experiment. The samples were weighed with a Mettler-Toledo microbalance with an accuracy of $\pm 2 \cdot 10^{-6}$ g. Some runs were rejected because of doubt about combustion completeness.

Thermal analysis

Power compensated calorimetry. A Perkin Elmer power compensated DSC (model 8500) was used for the measurement of the processes occurring during heating. Samples of about 0.4–0.9 mg of amino acid were sealed in aluminum pans. All samples were scanned at a heating rate 10 °C min^{-1}, in flowing nitrogen atmosphere (purity > 99.996%, 20 mL min^{-1}) from room temperature to 600 °C.

Heat flow calorimetry. The thermogravimetric data of the investigated inclusion compounds were performed using a simultaneous thermogravimetry-differential scanning calorimetry (TGA/DSC SETSYS Evolution 17). The heating rate used was 10 ºC min^{-1} from the ambient to 400 ºC, using Ar flow atmosphere and the samples mass was 1–1.4 mg.

CONCLUSIONS

The FT-IR results indicate that the vibrations and bends of the guest molecule (each of the EU, CA, TY) are restricted through encapsulation of molecule into the – CD cavity and formation of the inclusion complex.

The combustion data reveal a different behavior for TY which is rather enthalpically more stable when compared with the other isomeric monoterpene CA and EU, while in presence of HPβ-CD the trend of enthalpy of formation of the complexes increase following the order: HPβ-CD/EU < HPβ-CD/TY < HPβ-CD/CA.

Based on thermal analysis data, TY appears to be the most stable compound in the presence of HPβ-CD, as indicated by its relatively stable heat flow and minimal thermal transitions. Carvacrol follows, showing good stability, while eugenol shows moderate stability. Thus, thymol is likely to have the highest effectiveness when complexed with HPβ-CD.

The thermal curves indicate that the interaction between the essential oils (EU, CA, TY) and HPβ-CD results in the formation of inclusion complexes. The presence of HPβ-CD enhances the thermal stability of EU, CA, TY compounds, suggesting that enclosing them within the cavity can modify their properties.

Acknowledgements. This contribution is carried out within the research program "Chemical Thermodynamics" of the "Ilie Murgulescu" Institute of Physical Chemistry of the Roumanian Academy. Support of the EU (ERDF) and Roumanian Government, for the acquisition of the research infrastructure under Project INFRANANOCHEM- No. 19/01.03.2009 is gratefully acknowledged.

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