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Molecular calculations on β-cyclodextrin inclusion complexes with five essential oil compounds from *Ocimum basilicum* (sweet basil)

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ABSTRACT: Molecular docking and quantum chemistry calculations were used to establish the molecular model of β-cyclodextrin inclusion complex with five major compounds found in Thai sweet basil (*Ocimum basilicum*) essential oils, which includes linalool, eugenol, methyl eugenol, estragole, and eucalyptol. The electronic structures and the binding energies of 1:1 inclusion complexes of host:guest ratio for all five compounds were modelled by B3LYP/6-31G (d) calculations both in the gas phase and in the aqueous phase using polarizable continuum methods. The results agree with the experimental data, which show the ability of the compounds in Thai sweet basil essential oils to form an inclusion complex with β-cyclodextrin.

KEYWORDS: molecular docking, density functional calculation, solvent effect, polarizable continuous model

INTRODUCTION

Essential oils of Thai herbal plants are widely used in numerous applications including pharmaceutical, food, cosmetics, and spa products. The main drawback of herbal products is the rapid degradation of essential oil quality from sunlight exposure, oxidizing agent, and humidity. To overcome the degradation, preservation techniques of essential oil have become one of the most attractive research topics within the industry. Novel techniques aim to preserve the quality of the product and enhance shelf lifetime as well as stability improvement without changing the oil chemical properties. β-cyclodextrin (βCD) is widely used in many applications to preserve the active compounds by the encapsulation method in the form of an inclusion complex. βCD is a nontoxic cyclic oligosaccharide composed of seven α-D-glucoses with 1–4 glycosidic linkages. The inner hydrophobic cavity of βCD has a truncated-cone shape composed of carbon and hydrogen atoms. The rims of the cavity comprise primary and secondary hydroxyl groups, giving it a hydrophilic property. Judging by the X-ray structures, there are secondary hydroxyl groups at the C2 and C3 positions of the βCD located on the wider rim. The primary hydroxyl group at the C6 position is located on the narrower rim of the cone (Fig. 1). βCD unique properties lead to applications in which βCD serves as a host molecule forming inclusion complexes with different hydrophobic molecules as guest. The inclusion complex can enhance the aqueous solubility of these hydrophobic guest molecules[1]. βCD inclusion complexes have been applied in pharmaceutical, food, and cosmetics industries for solubility enhancement, drug delivery systems, separation technology, and chemical protection[1–3].

Thai sweet basil (*Ocimum basilicum*) is a well-known medicinal herb in traditional cuisine. The essential oil from Thai sweet basil provides many benefits such as anti-microorganism, anti-free radical, anti-carcinogen, anti-inflammation, cholesterol reduction, and peptic ulcer treatment. Thai sweet basil essential oil is mainly composed of linalool (3,7-dimethylocta-1,6-dien-3-ol), eugenol (4-allyl-2-methoxyphenol), and eucalyptol (1,3,3-trimethyl-2-oxabicyclo[2,2,2]octane) with a small amount of methyl eugenol (1,2-dimethoxy-4-prop-2-en-1-yl-benzene) and estragole (1-allyl-4-methoxybenzene)[4–6]. All chemical components are sensitive towards light, oxygen, humidity, and temperature. Compound encapsulation in βCD is therefore an interesting technique to enhance the stability of these compounds[7–9]. Experimental data report that linalool and eugenol can form an inclusion complex host:guest ratio of 1:1 with βCD[10–17]. Unfortunately, no experimental data has revealed the host-guest ori-

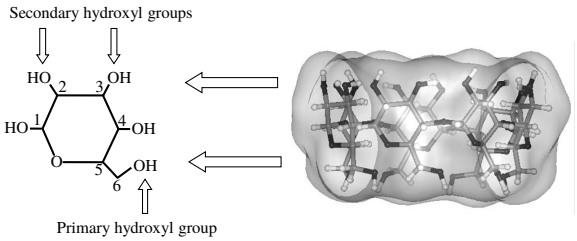

Fig. 1 Schematic representations of glucose unit and truncated cone shape of βCD.

entation within the complex and inclusion complex interactions, which are important to elucidate the encapsulation mechanism. The encapsulation mechanism could be essential to develop novel inclusion complex production at a pilot scale.

The study of host:guest interaction and preferred conformations of the inclusion complexes were investigated in this study by using molecular modelling techniques: molecular docking and quantum calculations. The combination of experimental and theoretical studies has been recognized as a powerful tool for the study of cyclodextrin inclusion complexes conformations[18–21]. Molecular docking can provide the probabilities of different preferred conformations for each individual complex. Quantum chemistry computations can provide optimized parameters for the molecular mechanics and electronic properties of the host and guest molecules. In addition, the calculations can also be applied in the selection of reliable conformations obtained from molecular docking simulation to yield the preferred conformations of the complexes.

The goal of this work is to study the possibility of using βCD to encapsulate the compounds in Thai sweet basil essential oils to prevent product degradation. The results from this work could lead to novel encapsulation of compounds in Thai sweet basil essential oils technique using βCD. The benefits of this method could also be applied to an advanced purification technique of specific active compounds in Thai sweet basil oil.

COMPUTATIONAL METHODS

Structure optimization

The βCD crystal structure was obtained from the Cambridge Crystallographic data Centre (code POBRON)[22]. Hydrogen atoms were added into the structure, which was then fully optimized by Density Functional Theory (DFT) at B3LYP/6-31G (d) level using GAUSSIAN09[23]. The obtained geometry was taken for further modelling of the inclusion complexes with five major compounds (guests) of Thai sweet basil essential oils. Guests compound structures were constructed with GAUSSVIEW. The structure of each guest was also fully optimized by DFT at B3LYP/6-31G (d) level. The logarithm partition coefficient ($\log P$) of compounds was calculated by ALOGPS[24,25] and HYPERCHEM Professional (Hypercube Inc., Gainesville FA).

Molecular docking

AUTODOCK 4.2[26] with Lamarckian Genetic Algorithm was used to generate the inclusion complex of βCD with guests. The complex was investigated in a three-dimensional volume divided into many small grid boxes. A box has a dimension of 24 Å × 24 Å × 24 Å with a grid spacing of 0.375 Å. Atomic charges were calculated by the Gasteiger-Marsili method[27]. The βCD molecule was kept as a fixed truncated-cone structure and guest structures were allowed free motion. One hundred docking calculations were executed for each guest structure.

Docking calculation results of each guest molecule were clustered into different groups based on the root mean-square deviation values of atomic position in the inclusion complex. Molecules in the same cluster must have a variation in position of less than 2 Å. The lowest energy host-guest inclusion complex conformation of each cluster was selected for further optimization using semi-empirical PM3 method. Optimized conformations of each inclusion complexes cluster were analysed.

Binding energy

A host-guest inclusion complex conformation from PM3 calculation of each group was selected based on the lowest binding energy. The selected conformations were further optimized using DFT calculations at B3LYP/6-31G (d) level to determine the binding energy of each complex. The binding energy (ΔE) of the inclusion complex was calculated as

$$\Delta E = E_{\text{complex}} - (E_{\text{guest}} + E_{\beta\text{CD}}),$$

where E_{complex} is the energy of the inclusion complex, E_{guest} is the energy of guest molecule, and $E_{\beta\text{CD}}$ is the energy of βCD.

The binding energies were estimated including basis set superposition error (BSSE) correction. The solvent effects on the inclusion complex conformations were investigated using the polarizable continuum model (PCM)[28] for water as a solvent with B3LYP/6-31G (d) calculations run on GAUSSIAN09.

Table 1 $\log P$ of compounds.

Compound	Free compound			Inclusion complex[b]
	Experiment[a]	ALOGPS	HYPERCHEM	
linalool	2.97	2.82	2.52	−7.66
eugenol	2.27	2.47	2.55	−7.33
methyl eugenol	3.45	2.75	2.59	−6.78
estragole	NA*	3.08	2.84	−8.60
eucalyptol	2.50	2.66	1.69	−8.37
βCD	NA*	−11.26	−8.52	–

[a] Refs. 29, 30.
[b] Calculated by HYPERCHEM.
* NA: not available.

RESULTS AND DISCUSSION

Chemical structures of five major compounds (guests) of essential oil from Thai sweet basil are depicted in Fig. 2. Distances between atoms of each optimized molecular conformation are also indicated. The truncated-cone cavity diameter of βCD (host) is in the range of 6.0–6.5 Å and the cavity height of βCD is 7.9 Å. Physicochemical properties of the guest molecule such as the size, charge, and polarity can influence the ability and stability of inclusion complex formation. In general, highly water-soluble and highly hydrophilic guests are not suitable for complex formation. The partition coefficients (P) are the ratios of concentrations of compounds in a mixture of two immiscible phases at equilibrium. These coefficients are the measurements of the difference in solubility of the compound in these two phases. The $\log P$ values have been used to indicate the level of lipophilicity of compounds.

Table 1 illustrates $\log P$ values of the host free compound, the guest free compound, and the inclusion complexes examined in this study. The results from the calculation compared to that of the experimental data reveal advantages and disadvantages of ALOGPS and HYPERCHEM for this study. ALOGPS provides more accurate $\log P$ values for guest molecules relative to the experimental data[29,30] than the value from HYPERCHEM. Unfortunately, ALOGPS is unable to calculate the $\log P$ of the inclusion complexes. HYPERCHEM is however able to calculate $\log P$ of the inclusion complexes and yields an acceptable $\log P$ values of guest compounds relative to the experimental data.

The $\log P$ values from both calculations and experimental data in Table 1 indicated all guests are hydrophobic compounds with positive partition coefficient (P) values. The βCD has the negative $\log P$ value of −8.52, which can dissolve in aqueous solution. After the encapsulation of guest in βCD in the form of inclusion complexes, the $\log P$ values of all inclusion complexes yield negative values vary from −6.78 to −8.60. Results indicate that the inclusion complexes in this study can dissolve in aqueous solution. Moreover, the formations of complex between βCD and guest molecules do not alter the βCD aqueous solubility.

Table 2 Molecular docking calculations.

Compound	# of rotatable bonds	Cluster	Frequency (%)	Energy (kcal/mol)	
				Lowest	Mean
linalool	5	1	68	−3.92	−3.76
		2	29	−3.84	−3.71
		3	3	−3.76	−3.68
eugenol	4	1	4	−3.74	−3.66
		2	62	−3.66	−3.55
		3	26	−3.64	−3.50
		4	4	−3.47	−3.39
		5	3	−3.35	−3.29
		6	1	−3.32	−3.32
methyl eugenol	4	1	66	−3.69	−3.57
		2	26	−3.64	−3.62
		3	3	−3.53	−3.50
		4	5	−3.53	−3.51
estragole	3	1	62	−3.65	−3.57
		2	38	−3.50	−3.48
eucalyptol	0	1	100	−4.82	−4.82

Molecular docking and PM3 optimization

AUTODOCK 4.2 was used to predict the preferred orientations of guest molecule with βCD in the inclusion complex formation. According to the simulations, all five guest molecules are able to form a 1:1 inclusion complex with βCD. The binding energies are listed in Table 2. An individual guest molecule was investigated to determine all atomic positions in three dimensions based on a hundred simulation runs to ensure all possible conformations of guest molecules in the inclusion complex.

The results of each guest molecule can be clustered in different groups based on the root mean-square deviation values of atomic position in the inclusion complex. Molecules in the same cluster must have a variation in position of less than 2 Å. Table 2 shows all clusters of each guest molecule conformations in the complex and the percentage of frequency. Only eucalyptol shows a single possibility conformation while other guest molecules provide more than one possible conformation. This phenomenon can be explained by the molecular structure of eucalyptol, with no available rotatable bond in the molecule (Fig. 2). Table 2 also shows the binding energies involved in the host-guest interactions determined by AUTODOCK simulations.

The molecular docking calculations utilize a basis

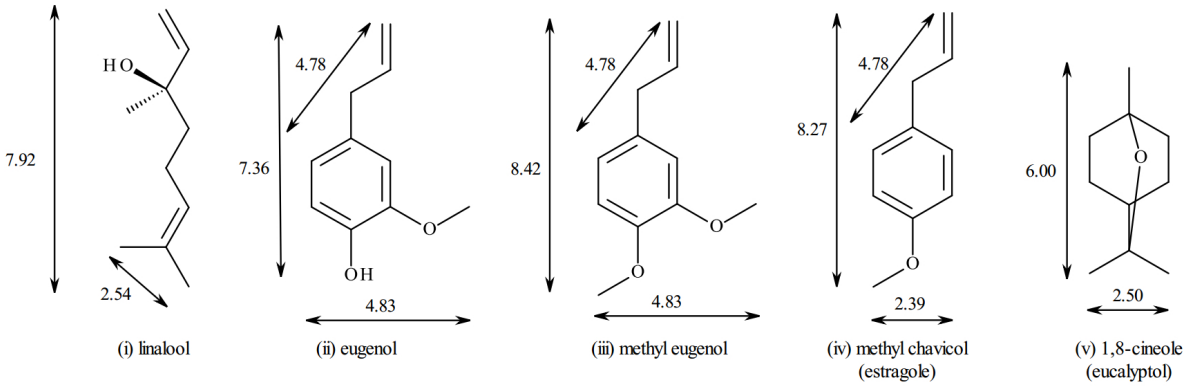

Fig. 2 Chemical structure of five components of Thai sweet basil essential oil (distances in Å).

Table 3 The binding energy (ΔE) of the inclusion complex structures optimized by PM3 calculations.

Guest	Cluster	ΔE (kcal/mol)	Inclusion complex conformation
linalool	1	−12.58	linalool-I[a]
	2	−10.18	linalool-I
	3	−7.02	linalool-II[a]
eugenol	1	−8.66	eugenol-I
	2	−7.57	eugenol-II
	3	−9.72	eugenol-I[a]
	4	−9.55	eugenol-II[a]
	5	−9.33	eugenol-I
	6	−8.20	eugenol-II
methyl eugenol	1	−13.53	methyl eugenol-I[a]
	2	−10.09	methyl eugenol-II[a]
	3	−13.20	methyl eugenol-I
	4	−13.16	methyl eugenol-I
estragole	1	−5.39	estragole-I[a]
	2	−7.01	estragole-II[a]
eugenol	1	−12.77	eucalyptol-I[a]

[a] selected conformation for DFT calculation

of flexible guest molecules and a fixed host system. Thus the conformation with the lowest binding energy of each cluster was selected for full optimization by PM3 calculations which provide free motions, both for host and guest molecules. The interaction energies of optimized inclusion complexes calculated by the PM3 method are presented in Table 3.

PM3 calculations coupled with geometry analysis yield two conformations for each guest molecule inclusion complex except for eucalyptol. Each conformation with the lowest binding energy was selected to be the representative conformation for further DFT calculations. Selected conformations are illustrated in Fig. 3.

Table 4 Binding energies in kcal/mol of inclusion complexes in water using PCM methods (ΔE^{PCM}) and in gas phase (without, ΔE, and with BSSE correction, ΔE^{cp}), at B3LYP/6-31G (d) levels.

Inclusion complex conformation	ΔE^{PCM}	Gas phase		
		ΔE	BSSE	ΔE^{cp}
linalool-I	−4.71	−13.57	11.11	−2.46
linalool-II	−5.61	−10.70	10.34	−0.36
eugenol-I	−2.44	−22.12	11.57	−10.55
eugenol-II	−8.18	−9.87	10.53	0.66
methyl eugenol-I	−7.15	−7.39	8.59	1.20
methyl eugenol-II	−7.74	−9.26	11.59	2.34
estragole-I	−4.20	−5.57	6.77	1.20
estragole-II	−4.21	−8.04	7.74	−0.30
eucalyptol-I	−2.86	−5.45	7.46	2.01

DFT calculations

The selected geometry of inclusion complex conformations of βCD with five compounds were further optimized by DFT at B3LYP/6-31G (d) level, and the binding energies including BSSE were estimated. Table 4 presents the B3LYP/6-31G (d) binding energies (ΔE) with and without BSSE correction of the lowest energy complex conformations in gas the phase. Effects of water solvation on binding energies of the complexes (ΔE^{PCM}) are listed in Table 4.

According to the calculations, the binding energies indicate that the inclusion complex formations of βCD with all five compounds are stabilized both in the gas phase and in the aqueous phase. The results show the complexes in water (ΔE^{PCM}) are more stable than those in the gas phase (ΔE^{cp}). The conformation of the complexes both in gas phase and water solvent are however similar. Fig. 4 presents the B3LYP/6-31G (d) optimized geometries for the most stable 1:1 host-guest inclusion complexes in water.

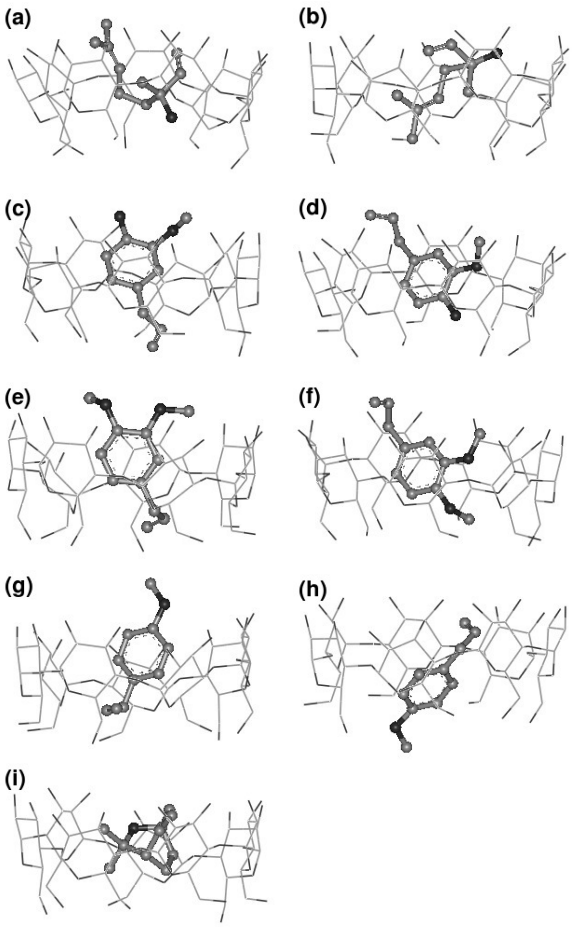

Fig. 3 PM3 optimized structures. βCD is presented as a line model and guest compounds are presented as ball and stick models (hydrogen atoms are omitted for clarity): (a) linalool-I; (b) linalool-II; (c) eugenol-I; (d) eugenol-II; (e) methyl eugenol-I; (f) methyl eugenol-II; (g) estragole-I; (h) estragole-II; (i) eucalyptol-I.

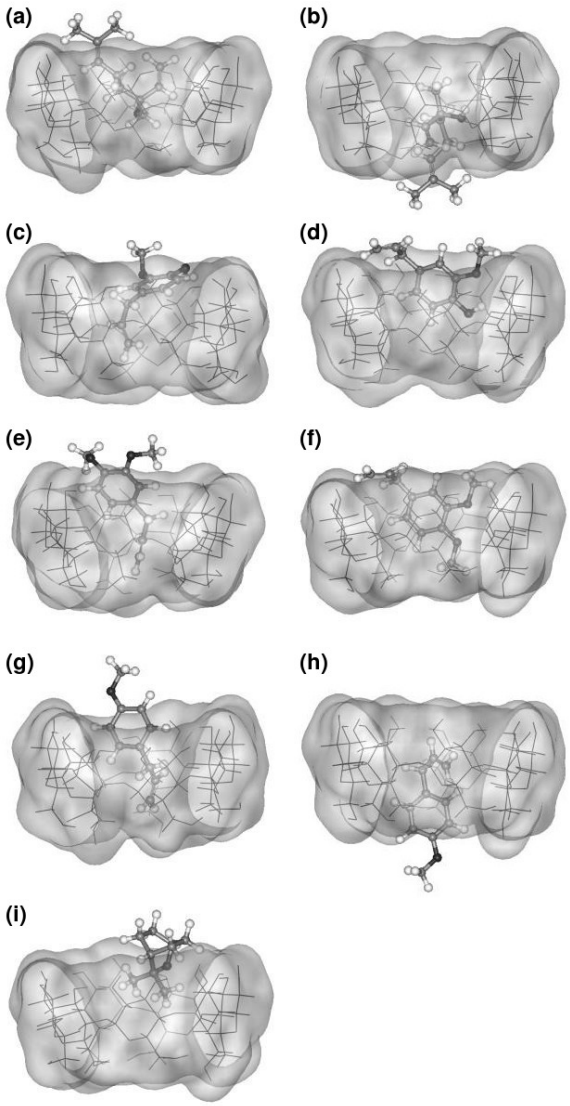

Fig. 4 DFT B3LYP/6-31G (d) optimized structures in water. βCD is presented as a line model with its surface with the probe radius 1.4 Å and guest compounds are presented as ball and stick models: (a) linalool-I; (b) linalool-II; (c) eugenol-I; (d) eugenol-II; (e) methyl eugenol-I; (f) methyl eugenol-II; (g) estragole-I; (h) estragole-II; (i) eucalyptol-I.

Linalool-βCD inclusion complex

Theoretical calculations provide two possible formations for 1:1 βCD-linalool inclusion complex in water solvent, (Fig. 4), with binding energy −4.71 and −5.61 kcal/mol. The results agree with the experimental data which indicated the stable 1:1 linalool-βCD inclusion complex with the formation constant (K_f) of 366 M^{-1} [11,12]. In both conformations, linalool-I and linalool-II, the linalool molecule was observed to be close to the βCD wider rim. The dimethyl group of linalool stays outside of the cavity on the wider rim. The calculations suggest that both linalool-I and linalool-II conformations are possible to occur in aqueous solution.

Eugenol-βCD inclusion complex

The calculations suggest two conformations of 1:1 eugenol-βCD inclusion complex (Fig. 4). In eugenol-I, the phenyl ring and the unsaturated end of eugenol molecule stay inside βCD cavity due to the hydrophobic interactions. The hydroxyl group and the methoxyl group of eugenol are located near the wider rim of βCD. In the gas phase, eugenol-I shows a cooperative hydrogen bonded chain occurs between

hydroxyl groups of eugenol and βCD resulting in very stable conformation with ΔE^{cp} −10.55 kcal/mol. However, no hydrogen bond was however observed in PCM calculations. The binding energy of this conformation in water solvent therefore increased from −10.55 kcal/mol to −2.44 kcal/mol (Table 4). For the second conformation, eugenol-II, the eugenol molecule is close to βCD wider rim with one H-bond between the hydroxyl group of eugenol and the ethereal oxygen (O4) of βCD. This H-bond is found both in gas the phase and in the aqueous phase. The experimental results show that eugenol with βCD can form 1:1 host-guest complex with K_f of 322 M^{-1} and 357 M^{-1} [14,15]. According to the difference in ΔE^{PCM} values, eugenol-II is about 5.7 kcal/mol more stable than eugenol-I.

Methyl eugenol-βCD and estragole-βCD inclusion complexes

Two possible conformations of the 1:1 inclusion complexes of methyl eugenol-βCD and estragole-βCD are demonstrated in Fig. 4. The phenyl ring of the two guest compounds, (methyl eugenol and estragole molecules) stay inside the βCD cavity. In conformation-I, the unsaturated end of these two guest molecules stay near the βCD narrow rim. In conformation-II, these unsaturated ends are near the βCD wider rim instead of the narrow rim. The negative binding energies of both conformations suggest the possibility of these complex formations with βCD in aqueous solution.

Eucalyptol-βCD inclusion complex

The structure of eucalyptol lacks bonding flexibility (Fig. 2) due to the presence of oxo bicyclo-configuration. The entrance of eucalyptol at the narrow rim of βCD is difficult due to the diameter of the βCD narrow rim is close to that of the widest part of eucalyptol. According to the steric hindrance, eucalyptol can enter βCD cavity at the wider rim and can form only eucalyptol-I inclusion complex conformation (Fig. 4). The dimethyl group of eucalyptol molecule provides the possibility of inclusion complex formation by hydrophobic interaction with a binding energy of −2.86 kcal/mol in aqueous phase. This result agrees with the experimental data which indicated the high possibility of the complex formation evidenced from the binding constant (K_s) of 1:1 eucalyptol to βCD inclusion [10].

Binding affinity of the inclusion complexes

In summary, the negative binding energies of all inclusion complex indicate the possible formation of 1:1 host:guest ratio inclusion complex in aqueous solution. The results also agree well with the experimental data of these complexes [10–12,14,15]. βCD and guest compounds are bound together to form complexes by electrostatic dipole-dipole, van der Waals, and hydrophobic interactions. The binding affinities of the inclusion complexes in water solvent determined from binding energy values are in the following order: eugenol-βCD > methyl eugenol-βCD > linalool-βCD > estragole-βCD > eucalyptol-βCD.

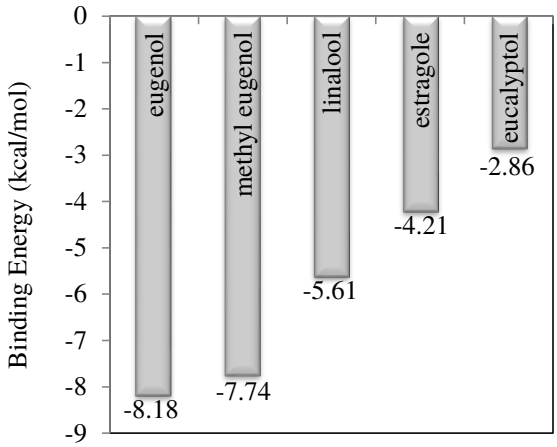

Fig. 5 The lowest binding energy of βCD inclusion complexes with five compounds calculated by B3LYP/6-31G (d) in water solvent.

According to the differences in binding affinities of the complexes, (Fig. 5), βCD could be used to separate and purify compounds in Thai sweet basil oil. The results from this study illustrate the possibility of a separation technique using βCD forming complexes with individual compound in different conditions, according to the binding affinities.

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