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Inclusion interactions of cyclodextrins and crosslinked cyclodextrin polymers with linalool and camphor in *Lavandula angustifolia* essential oil

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ABSTRACT

In the present study, we investigated the feasibility of preparation of novel controlled release systems for the delivery of essential oil used as ambient odors. The inclusion interactions of cyclodextrins (CDs) and β-cyclodextrin polymers with linalool and camphor in *Lavandula angustifolia* essential oil were investigated by static headspace gas chromatography (SH-GC). The stability constants with monomeric CD derivatives were determined for standard compounds and for the compounds in essential oil. All studied CDs and CD polymers reduce the volatility of the aroma compounds and stable 1:1 inclusion complexes are formed. The retention capacity of the CD derivatives was measured in static experiments. The feasibility of preparation of novel controlled release systems for the delivery of fragrances was investigated by multiple headspace extraction (MHE) experiments.

1. Introduction

Pure fragrance compounds and essential oils have been used traditionally in folk medicine, spa, cosmetics and toiletries, but also in many scented household and occupational products. Lavender is one of the most useful medicinal plants. Commercially, the lavender provides several important essential oils to the fragrance industry including soaps, colognes, perfumes, skin lotions and other cosmetics. In food manufacturing, lavender essential oil is employed in flavoring beverages, ice cream, candy, baked goods, and chewing gum. Recently, aromatherapy is becoming increasingly popular, and lavender is used in aromatherapy as a relaxant. Several therapeutic effects of lavender such as sedative, spasmolytic, antiviral, and antibacterial activities have been reported (Lehrner, Marwinski, Lehr, Johren, & Deecke, 2005; Wang & Chen, 2005a). Therefore, the development of support for aroma controlled release is of interest. Moreover, many of fragrance molecules are unstable due to their reactive functionalities, such as aldehyde, ketone and terpenes. Degradation not only causes changes in their sensory characteristics, but also, in many cases, creates allergenic products (Karlberg, Magnusson, & Nilsson, 1992; Matura et al., 2005, 2006).

It has been known that control of the volatilization rate and degradation is the heart of prolonging the sensory characteristics of fragrance materials. One way of doing so is encapsulation, which provides both stabilization and a controlled release of the entrapped materials (Madene, Jacquot, Scher, & Desobry, 2006; Reineccius, 1989).

Cyclodextrins (CDs) represent one of the simplest encapsulant systems (Marques, 2010). CDs are non-toxic macrocyclic oligosaccharides, consisting of (α-1,4)-linked α-D-glucopyranose units, with a hydrophilic outer surface and hollow hydrophobic interior (Szente & Szejtli, 2004). It has been reported that the inclusion complexes of guest compounds with CDs can enhance guest stability, improve the aqueous solubility, protect against oxidation, light-induced decomposition, and heat-induced changes, mask or reduce unwanted physiological effects, and reduce volatility (Hedges, Shiech, & Sikorski, 1995; Shieh & Hedges, 1996). These characteristics of CDs make them suitable for applications in food and flavors industries (Astray, Gonzalez-Barreiro, Mejuto, Rial-Otero, & Simal-Gándara, 2009).

Binding of aroma (guest) compounds to the β-CD molecule (host) leads to the formation of an inclusion complex. The nature of the interactions leading to complexation has been discussed elsewhere (Decock et al., 2006; Decock, Landy, Surpateanu, & Fourmentin, 2008; Szejtli, 1998). Essentially, complexation is

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dependent primarily on guest compound hydrophobicity as well as molecular size and geometry. Computer-aided molecular modeling has also been used to understand the spatial orientation of guest compound complex inclusions with β-CD (Decock et al., 2006; Lipkowitz, 1998).

Polymers with β-cyclodextrin (β-CD) have been extensively studied in different fields such as analytical chemistry (Crini & Morcellet, 2002; Yu, Jiang, Liu, Yu, & Zhang, 2003) or pharmaceutical industries (Binello, Robaldo, Barge, Cavalli, & Cravotto, 2008; Davis & Brewster, 2004; Gazpio et al., 2008; Layre, Gosselet, Renard, Sebille, & Amiel, 2002). One of the first and most frequently used crosslinker is epichlorohydrin (EP). EP can react with the hydroxyl groups of CDs in basic media to yield ethers. However, to the best of our knowledge, there are, so far, no report on the inclusion of essential oils and aroma with CD polymers. Moreover, there is scanty literature on the inclusion complex of *Lavandula* essential oil and CDs (Hădărugă et al., 2007; Wang & Chen, 2005b).

In the present study we investigated the feasibility of preparation of novel controlled release systems for the delivery of essential oil used as ambient odors. We focused on the complexation behaviour and the retention capacity of α-CD, β-CD, γ-CD, hydroxypropyl-β-cyclodextrin (HPBCD), randomly methylated-β-cyclodextrin (RAMEB), a low methylated-β-cyclodextrin (CRYSMEB) and crosslinked β-CD polymers for linalool and camphor two major components of *Lavandula angustifolia* essential oil. The complexation and the retention capacity of CDs and CD polymers were investigated under solid support or in aqueous media by static headspace gas chromatography (SH-GC). The release profile of aroma from solid support was investigated by multiple headspace extraction (MHE).

2. Materials and methods

2.1. Chemical

Sodium hydroxide, epichlorohydrin, linalool, camphor (Aldrich) all of analytical reagent grade were used as received. CRYSMEB (DS = 4.9) were provided from Roquette Frères (Lestrem, France), α-CD, β-CD, γ-CD, HPBCD (DS = 5.6) and RAMEB (DS = 12.6) were purchased from Wacker-Chemie (Lyon, France). Distilled deionized water was used throughout this work.

L. angustifolia essential oil was obtained by Soxhlet extraction. The flowers of *L. angustifolia* were produced by the company "Farmacia Naturii" from Bacau. The dried flowers were extracted using a soxhlet apparatus for 9 h in ethanol (40–60 °C). The essential oil obtained was dried under vacuum and stored at 4–6 °C before analysis.

2.2. Gas chromatography–mass spectrometry (GC–MS) analysis

Analysis of the essential oil was carried out on a Varian 1200 Quadrupole MS/MS with a CP-3800 GC (Varian) fitted with a split/splitless injector and a CP-8400 autosampler (Varian). An Agilent J&W FactorFour VF-5ms GC Column (30 m × 0.25 mm, df = 0.25 μm) was used. Temperature conditions were as follows: initial temperature of 40 °C for 5 min, increased to 310 °C at 5 °C/min and isothermally held for 1 min giving a total run time of 60 min. The flow of the carrier gas (helium) was maintained at 1.0 mL/min in constant flow mode. The injector was set at 280 °C, the transfer line was 320 °C and the ion source was 200 °C. The EI (Electron Impact Ionization) mode was used with electron energy of 70 eV. The GC–MS was programmed to perform a 1.0 μL splitless injection.

The identification of the components was based on the comparison of their mass spectra with those of reference spectra in the computer library, as well as by comparison of their retention indices with literature values and our data are in accordance with those previously reported.

Table 1
Experimental conditions for the synthesis of β-CD polymers.

Polymers	EP/BCD ratio	Soluble or insoluble
P1	3:1	Soluble
P2	5:1	Soluble
P3	8:1	Soluble
P4	10:1	Soluble
P5	15:1	Soluble
P6	23:1	Insoluble
P7	39:1	Insoluble

2.3. Synthesis of cyclodextrin polymers

The polymerization of β-CD with epichlorohydrin (EP) was carried out in aqueous media as described elsewhere (Crini et al., 1998; Mallard-Favier, Baudelet, & Fourmentin, 2011; Renard, Deratani, Volet, & Sebille, 1997). Briefly, sodium hydroxide (5 g) and water (15 g) were mixed together in a flask, while the mixture was heated under stirring (600 rpm) at 60 °C. β-CD was added slowly to the solution. Once the β-CD dissolved, epichlorohydrin was added dropwise to the stirred solution at the rate of about 2 mL per every 15 min. After addition, the reaction mixture was kept at 60 °C for 4 h. Polymer precipitation was realized with ethanol. The experimental conditions are summarized in Table 1.

Depending on the EP/CD ratio, soluble and insoluble polymers were obtained in agreement with literature (Renard et al., 1997). From our results, the occurrence of insoluble polymers is observed for an EP/CD ratio >15. Soluble polymers were dialysed during one night to remove all impurities. Insoluble polymers were sieved and the fraction <125 μm were used during the study.

2.4. Static headspace gas chromatography (HS-GC)

Headspace sampling is employed with gas chromatography (GC) in numerous fields and with a variety of applications (Kolb, 1999; Snow & Slack, 2002). A headspace sample is in principle a gas sample which has been previously in contact with a liquid or solid sample from which volatile compounds were released into the gas with subsequent analysis by gas chromatography. Headspace gas chromatography is therefore a technique of gas extraction and can be carried out comparable to a solvent extraction as a one-step extraction (static or equilibrium headspace) or as a continuous extraction (dynamic headspace) (Kolb & Ettre, 2006).

Measurements were conducted with an Agilent headspace autosampler under solid support or aqueous media. The oven-dried adsorbents were weighed in glass vials of 22 mL in volume. For studies under aqueous media 10 mL of distilled deionized water were added in the vial. After addition of the sorbate with a mycrosyringe, the vial was sealed using silicone septa and aluminium foil. The vials were then thermostated at 25 ± 0.1 °C. After the equilibrium was established (24 h), 1 mL of vapor from the above solution was drawn out from the vial using a gas-tight syringe and injected directly in the chromatographic column via a transfer line (Fig. 1).

This sample was then analyzed by gas chromatography (Perkin Elmer Autosystem XL) equipped with a flame-ionization detector using an Agilent J&W DB-5 column. The temperature conditions were the same as for GC–MS analysis. The obtained chromatograms allow quantitative analysis of the vapor above each sample. Blank experiments (without sorbents) were used to account for sorption losses.

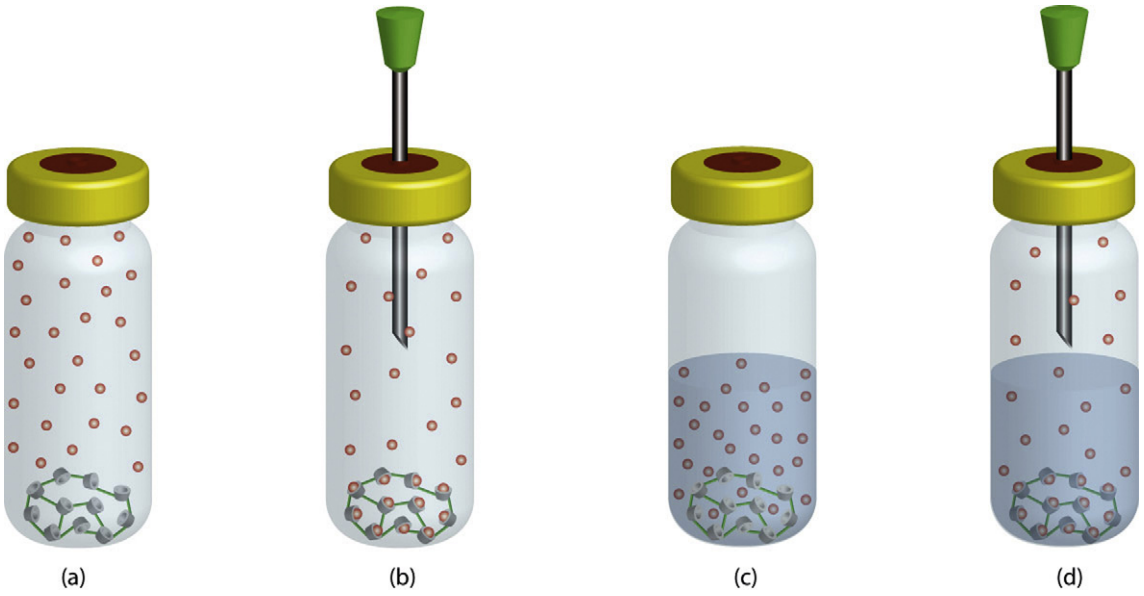

Fig. 1. Illustration of the sorption experiment: addition of the sorbate in gaseous phase (a) or in water (c) and after equilibrium (b) and (d).

2.5. Retention of aroma by cyclodextrin derivatives

The percentage of retention (r) of the studied aroma by the different CDs is expressed as follows:

$$r\ (\%) = \left(1 - \frac{A_{CD}}{A_0}\right) \quad (1)$$

with A_0 and A_{CD} the peak area of the aroma in the absence and in the presence of CD respectively. The percentage of retention was determined at 25 °C for a 10 ppm solution of the aroma and a weight of 30 mg for CDs and CD polymers. For each adsorbent, measurements were done in triplicate.

2.6. Formation constant determination

The host/guest system was studied by a SH-GC titration method developed in our laboratory for volatile organic compounds (Blach, Fourmentin, Landy, Cazier, & Surpateanu, 2008; Decock et al., 2008; Dron, Fourmentin, Cazier, Landy, & Surpateanu, 2008; Fourmentin et al., 2007). Different concentrations of CD were used at constant guest (G) concentration.

Assuming 1:1 ratio binding, the total concentration of guest in aqueous solution ($[G]_0$) and the total CD concentration ($[CD]_0$) were expressed as follows:

$$[G]_0 = [G] + [CD/G] \quad (2)$$

and

$$[CD]_0 = [CD] + [CD/G] \quad (3)$$

where [CD/G] was the concentration of the associated complex. The $[G]_0$ after equilibrium was determined by subtracting the number of moles of guest in the gaseous phase.

Then, in the presence of CD, the peak area can be expressed as follows:

$$A = \alpha([G]_0 - [CD/G]) \quad (4)$$

with A the integrated area counts of the GC peak for a given sample, and α a specific parameter of the headspace.

The association constant was given by:

$$K_f = \frac{[CD/G]}{[G][CD]} = \frac{[CD/G]}{([G]_0 - [CD/G]) \times ([CD]_0 - [CD/G])} \quad (5)$$

Thus, [CD/G] can be estimated by:

$$[CD/G] = -\frac{1}{2}\sqrt{\left[\left(\frac{1}{K_f} + [CD]_0 + [G]_0\right)^2 - 4[CD]_0[G]_0\right]} + \frac{1}{2}\left(\frac{1}{K_f} + [CD]_0 + [G]_0\right) \quad (6)$$

For a given value of K_f, [CD/G] was known, and thus a theoretical value was calculated for the peak area. An algorithmic treatment was then applied to minimize the difference between the experimental and theoretical values of the peak area leading to the adequate formation constant (K_f) (Landy, Fourmentin, Salome, & Surpateanu, 2000).

2.7. Multiple headspace extraction (MHE)

In order to study the dynamic release of aroma from CD or CD polymers we used multiple headspace extraction (MHE). In principle, MHE is a dynamic gas extraction carried out stepwise. If we take successive aliquots from the vial's headspace, the total amount of the analyte present will further decline, eventually becoming totally exhausted. In each step, part of the analyte present is removed until no analyte is left in the original sample. Thus, the sum of the amounts of the analyte removed in the individual extractions will be equal to the total amount of analyte present in the original sample (Kolb & Ettre, 2006).

100 mg of the adsorbate were placed in a sealed vial with 10 ppm of aroma at 60 °C. Fifty successive extractions were realized.

2.8. Molecular modeling

Simulations were realized by means of Macromodel (Mohamadi et al., 1990) with MMFFs force field and GB/SA simulation of water (Cheng, Best, Merz, & Reynolds, 2000). The host structure was based on a non distorded monomeric β-CD with C7 symmetry, while guests were constructed manually and submitted to appropriate minimization and conformational search, prior to inclusion simulations. The docking of each guest inside β-CD was realized by means of Monte Carlo searches, with generation of 25000 conformations (Polak-Ribiere Conjugate Gradient minimization, convergence fixed to 0.05 kJ/Å mol). The guest was freely modified

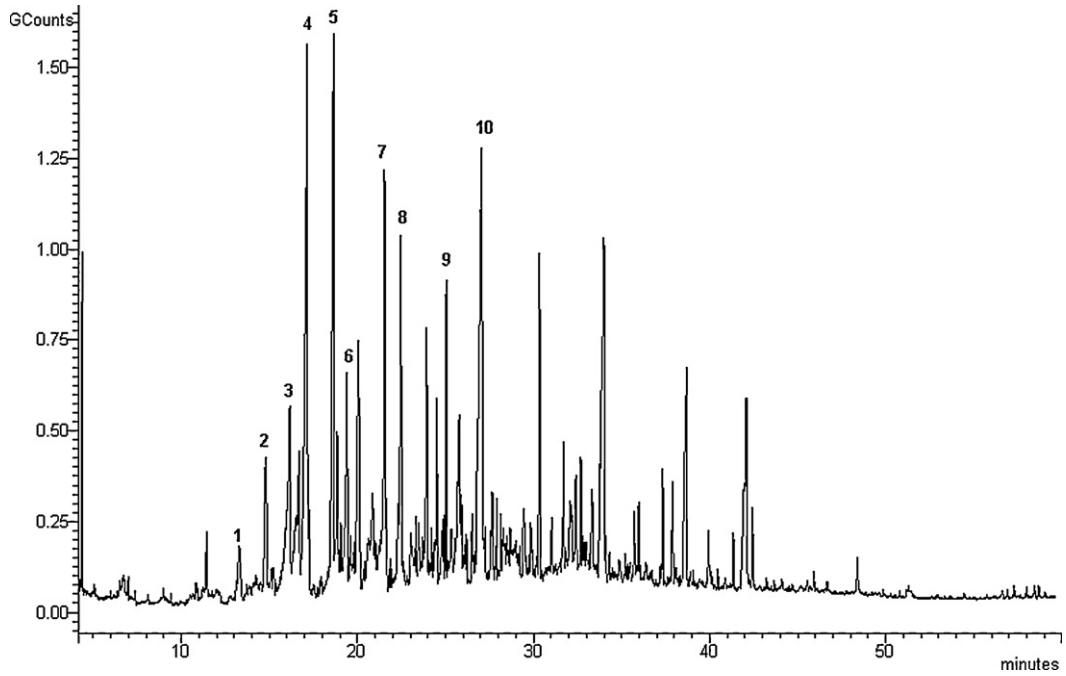

Fig. 2. *Lavandula angustifolia* essential oil profile with myrcene (1), eucalyptol (2), linalool oxide (3), linalool (4), camphor (5), isoborneol (6), linalyl acetate (7), lavandulyl acetate (8), geranyl acetate (9) and coumarin (10).

while β-CD was kept rigid. The most stable conformation for each inclusion compound was then completely relaxed (convergence fixed to 0.05 kJ/Å mol).

3. Results and discussion

3.1. GC–MS analysis of Lavandula essential oil

48 components have been identified from essential oil. Among them linalool (9.68%), camphor (8.35%), coumarin (7.5%), linalool oxide (4.1%), linalyl acetate (3.23%), lavandulyl acetate (2.76%), eucalyptol (2.46%), geranyl acetate (2.06%), isoborneol (1.25%), and myrcene (0.85%), have been identified as the major components. The composition of the *L. angustifolia* essential oil was similar to that reported in the literature (Da Porto, Decorti, & Kikic, 2009; Kim & Lee, 2002), the relative percentage of each component depending on the extraction method and on the *Lavandula* species. The GC/MS profile is presented in Fig. 2. Linalool and camphor, the two principal components, were used as model compounds for the study.

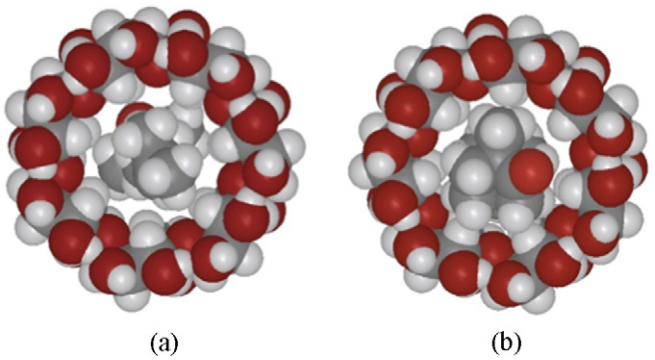

Fig. 3. β-CD complexes with linalool (a) and camphor (b).

3.2. Inclusion of aroma inside monomeric cyclodextrins

The determinations of the formation constant were done at 25 °C using four CDs concentration. The obtained variations of the peak area are in good agreements with a 1:1 host/guest ratio.

Few determinations of the formation constant between aroma and CDs have been performed (Astray, Mejuto, Morales, Rial-Otero, & Simal-Gándara, 2010; Decock et al., 2006, 2008; Saito, Tanemura, Sato, & Ueda, 1999; Saito, Tanemura, Ueda, & Sato, 1998; Tanemura, Saito, Ueda, & Sato, 1998; Tobitsuka, Miura, & Kobayashi, 2005). To the best of our knowledge, there is no data concerning the determination of the formation constant between CDs and aroma compounds present in an essential oil. This determination is only possible with chromatographic methods, since they can separate the different compounds. The variation of the area of each compound in the presence of CDs allows the simultaneous determination of formation constants for several compounds.

The formation constants calculated are reported in Table 2. It can be seen that the value obtained for the standard aroma compound and for the same compounds in *Lavandula* essential oil are in good agreement.

Table 2
Formation constant (M^{-1}) obtained by static headspace gas chromatography at 25 °C for the standard compounds and for the compounds in *Lavandula angustifolia* essential oil.

	Linalool		Camphor	
	3.213[a]		2.160[a]	
	Standard	In essential oil	Standard	In essential oil
ACD	32	78	184	285
BCD	366	804	2058	2385
RAMEB	833	1074	1194	2963
CRYSMEB	816	882	1901	2409
HPBCD	596	584	1280	1769
GCD	138	317	1048	1198

[a] Log *P*. http://www.molinspiration.com/cgi-bin/properties.

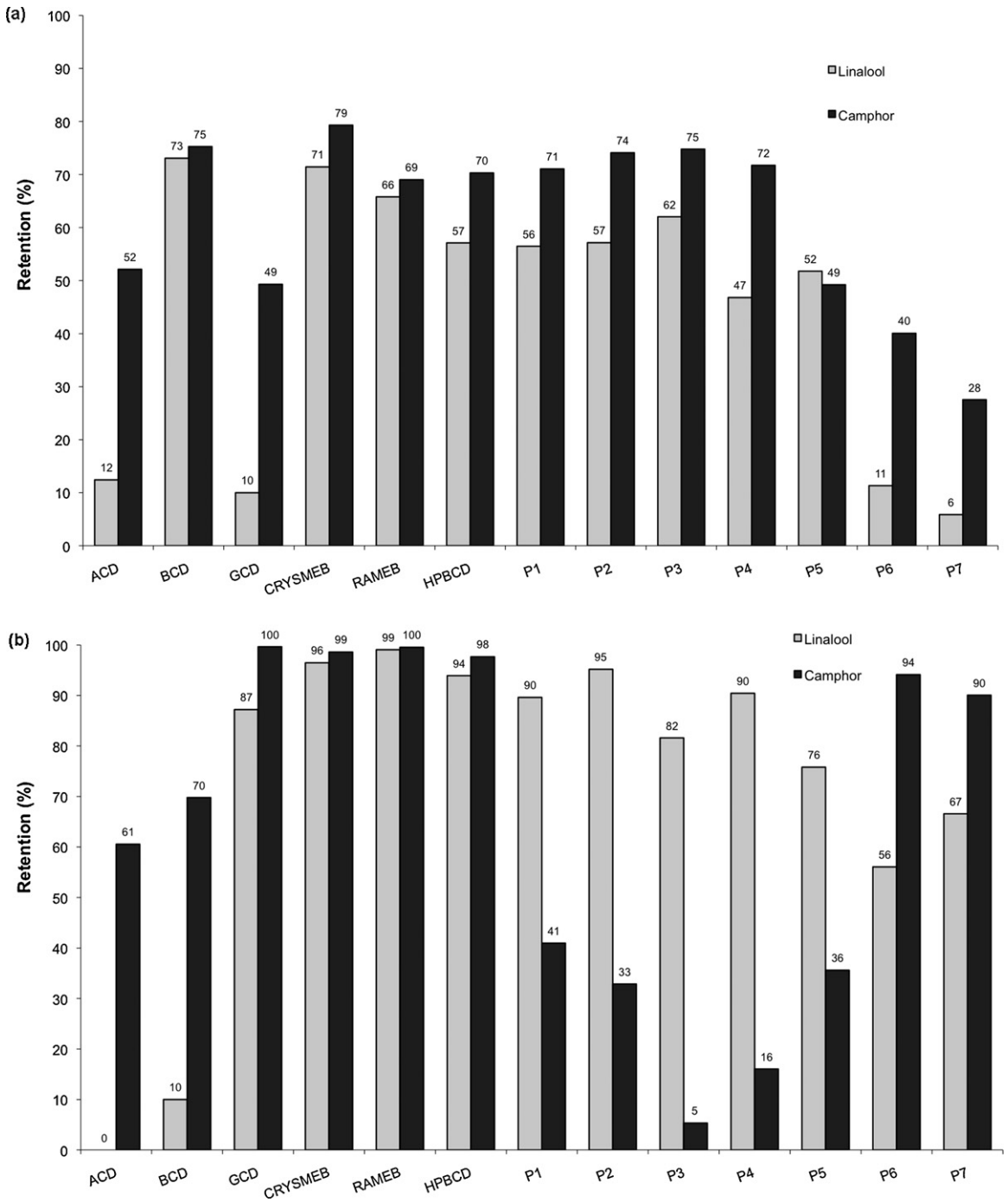

Fig. 4. Retention linalool and camphor by CDs and CD polymers in aqueous phase (a) and in gaseous phase (b).

Whatever the CD, camphor is always more recognized than linalool. β-CDs have more affinity for the two compounds than α- or γ-CD. β-CDs seem to be the most versatile CDs for aroma complexation, therefore β-CDs polymers where synthesized and evaluated for their retention ability.

Generally, the binding between CDs and aroma compounds depends on both guest hydrophobicity (estimated on the basis of log *P*) and on its geometric accommodation inside the CD cavity (Decock et al., 2008). In order to get better insights inside these inclusion phenomena, we have also studied the steric complementarity between camphor and linalool with β-CD by means of molecular modeling. The inclusion compounds have been submitted to Monte Carlo searches (MMFF force field), with an implicit representation of water (GB/SA). The most stable conformations which have been simulated are illustrated in Fig. 3. One can observe that both guest structures might be encapsulated in β-CD, but that much more space remains free in the cavity in the case of linalool. Thus, the influence of the steric complementarity probably explains the greater stability observed for camphor.

3.3. Retention of aroma by cyclodextrin derivatives

The presence of chemical agents in solution is known to impact the vapor–liquid equilibria (Kashiyama & Boving, 2004; Ladaa, Lee, Coates, & Falta, 2001) since they can change the solubility of

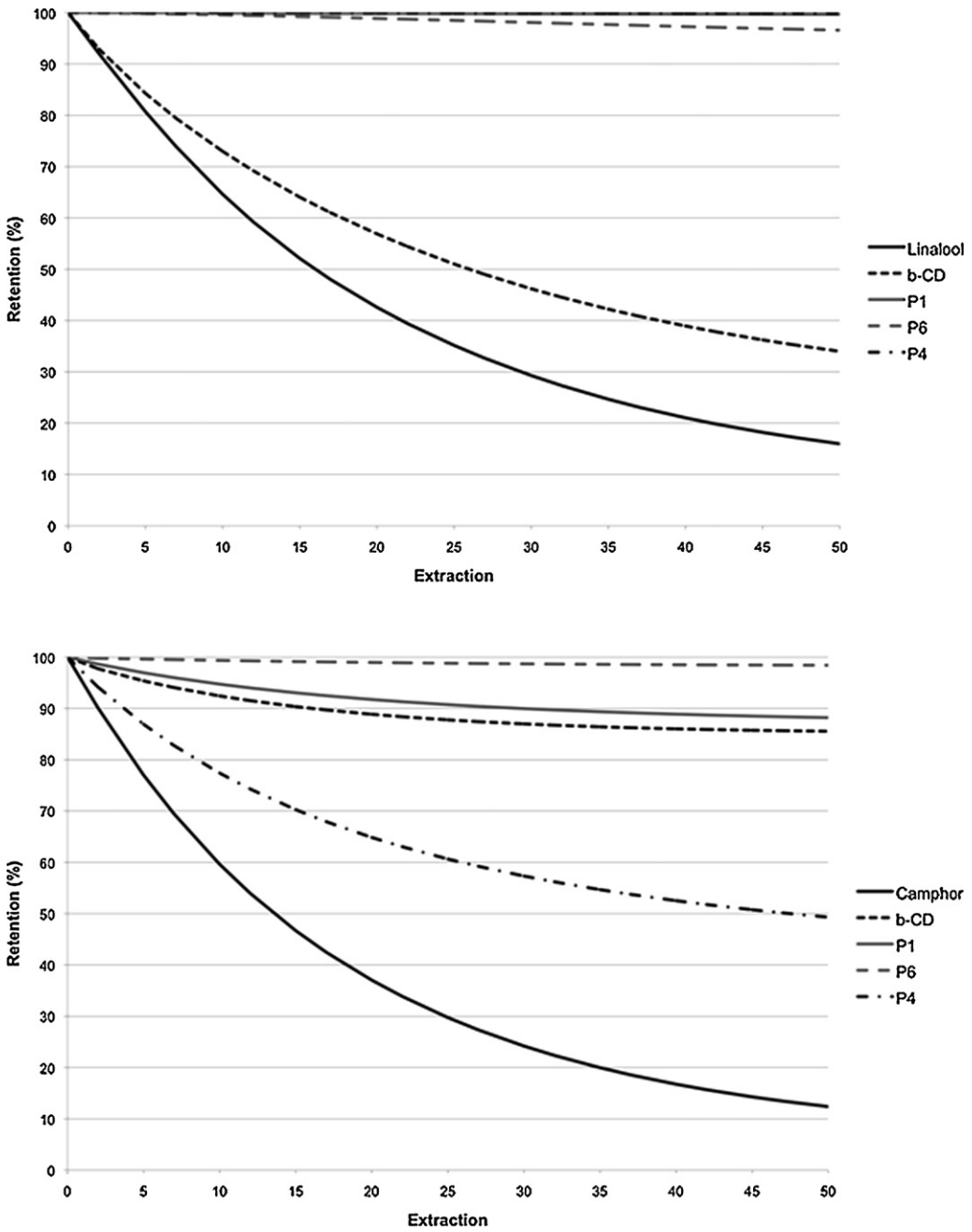

Fig. 5. Multiple headspace extraction for linalool and camphor.

hydrophobic compounds, for example, by forming inclusion complexes as in the case of CDs.

The presence of CDs or CD polymers modified the vapor–liquid equilibria for all the studied compounds, which were all more retained in aqueous solution in presence of CD derivatives. The results obtained for the different adsorbent in aqueous media and in gaseous phase are presented in Fig. 4.

No negative retention was observed as reported by Jouquand, Ducruet, and Giampaoli (2004) in the case of aliphatic ketones and β-CD, or by Reineccius, Reineccius, and Peppard (2005) for α-CD and methyl anthranilate. In aqueous medium soluble polymer trapped more efficiently the aroma compounds and camphor is always more retained than linalool. In gaseous phase, only CDs and insoluble polymers present a high retention capacity for camphor. Linalool is well retained by CDs derivatives except for native α- and β-CDs.

3.4. Multiple headspace extraction (MHE)

For the multiple release experiments we choose, β-CD, two soluble polymers (P1 and P4) and one insoluble polymer (P6). The same amount of the aroma is placed in a seal vial with solid support and without solid support (blank experiment). The amount of aroma present in the vial after each extraction is determined using the peak area. The sum of the amounts of the aroma removed in the individual extractions will be equal to the total amount of aroma present in the original sample. Thus the retention of the solid support can be evaluated and compared to the blank experiment. The retention percentages obtained for each successive extraction are presented in Fig. 5.

The results obtained in MHE extraction are correlated with the retention obtained in static experiments. If the release profiles with β-CD are already improved if compared to the blank experiments,

all studied polymers, which have high affinity for linalool and camphor, retained these compounds with a high efficiency. This means that the release of such species could be effective for a long period.

4. Conclusion

Static headspace gas chromatography has been successfully used to study the interactions between aroma compounds and CDs derivatives. Moreover, this method allows the simultaneous determination of several formation constants of compounds present in a mixture. β-CDs are the most versatile CDs for the two guests, leading to greater formation constant and retention ability in aqueous phase. MHE was used for the first time to investigate the release of fragrance compounds from CDs derivatives. The use of β-CD polymers allows the controlled release of aroma compounds.

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