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APPLICATION OF COMBINED THERMOANALYTICAL TECHNIQUES IN THE INVESTIGATION OF CYCLODEXTRIN INCLUSION COMPLEXES

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Citronellol and citronellyl acetate have been entrapped with α-, β- and γ-cyclodextrin (CD). Evolved gas detection and TG-MS coupling was applied to prove the actual inclusion complex formation between monoterpens and CDs. The terpene content was determined by UV-VIS specrophotometry and RP-HPLC and the effect of storage time on the terpene content was also investigated. The α- and γ-cyclodextrin inclusion complexes showed higher thermal stabilities *vs.* dynamic heating compared to the β-CD complexes. On the contray, the retention of guest using β-cyclodextrin even after 10 years of storage was much more pronounced. Experimental data other than 1:1 complex compositions are assumed. Molecular modeling experiments also suggested multiple complex compositions.

Keywords: *citronellol, citronellyl acetate, cyclodextrins, evolved gas detection, molecular modeling, TG-MS*

Introduction

Starting from the early sixties cyclodextrins (CDs) have risen a brilliant carrier. They are cyclic molecules with cylindrical shape and built up from α-D-glucopyranose units linking together with α-1,4 glycosidic bonds. The three most frequently used native CDs are called to α-, β- and γ-CD, consisting 6, 7 and 8 glucopyranose units, respectively. Due to the hydroxyl groups, the external surface of CDs is hydrophilic providing their water solubility. The internal part of the macrocyle has less polar character allowing the entrapment of molecules with appropriate shape and size. This special host-guest interaction (where the CD is the host and the entrapped molecule is the guest) leads to the formation of a so-called cyclodextrin inclusion complex.

CDs were used mainly for pharmaceutical purposes at first, aiming to increase the water solubility, bioavailability, to reduce side effects (e.g. stomach irritation) and to avoid unfavourable organoleptic properties (e.g. unpleasant tastes, odours), to increase thermal and chemical stability of the entrapped pharmaceutically active compounds, etc. Even today many research papers are dealing with the complexation of pharmaceuticals [1]. Then CDs are used for many other purposes, e.g. to stabilize pesticides [2], UV filters [3], to improve flavor retention in thermally processed foods [4]. CDs and their chemically modified derivatives are frequently applied alone for chiral resolution [5] and as stationer [6–8] or mobile phases [9] for separation of enantiomers.

CD inclusion complexes are mostly prepared in solution or using suspension technique. In this latter case just a small amount of solvent is added to the mixture of CD and guest in order to make it miscible. Sometimes mechanical processes as grinding and kneading are applied. The prepared CD inclusion complexes are used and stored mainly in solid state, so for their analytical investigation X-ray diffraction, spectroscopic, thermoanalytical techniques and hot-stage microscopy [1–3] are applied.

The systematic comparison of the matching curves of the pure CD and guest, their mechanical mixture and the putative complex supports or denies the complex formation.

Thermal analysis is a simple, fast and reliable technique having a distinguished role in the investigation of these compounds, since inclusion complex formation changes remarkably the original thermal properties of the complexed guest(s). The absence of the melting-, evaporation- and sublimation TG steps or DSC peaks or a shifted decomposition towards higher temperatures are the most representative fea-

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tures of the CD complexes [10]. However, sometimes, when the guest and/or the product are amorphous or in case of entrapment of volatile molecules, the application of the conventional thermoanalytical techniques does not lead to satisfactory results.

Experimental

Sample preparation

Raceme citronellol and citronellyl acetate have been complexed using α-, β- and γ-CDs The complexes were prepared using suspension technique in aqueous medium keeping 1:1 initial guest:host molar ratio. Besides the preparation and characterization of the formed inclusion complexes, the aim of the work was to investigate the effect of storage on the terpene content at room temperature.

Methods

Thermal analysis – mass spectrometry

DuPont 916 Thermal Evolution Analyser was used and TA Instruments 2960 STD TG-DTA unit was coupled to Balzers Thermostar GSD 300 mass spectrometer for the TG-MS measurements. (Experimental conditions: β=10 K min^{-1}, helium purging with a flow rate of 10 L h^{-1}, 1–1.5 mg sample masses for EGD and 6–7 mg initial sample masses for the TG-MS measurements.)

Guest content determination

The guest content was determined using UV-VIS and HPLC techniques.

For UV-VIS experiments GBC 916 UV-VIS spectrophotometer was used (λ=220 nm, the blank was 1:1 vol/vol% water:ethanol solution). The samples were dissolved in 1:1 vol/vol% water ethanol medium.

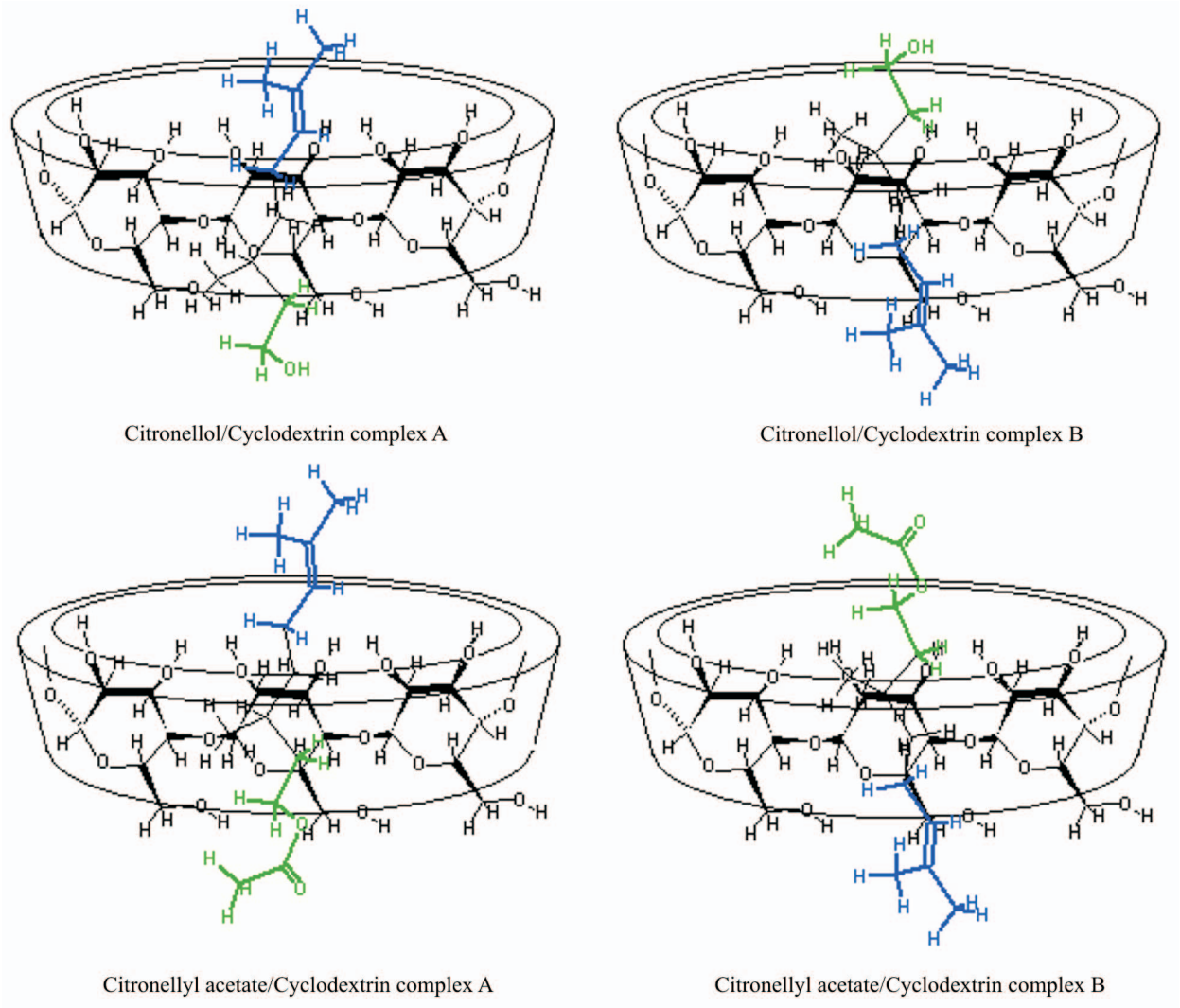

Fig. 1 Schematic view of citronellol/cyclodextrin and citronellyl acetate/cyclodextrin complexes (water is removed)

The HPLC experimental arrangement contained Chrompack ISOS isocratic pump was equipped with a solvent selection valve Rheodyne 7125 manual injector (with 25 μL loop) and with a Chrompack 204 UV/Visible detector (wavelength 220 nm). Chromspher C_{18}, 100×3.0 mm (Chrompack) was used for the separation. The evaluation of the experimental data was done using MOSAIC chromatographic data processing software (Chrompack).

Experimental conditions for HPLC

HPLC grade methanol for liquid chromatography (Merck, Darmstadt, Germany) and deionised water generated by Milli-Q_{Plus} Ultra Pure Water System from Millipore (Billerica, MA, USA) solution were used.

For citronellol 60:40 v/v% methanol:water solution as eluent at a 0.6 mL min^{-1} flow rate was applied, while for citronellyl acetate 75:25 v/v% methanol:water ratio was kept.

Molecular modeling

Molecules were built with HyperChem® 5.11 [11] based on crystal structure data. Molecular Mechanics optimization and simulation of the complexation processes (–0.5 nm to +0.5 nm of the centre of mass of guest from the geometric centre of the cyclodextrins) were performed with Tinker® 4.2 [12], using Allinger's MM3 force field [13–20] implemented in Tinker® 4.2. During the simulation full optimizations were done and total energies obtained from the MM calculations were graphed by states not the distances of centre of masses. Heats of formation were calculated with HyperChem® 5.11 on the MM3 optimized structures.

Calculations performed in a water box (17.5·2.0·17.5 nm^3) used external water molecules (200) to mimic solvated states. Arrangements of hosts in complexes due to their asymmetric character, is demonstrated in Fig. 1. Although that is not fully correct, for simulation purposes 'inclusion complex' means the states when the geometric centre of host and guest is overlapped. Due to the small asymmetry of the guest and host molecules it is an acceptable compromise for comparison of calculated energies.

Dynamic properties of the host guest interaction were simulated by moving in equidistant steps the geometric centre of guests inward and outward of the cyclodextrin cavities. Full MM geometry optimizations were performed in each step of molecular ensembles; the gradients of E_{Tot} were set to <0.004 kJ nm^{-1} mol^{-1}. Assembly the system for the 'reaction path' calculation is demonstrated in Fig. 2. Heats of formation were calculated at the deepest minima of MM-paths by AM1 method which seems to be the more reliable method in a hydrogen bonded system than PM3 [21].

Due to the computational limitations energy calculations on different host-guest ratios could not been performed.

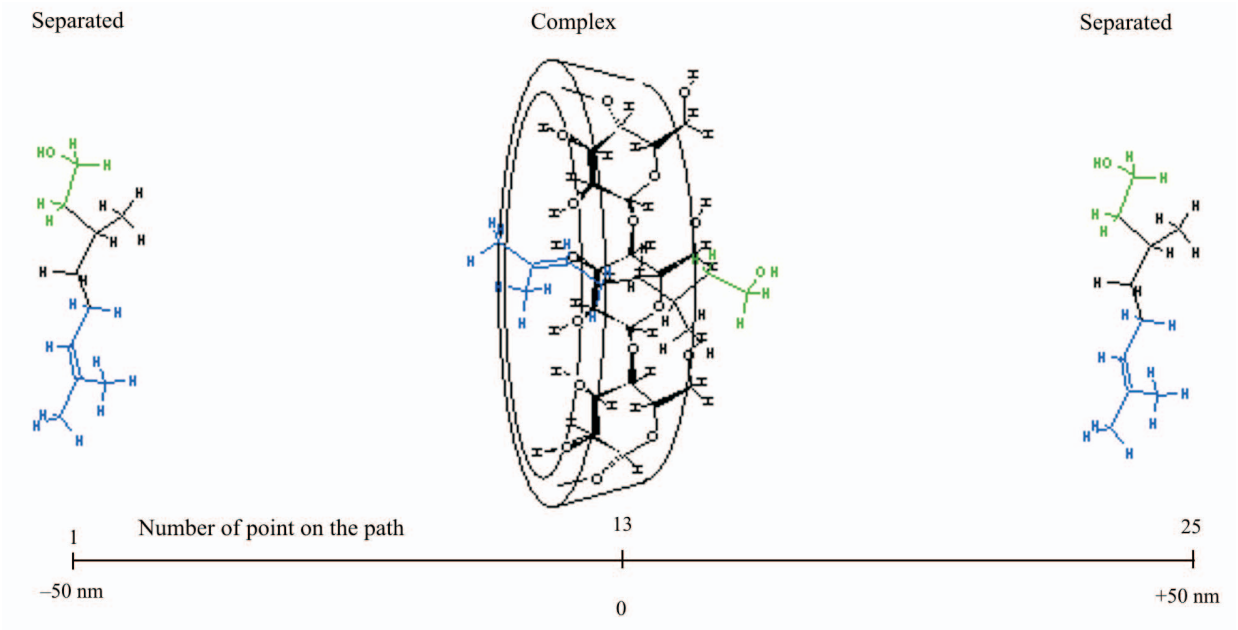

Fig. 2 Schematic view of simulation the complexation/dissociation path of citronellol/cyclodextrin complex (water is removed)

Results and discussion

Evolved gas detection experiments

Citronellol – cyclodextrin complexes

Since the pure guests are volatile and evaporate together with the water content of the cyclodextrin, the TG and DTA methods did not provide unambiguous evidence on the inclusion complex formation. By the aid of its hydrogen-air flame ionization detector, the DuPont 916 unit indicates the release of organic compounds but no signal is given for the inorganic ones.

The EGD curves of citronellol alone and citronellol-cyclodextrin complexes right after their preparation (continuous lines) and after ten years of storage (dashed lines) are summarized in Fig. 3. The intact citronellol evaporates between rt. and 100°C. It means that the peak at 74°C in the EGD curve of the citronellol – α-CD is related to the release of an amount of uncomplexed (surface adsorbed) guest. Over 100°C the EGD curve deviates from the baseline indicating the release of citronellol from the decomposed complex.

By the evaluation of the EGD curve of the citronellol – β-CD complex one can assume that the release of organic compounds starts over 50°C with the decomposition of a relatively weak thermostable fraction of the complex. The three peaks between 50–250°C can be attributed to the formation of complex fractions with different compositions consequently with different thermal stabilities. It can be also observed that the citronellol-γ-CD sample does not contain any adsorbed guest on the surface of the parent CD. Disregard of the release of the adsorbed citronellol from its α-CD complex, by the comparison of the initial temperatures of their decomposition, the relative heat stability of the investigated inclusion complexes varied in the β-CD<α-CD≈γ-CD order. Dashed lines are from the same complex systems after 10 years of storage. No adsorbed guest can be observed in case of citronellol – α-CD and it is also well visible that the thermal decomposition of the complex shifted towards higher temperatures in all cases.

Citronellyl acetate – cyclodextrin complexes

The EGD curves of citronellyl acetate and its cyclodextrin inclusion complexes right after their preparation (continuous curves) and after 10 years of storage (dashed curves) are summarized in Fig. 4. It can be seen that both α-CD and β-CD formulas contain uncomplexed amount of guest which evaporates up to 100°C. Then, with increasing temperature further on, the thermal decomposition of the inclusion complex takes place. Concluding from the shape of the EGD curve it seems that the composition of the citronellyl acetate – α-CD product is rather homogeneous. On the contrary, the peaks at 161, 210 and 237°C, respectively for the γ-CD complex may suggest the existence of fractions with different thermal

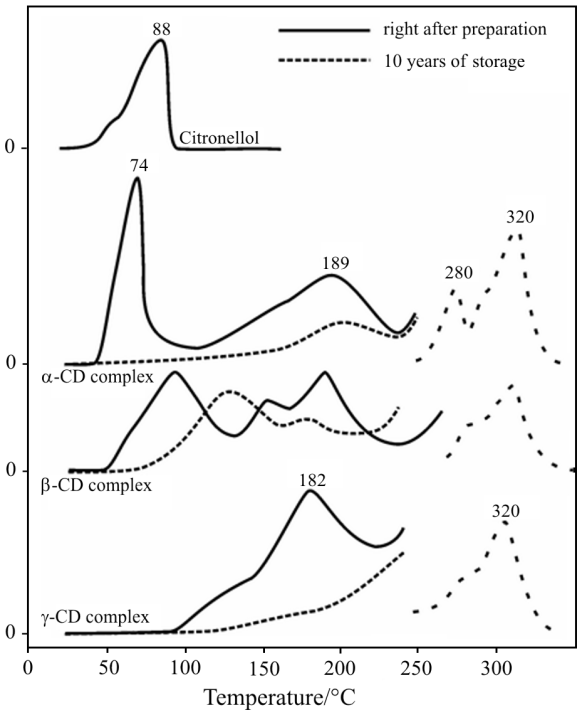

Fig. 3 EGD curves of citronellol and citronellol – CD complexes

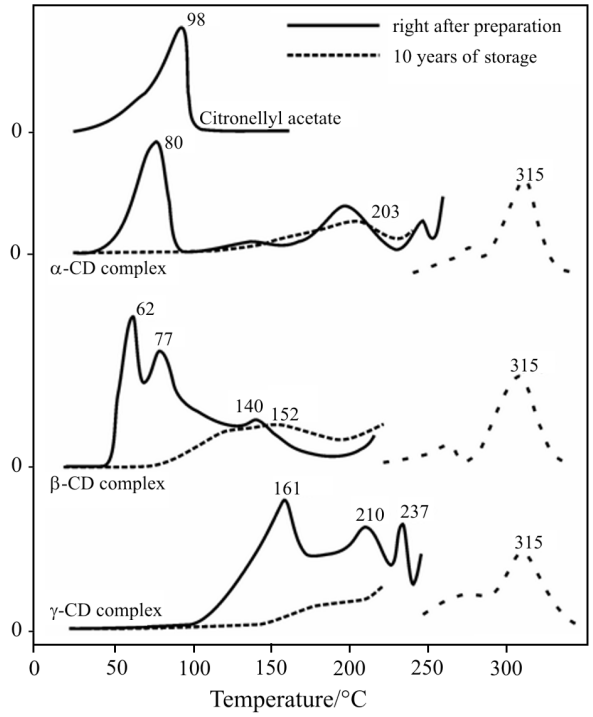

Fig. 4 EGD curves of citronellyl acetate and citronellyl acetate – CD complexes

stabilities. Taking into account the starting temperatures of the decompositions, among the three citronellyl acetate – cyclodextrin inclusion complexes the β-CD complex exhibited the lowest thermal stability against dynamic heating.

After 10 years of storage none of the inclusion complexes contains surface adsorbed guest. By the comparison of the curves recorded at zero time and after one decade of storage the change in the curvature is well visible. In one hand, it can be attributed to the loss of guest (consequently to the change of the composition of the samples) upon storage. On the other hand, it can be explained in the change of the thermal properties of the stored inclusion complexes, too.

The terpene content of all samples right after their preparation and time-to-time during storage was determined. These experimentally determined values were related to the theoretical guest content (taking into account 1:1 guest:host molar ratios). Describing these data *vs.* time of storage indicates well the variation of terpene content of the complexes (Fig. 5). It can be seen that the retention of citronellol is higher than of the citronellyl acetate in any samples. Among the three used cyclodextrins, the entrapped amounts for both citronellol and citronellyl acetate have decreased by 20–40% in the α- and β-CD inclusion complexes. Furthermore, the retardation efficiency of β-CD is the largest in comparison with the two other cyclodextrins. For the γ-CD formulas the continuous decrease and almost the total release of citronellol and citronellyl acetate after 10 years of storage can be observed.

Combined thermogravimetry – mass spectrometry

Despite the usefulness of TG, DSC/DTA techniques, they do not provide information on the chemical composition of the evolved products. Consequently fragments originating either from the decomposition of the parent CD or from the guest cannot be distinguished. The thermal properties of cyclodextrins have been investigated and reported in [10 and references therein]. However, an alternate method for TG-MS coupling has been developed [22, 23] in order to follow selectively the escape of guest from its inclusion complex.

Theoretically, mass spectrometry is a selective analytical tool for the investigated compounds. However, the TG-MS coupling is somewhat different. The main difference between the 'classical' mass spectrometric investigation and the TG-MS arrangement is that in this latter case quite frequently the products of thermal decomposition/fragmentation are introduced to the mass spectrometer. This way of sampling makes somewhat uniform the composition of the products which reach the detector unless the guest is volatile, easy-to-sublime or exhibiting high thermal stability.

Some representative multiple ion detection curves (MID) together with the molecular structure of

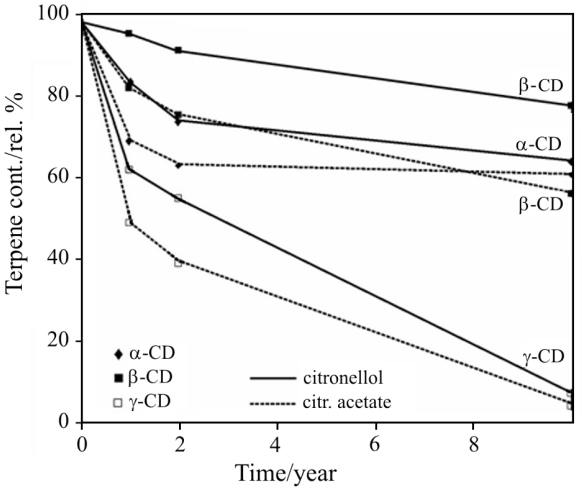

Fig. 5 Release of citronellol and citronellyl acetate from their inclusion complexes *vs.* time of storage

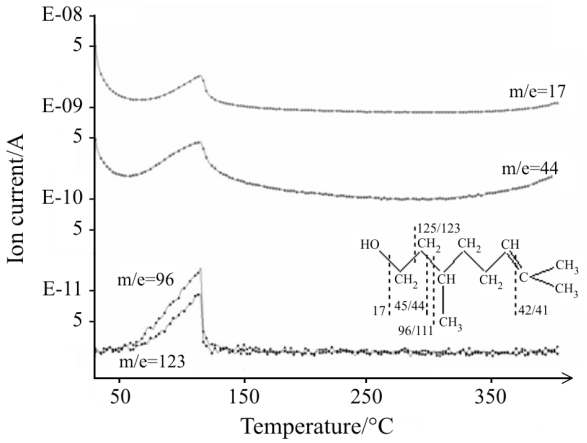

Fig. 6 MID curves of citronellol

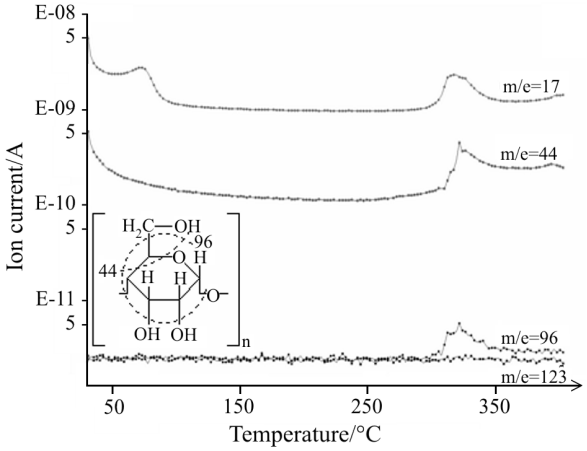

Fig. 7 MID curves of β-CD

citronellol are given in Fig. 6. The MID curves of β-CD with the same specific mass/charge units and the molecular scheme of one glucopyranose unit are summarized in Fig. 7. By the comparison of Figs 6 and 7 one can see that curves at *m*/*e*=17, 44 and 96 indicate the evolution of water and organic fragments. However, at *m*/*e*=123 only the citronellol gives signal, while for β-CD the curve at *m*/*e*=123 is running horizontally, no deviation was observed. It means that in the citronellol – cyclodextrin multicomponent system the signal at *m*/*e*=123 indicate the fragmentation of citronellol only and consequently is selective for the guest.

Some fragmentation curves for the citronellol – β-CD mechanical mixture are indicated in Fig. 8. The curves look like the superposition of the MID curves of the pure terpene and β-CD. It is well visible that signals at *m*/*e*= 44, 96 and 123 indicate the evaporation of citronellol in the 30–130°C temperature range. On the contrary, there is no deviation for *m*/*e*= 123 between 270–370°C.

Disregard of the water release (*m*/*e*=17) the left side of Fig. 8 represents the evaporation of citronellol, while the right part is belonging to the thermal fragmentation of β-CD (dashed line is guide to eye). It can be seen, that together with some common *m*/*e* units, the signal at *m*/*e*=123 is representative only for citronellol.

Figure 9 contains the MID curves of the 10 years stored complex. The signal at *m*/*e*=123 indicates the liberation of citronellol from its CD inclusion complex proving evidence on the long-term retention ability of β-CD. The decomposition of the complex fractions with different thermal stabilities can be seen between 70–250°C and over 250°C the thermal degradation of the parent β-CD takes place.

Molecular modeling

It is necessary to note that all computed energies, particularly those which were obtained from MM calculations, have few relationships to the physically measurable energies. Additionally, a deep minimum for a complex does not mean automatically its experimental realization. Multiple minima of the MM-path curves suggest that in solution the most favourable arrangements of the molecules are rather 'second sphere' complexes than real inclusion complexes. The occurrence of other than 1:1 host-guest species should be more typical.

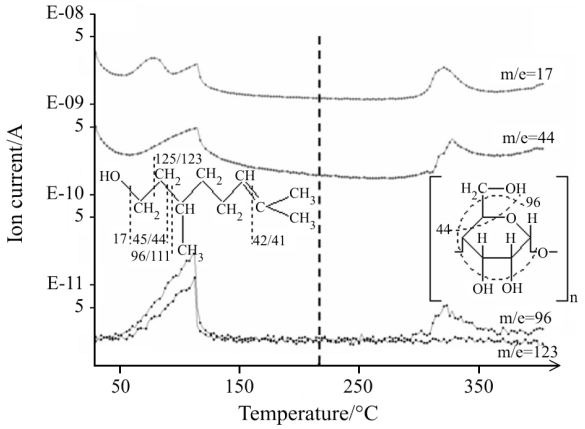

Fig. 8 MID curves of citronellol – β-CD mech. mixt.

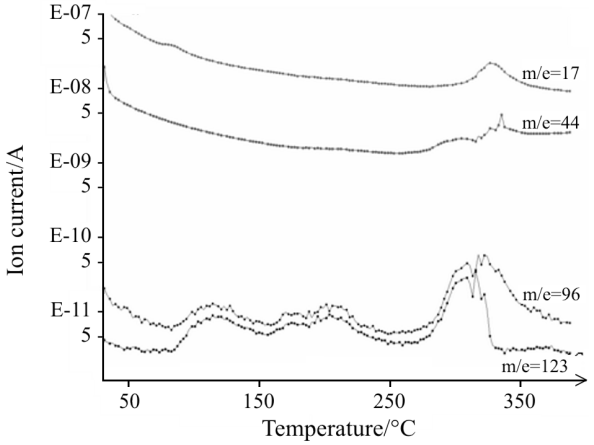

Fig. 9 MID curves of citronellol – β-CD complex

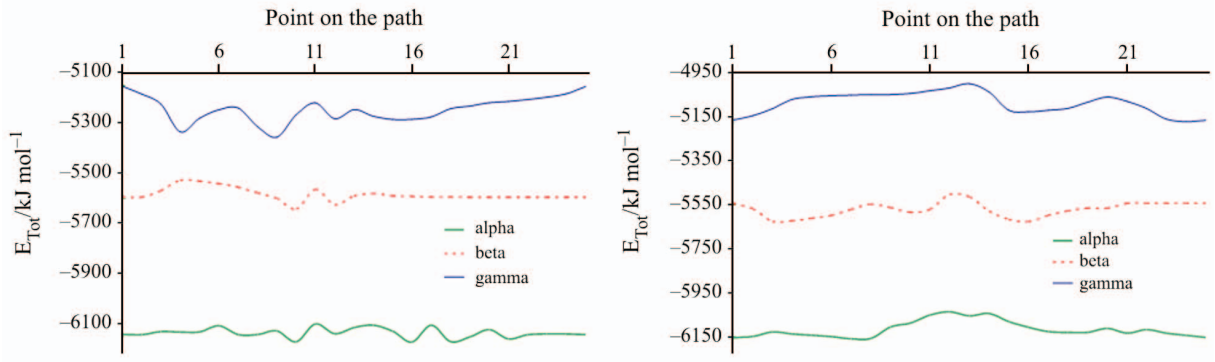

Fig. 10 Molecular Mechanics total energies of citronellol/cyclodextrin and citronellyl acetate/cyclodextrin systems

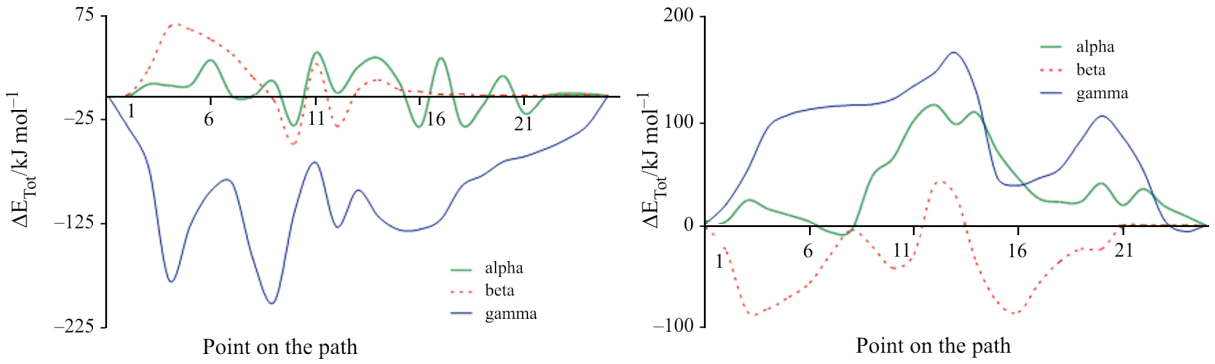

Fig. 11 Molecular Mechanics total energy differences of citronellol/cyclodextrin and citronellyl acetate/cyclodextrin systems

Due to the nature of molecular mechanics calculations the increasing number of atoms increases the total energy by larger number of energy contributions, therefore the energy curve itself serves only for qualitative comparisons (Fig. 10).

Citronellol – cyclodextrin complexes

MM energy curves of citronellol/α-, β- and γ-cyclodextrins show multiple minima around the inclusion complex state (note: in terms of calculation the 'inclusion complex' means the overlapping of geometric centres of host and guest molecules) in both systems there are an energy barriers between the minima around the exact matches of the geometrical centres of host and guests. Small shifts of the citronellol in both directions suggest the strong interactions of the hydroxyls of cyclodextrins and polarizable parts of citronellol (hydroxyl and double bond, Fig. 11). Analysis of the structures along the energy curves it can be concluded that only partially penetration of guest onto the cyclodextrin cavity is energetically favoured. Comparison of the arrangements of molecules at the local minima more than 1:1 molar ratio can be assumed in aqueous solution.

Due to computational limitations (using 1:1 complexes) only qualitative conclusions can be made. Apart from the multiple compositions, from MM calculations more stable β- and γ-cyclodextrin complexes can be concluded. In case of γ-cyclodextrin all MM energies are significantly lower than the sum of E_{Tot} of separated molecules, but it is true that a real inclusion

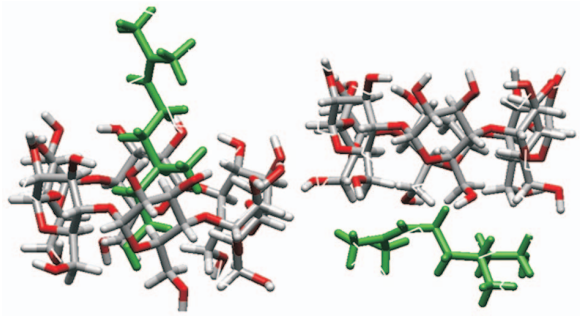

Fig. 12 Position of the citronellol/α-cyclodextrin molecules in two local minima: at the secondary side and at the primary side (cf.: Table 1)

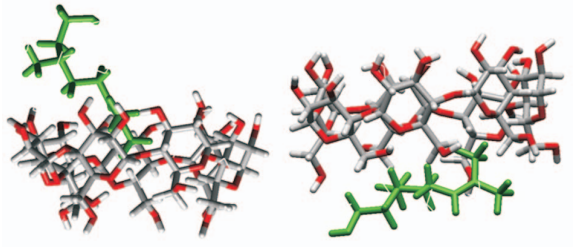

Fig. 13 Position of citronellol/β-cyclodextrin molecules in two local minima: at the secondary side and at the primary side (cf.: Table 1)

Table 1 MM total energy and AM1 heat of formation differences of citronellol/cyclodextrin relaxed systems, significant values are in bold (base: host and guest are enough far from any interactions)

Citronellol	ΔE_{Tot}/kJ mol^{-1}	ΔH_F/kJ mol^{-1}	ΔE_{Tot}/kJ mol^{-1}	ΔH_F/kJ mol^{-1}	ΔE_{Tot}/kJ mol^{-1}	ΔH_F/kJ mol^{-1}
	α-cyclodextrin		β-cyclodextrin		γ-cyclodextrin	
Inclusion complex A	3.8	–106.3	28.8	–49.6	–32.1	11.3
Inclusion complex B	–1.7	–22.1	38.8	20.0	–18.3	–3.3
Minimum at secondary OH side	–28.8	–119.7	–46.3	–144.3	–203.1	–141.8
Minimum at primary OH side	–30.0	–119.3	–3.8	–110.1	–130.1	–125.9

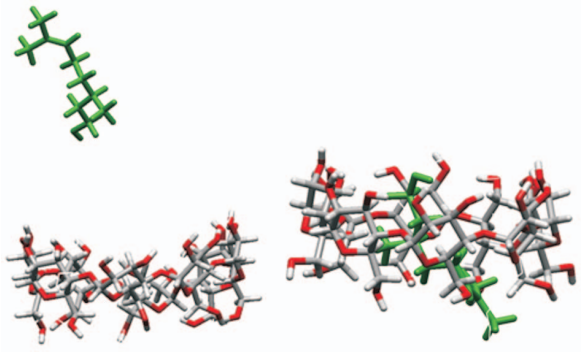

Fig. 14 Position of citronellol/γ-cyclodextrin molecules in two local minima: at the secondary side and at the primary side (cf.: Table 1)

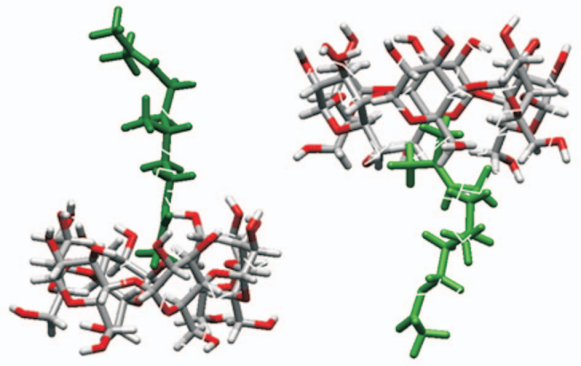

Fig. 15 Position of citronellyl acetate/α-cyclodextrin molecules in two local minima: at the secondary side and at the primary side (cf.: Table 2)

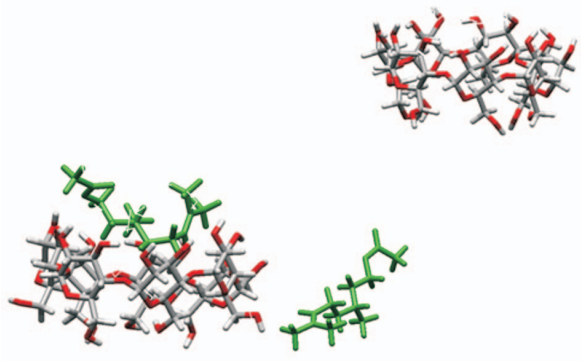

Fig. 16 Position of citronellyl acetate/β-cyclodextrin molecules in two local minima: at the secondary side and at the primary side (cf.: Table 2)

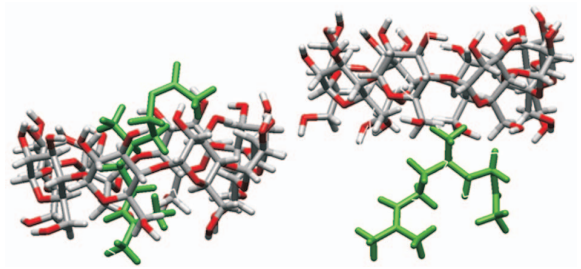

Fig. 17 Position of citronellyl acetate/γ-cyclodextrin molecules in two local minima: at the secondary side and at the primary side (cf.: Table 2)

complex of citronellol/γ-cyclodextrin is far from any local minima. In case of γ-cyclodextrin deep minima are far from any inclusion (Figs 12–14). It can be also seen from the MM energies that although the theoretical inclusion complexes do not represent minima, the energies of complexes follows the γ>β>α order. The large energy gain of complexed and dissociated states minima in case of γ-cyclodextrin suggests that the citronellol/γ-cyclodextrin complex is relatively weak, easy to dissociate. At the same time more stable complexes can be assumed for β-cyclodextrin – where energy is necessary to dissociate –, and α-cyclodextrin, where numerous complex states have energy gains. By this way α- and β-cyclodextrins form complexes with practically similar stability.

From the heat of formations the β≈α>γ order can be concluded for the stability of complexes. For α-cyclodextrin practically all complexed forms are in significantly lower energy state in comparison with the separated state, while β-cyclodextrin ensembles are in deeper minima.

Citronellyl acetate – cyclodextrin complexes

Calculation results show more complex picture. This can be partly assigned to the enhanced lipophilicity of citronellyl acetate to citronellol. That means more

Table 2 MM total energy and AM1 heat of formation differences of citronellyl acetate/cyclodextrin relaxed systems, significant values are in bold (base: host and guest are enough far from any interactions)

Citronellol	ΔE_{Tot} /kJ mol^{-1}	ΔH_F /kJ mol^{-1}	ΔE_{Tot} /kJ mol^{-1}	ΔH_F /kJ mol^{-1}	ΔE_{Tot} /kJ mol^{-1}	ΔH_F /kJ mol^{-1}
	α-cyclodextrin		β-cyclodextrin		γ-cyclodextrin	
Inclusion complex A	130.1	113.0	77.6	56.3	192.2	122.2
Inclusion complex B	102.6	103.8	48.8	115.9	–39.2	–50.9
Guest at secondary OH side	81.3	–9.6	200.2	–131.8	26.7	–79.2*
Guest at primary OH side	224.3	–174.7	2.9	–217.7	196.8	–55.0

*primary side also

unfavoured interactions of the very lipophylic citronellyl acetate and cyclodextrins. The smallest α-cyclodextrin has no enough room for energy compensation of lipophyl-hydrophyl interactions. From both MM and quantumchemical calculations the γ≈β>α complex stabilities can be concluded as seen in Figs 15–17. More complex composition of citronellyl acetate/cyclodextrin can be also assumed.

Conclusions

Inclusion complex formation between the selected monoterpenes and three native cyclodextrins could be successfully revealed. The thermal stabilities of the complexes varied in β-CD<α-CD≈γ-CD order. In the aspect of long term storage the application of β-cyclodextrin is preferred. It can be explained with its optimal internal cavity size, since in this case the 'best fit' arrangement between guest and host could be achieved.

Conclusions from experimental data have not uniformly been confirmed by molecular modeling but both types of experiments make probable the presence of multicomponent complexes. The restricted calculations to 1:1 compositions suggest loose complexes for γ-CD and the β-CD as most favorable host.

Slow release of citronellol and citronellyl acetate in solid state can be explained by the weak interaction of host and guests. Molecular modeling experiments reflect better to the dynamic behavior of complexes, therefore only restricted information can be obtained for the solid state.

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