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Structural investigation of the β-cyclodextrin complexes with linalool and isopinocampheol – Influence of monoterpenes cyclicity on the host–guest stoichiometry

Magdalena Ceborska

Institute of Physical Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

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ABSTRACT

The crystal structures of the complexes of β-cyclodextrin with two chiral terpene alcohols are presented. (−)-Linalool forms the complex of a 2:2 host–guest stoichiometry, while the complex with (−)-isopinocampheol exhibits a 2:3 stoichiometry. The comparison of the crystal structures with the data for other complexes of β-cyclodextrin with chiral monoterpene alcohols obtained from Cambridge Structural Database (CSD) highlights the tendency of linear and monocyclic alcohols to form complexes of 2:2 stoichiometry whereas bicyclic alcohols prefer to form 2:3 host–guest inclusion complexes.

1. Introduction

Terpenes are organic constituents of essential oils [1] which are commonly found in flowers, leaves, and fruits. The core structure of terpenes is based on isoprene unit, to which additional functional groups, such as hydrocarbons, alcohols, ketones, can be attached. Linear monoterpenes may also be considered as derivatives of 2,6-dimethyloctane. They include, among others, chiral linalool and citronellol, as well as achiral nerol and geraniol. Monocyclic terpene alcohols include menthol, terpineol, and isopulegol, while the class of bicyclic monoterpene alcohols consists of borneol, isoborneol, isopinocampheol, myrtenol and verbenol. Native cyclodextrins, i.e. alpha cyclodextrin (α-CD), beta-cyclodextrin (β-CD), and gamma-cyclodextrin (γ-CD) belong to the class of cyclic oligosaccharides composed of six, seven or eight α-(1,4)-linked glucopyranose units. They are produced after enzymatic degradation of starch. Cyclodextrins possess hydrophobic cavity which is able to accommodate various compounds and hydrophilic outer space which render them readily soluble in water. They can, by the process of complexion of the guest compound, change its properties, e.g. solubility, stability or bioavailability. Unique properties of CDs make them invaluable for pharmaceutical [2,3] and food [4] industries. Chiral terpene alcohols are known for forming host:guest inclusion complexes with β-CD both in solution [5–7] and in the solid state [8–14]. Inclusion complexes of linalool in various CDs were studied by Fourmentin et al. [15]. The highest association constants were obtained for β-CD and its derivatives. β-CD/(−)-linalool complex was also studied in detail by Araujo et al. [16]. In the present Letter solid-state complexes of β-CD with linear (−)-linalool and bicyclic (−)-isopinocampheol (Figure 1) are presented and characterized in detail and subsequently these structures are compared with other known β-CD complexes with chiral monoterpene alcohols.

2. Experimental

2.1. Materials

β-CD was purchased from Cyclolab, (−)-linalool and (−)-isopinocampheol were obtained from Sigma–Aldrich. All the reagents were used as received. Distilled water was used to prepare aqueous solutions of CDs and terpenes.

2.2. Sample preparation

To the 0.01 M water solution of β-CD (10 mL) the solution of (−)-linalool or (−)-isopinocampheol (15.4 mg, 0.01 mM) in methanol (0.5 mL) was added and the obtained solution was left at RT without stirring. Monocrystals appropriate for X-ray measurement were obtained after one week [(−)-isopinocampheol] or one month [(−)-linalool].

2.3. X-ray data collection, structure solution and refinement

The X-ray data were collected at 100(1)K on an Agilent SuperNova Dual diffractometer equipped with Eos CCD detector using

E-mail address: mceborska@ichf.edu.pl

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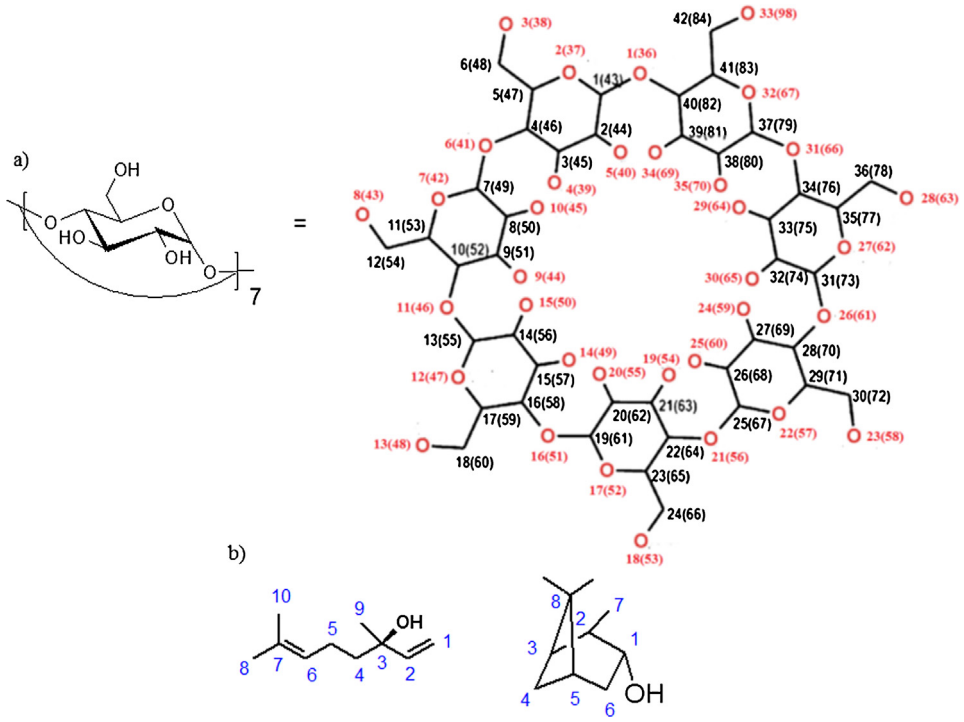


Figure 1. Molecular structures of (a) β-CD (numbers in parentheses refer to the second symmetry independent molecule), (b) (−)-linalool c) (−)-isopinocampheol; letters after the atom number were used to distinguish the two symmetry independent molecules ('A' and 'B' for the (−)-linalool molecule and letters 'C' and 'D' for (−)-isopinocampheol molecule), hydrogen atoms were omitted for clarity.

CuKα radiation (λ = 1.54184 Å). The data were processed with CrysAlisPro [17]. Structures were solved with SUPERFLIP [18] and refined using SHELXL-2013 [19]. All hydrogen atoms were placed in geometric positions and treated as riding on their parent atoms with d_{C-H} = 0.95–1.00 Å (depending on the hybridization of carbon atom) and d_{O-H} = 0.84 Å. Hydrogen atoms of water molecules were not included in the structural model.

2.3.1. Crystal data for β-CD/(−)-linalool

$C_{42}H_{70}O_{35}\cdot C_{10}H_{18}O\cdot 8H_2O$, M = 1433.3, colorless plate, 0.20 × 0.15 × 0.03 mm^3, triclinic, space group $P1$, V = 3310.2(5) Å^3, Z = 2, D_c = 1.422 g/cm^3, F_{000} = 1504, T = 100(2) K. Final $GooF$ = 1.636, R = 0.013, wR = 0.034, R indices based on 13 596 reflections with $I > 2\sigma(I)$ (refinement on F^2), Lp and absorption corrections applied, μ = 1.094 mm^{-1}. Absolute structure parameter x = 0.0(2) [20]. CCDC 1439675.

2.3.2. Crystal data for β-CD/(−)-isopinocampheol

$C_{42}H_{70}O_{35}\cdot 1.5\,C_{10}H_{18}O\cdot 12H_2O$, M = 1582.5, colorless plate, 0.18 × 0.12 × 0.05 mm^3, orthorhombic space group $C222_1$, V = 150 492(9) Å^3, Z = 8, D_c = 1.369 g/cm^3, F_{000} = 6584, T = 100(2) K, Final $GooF$ = 1.133, R = 0.088, wR = 0.169, R indices based on 5131 reflections with $I > 2\sigma(I)$ (refinement on F^2), Lp and absorption corrections applied, μ = 0.121 mm^{-1}. Absolute structure parameter x = 0.0(2). CCDC 1439846.

3. Results and discussion

3.1. Description of structures

3.1.1. β-CD/(−)-linalool

The β-CD/(−)-linalool complex crystallizes in triclinic space group $P1$. There are two guest molecules (A and B) included in head-to-head β-CD dimer, resulting in a 2:2 stoichiometry of the formed complex (Figure 2). Every barrel-like-shaped dimer is stabilized by a net of hydrogen bonds between secondary hydroxyl groups. In each cyclodextrin forming head-to-head dimer five out of seven primary hydroxyl groups are directed outwards and two point inwards (O8, O23 and O50, O70 respectively). Guest molecules are oriented in head-to-tail mode, with hydroxyl groups pointing toward narrow rim and aliphatic chain stretched toward interspatial region of the dimer. In depth crystal analysis reveals absence of any hydrogen bonds or C–H···O interactions between guest molecules within the complex, although both of (−)-linalool molecules (denoted as A and B) are connected with the host molecules via C–H···O interactions (C23–H23···O1A and C47–H47···O1B) and via hydrogen bonds with symmetrically related β-CDs (O1A–H1A···O50 and O8–H8X···O1B) (Figure 2(a), Table 1).

It is known that β-CD dimers exhibit four main possible ways of molecular packing: channel (CH), chessboard (CB), intermediate (IM), screw channel (SC) and tetrad (TT) [21,22]. β-CD/(−)-linalool inclusion complex exhibits screw channel packing along a axis (Figure 3(a)).

Table 1
Analysis of host–guest and guest–water interactions in β-CD/(−)-linalool and β-CD/(−)-isopinocampheol complexes.

Donor–H···Acceptor	D–H	H···A	D···A	D–H···A
β-CD/(−)-linalool [2:2]				
O1A–H1A···O50[a]	0.84	2.064	2.857	157
C23–H23···O1A	1.00	2.487	3.399	151
O8[b]–H8X[b]···O1B	0.84	2.180	2.875	140
C47–H47···O1B	1.00	2.644	3.495	143
β-CD/(-)-isopinocampheol [2:3]				
C10–H10···O1C	1.00	2.681	3.427	132
O21–H21B···O1D	0.84	2.090	2.732	124
O1D–H1X···O1W[c]	0.84	2.590	3.260	137

Symmetry equivalent positions: (a) $x, y, 1+z$, (b) $x, y, -1+z$, (c) $\frac{1}{2}+x, -\frac{1}{2}+y, z$.

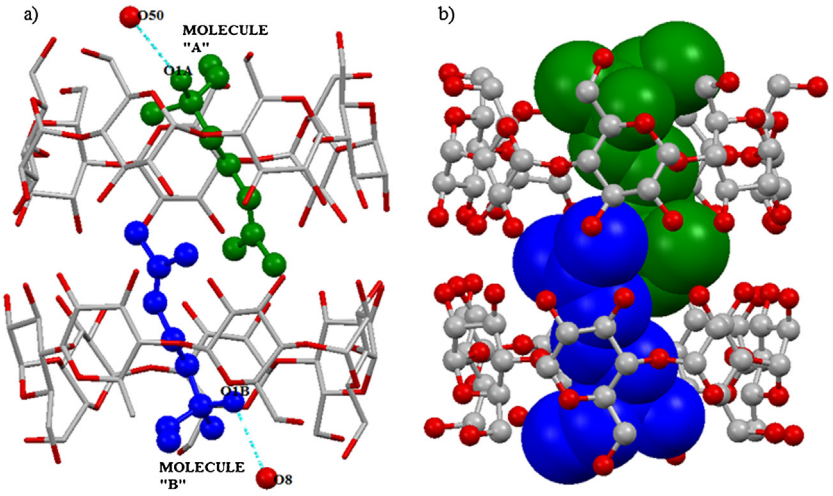


Figure 2. (a) X-ray structure of the β-CD/(−)-linalool [2:2] dimeric complex, from top-to-bottom: guest molecule 'A' and 'B', dashed lines indicate O–H···O hydrogen bonds host and guest molecules; (b) structure of the dimeric complex where guest molecules are shown in space-filling mode.

3.1.2. *β-CD/(−)-isopinocampheol*

The β-CD/(−)-isopinocampheol inclusion complex crystallizes in an orthorhombic space group $C222_1$. Two β-CD molecules form head-to head dimer which is stabilized by hydrogen bonds formed between secondary hydroxyl groups of adjacent β-CD molecules. The stoichiometry of the formed complex is 2:3 (host:guest ratio). Two of the guests molecules (denoted as 'D') are included in the cyclodextrin cavities while highly disordered third molecule (denoted as 'C') is accommodated at the dimeric interface (Figure 4). There are no interactions between isopinocampheol molecules within the β-CD capsule. Molecule 'C' is disordered in two positions and takes part in one week C–H···O interaction (C10–H10···O1C) whereas molecule 'D' forms two hydrogen bonds of type O–H···O (Figure 4(a), Table 1). The first one is formed between oxygen atom of O1W water molecule and hydroxyl group of (−)-isopinocampheol acting as hydrogen bond donor. The second one is formed between hydroxyl group of symmetrically related β-CD (O21–H21B) and O1D.

The β-cyclodextrin/(−)-isopinocampheol crystallizes in chessboard mode (the packing along *a* axis is presented in Figure 5(a), packing along *c* axis is shown in Figure 5(b))

3.2. *Comparison of solid state inclusion complexes of β-CD with optically active monoterpene alcohols*

To date, there are in total ten structures of inclusion complexes of β-CD with optically active monoterpene alcohols, namely one linear [(−)-(linalool)], six monocyclic [(+)-menthol, (−)-menthol, (+)-isopulegol, (−)-isopulegol, (+)-α-terpineol, (−)-α-terpineol], and three bicyclic [(+)-borneol, (−)-borneol, (−)-isopinocampheol] (Table 2). Solid state structures were derived from a CSD survey [23]. Linear (−)-linalool crystallizes in *P*1 space group and forms a complex of 2:2 stoichiometry where two guest molecules are included in two adjacent cavities of β-CD dimer. Guest molecules are oriented in head-to-head manner which is typical for β-CD solid-state inclusion complexes. No interactions between guest molecules are observed but each (−)-linalool molecule is held in its position by one C–H···O interaction with the host molecule and one O–H···O interaction with symmetrically related β-CD. All of six complexes with monocyclic terpene alcohols exhibit 2:2 host–guest stoichiometry, but isomeric isopulegols and terpineols are oriented in typical head-to-head mode, while both enantiomers of menthol are located inside the dimeric host in head-to-tail mode.

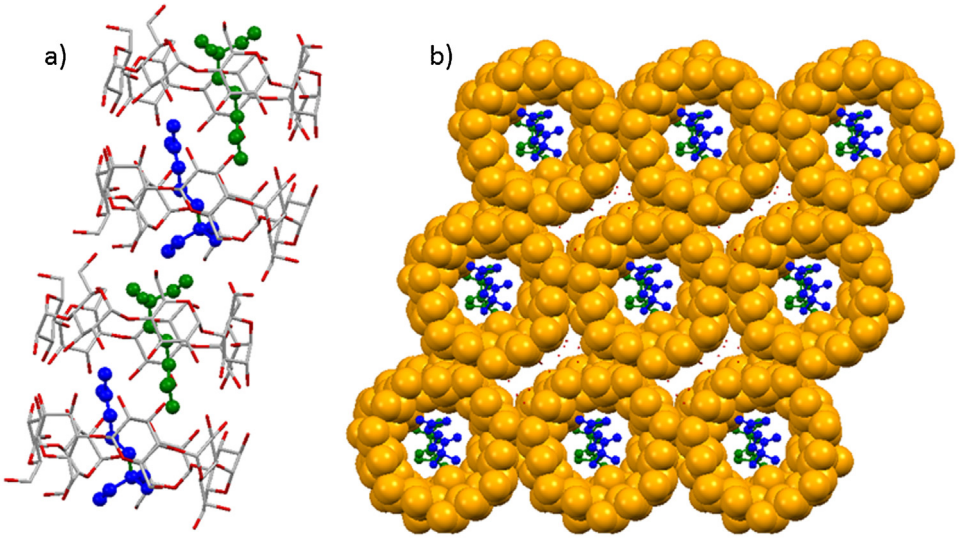


Figure 3. Molecular packing of the β-CD/(−)-linalool complex (a) view along *a* axis; (b) view along *c* axis.

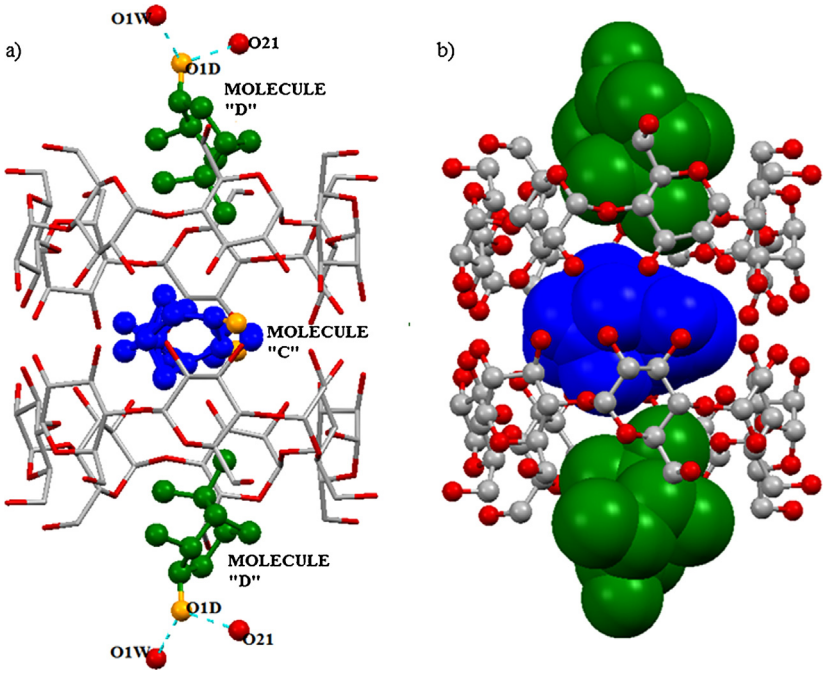


Figure 4. (a) The β-CD/(−)-isopinocampheol [2:3] dimeric complex from top-to-bottom: guest molecule 'D', 'C', and 'D'; dashed lines indicate O–H···O hydrogen bonds involving guest molecules; (b) structure of the dimeric complex where guest molecules are shown in space-filling mode to illustrate partial inclusion of the guest molecules 'D' caused by steric effects.

There are no interactions between guest molecules in any of these structures. In a 2:2 β-CD/(−)-α-terpineol complex each guest molecule interacts with the host β-CD molecule via two C–H···O interactions and via one O–H···O with the adjacent capsule. (+)-α-terpineols are disordered inside a β-CD complex and depending on their orientation form O–H···O and C–H···O bonds with the host capsule, while in the other orientation the same bonds are formed with symmetrically related β-CDs. In β-CD/(−)-isopulegol only one C–H···O interaction between host and guest may be observed and in the (+) enantiomer there are neither O–H···O nor C–H···O interactions between host and guests. Menthols may be considered as derivatives of isopulegols due to fact that they differ only by the presence or absence of a double bond in the ring. In the 2:2 complex of both menthol enantiomers, i.e. (−)-menthol and (+)-menthol, one of the guest molecules is disordered and does not form any O–H···O or C–H···O bonds and the second one is bonded with the host β-CD via one C–H···O interaction. It seems likely that structure of a α-terpineol is better fitted for the β-CD cavity than (+)- and (−)-enantiomers of menthol due to fact that former one produces more O–H···O and C–H···O interactions than (+)- and (−)-menthols. This assumption is further confirmed by studies of the complex formation in the solution, which provide the corresponding affinity constants: 413 [M^{-1}] for (−)-α-terpineol, 399 [M^{-1}] for (+)-α-terpineol, 243 [M^{-1}] for both enantiomers of isopulegols, and 163 for (+)- and (−)-menthols. There are known three solid state structures of β-CD complexes with bicyclic monoterpene alcohols: with both enantiomers of borneol and with (−)-isopinocampheol. They all crystallize in $C222_1$ space group and exhibit 2:3 host–guest

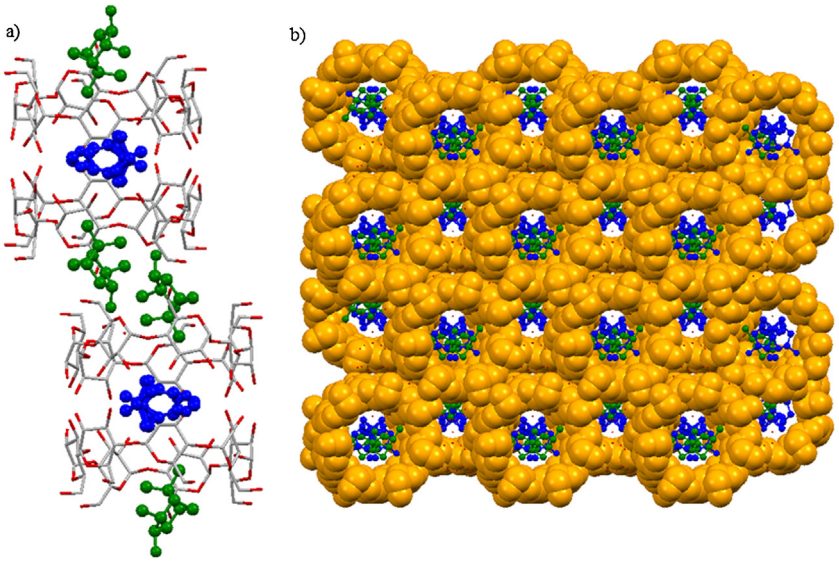
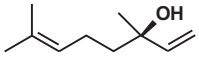
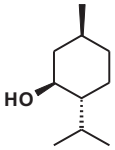
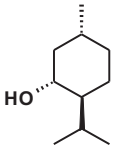
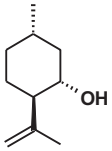
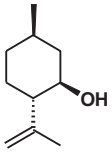
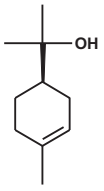
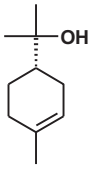
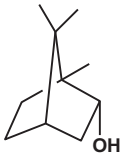
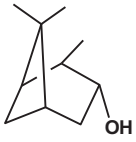


Figure 5. Molecular packing of the β-CD/(−)-isopinocampheol complex (a) view along *a* axis; (b) view along *c* axis.

Table 2
Comparison of solid state inclusion complexes of β-cyclodextrin with optically active monoterpene alcohols.

	Name of the guest terpene molecule	Molecular structure of monoterpene	Stoichiometry of the host:guest inclusion complex with β-CD	Space group
Linear alcohols	(−)-Linalool		2:2	*P*1
Monocyclic alcohols	(+)-Menthol		2:2	$P2_1$
	(−)-Menthol		2:2	$P2_1$
	(+)-Isopulegol		2:2	*P*1
	(−)-Isopulegol		2:2	*P*1
	(+)-α-Terpineol		2:2	$P2_1$
	(−)-α-Terpineol		2:2	$P2_1$
Bicyclic alcohols	(+)-Borneol		2:3	$C222_1$
	(−)-Borneol		2:3	$C222_1$
	(−)-Isopinocampheol		2:3	$C222_1$

stoichiometry with two guest molecules encapsulated in β-CD cavities and one disordered guest molecule located at the dimeric interface. For all three guest molecules, i.e. (+)-borneol, (−)-borneol, and (−)-isopinocampheol, two hydrogen bonds may be identified – one with water molecule and the other with symmetrically related β-CD. The space filling projection of the (−)-isopinocampheol complex as well as that for both borneol complexes show very efficient packing within the β-CD dimer, with two guest molecules occupying the rims of primary hydroxyls and the third lying in the interspace of the supramolecular capsule. In complexes of linear and monocyclic terpenes exhibiting 2:2 stoichiometry, guest molecules are tightly fitted into β-CD cavities leaving no space for the third terpene molecule. Tight fitting is also observed for complexes with bicyclic terpene alcohols. It suggests that shape fitting is the key for the formation of the given stoichiometry. Nevertheless, another bicyclic monoterpene – hydrocarbon fenchene [24], which is structurally related to isopinocampheol, forms a 2:2 inclusion complex with β-CD. In this complex, fenchene is not fully encapsulated in the β-CD cavity (contrary to borneol and isopinocampheol complexes) and some part of this hydrophobic guest molecule is occupying the rims of highly hydrophilic primary hydroxyls, thus preventing binding of the other guest molecule at the interface of β-CD supramolecular dimer. Combined, these results suggests that apart from shape adjustment between β-CD cavity and guest molecule, weak interactions should also be considered. It is known, that non-covalent interactions are mainly responsible for the most efficient packing of organic molecules in the solid state leading to the structures with minimal lattice energy [25,26]. Highly hydrophobic hydrocarbon fenchene does not form any weak interactions with β-CD molecule whereas isopinocampheol and both borneols bearing hydrophilic alcohol group are kept at their positions via C–H···O interactions with host β-CD and adjacent capsules.

4. Conclusions

Solid-state analysis of the inclusion complexes of β-CD with linear (−)-linalool and monocyclic (−)-isopinocampheol reveal different host–guest stoichiometry, i.e. 2:2 for (−)-linalool and 2:3 for (−)-isopinocampheol, respectively. The CSD survey for all solid-state complexes of β-CD with chiral terpene alcohols (linear, monocyclic and bicyclic) highlights the tendency of formation of 2:2 host–guest complexes with linear and monocyclic alcohols whereas bicyclic terpenes prefer to form 2:3 host–guest complexes.

Acknowledgments

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