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Determination of stoichiometric coefficients and apparent formation constants for α- and β-CD complexes of terpenes using reversed-phase liquid chromatography

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Abstract

The stoichiometric coefficients and apparent formation constants for (±)-α-pinene, (±)-β-pinene, (±)-camphene and (±)-limonene with α- and β-cyclodextrins were determined using high-performance liquid chromatography. These measurements were performed in 55 : 45 0.1% orthophosphoric acid in water–methanol using a Vydac C_4 column (15.0×0.46 cm I.D., 10 μm, 300A). Using α-cyclodextrin (α-CD), 1:2 guest–CD complexes were found for the three bicyclic compounds, α- and β-pinene and camphene; a 1:1 guest–CD complex was found for limonene. Using β-cyclodextrin (β-CD), 1:1 guest–CD complexes were found for all compounds. Recognition of the terpene enantiomers was only achieved for the bicyclic compounds using α-CD. For α- and β-CD, the apparent formation constant for each terpene–CD complex was calculated.

Keywords: Chiral mobile phase additive; Cyclodextrins; Enantiomer separation; Apparent formation constants; Stoichiometric coefficients; Terpenes

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides constructed from α-(1,4)-linked glucose units arranged in a torus [1]. The most common CDs are α-, β- and γ-CD, containing six, seven and eight units, respectively. In an aqueous environment, the interior of the cavity is relatively hydrophobic, consisting of a circular configuration of hydrogen atoms and glucoside oxygen atoms, while all hydroxyl groups are outside the molecule. This configuration explains the ability of CD to form inclusion complexes with various hydrophobic solutes in aqueous solutions [2].

The unique inclusion property of CDs has been successfully used to separate geometric, structural and stereo-isomers by thin-layer chromatography (TLC) [3,4], gas chromatography (GC) [5,6] and high-performance liquid chromatography (HPLC) [7,8]. Two different uses of CDs have emerged in HPLC. CDs have been bonded to silica to make chiral stationary phases [9,10] and have been used as chiral mobile-phase additives [11–13].

Terpenes are a class of chiral hydrocarbons found in plant leaves, flowers and fruits [14], the most prevalent of which is α-pinene. Pinene and other

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terpenic derivatives have been used therapeutically in the treatment of various liver [15] and kidney [16] diseases as well as synthetically in the preparation of enantiospecific reducing agents used in the synthesis of chiral alcohols from their corresponding ketones [17].

The separation of enantiomeric terpenes is difficult since they lack functional groups that provide hydrogen bonding, dipole, $\pi-\pi$ or charge transfer interactions required for most chiral recognition mechanisms. CDs have been very successful in the separation of these compounds because of their ability to provide enantiomeric selectivity through an inclusion mechanism.

The most successful technique used in the separation of terpenes is their direct resolution by GC using CD bonded stationary phases [18,19]. Recently, the direct resolution of enantiomeric terpenes has been achieved using HPLC with an α-CD bonded stationary phase [20]. Terpene enantiomers have also been separated using α-CD as a mobile-phase additive [21,22].

Several techniques have been used in the determination of apparent formation constants and stoichiometric coefficients of the guest–CD complex, such as NMR spectrometry [23], potentiometry [23], spectroscopic techniques [24,25,31] and reversed-phase HPLC [26,28,33]. While spectroscopic techniques are sensitive and rapid methods for the determination of apparent formation constants, unfortunately, inclusion of the guest in the CD cavity is not necessarily accompanied by significant spectral changes. Thus, the practical application of these techniques could be limited. HPLC has proven to be a powerful technique for the investigation of the CD inclusion phenomenon [27–29,32]. We wish to report here the determination of apparent formation constants and stoichiometric coefficients of terpene–CD inclusion complexes using HPLC with α- and β-CD as chiral mobile-phase additives.

2. Experimental

2.1. Apparatus

The liquid chromatograph consisted of a Spectra-Physics (Piscataway, NJ, USA) SP-P4000 Pump and Spectra-Physics AS3000 autosampler equipped with a Rheodyne (Cotati, CA, USA) Model 7010 injection valve and 10-μl injection loop. The mobile phases were continually sparged with helium and the column temperature was held at 30±1°C. A Kratos ABI Model 783A variable-wavelength detector (Foster City, CA, USA) set at 210 nm was used. The column was a Vydac (Hesperia, CA, USA) C_4 (15.0×0.46 cm I.D., 10 μm, 300A). The data analysis was performed using P.E. Nelson (Cupertino, CA, USA) Access*Chrom software. Linear regressions and polynomial fits were done using Origin from Microcal Software (Northampton, MA, USA).

2.2. Reagents

The organic modifier, methanol, was HPLC-grade from Fischer (Fair Lawn, NJ, USA). The water was ultra-pure from a Waters (Medford, MA, USA) purification system in the laboratory. Orthophosphoric acid was from Fischer. α-Cyclodextrin, (+)- and (−)-α-pinene, (+)- and (−)-camphene, (+)- and (−)-β-pinene, and (+)- and (−)-limonene were from Aldrich (Milwaukee, WI, USA) and used without further purification. β-CD was obtained from Sigma (St. Louis, MO, USA) and used without further purification.

2.3. Sample preparation

Samples were prepared at a concentration of ca. 0.1 mg/ml of each enantiomer in methanol.

2.4. Mobile-phase preparation

Solutions of 1 l of 0.1% orthophosphoric acid were prepared by dissolving 1 ml of orthophosphoric acid in 1000 ml of ultra-pure water. Amounts of α-CD were added to prepare four mobile-phase solutions with concentrations ranging from 8.3 to 33.1 m*M* α-CD. Similarly, amounts of β-CD were added to a separate set of solutions such that the resulting aqueous concentrations ranged from 0.2 to 1.4 m*M* β-CD. The mobile phases were pump-mixed at a ratio of 55 : 45 aqueous–methanol. The final

mobile-phase composition ranged from 5 to 20 m*M* α-CD and from 0.1 to 0.8 m*M* β-CD.

2.5. Chromatography

The mobile-phase reservoirs were sparged with He for at least 30 min before each run. The column was equilibrated with the mobile phase for at least 30 min at a flow-rate of 1.5 ml/min. As the aqueous mobile phase was changed, the same procedure was applied. Overnight, the system was washed with 55:45 0.1% orthophosphoric acid in water (without CD additive)–methanol. The column void time, t_o, was determined by injecting methanol and recording the first baseline perturbation. Duplicate injections of each compound were performed at each mobile-phase concentration. The average retention time was calculated, t_{ave}, and the k' was determined using the following formula:

$$k' = \frac{t_{ave} - t_o}{t_o}$$

After the studies, the column was re-equilibrated with 55:45 0.1% orthophosphoric acid (without CD additive)–methanol. The samples were injected once again, the retention times of the analyte peaks were recorded. The retention times were the same before and after the column was exposed to CD mobile-phase additive. Thus, the CD additive did not modify the column stationary phase over the duration of the study.

3. Results

3.1. Equilibria and equations

Several competing equilibria occur when a solute is introduced to a reversed-phase chromatographic system (aqueous–organic) with cyclodextrin (CD) as a mobile-phase additive. Studies have examined the relationship between the capacity factor (k') of the solute and the concentration of the CD in the mobile phase [28–32]. Mohseni and Hurtubise [28] proposed the following equilibrium where 1:1 guest–CD complex is observed between a guest solute (S) and CD:

$$\begin{array}{ccc} Sm + (CD)_m & \xleftrightarrow{K_f} & (CD \cdot S)_m \\ \updownarrow K_o \quad + & & \updownarrow K_1 \\ S_s \quad M & & (CD \cdot S)_s \\ \updownarrow K_m & & \\ (CD \cdot M)_m & & \end{array}$$

The subscripts 'm' and 's' refer to the mobile and stationary phase, respectively. M denotes the organic modifier of the mobile phase. K_m describes the affinity of the organic modifier for the CD cavity [33]. Since the organic modifier competes with the solute for the CD cavity, the effective CD concentration in the mobile phase must be calculated using the following equation [34]:

$$[CD]_m = \frac{[CD]}{1 + K_m[M]}$$

The K_m for methanol has been determined to be 0.93 and 0.32 [33] at 25°C for α-CD and β-CD, respectively.

Assuming that the interaction of the guest–CD complex with the stationary phase is negligible [32], the relationship between the capacity factor, k', and the effective cyclodextrin mobile-phase concentration, $[CD]_m$, can be derived:

$$\frac{1}{k'} = \frac{1}{k'_o} + \frac{K_f}{k'_o}[CD]_m \qquad (1)$$

Using k'_o, the capacity factor of the analyte in the absence of the CD modifier, the apparent formation constant, K_f, for the guest–CD complex may be calculated.

We wish to expand on the equilibria proposed by Mohseni and Hurtubise [28] to allow for 1:2 guest–CD complexation. The equilibria below show the formation of a 1:2 guest–CD complex via a precursor 1:1 guest–CD complex:

$$\begin{array}{ccccc} Sm + (CD)_m & \xleftrightarrow{K_{f1}} & (CD \cdot S)_m & \xleftrightarrow{K_{f2}} & (CD \cdot S \cdot CD)_m \\ \updownarrow K_o \quad + & & \updownarrow K_1 & & \updownarrow K_2 \\ S_s \quad M & & (CD \cdot S)_s & & (CD \cdot S \cdot CD)_s \\ \updownarrow K_m & & & & \\ (CD \cdot M)_m & & & & \end{array}$$

Following the derivation of Mohseni and Hurtubise [28] assuming that the interaction of the guest–CD complex with the stationary phase is negligible ($K_1 \cong 0$ and $K_2 \cong 0$) [32] and including terms that account for the possibility of a 1:2 guest–CD complex, a similar mathematical expression can be derived that describes the dependence of the capacity factor, k', of the guest solute on the effective concentration of CD in the mobile phase, $[CD]_m$:

$$\frac{1}{k'} = \frac{1}{k'_o} + \frac{K_{f1}}{k'_o}[CD]_m + \frac{K_{f1}K_{f2}}{k'_o}[CD]_m^2 \quad (2)$$

Eq. 2 is an extension of Eq. 1 that includes a second-order term that accounts for the possibility of a 1:2 guest–CD complex formation. K_{f1} is the apparent formation constant for the 1:1 guest–CD complex, K_{f2} is the apparent formation constant for the 1:2 guest–CD complex and k'_o is the capacity factor of the solute in the absence of the CD modifier.

Eq. 2 simplifies to Eq. 1 when a 1:1 guest–CD complex is the only complex formed; the apparent formation constant of the 1:2 guest–CD complex (K_{f2}) is zero. In this case, a plot of the reciprocal of k' vs. $[CD]_m$ should give a straight line (demonstrated by Mohseni and Hurtubise [28]). In the case of a 1:2 guest–CD complex formation, a plot of reciprocal of k' vs. $[CD]_m$ should give a parabolic curve that fits Eq. 2. The values of K_{f1} and K_{f2} can be obtained by performing a second-order polynomial fit to the data. This polynomial model is used for the four terpene compounds of this study.

A 1:2 guest–CD complex has been reported for pyrene using β-CD as a mobile-phase additive by Anigbogu et al. [35]. In this study, a linear relationship was obtained by plotting the reciprocal of k' vs. the square of the effective β-CD concentration:

$$\frac{1}{k'} = \frac{1}{k'_o} + \frac{K_f}{k'_o}[CD]_m^2 \quad (3)$$

Eq. 3 is similar to Eq. 2 lacking the first-order term, the term that holds the apparent formation constant of the 1:1 guest–CD complex. A linear relationship obtained by plotting the reciprocal of k' vs. the square of the effective β-CD concentration indicates, in the case of pyrene, that the apparent formation constant of the 1:1 guest–CD complex is negligible relative to the apparent formation constant of the 1:2 guest–CD complex ($K_{f1} < K_{f2}$). Thus, Eq. 2 reduces to Eq. 3 where the observed K_f in Eq. 3 is actually equal to $K_{f1}K_{f2}$.

Because the probability of a three-molecule collision resulting in a 1:2 guest–CD complex is very small, the formation of a 1:2 guest–CD complex most likely occurs via a precursor 1:1 guest–CD complex. Therefore, in the cases where 1:2 guest–CD complexation is possible, it may not always be correct to assume that the formation of the 1:1 complex is negligible. By using Eq. 2, the significance of the precursor 1:1 complex in the overall equilibrium can be understood from the magnitude of K_{f1} relative to K_{f2}. In this paper, we examine guest–CD complex formation of four terpenes and α- and β-CD using Eqs. 1, 2 and 3. The apparent formation constants and stoichiometric coefficients of the complexation were calculated and compared with the results obtained using the alternative equations.

3.2. Determination of apparent formation constants

Figs. 1 and 2 show chromatograms of α-pinene and limonene enantiomers with increasing concentrations of α-CD mobile-phase additive. The decrease in k' with increasing concentration of each CD additive indicates that α-pinene forms an inclusion complex with α- and β-CD in the mobile phase. This same trend was observed for all of the terpenes studied with both α- and β-CD.

For each terpene, the reciprocal of k' was plotted vs. the effective CD mobile-phase concentration, $[CD]_m$. In cases where chiral recognition was achieved, each enantiomer was plotted individually and the apparent formation constant was determined for each enantiomer. In cases where chiral recognition is not achieved, the apparent formation constants for the enantiomers are equivalent. As an example, the reciprocal of k' vs. effective α-CD concentration in the mobile phase for (±)-α-pinene and (±)-limonene is shown in Fig. 3. Note that chiral recognition is only observed for (+)- and (−)-α-pinene.

Following Eq. 2, all plots were fit to a second-order polynomial equation to obtain values for K_{f1} and K_{f2}. For (±)-limonene and α-CD and all terpenes and β-CD, a good fit of the data could not

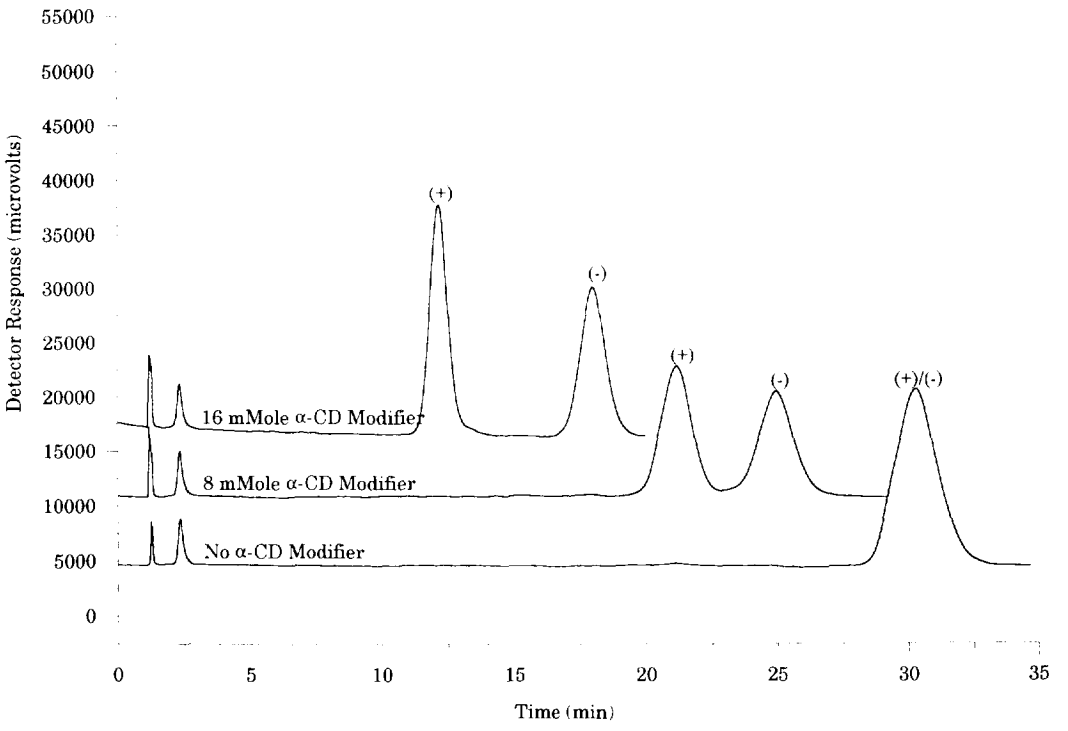

Fig. 1. α-Pinene enantiomers with α-CD mobile phase additive. For chromatographic conditions, see Section 2.

be obtained when the K_{f2} term was included. Therefore, the data was fit to the linear relation of Eq. 1. The values for the apparent formation constants are given in Table 1.

3.3. Determination of stoichiometric ratios

Analysis of K_{f1} and K_{f2} for (±)-α-pinene, (±)-β-pinene and (±)-camphene with α-CD (Table 1) shows that the K_{f2} for each terpene is between at least one order of magnitude larger than K_{f1}. This suggests that both enantiomers of α-pinene, β-pinene, and camphene favor the formation of a 1:2 guest–CD complex. For (±)-limonene, the linear relationship that fits Eq. 1 indicates that a 1:1 guest–CD complex is preferred. Using β-CD as a mobile-phase additive, the fit of the data to Eq. 1 indicates that a 1:1 guest–CD complex is favored. A summary of the stoichiometric coefficients determined for each terpene with α and β-CD is given in Table 2.

For (±)-α-pinene, (±)-β-pinene and (±)-camphene, further confirmation of a 1:2 guest–CD complex was obtained by plotting the reciprocal of k' vs. $[CD]_m^2$ and observing the linear relationship predicted by Eq. 3. Linear regression was performed on each plot and the apparent formation constants were determined from the slope and intercept of each line. The apparent formation constants obtained by the linear plots were then compared to the corresponding constants determined for the polynomial Eq. 2. The K_f from Eq. 3 corresponds to $K_{f1}K_{f2}$ in Eq. 2. Results from the two determinations are shown in Table 3.

As can be seen for each terpene–α-CD system, excellent agreement was obtained between the polynomial and linear equations. It is not surprising that Eqs. 2 and 3 yield equivalent results for the terpenes that form 1:2 complexes with α-CD ((±)-α-pinene, (±)-β-pinene, and (±)-camphene) because $K_{f1} < K_{f2}$ for these terpenes (Table 1). As mentioned above, this condition effectively reduces Eq. 2 to Eq. 3.

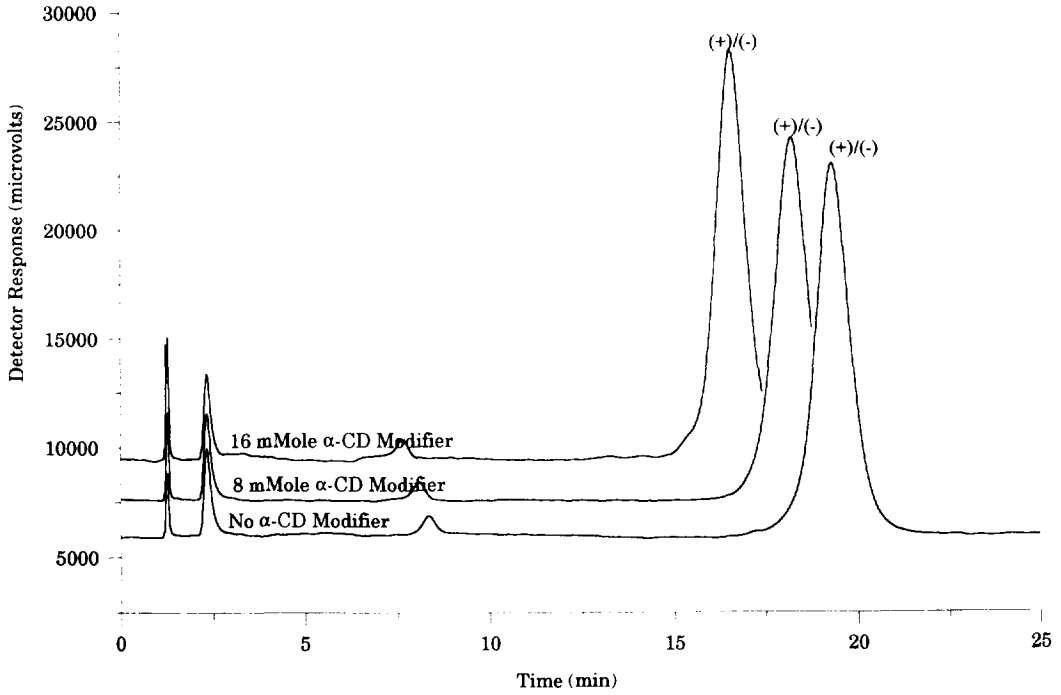

Fig. 2. Limonene enantiomers with α-CD mobile-phase additive. For chromatographic conditions, see Section 2.

4. Discussion

The four terpenes studied (see Fig. 4) contain the same number (10) of carbons. Three compounds (α-pinene, β-pinene and camphene) are bicyclic in structure, one is monocyclic (limonene). Only the bicyclic terpenes were observed to form 1:2 terpene–α-CD inclusion complexes. It was also observed that only the bicyclic molecules (α-pinene, β-pinene, camphene) could be resolved into enantiomers using α-CD. The monocyclic terpene, limonene, was observed to form a 1:1 guest–α-CD complex and its enantiomers were not resolved. All four terpenes formed 1:1 guest complexes with β-CD, enantiomeric resolution was not observed.

The differences in the stoichiometric ratios with α-CD may be explained by the structural differences between the terpenes. The bicyclic terpenes possess two fused rings that contribute to considerable molecular rigidity. It is possible that upon forming an inclusion complex with the first α-CD molecule, the bicyclic terpenes are too inflexible for complete inclusion into the cavity of the α-CD. The hydrophobicity of the protruding portion may then drive a complexation with a second α-CD molecule. Limonene does not possess a fused ring structure and is a longer, more planar molecule. When limonene forms an inclusion complex with an α-CD molecule, its more planar, flexible structure allows for better inclusion in a single α-CD cavity. This precludes complexation with a second α-CD molecule.

The rationale presented above is supported by the observation that the apparent formation constants of the 1:2 terpene–CD complex, K_{f2}, for (+)- and (−)-α-pinene are much larger than for the corresponding β-pinene enantiomers (Table 1), even though the two molecules differ only in the placement of the double bond. For α-pinene, the double bond is within the ring structure of the molecule thereby providing greater molecular rigidity relative

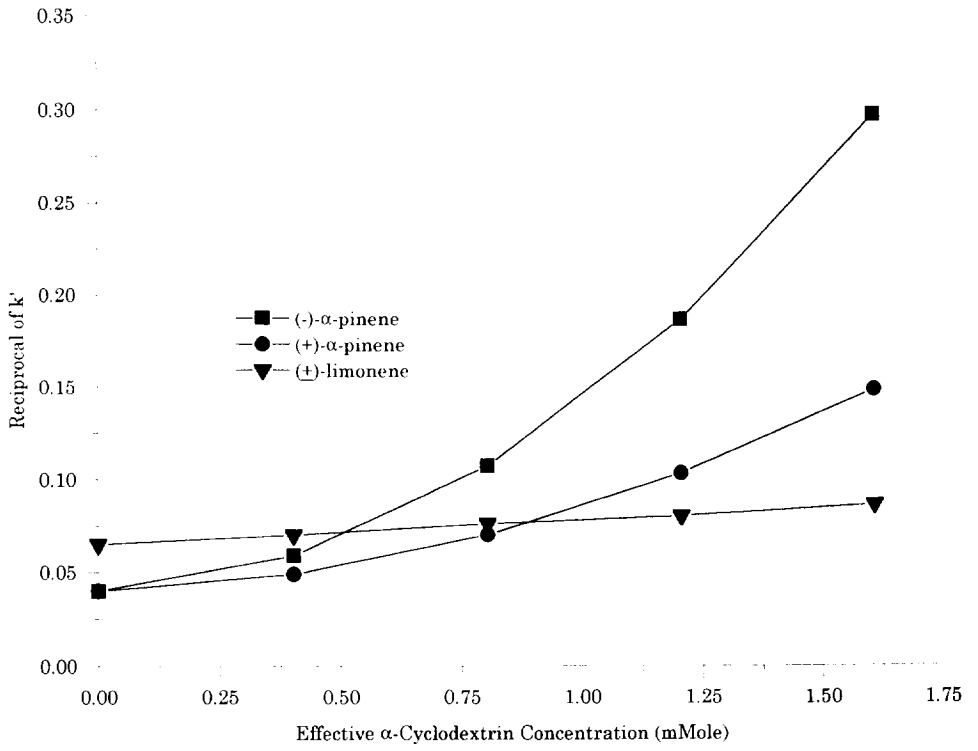

Fig. 3. Reciprocal of k' vs. α-CD concentration for (±)-α-pinene and (±)-limonene. For chromatographic conditions, see Section 2.

to β-pinene, where the double bond is outside of the ring. More rigidity may result in a larger portion of the terpene molecule protruding from the first α-CD molecule and resulting in the formation of a 1:2 terpene–CD complex.

Table 1
Summary of apparent formation constants of terpene complexes with α- and β-CDs

Compound	Apparent formation constants ($\cdot 10^3$)		
	α-CD		β-CD[a]
	K_{f1}	K_{f2}	K_f
(−)-α-Pinene	0.195	12.0	6.08
(+)-α-Pinene	0.190	4.88	
(−)-β-Pinene	0.201	3.91	6.12
(+)-β-Pinene	0.200	1.87	
(−)-Camphene	0.335	9.29	6.04
(+)-Camphene	0.249	2.80	
(±)-Limonene	0.199		3.92

[a] (±)-Enantiomers were not resolved using β-CD.

For the β-CD systems, the 1:1 guest–β-CD stoichiometric ratios observed for all of the terpenes studied can be understood by considering the larger capacity of β-CD relative to α-CD. The larger β-CD cavity poses less steric hindrance to an entering molecule and allows for better inclusion of each terpene into the cavity of the β-CD. This precludes complexation with a second β-CD molecule. The apparent formation constant of a 1:1 terpene–β-CD

Table 2
Summary of stoichiometric coefficient of terpene complexes with α- and β-CDs

Compound	Stoichiometric ratios (guest–CD)	
	α-CD	β-CD
(±)-α-Pinene	1:2	1:1
(±)-β-Pinene	1:2	1:1
(±)-Camphene	1:2	1:1
(±)-Limonene	1:1	1:1

Table 3
Summary of apparent formation constants of terpene complexes with α-CDs: method comparison

Compound	Apparent formation constants ($\cdot 10^5$)	
	Polynomial $K_{f1}K_{f2}$	Linear K_f
(−)-α-Pinene	23.3	23.4 (R^2=0.9999)
(+)-α-Pinene	9.28	9.84 (R^2=0.9995)
(−)-β-Pinene	7.86	8.55 (R^2=0.9992)
(+)-β-Pinene	3.73	4.64 (R^2=0.9976)
(−)-Camphene	3.11	3.05 (R^2=0.9998)
(+)-Camphene	6.97	8.00 (R^2=0.9987)

complex, K_{f1}, is significantly larger than the corresponding apparent formation constant of the 1:1 terpene–α-CD complex, K_{f1}. For β-CD, a strong 1:1 terpene–β-CD complex is formed. Alternatively, the relatively small apparent formation constants of the 1:1 terpene–α-CD complexes indicate that a weak 1:1 terpene–α-CD complex is formed that is stabilized by complexation with a second α-CD molecule to give a 1:2 terpene–α-CD complex. This is indicated by the relatively large K_{f2} values observed for these complexes.

All of the terpenes studied lack functional groups that can interact with the secondary hydroxyl groups on the rim of the CD cavity. Therefore, instances of enantiomeric resolution can be attributed to steric differences between the enantiomers upon inclusion in the CD cavity. When these steric differences are pronounced, the observed apparent formation constant for each enantiomer–CD complex is different; enantiomeric resolution is observed.

Enantiomeric resolution for each terpene also appears to depend on the stoichiometry of the terpene–CD complex. With the exception of camphene, the 1:1 terpene–CD apparent formation constants (K_{f1}) for the (+)- and (−)-enantiomers of each terpene are equal using both α-CD and β-CD. As a result, no enantiomeric resolution is seen in cases where a 1:1 terpene–CD complex is observed. A 1:1 complex is observed between (±)-limonene and α-CD and enantiomeric resolution is not achieved. Also, a 1:1 complex is observed between all terpenes and β-CD and enantiomeric resolution is not achieved. However, for the bicyclic terpenes that form 1:2 terpene–α-CD complexes, the 1:2 complex apparent formation constants (K_{f2}) are significantly different for each enantiomer resulting in enantiomeric resolution. This suggests that for (+)- and (−)-α-pinene, (+)- and (−)-β-pinene and (+)- and (−)-camphene enantiomeric resolution occurs only after complexation of the precursor 1:1 terpene–α-CD complex with a second α-CD molecule.

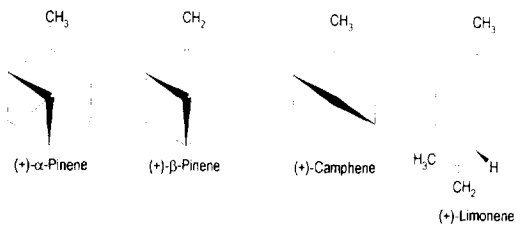

Fig. 4. Structures of terpenes.

5. Conclusion

We have tested a series of terpene compounds and determined their stoichiometric coefficients of complexation and their apparent formation constants. Chiral recognition, a result of the difference between the apparent formation constants of the enantiomers, was achieved for the bicyclic terpenes with α-CD. A difference in apparent formation constants was only observed when a 1:2 terpene–CD complex was formed. α-Pinene, β-pinene and camphene formed a 1:2 terpene–α-CD complex; their enantiomers were resolved. Enantiomeric separation was not achieved using β-CD.

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