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CHIRAL SEPARATIONS OF PHYRETROIC ACIDS USING CYCLODEXTRIN SELECTORS

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The pyrethroid insecticides are broadly used insecticides. They are used also near food insecticides in households because they have low toxicity for warm blooded living creatures. On the other hand, they show high toxicity not only for insecticides but for fishes too. Therefore, it is important to decrease the environmental burden of the pyrethroids. One of the effective ways to decrease the pollution using chiral pure insecticide products instead of their racemic mixtures. For example, the chiral pure deltamethrin has same insecticide effect than the eight times more amount racemic mixture of deltamethrin. The enantiomer pure products require enantiomer selective synthesis and analysis. The pyrethroic acids are chiral compounds. Their chiral selective syntheses are necessary therefore their chiral selective analyses are crucial. The chiral selective analyses of pyrethroic acids are also important from the point of view of their degradation metabolism in the environment. This study shows various enantiomeric selective chromatographic methods: gas chromatography, supercritical fluid chromatography and capillary electrophoresis for separation of various pyrethroic acids. The used chiral selective agents were based on cyclodextrin derivatives. To find the appropriate chiral selective selector is the result of a trial-and-error method development. This systematic study explores the correlation of chiral selectivity-analyte structure using different pyrethroic acids in various derivatives forms.

Key words: *pyrethroic acids, chiral separations, gas chromatography, capillary electrophoresis, chiral selectivity-structure relationships*

INTRODUCTION

Phenomenon of the chirality

The chiral molecules are asymmetric molecules [1]. They are not same with their mirror images. A chiral molecule and its mirror image molecule are called enantiomers, or an enantiomeric pair (Figure 1).

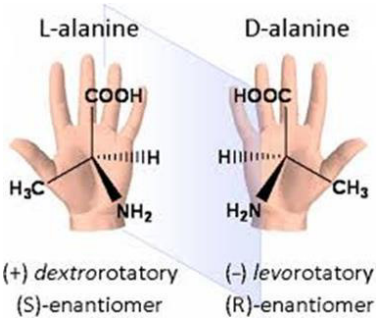

Figure 1. The structure of enantiomeric pair. They are asymmetric molecules. they are mirror images of each other, and they have not superimposable structures.

The properties of the member of an enantiomer pair are same in homogeneous (achiral) environment. However, they show different properties in inhomogeneous, chiral environment (e.g., magnetic field, receptor sites and interactions with other asymmetric molecules). The molecules of living organisms (e.g., amino acids, sugars, receptors etc.) of nature are dominantly asymmetric and several inorganic molecules are also chiral (e.g., quartz). The members of an enantiomeric pairs show different biological effects frequently. Every essential amino acid has only one member (L) of their enantiomeric pairs in the proteins. The proteins consist of enantiomerically pure amino acids.
The importance of chiral pure pharmaceutical is evident since the Contergan scandal [2]. Contergan (Thalidomide) pharmaceutical medicine was a mixture of enantiomer molecules, in which one enantiomer produced a desirable antiemetic effect. The other isomer of enantiomeric pair was toxic and produced teratogenicity side-effects. More than 10,000 children were born with serious deformations (phocomelia) if their mothers had taken Contergan during their pregnancy. Recently, the authorities allow only enantiomer pure medication products [3]. Chiral drug can contain less than 0.1% of its optical isomer. The use of enantiomer pure agrochemicals is increasingly making its way [4].

Pyrethroids

Pyrethroids are broadly used synthetic insecticides [5]. They have more intensive effects than their natural analogues: pyrethrum, produced by chrysanthemum flowers. The pyrethroids have low toxicity to mammalians, but high to bees and fishes [6, 7]. They have neurotoxic effects through the sodium channel [7]. Commercially available pyrethroids are esters. The acidic parts usually have two chiral centres in their cyclopropane rings (Figure 2).

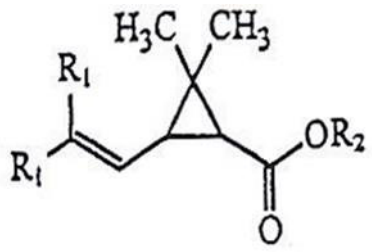

Figure 2. The general structure of tested pyrethroic acids. The R_1 can be methyl (chrysantemic acid), chlorine (permethrinic acid) or bromine (delthametrinic acid). The R_2 can hydrogen (free acid) or any alkyl substituents (ester).

The diastereomers are called cis/trans isomers according to the relative configuration of the carboxyl and substituted alkene (e.g., dimethyl-, dichloro-, dibromo-vinyl) groups on the cyclopropane ring. These acids are frequently esterified with optically active alcohols (cypermethrin, cyfluthrin and delthametrin) creating additional stereoisomers of the insecticidal products. The structural isomers have different biological effects [6-10].
The 1R-cis isomers of acids show much more effective insecticidal activity than the other isomers. For example, the deltamethrin pesticide has 3 chiral centres, but only one of the eight isomers (αS,1R,3R′-) has a really good and effective pesticide effect. On the other hand, every isomer has toxic side effects toward fishes [11].
In this way, a certain amount of the enantiomeric pure deltamethrin cause the same useful effect than the eight time more amount stereoisomeric mixture of deltamethrin. The same insecticidal effects cause eight times less environmental load with enantiomer pure products, than the mixture of all stereoisomers.
The large difference in their biological activity of these enantiomers require their chiral selective syntheses [4, 12,], and highly efficient chiral analyses with HPLC [6, 8- 13], SFC [14, 15] and GC [16]. The enantiomer selective analyses of pyrethroic acids are also important from the point of view of production processes and metabolism control in the environment. The GC [17], SFC [18] or CE [19-21] are also important in the chiral separation of pyrethroic acids.

Separation of enantiomers

There is no general chiral selector for every enantiomeric pair [22]. Chiral chromatographic separations request exact fits among the interaction groups of the selector and interaction groups of analytes [23, 24]. Namely, the three-point interaction recognition mechanism requires fair geometrical arrangements and chemical appropriateness among the interacting groups of the selectors and selectands.

A good chiral separation is the result of trial-and-error process on several occasions. However, certain rules can be established for the chiral recognition conditions with systematic studies using model compounds. These rules can be employed for other chiral separations, to gain a good chiral separation in a faster way than the trial-and-error method.

In this study, we present a systematic study to show the chiral selectivity structure relationships using pyrethroic acids.

Cyclodextrins

The cyclodextrins (CDs) are the most frequently used chiral selectors in the capillary column separations [25-27], therefore cyclodextrin were used for the chiral separation of pyrethroic acids in this study.

The CDs are cyclic oligosaccharide molecules [28]. The glucose units join together with α-1,4-glycosidic linkages. The most important members of CDs consist of six, seven or eight D (+)-glucopyranose units, to which the letters Greek, α, β and γ were assigned respectively. The structures of the β-CD are in Figure 3. The CDs have twisted truncated cone shape. They can include as host guest molecules insides in their cavities.

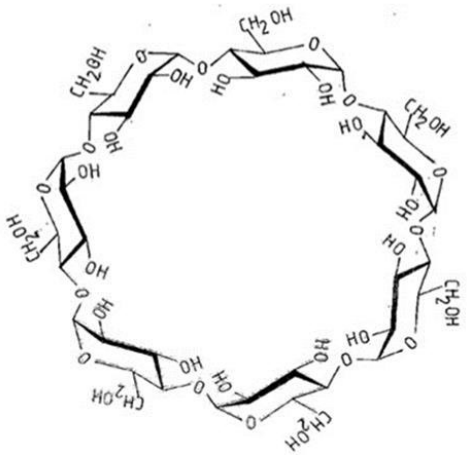

Figure 3. The structure of β-cyclodextrin

The most important features of the CDs are their excellent chiral recognition characters toward to extreme broad spectra of the enantiomers in the analytical chemistry. CD molecules are the most popular chiral selectors using capillary columns in gas chromatography (GC) and capillary electrophoresis (CE).

Enantiomers, having any functional groups or structures, can be separated with CD based selectors [17 24-30]. The reason of the broad chiral selectivity spectra of CDs are the following:

- The CDs have numerous, non-uniform chiral centres, (35 in β-CD), because the CDs have twisted truncated cone structures [25].
- The hydroxyl groups of CDs can substitute with different functional groups (e.g., methyl, phosphate, sulphate, amino, naphthyl, acetate) add extra interaction ability to the interaction potentials of underivatized CDs [28]. Some substitutions groups (such as hydroxypropyl and naphthyl-ethyl carbamoyl) add extra chiral centres to CDs, further broadening their recognition spectra [25].
- The most CD derivatives are randomly substituted molecules. They are mixtures of large number of isomers [28]. They differ from each other in the numbers and the positions of the

substituents, and almost every isomer has different chiral recognition features. Moreover, the substituents can be different in their chemical structures and arrangements in a derivatized CD [28].

- The derivatized CDs have rather flexible structure. CDs can change their shape to interact with analytes with the "induced fit" mechanism [28]. A CD can change its shape to produce stronger interactions resulting in further enlarged chiral selectivity spectra.
- The ionizable CDs can change their selectivity spectra according to their ionization states according to the pH value of their solutions [31].
- The types of the background buffer or mobile phases (normal, revers and polar-organic) influence also the selectivity features of CDs [25].

The CDs can also separate enantiomers, not only with carbon atom centre, but they can also separate enantiomers with phosphorus, nitrogen or sulphur atom centres. Chiral molecules can be also separated with planar or axial chirality with CDs [29].
We used cyclodextrin chiral selectors in our study. Our generalizable conclusions (structure-chiral selectivity correlations) can be used for solutions of several other chiral separations.

EXPERIMENTAL METHOD

The tested pyrethroic acids: chrysantemic acids, ($C_{10}H_{16}O_2$), permethrinic acids ($C_9H_{12}Cl_2O_2$) and deltamethrinic acids ($C_9H_{12}Cl_2O_2$) were products of Ciba-Geigy.
The used solvents and reagents: hexane, ethyl acetate, diethyl ether, and BF_3 methanol, ethanol, n-propanol, i-propanol, n-butanol, s-butanol and t-butanol were purchased from Merck, which were used for GC measurements. The syntheses of ester derivatives of pyrethroic acids were made using reaction of BF_3 with various alcohols.
The chemicals of background electrolyte of CE measurements were boric, acetic and phosphoric acids and sodium hydroxide from Sigma-Aldrich. The used deionized water was made by MilliQ instrument.
The permethyl monoamino β-cyclodextrin (PMMA βCD), monoamino β-cyclodextrin (MA βCD), permethyl β-cyclodextrin (TRIMEB), dimethyl β-cyclodextrin (DIMEB), hydroxypropyl β-cyclodextrin (HP βCD) were products of Cyclolab.
The gas chromatographic experiments were done on Chirasil-Dex, a polysiloxane anchored permethylated β-cyclodextrin coated. Column (10 m x 0.1 mm I.D.) and 25 m x 0.22 mm; stationary phase, Cydex-B (0.25 μm). Carlo Erba Mega was the GC instrument [17, 18]. Every tested molecule was separated at least 3 temperatures to calculate the selectivity values at 100° C.
The capillary electrophoresis measurements were carried out on a Hewlett Packard 3DCE system with diode array UV detector (202 and 220 nm) at 25 °C. Uncoated fused-silica capillary (58.5 cm x 50 μm I.D.) was applied [19, 20]. The background electrolyte (BGE) consisted of 40 mM boric, acetic and phosphoric acid buffers in ratio of 1:2:2 (Britton-Robinson). The exact pH values of BGEs were adjusted with 0.1 m NaOH solution.

RESULT AND DISCUSSIONS

Results of gas chromatographic measurements
Every enantiomer of pyrethroic acids were separated somehow (Table 1) under GC conditions. The measurements were done at different temperatures. For the sake of comparison, the measurements were done at 100° C, or calculated for this temperature.
The calculations were based on the linearity of lnα-1/T correlations where α is the chiral selectivity and T is the absolute temperature [29]. The linearity values are checked with regression calculations. The linearity of these regression calculations proved that the separation processes belong to only one chiral recognition mechanism for a given enantiomeric pair.
Probably, the rigid cyclopropane ring structure of the pyrethroic acids fit well to the cavity of the permethylated β-cyclodextrin. This inclusion process offers a good chiral recognition toward to pyrethroic acids.

Table 1. The chiral selectivity of pyrethroic acids at 100° C

Structures of the racemates			Selectivity (α)
cis/trans	R_1	R_2	
cis	Me	H	1.275
trans	Me	H	1.153
cis	Me	Me	1.013
trans	Me	Me	<1.01
cis	Me	Et	<1.01
trans	Me	Et	<1.01
cis	Br	Me	1.046[b]
trans	Br	Me	1.040[b]
cis	Cl	H	1.284[b]
trans	Cl	H	1.194[b]
cis	Cl	Me	1.043
trans	Cl	Me	1.010
cis	Cl	Et	1.023
cis	Cl	Pr	1.019
cis	Cl	iPr	<1.01
cis	Cl	Bu	1.014
cis	Cl	sBu	1.034
cis	Cl	tBu	<1.01

[a]10 m x 100 μm i.d. column, coated with Chirasil-Dex (d_f = 0.25 μm), at 100°C.
[b]Extrapolated values.

R_1, substitution in vinyl group; R_2, substituent in acid function

The free acids were excellent forms for chiral separations, because the free acid forms showed higher chiral selectivity than the ester forms (Table 1). Probably the H-bond donor ability of analytes play an important role in the chiral recognition. Even the chrysanthemic acid isomers showed excellent separations (Figure 4). It is interesting to note the trans isomers elutes among the cis isomers on Figure 4.

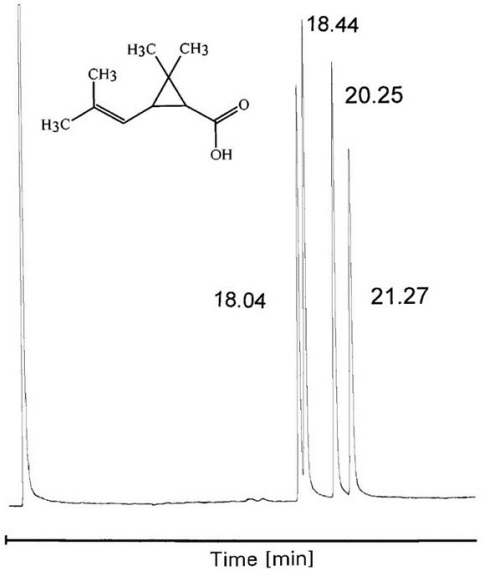

Figure 4. Chiral and cis-trans separation of Chrysanthemic acid isomers as free acids. The peaks of trans isomers elute between the peaks of cis isomers. Conditions: instument, Carlo Erba Mega; column, 25 m x 0.22 mm; stationary phase, Cydex-B; carrier, H_2 (50 cm/sec); temperature, 120° C.

The cis isomers showed higher selectivity values than trans isomers. The ester forms of pyrethroic acids, where R2are alkyl groups, show smaller chiral selectivity values than their free acid forms except for s-butyl derivative of c-permethrinic acid. Generally, the chiral selectivity values decrease with the increasing alcohol part of the esters (Me>Et>Pr>Bu) in the case of normal alcohol substitution. On the other hand, the chiral selectivity of different pyrethroic acids increase with the volumes of substituents of vinyl groups (R_1). Highest selectivity was measured for deltamethrinic acid (R_1 = Br), which was followed the permethrinic acids (R_1 = Cl) and the chrysantemic acid (R_1 = Me) showed the lowest selectivity. Probably, not only the volume of the R_1 groups can play role int the chiral recognitions, but the electron donor abilities of substituents too. The (+) isomers eluted before (-) isomers on every occasion.

Results of capillary electrophoretic measurements

The pyrethroic acids enantiomers can be effectively separated using various cyclodextrins in capillary electrophoresis [19-21]. The best resolution values are summarized in Table 2. The numbers of the Table 2 show the permethyl monoamino β-cyclodextrin (PMMAβCD) is the best chiral selective agents from the tested CDs. The permethyl β-cyclodextrin (TRIMEB) is also good for these purposes. The monoamino β-cyclodextrin (MA βCD), permethyl β-cyclodextrin (TRIMEB), dimethyl β-cyclodextrin (DIMEB), hydroxypropyl β-cyclodextrin (HP βCD are less effective separation agents toward to pyrethroic acids.

Table 2. The resolution values of pyrethroic acid using various cyclodextrin derivatives at pH 6.5 buffer

Resolution (pH 6.5)	15 mM PMMAβCD	15 mM TRIMEB	15 mM MAβCD	15 mM DIMEB	15 mM HPβCD
trans-deltamethinic acid	11.56	3.24	<0.5	<0.5	<0.5
cis-deltamethrinic acid	20	5.64	<0.5	<0.5	<0.5
trans-permethrinic acid	6.62	1.69	<0.5	<0.5	<0.5
cis-permethrinic acid	17.23	2.37	<0.5	<0.5	0.55
trans-chrysanthemic acid	1.08	<0.5	<0.5	<0.5	<0.5
cis-chrysanthemic acid	8.5	1.56	2.57	1.93	1.67

The PMMAβCD can separate every tested chiral pyrethroic acids (Figure 5). The trans-chrysanthemic acid enantiomers can also be baseline separated using 17.5 mMol PMMAβCD, but the increased concentration of the selector results in more than one over migration times.

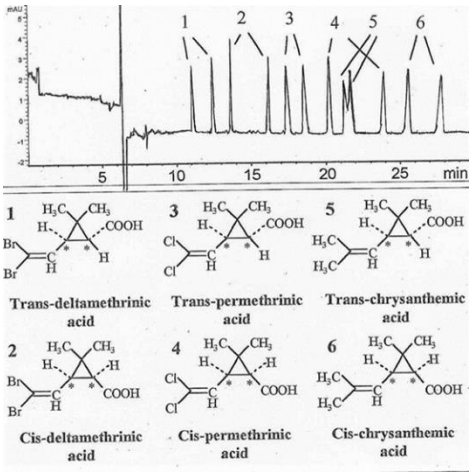

Figure 5. Simultaneous enantioseparation of 6 pyrethroic acids. Conditions: column 50 cm effective length x 0.050 mm i. d. uncoated fused-silica capillary; 15 mM PMMAβCD concentration;

background buffer, 40 mM boric, acetic and phosphoric acid buffers (1:2:2); potential, 30 kV; detection, 220 nm.

The resolution values highly depend on the pH of the background electrolyte [20]. The best resolutions were gained at pH 6.5 (Figure 6).

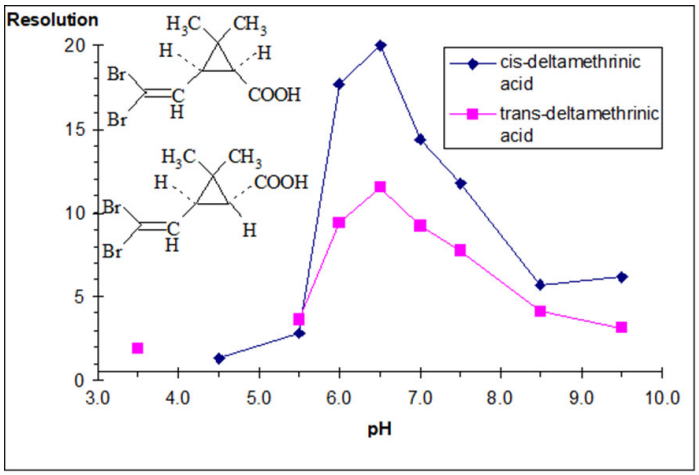

Figure 6. Resolution of enantiomers of cis- and trans-deltamethrinic acids depending on pH at Conditions: column 50 cm effective length x 0.050 mm i. d. uncoated fused-silica capillary; 15 mM PMMAβCD concentration; background buffer, 40 mM boric, acetic and phosphoric acid buffers (1:2:2); potential, 30 kV; detection, 220 nm.

The highest resolution can be achieved in a pH range, where the analytes and selector both are in ionized states. Namely the oppositely charged selector and analytes gained pseudo elongation of their separation length [30], because the analytes have opposite migration directions in complexed and uncomplexed states. The selectivity values of other tested pyrethroic acids showed similar pH dependency trend.

The TRIMEB is also a very good chiral separation agent toward to pyrethroic acids. The resolution values of cis-permethrinic acid enantiomers show maximum in the function of concentration of TRIMEB according to the theory of Wrenn [32]. The 12.5 mMol concentration of the TRIMEB showed the maximum value. The TRIMEB was also excellent to analyse the result of salt resolvation process [21.]. Using this selector, the simultaneous determination of anionic, cationic compounds and the enantiomeric ratio of the anionic compound were determined during one analysis run.

CONCLUSION

The enantiomeric separations of pyrethroic acids were solved with various gas chromatographic and electrophoresis methods. The highly methylated cyclodextrins TRIMEB and PMMAβCD selectors were the most effective for this task. The cis isomers showed higher selectivity than their trans isomers. The selectivity values gained the following tendency: deltamethrinic acids> permethrinic acids> chrysantemic acids. The selectivity of the permethrinic acids were influenced with the derivatization of these compounds in GC mode. The CE experiments show maximum resolution values in the function of pH and concentration selectors. The high chiral recognition properties of the pyrethroic acid partly come from their rigid cyclopropane structure. The chiral recognition improved by the H-bond donor and acceptor properties of the analytes. Our finding and conclusions concerning the chiral recognition mechanisms are also useful to find appropriate selectors for other chiral separations.

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