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Application of cyclodextrin-modified micellar electrokinetic chromatography to the separations of selected neutral pesticides and their enantiomers

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Abstract

The environmental chemistry of chiral pesticides is receiving increased attention — enantiomeric ratios are being measured and enantioselective degradation processes are being reported. The requisite analysis involves separation of the various enantiomers. Mixtures of three classes of chiral pesticides — organophosphorus, DDT congeners and methyl esters of phenoxy acids — were separately tested for separation, first by non-chiral micellar electrokinetic chromatography (MEKC). Generally, the components of each mixture were so strongly adsorbed by the micelles that they coeluted with the micelles. Then, different concentrations of an organic modifier, methanol or acetonitrile, were added. Only the five organophosphorus pesticides were separated efficiently; components of the other mixtures still migrated with the micelles. Each of six cyclodextrins (CD) — α-, β-, γ-, hydroxypropyl-β-, dimethyl-β- and trimethyl-β-CD, were then added to the borate–SDS buffer, with and without the organic modifier, to test for separation of the non-chiral compounds and the enantiomers of the chiral racemates by CD-MEKC. The enantiomers of malathion, ruelene and dialifos were separated by hydroxypropyl-β-CD, β-CD and/or γ-CD, while the enantiomers of isofenfos and fenamifos could not be separated. γ-CD with methanol modifier allowed baseline separation of the three phenoxy acid methyl esters and of the enantiomers of fenoprop methyl ester, but none of the CDs separated the enantiomers of mecoprop and dichlorprop methyl esters. The use of γ-CD with acetonitrile modifier resulted in excellent separation of six DDT congeners, o,p′- and p,p′-DDT, -DDD and -DDE, as well as baseline separation of the enantiomers of the chiral members of this series, o,p′-DDT and -DDD. Finally, attempts were made to separate the four enantiomers of the herbicide metolachlor; three of the enantiomers were separated by γ-CD with methanol. © 1997 Elsevier Science B.V.

Keywords: Enantiomer separation; Buffer composition; Pesticides; Organophosphorus compounds; DDT congeners; Phenoxy acids, methyl esters; Metolachlor; Cyclodextrins

1. Introduction

Many chemical products used in the pharmaceutical and agrochemical industries contain chiral centers and are used as racemates. A recent study showed that chiral compounds accounted for 25% of all agrochemicals in 1995 (26% of the total agrochemical market value) as compared to 19% in 1980; the compounds sold as single isomers accounted for only 7% of the total market value [1]. After their field application, pesticides generally undergo a series of biologically mediated reactions in which the differences in activity of the isomers may have important consequences [2]: in some cases only one

of the isomers has a pesticidal activity while the other may have toxic effects against non-target organisms. The use of racemates contributes to useless environmental loading; furthermore, additional costs are involved in both production and removal processes of the non-active isomers. For materials used in pharmacological, toxicological and clinical studies the quantitative stereoisomeric composition of drugs with chiral centers must be known, as dictated by the policy of the US Food and Drug Administration [3]. For chiral herbicides such as dichlorprop and mecoprop, for which only one form is herbicidally active, regulatory actions already limit the use of racemates in the Netherlands and in Switzerland [1].

The interest in analytical techniques for the separation of environmental chiral compounds is thus increasing because the understanding of enantiomeric discrimination in environmental compartments is becoming important [4,5].

1.1. Application of capillary electrophoresis to the analysis of pesticides

Applications of capillary electrophoretic (CE) methods to pesticides and environmental samples have been reviewed [6,7]. Isotachophoretic methods were the first capillary electrophoretic applications; e.g., in the analysis of pyrethroids (alphametryne, cypermetryne) [8], bipyridilium salts (diquat and paraquat) [9] or s-triazines [10]. Capillary zone electrophoresis (CZE) enables the rapid separation of ionic compounds and has been successfully applied to the analysis of anionic phenoxy acid herbicides (MCPA, MCPP, 2,4-D, fenoprop, dichlorprop) [11–15], organophosphoric acids (glyphosate, MPA, ENPA, PMPA...) [16], sulfunylureas (metsulfuron and chlorsulfuron) [17], cationic bipyridilium salts (diquat and paraquat) [18,19] and s-triazines [20–23].

Neutral pesticides are analysed by micellar electrokinetic chromatography (MEKC); charged micelles are added to the running buffer and the separation of the pesticides is based on their relative partitioning between the water and the micellar phase [24,25]. Several classes of pesticides and their degradation products have been separated with MEKC, for example chloroanilines [26], triazoles

[27], phenoxy acids [28,29], carbamates [30], s-triazines [31–33] or urea herbicides [34]. Finally, the addition to the running buffer of chiral selectors that selectively bind the different enantiomers allows the electrophoretic separation of enantiomers of charged or neutral chiral compounds [35,36].

The aims of this study were:

– to separate neutral chiral pesticides (organophosphorus, organochlorine, acetamide, phenoxy acid methyl esters) with MEKC,

– to analyse the influence of six different cyclodextrins on the separation of enantiomers of these pesticides by CD-MEKC,

– to optimize the enantioselective separation by addition of organic modifiers.

2. Experimental

2.1. Apparatus

Separations were performed with a Beckman P/ACE 5000 Series HPCE with Beckman SYSTEM GOLD chromatography software version 8.1.

The fused-silica CE column (75 μm I.D.; 375 μm O.D.; 50 cm length to detector and total length of 57 cm) was obtained from Beckman Instruments.

2.2. Separation and washing cycles

The separation runs were done at constant temperature (30°C) and variable voltage (15–30 kV) with UV–vis filter detection at 200 nm. Hydrodynamic sample injection for 10 s was the sample introduction mode for all experiments. The separation solutions were prepared from 40 mM borate buffer (pH 9) and 100 mM sodium dodecyl sulphate (SDS) stock solutions purchased from Applied Biosystems (Foster City, CA, USA).

A 2-min washing cycle (high pressure, 20 p.s.i.) with 0.1 M NaOH was followed by a 2-min conditioning of the capillary with the run buffer before the sample injection; each measurement was ended with a 2-min 0.1 M NaOH washing cycle; this washing cycle between the measurements assured good conditioning of the capillary wall surface, thus avoiding hysteresis effects with changes in the pH of

the running buffer. This buffer washing was not combined with electrophoretic conditioning.

2.3. Chemicals

The non-ionizable pesticides analysed in this study are presented in Fig. 1. They were purchased in greater than 99% purity grade from Riedel de Haen (Pestanal grade), Munich, Germany. Most of them contain a chiral center because of asymmetry about a carbon or phosphorus atom; they fall into four classes:

1. organophosphorus: ruelene (R), isofenphos (I), dialifor or dialifos (D), fenamifos (F), malathion (M)
2. phenoxy acid methyl esters: fenoprop-, meco-prop-, dichlorprop-methyl ester
3. organochlorine: p,p′-DDT, p,p′-DDD, o,p′-DDT, o,p′-DDD, p,p′-DDE, o,p′-DDE
4. acetamide: metolachlor.

Pesticide stock solutions were prepared by dissolving 10 mg of each compound in 10 ml of pesticide grade methanol; a 20-μl volume of this solution was mixed with 380 μl distilled water to reach a final concentration of 50 ppm each.

Organic modifiers, all p.a. grade, were obtained from Fisher Scientific (Springfield, NJ, USA). Cyclodextrins were α-CD (cyclohexaamylose), β-CD (cycloheptaamylose), γ-CD (cyclooctaamylose), DM-β-CD (heptakis (2,6-di-o-methyl)-β-cyclodextrin), TM-β-CD (heptakis (2,3,6-tri-o-methyl)-β-cyclodextrin) and HP-β-CD (hydroxypropyl-β-cyclodextrin) and were obtained from Sigma (St. Louis, MO, USA). Sudan III was used as the micellar marker and was purchased from Micro-Solve CE (Scientific Resources, Eatontown, NJ, USA). All buffers and stock solutions were kept under refrigeration (4°C).

3. Results and discussion

3.1. Micellar electrokinetic chromatography (MEKC)

The micellar electrokinetic chromatography (MEKC) as developed by Terabe et al. (1985) [25] allows the separation of neutral pesticides in the presence of charged micelles (i.e. sodium dodecyl sulfate — SDS in our study) and an electroosmotic flow (EOF). The relative distribution of the pesticides between the mobile aqueous and charged micellar phase is a function of the hydrophobicity of the pesticides and will determine the selectivity of the separation (Fig. 2).

The analyte must migrate with a velocity between the electroosmotic velocity and the velocity of the micelle (measured with the micellar marker Sudan III). In other words, the elution time of the analyte, t_i, must fall between the elution time of the bulk solution, t_0, and that of the micelle, t_{mc}; this is the migration time window.

A capacity factor k' can be defined, as in classical liquid chromatography, as the partition of the analyte between the aqueous and the micellar phase:

$$k' = \frac{n_{mc}}{n_{aq}} \tag{1}$$

with n_{mc} and n_{aq} the amounts of analyte in the micellar and aqueous phase respectively. The capacity factor k' can be expressed as a function of the elution times:

$$k' = \frac{t_i - t_0}{t_0(1 - t_i/t_{mc})} \tag{2}$$

Eq. (2) is equivalent to:

$$k' = \frac{\mu_i - \mu_0}{\mu_{mc} - \mu_i} \tag{3}$$

where μ_i, μ_{mc} and μ_0 are the electrophoretic mobilities of the analyte, the micelle and the EOF respectively.

The capacity factor k' is directly correlated to the partition coefficient K_p of the pesticide between the aqueous and the micellar phase [25]; k' was calculated for most of the separations in this study and could be taken as a quantitative indicator of K_p. In a related study the partitioning of s-triazines between water and a dissolved organic phase (humic substances) could be calculated by using humic substances as charged micelles in MEKC [37].

3.2. Influence of organic modifiers

For all studies we used a 20 m*M* borate buffer (pH 9.0) under a voltage of 30 kV to produce a high electroosmotic flow for rapid separations. It was
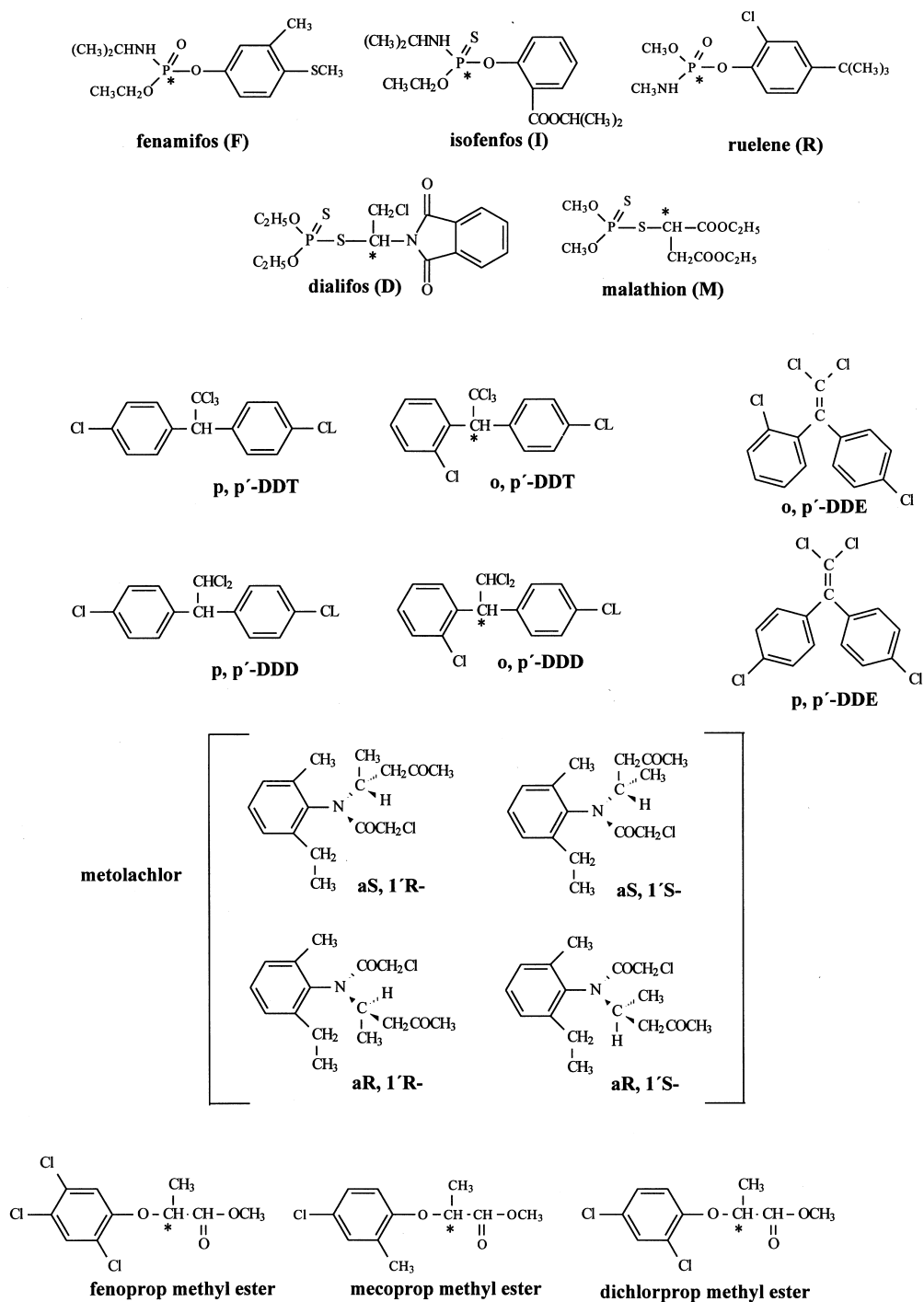
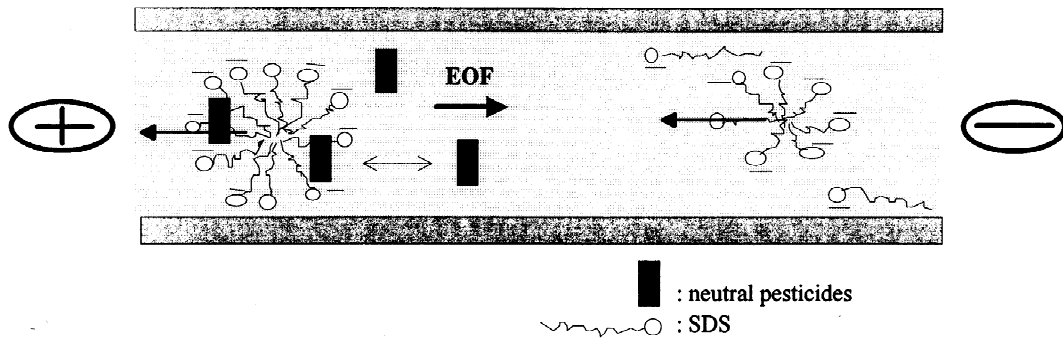Fig. 1. Pesticides analysed by CD-MEKC.

Fig. 2. Schematic of the separation principle of MEKC.

shown by other authors that changes in the SDS or borate concentrations, pH, temperature and applied voltage did change the capacity factor k' a little, but did not significantly change enantiomeric separation at constant cyclodextrin concentration [38]; for this reason the effects of changes of these parameters on the separation were not investigated. SDS was used at a constant concentration of 100 mM (more than ten times the critical micellar concentration of 8.1 mM at 25°C). Under these experimental conditions all the pesticides were strongly adsorbed by the micelles and coeluted with the micellar marker (Sudan III). This is shown in Fig. 3a using five organophosphorus insecticides. Malathion (M) is the

only compound partitioned enough in the water phase to show up as single peak.

The addition of organic modifiers like methanol or acetonitrile changes the partitioning behaviour of the five pesticides so that they can be baseline-separated in less than 30 min (Fig. 4). Good separation (Fig. 3b) is achieved with addition of 20% methanol (identical separation with only 15% acetonitrile); the increase in migration times and the larger migration time window is due to the combined effect of changes in viscosity and EOF.

The other pesticides studied were mixtures of organochlorine (p,p′-DDT, o,p′-DDT, p,p′-DDD, o,p′-DDD, p,p′-DDE and o,p′-DDE) and phenoxy
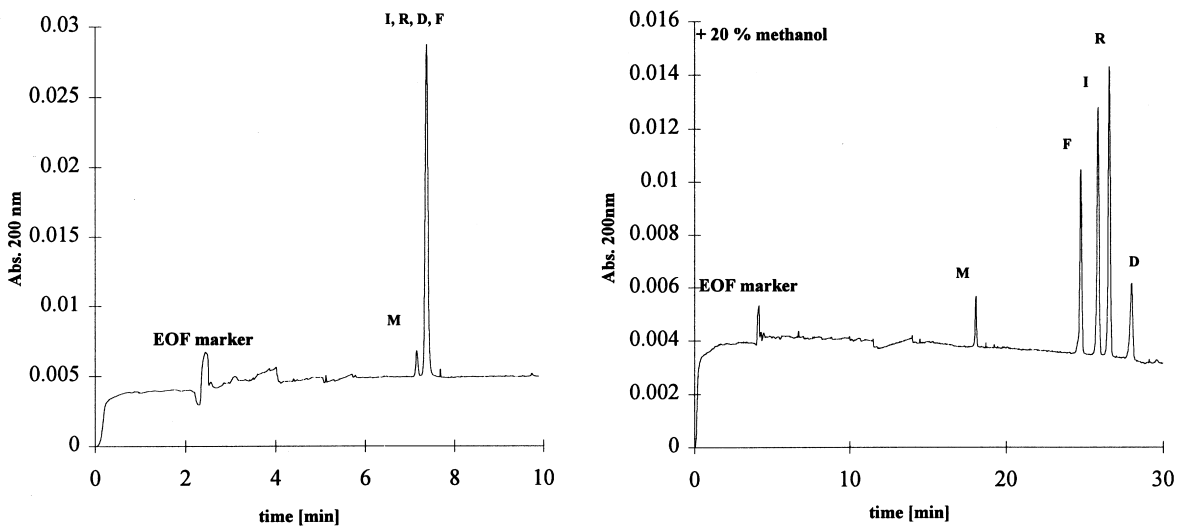

Fig. 3. Electropherogram of malathion (M), isofenfos (I), ruelene (R), dialifos (D) and fenamifos (F) in MEKC (a) without addition of methanol, (b) with addition of 20% methanol [20 mM borate buffer (pH 9.0) 100 mM SDS, 30°C, 30 kV].
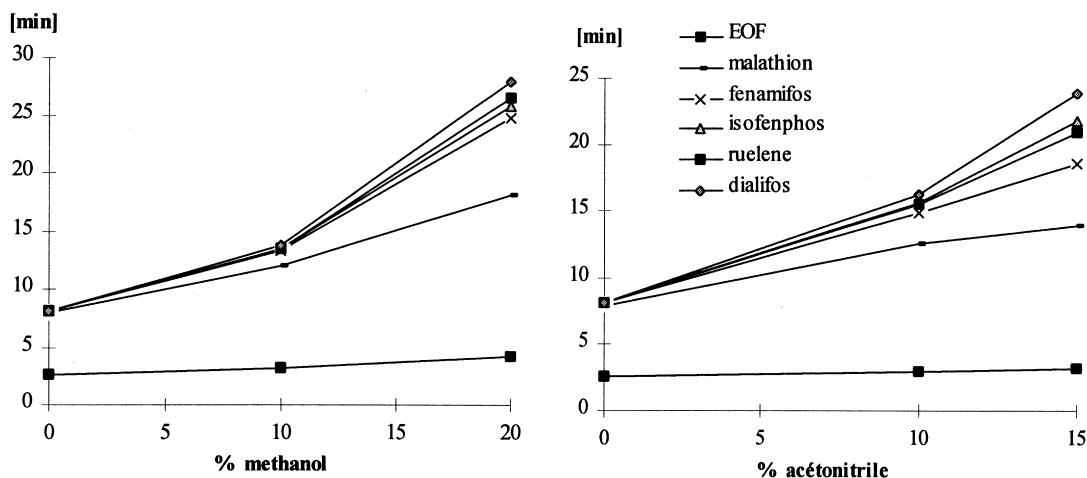
Fig. 4. Variations of migration times of the five organophosphorus pesticides as a function of organic modifier [20 mM borate buffer (pH 9.0) 100 mM SDS, 30°C, 30 kV].

methyl ester (mecoprop-, fenoprop- and dichlorprop-methyl ester) compounds. The addition of the modifiers (methanol or acetonitrile) did not improve the separation of these; there was only a sharp micellar peak on the electropherogram. The organochlorine pesticides have higher hydrophobicities and are thus more strongly adsorbed by the micelles than are the organophosphorus pesticides.

3.3. Cyclodextrin-modified MEKC

Cyclodextrins (CD) are well known for their potential to increase the apparent aqueous solubility of low polarity compounds [39]; they can be added to CE separation buffers to increase the selectivity and efficiency of CE separations [40].

Six cyclodextrins, different in the diameter of their cavity and/or the lipophilicity of the external portion of the CD molecule were tested for their effect on MEKC-separation of the selected pesticides. For each class of pesticides the CD were systematically added to the separation buffer at different concentration (0, 10, 20, 40 and 60 mM) with and without organic solvents (methanol or acetonitrile at 0, 5, 10, 20 and 30%). Experiments with hydroxypropyl-β-cyclodextrin (HP-β-CD), as well as α-CD, β-CD, γ-CD, DM-β-CD and TM-β-CD which were already tested by the authors for optimization of the CZE

separation of phenoxy acids [13,14] showed that chiral recognition was dependant on the structure of both the CD and the pesticide.

Possible reactions occurring in the MEKC capillary are shown in Fig. 5. The addition of cyclodextrins to the buffer displaces the distribution of the pesticides from the micellar to the water phase as a function of the possible interaction between the water soluble cyclodextrins and the pesticides. Inclusion complexes can be formed if the cavity of the cyclodextrins are large enough leading in the best cases to chiral recognition of the pesticides and the separation of their enantiomers [41,42]. The addition of other chiral selectors (dextran [43], serum albumin [44], vancomycin [45] to the separation buffer can also lead to enantiomeric selectivity.

3.3.1. Organophosphorus pesticides

Good separation was obtained in 7 min for the five organophosphorus compounds by addition of DM-β-CD and TM-β-CD to the MEKC buffer, but without chiral selectivity (Fig. 6). Addition of HP-β-CD, β-CD or γ-CD resulted in separation of only three of the five pesticides. No changes in the migration times relative to MEKC without the addition of a CD occurred with even 40 mM α-CD. The cavity of the α-CD is too small to allow formation of an inclusion complex.
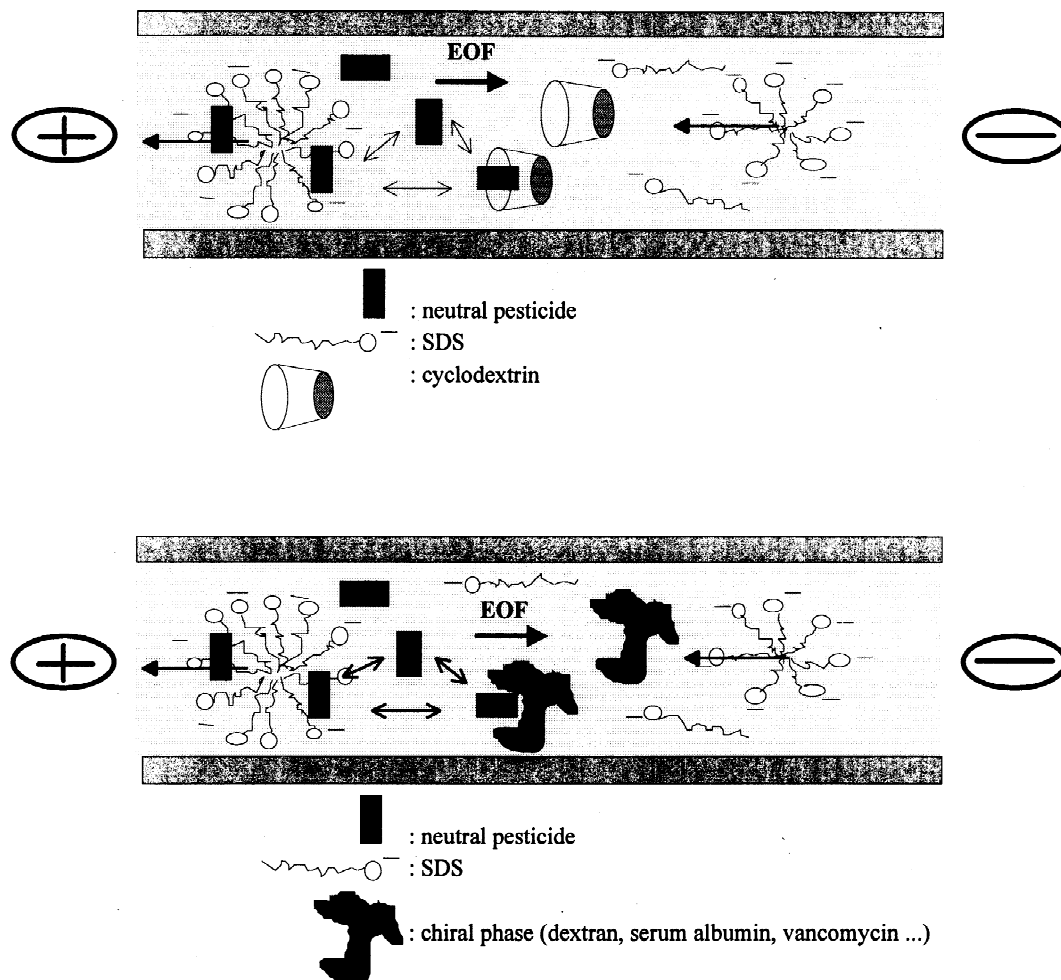
Fig. 5. Reactions occurring in the capillary during the separation of pesticides by addition of cyclodextrins or other chiral phases to the MEKC separation buffer.

The variations of the cyclodextrins, of their concentration and of addition of organic modifier allowed the few chiral separations summarized in Table 1. The best separations for malathion, ruelene and dialifos are shown in Fig. 7.

The enantiomers of isofenfos and fenamifos could not be separated under these experimental conditions. These two molecules contains more bulky groups bound to the chiral phosphorus atom than does ruelene, which is separable; this may limit formation of inclusion complexes with the cyclodextrins.

3.3.2. Phenoxy acid methyl esters

Within the experimental conditions of CD and modifier concentrations, only the γ-CD (60 mM) with 15% methanol allowed any enantiomer separation; we observed baseline separation of the three herbicides and chiral separation of fenoprop (α = 1.008) under these conditions (Fig. 8). In a previous study it was shown that the phenyl moieties of the corresponding phenoxy acids are involved in the formation of inclusion complexes with the cyclodextrins [13]; the size of the cavity of the cyclodextrins as well as that of the phenyl moiety
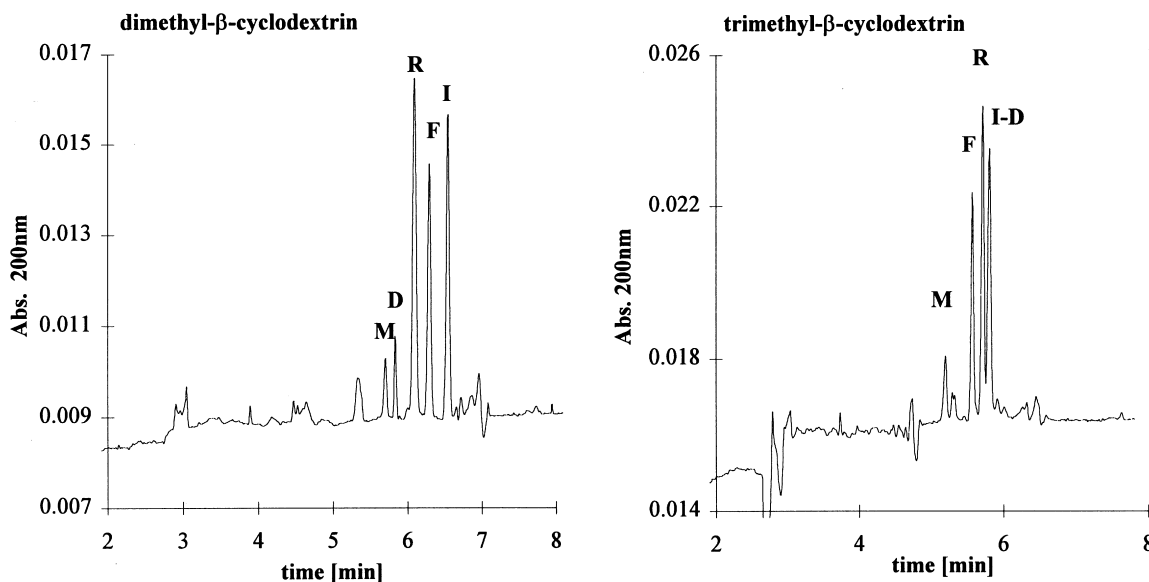
Fig. 6. Separation of the organophosphorus pesticides with addition of 40 m*M* of DM-β-CD or TM-β-CD to the MEKC buffer [20 m*M* borate buffer (pH 9.0) 100 m*M* SDS, 30°C, 30 kV].

governed the chiral separation. For successful chiral recognition with cyclodextrins, hydrophobic interactions between the cavity interior and the analytes are assumed, whereas hydrogen bonding at the cavity edge presumably determines a compound's access to the cavity entrance [46]. Partitioning of the methyl esters to the CD is probably of a different nature than that of the corresponding acids; the alkyl moieties of

Table 1
Best CD–methanol combination for chiral separation of the organophosphorus pesticides

Pesticide	CD (conc.)	Methanol %	α^{a}
Malathion	γ-CD (40 m*M*)	15%	1.013
	HP-β-CD (65 m*M*)	None	1.014
Ruelene	α-CD (40 m*M*)	15%	1.007
	β-CD (40 m*M*)	15%	1.006
	DM-β-CD (40 m*M*)	15%	1.024
	HP-β-CD (60 m*M*)	20%	1.009
Dialifos	γ-CD (40 m*M*)	None	1.039
	γ-CD (40 m*M*)	10%	1.057
Isofenfos	None	–	–
Fenamifos	None	–	–

[a] $\alpha = t_{\text{R2}}/t_{\text{R1}}$, where R1 and R2 are the migration times of the later-eluting peak and the first peak, respectively.

the esters may also be involved in the inclusion complex without possible chiral recognition.

3.3.3. DDT congeners

The goal here was to develop an analytical technique for the simultaneous separation of p,p′-DDT, p,p′-DDD, p,p′-DDE, o,p′-DDE and the enantiomers of o,p-DDT and o,p-DDD. Although these compounds and enantiomers have been efficiently separated by high-resolution gas chromatography (HRGC), that technique requires special capillary columns that are not commercially available [5,47].

A mixture of the six compounds was first analysed after addition of each cyclodextrin at a concentration of 40 m*M* to the MEKC buffer. Partial separation only was achieved with γ-CD, DM-β-CD and β-CD; the other cyclodextrins did not show any improvement in separation even with addition of solvents, only the micellar peak was seen on the electropherograms.

Chiral recognition of o,p′-DDT and o,p′-DDD was possible only with the γ-CD. The enantiomeric separation of o,p′-DDT, expressed as α (ratio of the migration times of the two enantiomers), is given in Fig. 9 as a function of the concentration of γ-CD and
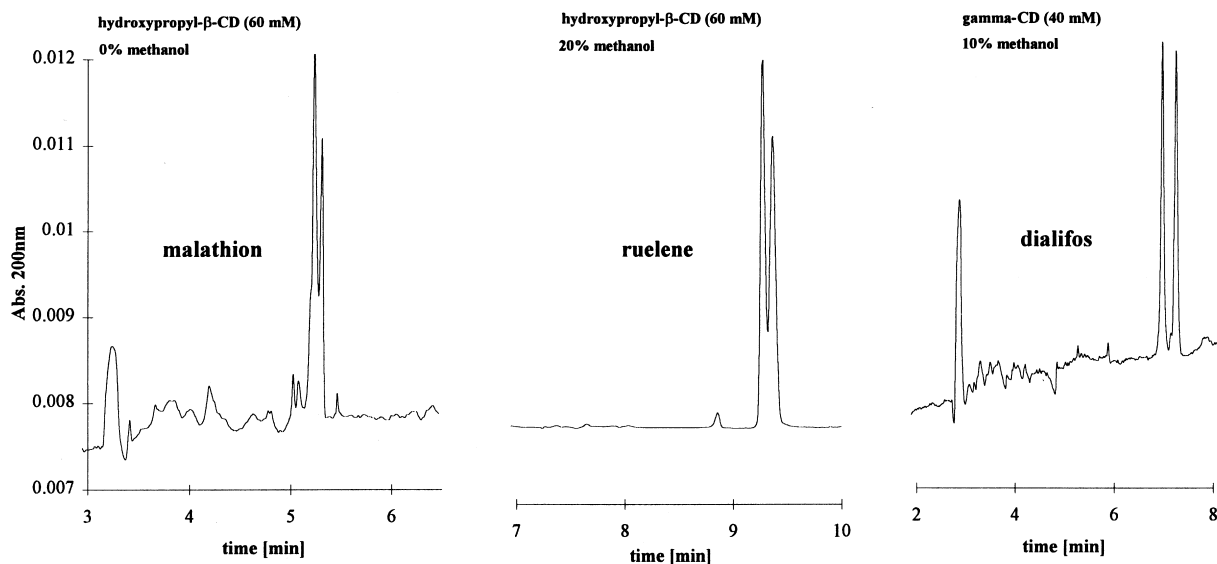
Fig. 7. Enantioselective separations by CD-MEKC of malathion, ruelene and dialifos [20 m*M* borate buffer (pH 9.0) 100 m*M* SDS, 30°C, 30 kV].

methanol in the separation buffer. The best separation is achieved with 40 m*M* γ-CD and 20% methanol.

As already shown with the organophosphorus insecticides, the addition of acetonitrile allows better selectivities at lower concentrations than with metha-

Fig. 8. Electropherogram of the best CD-MEKC separation of mecoprop-, fenoprop- and dichlorprop methyl esters with addition of 60 m*M* γ-CD and 15% methanol [20 m*M* borate buffer (pH 9.0) 100 m*M* SDS, 30°C, 30 kV].

nol. Examples of separation of the DDT compounds are shown in Fig. 10. The best separation for a mixture of all six compounds was achieved with 20 m*M* γ-CD, 20% acetonitrile and 50 m*M* SDS at 25°C and 25 kV.

3.3.4. Metolachlor

Metolachlor, an acetamide herbicide, consists of four stereoisomers (Fig. 1) resulting from axial chirality (hindered rotation about the phenyl-nitrogen and asymmetric substitution of the phenyl ring) and
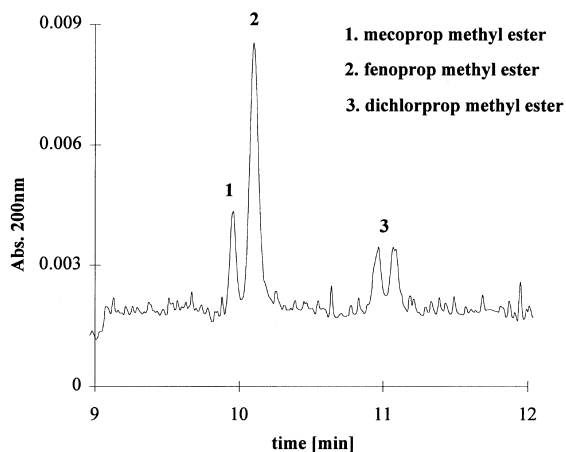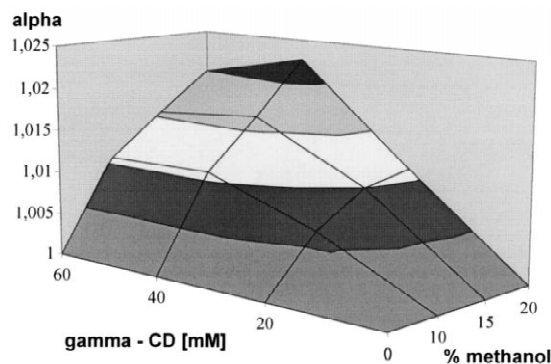

Fig. 9. Enantiomeric separation of o,p′-DDT (expressed by alpha) as a function of the concentrations of γ-CD and methanol.

40 mM gamma CD, 0% acetonitrile

20 mM gamma CD, 10% acetonitrile

20 mM gamma CD, 20% acetonitrile

20 mM gamma CD, 20% acetonitrile, 50 mM SDS

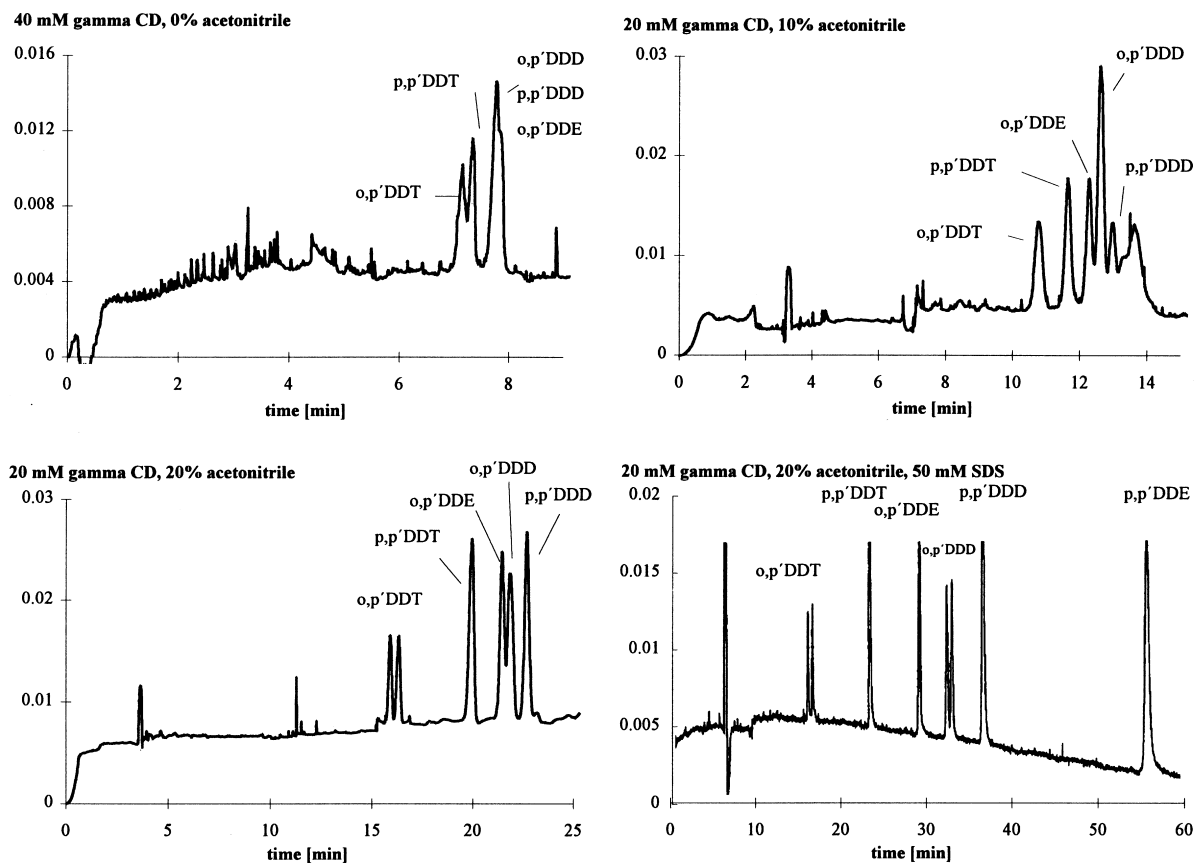Fig. 10. Separation of p,p′-DDT, p,p′-DDD, o,p′-DDE, p,p′-DDE and the enantiomers of o,p′-DDT, o,p′-DDD as a function of the addition of γ-CD and acetonitrile to the separation buffer; (a), (b) and (c) with 20 mM borate buffer (pH 9.0) 100 mM SDS, 30°C, 30 kV, (d) with 20 mM borate buffer (pH 9.0) 50 mM SDS, 25°C, 20 kV.
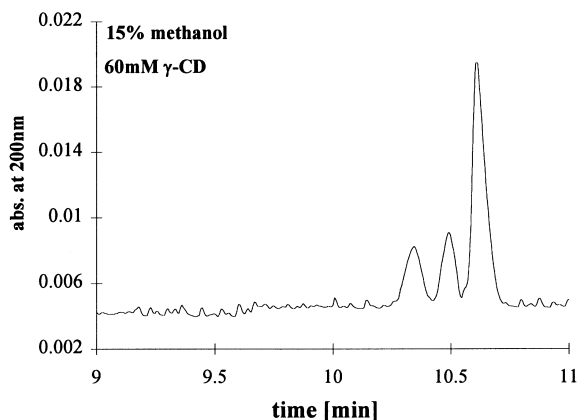

Fig. 11. Separation by CD-MEKC of three of the four isomers of metolachlor [20 mM borate buffer (pH 9.0) 100 mM SDS, 30°C, 30 kV].

C-chirality (asymmetrically substituted carbon-atom in the N-alkyl moiety). With chiral HRGC and high-performance liquid chromatography (HPLC) three of the four isomers could be analysed but without baseline separation [4]. Capillary electrophoresis by CD-MEKC gives better separation of three of the four isomers, as shown in Fig. 11.

4. Conclusions

Highly hydrophobic compounds such as DDT and many other pesticides absorb so strongly to the micelles in MEKC that the addition of organic modifiers such as methanol or acetonitrile is required for their separation from the micelle and from other

analytes. For chiral separation, cyclodextrin selectors along with the modifier usually provide at least some enantiomeric resolution. Good separation was shown here, for example, for six DDT congeners and their enantiomers and for several organophosphorus pesticides and some of their enantiomers. Enantiomeric separation by CD-MEKC is often superior to that obtained by HRGC or HPLC, and is much simpler in operation. However, the sensitivity of CD-MEKC with most pesticides is considerably less than that of classical chromatographic methods (ppm levels of sample needed as compared to ppb levels in routine applications with HRGC or HPLC). Its application to studies of most chiral chemistry in the environment will be limited until more sensitive detectors are developed.

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