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Journal of Chromatography A, 790 (1997) 225–234

JOURNAL OF CHROMATOGRAPHY A

Enantiomeric and isomeric separation of herbicides using cyclodextrin-modified capillary zone electrophoresis

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Received 26 March 1997; received in revised form 10 June 1997; accepted 3 July 1997

Abstract

Cyclodextrin-modified capillary zone electrophoresis (CD-CZE) was applied successfully to the enantiomeric and isomeric separation of three herbicides (imazaquin, diclofop and imazamethabenz). Commercially available cyclodextrins were evaluated for separation of the enantiomers and isomers of the three herbicides having varied molecular structures. The enantiomers of imazaquin and diclofop, and the isomers of imazamethabenz could be resolved with a resolution of ≥ 1.5. The resolution was found to depend on pH of the run buffer, cyclodextrin type and cyclodextrin concentration. By employing mixed cyclodextrins in the running buffer, the three herbicides were simultaneously separated in a single run. In addition, rapid (less than 3 min) enantiomeric separation is demonstrated using imazaquin as a model herbicide. The reported capillary electrophoresis (CE) methods are simple, rapid, efficient and reproducible and our results demonstrate that CE provides a powerful analytical tool for enantiomeric and isomeric separation of herbicides. © 1997 Elsevier Science B.V.

Keywords: Enatiomer separation; Pesticides; Imazaquin; Diclofop; Imazamethabenz

1. Introduction

About 25% of compounds used in the agrochemical industry contain chiral centers and are produced and used as racemic mixtures [1]. These compounds usually show enantiomeric selectivity, with biological activity generally residing in only one of the enantiomers. It was shown, for example, that only the (+)-isomers of dichlorprop, mecoprop and diclofop-methyl are herbicidally active [2]. In addition, when racemic mixtures are applied, they often are degraded in the environment at different rates [3,4]. This enantioselective phenomena has important implications in the manufacture and use of chiral agrochemicals. Thus, separation and identification of the desired isomer is essential during the discovery of such compounds and also to support a product through development, registration and production (quality assurance). A few HPLC and GC methods have been reported for analysis of chiral agrochemicals [5–10]. These methods have proved to be effective for chiral separations but have two main disadvantages: (1) relatively expensive chiral columns are required for analysis and (2) many different types of columns are required for analysis of several chiral compounds.

The recent advent of capillary electrophoresis (CE) provides a powerful analytical tool for highly efficient separations of chiral compounds compared to more conventional chromatographic techniques.

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0021-9673/97/$17.00
PII S0021-9673(97)00765-6

The inherent ability of CE to provide high separation efficiencies combined with rapid method development and minimal use of expensive chiral reagents makes it an ideal technique for chiral separations. CE has been used extensively for separation of drug enantiomers [11–16]. In contrast, only a handful of reports describe the use of CE for separation of chiral agrochemicals [17–19].

In this study, we investigate the use of commercially available cyclodextrins (CDs) for capillary electrophoretic separation of the enantiomers and isomers of three commonly used herbicides (imazaquin, diclofop and imazamethabenz). Imazaquin and imazamethabenz belong to the imidazolinone family of herbicides. The imidazolinones are a new class of low-use-rate, reduced-environmental-risk herbicides for protection of a wide variety of agricultural crops. Imazaquin (Scepter) can be applied as a preemergence or postemergence herbicide for control of weeds in soybeans. It is applied at a rate of 56.7 g acid equivalent/4047 m^2. Imazamethabenz (Assert) is applied as a postemergence herbicide for control of weeds in wheat and barley. It is applied at a rate of 141 to 218 g active ingredient/4047 m^2. The herbicidal activity of imidazolinones resides in the (*R*)-enantiomer, and it was shown that the (*R*)-enantiomer is about eight-times more active than the (*S*)-enantiomer [20]. Diclofop (Hoelon) belongs to aryloxyphenoxy propionate family of herbicides. It is applied as a postemergence herbicide for control of weeds in wheat and barley. It is applied at a rate of 227 to 454 g active ingredient/4047 m^2. The use of racemic mixtures of these herbicides is not a problem; however, if the active isomer is used alone, smaller quantities can be applied to crops, thereby reducing the environmental load. Because, these herbicides are gaining in popularity for weed control, we decided to use them as model compounds for separation by CE.

In this study, the importance of parameters such as pH of run buffer, CD type and CD concentration, in optimizing resolution of the three herbicides are investigated. Finally, rapid (2 to 3 min) enantiomeric separation is demonstrated for imazaquin. To our knowledge this is the first report describing the use of CD-capillary zone electrophoresis (CZE) for separation of imazaquin and diclofop enantiomers and imazamethabenz isomers.

2. Experimental

2.1. Materials

Imazaquin (99%) was obtained from Chem Service (West Chester, PA, USA). Diclofop (97.5%) was a generous gift from AgrEvo USA Company (Pikeville, NC, USA). Imazamethabenz (96.6%) was a generous gift from American Cyanamid Company (Princeton, NJ, USA). Heptakis(2,6-di-O-methyl)-β-cyclodextrin (DM-β-CD), Heptakis(2,3,6-tri-O-methyl)-β-CD (TM-β-CD) and all buffers were obtained from Sigma (St. Louis, MO, USA). 2-Hydroxypropyl-γ-cyclodextrin (HP-γ-CD) was obtained from Fluka (Buchs, Switzerland). The fused-silica column used for CE was obtained from Polymicro Technologies (Phoenix, AZ, USA).

2.2. Apparatus

A Beckman P/ACE 2200 (Fullerton, CA, USA) unit equipped with ultraviolet detection was employed for CE analysis. The capillary used for separation was 50 μm I.D. housed in a cartridge configured for UV detection. The length of the capillary was either 57-cm long (50-cm to detector) or 27-cm long (20-cm to detector). Standard injections were made using pressure injection (3.45 kPa) for 2 s, corresponding to an injection volume of 2.4 nl. The separations were performed at 25°C and the separation voltage was 25 kV. All operations of the P/ACE unit were controlled by an IBM personal computer with Beckman Gold Software. At the beginning of each day the capillary was rinsed with 0.1 *M* NaOH for 10 min, followed by 5 min with deionized water and 15 min with run buffer. Before each standard injection, the capillary was rinsed for 2 min with 0.1 *M* NaOH followed by 2 min with run buffer. At the end of each day, the capillary was rinsed with 0.1 *M* NaOH for 10 min followed by 5 min with deionized water. When the instrument was not in use, the electrodes were left immersed in deionized water.

2.3. Preparation of buffers and herbicide standards

The electrophoresis buffers were prepared by

dissolving appropriate amounts of sodium acetate and CD in water and adjusting the pH with 1.0 *M* acetic acid. All buffers were filtered through a 0.45 μm filter before use. The description of each buffer used is given under the appropriate figure legend.

The stock solutions of the herbicides were prepared in methanol at a concentration of 1 mg/ml. Working standards were prepared by making a 1 to 10 dilution of the stock solution in methanol to obtain a concentration of 100 μg/ml. This working standard was used directly for CE analysis. A 10 μg/ml standard was used for determining detection limits and to carry out reproducibility studies. The stock and working standards were stored in the dark at −20°C.

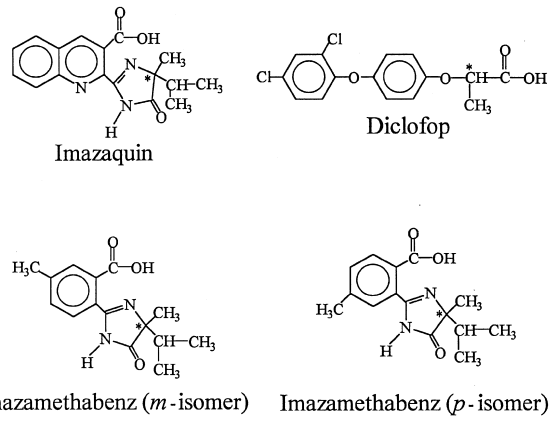

Fig. 1. Structures of herbicides; chiral center is indicated with an asterisk (*).

3. Results and discussion

CDs make extremely versatile chiral selectors for CE because they have numerous chiral recognition centers. CDs are oligosaccharides with truncated cylindrical molecular shapes. Their outside surfaces are hydrophilic, while their cavities are hydrophobic [21]. Details of CDs and mechanisms of interaction with chiral molecules have been extensively studied and reported in the literature [22,23]. In this study, we investigated the effect of pH and CD type and concentration on the enantiomeric and isomeric separation of three commonly used herbicides. The structures of the herbicides investigated in this study are shown in Fig. 1. Imazaquin and diclofop are chiral and each have a pair of enantiomers [2,24]. Imazamethabenz is a 3:2 mixture of *para* and *meta* isomers [24]. The pK_a values for imazaquin, diclofop and imazamethabenz are 3.8, 3.6 and 2.9, respectively [24]. The resolution (R_s) of enantiomers/isomers was calculated using the equation [25]

$$R_s = 2\Delta t_r/(W_1 + W_2) \quad (1)$$

where Δt_r is the difference in migration times and W is the peak width at the peak base.

3.1. Effect of run buffer pH on enantiomeric and isomeric separations

The pH of the run buffer influences the ionic state at the capillary wall, thereby altering electroosmotic flow (EOF). At acidic pH the EOF is decreased. If one enantiomer has a greater stability constant with the CD, it will migrate more slowly and chiral resolution is improved. In addition, it has been shown that in CD-based CE separations, chiral selectivity varies according to three fundamentally different situations depending on whether (a) only the non-dissociated, (b) dissociated or (c) both forms of the two enantiomers interact differently with CD [26]. Thus, pH of the running buffer can significantly influence the chiral selectivity in CD-CZE [13]. We optimized the separation of our herbicides by varying the pH of the run buffer from 3.6 to 5.6. Fig. 2 shows the influence of pH on the resolution of imazaquin and diclofop enantiomers, and imazamethabenz isomers. A 50 m*M* sodium acetate buffer (pH 3.6 to 4.6) gave the best separation; higher pH acetate buffers decreased resolution. This could be due to increased EOF at higher pH [13] and/or a decrease in the differential interaction of the enantiomers with the CD as the fraction of the conjugate-base form increases at higher pH. If the latter was happening one might expect a decrease in resolution at lower pH values than we observed in Fig. 2, that is below the listed pK_a values. However, the apparent pK_a values of the herbicides could shift to higher values when complexed to the CD, as is often the case with complexation by micelles [27,28]. Regardless of the underlying mechanism, it is apparent from this study that at pH 3.6 and 4.6, the

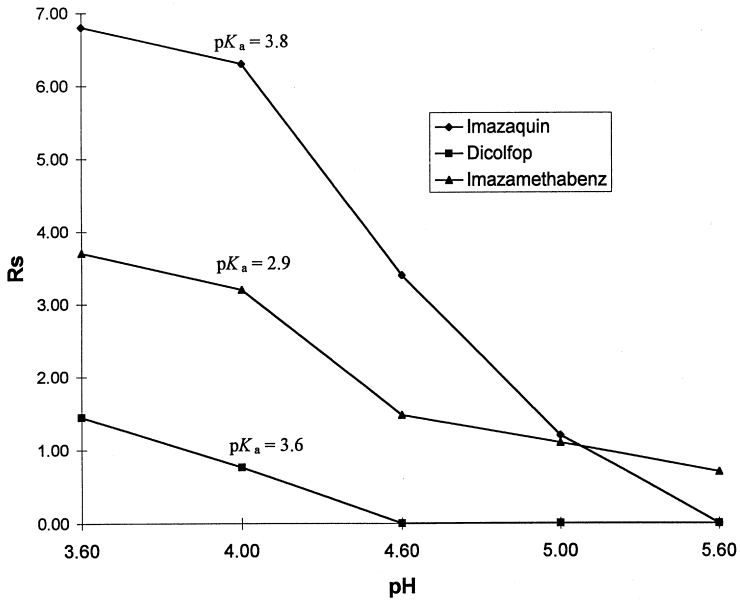

Fig. 2. Resolution of herbicide enantiomers and isomers as a function of pH. Analysis conditions: as in Fig. 3.

EOF is reasonably small, efficiency is high, and selective interaction with the CDs are evident, producing baseline separation of the enantiomers and isomers of these compounds.

3.2. Effect of CD type on enantiomeric and isomeric separations

Enantiomeric separations with CDs often hinge on favorable interactions between analytes and the CD cavity. The diameter of the CD cavity varies with the number of glucose units in the ring. The work reported herein illustrates the importance of the type of CD employed for analysis of the model herbicides. We evaluated DM-β-CD, TM-β-CD and HP-γ-CD for separation of the enantiomers of imazaquin and diclofop, and the isomers of imazamethabenz. Table 1 summarizes the separation of the three herbicides using the three different CDs. The buffer consisted of 50 m*M* sodium acetate with 10 m*M* of DM-β-CD or TM-β-CD or HP-γ-CD, pH 3.6 or 4.6. In the case of imazaquin, baseline resolution of the two enantiomers was obtained only with DM-β-CD. The other two CDs were not successful in resolving

Table 1
Effect of cyclodextrin type on enantiomeric and isomeric separation of herbicides[a]

Compound	DM-β-CD			TM-β-CD			HP-γ-CD		
	t_r	α	R_s	t_r	α	R_s	t_r	α	R_s
Imazaquin	9.89 10.23	1.053	3.40	10.60	1.000	ns	10.64	1.000	ns
Diclofop	7.81	1.000	ns	16.15 16.40	1.030	1.50[b]	8.07	1.000	ns
Imazamethabenz	9.57	1.000	ns	9.49 9.65	1.030	1.50	9.48 9.59	1.019	1.10

[a] 50 m*M* sodium acetate + 10 m*M* CD, pH 4.6.
[b] pH 3.6; ns, no separation; t_r, migration time in minutes; α (selectivity) = μ_2/μ_1 (where, μ_2 and μ_1, are the electrophoretic mobilities of enantiomer 2 and 1, respectively); R_s, resolution.

the enantiomers of imazaquin. Similarly, baseline resolution of diclofop was obtained only with TM-β-CD at pH 3.6. At pH 4.0, partial resolution (R_s 0.76) of the enantiomers was obtained and no resolution was obtained when the pH was increased above 4.0. In addition, no resolution of diclofop was obtained with either DM-β-CD or HP-γ-CD. The isomers of imazamethabenz were baseline resolved with 10 m*M* TM-β-CD. Partial resolution of imazamethabenz isomers (R_s 1.10) was obtained with HP-γ-CD and no separation was obtained with DM-β-CD. Fig. 3 shows the separation of imazaquin and diclofop enantiomers and imazamethabenz isomers by CD-CZE. The absolute confirmation of the (+) and (−) enantiomers of imazaquin and diclofop was not carried out because the pure enantiomers were not available to us.

Both the cavity size and hydrogen bonding and/or hydrophobic interactions at the larger lip of the truncated CDs may play a role in complexation with the herbicides used in this study [21,25,29]. We calculated the molecular volumes of our herbicides using Molecular Modeling Pro (WindowChem Software, Fairfield, CA, USA). The molecular volumes for diclofop, imazaquin and imazamethabenz were 260 $Å^3$, 273 $Å^3$ and 249 $Å^3$, respectively. The cavity volume of β-CDs and γ-CDs is about 262 $Å^3$ and 427 $Å^3$, respectively [30]. In addition, the cross sectional areas of the three herbicides (in many orientations) are similar to the opening of the β-CDs. Among the three CDs, only the derivatized β-CDs were able to separate the enantiomers/isomers of the herbicides because the size similarity of the herbicides and the β-CDs apparently results in a ''snug fit'' and stronger inclusion complexation. However, the fact that imazaquin racemate is separated only by DM-β-CD and diclofop racemate is separated only by TM-β-CD, which have the same cavity volume, implies an additional complexation mechanism. The isomers of imazamethabenz are separated by TM-β-CD and to a small extent by HP-γ-CD, but not at all by DM-β-CD. This apparent anomaly also implies an additional interaction mechanism. These results suggest that, cavity size of CD alone does not determine whether there is sufficient difference in the complexation constants of the *R* and *S* isomers of the herbicides to cause separation. The exact mechanism of interaction of our test solutes with the different CDs is not known at this point. Nuclear magnetic resonance (NMR) experiments will have to be conducted to fully understand the actual interaction of the herbicides used in this study with the different CDs [23].

3.3. Effect of CD concentration on enantiomeric separations

The concentration of the CD in the mobile phase affects the enantiomeric resolution [13]. We conducted experiments to determine the effect of CD concentration on the resolution of imazaquin enantiomers. Fig. 4 is a plot of the experimentally determined mobilities of imazaquin enantiomers as a function of DM-β-CD in the mobile phase. At low (2 m*M*) concentration, mobilities are similar and no enantiomeric resolution was obtained for the enantiomers. As the CD concentration increases, enantiomer 1 increasingly finds enantiomerically favorable interaction with the neutral CD, thereby decreasing its negative mobility. The differences in mobility of the two enantiomers was sufficient at 10 m*M* CD concentration, resulting in baseline resolution of the two enantiomers. Higher concentrations of CD (up to 20 m*M*) resulted in an increase in the resolution of the enantiomers with a slight increase in migration time, which is probably due to an increase in the viscosity of the buffer at higher CD concentrations thus, decreasing the mobility of the analyte [31]. We also found that CD concentrations higher than 20 m*M* did not give us any significant improvement in resolution.

3.4. Separation of imazaquin and diclofop enantiomers, and imazamethabenz isomers by mixed CDs

We observed during our experiments that various CDs exhibited different selectivity toward the three model herbicides. These results suggest that running buffers composed of mixed CDs should yield a unique selectivity that cannot be achieved by either of the CDs alone. Experiments were conducted to investigate the enantiomeric and isomeric separation of the herbicides with electrolyte systems composed of DM-β-CD and TM-β-CD. The enantiomers of imazaquin and diclofop, and the isomers of im-

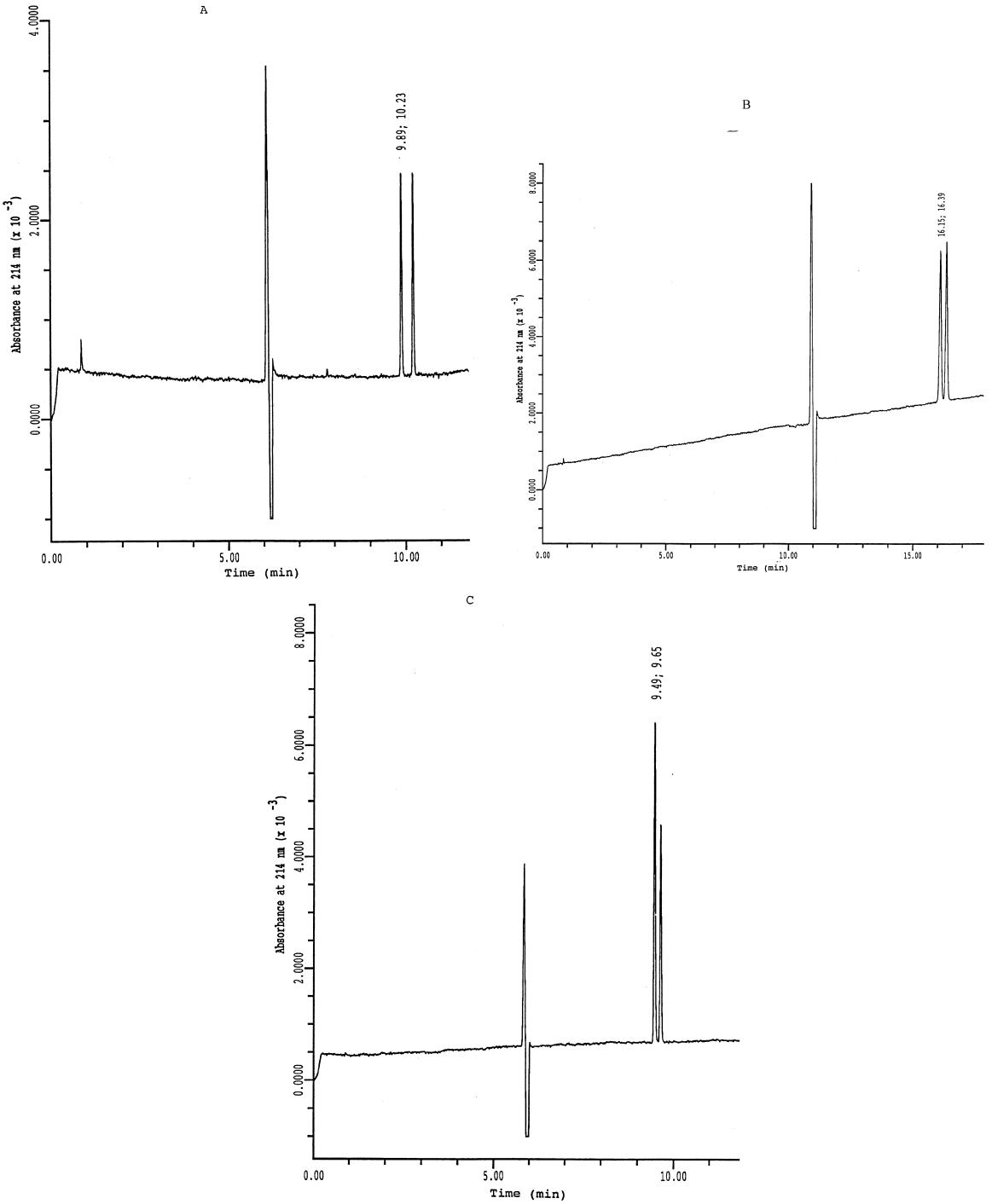

Fig. 3. Separation of (A) imazaquin enantiomers, (B) diclofop enantiomers and (C) imazamethabenz isomers (9.49 min, *para* and 9.65 min, *meta* isomers) Analysis conditions: 57 cm (50 cm to detector)×50 μm I.D. capillary column; pressure injection (2 s=2.4 nl); 25 kV (35 μA); 214 nm UV absorbance. Buffer: (A) 50 m*M* sodium acetate+10 m*M* DM-β-CD buffer, pH 4.6, (B) 50 m*M* sodium acetate+10 m*M* TM-β-CD buffer, pH 3.6 and (C) 50 m*M* sodium acetate+10 m*M* TM-β-CD buffer, pH 4.6.

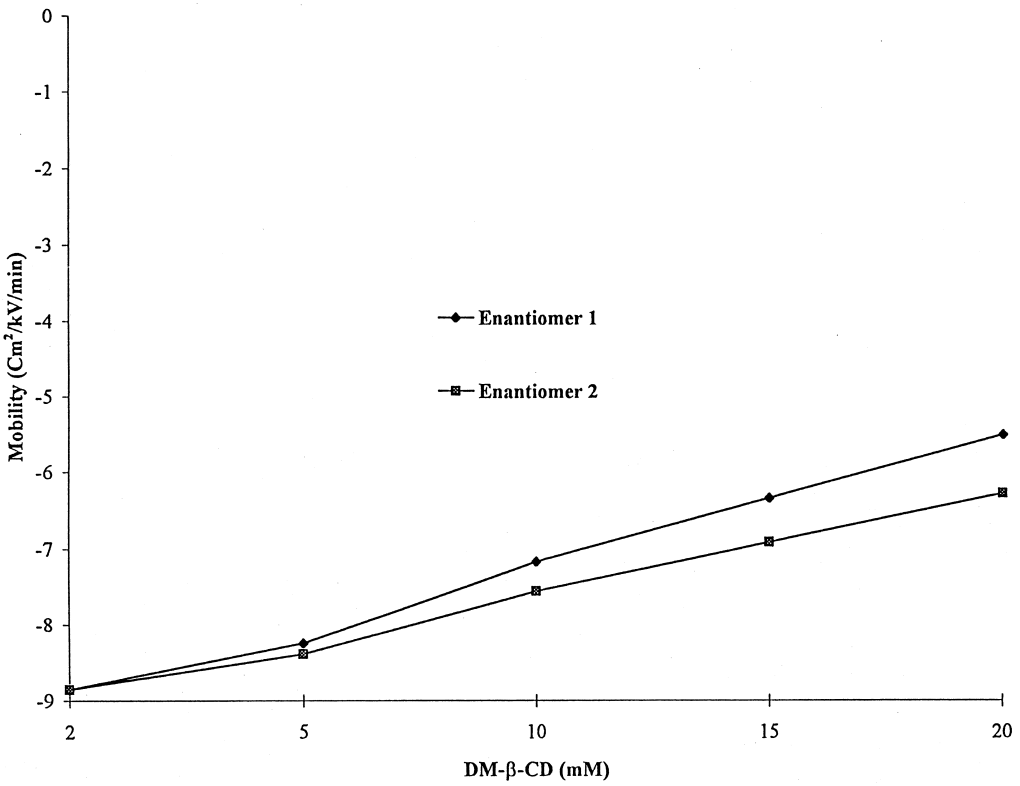

Fig. 4. Plot of the observed mobility of imazaquin enantiomers as function of DM-β-CD concentration. Other conditions as in Fig. 3.

azamethabenz were simultaneously separated in a single run using a buffer consisting of 50 m*M* sodium acetate + 10 m*M* DM-β-CD + 10 m*M* TM-β-CD (pH 3.6), as shown in Fig. 5.

3.5. Detection and reproducibility of the enantiomers/isomers

Detection limit and reproducibility studies were conducted using a 10 μg/ml standard of the herbicides. Detection limits were calculated for a signal-to-noise ratio of 3 and were 10 μg/ml for imazaquin, diclofop and imazamethabenz. This corresponds to an injection on-column of about 24 pg of each herbicide. The detection limits for these herbicides using CE with ultraviolet detection are comparable to those obtained for other herbicides using CE in our previous investigations [32]. The reproducibility of migration times and peak area was tested by repeated injections of a 10 μg/ml standard. The results indicate good reproducibility and quantitative accuracy of the method (Table 2). The reproducibility of migration times and peak areas are comparable to those obtained for other herbicides using CE in our previous research projects [32,33] and by other investigators [34,35].

3.6. Rapid analysis by CD-CZE

Rapid separations (analysis times on the order of 2 to 3 min) can be readily attained in CE. Parameters such as applied voltage, capillary length and internal diameter are critical in determining the speed and quality of separation [36]. A high EOF is required to rapidly transport the analytes through the capillary to the detector window. In CZE, the EOF usually increases with an increase in the applied voltage. Rapid separations in CE, can be carried out in relatively short capillaries with narrow internal diameter. We used a 27 cm (20 cm to detector) × 50 μm

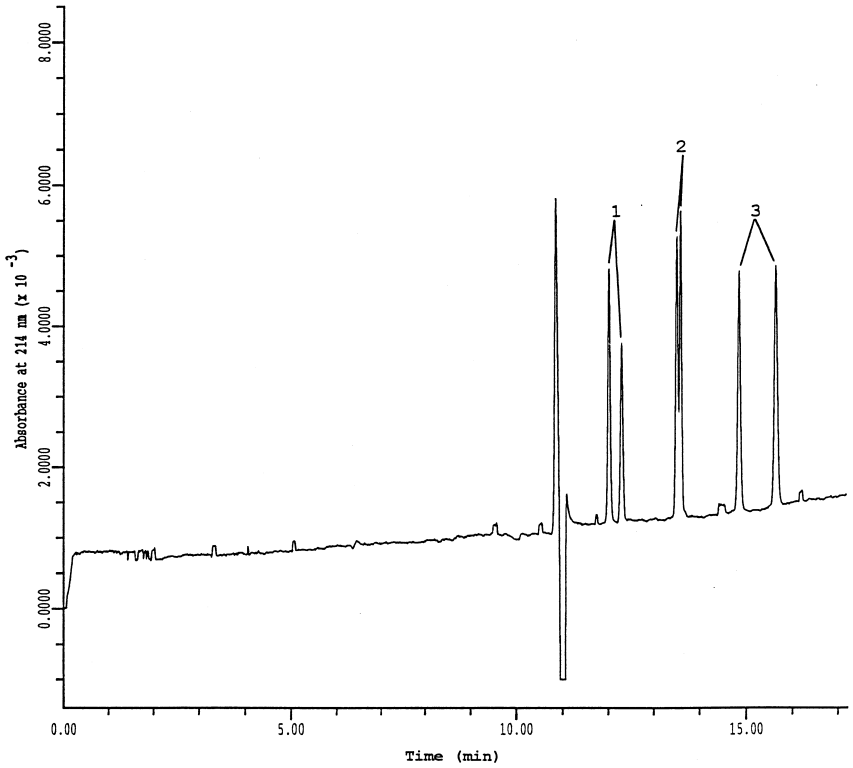

Fig. 5. Simultaneous separation of herbicides using mixed cyclodextrins. (1) Imazamethabenz isomers, (2) diclofop enantiomers and (3) imazaquin enantiomers. Analysis conditions: 57 cm (50 cm to detector)×50 μm I.D. capillary column; pressure injection (2 s=2.4 nl); 50 m*M* sodium acetate+10 m*M* DM-β-CD+10 m*M* TM-β-CD buffer, pH 3.6; 25 kV (35 μA); 214 nm UV absorbance.

I.D. capillary column to obtain rapid separation of imazaquin enantiomers, as shown in Fig. 6A. By decreasing the length of the capillary from 57 cm to 27 cm, the analysis of imazaquin was complete under 3 min with baseline resolution of the two enantiomers. The analysis time for imazaquin was less than 12 min to begin with when a 57 cm long capillary was used. We were able to decrease the analysis time even further by simply using a shorter capillary, saving about 8 min in analysis time. We used a similar approach to obtain rapid simultaneous separation of the three herbicides used in this study. Fig. 6B shows the rapid simultaneous separation for the three herbicides using mixed CDs in the running buffer. The analysis was complete under 6 min; however, the *R* and *S* enantiomers of diclofop coeluted under these experimental conditions.

Table 2
Reproducibility of CE data for herbicide enantiomers and isomers.

Herbicide	Migration time (min)	Peak area
Imazaquin	9.59[a]±0.07	0.00908±0.001
	9.88[b]±0.07	0.00865±0.001
Diclofop	16.28[a]±0.15	0.03561±0.001
	16.47[b]±0.15	0.03400±0.001
Imazamethabenz		
p-isomer	9.60±0.01	0.01607±0.001
m-isomer	9.74±0.02	0.01123±0.001

Data are mean±S.D. of six injections of 10 μg/ml concentration, 2.4 nl injection volume.
[a] First eluting enantiomer.
[b] Second eluting enantiomer.

A potentially important application of rapid CD-CZE separations is during the discovery and development of chiral agrochemical and pharmaceutical compounds. In the pharmaceutical and agrochemical industry, optical purity assessment is routinely carried out for a number of chiral compounds.

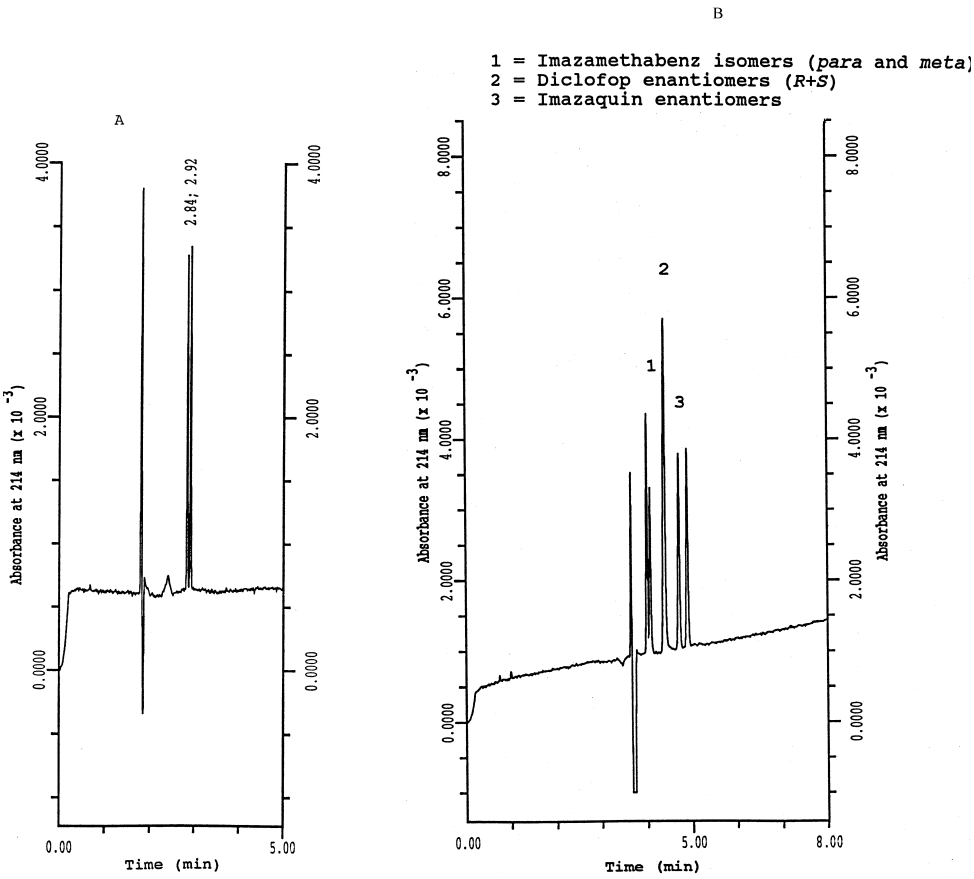

Fig. 6. (A) Rapid separation of imazaquin enantiomers and (B) rapid simultaneous separation of the three herbicides. Analysis conditions: 27 cm (20 cm to detector)×50 μm I.D. capillary column; pressure injection (1 s=2.4 nl); 12 kV (36 μA); 214 nm UV absorbance. Buffer: (A) 50 m*M* sodium acetate+10 m*M* DM-β-CD, pH 4.6 and (B) 50 m*M* sodium acetate+10 m*M* DM-β-CD+10 m*M* TM-β-CD, pH 3.6.

This is especially important in situations where one enantiomer elicits undesirable physiological response or has toxic effects in the case of drugs or one enantiomer elicits toxic effects to non-target species in the case of agrochemicals. Thus, the application of rapid CD-CZE separations for determining the optical purity of chiral agrochemical and pharmaceutical compounds shows great promise.

4. Conclusions

Enantiomeric and isomeric separations of three commonly used herbicides with varied molecular structures were successfully performed by CD-CZE. The resolution was found to depend on pH of the run buffer, CD type and CD concentration. Reproducibility of migration times and peak area for the three herbicides using CE was good. In addition, rapid CD-CZE separation was demonstrated for enantiomers of imazaquin. Our results from this study clearly demonstrate that CE provides a powerful analytical tool for enantiomeric and isomeric separation of agrochemicals. We believe, the application of CE for chiral separations in the agrochemical industry shows significant potential in the near future.

Acknowledgements

The authors wish to acknowledge United States

Environmental Protection Agency and United States Fish and Wildlife Service for financial support. The authors would like to thank Dr. John Schupner at AgrEvo USA Company for his help in obtaining the standard of diclofop and Dr. Hans Nejad and Dr. Maximilian M. Safarpour at American Cyanamid Company for their help in obtaining the standard of imazamethabenz. The authors would also like to thank Stephen E. Graham for helping with Molecular Modeling. K.V.P. is the recipient of The United States Environmental Protection Agency Pre-Doctoral Fellowship. The use of trade names does not imply endorsement by the North Carolina Agricultural Research Service of the products named or criticism of similar ones not mentioned.

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