Characterization of racemization of chiral pesticides in organic solvents and water

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ARTICLE INFO

Article history:

Received 26 March 2010

Received in revised form 3 July 2010

Accepted 10 July 2010

Available online 16 July 2010

Keywords:

Chiral pesticides
Chiral stability
Racemization
Organic solvents
Enantioselectivity

ABSTRACT

Eight chiral pesticides, which were selected to cover different pesticide species and origins of chirality, were investigated to explore their chiral stability in organic solvents and water. Profenophos, fenamiphos, quinalofop-ethyl, dichlorprop-methyl (DCPP-methyl) and acetochlor were showed stable under all test conditions. However, significant racemization was observed for malathion, phenthoate and fenpropathrin in methanol, ethanol and water, but not in *n*-hexane, isopropanol, acetone or methylene chloride. The kinetic parameters (rate constant *k* and half-life $T_{1/2}$) of the abiotic racemization were calculated through a mathematical model of the first-order reaction. Furthermore, the extent of racemization varied among the solvents and was also affected by temperature dependence. The racemization of malathion, phenthoate and fenpropathrin in water was documented to be pH-dependent and took place more rapidly at pH 7.0 than at pH 5.8. The observed racemization was deduced to occur via a proton exchange process at the chiral center, and the relationship between the abiotic racemization and pesticide structure was further explored. Findings from this study are useful for better understanding enantioselectivity of chiral pesticides in environment and also for proper analysis, formulating or handling of enantiopure products.

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1. Introduction

Chiral pesticides account for more than a quarter of currently used pesticides and this ratio is still increasing [1]. According to the number of chiral centers in the structure, a chiral pesticide may consist of two or multiple enantiomers or stereoisomers. Different enantio-/stereoisomers of a chiral pesticide often exhibit different biological property, toxicity and metabolism behavior in the environment, and the pesticidal activity of a chiral pesticide usually resides in one or several enantio-/stereoisomers [2]. To lower application rates and thus smaller amounts of chemicals released into the environment, efforts are being made to replace pesticide racemates (i.e., mixtures of enantio-/stereoisomers) by single biologically active enantio-/stereoisomer or enantio-/stereoisomerically enriched compounds [3,4]. The enantio-/stereoisomer-specific profiles of chiral pesticides have become important topics at the forefront of chemistry and toxicology research [5–7].

More recently, studies have shown that under certain conditions some chiral pesticides were configurationally unstable

and could undergo significant isomer conversion. For instance, some pyrethroids, such as cypermethrin and cyfluthrin, were found to epimerize at the asymmetric carbon in the benzylic moiety (i.e., α -carbon chiral center) in short-chain alkyl alcohols (e.g., methanol and ethanol) or in water-alcohol mixtures [8–11]. It is obvious such conversion would reduce the efficacy of biologically active enantio-/stereoisomer due to the formation of nonactive enantio-/stereoisomer, and even make the use of enantio-/stereopure product pointless when conversion is fast enough. Moreover, as alcohols and water are often used in sample extraction, storage and analysis processes, isomer conversion may occur, causing analytical biases in chiral selective analysis. Potential isomer conversion must be considered significantly to ensure accurate and rigorous data from sample preparation and separation processes.

Researchers have observed interconversion between enantiomers in solvents for many chiral compounds with different stereolabile units [12–16]. The interconversion profiles can be determined by classical interconversion experiments of single enantiomers or by dynamic and stopped-flow chromatographic techniques. Assuming that the conversion between a pair of enantiomers was a process of equilibrium and the conversion in both directions obeyed first-order kinetics, the following equations can describe the dissipation of the starting enantiomer and the forma-

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Fig. 1. Chemical structures of chiral pesticides (* indicates chiral position).

tion of the converted enantiomer [9,16,17]:

$$C_1 = 0.5C_0(1 + e^{-kt}) \quad (1)$$

$$C_2 = 0.5C_0(1 - e^{-kt}) \quad (2)$$

where C_1 is the concentration of the starting enantiomer at time t , C_0 is the initial concentration of the starting enantiomer, C_2 is the concentration of the resulted enantiomer at time t and k is the rate constant of conversion. The half-life of conversion ($T_{1/2}$) can be calculated via

$$T_{1/2} = \ln \frac{2}{k} \quad (3)$$

From the kinetic rate constants, the apparent free energy barriers $\Delta G^\ddagger$ (T) can be calculated by the Eyring equation [15,16]:

$$\Delta G^\ddagger = -RT \ln \left(\frac{k \cdot h}{k_b \cdot T} \right) \quad (4)$$

where k is kinetic rate constant, k_b is the Boltzmann constant, h Planck's constant, R the universal gas constant and T is the temperature in K.

In the case of chiral pesticides, however, up to now only several pyrethroids have received some considerations on their abiotic isomer conversion. Information related to the chiral stability of many other chiral pesticide species is still poorly learn [18,19]. In a recent study, we investigated the chiral stability of triazole pesticides, i.e., triadimefon and diniconazole, in various organic solvents and water [20]. The results revealed rapid racemization for triadimefon in methanol, ethanol and water, whereas diniconazole was chirally stable. In this study, eight chiral pesticides, which were selected to cover different pesticide species and origins of chirality, were investigated to explore their chiral stability in organic solvents and water. The pesticides included four organophosphorus insecticides (malathion, phenthoate, profenophos and fenamiphos), one pyrethroid insecticide (fenpropathrin), two phenoxyalkanoic ester herbicides (quinalofop-ethyl and dichlorprop-methyl or DCP-methyl) and one acetamide fungicide (acetochlor). As seen in Fig. 1, each of the pesticides has one chiral center and thus consists of two enantiomers. Among them, profenophos and fenamiphos are P-chiral insecticides and acetochlor displays axial chirality. The other five pesticides are all C-chiral compounds. The relationship between the abiotic racemization and pesticide structure was further explored in this study.

The purpose of this study is not to add the fundamental knowledge of chiral pesticide chemistry, but rather to demonstrate that

potential racemization of chiral pesticides due to solvents must be considered significantly during chiral selective analysis. Findings from this study are useful for better understanding enantioselectivity of chiral pesticides in environment and also for proper analysis, formulating or handling of enantiopure products.

2. Materials and methods

2.1. Chemicals and reagents

Analytical standards of phenthoate (98.0%) and DCP-methyl (98.2%) were purchased from Dr. Ehrenstorfer (Germany). Standards of malathion (99.0%), profenophos (97.8%), fenpropathrin (99.5%) and quinalofop-ethyl (96.4%) were provided by National Pesticide Quality Inspection Center of China, and fenamiphos (98.5%) and acetochlor (93.7%) were from Shanghai Pesticide Research Institute. Stock solutions of the pesticides were made up at a concentration of 1 mg mL^{-1} in 100:10 hexane/isopropanol (v/v) and preserved at 4°C . *n*-Hexane, methanol, ethanol, isopropanol, acetone and methylene chloride were all of analytical grade, redistilled and filtered through a $0.45\text{-}\mu\text{m}$ filter before use. Other solvents and chemicals were of analytical grade.

2.2. Enantioselective analysis and isolation of enantiomers of chiral pesticides

A Shimadzu LC-20AB high-performance liquid chromatography (HPLC) system (Shimadzu Corporation, Japan) consisted of a LC-20AB pump, a SPD-20A UV/VIS detector, a CTO-10AS column oven and a SIL-20A manual injector with a $20\text{-}\mu\text{L}$ sample loop. The signal was acquired and processed by a LC-20AB solution workstation. The HPLC columns used for enantioselective separation were a Chiralcel OD-H column (Daicel Chemical Industries Ltd. Japan, $250 \text{ mm} \times 4.6 \text{ mm}$ i.d., $5\text{-}\mu\text{m}$ particle size) and a Chiralcel OJ-H column (Daicel Chemical Industries Ltd. Japan, $250 \text{ mm} \times 4.6 \text{ mm}$ i.d., $5\text{-}\mu\text{m}$ particle size), each protected with a guard column of the same phase. The enantioselective separation was performed at 20°C and the flow rate was set at 1.0 mL min^{-1} . The mobile phase was *n*-hexane with appropriate percentage of isopropanol modifier. Complete separation of the two enantiomers of each pesticide was accomplished after optimization of resolution conditions on the two chiral columns. The retention times of individual enantiomers are given in Table 1. For the purpose of station more clearly,

Table 1
Enantioselective separation results of chiral pesticides.

Compound	Column	Mobile phase ^a	Wave length/nm	<i>t</i> ₁ /min	<i>t</i> ₂ /min	<i>R</i> _s
Malathion	OD-H	100:3	230	15.6	18.5	3.79
Phenthoate	OD-H	100:1	230	11.9	12.8	1.83
Profenophos	OJ-H	100:3	230	9.5	10.5	2.61
Fenamiphos	OJ-H	100:1	254	40.2	49.4	1.79
Fenpropathrin	OD-H	100:1	235	10.4	14.8	4.64
Quinalofop-ethyl	OD-H	100:1	235	30.1	34.8	2.16
DCPP-methyl	OJ-H	100:1	230	13.2	14.5	2.16
Acetochlor	OD-H	100:0.9	254	13.1	15.0	1.43

^a The mobile phase was *n*-hexane:isopropanol (v/v).

the enantiomer first eluted was all labeled as pesticide-1 (e.g., malathion-1), and the second eluted enantiomer as pesticide-2 (e.g., malathion-2).

Individual enantiomers were prepared in this study via enantioselective separation of corresponding pesticide racemates by enantioselective HPLC. In this step, pesticide racemates of known quantity were injected into the enantioselective HPLC system and the mobile phase fractions corresponding to individual enantiomers were collected manually by observing their UV signals. The collected samples were then gently concentrated to dryness and used as enantiomer standards. The enantiopurity of the prepared enantiomers was >99% checked under corresponding enantioselective HPLC conditions.

2.3. Chiral stability experiments in organic solvents

0.1 mL pesticide enantiomer in hexane/isopropanol (100:10, v/v) mixture was pipetted into a 10 mL brown glass vial. After blown to dryness, 10 mL of a solvent, i.e., *n*-hexane, methanol, ethanol, isopropanol, acetone or methylene chloride, was added to give a final concentration of 10 µg mL⁻¹. The sample vials were capped with capsule, covered with parafilm, and incubated in the dark at 25 ± 1 °C. After 0, 1, 2, 4, 7 and 9 d of incubation, 1.0 mL solution samples in separate vials were removed. After blown to dryness under nitrogen and redissolved in 0.3 mL hexane/isopropanol (100:10, v/v) mixture, the samples were analyzed by enantioselective HPLC to determine the enantiomer composition. If racemization was observed, further incubation was performed at 20 ± 1 and 35 ± 1 °C for enantiomer-1 of corresponding pesticides to evaluate the influence of temperature on the racemization. All the experiments were performed in duplicate. Peak areas were directly used to calculate enantiomer composition, assuming the same instrument response for enantiomers from the same compound.

2.4. Chiral stability experiments in buffer solutions

Buffers with pH 5.8 and 7.0 were prepared by dissolving different proportions of KH₂PO₄ and Na₂HPO₄ in 1000 mL sterilized distilled water. Individual enantiomer-1 of each pesticide was first incubated in the buffers for 3 and 7 d followed with enantioselective analysis to elucidate if racemization took place during the incubation. When racemization was observed, corresponding enantiomer-1 was then reincubated in the buffers and sampled for analysis at intervals to determine the racemization kinetics. All the experiments were performed in duplicate. It is worth mentioning that only enantiomer-1 was investigated due to the fact that the results observed in achiral media are considered similar for both enantiomers, which has been validated by the racemization experiments in organic solvents (see Sections 2.3 and 3.1).

The buffer experiment was conducted as follows: a 500 mL buffer solution of individual enantiomer was prepared in a 500 mL conical flask at 1.0 µg mL⁻¹. The solution was capped, covered with

parafilm and incubated in the dark at 25 ± 1 °C. During the incubation, 30 mL solution samples were removed periodically and extracted with three 20 mL methylene chloride. The combined methylene chloride was dried with 20 g anhydrous sodium sulfate and carefully blown to dryness. After redissolved in 0.3 mL hexane/isopropanol (100:10, v/v) mixture, an aliquot was analyzed by enantioselective HPLC. As for fenpropathrin, due to its low water solubility (0.33 µg mL⁻¹ [21]), the incubation concentration was set at 0.1 µg mL⁻¹. During the incubation 100 mL buffer solution samples were taken at intervals and extracted with three 50 mL methylene chloride. Preliminary experiments showed no interconversion between enantiomers occurred during extraction and HPLC separation processes.

3. Results and discussion

3.1. Racemization of chiral pesticides in organic solvents

During incubation of enantiomers of profenophos, fenamiphos, quinalofop-ethyl, DCP-methyl and acetochlor in any of the organic solvents, enantioselective analysis always showed a single peak corresponding to the starting enantiomer. The results suggest that the five pesticides were configurationally stable in the studied organic solvents. Similar results were obtained when enantiomers of malathion, phenthoate or fenpropathrin were incubated in *n*-hexane, isopropanol, acetone or methylene chloride. However, during the incubation of enantiomer-1 of malathion, phenthoate or fenpropathrin in methanol or ethanol, enantioselective analysis showed the appearance of corresponding enantiomer-2. The amount of enantiomer-2 increased steadily until it nearly equaled to that of enantiomer-1. Similar pattern was observed for incubation of enantiomer-2 of malathion, phenthoate or fenpropathrin in methanol or ethanol, which resulted in the formation of corresponding enantiomer-1. Therefore, it is concluded that significant racemization took place when enantiomers of malathion, phenthoate or fenpropathrin incubated in methanol or ethanol. As an illustration, chromatograms in Fig. 2 show the racemization of phenthoate-1 in methanol at different incubation time.

Racemization of enantiomer-1 of malathion, phenthoate or fenpropathrin as a function of time in methanol and ethanol is plotted in Fig. 3. The pattern for enantiomer-2 was almost the same for that of enantiomer-1. Racemization of the three pesticides was significantly faster in methanol than in ethanol. For example, after 9-d incubation, 38.6% of fenpropathrin-1 was converted to fenpropathrin-2 in ethanol, while nearly 49.1% of conversion was observed in methanol, which indicated a nearly complete conversion.

According to Eqs. (1)–(4), the *k* (d⁻¹), *T*_{1/2} (d) and Δ*G*[#] (kJ mol⁻¹) values for racemization of malathion, phenthoate and fenpropathrin enantiomers in methanol and ethanol were calculated and are listed in Table 2. The fit was good with *r*² > 0.98 in most cases. It can be expected that the *k* values of a pair of

Fig. 2. Chromatograms showing racemization of phenthoate-1 in methanol at (a) 1 d, (b) 3 d and (c) 7 d incubation time.

Fig. 3. Racemization of (a) malathion-1, (b) phenthoate-1 and (c) fenpropathrin-1 in methanol and ethanol. Open dots refer to starting enantiomer and solid dots refer to converted enantiomer.

enantiomers are almost the same, as the reaction occurred in an achiral medium. The average half-lives for malathion, phenthoate and fenpropathrin were 4.4, 3.6 and 1.0 d in methanol or 40.1, 18.3 and 3.6 d in ethanol, respectively. Moreover, in both methanol and ethanol, $T_{1/2}$ of the three pesticides decreased in an order

malathion > phenthoate > fenpropathrin, indicating fenpropathrin underwent the most rapid racemization.

Influence of temperature on racemization of the three pesticides was further evaluated by measuring enantiomer-1 stability at 20 °C and 35 °C. The same racemization patterns were observed

Table 2

Kinetic rate constant k (d^{-1}), half-life $T_{1/2}$ (d) and energy barrier $\Delta G^\ddagger$ (kJ mol^{-1}) for the racemization of malathion, phenthoate and fenpropathrin in methanol and ethanol.

Solvent	Compound	25 °C			20 °C			35 °C		
		$k (\times 10^3)$	$T_{1/2}$	$\Delta G^\ddagger$	$k (\times 10^3)$	$T_{1/2}$	$\Delta G^\ddagger$	$k (\times 10^3)$	$T_{1/2}$	$\Delta G^\ddagger$
Methanol	Malathion-1	160	4.4	105.7	91.0	7.6	105.3	372	1.9	107.2
	Malathion-2	157	4.4	105.8	ND			ND		
	Phenthoate-1	196	3.6	105.2	138	5.1	104.3	610	1.2	105.9
	Phenthoate-2	195	3.5	105.3	ND			ND		
	Fenpropathrin-1	724	1.0	102.0	374	1.9	101.9	932	0.8	104.9
	Fenpropathrin-2	758	0.9	101.9	ND			ND		
Ethanol	Malathion-1	16.6	41.7	111.4	8.6	81.0	111.1	36.2	19.2	113.2
	Malathion-2	18.0	38.5	111.2	ND			ND		
	Phenthoate-1	38.6	18.0	109.3	14.6	47.5	109.8	112	6.2	110.3
	Phenthoate-2	37.6	18.5	109.3	ND			ND		
	Fenpropathrin-1	190	3.7	105.3	68.6	10.1	106.0	414	1.7	106.9
	Fenpropathrin-2	199	3.5	105.2	ND			ND		

ND: not detected.

Table 3

Kinetic rate constant k (d^{-1}), half-life $T_{1/2}$ (d) and energy barrier $\Delta G^\ddagger$ (kJ mol^{-1}) for the racemization of malathion, phenthoate and fenpropathrin in buffer solutions at 25°C .

Compound	pH 5.8			pH 7.0		
	$k (\times 10^3)$	$T_{1/2}$	$\Delta G^\ddagger$	$k (\times 10^3)$	$T_{1/2}$	$\Delta G^\ddagger$
Malathion-1	136	5.1	106.1	1412	0.5	100.3
Phenthoate-1	414	1.7	103.4	3104	0.2	98.4
Fenpropathrin-1	11.0	63.0	112.4	118	5.9	106.5

in methanol and ethanol, but the extent of conversion was smaller at 20°C and greater at 35°C (Table 2). For instance, the $T_{1/2}$ of malathion-1 racemization in methanol increased from 1.9 to 7.6 d when the incubation temperature decreased from 35°C to 20°C . The temperature dependent effect is consistent with the observation of Qin that the epimerization of cypermethrin in alcohols was much slower at 4°C than at 20°C [9].

3.2. Racemization of chiral pesticides in buffer solutions

Many pesticides could move into water systems after application. In addition, water is often used to prepare pesticide solutions prior to spray application. For this reason, the stability of chiral pesticides in water was also investigated. Similar to the results in organic solvents, profenophos, fenamiphos, quinalofop-ethyl, DCP-methyl and acetochlor were found configurationally stable at 25°C in buffer solutions of pH 5.8 and 7.0. However, significant racemization was observed during the incubation of enantiomer-1 of malathion, phenthoate or fenpropathrin in the two buffers. The kinetic data of the racemization were further estimated and listed in Table 3. The pH value seemed to extensively influence the racemization process. The racemization half-lives for malathion, phenthoate and fenpropathrin were 5.1, 1.7 and 63.0 d at pH 5.8, or 0.5, 0.2 and 5.9 d at pH 7.0, respectively. It can be seen that the racemization of the three pesticides occurred more rapidly at pH 7.0 than at pH 5.8. Moreover, faster racemization was observed for malathion and phenthoate in water (pH 7.0) than in methanol or ethanol. However, as for fenpropathrin, racemization in the two buffers was much slower than in methanol or ethanol. Qin and Liu investigated the chiral stability of cypermethrin and also found rapid epimerization of cypermethrin in alcohols and slow epimerization in pure water [8–10]. This may be due to the very low solubility of pyrethroid insecticides in water [8].

3.3. Mechanism and structural consideration of the racemization

Chiral conversion has been observed in the case of some synthetic pyrethroids with chirality on the α -carbon. These included cypermethrin [8–10], cyfluthrin [11], deltamethrin [22,23] and fenvalerate [24]. However, permethrin, which does not have the α -C chiral center, did not undergo such conversion [9]. The conversion was generally attributable to the fact that an active proton at the chiral center exchanged with the protic solvent. In the proposed

mechanism, the proton on the chiral center is relatively acidic and is thus easily lost to create an intermediate carbanion. In protic solvents, such as alcohols and water, reprotonation regenerates the parent compound from either the top or bottom face of the anion, thus interconverting enantiomers [9]. Fenpropathrin shares a similar structure to cypermethrin and cyfluthrin, and also has an active proton at the α -C chiral center (Fig. 1), therefore its racemization likely occurred via the same proton exchange mechanism (Fig. 4).

Moreover, we argue the racemization of malathion and phenthoate occurred via a comparable pathway. The acid-decelerated effect of the racemization of malathion, phenthoate and fenpropathrin further supports the mechanism. The observed pH dependence is consistent with the results of the study by Perschke and Hussain, who reported the isomerization of detamethrin in alcohols and found that addition of HCl or HBr would block the isomerization [23]. In addition, the different racemization rates in water and alcohols can be ascribed to different acidity and polarity of the solvents [8,25]. In the case of isopropanol, the absence of racemization may also be due to the steric hindrance of secondary alcohols [8].

In a recent study, we investigated the chiral stability of triadimefon and diniconazole in organic solvents and water [20]. The results indicated similar racemization for triadimefon in methanol, ethanol and water, whereas diniconazole was chirally stable. In Fig. 1, we also give the structures of triadimefon and diniconazole. Among the 10 pesticides, malathion, phenthoate, fenpropathrin and triadimefon were found to undergo abiotic racemization in methanol, ethanol and water. It seems that the observed racemization in this study is closely related to acidity of the proton on the chiral carbon. Although no acidity value of the acidic proton at the chiral position is available, a tentative explanation of the relationship between racemization and chemical structure is given. It is known that any molecule containing a C-H can lose a proton forming the carbanion and the stability of the resulted carbanion can greatly affect the acidity of the proton. Carbanions vary widely in stability, depending on the hybridization of the carbon atom and the ability of substituent groups to stabilize the negative charge [26–28]. The proton acidity can then be increased or decreased by the carbanion stabilizing or destabilizing effect of adjacent substituent groups. The carbanion stabilizing substituents mainly include electron-withdrawing groups, conjugated functional groups as well as third row elements, particularly phosphorus and sulfur [26–28].

As seen in Fig. 1, the 10 pesticides can be classified into three groups according to the chiral structure of the analyte. (1) Molecules with one chiral center having no proton, i.e., profenophos, fenamiphos or acetochlor. The three pesticides are configurationally stable in protic solvents. (2) Molecules with one chiral center having one proton and one carbanion stabilizing group, i.e., quinalofop-ethyl, DCP-methyl and diniconazole. There is only one carbanion stabilizing group at the chiral position. Moreover, the alkyl substituent attached to the chiral carbon in the three pesticides exhibits an electron-donating property, resulting in a decrease of stability of the carbanion. Thus, the proton on

Fig. 4. Racemization scheme of fenpropathrin in protic solvents.

the chiral carbon shows relatively weak acidity and is only lost with difficulty. As a consequence, the three chiral pesticides are also configurationally stable in protic solvents. (3) Molecules with one chiral center having one proton and two or three carbanion stabilizing groups, i.e., malathion, phenthoate, fenprothrin and triadimefon. Taking fenprothrin as an example, the α -C holds an electron-withdrawing cyano group and a conjugated benzyl group. Similar cases are shared with malathion, phenthoate and triadimefon. Therefore, the proton on the chiral carbon is relatively acidic and racemization occurs in protic solvents.

4. Conclusions

To our knowledge, this is the first study related to abiotic racemization of malathion and phenthoate, two widely used organophosphorus insecticides. In fact, many pharmaceuticals have been shown to racemize in aqueous media and have received extensive investigations [29–31]. However, only limited information is available regarding the abiotic isomer conversion of chiral pesticides. Much more attention should be paid to the abiotic isomer conversion to ensure proper evaluation of environmental fate and toxicology of relevant chiral pesticides. This is particularly important as more and more enantiopure products are introduced into market. Moreover, a chiral pesticide possessing a similar chiral structure to malathion, phenthoate, fenprothrin and triadimefon is expected to racemize in protic solvents. The rule is also thought to apply universally to other chiral compounds, such as chiral drugs. Findings from our study are useful for analysis and investigation of such compounds on the enantiomeric level.

Acknowledgement

This work was supported by National Natural Science Foundation of China (no. 20707005).

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