DOI:10.1021/jf900921g

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

Epimerization of Cypermethrin Stereoisomers in Alcohols

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Isomerization induced by light, heat, and organic solvents has been shown to occur for some pyrethroid insecticides. Alcohols are popular solvents that are used in sample extraction, storage, and analysis. Thus, alcohol-induced epimerization may contribute to the incorrect interpretation of results from enantioselective chemical analysis and bioassay of pyrethroids like cypermethrin. In this study, we investigated the relationship between the rate of epimerization of cypermethrin stereoisomers: 1*R*-*cis*-α*R* and 1*R*-*trans*-α*R* and short-chain alkyl alcohol properties. In this study, complete epimerization of 1*R*-*cis*-α*R* produced an almost equal fraction of 1*R*-*cis*-α*S*, and that of 1*R*-*trans*-α*R* yielded 1*R*-*trans*-α*S*. For both stereoisomers, epimerization was most rapid in ethanol. The same stereoisomers underwent relatively rapid epimerization in methanol, *n*-propanol, 2-methyl-1-propanol, and *n*-butanol but were stable in 2-butanol, suggesting that secondary alcohols have reduced reactivity, likely due to steric hindrance. We further evaluated epimerization of 1*R*-*cis*-α*R* and 1*R*-*trans*-α*R* stereoisomers of cypermethrin as a function of water content in methanol. The presence of water in methanol generally increased the epimerization rate. For 1*R*-*cis*-α*R*, epimerization was most rapid with a water content of ≤2%, while for 1*R*-*trans*-α*R*, epimerization was most rapid with a water content of 10%. Results from this study clearly show that contact with commonly used primary alcohols may result in rapid abiotic epimerization, underscoring the importance of considering configurational stability in ensuring the analytical integrity and correct interpretation of bioassay data for stereoisomers of cypermethrin and similar pyrethroids.

KEYWORDS: Epimerization; epimers; cypermethrin; configurational stability; chiral contaminants

INTRODUCTION

The past two decades saw a dramatic increase in the use of pyrethroids in agriculture and urban/household insect control (*1*, *2*). The popularity of pyrethroid insecticides may be attributed to their "ideal" characteristics as broad-spectrum and low-application rate insecticides (*2*), with low mammalian and avian toxicity (*3*). However, pyrethroids are highly toxic to fish and other aquatic organisms (*4*). In addition, recent reports indicate ubiquitous pyrethroid contamination of agricultural and urban creeks in regions such as California, often at concentrations acutely toxic to aquatic invertebrates (*2*, *5*−*7*).

Because of the presence of multiple asymmetric centers in their structure, most pyrethroids are chiral and can consist of up to four to eight stereoisomers, of which only one or two stereoisomers are responsible for the insecticidal activity (*8*, *9*). For instance, in *cis*-bifenthrin, only the 1*R*-*cis* enantiomer is insecticidally active, while the corresponding 1*S*-*cis* enantiomer is "inactive" (*10*). Previous studies reported large differences in toxicity to nontarget organisms (*9*, *11*) as well as in environmental degradation rates between stereoisomers of the same pyrethroids (*9*, *12*).

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Cypermethrin [CP, (*RS*)-α-cyano-3-phenoxybenzyl (1*RS*)-*cis*, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate] is a type II pyrethroid insecticide containing three chiral centers, including an asymmetric α-carbon (**Figure 1**). It thus consists of eight stereoisomers, four of which occur in two *cis* diastereomers (1*R*-*cis*-α*R* and 1*S*-*cis*-α*S*, and 1*S*-*cis*-α*R* and 1*R*-*cis*-α*S*) and two *trans* diastereomers (1*R*-*trans*-α*R* and 1*S*-*trans*-α*S*, and 1*S*-*trans*-α*R* and 1*R*-*trans*-α*S*) (*13*−*15*). Considerable differences have been observed between CP stereoisomers in acute toxicity to aquatic invertebrates (*14*). Moreover, stereoselective degradation of CP stereoisomers has been observed in soils and sediments (*12*, *16*, *17*). Similar to cyfluthrin and deltamethrin, only two (1*R*-*cis*-α*S* and 1*R*-*trans*-α*S*) of the eight stereoisomers in CP are insecticidally active, suggesting that the 1*R* configuration and an *S* configuration of the α-carbon containing the cyano group are essential for the desired activity (*10*, *18*).

Chirality is an important consideration in green chemistry, as the use of stereoisomer-enriched formulations, including those for pyrethroids, reduces the amount of chemicals released into the environment without sacrificing the pest control effectiveness (*19*). However, chiral structures require more rigorous analytical methods, and extra caution must be used to ensure integrity in toxicological assessment (*20*). In the case of type II pyrethroids, including CP (**Figure 1**), the presence of an α-carbon chiral center renders them susceptible to isomerization resulting from exposure

 Published on Web 07/09/2009

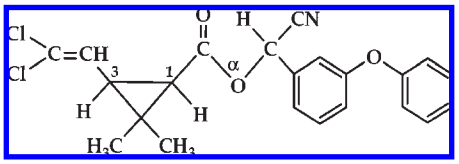


Figure 1. Chemical structure of cypermethrin showing chiral positions (labeled with 1, 3, or α) in the structure.

to light (*22*), heat (*21*−*23*), or organic solvents (*13*, *18*, *22*, *24*, *25*). However, despite the fact that configurational stability could be an important consideration in the development of analytical methods (*26*) and the interpretation of enantioselective toxicity data (*13*, *18*), abiotic isomerization is often overlooked in chiral pesticides.

In a recent study, we evaluated the configurational stability of permethrin and CP stereoisomers in a range of polar and nonpolar solvents, including methanol, 2-propanol, acetone, and hexane (*24*). Permethrin, which is similar in structure to CP except for the absence of an α-carbon chiral center, was found to be stable in all solvents in the dark at room temperature (25 ± 2 °C). In contrast, CP stereoisomers underwent rapid interconversion in methanol and 2-propanol, with an enhanced rate in methanol/water mixtures. Given that alcohols are among the most widely used solvents in chemical analysis and bioassays, as well as in pesticide formulations, this study was designed to further explore alcohol-induced isomerization of CP stereoisomers (1*R*-*cis*-α*R* and 1*R*-*trans*-α*R*) by considering the influence of alcohol structure (i.e., chain length and branch chains) and water content. As several other commonly used pyrethroids (e.g., cyfluthrin, cyhalothrin, and deltamethrin) share structures similar to that of CP, findings from this study are expected to have broad implications for the fate and effects of these compounds in the environment.

MATERIALS AND METHODS

Chemicals. The analytical standard of CP (98%) was purchased from Chem Service (West Chester, PA). By using previously established chiral selective high-performance liquid chromatography (HPLC) methods (*27*), individual stereoisomers were resolved and collected for use in further analysis. Two stereoisomers from two different diastereomers of CP, 1*R*-*cis*-α*R*-CP and 1*R*-*trans*-α*R*-CP, were obtained. The purity of the isolated stereoisomers was determined to be >99% by HPLC and gas chromatography (GC) analysis prior to their use. Other solvents or chemicals used in this study were of analytical or HPLC grade.

Stability of Cypermethrin Stereoisomers in Pure Alcohols. To understand the dependence of CP stereoisomer stability on alcohol structures, isomerization was first assessed in a range of alkyl alcohols. Individual CP stereoisomers were added to 1.0 mL of a solvent in amber glass GC vials at 10 μg/mL. Epimerization was evaluated in six different alcohols (methanol, ethanol, *n*-propanol, 2-methyl-1-propanol, *n*-butanol, and 2-butanol). The sample vials were capped with crimp seals, covered with aluminum foil, and kept in the dark at room temperature (20 ± 1 °C). After incubation for 8, 24, 48, 96, and 192 h, duplicate samples in separate vials were removed and solvent evaporated to dryness under nitrogen and redissolved in 0.5 mL of *n*-hexane. The samples were analyzed via GC using a previously developed method to determine the stereoisomer composition (*27*).

Stability of Cypermethrin Stereoisomers in Methanol/Water Mixtures. The second set of experiments was conducted to evaluate the effect of water in methanol on epimerization of CP stereoisomers. A 5.0 mL solution of the CP stereoisomer (1*R*-*cis*-α*R*-CP or 1*R*-*trans*-α*R*-CP) was prepared in a 20 mL glass vial at a concentration of 1.0 μg/mL. The solution was a mixture of water and methanol at different ratios. Fifteen water:methanol ratios [100:0, 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, 10:90, 8:92, 6:94, 4:96, 2:98, and 0:100 (v/v)] were used, which represented the water content in methanol ranging from 0 to 100%. Finer increments (between 0 and 10% water for 1*R*-*trans*-α*R*-CP and between 0 and 2% water for 1*R*-*cis*-α*R*-CP) were also evaluated because preliminary experiments showed that the most rapid isomerization occurred in these ranges. The samples were capped, covered with aluminum foil, and kept in the dark at room temperature (20 ± 1 °C). After incubation for 4, 8, 24, and 48 h, duplicate samples were removed and 10 g of anhydrous sodium sulfate was added to each sample vial to absorb the water. Five milliliters of methylene chloride was then added, and the sample was mixed on a vortex for 1 min. The methylene chloride extracts were combined and then filtered through 10 g of anhydrous sodium sulfate. The combined extract was evaporated to dryness under a stream of pure nitrogen and redissolved in 0.5 mL of hexane. The stereoisomer composition was analyzed with GC instrument equipped with a chiral selective column.

GC Analysis. Analysis of stereoisomer composition was conducted on an Agilent 6890 GC instrument equipped with an electron capture detector (ECD) (Agilent Technologies, Palo Alto, CA) using a BGB-172 capillary column [30 m × 0.25 mm × 0.25 μm, *tert*-butyldimethylsilyl-β-cyclodextrin dissolved in 15% diphenyl- and 85% dimethylpolysiloxane (BGB Analytik, Adliwil, Switzerland)]. The detector temperature was 310 °C, and the makeup gas was nitrogen flowing at a rate of 60 mL/min. The inlet temperature was 160 °C. The column was initially held at 160 °C for 1 min, ramped to 230 at a rate of 1 °C/min, and then held at 230 °C for 90 min until all stereoisomers were eluted. Under the conditions used, all enantiomeric pairs from the *cis* diastereomers were well separated, while the enantiomeric pairs from the *trans* diastereomers of CP were not resolved. Preliminary experiments showed that the method detection limits for the selected stereoisomers were 1−2 ng/mL. Peak areas were directly used to calculate stereoisomer composition, assuming the same instrument response for the two stereoisomers.

RESULTS AND DISCUSSION

Recent advances in separation and synthesis techniques have helped facilitate the routine separation of stereoisomers of a significant number of chiral compounds for stereoselective environmental and toxicity assessment (*28*−*30*). One complicating factor in studies related to chiral chemicals is the presence of a configurationally unstable stereogenic center that is susceptible to enzymatic and/or nonenzymatic stereoisomer interconversion (*13*, *18*−*20*, *22*, *24*, *25*). However, the terms used to define configurational lability have always been a source of confusion, particularly in the determination and reporting of rate constants that refer to the interconversion process. Reist et al. (*31*) provided a detailed discussion of semantics and processes involved in configurational instabililty. In broad terms, configurational instability could result in interconversion between enantiomers (defined as chiral inversion) in compounds with a single element of chirality, or interconversion between epimers (defined as epimerization) in compounds that contain two or more elements of chirality (*20*).

Epimerization of Cypermethrin Stereoisomers in Alcohols. The enantioselective separation and identification of selected pyrethroids via GC were described in a previous study (*27*). The conversion of CP stereoisomers induced by the heated GC inlet was relatively small (≤3%) under the analytical conditions. During each sequence of analysis, pure stereoisomers prepared in *n*-hexane were included in the analysis to quantify the stereoisomer conversion caused by analysis. The calculation of the rate of epimerization from the various treatments accounted for this fraction of conversion. A previous study showed that CP stereoisomers were relatively stable in *n*-hexane and methylene chloride used in the sample preparation (*24*). In addition, as all samples were incubated in the dark, the potential contribution from light to the observed epimerization was considered to be insignificant.

Incubation of 1*R*-*cis*-α*R*-CP in all primary alcohols (ethanol, methanol, *n*-propanol, 2-methyl-1-propanol, and *n*-butanol) resulted in the formation of 1*R*-*cis*-α*S*-CP. Similarly, 1*R*-*trans*-α*R* epimerized to 1*R*-*trans*-α*S* CP. However, under the analytical conditions used in this study, the enantiomer pair from the *trans* diastereomer (1*R*-*trans*-α*S* and 1*S*-*trans*-α*R*) was not completely resolved. However, as with the *cis* stereoisomers, given that

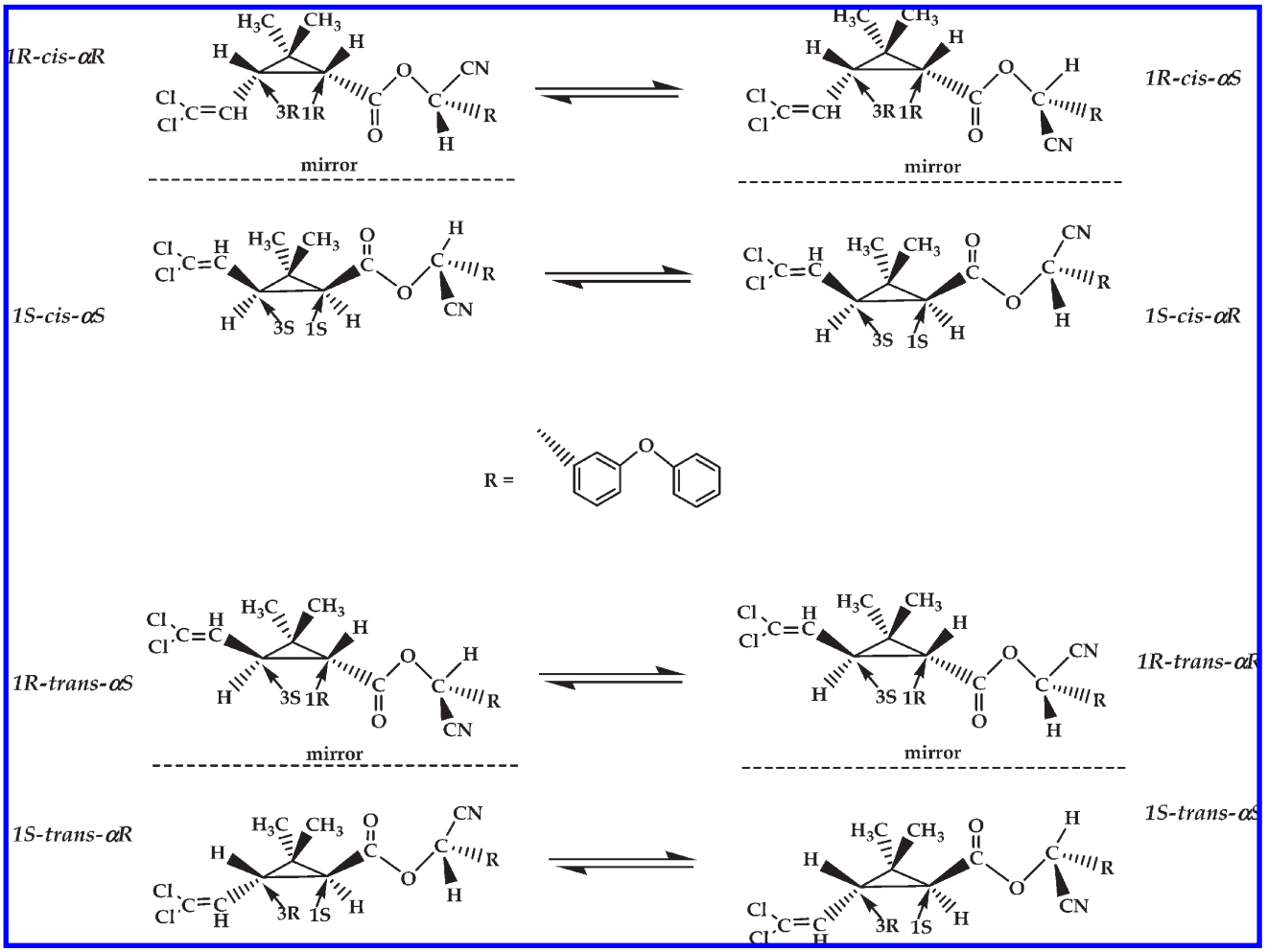


Figure 2. Predicted pathways for interconversion of cypermethrin stereoisomers in protic solvents (interconversion of the 1*R-cis*-α*R* and 1*R-trans*-α*R* stereoisomers was considered in this study).

interconversion likely occurred at the α-carbon, it may be assumed that 1*R-trans*-α*R* was converted to the 1*R-trans*-α*S* epimer in the alcohols (**Figure 2**). This also means that the epimers can be analyzed without the need for complete resolution of enantiomers in a given diastereomer (*20*).

After incubation for 8 days in the alcohols, the degree of isomer conversion ranged from 4 to 46% and from 5 to 49% for 1*R-cis*-α*R* and 1*R-trans*-α*R*, respectively (**Figure 3**). The most rapid conversion was observed with ethanol for both stereoisomers. Within 8 h (the first sampling time point), equal fractions (46−49%) of 1*R-cis*-α*R* (or 1*R-trans*-α*R*) and 1*R-cis*-α*S* (or 1*R-trans*-α*S*) were observed, suggesting a nearly complete conversion (50:50 mixture of epimers). Except for 2-butanol, relatively rapid conversion also occurred in the other primary alcohols, reaching completion at 192 h (in *n*-butanol and 2-methyl-1-propanol for 1*R-trans*-α*R*) or at 96 h (for the other solvent−-stereoisomer combinations) (**Figure 3**). In 2-butanol, the only secondary alcohol considered in this study, both stereoisomers were found to be relatively stable with limited formation of the corresponding epimer.

Assuming that the epimerization is an equilibrium process and that the conversion obeys pseudo-first-order kinetics, the concentration fraction change of a given stereoisomer can be described by

$$[S] = 0.5[S]_0(1+e^{-kt}) \quad (1)$$

where [S] is the fraction of the starting stereoisomer at time t, $[S]_0$ is the initial fraction of the starting stereoisomer, and k is the conversion rate constant (inverse days). The time-dependent concentrations of stereoisomers were fitted to eq (1) to estimate k, from which the half-life $T_{1/2}$ (days) was derived (**Table 1**). Epimerization occurred most rapidly in ethanol but was almost negligible in 2-butanol for both *cis* and *trans* stereoisomers. The estimated $T_{1/2}$ was 0.07 days (~1.7 h) for both stereoisomers in ethanol, with 99% conversion occurring in < 8 h. The stability of 1*R-trans*-α*R* followed the order ethanol < methanol < *n*-propanol < 2-methyl-1-propanol < *n*-butanol (**Table 1**). Significant differences were observed in the rates of epimerization of 1*R-trans*-α*R* in the different alcohols.

The derived $T_{1/2}$ values of 1*R-cis*-α*R* in ethanol, methanol, *n*-propanol, 2-methyl-1-propanol, and *n*-butanol ranged from 0.07 to 1.75 days, suggesting comparable stability of the 1*R-cis*-α*R* CP in these alcohols and a lack of strong structural influence. In the study by Perschke and Hussain (*25*), deltamethrin was found to epimerize faster in short- and straight-chain alcohols relative to long- or branched-chain alcohols.

On the basis of the results of this study and previous studies (*14*, *18*, *21*, *24*, *25*), the interconversion of the CP stereoisomers in alcohols likely occurred at the α-carbon chiral center via an intermediate (transition state) carbanion formation (**Figure 4**). In the proposed mechanism, the proton on the carbon that holds the cyano group in CP is relatively acidic (*20*), so that it can be easily lost, creating an anion that is stabilized by both the cyano group and the aromatic ring. Reprotonation in protic solvents (which contains a dissociable H^+) regenerates the parent compound

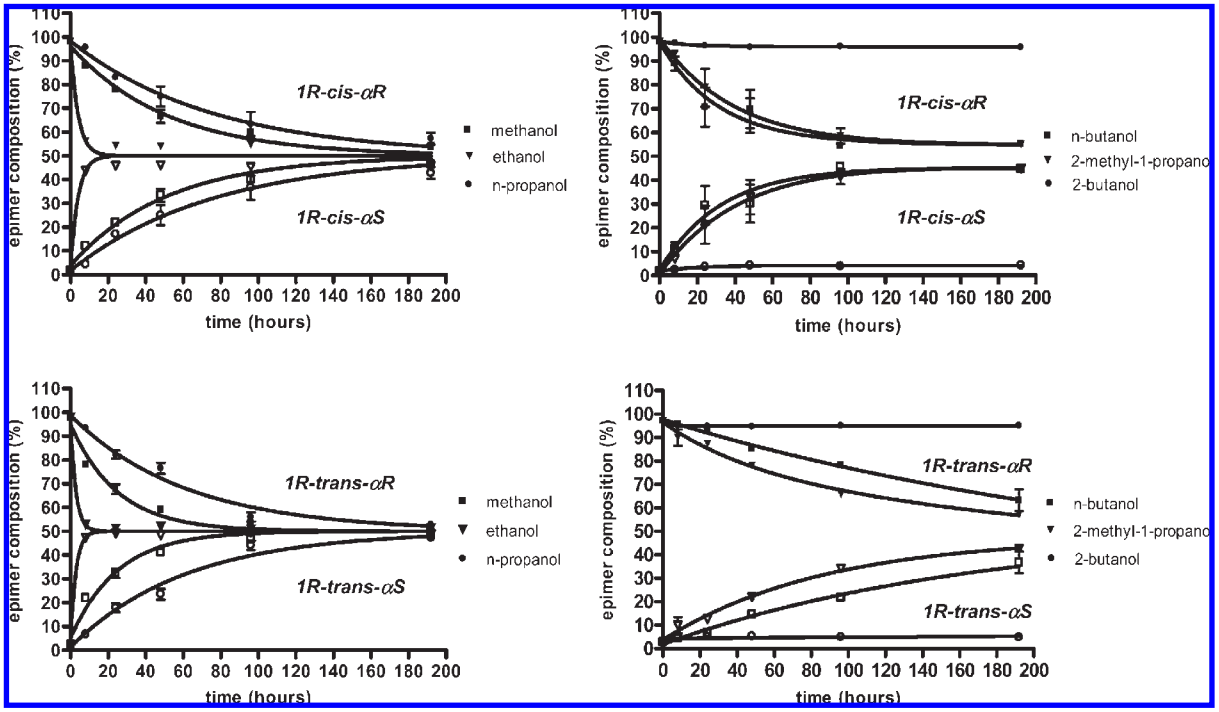
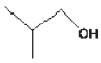
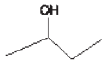


Figure 3. Stereisomer interconversion of (**A**) 1*R*-*cis*-α*R* to 1*R*-*cis*-α*S* and (**B**) 1*R*-*trans*-α*R* to 1*R*-*trans*-α*S* cypermethrin.

Table 1. Pseudo-First-Order Kinetic Constants [k (d^{-1}) (mean ± standard error)] for the Interconversion of Cypermethrin Stereoisomers in Selected Alcohols[a]

	Water solubility (g/100g)	Structure of alcohols	1*R*-cis-α*R*		1*R*-trans-α*R*	
			k (d^{-1})	$T_{1/2}$ (d)	k (d^{-1})	$T_{1/2}$ (d)
Methanol	∝		0.61 ± 0.09	1.14	1.05 ± 0.08	0.66
Ethanol	∝		9.71 ± 5.04	0.07	10.48 ± 3.19	0.07
n-Propanol	∝		0.40 ± 0.06	1.75	0.41 ± 0.03	1.69
2-Methyl-1-propanol	~4.0		0.61 ± 0.09	1.14	0.26 ± 0.02	2.64
n-Butanol	~7.4		0.74 ± 0.11	0.94	0.15 ± 0.01	4.50
2-Butanol	~6.7		0.01 ± 0.01	123.4*	0.00 ± 0.00	291.30*

[a] Incubation was conducted in the dark at room temperature (∝ indicates complete miscibility with water at room temperature; estimated values are denoted with an asterisk).

from either the top or bottom face of the anion (*31*), thus interconverting the stereoisomers. This mechanism is consistent with the results of the study by Perschke and Hussain (*25*), who reported that the addition of 0.2 μmol of HCl to 2 μmol of deltamethrin in 1 mL of alcohol prevented the isomerization of deltamethrin, thus indicating that the exchange of the α-proton with the solvent was blocked (*25*).

The proposed mechanism further suggests that for a secondary alcohol, the hydroxyl group may have difficulty approaching the α-carbon, resulting in much reduced activity, as observed for 2-butanol in this study. Moreover, epimerization at the α-carbon in this study is a reversible interconversion process approaching a 50:50 mixture of the epimers, but not exactly racemic (*31*). This is due to the fact that epimerization is essentially a diastereomerization process and diastereomers differ in their energy content and molecular properties (*20*, *31*). Unlike chiral inversions, where the end point equilibrium (a racemic mixture) can be known beforehand, the equilibrium between epimers depends heavily on the internal energy of the epimers and more importantly on the environmental conditions, particularly the solvent properties (*31*).

Results from this study and previous studies suggest that the presence of a chiral center on the α-carbon adjacent to a cyano group renders CP and other similar pyrethroids (or all type II pyrethroids) susceptible to chemical, photochemical, and thermal epimerization (**Figure 2**) (*13*, *14*, *18*, *24*, *25*). Results from our recent investigations with permethrin, which is similar in structure to CP but lacks an α-carbon chiral center, suggest that the chiral centers on positions 1 and 3 of the cyclopropyl ring on the acid moiety are relatively stable in various solvents and solvent/water mixtures in the dark at ambient temperature (*24*).

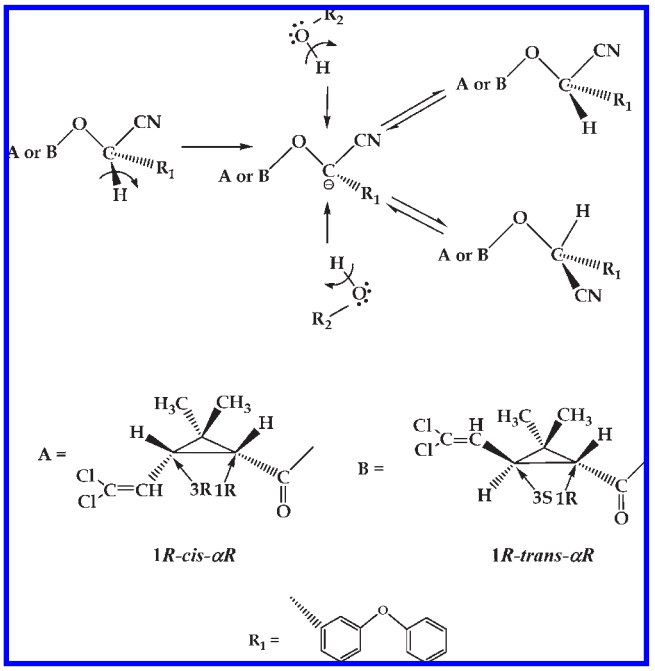


Figure 4. Proposed mechanism for the epimerization of cypermethrin stereoisomers in protic solvents.

Epimerization in Water/Methanol Mixtures. In a previous study, water was found to enhance epimerization when present in methanol, 2-propanol, or acetone (*24*). To improve our understanding of the effect of water in solvent systems, epimerization of 1*R*-*cis*-α*R*-CP and 1*R*-*trans*-α*R*-CP was further evaluated as a function of water content in methanol. Chiral interconversion was observed for CP stereoisomers in all methanol/water mixtures, and as expected, the rate of epimerization depended closely on the relative water:methanol ratio, or water content in methanol (**Table 2**). No detectable epimerization was found for either stereoisomer in water alone, presumably due to the very low water solubility of CP (water solubility of 4 ppb) (*32*). Compared to the interconversion in the unamended methanol, epimerization was significantly faster in the water-amended solvent. This may be due to the fact that among the polar protic solvents, water is the most polar and would contain a more readily dissociable H^+ as compared to alcohols (*33*). For 1*R*-*trans*-α*R*, the water content at which maximum epimerization occurred was ~10%. However, for 1*R*-*cis*-α*R*, epimerization was further accelerated as the water content decreased, and the water content with the highest rate of epimerization was found to be ~1.5%. When compared to the methanol-only treatment, epimerization of 1*R*-*trans*-α*R* was enhanced in water/methanol mixtures. However, for the 1*R*-*cis*-α*R* stereoisomer, the extent of epimerization decreased as the water content was increased from 70 to 100%, again likely due to an effect on the solubility of the compound.

Observations in this study suggest that water alone did not induce epimerization of CP, likely because CP was insoluble in water. However, the presence of water in an alcohol such as methanol, especially at a relatively low water content, was found to substantially enhance epimerization of both CP stereoisomers. Our finding that water in methanol enhanced epimerization of CP was consistent with a previous study by Leicht et al. (*18*), who also reported rapid isomer interconversion for cyfluthrin diastereomers in a 9:1 (v/v) methanol/water mixture in the dark, although only one water content was examined in that study.

Table 2. Pseudo-first order kinetic constants (k, d^{-1}) (mean ± standard error) for interconversion of cypermethrin stereoisomers in water-methanol mixtures (% water content)

water content (%)	1*R*-*cis*-α*R*	1*R*-*trans*-α*R*
0 (methanol alone)	0.67 ± 0.24	0.88 ± 0.20
0.5	7.38 ± 0.64	—[a]
1.0	12.04 ± 1.55	—[a]
1.5	19.61 ± 2.90	—[a]
2	13.30 ± 3.73	2.41 ± 0.40
4	10.95 ± 1.06	2.92 ± 0.25
6	8.96 ± 1.69	3.25 ± 0.38
8	6.39 ± 0.40	3.24 ± 0.53
10	5.43 ± 0.45	4.86 ± 0.52
20	3.00 ± 0.37	3.94 ± 0.32
30	2.88 ± 0.42	3.46 ± 0.16
40	0.94 ± 0.22	2.48 ± 0.23
50	0.78 ± 0.18	1.92 ± 0.16
60	0.70 ± 0.11	1.73 ± 0.16
70	0.66 ± 0.12	1.32 ± 0.13
80	0.46 ± 0.09	1.30 ± 0.19
90	0.44 ± 0.12	1.23 ± 0.37
100 (water alone)	0	0

[a] Not tested.

The occurrence of nonenzymatic chiral interconversion for bioactive compounds like pyrethroids is important for several reasons. While enantioselectivity can be readily expected in interactions of biomolecules with chiral chemicals, enzymatic routes of chiral center interconversion, particularly epimerization, are not very common (*13*, *20*), and nonbiological chiral inversion could be incorrectly attributed to biological processes, consequently leading to an incorrect interpretation of toxicological results if left unchecked (*13*). Alcohols, especially methanol and ethanol, have vast industrial and laboratory applications. The presence of water in alcohols may be expected in many scenarios, such as in low-grade alcohol products, and when nondehydrated environmental samples are extracted with an alcohol, resulting in extract mixtures of alcohol and water. In addition, alcohols are often used in dissolving and storing individual stereoisomers prior to use. Water is often used to prepare pesticide solutions prior to spray application. Findings from this study show that caution must be used when alcohols are involved in sample extraction, storage, and analysis (especially toxicological analysis) to ensure integrity and correct interpretation of analytical and toxicological assessment results at the enantiomer level (*13*).

Findings from this study and previous studies indicated that the factors affecting the rate of epimerization of CP and related pyrethroids in alcohols are not readily discernible from typical physical and chemical properties of alcohols (e.g., viscosity, density, water solubility, and chemical structures such as straight vs branched-chain) (*25*). However, it may be expected that epimerization is rapid in most short-chain primary alcohols, whereas the stereoisomers are relatively stable in secondary alcohols. It will be of interest in future research to consider alcohols with longer chains or more bulky substituents and to derive quantitative structure−activity relationships.

ACKNOWLEDGMENT

We acknowledge the University of California Toxic Substances Research and Training Program (UC-TOXICS) for the support of M.G.N. This study was partially supported by USDA-National Research Initiatives Grant 2005-35107-16189.

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Received March 18, 2009. Revised manuscript received June 19, 2009. Accepted June 23, 2009.