Chemical Isomerization of Deltamethrin in Alcohols

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Deltamethrin containing 96.3% DM1 epimer (*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylate was allowed to stand in the dark at 21 ± 1 °C in 19 different solvents to study the effect of solvents on isomerization of this insecticide. DM1 was converted to DM(2+2′) epimer in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, 1-pentanol, acetone, and acetonitrile. Reaction was faster in the first four solvents than in the others and resulted in the formation of a equilibrium mixture of DM1 and DM(2+2′) after 2–3 days. The reaction followed first-order kinetics and could be blocked by the addition of HCl or HBr. Bioassay of DM1 and DM(2+2′) on 1-day-old female tsetse flies showed that DM1 was very toxic but DM(2+2′) was relatively nontoxic to these insects. No isomerization of DM1 took place in *n*-hexane, diethyl ether, ethyl acetate, *p*-dioxane, benzene, toluene, 2-methyl-2-propanol, 1-octanol, and 2-octanol in the dark.

INTRODUCTION

Deltamethrin [(*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylate] was the first synthetic pyrethroid insecticide used successfully in tsetse fly control (Gruvel and Tazé, 1978; Spielberger et al., 1979). Several formulations of deltamethrin are currently being marketed in African countries. These include Glossinex 200 S.C., a formulation developed for use on tsetse fly target screens (Wellcome Foundation, 1986). However, deltamethrin degrades quickly on tsetse fly targets, and there is a need for formulations that will confer stability against environmental effects such as sun and rain (Torr, 1985). Allan and Miller (1987) invented silicone polymer based formulations for this purpose. However, several of these formulations include ethanol and 2-propanol as volatile carriers.

Chemical and photochemical isomerization of deltamethrin has been investigated by Ruzo et al. (1977), Maguire (1990), and Day and Maguire (1990). Deltamethrin has eight possible stereoisomers as described by Ruzo et al. (1977) and shown in Figure 1. According to Elliott et al. (1974) the cis-1*R*,3*R* configuration about the cyclopropane ring and the *S* configuration for the cyano group at the benzylic carbon are essential for insecticidal activity. Studying the effect of alcohols on isomerization of deltamethrin exposed to sunlight Ruzo et al. (1977) reported the formation of the insecticidally inactive DM2 (α*R*,1*R*-cis) isomer. The yield of DM2 decreased in the solvent order methanol ≃ ethanol > 2-propanol. Only a portion of the DM2 formed in alcohols was attributed to photochemical process, and most of it resulted apparently from a ground-state reaction in which the α-proton of deltamethrin exchanged with the solvent.

Since alcohols are used in some deltamethrin formulations (Allan and Miller, 1987), it would be of interest to study the effect of organic solvents, particularly alcohols, on the stability of deltamethrin in the dark. In this paper we report studies of the effects of different aliphatic alcohols and other common solvents on the isomerization of deltamethrin in the dark and its effect on the insecticidal activity to tsetse flies.

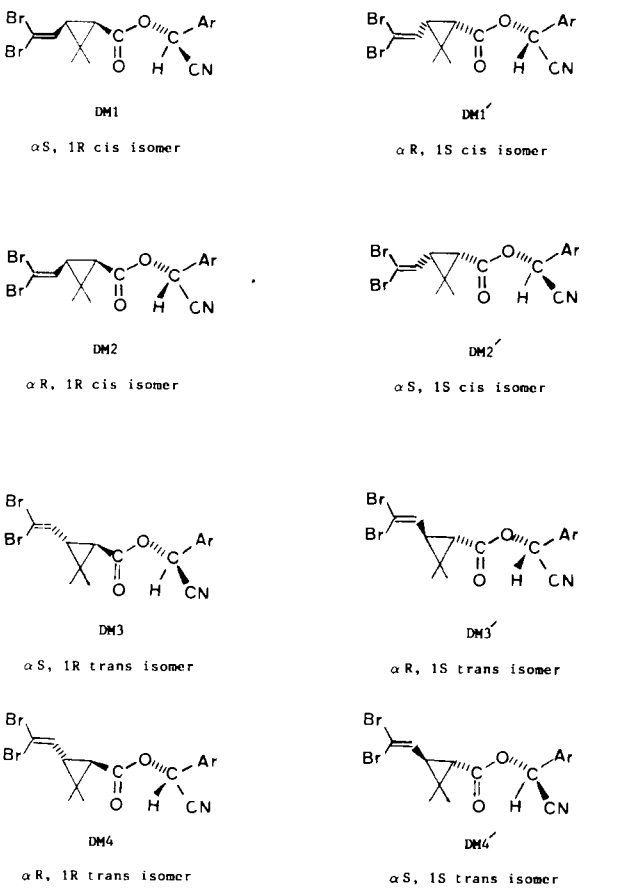

Figure 1. Structures of eight possible isomers of deltamethrin.

MATERIALS AND METHODS

Materials. Analytical standards of deltamethrin isomers DM1, DM2, DM3, and DM4 were provided by Roussel Uclaf, Paris. The purity of the isomers was greater than 95%. Pesticide grade and reagent grade organic solvents were obtained from E. Merck (Darmstadt) and Rathburn Chemicals Ltd. (Walkerburn, U.K.). Hexane used for gas chromatographic analysis was glass distilled prior to use. All glassware was rinsed with pesticide grade solvents prior to use.

Isomerization of Deltamethrin. Isomerization of DM1 was studied in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol,

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2-methyl-1-propanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 1-octanol, 2-octanol, acetone, acetonitrile, *p*-dioxane, *n*-hexane, diethyl ether, ethyl acetate, benzene, and toluene. Depending on the solubility of deltamethrin in these solvents, a 0.1–1.0 mg/mL solution of deltamethrin (DM1) was prepared in 10 mL of solvent in a glass vial and allowed to stand in the dark at room temperature (21 ± 1 °C). The solutions were analyzed at intervals of 24 h for 96 h.

For determining the rate of isomerization, DM1 was allowed to stand in ethyl alcohol in the dark at 21 ± 1 °C for 10 h. Samples were taken at intervals of 30, 60, 110, 180, and 240 min and analyzed for the conversion of DM1 to DM2. Then by using eq 1 for first-order reaction (Maron and Prutton, 1969), reaction rate constant K was calculated

$$K = (1/t)2.303 \log [a/(a - x)] \quad (1)$$

where a is the initial concentration of DM1 and $a - x$ its concentration at time t.

Reactions of Alcohols with Other Pyrethroid Insecticides. The isomerization reaction of aliphatic alcohols with cypermethrin, *lambda*-cyhalothrin, cyfluthrin, and permethrin was also studied by allowing solutions of technical standards of these compounds in methanol and ethanol to stand in the dark at 21 ± 1 °C and analyzing the products.

Analysis. For analysis, an aliquot of the sample was first applied on a TLC plate and the plate developed in a solvent mixture. For qualitative analysis, a droplet containing an equivalent of 10 μg of DM1 was applied to the TLC plate, and for quantitative analysis a solution containing an equivalent of 500 μg of DM1 was streaked as a band on the plate. TLC analysis was carried out on 0.25 mm thick chromatoplates precoated with silica gel 60 F-254 (Merck). The developing solvent systems included (A) *n*-hexane/ethyl acetate (9:1 v/v) and (B) benzene/carbon tetrachloride (1:1 v/v). After development of the plate, the solvents were evaporated from the plate and the plate was viewed under a short-wave UV lamp (254 nm) for quenching of the fluorescent gel. The areas for reaction products were scraped out and extracted with ethyl acetate, and this extract was directly analyzed by HPLC. A 10-μL aliquot was injected into a Waters Associates HPLC (Waters Associates, Milford, MA) equipped with a Waters Model 45 solvent delivery system, Lambda-Max Model 481 UV detector, and a Data Module integrator. The column was a Merck Lichrosorb RP-18, 4 mm × 25 cm, 7 μm spherical partical size. The eluant was methanol/water (75:25 v/v), and the flow rate was 1 mL/min. The detector wavelength was 226 nm. For GC analysis the ethyl acetate extract was diluted with *n*-hexane to $^1/_{100}$ dilution, and 1-μL aliquots were injected in the GC. Gas chromatographic analysis was carried out on a Hewlett-Packard Model 5890 Series II instrument (Hewlett-Packard, Avondale, PA) with an electron capture detector using a 0.5 mm × 30 m long Supelco capillary column, Type SPB-608 (Supelco, Bellefonte, PA). The column temperature was programmed (55 °C for 2 min, 20 °C/min to 270 °C, 15 min at 270 °C). Detector and injection port temperatures were 300 °C. Nitrogen was used as a carrier gas, and the flow rate was 27 mL/min. One-microliter aliquots of solutions were injected in the column. Products of reaction were identified by comparing R_f values from the TLC and GC and HPLC retention times with those of authentic standards. The concentrations of the products were estimated by using a standard curve.

Bioassay of DM1 and DM(2+2′) on Tsetse Flies. Bioassay of DM1 and DM(2+2′) on tsetse flies was conducted according to the method of Hussain et al. (1990). One-day-old unfed female tsetse flies (*Glossina palpalis palpalis*) were used in this method. The inside rim of a 5.5 cm diameter plastic Petri dish was lined with a 1 cm wide × 16 cm long strip of cotton fabric which had been treated with DM1 or DM(2+2′) (29 μg/cm²). Cotton was used in this test because insecticide-treated targets used for tsetse fly control in Africa are made of cotton (Takken et al., 1986). DM(2+2′) used in this test was obtained from TLC of the reaction mixture of DM1 and ethanol. An untreated fabric strip was used as a control. Five flies, immobilized by chilling with cold air, were transferred into the Petri dish and the dish was covered with the top. The flies, which prefer to sit on the vertical surface, were exposed for 10 min to the treated cotton surface and then transferred into a holding cage. Mortality was observed at 10 min, 1.5 h, and 24 h after the exposure of the flies.

Table I. R_f Values of Deltamethrin Epimers on TLC Plates Developed in Two Different Solvent Mixtures[a]

reference standards			reaction products		
	R_f in solvent mixture			R_f in solvent mixture	
epimer	A	B	epimer	A	B
DM1	0.50	0.50	DM (1+1′)	0.49	0.51
DM2	0.55	0.51	DM (2+2′)	0.55	0.51
DM3	0.47	0.41	DM (3+3′)	ND[b]	ND
DM4	0.50	0.41	DM (4+4′)	ND	ND

[a] Solvent mixture A was *n*-hexane/ethyl acetate (9:11 v/v) and B was benzene/carbon tetrachloride (1:1 v/v). [b] ND, not detected.

RESULTS AND DISCUSSION

Neither the TLC system nor the GC and HPLC columns used were chiral and, hence, capable of distinguishing between individual stereoisomers. However, these chromatographic methods were capable of distinguishing the four epimers: (1+1′), (2+2′), (3+3′), and (4+4′). Therefore, our products of reaction may include either one or both stereoisomers. For example, product DM2 may be either DM2 alone or a DM(2+2′) mixture. As shown in Table I TLC system A resolved DM2 (R_f = 0.55) from the other three epimers (R_f = 0.47–0.50). DM3 (R_f = 0.47) and DM1 or DM4 (R_f = 0.50) were not clearly separable from one another in this solvent system. Solvent system B, however, separated DM1 and DM2 (R_f = 0.50, 0.51) from DM3 and DM4 (R_f = 0.41). Similarly, DM1 was separated from DM2 and DM3 but not from DM4 on HPLC as shown in Figure 2. Gas chromatography, on the other hand, could only partially resolve DM2 from the other products which yielded a broad peak with a slight shoulder as shown in Figure 3.

As the reaction was run in the dark, no light-induced cis–trans isomerization and, hence, no photoproducts including DM3 or DM4 were expected. Deltamethrin epimer DM1 reacted with some of the aliphatic alcohols (Table II) and, to a lesser degree, with acetone and acetonitrile in the dark. No reaction with hexane, diethyl ether, ethyl acetate, *p*-dioxane, benzene, toluene, 2-methyl-2-propanol, 1-octanol, and 2-octanol took place. This supports the report of Maguire (1990) that deltamethrin does not isomerize or degrade in hexane in the dark. TLC analysis of the reaction mixture after it had stood for 24 h in alcohols, acetone, or acetonitrile showed two spots in solvent system A. One of these spots had R_f = 0.49 and the second R_f = 0.55 (Table I). Only one spot was seen (R_f = 0.51) in solvent system B. This indicated that no DM3 or DM4 was formed and the only product of the reaction of DM1 with alcohols, acetone, or acetonitrile was possibly DM(2+2′). HPLC analysis of the reaction mixture showed two peaks (Figure 2), and GC also showed two peaks (Figure 3). Comparison of the retention times of these peaks with those for authentic standards indicated that DM(2+2′) was the only product. Since no trace for DM3 was seen on HPLC chromatogram and no spot for DM3 or DM4 was observed on TLC, the analyses confirmed that DM(2+2′) was the only product. As data in Table II show, conversion of DM1 to DM(2+2′) reached an equilibrium at about 24–28 h in ethanol. Equilibrium in methanol, 1-propanol, and 1-butanol was obtained in 2–3 days, but isomerization was slower in other alcohols, acetone, and acetonitrile. After 4 days of reaction, 40.4%, 35.1%, 9.8%, and 8.7% of DM1 was converted to DM(2+2′) in 1-pentanol, 2-propanol, 2-methyl-1-propanol, and 2-butanol, respectively. Reaction with acetone converted

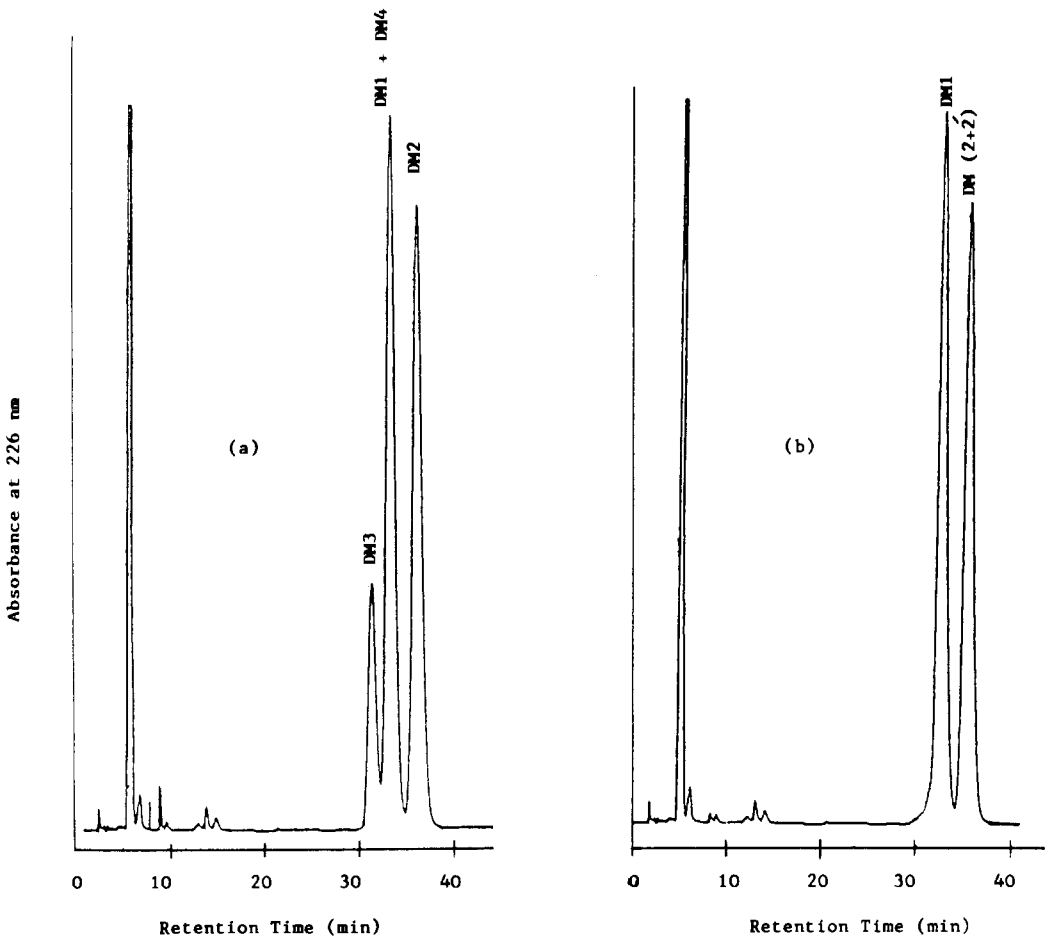

Figure 2. HPLC chromatograms of (a) a mixture of reference standards of deltamethrin epimers DM1, DM2, DM3, and DM4 and (b) a mixture of DM1 and DM(2+2′) at equilibrium in ethanol in the dark.

26.5% DM1 to DM(2+2′) during the same time, and only 15.2% DM1 isomerized to DM(2+2′) epimer in acetonitrile after 5 days.

Ruzo et al. (1977) reported that the rate of isomerization of DM1 to DM2 in alcohols in the presence of light was related to solvent viscosity. However, in our reactions, which were run in the dark, we did not see a direct relationship. Thus, in spite of differences between the viscosities of methanol, ethanol, and 1-propanol (0.6, 1.2, and 2.6 cP at 20 °C, respectively), the rates of conversion of DM1 to DM(2+2′) in these solvents were not very different and equilibrium was attained in approximately the same time. Also, isomerization was in some cases faster in more viscous alcohols; for example, 40.4% DM1 was converted to DM(2+2′) in 1-pentanol which has a viscosity of 4.65 cP at 15 °C, and 35.1% DM1 was converted to DM(2+2′) in 2-propanol with a viscosity of 2.86 cP. Similarly, 2-methyl-1-propanol and 1-pentanol have comparable viscosities but the rate of isomerization of DM1 to DM(2+2′) was 4-fold faster in 1-pentanol. There is an indication that the branching of the carbon chain, which increased steric hindrance, affected the rate of this ground-state reaction which, according to Ruzo et al. (1977), proceeds through α-proton exchange with the solvent. Maguire (1990) reported a similar reaction with water and showed that DM(2+2′) was the main product. An addition of 0.2 μmol of HCl or HBr to 2 μmol of deltamethrin in 1 mL of alcohol prevented the epimerization reaction, indicating that the exchange of α-proton of DM1 with the solvent was blocked.

Similar reactions were observed in the case of other synthetic pyrethroids which also contain an α-cyano group and an α-proton on an asymmetric carbon in the benzylic moiety. These included cyfluthrin, cypermethrin, and *lambda*-cyhalothrin. However, permethrin, which does not have an asymmetric carbon in the benzylic moiety, did not undergo these reactions.

Table III shows data on the rate of epimerization of DM1 to DM(2+2′) in ethanol at 21 ± 1 °C in the dark. The reaction rate constant was calculated to average 2.25×10^{-5} s^{-1}, and the correlation coefficient was 0.999, which indicates that the epimerization follows first-order rate of reaction. The resulting DM(2+2′) epimer was extracted from the TLC plates and dissolved in ethanol. On standing in the dark it underwent isomerization and a mixture of DM(1+1′) and DM(2+2′) was formed, which again reached equilibrium.

Bioassay of the DM1 epimer on tsetse flies resulted in the mortality of all flies within 10 min. On the other hand, all flies exposed to cotton fabric treated with a similar concentration of the DM(2+2′) epimer were still alive after 10 min. However, after 1.5 h these were moribund. After 24 h, the flies treated with DM1 were still dead but those treated with DM(2+2′) had all recovered. This indicated that DM(2+2′) had some, but very low, toxicity to the flies. This finding is consistent with the reports of Elliott et al. (1974) and Tessier (1982) that the DM2 epimer is nontoxic to insects. However, when DM(2+2′) was added to ethanol and the mixture bioassayed after 24 h, all flies were killed within 10 min, indicating the formation of the insecticidally potent DM1 epimer.

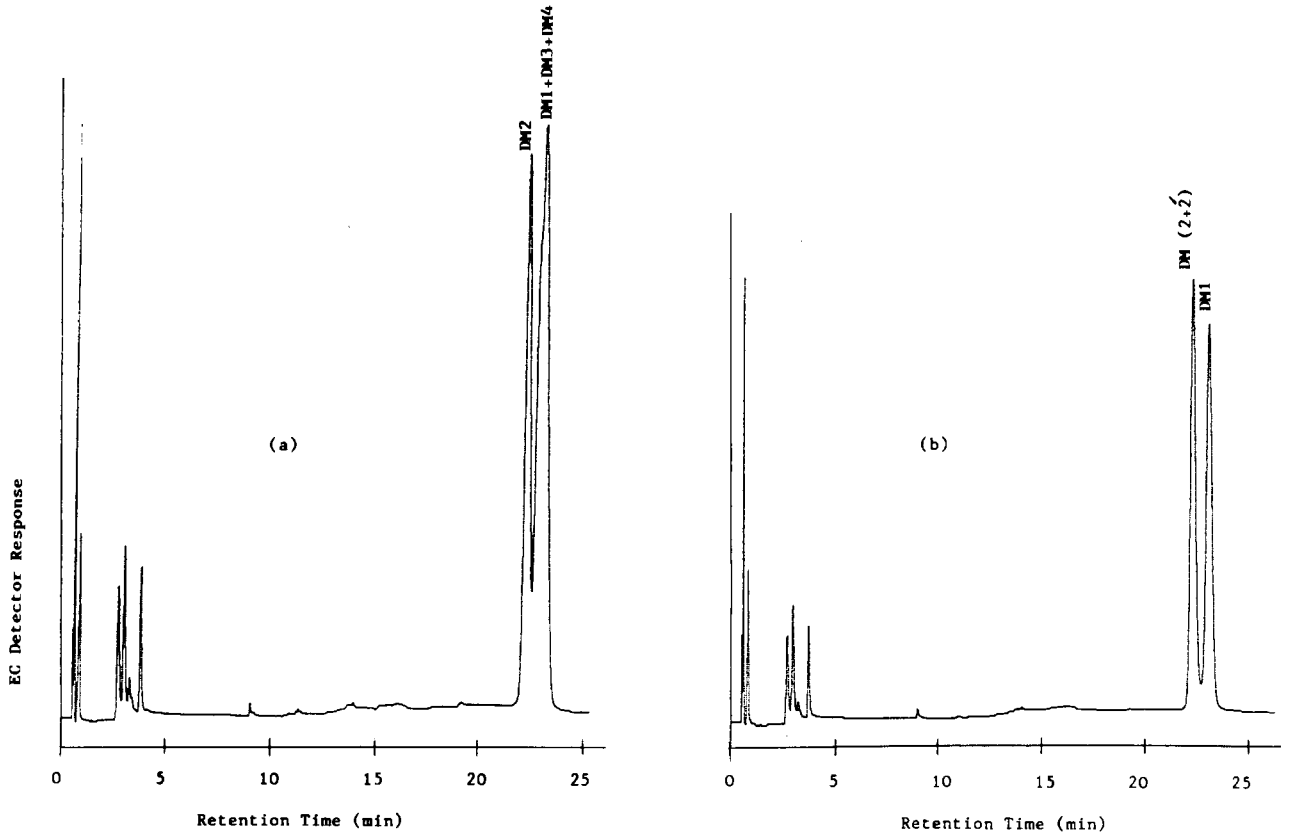

Figure 3. GC chromatograms of (a) a mixture of reference standards of deltamethrin epimers DM1, DM2, DM3, and DM4 and (b) a mixture of DM1 and DM(2+2′) at equilibrium in ethanol in the dark.

Table II. Percent Conversion of Deltamethrin (DM1) to Epimer DM(2+2′) in Alcohols

solvent	24 h	48 h	72 h	96 h
methanol	46.8	50.3	50.5	50.8
ethanol	49.8	51.5	51.5	51.5
1-propanol	45.1	49.5	51.2	51.4
1-butanol	30.8	45.9	51.0	52.8
1-pentanol	20.8	30.2	36.7	40.4
2-propanol	22.1	28.8	33.0	35.1
2-methyl-1-propanol	4.4	5.9	8.0	9.8
2-butanol	3.1	5.2	7.1	8.7

Table III. Rate of Isomerization of Deltamethrin (DM1) in Ethanol at 21 ± 1 °C in the Dark

period of reaction t, min	% of DM1[a] isomerized to DM(2+2′) (x)	reaction rate constant K, $\times 10^{-5}$ s^{-1}
30	4.0	2.26
60	7.9	2.28
110	13.9	2.26
180	21.1	2.20
240	27.5	2.23

[a] Initial amount of DM1 (a) = 100%.

CONCLUSIONS

Technical grade deltamethrin containing 96.3% DM1 epimer isomerizes in aliphatic alcohols including methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, 2-butanol, and 1-pentanol and in acetone and acetonitrile in the dark. The rate of epimerization follows first-order kinetics and results in a mixture of DM1 and DM(2+2′) in equilibrium. The reaction is faster in short- and straight-chain alcohols than in long- and branched-chain alcohols, and DM(2+2′) is the only epimer formed in the dark. The epimerization does not take place in 2-methyl-2-propanol, 1-octanol, 2-octanol, diethyl ether, ethyl acetate, hexane, benzene, toluene, and *p*-dioxane.

The DM(2+2′) epimer was found to be much less insecticidal than DM1. All tsetse flies exposed to DM1 were killed within 10 min, but all those exposed to DM-(2+2′) were alive 24 h after a 10-min exposure. Alcohols are sometimes used in deltamethrin formulations, and this can result in reduced toxicity of the formulations.

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