Original Article

Structure-activity Relationships of Insecticidal α -Cyanobenzyl Cyclopropanecarboxylates*

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The structure-activity relationships of α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates having various substituents at the 3-position of the benzyl group have been analyzed with physicochemical substituent parameters and regression techniques. The knockdown activity with and without synergists, PB and NIA, against the housefly, *Musca domestica* L., is correlated to the hydrophobicity, steric bulkiness, and stereo-electronic properties of the 3-substituents. Without synergists, the variation in the knockdown activity is related to that in the lethal activity with the addition of the hydrophobic term, while with synergists, both variations are directly related to each other. Synergistic effects on the knockdown activity are not so remarkable, and these compounds are detoxified depending on the structure of the 3-substituent even under synergistic conditions.

INTRODUCTION

Pyrethroid insecticides have high knockdown activity as well as potent lethal activity. Generally, flying insects such as flies and mosquitoes are knocked down and crawling insects such as cockroaches are knocked over onto their backs when they are poisoned by pyrethroids. They may recover depending on the structure and/or concentration of the chemicals.

It has been pointed out that there are different optimum hydrophobicities for knockdown and lethality, and knockdown pyrethroids are less hydrophobic than lethal ones.^{1,2)} Fujita and his co-workers quantitatively analyzed the substituent effects on knockdown activities of substituted benzyl (1*R*)-*trans*-chrysanthemates against American cockroaches³⁾ and

houseflies⁴⁾ using hydrophobic, electronic, and steric parameters. They reported that the most significant parameter in determining both activities is the steric bulkiness of the substituents at the benzene ring represented by the van der Waals volume.

Pyrethroids are detoxified by oxidative and hydrolytic mechanisms in the insect body. To minimize these detoxication mechanisms, generally, the synergists PB (piperonyl butoxide) and NIA (NIA-16388 or propargyl propyl benzenephosphonate) are used.^{4–6)}

In this paper we have analyzed the relationship between the knockdown activity of 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates against houseflies with and without synergists and their chemical structures.

MATERIALS AND METHODS

1. Compounds

All α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates used are the same as those described in our previous paper.⁷⁾

* Studies on Insecticidal Pyrethroids (Part III).
For earlier study, see Ref. 7).

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Table 1 3-Substituted- α -cyanobenzyl 3-(2,5-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates and their knockdown activity against houseflies.

R	$\pi^a)$	$\Delta V_w^b)$	$I_\pi^c)$	log 1/KD ₅₀			
				Alone		PB+NIA	
				Obsd.	Calcd. ^{d)}	Obsd.	Calcd. ^{e)}
H	0.00	0.00	0	3.28	3.22	3.70	3.79
F	0.14	0.33	0	3.65	3.29	3.91	3.87
Cl	0.71	0.95	0	3.50	3.49	3.94	4.07
Br	0.86	1.26	0	3.51	3.57	4.13	4.15
C ₂ H ₅	1.02	2.14	0	3.56	3.73	4.53	4.34
CH ₂ CH=CH ₂	1.10	2.72	1	4.40	4.68	5.18	5.10
CH ₂ OCH ₃	-0.78	2.51	0	3.23	3.43	4.44	4.14
CH ₂ OC ₂ H ₅	-0.24	3.53	0	3.50	3.69	4.32	4.41
CH ₂ OCH ₂ CH=CH ₂	-0.25	4.11	0	4.01	3.77	4.39	4.52
CH ₂ OCH ₂ C≡CH	-1.12	4.12	0	3.71	3.60	4.42	4.39
OCH ₃	-0.02	1.44	0	3.15	3.42	4.16	4.05
OC ₂ H ₅	0.38	2.51	0	3.57	3.66	4.22	4.32
OC ₃ H ₇ (i)	0.85	3.53	0	4.30	3.90	4.62	4.58
OC ₄ H ₉ (s)	1.39	4.55	0	3.82	4.15	4.47	4.85
OCH=CH ₂	-0.04	2.07	1	4.45	4.36	4.60	4.81
OCH=CHCH ₃	0.50	3.09	1	4.51	4.61	4.89	5.08
OCH ₂ C(CH ₃)=CH ₂	0.86	4.20	0	4.12	4.00	4.95	4.71
CH ₂ C ₆ H ₅	2.01	5.36	1	5.02	5.24	5.75	5.74
OC ₆ H ₅	2.08	4.65	1	5.77	5.15	6.20	5.61
OC ₆ H ₄ Cl(p)	2.79	5.60	1	5.31	5.42	5.62	5.90

^{a)} Taken from Ref. 11). ^{b)} Taken from Ref. 14). ^{c)} I_π is an indicator variable that takes 1 for the compounds having π electrons at the $\beta\gamma$ -position of the substituents and zero for the others.

^{d)} By Eq. (2). ^{e)} By Eq. (3).

The structures of the compounds are listed in Table 1.

2. Knockdown Activity

The knockdown activity against adult female houseflies, *Musca domestica* L., was determined with and without synergists by the method described previously except for the observation time.⁷⁾ Houseflies poisoned by pyrethroids show a progressive series of poisoning symptoms: hyperactivity, ataxia, convulsions, and paralysis. With the α -cyano-3-phenoxybenzyl esters, symptoms of excitation are absent. Instead, ataxia and a lethargic stage, then finally flaccid paralysis develop.⁸⁾ In this experiment, houseflies were regarded as knocked down when the insects were para-

lyzed. As synergists, PB and NIA were used to avoid metabolic detoxication. PB and NIA show toxicity against houseflies at high concentrations,^{7,9)} so the knockdown activity of the synergists alone was first determined. Insects poisoned by pyrethroids may recover when the additional amount of synergists is insufficient. The additional ratio of synergists to pyrethroid for the desired effect was also examined. Next, the observation time for the knockdown activity was investigated under the conditions determined above. The knockdown activity was expressed as the negative logarithm of the molar KD₅₀ value, the concentration required for 50% knockdown, and is listed in Table 1.

3. Structure-Activity Correlations

The structure-activity correlations were analyzed with the multiple regression technique¹⁰⁾ using such physicochemical substituent parameters as the hydrophobic π ,¹¹⁾ Taft-Kutter-Hansch steric substituent constant E_s ,^{12,13)} van der Waals volume ΔV_w ,¹⁴⁾ and electronic σ .^{15,16)} The ΔV_w value is defined by $\Delta V_w(X) = V_w(X) - V_w(H)$, where $V_w(X)$ and $V_w(H)$ are the van der Waals volumes of X -substituents and H , respectively. The ΔV_w value used here is scaled by 0.1 to make the size comparable to that of the other parameters.

RESULTS AND DISCUSSION

As shown in Table 2, both synergists, PB and NIA, showed almost no knockdown activity within 6 hr even at the concentration that caused toxicity 48 hr after treatment. When PB and NIA were mixed together, 7.09

mm PB and 10.08 mm NIA showed no knockdown activity within 6 hr. The upper limits of synergists for this experiment were thus determined to be 7.09 mm PB and 10.08 mm NIA. As shown in Fig. 1, no recovery of the houseflies was observed within at least 3 hr when pyrethroid, PB, and NIA were mixed at the weight ratio of 1:7:7. To obtain the maximal synergistic effects in the combination of PB and NIA and furthermore to minimize the additional quantity of synergists to pyrethroid, this ratio was chosen for the following experiment. As shown in Fig. 2, the knockdown symptom became stable enough 3 hr after treatment, so the activity with synergists was measured at this time. The knockdown activity without synergists was also measured 3 hr after treatment.

First, the correlation between the knockdown activity with synergists and that with-

Table 2 Knockdown activity of synergists against houseflies.

Synergist(s)	Conc. (mm)	Time after treatment—% of knockdown					
		0.5	1	2	3	6	48 hr ^{a)}
PB	14.18	0	0	0	0	0	15
NIA	20.15	0	0	0	0	5	100
PB+NIA	7.09+10.08	0	0	0	0	0	55

^{a)} Values for mortality.

Fig. 1 Enhancement of the knockdown activity of pyrethroids against houseflies by synergists.

○: 1 hr, ●: 2 hr, △: 3 hr after treatment. (a) 3-fluorobenzyl derivative, (b) 3-phenoxybenzyl derivative. Test solution contains pyrethroid and synergists at each ratio. The upper limits of the concentration of PB and NIA are 7.09 mm and 10.08 mm, respectively.

Fig. 2 Log $1/KD_{50}$ /time curves for (a) 3-fluorobenzyl derivative and (b) 3-phenoxybenzyl derivative.

The test solution contains the pyrethroid, PB, and NIA in the weight ratio of 1: 7: 7.

out synergists shown in Table 1 was investigated to yield Eq. (1).

$$\begin{aligned} \log [1/KD_{50} (PB+NIA)] \\ = 1.295 + 0.828 \log [1/KD_{50} (\text{alone})] \\ (\pm 0.712) (\pm 0.175) \\ n=20, s=0.260, r=0.920, \quad (1) \\ F=99.2 \end{aligned}$$

In this and the following equations, n is the number of compounds, s is the standard deviation, r is the correlation coefficient, and F is the F -value of the correlation. The figures in parentheses are the 95% confidence intervals of the corresponding coefficients. The addition of the hydrophobic π , steric ΔV_w or E_s , electronic σ to Eq. (1) did not afford any significant improvement. Figure 3 was obtained by plotting $\log [1/KD_{50}(PB+NIA)]$ against $\log [1/KD_{50}(\text{alone})]$. If PB and NIA show no synergistic effect, the lower straight line whose slope and intercept are 1 and zero, respectively, must be obtained for that plotting. As a matter of fact, however, the slope and intercept of the straight line expressed by Eq. (1) are 0.828 and 1.295, respectively. The distance between two straight lines in each $\log [1/KD_{50}(\text{alone})]$ value means the additional effect of synergists. From Fig. 3, it is obvious that the less the knockdown activity without synergists, the greater the enhancement of the knockdown activity with synergists.

Knockdown activity without synergists was

Fig. 3 Relationship between knockdown activities with and without synergists.

expressed by Eq. (2) with π , ΔV_w , and I_π .

$$\begin{aligned} \log [1/KD_{50} (\text{alone})] \\ = 3.217 + 0.194\pi + 0.146\Delta V_w \\ (\pm 0.278) (\pm 0.175) (\pm 0.096) \\ + 0.849I_\pi \quad (2) \\ (\pm 0.349) \\ n=20, s=0.276, r=0.936, F=37.5 \end{aligned}$$

In Eq. (2), I_π is an indicator variable that takes 1 for the compounds having π electrons at the $\beta\gamma$ -position of the substituents and zero for the others. The development of Eq. (2) is given in Table 3 and the degree of collinearity

Table 3 Development of QSAR of Eq. (2).

Intercept	I_π	π	ΔV_w	s	r	$F_{1,n-m-1}^{a)}$
3.636	1.274			0.408	0.834	41.03
3.561	0.957	0.279		0.344	0.891	8.23
3.217	0.849	0.194	0.146	0.276	0.936	10.40

^{a)} $F_{1,18,0.05}=4.41$, $F_{1,17,0.05}=4.45$, $F_{1,16,0.05}=4.49$

between variables is shown in Table 4. The positive sign of the π and ΔV_w terms in Eq. (2) means that the more the hydrophobicity and steric bulkiness, the higher the knockdown activity. The positive coefficient of the I_π term, 0.849, means that the presence of π electrons at the $\beta\gamma$ -position is favorable for high activity.

The synergistic activity was represented by Eq. (3).

$$\begin{aligned} \log [1/\text{KD}_{50} (\text{PB+NIA})] \\ = 3.785 + 0.152\pi + 0.189\Delta V_w \\ (\pm 0.241) (\pm 0.151) (\pm 0.083) \\ + 0.636I_\pi \quad (3) \\ (\pm 0.302) \\ n=20, s=0.239, r=0.941, F=41.0 \end{aligned}$$

The development of Eq. (3) is given in Table 5. The physicochemical meaning of Eq. (3) is the same as that of Eq. (2), but statistically Eq. (3) is better than Eq. (2). Equation (3) shows that the substituents exert hydrophobic, steric, and stereo-electronic effects on the knockdown activity with synergists. These substituent effects are similar to those on the lethal activity reported previously.⁷⁾ Nishimura *et al.*⁴⁾ confirmed that the synergistic knockdown and lethal activities of 3-substituted benzyl (1 *R*)-*trans*-chrysanthemates against houseflies were expressed by the hydrophobicity and van der Waals volume of the substituents. Their results are similar to ours. In Eqs. (2)

Table 4 Squared correlation matrix of variables used in Eqs. (2) and (3).

	π	ΔV_w	I_π
π	1.000		
ΔV_w	0.220	1.000	
I_π	0.301	0.166	1.000

and (3) I_π terms are involved, but not in the equations obtained by Nishimura *et al.*⁴⁾ This difference may be attributed to only a few compounds with $\beta\gamma$ -unsaturated substituents being involved in the data set used by them. The coefficients of each of the π and ΔV_w terms are very similar between Eq. (3) and the equation for the knockdown activity obtained by Nishimura *et al.*⁴⁾ Thus, the effect of substituents on the knockdown activity against houseflies are very similar between 3-substituted-benzyl chrysanthemates and the corresponding α -cyano-dichlorovinyl analogs.

The coefficient of $\log [1/\text{KD}_{50}(\text{alone})]$ term in Eq. (1) is somewhat smaller than 1. This means that these compounds are detoxified depending on the structure of the 3-substituent even under synergistic condition. The coefficients of each term in Eqs. (2) and (3) are not so different. This is consistent with the meaning of Eq. (1) because the coefficient of $\log [1/\text{KD}_{50}(\text{alone})]$ term in Eq. (1) is near to 1. Comparing the intercept in Eq. (2) with that in

Table 5 Development of QSAR of Eq. (3).

Intercept	I_π	ΔV_w	π	s	r	$F_{1,n-m-1}^{a)}$
4.300	1.073			0.415	0.781	28.09
3.759	0.771	0.215		0.263	0.923	27.89
3.785	0.636	0.189	0.152	0.239	0.941	4.55

^{a)} $F_{1,18,0.05}=4.41$, $F_{1,17,0.05}=4.45$, $F_{1,16,0.05}=4.49$

Eq. (3), the latter is somewhat larger than the former, and the difference is 0.568. This value represents synergistic effect on the nonsubstituted derivative. It can be said that synergistic effects on the knockdown activity is not so remarkable in this series of compounds, that is, 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates. These results are consistent with the experimental facts described below. Chrysanthemates of pyrethroids such as allethrin, pyrethrin I, and tetramethrin are mainly detoxified oxidatively at the isobutenyl moiety in the insect body.^{5,17-21)} This detoxication can be reduced greatly by the replacement of two methyl groups of that moiety to chlorine atoms (isobutenyl to dichlorovinyl).²²⁾ Furthermore, pyrethroids which have a cyano group at the α -position of the benzyl moiety are hydrolytically detoxified more slowly than the corresponding ones which do not have α -cyano group.^{23,24)} The compounds used in this study have the dichlorovinyl and cyano groups in the proper positions of acidic and alcoholic portion, respectively.

Table 1 shows that the phenoxy derivative has the highest knockdown activities. However the calculations by Eqs. (2) and (3) do not give the phenoxy derivative the highest knockdown activities, that is, the calculated values are rather smaller than the observed ones. The reason is not clear now. The three-dimensional factor which is not contained in Eqs. (2) and (3) may be to be considered. The phenoxy derivative may be able to take a favorable three-dimensional conformation for the activity compared with the other derivatives, including benzyl and *p*-chlorophenoxy ones. Further examination should be carried out.

Equations (4) and (5) were obtained by the analysis of the relationship between the knockdown and lethal activities. The latter activity values were taken from our previous paper.⁷⁾

$$\begin{aligned} \log [1/LC_{50}(\text{alone})] \\ = 1.631 + 0.222\pi \\ (\pm 0.615) (\pm 0.177) \\ + 0.495 \log [1/KD_{50}(\text{alone})] \quad (4) \\ (\pm 0.239) \\ n=20, s=0.246, r=0.917, F=44.7 \end{aligned}$$

$$\begin{aligned} \log [1/LC_{50}(\text{PB+NIA})] \\ = 2.297 + 0.593 \log [1/KD_{50}(\text{PB+NIA})] \\ (\pm 0.615) (\pm 0.132) \\ n=20, s=0.177, r=0.912, \quad (5) \\ F=89.1 \end{aligned}$$

The addition of the hydrophobic π , steric ΔV_w or E_s , electronic σ , or indicator variable I_π to Eq. (5) did not afford any significant improvement. According to Eq. (5), which was obtained for the synergistic activities, the greater the knockdown activity of a compound, the greater the lethal activity. Since the coefficient of the synergistic knockdown activity term in Eq. (5) is considerably smaller than 1, it is clear that the less the knockdown activity, the greater the difference of the concentration required for the definite activity between the knockdown and lethality caused by a compound. Unlike Eq. (5), Eq. (4) includes the π term. This term may relate to the detoxication process, because Eq. (5) was obtained for the activities measured in conditions that detoxication was depressed by the addition of synergists. According to Eq. (4), the more the knockdown activity and hydrophobicity of compounds, the greater the lethal activity.

In conclusion, the knockdown activity of 3-substituted- α -cyanobenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylates against houseflies is represented by the hydrophobicity, steric, and stereo-specific electronic properties of the substituents. Synergistic effects on the knockdown activity is not so remarkable.

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要 約

殺虫剤 α -シアノベンジルシクロプロパンカルボン酸エステル類の構造活性相関*

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α -シアノベンジル 3-(2,2-ジクロルビニル)-2,2-ジメチルシクロプロパンカルボキシレートのベンジル基の3位に種々の置換基を持つ化合物の構造活性相関を、物理化学的パラメータと回帰分析を用い解析した。共力剤添加、無添加状態で得られたイエバエ成虫に対するノックダウン活性の大きさの変化は、3位置換基の疎水性、立体的かさ高さおよび位置特異的な電子的効果と関係づけられる。共力剤無添加状態では、ノックダウン活性の変化は致死活性の変化と疎水性により関係づけられる。一方、共力剤添加状態では、ノックダウン活性の変化は致死活性の変化により良好に関係づけられる。

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