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Structure-Activity Relationships in Triaryl Phosphite Fungicides†

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Quantitative structure-activity relationship studies on triaryl phosphite fungicides show that the variation in fungicidal activity among the members of the series against *Pyricularia oryzae*, *Helminthosporium oryzae*, *Alternaria alternata* and *Pythium aphanidermatum* depends on changes in hydrophobicity of substituents in the phenyl ring. On the other hand, the variation in fungicidal activity against *Rhizoctonia bataticola* was found to depend on changes in both hydrophobicity and electronic character of substituents in the phenyl ring. Good correlation could be obtained only in the cases of *P. aphanidermatum* and *R. bataticola*.

Key Words: Triaryl phosphites, Fungicidal activity, Quantitative structure-activity relationship, Hydrophobicity, Electronic character

Introduction

Quantitative structure activity relationships on different series of organophosphorus fungicides have been reported recently (Nidiry et al. 1988, Gupta et al. 1988, Roy et al. 1988 and Nidiry et al. 1989). The present study deals with the QSAR of triaryl phosphites (Vasu et al. 1985) based on Hansch (1964) approach.

Materials and Methods

Parameters chosen

EC_{50} values given in the earlier paper (Vasu et al. 1985) were converted to molar activity for QSAR study. Thus in all cases, $-\log EC_{50}$, where EC_{50} is the median effective molar concentration for mycelial growth inhibition was taken as the dependent variable.

Hansch π values, which are measured of relative hydrophobicity of substituents and Hammett's electronic parameters σp and σm which were developed as measures of relative electronic influence of substituents on the ionization of benzoic acid in water were taken from literature (Hansch et al. 1979). The hydrophobicity parameter ($\Sigma\Pi$) and electronic character ($\Sigma\sigma$) for individual compounds were calculated by simple additivity principle and are presented in table 2. The parameters were considered only for phenyl ring since substitution pattern on all the three rings were similar in all the compounds.

Swain-Lupton constant (F) for proximity polar effect as suggested by Fujita and Nishioka, 1976, Taft's steric parameters (Es) and molar refractivity (MR) for *o*, *m* and *p* substitutions were also tested but showed no significant contribution towards

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Table 1 Regression equations obtained in the QSAR study with their statistical values

Sl.	Organism	Regression equation (No.)	n	R	S	F	Value of F showing significance at 1% level (Gupta 1984)
1.	*Pyricularia oryzae*	$-\log EC_{50} = 3.080 + 0.110(\Sigma\pi)^2$ (± 0.082) (1)	17	0.627	0.157	9.74	8.68
2.	*Helminthosporium oryzae*	$-\log EC_{50} = 3.112 + 0.153(\Sigma\pi)^2$ (± 0.083) (2)	17	0.684	0.187	13.18	8.68
3.	*Rhizoctonia*	$-log\ EC_{50} = 3.625 + 0.788(\Sigma\pi)$ (± 0.325) (3)	17	0.774	0.210	22.42	8.68
		$-\log EC_{50} = 3.040 + 0.529(\Sigma\pi)$† $+(\pm 0.318)$ $(+0.266)\,\Sigma\sigma$ ± 0.178 (4)	17	0.867	0.172	21.13	6.51
4.	*Alternaria alternata*	$-\log EC_{50} = 2.920 + 0.328\ (\Sigma\pi)$ (± 0.171) (5)	17	0.697	0.196	14.14	8.68
5.	*Pythium aphanidermatum*	$-log\ EC_{50} = 2.902 + 0.211(\Sigma\pi)^2$ (± 0.076) (6)	17	0.810	0.173	28.74	8.68

the variability in fungicidal activity. The square terms of $\Sigma\pi$ and MR(p) were also taken into consideration.

Results and Discussion

The significant equations for each test organism, obtained by carrying out step-wise multiple regression analysis provided in the S.P.S.S.G. Package (Anonymous 1979) are presented in table 1, with their statistical values: n = number of compounds considered, R = correlation coefficient, S = standard deviation and F = significance index with respect to the equation. The figures in paranthesis are for 95% confidence intervals.

Introduction of parameters like ΣF, ΣEs(o), ΣEs(m), Es(p), ΣMR(o), ΣMR(m) and MR(p) did not significantly improve the correlation. Introduction of $\Sigma\sigma$ significantly improved the correlation only in the case of *Rhizoctonia bataticola*. Introduction of square terms of hydrophobicity in the cases of *R. bataticola* and *Alternaria alternata* and introduction of linear terms of hydrophobicity in the cases of *Pyricularia oryzae*, *Helminthosporium oryzae* and *Pythium aphanidermatum* also did not significantly improve the correlation. The calculated values of fungicidal activity by regression equations with their experimental values are presented in table 2 for comparison purpose.

The study clearly shows that change in hydrophobicity of phenyl substituents is probably the most decisive factor in the variation in fungicidal activity among the members of the series against all the fungi studied. The variation in hydrophobicity alone accounted for 39.3% of the variation in fungicidal activity against *P. oryzae*, 46.8% against *H. oryzae*, 59.9% against *R. bataticola*, 48.6% against *A. alternata* and 65.6% against *P. aphanidermatum*. The variations in hydrophobicity and electronic character of the substituents together accounted for 75.2% of the variation against *R. bataticola*. Steric factors were not found to play any significant role in determining the fungicidal activity against any of the test fungi studied.

Table 2 *Physico chemical parameters* of triaryl phosphites with experimental and calculated fungicidal activity data* ($P-(O-\langle O\rangle-R)_3$)

Sl.	R	Σπ	Σσ	−log EC_{50} against									
				P. oryzae		*H. oryzae*		*R. bataticola*		*A. alternata*		*P. aphanidermatum*	
				Exp.	Calc.[1]	Exp.	Calc.[2]	Exp.	Calc.[3]	Exp.	Calc.[4]	Exp.	Calc.[5]
1	H	0.00	0.00	3.00	3.08	3.01	3.11	2.76	3.04	2.83	2.92	2.51	2.90
2	2-Cl	0.71	0.23	3.07	3.13	2.99	3.19	2.97	3.35	3.28	3.15	3.14	3.01
3	4-Cl	0.71	0.23	3.21	3.13	3.58	3.19	3.56	3.35	3.79	3.15	3.26	3.01
4	2-CH_3	0.56	−0.17	3.26	3.12	3.24	3.16	3.22	3.10	3.16	3.10	2.74	2.97
5	3-CH_3	0.56	−0.07	3.02	3.12	3.11	3.16	3.40	3.15	2.96	3.10	3.06	2.97
6	4-CH_3	0.56	−0.17	2.94	3.12	2.79	3.16	2.74	3.10	2.93	3.10	3.21	2.97
7	2-OCH_3	−0.02	−0.27	3.31	3.08	3.29	3.11	2.93	2.89	2.95	2.91	3.04	2.90
8	4-OCH_3	−0.02	−0.27	3.11	3.08	2.99	3.11	2.99	2.89	2.98	2.91	2.83	2.90
9	4-SCH_3	0.61	0.00	3.31	3.12	3.34	3.17	3.03	3.20	3.12	3.12	3.12	2.98
10	2,4-Cl_2	1.42	0.46	3.34	3.30	3.49	3.42	3.47	3.66	3.77	3.39	3.28	3.33
11	4-Cl, 3-CH_3	1.27	0.16	3.33	3.26	3.45	3.36	3.54	3.46	3.62	3.34	3.20	3.24
12	2,3-$(CH_3)_2$	1.12	−0.24	3.34	3.22	3.33	3.31	3.20	3.21	3.17	3.29	3.16	3.17
13	2,4-$(CH_3)_2$	1.12	−0.34	2.96	3.22	3.15	3.31	3.10	3.16	3.23	3.29	3.21	3.17
14	2,6-$(CH_3)_2$	1.12	−0.34	3.12	3.22	3.44	3.31	3.28	3.16	3.12	3.29	3.15	3.17
15	3,4-$(CH_3)_2$	1.12	−0.24	2.92	3.22	3.10	3.31	3.31	3.21	3.17	3.29	2.95	3.17
16	3,5-$(CH_3)_2$	1.12	−0.14	3.32	3.22	3.40	3.31	3.20	3.26	3.30	3.29	3.11	3.17
17	2,4,5-Cl_3	2.13	0.83	3.65	3.58	3.76	3.81	3.57	4.05	3.86	3.62	3.91	3.86

* Considered for one phenyl ring only; calculated by eq. (1); calculated by eq. (2); 3, calculated by eq. (4); 4, calculated by eq. (5); 5, calculated by eq. (6).

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