Proc. Indian natn. Sci. Acad. **B54** No.6 pp. 395-398. (1988)

Quantitative Structure Activity Studies of Fungicidal *O,O*-Bisaryl Methyl Phosphonates*

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(Accepted on 6 December 1988)

Quantitative structure activity relationship studies on O,O-bisaryl methyl phosphonate fungicides were carried out. The variation in fungicidal activity against *Pyricularia oryzae Helminthosporium oryzae* and *Rhizoctonia bataticola* was found to depend on changes in hydrophobicity of substituents of the phenyl ring and variation in fungicidal activity against *Alternaria alternata* and *Pythium aphanidermatum* was found to depend on changes in electronic character of substituents on the phenyl ring. Excellent correlation could be obtained particularly in the cases of *Alternaria alternata* and *Helminthosporium oryzae.*

Key Words: Quantitative structure activity relationship, Fungicidal activity, *O,O*-bisaryl methyl phosphonates, Hydrophobicity, Electronic character

Introduction

The variation of fungicidal activity in a congeneric series of compounds is influened by different hydrophobic, electronic and steric properties of the members of the series. These possible influences can be studied in a quantitative way with multiple regression analysis using substituent constants for the properties mentioned.

We present here our study on the correlation of physico-chemical parameters of *O,O*-bisaryl methyl phosphonates (Vasu & Roy 1983) with their fungicidal activity against *Pyricularia oryzae, Helminthosporium oryzae, Alternaria alternata, Rhizoctonia bataticola* and *Pythium aphanidermatum*.

Materials and Methods

Parameters chosen

EC_{50} values given in our earlier paper (Vasu & Roy 1983) has been converted to molar activity for the 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 measures of relative hydrophobicity of substituents were taken from literature (Hansch & Leo 1979). 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 also were taken from literature. For ortho substituents, σp alongwith F, Swain-Lupton constant for proximity polar effect suggested by Fujita and Nishioka (1976) was used. Taft's ES parameters (Jaffe 1953) which were developed in the studies of organic reaction meachnism of aliphatic esters were taken to study the steric influence of substituents. Since substituents are placed at different positions of the phenyl ring, this was separated into three: Es(o) denotes Taft's steric constant for ortho-substituent, Es(m) for the meta-substituent and Es(p) for the para-substituent. The

*Contribution No. 414
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additive nature of all substituent parameters was presumed. The parameters were considered only for one phenyl ring since substituents on both rings are the same. The various parameters taken for individual compound are presented in table 1. A squared correlation matrix for the same is given in table 2.

Multiple Regression

The multiple regression analysis was carried out by a computerised method the parameters minimising the sum of squared deviations being introduced step by step. The stepwise regression provided in the SPSS Package (Anonymous 1979) through Burrough's 4700 electronic computer at Indian Agricultural Statistical Research Institute was used for this purpose.

Results and Discussion

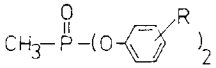
The significant equations for each test organism are given below together with their statistical values n=number of compounds considered, R=correlation coefficient, s=standard deviation and F=significance index with respect to the equation. The figures in parenthesis are for 95% confidence intervals.

Pyricularia oryzae

The following regression equation was obtained between fungicidal activity and hydrophobicity parameter $\Sigma\pi$.

$$-\log EC_{50}=3.214 + \underset{(+\ 0.137)}{0.412}\ \Sigma\pi \qquad \ldots(1)$$

$n=18$, $R=0.815$ $s=0.254$, $F=31.13$

Table 1 *Physico-chemical parameters of O,O-*bisaryl methyl phosphonates 

Sl. No.	R	ΣΠ	Σσ	ΣF	$\Sigma E_S(o)$	$\Sigma E_S(m)$	$E_S(P)$
1.	H	0.00	0.00	0.00	0.00	0.00	0.00
2.	2-Cl	0.71	0.23	0.41	-0.97	0.00	0.00
3.	4-Cl	0.71	0.23	0.00	0.00	0.00	-0.97
4.	$2\text{-}CH_3$	0.56	-0.17	-0.04	-1.24	0.00	0.00
5.	$3\text{-}CH_3$	0.56	-0.07	0.00	0.00	-1.24	0.00
6.	$4\text{-}CH_3$	0:56	-0.17	0.00	0.00	-0.00	-1.24
7.	$2\text{-}OCH_3$	-0.02	-0.27	0.26	-0.55	0.00	0.00
8.	$4\text{-}OCH_3$	-0.02	-0.27	0.00	0.00	0.00	-0.55
9.	$4\text{-}SCH_3$	0.61	0.00	0.00	0.00	0.00	-1.07
10.	$2,4\text{-}Cl_2$	1.42	0.46	0.41	-0.97	0.00	-0.97
11.	$3\text{-}CH_3$, 4-Cl	1.27	0.20	0.00	0.00	-1.24	-0.97
12.	$2,3\text{-}(CH_3)_2$	1.12	-0.24	-0.04	-1.24	-1.24	0.00
13	$2,4\text{-}(CH_3)_2$	1.12	-0.34	-0.04	-1.24	0.00	-1.24
14.	$2,6\text{-}(CH_3)_2$	1.12	-0.34	-0.08	-2.48	0.00	0.00
15.	$3,4\text{-}(CH_3)_2$	1.12	-0.24	0.00	0.00	-1.24	-1.24
16.	$3,5\text{-}(CH_3)_2$	1.12	-0.14	0.00	0.00	-2.48	0.00
17.	$2,4,5\text{-}Cl_3$	2.13	0.83	0.41	-0.97	-0.97	-0.97
18.	Cl_5	3.55	1.43	0.82	-1.94	-1.94	-0.97

Table 2 *Squared correlation matrix for the physico chemical parameters*

	ΣΠ	Σσ	ΣF	$\Sigma E_S(O)$	$\Sigma E_S(m)$	$E_S(p)$
ΣΠ	1	0.64	0.47	0.28	0.32	0.14
Σσ		1	0.76	0.07	0.12	0.10
ΣF			1	0.14	0.05	0.02
$\Sigma E_S(o)$				1	0.00	0.03
$\Sigma E_S(m)$					1	0.00
$E_S(p)$						1

Introduction of any other parameter like $(\Sigma\pi)^2$, σ, F, E_S (o), E_S (m) or E_S (p) did not significantly contribute towards the correlation. The F value of equation (1) shows significance at 1% level (Gupta 1984) $[F^1_{16}(0.01)=8.56]$ and the equation can explain 66.5% of the variation exhibited by the members of the series. The observed and calculated values are given in table 3. Marked difference between observed and calculated value is shown by one compound i.e. *O,O*-bis (2,4,5-trichlorophenyl) methyl phosphonate which possesses exceptionally higher activity than the calculated value.

Helminthosporium oryzae

The following regression equation was obtained between fungicidal activity and hydrophobicity parameter $\Sigma\ \pi$

$$-\log EC_{50} = 3.174 + \underset{(\pm\ 0.116)}{0.390}\ \Sigma\ \pi \qquad \ldots(2)$$

$$n=18,\ R=0.856,\ s=0.205,\ F=43.78$$

Introduction of other parameters did not significantly improve the correlation. F value of equation (2) shows significance at 1% level $[F^1_{16}\ (0.01)=8.56]$ and explains 73.2% of the variation exhibited by the members of the series. The observed and calculated values presented in table 3 shows that they are close to each other except for *O,O*-bis (2,4,5-trichlorophenyl) methyl phosphonate.

Alternaria alternata

Hammett's electronic parameter $\Sigma\sigma$ minimised the sum of squared derivatives to the maximum extent and the following reqression equation was obtained.

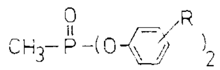
$$-\log EC_{50}=3.600 + \underset{(\pm\ 0.176)}{0.690}\ \Sigma\sigma \qquad \ldots\ (3)$$

$$n=18,\ R=0.888,\ s=0.170,\ F=59.24$$

Introduction of other parameters did not significantly improve the correlation. The equation (3) shows significance at 1% level $[F^1_{16}\ (0.01)=8.56]$ and explains 78.8% of the variation in fungicidal activity exhibited by the members of the series. The observed and calculated values in table 3 are very close to each other except for *O,O*-bis (2,4,5-trichloro phenyl) methyl phosphonate.

Rhizoctonia bataticola

When hydrophobicity parameter $\Sigma\pi$ alone was taken as the independent variable, the following equation was obtained.

Table 3 *Observed and calculated fungitoxicity data of O,O*-bisaryl methyl phosphonates 

$-\log EC_{50}$

Sl. No.	R	Pyricularia oryzae Obs.	Calc[1]	Helminthosporium oryzae Obs.	Calc[2]	Alternaria alternata Obs.	Calc[3]	Rhizoctonia bataticola Obs.	Calc[4]	Pythium aphanidermatum Obs.	Calc[5]
1	H	3.22	3.12	3.10	3.17	3.42	3.60	3.34	3.36	3.29	3.47
2.	2-Cl	3.63	3.51	3.27	3.45	3.58	3.76	3.41	3.61	3.34	3.65
3.	4-Cl	3.69	3.51	3.41	3.45	3.64	3.76	3.58	3.61	4.10	3.65
4.	$2\text{-}CH_3$	3.53	3.45	3.42	3.39	3.46	3.48	3.50	3.56	3.45	3.34
5.	$3\text{-}CH_3$	3.63	3.45	3.38	3.39	3.49	3.55	3.49	3.56	3.47	3.42
6.	$4\text{-}CH_3$	3.21	3.21	3.41	3.39	3.58	3.48	3.50	3.56	3.73	3.34
7.	$2\text{-}OCH_3$	3.13	3.21	3.22	3.17	3.48	3.41	3.52	3.35	3.12	3.26
8.	$4\text{-}OCH_3$	3.36	3.21	3.46	3.17	3.42	3.41	3.52	3.35	3.01	3.26
9.	$4\text{-}SCH_3$	3.33	3.47	3.26	3.41	3.48	3.60	3.15	3.58	3.32	3.47
10	$2,4\text{-}Cl_2$	3.61	3.80	3.84	3.73	3.60	3.92	3.57	3.87	3.33	3.83
11.	$3\text{-}CH_3$, 4-Cl	3.72	3.74	3.84	3.67	3.66	3.74	3.66	3.81	3.51	3.63
12.	$2,3\text{-}(CH_3)^2$	3.67	3.68	3.82	3.61	3.65	3.43	3.93	3.76	3.53	3.29
13.	$2,4\text{-}(CH_3)_2$	3.40	3.68	3.40	3.61	3.51	3.37	3.60	3.76	3.41	3.21
14.	$2,6\text{-}(CH_3)_2$	3.54	3.68	3.38	3.61	3.45	3.37	3.58	3.76	2.91	3.21
15.	$3,4\text{-}(CH_3)_2$	3.54	3.68	3.49	3.61	3.46	3.43	4.05	3.76	3.03	3.29
16.	$3,5\text{-}(CH_3)_2$	3.54	3.68	3.41	3.61	3.49	3.50	4.14	3.76	3.74	3.37
17.	$2,4,5\text{-}Cl_3$	4.88	4.09	4.51	4.01	4.58	4.17	4.88	4.12	4.70	4.12
18.	Cl_5	4.45	4.68	4.39	4.56	4.63	4.59	4.34	4.63	4.41	4.59

[1]Calculated by eq. (1); [2]Calculated by eq. (2); [3]Calculated by eq. (3); [4]Calculated by eq. (4); [5]Calculated by eq. (5);

$$-\log EC_{50}=3.358 + 0.358\ \Sigma\Pi \ldots (4)$$
$$(\pm\ 0.165)$$
$$n=18,\ R=0.727,\ s=0.294,\ F=17.98$$

Other parameters did not significantly improve the correlation. Although F value shows significance at 1% level [F^1_{16} (0.01) = 8.56], the equation explains only 52.9% of the variation in fungicidal activity against *R. bataticola* exhibited by the members of the series. Marked difference between observed and calculated values are shown by compounds, viz, *O,O*-bis (3,4-dimethyl phenyl) methyl phosphonate and *O,O*-bis (2,4,5-trichlorophenyl) methyl phosphonate.

Pythium aphanidermatum

The following regression equation was obtained between fungicidal activity and Hammett's electronic parameter $\Sigma\sigma$

$$-\log EC_{50} = 3.474 + 0.782\ \Sigma\sigma \ldots (5)$$
$$(\pm\ 0.333)$$
$$n=18,\ R=0.755,\ s= 0.321,\ F= 21.25$$

Introduction of other parameters did not significantly improve the correlation. Although F value shows significance at 1% level [$F^1{}_{16}$ (0.01)=8.56] equation (5) explains only 57.1% of the variation in fungicidal activity exhibited by the members of the series. Marked difference between observed and calculated values is shown in the case of two compounds, viz, *O,O*-bis-(2-4-dichloro phenyl) methyl phosphonate and *O-O*-bis (2-4-5-trichlorophenyl) methyl phosphonate.

Conclusion

Thus variation in fungicidal activity exhibited by the members of the series against *Pyricularia oryzae, Helminthosporium oryzae* and *Rhizoctonia bataticola* mainly depended on change in hydrophobicity of substitutents ($\Sigma\pi$) on the phenyl ring, while variation in fungicidal activity against *Alternaria alternata* and *Pythium aphanidermatum* depended mainly on changes in the electronic character ($\Sigma\sigma$) of substituent on the phenyl ring.

Since there is an intercorrelation between hydrophobicity and electronic character (table 2), both these factors may be contributing towards fungicidal activity against all other test fungi. Comparison of calculated and observéd value (table 3) shows that *O,O*-bis (2,4,5-trichlorophenyl) methyl phosphonate possesses exceptionally high activity than the calculated value against all the test fungi. This indicates that optimum hydrophobicity alongwith electronic parameters may be contributing towards the high activity of this compound. Besides, there could be some unknown mechanism which might be responsible for its high activity.

References

Anonymous 1979 Burrough's Medium System SPSSG; CCIMS Teacher's College Columbia University

Fujita T and Nishioka T 1976 The analysis of ortho-effect; *Progr. Phys. Org. Chem.* **12** 49

Gupta S P 1984 *Statistical Methods* (New Delhi: Sultan Chand and Sons) xxxviii pp.

Hansch C and Leo A 1979 *Substituent Constants for Correlation Analysis in Chemistry and Biology pp 50-51* (New York: John Wiley & Sons. N.Y.)

Jaffe H H 1953 A re-examination of Hammett equation; *Chem. Rev.* **53** 191-261

Vasu K and Roy N K 1983 Synthesis and fungicidal activity of diaryl methyl phosphonates; *Agric. Biol. Chem.* **47** 2657-2659