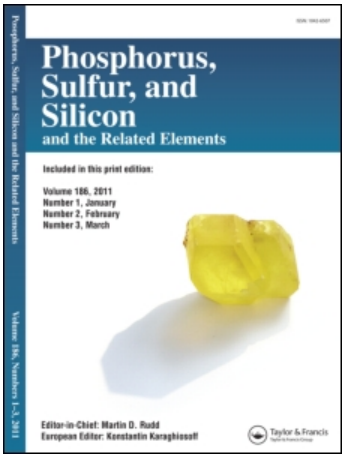

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STRUCTURE-ACTIVITY STUDIES OF AMINOPHOSPHONIC DERIVATIVES OF FLUORENE

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STRUCTURE-ACTIVITY STUDIES OF AMINOPHOSPHONIC DERIVATIVES OF FLUORENE

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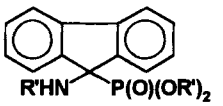
Structure-activity dependence of 51 aminofluorenephosphonic acid derivatives was studied. It was found that herbicidal activity of the studied compounds depends on the hydrophobic parameters, and to a smaller extent to the electronic parameters of the substituents on nitrogen and phoshorus atoms and is independent on their steric parameters.

Key words: Aminophosphonic acid, morphactin, fluorene, QSAR.

INTRODUCTION

The aminophosphonic acid derivatives of fluorene of the general structure:



represent an interesting class of plant growth regulators.[1-13] We have been studying this class of compounds since 1974. Some of our compounds happen to be of high biological activity, comparable with the known herbicide-N-phosphonomethylglycine. In this paper we are trying to build a mathematical model of biological activity in order to explain the variance of activity in terms of molecular features.

Any way which can help to plan a synthesis of a new potentially active compound can be of some value as it can diminish an effort of investigators. Structure-activity studies are also of enormous commercial interest, since "trial and error" approach has become extremely expensive. Among various methods, the classic one developed by Hansch[14] is still commonly applied in drug design research. In general, this method is based on an assumption that variations of the biological activity shown by a set of compounds, can be explained in terms of physicochemical, molecular and structural parameters of the compounds. The goal is to find an equation which correlates the observed biological activity with the structural parameters BA = f (structure parameters) There are some very successful predictions (see for example a review by Y. C. Martin[15]) as well as a lot of failures. Hansch himself stated: "predicting QSAR is somewhat like a blind man defining an object or a room by exploring it with hands: eventually a good image can be developed."[10] Correlation coefficient, standard error of estimate and Fisher test are used very frequently to evaluate the quality of the model. In the presented paper we tried to find out whether certain physicochemical properties can explain the variations in biological activity

found for the series of compounds, and which of the parameters are of great importance.

MATERIALS AND METHODS

The calculations were done for a set of 51 aminophosphonic acid derivatives synthesised in our laboratory.

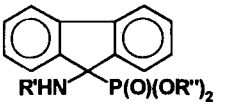
Methods of syntheses as well as biological activity were presented previously.[1,7,8,10] The following criteria were used in selection of these 51 compounds from all we have synthesized: all compounds were tested in the same biological test and in the same conditions, all compounds were well purified, the structure of each compound has been proven, the calculations of the physicochemical parameters were consistent within the whole data set. All the considered compounds are listed in the Table I. The biological tests were done in the Institute of Industrial Chemistry in Warsaw. Two week old plants were sprayed to get a 5 kg/ha dose. Two weeks later the effect was estimated in a five point scale (0—no effect, 1—low, 2—medium, 3—good, 4—very good). Ten plants were used as bioindicators and they are ordered in the following manner:

1. ryegrass (*Arrhenatherum elatius*)
2. oats (*Avena sativa*)
3. maize (*Zea mays*)
4. mustard (*Sinapis arvensis*)
5. peas (*Pisum sativum*)
6. bean (*Phaseolus vulgaris*)
7. cucumber (*Cucumis sativus*)
8. flox (*Linum usitatissimum*)
9. red beet (*Beta esculenta*)
10. buckwheat (*Fagopyrum sagittatum*)

Thus every compound is characterized by ten numbers i.e. it is represented by a point in a ten dimensional vector space, whereas each number corresponds to an activity towards particular plant. In the column 4 the activity vector in a postemergence test is presented. Column 5 shows the average activity. As it has been calculated in a separate experiment[17] it contains about 65% of the original variance given by the whole response vector. We call this value—biological activity and we use it as a dependend variable in multivariate linear regression analysis. Three molecular parameters were used in the regression equation as the independent variables. They are presented in columns 6–8. The partition coefficients (column 6) were calculated using the fragmental constants as described by Rekker[18] and were taken from Reference 19. The fragmental constants for electronic parameters (column 7) were taken from Reference 19. Steric parameters (column 8) were taken from the papers by Chartonet and all.[20–22]

TABLE I

Fluorene derivatives used in calculations

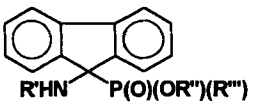


No.	R'	R''	activity vector	BA	v	s	log(P)
1	H	Et	2223233333	2.6	0.96	-2.202	2.341
2	H	nPr	0001001111	0.5	1.12	-2.354	3.495
3	H	iPr	3303033333	2.4	1.5	-2.6	3.163
4	H	nBu	0002220002	0.8	1.16	-2.438	4.549
5	H	nC_5H_{11}	0001001000	0.2	1.16	-2.59	5.603
6	H	nC_8H_{17}	0000000000	0	1.16	-2.38	8.765
7	H	$nC_{11}H_{23}$	0001000000	0.1	1.16	-2.586	11.927
8	H	$nC_{16}H_{33}$	0000000001	0.1	1.16	-2.738	17.197
9	H	$nC_{16}H_{35}$	0000011001	0.3	1.16	-2.738	18.603
10	H	$nC_{18}H_{37}$	0000000000	0	1.16	-2.738	19.305
11	nPr	Et	2303033332	2.2	1.64	-3.379	3.613
12	nPr	nPr	3304023333	2.4	1.8	-3.531	4.667
13	nPr	iPr	3304034433	2.7	2.18	-3.777	4.435
14	nPr	nBu	3334344444	3.6	1.84	-3.615	5.721
15	iPr	iPr	3304233443	2.9	2.26	-3.9	4.319
16	nBu	Et	1203033332	2	1.64	-3.421	4.14
17	nBu	nPr	3434334334	3.4	1.8	-3.573	5.194
18	nBu	iPr	3334334343	3.3	2.18	-3.819	4.962
19	nBu	nBu	2334333344	3.2	1.84	-3.657	6.248
20	nBu	nC_8H_{17}	0001011100	0.4	1.84	-3.599	10.464
21	nBu	$nC_{11}H_{23}$	0000000000	0	1.84	-3.805	13.626
22	nBu	$nC_{16}H_{33}$	0000000000	0	1.84	-3.957	18.896
23	nBu	$nC_{18}H_{37}$	0000000000	0	1.84	-3.957	21.004
24	nBu	Ph	0001222203	1.2	2.08	-2.181	5.474
25	iBu	Et	4434444444	3.9	1.94	-3.499	4.024
26	iBu	nBu	2104334344	2.8	2.14	-3.735	6.132
27	iBu	nC_8H_{17}	0001000100	0.2	2.14	-3.677	10.348
28	iBu	$nC_{11}H_{23}$	0000000000	0	2.14	-3.883	13.51
29	iBu	$nC_{16}H_{33}$	0000000000	0	2.14	-4.035	18.78
30	secBu	Et	3334344343	3.4	1.98	-3.571	4.024
31	secBu	nBu	3324343344	3.3	2.18	-3.807	6.132
32	secBu	nC_8H_{17}	0000000000	0	2.24	-4.107	20.888
33	nC_5H_{11}	iPr	2324244443	3.2	2.18	-3.895	5.489
34	nC_7H_{15}	Et	0004333343	2.3	1.69	-3.312	5.721
35	Ph	Me	0000020002	0.4	2.38	-2.411	2.699
36	Ph	nBu	0002032203	1.2	2.82	-2.919	5.861

CALCULATIONS

The calculations were done for all compounds presented in the Table I by constructing a multiple linear regression model. The multiple linear regression problem can be stated as looking for a linear relationship between a set of independent variables (molecular features) and the dependend variable (biological activity) in a form:

TABLE I (*Continued*)



R"'=Ph

No.	R'	R''	activity vector	BA	v	s	log(P)
37	H	Et	0000000000	0	2.14	-1.582	4.253
38	nBu	Et	0002032123	1.3	2.82	-2.801	6.343
39	iBu	Et	0003022223	1.4	3.12	-2.879	6.227
40	nC_5H_{11}	Et	0003223343	2	2.82	-2.877	6.87
41	C_7H_{15}	Et	0003233322	1.6	2.87	-2.692	7.924
42	C_9H_{19}	Et	0034334333	2.6	2.82	-2.852	2.82
43	$C_{12}H_{25}$	Et	2234333333	2.9	2.84	-2.139	10.559
44	$PhCH_2$	Et	0000002002	0.4	2.82	-2.951	6.483
45	nBu	H	0000000000	0	2.66	1.7	5.307
46	C_5H_{11}	H	0000000000	0	2.66	1.776	5.834
47	C_8H_{17}	H	0000000000	0	2.66	1.671	7.415
48	C_9H_{19}	H	0000000000	0	2.66	1.751	7.007
49	$C_{12}H_{25}$	H	0000000000	0	2.66	1.85	9.523
50	$PhCH_2$	H	0000000000	0	1.76	-1.038	5.447
51	nBu	Et	0002032011	0.9	1.76	1.253	5.034

$$Y = a_1x_1 + a_2x_2 + a_3x_3 + \cdots + a_nx_n + a_0 + e$$

where: Y = biological activity; x_1–x_n = molecular features; a_0–a_n = coefficients of the equation; e = prediction error (residual).

The task is to find a single set of coefficients, such that the sum of squared errors (residuals) is minimised. The algorithms can be found elsewhere.[23] The quality of the model can be estimated by correlation coefficient R, standart deviations and F-statistics.

RESULTS AND DISCUSSION

In the first part the diagrams of the biological activity dependence as a function of different physiocochemical properties are shown.

From the Diagram 1 one can see that there is some optimal range of log(P) in which the most active compounds were found. This is in agreement with some of our earlier publications in which we show that the transport of the molecule to the cell is important. It was previously found that peptides with phosphonic analogues of morphactins as a P terminal fragment were slightly more active than the "naked" compound. Our conclusion was that attaching a "transporter" makes the molecule more readily transportable to the iterior of the plant cell. Thus very hydrophilic compounds are not able to cross the lipid barrier, whereas the very lipophilic compounds are trapped by the lipophilic part of a membrane.

This is even better shown in Diagram 1a which is constructed as follows.

The whole data points were divided into 8 groups (which is close to $\sqrt{n}$, where n is the number of data points). For every group the average biological activity was

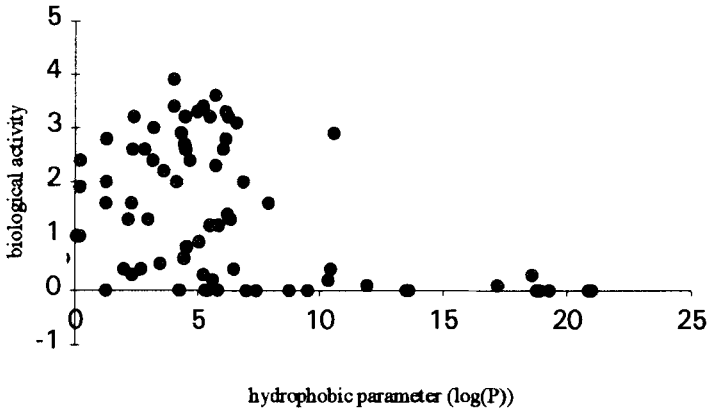


DIAGRAM 1 Biological activity as a function of hydrophobic parameter.

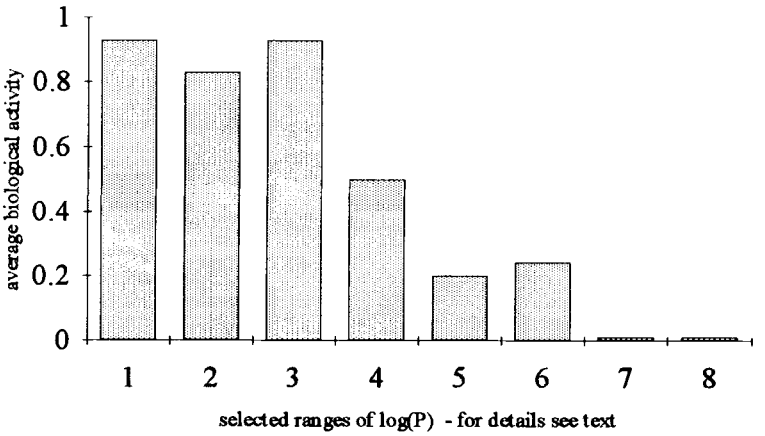


DIAGRAM 1a Average biological activity for a selected range of log(P).

calculated. The results are shown in Diagram 1a. The ranges of log(P) were as follows: 1: 2.341–4.024; 2: 4.024–4.667; 3: 4.667–5.489; 4: 5.489–6.132; 5: 6.132–7.415; 6: 7.415–11.927; 7: 11.927–19.305; 8: 19.305–21.004;

From Diagrams 2 and 3 one can see, that the increase of the electronic parameter causes a very small decrease of biological activity and no influence of the steric parameter of the substituent on determined biological activity is observed. Thus these two parameters are less critical to herbicidal activity of phosphonic analogues of morphactines.

In the next step we tried to build with the help of Microsoft Excel a mathematical model by a regression analysis, in a Hansh like approach. This was done by constructing a multiple regression model of the type:

$$BA = a_1\nu + a_2\sigma + a_3 \log(P) + a_4 \log^2(P) + a_5 \log^3(P) + \text{const}$$

where: BA = biological activity, log(P) = hydrophobic parameter, ν = steric parameter, σ = electronic parameter. The results are shown in Table II.

The description of the data by this polynomial is rather poor as estimated by R = 0.571404. The only statistically significant coefficient appears to be the a_4 parameter,

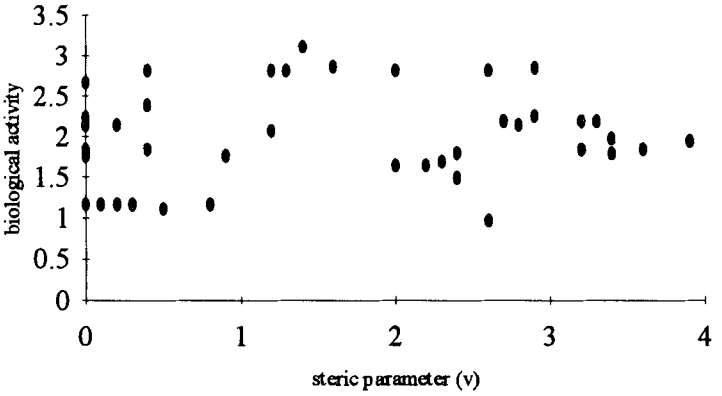


DIAGRAM 2 Biological activity as a function of steric parameter.

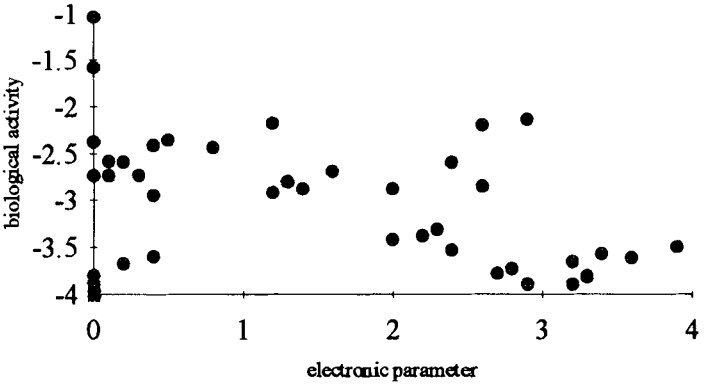


DIAGRAM 3 Biological activity as a function of electric parameter.

TABLE II

Coefficient of the regression analysis and their standard deviations

	a_1	a_2	a_3	a_4	a_5	const
coefficient	0.001041	-0.03176	0.09709	-0.4325	0.203523	0.531931
standard error	0.00125	0.042846	0.426651	0.081415	0.258279	1.171469

what means that the statistically acceptable model can be the one described only by the equation: $BA = -0.4325 \log^2(P)$. The conclusion is that there exists an optimal range of hydrophobic parameters resulting in herbicidal activity. This strengthens our previous statement that the most important parameter for explaining the activity is the ability of the compound to reach the target plant cell.

Using STATGRAPHICS we have developed another multiple regression model with stepwise variable parameters selection. In each step the most significant parameter was selected. The significance of the parameter was controlled by the Fisher F value. The selection was stopped when no variable had a F value greater than 4. In

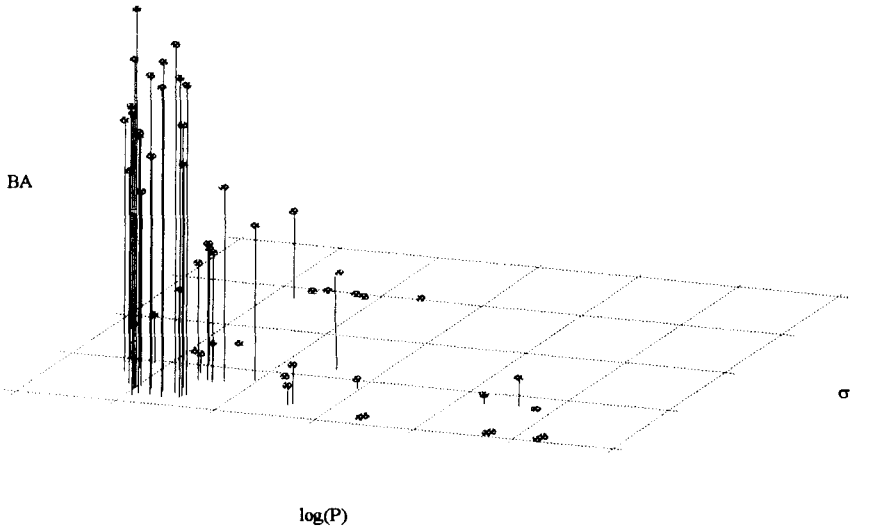


DIAGRAM 4 Biological activity as a function of hydrophobic (log(P)) and electronic (σ) parameters.

this way we have built the following model: $BA = -0.006785 \log^2(P) - 0.43472\sigma + 0.84033$ which states that biological activity depends on the square value of log(P) and electronic parameter σ.

CONCLUSION

Concluding we can say that the biological activity of the tested compounds can not be adequately described by the Hansch model. From our analysis we have developed two models, both of rather low correlation coefficient. Although quite different, both models gave similar results showing that activity decreases with the increase of lipophilicity of the compound and to a smaller extent with the increase of the electronic parameters. There are optimal ranges for both of these parameters which are expressed in the Diagram 4.

Steric parameters seem to have no influence on the biological activity which suggests that these compounds act on a receptor having no great steric demands or they act in the solution outside any receptor. Since our compounds, similarly like Trakephon®, seem to disrupt functioning of plant membranes[24,25] the obtained results are quite logic.

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