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Interaction of Pesticides with a β-Cyclodextrin Derivative Studied by Reversed-phase Thin-layer Chromatography and Principal Component Analysis

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Abstract

The interaction of 18 pesticides with a water-soluble β-cyclodextrin polymer (BCDP) was studied by reversed-phase thin-layer chromatography and principal component analysis (PCA) was employed for the elucidation of the relationship between the relative strength of interaction and the calculated surface parameters of the guest molecules. Except for penconazole the lipophilicity of the pesticides decrease in the presence of BCDP. PCA indicated that apolar surface parameters are highly positively correlated with the strength of interaction. The data indicate that the agrochemical characteristics (adsorption, leakage, decomposition, etc) of complexed pesticide molecules can be different from those of uncomplexed ones resulting in modified efficacy.

Introduction

Cyclodextrins (cyclomalto-oligosaccharides containing 6–8 glucose units) are able to form inclusion complexes with various organic and inorganic molecules [1,2]. The formation of an inclusion complex can considerably modify the physicochemical parameters and consequently the biological activity of the guest molecule. Thus, cyclodextrin (CD) complexation changes oxidation [3] and decomposition rates [4], promotes microbial transformation [5], increases the release of the active ingredient from the formulation [6], improves delivery through the skin [7], etc. Because of the beneficial effect of the formation of inclusion complexes CDs have also found application in up-to-date agrochemical practice [8]. It has been proven many times that the formation of CD – pesticide complexes markedly influences the physicochemical parameters and biological activity of the guest molecule. Thus, it was established that the rate of alkaline hydrolysis of organo-phosphothioate pesticides [9–11] was reduced and their chemical and heat stability were enhanced when they were complexed with β-CD [12]. The various aspects of the complexation of pesticides with CDs has been previously reviewed [13]. It has been recently found that complexation modifies the stability of n-butyl-9-fluorenyl-9-carboxylate [14], enhances the solubility of chlorpyrofos [15], 2,4-D [16] and carbaryl [17], and may increase desorption [18].

The character of the interactive forces involved in the formation of inclusion complexes has been vigorously discussed. The importance of hydrophobic [19, 20], electrostatic and hydrophobic [21], dipolar and hydrogen bonding [22], and van der Waals forces have been emphasized [23].

Lipophilicity is one of the most important physicochemical parameters of bioactive compounds used in quantitative structure-activity relationship (QSAR) studies [24, 25]. It has been established that lipophilicity influences significantly the toxicity of organophorporus pesticides towards *Daphnia magna* and honebees [26], the acute toxicity of pesticides to *Oncorhynchus mykiss* [27], and the accumulation of organochlorine pesticides in perch (*Perca fluviatilis* L) [28].

Besides the traditional partition method between *n*-octanol and water, lipophilicity can be determined by various chromatographic methods such as reversed-phase thin-layer chromatography (RP-TLC) [29, 30], reversed-phase high-performance liquid chromatography [31], and micellar liquid chromatography [32]. RP-TLC has been employed not only for the determination of lipophilicity but also for the study of the effect of CDs on the lipophilicity of various compounds such as normal alcohols [33], unconjugated and conjugated bile acids [34], etc. The relative strength of the inclusion complex formation can be calculated from the dependence of lipophilicity on the concentration of CD or CD derivative in the mobile phase [35, 36]. A higher change in lipophilicity means a higher relative strength of host–guest interaction.

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Principal component analysis (PCA) is a multivariate technique that reduces the dimensionality of a large data matrix whilst retaining the maximum amount of variation in the data. It works by exploiting the correlation structure of the variables [37, 38]. PCA has also been frequently used for the evaluation of large data matrices in chromatography [39]. However, the matrices of PC loadings and variables are generally multidimensional and their evaluation by visual methods is cumbersome and subjected to errors. A nonlinear mapping technique (NLMAP) has been developed for the reduction of the dimensionality of such matrices [40]. Two-dimensional NLMAP projects the points of PC loading or variables onto a plane in such a manner that the distances between the points on the plane represent the best approximation of the distances between the points in the multidimensional space.

The aims of the work were the elucidation of the effect of a water-soluble β-CD polymer (BCDP) on the apparent lipophilicity of some pesticides and the elucidation of the correlation between the surface parameters of pesticides and their capacity to form inclusion complexes with BCDP by PCA.

Experimental

Reversed-phase ready made plates (RP-18W/UV_{254}) were purchased from Macherey-Nagel GmbH&Co (Düren, Germany) and were used for the measurement of the effect of CD on the lipophilicity of pesticides without any pretreatment. The water-soluble β-CD polymer (BCDP) was the gift of Dr. Éva Fenyvesi (CYCLOLAB Research and development Laboratory, Budapest, Hungary) and was employed as received. BCDP (β-CD content 59.3%) was synthesized by binding β-CD monomers with ethyleneglycol diepoxypropylether. The polymer contained two or three β-cyclodextrin units per molecule, the average molecular mass has not been determined. The use of the highly water-soluble BCDP was necessitated by the low solubility of monomer β-CD in water and aqueous solutions. The common and IUPAC names and the biological activity of the pesticides used in this investigation are compiled in Table 1.

Pesticides were dissolved in methanol at a concentration of 5 mg/mL, and 4 μL of the solutions were spotted separately onto the plates. This experimental design was motivated by the fact that the objective of the measurements was the determination of the effect of BCDP on the apparent lipophilicity of pesticides and not the assessment of the impact of BCDP on the separation of pesticides. Furthermore, this experimental design excluded the competition between pesticides for the binding sites of BCDP. Mobile phases were mixtures of water and methanol, the methanol concentration varying from 30 to 60 vol.% in steps of 5 vol.%. Methanol was chosen as organic component because it forms only weak complexes with CDs [41, 42]. BCDP was added to the mobile phase in the concentration range of 0–50 mg/mL in steps of 10 mg/mL. Each pesticide has been investigated in each mobile phase system (altogether 42 combinations of mobile phase). Measurements were performed in sandwich chambers (22 × 22 × 3 cm) at ambient temperature, the distance of development being about 16 cm. After development the plates were dried at 105 °C and pesticides were detected by their UV absorbance or by iodine vapors. Each measurement was run in quadruplicate. The lipophilicity (R_M) value was calculated by

$$R_M = \log(1/R_f - 1). \quad (1)$$

When the relative standard error of the parallel measurements was higher than 5% the data were omitted from the subsequent calculations. This procedure was motivated by the fact that the standard error of traditional TLC measurements is generally lower than 5%. A higher standard error indicates inadequate experimental conditions and biased data.

In order to separate the impact of the organic modifier and BCDP on the lipophilicity of pesticides the following equation was fitted to the experimental R_M values:

$$R_M = R_{M0} + b_{\mathrm{BCDP}}.C_{\mathrm{BCDP}} + b_M.C_M, \quad (2)$$

where R_M is the R_M value measured at a given concentration of methanol and BCDP, R_{M0} is the R_M value extrapolated to zero concentrations of BCDP and methanol (best estimation of molecular lipophilicity), b_{BCDP} is the decrease in the R_M value caused by a concentration increase of 1 mg BCDP/mL mobile phase (related to the relative strength of interaction), b_M is the decrease in the RM value caused by a 1 vol.% increase of methanol concentration in the mobile phase (related to the specific hydrophobic surface area of pesticides) [43]. CBCDP and CM are the concentrations of BCDP (mg/mL) and methanol (vol.%) in the mobile phase, respectively. A similar method has been employed for the study of the complex formation of other sets of pesticides with BCDP [44].

In order to verify that the relative strength of the pesticide – BCDP interaction does not depend significantly on the concentration of methanol in the mobile phase the following equation was employed for some randomly selected pesticides (comps 3, 4, 8–10 and 12):

$$R_M = R_{M0} + b_{\mathrm{BCDP}}.C_{\mathrm{BCDP}} + b_M.C_M + B_{\mathrm{BCDP}xM}.C_{\mathrm{BCDP}}xC_M. \quad (3)$$

It has to be emphasized that Equations (2) and (3) are general forms for bi- and trilinear relationships, therefore, the signs of the coefficients of correlation are always positive. The real signs of the calculated coefficients can be found in Table 2.

Principal component analysis has been employed for the elucidation of the relationship between the measured physicochemical characteristics of the pesticides and their calculated surface parameters. These surface parameters have been chosen because it has been previously proven that these parameters influence significantly the strength of the interaction of other pesticides with BCDP [44]. The variables were the R_{M0} (variable I), b_M (II) and b_{BCDP} (III), values of Equation (2), the nonpolar saturated surface area (NPSSA, IV), the nonpolar unsaturated surface area (NPUSA, V), the nonpolar surface area (NPSA, VI), the polar surface area (PSA,

Table 1. The common and IUPAC names and biological activities of the pesticides used in this investigation [45]

Identifying No.	Common name	IUPAC name and biological activities in italics
1	Acifluorfen	5-(2-Chloro-α,α,α-trifluro-*p*- tolyloxy-)-2-nitrobenzoic acid. *Herbicide*
2	Benoxacor	(±)-4-(Dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine safener. *Herbicide*
3	Cyprofuram	(±)-α-[N-(3-Chlorophenyl)cyclopropanecarboxamido]-τ-butyrolactone. *Fungicide*
4	Diclobutrazole	(2RS, 3RS)-1-(2,4-Dichlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-ol. *Fungicide*
5	Dimethomorph	(E, Z)-4-[3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl] morpholine. *Fungicide*
6	*cis*-Dodemorph	4-Cyclododecyl-2,6-dimethylmorpholine. *Fungicide*
7	*trans*-Dodemorph	
8	Dodine	1-Dodecylguanidinium acetate. *Fungicide*
9	Metconazole	(1RS, 5RS:1RS, 5RS)-5-(4-Chlorobenzyl)-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentanol. *Fungicide*
10	Paclobutrazole	(1RS, 3RS)-1-(4-Chlorophenyl-4,4-dimethyl-2-(1H-1,2,4-triazole-1-yl)pentan-3-ol. *Plant growth regulator*
11	Penconazole	1-(2,4-Dichloro-β-propylphenethyl)-1H-1,2,4-triazole. *Fungicide*
12	Pretilachlor	2-Chloro-2′,6′-diethyl-*N*-(2-propoxyethyl) acetanilide. *Herbicide*
13	Thiram	Bis(dimethylthiocarbamoyl) disulfide. *Fungicide*
14	Triadimefon	1-(4-Chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one. *Fungicide*
15	Triadimenole	(1RS, 2RS; 1RS, 2SR)-1-(4-chlorophenoxy)-3,3-dimethyl-1-H- 1,2,4-triazol-1-yl)butan-2-ol. *Fungicide*
16	Tridemorph	4-*Alkyl*-2,6-dimethylmorpholine. *Fungicide*
17		2-Amino-4-methyl-5-carboxanilidotriazole. *Fungicide*
18		*N*-Isoxazole-5-yl-*N*-(2,6-xylyl)-DL-alaninate. *Fungicide*

VII), the total surface area (TSA, VIII) and the corresponding surface energies (NPSSE, IX; NPUSSE, X; NPSE, XI; PSE, XII, and TSE, XIII). The individual pesticides were the observations. The variation explained was set to 95% thus ensuring that enough principal components were extracted so that 95% of the variation in the data was explained. The dimensionality of the matrix of PC loadings and variables was reduced to two by NLMAP. Iteration was carried out to the point where the difference between the last two iterations was lower than 10^{-8}.

Surface parameters were calculated by the PCMODEL 4.0 software (Serena Software, Bloomington, USA). Software for PCA and NLMAP were prepared by Dr. Barna Bordás (Plant Protection Institute, Budapest, Hungary).

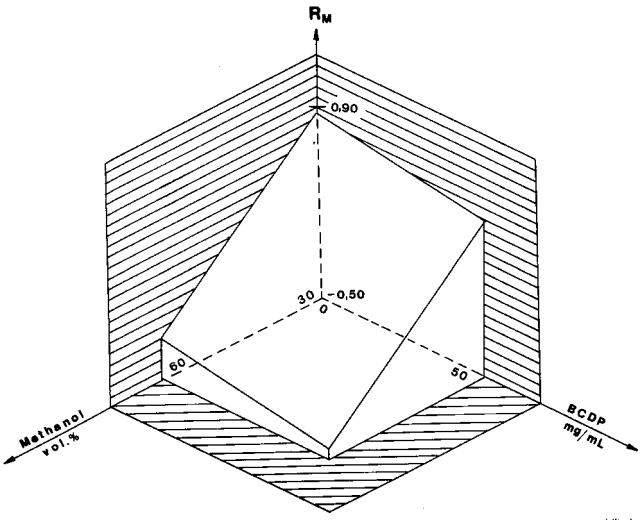

Figure 1. Effect of methanol and a water-soluble β-cyclodextrin (BCDP) concentrations on the lipophilicity (R_M value) of cyprofuram.

Results and discussion

The more lipophilic pesticides remained on the start in mobile phases containing lower concentrations of methanol and BCDP while the more hydrophilic pesticides moved with the eluent front in mobile phases containing higher concentrations of organic modifier and BCDP. The number of R_M values of the pesticides were, therefore, always lower than the total number of mobile phase systems (42) used for the investigation. The concrete number of valid measurements can be found in Table 2.

The influence of both BCDP and methanol concentrations on the lipophilicity of cyprofuram is shown in Figure 1. The figure represents the outline of the fitted model without showing the original lipophilicity values distributed inside the limits of the three-dimensional model. The apparent lipophilicity (R_M value) of cyprofuram decreased linearly with increasing concentration of methanol in the mobile phase, indicating that it exhibits regular retention behavior and Equation (2) can be safely used for the calculation of hydrophobicity parameters and the relative strength of the pesticide-BCDP interaction. Increasing concentration of BCDP in the mobile phase also resulted in the reduced apparent lipophilicity of the guest molecules indicating complex (probably inclusion complex) formation. The less hydrophobic BCDP decreases the lipophilicity of the more hydrophobic pesticides.

The parameters of Equation (2) are compiled in Table 2. Except for penconazole the interaction of pesticides with BCDP has been proven at the significance level of 95%. Equation (2) fitted well to the experimental data, the variance explained varied between 69.92–98.79% (see r^2 % values).

Table 2. Parameters of linear relationships between the lipophilicity (R_M) of pesticides and the water-soluble β-cyclodextrin (C_{BCDP}) and methanol (C_M) concentration in the mobile phase. Numbers refer to the pesticides in Table 1

Parameter	Compound no.					
	1	**2**	**3**	**4**	**5**	**6**
n	20	18	15	15	21	24
R_{M0}	1.80	3.39	1.94	3.61	3.10	2.05
S_M	0.09	0.06	0.05	0.12	0.11	0.12
$-b_{\mathrm{BCDP}} \times 10^{-3}$	9.02	8.57	4.49	13.07	13.57	10.87
$S_{b\mathrm{BCDP}} \times 10^{-3}$	1.21	0.97	0.89	2.21	1.42	1.42
$-b_M \times 10^{-2}$	3.83	5.20	3.58	5.48	4.88	2.91
$S_{bM} \times 10^{-3}$	2.85	2.12	1.61	4.61	3.42	3.58
r^2 (%)	91.90	97.77	98.22	93.16	92.66	81.86
$F_{\mathrm{calc.}}$	90.71	306.82	303.34	74.96	107.35	45.12
$p.10^5$ (%)	0	0	0	11	0	1
b'_{BCDP} (%)	35.76	26.50	18.49	33.23	40.05	48.39
b'_M (%)	64.24	73.50	81.51	66.77	59.95	51.61
Parameter	Compound no.					
	7	**8**	**9**	**10**	**11**	**12**
n	24	23	15	15	13	15
R_{M0}	2.07	2.72	3.47	2.59	3.00	3.63
S_M	0.13	0.22	0.18	0.06	0.12	0.05
$-b_{\mathrm{BCDP}} \times 10^{-3}$	12.47	23.47	19.97	9.39	–	5.22
$S_{b\mathrm{BCDP}} \times 10^{-3}$	1.45	2.67	3.33	1.06	–	1.07
$-b_M \times 10^{-2}$	2.56	3.67	4.61	4.19	3.93	5.33
$S_{bM} \times 10^{-3}$	3.63	6.84	6.96	2.22	3.52	1.86
r^2 (%)	81.97	80.71	81.38	97.23	92.57	98.79
Fcalc.	45.47	39.73	24.03	193.03	124.67	530.52
$p.10^5$ (%)	1	3	1223	0	16	0
b'_{BCDP} (%)	35.76	62.11	47.48	31.89	–	15.07
b'_M (%)	64.24	37.89	52.52	68.11	–	84.93
Parameter	Compound no.					
	13	**14**	**15**	**16**	**17**	**18**
n	22	24	16	22	24	15
R_{M0}	1.06	2.74	2.97	2.27	1.40	2.14
S_M	0.12	0.08	0.06	0.17	0.04	0.05
$-b_{\mathrm{BCDP}} \times 10^{-3}$	8.34	8.52	10.93	19.82	5.36	3.28
$S_{b\mathrm{BCDP}} \times 10^{-3}$	1.68	0.87	1.08	2.21	0.49	0.93
$-b_M \times 10^{-2}$	2.53	4.15	4.62	2.66	2.91	3.98
$S_{bM} \times 10^{-3}$	4.11	2.18	2.26	5.62	1.23	1.69
r^2 (%)	69.92	94.86	97.34	81.70	96.56	98.54
$F_{\mathrm{calc.}}$	20.92	184.42	219.35	40.19	280.31	371.97
$p.10^5$ (%)	257	0	0	4	0	4779
b'_{BCDP} (%)	44.64	34.06	32.66	65.48	31.67	12.97
b'_M (%)	55.36	65.94	67.34	34.52	68.33	87.03

R_{M0} = Intercept value of Equation (2); b_{BCDP} and b_M = Coefficients of regression; S_M, $S_{b\mathrm{BCDP}}$ and S_{bM} = Standard errors of R_{M0}, b_{BCDP} and b_M; r_2 (%) = Coefficient of determination indicating the ratio of variance explained by the independent variables; $F_{\mathrm{calc.}}$ = Calculated F value indicating the fitness of Equation (2) to the experimental data; p = related to the significance of regression; b'_{BCDP} (%) and b'_M (%) = Standard partial regression coefficients normalized to unity.

$$R_M = R_{M0} + b_{\mathrm{BCDP}}.C_{\mathrm{BCDP}} + b_M.C_M.$$

The hydrophobicity parameters and the relative strength of interaction showed marked variations between the analytes suggesting that the lipophilicity, specific hydrophobic surface area and the relative strength of the BCDP-pesticide complexes strongly depend on the chemical character of the molecule. The path coefficients (b' % values) are standard partial regression coefficients normalized to unity showing the relative impact of the individual independent variables on the dependent variables. They are commensurable for methanol and BCDP suggesting that the reversed-phase mobility of pesticides can be equally modified by changing the concentration of methanol and/or BCDP in the mobile phase. No significant interaction was found between the concentrations of methanol and BCDP in the mobile phase (the third term in Equation (3) did not deviate significantly from zero). This fact supports the previous results that methanol forms only a very weak complex also with BCDP, therefore, its concentration does not affect the relative strength of the pesticide – BCDP interaction.

The results of PCA are compiled in Table 3. Four PC components explain the overwhelming majority of the variation present in the original 13 variables. Unfortunately, PCA does not define these background (theoretical) variables as concrete physicochemical or physical entities, it only indicates their mathematical possibility. The variable b_{BCDP} and more than one surface and surface energy parameters have high loadings in the first principal component. This finding suggests that the relative strength of the pesticide-BCDP interaction depends on more physicochemical characteristics which suggests the involvement of various binding forces in the formation of inclusion complexes.

The two-dimensional nonlinear map of principal component loadings is shown in Figure 2. The scales of the maps are dimensionless numbers indicating only the distribution of points on the two-dimensional plane. The results entirely support the previous qualitative conclusions. The relative strength of the pesticide-BCDP interaction (point III) forms a clear-cut cluster with NPSSA (IV), NPSA (VI), TSA (VIII), NPSSE (IX) and NPSE (XI) indicating again the mixed mode of interaction. The fact that the polar surface (VII) and surface energy (XII) parameters are far away from the cluster proves the decisive role of hydrophobic forces in the interaction.

The two-dimensional nonlinear map of pesticides is shown in Figure 3. The majority of pesticides form a loose cluster suggesting that they do not differ considerably from each other. Only pesticides with a morpholine ring (5 and 16) are well separated from the other pesticides proving the considerable impact of the large ring structure on the physicochemical characteristics of pesticides.

It can be concluded from the results that BCDP interacts with the majority of pesticides decreasing their apparent lipophilicty. The strength of the BCDP-pesticide inclusion complexes depends considerably on the apolar surface characteristics of the guest molecules. RP-TLC combined with PCA is suitable for the study of such interactions.

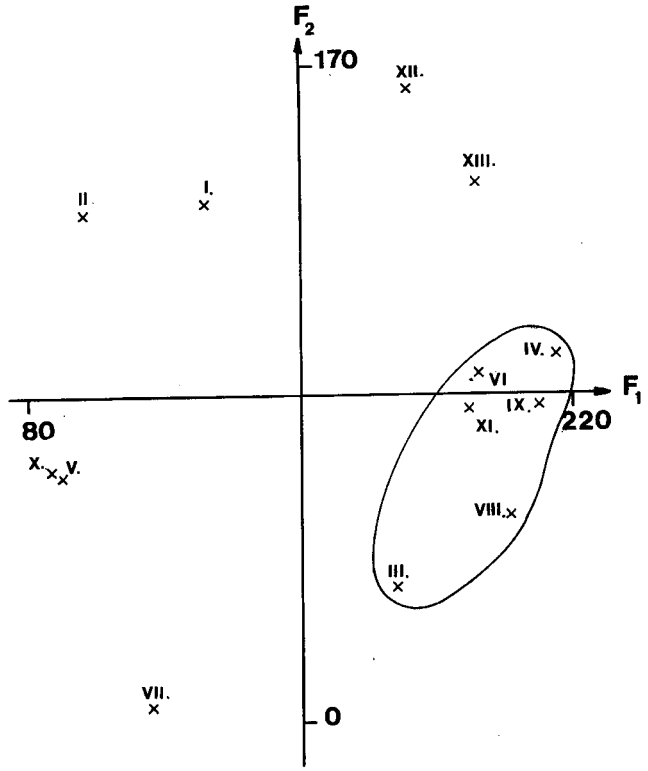

Figure 2. Similarity and dissimilarity between the measured and calculated physicochemical parameters of pesticides. Two-dimensional nonlinear map of principal component loadings. No. of iterations: 161; maximum error: 2.29×10^{-2}. Roman numbers refer to the physicochemical parameters in the Experimental section. The scales of the map are dimensionless numbers indicating only the distribution of points on the two-dimensional plane.

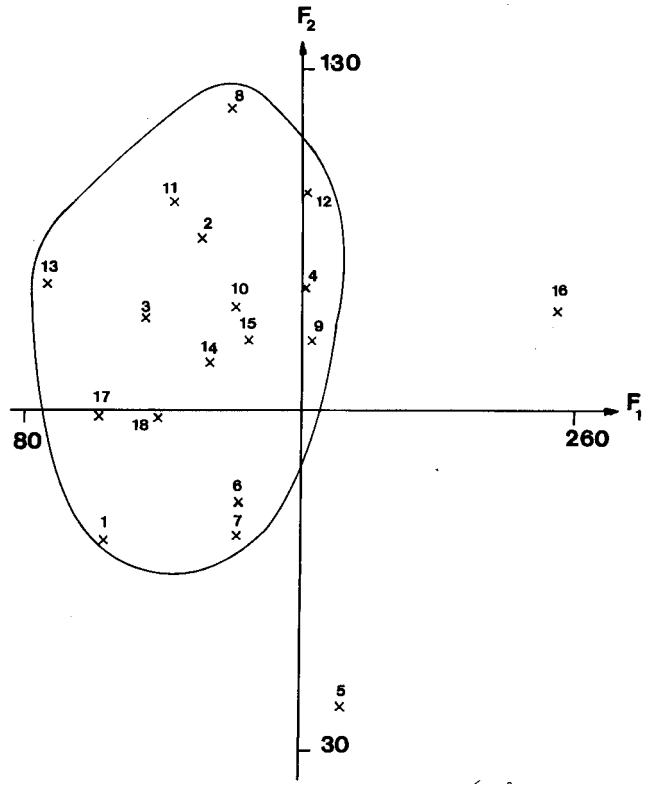

Figure 3. Similarity and dissimilarity between pesticides. Two-dimensional nonlinear map of principal component variables. No. of iterations: 157; maximum error: 2.68×10^{-2}. Arabic numbers refer to the pesticides in Table 1. The scales of the map are dimensionless numbers indicating only the distribution of points on the two-dimensional plane.

Table 3. Similarities and dissimilarities between the physico-chemical parameters of pesticides. Results of principal component analysis. For symbols see Experimental

No. of principal component	Eigenvalue	Variance explained (%)	Total variance explained (%)
1	5.76	44.30	44.30
2	3.04	23.39	67.68
3	2.43	18.69	86.37
4	1.07	8.22	94.60

Parameter	Principal component loadings No. of principal component			
	1	2	3	4
R_{M0}	0.41	−0.37	*0.74*	0.36
b_M	0.04	−0.25	*0.80*	0.47
b_{BCDP}	*0.59*	0.21	−0.17	*0.57*
NPSSA	*0.96*	0.14	−0.15	−0.01
NPUSSA	-0.11	*0.59*	*0.73*	-0.28
NPSA	*0.94*	0.30	0.05	-0.09
PSA	-0.49	*0.82*	-0.13	0.20
TSA	*0.76*	*0.54*	-0.05	0.14
NPSSE	*0.94*	0.24	-0.15	-0.06
NPUSSE	-0.10	*0.51*	*0.77*	-0.34
NPSE	*0.91*	0.35	0.02	-0.14
PSE	0.48	*-0.82*	0.11	-0.23
TSE	*0.80*	*-0.51*	0.08	-0.24

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