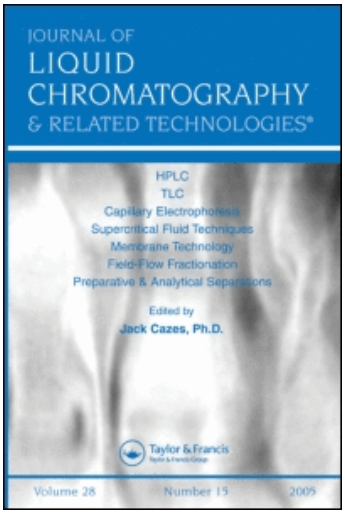

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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Online publication date: 18 January 2000

To cite this Article Cserháti, T. , Forgács, E. and Oros, Gy.(2000) 'BINDING CHARACTERISTICS OF A WATER-SOLUBLE β-CYCLODEXTRIN POLYMER', Journal of Liquid Chromatography & Related Technologies, 23: 3, 411 — 421
To link to this Article: DOI: 10.1081/JLC-100101460
URL: http://dx.doi.org/10.1081/JLC-100101460

J. LIQ. CHROM. & REL. TECHNOL., 23(3), 411–421 (2000)

BINDING CHARACTERISTICS OF A WATER-SOLUBLE β-CYCLODEXTRIN POLYMER

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ABSTRACT

The interaction of 18 commercial pesticides with a water-soluble β-cyclodextrin polymer (BCDP) was determined by charge-transfer reversed phase thin layer chromatography and the relative strength of interaction was calculated. The relationship between the calculated surface parameters of pesticides and their capacity to interact with BCDP was elucidated by stepwise regression analysis. BCDP decreased the lipophilicity of the majority of pesticides probably by the formation of inclusion complexes. Significant quadratic relationships were found between the relative strength of interaction and the polar surface area and polar surface energy of pesticides emphasizing the impact of surface characteristics on the relative strength of interaction. The result suggests that the agrochemical properties (adsorption, uptake, half-life, etc.) of pesticide - BCDP complex may be different from those of uncomplexed compounds resulting in modified effectivity.

INTRODUCTION

Cyclomalto-oligosaccharides (cyclodextrins, CDs) can form inclusion complexes with a wide variety of inorganic and organic compounds.[1,2] Due to their favourable physicochemical characteristics various CDs and CD derivatives have been frequently used in agrochemical formulations to enhance the efficacy of the active ingredient and/or to improve the application parameters of the formulation. CDs and CD derivatives interact with many pesticides too.[3] It was established that CDs can enhance or inhibit the photodegradation of the organophosphorus pesticides parathion and paraoxon depending on the type of CD.[4] Another study indicated that the formation of inclusion complexes of organophosphothioate pesticides with β-CD inhibit their alkaline hydrolysis[5] and improve heat and chemical stability.[6] Besides physicochemical methods, various chromatographic techniques such as high performance liquid chromatography,[7] free solution capillary electrophoresis,[8] gas liquid chromatography,[9] and reversed phase thin layer chromatography (RP-TLC)[10] have also been used for the study of the interaction of CDs with various organic molecules. The advantages of the chromatographic methods are the low quantity of guest compound used for the determination of the complex stability and the low requirement concerning its purity (impurities are separated during the chromatographic process). The character of interactive forces involved in host - guest interactions has been vigorously discussed. The preponderant role of hydrophobic forces,[11] the importance of hydrogen bond,[12] and electrostatic interactions[13] have been discussed in detail. The wide variety of interactive forces involved in the formation of host - guest inclusion complexes suggests that the character of the interactive forces strongly depends on the original molecular characteristics of both the host and guest molecules.

The objectives of the study was the determination of the interaction of some commercial pesticides with a water-soluble β-CD polymer (BCDP) and the assessment of the relationship between the surface characteristics of pesticides and their complex forming capacity. The elucidation of the formation of inclusion complexes between commercial pesticides and BCDP may promote the development of new, more effective formulations with higher biological efficiencies and lower toxic side effects. To the best of our knowledge the interaction of pesticides with BCDP has never been studied in detail.

EXPERIMENTAL

Reversed-phase RP-18W/UV_{254} plates (Macherey-Nagel, Dürren, Germany) were used for the determination of the relative strength of interaction without any pretreatment. The water-soluble b-CD polymer (BCDP) was prepared by Dr. Éva Fenyvesi (CYCLOLAB Research and Development Laboratory, Budapest, Hungary) and was used as received. BCDP was prepared

Table 1

Common and IUPAC Names of Commercial Pesticides

No.	Common Name	IUPAC Name
1	Benomyl	Methyl 1-(butylcarbamoyl)benzimiazol-2 lycarbamate
2	Carbendazim	Methyl benzimidazol-2-ylcarbamate
3	STB	3-Butyl-2,4-dioxo[1,2-α]-s-triazinobenzi-midazole
4	Thiabendazol	2-(1,3-Thiazol-4-yl)benzimidazole
5	Fuberidazol	2-(2'-furyl)benzimidazole
6	Mebendazol	(5-Benzoyl-1H-benzimidazol-2-yl)carbamic acid methyl ester
7	Diethofencarb	Isopropyl 3,4-diethoxycarbanilate
8	Fenarimol	(±) -2,4'-Dichloro-α–(pyrimidin-5-yl)benzhydryl alcohol
9	Nuarimol	(±)-2-Chloro-4'-fluoro-α-(pyrimidin-5-yl)-benzhydryl alcohol
10	Prochloraz	N-Propyl-N-[2-(2,4,6-trichlorophenoxy)-ethyl]imidazole-1-carboxiamide
11	Myclobutanyl	2-p-Chlorophenyl-2-(1H-1,2,4-triazol-1-yl-methyl) hexanenitrole
12	Benalaxyl	Methyl N-phenylacetyl-N-2,6-xylyl-DL-alaninate
13	Furalaxyl	Methyl N-(2-furoyl)-N-(2,6-xylyl)-DL-alaninate
14	Ofurace	(±)-α-(2-Chloro-N-2,5-xylylacetamido)-τ-butyrolactone
15	Oxadixyl	2-Methoxy-N-(2-oxo-1,3-oxazolidine-3-yl)-acet-2'6'-xylide
16	Metalaxyl	Methyl N-(20 methoxyacetyl)-N-2,6-xylyl)-DL-alaninate
17	Carboxin	5,6-Dihydro-2-methyl-N-phenyl-1,4-oxathi-in-3-carboxamide
18	Ziram	Zinc bis(dismethyldithiocarbamate)

by binding β-CD monomers with ethyleneglycol diepoxypropylether. The end product contained 59.3% β-CD. The common and IUPAC names of commercial pesticides are compiled in Table 1. Commercial pesticides were dissolved in methanol at a concentration of 5 mg/mL, and 4 μL of the solutions were spotted separately on the plates. As the object was the study of the interac- tion between pesticides and BCDP and not the elucidation of the influence of BCDP on their separation, the pesticides were separately spotted on the plates.

Mobile phases were water: methanol mixtures the methanol concentration varying between 30 - 60 vol. %. in steps of 5 vol. %. Methanol was chosen as organic modifier because it forms only weak complexes with CDs.[14,15] The concentration of BCDP in the mobile phase varied between 0 and 50 mg/mL in steps of 10.0 mg/mL. Developments were carried out in sandwich chambers (22x22x3 cm) at room temperature, with the distance of development at about 16 cm.

After development the plates were dried at 105°C and the spots of solutes were revealed by their UV absorption spectra or by iodine vapors. Each experiment was run in quadruplicate. The R_M value characterising the molecular lipophilicity in reversed phase thin layer chromatography was calculated

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

When the coefficient of variation of the parallel determinations was higher than 5% the R_M value was omitted from the following calculations. To separate the effects of methanol and BCDP on the lipophilicity of the pesticides the following equation was fitted to the experimental data:

$$R_M = R_{M0} + b_1.C_1 + b_2.C_2 \quad (2)$$

where $R_M = R_M$ value for a pesticide determined at given methanol and BCDP concentrations; $R_{M0} = R_M$ value extrapolated to zero methanol and BCDP concentrations; b_1 = decrease in the R_M value caused by a 1% increase in the methanol concentration in the eluent (related to the specific hydrophobic surface area of pesticides),[16] b_2 = decrease in the R_M value caused by a 1 mg/mL concentration change of BCDP in the eluent (related to the relative strength of interaction); C_1 and C_2 = concentrations of methanol and BCDP, respectively. Eq.2 was applied separately for each pesticide. As it was previously indicated that in the case of homogenous solutes the lipophilicity (R_{M0}) and specific hydrophobic surface area (b_1) are strongly intercorrelated[17] linear correlation was calculated between these two hydrophobicity parameters.

The relationship between the relative strength of BCDP-pesticide interaction and their calculated surface characteristics was assessed by stepwise regression analysis.[18] The relative strength of interaction was the dependent variable, and the nonpolar saturated surface area (NPSSA), nonpolar unsaturated surface area (NPUSA), nonpolar surface area (NPSA), polar surface area (PSA) and total surface area (TSA) and the corresponding surface energy values (E) were the independent variables.

As the linear character of the relationship between the relative strength of interaction and the surface parameters has never been assessed the quadratic forms of the independent variables were also included in the calculation. The number of independent variables in the selected equation was not previously determined, acceptance limit for the independent variables was set to 95% significance level. In the traditional multivariate regression analysis the presence of the independent variables that exert no significant influence on the dependent variable lessens the significance level of independent variables that

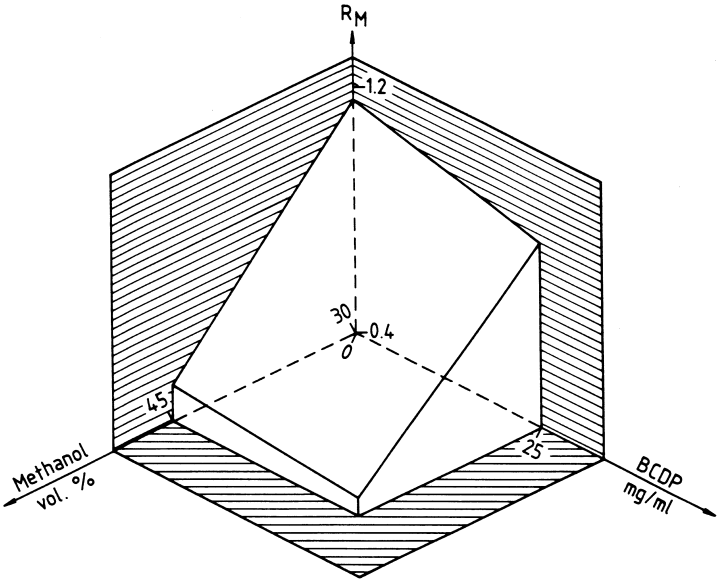

Figure 1. Effect of methanol and a water-soluble b-cyclodextrin (BCDP) concentrations on the R_M value of Furalaxyl.

significantly influence the dependent variable. To overcome this difficulty, stepwise regression analysis automatically eliminates from the selected equation the insignificant independent variables increasing in this manner the information power of the calculation. Surface parameters were calculated by the PCMODEL 4.0 software (Serena Software, Bloomington, USA). Software for stepwise regression analysis was purchased from Compudrug, Ltd. (Budapest, Hungary).

RESULTS AND DISCUSSION

The simultaneous effect of methanol and BCDP concentrations on the R_M values of the pesticides furalaxyl and ziram are shown in Figures 1 and 2, respectively. The R_M values of each compound decreased with increasing concentration of methanol in the mobile phase, i.e. the pesticides do not show any anomalous retention behaviour in this concentration range that would invalidate the evaluation using eq.2. An increase in the BCDP concentration also caused a decrease in R_M values indicating complex (probably inclusion complex) formation. Interaction of the more hydrophilic BCDP with the commercial pesticides decreases the lipophilicity of the latter.

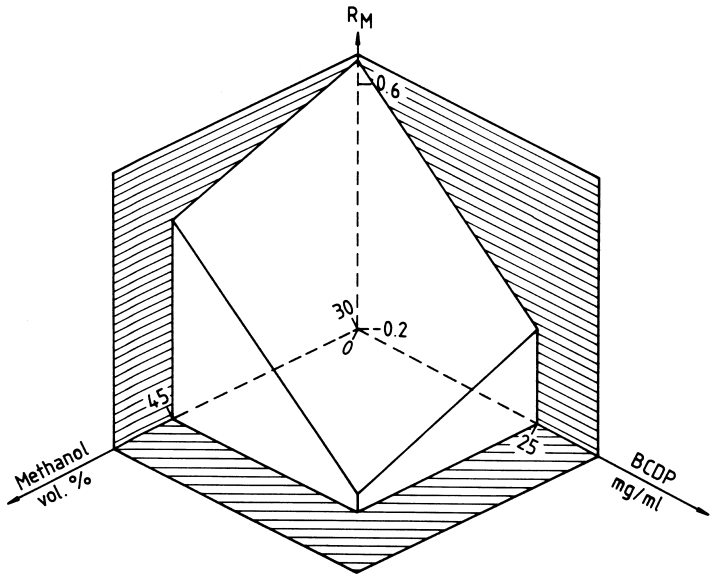

Figure 2. Effect of methanol and a water-soluble b-cyclodextrin (BCDP) concentrations on the R_M value of Ziram.

This result suggests that the agrochemical properties (adsorption, uptake, half-life, etc.) of pesticide-BCDP complex may be different from those of uncomplexed compound resulting in modified effectivity. The parameters of eq.2 are compiled in Tables 2 and 3. The equation fits the experimental data well; the significance levels in each instance being over 99.9% (compare calculated F values with tabulated ones). The ratios of variance explained varied between 73.99 and 99.05% (see r^2 values).

The interaction of commercial pesticides with BCDP means that in agrochemical formulations containing both pesticides and BCDP their interaction must be taken into consideration. The parameters in Tables 2 and 3 show marked variations proving that the lipophilicity, specific hydrophobic surface area, and the capacity of pesticides to form complexes with BCDP differ considerably. This result further suggests that the complex formation may influence differently the biological activity of individual commercial pesticides.

The path coefficients (b'% values) indicate that the effect of the change of methanol and BCDP concentrations exert a similar impact on the mobility of pesticides under reversed phase chromatographic conditions. This means that the retention can be equally modified by changing either the methanol or the BCDP concentration in the mobile phase.

Table 2

Parameters of Linear Correlations Between the Lipophilicity (R_M) of Commercial Pesticides and the Methanol (C_1 vol. -%) and Water-Soluble β-Cyclodextrin Polymer (C_2 mg/mL) Concentrations in the Mobile Phase*

$$R_M = R_{MO} + b_1 . C_1 + b_2 . C_2$$

Parameter	No. of Commercial Pesticides 1	2	3	4	5
n^a	14	14	14	21	21
R_{MO}	1.32	1.32	1.39	2.20	1.48
$-10^2 xb_1$	2.35	2.35	2.53	3.99	2.98
$10^3 xs_{b1}{}^b$	1.44	1.61	1.07	0.55	1.37
$-10^2 xb_2$	0.50	0.53	0.59	0.89	0.49
$10^3 xs_{b2}{}^b$	0.70	0.79	0.52	2.13	0.53
b'_1 (%)^c	69.51	68.41	67.72	63.54	70.23
b'_1 (%)^c	30.49	31.59	32.28	36.46	29.77
r^{2d}	0.9580	0.9477	0.9795	0.7399	0.9615
$F_{calc}{}^e$	136.98	108.69	287.26	27.02	237.16

Parameter	No. of Commercial Pesticides 6	7	8	9	10
n^a	21	21	13	14	14
R_{MO}	2.60	2.46	3.36	2.94	3.59
$-10^2 xb_1$	4.05	4.10	4.95	4.70	4.69
$10^3 xs_{b1}{}^b$	0.33	1.34	0.33	1.97	4.78
$-10^2 xb_2$	1.70	0.49	1.22	0.10	---
$10^3 xs_{b2}{}^b$	1.29	0.53	1.60	0.96	---
b'_1 (%)^c	48.17	76.81	66.12	70.52	---
b'_1 (%)^c	51.83	23.19	33.88	29.48	---
$r^{2,d}$	0.9209	0.9802	0.9546	0.9802	0.8813
$F_{calc}{}^e$	110.58	469.30	115.62	296.62	96.491

* Numbers refer to commercial pesticides in table 1; b_1 = decrease in the R_M value caused by 1% increase in methanol concentration in the eluent (related to the specific hydrophobic surface area of commercial pesticides; b_2 = decrease in the R_M value caused by 1 mg/mL concentration change of BCDP in the eluent (related to the relative strength of interaction; [a] Number of data points; [b] Standard deviations of b_1 and b_2; [c] Standard partial regression coefficients of b_1 and b_2, which are normalized to unity; [d] Coefficient of determination; [e] Calculated F value indicating the fitness of Eq. 2 to the experimental data.

Table 3

Parameters of Linear Correlations Between the Lipophilicity (R_M) of Commercial Pesticides and the Methanol (C_1 vol. -%) and Water-Soluble β-Cyclodextrin Polymer (C_2 mg/mL) Concentrations in the Mobile Phase*

$$R_M = R_{MO} + b_1 . C_1 + b_2 . C_2$$

Parameter	No. of Commerical Pesticides 11	12	13	14
n^a	13	16	21	22
R_{MO}	3.41	3.39	2.45	2.08
$-10^2 xb_1$	5.21	5.20	4.29	3.97
$10^3 xs_{b1}{}^b$	2.52	2.12	1.47	4.84
$-10^2 xb_2$	0.64	0.86	0.26	0.61
$10^3 xs_{b2}{}^b$	1.21	0.97	0.58	1.93
b'_1 (%)^c	79.56	73.50	86.82	72.06
b'_2 (%)^c	20.44	26.50	13.18	27.94
r^{2d}	0.9809	0.9777	0.9795	0.7711
$F_{calc}{}^c$	282.87	306.82	454.54	33.68

Parameter	No. of Commercial Pesticides 15	16	17	18
n^a	13	12	22	20
R_{MD}	1.27	1.81	1.63	1.20
$-10^2 xb_1$	2.72	3.37	2.88	1.68
$10^3 xs_{b1}{}^b$	1.31	1.18	1.22	5.63
$-10^2 xb_2$	0.24	0.35	0.62	2.32
$10^3 xs_{b2}{}^b$	0.72	0.70	0.49	2.30
b'_1 (%)^c	86.13	84.97	65.07	22.78
b'_2 (%)^c	13.87	15.03	34.93	77.22
r^{2d}	0.9809	0.9905	0.9663	0.8598
$F_{casc}{}^c$	282.69	523.97	287.04	55.20

* Numbers refer to commercial pesticides in Table 1; [f] for symbols see Table 2.

Significant linear relationship was found between the lipophilicity (R_{M0}) and specific hydrophobic surface area (b_1) of commercial pesticides indicating that from a chromatographic point of view these compounds behave as a homologous series of solute, although their chemical structures are different:

$$R_{M0} = -0.50 + (0.74 \pm 0.06).b_1 \qquad (3)$$
$$n = 18 \quad r_{calc.} = 0.9549$$

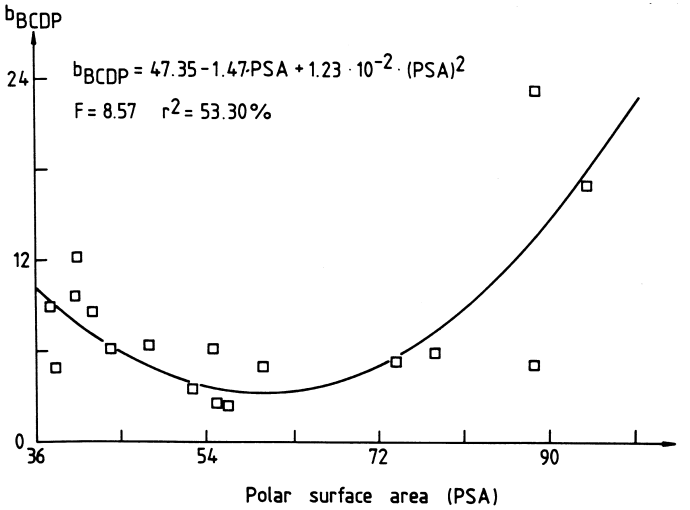

Figure 3. Relationship between the capacity of commercial pesticides to bind to a water-soluble b-cyclodextrin polymer (b_{BCDP}) and their polar surface area (PSA).

Significant correlations were found between the relative strength of pesticide - BCDP interaction (RSI) and the surface area and surface energy values (see Figure 3 and eq. 4):

$$RSI = 31.66 - 0.90.PSA + 1.37.PSE^2 \quad (4)$$
$$n = 18 \quad F_{calc.} = 9.55; \; r^2 = 0.5600$$

The results clearly show that the surface area and surface energy of pesticides influence significantly their capacity to interact with BCDP. However, the relationships are markedly nonlinear. This result can be tentatively explained by the supposition that that pesticides with too small or too big surfaces cannot fit well to the BCDP cavity. Small pesticide molecules are not able to fill the BCDP cavity resulting in weak interaction, whereas too big guest molecules are not able to enter the BCDP cavity. The fact that the ratio of variance was fairly low in both equations, indicates that other than surface characteristics of pesticides may exert a considerable effect on their capacity to interact with BCDP.

It can be concluded from the data that commercial pesticides readily form complexes with BCDP. Stepwise regression analysis indicated that the surface areas and surface energies exert a significant impact on the strength of inclusion complexes. Complex formation may modify physicochemical parameters of the guest nucleoside molecule resulting in modified biological efficiency.

ACKNOWLEDGMENT

This work was supported by the grant OTKA T 023422.

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Received June 10, 1999
Accepted June 26, 1999
Manuscript 5102