CHARACTERIZATION OF PESTICIDE-β-CYCLODEXTRIN INCLUSION COMPLEXES IN AQUEOUS SOLUTION

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Abstract. *The solubility of four different pesticides, "dimethoate", "simazine", "linuron" and "thiram", poorly soluble or non-soluble in water, were measured in water and in aqueous solution of β-cyclodextrin by ultraviolet spectrophotometry. Standard water solutions of pesticides were prepared in the range of concentrations up to the maximum solubility of each pesticide in water. Concentrations of the pesticides were determined as absorbance on the absorption maximum. The obtained results show that the aqueous solution of β-cyclodextrin was a powerful solubilizer of investigated pesticides due to the formation of inclusion complexes. Effective solubility of some of the pesticides in aqueous β-cyclodextrin solution was up to three orders of magnitude higher than those in water. Thermodynamic parameters and complex stability constant of the obtained inclusion complexes were determined by the calorimetric measurements.*

Key words: *β-cyclodextrin, complexes, pesticides, solubility*

INTRODUCTION

β-Cyclodextrin (cyclomaltoheptaose) is a cyclic oligomer of 7 glucose residues. These glucose residues are arranged in a circle with a toroidal shape in which all the primary hydroxy groups are on the narrower base and secondary hydroxy groups are on the wider base of the toroid. The cavity of the torus has a non-polar character and in a hydrated state, it is filled with 11 water molecules. These molecules of water may be replaced with a gain in energy by molecules of a compound that is less polar than water and can form stable inclusion complexes [1]. The formation of such complexes is a fast reversible reaction and these complexes exist both in solution and in crystalline state and can considerably modify the physicochemical parameters and consequently the biological activity of the guest molecule. Thus, cyclodextrin complexation changes oxidation and decomposition rates, promotes microbial transformation, increases the release of the active ingradient from the formulation, etc [2,3]. As β-cyclodextrin (βCD) is a water-soluble compound, the effective solubility of lipophilic substances in aqueous β-cyclodextrin

solutions increases. The extent of this solubility enhancement depends on the concentration of βCD, temperature, etc. but mainly on the chemical nature of the "guest" molecule [4,5].

Complexation thermodynamic is also a very important factor that governs the complexation phenomena between molecular receptor "host" and substrate "guest" molecule. The driving force leading to the inclusion complexation of cyclodextrins include electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, release of conformational strain, exclusion of cavity-bound high-energy water and charge-transfer interactions [6]. The character of the interactive forces involved in the formation of inclusion complexes has been vigorously discussed many times. In spite of the anthalpy-entropy compensation, the enthalpy and entropy changes of the complex formation can be useful in predicting which driving forces are important. Due to the fact that the cost of cyclodextrins is declining, the potential use of β-cyclodextrin could be of great interest in the pesticide solutions formulations and enhancement of their biological activity [7].

2. EXPERIMENTAL

The active components of the "dimethoate", "simazine", "linuron" and "thiram" (generic names of the pesticides) were obtained from "Zupa" (Serbia) and were used without further purification. Chemical names of active ingredients are: O,O-dimethyl S-methyl-carbamoylmethyl phosphorodithioate, 6-chloro-N^2,N^4-diethyl-1,3,5-triazine-2,4-diamine, 3-(3,4-dichlorophenyl)-1-metoxy-1-methylurea and bis (dimethylthio-carbamoyl) disulfide, respectively. β-Cyclodextrin was purchased from Merck (Germany) and dried in vacuum oven at 80°C, till constant weight. All other chemicals were of analytical grade.

Ultraviolet spectra were recorded using a Perkin Elmer Lambda 15 spectrophotometer. A TRONAC model 458 isoperibol titration calorimeter was used for all of the thermodynamic measurements.

Standard aqueous solutions of pesticides were prepared in the range of concentrations up to the maximum solubility of each pesticide in water. Analytical curves of pesticides are shown in Figure 1-4 respectively. Some of the pesticides had to be dissolved in a small amount of ethanol and diluted with water (15% v/v) because of their insolubility in water.
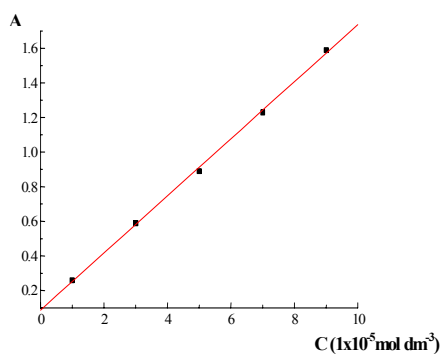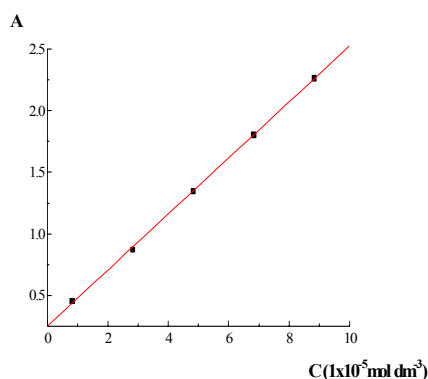

Fig. 1. Analytical curve of "dimethoate"   Fig. 2. Analytical curve of "simazine"
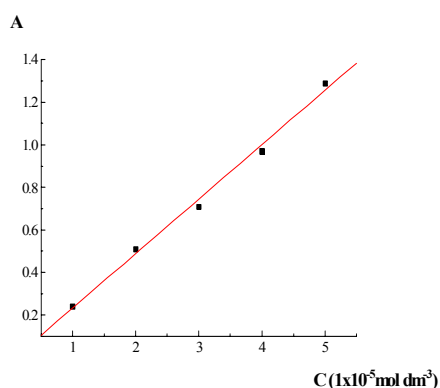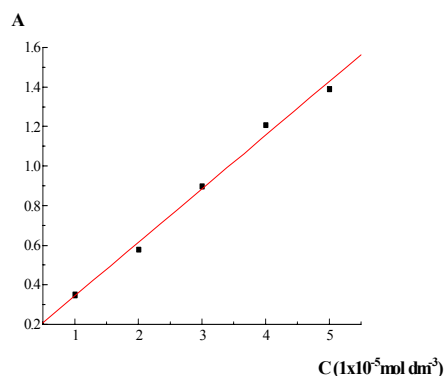
Fig. 3. Analytical curve of "linuron"   Fig. 4. Analytical curve of "thiram"

An aqueous solution of β-cyclodextrin (1×10^{-4} moldm^{-3}) was placed in a screw-cap vial and an excess of pesticide was added. Vials were shaken at room temperature (ca. 22°C) for at least 48h. Contents of the vials were centrifuged, aliquots of the clear supernatant were diluted, and the concentrations of pesticides in these solutions were measured by UV spectrometry [8].

Calorimetric measurements were performed by the calorimetric titrations in an aqueous phosphate buffer solution at pH 7.20 in a temperature-controlled water bath maintained at 22°C. A titration curve was obtained by plotting the temperature change against the amount of the pesticide solution added, from which the complex stability constant (K) and the enthalpy change (ΔH) were calculated [9].

3. RESULTS AND DISCUSSION

Concentrations of the pesticides were determined as absorbance at the wavelength at which absorbance was maximum (Table 1). There is no significant difference in the position of the absorption band between pesticides solutions in water and in the β-cyclodextrin solutions due to very weak intermolecular bonds between "host" (βCD) and "guest" (pesticide) molecules [10].

Table 1. λ_{max} and absorbences of the dilute βCD-pesticide complexes

Pesticide	λ_{max} (nm)	A
Dimethoate	192	1,49
Simazine	221	0,23
Linuron	244	0,63
Thiram	207	0,62

Obtained results show that the effective solubility of the investigated pesticides was substantially increased in the presence of dissolved β-cyclodextrin. Solubility of some of the pesticides in aqueous β-cyclodextrin solutions was up to three orders of magnitude higher than those in water (Table 2).

The difference between the solubility enhancements is due to the molecular structure of the investigated pesticides and binding ability and selectivity of the molecular guest accommodated in the cyclodextrin cavity.

Table 2. Increase in the solubility of investigated pesticides

Pesticide	Solubility in water (mol dm^{-3})	Solubility in aqueous βCD (mol dm^{-3})	Increase in solubility
Dimethoate	1.70×10^{-4}	8.5×10^{-2}	500
Simazine	1.44×10^{-7}	5.0×10^{-5}	347
Linuron	3.19×10^{-6}	9.5×10^{-5}	30
Thiram	1.15×10^{-6}	1.0×10^{-4}	87

Assuming a 1:1 stoichiometry for the inclusion complexation of selected guest molecules (G) with β-cyclodextrin (Eq. 1), the complex stability constant (K) and the enthalpy change ($\Delta H°$) were determined simultaneously (Eq. 2) by using the least-squares method to minimize the error square sum (U).

$$G + \beta CD \rightleftharpoons G \cdot CD \qquad (1)$$

$$U(K, \Delta H^o) = \sum_{t=1}^{m} (Q_t - \Delta H^o \times N_t)^2 \qquad (2)$$

Where Q_t refers to the net heat of complexation measured at time t in minutes and N_t denotes the amount in moles of the complex formed at time t and is directly related to the complex stability constant K.

The stability constant K and the enthalpy change $\Delta H°$ were calculated by computer simulation by continuously changing K, i.e. N_t, to minimize the U value. The measurements were repeated more than three times and the U value obtained was minimized satisfactorily to give the optimized set of K and $\Delta H°$ with standard deviations. No serious deviation was found in the fitting process, verifying the 1:1 stoichiometry of complexation. The complex stability constants and thermodynamic parameters obtained are listed (Table 3).

Table 3. Complex stability constants and thermodynamic parameters (kcal mol^{-1})

Pesticide	log K	$-\Delta G°$	$-\Delta H°$	$T\Delta S°$
Dimethoate	3.36 ± 0.06	4.58	1.47 ± 0.09	3.11
Simazine	3.68 ± 0.03	5.02	2.62 ± 0.05	2.40
Linuron	3.42 ± 0.02	4.67	4.00 ± 0.09	0.67
Thiram	3.93 ± 0.05	5.36	6.63 ± 0.04	-1.27

As can be seen, the ΔH values for the inclusion complexation of β-cyclodextrin with the pesticide molecules are all negative and stabilizing, whereas the $T\Delta S$ values are either negative or positive. Combination of dimethoate and simazine with βCD formed typical entropy-driven complexes. Thus, the complexes are inferred to be stabilized by the entropic gain arising from the desolvation of the host and guest molecules upon complexation, as well as the release of water molecules trapped originally in the cavity. On the

other hand, inclusion compexation of β-cyclodextrin with the linuron and thiram are enthalpy-driven reactions. In the case of linuron, negative enthalpy change indicates the dominance of van der Waals interactions but also the entropy evidently assists the process. Although it affords a comparable K value with those of dimethoate, their thermodinamic profiles are completely different. Thiram gives the most stable inclusion complex which is evidently enthalpy-driven, although the enthalpic gain is partialy canceled out by the accompanying loss in entropy.

REFERENCES

1. J. Szejtli, *Carbohydr. Polym.*, **12**, 375 (1990).
2. T. Loftsson, B. Jonsdottir, J. Baldwinsdottir, H. Fridriksdottir, *STP Pharm. Sci.*, **4**, 354 (1994).
3. K. Takeda, A. Asou, K. Matsuda, K. Okamura, R. Okamoto, J. Sasaki, T. Adachi, *J. Ferment. Bioeng.*, **78**, 380 (1994).
4. Y.L. Loukas, E.A. Vyza, A.P. Valiraki, *Analyst*, **120**, 533 (1995).
5. M.E. Brewster, J.W. Simpkins, M.S. Hora, W.C. Stern and N. Bodor, *J. Parent. Sci. and Tech.*, **43**, 231 (1989).
6. L. Liu and Q.-X. Guo, *J. Incl. Phenom.*, **42**, 1 (2002).
7. O.I. Corrigan, M.A. Forvar and W.I. Higuchi, *Int. J. Pharm.*, **5**, 229 (1980).
8. J. Pitha, J. Milecki, H. Fales, L. Pannell and K. Uekama, *Int. J. Pharm.*, **29**, 73 (1986).
9. Y. Liu, B.-H. Han, Y.-M. Li, P. Zhao, Y.-T. Chen, M. Ouchi and Y. Inoue, *J. Phys. Chem.*, **100**, 17361 (1996).
10. F. De Jong and D.N. Reinhoudt, Stability and Reactivity of Crown Ether Complexes, Academic Press, New York 1981.

KARAKTERIZACIJA INKLUZIONIH KOMPLEKSA PESTICIDA U VODENOM RASTVORU β-CIKLODEKSTRINA

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Promena rastvorljivosti u vodenom rastvoru β-ciklodekstrina četiri različita pesticida: dimetoata, linurona, simazina i cirama; veoma slabo rastvornih ili nerastvornih u vodi, određivana je primenom UV spektrofotometrije. Standardni rastvori pesticida pripremljeni su u opsegu koncentracija do maksimalne rastvorljivosti svakog pesticida u vodi. Koncentracija pesticida određivana je merenjem apsorbancije na položaju apsorpcionog maksimuma. Dobijeni rezultati ukazuju da se rastvorljivost ispitivanih pesticida u vodenom rastvoru β-ciklodekstrina u mnogome povećava građenjem inkluzionih kompleksa. Efektivna rastvorljivost nekih pesticida je porasla za tri reda veličine. Termodinamički parametri i konstante stabilnost nastalih inkluzionih kompleksa određivani su kalorimetrijskim merenjima.