

## Inclusion Complex of Butachlor with $\beta$ -Cyclodextrin: Characterization, Solubility, and Speciation-Dependent Adsorption

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Due to soil adsorption, higher amounts of the herbicide butachlor are necessary to achieve its herbicidal activity, hence increasing its environmental risks. In this study, the effects of  $\beta$ -cyclodextrin ( $\beta$ -CD) on solubility and soil adsorption of butachlor were investigated. Formation of a 1:1 stoichiometric inclusion complex between them with an apparent stability constant of  $443 \text{ L mol}^{-1}$  was confirmed in the solution. Fourier transform infrared spectroscopy showed that the (N–CO) amide bond and alkyl ether moiety of butachlor molecule could enter into the cavity of  $\beta$ -CD, but the double-substituted aromatic ring was excluded because it was larger size than the cavity. Significant enhancing dissolution of butachlor in the inclusion complex occurred in comparison to the free herbicide. The adsorption of butachlor on soil was reduced with an increase of  $\beta$ -CD concentration because of the formation of the inclusion complex with low adsorption potency. Although the sorption distribution coefficient of complexed butachlor (i.e., butachlor/ $\beta$ -cyclodextrin inclusion complex) ( $K_{d,c} = 6.14$ ) was about 14% of that of the free herbicide ( $K_{d,f} = 44.54$ ), the proportion of the adsorbed amount of complexed butachlor to the total adsorbed amount rose with the increase of  $\beta$ -CD concentration. Thus, the adsorption of inclusion complex cannot be neglected in the presence of high concentrations cyclodextrins, although its water solubility was much higher than that of the free herbicide. These results indicate that  $\beta$ -CD may be used as a formation additive to improve the solubility of butachlor, reduce its adsorption on soil, and increase the availability of butachlor for weeds.

**KEYWORDS:** Butachlor; inclusion complex;  $\beta$ -CD; solubility; speciation-dependent adsorption

### INTRODUCTION

Butachlor [2-chloro-*N*-(2,6-diethylphenyl)-*N*-(butoxymethyl)-acetamide] is a chloracetamide herbicide widely used in Asia and South America for the control of annual grasses. Nearly 10000 tons of butachlor active ingredient is applied annually in China (1). Butachlor is highly toxic to some aquatic organisms such as green algae (2) and fish (3) and influences soil microbial populations and enzyme activities (4, 5) as well as does harm to earthworms (6). Moreover, some researchers have demonstrated that butachlor can induce sister chromatid exchanges in rat tracheaepithelial cells (7) and stomach tumors in Sprague–Dawley rats (8) and result in chromosomal aberrations in Chinese hamster ovary cells or cultured human lymphocytes (9, 10).

Previous studies have determined that soil adsorption/desorption is one of the key factors influencing bioavailability of hydrophobic chemicals (11, 12). Due to its low water solubility ( $20 \text{ mg L}^{-1}$  at  $20 \text{ }^\circ\text{C}$ ) (13) and high hydrophobicity ( $\log K_{ow} =$

4.50) (14), butachlor presents high adsorption in soils with medium-high organic matter (13, 15, 16). This behavior of butachlor not only may lead to its inactivation, with the consequent result that higher amounts of herbicide have to be applied to obtain the desired control, but also could reduce its bioavailability and thereby increase its environmental persistence.

Pesticides are formulated to make them easy, safe, and efficient to apply and also reduce the environmental risk associated with overdosing. The appropriate pesticide formulation additives should not only improve the physicochemical properties of pesticides but also be environmentally friendly. Cyclodextrins, cyclic oligosaccharides made by six, seven, or eight glycosidic units that are linked together by  $\alpha$ -1,4 glycosidic bonds, have a doughnut-shaped structure with a hydrophobic interior cavity and hydrophilic faces. Due to their structural features, cyclodextrins could form soluble inclusion complexes with a large variety of chemicals (e.g., hydrophobic pesticides, polycyclic aromatic hydrocarbons) to improve their physicochemical properties such as solubility, bioavailability, photostability, soil sorption, and leaching (17–23). Moreover, cyclodextrins, as biodegradable

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enzyme-modified starch derivatives, are nontoxic, harmless to microorganisms, and hence environmentally benign.

One aim of this study was to confirm and characterize the formation of butachlor/ $\beta$ -cyclodextrin ( $\beta$ -CD) inclusion complexes by phase-solubility determination, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry analysis (DSC), and X-ray diffraction (XRD). The other aim was to investigate the effect of the inclusion complexation between them on the adsorption of butachlor in relation with its soil mobility and environmental availability.

## MATERIALS AND METHODS

**Materials.** Technical grade butachlor (94.2%) was purchased from Shandong Binnong Technology Co., Ltd. (Binzhou, China).  $\beta$ -CD (purity > 99%) was purchased from Tianjin Bodi Chemical Co., Ltd. (Tianjin, China), recrystallized from doubly distilled water, and then dried under vacuum prior to use. The soil employed to carry out the adsorption experiments was taken from the superficial horizon (0–20 cm) of the farmland of Baiyangdian (Hebei Province, China). The main physico-chemical properties of the soil were as follows: pH, 8.07; cationic exchange capacity, 26.71 cmol kg<sup>-1</sup>; organic carbon, 33.7 g kg<sup>-1</sup>; sand, 75.9%; silt, 18.7%; and clay, 5.4%.

**Preparation and Characterization of Solid Complexes.** Equimolar butachlor and  $\beta$ -CD were employed for the preparation of the solid complexes. The inclusion complexes were prepared by the kneading method. Butachlor and  $\beta$ -CD were mixed in a mortar and kneaded for 60 min. The obtained mass was dried at 37 °C for 48 h. The dried residue was ground to fine powder and characterized. A physical mixture of butachlor and  $\beta$ -CD (1:1) has also been prepared for use as a reference in characterization.

DSC data were obtained using a TA Instruments DSC 910S equipped with an aluminum pan. The heating rate was 10 °C min<sup>-1</sup> over the temperature range from 40 to 400 °C, under nitrogen gas flow.

FTIR spectral studies were carried on a Shimadzu IR Prestige-21 between 4000 and 400 cm<sup>-1</sup>. Samples were prepared as KBr disks.

X-ray diffraction patterns were obtained from a Shimadzu XRD-6000 automatic X-ray diffractometer. The samples were irradiated with monochromatized Cu K $\alpha$  radiation, mounted on a sample holder, and scanned with a step size of 0.04° between 2 $\theta$  = 5 and 60°. The voltage and current were 40 kV and 30 mA, respectively.

**Experimental Systems.** The phase-solubility studies were performed in triplicate using the Higuchi and Connors method (24). Butachlor (0.08 mmol) was added to 50 mL of aqueous solutions containing various concentrations of  $\beta$ -CD ranging between 0 and 12 mmol L<sup>-1</sup>. The solutions were shaken at 25 °C for 3 days to reach equilibration of inclusion complexation. After the above steps, the solutions were centrifuged and the concentration of butachlor in the supernatants was determined by HPLC.

The dissolution rate studies of the inclusion complexes were carried out according to the USP 25 paddle method (25). The amount of each solid complex sample employed was 100 mg, containing 24.0 mg of the herbicide. The dissolution medium was deionized water (1000 mL), the stirring speed was 50 rpm, and the temperature was maintained at 37 ± 0.5 °C. At various sampling times, aliquots were withdrawn, filtered through 0.22  $\mu$ m membrane filters, and analyzed by HPLC for butachlor concentration at 215 nm. The experiments were performed in triplicate.

Adsorption experiments were performed using a batch equilibration technique (26). Twenty-five milliliters of a 0.01 mol L<sup>-1</sup> CaCl<sub>2</sub> solution containing various concentrations (0, 2, 4, 6, 8, and 10 mg L<sup>-1</sup>) of butachlor and various concentrations (0, 1.135 × 10<sup>3</sup>, 3.405 × 10<sup>3</sup>, 6.810 × 10<sup>3</sup>, and 1.022 × 10<sup>4</sup> mg L<sup>-1</sup>) of  $\beta$ -CD was added into 50 mL centrifuge glass bottles with screw caps and shaken at 25 °C for 3 days. Then 0.5 g of soil was placed in the bottles. One series of vials without soil as control was also monitored. The samples were then shaken for 24 h for equilibration at 25 °C. Preliminary kinetic studies showed that 24 h of shaking was sufficient to reach pseudoequilibrium. After that, equilibrium phases were separated by centrifugation, and the supernatant was filtered through a 0.22  $\mu$ m Millipore glass fiber membrane filter; butachlor concentration was determined in the filtrate by HPLC. All of the experiments were carried out in triplicate.

The amount of adsorbed butachlor was calculated by the mass balance equation

$$C_s = (C_0 - C_e)V/m \quad (1)$$

where  $C_s$  is the adsorbed amount of solute (mg kg<sup>-1</sup>),  $C_0$  and  $C_e$  represent, respectively, the initial and equilibrium concentrations of butachlor (mg L<sup>-1</sup>),  $V$  is the volume of the equilibrium solution, and  $m$  is the weight of soil.

Sorption isotherms were fitted to the Freundlich equation

$$C_s = K_f C_e^n \quad (2)$$

where  $K_f$  is the Freundlich constant that is indicative of relative sorption affinity and  $n$  is an exponent that indicates relative linearity.

The adsorption of  $\beta$ -CD on the soil was also investigated following the same procedure as that of butachlor, and its concentration was determined using the phenolphthalein method proposed by Li and Zhang (27). A comparable level of  $\beta$ -CD was observed compared to its initial concentration (data not shown), indicating poor adsorption of  $\beta$ -CD on the soil.

**Analytical Determination.** HPLC analyses were carried out using an Agilent 1100 HPLC equipped with a diode array UV detector and a YWG C-18 reversed-phase column (4.6 × 250 mm, 10  $\mu$ m; Dalian Elite Analytical Instruments Co., Ltd., Dalian, China). The mobile phase was composed of 80% acetonitrile and 20% water, which was acidified to pH 3 with phosphoric acid. The flow rate was 1.0 mL min<sup>-1</sup>, and the temperature of the column was kept at 30 °C. The wavelength was set at 215 nm. Butachlor was eluted at 8.2 min. The presence of  $\beta$ -CD was not found to interfere with the assay.

## RESULTS AND DISCUSSION

**Phase Solubility.** The solubility of butachlor in water increased linearly with the increase of  $\beta$ -CD concentration, and a solubility limit was not observed in the range of  $\beta$ -CD concentrations used (Figure 1). This is in accordance with an  $A_L$  classification according to Higuchi and Connors (24), indicating the formation of a 1:1 complex stoichiometry in solution. The apparent stability constant ( $K_c$ ) can be calculated using

$$K_c = \text{slope}/S_0(1 - \text{slope}) \quad (3)$$

where  $S_0$  is the solubility of butachlor in pure water. The slope of the line in Figure 1 was 0.01508, and the determined apparent stability constant of the butachlor/ $\beta$ -CD complex was 443 L mol<sup>-1</sup>, which suggests strong interactions between  $\beta$ -CD and butachlor in water.

Besides hydrophobicity, the inclusion complexation may also be affected by other factors, such as the size and steric conformation of the guest compound. When the guest molecule cannot be completely accommodated within the cyclodextrin cavity, steric effects may play a dominant role. For example, the apparent stability constant of the butachlor/ $\beta$ -CD complex is smaller than that of the naphthalene/ $\beta$ -CD ( $K_c$  = 678.3 L mol<sup>-1</sup>) (28), despite the higher hydrophobicity of butachlor (log  $K_{ow}$  = 4.50)

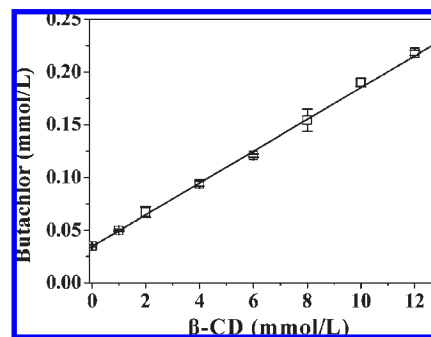
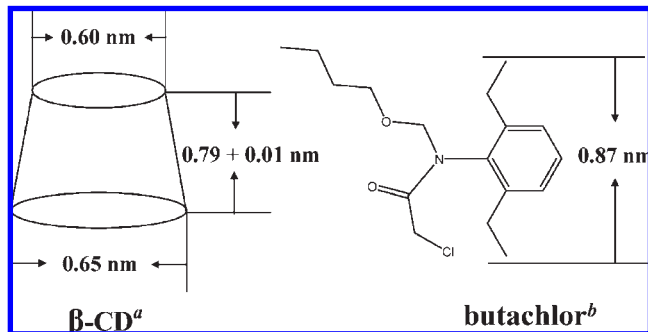
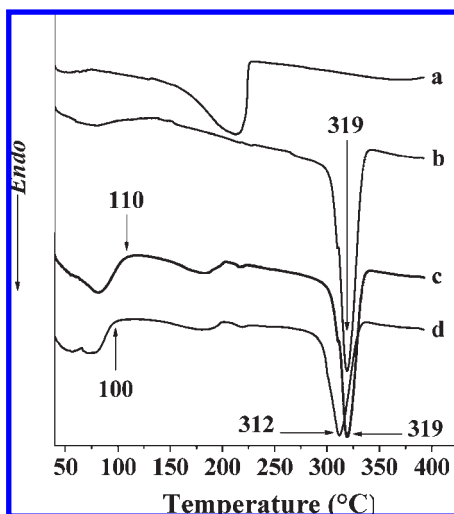


Figure 1. Phase-solubility diagram of butachlor in the presence of  $\beta$ -CD.



**Figure 2.** Molecular sizes of  $\beta$ -CD and butachlor. <sup>a</sup>Data are from the literature (33). <sup>b</sup>The sizes of molecules were calculated with the CS ChemOffice program.

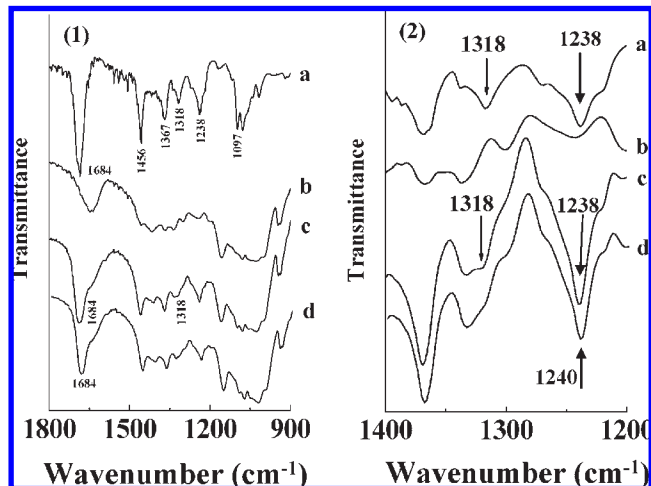


**Figure 3.** DSC thermograms of (a) butachlor, (b)  $\beta$ -CD, (c) physical mixture, and (d) inclusion complex.

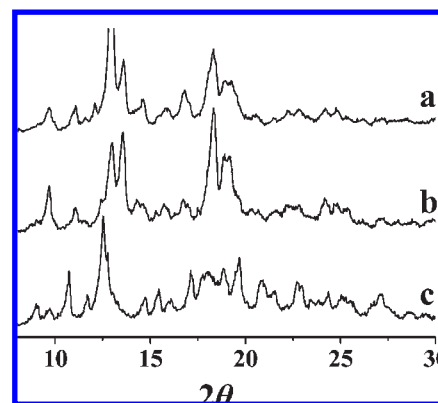
relative to that of naphthalene ( $\log K_{ow} = 3.33$ ) (29). It can be seen from **Figure 2** that the distance between two ethyl groups in butachlor at the ortho position of the benzene ring (0.87 nm) is larger than the cavity of  $\beta$ -CD (0.60–0.65 nm), which prevents the benzene ring from penetrating into the  $\beta$ -CD cavity.

**DSC.** The DSC curve of butachlor shows a broad endothermic peak in the range of 150–220 °C (**Figure 3a**), corresponding to an evaporation process. Liberation of crystal water from  $\beta$ -CD and characteristic endothermic fusion of  $\beta$ -CD were observed as a low broad endothermic peak between 50 and 110 °C and a peak about 319 °C, respectively (**Figure 3b**). The DSC thermogram of the physical mixture (**Figure 3c**) displayed the characteristic events corresponding to butachlor and  $\beta$ -CD, indicating that physical mixing of butachlor and  $\beta$ -CD did not result in obvious and direct interactions. In comparison with the thermogram of the physical mixture, a small diminution of the dehydration effect of  $\beta$ -CD (an endothermic peak between 50 and 100 °C) was observed in that of the solid complex (**Figure 3d**) prepared by the kneading method, indicating that a lower amount of water molecules is present at the internal cavity of  $\beta$ -CD. The diminution of the endothermic peak corresponding to  $\beta$ -CD dehydration could indicate complexation of a small percentage of the herbicide used in the CD cavity. In addition, the endothermic peak corresponding to endothermic fusion of  $\beta$ -CD is displaced to lower temperatures (from 319 to 312 °C), indicating also the formation of the complex.

**FTIR.** In the FTIR spectrum of pure butachlor, the band at 1684  $\text{cm}^{-1}$  was assigned to the stretching of the C=O group, that



**Figure 4.** FTIR spectra of (a) butachlor, (b)  $\beta$ -CD, (c) physical mixture, and (d) inclusion complex.

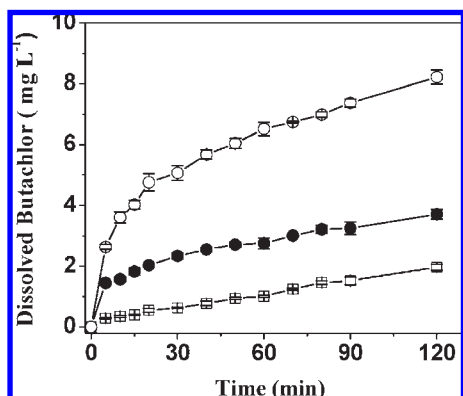


**Figure 5.** XRD patterns of (a)  $\beta$ -CD, (b) physical mixture, and (c) inclusion complex.

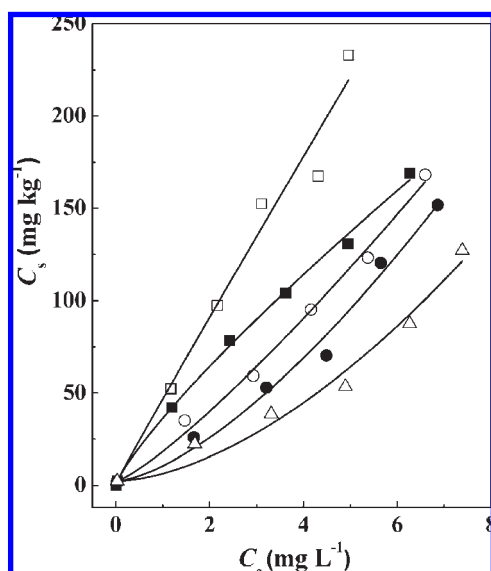
at 1456  $\text{cm}^{-1}$  to the stretching of the C=C bond in the aromatic ring, that at 1367  $\text{cm}^{-1}$  to the deformation vibration of methyl, that at 1318  $\text{cm}^{-1}$  to the aromatic C—N stretching, that at 1238  $\text{cm}^{-1}$  to the methylene deformation vibration of  $-\text{CH}_2-\text{Cl}$ , and that at 1097  $\text{cm}^{-1}$  to the ether stretching (**Figure 4a**). Due to the overlapping of butachlor characteristic bands with those of  $\beta$ -CD, the changes in the spectrum of the solid inclusion complex were very subtle. However, the band at 1318  $\text{cm}^{-1}$  corresponding to the aromatic C—N stretching for the inclusion complex disappeared, and the band corresponding to the methylene deformation vibration of  $-\text{CH}_2-\text{Cl}$  shifted from 1238 to 1240  $\text{cm}^{-1}$  (**Figure 4d**), in comparison with the spectrum of the physical mixture (**Figure 4c**), suggesting the (N—CO) amide bond and alkyl ether moiety of butachlor molecule could enter into the cavity of  $\beta$ -CD.

**XRD.** In the XRD pattern of pure  $\beta$ -CD (**Figure 5a**), sharp diffraction peaks were present, representing high crystallinity. The XRD pattern corresponding to the physical mixture (**Figure 5b**) was similar to that of isolated  $\beta$ -CD. In the XRD diagram of the solid sample obtained by the kneading method (**Figure 5c**), some new diffraction peaks (e.g., 19 and 21°  $2\theta$ ) corresponding to a new crystalline compound appeared, suggesting the formation of the butachlor/ $\beta$ -CD inclusion complex.

**Dissolution Rates.** The dissolution profiles in water of butachlor and butachlor/ $\beta$ -CD binary systems are shown in **Figure 6**. The measured concentration of butachlor by itself in deionized water was only 1.97  $\text{mg L}^{-1}$  2 h after mixing. In contrast, an



**Figure 6.** Dissolution profiles in water of butachlor (□), physical mixture (●), and inclusion complex (○).



**Figure 7.** Freundlich sorption isotherms of butachlor at different  $\beta$ -CD concentrations. Experimental data: 0 mg L<sup>-1</sup> (□); 1.135 × 10<sup>3</sup> mg L<sup>-1</sup> (■); 3.405 × 10<sup>3</sup> mg L<sup>-1</sup> (○); 6.810 × 10<sup>3</sup> mg L<sup>-1</sup> (●); 1.022 × 10<sup>4</sup> mg L<sup>-1</sup> (△).

improvement of the dissolution profile was observed for the physical mixture with respect to the free herbicide. The rapid dissolution of the herbicide observed in the physical mixture indicates the rapid formation of a soluble butachlor/ $\beta$ -CD inclusion complex in solution, corroborating the high  $K_c$  value obtained for this complex (443 L mol<sup>-1</sup>). Under the same conditions, a stronger increase of the dissolution profile for the systems obtained by the kneading method can be observed (Figure 6).

**Effects of the Complexing Role of  $\beta$ -CD on Adsorption of Butachlor.** The butachlor adsorption isotherm in the absence of  $\beta$ -CD was well described by the Freundlich equation (Figure 7). The  $n$  value of the Freundlich equation approached 1.0 for butachlor alone (Table 1), indicating that the sorption of butachlor by the soil proceeded largely by a partitioning process. This observation agreed with the results on butachlor adsorption by nine Taiwan soils reported by Chiang et al. (30). Furthermore, the ratio of clay content to the total organic carbon content of the soil used in this study is 1.60, which is consistent with the finding that soils with the ratio of clay content to total organic carbon content values of <60 adsorbed butachlor mainly by partition into the soil organic matter matrix, as reported by Liu et al. (26).

**Table 1.** Freundlich Parameters ( $K_f$  and  $n$  Values) and Coefficients of Determination ( $R^2$ ) for Butachlor Sorption and Sorption Distribution Coefficients of Complexed Butachlor ( $K_{d,c}$ )

$\beta$ -CD concn (mg L <sup>-1</sup> )	$K_f$	$n$	$R^2$	$K_{d,c}^a$
0	45.72	0.977	0.95	0
1.135 × 10 <sup>3</sup>	36.26	0.827	0.99	5.80
3.405 × 10 <sup>3</sup>	16.58	1.212	0.99	6.04
6.810 × 10 <sup>3</sup>	8.53	1.492	0.98	7.60
1.022 × 10 <sup>4</sup>	4.21	1.675	0.96	5.10

<sup>a</sup> Values are the average of five concentration levels of butachlor at certain concentrations of  $\beta$ -CD.

After butachlor formed inclusion complexes with  $\beta$ -CD, the corresponding adsorption isotherms were also well described by the Freundlich equation ( $R^2 > 0.95$ ) (Figure 7). A large decrease in butachlor adsorption capacity was observed with an increase of the concentration of  $\beta$ -CD (Table 1). Apparently it was ascribed to the formation of the butachlor/ $\beta$ -CD inclusion complex that had higher water solubility than pure herbicide and thus a higher tendency to be retained in solution than to be adsorbed in the soil. As such, butachlor would be highly mobilized in soil, which would increase its leachability. However, this behavior for the soil with a high adsorption capacity for butachlor would increase the availability of butachlor for weeds, avoiding the use of higher amounts of herbicide with the consequent disadvantage and in turn reducing its leaching potential.

To better understand the effect of the complexing role of  $\beta$ -CD on the adsorption of butachlor, it was assumed that the adsorbed butachlor in the soil resulted from free butachlor and complexed butachlor (i.e., butachlor/ $\beta$ -cyclodextrin inclusion complex) in solution. Then apparent sorption distribution coefficient of butachlor ( $K_d$ ), sorption distribution coefficient of free butachlor ( $K_{d,f}$ ), and sorption distribution coefficient of complexed butachlor ( $K_{d,c}$ ) can be expressed as

$$K_d = C_s/C_e = (C_{s,c} + C_{s,f})/(C_{e,c} + C_{e,f}) \quad (4)$$

$$K_{d,c} = C_{s,c}/C_{e,c} \quad (5)$$

$$K_{d,f} = C_{s,f}/C_{e,f} \quad (6)$$

where  $C_{e,f}$  and  $C_{e,c}$  are free butachlor equilibrium concentration and complexed butachlor equilibrium concentration in solution and  $C_{s,f}$  and  $C_{s,c}$  are the adsorbed amount of free butachlor and complexed butachlor in soil, respectively.

$C_{e,f}$  and  $C_{e,c}$  can be calculated on the basis of the equation

$$K_c = C_{e,c}/(C_{e,f}C_{CD}) \quad (7)$$

where  $K_c$  is the apparent stability constant of the complexes and  $C_{CD}$  is the concentration of  $\beta$ -CD in solution. As  $\beta$ -CD was poorly adsorbed in the soil and its initial concentration was far higher than that of butachlor,  $C_{CD}$  was treated as a constant.

$K_{d,f}$  was assumed to be constant, which was an average value of  $K_d$  (44.54) at  $C_{CD} = 0$ . Then  $K_{d,c}$  and  $K_d$  can be written as

$$K_{d,c} = (C_s - K_{d,f}C_{e,f})/C_{e,c} \quad (8)$$

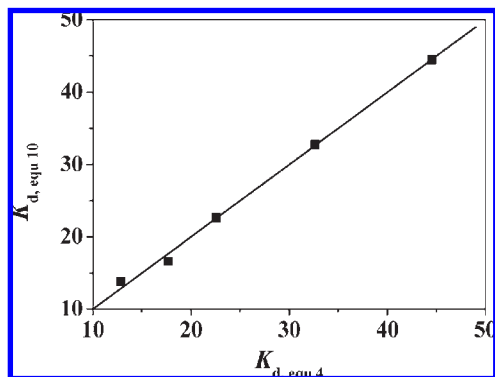
$$K_d = (K_{d,f} - K_{d,c})/(1 + K_c C_{CD}) + K_{d,c} \quad (9)$$

If an average value of  $K_{d,c}$  (6.14) was used in eq 9, then

$$K_d = 38.40/(1 + 443C_{CD}) + 6.14 \quad (10)$$

As shown in Table 1, calculated values of  $K_{d,c}$  from eq 8 (average value of 6.14) were 14% of  $K_{d,f}$  (44.54), suggesting that





**Figure 8.** Relationship between calculated values of  $K_d$  from eq 10 and those from eq 4.

the adsorption of butachlor in soil is speciation-dependent in the presence of  $\beta$ -CD. A good linear relationship between the calculated values of  $K_d$  from eq 10 and those from eq 4 ( $R = 0.99$ ,  $p < 0.001$ ) (Figure 8) was obtained, indicating that eq 10 can be used to calculate  $K_d$  at various concentrations of  $\beta$ -CD.

Although the inclusion complex was less adsorbed than the free herbicide, the proportion of the adsorbed amount of complexed butachlor to the total adsorbed amount rose with the increase of  $\beta$ -CD concentration, corresponding with the increase of complexed butachlor concentration in solution. For example, the proportion of the adsorbed amount of complexed butachlor to the total adsorbed amount was  $> 30\%$  in the presence of  $1.022 \times 10^4$  mg L<sup>-1</sup>  $\beta$ -CD. Therefore, the adsorption of complexed butachlor cannot be neglected in the presence of high concentrations cyclodextrins. This differs from the adsorption in the presence of hydroxypropyl- $\beta$ -cyclodextrin, which has shown that the adsorption of complexed solutes, such as phenanthrene, naphthalene, and 2,4,6-trinitrotoluene, is negligible (31, 32).

In summary, the interaction of butachlor with  $\beta$ -CD produced the formation of an inclusion complex with a stoichiometry of 1:1 and an apparent stability constant of 443 L mol<sup>-1</sup>. By complexation, not only is the solubility of butachlor greatly improved, but also the butachlor aqueous dissolution rate is remarkably enhanced. Moreover, the complexation significantly reduces the sorption of butachlor by soil. Therefore,  $\beta$ -CD as formation additive may obtain controlled release of butachlor, increase the availability of butachlor for weeds, avoid the use of higher amounts of herbicide, and diminish the use of organic solvents.  $\beta$ -CD may also be used as a remediation agent to enhance the mobility of butachlor and thus the bioavailability of butachlor in contaminated soil.

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