Preparation and Characterization of Cyclodextrin Complexes of the Insecticides Aldicarb and Sulprofos

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The β-cyclodextrin (BCD) complexes of the insecticides sulprofos and aldicarb have been prepared in an aqueous medium. Attempts to form a BCD complex of the insecticide thiodicarb were apparently unsuccessful. The BCD complexes were characterized by solubility properties, elemental analyses, and spectral studies. Spectral studies included ultraviolet, infrared, proton NMR, and ^{13}C NMR spectroscopy. The spectral differences between the BCD complex and its individual components were greatest in the case of aldicarb, providing evidence confirming the formation of a true inclusion complex. Since the spectral differences between the sulprofos–BCD complex and its components were small, it was analyzed by differential scanning calorimetry (DSC). The DSC thermogram of the complex differed markedly from that of sulprofos or BCD, suggesting the formation of an inclusion complex; however, an external associative complex cannot be ruled out.

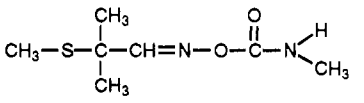
INTRODUCTION

Recently, concern over the contamination of groundwater by pesticides has mounted. In 1986, the U.S. Environmental Protection Agency disclosed that at least 17 pesticides used in agriculture had been found in groundwater in 23 states (Cohen et al., 1986). According to a 1988 interim report, 74 different pesticides from all sources have been detected in the groundwater of 38 states. Contamination attributable to normal agricultural use has been confirmed for 46 different pesticides detected in 26 states (Williams et al., 1988). The preparation and characterization of the β-cyclodextrin (BCD) or γ-cyclodextrin (GCD) complexes of five herbicides frequently implicated in groundwater contamination have been reported (Dailey, 1991). The chief objectives of our research are to develop pesticide formulations that will maintain or increase efficacy on target organisms when applied and that will not adversely impact the environment or groundwater while maintaining effective pest control.

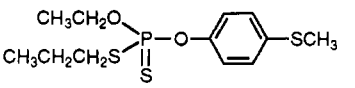
Cyclodextrins are macrocyclic torus-shaped oligomers consisting of six or more D-glucose residues. β-Cyclodextrin (BCD) is composed of seven D-glucose units connected by glycosidic bonds between the 1 and 4 carbon atoms of adjacent glucose units. In aqueous solution, the cyclodextrin molecule can readily accept a guest molecule in its hydrophobic central cavity, forming a stable complex. It is necessary for only a portion of the molecule to fit in the cavity for an inclusion complex to form (Pagington, 1987; Szejtli, 1982, 1985; Pszczola, 1988; Saenger, 1980).

Many synthetic pesticides can form inclusion complexes with cyclodextrins, often resulting in improvements in the properties of the complexed substances. Cyclodextrins have found particular application for the formulation of poorly water soluble, volatile, or unstable herbicides. Among the advantages of cyclodextrin complexes of pesticides are enhanced stabilization, reduced volatility, masked bad odor, enhanced wettability, solubility, and bioavailability, and controlled-release properties (Szjetli, 1985).

In this paper, the methods of preparation of the BCD complexes of the insecticides aldicarb and sulprofos will be described. In addition, evidence confirming the formation of true inclusion complexes (solubility properties, spectral studies, differential scanning calorimetry) will be presented.



aldicarb



sulprofos

Aldicarb is probably the insecticide receiving the most attention regarding groundwater contamination (Jones, 1986; Harkin et al., 1986; Lorber et al., 1989; Miller et al., 1989; Dierberg et al., 1986). According to the 1986 EPA report (Cohen et al., 1986), it was the most widely found pesticide, having been detected in 14 of 23 different states. By 1989 it had been found in 19 states overall (Lorber et al., 1989). Groundwater contamination of aldicarb is of particular concern owing to its acute toxicity to mammals (Miller et al., 1989). Sulprofos is an organophosphorus insecticide recommended to control the beet armyworm and larvae of the cotton bollworm and tobacco budworm on cotton. It is expected that complexation of sulprofos may not only provide a much needed longer residual effect but also cause reduction in phytotoxicity and operator hazards.

MATERIALS AND METHODS

Materials. Sulprofos was furnished by Mobay Corp., Kansas City, MO, as technical Bolstar, 89.8% active ingredient. The carbamate thiodicarb was provided by Rhone-Poulenc, Research Triangle Park, NC, as Larvin 90 MC, 90% active ingredient. Aldicarb was supplied by Rhone-Poulenc, Statesboro, GA, as Temik 15G. Pure aldicarb was obtained by percolation with dichloromethane in a hood following appropriate safety precautions. While handling aldicarb, a cholinesterase inhibitor, one should wear a respirator, gloves, and laboratory coat to protect exposed skin and nasal passages. The material should never be handled alone. Atropine and possibly other cholinesterase reactivators should be immediately accessible. All glassware and other equipment used were treated with a 10% sodium hydroxide

Table I. Cyclodextrin Complexation of Selected Insecticides

insecticide	complex formation?	reaction conditions (aqueous solution)	analysis[a]
sulprofos	yes	65–70 °C, 2–24 h	1.2:1:3
		20 °C, 1–20 h	1.4:1:3
aldicarb	yes	60 °C, 24 h	1:1:2
thiodicarb	no	100 °C, 17 h	

[a] Insecticide:BCD:water molar ratio as determined by elemental analysis. (Analysis of the BCD used in the preparations indicated the presence of 5 mol of water/mol of BCD.)

solution for at least 24 h to remove traces of aldicarb. Larger quantities of aldicarb were decomposed with 50% aqueous sodium hydroxide.

Preparation of BCD Complexes. The following insecticides were selected for complexation with BCD: aldicarb, sulprofos, and thiodicarb. Typical reaction conditions for the formation of BCD complexes of these insecticides are shown in Table I.

Preparation of BCD Complex of Sulprofos. BCD (25.97 g, 21.2 mmol) was dissolved in 500 mL of deionized water under an argon atmosphere at 65–70 °C over a 1-h period. Thereupon, 6.00 mL (6.47 g, 20.1 mmol) of sulprofos (89.8%) was added. The reaction mixture was stirred at 65–70 °C for 24 h. However, complexation of sulprofos appeared to be complete within 2 h. The reaction mixture was allowed to cool to room temperature, and the white precipitate was filtered and dried thoroughly in a vacuum desiccator, affording 25.16 g of sulprofos–BCD complex: mp 218–222 °C (dec). Anal. Calcd for 1.2 $C_{12}H_{19}O_2PS_3{\cdot}C_{42}H_{70}O_{35}{\cdot}3H_2O$: C, 42.98; H, 6.32; P, 2.36; S, 7.33. Found: C, 43.10; H, 6.21; P, 2.48; S, 7.31.

The preparation was repeated at 20 °C. The sulprofos was added to an aqueous slurry of BCD. There was no evidence of the oily sulprofos after 1 h. After 20 h, the white solid was filtered, washed with 2-propanol (100 mL), air-dried, and further dried in a vacuum desiccator, affording 23.16 g of complex: mp 221–225 °C (dec). Anal. Calcd for 1.4 $C_{12}H_{19}O_2PS_3{\cdot}C_{42}H_{70}O_{35}{\cdot}3H_2O$: C, 43.05; H, 6.30; P, 2.64; S, 8.21. Found: C, 42.90; H, 6.27; P, 2.64; S, 8.18.

Preparation of BCD Complex of Aldicarb. A mixture of 1.133 g (5.95 mmol) of aldicarb and 7.29 g (5.95 mmol) of BCD in 150 mL of water under argon was heated at 60 °C for 24 h. The hot solution was filtered, removing 56 mg of insoluble material. The filtrate was kept at 5 °C for 24 h. Filtration removed an additional 218 mg of solids. Removal of the solvent *in vacuo* at 60 °C and subsequent drying afforded 6.91 g of BCD complex: mp 298–300 °C. Anal. Calcd for $C_7H_{14}N_2O_2S{\cdot}C_{42}H_{70}{\cdot}O_{35}{\cdot}2H_2O$: C, 43.23; H, 6.52; N, 2.06. Found: C, 43.08; H, 6.42; N, 1.92.

Several attempts were made to prepare a BCD complex of thiodicarb under conditions as described above. No complex was formed in reactions run at 20, 60, or 100 °C. At 100 °C, thiodicarb began to decompose.

Molecular Modeling. Aldicarb, sulprofos, and BCD were modeled using the ChemX (Chemical Design, Ltd.) molecular modeling software on a Gateway 2000 486/25 and/or Vax station 4000/90. Using space-filling models, minimum energy structures of aldicarb and sulprofos were visually fitted or "docked" with BCD to determine if an inclusion complex would be sterically allowed.

Characterization of BCD Complexes. The two BCD complexes were characterized by physical properties, NMR, IR, and UV spectra, and elemental analysis (Table I). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and Oneida Research Services, Inc., Whitesboro, NY. Elemental analysis of the BCD used in the complex preparations showed a 5:1 water/BCD ratio.

Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded in DMSO-d_6 solution at 25 °C on a Varian VXR-200 NMR spectrometer at 200 and 50.3 MHz, respectively. Chemical shifts are reported in parts per million from internal tetramethylsilane (TMS). APT spectra were obtained for carbon peak determination. Ultraviolet (UV) spectra were recorded on a Gilford Response UV–visible spectrometer using deionized water as solvent. Infrared (IR) spectra were recorded on a Beckman AccuLab 8 spectrometer and were calibrated with the 3027.9, 1601.8, and 1028.3 cm^{-1} bands of polystyrene. Potassium bromide (KBr) disks were used for all samples except sulprofos, which was analyzed as a dichloromethane solution.

All thermal analyses were performed using a TA Instruments 2100 thermoanalyzer. A differential scanning calorimeter (DSC) Module 910 with a dual-sample cell base was used. DSC samples were 4.3 to 6.0 mg in mass. All samples were tested under flowing nitrogen and were heated under programmed conditions. Samples were held at 60 °C for 3 min, heated at a rate of 15 °C/min to 400 °C, and held isothermally for 3 min. All samples were tested at least in duplicate. When plotted, the curves were overlaid using data from a specified temperature interval (75–375 °C) and shifted to zero on the milliwatt scale.

RESULTS AND DISCUSSION

Physical Properties of BCD Complexes. A number of physical properties were taken into account in determining whether or not the aforementioned insecticides did indeed form true cyclodextrin inclusion compounds. In general, BCD complexes are less soluble in water than BCD itself. The solubility of BCD in water at 25 °C is 1.85 g/100 mL (Pszczola, 1988; Saenger, 1980). The BCD complex of aldicarb, however, was considerably more soluble in water. This increased solubility was also observed in the BCD complexes of the herbicides atrazine and metribuzin (Dailey, 1991). The BCD complex of sulprofos was essentially insoluble in water at room temperature. However, upon heating in water at 100 °C the complex dissociated into BCD and free sulprofos. The pronounced changes observed in the solubility of BCD are consistent with complex formation.

Infrared (IR) Spectra. In general, IR spectroscopy is not useful in the characterization of cyclodextrin complexes owing to little or no observable change due to complex formation (Saenger, 1980; Szejtli, 1982). However, in the cases of the BCD complexes of aldicarb and sulprofos, there are definite observable changes. IR spectra were recorded for the aldicarb–BCD complex and for a proportional mechanical mixture of aldicarb and BCD. Upon visual inspection, the most significant differences between the two spectra occurred in the 1000–1150- and 1600–1650-cm^{-1} range; however, there were band shifts throughout the IR region. Prominent absorbance bands for the aldicarb–BCD mixture occurred at 3398, 3310, 2915, 1713, 1489, 1365, 1335, 1148, 1073, 1026, 937, 840, 750, and 700 cm^{-1}. Prominent bands for the complex occurred at 3355, 3250, 2878, 1708, 1605, 1489, 1400, 1346, 1318, 1140, 1000, 920, 840, 740, and 680 cm^{-1}. Significant bands shifts were also observed for the sulprofos–BCD complex. Prominent bands were as follows: sulprofos—2965, 1597, 1420, 1196, 1158, 1020, 910, 895, 820, 760, and 660 cm^{-1}; BCD—3360, 3300, 3240, 2885, 1613, 1390, 1327, 1148, 1065, 1015, 938, 840, 743, and 700 cm^{-1}; complex—3360, 3265, 2873, 1610, 1474, 1320, 1186, 1137, 1035, 1010, 998, 920, 843, 810, 740, 683, and 655 cm^{-1}.

Ultraviolet (UV) Spectra. For the UV analyses of the BCD complexes of aldicarb and sulprofos, all solutions were prepared in deionized water and analyzed immediately. Samples were scanned over the 200–400-nm range at 0.5-nm increments (bandwidth = 1.0 nm). The UV spectra of sulprofos (λ_{max} 254 nm) and its BCD complex (λ_{max} 253) were essentially identical. The UV spectrum of aldicarb exhibited peaks at 218 and 242 nm, whereas the UV spectrum of its BCD complex showed peaks at 210 and 244.5 nm (Figure 1). These differences suggest that the BCD complex of aldicarb is stronger than that of sulprofos.

Proton NMR Spectra. The proton resonance signals for aldicarb, BCD, and the aldicarb–BCD complex are

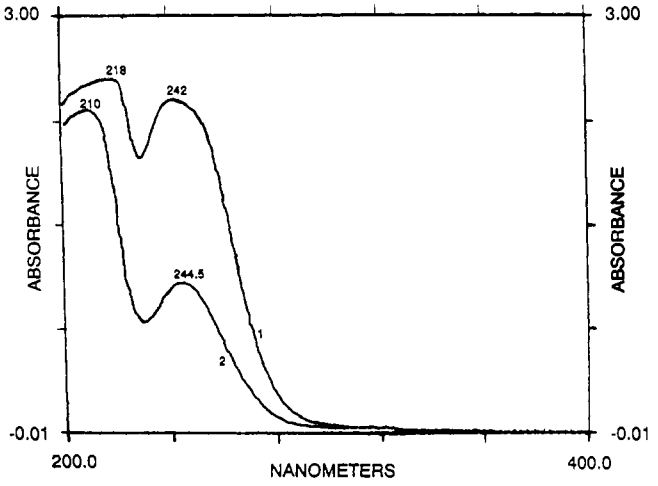
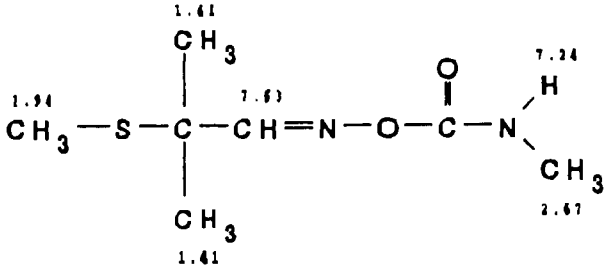


Figure 1. Composite of UV spectra of aldicarb (1) and its BCD complex (2).

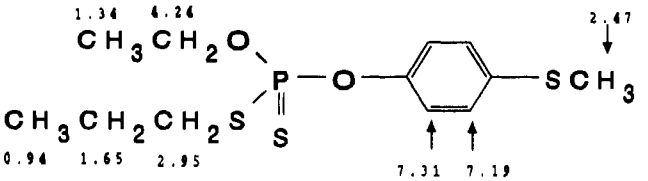
Table II. Proton NMR Spectra of Aldicarb and Its BCD Complex[a]



aldicarb	aldicarb–BCD complex		BCD
1.41 (s)	1.39 (s)	5.71	5.72 (OH-2)
1.94 (s)	1.92 (s)	5.67	5.67 (OH-3)
2.67 (d)	2.66 (s)	4.83	4.83 (H-1)
7.24 (s)	7.18 (s)	4.49	4.46 (OH-6)
7.63 (s)	7.61 (s)	3.63–3.29	3.63–3.30 (remaining H)

[a] Chemical shifts are recorded in ppm from internal TMS. All samples were dissolved in DMSO-d_6 at a concentration of 0.182 M. s, single; d, doublet.

Table III. Proton NMR Spectra of Sulprofos and Its BCD Complex[a]

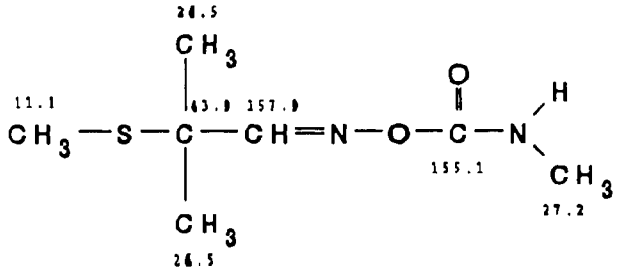


sulprofos	suprofos–BCD complex		BCD
0.94 (t)	0.92 (t)	5.73	5.72 (OH-2)
1.34 (t)	1.32 (t)	5.70	5.67 (OH-3)
1.65 (m)	1.63 (m)	4.84	4.83 (H-1)
2.47 (s)	2.46 (s)	4.48	4.46 (OH-6)
2.95 (m)	2.93 (m)	3.64–3.31	3.63–3.30 (remaining H)
4.24 (m)	4.23 (m)		
7.19 (d)	7.18 (d)		
7.31 (d)	7.29 (d)		

[a] Chemical shifts are recorded in ppm from internal TMS. All samples were dissolved in DMSO-d_6 at a concentration of 0.182 M. s, singlet; d, doublet; t, triplet; m, multiplet.

given in Table II. The proton NMR spectrum of BCD in DMSO-d_6 at 60 °C has been reported by Vincendon (1981); the proton NMR spectrum of aldicarb has also been reported (Payne et al., 1966). The proton NMR data for sulprofos and its BCD complex are presented in Table III. In general, changes in the chemical shifts of protons of the guest molecules were small (0.01–0.06 ppm) but measurable and reproducible.

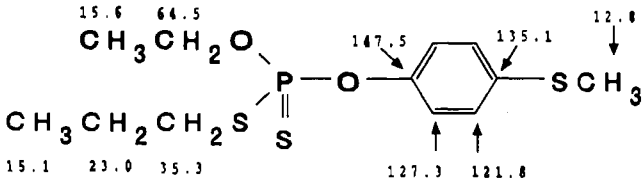
Table IV. ^{13}C NMR Spectra of Aldicarb and Its BCD Complex[a]



aldicarb	aldicarb–BCD complex		BCD
157.9	157.6	101.6	101.6 (C-1)
155.1	154.9	81.2	81.3 (C-4)
43.9	43.6	72.7	72.7 (C-3)
27.2	26.9	72.1	72.1 (C-2)
24.5	24.2	71.7	71.7 (C-5)
11.1	10.8	59.6	59.6 (C-6)

[a] Chemical shifts are recorded in ppm from internal TMS. All samples were dissolved in DMSO-d_6 at a concentration of 0.182 M.

Table V. ^{13}C NMR Spectra of Sulprofos and Its BCD Complex[a]



sulprofos	sulprofos–BCD complex		BCD
147.5	147.3	101.7	101.6 (C-1)
135.1	134.9	81.3	81.3 (C-4)
127.3	127.1	72.8	72.7 (C-3)
121.8	121.6	72.2	72.1 (C-2)
64.5	64.3	71.8	71.7 (C-5)
35.3	35.2	59.7	59.6 (C-6)
23.0	22.8		
15.6	15.4		
15.1	14.9		
12.8	12.6		

[a] Chemical shifts are recorded in ppm from internal TMS. All samples were dissolved in DMSO-d_6 at a concentration of 0.182 M.

^{13}C NMR Spectra. The ^{13}C NMR spectral data for aldicarb and its BCD complex are presented in Table IV, and the data for sulprofos and its BCD complex are given in Table V. The assignments of the carbons of BCD are based upon the data of Vincendon (1981). As expected, complexation has only a slight influence on the chemical shifts of the carbons of the guest molecule (0.3 ppm for aldicarb and 0.2 ppm for sulprofos). There was virtually no change in the chemical shifts of the BCD carbon atoms.

Differential Scanning Calorimetry. In some instances, DSC can verify the formation of a BCD inclusion complex (Szejtli, 1982). In Figure 2 are representative DSC thermograms of BCD, sulprofos and their complex. The β-cyclodextrin showed water loss in the first peak and then began to decompose between 290 and 330 °C with endothermic activity. In comparison, the thermogram of the sulprofos showed smaller endothermic peaks from near 200 °C to approximately 330 °C. In contrast to these two curves was the thermogram of the complex. Its DSC profile was dominated by an endothermic portion that began near 225 °C, corresponding to melting, and then changed dramatically to a sharp exothermic decomposition peak. The exothermic peak is highly indicative of a cyclodextrin inclusion complex (Szejtli, 1982).

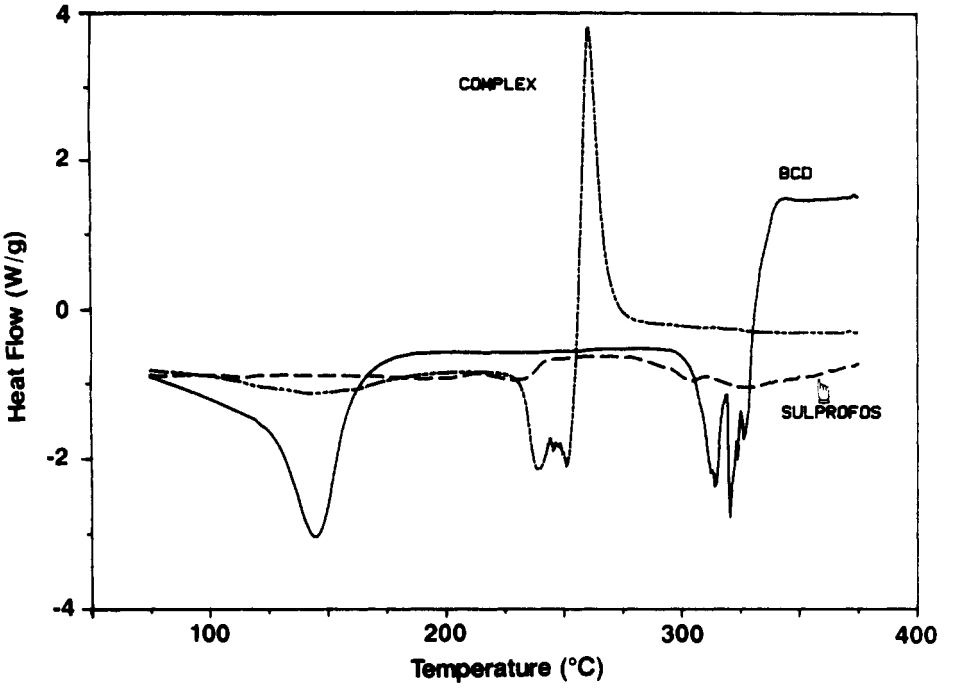


Figure 2. Composite of overlaid DSC thermograms of BCD, sulprofos, and sulprofos–BCD complex.

These same features were observed upon comparison of thermograms of two additional preparations of complexes with BCD and sulprofos. In all DSC thermograms of complexes that we studied, the exothermic peak was present and occurred at a mean temperature of 264.1 °C with a standard error of ±0.52 (12 determinations of three discrete preparations of the complex). These profiles cannot be explained by simple additivity of individual thermal characteristics. We tested this possibility by normalizing the DSC thermograms of the two components to the proportions used to prepare the complex and adding the thermograms (not shown).

Molecular Modeling Studies. In the molecular modeling studies, aldicarb was easily contained within the BCD ring with no van der Waals contacts. The aromatic ring of sulprofos fits comfortably within the BCD ring, satisfying the condition for inclusion complex formation. Formation of each complex resulted in a decrease in van der Waals energy of approximately 12 kcal/mol. Thus, the molecular modeling studies predict that both aldicarb and sulprofos should be able to form a BCD inclusion complex. Thiodicarb was also modeled, showing a complete inability to form an inclusion complex with BCD because of its bent structure.

Several properties of the sulprofos–BCD complex suggest that it may be an external associative complex instead of an inclusion complex. However, we believe that formation of an inclusion complex is more likely. First, elemental analyses of complex samples gave a variable nonstoichiometric ratio of sulprofos to BCD. However, crystalline cyclodextrin complexes rarely are of strictly stoichiometric composition. Guest molecules are located both within the central cavity and between cyclodextrin molecules, and some cyclodextrin molecules may contain only water molecules (Szejtli, 1987). Second, the spectral changes observed for the complex were small or negligible, particularly in the case of the UV spectrum. Inclusion complex formation often results in changes in the absorption spectra of guests, but not always (Bender and Komiyama, 1978). Lack of spectral changes does not negate inclusion complex formation. Third, the dissociation of the sulprofos–BCD complex was observed in an aqueous medium at 100 °C. However, this observation is in keeping with the fact that cyclodextrin inclusion complexes do dissociate when the temperature is increased (Saenger, 1980; Bender and Komiyama, 1978). Furthermore, since sulprofos is a nonpolar compound, it is more likely to form a complex within the hydrophobic central cavity of BCD than an external complex via hydrogen bonds with hydroxyl groups. The DSC curve of the sulprofos–BCD complex is more consistent with an inclusion complex than an external associative complex. One would not expect such dramatic changes in a relatively weak external complex.

Conclusion. The BCD complexes of the insecticides aldicarb and sulprofos have been prepared and characterized by their physical properties and their IR, UV, and NMR spectra to establish them as true inclusion complexes. In general, the spectral differences between the complexes and their individual components were small, as expected, but they were measurable and reproducible. It is noteworthy that there were observable changes in the ^{13}C NMR spectra of the BCD complexes of aldicarb and sulprofos. Our findings do not rule out the possibility that sulprofos formed an external associative complex with BCD instead of an inclusion complex. However, we believe that an inclusion complex is more likely, on the basis of the nonpolar nature of sulprofos, the DSC thermogram of the complex, and molecular modeling studies. The BCD complexes of aldicarb and other acutely toxic insecticides should be much safer to handle and may find use in formulations. The BCD complex of sulprofos is being formulated for studies of its controlled-release properties in the control of cotton pests.

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