

Kinetic Study on the Interactions of Cyclodextrins with Organic Phosphates and Thiophosphates

Takuya Nagata, Kenta Yamamoto, Keisuke Yoshikiyo, Yoshihisa Matsui, and Tatsuyuki Yamamoto*

Faculty of Life and Environmental Science, Shimane University, 1060 Nishikawatsu, Matsue 690-8504

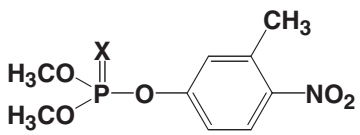
Received July 14, 2008; E-mail: tyamamot@life.shimane-u.ac.jp

α-Cyclodextrin (α-CD) and 6-*O*-α-D-glucopyranosyl-β-cyclodextrin (G1-β-CD) affected the rates of phenol release from a few dimethyl(nitrophenyl) phosphates and the corresponding thiophosphates in aqueous alkaline solutions. Curve-fitting analysis of changes in the rate constants with CD concentrations showed that both α-CD and G1-β-CD form not only 1:1 but also 2:1 (host:guest) complexes with the phosphates and thiophosphates. In 1:1 complexes, phenol release from the phosphates was mostly accelerated, and that from the thiophosphates was decelerated. In 2:1 complexes, the reactions both of the phosphates and thiophosphates were strongly retarded. Binding constants and rate constants determined showed significant host and substrate specificities.

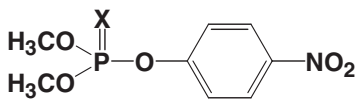
A number of organophosphorus compounds have been developed as pesticides. Among them, *O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) thiophosphate (fenitrothion, **1S**) is one of the most widely used insecticides. The compound is chemically or biochemically converted to the corresponding phosphate (**1O**), which acts as an acetylcholinesterase inhibitor.[1] Cyclodextrins (CDs) are cyclic oligomers composed of six (α-CD), seven (β-CD), eight (γ-CD), or more α-D-glucopyranose units and have the shapes of hollow truncated cones. They are able to accommodate a variety of organic molecules, including organophosphorus compounds, within their interior cavities to form inclusion complexes. According to van Hooidonk et al.,[2] α-CD is a simple and good model for the inhibition of acetylcholinesterases by organophosphorus insecticides. Mochida et al.[3] showed that CDs accelerate the cleavage of organic phosphates but decelerate that of corresponding thiophosphates in alkaline solutions. Vico et al.[4] also showed that β-CD inhibits the alkaline hydrolysis of **1S**. On the other hand, Kamiya et al.[5] examined interactions of CDs with organophosphorus pesticides from the viewpoint of environmental chemistry. Recently, Luo et al.[6] reported toxicological studies on CD complexes with *O*,*O*-dimethyl *O*-4-nitrophenyl thiophosphate (methyl parathion, **2S**). Computational studies with molecular dynamics were also reported on the interactions of CDs with a few organophosphorus pesticides.[7,8] It is noteworthy that all the above works assumed that CDs form only 1:1 (host:guest) inclusion complexes with organophosphorus compounds. However, Yamamoto et al.[9] have isolated β-CD complexes with **2S** with molar ratios not only 1:1 but also 2:1 (host:guest). Recently, we also found that an effect of 6-*O*-α-D-glucopyranosyl-β-CD (G1-β-CD) on the alkaline hydrolysis of **1S** is difficult to explain by simple 1:1 complexation but is explicable by consecutive formation of 1:1 and 2:1 complexes. The present study was undertaken to examine the generality of consecutive formation of 1:1 and 2:1 complexes between CDs and organophosphorus compounds, using α-CD and G1-β-CD as hosts and **1S**, **1O**, and their analogs such as **2S**, *O*,*O*-dimethyl *O*-3-nitrophenyl thiophosphate (**3S**) and their corresponding phosphates (**2O** and **3O**) as guests (Figure 1). G1-β-CD was selected as a host instead of native β-CD, since the water solubility of β-CD is too low for us to observe consecutive formation of 1:1 and 2:1 complexes. The water solubility of G1-β-CD is about 50 times greater than that of β-CD.[10]

Results and Discussion

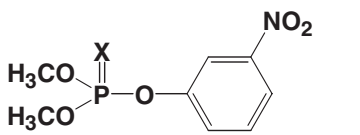
Stoichiometry. The rate of phenol release from **1S** was measured by following the appearance of the absorption due to



X = S, **1S** X = O, **1O**



X = S, **2S** X = O, **2O**



X = S, **3S** X = O, **3O**

Figure 1. Structures and abbreviations of organophosphorus compounds examined.

Published on the web January 14, 2009; doi:10.1246/bcsj.82.76

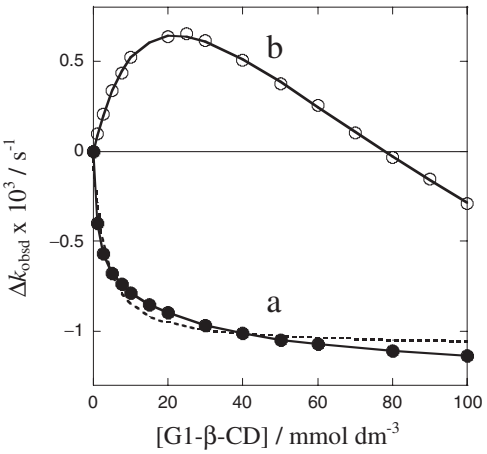


Figure 2. The plots of Δk_{obsd} vs. G1-β-CD concentration for **1S** (a) and **1O** (b) in 0.20 and 0.05 mol dm^{-3} NaOH, respectively, at 308 K and $I_c = 0.65$ mol dm^{-3}. A solid line was obtained by curve-fitting analysis upon an assumption of consecutive 1:1 and 2:1 complexation. A dotted line was obtained upon an assumption of simple 1:1 complexation. The k_{un} values were 1.22×10^{-3} s^{-1} for **1S** and 2.73×10^{-3} s^{-1} for **1O**.

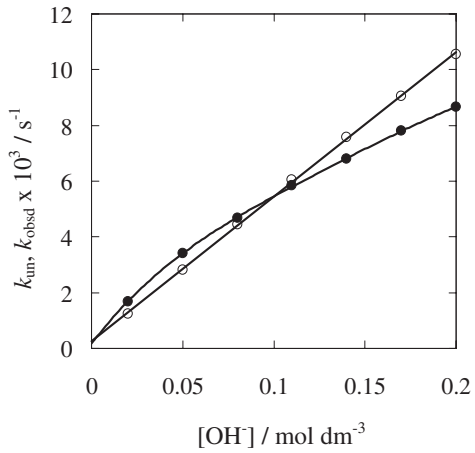


Figure 3. The plots of k_{un} (○) and k_{obsd} (●) vs. OH^- concentration for a 20 mmol dm^{-3} G1-β-CD–**1O** system at 308 K and $I_c = 0.65$ mol dm^{-3}.

the corresponding phenoxide ion at 410 nm in 0.20 mol dm^{-3} NaOH at 308 K. Changes in absorbance with time obeyed good first-order kinetics with respect to **1S** in both the absence and presence of α-CD or G1-β-CD. Figure 2a shows the plot of differences (Δk_{obsd}) between the rates in the presence (k_{obsd}) and in the absence (k_{un}) of G1-β-CD vs. G1-β-CD concentrations (c_0). As have already been reported for a β-CD–**1S** system,[3] the phenol release was significantly decelerated by the addition of G1-β-CD. However, the curve-fitting analysis of the relationship between Δk_{obsd} and c_0 upon an assumption of simple 1:1 complexation of G1-β-CD with **1S** gave an unsatisfactory correlation coefficient of 0.9836, and the calculated curve (dotted line) was apparently ill-fitted to the observed data. Then, the relationship between Δk_{obsd} and c_0 was analyzed by an equation derived by Tee and Du[11] for such a case that 1:1 complexation is followed by 2:1 (host:guest) complexation. The obtained curve (solid line) was well-fitted to the data with a correlation coefficient of 0.9998, suggesting that not only 1:1 but also 2:1 complexes are formed in solution.

More clear results were obtained for a G1-β-CD–**1O** system in 0.05 mol dm^{-3} NaOH at 308 K (Figure 2b). The rate (k_{obsd}) of phenol release increased with an increase in c_0 up to ca. 20 mmol dm^{-3}, whereas it decreased above 25 mmol dm^{-3} G1-β-CD. At $c_0 \geq 80$ mmol dm^{-3}, the k_{obsd} value became smaller than k_{un} ($\Delta k_{obsd} < 0$, deceleration). Similar results have been reported by Tee and Du,[11] who examined the cleavage of aryl alkanoates by α-CD in basic aqueous solution. They found that the cleavage of 4-carboxy-2-nitrophenyl hexanoate, for example, is accelerated at low α-CD concentrations but decelerated at high α-CD concentrations. They concluded that α-CD consecutively forms 1:1 and 2:1 complexes, and 1:1 complex accelerates, whereas 2:1 complex decelerates, the cleavage. The curve-fitting analysis of our data upon the same assumption, in fact, gave a well-fitted curve (solid line in Figure 2b) with a correlation coefficient 0.9996. van Hooidonk et al.[2] have shown that α-CD accelerates the cleavage of a few organophosphorus compounds in aqueous alkaline solutions, and the acceleration is due to the nucleophilic attack of the alkoxide ion derived from α-CD on the phosphates. Thus, the acceleration of the cleavage of **1O** by G1-β-CD in a 1:1 complex will also be due to the nucleophilic attack of the alkoxide ion on the phosphate group of **1O**. On the other hand, the deceleration observed for a 2:1 complex will be brought about by the second G1-β-CD molecule, which pulls apart the phosphate group from the alkoxide ion and also protects the phosphate group from nucleophilic attack of the hydroxide ion from bulk solution by steric hindrance.

In order to learn the detailed roles of the alkoxide and hydroxide ions in the reaction of **1O**, the reaction rates were measured at various alkaline concentrations in the absence and in the presence of 20 mmol dm^{-3} G1-β-CD (Figure 3). The plot of the rate constants (k_{un}) for free **1O** vs. OH^- concentrations gave a good straight line passing through the point of origin. The rate constant at $[OH^-] = 0.1$ mol dm^{-3} was about twice that at $[OH^-] = 0.05$ mol dm^{-3}, indicating that phenol release from free **1O** is brought about by the nucleophilic attack of the hydroxide ion from bulk solution. On the other hand, the plot of the rate constants (k_{obsd}) in the presence of 20 mmol dm^{-3} G1-β-CD vs. OH^- concentrations gave a hyperbolic curve: The k_{obsd} values at low OH^- concentrations were larger than the corresponding k_{un} values, but those at high OH^- concentrations were smaller than the corresponding k_{un} values. The **1O** molecule included within the G1-β-CD cavity is subject to nucleophilic attack by the alkoxide ion derived from G1-β-CD, together with the attack by the hydroxide ion from bulk solution.[3] Although the pK_a value of G1-β-CD is not known, it will virtually be equal to that of native β-CD (p$K_a = 12.09$ at 303 K and 11.91 at 313 K[12]). Therefore, the G1-β-CD molecule will almost completely be ionized to give the alkoxide ion at any OH^- concentrations above 0.05 mol dm^{-3} (pH ca. 12.7). Then, the rate constants for the nucleophilic attack by the alkoxide ion are regarded as constant at OH^- concentrations above 0.05 mol dm^{-3}. On the other hand, the rate constants for the attack on the included **1O** by the hydroxide ion from bulk solution will be smaller than those for free **1O**, owing to steric

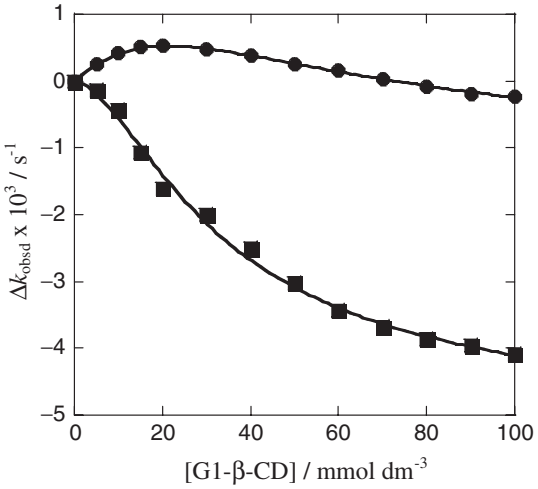


Figure 4. The plots of Δk_{obsd} vs. G1-β-CD concentration for **1O** in 0.03 (●) and 0.20 mol dm^{-3} (■) NaOH at 308 K and $I_c = 0.65$ mol dm^{-3}. Solid lines were obtained by curve-fitting analysis upon an assumption of consecutive 1:1 and 2:1 complexation. The k_{un} values were 1.75×10^{-3} and 10.09×10^{-3} s^{-1} in 0.03 and 0.20 mol dm^{-3} NaOH, respectively.

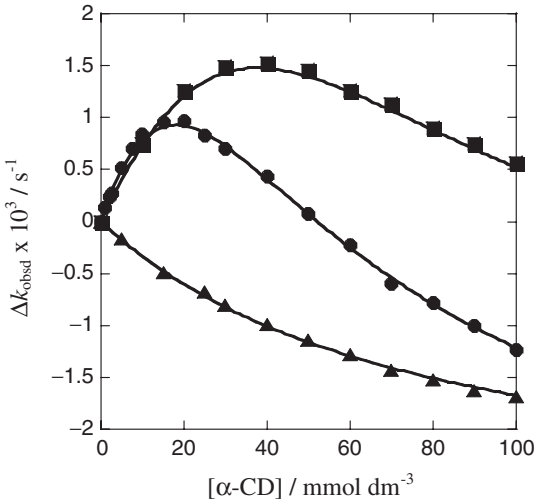


Figure 5. The plots of Δk_{obsd} vs. α-CD concentration for **1O** (▲), **2O** (●), and **3O** (■) in 0.05 mol dm^{-3} NaOH at 308 K and $I_c = 0.65$ mol dm^{-3}. Solid lines were obtained by curve-fitting analysis upon an assumption of consecutive 1:1 and 2:1 complexation. The k_{un} values were 2.73×10^{-3} s^{-1} for **1O**, 4.33×10^{-3} s^{-1} for **2O**, and 2.60×10^{-3} s^{-1} for **3O**.

hindrance. Hence, the k_{obsd} values at high OH^- concentrations become smaller than the corresponding k_{un} values. Figure 4 shows the plots of Δk_{obsd} versus c_0 for a G1-β-CD–**1O** system in 0.03 and 0.20 mol dm^{-3} NaOH. The plot for a G1-β-CD–**1O** system in 0.03 mol dm^{-3} NaOH was similar to that in 0.05 mol dm^{-3} NaOH: The Δk_{obsd} value increased at low concentrations, whereas it decreased at high concentrations of G1-β-CD. On the other hand, the Δk_{obsd} value for the system in 0.20 mol dm^{-3} NaOH decreased even at low concentrations of G1-β-CD, indicating that the included **1O** is less reactive than the free **1O** in such a strong basic solution. The plot also shows that the extent of retardation by G1-β-CD is more pronounced at high G1-β-CD concentrations than that at low G1-β-CD concentrations, suggesting that **1O** included in a 2:1 complex is more effectively protected from the attack of OH^- in bulk solution than that in a 1:1 complex. The curve-fitting analysis of these data based on the consecutive formation of 1:1 and 2:1 complexes gave well-fitted curves (solid lines).

In order to examine the generality of consecutive formation of 1:1 and 2:1 complexes between CDs and organophosphorus compounds, we also used **2O**, **2S**, **3O**, and **3S** as substrates and α-CD as well as G1-β-CD as hosts. Every combination of the host and substrate showed the consecutive formation of 1:1 and 2:1 complexes between them. The effects of α-CD on the rates of phenol release from **1O**, **2O**, and **3O** are shown in Figure 5 as examples. The curves (solid lines) obtained by calculation were well-fitted to the observed data with correlation coefficients of about 0.999. Thus, it is evident that the consecutive formation of 1:1 and 2:1 complexes is general, at least, in α-CD and G1-β-CD complexation with dimethyl(nitrophenyl) phosphates and thiophosphates. Hamai[13] showed that, in the 2:2 inclusion complex of γ-CD with 1-chloronaphthalene in alkaline solution, the primary hydroxy-group sides of the CD cavities face each other. Unfortunately, there is no experimental evidence showing how the 2 molecules of CD are bound to dimethyl(nitrophenyl) phosphates and thiophosphates in our 2:1 complexes at the present stage of investigation.

Kinetic Parameters. Kinetic parameters determined for the alkaline hydrolyses of the organic phosphates and thiophosphates in the presence of α-CD and G1-β-CD are shown in Table 1, where k_1 and k_2 are the rate constants for 1:1 and 2:1 complexes, respectively, and K_1 and K_2, the binding constants for 1:1 and 2:1 complexes, respectively. A few notable features were found in the obtained parameters: First of all, the k_2/k_{un} values were always smaller than the k_1/k_{un} values, implying that the 2:1 complexes of the phosphates and thiophosphates are less reactive than the 1:1 complexes. The substrates will be effectively protected by the second CD molecules in the 2:1 complexes from the nucleophilic attack of the hydroxide ion from bulk solution by steric hindrance. It is also notable that the k_1/k_{un} values for the phosphates, except a α-CD–**1O** system, were larger than 1, whereas those for the thiophosphates were smaller than 1. This tendency was especially clear when G1-β-CD was used as a host. The binding constants K_1 for G1-β-CD–thiophosphate systems were much larger than those for G1-β-CD–phosphate systems, suggesting that the thiophosphates are too deeply included within the cavity of G1-β-CD to be attacked by the alkoxide ion derived from the secondary hydroxy groups of G1-β-CD, as well as by the hydroxide ion from bulk solution. The electronegativity of sulfur is less than that of oxygen, and the atomic radius of sulfur is larger than of oxygen. Therefore, the thiophosphates are more hydrophobic than the corresponding phosphates. On the other hand, the phosphates are less deeply included within the G1-β-CD cavity and susceptible to the nucleophilic attack by the alkoxide ion and the hydroxide ion from bulk solution. In this context, it is interesting that the k_1/k_{un} value for a α-CD–**3O** system was the largest among systems examined. **3O** has a *m*-nitrophenyl group. It is well known that the cleavage of

Table 1. Kinetic (k_1/k_{un} and k_2/k_{un})[a] and Equilibrium (K_1 and K_2) Parameters for Complexes of CDs with Organic Phosphates and Thiophosphates in NaOH Solution ($I_c = 0.65\,mol\,dm^{-3}$) at 308 K

Compound	$[OH^-]$ /mol dm^{-3}	k_1/k_{un}	k_2/k_{un}	K_1 /mol^{-1} dm^3	K_2 /mol^{-1} dm^3	r[b]
			α-Cyclodextrin			
1S	0.20	0.49	0.00	21	11	0.9961
2S	0.20	0.95	0.00	5	61	0.9994
3S	0.20	1.00	0.26	4	47	0.9946
1O	0.05	0.66	0.00	44	9	0.9990
2O	0.05	2.54	0.05	22	31	0.9992
3O	0.05	6.51	0.08	7	41	0.9987
			G1-β-Cyclodextrin			
1S	0.20	0.44	0.00	1300	33	0.9998
2S	0.20	0.32	0.01	750	33	0.9993
3S	0.20	0.34	0.04	640	57	0.9998
1O	0.05	1.68	0.00	48	7	0.9996
2O	0.05	2.23	0.33	11	25	0.9980
3O	0.05	1.06	0.11	7	31	0.9980

a) $k_{un} = 1.22 \times 10^{-3}\,s^{-1}$ (**1S**), $1.78 \times 10^{-3}\,s^{-1}$ (**2S**), $1.24 \times 10^{-3}\,s^{-1}$ (**3S**), $2.73 \times 10^{-3}\,s^{-1}$ (**1O**), $4.33 \times 10^{-3}\,s^{-1}$ (**2O**), and $2.60 \times 10^{-3}\,s^{-1}$ (**3O**). b) Correlation coefficient.

m-nitrophenyl acetate in an alkaline solution is greatly accelerated by α-CD, since the alkoxide ion of α-CD and the acyl carbonyl of the substrate lie close together in their inclusion complex.[14] Thus, the phosphate group of **3O** will also lie close to the α-CD alkoxide ion in a 1:1 complex. Only a α-CD–**1O** system showed weak deceleration by 1:1 complexation: No clear reasoning is possible at the present stage of investigation. The K_1 values for the α-CD complexes with thiophosphates were smaller than those for the corresponding phosphate complexes, suggesting that the thiophosphates are more shallowly included within the α-CD cavity than the phosphates. Probably, the relatively bulky thiophosphate group will retard deep inclusion within the small cavity of α-CD. In such cases, the reaction sites of the thiophosphates locate at the outside of the α-CD cavity and too far apart from the alkoxide ion of α-CD to be attacked. The weak or no deceleration observed for **2S** ($k_1/k_{un} = 0.95$) or **3S** ($k_1/k_{un} = 1.00$) implies that the α-CD cavity hardly hinders the attack of the hydroxide ion from bulk solution on the complexed thiophosphates. Another notable point of data shown in Table 1 is that there are several cases in which the K_2 values are larger than the K_1 values. This fact suggests that the second CD molecule interacts not only with part of a substrate molecule but also with the first CD molecule, probably by hydrogen bonding.

^{1}H NMR Spectroscopy. The solubilities of the examined phosphates and thiophosphates in D_2O were too low for us to record their ^{1}H NMR spectra. However, **2S** was soluble enough for NMR measurement in a 1:1 (v/v) mixture of D_2O with dimethyl sulfoxide-d_6. The chemical shifts (δ) for the protons of **2S** ($3.1\,mmol\,dm^{-3}$) in the solvent were significantly changed by the addition of α-CD and G1-β-CD. For example, changes ($\Delta\delta$) in chemical shifts for the ortho protons of the *p*-nitrophenyl group of **2S** were 0.027 and -0.019 when α-CD ($50\,mmol\,dm^{-3}$) and G1-β-CD ($21\,mmol\,dm^{-3}$) were added, respectively. On the other hand, the $\Delta\delta$ values for the methyl protons of **2S** were only 0.003 and –0.005 for α-CD and G1-β-CD, respectively. Significant upfield shifts of the C(3)- and C(5)-Hs of α-CD and G1-β-CD were also observed by the addition of **2S**. These results suggest that the *p*-nitrophenyl group of **2S** interact with α-CD and G1-β-CD more strongly than the methoxy groups of **2S**.

Conclusion

α-CD and G1-β-CD form not only 1:1 but also 2:1 complexes with the organic phosphates and thiophosphates examined in aqueous alkaline solutions. In 1:1 complexes, phenol release from the phosphates was mostly accelerated, and that from the thiophosphates was decelerated. In 2:1 complexes, the reactions both of the phosphates and thiophosphates were strongly retarded.

Experimental

Apparatus. The absorption and NMR spectra were recorded using a Shimadzu UV-2100 UV/Vis spectrophotometer and a JEOL Model JNM-A400 FT NMR spectrometer (400 MHz), respectively. The mass spectra were recorded using a Waters Quattro Micro tandem quadrupole MS system with positive ion electrospray ionization (ESI).

Materials. The α-CD and G1-β-CD were kindly supplied by Ensuiko Sugar Refining Co., Ltd. They were dissolved in water, treated with activated charcoal, and lyophilized to dryness before use. Reagent-grade *m*-nitrophenol (*m*-NP) and *m*-chloroperbenzoic acid (*m*-CPBA) were purchased from Wako Pure Chemical Industries, Ltd. The potassium salt of *m*-NP was prepared by neutralization of *m*-NP with aqueous KOH, followed by lyophilization. Reagent-grade *O*,*O*-dimethyl chlorothiophosphate was purchased from Sigma-Aldrich and used without further purification. Silica gel 60 (Merck, 0.040–0.063 mm) was used for column chromatography.

1S was extracted from MEP water-dispersible powder (MEP 40%, Nihon Nohyaku Co., Ltd.) and purified as follows: An aliquot of the MEP powder was suspended in aqueous NaCl (10%) solution and extracted twice with dichloromethane. The organic

layer was dried over Na_2SO_4, filtered, and evaporated in vacuo at 40 °C to dryness. The residue was suspended in hexane and chromatographed on a 3.0 × 50 cm silica gel column with hexane, followed by hexane/ether (3:1 v/v), as eluents. The hexane/ether fractions were assayed by an UV spectrophotometer. Fractions which gave absorption at 265 nm were combined and evaporated to afford a yellow-brown liquid, which was identified to be **1S** by ^{1}H NMR spectroscopy and mass spectroscopy.

2S was a stored sample used in previous work.[3] **3S** was prepared by the reaction of *O*,*O*-dimethyl chlorothiophosphate with potassium *m*-nitrophenoxide in xylene.[15] Crude **2S** and **3S** were purified by column chromatography and identified as described above.

1O, **2O**, and **3O** were prepared by the reaction of corresponding thiophosphates, **1S**, **2S**, and **3S**, with *m*-CPBA.[16] For example, a solution of *m*-CPBA in chloroform was added to a solution of **1S** in chloroform cooled below 0 °C. After stirring overnight at room temperature, the mixture was washed with 5% $NaHCO_3$ aqueous solution and then with water. The chloroform layer was dried over Na_2SO_4, filtrated, and evaporated in vacuo at 40 °C to dryness. The residue was dissolved in hexane/ethyl acetate (1:1 v/v) and chromatographed on a 3.0 × 50 cm silica gel column with hexane/ethyl acetate (1:1 v/v) as an eluent. Fractions which gave absorption at 265 nm were combined and evaporated to dryness to afford a yellow-brown liquid. The liquid was identified to be **1O** by ^{1}H NMR spectroscopy and mass spectroscopy.

Kinetics. The alkaline hydrolyses of organic phosphates and thiophosphates were carried out in 0.05 and 0.20 mol dm^{-3} NaOH, respectively, at 308 ± 0.1 K. The ionic strengths (I_c) of the solutions were maintained at 0.65 mol dm^{-3} with Na_2SO_4. The reaction rates were measured by following the appearance of the absorption due to the corresponding phenoxide anions at 410 nm for **1S**, **2S**, **1O**, and **2O** and at 390 nm for **3S** and **3O**. In a typical run, 2.00 mL of a base solution was pipetted into a pair of 1.00-cm quartz cells, one of which was used as a reference cell, and the other, as a sample cell, in a spectrophotometer. After thermal equilibrium had been reached, 5 to 20 μL of a ca. 20 mmol dm^{-3} ester in methanol was added to the sample cell and the change in absorbance was followed. The rate constants (k_{obsd}) were determined by a nonlinear least-squares curve-fitting analysis of the data according to the ordinary first-order rate equation. All the reactions examined obeyed good first-order kinetics with respect to substrates in both the absence and presence of α-CD and G1-β-CD.

Kinetic Determination of the Binding Constants and Rate Constants of Cyclodextrin–Substrate Complexes. As is shown in Figure 2b for a G1-β-CD–**1O** system as an example, the observed first-order rate constant (k_{obsd}) increased, approached maximum, and then decreased as the CD concentration (c_0) increased. This behavior suggests that the rate process involves the prior formation of not only 1:1 but also 2:1 (host:guest) inclusion complexes of the CD with the substrate. In such a case, we can derive eq 1:[11]

$$K_1K_2c^3 + (K_1 + 2K_1K_2s_0 - K_1K_2c_0)c^2 + (1 + K_1s_0 - K_1c_0)c - c_0 = 0 \quad (1)$$

where K_1 and K_2 are binding constants for 1:1 and 2:1 complexes, respectively, c_0 and s_0, initial concentrations of CD and substrate, respectively, and c, equilibrium concentration of CD.

On the other hand, the rate constant k_{obsd} at any CD concentration is represented by:

$$k_{obsd} = k_{un}(s/s_0) + k_1(x/s_0) + k_2(y/s_0) \quad (2)$$

or

$$\Delta k_{obsd} = \Delta k_1 x/s_0 + \Delta k_2 y/s_0 \quad (3)$$

where k_{un} and s are the rate constant and equilibrium concentration for free substrate, respectively, k_1, and x, those for 1:1 complex, k_2 and y, those for 2:1 complexes, $\Delta k_{obsd} = k_{obsd} - k_{un}$, $\Delta k_1 = k_1 - k_{un}$, and $\Delta k_2 = k_2 - k_{un}$. Thus, we determined the values of K_1, K_2, Δk_1, and Δk_2 by a nonlinear least-squares curve-fitting analysis of the change in Δk_{obsd} with c_0 using the software Equatram-G available for numerical analysis.

References

1 T. Kasagami, T. Miyamoto, I. Yamamoto, *Pest Manag. Sci.* **2002**, *58*, 1107.

2 a) C. van Hooidonk, J. C. A. E. Breebaart-Hansen, *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 289. b) C. van Hooidonk, C. C. Groos, *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 845. c) C. van Hooidonk, J. C. A. E. Breebaart-Hansen, *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 680.

3 K. Mochida, Y. Matsui, Y. Ota, K. Arakawa, Y. Date, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3119.

4 R. V. Vico, E. I. Buján, R. H. de Rossi, *J. Phys. Org. Chem.* **2002**, *15*, 858.

5 a) M. Kamiya, S. Mitsuhasi, M. Makino, *Chemosphere* **1992**, *25*, 1783. b) M. Kamiya, K. Nakamura, C. Sasaki, *Chemosphere* **1994**, *28*, 1961. c) M. Kamiya, K. Nakamura, *Pestic. Sci.* **1994**, *41*, 305. d) M. Kamiya, K. Nakamura, C. Sasaki, *Chemosphere* **1995**, *30*, 653. e) M. Kamiya, K. Nakamura, *Environ. Int.* **1995**, *21*, 299. f) S. Ishiwata, M. Kamiya, *Chemosphere* **1999**, *38*, 2219. g) S. Ishiwata, M. Kamiya, *Chemosphere* **1999**, *39*, 1595. h) S. Ishiwata, M. Kamiya, *Chemosphere* **2000**, *41*, 701. i) M. Kamiya, K. Kameyama, S. Ishiwata, *Chemosphere* **2001**, *42*, 251.

6 a) Y. C. Luo, Q. R. Zeng, G. Wu, Z. K. Luan, R. B. Yang, B. H. Liao, *Bull. Environ. Contam. Toxicol.* **2003**, *70*, 998. b) Q. Zeng, B. Liao, Y. You, C. Liu, H. Tang, *Bull. Environ. Contam. Toxicol.* **2003**, *71*, 668.

7 B. Manunza, S. Deiana, M. Pintore, C. Gessa, *Glycoconjugate J.* **1998**, *15*, 293.

8 D. Churchill, J. C. F. Cheung, Y. S. Park, V. H. Smith, G. vanLoon, E. Buncel, *Can. J. Chem.* **2006**, *84*, 702.

9 I. Yamamoto, K. Ohsawa, F. W. Plapp, Jr., *J. Pestic. Sci.* **1977**, *2*, 41.

10 Y. Okada, Y. Kubota, K. Koizumi, S. Hizukuri, T. Ohfuji, K. Ogata, *Chem. Pharm. Bull.* **1988**, *36*, 2176.

11 O. S. Tee, X.-X. Du, *J. Org. Chem.* **1988**, *53*, 1837.

12 R. I. Gelb, L. M. Schwartz, J. J. Bradshaw, D. A. Laufer, *Bioorg. Chem.* **1980**, *9*, 299.

13 S. Hamai, *J. Mater. Chem.* **2005**, *15*, 2881.

14 R. L. VanEtten, J. F. Sebastian, G. A. Clowes, M. L. Bender, *J. Am. Chem. Soc.* **1967**, *89*, 3242.

15 W. Loremz, G. Schrader, *Chem. Abstr.* **1963**, *58*, 11402e.

16 T. Miyamoto, I. Yamamoto, *J. Pestic. Sci.* **1997**, *2*, 303.