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Catalytic properties of novel cyclodextrin dimers in the hydrolytic cleavage of *p*-nitrophenyl alkanoates

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ABSTRACT: Novel cyclodextrin (CD) dimers (**3a–c**) linked by multidentate ligands were prepared by reacting 6-deoxy-6-(hydroxyethylamino)-β-CD (**2**) with *p*- and *m*-bis(bromomethyl)benzene and 2,6-bis(bromomethyl)pyridine, respectively. The catalytic properties of **2, 3b** and **3c** in the hydrolytic cleavage of *p*-nitrophenyl alkanoates, namely acetate (PNPA), butanoate (PNPB), hexanoate (PNPH) and octanoate (PNPO), were examined. CD dimers **3b** and **3c** showed modest rate enhancements around neutrality. Although the catalytic rate constants (k_c) in the presence of **3b** or **3c** did not vary significantly with the chain length of the esters, the Michaelis constants, K_M, for 'long-chain' esters (PNPH and PNPO) were much smaller than those for 'short-chain' esters (PHPA and PNPB), and consequently the selectivity factors (k_c/K_M) for 'long-chain' esters were much larger than those for 'short chain' esters, indicating that the CD dimers had good dimensional recognition ability and substrate selectivity in the hydrolytic cleavage of *p*-nitrophenyl alkanoates. Addition of Cu^{2+} to the reaction media did not have much impact on K_M, but led to an appreciable increase in k_c, and therefore increases in k_c/k_u and k_c/K_M. The monomeric CD compound **2** showed essentially no selectivity in the hydrolysis of these esters. Kinetic consequences are briefly interpreted. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: catalytic hydrolysis; cyclodextrin dimer; *p*-nitrophenyl alkanoates; synthesis

INTRODUCTION

The effects of cyclodextrins (CDs) on the hydrolytic cleavage of esters in basic solutions have been intensively investigated.[1] The clearly established mechanism involves inclusion of the hydrophobic moiety of an ester and then acyl transfer from the ester to the anionic form of a secondary hydroxyl group ($pK_a = 12.2$) of CD. The acylated CD then reacts with hydroxide anion to release CD. This CD-catalyzed process proceeds similarly to enzymatic hydrolysis, and CDs have been extensively studied as a hydrolase model. However, in the ester hydrolysis, CD is only a reactant rather than a real catalyst since the deacylation of acylated CD is even slower than the hydrolysis of the substrate.[2,3] Even for the first acyl transfer step, appropriate alkaline conditions are required to activate the CD hydroxyl group.[1a,2] Moreover, the binding ability of a single CD to the substrate is usually weaker than that of natural enzymes.[4] Introduction of a functionality other than a hydroxyl group,[5] such as imidazolyl among many others, and synthesizing CD dimers (for other CD dimers, see Refs. 4 and 6), which have the potential to bind a substrate with their two hydrophobic CD cavities, have proven effective approaches for the improvement of the catalytic activity and binding ability of CD enzyme models to substrates. Given that the linkage of a CD dimer is catalytically active, and the reaction site of the substrate is situated between its two hydrophobic ends, the ditopic binding of the substrate to the CD dimer would locate the reaction site in the vicinity of the catalytic group of the CD dimer, taking advantage of the proximity effect resulting in rate acceleration and catalytic specificity near neutral conditions.

Various metal ions exist in the active center of natural enzymes and play an essential role in catalysis.[7] However, the linkage of CD dimers so far reported capable of complexing metal ion as catalytically active site is limited to that derived from 2,2′-bipyridine and porphyrin moieties.[6g,o] We herein wish to report the syntheses of novel CD dimers which are bridged by multidentate catalytic matrix, and their catalytic behavior in the hydrolytic cleavage of *p*-nitrophenyl alkanoates.

RESULTS AND DISCUSSION

Syntheses of CD dimers

The synthetic route for CD dimers (**3a–c**) is depicted in

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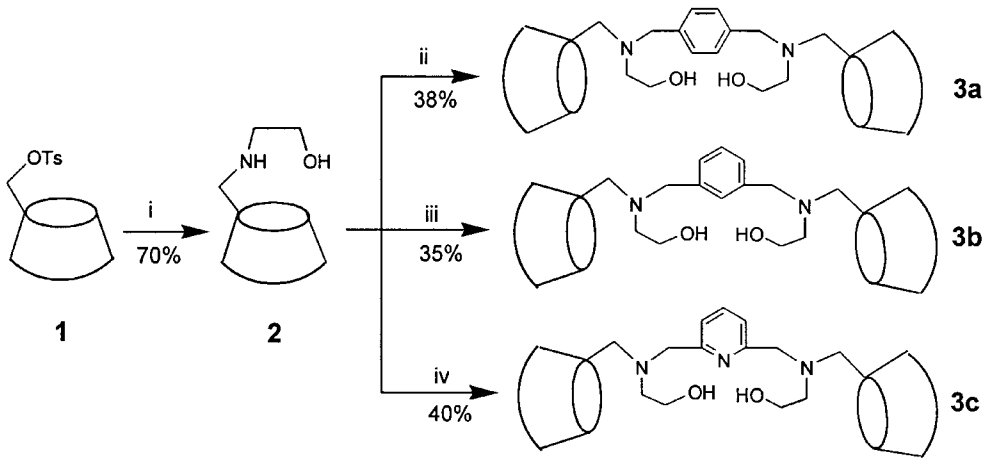

Scheme 1. Reagents and conditions: i, aminoethyl alcohol, 80 °C, 3 h; ii, *p*-bis(bromomethyl)benzene, Na_2CO_3, DMF,. rt,. 24 h; iii, *m*-bis(bromomethyl)benzene, Na_2CO_3, DMF, r.t., 24 h; iv, 2,6-bis(bromomethyl)pyridine, K_2CO_3, DMSO, r.t., 24 h

Scheme 1. 6-Deoxy-6-hydroxyethylamino-β-CD (**2**) was obtained by reaction of β-CD tosylate (**1**) with excess of aminoethyl alcohol at 70 °C under nitrogen. Recrystallization of the crude product from water gave **2** in 70% yield. Reaction of **2** with *p*-bis(bromomethyl)benzene and *m*-bis(bromomethlyl)benzene in DMF in the presence of anhydrous Na_2CO_3 at room temperature, followed by chromatographic purification on a Sephadex column, gave CD dimers **3a** and **3b** in 38 and 35% yield, respectively. CD dimer **3c** was prepared by treating **2** with 2,6-bis(bromomethyl)pyridine in DMSO in the presence of anhydrous K_2CO_3. We found that important factors affecting the yield of **3c** are the variety of solvent and base. Experimental results showed that DMSO was preferable to DMF, and K_2CO_3 to Na_2CO_3. With DMSO–K_2CO_3 condition, **3c** was obtained in 40% yield, whereas in DMF and with Na_2CO_3 as the base, the yield was only 15%. Compounds **2** and **3a–c** are unprecedented. Their structures were identified by their mass, ^{1}H NMR and ^{13}C NMR spectra and elemental analyses. Thermogravimetric and elemental analyses showed that all of these compounds are hydrates. The success of selective syntheses of CD dimers **3a–c** demonstrates the greater neucleophilicity of the secondary amino substituent compared with the primary and secondary hydroxyl groups in **2**. This synthetic route provides a convenient approach for the preparation of CD dimers capable of locating a metal ion in the linkage as a catalytically active center.

Complex of CD dimer 3c with Cu^{2+}

Addition of $CuSO_4 \cdot 5H_2O$ to a solution of CD dimer **3c** at pH 8.04 afforded a green solution. The plot of absorbance at 298 nm versus $[Cu^{2+}]/[\mathbf{3c}]$ (Fig. 1) gave an inflection point around $[Cu^{2+}]/[\mathbf{3c}] = 1.0$, indicating the formation of a 1:1 complex between Cu^{2+} and dimer **3c**. The solution turned turbid when $[Cu^{2+}]/[\mathbf{3c}]$ exceeded 2.0. The stability constant for the complex was 1.22×10^6 l mol^{-1} as calculated with least-squares treatment of the spectrophotometric data.

Hydrolytic cleavage of *p*-nitrophenyl alkanoates

The catalytic properties of CD dimers and related compounds were examined with regard to the hydrolysis reaction of *p*-nitrophenyl alkanoates, in the form of acetate (PNPA), butanoate (PNPB), hexanoate (PNPH) and octanoate (PNPO). These substrates have already been used in previous studies[8] of enzyme models with the aim of achieving hydrophobic binding of the acyl group of the ester to the enzyme model, and for the convenience of automatic measurements. For long-chain alkanoates, especially PNPO in our case, rate measurements in the

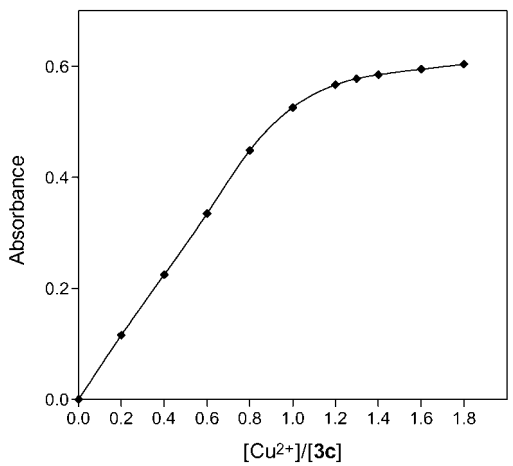

Figure 1. Plot of the absorbance at 298 nm vs $[Cu^{2+}]/[\mathbf{3c}]$. Conditions: 0.1 M phosphate buffer (pH 8.0), 30 °C; $[\mathbf{3c}] = 2.0 \times 10^{-4}$ M

Table 1. Kinetic parameters for hydrolysis of *p*-nitrophenyl alkanoates[a]

Catalyst	Substrate[b]	$10^3 k_c(s^{-1})$	$10^3 K_M(M)$	k_c/k_u	$k_c/K_M(s^{-1}\ lmol^{-1})$
2	PNPA	3.52	4.79	29.1	0.735
	PNPB	1.44	3.90	20.0	0.369
	PNPH	1.30	1.88	15.9	0.692
	PNPO	0.890	1.34	11.9	1.33
3b	PNPA	0.561	1.54	4.64	0.364
	PNPB	0.254	1.08	3.53	0.235
	PNPH	0.169	0.00580	2.06	29.1
	PNPO	0.208	0.0612	2.77	6.78
3c	PNPA	0.271	1.22	2.24	0.222
	PNPB	0.151	0.917	2.10	0.165
	PNPH	0.149	0.00700	1.82	21.3
	PNPO	0.189	0.0675	2.51	5.59
Cu^{2+}–**3b**	PNPH	0.427	0.00681	5.21	62.7
	PNPO	0.403	0.0610	5.37	13.2
Cu^{2+}–**3c**	PNPA	1.82	0.993	15.0	1.83
	PNPB	1.89	0.789	26.3	2.40
	PNPH	0.892	0.00620	10.9	144
	PNPO	0.720	0.0562	9.60	25.6

[a] At 35 ± 0.1 °C in 0.1 M phosphate buffer (pH 8.04). [Substrate] = 1×10^{-5} M, [catalyst] = 2×10^{-4}–2×10^{-3} M.
[b] PNPA = *p*-nitrophenyl acetate; PNPB = *p*-nitrophenyl butanoate; PNPH = *p*-nitrophenyl hexanoate; PNPO = *p*-nitrophenyl octanoate.

absence of CDs are complicated by low solubility or aggregation. We carried out our kinetic experiments by adjusting the ester concentration to 1×10^{-5} M in accordance with the procedure of Guthrie.[9]

The hydrolyses of *p*-nitrophenyl alkanoates were measured spectroscopically at 35 °C in 0.1 M phosphate buffer at pH 8.04, in the presence or absence of an excess of CDs with added 2% (v/v) CH_3CN. All of the substrates gave saturation-type kinectics. Treatment of the kinetic data by the Eadie–Hofstee approach gave the Michaelis constants (K_M), the maximum catalytic rate constants (k_c), the rate enhancements (k_c/k_u) and selectivity factors (k_c/K_M) (Table 1). In the case of the monomeric CD **2** as catalyst, it is apparent that the Michaelis constants (K_M) and rate enhancements (k_c/k_u) decrease regularly with increase in the alkyl chain length of the esters, which can probably be attributed to the competitive inclusion of aryl and alkyl groups in the CD cavity. The poorly productive or non-productive alkyl insertion complexes[10] possibly result in decreases of the rate enhancements as the hydrocarbon chain increasingly occupies the CD cavity. No remarkable variations were seen in the selectivity factors (k_c/K_M) of **2** for all of the substrates, indicating that the monomeric CD **2** shows no selectivity in the hydrolytic cleavage of *p*-nitrophenyl alkanoates.

It is worth noting that the K_M values of CD dimers **3b** and **3c** for 'long-chain' esters (PNPH, PNPO) are much smaller than those for 'short-chain' esters (PNPA, PNPB). For example, K_M of **3b** for PNPH is about 265 times less than that for PNPA, and K_M of **3c** for PNPH is 170 times less than that for PNPA. Similar trends also occur in the binding of CD dimers to PNPH and PNPB, demonstrating that CD dimers bind to 'long-chain' esters much more strongly than to 'short-chain' esters. The binding of the alkyl chain to the CD cavity is documented in the literature. For instance, CDs form inclusion complexes with linear alcohols, alkylphenols, acylphenols[11] and surfactants.[12] It is also known that two separate CDs in high concentrations can bind *p*-nitrophenyl and alkyl groups of 'long-chain' alkanoates simultaneously.[13] Thus, in the present case of our CD dimers, it can be visualized that the *p*-nitrophenyl group is included in one of the two linked CD cavities and the comparatively long alkyl chain in another. Nevertheless, for the 'short-chain' esters, when *p*-nitrophenyl is included in one CD cavity, the alkyl group is too short to occupy another cavity of the CD dimers. The synchronous binding of CD dimers to double-ended substrates is responsible for the far smaller K_M of CD dimers for 'long-chain' esters. Moreover, even for 'long-chain esters' (PNPH and PNPO), the Michaelis constants of the CD dimers also vary significantly. For example, K_M of **3b** for PNPH is about 10 times smaller than that for PNPO, K_M of **3c** for PNPH is nine times smaller than that for PNPO. CD dimers **3b** and **3c** bind to the relatively long ester PNPO more weakly than to PNPH. We take these results to means that the CD dimers have reasonable molecular recognition ability, here virtually length recognition for *p*-nitrophenyl alkanotes. Dimensional fitting contributes much to the stability of the inclusion complex; too short or too long hydrocarbon chains lead to weaker binding.

Another noteworthy feature about the CD dimers in Table 1 is the selectivity factors (k_c/K_M). Whereas the k_c/K_M values of CD dimers for PNPA and PNPB do not change appreciably, those for PNPH and PNPO increase significantly. k_c/K_M of **3b** for PNPH is about 80 times

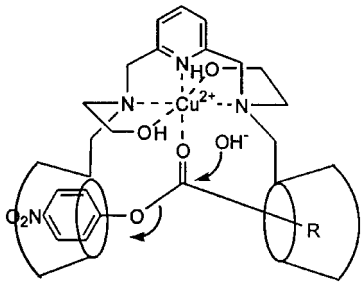

Figure 2. Proposed mechanism for ester hydrolysis catalyzed by the Cu^{2+}–**3c** complex

larger than that for PNPA and k_c/K_M of **3c** for PNPH is approximately 95 times larger than that for PNPA. For PNPH and PNPO, k_c/K_M of CD dimers also varies considerably. k_c/K_M of CD dimers **3b** and **3c** for PNPH is about four times larger than that for PNPO. These observations imply good substrate selectivity of the CD dimers in the hydrolytic cleavage of *p*-nitrophenyl alkanoates. Since the k_c values of the CD dimers for all of the substrates do not change significantly, the differences in k_c/K_M result mainly from the great variations of K_M, suggesting that selective binding of CD dimers to substrates contributes to the selective catalyses.

The rate enhancements (k_c/k_u) in the presence of CD dimers (**3b** and **3c**) are about 2–5-fold, displaying modest catalyses near neutral conditions. That the k_c and k_c/k_u values of CD dimers **3b** and **3c** are smaller than those of **2** is probably due to the different nucleophilicities of the secondary and tertiary amines.

Addition of Cu^{2+} to the reaction media containing CD dimers does not have much impact on K_M, but leads to significant increase in the catalytic rate constants (k_c) and therefore increases in the rate enhancements (k_c/k_u) and selectivity factors (k_c/K_M). The increase in k_c for **3c** caused by Cu^{2+} is 4–12-fold, which is larger than that for **3b** by Cu^{2+}. This observation suggests that the pyridine nitrogen plays an important role in the coordination of **3c** to Cu^{2+} and in the cleavage of *p*-nitrophenyl alkanoates. The proposed mechanism of ester hydrolysis catalyzed by the Cu^{2+}–**3c** complex is illustrated in Fig. 2. Cu^{2+} is coordinated by oligoazadiols in the linkage of the CD dimer, and situated near the center of the substrate. Electrophilic activation of the ester carbonyl by the approaching Cu^{2+} and locally effective concentrated hydroxide anion around Cu^{2+} by electrostatic interaction poses an essential ensemble of catalysis resulting in an increase in k_c. The hydrolysis of the substrates in the absence of a Cu^{2+} ion might be explained similarly through an Na^+–CD dimer complex. Unfortunately, kinetic measurements of **2** in the presence of Cu^{2+} for ester hydrolysis were not made because the solution turned turbid when $CuSO_4$ was added.

CONCLUSIONS

Novel CD dimers (**3a–c**) in which the two CDs are bridged by an oligoazadiol, a kind of multidentate ligand, were conveniently prepared by reaction of 6-deoxy-6-hydroxyethylamino-β-CD (**2**) with *p*- and *m*-bis(bromomethyl)benzene and 2,6-bis(bromomethyl)pyridine. CD dimer **3c** forms stable complex with Cu^{2+}. These CD dimers **3b, 3c** and their Cu^{2+} complexes show good substrate selectivity in the hydrolysis of *p*-nitrophenyl alkanoates by virtue of length recognition, which is attributed to stronger binding of CD dimers to 'long-chain' esters, resulting from the simultaneous binding of the two hydrophobic ends, aromatic and alkyl groups, of the 'long-chain' esters to the two CD cavities. It may be suggested that in the presence of Cu^{2+}, the electrophilic activation of the ester carbonyl by the nearby Cu^{2+} and the relatively high concentration of hydroxide anion around Cu^{2+} contribute to the increase in catalytic rate constants in hydrolytic cleavage of *p*-nitrophenyl alkanoates.

EXPERIMENTAL

Melting-points were measured on a DuPont Model 1090B differential thermal analyzer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument in DMSO-d_6 with TMS as the internal standard. Mass spectra were obtained on a VG Autospec 3000 mass spectrometer, UV–visible spectra were obtained with a Shimadzu UV265FW spectrophotometer. Elemental analyses were carried out with a Carlo Erba Model 1106 instrument.

Aminoethyl alcohol was freshly distilled. β-CD was recrystallized from water and dried with a P_2O_5 trap before use. DMF was dried with CaH_2. *p*-Bis(bromomethyl)benzene,[14] *m*-bis(bromomethyl)benzene[14] and 2,6-bis(bromomethyl)pyridine[15] were prepared according to the literature procedures. β-CD tosylate (**1**) was synthesized by a slight modification of the literature procedure.[16] *p*-Nitrophenyl alkanoates were obtained from the reaction of *p*-nitrophenol with the appropriate acid anhydride or acyl chloride. The purity of the alkanoates was satisfactory by TLC and ^1H NMR spectra.

*6-Deoxy-6-hydroxyethylamino-β-CD (**2**).* A mixture of β-CD tosylate (**1**) (1.34 g, 1.0 mmol) and aminoethyl alcohol (5 ml) was heated at 80 °C with stirring for 3 h under nitrogen. After cooling, the mixture was poured into acetone (50 ml), and a copious of white precipitate appeared. The precipitate was collected by filtration and dissolved in a small amount of hot water, and precipitated again with acetone. The resulting crude product was recrystallized three times from water to afford 0.88 g of **2** as white needles (70% yield), m.p. 278 °C (decomp.). ^1H NMR: δ 5.75–5.70 (m, 14H), 4.82 (s, 7H), 4.53–4.33 (m,

6H), 3.83–3.53 (m, 30H), 3.45–3.30 (m, overlaps with HOD). ^{13}C NMR: δ 102.3, 83.6, 81.9, 73.2, 72.7, 72.3, 70.7, 60.6, 60.2, 51.8, 49.4. Fast atom bombardment mass spectrometry (FAB-MS) (methanol): *m/z* 1179 $(M + 1)^+$. Anal. Calcd for $C_{44}H_{75}NO_{35}\cdot 4H_2O$: C, 42.27; H, 6.69; N, 1.12. Found: C, 41.97; H, 6.40; N, 1.31%.

*General procedure for preparation of **3a** and **3b**.* To a solution of **2** (250 mg, 0.2 mmol) in DMF (4 ml) were added anhydrous Na_2CO_3 (106 mg, 1.0 mmol) and bis(bromomethyl)benzene (26.4 mg, 0.1 mmol). The mixture was stirred at room temperature for 24 h. The solid in the reaction solution was filtered off and the filtrate was precipitated by addition of acetone (30 ml). The precipitates were collected by suction and dried at 80 °C to give a white crude product. This crude product was dissolved in water (2 ml) and applied to a column (40×3 cm i.d.) of CM-Sephadex C-25 resin (NH_4^+ form). The column was eluted with 0.05 M ammonium hydrogencarbonate to afford the product as white crystals.

Compound **3a**: yield 99 mg (38%), m.p. 298.4 °C (decomp.). ^{1}H NMR: δ 7.24 (s, 4H), 6.08–5.74 (m, 28H), 4.82 (s, 14H), 4.49–4.35 (m, 14H), 3.62 (br s, 56H), 3.34 (br s, overlaps with HOD), 2.84–2.42 (m, overlaps with DMSO). ^{13}C NMR: δ 138.1, 128.7, 102.3, 84.2, 81.7, 73.3, 72.7, 72.3, 71.2, 60.2, 59.2, 55.8, 55.5. FAB-MS [DMSO–glycerol–*m*-nitrobenzyl alcohol (1:1:1)]: *m/z* 2458 (M^+). Anal. Calcd for $C_{96}H_{156}N_2O_{70}\cdot 8H_2O$: C, 44.31; H, 6.67; N, 1.08. Found: C, 44.15; H, 6.40; N, 1.12%.

Compound **3b**: yield 91.7 mg (35%), m.p. 294.6 °C (decomp.). ^{1}H NMR: δ 7.20 (s, 4H), 5.96–5.74 (m, 28H), 4.82 (s, 14H), 4.60–4.38 (m, 14H), 3.59 (br s, 56H), 3.37 (br s, overlaps with HOD), 2.81–2.40 (m, overlaps with DMSO). ^{13}C NMR: δ 139.6, 129.8, 128.2, 102.4, 84.4, 81.8, 73.4, 72.8, 72.4, 71.3, 60.3, 59.3, 56.1, 55.5. FAB-MS [DMSO–glycerol–*m*-nitrobenzyl alcohol (1:1:1)]: *m/z* 2458 (M^+). Anal. Calcd for $C_{96}H_{156}N_2O_{70}\cdot 9H_2O$: C, 44.00; H, 6.69; N, 1.07. Found: C, 44.29; H, 6.51; N, 1.10%.

Compound **3c** was prepared by a procedure similar to that for **3a** except for using DMSO and K_2CO_3 instead of DMF and Na_2CO_3. Yield 108 mg (40%), m.p. 290.4 °C (decomp.). ^{1}H NMR: δ 7.52 (s, 1H), 7.39 (s, 2H), 6.12–5.77 (m, 28H), 4.82 (br s, 21H), 4.53 (br s, 7H), 3.63 (br s, overlaps with HOD), 2.88–2.49 (m, overlaps with DMSO). ^{13}C NMR: δ 159.3, 137.3, 121.1, 102.3, 84.1, 81.6, 73.2, 72.7, 72.3, 71.5, 60.1, 59.4, 56.8, 55.9. FAB-MS [DMSO–glycerol–*m*-nitrobenzyl alcohol (1:1:1)]: *m/z* 2459 (M^+). Anal. Calcd for $C_{95}H_{155}N_3O_{70}\cdot 14H_2O$: C, 42.08; H, 6.80; N, 1.55. Found: C, 42.34; H, 6.66; N, 1.31%.

Kinetic study. Rate measurements were made for solutions of the esters at a concentration of 1×10^{-5} M using 6–10 different CD concentrations from 2×10^{-4} to 2×10^{-3} M. Each run was initiated by adding 60 µl of a stock solution of ester in CH_3CN to 3 ml of 0.1 M phosphate buffer (pH 8.04) containing a suitable amount of CD derivative, pre-equilibrated at 35 ± 0.1 °C in the thermostated cell holder of a Shimadzu 265 FW spectrophotometer. The ester cleavage was followed by monitoring the first-order appearance of the *p*-nitrophenolate ion at 400 nm. In the presence of CDs, all of the substrates gave saturation-type kinetics. The Eadie–Hofstee approach[1a] was used to provide the constants k_c and K_M as given in Table 1.

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