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A New Ligand-Functionalized β-Cyclodextrin as a Esterolytic Reagent at Neutral pH

ROBERTO FORNASIER, ENNIO SCARPA, PAOLO SCRIMIN,*
PAOLO TECILLA, and UMBERTO TONELLATO*
Department of Organic Chemistry and Centro CNR Meccanismi Reazioni Organiche, Universita' di Padova, Via Marzolo 1, 35131 Padova, Italy

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Abstract. The paper reports the synthesis of a β-cyclodextrin (β-CD) derivative (**1**) functionalized with a ligand subunit at the secondary-hydroxyl rim. The ligand subunit is 2-hydroxymethyl-6-thiomethyl pyridine connected to the macrocycle via a thioether bond. In the presence of Cu(II) ions **1** accelerates the cleavage of the *p*-nitrophenyl esters of picolinic acid (PNPP), quinaldic acid (PNPQ) and its 6-phenyl derivative (PNPQPh) via the nucleophilic attack of the hydroxyl of the pyridine subunit. However, the β-CD derivative is less effective than the ligand 2-hydroxymethyl-6-methylthiomethyl pyridine (**2**), indicating no cooperation between the hydrophobic and metal ion recognition sites. However, in the case of PNPQPh, the observed rate constants in the presence of Cu(II) ions are close to that of model **2** and this suggests we are approaching a binding mode appropriate for taking advantage of the two binding sites of the metal receptor **1** · Cu(II). Interestingly, the most reactive derivative with native β-CD is the *p*-nitrophenyl quinaldate (PNPQ) in accord with its mode of complexation to the macrocycle and the location of the actual nucleophile (one of the secondary hydroxyls of β-CD).

Key words. Cyclodextrin, transacylation, metal, Cu(II), catalysis, ester, supramolecule.

1. Introduction

The synthesis of functionalized cyclodextrins (CDs) [1] provides new receptors with molecular recognition properties and catalytic behavior often quite different from those of native CDs. For instance, CD derivatives bearing a pendant imidazole [2] may act as catalysts in the cleavage of complexed esters in neutral aqueous solutions, in contrast to native CDs, which react at much higher pHs through a transacylation process [3]. The ability of transition metal ions to act as additional recognition and/or catalytic sites for several substrates [4] has stimulated the investigation of modified cyclodextrins bearing ligand subunits for transition metal ion complexation which may behave as polytopic receptors. Ligand modified CDs have been synthesized by Breslow [5], Tabushi [6], Willner [7], Vögtle [8], Czarnik [9], Schneider [10], and Rizzarelli [11]. Cooperativity between the hydrophobic CD cavity and the metal ion in binding proper substrates [6, 7] as well as catalysis of the hydrolysis of activated esters complexed within the cavity [5, 9, 10] have been reported.

We address here the problem of the competition between the two binding sites of a ligand functionalized CD (i.e., the macrocycle's cavity and the metal ion

* Authors for correspondence.

complexed to the ligand subunit of the receptor) with a kinetic study of the hydrolytic cleavage of activated esters of selected α-amino acids. These substrates are also effective ligands for metal ions such as Cu(II) and are good candidates for inclusion in the CD cavity. The reactivity of the functionalized derivative will be compared with that observed with native cyclodextrin in order to highlight possible differences due to the shape of the substrate and the different nature and location of the actual nucleophilic group.

For this purpose, β-CD has been functionalized with a hydroxymethylpyridine ligand subunit at the secondary-hydroxyl rim leading to compound **1**. Esters PNPP, PNPQ and PNPQPh have been used as substrates. From previous studies in our laboratory [12, 13] it was known that a 2-hydroxymethylpyridine ligand, in the presence of Cu(II) or Zn(II) ions, becomes a powerful catalyst for the cleavage of PNPP and other α-amino acid esters. We now report on the reactivity of **1** in the presence of Cu(II) in the esterolytic cleavage of these three substrates. The kinetic effects observed are compared with those obtained using ligand **2** [12], devoid of a hydrophobic recognition site, and also with those obtained with native β-CD. A rationale for the observed differences in reactivity is offered.

2. Experimental

2.1. GENERAL

NMR spectra were recorded on Bruker AC200 or AM400 spectrometers operating at 200 or 400 MHz, respectively. UV spectra were obtained using a Perkin-Elmer Lambda 5 instrument equipped with a thermostatted cell holder. $Cu(NO_3)_2$ solutions were titrated according to standard procedures [13]. The buffer 4-morpholinoethanesulfonic acid, MES, was a Fluka product, used as received. β-Cyclodextrin (β-CD) was purchased from Sigma as the heptahydrate. Dry β-Cd was obtained by keeping the compound *in vacuo* at 60°C over P_2O_5 for 24 h. Quinaldic acid was purchased from Aldrich. The synthesis of compound **2** has already been reported [12], as has that of PNPP [14].

2.2. SYNTHESIS

2.2.1. *3-(2-Thiomethyl-6-hydroxymethylpyridine)-β-cyclodextrin* (**1**)

2-(*O-p*-toluensolfonyl)-β-CD (2.15 g, 1.7 mmol), prepared according to Breslow's procedure [18], was dissolved in 20 mL of H_2O containing 1.7 mmol of $NaHCO_3$ and 1.7 mmol of 2-hydroxymethyl-6-mercaptomethyl pyridine [12] kept at 60°C under a nitrogen atmosphere. The reaction mixture was stirred under these conditions until all the thiol had disappeared (26 h). The hot reaction mixture was then filtered with suction to remove any precipitate. Subsequently 1 L of acetone was slowly added under stirring. The solid obtained was filtered off and purified by chromatography over Sephadex G-15 (eluant: H_2O). After freeze drying the proper fractions, 900 mg of pure **1** (40% yield) was obtained: ^{1}H-NMR (D_2O)δ 3.3–4.0 (*m*, 42H, H2, H3, H4, H5, H6), 5.0–5.2 (*m*, 7H, H1), 7.40 and 7.48

(two *d*, 2H, Py H3 and H5), 7.85 (*t*, 1H, Py H4); FAB mass spectrum, *m/z*(relative intensity): 1272 (M + 1, 75%), 1294 (M + Na, 100%).

Anal. Calcd. for $C_{49}H_{78}NO_{35}S \cdot 7H_2O$: C, 30.28; H, 4.77; N, 0.72. *Found:* C, 30.33; H, 4.35; N, 0.80.

2.2.2. *6-Phenylquinaldic Acid*

4-Aminodiphenyl (3.38 g, 20 mmol) was reacted in toluene (100 mL) with freshly distilled ethyl glyoxylate [15] to give the imine derivative. The reaction is fast (5–10 min) and occurs at room temperature with occasional heating (heating gun). After evaporation of the toluene the above crude imine was dissolved, at −78°C, in CH_2Cl_2 containing ethyl vinyl ether (2.4 mL) and boron trifluoride etherate (3.68 mL). The reaction was kept at this temperature for 10 h, then allowed to reach room temperature. The solvent was rotary evaporated and the crude material purified by medium pressure chromatography (SiO_2, 3% ethyl acetate in toluene). Evaporation of the proper fractions gave 2-ethyloxycarbonyl-6-phenyl quinoline (0.95 g). The above ester was subsequently hydrolyzed in dioxane (60 mL) containing 1N NaOH (15 mL) during *ca.* 1 h at room temperature. The solution was then acidified to pH = 3 (HCl), the dioxane removed with the rotary evaporator and the remaining solution extracted with $CHCl_3$. Evaporation of the dried chloroform gave the acid quantitatively: ^{1}H-NMR ($CDCl_3$) δ 7.53 (*m*, 3H), 7.74 (*d*, 2H), 8.11 (*m*, 2H, H7 and H5), 8.26 (*d*, 1H, H8), 8.31 (*d*, 1H, H3), 8.47 (*d*, 1H, H4).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.88; H, 4.45; N, 5.64. *Found:* C, 77.63; H, 4.51; N, 5.58.

2.2.3. *General Procedure for the Synthesis of Esters PNPQ and PNPQPh*

The acid, *p*-nitrophenol and dicyclohexylcarbodiimide were dissolved in equimolar amounts in dry pyridine. The mixture was stirred at room temperature until all the acid had disappeared (2 to 3 d). A white precipitate of dicyclohexyl urea formed during this period. The slurry was cooled to 0°C, filtered with suction and the pyridine distilled at reduced pressure. The crude material was crystallized from methanol.

PNPQ: m.p. 184–187°C.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.33; H, 3.43; N, 9.52. *Found:* C, 65.16; H, 3.35; N, 9.55.

PNPQPh: m.p. 191–193 (dec)°C.

Anal. Calcd. for $C_{22}H_{14}N_2O_4$: C, 71.32; H, 3.81; N, 7.56. *Found:* C, 71.27; H, 4.00; N, 7.11.

2.3. KINETICS

The cleavage of the esters was followed spectrophotometrically at 400 nm and 25 ± 0.1°C. Kinetics were started by adding 20–40 μL of a 1×10^{-3}M stock solution of the ester in CH_3CN to 2 mL of the reaction mixture containing the proper concentration of reagents. The release of *p*-nitrophenoxide followed first order kinetics up to 90% of the reaction. Rate constants were obtained from the

absorbance *vs.* time data by nonlinear regression analysis using a PC and the software package ENZFITTER [16].

2.4. COMPLEX INDUCED SHIFTS (CIS) MEASUREMENTS

^{1}H-NMR spectra were recorded at 25 ± 1°C on a Bruker AC200 instrument operating at 200 MHz for PNPP and on a Bruker AM400 instrument operating at 400 MHz for PNPQ and PNPQPh. Two solutions were prepared: one containing the substrate (concentrations: 1.3×10^{-3}M for PNPP, 1.5×10^{-4}M for PNPQ, and 5.1×10^{-5}M for PNPQPh) in the proper deuterated solvent mixture; the other contained the substrate at the concentration indicated above and β-CD (1.4×10^{-2}M). The signal of CHD_2CN was used as internal reference and the resolution of the instrument was always better than 0.4 Hz (0.002 and 0.001 ppm for the instrument working at 200 and 400 MHz, respectively). From the observed shifts of selected protons of the substrate, CIS values were calculated by using the K_b values determined from the kinetics plots of Fig. 4. Direct determination of the binding constants from NMR was not possible due to the low solubility of the substrates in the solvent mixture.

3. Results and Discussion

3.1. SYNTHESIS OF THE LIGANDS AND THE SUBSTRATES

The ligand-functionalized β-CD, **1**, has been synthesized following the general procedure described by Breslow *et al.* [18, 9] by reacting mono 2-*O*-tosyl-β-CD with 2-hydroxymethyl-6-mercaptomethylpyridine. From the outcome of similar reactions [9] and from the analysis of the ^{1}H-NMR spectrum (the signal pattern of the protons bound to C(1) is remarkably different in C(2) or C(3) substituted βCDs and is in agreement with data reported [18] for other β-CDs functionalized at the secondary hydroxyl rim) we infer that the substituent is bound to C(3) of one of the glucose residues of β-CD, thus leaning towards the bulk water solution rather than the cavity of the macrocycle.

The synthesis of ligand **2** has already been reported [12], while the three esters PNPP, PNPQ, and PNPQPh have been obtained from the corresponding acids *via* standard dicyclohexylcarbodiimide-mediated condensation. The 6-phenyl quinaldic acid has been synthesized following the general procedure described by Scorrano *et al.* [19] for the synthesis of 2,6-substituted quinoline derivatives.

3.2. Cu(11) COMPLEXATION WITH LIGANDS **1** AND **2**

The complexation of Cu(11) ions by ligands **1** and **2** is evident by the formation of an absorption band in the UV spectrum (MES buffer, pH = 6.3) at 320 nm and an increase in the intensity of the 268 nm band already present with the free ligands. The 320 nm band is due to an S→Cu transition as shown for similar ligands [20, 21]. No differences were observed between the two ligands as to the position of the maximum and intensity of the band: this indicates that the β-CD cavity does not perturb the binding ability of the ligand subunit of the new molecule. Both

ligands **1** and **2** show a similar tendency to form ternary complexes (two ligands for a single Cu(11) ion) under conditions [ligand] > [Cu(11)]. This is in line with the available evidence that the ligand is bound at one of the C(3) carbons of the β-CD, i.e. in a position removed from the cavity. The formation of analogous ternary complexes with Cu(II) and a ligand-functionalized β-CD has been recently reported by Schneider [10]. The binding constants for the 1 : 1 complex with Cu(11) have not been determined. However they must be close to the value of $10^{4.6}$ M^{-1} determined for similar ligands [21].

3.3. INCLUSION MODE OF SUBSTRATES: ^{1}H-NMR INDUCED SHIFT STUDIES

It is well known that, in aqueous solutions, the ^{1}H-NMR signals of the protons of aromatic subunits of molecules inserted in CDs are shifted upfield [23]. Complexation-induced shifts (CIS) for the 100% complexed substrates (see Figure 1) using the native β-CD, in 4:1 D_2O/CD_3CN (PNPP) and in 3:2 D_2O/CD_3CN (PNPQ and PNPQPh), the solvent mixtures used in the kinetic studies, are reported in Figure 1. Since a mixed solvent of lower polarity than water is being used, lower binding constants [24] are expected and, in fact, are obtained. The low CIS values may also reflect a minor environmental change experienced by the protons of the substrates on moving from the mixed solvent to the CD cavity.

Analysis of these values indicates the *preferential* binding modes for the three substrates. PNPP appears to bind to β-CD with the *p*-nitrophenyl moiety included in the cavity. In contrast, in the case of PNPQPh, the phenyl substituent at the 6 position of the quinoline appears to be inserted. Complexation of PNPQ appears less selective and both modes of inclusion (quinoline or *p*-nitrophenol inside) appear possible: this partition between two different binding modes may justify the low CIS values observed for this substrate. Because of the substitution of the ligand

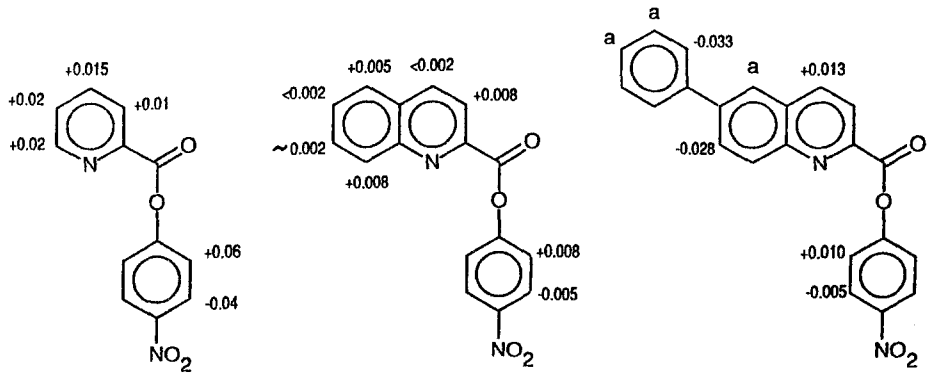
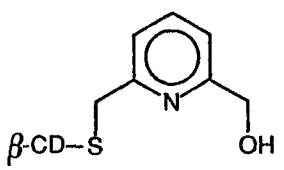


Fig. 1. Complexation-induced shifts (ppm) for the three substrates fully included in β-CD. Data were extrapolated using the binding constants obtained kinetically from the plots of Figure 4. Assignments of the protons indicated by "a" was hampered by their clustering.

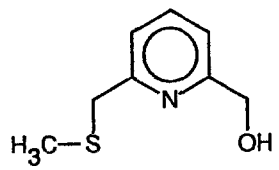
at a position which is removed from the cavity, it is conceivable that the binding mode of the substrates in **1**, with no Cu(II) ions added, is similar to that of native β-CD.

3.4. KINETICS

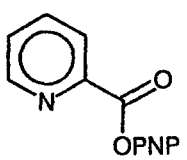
The effects of ligands **1** and **2** on the Cu(11) catalyzed hydrolysis of PNPP [22], PNPQ and PNPQPh were determined in mixed solvents (4:1, H_2O/CH_3CN, for PNPP and PNPQ; 3:2, H_2O/CH_3CN, for PNPQPh) due to the quite low solubility of the hydrophobic substrates PNPQ and PNPQPh in a pure aqueous medium. The pH of the aqueous component was 6.3 (0.05M 4-morpholinoethanesulphonic acid, MES) and the concentration of Cu(11) was kept constant: 1.4×10^{-4}M. The relative rate constants, k_ψ/k_0, observed for the release of *p*-nitrophenol *vs.* the ligand concentration are reported in Figure 2. Table I shows the rate data at [ligand] $= 8 \times 10^{-4}$M. The addition of either ligand **1** or **2** accelerates the cleavage of



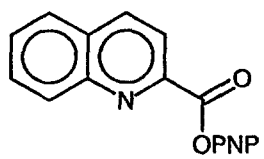
(1)



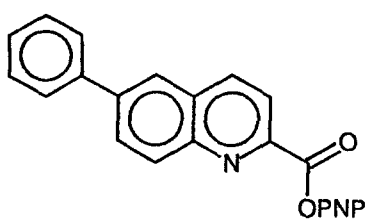
(2)



PNPP



PNPQ



PNPQPh

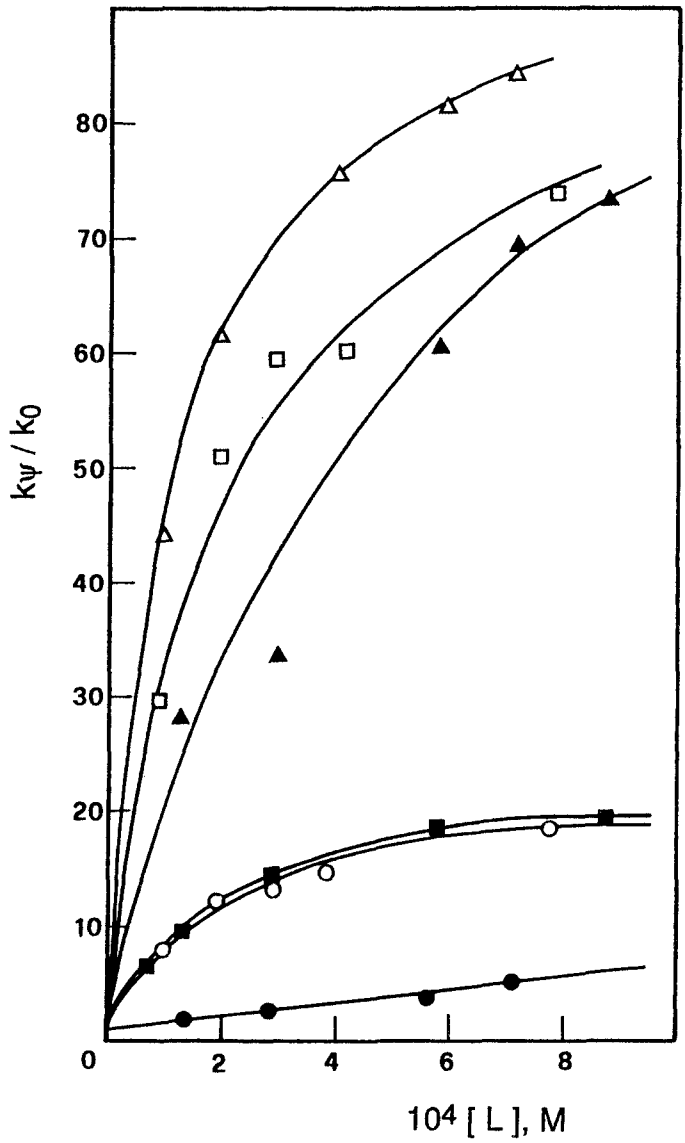


Fig. 2. Relative rate constants (k_ψ/k_0) observed with ligands **1** and **2** for the cleavage of PNPP, PNPQ and PNPQPh in the presence of Cu(II) ([Cu(II)] = 1.4×10^{-4}M) at 25°C and pH = 6.3. Black symbols refer to **1**, white to **2**. ●, ○: PNPP; ■, □: PNPQ; ▲, △: PNPQPh.

the three esters. Under the same conditions, β-CD does not affect the metal ion-catalyzed hydrolysis of the substrates.

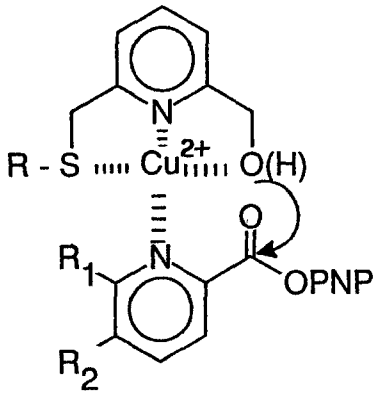
The rate accelerations observed by the addition of **1** and **2** are, quite likely, due to the formation of a ternary complex ligand/metal ion/substrate and to the nucleophilic attack of the hydroxy group of the methylpyridine moiety in a pseudo-intramolecular process as shown for analogous systems [12] and schematically indicated in **3**.

Table I. Observed rate constants, $k_\psi(s^{-1})$, for the cleavage of the substrates PNPP, PNPQ and PNPQPh by ligands **1** and **2** in the presence of Cu(II) ions[a]

Substrate	ligand			
	1		**2**	
	$10k_\psi$, s^{-1}	k_ψ/k_0[d]	$10k_\psi$, s^{-1}	k_ψ/k_0[d]
PNPP[b]	1.76	5.5	5.92	18.5
PNPQ[b]	0.21	19.4	0.81	74.0
PNPQPh[c]	1.93	71.5	2.29	85.0

[a] Conditions: [ligand] = 8×10^{-4}M, [Cu(II)] = 1.4×10^{-4}M, pH = 6.3, 25°C.
[b] $CH_3CN/H_2O = 1:4$.
[c] $CH_3CN/H_2O = 2:3$.
[d] k_0 Refers to the rate constant determined with only Cu(II) added.

The rate data of Figure 2 and Table I, indicate that the functionalized CD, **1**, is less effective than the model ligand **2** in the case of PNPP and PNPQ and virtually just as effective in the case of PNPQPh. If we consider ligand **2** as a reference system for the formation of the ternary complex and its reactivity, the results suggest that PNPP and PNPQ, when included in the cavity of **1** are not allowed to easily assume the proper position for the formation of such a complex whereas such a productive mode of inclusion is approached in the case of PNPQPh, although not completely reached. This means that the geometry of PNPQPh within the complex is such as to fill the cavity and locate the ester group in the proximity of the metal ion activated hydroxy group (Figure 3A), as suggested by the results of the ^{1}H-NMR analysis of the β-CD induced shifts (see above) and indicated as the most likely by inspection of CPK models.



(3)

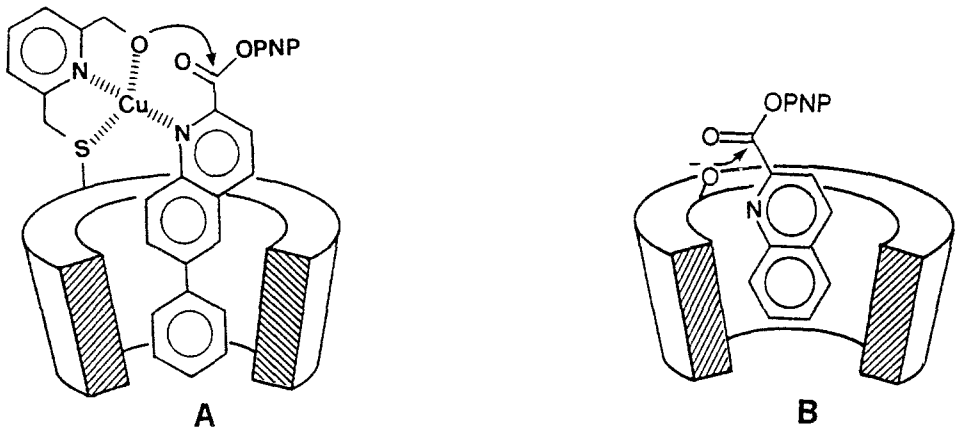


Fig. 3. Schematic representation of the mode of inclusion of substrate PNPQPh in 1·Cu(II) (A), and substrate PNPQ in β-CD (B).

The transacylation rates determined for the same substrates and native β-CD (at pH = 9.81, 0.02M carbonate buffer) are shown in Figure 4. The highest accelerations are achieved here with PNPQ, while the kinetic effects are quite modest with either PNPP or PNPQPh. Again, CPK models, in agreement with the ^{1}H-NMR induced shifts, suggest that this reactivity is due to the geometry of complexation of PNPQ in the β-CD cavity. In fact, with the quinoline moiety inserted into the cavity, the ester group faces the secondary hydroxyl of the β-CD, which is the nucleophilic species [18] (Figure 3B). Such a productive geometry of inclusion is not obtained with the other two esters.

4. Conclusion

The kinetic data reported here for the cleavage of substrates PNPP, PNPQ and PNPQPh by the native and the ligand-functionalized β-CD without or with added Cu(11) ions, respectively, show interesting differences in the observed accelerations.

The 'best' substrate for native β-CD is PNPQ while the 'best' one for **1** is PNPQPh. This may be explained by taking into account the geometry of binding of the three substrates in the β-CD cavity and the position of the effective nucleophile in the two systems.

Comparison of the kinetic data obtained with the ligand model **2** and the modified cyclodextrin, **1**, suggests, for the three substrates a competition between the two binding sites present in the modified cyclodextrin (i.e. the hydrophobic cavity and the metal ion). Although in no cases is co-operativity observed, the small difference in rate observed between **2** and **1**, suggests that with substrate PNPQPh its binding mode is suitable for taking advantage of both binding sites.

Recently Czarnik [9] observed a remarkable difference in the acceleration of the cleavage of *p*-nitrophenyl acetate (PNPA) using β-CDs functionalized at the primary or secondary hydroxyls with a Co(III)-cyclen group, the former one being the more effective catalyst. The suggested explanation of a hindered rotation of the cyclen-Co(III) group in the secondary hydroxyl-substituted derivative that would

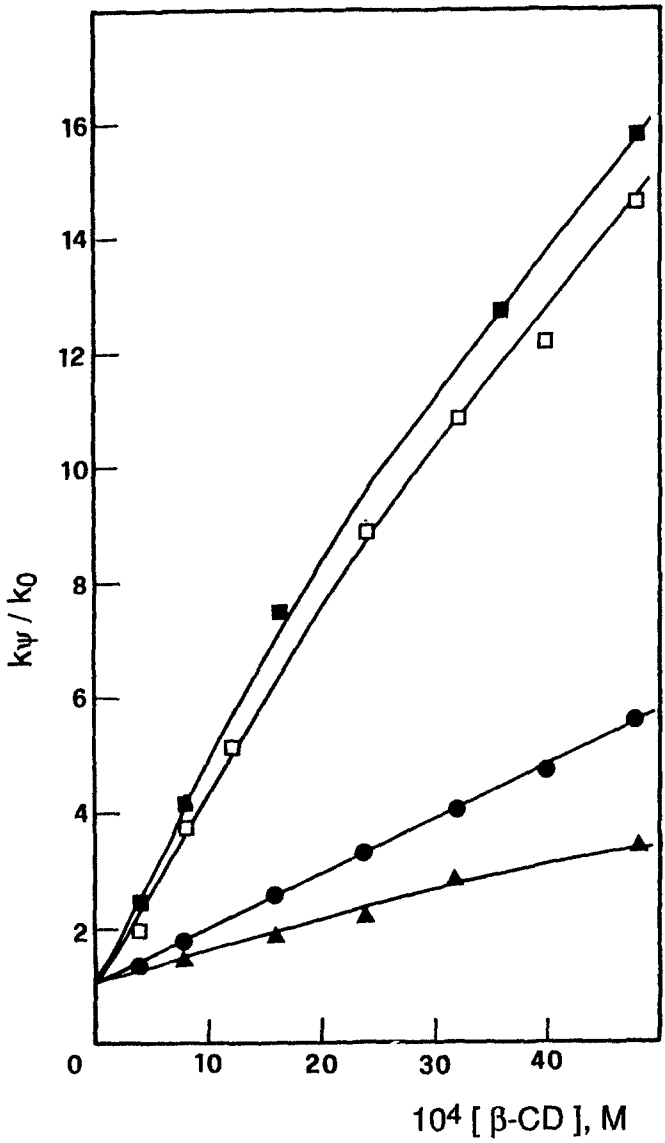


Fig. 4. Relative rate constants (k_ψ/k_0) observed for the cleavage of PNPP (●, 4:1 H_2O/CH_3CN), PNPQ (■, 4:1; □, 3:2 H_2O/CH_3CN), PNPQPh (▲, 3:2 H_2O/CH_3CN) with native β-CD (25°C, pH = 9.8).

make the interaction with CD-bound PNPA less favorable could also be associated with an unfavorable binding of the substrate located too far away from the catalytic site as for PNPP in our case. The difference between PNPA and PNPP is that, with the latter also being able to act as a ligand, it may be removed from the cavity in order to be involved in the co-ordination sphere of Cu(11) (the affinity constant of PNPP for a 1:1 complex with Cu(11) may be estimated to be close to that of pyridine, i.e. $\sim 300\ M^{-1}$) while this is not possible for PNPA.

On the basis of these data we think that a non-ligand molecule with a geometry similar to that of PNPQPh could be a good substrate for this metallocatalyst: work aimed to design such a compound is in progress in our laboratory.

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