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One Step Synthesis of New Urea-linked β-Cyclodextrin Dimers

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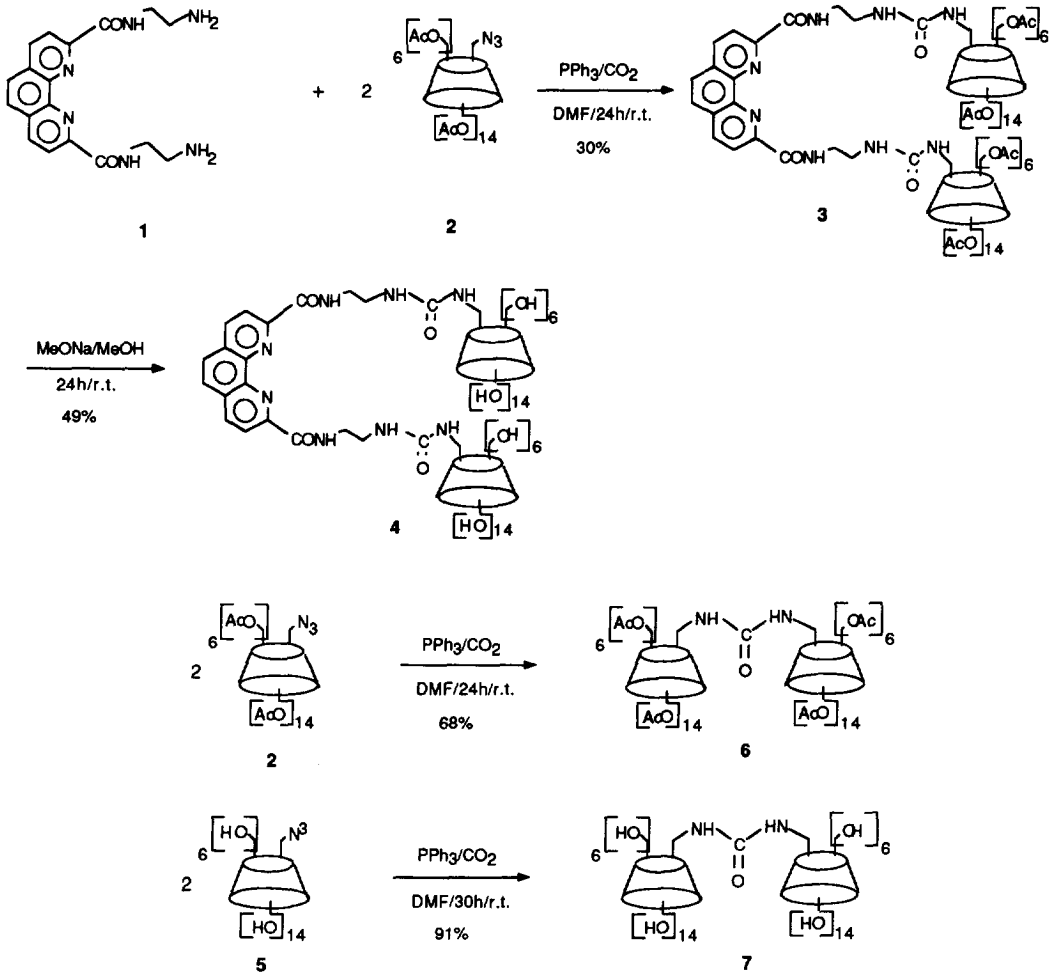
Abstract : The synthesis of new bridged β-cyclodextrin dimers (CDs) has been successfully achieved by a one pot transformation of 6-monoazido-6-monodeoxy-β-CDs **2** and **5** *via* the phosphinimines. Pseudo-first-order rate constants hydrolysis of bis-(-*p*-nitrophenyl)-phosphate (PNPP) by metal-complexes of **4** have been measured. Copyright © 1996 Elsevier Science Ltd

Although a large number of synthetic compounds have been designed as biomimetic host molecules[1], only few of them reproduce characteristics of enzymatic action. Enzymes generally bind their substrates and then use the action of cooperative interactions with appropriate well-placed functional groups to achieve catalysis. In the design of artificial enzymes, cyclodextrins hosts are very available compounds and have many interesting properties. Hydrophobic binding of non-polar substrates in water can be achieved with hydrophobic cavities of natural or modified cyclodextrins (CDs). Among numerous published cyclodextrins conjugate[2], cyclodextrin dimers have a special status and notably can bind appropriate substrates very strongly[3]. Another important feature of CD dimers is that the doubly-bound substrate is normally streched along the linker. In the case of linkers containing a catalytic group, this leads to striking rate accelarations. A representative example was reported recently by Breslow [4]. This latter including a bipyridine moiety is able to coordinate a La^{3+} ion and a hydrogen peroxide molecule and realize oxidative hydrolysis of phosphate anion or neutral phosphate triester with high rate accelerations.

Considering the increasing interest of this field and the necessity to develop new systems for exploring and improving the properties of the earlier described molecules (*e.g.* selectivity, rate acceleration, chelate effect...), we wish to report here the syntheses and characterization of three new symmetrical cyclodextrin dimers linked with phenantroline **4** and/or urea **6** and **7** spacers. Hitherto, direct condensation condensation of dithiols and heterodithiols with two equivalents of 6-iodo-6-deoxy-β-CD has been described for the synthsesis of the desired CD dimers[5] in which the CDs are briged by covalent carbon-sulfur single bonds.

We describe here a one-pot reaction leading to a new class of carbon-nitrogen bounded CD dimers which exploits an interesting and simple procedure, early described by Kovács and Pintér[6]. This reaction proceeds *via* a phosphinimine intermediate (not isolated in the present case). Application of the reaction to the diamino derivative **1** of phenantroline with the peracetylated 6-azido-6-deoxy-β-CD **2** in the presence of

CO_2 readily afforded the adduct **3** (yield 30%) from which dimer **4** was obtained by deacetylation in 49%. Similarly, but without additional amine, **2** or **5** gave dimers **6** or **7**, having urea spacer, in 68% and 91% yields respectively. Compound **6** was also obtained by acetylation of **7** at 80°C (Scheme 1).



Scheme 1.

New compounds were analyzed by NMR and FABMS and the collected data are in agreement with the proposed structures[7]. Considering the structure of the synthesized dimers, we can conclude positively that this methodology can be used to access rapidly a large panel of new dimers or oligomers.

The potential catalytic *in vitro* esterase activity of the *in situ* formed Cu (II), Eu (III) and Zn (II) complexes of **4** towards phosphodiester bonds was tested along with those of the corresponding free metals. The kinetic measurements were carried out in HEPES buffer (pH 7.06) at 25°C, using a 0.2mM dimer **4**, 0.2mM metal-ion, 48mM H_2O_2 and 0.06 mM of the substrate bis-(*p*-nitrophenyl) phosphate (BNPP).

Pseudo-first order conditions were used. The obtained rate constants (Table 1) show the following order efficiency in cleaving phosphodiester bonds : Cu (II) > Eu (III) > Zn (II).

Table 1. Pseudo-First-Order Rate Constants of BNPP hydrolysis[a] by metal complexes of dimer **4**.

Complexes and metals	Time (s)	k_{obs} (s^{-1})
[**4** - Cu_2^+]	0 to 180	$9.55\ 10^{-4}$
Cu_2^+	0 to $1.08\ 10^4$	$8.62\ 10^{-6}$
[**4**-Eu_3^+]	0 to 240	$3.10\ 10^{-4}$
Eu_3^+	0 to $7.02\ 10^4$	$6.45\ 10^{-7}$
[**4**-Zn_2^+]	0 to $7.20\ 10^3$	$8.03\ 10^{-6}$
Zn_2^+	no hydrolysis after 72h	

[a]Reactions were monitored by UV/Vis absorbance at 400 nm at 25.0 ± 0.2°C.

As expected, high rate accelerations were observed with Cu (II) and Eu (III) complexes, indicating the binding of the substrate into the CDs cavities and a cooperative interaction betweeen the hydrophobic CD hosts and the metal coordination site. Further investigations are currently in progress to synthesize new hosts with different structure of the linkers and modified CD hosts to reach high selectivities in DNA *in vitro* cleavage experiments. N,N'-carbonyl dimers **6** and **7** are also under study for their interesting complexation properties as potent new drug carrier hosts.

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7. Structures of all compounds were assigned by ^1H and ^{13}C NMR on Bruker-DRX 400 and Varian VXR-400 spectrometers; some of the chemical shifts assignments are based on 2D-HETCOR and COSY experiments, H_a were designed as protons of the substituted CD-glucosyl residue and H_b are those of

the unsubstituted glucosyl units. UV/Vis spectra are recorded on a Beckman DU-64 and on Shimadzu UV-160, FTIR spectra on a Perkin-Elmer-1600 and a Nicolet 205. Mass spectra were recorded on a R-1010 Nermag in EI mode or a Fisons-ZABIISEQ spectrometer in FAB^+ mode with NBA or thioglycerol as matrix. All new compounds gave satisfactory spectroscopic data and analyses.

1 : Pale yellow powder (0.535 g, 90%). UV (H_2O) : 234 (32570), 284 (19806); IR : 3362 (N-H); 3100-3000 (C-H, phen); 2900-2800 (C-H, alkyl); 1661 (C=O); 1553 (C=N phen); 1495 (C=C); ^1H NMR (D_2O) δ (ppm) 7.87 (d, 2H, J = 8.25); 7.72 (d, 2H, J = 8.25); 7.23 (s, 2H); 3.43 (t, 2H, J = 6.20); 2.9 (t, 2H, J = 6.20); ^{13}C NMR (D_2O) δ (ppm) 165.3 (C=O); 147.7 (O=C-*C*=N); 141.7 (C-*C*=N); 137.8 (C_4, C_7); MS (EI, direct probe) m / z (relative intensity) 353 ($[M+H]^+$); 323 ($[M-CH2NH2]^+$); 179 ([M-CO-NH-(CH2)2-NH2]$^+$). Elemental analysis $C_{18}H_{20}N_6O_2$. $2H_2O$ (388.0) : Required C% 55.67, H% 5.67, N% 21.65; Found : C% 55.6, H% 5.4, N% 21.6.

4 : White powder (0.03g, 49%); UV (H_2O) : 237 (17023), 284 (11085); IR : 3851-3332 (N-H, O-H); 2928 (C-H, phen); 1652 (C=O); 1558 (C=N, phen); 1498 (C=C, phen); ^1H NMR (D_2O) δ (ppm) : 9.70 (s, 1H, (NH)); 8.70 (d, 2H); 8.42 (d, 2H); 8.10, (s, 2H); 6.40 (s, 1H, (NH)); 6.10 (s, 1H, (NH)); 5.05 - 5.00, (t, $H_{a,b}1$, 14 H); 4.40 (s, 1H, (NH)); 3.90 (t, H_a4); 3.80-3.60 (complex m, 84H, (H_2, H_3, H_b4, H_5, H_6)); 3.30 (m, 4H); 3.20 (m, 4H). (MS (FAB^+): 2694.1 ($M+Na^+$), 2672 ($M+H^+$); HRMS (FAB^+): 2671.8796 ($M+H^+$). Elemental analysis $C_{104}H_{159}N_{72}O_8$. $24H_2O$ (3104.9) : Required C% 40.21, H% 6.67, N% 3.61; Found C% 40.2, H% 6.9, N% 3.3.

6 :White amorphous powder, (0.136g, 68%), m.p. 168-175°; IR : 1755,1680 (C=O); ^1H NMR ($CDCl_3$, 60°) δ (ppm) : 5.35-5.25 (m, 7H, (H3)); 5.18 (d, 1H, J = 2, (H_a1)); 5.07 (m, 1H, (NH)); 5.11-5.01 (m, 6H, (H_b1)); 4.88-4.73 (m, 7H, (H2)); 4.60-4.48 (m, 6H, (H_b6)); 4.35-4.22 (m, 6H, (H_b6')); 4.21-411 (m, 6H, (H_b5)); 3.99 (m, 1H, (H_a5)); 3.82 (m, 1H, (H_a6)); 3.77-3.65 (m, 7H, (H4)); 3.48 (m, 1H, (H_a6')); 2.16-2.03 (several s, 60H, 20 CH_3CO). ^{13}C NMR ($CDCl_3$, 25°) δ (ppm) : 180.0-170.4, 169.6-169.3 (CH_3CO); 158.2 (NH-*C*O-NH); 96.9-96.6 (C1); 77.9-76.5 (C4); 71.3-69.4 (C2, C3, C5); 62.9-62.4 (C_b6); 40.4 (C_a6); 20.9-20.8 (CH_3CO). MS (FAB^+) : 3976.4 ($M+H^+$). Elemental analysis $C_{165}H_{220}N_2O_{109}$ (3975.6) : Required C% 49.85, H% 5.58, N% 0.70; Found : C% 50.3, H% 5.5, N% 0.7.

7 : Microcrystalline white powder (1.10g, 91%), m.p. > 315° (decomp.); IR : 1647 (C=O urea); ^1H NMR ($DMSO_6$d, 80°) δ (ppm) : 5.74 (t, 1H, (NH)); 5.5-5.4 (m, 14H, (OH2, OH3)); 4.86-4.80 (m, 7H, (H_b1)); 4.38, 4.20, 4.15 (3m, 1H, 1H, 4H, (OH6)); 3.80-3.55 (m, 26H, (H_b3, H_b5, H_b6)); 3.45-3.35(m, 1H, (H_a6)); 3.40-3.25 (m, 14H, (H2, H4)). ^{13}C NMR ($DMSO_6$d, 25°) δ (ppm) : 158.9 (NH-*C*O-NH); 102.3-102.1 (C1); 82.6-81.6 (C4); 73.3-72.2 and 70.0 (C2, C3, C5); 67.0 (C_5'); 60.6-60.0 (C_b6); 40.6 (C_a6). MS (FAB^+) : 2294.6 ($M+H^+$). Elemental analysis $C_{85}H_{140}N_2O_{69}.7H_2O$ (2420.2) : Required *C*% 42.18, H % 6.41, N % 1.16; Found : C% 42.2, H% 6.5, N% 1.1.

8. The 6-monoazido-6-monodeoxy-β-cyclodextrin **5** was prepared according to the literature[9, 10], but with only a slight excess of sodium azide (1.2 mol).

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