Synthesis and Study of New β-Cyclodextrin 'Dimers' Having a Metal Coordination Center and Carboxamide or Urea Linkers

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The synthesis of new 'bridged' β-cyclodextrin (β-CD) 'dimers' **7**–**12** was successfully achieved by two one-pot reactions from β-CD (**3**) and 6^A-azido-6^A-deoxy-β-CD (**4**). The 'phosphine imine' reaction was shown to be a superior approach compared to the *Mitsunobu* reaction as coupling strategy for the preparation of these 'dimers'. NMR Data, along with molecular-modelling calculations, suggest a 'helical-like' arrangement for the phenanthroline-diyl-linked 'dimer' derivative **9**. Complexation properties of **9** were established by UV-VIS-spectrophotometric titration toward four metals. Among them Cu^{II} or Eu^{III} ions were complexed selectively by **9**, but no complexation occurred with La^{III} and Zn^{II}. In addition a specific and interesing esterase activity toward the phosphodiester bond of bis(4-nitrophenyl) phosphate anion was found in the case of the Cu^{II} complex of **9**.

Introduction. – Although a large number of synthetic compounds have been designed as biomimetic host molecules [1], only few of them reproduce characteristics of enzymic action. Enzymes generally bind their substrates and then use the action of cooperative interactions with appropriate well-placed functional groups to achieve catalysis. In addition, more effective molecular recognition of the transition state is required to achieve high-rate acceleration.

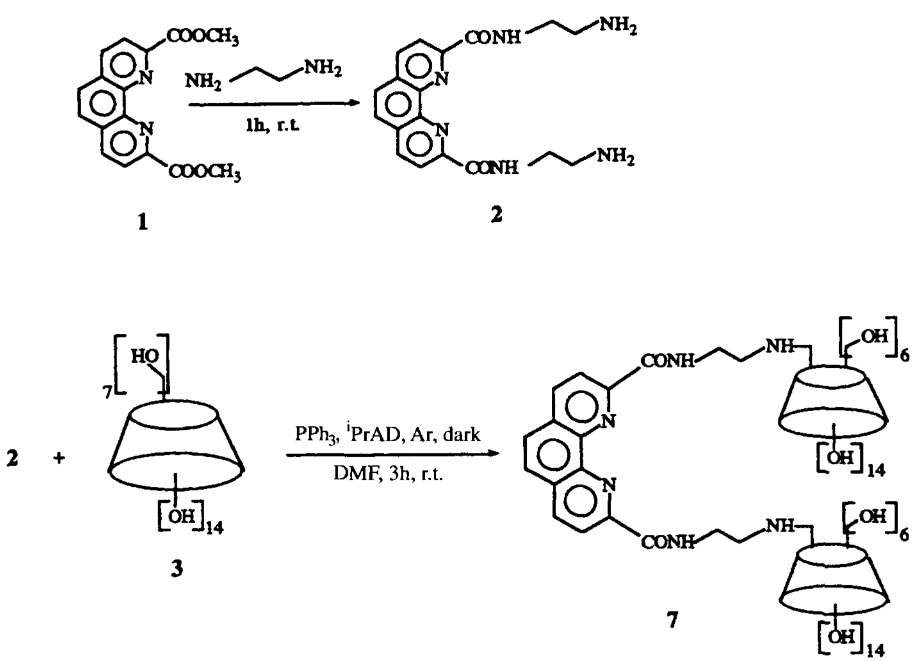
Binding can be obtained by metal, *Lewis*-acid-base coordination, and H-bonding or hydrophobic interaction. It is well-known also that enzymes, antibodies, and biological receptors use the hydrophobic effect in H_2O solution to help them bind their substrates. Hydrophobic binding of nonpolar substrates in H_2O can be achieved with hydrophobic cavities of natural or modified cyclodextrins (CDs).

In the design of artificial enzymes, cyclodextrin hosts are highly available compounds and have many interesting properties. Among numerous known cyclodextrin conjugates [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 accelerations. A representative example was reported by *Breslow* and *Zhang* [4]. Their 'dimer' containing a bipyridine moiety in the linker is able to coordinate a La^{3+} ion and a H_2O_2 molecule to realize an oxidative hydrolysis of an anionic phosphoric acid diester or a neutral phosphoric acid triester with high-rate accelerations.

Considering the increasing interest in this field and the necessity to develop new systems to improve the properties of the previously described enzyme mimics (*e.g.*, selectivity, rate acceleration, chelate effect, *etc.*), we decided to provide a new contribution to this field with the preparation of a full family of novel β-CD 'dimers'.

Results and Discussion. – We wish to report here the syntheses and characterization of six new cyclodextrin 'dimers', *i.e.*, of **7**–**10**, bearing a phenanthroline moiety in the linker, and **11** and **12** having an urea spacer. Until now, direct condensation of dithiols and heterocyclic dithiols with 2 equiv. of 6^A-deoxy-6^A-iodo-β-cyclodextrin was most often used to synthesize CD 'dimers' [5] in which the CD moieties are connected to the linker by covalent C–S bonds. Recently, multistep syntheses of C–N connected CD 'dimers' were reported [6].

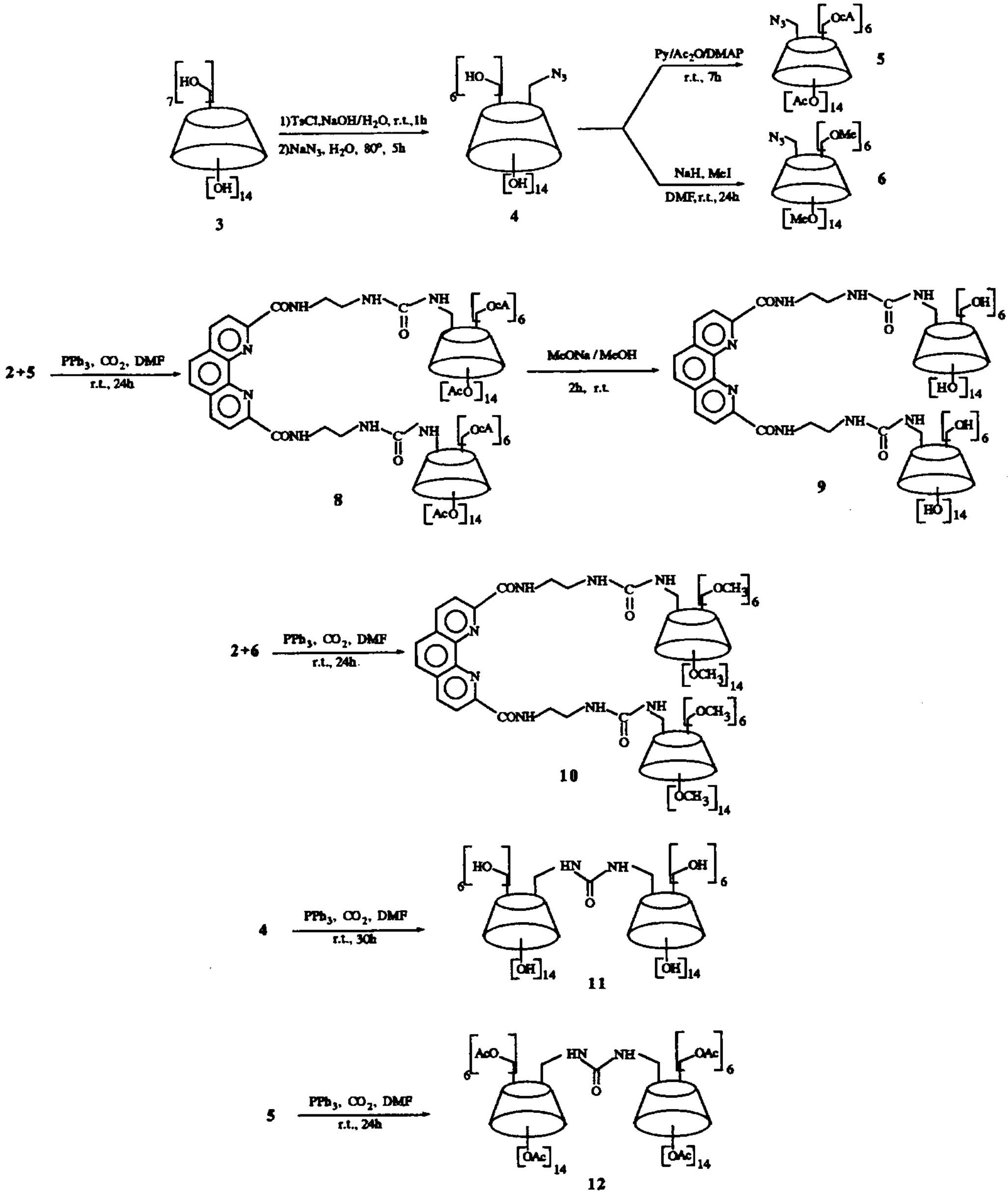
Scheme 1



We propose now two one-pot procedures leading to CD 'dimers' which are C–N connected to the linker. Thus, the phenanthroline-derived diamine **2** (obtained from **1** [9]) was coupled with 2 equiv. of unprotected β-CD (**3**) using the modified *Mitsunobu* conditions previously reported by us for the synthesis of C–S connected CD derivatives [7]. The first approach gave the pure dimer **7** in 1.75% yield (*Scheme 1*) after a laborious purification by reversed-phase column chromatography (*Nucleosil*® C_{18}, MeOH/H_2O gradient).

The second approach exploited an interesting reaction described by *Kovacs et al.* [8] for the synthesis of monosaccharide urea derivatives from azido-sugar anomers in the presence of triphenylphosphine (PPh_3) and CO_2 in a simple one-pot procedure. Applied to 6^A-azido-6^A-deoxy-β-CD (**4**) [11][12], the per-*O*-acetylated 6^A-azido-6^A-deoxy-β-CD **5**, and the per-*O*-methylated 6^A-azido-6^A-deoxy-β-CD **6** [10], the β-CD 'dimers' **8**–**12** were readily obtained (*Scheme 2*). The 'dimers' **8**–**10** bearing a phenanthroline unit in the linker were obtained in 31, 49 (from **8** by deacetylation), and 20% yield, respectively, and **11** and **12** having an urea spacer in 91 and 68% yield, respectively.

Scheme 2



As indicated above, the efficiency of the direct substitution of a primary OH group in a cyclodextrin by a RCH_2NH_2 nucleophile under modified *Mitsunobu* by conditions was poor compared to the relatively good yields obtained with thiol reactants in the case of monosaccharides, disaccharides, or cyclodextrins [7][13]. On the other hand, the reaction of monoazido-monodeoxy-CDs with the same amine RCH_2NH_2 in the presence of CO_2 and PPh_3 was shown to be most efficient and represents a potential indirect access to 6^A-(alkylamino)-6^A-deoxy-CD 'dimers' after reduction of the C=O groups.

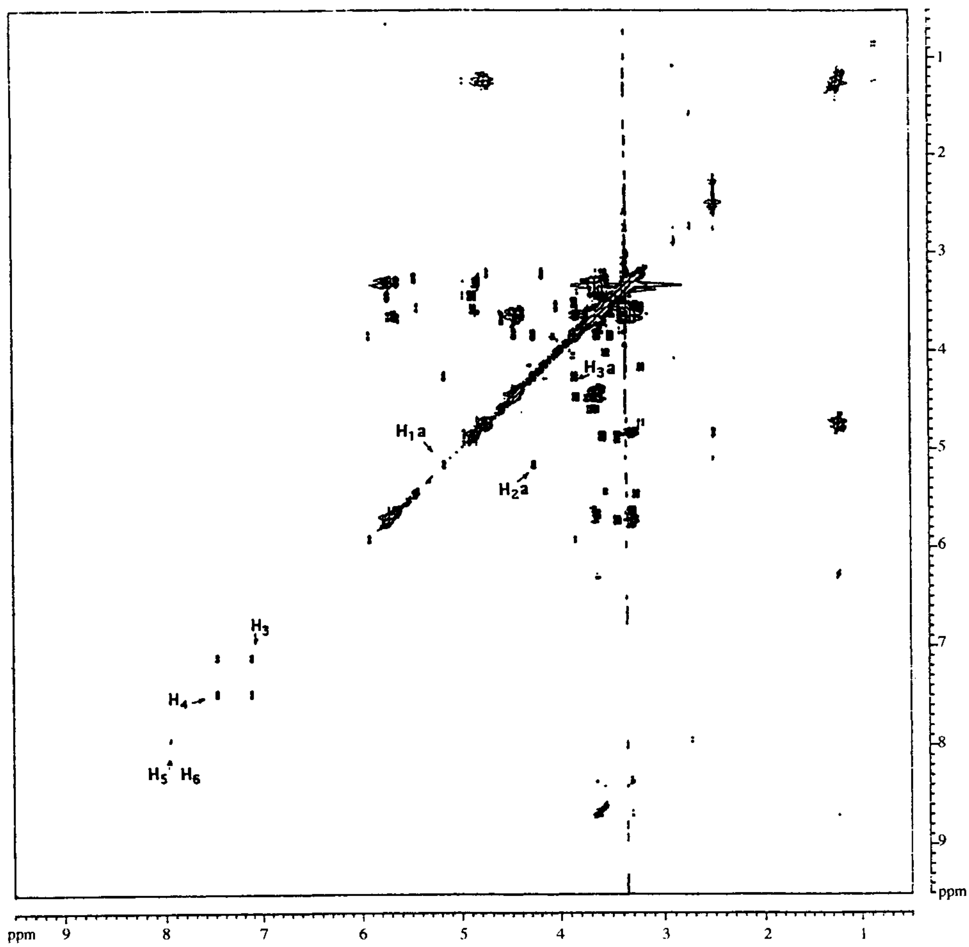
The relative complexity of the synthesized molecules made interpretation of their ^{1}H-NMR spectra speculative. Therefore, 2D-NMR methods were essential for resonance attributions. Moreover, to obtain mainly fundamental informations on their molecular conformation in solution, several technics were used: COSY-DQF (double quantum filtration correlation spectroscopy), NOESY (nuclear *Overhauser* spectroscopy), ROESY (rotating-frame *Overhauser* spectroscopy), and TOCSY (total-correlation spectroscopy).

While it was relatively easy to assign the ^{13}C-NMR spectrum of 'dimer' **7**, its ^{1}H-NMR spectrum did not allow a complete attribution of the protons. A COSY of **7** (*Fig. 1*) showed, besides the aromatic protons H–C(3), H–C(4), H–C(5), and H–C(6) of the phenanthroline (phen) moiety, numerous cross-peaks corresponding to each spin system from H–C(1) to 2H–C(6) of the β-CD glucose units. In case of the per-*O*-acetylated 'dimer' **8**, the same experiments were performed, and the same difficulties, essentially due to strong overlapping, were encountered for proton assignments.

In the ^{13}C-NMR spectrum of **9**, some lines were not detected under the conditions given in the *Exper. Part*, but a more complete analysis for **9** and **10** was achieved by the ^{1}H-NMR data at 500 MHz. A first assignment of the protons lying in the downfield and weakly-coupled part was directly available from the 1D spectra. On the contrary, chemical shifts of the strongly coupled protons in the high-field section and the determination of dipolar interactions occuring in the 'dimers' required 2D-NMR experiments. Thus, the recorded TOCSY and NOESY maps of **9** showed cross-peaks between the ureido NH, $NHCH_2CH_2NH$, and 2H–C(6^A) of the linker-connected glucose unit of β-CD which permitted their assignment (*Fig. 2*).

Further, the conformation of **9** in solution was examined by NOESY and ROESY maps that provided interesting complementary informations about the geometry of the spacer arms and the position of the β-CD moieties with respect to the phenanthroline-ring plane. On one hand, the NOEs (see *Exper. Part*) between the amido and ureido NH, and between NH and NCH_2CH_2N suggested that the $NHCH_2CH_2NHCONH$ chain should adopt a particular configuration of its three amino groups leading to a 'U' form of the $NHCH_2CH_2NH$ moiety. On the other hand, two ROE correlations (see *Exper. Part*) were also observed in **9**, one between an NH of $NHCH_2CH_2NH$ ($CONHCH_2CH_2N\mathit{H}CONH$) and the aromatic H–C(3) of the phenanthroline unit and another between protons of β-CD and H–C(5) or H–C(6) of the phenanthroline ring. The latter would suggest a folding of the spacers at the top and underneath of the aromatic ring probably giving a 'sandwich like' type molecular assembly for **9**, as illustrated in *Fig. 3,a*.

The above 'sandwich-like' structure, proposed on the basis of NOEs, can be supported by the fact that the NH protons are very probably engaged in strong intramolecular H-bonds, inside the spacer arms or between OH groups of the cyclodextrin hosts and



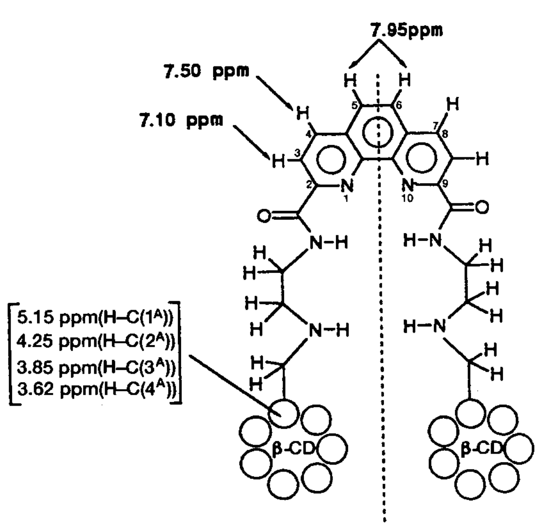


Fig. 1. *COSY Spectrum and proton attribution of* 7. H_3, H_4, H_5, H_6: H–C(3), H–C(4), H–C(5), H–C(6) of the phenanthroline unit; H_{1a}, H_{2a}, H_{3a}: H–C(1^A), H–C(2^A), H–C(3^A) of the β-CD glucose unit A (connected to the linker)

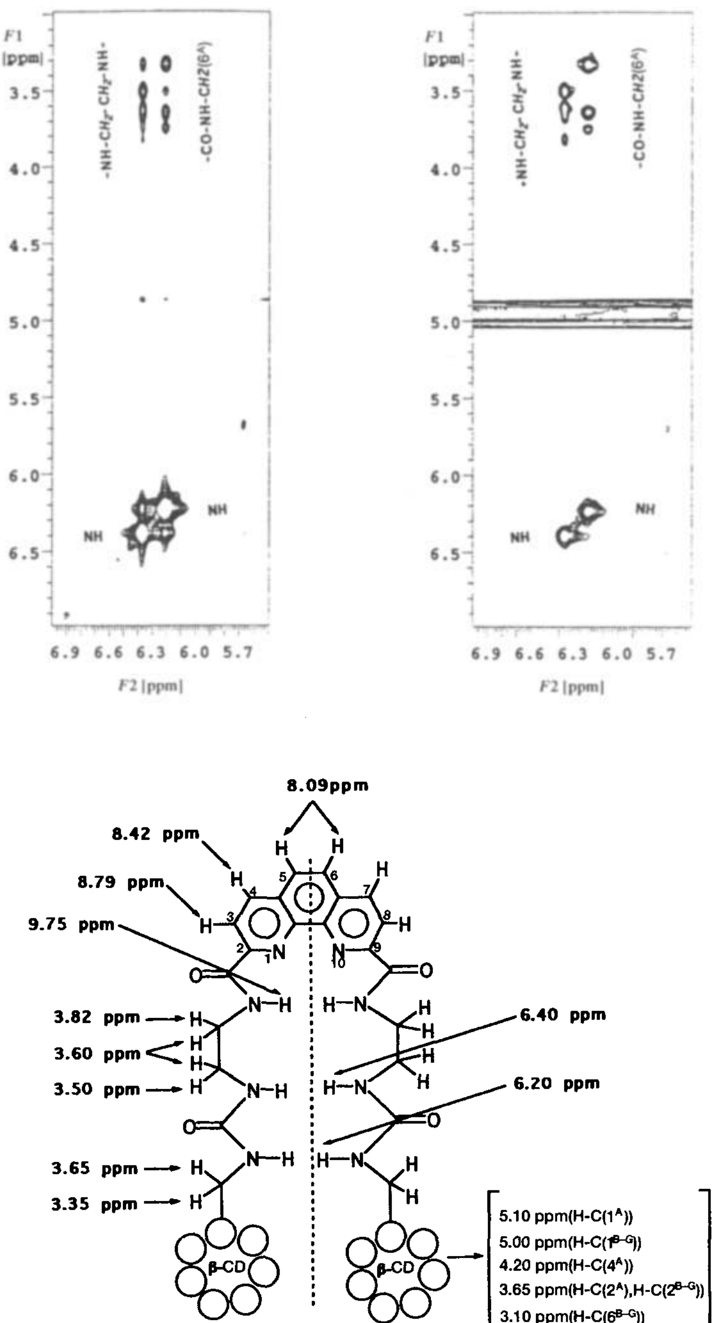


Fig. 2. *TOCSY and NOESY partial contour plots and proton attributions of* **9**. The locants 1^A, 2^A refer to the β-CD glucose unit A (connected to the linker)

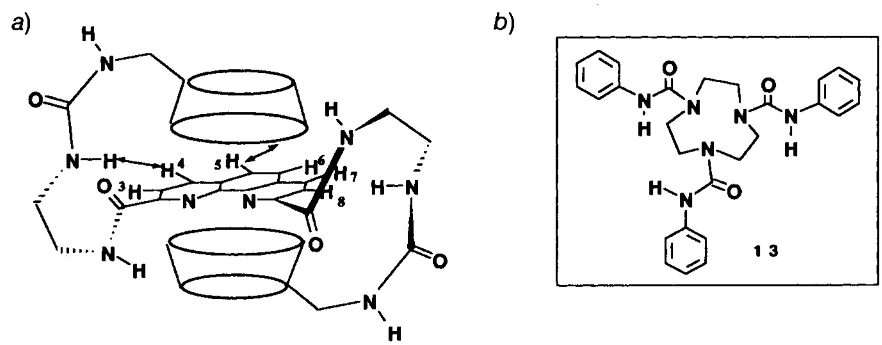


Fig. 3. a) *Schematic representation of the probable conformation of* **9** *in solution.* b) *Structure of the new ligand* **13** *used for the* ^{1}*H-NMR exchange*

these NH. This is due to the stacking of the *β*-CD moieties on both the hydrophobic phenanthroline ring sides (see also illustration of the most preferred conformations obtained by molecular-dynamic computations in *Fig. 5,b* (below)). In such a situation, the NH protons probably do not or very slowly exchange. To support this statement, we report recent results obtained from the ^{1}H-NMR spectrum of the new urea-like ligand **13** (*Fig. 3,b*), recorded in $CHCl_3$ after addition of D_2O. In that case, a very low exchange of the urea NHs was observed, showing unmodified signal intensities after 5 h; after 10 h, the intensity decrease was only 50% [14]. Actually, despite the lack of X-ray data, these observations are also supported by some literature results, describing a ditosyl-substituted azacrown ether in corporating a methyl-1,10-phenanthroline moiety [15] in which a similar double-spiral arrangement of its azacrown ether arms exists.

MM3 Calculations effected both on the diamine precursor **2** and a computer-simulated *N,N*-bis(6-deoxyglucos-6-*C*-yl) derivative of **2** (*Fig. 4*), display favoured geometries of the spacer arms similar to the ones suggested by the above NMR observations. In extension, supplementary molecular-dynamics computations were conducted on the full structure of **9** using software from *Biosym/MSI* of *San Diego-Dynamics*. Calculations and minimization were done with the Discover® program [16] using the CVFF force field. A simulated high-temperature annealing experiment *in vacuo* (2000–300 K) [17] led to a

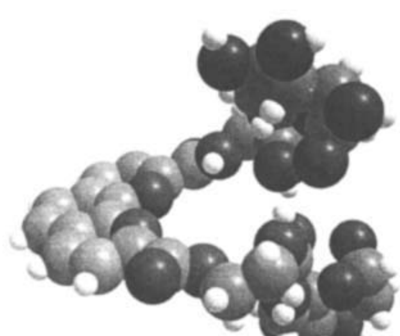


Fig. 4. *MM3* (MAD-CHIMISTE®) *Molecular-modelling structure of the* N,N'-*bis*(*6-deoxyglucos-6-*C-*yl*) *derivative of* **2** *showing the double spiral arrangement of the spacer arms*

representative sample of the 100 most stable conformations of **9** (*Fig. 5, a*). Among them, the four conformers (over 20.9 kJ · mol^{-1}) of the lowest energies were retained and printed out from the Insight II® molecular modelling system. Looking at the conformer of the lowest energy (−1563 kJ · mol^{-1}), *i.e.*, No. 30 CPK frame (*Fig. 5, b*), one can see that the phenanthroline ring appears almost totally inserted between the two β-CD cavities, thus supporting the high probability of the expected 'sandwich-like' assembly for **9**. It should be noted that the remaining three conformers of the lowest energies (not shown) display also close packing arrangements with partial inclusion of the phenanthroline moiety in the β-CD cavity.

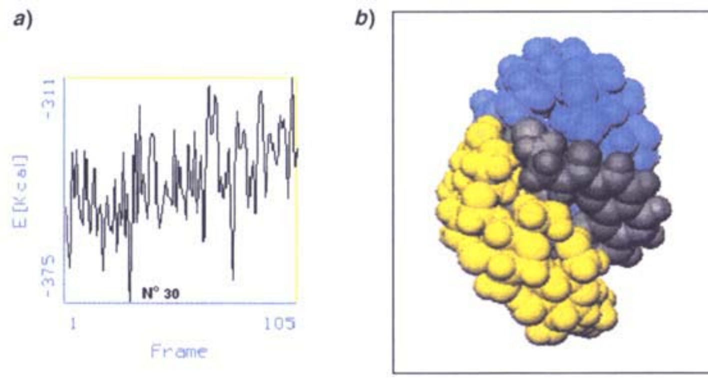


Fig. 5. a) *Sample of 100 conformations obtained by the simulated annealing experiment with DISCOVER®*. b) *CPK Structure of the most stable conformer of dimer* **9** *obtained by Insight II® molecular modelling program*

Metal Complexes of Ligand 9. – Spectrophotometric titration of a water solution of **9** (*Fig. 6, a*) at 285 nm, with a $CuCl_2$, $LaCl_3$, $EuCl_3$, or $ZnCl_2$ solution (*Fig. 6, b*) showed that, in the case of $CuCl_2$ and $EuCl_3$, the formed species have a composition of *ca.* 0.2 Cu^{II} or Eu^{III} atoms, respectively, for 1 equiv. of **9**, *i.e.*, they have not the expected 1:1 stoichiometry. These results indicated that only 20% of the metal ion is coordinated at the bidendate phenanthroline site; the remaining 80% of the metal might be complexed by β-CD moieties since the formation of a complex [C^{II}(β-CD)] on mixing H_2O solutions of Cu^{2+} ions and β-CD was reported [18]. This hypothesis was confirmed by titrations performed under the same conditions with the phenanthroline-derived diamine **2**. Thus, in absence of β-CD complexing sites, a 'normal' stoichiometry of 1 Cu^{II} or Eu^{III} atom for 1 equiv. of **2** was observed.

Regarding the metal-complexation selectivity of **9**, the titration curves (*Fig. 6, b*) clearly indicated the best selectivity for the Cu^{II} ion followed by the Eu^{III} ion. No complexation seems to occur with La^{III} and Zn^{II} ions, neither **9** nor with diamine **2**. These results were also confirmed by a total absence of catalytic phosphodiesterase activity of Zn^{II} and La^{III} in the presence of **9** toward bis(4-nitrophenyl) phosphate anion (see below).

The potential catalytic *in vitro* esterase activity of the *in situ* formed Cu^{II}, Eu^{III}, and Zn^{II} complexes of **9** toward phosphodiester bonds was tested using bis(4-nitrophenyl) phosphate anion as substrate in the presence of H_2O_2 (see *Table*). For comparison, the phosphodiesterase activity of the corresponding complexes of **2** and of the metal-free

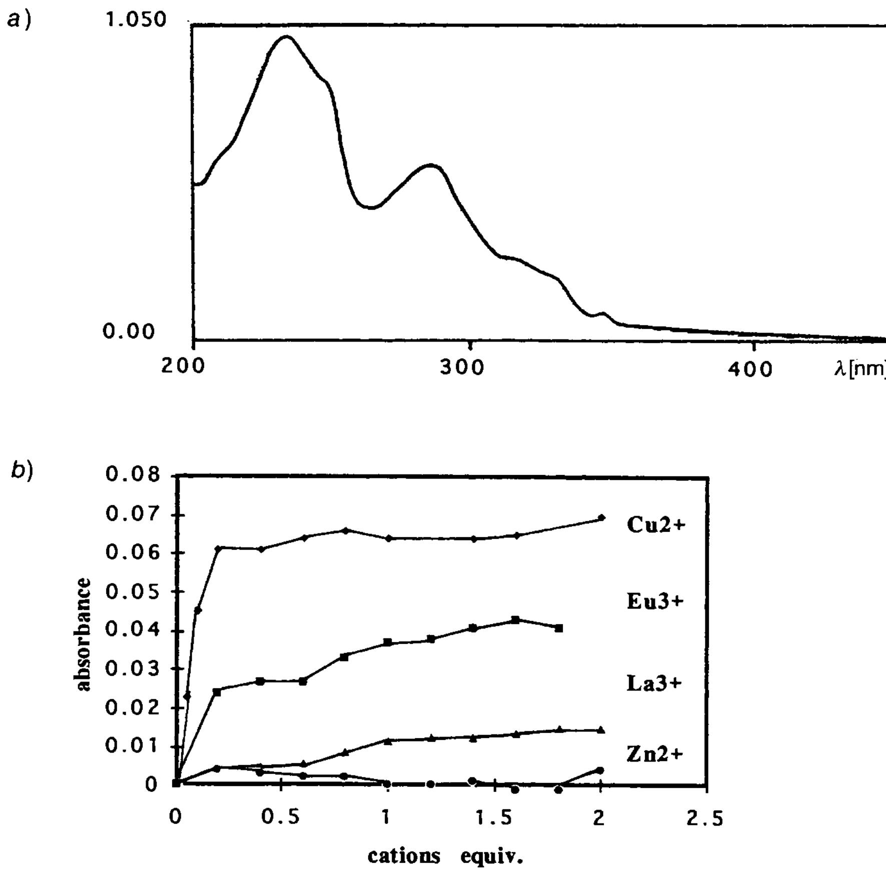


Fig. 6. a) *UV/VIS Spectrum of* **9** *in* H_2O ($c = 3.0 \cdot 10^{-5}$ mol · dm^{-3}); b) *spectrophotometric titration of the ligand* **9** *at 285 nm with four cations in* H_2O (c(**9**) $= 3.0 \cdot 10^{-5}$ mol · dm^{-3}; counter ions: Cl^-)

ligands **2** and **9** were also determined. The kinetic measurements were carried out under pseudo-first-order conditions according to *Takasaki* and *Chin* [19]. The obtained rate constants [20] show the following order efficiency in cleaving the phosphodiester bond by complexes: $Cu^{II} > Eu^{III} > Zn^{II}$. As expected, high-rate accelerations were observed with the Cu^{II} complex (*Fig. 7*), indicating the binding of the substrate into the β-CD cavities of **9** and a cooperative interaction between the hydrophobic β-CD hosts and the metal coordination site.

Conclusion. – The synthesis of the 'dimers' **7**–**12** represents an interesting application of the 'phosphine imine' methodology allowing a rapid access to a large panel of complex CD oligomers. The poor efficiency of the *Mitsunobu* methodology in these syntheses is probably due to the low reactivity of the diamine **2** and to the problematic HPLC workup accompanied by important losses of product.

Future work will be oriented towards the synthesis of new CD multisite receptors or controlled linear 'oligomers', the determination of X-ray structures, and advanced com-

Table. *Pseudo-First-Order Rate Constants for the Hydrolysis of Bis(4-nitrophenyl) Phosphate Anion by Complexes of Diamine **2** and 'Dimer' **9**[a]).* $k_{rel} = k_{obs}/k_0$ ($k_0 = 1.1 \cdot 10^{-11}$ s^{-1}), k_0 = rate constant for the non-catalyzed hydrolysis in absence of any metal and H_2O_2 [20].

	Time [s]	k_{obs} [s^{-1}]	k_{rel}
[Cu^{II}(**9**)]	0–480	$9.12 \cdot 10^{-6}$	$8.29 \cdot 10^{6}$
	480–1980	$9.02 \cdot 10^{-5}$	$8.20 \cdot 10^{6}$
	1980–2340	$2.01 \cdot 10^{-5}$	$1.98 \cdot 10^{6}$
	2340–5100	$2.18 \cdot 10^{-6}$	$1.98 \cdot 10^{5}$
[Cu^{II}(**2**)]	0–900	$-1.07 \cdot 10^{-5}$	$-9.72 \cdot 10^{5}$
	900–7200	$4.31 \cdot 10^{-5}$	$3.92 \cdot 10^{6}$
[Eu^{III}(**9**]	0–1200	$1.19 \cdot 10^{-5}$	$1.08 \cdot 10^{6}$
	1200–5700	$2.76 \cdot 10^{-6}$	$2.50 \cdot 10^{5}$
[Eu^{III}(**2**)]	0–300	$3.59 \cdot 10^{-5}$	$3.26 \cdot 10^{6}$
	300–1500	$1.05 \cdot 10^{-5}$	$9.54 \cdot 10^{5}$
	1500–7200	$1.07 \cdot 10^{-5}$	$9.72 \cdot 10^{5}$
[Zn^{II}(**9**)]	0–300	$9.41 \cdot 10^{-6}$	$8.85 \cdot 10^{5}$
	300–7200	$7.59 \cdot 10^{-7}$	$6.90 \cdot 10^{4}$
[Zn^{II}(**2**)]	0–900	$2.42 \cdot 10^{-6}$	$2.22 \cdot 10^{5}$
	900–7200	$7.97 \cdot 10^{-7}$	$7.26 \cdot 10^{4}$

[a]) Experimental conditions: HEPES buffer (pH 7); *T* 25°; [M^+] = 0.2 mM; [L] = 0.2 mM; [H_2O_2] = 48 mM; [$(O_2NC_6H_4O)_2P(O)C$] = 0.06 mM. The reaction was followed by UV/VIS monitoring of the 4-nitrophenol absorbance at λ_{max} 400 nm.

puting simulations of the 'dimers' in solvent (H_2O). The Cu^{II} complex of **9** is a powerful potential artificial esterase and will be used in a near future in studies for the selective binding and oxidative hydrolysis of other esters and biological macromolecules such as DNA. In addition, structural modifications of the spacer arms are planned to study their influence on catalytic activities.

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Experimental Part

General. The 6^A-azido-6^A-deoxy-β-cyclodextrin (**4**) was prepared according to [11][12], but using only a slight excess of NaN_3 (1.2 equiv.). All commercially available chemicals used were of *p.a.* quality or purified according to standard methods. All reactions were carried out under Ar unless otherwise stated. Solvents were dried by distillation before use: DMF from CaH_2 and stored over 4-Å molecular sieves under Ar, pyridine from P_2O_5 and stored over CaH_2. MeOH and CH_2Cl_2 were obtained from *Merck*, Et_2O from *Gifrer*; CH_2Cl_2 was purified by distillation before use. β-Cyclodextrin (β-CD) was a generous gift of *Roquettes-Freres* (Lestrem, France) and was vacuum-dried for 12 h at 120° prior to use. TLC: precoated silica gel *60 F_{254}* plates (*Merck*); detection by charring with H_2SO_4. M.p.: uncorrected. Optical rotations: *Zeiss Polamat A*; at 25°. UV/VIS Spectra: *Beckman DU-64* and *Shimadzu UV-160*. λ_{max} (ε) in nm. FT-IR spectra: *Perkin-Elmer-1600 and Nicolet 205*; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX 400*, *Varian VXR-400*, and *Bruker DRX-500*; δ in ppm rel. to $SiMe_4$, some assignments based on 2D-HETCOR and COSY; locants 1^A, 2^A *etc.* refer to the linker-connected glucose unit of β-CD and locants 1^{B-G}, 2^{B-G} *etc.* to the remaining glucose units. 2D-NMR experiments of **9**: phase-sensitive mode

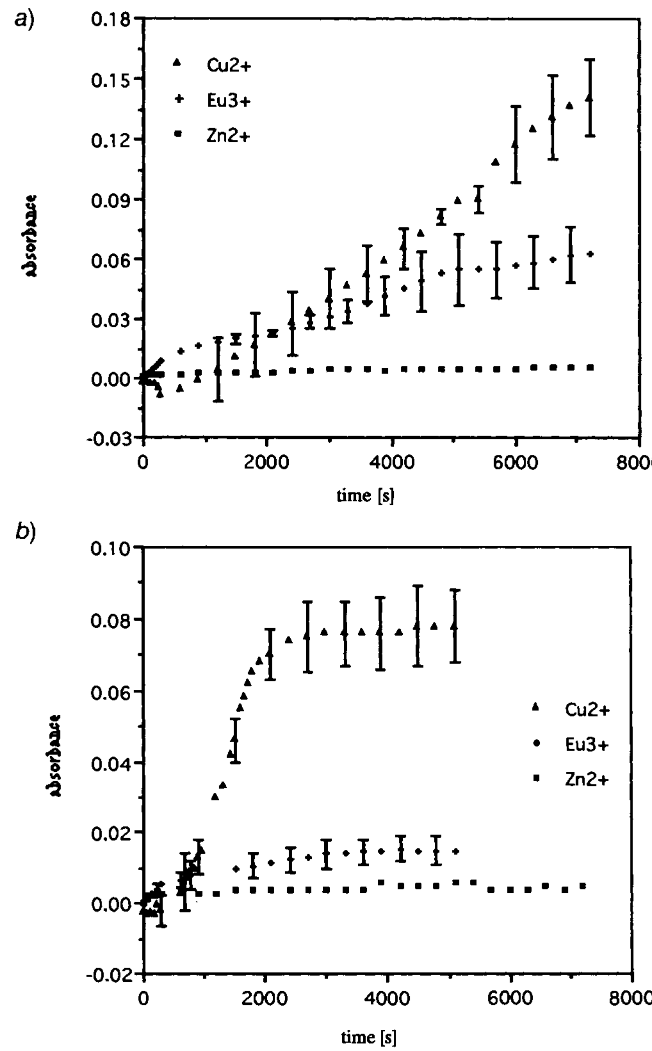

Fig. 7. *Kinetics* (*A* = f(*t*)) *of the hydrolysis of bis(4-nitrophenyl) phosphate anion by* a) *metal complexes of* **2** *and* b) *metal complexes of* **9**

at *T* 293 K with H_2O-signal presaturation (presaturation delay 1.2 s); COSY-DQF: *SW* 6000 Hz (in the two dimensions), *SI* 4K, *NE* = 600 increments for the second dimension; data processing with the STATE package in the phase-sensitive mode with a square sine bell window function in the two dimensions and a final matrix size of 1K × 1K of reals; TOCSY: *SW* 6000 Hz, spin locked, *SI* 4K, relaxation delay *D*1 1.2 s, mixing time τ_m 50 ms, *NE* = 256 increments in the second dimension; NOESY: *SW* 6000 Hz, *SI* 4K, relaxation delay *D*1 1.2 s, mixing time τ_m 200 ms, *NE* = 256 increments in the second dimension; ROESY: *SW* 6000 Hz, *SI* = 2K, relaxation delay *D*1 1.2 s, mixing time τ_m 300 ms, *NE* = 256 increments in the second dimension, final matrix size of 0.5 K × 0.5 K of reals. FAB-MS (pos. mode): *Fisons-ZABIISEQ*; in 3-nitrobenzyl alcohol or thioglycerol matrix. ESI-MS (pos. mode): *Micromass* (UK) *VG*-platform *II*.

N,N′-*Bis(2-aminoethyl)-1,10-phenanthroline-2,9-dicarboxamide* (**2**). A mixture of dimethyl 1,10-phenanthroline-2,9-dicarboxylate **1** [9] (0.5 g, 1.69 mmol) and freshly distilled anh. ethane-1,2-diamine (20 ml) was stirred for

30 min at r.t. Ethane-1,2-diamine was then evaporated and an excess of Et_2O added. The resulting precipitate was filtered to give crude **2** which was stored in a dessicator and used without further purification: 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). ^{1}H-NMR (D_2O): 7.87 (*d*, *J* = 8.25, 2 H); 7.72 (*d*, *J* = 8.25, 2 H); 7.23 (*s*, 2 H); 3.43 (*t*, *J* = 6.20, 2 H); 2.9 (*t*, *J* = 6.20, 2 H). ^{13}C-NMR (D_2O): 165.3 (C=O); 147.7 (O=C–*C*=N); 141.7 (C–*C*=N); 137.8 (C(4), C(7)). EI-MS: 353 ([*M* + H]$^+$), 323 ([*M* – CH_2NH_2]$^+$), 179 ([*M* – $CONH(CH_2)_2NH_2$]$^+$). Anal. calc. for $C_{18}H_{20}N_6O_2 \cdot 2\,H_2O$ (388.0): C 55.67, H 5.67, N 21.65; found: C 55.60, H 5.70, N 21.61.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G$-Icosa-O-acetyl-$6^A$-azido-$6^A$-deoxy-β-cyclodextrin (**5**). At 80°, 6^A-azido-6^A-deoxy-β-cyclodextrin (**4**; 1.0 g, 0.86 mmol) was acetylated for 7 h with Ac_2O/pyridine 3:5 (8 ml). The mixture, was evaporated, the residue dried by repeated treatment with anh. toluene and MeOH, followed by distillation, and the crude product treated with H_2O, filtered, and dried in a dessicator over KOH: white powder (1.57 g, 91%). M.p. 155–157°. $[\alpha]_D$ = + 132 (*c* = 1.6, $CHCl_3$). IR (KBr): 2108, 1754–1751, 1373. ^{1}H-NMR (400 MHz, 60°, $CDCl_3$): 5.36–5.20 (*m*, 7 H, H–C(3^{A-G})); 5.14 (*d*, *J* = 2.3, H–C(1^A)); 5.12–5.02 (*m*, 6 H, H–C(1^{B-G})); 4.85–4.75 (*m*, 7 H, H–C(2^{A-G})); 4.62–4.52 (*m*, 6 H, H–C(6^{B-G})); 4.34–4.20 (*m*, 6 H, H–C(6^{B-G})); 4.20–4.04 (*m*, 7 H, H–C(5^{A-G})); 3.81–3.67 (*m*, 9 H, H–C(4^{A-G}), 2 H–C(6^A)); 2.16–2.02 (several *s*, 60 H, MeCO). ^{13}C-NMR ($CDCl_3$): 170.7–169.4 (Me*C*O); 96.9–96.5 (C(1)); 71.2–69.9 (C(2), C(3)); 69.5 (C(5)); 62.4 (C(6^{B-G})); 50.7 (C(6^A)), 20.7 (*Me*CO). FAB-MS: 2024.4 ([*M* + Na]$^+$), 2002.5 ([*M* + H]$^+$). ESI-MS: 2002.4 ([*M* + H]$^+$).

N,N'-*Bis{2-[(6^A-deoxy-β-cyclodextrin-6^A-*C*-yl)amino]ethyl}-1,10 phenantroline-2,9-dicarboxamide* (**7**). β-Cyclodextrin (**3**; 0.5 g, 0.44 mmol) and PPh_3 (2.08 g, 7.93 mmol, 12 equiv.) were added to a suspension of **2** (0.93 g, 2.64 mmol, 6 equiv.) in dry DMF (10 ml) under Ar and protected from light. Then, ^{i}PrAD (1.04 ml, 12 equiv.) was added dropwise, and the soln. was stirred for 3 h at r.t. The solvent was evaporated, aceton (50 ml) added to the residue, and the precipitate of sugar products filtered off and washed with aceton (3 ×). The crude material was then purified by reversed-phase column chromatography (*Nucleosil*® C_{18}, MeOH/H_2O discontinueous gradient). Pure **7** was eluted with MeOH/H_2O 1:9: white powder (0.01 g, 1.75%) UV (H_2O): 277 (1522). ^{1}H-NMR (500 MHz, (D_6)DMSO): 8.95 (*t*, ArCON*H*); 7.95 (*s*, 2 H, phen); 7.50 (*d*, 2 H, phen); 7.10 (*d*, 2 H, phen); 5.15 (*d*, H–C(1^A)); 4.50 (*dd*, H–C(2^A)); 3.85 (*dd*, H–C(3^A)); 3.62 (*m*, H–C(4^A)). ^{13}C-NMR ((D_6)DMSO): 166.8 (C=O); 162.4 (O=C–*C*=N); 156.2 (*C*–C=N); 102.0 (C(1)); 81.6 (C(4)); 73.1–72.1 (C(2), C(3)); 67.9 (C(5)); 60.0 (C(6^{B-G})); 35.9 (C(6^A)); 21.9 (NCH_2CH_2N). FAB-MS: 2656 ([*M* + H + 3Na]$^+$).

N,N'-*Bis{2-{[($2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F$-Icosa-O-acetyl-$6^A$-deoxy-β-cyclodextrin-$6^A$-*C*-yl-amino)carbonyl]amino}ethyl}-1,10-phenanthroline-2,9-dicarboxamide* (**8**). Under Ar, **2** (0.053 g, 0.15 mmol) was added portionwise to a soln. of PPh_3 (0.66 g, 2.5 mmol) and **5** (0.5 g, 0.25 mmol) in dry DMF (40 ml) while bubbling continuously dry CO_2 through the mixture. After 24 h, the mixture was evaporated, H_2O added, and the soln. extracted with CH_2Cl_2 (150 ml). The org. phase was dried ($MgSO_4$), evaporated, and the crude product chromatographed (silica gel, CH_2Cl_2/MeOH gradient). Pure **8** was eluted with CH_2Cl_2/MeOH 93:7: pale-brown powder (0.2 g, 31%). UV (MeOH): 237 (47391), 284 (26273). IR: 3750 (N–H), 2958 (C–H, phen), 1748–1654 (C=O), 1559 (C=N, phen), 1498 (C=C). ^{1}H-NMR ($CDCl_3$): 10.00 (br. *s*, N); 8.73 (*d*, 2 H, phen); 8.60 (*d*, 2 H, phen); 8.25 (br. *s*, NH); 8.12 (*s*, phen); 7.90 (br. *s*, NH); 6.80 (br. *s*, NH); 6.00 (br. *s*, NH); 5.32 (*m*, H–C(3^{B-G})); 5.25 (*m*, H–C(3^A)); 5.07 (*d*, H–C(1^A)); 5.02 (*m*, H–C(1^{B-G})); 4.75 (*m*, H–C(2^A)); 4.70 (*m*, H–C(2^{B-G})); 4.55 (*m*, 4 H, NC*H*$_2$CH$_2$N); 4.40 (*m*, 4 H, NC*H*$_2$C*H*$_2$N); 4.35–4.25 (*m*, H–C(6^{A-G})); 3.82 (*m*, H–C(4^A)); 3.70 (*m*, H–C($^{B-G}$)); 2.20–1.80 (MeCO). FAB-MS: 4353.9 ([*M* + H]$^+$).

N,N'-*Bis{2-{(6^A-deoxy-β-cyclodextrin-6^A-*C*-yl-amino)carbonyl]amino}ethyl}-1,10-phenanthroline-2,9-dicarboxamide* (**9**). A 1M NaOMe soln. (0.12 ml) was added to **8** (0.1 g, 0.023 mmol) in MeOH (5 ml). The mixture was stirred for 2 h at r.t. Then, aq. 1M NaOH (0.4 ml) was added to dissolve the white precipitate of NaOAc. After stirring overnight at r.t., small amounts of *IRN 77*® resin were added until neutralization. The mixture was then filtered, the soln. discarded, and the solid product dissolved by addition of H_2O. The resulting aq. soln. was evaporated *in vacuo* to give pure **9**: white powder (0.03 g, 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). ^{1}H-NMR (D_2O): 9.75 (*s*, 1 H, NH); 8.79 (*d*, 2 H, phen); 8.42 (*d*, 2 H, phen); 8.09 (*s*, 2 H, phen); 6.40 (*s*, 1 H, NH); 6.20 (*s*, 1 H, NH); 5.10 (*s*, H–C(1^{B-G})); 5.00 (*s*, H–C(1^A)); 4.20 (*m*, H–C(4^A)); 3.82 (*m*, 2 H, NC*H*$_2$C*H*$_2$N); 3.65 (*m*, H–C(2^{A-G}), 1 H–C(6^A)); 3.60 (*m*, 4 H, NC*H*$_2$C*H*$_2$N); 3.50 (*m*, 2 H, NC*H*$_2$C*H*$_2$N); 3.35 (*m*, 1 H–C(6^A)); 3.10 (*m*, 2 H–C(6^{B-G})). FAB-MS: 2672 ([*M* + H]$^+$).

N,N'-*Bis{2-{[(6^A-deoxy-$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G$-Icosa-O-methyl-β-cyclodextrin-6^A-*C*-yl-amino)carbonyl]amino}ethyl}-1,10-phenanthroline-2,9-dicarboxamide* (**10**): As described for **8**, with (0.074 g, 0.21 mmol, 0.6 equiv.), PPh_3 (0.91 g, 3.47 mmol), permethylated 6^A-azido-6^A-deoxy-β-cyclodextrin

6 [9] (0.5 g, 0.35 mmol), DMF (40 ml), and CO_2. Pure **10** was eluted with CH_2Cl_2/MeOH 92:8: white powder (0.224 g, 20%). UV (MeOH): 232 (22891), 284 (128.38). IR: 3348 (N–H); 2927–2834 (C–H, phen), 1733–1652 (C=O), 1567 (C=N, phen), 1498 (C=C, phen). ^{1}H-NMR (D_2O): 9.40 (br. *s*, 1H, NH); 8.60 (*d*, 2 H, phen); 8.50 (*d*, 2 H, phen); 8.20 (br. *s*, 1 H, NH); 7.90 (*s*, 2 H, phen); 6.00 (br. *s*, 1 H, NH); 5.30 (*m*, H–C(3^{A-G})); 5.15 (*s*, H–C(1^A)); 5.10 (*s*, H–C(1^{B-G})); 4.80 (*m*, H–C(2^{A-G})); 4.50–4.30 (*m*, H–C(6^{A-G})); 4.10 (H–C(5^{A-G})); 4.00 (NCH_2CH_2N); 3.70 (H–C(4^{A-G})); 3.40 (NCH_2CH_2N); 2.10 (*m*, MeO). FAB-MS: 3270.7 ([*M* + K]$^+$).

N,N′-*Bis(6^A-deoxy-β-cyclodextrin-6^A-*C*-yl)urea* (**11**). To a soln. of **4** (1.16 g, 1 mmol) in DMF (12 ml) previously saturated with dry CO_2, a soln. of PPh_3 (0.39 g, 1.5 mmol) in DMF (6 ml) was added during 10 min. Then CO_2 bubbling was continued for 30 h. TLC (dioxane/conc. aq. NH_3 soln. 10:7): no **4** left, product at R_f 0.1, PPh_3O at R_f 0.9. After evaporation, the residue was treaded with acetone (20 ml) and filtered off. The resulting crude product (1.16 g, 96%) was purified by precipitation with acetone (700 ml) from an aq. soln. (90 ml): microcrystalline **11** · 7 H_2O (1.10 g, 91%). M.p. > 315° (dec.). $[\alpha]_D$ = + 146 (*c* = 1.2, DMF). IR: 1647 (C=O, urea). ^{1}H-NMR ((D_6)DMSO, 80°): 5.74 (*t*, 1 H, NH); 5.5–5.4 (*m*, 14 H, OH–C(2^{A-G}), OH–C(3^{A-G})); 4.86–4.80 (*m*, 7 H, H–C(1^{A-G})); 4.38, 4.20, 4.15 (3*m*, 1 H, 1 H, 4 H, OH–C(6^{B-G})); 3.80–3.55 (*m*, 26 H, H–C(3^{A-G}), H–C(5^{A-G}), H–C(6^{B-G})); 3.45 (*m*, 1 H, H–C(6^A)); 3.40–3.35*m*, 1 H, H–C(1^A)); 3.40–3.25 (*m*, 14 H, H–C(2^{A-G}), H–C(4^{A-G})). ^{13}C-NMR ((D_6)DMSO, 25°): 158.9 (C=O); 102.3–102.1 (C(1)); 82.6–81.6 (C(4)); 73.3–72.2 (C(2), C(3), C(5^{B-G})); 67.0 (C(5^A)); 60.6–60.0 (C(6^{B-G})); 40.6 (C(6^A)). FAB-MS: 2294.6 ([*M* + H]$^+$). ESI-MS: 2317.6 ([*M* + Na]$^+$). Anal. calc. for $C_{85}H_{140}N_2O_{69}$ · 7 H_2O (2420.18): C 42.18, H 6.41, N 1.16; found: C 42.25, H 6.48, N 1.11.

N,N′-*Bis(2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosa-*O*-acetyl-6^A-deoxy-β-cydodextrin-6^A-*C*-yl)urea* (**12**). a) A soln. of **5** (0.2 g, 0.1 mmol) in dry acetone (6 ml) was saturated with CO_2, and a soln. of PPh_3 (0.04 g, 0.15 mmol) in acetone (6 ml) was added dropwise over 20 min. CO_2 bubbling was continued for 24 h. TLC (AcOEt/EtOH 95:5): no **5** left (R_f 0.7), at R_f 0.4, Ph_3PO at R_f 0.5. The mixture was then evaporated and the residue treated with EtOH (3 ml). After cooling to 5°, the mixture was filtered and the residue washed with cold EtOH and petroleum ether: white amorphous powder (0.136 g, 68%). R_f (AcOEt/EtOH 95:5) 0.4. M.p. 168–175°. $[\alpha]_D$ = + 121 (*c* = 1, $CHCl_3$). IR: 1755, 1680 (C=O). ^{1}H-NMR ($CDCl_3$, 60°): 6.35–5.25 (*m*, 7 H, H–C(3^{A-G})); 5.18 (*d*, *J* = 2, 1 H, H–C(1^A)); 5.07 (*m*, 1 H, NH); 5.11–5.01 (*m*, 6 H, H–C(1^{B-G})); 4.88–4.73 (*m*, 7 H, H–C(2^{A-G})); 4.60–4.48 (*m*, 6 H, H–C(6^{B-G})); 4.35–4.22 (*m*, 6 H, H–C(6^{B-G})); 4.21–411 (*m*, H–C(5^{B-G})); 3.99 (*m*, 1 H, H–C(5^A)); 3.82 (*m*, 1 H, 1 H–C(6^A)); 3.77–3.65 (*m*, 7 H, H–C(4^{A-G})); 3.48 (*m*, 1 H, 1 H–C(6^A)); 2.16–2.03 (several *s*, 60 H, 20 MeCO). ^{13}C-NMR ($CDCl_3$, 25°): 180.0–170.4, 169.6–169.3 (MeCO); 158.2 (NHCONH); 96.9–96.6 (C(1)); 77.9 (C(4^A)); 77.0–76.5 (C(4^{B-G})); 71.3–69.4 (C(2), C(3), C(5)); 62.9–62.39 (C(6^{B-G})); 40.4 (C(6^A)); 20.9–20.8 (*Me*CO). FAB-MS: 3976.4 ([M + H]$^+$). ESI-MS: 1989.9 (M^+/2), 1326.8 (M^+/3). Anal. calc. for $C_{165}H_{220}N_2O_{109}$ (3975.59): C 49.85, H 5.58, N 0.70; found: C 50.34, H 5.49, N 0.71.

b) The heptahydrate **11** · 7 H_2O (0.048 g, 0.2 mmol) was acetylated with Ac_2O (0.3 ml) and pyridine (0.5 ml) and worked up as described for **5**. White amorphous powder. M.p. 173–178°. TLC, IR, NMR: identical with the product obtained in *a*.

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