NEW TYPE OF BRIDGED MONOAMINO-β-CYCLODEXTRINS

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ABSTRACT

The synthesis of new urea-bridged ß-cyclodextrin dimers (CDs) has been successfully achieved by a one-pot transformation of 6-monoazido-6-monodeoxy-ß-CDs (**1** and **2**) *via* the phosphinimines. Pseudo-first-order rate constants for hydrolysis of bis-(*p*-nitrophenyl)-phosphate (BNPP) by metal-complexes of **7** have been measured.

1. INTRODUCTION

Although a large number of synthetic compounds have been designed as biomimetic host molecules [1], only few of them reproduce characteristics of enzymatic action.

In the design of artificial enzymes cyclodextrin hosts are highly available compounds and have 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 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 stretched along the linker. In the case of linkers containing a catalytic group, this leads to striking rate acceleration. A representative example was recently reported by Breslow [4]. The dimer including bipyridine moiety is able to coordinate La^{3+} ion and hydrogen peroxide molecule to result in oxidative hydrolysis of phosphate anion or neutral phosphate triester with high rate acceleration.

Considering the increasing interest of this field and the necessity to develop new systems to improve the properties of the previously described enzyme mimics (*e.g.*, selectivity, rate acceleration, chelation) we decided to bring a new contribution with the synthesis of a full family of novel ß-cyclodextrin dimers.

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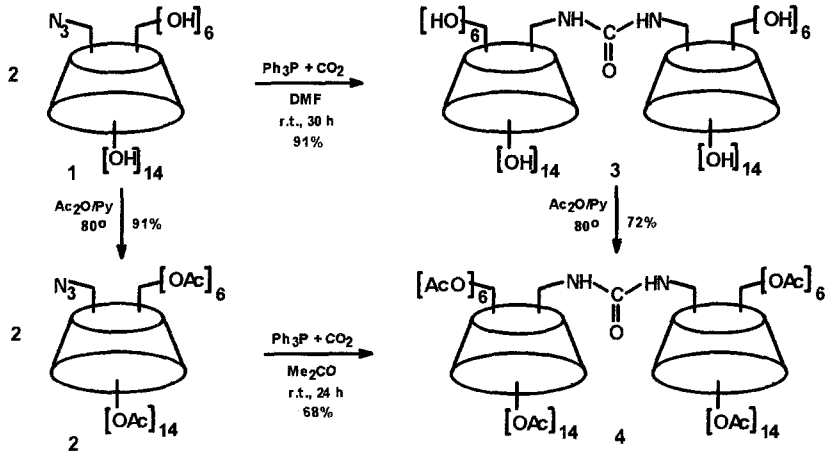
2. MATERIALS AND METHODS

6-Monoazido-6-deoxy-ß-cyclodextrin (**1**) was prepared according to the literature [5, 6] but with only a slight excess of sodium azide (1.2 mol). Acetylation of **1** with pyridine/ acetic anhydride at 80°C afforded the peracetylated **2** as white powder (m.p. 155-157°C) in 91% yield. Phenanthroline-2,9-bis-(2-aminoethyl)-carboxamide (**5**) was obtained as yellow powder from phenantroline-2,9-dicarboxylic acid dimethyl ester with ethylene diamine in 90% yield. Hydrocortison, Ketoconazole and Itraconazole were isolated from commercially available drug formulations by extraction with organic solvents.
Solubility isotherms were measured at 25 ± 1°C, with 48 h equilibration in a Millipore reverse osmotic purified water. Stability constants were determined for 1 : 1 complex composition by linear curve fitting to the solubility isotherms (Table 1). Kinetic measurements were carried out in HEPES buffer (pH 7.06) at room temperature, using dimer **7** (0.2mM), $CuCl_2$, $ZnCl_2$ or $EuCl_3$ (0.2mM), H_2O_2 (48mM) and bis-(*p*-nitrophenyl)-phosphate (BNPP) (0.06mM). Concentration of *p*-nitrophenol, resulted by the hydrolysis, was determined by UV/vis spectrometer at λ_{max} = 400 nm and the rate constants were calculated (Table 2).

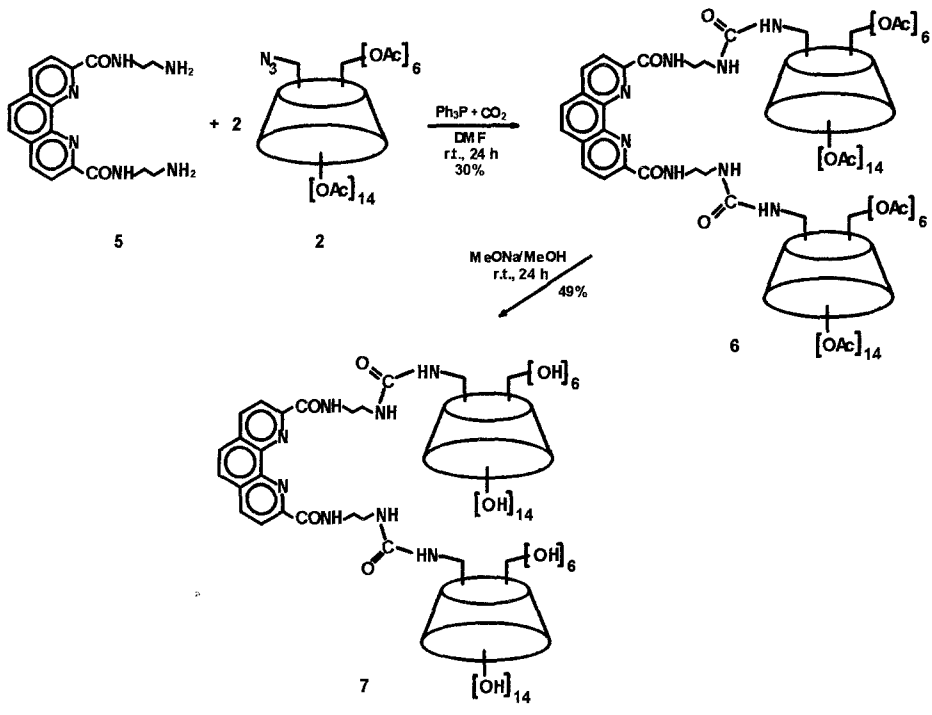
3. RESULTS AND DISCUSSION

Hitherto, CD dimers bridged with carbon-sulfur single bonds were obtained by direct condensation of dithiols with 6-monoiodo-6-mono-deoxy-ß-cyclodextrin [7].
We report here the synthesis and characterization of four original symmetrical CD dimers with urea linkage or with a spacer which contains diamino and urea moieties.
For the synthesis we used the sugar phosphinimine reaction, *i. e.*, conversion of azido sugars with triphenylphosphine and CO_2. From protected azidosugars the reaction leads to the formation of carbodiimides [8] in which two sugar units are linked with carbodiimide bridge. In contrast, from unprotected sugar azides cyclic carbamates [9] were obtained. Both syntheses were carried out either in two steps or under one-pot conditions. Recently, we have found that similar transformation of azidosugars, in the presence of amines, furnishes urea derivatives of the aminosugars corresponding to the starting azides [10].
Application of the reaction to 6-monoazido-6-monodeoxy-ß-cyclodextrin (**1**) gave readily the dimer **3** in which the two CD units are bound with urea linkage (Scheme 1). Similarly, the peracetyl compound **2** afforded the acetylated urea-linked dimer (**4**) and not the corresponding carbodiimide. Formation of **4** can be attributed, very probably, to the presence of water molecules complexed by ß-CD. Dimer **4** was also obtained by acetylation of **3** in pyridine/acetic anhydride at 80°C providing evidence for the structure of both molecules (Scheme 1).
Under similar conditions, but in the presence of phenantroline-2,9-bis-(2-aminoethyl)-carboxamide (**5**) **2** gave a new dimer (**6**) in which the two ß-CD units are linked symmetrically to the phenantroline-bis-carboxamide moiety with urea units. Deacetylation of **6** by the Zemplén method gave the hydroxy derivative **7** (Scheme 2).
The structures of the new dimers were corroborated by NMR showing the characteristic signals of the CD, phenantrolyl and urea moieties. Data of FABMS analyses matched

also the proposed structures.



Scheme 1



Scheme 2

Stability constants of dimers **3** and **7** were determined and compared with those of ß-CD (Table 1).

Table 1. Stability constants of urea-bridged ß-CDs and ß-CD with various drugs

	K [$dm^3.mole^{-1}$]		
CD-compound	Ketoconazole	Itraconazole	Hydrocortisone
3	131	101	2481
7	55	28	
ß-CD	939	250	6111

Complexes of dimer **7** with cations were formed and the rate constants of BNPP hydrolysis were measured under pseudo-first-order conditions (Table 2).

Table 2. Rate constants of BNPP hydrolysis by dimer 7

Compounds	Time(s)	$k_1(s^{-1})$	Time(s)	$k_2(s^{-1})$
7-Cu^{2+}	$0<t<180$	$9.55x10^{-4}$	$180<t<7.2.10^3$	$1.60x10^{-5}$
Cu^{2+}	$0<t<10.8x10^3$	$8.62x10^{-6}$	$64.8x10^3<t<97.2x10^3$	$5.69x10^{-8}$
7-Eu^{3+}	$0<t<240$	$3.10x10^{-4}$	$300<t<90x10^3$	$2.10x10^{-6}$
Eu^{3+}	$0<t<70.2x10^3$	$6.45x10^{-7}$	$75.6x10^3<t<163.8x10^3$	$2.39x10^{-7}$
7-Zn^{2+}	$0<t<7.2x10^{-3}$	$8.03x10^{-6}$	$9.0x10^3<t<14.4x10^3$	$1.80x10^{-7}$
Zn^{2+}	no hydrolysis after 72 h			

4. CONCLUSION

Structures of the new CD dimers allow to conclude positively for the scope of this methodology in the synthesis of such derivatives. The calculated complex constants for 1:1 complex compositions are in a similar range to those of ß-CD. Complexation of Hydrocortison by the dimer **7,** however, is more complicated. The low solubility of the complexes are the limits of their application to steroids and conazole-like drugs.

5. ACKNOWLEDGEMENTS

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