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A Simple Synthesis of a Highly Water Soluble Symmetrical β-Cyclodextrin Derivative

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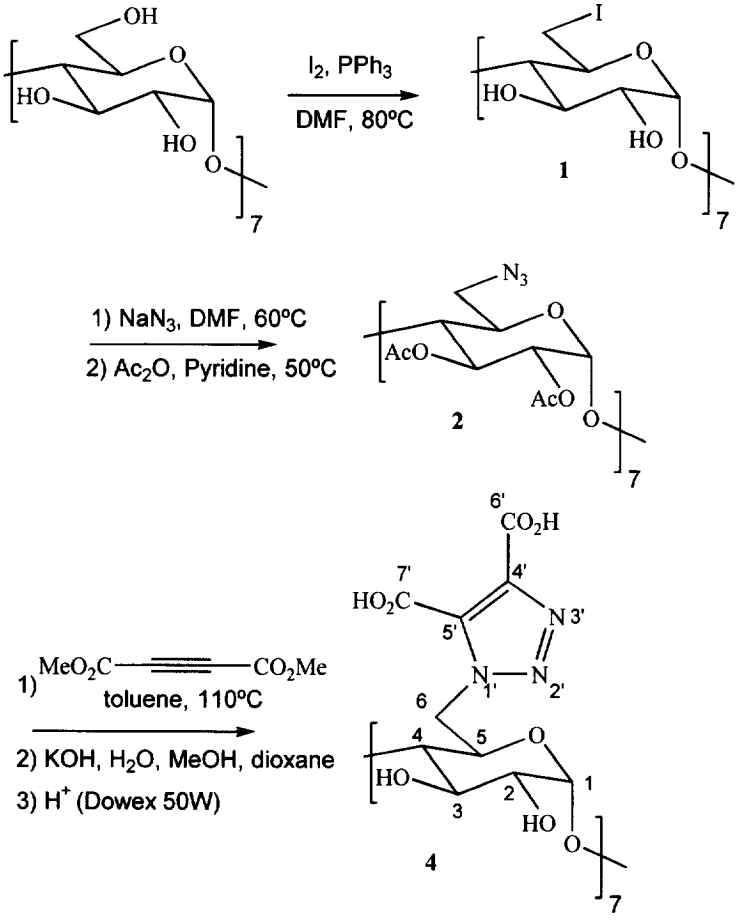
Abstract: 1,3-dipolar cycloaddition between peracetyl-heptakis-6-azido-6-deoxy-β-cyclodextrin and the dimethylester of 2-butyne dicarboxylic acid is a highly efficient route for the introduction of seven 1,2,3-triazole heterocycles and fourteen carboxyl groups on the small rim of the macrocycle.

α-, β- and γ-cyclodextrins (CDs) are naturally occurring commercially available macrocyclic oligosaccharides of, respectively, six, seven and eight α-1,4-linked D-glucose monomers.[1] Their thoroughly investigated ability to accommodate a large variety of organic compounds in their relatively hydrophobic macrocyclic cavities (formation of inclusion complexes) finds applications in numerous fields[1,2] such as enzyme mimicking, chiral chromatographic separations, solubilization in water of lipophilic compounds, transport, improvement of drug bioavailability, protection against chemical and photochemical degradations... In addition, much synthetic work has been devoted to elaborating chemically modified CDs[1,3-6] for better activities in catalysis and transport, more specific molecular recognition... Because of its low cost and availability in large quantities, β-CD is the most commonly chosen starting material in spite of its relatively low water solubility. Therefore, it could be desirable that chemical modifications of β-CD aimed at a specific purpose be accompanied by an increase in water solubility.

The straightforward modifications of β-CD reported here (Scheme 1) not only provide a deeper symmetrical macrocyclic cavity but also markedly enhance water solubility. In the first step, β-CD was converted into heptakis 6-deoxy-6-iodo-β-CD (**1**) upon treatment by iodine and triphenylphosphine in DMF (yield: 85%).[7] In the second step, **1** was reacted with sodium azide (5 equiv. per iodide atom) in DMF (60°C, overnight) to give heptakis 6-azido-6-deoxy-β-CD which was further peracetylated by acetic anhydride in pyridine to afford **2** (overall yield: 65%).[8] In the key step, a toluene solution of **2** and the dimethylester of 2-butyne dicarboxylic acid (3 equiv. per azido group) was refluxed for 17 hours. HPLC analysis (gradient elution from 0.1% HCO_2H in CH_3CN-H_2O (20:80) to 0.1% HCO_2H in CH_3CN-H_2O (60:40), UV detection at 242 nm)

showed the quantitative conversion of **2** into a single β-CD derivative (**3**). The ^{1}H- and ^{13}C-NMR spectra of **3**,[9] which displayed the simple pattern typical of symmetrical β-CD derivatives with identical monomeric units, were consistent with the conversion of the seven azido groups of **2** into seven 1,2,3-triazolyl rings bearing two methylcarboxy groups on their 4 and 5 positions (yield: 91% after chromatography on silica, eluent: toluene-ethanol 9:1, then 8:2). This was confirmed by IR (complete disappearance of the azido band around 2100 cm^{-1}) and mass analysis.[9] Complete ester hydrolysis (acetates + methylesters) could be achieved upon prolonged treatment of **3** by potassium hydroxide (2 equiv. per ester group) in dioxane-CH_3OH-H_2O (50:6:3) at room temperature (heating caused decarboxylation of the triazolyl rings). The reactional mixture was then acidified to pH 2 by a strong cation exchanger under H^+ form (Dowex 50W), filtered, concentrated and dried under vacuum over P_2O_5. From mass and ^{1}H- and ^{13}C-NMR analysis,[10] the white powder thus obtained was shown to be heptakis 6-deoxy-6-(1-(4,5-dicarboxyl)-1,2,3-triazolyl)-β-CD (**4**).



Scheme 1

This short synthesis is high yielding, devoid of tedious chromatographic purification and allows to prepare several grams of **4**. In the key step, 1,3-dipolar cycloaddition between the seven azido groups of **2** and the dimethylester of 2-butyne dicarboxylic acid proves to be a highly efficient route for the introduction of seven 1,2,3-triazole heterocycles and fourteen carboxyl groups on the small rim of β-CD. As expected, the carboxyl groups markedly increase the water solubility of the macrocycle: whereas the solubility of β-CD in 100 ml of water at room temperature is less than 2 g ($1.6x10^{-2}$ M), it is roughly 17 g ($8x10^{-2}$ M) for **4** under its neutral form and 70 g (0.3 M) for **4** whose carboxyl groups have been replaced by ammonium carboxylate groups (excess aqueous NH_3, then concentration to dryness). On the other hand, the seven 1,2,3-triazolyl moieties may well favour the formation of inclusion complexes, for instance, through π-stacking interactions with aromatic guests. β-CD derivatives bearing positively charged amino groups have been shown to possess increased affinities for anionic guests (carboxylates and phenolates,[11] nucleotides[12]...) due to the development of favourable electrostatic interactions in the inclusion complexes. Conversely, the fourteen carboxyl groups may confer on **4** a special affinity for cationic guests. Finally, β-CDs functionalized by carboxylate groups can be used for the simultaneous complexation of organic guests and metal ions.[13] Similarly, **4** may find applications in metal coordination chemistry. Investigations of these various potentialities are under way.

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9. Compound **3**
   ^{1}H-NMR (200 MHz, CD_3CN, δ in ppm, J in Hz): 5.54 (t, 7H, J = 9.0, 3-H), 5.51 (d, 7H, J = 3.5, 1-H), 4.96 (m, 14H, 6-Ha, 6-Hb), 4.61 (dd, 7H, J = 9.0, 3.5, 2-H), 4.50 (m, 7H, 5-H), 3.89 (s, 21H, CO_2Me), 3.85 (s, 21H, CO_2Me), 3.65 (t, 7H, J = 9.0, 4-H), 2.03 (s, 42H, acetates)

^{13}C-NMR (50 MHz, $CDCl_3$, δ in ppm): 170.0, 169.2 (CO from acetates), 160.1, 158.9 (CO from CO_2Me), 139.7, 132.2 (4'-C, 5'-C), 96.6 (1-C), 76.6 (4-C), 69.6 (2-C, 3-C, 5-C), 53.8, 52.8 (Me from CO_2Me), 49.1 (6-C), 20.6 (Me from acetates)

Mass (FAB, positive mode, thioglycerol, NaI): m/Z = 2916 (**3**-Na^+ adduct)

Microanalysis:

calc. (from $C_{112}H_{133}N_{21}O_{70}$): C: 46.5% H: 4.6% N: 10.2%

found: C: 46.15% H: 4.66% N: 9.83%

UV-vis (CH_3CN): λ_{max} = 242 nm

10. Compound **4**

^{1}H-NMR (400 MHz, D_2O, 60°C, $(CD_3)_2CO$ as internal reference): 5.03 (d, 7H, J = 3.5, 1-H), 4.82 (dd, 7H, J = 14.0, 3.0, 6-Ha), 4.52 (dd, 7H, J = 14.0, 6.5, 6-Hb), 4.14 (m, 7H, 5-H), 3.82 (t, 7H, J = 9.5, 4-H), 3.46 (dd, 7H, J = 9.5, 3.5, 2-H), 3.37 (t, J = 9.5, 3-H)

^{13}C-NMR (50 MHz, D_2O, $(CD_3)_2CO$ as internal reference): 162.6, 159.9 (6'-C, 7'-C), 138.7, 132.7 (4'-C, 5'-C), 101.0 (1-C), 82.1 (4-C), 71.7, 70.9, 69.0 (2-C, 3-C, 5-C), 48.2 (6-C)

Mass (electrospray, positive mode, figures in brackets refer to relative intensity): m/Z = 535.51 (Z = 4, **4**-K^+ adduct, 70), 526.06 (Z = 4, 100), 428.30 (Z = 5, **4**-K^+ adduct, 70), 420.60 (Z = 5, 90)

UV-vis (Tris buffer, pH 8): λ_{max} = 252 nm

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