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ORIGINAL ARTICLE

Supramolecular structures based on dimeric combinations of cyclodextrin and adamantane via click chemistry

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Abstract We describe the synthesis of 1-mono-β-cyclodextrin-4-[4-(1-mono-β-cyclodextrin-1*H*-1,2,3-triazol-4-l)butyl]-1*H*-1,2,3-triazole (CD–CD) **3**, 1-mono-β-cyclodextrin-4-[4-(1-adamantane-1*H*-1,2,3-triazol-4-yl)butyl]-1*H*-1,2,3-triazole (CD–Ad) **4**, and 1-adamantane-4-[4-(1-adamantane-1*H*-1,2,3-triazol-4-yl)butyl]-1*H*-1,2,3-triazole (Ad–Ad) **5** via microwave-assisted cycloaddition of 6I-azido-6I-deoxycyclomaltoheptaose and 1-azidoadamantane with 1,7-octadiyne. Dynamic light scattering (DLS) was used to investigate the host-guest interactions and the self-assembly properties of the complexes formed by the compound **3** with the dimers **4** and **5**.

Keywords Cyclodextrin and adamantane dimers · Microwave-assisted cycloaddition · Supramolecular structures

Introduction

Supramolecular chemistry based on fundamental principles like non covalent interactions, molecular recognition and self-assembly processes received a great consideration in the last years mainly due its role to connect the world of single molecules with that of nano-biotechnology [1]. The recent progresses in this field are also the contribution of 'click' methodology, a powerful strategy that affords the modular assembly of new molecular entities [2–7]. The strong interrelation between the two research areas imposed the new concept of 'supramolecular click chemistry' [8], as a valuable tool in bioconjugation [7, 9], drug discovery [10–13] and material science [14–16]. The reference host compounds and the most important molecular receptors studied in supramolecular chemistry are cyclodextrins (CD), being appealing and versatile structures for the design of inclusion complexes with hydrophobic guests [17–21]. The strong binding of hydrophobic ditopic substrates into dimeric cyclodextrins, with potential application as antibody or enzyme mimics was demonstrated by Breslow [22–30]. Regarding the guest-modified CD, the couple cyclodextrin/adamantane has been intensive investigated, due its complementarity and reversible interaction [17], these features being of great interest for the design of self-associating biopolymers [31–33]. The use of microwave (MW)-assisted 'click' methodology to prepare CD-dimers and guest-dimers has not been reported. In the present research we thus describe the synthesis of three types of dimers via Cu(I)-mediated cycloaddition of 6I-azido-6I-deoxycyclomaltoheptaose and 1-azidoadamantane with 1,7-octadiyne (Scheme 1), respectively the study of their water-soluble inclusion complexes.

Experimental

IR spectra were recorded with a Nicolet 5 SXB FT-IR Spectrometer, equipped with an ATR unit. NMR spectra were recorded with a Bruker AC 500 at 20 °C. Chemical shifts were referenced to the solvent value δ 2.51 for DMSO-d_6, δ 4.79 for D_2O and δ 7.26 for $CDCl_3$. MALDI-TOF-MS was performed on a Bruker Ultraflex TOF time-of-flight mass spectrometer using a 337 nm nitrogen laser. GC-MS measurements were realised with a Thermo Finnigan Trace DSQ system. Dynamic Light Scattering (DLS) experiments

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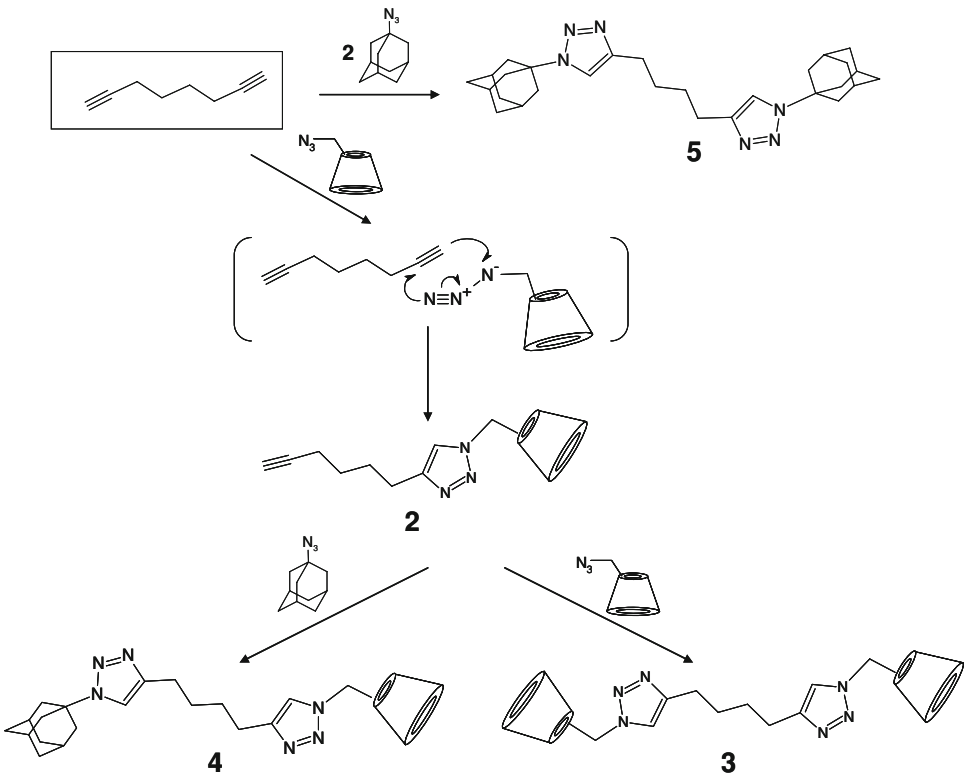
Scheme 1 Dimer synthesis via click methodology



were carried out with a Malvern HPPS-ET at a temperature value of 25 °C. The particle size distribution was derived from a deconvolution of the measured intensity autocorrelation function of the sample by the *general purpose mode* algorithm included in the *DTS* software. Each experiment was performed five times to obtain statistical information. MW-assisted synthesis was performed using a CEM Discover Synthesis Unit (monomode system). The temperature was measured by infrared detection with continuous feedback temperature control, and maintained at a constant value by power modulation. Reactions were performed in closed vessels under controlled pressure. Commercially available reagents and solvents were used without further purification. Cyclodextrin (β-CD) was obtained from Wacker-Chemie GmbH, Burghausen, Germany and used after drying overnight in vacuum oil-pump, on P_4O_{10}. 6I-Azido-6I-deoxycyclomaltoheptaose (**1**) was prepared according to a method described in literature [34].

6I-Azido-6I-deoxycyclomaltoheptaose **1**

6I-Azido-6I-deoxycyclomaltoheptaose was prepared from mono-(6-O-(p-tolylsulfonyl))-β-Cyclodextrin and sodium azide [34]. The product was dried in oil-pump and maintained in dessicator over P_4O_{10}. IR: ν 1,025, 1,077, 1,152, 1,364, 2,043, 3,316 cm^{-1}; ^{1}H-NMR (500 MHz; DMSO-d_6) δ: 3.32 (14H, CH), 3.60–3.84 (br, 28H), 4.44–4.60 (br, 6H), 4.85 (d, 6H), 4.92 (H, CH), 5.73 (14H); *m/z* 1,182.4 [M + Na^+].

Mono-(1*H*-1,2,3-triazol-4-yl)-4-hex-5-ynyl-β-cyclodextrin **2**

The compound **2** was prepared according to the following method: 1,7-octadiyne (4.55 mg, 0.043 mmol) was added to a solution of 6I-azido-6I-deoxycyclomaltoheptaose (100 mg, 0.086 mmol) in 2 mL DMF in a pressure-resistant test tube. To the clear solution were added sodium ascorbate (0.85 mg, 0.0043 mmol) and copper (II) sulfate pentahydrate (0.5 mg, 0.0021 mmol). The tube was sealed and placed in the CEM monomode MW and irradiated at 150 °C and 130 W for 30 min. The product was collected by filtration, after precipitating with acetone (50 mL). In order to remove the unreacted 6I-azido-6I-deoxycyclomaltoheptaose, the white solid was re-dissolved in methanol (50 mL), than the compound **2** was isolated by evaporating the methanolic solution. IR: ν 1,020, 1,081, 1,153, 1,388, 1,655, 2,930, 3,309 cm^{-1}; ^{1}H-NMR (500 MHz; DMSO-d_6) δ: 1.24 (1H), 1.51–1.69 (8H), 3.32 (14H), 3.57–3.65 (br, 28H), 4.48 (6H), 4.84 (7H), 5.79 (14H), 8.47 (1H); *m/z* 1,288.5 [M + Na^+].

1-Mono-β-cyclodextrin-4-[4-(1-mono-β-cyclodextrin-1*H*-1,2,3-triazol-4-yl)butyl]-1*H*-1,2,3-triazole **3**

The compound **3** was obtained from compound **2** (54 mg, 0.043 mmol) and compound **1** (100 mg, 0.086 mmol), which were solved in 2 mL DMF in a pressure-resistant test

tube. To the reaction mixture was added the catalytic system, consisting of sodium ascorbate (0.85 mg, 0.0043 mmol) and copper (II) sulfate pentahydrate (0.5 mg, 0.0021 mmol). The tube was irradiated at 150 °C and 130 W for 30 min. in the CEM monomode MW. The white solid collected by filtration, after precipitating with acetone (50 mL) was suspended in methanol (50 mL) and the dimer **3** was isolated by filtration. We tried also to obtain the compound **3** from the direct reaction of 1,7-octadiyn (4.55 mg, 0.043 mmol) with 6I-azido-6I-deoxycyclomaltoheptaose (100 mg, 0.086 mmol), solved in 2 mL DMF, in the presence of sodium ascorbate (1.7 mg, 0.0086 mmol) and copper (II) sulfate pentahydrate (1 mg, 0.0043 mmol). After irradiating the reaction mixture at 150 °C and 130 W for 60 min, we obtained a mixture of compounds 2 and 3, with a ratio of 2:1. IR: *v* 1,025, 1,086, 1,148, 1,337, 1,655, 2,925, 3,319 cm^{-1}; ^{1}H-NMR (500 MHz; D_2O) δ: 1.49–1.94 (16), 3.59–3.66 (28 H), 3.85–3.96 (br, 6H), 4.44–4.60 (br, 12H), 4.87 (d, 12H), 4.92 (2H), 5.07 (28H), 8.38 (2H); *m/z* 2,447.7 [M + Na^+].

1-Mono-β-cyclodextrin–4-[4-(1-adamantane-1*H*-1,2,3-triazol-4-yl)butyl]-1*H*-1,2,3-triazole **4**

The compound **4** was prepared using the monomer **2** (176.6 mg, 0.14 mmol) and azido-adamantane (100 mg, 0.56 mmol) as starting materials, solved in 2 mL DMF, in a pressure-resistant test tube, in the presence of sodium ascorbate (5.5 mg, 0.028 mmol) and copper (II) sulfate pentahydrate (3.4 mg, 0.014 mmol). The reaction mixture was irradiated 120 °C and 130 W for 30 min, than poured in 50 mL acetone, and the solid product isolated by filtration and dried at room temperature. IR: *v* 1,020, 1,076, 1,143, 1,352, 1,655, 1,685, 2,852, 2,930, 3,309 cm^{-1}; ^{1}H-NMR (500 MHz; DMSO-d_6) δ: 1.51 (6H), 1.65 (6H), 2.17 (4H), 3.32 (14H), 3.57–3.65 (br, 28H), 4.48 (6H), 4.84 (6H), 4.88 (2H), 4.92 (H), 5.70 (14H), 7.79, 8.44; *m/z* 1,465.8 [M + Na^+].

1-Adamantane-4-[4-(1-adamantane-1*H*-1,2,3-triazol-4-yl)butyl]-1*H*-1,2,3-triazole **5**

The compound **5** was obtained from 1,7-octadiyne (14.87 mg, 0.14 mmol) and azido-adamantane (100 mg, 0.56 mmol) as starting materials, which were solved in 2 mL DMF, in a pressure-resistant test tube. After adding sodium ascorbate (5.5 mg, 0.028 mmol) and copper (II) sulfate pentahydrate (3.4 mg, 0.014 mmol), the reaction mixture was heated at 120 °C and 130 W for 20 min. The solid product precipitated during the reaction was isolated by filtration and washed with acetone, in order to remove the unreacted azido-adamnantane, than was and dried at room temperature. IR *v*: 1,015, 1,255, 1,358, 1,434, 1,542, 1,675, 2,858, 2,904, 3,099 cm^{-1}; 1H-NMR (500 MHz; $CDCl_3$) δ: 1.20–1.41 (br, 12H, CH_2), 1.71 (4H), 2.24 (4H) 2.74 (br, 12H, CH_2), 7.36 (6H, CH), 7.70 (2H, CH); *m/e* 461.

Results and discussions

6I-Azido-6I-deoxycyclomaltoheptaose was synthesized according to a method described in literature [34]. In order to obtain CD–CD and CD–adamantane (CD–Ad) dimers, we prepared first the monomer **2** from 6I-azido-6I-deoxycyclomaltoheptaose and 1,7-octadiyne, applying Cu(I)-catalysed cycloaddition under microwave conditions (Scheme 1). Using this monomer for the synthesis of CD–CD dimer (**3**) in a two steps-procedure instead of the direct reaction of 6I-azido-6I-deoxycyclomaltoheptaose with 1,7-octadiyne provided the complete conversion into dimer, while the direct reaction led to a mixture of monomer (**2**) and dimer (**3**), with a ratio of 2:1. CD-monomer **2** was further used for the synthesis of the mix dimer CD–Ad (**4**). The guest adamantane-adamantane (Ad–Ad) dimer **5** was also obtained by MW-assisted 'click' reaction of azido-adamantane with 1,7-octadiyne, the reaction being easier to perform than the procedure applying to 6I-azido-6I-deoxycyclomaltoheptaose. The compounds isolated after cycloaddition were characterised by ^{1}H-NMR, FT-IR, MALDI-TOF and GC-MS spectroscopy. The ^{1}H-NMR spectra confirmed all proposed structures, the chemical shifts of the triazolic proton being observed at 8.47 ppm (**2**), 8.38 ppm (**3**), 7.79 and 8.44 ppm (**4**), respective 7.70 ppm (**5**) (Fig. 1). The successful completion of each reaction was also proven by the absence of the specific N_3 vibrations at 2,043 cm^{-1} for 6I-azido-6I-deoxycyclomaltoheptaose and 2,090 cm^{-1} for 1-azidoadamantane and also of the band detected at 2,100 cm^{-1} for 1,7-octadiyne in the FT-IR spectra. Instead, we could observe new peaks at 1,655 cm^{-1}, specific for carbon-carbon double bond which, associated with the vibration of carbon-nitrogen bond at 1,020 cm^{-1}, proving the existence of triazole. For the mixed dimer **4** we identified, beside the specific peaks for triazole, both the vibrations for hydroxyl groups of CD at 3,344 cm^{-1} and for methylene groups of adamantane at 2,853 cm^{-1}. The molecular weight of the compounds **2**, **3** and **4** was measured by MALDI-TOF mass spectroscopy, the values [M + Na^+] being 1,288.4, 2,447.7, respectively 1,465.8. Regarding the dimer **5**, we obtained a molecular weight of 461 g/mol.

We investigated the tendency of synthesized dimers to form supramolecular complexes in water, using dynamic light scattering. An interesting behavior was observed for distinct water-soluble CD–CD (**3**) and CD–Ad (**4**) dimers. Therefore, the mean hydrodynamic radius size of 40 nm and 49 obtained for a complexation time of 1 h and for a

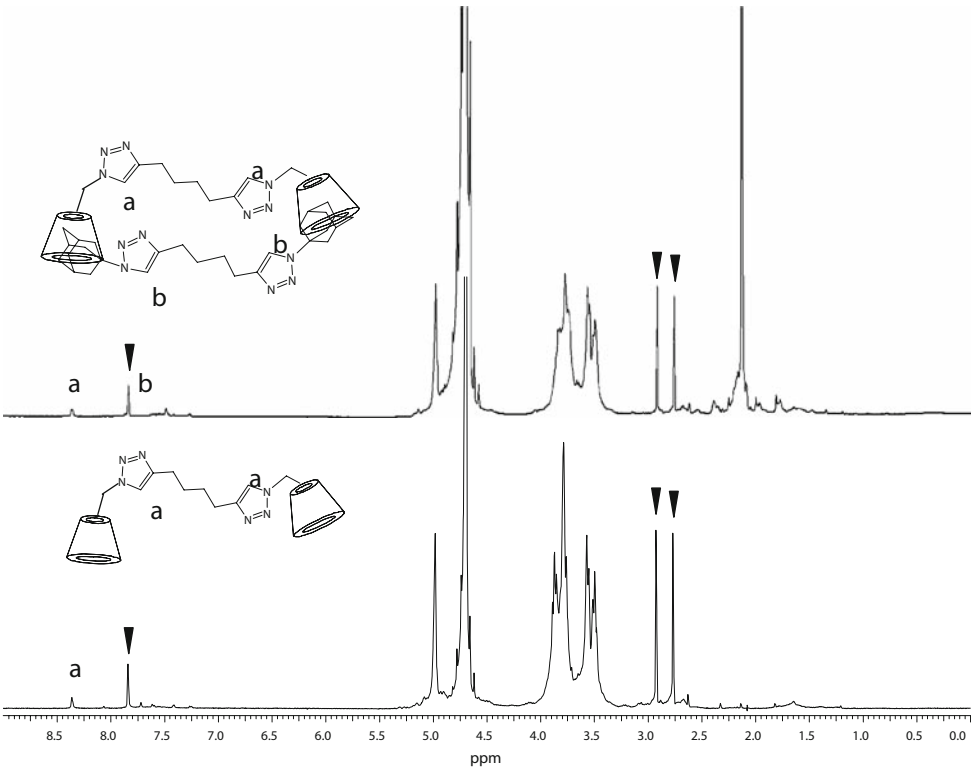


Fig. 1 ^{1}H-NMR (500 MHz, D_2O) spectra showing signals for the protons of the triazole on CD–CD dimer (**a**) as well as on Ad–Ad (**b**) complexed with CD–CD (▼: signals of solvent (DMF))

Table 1 Size distribution of synthesized dimers

Compound (No.)	Concentration (g/l)	Time of complexation (h)	Mean of size distribution by number (nm)
CD–CD (**3**)	10	1	40
		24	240
CD–CD (**3**)	20	1	49
		24	310
CD–Ad (**4**)	10	1	65
		24	415
CD–Ad (**4**)	20	1	92
		24	695

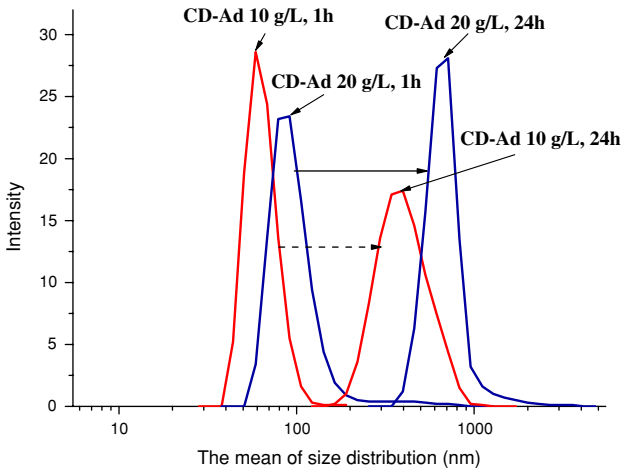


Fig. 2 Hydrodynamic volumes of CD–Ad dimer depending on concentration and complexation time

concentration of 10 g/L, respective 20 g/L, which increased up to 240 nm and 310 nm after 24 h, suggests that this dimer is self-associated through hydrogen bonds in water (Table 1).

The results confirm these reported by Bonini et al., according with β-CD monomers do aggregate in water at room temperature, with a mean value of hydrodynamic radius size of 90 nm [35, 36]. The same effect was observed for the mix dimer CD–Ad (**4**), the increased concentration and complexation time being favorable for the self-assembly process in water (Fig. 2). A greater hydrodynamic radius of 695 nm was obtained for higher concentration (20 g/L) after 24 h, in contrast to 310 nm obtained for the CD–CD (**3**) dimer in the same conditions.

These results suggest the preference for self-association to hydrogen bonds detriment. This preferential behavior of CD–Ad dimer (**4**) is proved also by the decreased value of hydrodynamic radius in the presence of CD–CD (**3**) dimer for a low time of complexation, while increasing the time to 24 h lead to higher radius size (700 nm for a concentration of 10 g/L and 1,820 nm for 20 g/L). In this case we can postulate that the two dimers CD–CD (**3**) and CD–Ad (**4**) are associated, beside specific host-guest interactions, through hydrogen bonds between the cyclodextrin units.

Table 2 Size distribution of supramolecular complexes based on synthesized dimers

Compound	Concentration (g/l)	Time of complexation (h)	Mean of size distribution by number (nm)
CD–CD + CD–Ad	10	1	53
		24	700
CD–CD + CD–Ad	20	1	62
		24	1,820
CD–CD + Ad–Ad	10	1	55
		24	1,740
CD–CD + Ad–Ad	20	1	64
		24	3,610

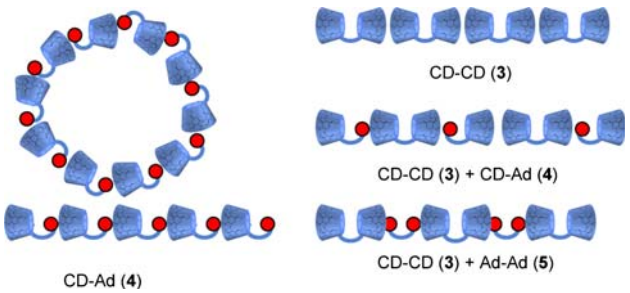


Fig. 3 Proposed supramolecular structures for synthesized dimers and their complexes

We investigated also the specific host-guest interactions of CD–CD dimer (**3**) with Ad–Ad (**5**). An interesting behaviour of these complexes was observed by comparing them with the self-assembly CD–CD (**3**) dimer in water. Lower concentration and complexation time strongly suggested the specific host-guest interaction, while increasing the concentration and the time of guest complexation had as consequence association and aggregation phenomena, expressed by a mean of hydrodynamic volume of 1,740 nm for a concentration of 10 g/L and 3,610 nm for 20 g/L (Table 2).

These values clearly indicate the presence of host-guest processes, which are favoured not only by the complementarity cyclodextrin-adamantane, but also by the flexibility of the butylene (tetramethylene) which connects each two units. Based on hydrodynamic radius size values obtained by DLS measurements we proposed the supramolecular structures of synthesized dimers and their complexes (Fig. 3).

Conclusions

Cyclodextrin- and guest adamantane-dimers were successfully prepared via click methodology, under MW conditions, using Cu(I) as catalyst. DLS measurements performed for CD–CD (**3**) and CD–Ad (**4**) dimers and also for the supramolecular complexes of CD–CD (**3**) with CD–Ad (**4**) and Ad–Ad (**5**) confirmed the ability of cyclodextrin to self-assembly in water, as well as its capacity to recognize and include adamantane moieties placed on the same dimer (as in the case of CD–Ad (**4**) compound) or on a different one (the interaction of CD–CD (**3**) with Ad–Ad (**5**)). By varying the solution concentration and the complexation time, we showed that the dimer CD–CD (**3**) has the tendency to self-associate through hydrogen bonds, while the inclusion phenomena are specific for CD–Ad (**4**) compound. Regarding the complexes of CD–CD (**3**) with the other dimers, we postulate that both types of interactions are possible in the presence of CD–Ad (**4**) and Ad–Ad (**5**) compounds, the host-guest complexation being characteristic for the supramolecular structures based on these dimeric combinations.

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