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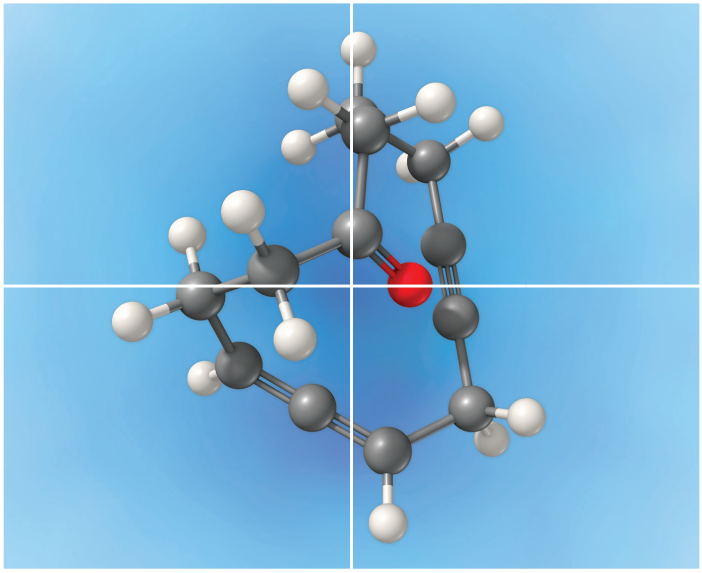

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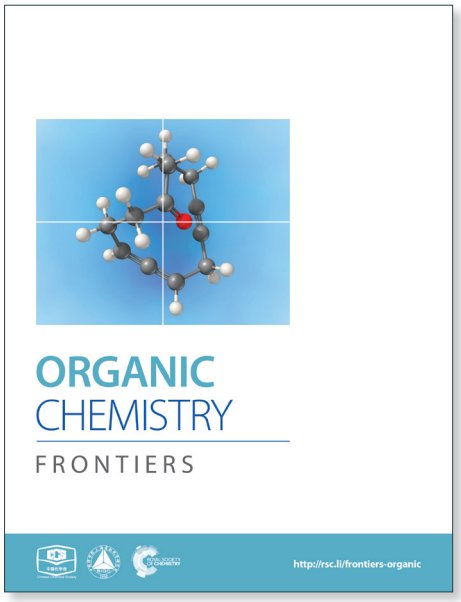

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ARTICLE

Cyclodextrin-adamantane conjugates, self-inclusion and aggregation versus supramolecular polymer formation

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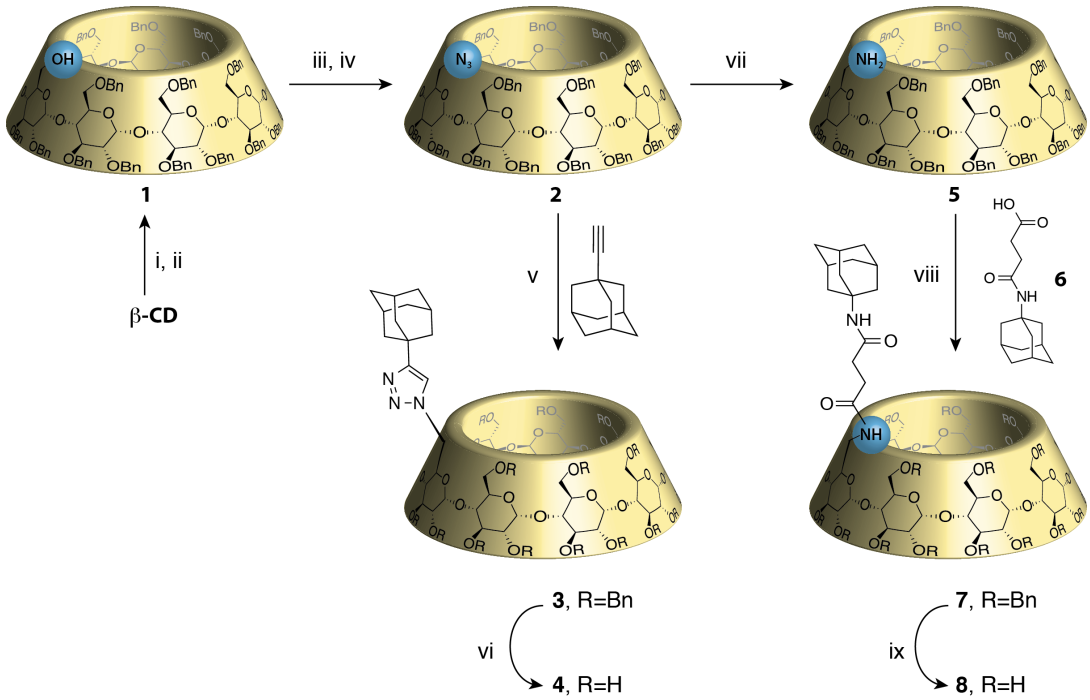
Cyclodextrin-adamantane conjugates have been prepared and their ability to form supramolecular polymers tested. It appears that they are either insoluble when the link is too rigid or they form self-included derivatives inhibiting the formation of the polymer.

Introduction

Cyclodextrins (CDs) are hydrosoluble cyclic oligosaccharides presenting a lamp-shade shape delineating a hydrophobic cavity. Due to this shape they can form inclusion complexes in water with hydrophobic guests. Consequently, CDs conjugated to a hydrophobic moiety have been widely studied for their ability to form supramolecular oligomeric assemblies.[1] In these assemblies the hydrophobic moiety linked to a given CD is included in the cavity of the next etc… The size of the assembly is generally governed by the affinity of the hydrophobic guest for the CD cavity, in an isodesmic model, according to the Carothers equation.[2] In this context, the well-known high affinity of adamantane for the β-CD cavity should have been exploited and studied in detail to form supramolecular polymers. But, rather surprisingly, only few examples are reported in the literature. This might be due to the report by Lincoln on a β-CD-adamantane conjugate with a flexible linker in which the adamantane moiety is included in the cavity of the CD bearing it.[3] The self-included adamantane complex was not displaced by 2 equivalents of adamantane carboxylate illustrating the high stability of this complex. The authors actually question the reason for this high stability that might be due to the synthesis where the arm could be already self-included and its functionalization with adamantane would form a stable "slip-knot". This report prompted Tato to use a very short and rigid linker to conjugate β-CD and adamantane to prevent self-inclusion, which afford a linear polymer described in the solid state.[4] Harada conjugated α-CD with adamantane through its secondary rim, no self-inclusion was reported here.[5] Finally, Ritter reported a series of triazol-linked β-CDs with various hydrophobic groups[6] including adamantane.[7] The link here is semi-rigid and the association in water was characterized using dynamic light scattering (DLS). This technique showed that the conjugate produced assemblies with higher hydrodynamic radii than in the absence of adamantane. However, those radii increased with time, which was attributed to some association through hydrogen bonding rather than inclusion.

Results and discussion

Based on those observations, we designed a first CD-adamantane conjugate **4** with a very rigid triazol link. The synthesis started by the classical benzylation/monodebenzylation sequence on β-CD to give alcohol **1**,[8] which was then converted into the azido-CD **2**[9] through mesylation followed by nucleophilic azidation.[10] Copper assisted azide-alkyne cycloaddition of **2** with 1-adamantylacetylene under micro-waves gave protected conjugate **3** in 86% yield, which was deprotected through hydrogenolysis to give the desired conjugate **4**. (Scheme 1) Unfortunately, compound **4** appeared to be insoluble in water rendering the study of its self-assembly impossible. This might also explain why Tato's conjugate's assembly was only described in the solid phase. We then turned our attention to a more flexible and potentially more soluble linker, and inspired by another work by Tato[11] we oriented our study toward CD **8**. Azido CD **2** was therefore reduced to the amine using $LiAlH_4$ to give CD **5** in 65% yield.[9] Peptide coupling of **5** with adamantane linked to an acid **6** was operated in 56% yield to give **7**, which in turn was deprotected in 81% yield to give the desired CD conjugate **8**. (Scheme 1)



Scheme 1. Synthesis of CD-adamantane conjugates. Reagents and conditions: i) BnCl, NaH, DMSO, 30 h, 98%; ii) DIBAL-H, toluene, 50°C, 45 min., 75%; iii) Mesyl chloride, Et_3N, CH_2Cl_2, 1h30, RT, 83%; iv) NaN_3, DMF, 80°C, 2h, 90%; v) $Cu(CH_3CN)_4PF_6$, tris[1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA), diisopropylethylamine (DIPEA), DMF, μW 150°C, 1h, 86%; vi) H_2, $Pd(OH)_2/C$, THF/MeOH, H_2O,12h, >98%; vii) $LiAlH_4$, THF, 80°C, 2h, 62%; viii) **6**, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, (EDC), DIPEA, 1-hdroxy-benzotriazol (HOBt), DMF, RT, 22h, 56%; ix) H_2, $Pd(OH)_2/C$, THF/MeOH, H_2O,12h, >98%.

CD **8** is soluble in water and the study of its self assembly could be performed using DLS, NMR, vicosimetry and ITC. First, it has to be said that the solubility of CD **8** is not very high as the solution becomes turbid above 5mM concentration. At this concentration, in an aqueous solution containing NaN_3, DLS showed formation of species with a hydrodynamic radius of 145nm, corresponding to the previously reported assembly sizes. Such a hydrodynamic radius is actually much larger than what is expected if the only interaction involved is host-guest complexation. Indeed, the association constant between adamantane derivatives and β-CD is at best on the order of K = 10^5 L/mol, which translates into a number average degree of polymerization of $DP_n \sim (KC)^{0.5} \sim 20$ (at a concentration C = 5mM), based on a classical mass action law model.[12] Therefore, the curvilinear end-to-end distance of the chains should be on the order of 20nm. The one order of magnitude larger hydrodynamic radius measured is therefore a clear indication that other interactions than simple host-guest complexation are driving the assembly.

We further studied our system by NMR. In a standard study, we performed a dilution, hoping to observe shifts and sharpening of signals. However, no chemical shift changes could be observed, nor sharpening of the signals upon 10 and 100 times dilutions starting from a 7mM solution of CD **8**. (Figure 1) We then operated a detailed assignment of the ^1H NMR spectrum and we were lucky enough to observe that two H-5s and two H-3s were clearly identifiable. (See SI Figures SI9-SI16) ROESY experiment then showed that adamantane was indeed inside the cavity but upside down. The 2D spectrum clearly shows cross-correlations only between H-5s of the CD and Ha of the adamantane, when the H-3s of the CD cross-correlate with Hb and Hc of the adamantane moiety. (Figures 2 and 3) Consequently compound **8** is in a self included form. We next performed DOSY experiments depending on the concentration of CD **8**, and observed that whatever the concentration the diffusion coefficient remains in the same range as the one of monomeric CD.[13] (Figure 4)

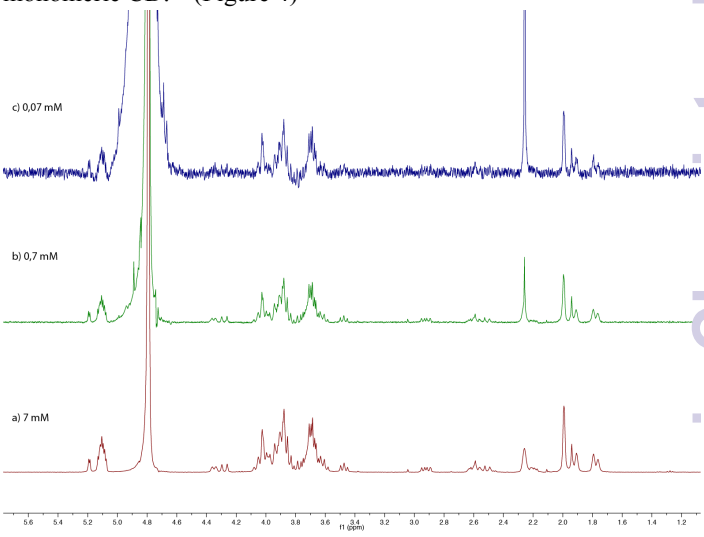


Figure 1. Effect of the dilution of CD **8** in D_2O on ^1H NMR: a) 7mM, b) 0.7mM, C) 0.07mM.

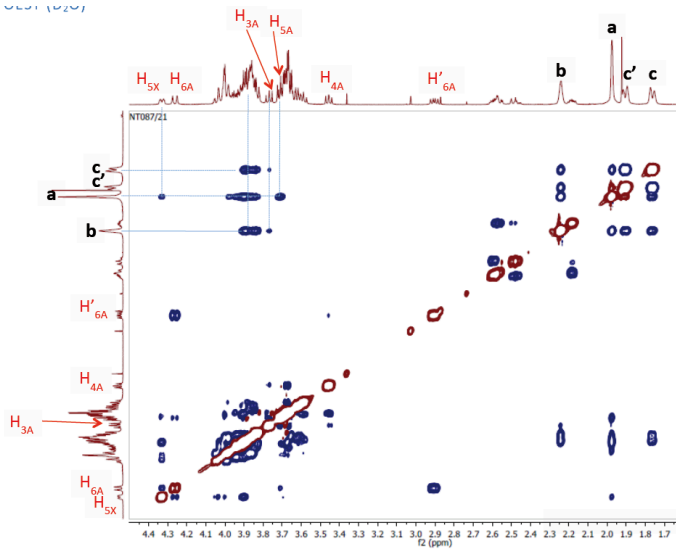


Figure 2. ROESY spectrum of CD **8** (D_2O, 600MHz), unit A is bearing the adamantine moiety.

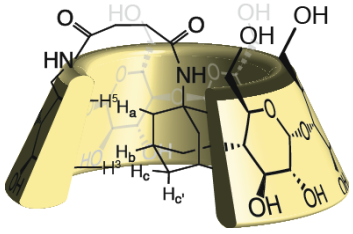


Figure 3. Proposed conformation for CD **8**, based on the ROESY.

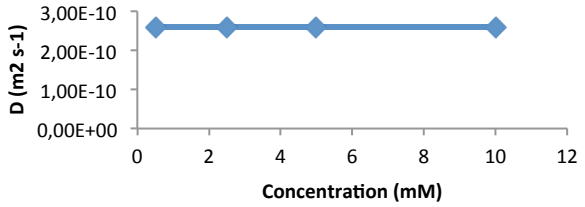


Figure 4. Diffusion coefficient (D) obtained by DOSY experiments (D_2O, 600 MHz) as a function of the concentration of CD **8**.

We next performed capillary viscosity measurements, and observed no difference in flow time between the blank and the 5mM solution of CD-adamantyl **8**. Finally, we probed intermolecular interactions by Isothermal Titration Calorimetry (ITC). Dilution of a 2.5mM solution of CD-adamantyl **8** into water produced a weak and concentration independent heat exchange (Figure 5). In contrast, dilution of an equimolar solution of β-CD and succinic acid linked adamantane **6** produced a strong endothermic effect that can be quantitatively fitted with a simple 1 to 1 association model, yielding an association constant K = 3.5 10^4 L/mol and a favourable association enthalpy ΔH_{assoc} = -4.4kcal/mol. This means that in the concentration range probed (0.01 to 2.5mM) CD-adamantyl **8** is not affected by dilution, which rules out the presence of a supramolecular polymer at 2.5mM, and is in agreement with the presence of self-included monomers and/or very stable aggregates. This result was also confirmed using NMR through successive additions of adamantylcarboxylate to a 5mM solution of CD **8** in D_2O. It is only when we added between 2.8 and 4.5 equivalents of adamantylcarboxylate that chemical shifts of the CD started to be modified. (See Figure SI17) The self-included complex is therefore particularly stable.

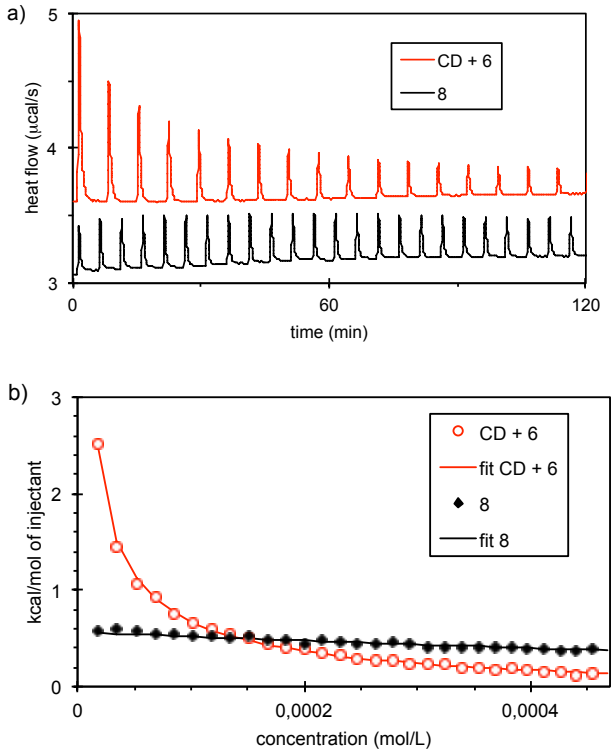
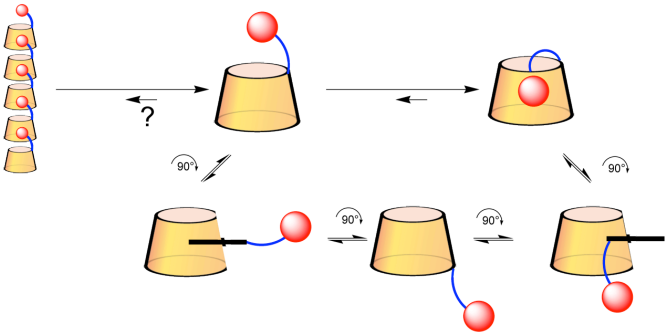


Figure 5. (a) Heat flow curves obtained by dilution of a 2.5mM solution of CD **8** or by dilution of a 2.5mM equimolar mixture of β-CD and adamantyl derivative **6**. (b) Corresponding ITC enthalpograms. The continuous curves are fits according to reference 14.

From all those results, we tend to conclude that CD **8** does not form supramolecular polymers because the self-included complex is highly stable. DOSY also does not detect any association whatever the concentration, and no viscosity enhancement could be observed. That leaves us with the DLS results that show the presence of large species. We believe that this signal is due to the well-known aggregation[15] of CDs undetectable by NMR because the aggregates are too large. Furthermore, we can answer to Lincoln interrogation whether the self-included compound was in equilibrium with the empty one, or if the self-included compound was obtained in the conjugation step.[3] In our case the conjugation is operated on a benzylated CD **5** excluding self-inclusion at that stage. The self-inclusion therefore, most probably uses the inversion or tumbling mechanism, which was mainly observed on CD-

dimers[16] so-far, but which seems to be a rather general mechanism. (Scheme 2) In our case, this mechanism could also be favoured by the 12 kJ.mol^{-1} free energy difference in favour of the complexation of adamantane from the secondary rim over the one from the primary rim.[17]



Scheme 2. Proposed behaviour for CD **8** in water.

Conclusions

In conclusion, the conjugation of a hydrophobic moiety to β-CD is a rather arduous task: if the linker is too rigid the conjugate tends to aggregate and be insoluble, if the linker is more flexible it can form self-included complexes inhibiting the self-association to yield polymers.

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Notes and references

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Electronic Supplementary Information (ESI) available: experimental section, NMR analysis, ITC experimental and adamantine carboxylate addition experiments. See DOI: 10.1039/b000000x/

1 A. Harada, Y. Takashima, H. Yamaguchi, *Chem. Soc. Rev.* 2009, **38**, 875-882.
2 A. Ciferri, Ed. *Supramolecular Polymers,* 2nd ed.; Taylor & Francis: New York, 2005. 397.
3 B. L. May, P. Clements, J. Tsanaktsidis, C. J. Easton, S. F. Lincoln, *J. Chem. Soc., Perkin Trans. 1* 2000, 463-469.
4 V. H. Soto Tellini, A. Jover, L. Galantini, F. Meijide, J. Vazquez Tato, *Acta Cryst. B* 2004, **60**, 204-210.
5 M. Miyauchi, A. Harada, *J. Am. Chem. Soc.* 2004, **126**, 11418-11419 ; A. Miyawaki, M. Miyauchi, Y. Takashima, H. Yamaguchi, A. Harada, *Chem. Commun.* 2008, 456-458.
6 M. Munteanu, U. Kolb, H. Ritter, *Macromol. Rapid Commun.* 2010, **31**, 616-618 ; A. Maciollek, H. Ritter, R. Beckert, *Beilstein J. Org. Chem.* 2013, **9**, 827-831.
7 M. Munteanu, S. Choi, H. Ritter, *J. Incl. Phenom. Macrocycl. Chem.* 2008, **62**, 197-202.
8 T. Lecourt, A. Herault, A. J. Pearce, M. Sollogoub, P. Sinaÿ, *Chem. Eur. J.* 2004, **10**, 2960-2971; S. Guieu, M. Sollogoub *J. Org. Chem.* 2008, **73**, 2819-2828.
9 S. Guieu, M. Sollogoub *Angew. Chem. Int. Ed.* 2008, **47**, 7060-7063.
10 S. Hanessian, A. Benalil, C. Laferriere, *J. Org. Chem.* 1995, **60**, 4786-4797.
11 Álvaro Antelo Queijo, PhD thesis, Santiago de Compostela, may 5th, 2008
12 V. Simic, L. Bouteiller, M. Jalabert, *J. Am. Chem. Soc.* 2003, **125**, 13148-13154.
13 Y. Cohen, L. Avram, L. Frish, *Angew. Chem. Int. Ed.* 2005, **44**, 520-554.
14 A. Arnaud, L. Bouteiller *Langmuir* **2004**, *20*, 6858-6863.
15 A. W. Coleman, I. Nicolis, N. Keller, J. P. Dalbiez, *J. Incl. Phenom. Macrocycl. Chem.* 1992, **13**, 139-143 ; M. Bonini, S. Rossi, G. Karlsson, M. Almgren, P. Lo Nostro, P. Baglioni, *Langmuir* 2006, **22**, 1478-1484 ; Y. He, P. Fu, X. Shen, H. Gao, *Micron* 2008, **39**, 495-516.
16 T. Yamada, G. Fukuhara, T. Kaneda, *Chem. Lett.* 2003, **32**, 534-535; K. Yamauchi, A. Miyawaki, Y. Takashima, H. Yamaguchi, A. Harada, *Org. Lett.* 2010, **12**, 1284-1286; S. Menuel, N. Azaroual, D. Landy, N. Six, F. Hapiot, E. Monflier, *Chem. Eur. J.* 2011, **17**, 3949-3955; V. Legros, C. Vanhaverbeke, F. Souard, C. Len, J. Désiré, *Eur. J. Org. Chem.* 2013, 2583-2590; J. Potier, S. Menuel, N. Azaroual, E. Monflier, F. Hapiot, *Eur. J. Org. Chem.* 2014, 1547-1556.
17 J. Carrazana, A. Jover, F. Meijide, V. H. Soto, J. V. Tato *J. Phys. Chem. B* 2005**, 109**, 9719-9726.