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# Synthesis and inclusion ability of anthracene appended β-cyclodextrins: unexpected effect of triazole linker

Isabelle Mallard [a,b,*], David Landy [a,b], Nadia Bouchemal [c], Sophie Fourmentin [a,b]

[a] *Univ Lille Nord de France, F-59000 Lille, France*
[b] *ULCO, UCEIV, F-59140 Dunkerque, France*
[c] *Univ Paris XIII, ANBiophy FRE 3207, F-93017 Bobigny, France*

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ABSTRACT

A new fluorescent β-cyclodextrin has been synthesized by coupling an anthracene moiety to the cyclic oligosaccharide via click chemistry. The influence of the triazole spacer was compared to the simple amino and amido linkers. While a sensing ability toward adamantan-1-ol was observed with the latter two spacers, the absence of inclusion capacity prevents the triazole modified cyclodextrin from showing any fluorescence variations. The difference in the binding behaviors studied by Isothermal Titration Calorimetry, UV–vis and fluorescence spectroscopies, was highlighted by the NOESY NMR spectra of the modified cyclodextrins: whereas a free cavity was observed for the amino and amido linkers, an important obstruction was obtained in the case of the triazole.

## 1. Introduction

To evaluate environmental pollution, new efficient systems of detection should be developed. For several years, we have focused on the design and synthesis of novel cyclodextrin sensors for the detection of volatile organic compounds (VOCs).[1–3] Within this scope, cyclodextrins should be modified by a chromophore to be used as a tool for detection.[4–6]

In the past few years, click chemistry has received much attention in the cyclodextrin field, as it allows for the development of new synthetic methods, leading to modified cyclodextrins used in catalysis,[7,8] chiral stationary phases[9], and cation detection.[10] According to the literature, triazole cyclodextrin derivatives have not been exploited for organic compound detection. A question thus arises: could we take advantage of the triazole ring for the detection process? As a consequence, we decided to investigate the effect of the triazole ring associated with a fluorescent anthracene moiety as a chromophoric model. Some anthracene derivatives have high quantum yield[11] and are used for metal detection[12–14] or medical diagnosis.[15] The synthesis of anthracene cyclodextrin derivatives has been reported for controlling stereochemistry of bimolecular interactions and reactions,[16] photophysical studies[17], and the molecular recognition.[18]

This paper describes the synthesis and the inclusion ability of three anthracene cyclodextrin derivatives (Fig. 1). Our target compound, **CD1**, consists of an anthracene moiety connected to β-CD via an imidazole ring spacer. The triazole ring is introduced via a Hugsen [1,3] dipolar cycloaddition, with an attempt to carry out the click chemistry on the anthracene derivative rather than on cyclodextrin. To validate the eventual efficiency of the triazole ring arm, the linker between anthracene moiety and cyclodextrin was varied. Sensor **CD2** was constructed according to the same design as **CD1**, except that the spacer was an amide linkage without the triazole ring. The last sensor, **CD3**, was based on an amine linkage and was prepared by means of a Schiff base reaction.

The inclusion ability of **CD1**, **CD2,** and **CD3** toward adamantan-1-ol as a model for organic compounds was studied by UV–vis and fluorescence spectroscopy and also by Isothermal Titration Calorimetry (ITC). On the basis of these results, we were able to elucidate the effect of the spacer on the binding ability of these fluorescent cyclodextrins.

## 2. Results and discussion

### 2.1. Synthesis of β-CD precursors

Mono 6$^{I}$-amino-6$^{I}$-deoxy-β-cyclodextrin was synthesized according to well known described procedures:[19–21] tosylation of the native β-CD followed by sodium azide substitution gave mono 6$^{I}$-azido-6$^{I}$-deoxy-β-cyclodextrin which was reduced to mono 6$^{I}$-amino-6$^{I}$-deoxy-β-cyclodextrin.

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[*] Corresponding author. Tel.: +33 (0) 328658257; fax: +33 (0) 328237605.
*E-mail address:* isabelle.mallard@univ-littoral.fr (I. Mallard).

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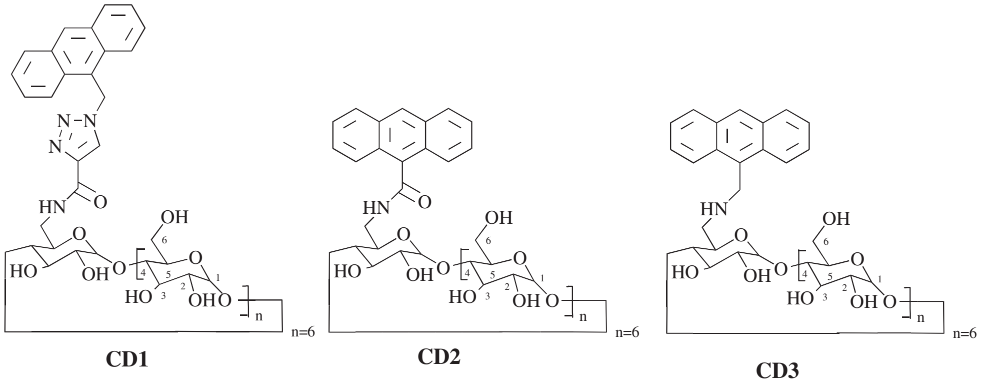


**Figure 1.** Structure of modified CDs.

## 2.2. Synthesis of CD1

The formation of **CD1** was conducted in six steps as shown in Scheme 1. Commercial anthracene **1** was converted to anthracene-9-carbaldehyde **2** via a slightly modified Vilsmeyer reaction.[22] Reduction[11] of **2** with $NaBH_4$ leads to compound **3**. Nucleophilic substitution[23] with thionyl chloride gave **4**. Azidation of **4** was slightly different from the usual treatment.[11] Following HSAB theory, the reaction was performed in the presence of quaternary tetrabutyl ammonium bromide salt,[24] used in catalytic amount to reduce reaction time from 5 h to 1 h. Propynoic acid-4-nitrophenylester was synthesized in 60% yield according to literature precedent,[25] by reacting *para*-nitrophenol and propiolic acid with dicyclohexyl-carbodiimide as activating agents and dimethylaminopyridine.

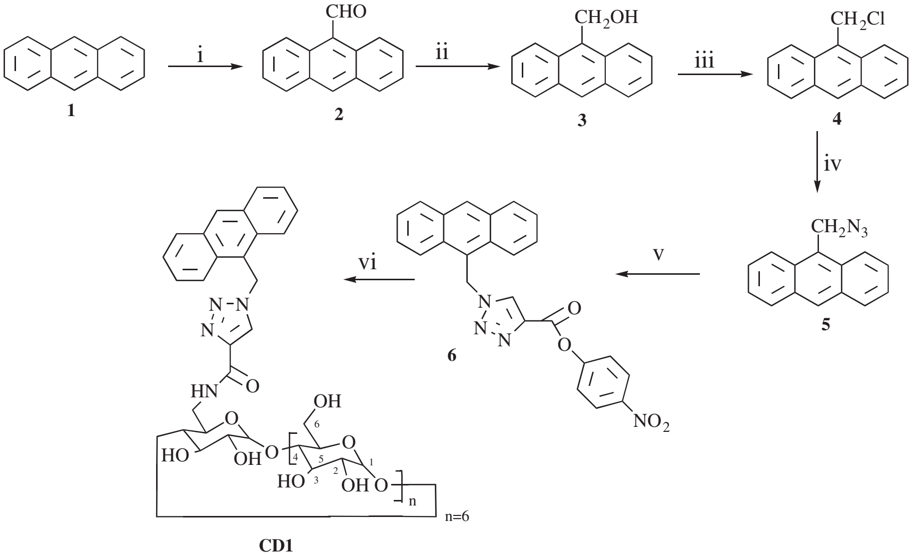
Huigsen 1,3-dipolar cycloaddition using copper iodide as a catalyst was performed between azide **5** and propynoic acid-4-nitrophenylester in a THF–water (1:1) solvent mixture at room temperature for one week to give **6**. Without heating, the cycloaddition proceeded regioselectively, however, a much longer reaction was required.[26] Although the click azide–alkyne cycloaddition reaction was reported with various different solvents[27,28] and copper salt catalysts,[28,29] we decided to use copper iodide and heterogeneous conditions to make the purification process less complicated instead of reduction in situ with copper sulfate and sodium ascorbate. Moreover, because of the size of anthracene, the reaction was applied to anthracene and not on cyclodextrin.[30–33]

The formation of the fluorescent triazole product is easily visible upon irradiation at 365 nm with a hand-held UV lamp. Copper catalyst was removed by washing with EDTA, then compound **6** was purified on silica gel to afford the pure product with a 72% yield. The triazole ring protons produced a singlet at 7.75 ppm. No other singlet was observed, confirming the formation of only one regioisomer. $CDNH_2$ was treated with **7** at 60 °C for two days; **CD1** was formed with a yield of 80%.

## 2.3. Synthesis of CD2

Our attempts to synthesize **CD2** with anthracene-9-carboxylic acid as a precursor and $6^I$-amino-$6^I$-deoxy-β-cyclodextrin using DCC–DMAP provided moderate yield, so we reverted to fluoride acid synthesis. Commercial carboxylic anthracene acid was converted to compound **8** in 80% yield using cyanuric fluoride,[34] pyridine, and dichloromethane. Condensation of **8** with $CDNH_2$ leads to compound **CD2** in a 73% of yield (Scheme 2).

It should be noted that **CD2** was prepared under mild conditions and that the purification methods were less fastidious than those required for carboxylic or chloride acid methods.



**Scheme 1.** (i) $POCl_3$, *N*-methylformanilide, *o*-dichlorobenzene, 363–368 K, 2 h; (ii) $NaBH_4$, ethanol, rt, 4 h; (iii) $SOCl_2$, $CH_2Cl_2$, RT, 2 h; (iv) $NaN_3$, tetrabutylammonium bromide, DMF, 353 K, 1 h; (v) propynoic acid-4-nitrophenylester, $H_2O$–THF, CuI, rt, one week; (vi) $CDNH_2$, 333 K, two days.