



Preliminary communication / Communication

In search for internal complexation in cyclodextrin-fullerene conjugates

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Abstract

Three new 2:1 cyclodextrin-fullerene (CD-F) conjugates have been prepared, two β -CD-F (**1b** and **1c**) and one γ -CD-F (**1d**), of general formula $C_{60}[C(COO-X-COOR)_2]$ (**1b**: X = CH₂, **1c**, X = CH₂CH₂OCH₂; R = NH-PMBCD (**1b,c**) or NH-PMGCD (**1d**), i.e. a β - (**1b,c**) or γ - (**1d**) CD, fully methylated except at one primary position, where OH is substituted by NH); they have been compared with the previously described compound **1a** (X = (CH₂)₁₁, R = NH-PMBCD). The solubility in water at neutral pH of the new molecules is the highest reported to date, greater than 250 mg ml⁻¹. UV and NMR spectra show that aggregates are present in these water solutions. The UV spectra suggest that, at the same concentration of conjugate in water, the percentage of aggregates decreases in the order **1a** > **1b** ~ **1d** > **1c**. No evidence of internal complexation of the fullerene moiety by the CD was detected. **To cite this article:** S. Filippone, A. Rassat, C. R. Chimie 6 (2003) 83–86.

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Résumé

On a préparé trois nouveaux conjugués 2:1 de cyclodextrine (CD) et de fullerène, deux dérivés de β -CD (**1b** et **1c**) et un de γ -CD (**1d**), de formule générale $C_{60}[C(COO-X-COOR)_2]$ (X = CH₂ (**1b**), X = CH₂CH₂OCH₂ (**1c**, **d**), R = NH-PMBCD (**1b,c**) ou NH-PMGCD (**1d**), c'est-à-dire une β - (**1b,c**) ou γ - (**1d**) CD, complètement méthylée, sauf à une position primaire, sur laquelle OH est substitué par NH) et on les a comparés avec le conjugué **1a** (X = (CH₂)₁₁, R = NH-PMBCD) déjà décrit. La solubilité dans l'eau à pH neutre des nouveaux conjugués (supérieure à 250 mg ml⁻¹) est la plus grande connue actuellement pour des dérivés de fullerènes. Les spectres UV et RMN montrent que des agrégats sont présents dans ces solutions aqueuses. Les spectres UV suggèrent que, pour une même concentration en conjugué, le pourcentage d'agrégats décroît dans l'ordre **1a** > **1b** ~ **1d** > **1c**. Nous n'avons pas trouvé d'indice de complexation interne du fullerène par les cyclodextrines. **Pour citer cet article :** S. Filippone, A. Rassat, C. R. Chimie 6 (2003) 83–86.

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Keywords: permethylcyclodextrin; methanofullerene; aggregates; solubility in water; complexation

Mots clés : perméthylcyclodextrine ; léthanofullerène ; agrégats ; solubilité dans l'eau ; complexation

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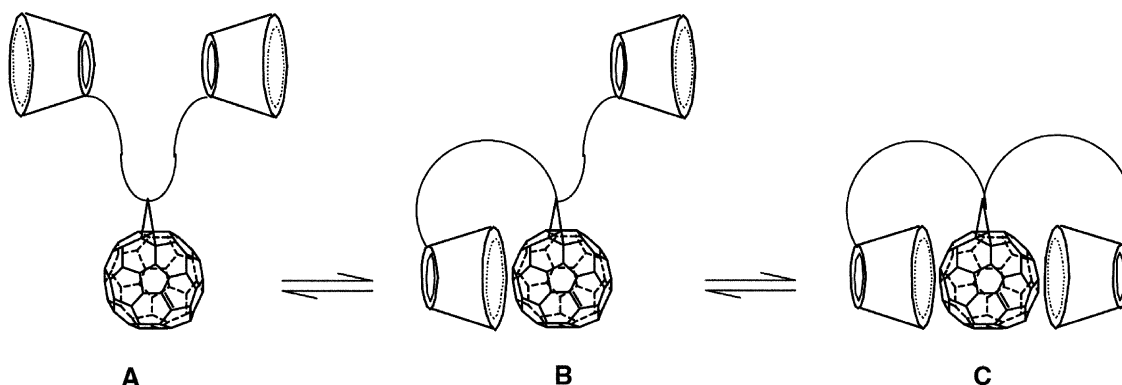


Fig. 1. Possible equilibria between conformers **A**, **B** and **C** of **1a**.

Recently, we described the synthesis of a 2:1 cyclodextrin–fullerene conjugate **1a** [1], designed to be highly soluble in water for biological and biophysical applications [2]. It was hoped that solvent-dependent equilibria between conformers such as **A**, **B** and **C** (Fig. 1) could occur.

In water, **A** and **B** could form micelle-like aggregates, while if the cyclodextrins (CD) insure a sufficient hydrophilic protection, **C** could exist as a non-associated species. It was found on the basis of UV and NMR spectra that aggregates were present in water solution, and this has since been confirmed by photophysical measurements [3]. In order to study the influence of the linker on solubility and/or aggregation, we have prepared the other conjugates **1b** and **1c** (Fig. 2).

In **1a**, a rather long and hydrophobic linker (**2a**) connected the methanofullerene moiety to the two β -CD derivatives. Two different linkers, **2b** and **2c**, have now been used: **2b** is less hydrophobic than **2a** and too small to be compatible with internal complexation (conformation **C**), while **2c**, longer and more hydrophilic, could allow both internal complexation

and a better solubility in water. These two conjugates were prepared (Fig. 3) from **4a** and **4b**, obtained by standard methods (starting from 2-benzyloxy(ethanol) [4] for **4b**). Satisfactory MS, ^1H and ^{13}C NMR have been obtained for these new compounds.

1b and **1c** are very soluble in dichloromethane and in chloroform and have a very high solubility in water at 20 °C, greater than 250 mg ml $^{-1}$ for **1b** and 300 mg ml $^{-1}$ for **1c**. Clear solutions were obtained after dissolving **1b** (25 mg) in water (100 μl), and **1c** (90 mg) in water (300 μl). Contrary to the negative solubility coefficient previously found for **1a**, no precipitation occurred when the temperature of these water solutions was raised.

As for **1a**, aggregates are present in water solutions: the NMR spectra of **1b** and **1c** are much broader in water than in chloroform. The UV spectra of dichloromethane solutions of **1a** and **1b** are not distinguishable from those of **1c**. In water solution, these three compounds have slightly different UV spectra (Fig. 4): while **1a** presents a shoulder at 330 nm, a relative maximum is found for **1c**, **1b** being intermediate be-

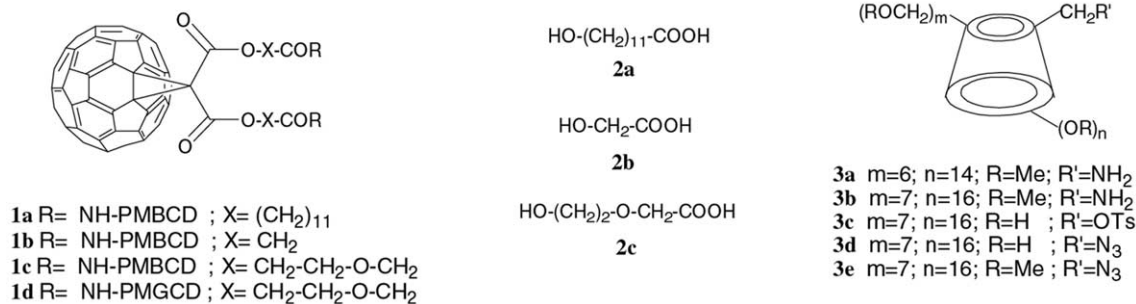


Fig. 2. Compounds **1a–d**, **2a–c**, **3a–e**.

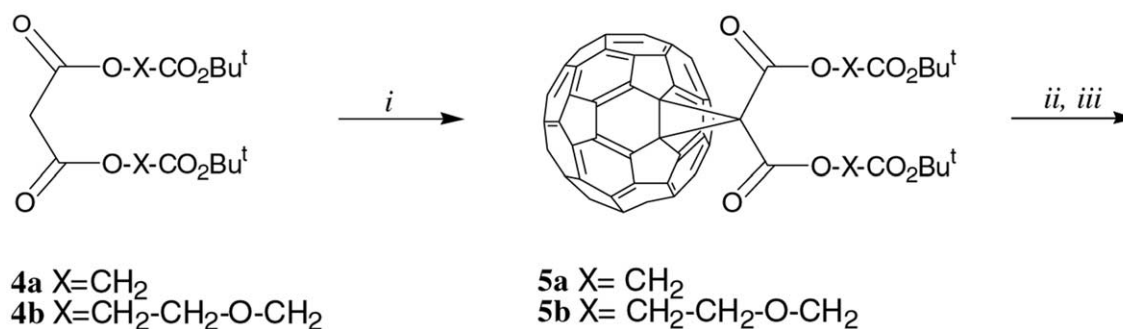


Fig. 3. Reagents and conditions. (i) C₆₀, I₂, DBU, toluene (**5a**: 43%; **5b**: 27%); (ii) TFA, CH₂Cl₂; (iii) **3a** (or **3b** for **1d**), 1-hydroxybenzotriazole (HOBt), DCC, CH₂Cl₂, rt, 48 h (**1b**: 79%; **1c**: 94%; **1d**: 59%).

tween **1a** and **1c**; none of these spectra display the absorption peak at 430 nm observed in dichloromethane solutions. As found for **1a**, these NMR [5] and UV [6,7] spectra show the presence of aggregates in water solutions. The UV spectra suggest that at the same total concentration, the proportion of aggregates decreases in the order **1a** > **1b** > **1c**, which is confirmed by photophysical measurements [3].

As again for **1a**, water solutions (concentrations 10⁻⁴–10⁻⁵M) of these conjugates did not show any circular dichroism in the absorption band of C₆₀, between 200 and 700 nm, although induced circular dichroism has been observed for a γ -CD/C₆₀ complex [8].

There is thus no evidence of internal complexation in these three conjugates. Since it is possible that the

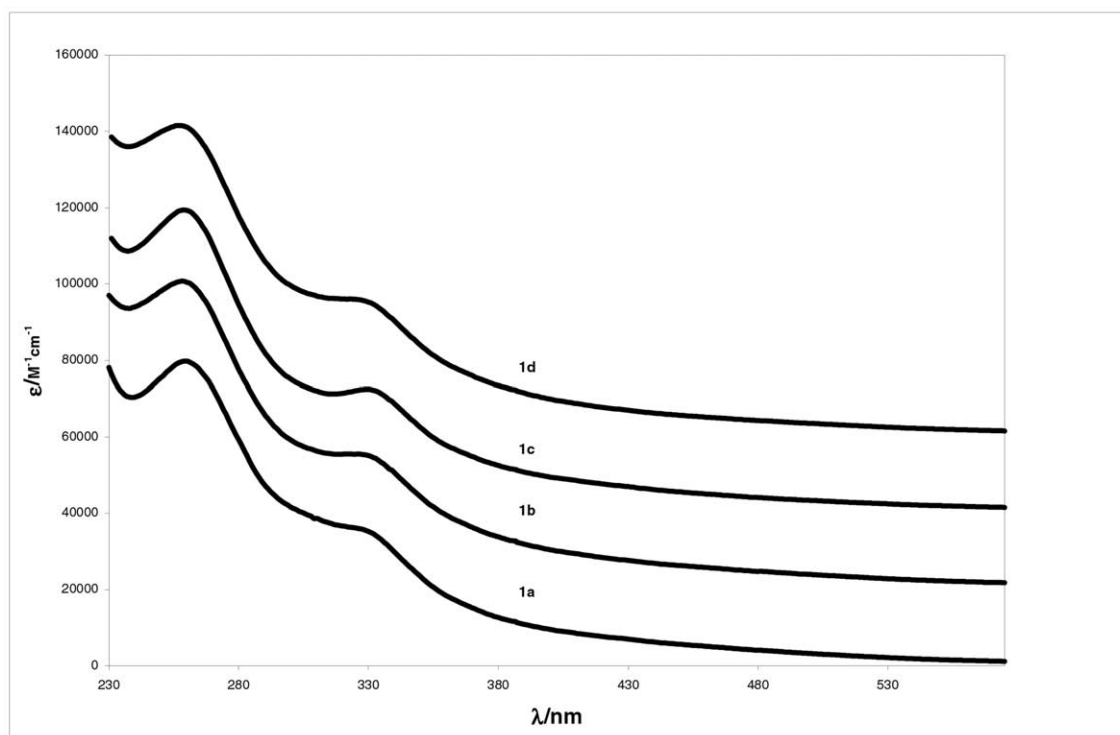


Fig. 4. Absorption spectra of water solutions of the CD-fullerene conjugates. The spectra of **1a**, **1b**, **1c** and **1d** have been shifted upwards by increments of $2 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$, in that order.

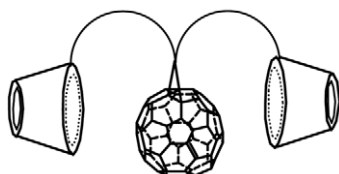


Fig. 5. Modified molecules under study: various different linkers are attached to a secondary hydroxyl groups and the β - and γ -CDs are methylated or not.

affinity of β -CD for the fullerene moiety is not sufficient to induce this type of complexation, a γ -CD conjugate **1d** was also prepared. NH_2 -PMGCD **3b** was obtained in total 6% yield from γ -CD, through the sequence of reactions (γ -CD \rightarrow **3c** \rightarrow **3d** [9] \rightarrow **3e** \rightarrow **3b**) similar to the one previously used for the preparation of NH_2 -PMBCD **3a**; **3b** was converted to **1d** as shown in Fig. 3. In the two last steps, we used conditions previously applied to the transformation of the corresponding β -CD derivatives [10] (see also [1]). Here again, a very soluble molecule was obtained, with solubility in water at 20 °C greater than 300 mg ml⁻¹ to a clear solution was obtained after dissolving **1d** (8 mg) in water (25 μ l). As before, the UV and NMR spectra in water indicated the presence of aggregates, but the peak at 330 nm present in **1c** was now replaced by a shoulder, as in **1b**, a possible indication of a similar degree of aggregation. Again, no induced circular dichroism was observed in water solutions of **1d**.

The CD-fullerene conjugates described in this communication are very soluble. They have the greatest solubility in neutral water ever reported for fullerene

derivatives [1,2,11,12]. The UV spectra show that aggregates are present in these solutions, the linewidths suggesting a degree of aggregation decreasing in the order **1a** > **1b** ~ **1d** > **1c**. Because the formation of aggregates could be due to the position of the linker and/or to the use of fully methylated cyclodextrins, modified conjugates of general formula **Z** (Fig. 5) are being studied.

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