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The water-soluble β-cyclodextrin–[60]fullerene complex

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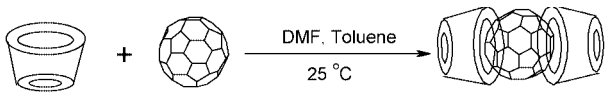
A stable inclusion complex of β-cyclodextrin with [60]fullerene is reported for the first time, synthesized by using a novel synthetic procedure; radical scavenging studies of the water-soluble complex indicate that it has potential for a number of medical applications.

The supramolecular chemistry of cyclodextrins (CD) in aqueous solution is a topic of commercial interest with a variety of biomedical applications.[1] Nonpolar drug molecules have been solubilized in water by making their inclusion complexes with cyclodextrins. Among the cyclodextrins, the β-cyclodextrin is the cheapest commercially available, being about four times cheaper than γ-cyclodextrin. [60]Fullerene is a nonpolar molecule and much of the research on the inclusion complexes of cyclodextrins and [60]fullerene has centered on γ-cyclodextrins,[2a–c] as recent research has shown the biological activity of water-soluble [60]fullerene derivatives such as its DNA-cleaving ability and anti-HIV activity.[3] There are only a few reports on inclusion complexation of [60]fullerene.[2] The procedures described are based on heterogeneous reaction media and all have reported that only γ-cyclodextrin forms an inclusion complex (2:1) and β-cyclodextrin or α-cyclodextrin do not form complexes. The reason given is the comparable size of the [60]fullerene and the cavity diameter of the γ-cyclodextrin molecule and that the C_{60} molecule does not intrude deeply into the γ-cyclodextrin cavity. In fact, these reports describe the experimental failure to prepare the inclusion complex of β-cyclodextrin with [60]fullerene.[2b,c]

There are only a few reports on the inclusion complexation of [60]fullerene by CD derivatives.[2d,e] However, when studying the data in detail and conducting molecular modeling studies, it becomes evident that the dimensions of the cyclodextrins do principally not rule out the formation of an inclusion complex between β-cyclodextrin and [60]fullerene. The larger cavity diameter of β-cyclodextrin is 780 pm and the outer rim diameter is 1530 pm on the polar side of the molecule as compared to 950 pm and 1690 pm, respectively, for the γ-cyclodextrin. Thus the cavity diameters are much smaller than the van der Waals diameter of [60]fullerene (~1000 pm). On the other hand, based on crystallographic studies it has been reported that the β-cyclodextrin cavity is suitable for spherically shaped guests such as adamantane derivatives[4] or naphthalene,[5] and the space enclosed by the head-to-head dimer is ~2.5 times wider than the cavity of the single molecule.[6] Consequently, the reason for the unsuccessful attempts to form inclusion complexes of β-cyclodextrin and [60]fullerene is not only the size but seems to also depend on the reaction conditions. Due to the lower cost of β-CD and its widespread applications, there are also considerably more data available on toxicity and other pharmacological studies. Here we report a novel method for a water-soluble, stable β-cyclodextrin–[60]fullerene inclusion complex.

The synthesis of the CD–C_{60} inclusion complex (Scheme 1) was achieved in a mixed organic solvent system containing DMF and toluene (typically 50–90% DMF, v:v), where both the β-cyclodextrin and [60]fullerene formed a homogeneous reaction medium. The inclusion of the fullerene into the CD cavity was monitored over a period of two weeks by UV-Vis spectroscopy (Fig. 1). The CD–C_{60} complex was isolated by removing the organic solvents, and subsequent addition of distilled water, to yield a light yellow aqueous solution. The complex was purified in aqueous solution by membrane filtration using a polymer membrane with a molar mass cut-off of 2 kg mol^{-1} (Yield: 60%, solubility in water: 4 g L^{-1}).[7] The FTIR spectra of the inclusion complex showed the typical band at 527 cm^{-1} assigned to [60]fullerene. The UV-Vis spectrum showed the absorption at 342 nm and the peak broadening beyond 350 nm. Further corroboration for the formation of the inclusion complex was obtained by ^1H and ^{13}C NMR spectroscopy. The complex showed a slight shift in the resonances of the C^3 carbon of the CD unit, but no shift in the resonance of the C^5, indicating that the fullerene does not intrude into the cavity completely. This is supported by the energy minimization calculations (Fig. 2). These studies also showed that the visible and accessible fullerene surface in the complex is increased by a factor of ~8 compared to the γ-cyclodextrin complex, which is very important with respect to biological applications. Under these conditions, in contrast, the α-cyclodextrin did not form an inclusion complex.



Scheme 1 Synthesis of the β-cyclodextrin–[60]fullerene inclusion complex.

Generally, β-cyclodextrin can form a 2:1, 1:1, or 1:2 complex with a guest and the theoretical calculated mass content of β-cyclodextrin in the complex for these three types would be 75.9, 61.2, and 44.1%, respectively. Thermogravimetric analysis of the complex formed showed that the total mass loss of the cyclodextrin at 325 °C was 72.5%. This result clearly indicates that this inclusion complex is of the 2:1 type.

It is known that the two main driving forces for inclusion complexation are the repulsive forces between the included water molecules and the apolar cyclodextrin cavity on the one

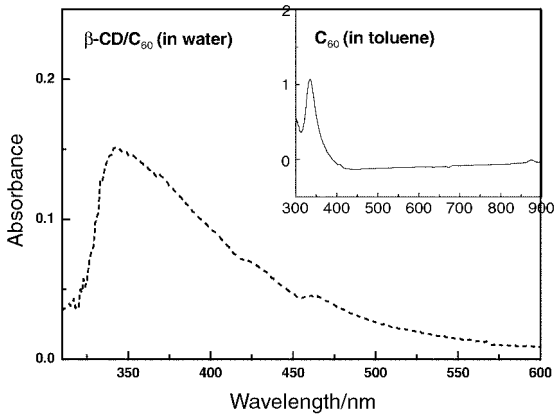


Fig. 1 UV-Vis spectra of C_{60} (in toluene) and the β-cyclodextrin–C_{60} inclusion complex (in water).

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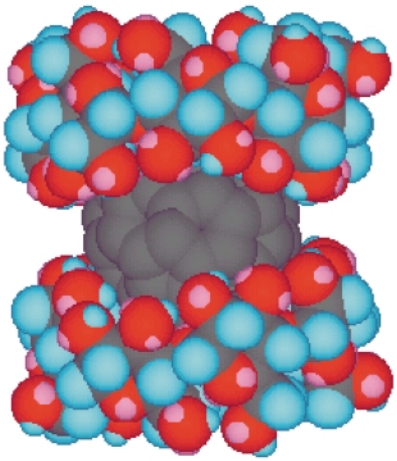

Fig. 2 Energy-minimized molecular model of the β-cyclodextrin–C_{60} inclusion complex (2:1).

hand, and between the apolar [60]fullerene and the bulk water on the other. However, the second factor is not relevant in the dry state and thus the product isolated from the solution could be just a fine dispersion of β-cyclodextrin and [60]fullerene. The X-ray diffraction pattern of the freeze-dried inclusion complex (Fig. 3), however, shows that the product isolated has neither the typical 2θ values of CD nor those of [60]fullerene. It can be seen that the complex has a different structure to the parent β-cyclodextrin (2θ = 9, 12.5, 19.6, 23.0, 27.0, 34.8°) and C_{60}[8] (2θ = 11.0, 17.5, 21.7°), with the total suppression of the crystalline

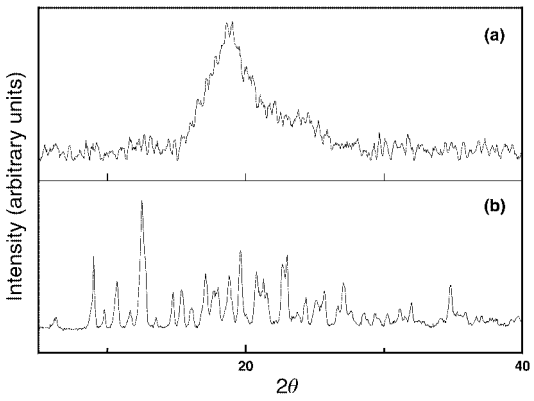

Fig. 3 X-ray diffractograms of (a) the inclusion complex of C_{60} with β-cyclodextrin and (b) the pristine β-cyclodextrin.

structure of β-CD. This is in accord with similar observations for the γ-CD complex.[2b]

Water-soluble fullerene compounds have potential biomedical applications and previous attempts involved its functionalization[9] with a significant modification of the fullerene molecule, which could lead to toxicity problems. The approach adopted here overcomes such problems, as at present only the parent β-CD has been cleared for human consumption. Radical scavenging studies were carried out using a screening test with the stable free radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH), developed in our laboratory.[10] There was a visual bleaching of the purple color of the DPPH solution with time, which was monitored by UV-Vis spectroscopy showing a gradual shift and decrease in the absorbance of the 517 nm peak of the DPPH solution. This shows that the [60]fullerene in the complex with β-cyclodextrin retains its radical scavenging activity in the aqueous solution.

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