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Short communication

Preparation and biological activity of novel cucurbit[8]uril–fullerene complex

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Abstract

The synthesis of a novel cucurbit[8]uril(CB_8)–fullerene[60] supramolecular complex using a simple and efficient pathway is reported for the first time. In the complex, which was found to be of the 1:2 type, the compounds interact weekly with each other. The complex was characterized by UV/Vis, FTIR, elemental analysis, X-ray diffraction (XRD), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). TEM analysis shows that the average particle diameter is about 19 nm. The *in vitro* antitumour activity of the complex has been tested and the result shows that the complex exhibits better antitumour activity against HeLa cells. The antitumour mechanism of the complex was investigated for the first time.

Keywords: Fullerene complex; C60; Cucurbit[8]uril; Solvent free; Antitumour activity

1. Introduction

Cucurbituril is a macrocyclic cavitand that is made of *n* glycoluril molecules and *n* formaldehyde units [1]. As cucurbituril has a rigid structure offering a hollow core, cucurbituril is attractive as synthetic receptor and useful building blocks of various supramolecular structures [2,3]. The cucurbituril family recently gained new members – CB_7, CB_8, and CB_{10}. Their broad utility in molecular recognition and self-assembly studies plays a central role in supramolecular chemistry and nanotechnology [4].

The family of cucurbituril hosts has been expanded [5,6]. Although cucurbituril (CB_6) is a molecular receptor with well established host properties [7–12], the larger-cavity homologues, cucurbituril (CB_7) and cucurbituril, (CB_8) have been recently isolated and have quickly attracted considerable attention as hosts for inclusion complexation [13–21]. Cucurbiturils have now been elicited for comparisons with cyclodextrins (CD) [22]. The cavity sizes of CB_6, CB_7, and CB_8 are similar to those of α-CD, β-CD, and γ-CD, respectively [13].

Fullerene (C_{60}), which has a spherical π-electron system, indicates interesting magnetic [23,24], superconductivity [25,26], electrical [27], and biochemical properties [28–30]. Not surprisingly, fullerenes and their derivatives have attracted a lot of attention in the recent years and have been successfully applied to materials science and biological technology. However, the application of fullerenes and their derivatives has now been limited because of their low solubility in water and frequently used solvents.

Since fullerenes show a poor solubility in common solvents (they are only soluble in a few solvents), many efforts have been made to modify these molecules in complex pathways [31]. One access to modified fullerenes through covalent and noncovalent binding describes a mechanochemical technique [31,32]. Also studies for the C_{60}-CD complex by mechanochemical synthesis have been reported [32]. Geckeler investigated the assembly behavior of the CB_7–fullerene complex [33,34]. Herein, we report the synthesis of the first supramolecular complex **3**

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between cucurbituril (CB_8) and fullerene through noncovalent binding.

2. Materials and methods

The glycoiuril **1** and cucurbituril(CB_8) **2** were synthesized according to the reported procedures [35]. Since another goal was to find a synthetic pathway, which should be as efficient as possible, we performed the synthesis as solid–liquid reaction between the solid guest molecule C_{60} and an alkaline aqueous solution of CB_8 as well as under high-speed vibration (HSVM) conditions of the solid compounds (Scheme 1) [36]. The stoichiometry of the complex was found to be 1:2 according to thermogravimetric analysis. The reaction conditions and yields are shown in Table 1. Furthermore, the assembly behavior of the CB_8–fullerene complex has been investigated by TEM and SEM. These special CB_8–fullerene complexes can not only form some classical micelles such as sphere and vesicle like those formed from CD–fullerene complex, but also organize into a novel "petal-like" morphology.

Typical procedure is as follows. (a) solid–liquid reaction: CB_8 (37 mg; 28 μmol) was dissolved in water (36 mL) by adding 1 M NaOH until a pH 12 was reached. After filtering, solid C_{60} (10 mg; 14 μmol) was added and the mixture was stirred at rt. Within 24 h of stirring, a brown solid started to precipitate indicating the formation of a complex. After six more days of stirring excess of C_{60} was removed by adding toluene, freezing the aqueous phase and decanting the organic phase. The aqueous phase was allowed to reach room temperature. Water was evaporated under reduced pressure. The solid was washed out by adding a few drops of water up to neutral pH. Finally the residual water was evaporated and the dark-brown product was dried in vacuo (10.8 mg; 56% yield). (b) solid–solid reaction: The mixture of solid C_{60} and solid CB_8 in different molar ratios was grinded on a mixer mill. The brown solid was flushed out by warm water followed by adding 1 or 2 M NaOH up to pH 12 and toluene to dissolve the excess of both CB_8 and C_{60}. The aqueous phase was frozen and the upper organic phase decanted. The aqueous phase was allowed to reach room temperature. Water was evaporated under reduced pressure. The solid was washed out by adding a few drops of water up to neutral pH. Finally the residual water was evaporated and the dark-brown product was dried it in vacuo.

Table 1
Synthesis of the CB_8–C_{60} complex performed as heterogeneous as well as solid state reaction

Entry	Preparation method	pH	Molar ratio CB_8/C_{60}	Temperature (°C)	Time (h)	Yield (%)
1	Heterogeneous	12	2/1	20	168	56
2	Solid state	Neutral	2/1	>30[a]	5	56
3	Solid state	Neutral	1/1	>30[a]	5	79
4	Solid state	Neutral	1/2	>30[a]	5	30

[a] Measurements of the temperature were performed inside the cups after 2 h of grinding.

3. Results and discussion

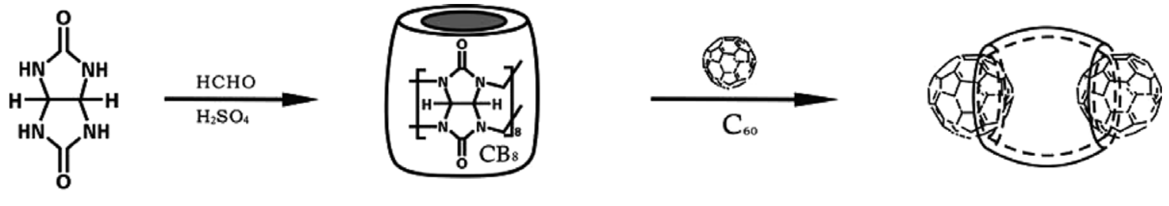
It can be seen from Table 1 that the rate increased significantly by synthesizing **3** under HSVM conditions compared to the solid–liquid synthesis (Table 1, entries 2–4 vs 1). After 5 h of milling the yields were similar to those which could be obtained after 7 days when the complexation was performed as solid–liquid reaction. Yields close to 80% could be achieved. Furthermore, contact with harmful solvents and waste was reduced to a minimum.

In all cases (entries 1–4) and independent of the molar ratio of CB_8 to C_{60} (entries 1–4), a dark-brown solid was formed. The complex was characterized by UV/Vis, FTIR, elemental analysis, X-ray diffraction (XRD), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), and transmission electron microscopy (TEM).

Theoretically, CB_8 can form a 1:1 exclusion complex, a 2:1 exclusion complex, and a 1:2 exclusion complex with a fullerene guest, as illustrated in Fig. 1.

The X-ray diffraction pattern (Fig. 2) shows that the product exhibits neither the typical 2θ values of CB_8 nor those of C_{60} at $2\theta = 11.2°$, 17.6°, and 21.6° [37]. In accordance with previous observations for C_{60} inclusion complexes, an exclusion complexation of the crystalline structure of the CB_8–fullerene takes place [38,39].

The absorption at 342 nm and the peak broadening beyond 351 nm in the UV/Vis spectrum of CB_8–fullerene complex were assigned to C_{60}. The FTIR spectra of CB_8–fullerene complex (Fig. 3) showed the typical band for C_{60} at 527 cm^{-1} in addition to the bands for CB_8. While the characteristic carbonyl band of CB_8 at 1729 cm^{-1} was slightly shifted to 1733 cm^{-1} due to complexation, the typical C_{60} band remained constant. The slight shift of the carbonyl band of CB_8 showed weak interactions, probably



1 **2** **3**

Scheme 1. Synthesis of **3**.