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Title

Preparation of 6-azafulleroid-6-deoxy-2,3-di-O-myristoylcellulose

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Abstract

6-Azafulleroid-6-deoxy-2,3-di-O-myristoylcellulose (3) was synthesized from 6-azido-6-deoxycellulose (1) by two reaction steps. The myristoylation of compound 1 with myristoyl chloride / pyridine proceeded smoothly to give 6-azido-6-deoxy-2,3-di-O-myristoylcellulose (2) in 97.0% yield. The reaction of compound 2 with fullerene (C_{60}) was carried out by microwave heating to afford compound 3 in high yield. It was found from FT-IR, ^{13}C-NMR, UV-vis, differential pulse voltammetry (DPV), SEC analyses that compound 3 was the expected C_{60}^-containing polymer. Consequently, maximum degree of substitution of C_{60} (DSC_{60}) of compound 3 was 0.33.

Keywords

Azafulleroid, Cellulose, Fullerene, Microwave heating
Cellulose is the most abundant biomacromolecule in nature, and is important as biodegradable and renewable organic material. Recently, new applications of cellulose derivatives as advanced materials such as shape memory-recovery material, and photoactive materials, have been reported. One of the proposals of cellulose derivatives for the advanced materials is the photocurrent generation system using porphyrin-containing cellulose derivatives as electron donor materials. Sakakibara and Nakatsubo reported the Langmuir-Blodgett film of porphyrin-fullerene ($C_{60}$) system using the porphyrin-containing cellulose derivative and $C_{60}$ with high photocurrent generation performance. Then, $C_{60}$-containing cellulose derivative is also attractive for the photocurrent generation system as an electron acceptor material, because it is expected to be useful for forming an electron transporting pathway in the system. However, there is no report for the preparation of $C_{60}$-containing cellulose derivative. Addition reaction of organic azides with $C_{60}$ has been widely applied to the preparation of $C_{60}$-bearing polymers. Then, this paper describes the preparation of 6-azafulleroid-6-deoxy-2,3-di-$O$-myristoylcellulose (3) from 6-azido-6-deoxycellulose (1). In the target compound 3, myristoyl group was selected as $O$-2 and $O$-3 substituent groups to enhance solubility for common organic solvents and formability of Langmuir-Blodgett film, because it was found to be preferable to the purposes in a preliminary experiment.

The synthetic route for 6-azafulleroid-6-deoxy-2,3-di-$O$-myristoylcellulose (3) from 6-azido-6-deoxycellulose (1) by two reaction steps is shown in Scheme 1. Myristoylation of 6-azido-6-deoxycellulose (1) with myristoyl chloride in the presence of pyridine in LiCl /DMAc afforded 6-azido-6-deoxy-2,3-di-$O$-myristoylcellulose (2) in 97.0 % yield.

Scheme 1 Synthetic route for 6-azafulleroid-6-deoxy-2,3-di-$O$-myristoyl cellulose (3)

![Scheme 1](image)

<table>
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<th>Reaction</th>
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<td>a</td>
<td>$C_{13}H_{27}COCl$ /Pyridine /LiCl-DMAc /70°C/ 24h</td>
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<tr>
<td>b</td>
<td>$C_{60}$ /ODCB /100-140°C (by microwave) /2-3h</td>
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</table>

Addition reaction of $C_{60}$ to compound 2 was carried out according to the modified method of Okamura et al. to give 6-azafulleroid-6-deoxy-2,3-di-$O$-myristoyl cellulose (3). That is, compound 2 and $C_{60}$ were reacted at...
140 °C for 3 h in o-dichlorobenzene (ODCB) to give product 3-i. Microwave (MW) heating was used for the reaction because it was reported that MW heating has an advantage of shortening reaction times compared with conventional heating (an oil bath method) in the preparation of cellulose derivatives \(^{14}\) and in the addition reaction of C\(_{60}\) to azido-compounds.\(^{12,15,16}\)

Product 3-i, which was easily soluble in organic solvents such as CHCl\(_3\), CH\(_2\)Cl\(_2\), THF, toluene, chlorobenzene and ODCB, was subjected to FT-IR, \(^{13}\)C-NMR, UV-vis, differential pulse voltammetry (DPV) and SEC measurement for its characterization. In FT-IR spectrum of product 3-i, the band at 2104 cm\(^{-1}\) from azido groups was completely disappeared, suggesting that heating time for 3 h by microwave heating was enough for the addition reaction. The small characteristic band at 527 cm\(^{-1}\) derived from C\(_{60}\) \(^{8,10}\) was newly appeared. \(^{13}\)C-NMR spectrum of product 3-i, the broad peak in the range of 130 to 150 ppm assigned to C\(_{60}\) moiety \(^{9,11}\) and the sharp peaks in the range of from 17 to 35 ppm derived from myristoyl groups were observed. Fig.1 shows UV-vis spectrum of product 3-i and C\(_{60}\). The characteristic peaks at 330 nm from C\(_{60}\) \(^{7,10}\) were found in the spectrum of product 3-i, although compound 2 has no absorption at the region. Electrochemical analysis such as cyclic voltammetry (CV) and differential pulse voltammetry (DPV) is one of the methods for characterization of substituted C\(_{60}\). It is reported that the reduction potential peaks, which are observed in CV or DPV of unsubstituted C\(_{60}\), are negatively shifted in CV or DPV of substituted C\(_{60}\) such as azafulleroid. \(^{10,17,18}\) Figure 2 shows the DPV curves of product 3-i and C\(_{60}\) in 0.1 M tetrabutylammonium perchlorate (TBAP) / ODCB. The negative shifts of three characteristic reduction peaks of C\(_{60}\) were observed in DPV of product 3-i. SEC is also important method for characterization of C\(_{60}\)-containing polymer. For example, Okamura et al. reported that C\(_{60}\)-pullulan derivatives were characterized by SEC with RI and UV (detective wavelength: 700 nm) detections.\(^{9}\)

Figure 3 shows SEC elution curves of product 3-i by RI and UV detectors. UV detection was performed by UV-600 nm, because of the detection ability of our UV-detector. The RI and UV elution curves showed nearly identical elution profiles. All data suggested that product 3-i was the desired C\(_{60}\)-containing cellulose derivative.

Figure 4 shows thermal gravimetric analysis (TGA) curve of product 3-i. The thermolysis of product 3-i started at 205°C, suggesting that product 3-i had an aza-bridged structure, but not triazol-bridged structure, because Ungurenasu and Pinteala reported that the thermolyses of aza-bridged type C\(_{60}\)-curdlan derivatives started at 205°C.\(^{11}\) There are two possibilities concerning aza-bridged types between nitrogen at C-6 position of the cellulose derivative and C\(_{60}\), that is, [6,6]-close type and [5,6]-open type, \(^{15,16,18,22}\) although it is reported that alkyl azides predominantly added at the [5,6]-open junction.\(^{19,22}\) The absence of the peak at 425 nm, which is a characteristic peak of [6,6]-close aza substructure,\(^{15,16,20}\) indirectly suggested that product 3-i had a [5,6]-open
type structure. This is also supported by $^{13}$C-NMR data. It is reported that the absence of the peak around 84 ppm accounted for a [5,6]-open type structure in $^{13}$C-NMR spectrum of C$_{60}$-curdlan derivative. Indeed, no peaks were observed in the range of 80 to 90 ppm in $^{13}$C-NMR spectrum of product 3-i.

The TGA method is widely used for determination of the weight percent of C$_{60}$ in C$_{60}$-bearing polymer. The degree of substitution of C$_{60}$ (DS$_{C_{60}}$) of product 3-i was calculated from TGA method, that is, it was determined using the weight change values of compounds 2 and 3-i at 600 ºC, and was found to be 0.25. The low DS$_{C_{60}}$ suggested that multi-addition of azido groups of compound 2 with C$_{60}$ might proceed, although further investigation is required. The degree of polymerization (DPn) of product 3-i was determined from SEC, and was found to be 14.5. The DPn of product 3-i was significantly lower than that of compound 2 (DPn =78.3), suggesting that depolymerization occurred under the reaction conditions for product 3-i.

Then, addition reaction of C$_{60}$ with compound 2 was carried out under various conditions with different concentration, amount of C$_{60}$, reaction time, temperature and so on to investigate the influence of the reaction conditions to DS$_{C_{60}}$ and DPn of the products and to get compound 3 with higher DS$_{C_{60}}$. The results are shown in Table 1. The reaction conditions for product 3-i (Entry 1) are regarded as criteria for the various reaction conditions.

The DS$_{C_{60}}$ of the products increased with increasing of the concentration of compound 2 (Entries 1-4) and with increasing of the amount of C$_{60}$ (Entries 1, 5-9), but leveled off when the concentration was 25 mM and when the amount of C$_{60}$ was 2 eq, respectively. The DPn of the products was not affected by the concentration of compound 2, but it slightly decreased with increasing of the amount of C$_{60}$. The DS$_{C_{60}}$ of the products did not increase but the DPn decreased with an increase of reaction time (Entries 1, 10-11). It was found that the band at 2104 cm$^{-1}$ from azido groups was completely disappeared after 1.5 h by the monitoring experiment of the reaction (Entry 1) (data not shown). The DS$_{C_{60}}$ of the products increased and leveled off, but the DPn decreased with an increase of reaction temperature (Entries 1, 12-13). Control experiments without addition of C$_{60}$, that is, microwave heating treatment of compound 2 with different temperature, were performed (Entries C1-C4). DPn of the products clearly decreased with an increase of reaction temperature, especially at 180 ºC, which is corresponded to the boiling point of the solvent (ODCB), serious degradation of compound 2 was confirmed by FT-IR analysis. It was found that high reaction temperature was responsible for decreasing of DPn of the products, although it was favorable to high DS$_{C_{60}}$. Product 3-xii, prepared at 100 ºC for 3 h, was insoluble in the solvents for product 3-i such as CHCl$_3$, CH$_2$Cl$_2$, THF, toluene, ODCB, product 3-xiii, prepared at 130 ºC for 3 h, became to be partially insoluble in the solvents two weeks later, while product 3-i, prepared at 140 ºC for 3 h, was easily soluble.
in the solvents two months later. These results suggest that higher DPn of the products 3 were undesirable to the solubility of the products 3. The DS\(_{C_60}\) of the product 3-xiv, which was prepared at 140°C for 48 h by oil-bath heating, was higher than that of product 3-i, but the DPn of product 3-xiv was almost same as that of product 3-i (Entries 1, 14). MW heating had an advantage of only a shortening of reaction time as expected. Considering the results described above, the addition reaction was carried out under the optimal reaction conditions for higher DS\(_{C_60}\) to afford product 3-xv with maximun DS\(_{C_60}\) of 0.33 and with DPn of 17.9 in 68.5% yield (Entry 15). It was thought that C\(_{60}\) was too bulky to be introduced to the cellulose derivative with DS\(_{C_60}\) of more than 0.33 by its steric hindrance.

1. Experimental

1.1. General

6-Azido-6-deoxycellulose (1) with DS\(_{N3}\) 0.88 was prepared according to the method of Matsui et al.\(^{13}\) Fullerene-C\(_{60}\) (98%) was purchased from Sigma-Aldrich (Tokyo, Japan) and all other chemicals were purchased from commercial sources and used without further purification.

FT-IR spectra were recorded in KBr pellets with a Shimadzu FTIR-8600 spectrophotometer. \(^{1}H\)- and \(^{13}\)C NMR spectra were recorded with a Varian INOVA300 FT-NMR (300 MHz) spectrometer with TMS as an internal standard in CDCl\(_3\). Chemical shifts (\(\delta\)) are given in \(\delta\) values (parts per million). The UV-vis spectra were recorded on a Jasco V-560 UV-vis spectrophotometer in CH\(_2\)Cl\(_2\). Differential pulse voltammetry (DPV) measurements were performed in a MCA micro cell (BSA, Japan) at room temperature at scan rate of 100 mVs\(^{-1}\) using a platinum electrode (1.6 mm diameter) as working electrode, Ag / AgCl (saturated KCl) as reference electrode, platinum wire as counter electrode by an ALS electrochemical analyzer (ALS650B). Ferrocene (Fc) was added as an internal standard. All potentials are given relative values to the ferrocenium / ferrocene couple (Fc\(^{+}\) / Fc). The electrolyte (0.1 M TBAP in ODCB) was degassed with nitrogen before use. SEC analyses were performed using a Shimadzu LC-10 system equipped with a Shimadzu UV-vis detector (SPD-10AVp) and a Shimadzu RI detector (RID-10A) (Conditions: column: KF-802.5 + KF-805, column temperature: 40 °C, eluent: THF, flow rate: 1.0 ml/min; standards; polystyrene standards (Shodex)). TGA was conducted in nitrogen with a Shimadzu TGA-50 thermal analyzer by heating from 100 to 700 °C at the programming rate of 10 °C min\(^{-1}\).

1.2. 6-Azido-6-deoxy-2,3-di-O-myristoylcellulose (2)

LiCl (1.2 g, 28.3mmol) was added to a suspension of 6-azido-6-deoxycellulose (1) (150 mg, 0.78mmol) in \(N,N-\)}}
dimethylacetamide (15 ml) at 60 °C. The reaction mixture became a clear solution within several minutes.

Pyridine (1.3 ml, 16.2 mmol) and myristoyl chloride (2.18 ml, 8.04 mmol) were added to the solution. After stirring at 70 °C for 24 h, the solution was diluted with CH₂Cl₂. The organic layer was washed with 1 M HCl, water and brine, dried over Na₂SO₄ and concentrated in vacuo to give an oil. The solution of the oil in a small amount of CH₂Cl₂ was dropped into EtOH (500 ml). The resulting precipitate was collected by centrifugation (15000 rpm, 15 minutes), and was purified by the re-precipitation method again to give 6-azido-6-deoxy-2,3-di-O-

myristoylcellulose (2) as a brown solid (470 mg, 97.0% yield).

Compound 2; DSmyristoyl: 2.02 (determined by elementary analysis); DPN: 78.3 (Mw/Mn: 3.36); ¹H NMR (CDCl₃): δ 5.13 (H-3), 4.76 (H-2), 4.50 (H-1), 3.75 (H-4), 3.61 (H-5,6a), 3.41 (H-6b), 2.23 (OC(=O)CH₂CH₂C₁₀H₂₀CH₃), 1.53 (OC(=O)CH₂CH₂C₁₀H₂₀CH₃), 1.26, (OC(=O)CH₂CH₂C₁₀H₂₀CH₃), 0.88 (OC(=O)CH₂CH₂C₁₀H₂₀CH₃) ppm; ¹³C NMR (CDCl₃): δ 172.5, 171.8 (C=O), 99.7 (C-1), 75.0–71.8 (C-2,3,4,5), 50.0 (C-6), 33.9, 31.9, 29.6, 24.7, 22.7 (OC(=O)C₁₂H₂₄CH₃), 14.1 (OC(=O)C₁₂H₂₄CH₃) ppm; FT-IR (KBr): ν 2104 ((N₃), 1757 (C=O) cm⁻¹.

1.3. 6-Azafulleroid-6-deoxy-2,3-di-O-

myristoylcellulose (3)

Typical method - 6-Azido-6-deoxy-2,3-di-O-

myristoylcellulose (2) (30 mg, 0.050 mmol) was reacted with fullerene (32 mg, 0.044 mmol) in ODCB (5 ml) at 140 °C for 3 h in a 10 ml-test tube by microwave heating with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC), which consists of a continuous focused microwave power delivery system with power output from 0 to 300 W at 2.45 GHz. The reaction mixture was purified by a silica gel column eluted firstly with toluene to remove unreacted C₆₀ and secondly with THF to be recovered, and concentrated in vacuo to give a crude product. The solution of the product in a small amount of CH₂Cl₂ was dropped into MeOH (200 ml). The resulting precipitate was collected by centrifugation (15000 rpm, 15 minutes), and was purified by the re-precipitation method again to give 6-Azafulleroid-6-deoxy-2,3-di-O-

myristoylcellulose (3-4) (31.9 mg, 85.1% yield).

Compound 3-4; DS₆₀: 0.25 (determined by TGA method); DPN: 14.5 (Mw/Mn: 3.64); ¹³C NMR (CDCl₃): δ 172.4 (C=O), 150 – 130 (C₆₀). 68–76 (C-2,3,4,5), 34.2, 32.2, 30.0, 25.0, 23.0, (OC(=O)C₁₂H₂₄CH₃), 14.4 (OC(=O)C₁₂H₂₄CH₃) ppm; FT-IR (KBr) : ν 1755 (C=O), 527 (C₆₀) cm⁻¹.

References
Captions (Scheme, Figures and Table)

Scheme 1 Synthetic route for 6-azafuleroid-6-deoxy-2,3-di-O-myristoylcellulose (3)

Figure 1 UV-vis spectra of product 3-i and C₆₀

Figure 2 DPVs of product 3-I, C₆₀ and compound 2

Figure 3 SEC elution curves of product 3-i

Figure 4 TGA curves of product 3-i and C₆₀

Table 1 Results of addition reaction of C₆₀ to compound 2 under various reaction conditions
Scheme 1  Synthetic route for 6-azafulleroid-6-deoxy-2,3-di-O-myristoylcellulose (3)
Figure 1  UV-vis spectra of product 3-‐i and C_{60}

Figure 2  DPVs of product 3-‐i and C_{60}

Figure 3  SEC elution curves of product 3-‐i

Figure 4  TGA curves of product 3-‐i, C_{60} and compound 2
Table 1 Results of addition reaction of C₆₀ to compound 2 under various reaction conditions

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<tr>
<th>Entry</th>
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<th>Temperature (°C)</th>
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C2 10 0 3 120 MW 3-ii - 49.6 2.64
C3 10 0 3 140 MW 3-iii - 16.5 2.57
C4 10 0 3 180 MW 3-iv - n.m. n.m.

a) per N₃-group  b) MW = microwave  c) DS₆₀ were calculated by TGA method.

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