JOC Note
pubs.acs.org/joc

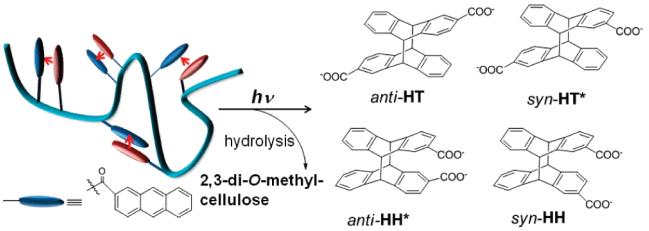
Diastereodifferentiating Photocyclodimerization of 2-Anthracenecarboxylate Tethered to Cellulose Scaffold

Gaku Fukuhara,* Tomohiro Nakamura, Cheng Yang, Tadashi Mori, and Yoshihisa Inoue*

Department of Applied Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan

gaku@chem.eng.osaka-u.ac.jp

Received March 30, 2010

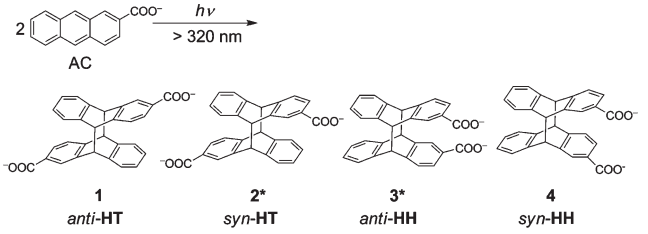


A series of anthracenecarboxylate(AC)-appended 2,3-di-*O*-methylcelluloses (**AC-Cell**s) of varying degrees of substitution (DS) were synthesized to examine their photochirogenic behavior under a variety of conditions. The product distribution and enantiomeric excess of the cyclodimers obtained upon photoirradiation and the subsequent saponification were critical functions of the DS and conversion, for which a conformational change of the flexible polymer backbone is likely to be responsible.

Photochirogenesis[1] enables the preparation of a variety of chiral compounds which are not readily accessible through thermal reactions, serving as an attractive and versatile alternative to the conventional catalytic or enzymatic methods.[2] Although the enantiomeric excesses (ee) of photoproducts obtained in previous studies were modest in general,[3] recent efforts in photochirogeneses with chiral templates have met with great success to give much higher ee's.[1c,4] We have also found that the product's ee and even chiral sense can be dynamically manipulated by the entropy-related variants such as temperature, pressure, and solvation, which led us to the concept of multidimensional control[5] of photochirogenic reaction to afford higher ee's under mild conditions.

In their pioneering work, Tamaki et al. reported the significant acceleration of the photocyclodimerization of anthracenecarboxylates and anthracenesulfonates in the presence of γ-cyclodextrin, but they did not determine the product's ee.[6] Recently, we examined the enantiodifferentiating [4 + 4] photocyclodimerization of 2-anthracenecarboxylate (AC) (Scheme 1) mediated by chiral supramolecular hosts, such as cyclodextrins[7] and biomolecules,[8] and determined the ee's of chiral cyclodimers **2*** and **3*** by using chiral HPLC. More recently, we have shown that the diastereodifferentiating photocyclodimerization of AC tethered to α-cyclodextrin can be mediated by γ-cyclodextrin or cucurbit[8]uril to afford the cyclodimers in much better stereoselectivities, where α-cyclodextrin functions as a bulky chiral auxiliary to remotely control the orientation and conformation of two AC moieties accommodated in the host cavity.[9]

SCHEME 1. Photocyclodimerization of 2-Anthracenecarboxylate



(The absolute configurations of **2*** and **3*** are arbitrary)

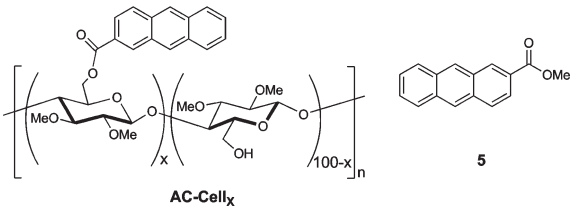
In this study to expand the range of photochirogenesis, we investigated the photophysical and photochemical behavior of AC anchored to 2,3-di-*O*-methylcellulose, which was used as a chiral polymer scaffold. Cellulose is a linear syndiotactic polysaccharide composed of D-anhydroglucopyranose units, which are linked together by β-1,4-glucosidic bonds,[10] while cyclodextrins are cyclic oligosaccharides consisted of α-1,4-D-glucopyranose units.[11] We synthesized a series of AC-appended methylcelluloses (**AC-Cell**) of varying degrees of substitution (DS) and examined their chiroptical properties, and then the **AC-Cell**s were subjected to the diastereodifferentiating photocyclodimerization under a variety of concentrations, temperatures, solvents, and pressures (as entropy-related variants), as well as irradiation period. The results will be discussed to elucidate the factors that control the photochirogenic process on a flexible polymer backbone.

By using the synthetic procedures previously reported for fluorophore-appended celluloses,[12] we performed the AC

(1) For reviews, see: (a) Griesbeck, A. G.; Meierhenrich, U. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3147. (b) Inoue, Y., Ramamurthy, V., Eds. *Chiral Photochemistry*; Marcel Dekker: New York, 2004. (c) Müller, C.; Bach, T. *Aust. J. Chem.* **2008**, *61*, 557. (d) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052.
(2) Nobel Lectures. See: (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024.
(3) Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256.
(4) (a) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982. (b) Albrecht, D.; Vogt, F.; Bach, T. *Chem.—Eur. J.* **2010**, *16*, 4284.
(5) Inoue, Y.; Wada, T.; Asaoka, S.; Sato, H.; Pete, J.-P. *Chem. Commun.* **2000**, 251.
(6) Tamaki, T.; Kokubu, T.; Ichimura, K. *Tetrahedron* **1987**, *43*, 1485.
(7) Yang, C.; Mori, T.; Inoue, Y. *J. Org. Chem.* **2008**, *73*, 5786.
(8) Nishijima, M.; Wada, T.; Mori, T.; Pace, T. C. S.; Bohne, C.; Inoue, Y. *J. Am. Chem. Soc.* **2007**, *129*, 3478.
(9) Yang, C.; Mori, T.; Origane, Y.; Ko, Y. H.; Selvapalam, N.; Kim, K.; Inoue, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8574.
(10) See: Cellulose and Cellulose Derivatives Special Issue. *Macromol. Chem. Phys.* **2000**, *201*, 1913.
(11) See: Cyclodextrins Special Issue. *Chem. Rev.* **1998**, *98*, 1741.
(12) Redl, F. X.; Lutz, M.; Daub, J. *Chem.—Eur. J.* **2001**, *7*, 5350.

DOI: 10.1021/jo100596n Published on Web 05/19/2010

CHART 1. 6-*O*-(2-Anthroyl)methylcelluloses (AC-Cell$_X$; X = 22, 42, and 53%) and Methyl 2-Anthracenecarboxylate (5) as a Reference Compound



esterification of 2,3-di-*O*-methylcellulose with EDC in THF/$CHCl_3$ to obtain 22−53% AC-substituted **AC-Cell**s, i.e., **AC-Cell$_{22}$** in 19%, **AC-Cell$_{42}$** in 44%, and **AC-Cell$_{53}$** in 54%, where the subscripts refer to %DS as shown in Chart 1. The better chemical yield for higher DS sample is attributable to the better solubility of the polymer obtained.

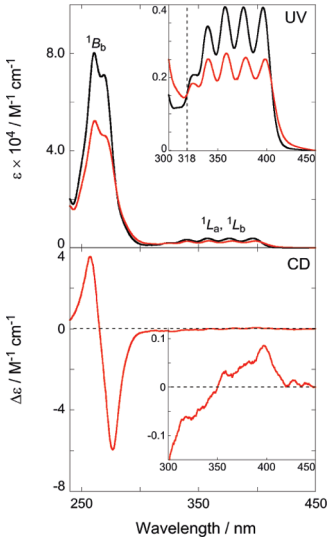


FIGURE 1. UV/vis and CD spectra of **AC-Cell$_{42}$** (0.22 mM in chromophore unit, red) measured in a 2-mm cell and **5** (35 μM, black) measured in a 1-cm cell in dichloromethane at room temperature; the insets show the UV/vis spectra of **AC-Cell$_{42}$** (50 μM in chromophore unit, red) and **5** (50 μM, black) measured in a 1-cm cell and the CD spectrum of **AC-Cell$_{42}$** (0.22 mM in chromophore unit, red) measured in a 1-cm cell.

First, the spectral behavior of **AC-Cell$_{42}$** in dichloromethane was compared with that of methyl 2-anthracenecarboxylate (**5**) as a reference compound. As shown in Figure 1, **AC-Cell$_{42}$** gave much reduced molar extinction coefficients over the entire absorption range with appreciable band-broadening and slight bathochromic shifts by ca. 3 nm, suggesting the aggregation of neighboring AC molecules attached to the polymer.[12,13] In the CD spectrum, **AC-Cell$_{42}$** exhibited a negative exciton couplet at the major ^1B_b band but only weak induced Cotton effects at the ^1L_a and ^1L_b bands. According to the exciton chirality theory,[14] the AC chromophores on the methylcellulose backbone of **AC-Cell$_{42}$** are oriented in the left-handed helical conformation on the average, as was the case with other chromophore-modified methylcelluloses.[12]

(13) Takeuchi, M.; Chin, Y.; Imada, T.; Shinkai, S. *Chem. Commun.* **1996**, 1867.

(14) Berova, N.; Bari, L. D.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914.

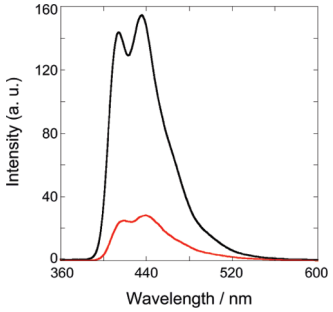


FIGURE 2. Fluorescence spectra of **AC-Cell$_{42}$** (50 μM in chromophore unit, red) and **5** (50 μM, black) excited at 318 nm in dichloromethane at room temperature.

The fluorescence spectral behavior of **AC-Cell$_{42}$** and **5** was comparatively investigated in dichloromethane at room temperature. To evaluate the relative fluorescence quantum yield, dichloromethane solutions of **AC-Cell$_{42}$** (in chromophore unit) and **5** at the same concentration (0.05 mM) were prepared and excited at such a wavelength (318 nm) that gives the same extinction coefficient for both compounds (Figure 1, inset). As shown in Figure 2, the fluorescence spectrum of **AC-Cell$_{42}$** was slightly red-shifted and weaker in intensity by a factor of 5.7, relative to **5**. The much smaller fluorescence quantum yield, as well as the lack of excimer emission at the longer wavelengths, may be rationalized by the efficient photodimerization of AC tethered to the methylcellulose scaffold, as was the case with the supramolecular photocyclodimerization of AC in γ-cyclodextrin cavity.[6,7]

As judged from the exciton-coupled CD spectrum and the reduced fluorescence intensity of **AC-Cell$_{42}$** compared to **5**, the AC moieties attached to the polymer backbone were likely to be located close enough to photocyclodimerize to each other. Indeed, the photoirradiation of **AC-Cell$_{42}$** in dichloromethane gave cyclodimers **1**−**4** as major photoproducts; see Table 1. However, photoreactive groups introduced to a polymer often cross-link two polymer chains.[15] Hence, we examined the effect of **AC-Cell$_{42}$** concentration on the photocyclodimerization behavior to find no essential difference[16] in product distribution or ee at least in the concentration range employed (0.07−0.28 mM in chromophore unit) (Table 1, runs 7−10), indicating no serious contribution of the intermolecular photocyclodimerization.

In the photocyclodimerization of **5** (run 1), the four stereoisomeric cyclodimers were almost randomly distributed to give an HH/HT ratio of 44:56. In contrast, the HH dimers (**3***and **4**) were favored upon photoirradiation of **AC-Cell$_{42}$** to give an averaged HH/HT ratio of 65:35 (runs 7−10). This is compatible with the idea that the photocyclodimerization occurs intramolecularly between the AC moieties tethered to a polymer scaffold. The chiral *syn*-HT (**2***) and *anti*-HH dimer (**3***) were obtained in 13% (run 7) and 22% ee (run 10), respectively, indicating the ability of 2,3-dimethylcellusose as a chiral scaffold.

(15) For recent examples, see: (a) Ide, N.; Tsuji, Y.; Fukuda, T.; Miyamoto, T. *Macromolecules* **1996**, *29*, 3851. (b) Yamaguchi, J.; Watanabe, J.; Takai, M.; Ishihara, K. *J. Appl. Polym. Sci.* **2007**, *104*, 44. (c) Ren, B.; Zhao, D.; Liu, S.; Liu, X.; Tong, Z. *Macromolecules* **2007**, *40*, 4501 and other references cited therein.

(16) Overall average, values in entries 7−10 were calculated as 21 ± 2 for **1**, 15 ± 1 for **2***, 42 ± 2 for **3***, and 22 ± 1 for **4** of the product distribution and as 11 ± 2 for **2*** and 20 ± 2 for **3*** of % ee.

TABLE 1. Product Distribution and Enantiomeric Excesses of Cyclodimers 1−4 Obtained in the Photocyclodimerization of AC-Cells in Dichloromethane under Various Conditions[a]

								product distribution/%					ee[i]/%	
run	substrate	concn[b]/mM	temp/°C	% toluene	pressure/MPa	irradiation time/min	convn/%	**1**	**2***	**3***	**4**	HH:HT[h]	**2***	**3***
1	**5**	0.10	25	0	0.1	60	80	27	29	23	21	44:56	0	0
2	**AC-Cell$_{42}$**	0.17	25	0	0.1	0.25[g]	6	11	7	54	28	82:18	17	7
3						0.5[g]	11	9	6	55	30	85:15	19	10
4						1[g]	20	10	7	53	30	83:17	20	10
5						3[g]	30	13	9	50	28	78:22	19	14
6						15[g]	55	14	10	49	27	76:24	18	16
7						62[g]	77	19	14	45	22	67:33	13	18
8		0.28	25	0	0.1	60	90	23	15	40	22	62:38	8	19
9		0.14	25	0	0.1	60	88	20	14	42	24	66:34	11	20
10		0.07	25	0	0.1	60	87	22	15	42	21	63:37	11	22
11			0				85	20	12	45	23	68:32	8	20
12		0.17	25	0	0.1[f]	60	34	13	10	49	28	77:23	18	16
13					100[f]		54	18	12	46	24	70:30	9	15
14		0.08	25	50	0.1	10[g]	54	13	10	52	25	77:23	14	14
15		[c]	[e]	0	0.1	60	4	23	11	30	36	66:34	10	−15
16	**AC-Cell$_{22}$**	[d]	25	0	0.1	3[g]	25	25	17	42	16	58:42	14	5
17						60	89	25	19	37	16	56:44	6	12
18	**AC-Cell$_{53}$**	0.17	25	0	0.1	0.25	4	6	4	58	32	90:10	18	−10
19						0.5[g]	9	6	4	57	33	90:10	16	−7
20						10[g]	58	9	7	52	32	84:16	15	5
21						60[g]	80	13	10	48	29	77:23	12	5

[a]Irradiated under a nitrogen atmosphere with an ultrahigh-pressure mercury lamp (500 W) fitted with a UV-35 glass filter, unless stated otherwise. [b]In chromophore units. [c]Solid state. [d]Value not determined due to the solubility problem. [e]Room temperature. [f]In a high-pressure vessel. [g]Irradiated under a nitrogen atmosphere with a xenon lamp (300 W) fitted with a band-pass filter (360 nm). [h]HH/HT = ([**3***] + [**4**])/([**1**] + [**2***]). [i]The first-eluted enantiomer is given a positive sign; error < 2% ee.

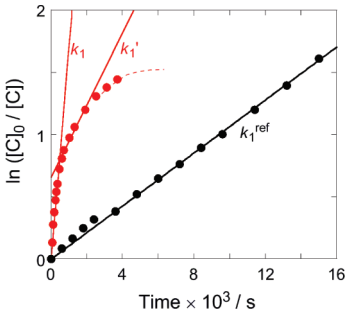


FIGURE 3. First-order kinetic plots for photocyclodimerization of **AC-Cell$_{42}$** (red) and **5** (black) in dichloromethane at 25 °C (correlation coefficient for k_1 = 0.98, k_1' = 0.99 and k_1^{ref} = 0.99).

Interestingly, the product distribution and ee obtained in the photocyclodimerization of **AC-Cell$_{42}$** turned out to be functions of the irradiation period. As shown in Table 1 (runs 2−7), the HH/HT ratio and the ee of **2*** were larger at shorter irradiation periods to give the best values of 85:15 ratio and 20% ee upon < 1 min irradiations (< 20% conversion), whereas the ee of **3*** was enhanced from 7% to 18% by extending the irradiation time from 15 s to 62 min.

To better understand the photocyclodimerization kinetics and the conversion dependency of HH/HT ratio and ee, we monitored the UV spectral changes of the anthracene chromophore upon irradiation of **AC-Cell$_{42}$** and **5** to obtain the first-order kinetics plots (Figure 3 and S6 (Supporting Information)). The reference compound **5** gave a linear plot, from which the rate constant was calculated as $k_1^{ref} = 1.1 \times 10^{-4}$ s^{-1}. In contrast, the UV spectral changes for **AC-Cell$_{42}$** showed saturating behavior, affording a good straight line in the initial stage (up to 40−50% conversion), a relatively good straight line thereafter (up to 70−80% conversion), and finally leveled off at 80−90% conversion. The rate constants for the first and second stages were calculated as $k_1 = 1.7 \times 10^{-3}$ s^{-1} and $k_1' = 2.9 \times 10^{-4}$ s^{-1}, respectively. Thus, the photocyclodimerization of **AC-Cell$_{42}$** is accelerated by a factor of 15 in the initial stage and by a factor of 2.6 even in the middle stage, compared to the photocyclodimerization of **5**.

In nice agreement with the conversion dependency of the rate constant, the HH:HT ratio, as well as the ee value of **2***, showed obvious link at ca. 50% conversion, as shown in Figure 4. Thus, the HH:HT ratio stayed almost constant at 8:2 up to 54% conversion but gradually decreased to reach an extrapolated value of 6:4 at 100% conversion. The enantioselectivity of **2*** was also kept constant at 19% ee up to 54% conversion and gradually decreased to 7% ee at 100% conversion. The ee of **3*** behaved somewhat differently, being steady increased (with a less-clear kink at 40−50% conversion) to reach the ultimate value of 22% ee.

The stereoselectivities of AC dimers obtained upon photocyclodimerization are thought to reflect the original conformation of AC moieties in **AC-Cell$_{42}$**. It is reasonable, therefore, to assume that the HH/HT ratio and ee value obtained in the initial stage (low conversions) represent the inherent stereoselectivities of **AC-Cell$_{42}$** upon photocyclodimerization, where neighboring, or closely located, AC moieties predominantly photocyclodimerize.

However, the HH/HT ratio and ee value at higher conversions are affected more or less by the intrachain cross-linking photocyclodimerization of the AC moieties located at more distant positions. The high HH selectivity (80%) at low conversions and the subsequent decrease at higher conversions seem reasonable, since an excited AC moiety can readily find the photocyclodimerization partner that is oriented in HH fashion at neighboring units, but has to seek for the partner in more distant positions in the later stage, which inevitably leads to the enhanced formation of HT dimers.

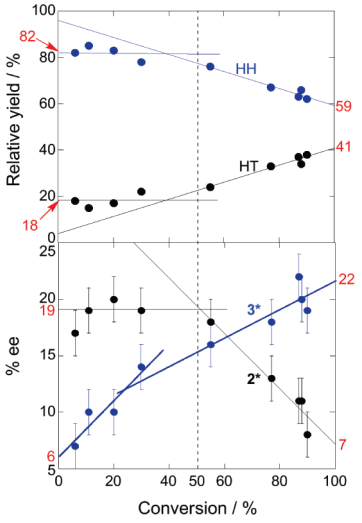


FIGURE 4. Plots of relative yields and ee's obtained upon irradiation of dichloromethane solutions of **AC-Cell$_{42}$** for varying conversions.

Similar behavior observed for the ee of **2*** indicates that the diastereoselectivity of photocyclodimerization to **2*** is higher in the initial, rather than later, stage.

However, this is not the case with the ee of **3***, which is more sensitive to the conversion even in the initial stage, growing from 7% to 22% ee by extending the irradiation time. Probably, the gradually reducing mobility of the polymer chain, caused by the intrachain cross-linking photocyclodimerization, effectively discourages the photocyclodimerization of HT-oriented AC pairs in less favorable conformations and/or more distant positions.

We further examined the effects of temperature, pressure, and solvent (Table 1, runs 11, 13, and 14). However, the photocyclodimerization of **AC-Cell$_{42}$** performed at 0 °C (run 11), at 100 MPa (run 13), or in a 1:1 toluene−dichloromethane mixture (run 14) showed no significant change in relative yield or ee. It is noted that the photocyclodimerization took place even in the solid state. Intriguingly, the chiral sense of **3*** was inverted to afford the antipode in 15% ee (run 15), probably reflecting the change of the initial AC orientation in the solid state.

Since the intramolecular cross-linking upon irradiation turned out to affect the stereochemical outcomes of photocyclodimerization, we prepared **AC-Cell**s of different DS, i.e., **AC-Cell$_{22}$** (DS = 0.22) and **AC-Cell$_{53}$** (DS = 0.53), and examined their photochemical behavior (Table 1). The HH/HT ratio obtained upon irradiation of **AC-Cell$_{22}$** (runs 16 and 17) did not depend on the irradiation time to give an average ratio of 57:43, which is however appreciably smaller than those obtained for **AC-Cell$_{42}$**, while the ee of **2*** decreased from 14% to 6% and that of **3*** increased from 5% to 12%, as was the case in the photoreaction of **AC-Cell$_{42}$**. In the photodimerization of **AC-Cell$_{53}$** (runs 18−21), the HH/HT ratio was greatly enhanced up to 90:10, reflecting the increased abundance of the HH-oriented neighboring AC moieties. The ee's of **2*** were comparable to those obtained for **AC-Cell$_{42}$**, including the decreasing tendency with irradiation time. However, the ee of **3*** behaved very differently with an accompanying inversion of the product chirality, starting from −10% ee at 4% conversion to reach +5% ee at 68−80% conversions. The formation of antipodal **3*** in the initial stage may indicate a significant change in the initial conformation of **AC-Cell$_{53}$**. The chirality switching observed for **3*** upon prolonged irradiations would be attributed to the more severe effect of photoinduced cross-linking on the mobility of AC moieties located at distant positions.

In the present study, we newly synthesized a series of **AC-Cell**s of DS = 0.22, 0.42, and 0.53, elucidated their chiroptical properties, and examined the diastereodifferentiating photocyclodimerization behavior under a variety of conditions to reveal that the HH/HT ratio can be enhanced up to 90:10 by increasing the DS to 0.53, while the ee's of chiral photocyclodimers **2*** and **3*** stay modest at 20−22%. It was also demonstrated that the intramolecular cross-linking photocyclodimerization plays critical roles in determining the HH/HT ratio as well as the ee of chiral products. Further studies on the photochirogenesis with chiral polymer scaffolds, such as polysaccharides, are currently in progress.

Experimental Section

General Procedure for the Synthesis of AC-Cell: AC-Cell$_{42}$. In a 100 mL, three-necked flask, 2,3-di-*O*-methylcellulose (Supporting Information) (300 mg, 1.58 mmol based on the glucose units), AC (525 mg, 2.37 mmol), and DMAP (780 mg, 6.30 mmol) were suspended in dry THF (50 mL) under N_2, to which was added EDC (300 mg, 1.58 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and for an additional 2 days at room temperature. After removal of the solvent, the residue obtained was dissolved in dry chloroform (50 mL), to which were added DMAP (190 mg, 1.58 mmol) and EDC (76 mg, 0.396 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C and for an additional 24 h at room temperature and then concentrated to ca. 10 mL under high vacuum. The concentrated solution was slowly poured into methanol (250 mL) to give a precipitate. The solid was dissolved in chloroform (50 mL) and filtered. The filtrate was slowly poured into methanol (200 mL) again, and the precipitate was collected by washing with acetone to give the **AC-Cell$_{42}$** polymer as yellow solid (190 mg, 0.69 mmol in monomer unit) in 44% yield: ^{1}H NMR (CD_2Cl_2, 400 MHz, 25 °C) δ_H 8.69−7.42, 4.81, 4.34, 4.00−3.29, 2.84; the DS was determined as 0.42 from the comparison of the aromatic and sugar peaks; ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C) δ_C 165.2, 133.4, 132.1, 131.6, 131.4, 131.0, 129.3, 127.7, 127.4, 127.2, 125.6, 125.2, 124.9, 123.0, 102.4, 102.1, 84.0, 82.9, 77.5, 73.8, 72.0, 69.2, 62.3, 60.8, 59.6, 58.1; IR (KBr) ν 3473, 2929, 2836, 2360, 1719, 1630, 1536, 1458, 1413, 1377, 1313, 1278, 1234, 1183, 1078, 957, 887, 807, 731 cm^{-1}; GPC ($CHCl_3$) M_n = 19700 and PDI = 1.8 at 254 nm.

Acknowledgment. We are grateful to Prof. Yoshio Aso and Dr. Makoto Karakawa for the GPC measurement. G.F. appreciates the generous support of a Grant-in-Aid for Young Scientists (start-up) (No. 20850023) from JSPS and also by the Shorai Foundation for Science and Technology. Y.I. acknowledges support of this work by a Grant-in-Aid for Scientific Research (A) (No. 21245011) from JSPS.

Supporting Information Available: General experimental methods and the spectroscopic data for **AC-Cell**s and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.